HERBAL AND DIETARY SUPPLEMENT USE IN THAI PATIENTS WITH CHRONIC KIDNEY DISEASE (CKD) AND THEIR ASSOCIATION WITH PROGRESSION OF CKD

MAYUREE TANGKIATKUMJAI, MSc

Thesis submitted to the University of Nottingham

for the degree of Doctor of Philosophy

NOVEMBER 2014

Abstract

There is limited scientific evidence of herbal and dietary supplement (HDS) safety amongst patients with renal insufficiency, including the prevalence, patterns and reasons for HDS use. The primary objective of this thesis was to determine any associations between HDS use and the fast progression of chronic kidney disease (CKD) in Thai outpatients with CKD. The other objectives were to determine 1) any associations between HDS use and CKD complications; 2) patterns of any other risk factors of CKD progression and its complications; 3) the prevalence, types, patterns and reasons for HDS use; 4) the demographic characteristics of Thai patients with CKD using HDS, compared with non-users; 5) any association between HDS use and the level of adherence to prescribed, conventional medication; 6) patients' experiences of the beneficial and adverse effects from using HDS; and 7) rate of non-disclosure of HDS use to a doctor and the reasons for that non-disclosure.

Following ethical approval in Thailand, a survey recruited 421 outpatients with stages 3 to 5 CKD from two kidney clinics in central Thailand, from January to June 2012. A prospective cohort study followed up these respondents, in particular noting their serum creatinine, as well as serum levels of potassium and phosphate, for 12 months. Three hundred and fifty-seven respondents were completely followed up. The exposed group was defined as the current and regular users of HDS and the primary outcome of the cohort study was defined as either a decline in the estimated glomerular filtration rate of at least 5 ml/min/1.73m^2/year or the initiation of renal replacement therapy. Sixteen HDS users were recruited from the survey to be interviewed about their reasons for using HDS, using open-ended questions to elicit information in the qualitative study. Exclusion criteria were those with had received renal replacement therapy before the recruitment.

Patients were interviewed face to face regarding demographics, use and disclosure of HDS, and adherence to prescribed, conventional medicine, which was assessed by the Thai version of the 8-Item Morisky Medication Adherence Scale®. Their co-morbidities, current use of conventional medicine and laboratory results were extracted from their medical notes. Univariate and multivariate analyses were performed to determine the associations using Chi-squared tests and multiple logistic regressions for dichotomous independent and dependent variables. Tests were 2-tailed and a *p*-value < 0.05 was considered statistically significant.

The prevalence of HDS use during the previous year in Thai patients with CKD was 45% (95%CI 40%-50%) and 99% of these used HDS together with conventional medicine. Most respondents used HDS for maintaining well-being (61%) whilst 30% used HDS for kidney diseases. Kariyat, turmeric and horse radish tree were the most commonly used HDS. The most frequently reported influences on HDS use in the survey and the qualitative study were family members, friends and perception of benefits gained from using HDS. Seventy-two percent did not inform their doctor about their HDS use. Those reporting a medium level of conventional medicine adherence (adjusted OR 0.53, 95% CI 0.32-0.87) were less likely to use HDS, compared with those reporting poor adherence.

An association between HDS use and CKD progression was not found (adjusted OR 1.16, 95%CI 0.66 – 2.03). Existing proteinuria at baseline had the strongest association with the fast progression of CKD (adjusted OR 4.22, 95% CI 2.52 – 7.05), followed by younger age (adjusted OR 1.91, 95% CI 1.14 – 3.18). Two respondents (0.6%) had acute kidney injury, which may be related to the use of unknown Chinese herbal medicines or river spiderwort combined with diclofenac; issues which were reported by their doctor in their medical note. Additionally, HDS use was associated with uncontrolled hyperphosphatemia (adjusted OR

3.53, 95%CI 1.20 – 10.43), possibly due to the HDS used in the cohort study which contained phosphate or vitamin D. Meanwhile, no association between HDS use and uncontrolled hyperkalemia was found (adjusted OR 0.59, 95%CI 0.25 – 1.38).

Health care providers, particularly in Thailand, should be aware of the high number of CKD patients using HDS; in particular that many may not inform their doctor about their HDS use. For this reason it is suggested enquiries about HDS use should be included in guidelines for CKD management. They should also closely monitor CKD patients using Chinese herbal medicine, river spiderwort or HDS containing phosphorus or vitamin D. Proteinuria raises more concerns about the fast progression of CKD than HDS use in Thai patients with CKD. A limitation of this cohort study was that it considered all HDS use and had a limited sample size. Further studies need to extend the follow-up period of this cohort study to 5 years to investigate any long-term effects of HDS, in a population-based cohort study, in order to confirm this present study's findings and to examine renal adverse effects of specific herbal medicines, particularly in relation to acute kidney injury.

Publications

Tangkiatkumjai M, Boardman H, Praditpornsilpa K, Walker DM. Association between herbal and dietary supplement use and the progression of chronic kidney disease. *American Journal of Kidney Disease* 2014;63(5):A108. This abstract was presented as a poster at the Spring Clinical Meeting held by the National Kidney Foundation, Las Vegas, April 2014.

Tangkiatkumjai M, Boardman H, Praditpornsilpa K, Walker DM. Prevalence of herbal and dietary supplement usage in Thai outpatients with chronic kidney disease: a cross-sectional survey. *BMC Complementary & Alternative Medicine* 2013;13:153.

Tangkiatkumjai M, Boardman H, Praditpornsilpa K, Walker DM. The prevalence and patterns of herbal and dietary supplement usage in Thai patients with chronic kidney disease. *Research in Complementary Medicine* 2013; 20 (suppl 1): 111. Poster presentation, International Congress on Complementary Medicine Research (ICCMR), London, April 2013 and awarded “Honorable Mention”.

Tangkiatkumjai M, Boardman H, Walker DM. The association between herbal and dietary supplement use and renal outcomes among pre-dialysis patients in Thailand. Poster presentation, Faculty Postgraduate Research Forum, University of Nottingham, June 2011, and won the prize for best poster.

Tangkiatkumjai M, Boardman H, Walker DM. The association between herbal and dietary supplement use and renal outcomes among pre-dialysis patients in Thailand: design and methods. Oral presentation, Alternative and Complementary Health Research Network conference (ACHRN), Manchester, July 2011.

Tangkiatkumjai M, Boardman H, Walker DM. Herbal and dietary supplement use in Bangkok: a survey. Journal of Complementary and Integrative Medicine 2014; 11(3): 203-211, see Appendix 1.

Acknowledgements

I would like to thank all the people who have contributed to this thesis. First of all, I would like to thank my supervisors, Dr. Dawn-Marie Walker and Dr. Helen Boardman for their support, being patient to regularly read and comment on my report and for their invaluable advice. Many thanks to Associate Professor Kearkiat Praditpornsilpa, my local supervisor, for his support and recommendations regarding the clinical aspects of my research; and to Assistant Professor Somratai Vadchravivad for her support.

I would like to thank the Royal Thai Government for funding this PhD study, and the patients and their family members who participated in the studies. Many thanks to the doctors, nurses and pharmacists in both King Chulalongkorn Memorial Hospital and HRH Princess Maha Chakri Sirindhorn Medical Center who provided access to their patients, and Professor Donald E. Morisky, Associate Professor Grace Kuo and Dr. Phantipa Sakthong for their permission to use their questionnaire. I would also like to thank Ms. Panjit Chaiyasanit and Mr. Piya Kaewkrachang for their help with data collection, Dr. Charoen Treesak for backward translation, and Professor Cees van der Eijk who provided recommendations concerning sample size determination.

Finally, I would like to thank my family for their endless support, as well as my friends and my colleagues for their help.

Table of contents

List of tables

List of figures

List of flowcharts

List of abbreviations and acronyms

A1C	Glycated haemoglobin
ACEIs	Angiotensin-converting enzyme inhibitors
ACR	Albumin and creatinine ratio
ACS	Acute coronary syndrome
AKI	Acute kidney injury
AOR	Adjusted odds ratio
ARBs	Angiotensin II receptor antagonists
BMI	Body mass index
BMQ	Brief Medication Questionnaire
CAM	Complementary and alternative medicine
CI	Confidence interval
CKD	Chronic kidney disease
CM	Conventional medicine
COX-2 inhibitors	Cyclooxygenase-2 inhibitors
CU	Chulalongkorn University
CVD	Cardiovascular disease
DDFQ	Dialysis diet and fluid non-adherence questionnaire
DS	Dietary supplement
eGFR	Estimated glomerular filtration rate
ESRD	End-stage renal disease
FDA	Food and Drug Administration
GFR	Glomerular filtration rate
HCP	Health care professionals
HDS	Herbal and dietary supplement
HIV	Human immunodeficiency virus
IBD	Inflammatory bowel disease
ICC	Intraclass correlation coefficient
IM	Integrative medicine
KDIGO	Kidney Disease Improving Global Outcomes
Kg/m^2	Kilogram per square meter
LDL	Low-density lipoprotein
MARS	Medication Adherence Rating Scale
MDRD	Modification of Diet in Renal Disease
mg/dl	Milligram per deciliter
$ml/min/1.73m^2$	Milliliter per minute per 1.73 square meter

MMAS®	Morisky Medication Adherence Scale®
mmol/l	Millimole per liter
NCCAM	National Center for Complementary and Alternative Medicine
NICE	National Institute for Health and Clinical Excellence
NKF-KDOQI™	National Kidney Foundation Kidney Disease Outcomes Quality Initiative
NSAIDs	Non-steroidal anti-inflammatory drugs
OR	Odds ratio
PCR	Protein and creatinine ratio
RPPPS	Restriction of Protein, Potassium, Phosphate and Salt diet
SEEK	Screening and early evaluation of kidney disease
SMAQ	Simplified Medication Adherence Questionnaire
SWU	Srinakharinwirot University
TM	Traditional medicine
UK	United Kingdom
US	United States
WHO	World Health Organisation

1. Introduction to the study

The prevalence of the use of herbal and dietary supplements (HDS) has been increasing worldwide, particularly in Asian populations.[1] Patients with stages 3 to 5 chronic kidney disease (CKD) are more vulnerable to renal adverse effects of HDS and there are several reports of nephropathy from using HDS in general populations.[2-7] Therefore, health professionals have raised safety concerns about HDS use in patients with CKD.[8-10] The US National Kidney Foundation Kidney Disease Outcomes Quality Initiative in 2012 (NKF-KDOQI®), and the Thai guideline for CKD management in 2009, have both recommended patients with CKD should avoid using herbal medicines, although they have only a few case reports of products containing aristolochic acid use related to acute kidney injury to support this recommendation.[11,12] Case reports are the main source of evidence regarding renal adverse effects from HDS use[2,3] although there have been cross-sectional and case-control studies in Thailand and Taiwan reporting the use of herbal medicine relating to individuals newly diagnosed with CKD or end stage renal disease.[4,5,7] There is limited evidence of HDS use being associated with progression of CKD and its complications amongst patients with advanced CKD, particularly in prospective studies.[13]

Despite the high prevalence of HDS use in Asian populations, there is a lack of studies investigating the use and effects of HDS amongst patients with CKD.[14] Most epidemiological studies in Thailand and Taiwan have investigated general populations using herbal medicines and have measured end-stage renal disease or developing CKD as an outcome.[4-7,13] There is limited information from a small number of surveys about HDS use in Western populations with CKD.[15,16] These issues need to be investigated in order for health care professionals to be aware of likely HDS use in such patients, and to identify and monitor the effects of HDS in those patients.

The association between HDS use and adherence to prescribed, conventional medication is unknown. Literature reports HDS use being associated with poor adherence to conventional medication or that there is no relationship between these two variables.[17-19] Further studies are required to ascertain any association as conventional medication adherence is a crucial factor related to the achievement of pharmacotherapeutic outcomes in patients.

The primary aim of this thesis, in a prospective cohort study, was to determine any associations between HDS use and the progression of CKD, including its complications in Thai patients with advanced CKD. This would provide further evidence of the safety of HDS in these patients and provide evidence for health care providers, when advising on the use of HDS with this population. The other aims were to determine 1) the patterns of any other risk factors of CKD progression and its complications; 2) the prevalence, types, patterns, and reasons for HDS use; 3) the demographic characteristics of Thai patients with CKD using HDS, compared with non-users; 4) any association between HDS use and the level of adherence to prescribed, conventional medication; 5) patients' experiences of the beneficial and adverse effects from using HDS; and 6) rate of non-disclosure of HDS use to a doctor and reasons for non-disclosure.

Structure of the thesis

Following this introduction, this thesis consists of a further nine chapters and these chapters are summarised below.

Chapters 2 to 4 present the literature review, gaps in research and content of each chapter is as follows:

Chapter 2 presents an overview of herbal and dietary supplements – definitions of HDS, the prevalence of HDS use in patients with CKD and demographic characteristics of those using HDS. This chapter then presents about attitudes towards HDS use and disclosure of HDS use. Evidence for relationships between

HDS use and adherence to prescribed conventional medicine is examined. Finally, this chapter presents the regulations regarding availability and recommended use of HDS, and details of a post-marketing surveillance system for adverse effects from HDS use in Thailand.

Chapter 3 gives an overview of chronic kidney disease, including its definition and classification of CKD. Then the prevalence of CKD in Thailand is described, together with the symptoms and complications of CKD, risk factors for and the measurement of the progression of CKD and CKD complications. This is followed by the presentation of treatment options in CKD, and recommendations for HDS use, based on guidelines for the management of CKD.

Chapter 4 describes the negative and positive effects of HDS use on the renal system.

Chapters 5 and 6 present the study's aims and an overview of the methods used. There are two main studies described in this thesis; a cross-sectional survey of CKD patients attending an outpatient clinic and these patients then formed a cohort which was followed prospectively for one-year. The survey determined the prevalence, types, patterns and reasons for HDS use; the demographic characteristics of Thai patients with CKD using HDS compared with non-users; any association between HDS use and the level of adherence to prescribed, conventional medication; patients' experiences of the beneficial and adverse effects from using HDS; and the rate of non-disclosure of HDS use to a doctor and reasons for such non-disclosure. Meanwhile the cohort study determined associations between HDS use, the progression of CKD and its complications, and the patterns of any other risk factors of CKD progression and its complications. The method chapter explains the reasons for the inclusion and exclusion criteria, and selected settings for both studies.

Chapter 7 describes the development and testing of researcher administered questionnaires regarding demographics, types, patterns, purposes and disclosure of HDS use, perception of benefits and adverse effects of HDS for a survey, and researcher administered open-ended questions about attitudes towards HDS use for a qualitative study. The validity and reliability of the Thai-version of the 8-item Morisky Medication Adherence Scale® and the Restriction of Protein, Potassium, Phosphate and Salt Diet (RPPPS) Questionnaire for pre-dialysis patients were tested with a group of Thai CKD patients. Further aims were to test the recruitment process, to estimate the time needed to recruit for the main study, and to analyse the completeness of routinely collected information from patients' records in the two settings.

Chapter 8 presents the findings from the survey of the prevalence, types, patterns, and disclosure of HDS use; the demographic characteristics of Thai patients with CKD using HDS, compared with non-users; perceptions of benefits and adverse effects of HDS use amongst Thai outpatients with CKD, including analysis of the association between HDS use and adherence to prescribed conventional medicine. Reasons for HDS use are presented based on data from both the survey and the qualitative study. This chapter supports the other aims of the thesis and explains the reasons for the study's design.

Chapter 9 presents the findings from the cohort study, which investigated any associations between HDS use, the progression of CKD and its complications. There are explanations concerning reasons for study design and definitions of exposed and unexposed groups, risk factors and study outcomes.

Chapter 10 summarises and concludes the thesis – key findings, summary of discussion, strengths and weaknesses of the study, implications for clinical practice and policy, and recommendations for further studies.

2. Herbal and dietary supplements

There is widespread usage of herbal and dietary supplement (HDS). The World Health Organisation (WHO) reports over 75% of the population, in some Asian countries, use herbal medicine whilst 38-75% of Western populations use complementary and alternative medicine.[1] In the last decade research in this field has been increasing. Many Asian countries have established a research institution of herbal medicine, such as China, South Korea, Thailand, Indonesia and Viet Nam.[1] Funding for alternative medicine research has been increasing in both the US and UK.[1] Various definitions of HDS have been reported in the literature and are discussed in this chapter. An overview of complementary, alternative and integrative medicine, the prevalence of HDS use, attitudes about and influences on HDS use, and the regulatory and safety environment for HDS in Thailand, are presented in this chapter.

2.1 Overview of complementary, alternative and integrative medicine

2.1.1 Definitions of complementary, alternative and integrative medicine

There are two terms commonly used to describe non-conventional medicine: i) complementary and alternative medicine (CAM) and ii) integrative medicine (IM). CAM is used more often to describe a new choice of therapy, instead of conventional medicine, whilst IM refers to integrated use of alternative medicine with conventional medicine.[20,21]

CAM has been defined by WHO, the National Center for Complementary and Alternative Medicine (NCCAM) in the US and the House of Lords in the UK. The definitions are similar in their meanings and enable them to be used worldwide.

"*CAM are used to refer to a broad set of health care practices that are not part of a country's own tradition, or not integrated into its dominant health care system*" (World Health Organization, 2002:7).[1]

NCCAM defines CAM as "*a group of diverse medical and health care systems, practices and products that are not generally considered part of conventional medicine*".[22] Similarly, the House of Lords defines CAM as "*a diverse group of health-related therapies and disciplines which are not considered to be a part of mainstream medical care*".[23] These definitions are defined from a Western perspective. From an Asian perspective, the term 'traditional medicine' (TM) is more likely to be used rather than CAM, as in most Asian countries TM is embedded in health care systems as a mainstay or self-care management of a wide variety of conditions. In such countries as India, China and Thailand, individuals are likely to turn to TM before treatment is sought from Western or conventional medicine.[21]

In Thailand, the Practice of the Arts of Healing Act 1999 defined Thai traditional medicine as "*the medical processes dealing with the examination, diagnosis, therapy, treatment, or prevention of diseases, or promotion and rehabilitation of the health of humans or animals, midwifery, Thai massage, as well as the preparation, production of Thai traditional medicines and the making of devices and instruments for medical purposes. All of these are based on the knowledge or textbooks that were passed on and developed from generation to generation*".[24] Recently, the National Health Care System in Thailand has included alternative medicine, i.e. herbal medicine, acupuncture and massage, and therefore most Thai people consider CAM with conventional medicine as a mainstream medicine and they will routinely use such treatments.

2.1.2 Types of CAM

The House of Lords (2000) classified CAM into three groups.[23] Firstly, professionally organised alternative therapies which claim to have an individual diagnostic approach including acupuncture, chiropractic, herbal medicine, homeopathy and osteopathy.[23] This group is the most frequently used in the UK. Secondly, complementary therapies, which are added to conventional medicine: the Alexander technique, aromatherapy, Bach and other flower remedies, body work therapies, including massage, counselling stress therapy, hypnotherapy, meditation, reflexology, Shiatsu, healing, Maharishi Ayurvedic medicine, nutritional medicine and yoga. Finally, alternative disciplines are divided into long-established and traditional systems of healthcare, and other alternative disciplines, which have limited evidence of effectiveness. Within the final group the first subgroup consists of anthroposophical, Ayurvedic medicine, Chinese herbal medicine, Eastern medicine, naturopathy and traditional Chinese medicine. The second subgroup is crystal therapy, dowsing, iridology, kinesiology and radionics.[23] A national survey in the UK found that herbal medicine was the most frequently used CAM (34%), compared with aromatherapy (21%), homeopathy (17%), acupuncture or acupressure (14%) and massage (6%).[23]

NCCAM classified types of CAM into natural products, mind and body medicine, manipulative and body-based practices, and other CAM practices.[22] Natural products refer to herbal medicines or dietary supplements. Mind and body medicine consists of meditation and acupuncture whilst manipulative and body-based practices include spinal manipulation, such as chiropractic and massage. Examples of other CAM practices are the Alexander technique and Feldenkrais method. A national survey in the US showed natural products were the most frequently used (22%), followed by chiropractic (8%), yoga (5%) and massage (5%).[25]

In Thailand, types of Thai traditional medicine are herbal medicine, Thai massage, hot herbal compresses and herbal steam baths, and meditation.[26] A survey of hospital patients in Thailand reported that folk remedies or herbal medicine was the most frequently used (72%), followed by massage (31%) and dietary supplements (12%).[27]

Therefore, herbal medicines and dietary supplements fall within the definitions of CAM and are the most frequently used types of CAM.

2.2 Definition of herbal and dietary supplement use

There are various terms and definitions of HDS across studies of HDS usage.[4,10,14,15,28-30] 'Natural products' was the term used by Grabe and Garrison (2004) and Laliberte et al. (2007), whilst 'natural herbs' was used by Kennedy (2005) and Gardiner et al. (2007). Grabe and Garrison (2004) defined 'natural products' as herbal or dietary supplements.[15] Likewise, Kennedy (2005) and Gardiner et al. (2007) used 'natural herbs', which include dietary supplements.[28,29] The term 'dietary supplements', which includes herbs, was used by Timbo et al. (2006).[10] However, Laliberte et al. (2007) did not define the term in their study.[30]

In Asian countries, some herbs are part of diet or are added to flavour food, rather than used for health reasons. Studies of herbal medicine use in Turkey and Taiwan[4,14] did not include herbal food consumption in their definition of herbal medicine usage. Therefore, studies of herbal medicine from Asian countries are less likely to include herbal food consumption, as this may overestimate prevalence of herbal medicine use.

There are widely used definitions of herbal medicine and dietary supplements defined by the WHO and the US Food and Drug Administration (US FDA),

respectively. The WHO defines a herbal medicine as "*a plant-derived material or preparation with therapeutic or other human health benefits which contains either raw or processed ingredients from one or more plants. In some traditions materials of inorganic or animal origin may also be present*" (World Health Organization, 2000: 27).[31] Dietary supplements are defined by the US FDA as products containing ingredients in order to supplement diet.[32] Dietary ingredients include vitamins, minerals, herbs or other botanicals, amino acids and substances, such as enzymes, organ tissues, glands and metabolites.[32] The Thai Drug Act 1967 defined herbal medicine as "*medicine [that] is derived from a plant, animal and mineral in a raw state*".[33]

In the present study, HDS was defined as products containing plant-derived material, which may be raw or processed ingredients from one or more plants; or products containing dietary ingredients, such as vitamins, minerals, amino acids and substances, for example enzymes, organ tissues, glands and metabolites, which combines the US FDA and WHO definitions.[31,32] Additionally, this study focused on HDS use for the treatment of illnesses or health promotion rather than consumption as daily food intake or for cosmetic purposes, due to HDS being less likely to be frequently used. Also the study did not include prescribed dietary supplements, which were a standard treatment for CKD.

2.3 The prevalence of CAM and HDS use and their characteristics

There is limited evidence reporting the prevalence and demographic characteristics of CAM or HDS use amongst patients with CKD, whilst large numbers of surveys have reported this information in both the general and other patient populations.

2.3.1 The prevalence of HDS and CAM use in patients with CKD

The prevalence of current HDS use amongst patients with CKD in Canada and the US ranges from 29 to 45%, see Table 2.1.[15,16] However, there is no evidence from Asian populations. In the US, the prevalence of HDS use amongst patients with CKD (29%)[15] was lower than patients with cardiovascular disease (57%)[34] and the general population (52-73%).[10,35] Similarly, the prevalence of herbal use in dialysis patients (28%) in Turkey[14] was lower than the general population (55%).[36] Whereas there was no difference in the prevalence of dietary supplement use between patients with CKD (45%) in Canada[16] and the general population (40%).[37]

Table 2.1 Studies reporting the prevalence of HDS or CAM use in patients with CKD, patients receiving dialysis or kidney transplant recipients (n=5)

Authors and country	Definition	Population and sample size	Prevalence (%)
Kara (2009), Turkey[14]	Herbal product use was defined as 'having ever used them for health maintenance or treatment of health problems rather than for food consumption'	114 haemodialysis patients	28.1
Hess et al. (2009), Switzerland[38]	CAM defined by Institute of Medicine of the National Academies	356 kidney transplant recipients	11.8 (CAM use) 1.9 (herbal use)
Nowack et al. (2009), Germany[39]	- CAM use was defined as 'having regularly consumed CAM in the last 12 months' - CAM use were herbal or dietary supplements	119 dialysis patients	57
		45 kidney transplant recipients	49
Spanner and Duncan (2005), Canada[16]	- DS use defined as 'current daily consumption' - DS defined by the Dietary Supplement Health and Education Act (1994)*	100 patients with CKD	45
Grabe and Garrison (2004) US[15]	- Natural products use defined as 'current use' - Natural products were defined as 'herbal or dietary supplements'	250 pre-dialysis patients	29

* Dietary supplement defined as a product intended to supplement the diet and not a conventional food[16]

2.3.2 The prevalence of CAM and HDS use in the general and patient populations

There are large numbers of studies measuring the prevalence of CAM or HDS use in the general population (n=15)[4,10,25,35-37,40-48], compared with such prevalence in patients with CKD (n=5).[14-16,38,39] The prevalence of CAM or HDS use varies considerably across both general and patient populations.[17-19,27,34,49-68] Some of the variation can be explained by the different periods used to measure prevalence and by the various definitions of CAM, dietary supplement (DS) or

HDS use, see Tables 2.2 and 2.3. 'One-year' is most frequently reported in the literature regarding the prevalence of HDS or CAM use in both general and patient populations (n=19, 48%). Definitions of CAM, DS or herbal use in the literature were mainly based on the NCCAM definition (n=11, 28%). However, 33% (n=13) and 25% (n=10) of surveys of such prevalence did not define a period of use and definition of CAM or HDS, respectively. Sixty-eight percent (n=27) of these surveys reported the prevalence of CAM use and 55% (n=22) showed the prevalence of HDS use.

Table 2.2 Studies reporting the prevalence of CAM and/or HDS use in general populations (n=15)

Authors and country	Definition and period for prevalence	Sample size	Prevalence (%)
Thomson et al. (2012), Australia[48]	CAM use was not defined	1,261	61.7
Hunt et al. (2010), UK[47]	CAM use in the last 12 months	7,630	26.3
Marques-Vidal et al. (2009), Switzerland[44]	DS defined by authors*	6,188	25.7 (DS use, including plant extracts)
Ock et al. (2009), South Korea[45]	- CAM use in the last 12 months - CAM defined by NCCAM	3,000	74.8 (CAM use) 65.4 (HDS use)
Aziz and Tey (2009), Malaysia[46]	- Herbal use in the last 12 months - Herbal medicine defined by authors**	1,601	33.9
Guo et al. (2009), Canada[37]	Vitamin and mineral supplements use in the last month	35,107	40.1
Aydin et al. (2008), Turkey[36]	- Herbal use in the last 12 months - Herbal medicine defined by NCCAM	873	55.4
Guh et al. (2007), Taiwan[4]	- Herbal use was not defined	1,740	21.6
Xue et al. (2007), Australia[43]	CAM use in the last 12 months	1,067	68.9
Timbo et al. (2006), US[10]	- DS use in the last 12 months - DS defined by the Dietary Supplement Health and Education Act (1994)***	2,743	73 (DS use, including herbal medicine)
Barnes et al. (2004), US[25]	- CAM use in the last 12 months - CAM defined by NCCAM	31,044	36 (CAM use) 18.9 (HDS use)
Radimer et al. (2004), US[35]	- Dietary supplements (DS) use in the last month - DS defined by the Dietary Supplement Health and Education Act (1994)***	4,862	52 (DS use, including herbal medicine)

Table 2.2 (continued)

Authors and country	Definition and period for prevalence	Sample size	Prevalence (%)
Singh et al. (2004), South Africa[42]	- CAM use in the last 12 months - CAM defined by the American National Institute of Health's Office of Alternative Medicine	200	38.5
Al-Windi et al. (2000), Sweden[40]	Herbal use in the last 12 months	1,312	31.8
Balluz et al. (2000), US[41]	- Vitamin and mineral supplements use in the last month - They defined by the Dietary Supplement Health and Education Act (1994)***	33,905	40

* Dietary supplements were defined as all possible dietary components not usually included in a regular diet, including herbal tea and plant and animal extracts.

** Herbal medicine was defined as all plant-derived products which contain either raw or processed ingredients from one or more plants used to prevent or treat diseases.

*** Dietary supplements were defined as a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients: a vitamin, a mineral, an herb or other botanical, an amino acid, or a dietary substance for use to supplement the diet by increasing the total dietary intake, or a concentrate, metabolite, constituent, extract, or combination of the above ingredients.

The prevalence of CAM use within a year in general populations ranges from 26% to 75%, see Table 2.2.[25,42,43,45,47] A similar range of prevalence is seen in studies amongst patients with chronic illnesses, which varies from 23% to 88%, see Table 2.3.[19,49,52,53,58,59]

Use of CAM is generally higher in Asian populations compared with Western populations. The prevalence in Western populations varies from 26% to 36% [25,47], whereas amongst Asian populations, the prevalence ranges from 38% to 75%.[42,45]

The one-year prevalence of HDS use amongst general populations ranges from 19% to 73% in the US and South Korea.[10,25,45] It would seem that the one-year prevalence of CAM and HDS use in general populations is quite similar (26-75% versus 19-73%).[25,42,43,45,47] Thus, this indicates that HDS is more likely to be used than other CAMs. However, it is not possible to accurately compare the one-year prevalence of HDS use between Western and Asian populations due to the low number of studies in both populations, and inconsistent prevalence of HDS use in the US, due to differences of HDS definitions. Likewise, there are insufficient studies to compare the one-year prevalence of HDS use between general and patient populations.

The one-year prevalence of herbal use amongst the general population in Sweden, Turkey and Malaysia ranges from 32% to 55%, see Table 2.2.[36,40,46] Kennedy (2005) in the US reported that the Asian population was more likely to use herbal medicine in the last 12 months compared with the Caucasian population (25% versus 19%).[29] However, there is limited evidence about the prevalence of herbal use in Thailand and two previous studies have not defined a period of herbal use.[5,69] These two studies were conducted by Ingsathit et al. (2010) and Satyapan (2010), and found that the prevalence of herbal use in Thailand and Bangkok were 33% and 29%, respectively. The main objective of Ingsathit's study was to determine risk factors influencing chronic kidney disease

(CKD), rather than the prevalence of herbal use in the Thai population.[5] Although Satyapan's study was to determine the prevalence of herbal use in Bangkok, respondents were recruited from Thai people attending or working at the Phramongkutklao hospital in Bangkok, and therefore, this may not represent the general population in Bangkok.[69]

Table 2.3 Studies reporting the prevalence of CAM and/or HDS use in patient populations (n=25)

Authors and country	Definition and period for prevalence	Population and sample size	Prevalence (%)
Strejilevich et al. (2013), Argentina and Colombia[68]	CAM defined by Barnes and Ernst (1997)[a]	200 outpatients with bipolar disease	46.7 (CAM use together with conventional medicine)
Ali-Shtayeh (2012), Palestinian territories[66]	Herbal medicine was not defined	1,883 diabetic patients	51.9
Weizman et al. (2012), Canada[18]	CAM defined by Zollman and Vicker (1999)[b]	380 patients with inflammatory bowel disease	56
Braun and Cohen (2011), Australia[65]	CAM use in the last 2 weeks before hospital admission	161 elective cardiac surgery inpatients	51
Krousel-Wood et al. (2010), US[17]	- CAM use was defined as the use of CAM at least several times or on a regular basis in the year before the baseline survey - CAM defined by NCCAM	2,000 elderly patients with hypertension	26.5
Shorofi and Arbon (2010), Australia[67]	- Herbal medicine have used daily - Defined by NCCAM	353 inpatients	38.2
Lambert et al. (2010), UK[63]	CAM defined by Eisenberg et al. (1993)[c]	92 outpatients with headache	32 (CAM use) 13 (herbal use) 10.9 (DS use)
Ogbera et al. (2010), Nigeria[64]	- CAM use was defined as the use of CAM more than once for any period of time - CAM defined by NCCAM	263 diabetic patients	46

Table 2.3 (continued)

Authors and country	Definition and period for prevalence	Population and sample size	Prevalence (%)
Hasan et al. (2009), Malaysia[61]	CAM was defined by authors[d]	321 outpatients	63.9
Wilkinson and Jelinek (2009), Australia[62]	- CAM use in the last 12 months - CAM defined by NCCAM	102 elderly patients with chronic illnesses	78 (CAM use) 54 (Vitamin and mineral use) 28 (herbal use)
Gohar et al. (2008), UK[19]	- CAM use in the last 12 months - CAM defined by NCCAM	153 patients with hypertension	43.1
Hori et al. (2008), Japan[59]	- CAM use in the last 12 months - CAM defined by NCCAM	496 outpatients	50 (CAM use) 28.4 (DS use)
Rossi et al. (2008), Italy[60]	CAM use in the last 12 months	100 patients with headache	10
Kumar et al. (2006), India[56]	CAM defined by NCCAM	493 diabetic patients	67.7
Saw et al. (2006), Malaysia[57]	Herbal medicine defined by WHO guidelines for the appropriate use of herbal medicines (1998)[e]	250 inpatients	42.4
Yeh et al. (2006), US[58]	- CAM use in the last 12 months - Biological based therapies defined by authors[f]	10,572 patients with CVD	68 (CAM use) 21.8 (biological based therapies)
Barraco et al. (2005), US[53]	- CAM use in the last 12 months - Listed types of CAM	223 inpatients with acute coronary syndrome	63
Hyodo et al. (2005), Japan[54]	CAM defined by WHO (2002)	3,100 patients with cancer	44.6
Molassiotis et al. (2005), 14 countries in Europe[55]	- Past and current use of CAM - CAM defined by Ernst et al. (1995)[g]	956 patients with cancer	35.9
Moolasarn et al. (2005), Thailand[51]	- CAM use in the last 3 months - CAM defined by Eisenberg et al. (1993)[c]	159 diabetic patients	47.8 (CAM use) 32 (herbal use)
Lee et al. (2004), Singapore[52]	CAM use in the last 12 months	488 patients with chronic illnesses	22.7

Table 2.3 (continued)

Authors and country	Definition and period for prevalence	Population and sample size	Prevalence (%)
Stys et al. (2004), US[34]	- Naturoceutical use in the last 12 months - Naturoceutical agents were vitamin, mineral or supplements.	187 patients with CVD	57 (including herbal medicine)
Moolasarn et al. (2003), Thailand[50]	CAM defined by Eisenberg et al. (1993)[c]	180 patients with cancer	41.1 (CAM use) 31.7 (herbal use)
Jiaranaikajorn et al. (2002), Thailand[27]	CAM defined by Eisenberg et al. (1993)[c]	200 inpatients and outpatients	52.5 (CAM use) 38 (herbal use)
Matthees et al. (2001), US[49]	- CAM use in the last 12 months - CAM defined by NCCAM	99 lung transplant recipients	88

CVD = Cardiovascular disease

[a] CAM was defined as a heterogenous group of practices which include several medical and health care practices and products that are not an integral part of conventional medicine due to insufficient proof of their safety and effectiveness.[70]

[b] CAM was defined as a therapy that falls beyond the realm of conventional medicine and is not based on rigorous scientific evidence for a particular indication.[71]

[c] CAM was defined as medical interventions and techniques that have neither been traditionally taught in medical schools nor included in residency training and that are not generally used in hospitals.[72]

[d] CAM was defined as a practice for an holistic approach other than conventional medicine.

[e] Herbal medicine was defined as plant derived materials or products with therapeutic or other human health benefits, which contain either raw or processed ingredients from one or more plants.

[f] Biological based therapies were chelation therapy, folk medicine, herbal products, large-dose vitamins, special diets, such as vegetarianism and macrobiotics.

[g] CAM was defined as any diagnosis treatment or prevention that complements mainstream medicine by contributing to a common whole, by satisfying a demand not met by orthodoxy or by diversifying the conceptual framework of medicine.[73]

Some surveys have reported the prevalence of CAM or HDS use amongst elderly people, see Table 2.4.[74-76] Comparing the one-year prevalence of CAM use

between general and elderly populations in the US, prevalence in elderly populations was more likely to be higher than the general population (63% versus 36%).[25,74]

Table 2.4 Studies reporting the prevalence of CAM and/or HDS use in elderly populations (n=3)

Authors and country	Definition and period for prevalence	Sample size	Prevalence (%)
Levine et al. (2009), Canada[76]	Natural health products (NHPs) use in the last 12 months NHPs defined by authors*	1,206	51 (NHP use)
Qato et al. (2008), US[75]	DS use at least daily or weekly	2,976	49 (DS use, including plant extracts)
Cheung et al. (2007), US[74]	- CAM use in the last 12 months - CAM defined by NCCAM	445	62.9 (CAM use) 44.3 (nutritional supplements) 28.3 (mega vitamins) 20.7 (herbal use)

* NHPs were defined as medicinal products derived from botanical or other natural sources (herbal products, vitamin, and mineral supplements.

2.3.3 Demographic characteristics of CAM and HDS users

A large number of cross-sectional surveys, amongst general populations worldwide, reported demographic characteristics related to the use of CAM, including HDS (n=18), see Table 2.5. Most studies in the general population have reported that older people and females are more likely to use CAM or HDS. There is inconsistent evidence that those who are highly educated or who take regular exercise are more likely to use CAM or HDS. There is evidence to suggest educated people in the US, Switzerland and the UK are more likely to use CAM or HDS[29,35,44,47,77,78], whereas those with a lower level of education are more likely to use them, amongst both Asian general and Asian patient populations in Turkey, South Korea and Thailand.[45,50,79] However, other studies have found no

relationship between educational level and CAM or HDS use in Japan, South Korea and Turkey.[36,80,81]

Table 2.5 Studies reporting characteristics of CAM or HDS users in general populations (n=18)

Authors and country	Study design and types of CAM	Sample size	Characteristics related to use CAM or HDS (AOR or OR, 95% CI)	No association
Thomson et al. (2012), Australia[48]	- An interview survey - CAM use	1,261	- Age (Ref. age < 65 yrs.) Age ≥ 65 yrs. (AOR 0.65, 0.47-0.89) - Male (AOR 0.69, 0.54-0.87) - Not married (AOR 0.78, 0.61-0.99) - Unemployed (AOR 0.76, 0.56-0.97)	Education, smoking Health status, BMI Physical activities Rural/urban areas
Chung et al. (2011), Hong Kong[82]	- Secondary analysis from the Hong Kong population representative thematic household survey 2007 dataset - Use of Chinese medicine	25,208	Age (Ref. age 15-29 yrs.) 30-39 yrs. (AOR 2.19, 1.28-3.72) 40-49 yrs. (AOR 2.68, 1.60-4.48) 50-59 yrs. (AOR 1.94, 1.11-3.41) 60-69 yrs. (AOR 2.17, 1.15-4.09) ≥ 70 yrs. (AOR 2.04, 1.07-3.88) - Male (AOR 0.7, 0.54-0.90) - Education (Ref. Primary school) Higher education (AOR 2.77, 1.78-4.30) - Self-reported health status (Ref. poor health status) Good (AOR 0.39, 0.29-0.51) - Having chronic illnesses (AOR 2.62, 1.96-3.49)	Personal income Secondary school education
Hunt et al. (2010), UK[47]	- Secondary analysis from the Health Survey for England 2005 - CAM use	7,630	- Male (OR 0.49, 0.42-0.58) - University education (OR 1.29, 1.09-1.54) - Employed (OR 1.42, 1.18-1.71) - Anxiety/depression (OR 1.34, 1.07-1.67) - Chronic illnesses (OR1.41, 1.19-1.66)	Household income

Table 2.5 (continued)

Authors and country	Study design and types of CAM	Sample size	Characteristics related to use CAM or HDS (AOR or OR, 95% CI)	No association
Araz et al. (2009), Turkey[79]	- A survey using a questionnaire - CAM use	988	- Education (Ref. Primary school) College degree (OR 0.36, 99%CI 0.20-0.63)	Age, sex, income Having chronic illnesses
Guo et al. (2009), Canada[37]	- A national survey - Use of vitamin and mineral supplements	35,107	- Female was more likely to use CAM. - Education (Ref. ≤ secondary school) College degree (AOR 1.37, 1.17-1.61) University education (AOR 1.41, 1.18-1.69) - Physical activities (Ref. active) Moderate (AOR 0.75,0.63-0.90) Inactive (AOR 0.64, 0.54-0.76)	Smoking, drinking BMI Chronic illnesses
Lee and Kim (2009), South Korea[81]	- Secondary analysis from the nationwide cross-sectional survey 2005 - Use of DS	4,775	Having higher household income was more likely to use DS.	Age, sex, education Smoking, drinking Health status Employment BMI, physical activities
Levine et al. (2009), Canada[76]	- A telephone interview survey - Use of NHPs	1,206 elderly people	- Younger (AOR 0.96, 0.94-0.98) - Smoking (Ref.-never smoking) Current smoking (AOR 0.62, 0.42-0.91)	Sex Education Health status
Marques-Vidal et al. (2009), Switzerland[44]	- A cross-sectional survey using interviews - HDS use	6,188	Elderly, female, higher educated people, having regular physical activities, having anxiety/depression and having normal BMI were more likely to use HDS	Alcohol consumption

AOR = Adjusted odds ratio; CI = confidence interval, BMI = Body mass index

Table 2.5 (continued)

Authors and country	Study design and types of CAM	Sample size	Characteristics related to use CAM or HDS (AOR or OR, 95% CI)	No association
Ock et al. (2009), South Korea[45]	- A national survey using interviews - CAM use	3,000	People aged 50-59 yrs., female, having less than high school education, having high household income, being married, being unemployed and living in an urban area were more likely to use CAM.	-
Aydin et al. (2008), Turkey[36]	- A cross-sectional population based study using interviews - CAM use	873	- Female (OR 1.42, 1.08-1.87) - Health status (Ref. good health) Fair (OR 1.36, 1.02-1.82) Bad (OR 2.35, 1.18-4.67) - Having chronic disease (OR 1.27, 1.54-2.49)	Education Smoking, drinking Marital status Income BMI
Cheung et al. (2007), US[74]	- A mailed survey - CAM use	445 elderly people	-	Sex, education Marital status Annual income
Xue et al. (2007), Australia[43]	- A national population based survey - CAM use	1,067	People aged 18-34 yrs., female, higher educated people and being employed were more likely to use CAM.	Health status
Imai et al. (2006), Japan[80]	- An interview survey - HDS use	2,259 aged 40-82 yrs	Middle aged people, female and having poor health status were more likely to use HDS.	Education Marital status Smoking Household income, BMI

Table 2.5 (continued)

Authors and country	Study design and types of CAM	Sample size	Characteristics related to use CAM or HDS (AOR or OR, 95% CI)	No association
Honda and Jacobson (2005), US[78]	- A national survey using both telephone interviews and mailed questionnaires - CAM use	4,242	Female and college educated people were more likely to use CAM.	Age Marital status
Kennedy (2005), US[29]	- Secondary analysis from the National Health Interview Survey 2002 - HDS use	30,412	People aged 45-64 yrs., female, higher educated people, having high household income, having good health status, former smokers and having regular exercise were more likely to use HDS.	-
Radimer et al. (2004), US[35]	- Secondary analysis from the National Health and Nutrition Examination Survey 1999-2000 - DS use	4,862	- Age (Ref. age 20-39 yrs.) 40-59 (OR 1.7, 1.4-2.1) ≥60 (OR 2.7, 2.2-3.3) - Female (OR 1.6, 1.3-1.8) - Education (Ref. less than high school) High school diploma (OR 1.5, 1.2-1.9) > High school (OR 2.4, 1.9-3.2) - BMI (ref. normal BMI) BMI ≥30 (OR 0.7, 0.6-0.9)	Health status BMI 25- < 30

In contrast with general populations, age, sex and educational level did not affect CAM or HDS use in patient populations reported by the majority of studies, see Table 2.6.[16,19,34,50,51,53,59,66,68]

With respect to most studies in both general and patient populations, there were no differences between CAM or HDS users and non-users regarding smoking, drinking, household income, marital status and body mass index (BMI), see Tables 2.5 and 2.6. Amongst general populations, there were inconsistencies in associations of living in urban or rural areas, self-reported health status and having chronic disease between CAM or HDS users and non-users. For instance, Ock et al. (2009) in South Korea reported that people living in an urban area were more likely to use CAM[45]; whilst Thomson et al. (2012) in Australia found that there were no associations between the users and non-users regarding living in urban or rural areas.[48] Three studies indicated that people who perceived poor health status were more likely to use CAM.[36,80,82] On the other hand, Kennedy et al. (2005) reported people with perceived good health status were more likely to use HDS.[29] Other studies found no association of health status and the users.[43,48,76,81]

Only one study reported demographic characteristics related to HDS use amongst patients with CKD.[16] There were no associations between the users and non-users regarding age, sex, education levels, smoking status, household income, the number of concurrent chronic illnesses and the number of prescribed medications.

Table 2.6 Studies reporting characteristics of CAM or HDS use in patient populations (n=13)

Authors and country	Study design and types of CAM	Sample size	Characteristics related to use CAM or HDS (AOR or OR, 95% CI)	No association
Strejilevich et al. (2013) Argentina and Colombia[68]	- A survey using a questionnaire - CAM use	200 patients with bipolar disease	-	Age, sex, education Marital status, employment No. of medications
Ali-Shtayeh et al. (2012) Palestinian territories[66]	- An interview survey - Herbal use	1,883 diabetic patients	-	Age, sex, education Marital status Having chronic illnesses
Weizman et al. (2012) Canada[18]	- A survey using a questionnaire - CAM use	380 patients with inflammatory bowel disease	- University education (AOR 1.72, 1.05-2.82) - Experienced adverse effects from using CM (AOR 2.54, 1.59-4.06)	Sex, smoking Marital status, employment Quality of life
Gohar et al. (2008) UK[19]	- A survey using a questionnaire - CAM use	153 patients with hypertension	-	Age, sex, education Marital status
Hori et al. (2008) Japan[59]	- A survey using a questionnaire - CAM use	496 outpatients	Female was more likely to use CAM.	Age, education Financial status

Table 2.6 (continued)

Authors and country	Study design and types of CAM	Sample size	Characteristics related to use CAM or HDS (AOR or OR, 95% CI)	No association
Yeh et al. (2006) US[58]	- Secondary analysis from the National Health Interview Survey (NHIS) 2002 - The use of CAM or herbal medicine	10,572 patients with CVD	CAM use - Age ≥ 65 yrs. compared with age < 30 (AOR 0.5, 0.4-0.7) - Female (AOR 1.7, 1.5-1.9) - Completed high school compared with less than high school (AOR 1.4, 1.2-1.7) - Higher household income (AOR 1.2, 1.1-1.5) - Asian population compared with whites (AOR 2.1, 1.4-3.1) - Poor health status compared with excellent health (AOR1.3, 1.1-1.6)	Age 30-64 yrs. Employment Fair health status
			Herbal use - Female (AOR 1.4, 1.2-1.6) - Completed high school compared with less than high school (AOR 1.3, 1.1-1.6) - Higher household income (AOR 1.2, 1.1-1.5) - Asian population compared with whites (AOR 2.5, 1.7-3.9)	Age
Barraco et al. (2005) US[53]	- An interview survey - Herbal use	223 inpatients with ACS	-	Age, education Marital status Income, BMI

Table 2.6 (continued)

Authors and country	Study design and types of CAM	Sample size	Characteristics related to use CAM or HDS (AOR or OR, 95% CI)	No association
Molassiotis et al. (2005), 14 countries in Europe[55]	- A survey using a questionnaire - CAM use	956 patients with cancer	Younger people, female and higher educated people were more likely to use CAM.	-
Moolasarn et al. (2005) Thailand[51]	- An interview survey - CAM use	159 diabetic patients	-	Age, sex, education Marital status, income Quality of life
Spanner and Duncan (2005) Canada[16]	- An interview survey - HDS use	100 patients with CKD	-	Age, sex, education Smoking, household income No. of concurrent chronic illnesses No. of prescribed medications
Stys et al. (2004) US[34]	- A cohort study over one year - HDS use	187 patients with CVD	-	Age, sex Smoking
Moolasarn et al. (2003) Thailand[50]	- An interview survey - CAM use	180 patients with cancer	- Education (Ref. having high educated) Less educated (OR 0.043, 0.004-0.415) - Having side effects from using CM (OR 3.054, 1.400-6.662)	Age, sex Marital status Income
Matthees et al. (2001) US[49]	- A mailed survey - CAM use	99 lung transplant recipients	- Female (OR 2.68, 1.02-7.03) - College degree compared to high school (OR 6.07, 1.62-22.73)	-

2.4 Reasons for HDS use

There are large numbers of surveys of attitudes towards reasons for HDS or CAM use worldwide (n=46). Meanwhile, qualitative studies about this issue are limited (n=4). Although most studies have been conducted amongst CAM users, no distinction was made between HDS and more generic CAM. Both the general population and patients with chronic illnesses, such as cardiovascular diseases, diabetes, hypertension, cancer, and arthritis, have been explored, regarding their attitudes towards HDS use. There are mainly no differences in attitudes across the populations using CAM or HDS. However, there are only limited studies of such attitudes amongst patients with CKD (n=1).

Quantitative studies show that the reasons most frequently reported for using CAM are the perception of benefit and safety; followed by dissatisfaction with conventional medicine (CM); willingness to try them; hope to gaining benefits from using them, including the use of CAM as a last resort; attitudes towards internal health locus of control and an holistic approach; and cultural and spiritual beliefs. CAM is perceived as a support for control over health whilst people who believe in a holistic approach to their wellbeing, perceive that CAM supports both physical and mental health. Cultural and spiritual beliefs are associated with decision-making in CAM use because they are embedded in the part of self-medication amongst citizens in some countries, such as China. These findings are consistent with the qualitative studies. Table 2.7 summarises seventeen studies of such attitudes in general populations.

In contrast, the perception of scepticism around the efficacy and safety of CAM, and satisfaction of CM, are most frequently reported in people who are unlikely to use CAM.[55,57,60,74]

Table 2.7 Studies reporting attitudes towards reasons for CAM or HDS use in general populations (n=17)

Authors and country	Study design and population	Attitudes towards reasons for CAM or HDS use	Interpretation of attitudes
DS use			
Conner et al. (2001), UK[83]	Database of self-reported DS use Qualitative analysis 303 female adults	- Perceived benefits of DS - Prevention of illnesses	Benefit
		- Intentions to use DS	Willingness to use DS
		- Highly perceived value of health and susceptibility to illness	-
Use of herbal medicine or natural products			
Aziz and Tey (2009), Malaysia[46]	Survey 1,601 adults	Agreed that herbal medicine was effective and safe	Benefit and safety
Levine et al. (2009), Canada[76]	Survey 1,206 elderly people	- Improvement of their health (73%) - Prevention of illnesses (47%) - Last resort for chronic illness (10%)	Benefit
		- Be able to tolerate more than CM (17%)	Safety
		- Less expensive than CM (4%)	-
Bruno and Ellis (2005), US[84]	Database of the 2002 National Health Interview Survey 31,044 elderly people	- Combination of herbal medicine and CM would help (48.8%)	Benefit
		- Willingness to try (45.6%)	Willingness to use
		- Ineffectiveness of CM (20%) - CM was too expensive (10.2%)	Dissatisfaction with CM

Table 2.7 (Continued)

Authors and country	Study design and population	Attitudes towards reasons for CAM or HDS use	Interpretation of attitudes
CAM use			
Thomson et al. (2012), Australia[48]	Survey 1,261 adults	- Treatment of their chronic illnesses (75.5%) - Prevention of illnesses (60%)	Benefit
McFadden et al. (2010), US[85]	Survey 65 healthy graduate students aged 22-45 years	- Holistic balance (r=0.52, p<0.001) - Internal health locus of control related to CAM use (r=0.33, p=0.007)	Internal health locus of control and holistic approach
		- Dissatisfaction with CM (r=0.25, p=0.045)	Dissatisfaction with CM
		- Philosophical congruence with CAM (r=0.41, p=0.001)	-
Araz et al. (2009), Turkey[79]	Survey 988 adults	- Perceived efficacy of CAM related to regular use of CAM (OR 1.74, 99%CI 1.06-2.85)	Benefit
		- There was no association between regular CAM use and internal health locus of control	Internal health locus of control
Ock et al. (2009), South Korea[45]	National survey 3,000 aged 30-69 years	- Health prevention and promotion (78.8%) - Treatment of illnesses (20.3%)	Benefit
Aydin et al. (2008), Turkey[36]	Cross-sectional population based survey 873 adults	- Perceived that herbs complemented CM (47.4%) - Prevention of illnesses (37.4%), treatment of illnesses (25.6%)	Benefit
		- Perceived that herbs were safe as they were natural (29.4%)	Safety
Smith et al. (2008), US[86]	Survey 276 undergraduate students	- Significant association between willingness to use herbs and spirituality and mood attention (r^2=0.078, F=11.48) - Significant association between willingness to use vitamin and optimism (r^2=0.026, F=7.29)	Willingness

Table 2.7 (Continued)

Authors and country	Study design and population	Attitudes towards reasons for CAM or HDS use	Interpretation of attitudes
CAM use			
Cheung et al. (2007), US[74]	Survey 445 elderly people	- Maintaining their general health (73.7%) - Treatment of illnesses (59.6%)	Benefit
		- Had more personal control over their health (50.2%)	Internal health locus of control
Vickers et al. (2006), UK[87]	Qualitative study the 18 female adults	- Natural and having no or little side effects.	Safety
		- Experienced side effects of CM	Dissatisfaction of CM
		- Last resort	Benefit
		- Had personal control over their health	Internal health locus of control
Honda and Jacobson (2005), US[78]	National survey 4,242 people aged 25-74 years	A personal trait of CAM users was more likely to have an open mind.	Willingness
Barnes et al. (2004), US[25]	National survey 31,044 adults	- Combined CAM with CM would help (54.9%)	Benefit
		- Wanting to try (50.1%)	Willingness to try
		- Belief in ineffectiveness of CM (28%) - CM were too expensive (13%)	Dissatisfaction with CM
Singh et al. (2004), South Africa[42]	Survey 200 people aged 26-60 years	- CAM was natural (61%) - Perceived that natural products were safe (23.4%)	Safety
		- Experienced or were concerned about side effects of CM (15.6%)	Dissatisfaction with CM
Thomas and Coleman (2004), UK[88]	National survey 1,794 adults	- Treatment of illnesses (62%) - Maintaining general health or prevent illnesses (34%)	Benefit
Astin (1998), US[89]	Survey 1,035 adults	Perceived benefits of CAM	Benefit

Table 2.8 shows twenty-nine studies of attitudes towards reasons for CAM or HDS use amongst patient population worldwide.

Table 2.8 Studies reporting attitudes towards reasons for CAM or HDS use in patients with chronic illnesses (n=29)

Authors and country	Study design, population and types of CAM use	Attitudes towards reasons for CAM or HDS use	Interpretation of attitudes
Yu et al. (2012), China[90]	Qualitative study 26 cancer patients Use of Chinese medicine	- Last resort - Perceived good experience	Benefit
		- safe and cheap	Safety
		- Desire to use	Willingness to use
		- Understanding of Chinese medicine due to their cultural and historical context	Cultural belief
Rausch et al. (2011), US[91]	Survey 153 cancer patients Use of herbal medicine	- Being used to taking it (19%) - Being interested in herbs (< 5%)	-
		- Dissatisfaction with CM (< 5%)	Dissatisfaction with CM
Sewitch et al. (2011), Canada[92]	Survey 103 cancer patients Use of natural health products	- Improving quality of life (98.8%) - Treatment of illnesses or maintenance of good health (20.7%) - Cure for cancer (9.8%) - Relief of symptoms or treatment of side effects from using CM (9.8%)	Benefit
Hyodo et al. (2005), Japan[54]	Survey 3,100 cancer patients CAM use	Expectation for CAM use - Dealing with cancer (67.1%), cure for cancer (44.5%) - Relieving symptoms (27.1%), combined CAM with CM (20.7%)	Benefit
Molassiotis et al. (2005), 14 countries in Europe[55]	Survey 956 cancer patients CAM use	- Improving their immune system (50.7%) - Improving physical health (40.6%) - Improving emotional health (35.2%)	Benefit

Table 2.8 (continued)

Authors and country	Study design, population and types of CAM use	Attitudes towards reasons for CAM or HDS use	Interpretation of attitudes
Verhoef et al. (2005)[93]	Systematic review 52 eligible quantitative studies during 1994-2004 Cancer patients CAM use	- Perceived benefits of CAM (38.4%)	Benefit
		- Last resort (9.6%), having hope (9.6%)	
		- Wanting to control their health (17.3%)	Internal health locus of control
		- A strong belief in CAM (17.3%)	-
		- Disappointment to CM (3.8%)	Dissatisfaction with CM
Wilkinson et al. (2002), US[94]	Survey 1,099 cancer patients CAM use	- Believed that CAM would extend life span and improvement of their quality of life (90%), having hope (81%)	Benefit
		- Relieved symptoms (60%), Expectation of disease cures (47%)	
		- Had control over their disease (63%)	Internal health locus of control
Chen et al. (2009), China[95]	Qualitative study 29 HIV patients, CAM use	- Relieving side effects of CM, dealing with other discomforts	Benefit
		- Enhancing good health	
Matthees et al. (2001), US[49]	Survey, 99 lung transplant recipients, CAM use	- Dealing with weight gain	Benefit
		- Maintaining good health or the immune system healthy	
Ali-Shtayeh et al. (2012), Palestinian territories[66]	Survey 1,883 diabetic patients Use of herbal medicine	- Slowing progression of their disease (45.7%)	Benefit
		- Relieving their symptoms (35%), cure for their disease (22.9%)	
		- Decreased side effects of CM (12.6%)	
Kumar et al. (2006), India[56]	Survey 493 diabetic patients CAM use	- Rapid and additional relief of their disease (86.8%)	Benefit
		- CAM was no side effects (26.1%)	Safety
		- There is low cost and easy availability (16.8%)	-
Yeh et al. (2006), US[58]	Survey 10,572 patients with cardiovascular disease, CAM use	- Combination of CAM and CM would help (59%)	Benefit
		- Trying (50%)	Willingness to try

Table 2.8 (Continued)

Authors and country	Study design, population and types of CAM use	Attitudes towards reasons for CAM or HDS use	Interpretation of attitudes
Moolasarn et al. (2005), Thailand[51]	Survey 159 diabetic patients, CAM use	Perceived that CAM complemented CM (13.2%)	Benefit
Kara (2009), Turkey[14]	Survey 114 hemodialysis patients Use of herbal medicine	- Treatment of their disease (81.3%) - Prevention of disease (12.5%)	Benefit
Spanner and Duncan (2005), Canada[16]	Survey 100 patients with CKD, DS use	- Prevention of illnesses (44%) - Treatment of illnesses (38%)	Benefit
Weizman et al. (2012), Canada[18]	Survey 380 outpatients with IBD CAM use	- Ineffectiveness of CM (40%), perceived side effects of CM (18%)	Dissatisfaction with CM
		- Safety of CAM (28%)	Safety
		- Sense of controlling their disease (30%)	Internal health locus of control
Rawsthorne et al. (1999), US, Canada, Ireland, Sweden[96]	Survey 289 patients with IBD CAM use	- Dissatisfaction with CM - Perceived their medical condition was hopeless	Dissatisfaction with CM
Lambert et al. (2010), UK[63]	Survey 92 outpatients with headache, CAM use	- Last resort (48%), belief in efficacy of CAM (21%)	Benefit
		- Unhappy with CM (17%)	Dissatisfaction with CM
Rossi et al. (2008), Italy[60]	Survey 100 patients with headache CAM use	- Perceived benefits of CAM (44.8%)	Benefit
		- Perceived that CAM was safer than CM or had fewer side effects than CM (27.5%)	Safety
		- Curiosity (24.1%)	-
		- Holistic approach to health (10.3%)	Holistic approach
		- Dissatisfaction with CM (4.6%)	Dissatisfaction with CM

Table 2.8 (Continued)

Authors and country	Study design, population and types of CAM use	Attitudes towards reasons for CAM or HDS use	Interpretation of attitudes
Strejilevich et al. (2013), Argentina and Colombia[68]	Survey 200 outpatients with bipolar disorder, CAM use	- Relieving their illness	Benefit
Braun and Cohen (2011), Australia[65]	Survey 161 inpatients, CAM use	- Improving their good health (71%), treatment of disease (30%) - Prevention of disease (20%)	Benefit
Hasan et al. (2009), Malaysia[61]	Survey 321 outpatients CAM use	- Belief in safety of CAM (66.3%)	Safety
		- Perceived efficacy of CAM and it was fewer side effects (15%)	Benefit and safety
		- Trying new alternative therapy (63.9%)	Willingness to try
		- Be used to take CAM (17.6%)	-
		- Experienced side effects of CM (7.8%) - Failure of CM to control their illnesses (2.9%) - Lack of trust in CM (4.9%)	Dissatisfaction with CM
		- Cultural belief (5.9%)	Cultural belief
Bishop et al. (2007)[97]	Systematic review during 1995-2005 94 eligible quantitative and qualitative studies in patients CAM use	- Belief in control and participation	Internal health locus of control and willingness

		- Illness perception
		  - Causes of illness
		  - Majority of the studies was among cancer patients
			-

		- Belief about holism and natural treatment	Holistic approach
		- Cultural or spiritual belief	Cultural or spiritual belief
Saw et al. (2006), Malaysia[57]	Survey, 250 inpatients Use of herbal medicine	- Maintaining good health (51.3%) - Treatment of chronic illnesses (42.1%)	Benefit

Table 2.8 (Continued)

Authors and country	Study design, population and types of CAM use	Attitudes towards reasons for CAM or HDS use	Interpretation of attitudes
Kuo et al. (2004), US[98]	Survey 322 primary care patients Use of herbal medicine	- Believed that combination of herbs and CM would be superior to using either alone - Believed that herbs were superior to CM - Using herbs for treatment and prevention of illnesses - Rapid relief of symptoms (47%)	Benefit
		- Trying (33%)	Willingness to try
		- Having their own treatment (20%)	Internal health locus of control
Jiaranaikajorn et al. (2002), Thailand[27]	Survey 200 outpatients and inpatients, CAM use	- Believed in efficacy of CAM (77.1%), - Alleviating minor ailments (27.6%)	Benefit
		- Failure to be treated by CM (13.3%)	Dissatisfaction with CM
Sirois and Gick (2002), Canada[99]	Survey 199 patients at health clinics CAM use	- Trying new things	Willingness to try
		- Medical need	-
		- Perceived ineffective of CM	Dissatisfaction with CM
Klepser et al. (2000), US[100]	Survey 794 outpatients, HDS use	- Positive attitude towards herbal effects on their health ($p < 0.05$)	Benefit
		- Perceived benefits and safety of HDS ($p < 0.05$)	Benefit and safety
Kappauf et al. (2000), Germany[101]	Survey 131 outpatients and inpatients, CAM use	Perceived that CAM complemented CM (75%)	Benefit

2.4.1 Perceived benefits from CAM and HDS use

The perception of CAM or HDS benefits has been reported as a reason for CAM or HDS use amongst both the general population and patients with chronic illnesses.[27,46,60,61,63,79,83,89,90,93,100] A survey in Turkish adults found that the perception of benefits was positively associated with regular use of CAM (Odds ratio (OR) 1.74, 99% CI 1.06-2.85).[79] The studies have also described benefits of CAM or HDS in terms of purposes of use, such as the treatment or prevention of illnesses, and the perception of gaining benefit when people combined CAM or HDS use with conventional medication.

Treatment or prevention of illnesses and maintaining good health are the most frequently reported reason for using CAM or HDS in both the general and patient populations.[14,16,36,46,48,49,57,65,66,68,76,83,88,92,94,95,98] Some patients with diabetes, cancer, human immunodeficiency virus (HIV) or receiving lung transplant have perceived that CAM relieved their symptoms, improved their immune system, physical and emotional health, or dealt with other discomforts or weight gain.[27,49,55,66,92,94,95] Patients with life-threatening illnesses, such as cancer, have reported using CAM to improve their quality of life.[92,94] Moreover, respondents with either cancer or diabetes have tried herbal medicine in order to cure their disease.[66,92] Some patients have reported using HDS or CAM to treat side effects from conventional medicine.[66,92,95]

The use of CAM or herbal medicine has been perceived to supplement conventional medication, or that their combination would be more effective than using either alone.[25,36,51,58,84,98,101] Moreover, some users perceive that herbal medicine is superior to conventional medicine, or it rapidly relieves their symptoms.[56,98]

Patients with life threatening illnesses hope or expect to gain benefits from using CAM.[54,93,94] Although both the general and patient populations want to use CAM

as a last resort for their chronic illnesses[63,76,87,90,93], it appears that this reason is more likely to be reported by patients rather than the general population.

2.4.2 The perception of safety of CAM and HDS

Respondents perceived that CAM or herbal medicine was safe.[18,46,61,90] CAM or herbal medicine has been perceived as being natural, leading to the belief that they are safe amongst both the general population and patients with chronic illnesses.[36,42,87] Some respondents thought that CAM had no, or fewer, adverse effects than conventional medication[56,60] and they could tolerate them more than those from CM.[76]

2.4.3 Dissatisfaction with conventional medication

Four studies in the general population[25,42,84,85] and nine studies in patient populations have reported the perception of dissatisfaction with CM as a reason for CAM use.[18,27,60,61,63,91,93,96,99] A survey in healthy graduate students has reported a significant association between dissatisfaction with conventional medication and CAM use ($r=0.25$, $p=0.04$).[85] However, Astin's study in the general population, and Eisenberg's study in adults who saw a doctor, tested this hypothesis and rejected it.[89,102] Despite inconsistencies with this reason for using CAM in the general population, it would seem that patients with chronic illnesses are likely to perceive dissatisfaction with CM as a reason for using CAM or herbal medicine, see Table 2.8.[18,27,60,61,63,91,93,96,99]

Dissatisfaction with CM was also described by both the general population and patients in terms of the ineffectiveness of CM, having either experienced or become concerned about adverse effects of CM, and the high costs of CM.[18,25,27,42,61,84,87,99] Some patients with inflammatory bowel disease (IBD) felt that "Their medical situation was hopeless", and thus they decided to use CAM.[96]

However, dissatisfaction with doctor-patient interaction was not related to CAM use.[52]

2.4.4 Willingness to try CAM and HDS

Willingness to try has been reported as a reason for using CAM or HDS in both the general population[25,84] and patients with chronic illnesses.[58,61,98,99] Having an open mind is a possible personality trait of CAM or HDS users, as they are willing to try new things.[61,78,99]

Some respondents desire to use CAM or HDS.[83,90] Patients using CAM are likely to actively search information on alternative medicine and discuss CAM with their friends and family in order to decide whether or not they will actually use CAM.[97]

2.4.5 Attitudes towards internal health locus of control, holistic approaches, cultural and spiritual beliefs

There are fewer studies of the relationship between CAM use and attitudes towards health locus of control, holistic approaches, cultural and spiritual beliefs. Perception of health locus of control is reported as a reason for CAM use in both the general and patient populations.[18,74,85,87,93,94,97] A survey in healthy graduate students shows a significant association between CAM use and internal health locus of control ($r=0.33$, $p<0.01$).[85] However, this attitude is inconsistent with Araz et al. (2009)[79], Conner et al. (2001)[83] and Sirois and Gick (2002).[99]

Attitudes towards a holistic approach is positively associated with CAM use in the general population ($r=0.52$, $p<0.01$).[85] This is consistent with Bishop and Rossi's studies of patient populations.[60,97]

There are cultural and spiritual beliefs linked to CAM use amongst patients with chronic illnesses.[61,97] Cultural belief related to CAM use is supported by Yu et al. (2012) who stated that Chinese patients with cancer use Chinese medicine, due

to their understanding of Chinese medicine, based on their cultural context.[90] Meanwhile Smith et al. (2008) in the UK reported that spiritual belief is significantly associated with CAM use amongst the general population.[86]

2.4.6 Attitudes towards CAM in people who are unlikely to use CAM

Negative attitudes towards CAM and the satisfaction of CM benefits prevent both general and patient populations from using CAM.[55,57,60,74] The negative attitudes are doubts regarding the efficacy and safety of CAM, and having either experienced or been concerned about the negative effects of CAM.[55,74] Saw et al. (2006) also report that non-users perceive that efficacy of herbal medicine is inferior to CM.[57]

2.5 HDS users' social networks and the media influence on HDS use

HDS users' social networks and the media are the most frequently reported sources of information or recommendations for the use of CAM or HDS, in both the general population and patients with chronic illnesses. This is supported by a large number of surveys (n=21), see Tables 2.9 and 2.10, but there is limited literature from qualitative research in the general population[83] and patients with CKD.[16]

Three quarters of the surveys in the general population report at least 40% of the users' social network influencing their decision making in CAM or HDS use, see Table 2.9.[45,74,76,88,103,104] Similarly, one of the top reasons why British people take CAM is because their family members recommend it.[105]

Table 2.9 Surveys of sources of information or recommendation for CAM or HDS use in the general population (n=8)

Authors and countries	The population, types of alternative medicine	Types and rates of sources
Chung et al. (2011), Hong Kong[82]	Secondary analysis of the Hong Kong Population Representative Thematic Household Survey 2007 dataset 25,208 people aged > 15 years Use of traditional Chinese medicine (TCM)	- TCM practitioners (59.5%) - Pharmacy sales personnel (24.6%) - Friends and relatives (19.8%) - Chinese herbal dispensers (12.2%) - Leaflets (10.4%)
McCrea and Pritchard (2011) in the US[103]	305 college students aged 18-50 years Use of herbal medicine	- Self-recommendation (60%) - Friends (40%)
Levine et al. (2009) in Canada[76]	1,206 elders Use of natural health products	- Friends and family (49%) - Self-experimentation (23%) - Advertisement (20%) - Doctors (18%) - Purveyor of the products (3%)
Ock et al. (2009) in South Korea[45]	3,000 adults CAM use	- Friends and family (66.9%) - The media (11.7%) - Doctors (4.1%) - Pharmacists (3%) - CAM practitioners (2.1%) - Distributor of CAM (1.8%)
Cheung et al. (2007) in the US[74]	445 elders CAM use	Friends and family (46.7%)
Alkhateeb et al. (2006) in the US[104]	456 adults Use of herbal medicine	- Friends and family (61.6%) - Newspapers/ magazine (43.8%) - TV and radio (37%) - Doctors or pharmacists (32.9%) - Internet (31.5%) - Herb professional (30.1%)
Singh et al. (2004) in South Africa[104]	200 adults CAM use	- Advised by someone or influenced by advertisement in newspapers, books or magazines (52%)
Thomas and Coleman (2004) in the UK[88]	1,794 people aged $\geq$ 16 years CAM use	- Friends or relatives (59%) - Health care providers (18%)

Amongst patients with chronic illnesses, half of the studies report more than 50% of CAM or HDS users regard family and friends as sources of information or recommendation, see Table 2.10.[50,51,54,55,60,63,106] However, amongst patients with CKD, Spanner and Duncan's survey in the US report the lowest rate of friends and family as an information source, because most respondents received information from their doctor (27%).[16] This is consistent with Kappauf's study in Germany[101], Wilkinson and Jelinek's study in Australia[62], and Braun and Cohen's study in Australia.[65] A doctor or pharmacist's recommendation for CAM use has been most frequently reported as influencing CAM use (41 to 53%).[62,65,101] Comparing health care professionals' recommendations for CAM or HDS use, between the general and patient populations, patients (8 to 53%) are more likely to receive recommendations from their health care providers, than the general population (3 to 33%), see Tables 2.9 and 2.10.

Table 2.10 Surveys of sources of information or recommendation for CAM or HDS use in patients with chronic illnesses (n=13)

Authors and country	Population, types of CAM	Types and rates of sources
Ali-Shtayeh et al. (2012), Palestinian territories[66]	1,883 diabetic patients Use of herbal medicine	- Family (40.2%) - Friends (37.1%) - Herbalists (16.4%) - The media (TV,radio) (12.3%) - Doctors and pharmacists (7.5%) - Internet, advertisement and text messages (5.6%)
Braun and Cohen (2011), Australia[65]	161 inpatients CAM use	- Pharmacists (44%) - Doctors (41%) - Health food store staff (23%) - CAM practitioners (22%) - Books or magazines (22%) - Friends and family (15%)
Lambert et al. (2010), UK[63]	92 outpatients with headache CAM use	- Friend or relatives (72%) - Doctors (16%) - Nurses (8%) - Self-recommendation (4%)
Hasan et al. (2009), Malaysia[61]	321 outpatients CAM use	- Friends (32.5%) - Health care professionals (25.9%) - Family (20.2%) - Advertisement (15.8%) - Folks or culture beliefs (4.4%)
Wilkinson and Jelinek (2009), Australia[62]	102 elderly people with chronic illnesses CAM use	- Doctors and pharmacists (53%) - Friends and family (28%) - Popular magazines (23%) - CAM practitioners (22%) - Internet (10%) - Medical/scientific journals (10%)
Rossi et al. (2008), Italy[60]	100 patients with headache CAM use	- Friends or relatives (54%) - Doctors (26%) - Self-recommendation (20%)
Kumar et al. (2006), India[56]	493 diabetic patients CAM use	- Friends (36.4%) - Neighbours (25%) - Relatives or family members (18.2%) - Doctors (17.9%)

Table 2.10 (continued)

Authors and country	Population, types of CAM	Types and rates of sources
Howell et al. (2006), US[106]	620 outpatients Use of herbal medicine	Family (66%)
Hyodo et al. (2005), Japan[54]	3,100 cancer patients CAM use	- Friends or family (77.7%) - Self-recommendation (23.3%)
Molassiotis et al. (2005), 14 countries in Europe[55]	956 cancer patients CAM use	- Friends (56.5%) - Family (29.1%) - The media (28.4%) - Doctors (18.6%) - CAM practitioners (12.9%) - Internet (9.3%)
Moolasarn et al. (2005), Thailand[51]	159 diabetic patients CAM use	- Friends, media and relatives (57.9%) - Doctors (28.9%)
Moolasarn et al. (2003), Thailand[50]	180 patients with cancer Use of herbal medicine	Friends, relatives and fellow patients (55.5%)
Kappauf et al. (2000), Germany[101]	131 outpatients and inpatients CAM use	- Doctors (41%) - Friends and relatives (21%) - Books and media (21%) - CAM practitioners (15%) - Fellow patients (2%)

Family and friends' recommendations influencing CAM or HDS use was most frequently reported in all studies amongst Asian patients, whilst 60% of studies amongst Western patients reported it.[50,51,54-56,60,61,63,106] It would seem that the Asian patient populations are more likely to receive information or recommendations from their social network, compared with Western patient populations. However, there is no difference in the general populations between Asian and Western countries, as family and friends are most frequently reported as sources of information or recommendations in both contexts, see Table 2.10.

The media, such as books, magazine, TV, radio and internet, as well as advertisements, seems to influence a person's decision to use CAM or HDS amongst both the general and patient populations, see Tables 2.9 and 2.10. No

more than one quarter of respondents reported this as a source, with the exception of Alkhateeb's study.[16,45,55,61,62,65,66,76,82,101]

Positive or negative effects of CAM have been reported by the media; Bubela et al. (2008) reviewed newspaper's perceptions of the efficacy and safety of herbal medicine during 1995-2005.[107] They reviewed the media in the UK, the US, Australia, New Zealand and Canada and found that 90% of newspapers reported benefits of herbal medicine, whilst no benefits were reported in only 4% of articles. The media under reported the side effects of herbal products.[107] This is consistent with a systematic review of the mass media and CAM use, in which the mass media was found to be more likely to report positive effects of CAM, rather than their risks.[108]

2.6 Disclosure of HDS use to health care providers

Herbal and dietary supplement use may affect conventional health management, particularly in patients with chronic illnesses. Theoretically, HDS users should inform their health care providers about their usage, in order to have their health properly managed. However, large numbers of surveys, worldwide, have reported high rates of non-disclosure of HDS or CAM use to health care professionals (HCP) in both the general population (n=10) and patients with chronic illnesses (n=12), see Tables 2.11 and 2.12, respectively.

Three surveys of general populations[42,74,82] and seven surveys of the patient populations have reported reasons for the non-disclosure, [53,61,63,65,68,101,102] whilst only two qualitative studies have reported them in the general population and patients.[87,109] The reasons are presented in section 2.6.2 below.

Table 2.11 Surveys of the non-disclosure of CAM or HDS use to HCP in the general population (n=10)

Authors and country	Population and types of CAM	Rates of the non-disclosure	Reasons for the non-disclosure
HDS use			
Chung et al. (2011), Hong Kong[82]	Secondary analysis of the Hong Kong Population Representative Thematic Household Survey 2007 dataset 25,208 people aged > 15 years Use of traditional Chinese medicine (TCM)	59.3%	- No interaction between CM and TCM (62.7%) - Doctors don't ask (25.9%) - Doctors don't understand (5.9%) - TCM wasn't based on modern, medical knowledge (4.5%) - Doctors would discourage from using TCM (4.1%)
McCrea and Pritchard (2011), US[103]	305 college students aged 18-50 years HDS use	75%	-
Chao et al. (2008), US[110]	Secondary analysis from the 2002 National Health Interview Survey and 2001 Health Care Quality Survey Use of folk medicine	67%	-
Mehta et al. (2008), US[111]	Secondary analysis from the 2002 NHIS Sample Adult Core and the Alternative Medicine Supplement HDS use	66.7%	-
Kennedy (2005), US[29]	31,044 adults Use of natural herbs	66.6%	-
CAM use			
Thomson et al. (2012), Australia[48]	1,261 adults CAM use	39.7%	-
Aydin et al. (2008), Turkey[36]	873 adults CAM use	73.6%	-
Cheung et al. (2007), US[74]	445 elders CAM use	46.7%	- Their practitioners don't ask (38.5%) - Unnecessary (22%)
Singh et al. (2004), South Africa[42]	200 adults CAM use	57.5%	- Unnecessary (53.6%) - Their doctor don't ask (28.6%) - The doctor may be upset (7.1%).

Table 2.11 (continued)

Authors and country	Population and types of CAM	Rates of the non-disclosure	Reasons for the non-disclosure
CAM use			
Thomas and Coleman (2004), UK[88]	1,794 adults CAM use	52%	-

Table 2.12 shows rates of the non-disclosure of CAM or HDS use to health care providers in patients, but the studies did not explore the reasons.

Table 2.12 Surveys of the non-disclosure of CAM or HDS use to HCP in patients (n=12)

Authors and country	Population and types of CAM	Rates of the non-disclosure
Ali-Shtayeh et al. (2012), Palestinian territories[66]	1,883 diabetic patients Use of herbal medicine	68%
Rausch et al. (2011), US[91]	153 cancer patients CAM use	47%
Sewitch et al. (2011), Canada[92]	103 cancer patients CAM use	31.7%
Shorofi and Arbon (2010), Australia[67]	353 inpatients Use of herbal medicine	51.6%
Wilkinson and Jelinek (2009), Australia[62]	102 elderly people with chronic illnesses CAM use	40%
Rossi et al. (2008), Italy[60]	100 patients with headache CAM use	62%
Yeh et al. (2006), US[58]	10,572 patients with cardiovascular disease Use of herbal medicine	56%
Moolasarn et al. (2005), Thailand[51]	159 diabetic patients CAM use	64.4%
Spanner and Duncan (2005), Canada[16]	100 patients with kidney disease Use of dietary supplement	33%
Grabe and Garrison (2004), US[15]	491 patients in primary care and nephrology units Use of natural products	67% for patients in primary care 45% for patients with kidney disease
Moolasarn et al. (2003), Thailand[50]	180 patients with cancer Use of herbal medicine	51.3%
Matthees et al. (2001), US[49]	41 lung transplant recipients HDS use	36.6%

Table 2.13 indicates both rates of the non-disclosure and the reasons amongst patients using CAM or HDS.

Table 2.13 Surveys of the non-disclosure of CAM or HDS use to HCP and its reasons in patients (n=7)

Authors and country	Population and types of CAM	Rates of the non-disclosure	Reasons for the non-disclosure
Strejilevich et al. (2013), Argentina and Colombia[68]	200 outpatients with bipolar disorder CAM use	48%	Patients were afraid that their doctor may ask them to stop using them (32%)
Braun and Cohen (2011), Australia[65]	161 inpatients CAM use	56%	- Doctors didn't ask (67%) - Unnecessary (54%) - Doctors would not understand (5%) - Didn't want to be judged negatively (5%)
Lambert et al. (2010), UK[63]	92 patients with headache CAM use	42%	- A doctor or nurse has never asked (80%). - Unnecessary (10%) - They wouldn't understand (10%)
Hasan et al. (2009), Malaysia[61]	321 outpatients CAM use	54.5%	- A doctor or pharmacist has never asked (45.5%). - Unnecessary (37.3%) - A doctor may disapprove (12.7%).

Barraco et al. (2005), US[53]	223 inpatients with acute coronary syndrome
	CAM use
		35.9%	- Doctors didn't ask (48%)
			- Other reasons
			  - Unnecessary
			  - They forgot
			  - Felt uneasy talking about it

Eisenberg et al. (2001), US[102]	831 outpatients CAM use	-	- HCP may be unable to understand their CAM use. - "It's not important for the doctor to know"
Kappauf et al. (2000), Germany[101]	131 outpatients and inpatients CAM use	44%	- Their use may be disapproved. - Patient-doctor relationship may be interrupted.

2.6.1 Comparison of rates of non-disclosure of CAM and HDS use to health care providers between general and patient populations

Forty to seventy-five percent of people using CAM or natural herbs do not disclose their CAM or HDS use to health care providers, see Table 2.9.[29,36,42,48,74,82,88,103,110,111] Amongst patients with chronic illnesses, the rate of the non-disclosure varies from 32% to 68%, see Tables 2.12 and 2.13.[49-51,53,58-63,65-68,91,92,101] The rate of non-disclosure in the general population is likely to be higher than that in patients as they have no, or only minor illnesses, so they may think that they do not need to inform their doctor, see Table 2.11.

Patients with life threatening illnesses, such as cancer, lung transplantation or CKD in Western populations, including Australian, are more likely to inform their health care providers about their CAM or HDS use (53 to 68%), compared with patients with other illnesses (33% to 64%) or the general population (25% to 60%).[15,16,49,91,92] However, cancer patients in Thailand were less likely to inform their doctor (49%), compared with Western countries.[50]

Asian populations, either general populations or patients with chronic illnesses, are less likely to inform their health care providers about their HDS or CAM use, compared with Western populations.[98,110,111] Nearly seventy per cent of Asian patients do not disclose their herbal use to their health care providers, compared with 33% of whites.[98] However, there is a lack of evidence on the rate of the non-disclosure in Asian patients with CKD, so the comparison between both populations cannot be made.

2.6.2 Reasons for non-disclosure of CAM and HDS use to health care providers

Surveys have reported the reasons why HDS or CAM users do not inform their use to health care providers in both the general population and patients with chronic illnesses (although not for CKD), see Tables 2.11 and 2.13. Amongst patient populations, the most frequently reported reasons for the non-disclosure are that doctors do not ask them about CAM or HDS use (46% to 80%), followed by reporting 'it is not important for their doctor to know' (10% to 54%).[53,61,63,65] The latter reason (22% to 54%) is more frequently reported than the former (29% to 39%) in the general population.[42,74]

Another reason for non-disclosure is concerns about receiving a negative response from health care providers, such as disapproval about their use of HDS or CAM, asking them to stop using HDS or CAM, or being upset by their use.[42,61,65,68,87,101] Moreover, some users thought that their doctor would not understand so they did not inform them.[63,65,82,102] However, there is a lack of literature about such reasons amongst patients with CKD.

It appears that the main types of reasons for the non-disclosure are likely to relate to a doctor's practice and their anticipated response.

2.6.3 Reasons for disclosure of CAM and HDS use to doctors

Only three studies have reported reasons for disclosure of CAM or HDS use to a doctor.[53,87,109] Vickers et al. (2006) report the main reasons why British females inform their doctor about their herbal use is because their doctor is open-minded about herbal medicine and that there is good relationship between the patient and doctor.[87] Farooqui et al. (2012) in Malaysia found that patients with cancer disclosed their CAM use to their doctor as their doctor advised well on CAM use.[109] Barraco et al. (2005) in the US found that the reasons for disclosure in patients were that respondents believe CAM affected their medical care, and

their doctor asked and is willing to listen to their ideas about CAM use.[53] This evidence seems to indicate that doctor's attitudes towards CAM use, and their response, play an important part in the disclosure, or lack thereof.

2.7 Association between HDS use and conventional medication adherence

Fewer studies have reported an association between CAM or HDS use and conventional medication adherence amongst patients with chronic illnesses, see Table 2.14.[19,68,112,113]. Other surveys have shown differences in adherence levels between the users and non-users.[17,18,49,64] The Morisky scale is the most frequently used to assess levels of adherence to conventional medication (CM). There are inconsistencies with such associations, differences amongst patients with chronic illnesses and a lack of literature in patients with CKD.

CAM or herb users are more likely to be non-adherent to CM. Gohar et al. (2008) report that there was a significant association between female users of CAM and poor adherence.[19] Herbal use has been found to related to non-adherence to antiretroviral agents (adjusted OR 6.67, 95% CI 3.12-14.24).[112] African-American users of CAM are likely to have poor adherence to CM (prevalence ratio 1.56, 95% CI 1.14-2.15) whilst the adherence in whites was not different between CAM users and non-users.[17] Bailey et al. (2012) report that a reason for non-adherence was CAM use (10%).[114] Only Krousel-Wood et al. (2010) explain possible reasons for such associations: depressive symptoms, high costs of CM and dissatisfaction with the doctor-patient relationship.[17] Gohar et al. (2008) suggest that further studies should investigate reasons why female CAM users have poorer adherence to CM.[19]

In contrast, five surveys found no association between CAM or HDS use and medication adherence in patients with different diseases.[18,49,64,68,113] Ogbera et al

(2010) and Cherniack (2011) did not define how they measured medication adherence.[64,113] The evidence suggests that CAM or HDS use may not influence CM adherence. Weizman et al. (2012) supports this position and explains that CAM users have more severe disease, and trust their doctor, so they are likely to adhere to their CM.[18] Despite the fact that Matthees's study also found no difference in levels of CM adherence between CAM users and non-users, the small number of CAM users (n= 30) and non-users (n=11) in that study means they cannot make this conclusion.[49] However, the remaining studies do not explain, or have unclear reasons, for such findings.

Table 2.14 Studies of any associations between CAM or HDS use and adherence to conventional medication (n=9)

Authors	Study design and population	Measurement of Adherence	Results
Strejilevich et al. (2013), Argentina and Colombia[68]	Survey 200 outpatients with bipolar disorder	Developed self-reported measurement of adherence	No association of adherence between CAM users and non-users (p > 0.05)
Bailey et al. (2012), US[114]	Survey 59 diabetic patients	MMAS-8-Item®	Reasons for non-adherence: CAM use (10%)
Weizman et al. (2012), Canada[18]	Survey 380 outpatients with inflammatory bowel syndrome	4-item Morisky medication adherence scale	No difference of adherence between CAM users and non-users (p=0.26)
Cherniack (2011), US[113]	Retrospective survey 300 charts in a geriatric clinic	Not defined	No association of adherence between CAM users and non-users (p = 0.46)
Krousel-Wood et al. (2010), US[17]	Survey 2,000 patients using hypertensive agents	MMAS-8-Item®	- Prevalence ratio of poor adherence in African-American CAM users = 1.56 (95%CI 1.14-2.15) - The prevalence ratio in Whites = 0.95 (95% CI 0.70-1.29)
Ogbera et al. (2010), Nigeria[64]	Survey 263 diabetic patients	Not defined	No difference of a percentage of adherence between herbal users and non-users (p > 0.05)
Peltzer et al. (2010), South Africa[112]	Cohort study 735 HIV patients	The 30-day visual analog scale	Herbal use associated with non-adherence to antiretroviral agents (adjusted OR 6.67, 95% CI 3.12-14.24)
Gohar et al. (2008), UK[19]	Survey 153 patients with hypertension	The Hill-Bone compliance	- Female CAM users related to non-perfect adherence (p = 0.02) - No association of adherence between CAM users and non-users (p = 0.11)
Matthees et al. (2001), US[49]	Survey 41 lung transplant recipients	4-item Morisky medication adherence scale	No difference of a percentage of reporting levels of adherence between CAM users and non-users

2.8 HDS situation in Thailand during the last two decades and the surveillance system for their adverse effects

Herbal medicine has been embedded in the Thai health system since the 11th century.[26] Thai herbal medicine has been influenced by India and China; some herbal medicines used by Thai people originate from Indian or Chinese herbal medicine, such as 'Tri pala' and ginseng.[26,115] However, this has declined as Western medicine has influenced the Thai health system since the 19th Century.[26]

The use of herbal medicine has become popular again in Thailand since 1999, because the government has promoted its use for self-reliance on health, in place of pharmaceuticals in order to decrease drug imports from Western countries.[116] The Act on the Protection and Promotion of Thai Traditional Medicine Wisdom 1999 is to promote the use of herbal medicine, and protect and develop knowledge of herbal medicine.[33] These issues have been established in Thai Public Health Development Plans since 2002. The Institute of Thai Traditional Medicine has also developed herbal products, disseminated knowledge of Thai herbal medicines, and promoted rational use of them since 1993.[117] The Medicinal Plant Research Institute in Thailand has developed herbal medicine knowledge, a standard of herbal medicine and Thai herbal pharmacopoeia since 1997.[118] Over 10,000 products have been produced during 1983-2004 and expenditure on herbal medicines was approximately 176 million GBP in 2005.[116]

In the past, most Thai herbal medicines were a mixture of herbal medicines called 'traditional medicine', such as 'Ya hom' for fainting and 'Ka sai' for muscle pain, but since the 20th century, single herbal medicines have been more popular

influenced by the philosophy of modern medicine. Clinical trials have been conducted on the first four herbal medicines: kariyat for pharyngotonsillitis, turmeric for dyspepsia, *Senna alata* for constipation and *Zingiber cassumunar* for muscle pain.[26] Recently, patterns of herbal medicine use in Thailand have been both herbal combinations and single herbal medicines. In general, herbal medicine plays an important role in self-reliance to health in Thai society. Kariyat for sore throats and common colds, turmeric for dyspepsia, and ginger for flatulence are most commonly used in Thailand; conclusions supported by data from a bus stop survey, see Appendix 1, and Satyapan's study.[69,119] There are limited studies about HDS use in Thailand, so the bus stop survey was conducted and aimed to determine the prevalence and pattern of HDS use amongst the Thai general population. This survey shows that the prevalence of HDS use is 52%; the main purpose of herbal medicine use is treating illnesses, whilst dietary supplements are used for maintaining well-being.

In the last decade, use of dietary supplements (DS) has frequently been used influenced by the US and beverages of DS imported from Japan; however there is a lack of evidence to report more on this situation.

2.8.1 Legislation relating to HDS

There has been a general debate on whether herbal and dietary supplements should be categorized as food or medicine, and whether they fall under the governing laws of food or medicine. In Thailand, herbal products are required by the Drug Act 1967 to be registered.[33] This Act has classified the products as either registered herbal products or over-the-counter traditional remedies. Meanwhile, dietary supplements are under the food law 1979.[33] If dietary supplements contain medicine or claim to prevent, cure or treat disease, or modify, restore or correct physiological function, they have to comply with the drug law.

To register the marketing authorisation of the products, both herbal products and dietary supplements must be tested to identify them, and assess maximum permissible levels of contaminants, amounts of bacteria, heavy metals and pesticides.[120] Herbal medicines must have proved their efficacy and safety by using scientific evidence or traditional medical pharmacopoeia,[120] whilst dietary supplements are required to prove their safety by using acute toxic and chronic toxic experiments in animal models.[121] Therefore, the registration of dietary supplements is less restricted than herbal products. However, the registration of herbal products is not subject to the same restrictions as for conventional medicine. For instance, companies which plan to register their herbal products are not required to prove efficacy and safety of their products by clinical trials, if up-to-date scientific evidence or traditional medical pharmacopoeia does not report serious side effects. As a result, there is a lack of safety evidence amongst herbal products and dietary supplements, particularly relating to patients with kidney and liver insufficiency.

Comparing the legislation of HDS in Thailand with the EU laws and WHO guidelines, HDS can be classified as either a medicine or food, depending on certain criteria under the EU laws. The European Directive 2004 has classified herbal medicines and dietary supplements as a medicine if they can "…..prevent, treat, or cure of a condition…., or can be administered with a view to restoring, correcting or modifying physiological functions in human beings" (Gulati and Ottaway, 2006:77).[122] However, they are defined as a food if they are intended to maintain the function of healthy organs and tissues and are regarded as a food ingredient.[122] If the products are identified as a food, they must be included under the EU food law. On the contrary, if they are defined as a medication, they must comply with the EU medicines law. Therefore, registered dietary supplements under the EU laws are more restricted than their legislation in

Thailand, in case some dietary supplements are classified as medication. If they are classified into food, the legislation, in both the EU and Thai laws, is similar.

Regarding legislation of safety of herbal products, the EU food law established the guidance on safety assessment of botanical preparations in 2009. These preparations must be tested for the identification of their scientific names and botanical parts. Moreover, manufacturers have to provide specific toxicity data as follows: genotoxicity data, reproductive toxicity, immunotoxicity and carcinogenicity. In the case of historic herbs, if they have no reports on toxic information, they need not to comply with this criterion.[123] Likewise, WHO guidelines for traditional medicine have suggested herbs, which have been traditionally used without any evidence of harm, do not have to provide any toxic data.[31] Amongst traditional herbal medicines, this is similar to the legislation in Thailand.

2.8.2 Post-marketing surveillance of HDS products

Post-marketing surveillance of herbal and dietary products under the Thai law is monitored by the Thai Health Product Vigilance Center and consumer complaint system. Initially, the center intensively monitored the side effects of five herbal products in 2000 and revealed minor side effects, which are described in herbal monographs.[124] In 2007, this intensive monitoring system has included eight herbal medicines: Kariyat, turmeric, *Zingiber officinale*, *Senna alata*, *Centella asiatica*, *Clinacanthus nutans*, *Capsicum frutescens*, and *Zingiber purpureum*, and found no renal adverse effects from using them.[125] The National spontaneous reporting system has also been established to monitor adverse effects from HDS products in Thailand since 1997 [126] and has encouraged both health care providers and consumers to report them. However, there is under reporting of adverse effects from HDS; for example there was only one report from dietary supplements in a monthly summary of the reports in 2012.[127]

The Thai Health Product Vigilance Center database, between 2000 and 2008, has reported that most side effects from using herbal medicines are gastrointestinal problems, with some are serious side effects, such as Stevens-Johnson syndrome and anaphylactic shock.[128] However, there are limited reports on any renal side effects from using HDS.

2.8.3 Accessibility to HDS products in Thailand

Registered herbal products are available at primary and secondary hospitals, health service centers, Thai traditional clinics and drug stores, but not in general shops.[116] Legislation of drug stores in Thailand has classified the stores as conventional medicine drug stores and traditional medicine drug stores. People who are likely to take herbal products can consult practitioners at these places. Additionally, general shops can sell over-the-counter traditional remedies. Medicinal plants in a raw state need not be registered as herbal products and are sold at traditional medicine drug stores. Many Thai people also grow medicinal plants in their garden. Therefore, raw herbal medicines are easy to access in Thailand, which may do harm if there is a lack of information on how to use them safely.

More than 1,000 dietary supplement products have been registered as a food in Thailand and can be categorised into 8 types of products: vitamins and minerals, antioxidant agents, anti-aging agents, laxatives, herbal extracts, cereal extracts, the agents of decreased lipid absorption and the agents of increased metabolism.[129] They are available at drug stores, dietary supplement stores and department stores.

2.8.4 Thai National List of Herbal Medicine Products

Since 2006, the Thai national drug committee has launched the National List of Herbal Medicine Products based on traditional knowledge, scientific evidence and Thai Herbal Pharmacopoeia in order to encourage good practice of the use of medicinal herbs.[124] Herbal medicines in the list are to alleviate minor ailments, such as fever, cold, gastrointestinal problems and muscle pain.

Seventy-one items of Thai herbal products, both herbal combinations (n=50) and single herbal medicines (n=21), are in the Thai National List of Herbal Medicine Products (2011): for example turmeric (*Curcuma longa*), ginger (*Zingiber officinale*), senna (*Senna alata*, *Cassia alata*), kariyat (*Andrographis paniculata*). Also included are Thai folk remedies such as 'Ya hom' and 'Ka sai'.[119] Appendix 2 shows commonly used herbal medicines in Thailand, their pictures and their medical purposes, which are either recommended by the Thai National List of Herbal Medicine Products or approved by Thai FDA.

2.8.5 Thai National Health System and traditional medicine

The Thai National Health System, called 'the Universal coverage of healthcare scheme', has been implemented nationwide since 2002.[130] Patients with advanced CKD in Thailand are referred from primary and secondary hospitals to tertiary hospitals, such as teaching hospitals, which provide a specialist, such as a nephrologist or cardiologist. Thus, these places are the primary source of advanced CKD health care in Thailand.

Herbal medicines in the Thai National List of Herbal Medicine Products are covered by Thai National Health System. However, only 3% of herbal products in government hospitals have been prescribed in 2012.[131]

Thai traditional medicine practitioners have to register under the Practice of the Art of Healing Act 1999.[33] There are two educational systems of Thai traditional

medicine, which are apprenticeship and undergraduate programmes.[24] However, most use of herbal medicine in Thailand is not under supervision by the practitioners as Thai people use it for self- care, such as treating common cold, dyspepsia and constipation.

2.8.6 The spectrum of herbal research in Thailand

Most studies of herbal medicines in Thailand have been conducted by researchers in Thai universities, the Medicinal Plant Research Institute, and the Institute of Thai Traditional Medicine. Most herbal research in Thailand has explored efficacy and toxicity of herbal medicine in animal models and in vitro.[132] Few clinical trial studies have been conducted. Examples of herbal medicines, which are studied are: *Curcuma longa, Andrographis paniculata, Centella asiatica, Boesenbergia pandurata, Zingiber officinale, Eugenia caryophyllus, Psidium guajava*.[132] The purposes of these herbal medicines are treatment of minor ailments, such as dyspepsia, diarrhoea, wound healing and the common cold. Additionally, research regarding the efficacy of well-known herbs such as *Momordica charantia, Allium sativum* and *Pueraria mirifica,* has been conducted frequently, compared with others, because they are consumed frequently. People have used them for diabetes, dyslipidaemia and breast enlargement, respectively.[133] There are limited clinical trials of benefits and adverse effects of herbal medicine in Thailand.[134-138] Case reports are the main information sources of side effects from use of herbal medicine in Thailand, and these have been limited.[139]

With respect to findings of herbal information supported by postgraduate research in Thailand, the majority of research areas are similar to the studies as described above. Many studies have examined anti-oxidant and anti-microbial effects of plants and have focused on medicinal plants for treating osteoarthritis, diabetes mellitus, cancer and acquired immune deficiency syndrome.[140] Beliefs

and attitudes regarding herbal products have been surveyed in many regions of Thailand.[141-143]

Despite plenty of animal studies on the beneficial effects of herbal medicine, there is a lack of human studies regarding positive and negative effects of herbal medicines in Thailand.

3. Chronic kidney disease

Chronic kidney disease (CKD) is an important condition, as it leads to an increase in morbidity and mortality worldwide. An overview of CKD, prevalence of this disease and assessment of kidney function are now presented.

3.1 Definition and classification of CKD

Chronic kidney disease is defined as either kidney damage or a glomerular filtration rate of less than 60 ml/min/1.73m^2 for at least 3 months.[144] The United States (US) National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI®) in 2002, the Kidney Disease Improving Global Outcomes (KDIGO) in 2012, and the National Institute for Health and Clinical Excellence (NICE) guideline for CKD in 2008, have classified the severity of CKD into five stages, see Table 3.1.[11,144,145] Stage one of CKD has the lowest kidney damage whilst stage five denotes the highest severity of CKD. The Thai guideline for CKD in 2009, which defined CKD and its classification, is based on the NKF-KDOQI® guideline.[12]

Table 3.1 Classification of CKD

Stage	Description	GFR (ml/min/1.73m^2)
1	Kidney damage with normal or an increase in GFR	$\geq$ 90
2	Kidney damage with a slight decline in GFR	60-89
3		
3a	Mild to moderate decline in GFR	45-59
3b	Moderate to severe decline in GFR	30-44
4	Severe decline in GFR	15-29
5	Kidney failure or end-stage renal disease	< 15 (or dialysis)

References: National Kidney Foundation. Definition and Classification of Stages of Chronic Kidney Disease. *Am J Kidney Dis* 2002;39(2 Suppl 1):S46.

Kidney Disease: Improving Global Outcome (KDIGO) CKD Work Group. The KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int Suppl* 2012;3(1):27.

The National Collaborating Centre for Chronic Conditions (Great Britain). *Chronic Kidney Disease: National Clinical Guideline for Early identification and Management in Adults in Primary and Secondary Care*. 1st ed. London: Royal College of Physicians, 2008.

This thesis is focused on CKD stages 3 to 5, as classified by GFR and defined as advanced CKD. Stage 1 to 2 CKD is classified by kidney damage – either structural or functional abnormality of the kidney.[144] The more GFR decreases, the more kidney function declines. Patients who either have less than 15 ml/min/1.73m^2 of GFR or are receiving dialysis therapy are defined as having end-stage renal disease (ESRD), meaning their kidneys fail to eliminate body waste.

3.2 Prevalence of CKD and characteristics of patients with CKD in Thailand

The prevalence of patients with less than 60 ml/min/1.73m^2 of estimated glomerular filtration rate (eGFR) in Thailand has ranged from 8.9-14.0%.[5,146,147] It appears that the prevalence of CKD in the Thai population, aged 35 years or older (8.9%),[147] was higher than the median prevalence of CKD worldwide in a population aged 30 years or over (7.2%).[148] Perkovic's study also showed that the prevalence of stage 3 CKD in Thailand was higher than in both the US and Taiwan.[147]

In Thailand, stage 3 of CKD has the highest prevalence, compared with stages 4 and 5, see Table 3.2.[5,146,147] Northeast Thailand has a high prevalence of CKD, whilst its prevalence in Bangkok is inconsistent: one study found the highest prevalence of CKD in Bangkok (23.9%)[5] and a national survey in 2000 showed the lowest prevalence (9.7%).[147]

Table 3.2 Prevalence of CKD in each stage and region amongst Thai patients

Authors	Study design	Population	Measurement of eGFR	Prevalence (%)
Perkovic et al. (2008)[147]	A national survey in 2000 using a stratified, multistage, cluster-sampling method (n=7,909)	Thai population aged 35 years or over	MDRD equation	Stage 3: 13.2 Stage 4: 0.6 Northeast: 16.9 North: 15.1 Central: 13.7 Bangkok: 9.7 South: 9.7
Ong-Ajyooth et al. (2009)[146]	A national health survey in 2004 (n=3,117)	Thai population aged 15 years or over	Chinese modified MDRD equation	Stage 3: 8.1 Stage 4: 0.2 Stage 5: 0.2
Ingsathit et al. (2010)[5]	The population-based Thai Screening and Early Evaluation of Kidney Disease (SEEK) study in 2007 (n=3,459)	Thai population aged 18 years or over	MDRD	Stage 3: 7.5 Stage 4: 1.1 Bangkok: 23.9 Northeast: 22.2 North: 20.4 South: 13.7 Central: 13.4

eGFR = Estimated glomerular filtration rate

MDRD = Modification of Diet in Renal Disease study

There are four relevant studies which reported characteristics of stages 3 to 5 CKD populations in four countries: Ong-Ajyooth's study (2009) in Thailand[146]; Zhang's study (2012) in China[149]; Imai's study (2010) in Japan[150]; and Martinez-Castelao's study (2011) in Spain[151], see Table 3.3. The mean age from the Thai survey (56.8) is younger than others. Most of the CKD population in Thailand and China is female, whilst those in Japan and Spain are male. The Thai population with CKD has the lowest proportion of hypertension and diabetes. There is no significant difference in mean BMI amongst Asian populations, which is lower than in Spain (28.4 kg/m^2). Fewer than 20% of CKD patients in Japan and China currently smoke, whilst 26% are either current or former smokers, as reported by the Thai survey. It appears that the characteristics of the Thai population are consistent with those in China.

Table 3.3 Characteristics of populations with stages 3 to 5 CKD aged 15-18 or over in several countries

Survey	Thailand[146] (n=3,117)	China[149] (n=47,204)	Japan[150] (n=2,977)	Spain[151]* (n=1,129)
Mean age	56.8	63.6	60.8	68
Female (%)	69.6	61.9	37.9	36.0
Mean BMI (kg/m^2)	24.4	24.4	23.5	28.4
Diabetes (%)	14.6	19.1	38.0	40.8
Hypertension (%)	50.0	60.5	92.0	92.7
Current smoking (%)	26.0**	19.4	16.4	-

* Stage 3-4 CKD population; ** Current or former smoking

3.3 Causes, symptoms of CKD and its complications

3.3.1 Causes of CKD and rate of CKD progression

There are several causes of CKD. Diabetes and hypertension are the main causes of CKD worldwide, followed by chronic glomerulonephritis, chronic interstitial nephritis and renovascular disease.[152] Chronic glomerulonephritis is a more common cause in Asia.[152] In Thailand, high numbers of renal tubular acidosis have been reported, particularly in northeast Thailand[153], which may lead to a high prevalence of CKD in northeast Thailand. There is an ongoing survey of CKD causes in Thailand – the population-based Thai screening and early evaluation of kidney disease (SEEK) study 2.

Several diseases can lead to CKD, such as human immunodeficiency virus (HIV), cancer and cirrhosis. Patients with HIV are six times more likely to develop kidney impairment than non-HIV patients, which mainly causes HIV-associated nephropathy.[154,155] CKD can be caused by cancer, due to paraneoplastic nephropathy and side effects from chemotherapy or radiation.[156] CKD in cirrhosis is related to hepatorenal syndrome impaired renal perfusion.[157]

Various causes of CKD have a different rate of decline in GFR, see Table 3.4.[18,19] Diabetes and chronic glomerulonephritis has a faster progression of CKD, compared to other causes. Fast progression has been defined as a decline in GFR of at least 5 ml/min/year.[11,145] There is a lack of evidence relating to the progression of CKD regarding those with cancer or cirrhosis.

Table 3.4 Mean rate of decline in GFR for various causes of CKD amongst patients with stage 3-5 CKD[158,159]

Causes of CKD	Mean GFR at baseline (ml/min)	Rate of decline in GFR (ml/min/year)
Diabetes	36	7.9
Hypertension	39	4
Chronic glomerulonephritis	43	4.6
Tubulointerstitial diseases	41	2
Polycystic kidney disease	47	3.8
HIV	< 60	2.3-2.6

References: National Kidney Foundation. Stratification of Risk for Progression of Kidney Disease and Development of Cardiovascular Disease. *Am J Kidney Dis* 2002;39(2 Suppl1):S173.

Campbell LJ, Ibrahim F, Fisher M, Holt SG, Hendry BM, Post FA. Spectrum of chronic kidney disease in HIV-infected patients. *HIV Med* 2009;10(6):329-36.

3.3.2 Symptoms and complications of CKD

Patients with early stage CKD are asymptomatic, whilst those with stages 3 to 5 CKD are likely to have symptoms of CKD complications: fatigue, weakness, a poor appetite, swollen feet, dry and itchy skin and frequent urination at night.[160,161]

Patients with less than 60 ml/min of GFR are more likely to develop complications of CKD, such as anemia, hypertension, hyperphosphatemia, hyperkalemia and metabolic acidosis. The prevalence of hypertension, amongst those with advanced CKD is over 70%, whilst the prevalence of anemia or hyperphosphatemia is less than 10%.[162] The more severe the CKD, the more complications of CKD patients suffer. Hyperkalemia is likely to occur when

patients have stages 4 to 5 of CKD.[163] The prevalence of hyperkalemia (serum potassium level > 5 mEq/L) in patients with stage 5 CKD is 54%.[164]

This thesis is focused on hyperphosphatemia and hyperkalemia, because herbal and dietary supplements may lead to these complications. CKD causes hyperphosphatemia and hyperkalemia as kidneys decline in eliminating phosphate and potassium.[163,165] However, patients with advanced CKD can develop hyperkalemia if they partake of a diet containing high amounts of potassium.[163] A high serum level of potassium (> 6.0 mEq/L) may cause electrocardiogram abnormality and is life-threatening. Severe hyperkalemia can induce ventricular arrhythmias, skeletal muscle weakness and respiratory failure.[157] Advanced CKD is linked to an abnormality of calcium-phosphate homeostasis leading to hyperparathyroidism. Hypercalcemia and hyperphosphatemia can increase cardiovascular calcification in patients with CKD.[166]

3.4 Risk factors related to progression of CKD and its complications

3.4.1 Risk factors linked to CKD progression

There are known factors that increase susceptibility to CKD, including older age, family history of CKD, diabetes, obesity, hypertension and dyslipidaemia, as well as nephrotoxic agents, such as non-steroidal anti-inflammatory drugs (NSAIDs).[167] Likewise, two surveys in Thailand have revealed factors related to CKD, which are being elderly, diabetes, hypertension, high body mass index (BMI) and a history of kidney stones.[5,168]

Established factors related to the progression of CKD have been younger age, male, obesity, smoking, proteinuria, high protein intake, hypertension, systolic blood pressure of more than 130 mmHg, hyperlipidaemia, and exposure to

nephrotoxic agents.[157,167] There have been many relevant cohort studies that have reported factors linked to the progression of CKD in patients with advanced CKD, see Table 3.5.[169-173]

These studies defined the progression of CKD as either a decline in eGFR of 5 ml/min/year or end-stage renal disease (ESRD). Levin et al. (2008) report a younger age has a faster progression (p-value < 0.01)[169] and Eriksen and Ingebretsen (2006) found that an increase of 10 years in age has less ESRD (HR 0.75, 95%CI 0.63-0.89).[173] Males are more likely to experience CKD progress in terms of severity, than females.[173] Proteinuria indicates a high risk of CKD progression[169] or ESRD[170,171], compared with diabetes, hypertension, smoking history and uncontrolled blood pressure.[170] Non-selective NSAIDs and rofecoxib are linked to ESRD in newly diagnosed CKD patients.[174]

Table 3.5 Factors related to the progression of CKD

Authors	Study design	Population	Definition of progression of CKD	Risk factors
Eriksen and Ingebretsen (2006), Norway[173]	A 10-year population-based study	Patients with stage 3 CKD (n=3,047)	End-stage renal disease	Age (10 year increase): HR 0.75, 95%CI 0.63-0.89 Female: HR 0.35, 95%CI 0.21-0.59
Levin et al. (2008), US[169]	Cohort analysis from PROMIS* database Median follow-up: 31 months	Patients with < 30 ml/min of eGFR (n=4,231)	Fast progression defined as -5 ml/min/yr of decline in eGFR	Younger age Proteinuria (> 1 g/day) Higher level of SBP
Obi et al. (2010), Japan[170]	Historical cohort study Median follow-up: 3.2 years	Patients with stage 3-5 CKD (n=461)	End-stage renal disease	Overt proteinuria (> 1 g/day): SHR 9.1, 95%CI 4.2-19.7 Diabetes: SHR 2.1, 95%CI 1.2-3.4 Hypertension: SHR 10.7, 95%CI 1.5-76.0 Smoking history: SHR 2.0, 95%CI 1.2-3.4
Nicola et al. (2011), Italy[171]	Prospective cohort study for 5 years	Patients with stage 3-5 CKD (n=1,248)	End-stage renal disease	Proteinuria ($\geq$ 0.5 g/day) Stage 3: HR 3.17, 95%CI 1.76-5.72 Stage 4: HR 2.02, 95%CI 1.41-2.88 Stage 5: HR 1.13, 95%CI 0.73-1.76
Goeij et al. (2011), Netherland[172]	Cohort analysis for a year from PREPARE-1 study	Patients with stage 4-5 CKD (n=508)	Rate of decline in eGFR	BP $\geq$ 130/80: Adjusted additional decline in eGFR 0.31 m/min/month, 95%CI 0.08-0.53

Table 3.5 (continued)

Authors	Study design	Population	Definition of progression of CKD	Risk factors
Samuelsson et al. (1997), Sweden[175]	A prospective, observational study Average follow-up: 3.2 years	Patients with GFR 15-75 ml/min/1.73m^2 and non-diabetes and (n=73)	Rate of decline in GFR	The more level of LDL increased, the more rate of GFR declined (p-value = 0.01) LDL level of 88-140 mg/dl had -4.7 of annual decline in GFR.
Kuo et al. (2010), Taiwan[174]	A cohort study	Newly diagnosed CKD patients (n=19,163)	End-stage renal disease	Non-selective NSAIDs: adjusted** HR 1.56, 95%CI 1.32-1.85 Aspirin: adjusted HR 1.96, 95%CI 1.62-2.36 Rofecoxib: adjusted HR 1.98, 95%CI 1.15-3.40

* Patient Registration and Outcomes Management Information System; eGFR = Estimated glomerular filtration rate; SBP = Systolic blood pressure

SHR = Subdistribution hazard ratio; HR = Hazard ratio, CI = Confidence intervals; PREPARE-1 = PREdialysis Patient Record-1 study

** Adjusted for age, sex. Comorbidities, such as diabetes and hypertension and use of other analgesics

There is limited evidence to support high protein intake relating to a progression of CKD in patients with advanced CKD. The Modification of Diet in Renal Disease (MDRD) study in 2004 has been the cornerstone of the recommendation for low protein intake in patients with CKD, and reports slightly slowed progression of CKD in a group with low protein intake (0.6-0.8 g/kg of body weight/day) amongst patients with 55-25 ml/min of eGFR, compared with a group of usual protein intake (1.0-1.2 g/kg of body weight/day).[176] There is no significant benefit in patients with less than 25 ml/min of eGFR and very low protein intake (0.4-0.6 g/kg of body weight/day), compared with a group of low protein intake.

3.4.2 Factors related to hyperkalemia and hyperphosphatemia

Theoretically, hyperkalemia in patients with CKD is caused by high potassium intake and/or drug-induced hyperkalemia, such as angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor antagonists (ARBs), NSAIDs or cyclooxygenase-2 (COX-2) inhibitors.[163,177] However, ACEIs or ARBs related to hyperkalemia in these patients are less likely to be clinically significant.[178] High phosphate intake mainly results in hyperphosphatemia amongst patients with advanced CKD.[179] Vitamin D also increases intestinal absorption of phosphate from 60% to 86% in patients with advanced CKD.[165]

There are limited studies of the association between risk factors and hyperkalemia and hyperphosphatemia. There is one cohort study with an average duration of 2.6 years, in the US, that report patients with CKD taking ACEIs or ARBs are more likely to have hyperkalemia.[180]

3.5 Measurement of kidney function, hyperkalemia and hyperphosphatemia

3.5.1 Measurement of kidney function and progression of CKD

Kidney function is assessed by measuring the glomerular filtration rate (GFR). Normal values of GFR in an adult are 120 ml/min for men and 100 ml/min for women. A decline in GFR represents worsening kidney function, particularly if less than 60 ml/min of GFR. Inulin is a gold standard marker for evaluating kidney function, as this substance is filtrated from renal tubules, and is not absorbed and secreted by renal tubules. In clinical practice, serum creatinine is a recommended marker for assessing kidney function due to being cheap and convenient. This is calculated to predict kidney function using the Cockcroft-Gault equation (CG equation), the MDRD equation or the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI equation), see Table 3.6.

Until 2005, the Cockcroft-Gault equation had been calculated to predict the creatinine clearance rate, which was assumed to be equal to GFR. This equation had been the most commonly used in clinical practice; nevertheless, it overestimates eGFR due to the fact that 15-20% of creatinine is secreted by renal tubules.[157]

To date, estimated GFR calculated using the MDRD equation has been recommended for adult patients with less than 60 ml/min/1.73m^2 of GFR by the National Kidney Disease Education Program in the US, the NICE guideline for CKD in UK and the Thai guideline for CKD.[12,145,181] This is adjusted for body surface area and is more accurate than the Cockcroft-Gault equation in patients with advanced CKD.[145] Meanwhile, the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI equation) has been recommended for those

with at least 60 ml/min/1.73m^2 of GFR.[11] Recently, epidemiologic studies are more likely to estimate kidney function using the MDRD equation, rather than the Cockcroft-Gault equation.[148]

Table 3.6 Equations of estimated glomerular filtration rate

eGFR equation	Formulas
Cockcroft-Gault equation (ml/min)	(140-Age) X Body weight/72 X Scr (ml/min) Female (X 0.72)
Reexpressed MDRD equation (ml/min/1.73 m^2)	(175 X Scr $^{-1.154}$ X Age$^{-0.203}$) Female (X 0.742)
Thai MDRD equitation (ml/min/1.73 m^2)	(175 X Scr $^{-1.154}$ X Age$^{-0.203}$) Female (X 0.742) X Thai (X 1.129)
CKD-EPI equation (ml/min/1.73 m^2)	Male: with Scr $\leq$ 0.9 mg/dL 141^{163} X (Scr/0.9)$^{-0.411}$ X (0.993)^{Age} Male: with Scr > 0.9 mg/dL 141^{163} X (Scr/0.9)$^{-1.209}$ X (0.993)^{Age} Female: with Scr $\leq$ 0.7 mg/dL 144^{166} X (Scr/0.7)$^{-0.329}$ X (0.993)^{Age} Female: with Scr > 0.7 mg/dL 144^{166} X (Scr/0.7)$^{-1.209}$ X (0.993)^{Age}

References: Cirillo M. Evaluation of Glomerular Filtration Rate and of Albuminuria/Proteinuria. *J Nephrol* 2010;23(2):127.

Levey AS, Coresh J, Greene T, Marsh J, Stevens LA, Kusek JW, et al. Expressing the Modification of Diet in Renal Disease Study Equation for Estimation Glomerular Filtration Rate with Standardized Serum Creatinine Values. *Clin Chem* 2007;53(4):771.

Praditpornsilpa K, Townamchai N, Chawatanarat T, Tiranathanagul K, Katawatin P, Susantitaphong P, et al. The Need for Robust Validation for MDRD-Based Glomerular Filtration Rate Estimation in Various CKD Populations. *Nephrol Dial Transplant* 2011;26(9):2780-85.

Scr = Serum creatinine

However, the MDRD equation has been validated in Caucasian populations and underestimates eGFR amongst Asian populations, such as Chinese people, due to a difference in muscle mass.[182] The Thai MDRD equation has been developed and recommended for Thai patients, see Table 3.6.[183] The limitation of the MDRD equation is that it should not be used for unstable serum creatinine and there

should be caution in using it for people aged over 70 years and those individuals with extremes of muscle mass, such as the obese or bodybuilders.

To estimate progression of CKD, based on eGFR, fast progression of CKD is currently defined as a decline in an eGFR of at least 5 ml/min/1.73m^2/year[11,145] although there is no conclusive definition as some studies define it as -3 or -4 ml/min/1.73m^2/year.[161,184] The NKF-KDOGI® guideline in 2002 has suggested that the CKD progression is estimated by a slope of the best fit linear regression line, which is plotted on a graph of eGFR levels and time under the assumption of a constant decline in kidney function over a period.[158] Both the NKF-KDOGI® guideline in 2002, and the NICE guideline for CKD in 2008, have recommended at least three measures of serum creatinine over a period in order to estimate GFR and precisely predict the progression of CKD; particularly slow rates of this progression.[145,158]

3.5.2 Measurement of hyperkalemia and hyper-phosphatemia

Serum levels of potassium and phosphate indicate abnormality of these electrolytes. Hyperkalemia is more than 5.5 mEq/L (mmol/l) of a serum potassium level[185] and hyperphosphatemia is more than 4.6 and 5.5 mg/dl (1.5 and 1.7 mmol/l) of a serum phosphate level for stages 3 to 4 CKD and stage 5 CKD, respectively.[186]

3.6 Slowing the progression of CKD and management of its complications

Management in slowing the progression of CKD has involved cessation of smoking, body weight loss for obesity, strict blood sugar control in diabetes, strict blood pressure control, use of ACEIs or ARBs for CKD with proteinuria and restricted protein intake.[145,158] The Thai guideline for CKD management in 2009,

and the NKF-KDOQI® for diabetes in 2007, have recommended controlled blood sugar of less than 7% of glycated haemoglobin (A1C) for diabetes and controlled blood pressure of equal or under 130/80 mmHg to slow the progression of CKD.[12,187] The NICE guideline for CKD management in 2008 has suggested controlled blood pressure of lower than 140/90 and 130/80 mmHg for non-diabetes and diabetes, respectively.[145] The Thai guideline for CKD management in 2009 has recommended 0.6-0.8 and 0.6 g of protein/kg of body weight/day for stage 3 and stages 4 to 5 of CKD, respectively, whilst the KDIGO guideline in 2012 has suggested 0.8 g of protein/kg of body weight/day for stages 4 to 5 of CKD.[11] A dietary protein restriction, of 0.6 g/kg/day, prevented 32% of non-diabetic patients from reaching end-stage renal disease.[188]

The principal management of CKD complications, hyperkalemia and hyperphosphatemia, has been the avoidance of potassium and phosphate rich foods.[12] Potassium-rich foods are fruit, such as oranges and bananas, dried fruit and potatoes, and phosphate-rich foods such as cereal, dairy products and coffee.[12,163] If a patient with CKD cannot control their serum potassium or phosphate levels under these diets, their doctor will consider prescribed medication therapy, such as sodium or calcium polystyrene sulfonate for hyperkalemia and phosphate binders, such as calcium carbonate or acetate, for hyperphosphatemia.[12,185]

There are common medications for other CKD complications, such as loop diuretics for peripheral oedema, iron supplements, folic acid, vitamin B12 and erythropoietin for anaemia, sodamint for metabolic acidosis and allopurinol for hyperuricemia.[185]

3.7 Use of nephrotoxic agents, herbal medicine and dietary supplements in patients with advanced CKD

NSAIDs and COX-2 inhibitors have been known as a nephrotoxic agent.[157] Both the NKF-KDOQI® guideline in 2002, and the Thai guideline for CKD management in 2009, have recommended avoiding nephrotoxic agents for patients with CKD, such as NSAIDs and COX-2 inhibitors, in order to prevent acute kidney injury on top of CKD.[158] The NICE guideline for CKD management in 2008 has suggested prolonged use of these medications only with caution for those with CKD, combined with close monitoring of their GFR.[145] There have been inconsistencies in the association between aspirin and progression of CKD. In case-control studies, aspirin is likely to be associated with end-stage renal disease (ESRD) in patients with newly diagnosed CKD[174,189]; however Perneger et al. in 1994 report no association.[190] Among patients with stages 4 to 5 of CKD, there is a positive association between aspirin and the progression of CKD in a prospective cohort study of 5-7 years duration.[191] However, this has been the only study reporting the positive association, so further studies are required to confirm and explain this result.

Patients with CKD should not use herbal medicine, as some Chinese herbal medicines may contain aristolochic acid, which can induce renal failure. Such patients should use dietary supplements only under the supervision of a doctor or pharmacist, as suggested by the KDIGO guideline in 2012.[11] The 2009 Thai guideline for CKD management has recommended using herbal medicine with caution.[12] However, neither guidelines have provided conclusive evidence to support their recommendation; in particular the KDIGO recommendation for herbal use is supported by only one Chinese herbal medicine related to kidney injury. The 2008 NICE guideline for CKD management did not mention herbal

medicine. Such guidelines suggest that there is only limited scientific evidence regarding the safety of herbal medicine for patients with CKD.

The 2011 Thai National List of Essential Medicines has advised patients with CKD to avoid senna for constipation, rosella flower for a diuretic effect, java tea for a diuretic effect and 'Ya hom' for fainting and 'Ka sai' for muscle pain, the last two being Thai folk remedies.[119] This is because high doses of senna may induce nephritis and its prolonged use affects water and electrolyte imbalance, particularly potassium imbalance. Java tea also contains high amounts of potassium and may cause water and electrolyte imbalance. Prolonged use of 'Ya hom' and 'Ka sai' accumulates camphor in the body leading to renal toxicity; particularly urinary retention, albuminuria and anuria.[192] Moreover, 'Ya hom' and 'Ya khom', which are Thai folk remedies, contain *Aristolochia*, which is related to renal failure and has a carcinogenic effect, so this ingredient has been withdrawn from these remedies in Thailand since 2013.[193]

The National Kidney Foundation in the US has suggested avoiding herbal medicine, which may be toxic or harmful to the kidneys, see Table 3.7.[194]

Table 3.7 Herbal medicines related to renal damage

Herbal medicine may injure the kidneys	
Artemisia absinthium (wormwood plant)	Periwinkle
Autumn crocus	Sassafras
Chuifong tuokuwan (Black pearl)	Tung shueh
Horse chestnut	Vandelia cordifolia
Herbal medicine may be harmful in CKD	
Alfalfa	Ginger
Aloe	Ginseng
Bayberry	Horsetail
Blue Cohosh	Mate
Broom	Nettle
Buckthorn	Noni juice
Capsicum	Rhubarb
Cascara	Senna
Coltsfoot	Vervain
Dandelion	

Reference: National kidney foundation. Use of herbal supplements in chronic kidney disease, 2013. www.kidney.org/atoz/content/herbalsupp.cfm. (accessed 17th December 2013).

4. Negative and positive effects of HDS on kidneys

This thesis is focused on investigating any adverse effects of herbal and dietary supplement on kidneys, rather than renal benefits of HDS.

4.1 Renal adverse effects of HDS

Adverse effects of HDS on renal function can be associated with their active ingredient which can cause kidney injury, adulteration of HDS with heavy metals and conventional medicines, or herbs/dietary supplements-drug interactions.

4.1.1 Herbal medicine-induced nephropathy

There are known herbal medicines which directly damage the kidneys, see Table 4.1.[2] Thai surveillance of herbal medicine also reports *Houttuynia cordata Thunb* can induce acute renal failure.[195] There is a case report that 'Ya hom' caused the renal failure and death of a 2-year-old girl, as it contained *Magnolia officinalis* which is associated with renal failure.[196] It appears that most of the information regarding medicine-induced nephropathy has been provided by case reports.

Table 4.1 Plants and herbal medicines and negative effects on renal function

Herbal medicine	Common name	Toxic component	Potential effects on renal function
Aristolochia spp.	-	Aristolochic acid	Chronic interstitial nephritis Renal tubular defects Urothelial malignancies
Lorrea tridentata	Chapparal	Nordihydroguaiaretic acid	Renal cysts, renal cell carcinoma
Ephedra sinica	Ma-Huang, ephedra	Ephedrine	Nephrolithiasis Obstructive nephropathy
Pithecolobium lobatum *P. jiringa*	Djengkol	Djenkolic acid	Nephrolithiasis Obstructive nephropathy
Averrhoa carambola	Star fruit	Oxalic acid	Nephrolithiasis Obstructive nephropathy
Vaccinium macrocarpon	Cranberry	Oxalic acid	Nephrolithiasis Obstructive nephropathy
Salix daphnoides	Willow bark	Salicin	Renal papillary necrosis
Pausinystalia yohimbe	Yohimbe	Yohimbe	Lupus nephritis
Rhizoma Rhei	Rhubarb	Anthraquinone	Chronic interstitial nephritis
Echinacea spp.	Coneflower	Arabinogalactan	Renal tubular acidosis

Reference: Jha V. Herbal medicines and chronic kidney disease. *Nephrology* 2010;15(Suppl S2):11.

A few observational studies in Taiwan and Thailand have reported a relationship between herbal products and new cases of CKD or end-stage renal disease (ESRD), see Table 4.2.[4-7,197,198] There are limited studies regarding this issue, particularly cohort studies or research involving populations with existing CKD. Most studies have been conducted in Taiwan and their focus is on those newly diagnosed with CKD (five out of six studies). Most studies have not reported the types of herbal medicines because most patients do not know the names of the herbal medicine or its active ingredients. There has been inconsistent association between herbal use and the progression of CKD.

Table 4.2 Studies of the association between herbal use and new cases of CKD or ESRD

Authors	Study design	Number of general population	Methods	Outcomes	Results
Guh et al. (2007), Taiwan[4]	Cross-sectional study	1,740	Interview	CKD	**Comparator:** non-herbal users **Herb users:** adjusted OR = 1.4 (95% CI = 1.2-1.7)
Lin et al. (2013), Taiwan[198]	Cross-sectional study	3,352	Interview	CKD	**Comparator:** non-herbal users **Chinese herb users:** adjusted OR = 0.8 (95% CI = 0.6-1.1)
Ingsathit et al. (2010), Thailand[5]	Cross-sectional study	3,459	Interview	CKD	**Comparator:** non-herb users **Herb users:** multivariate OR = 1.20 (95% CI = 1.02-1.42)
Hsieh et al. (2012), Taiwan[6]	Case-control study	424	Interview	CKD	**Comparator:** non-herbal users **Prescribed Chinese herb use:** Occasional use: adjusted OR = 1.9 (95% CI = 0.9-4.1) Regular use: adjusted OR = 1.2 (95% CI = 0.6-2.4) **Non-prescribed Chinese herb use:** Occasional use: adjusted OR = 6.2 (95% CI = 1.8-21.6) Regular use: adjusted OR = 3.1 (95% CI = 0.8-12.2)
Tsai et al. (2009), Taiwan[7]	Case-control study	200 cases and 200 controls	Interview	ESRD	**Comparator:** non-herbal users **Herbal users*:** crude OR = 6.26 (95% CI = 3.85-10.19)

Table 4.2 (continued)

Authors	Study design	Number of general population	Methods	Outcomes	Results
Lai et al. (2010), Taiwan[197]	Population-based case-control study	25,843 cases and 184,851 controls	Database analysis	ESRD	**Comparator:** 0 g of Mu tong **101-200 g of Mu tong**:** Multivariate OR = 2.42 (95% CI = 1.45-4.05) **> 200 g of Mu tong**:** Multivariate OR = 6.17 (95% CI = 3.62-10.53) **Comparator:** 0 g of Fangchi **> 200 g of Fangchi**:** Multivariate OR = 2.40 (95% CI = 1.43-4.04)

Note: CKD = chronic kidney disease, OR = odds ratio, CI = confidence intervals, ESRD = end-stage renal disease, * = regular herb used for 5 years before diagnosed with ESRD, ** = used herbal medicines more than once a week for at least 3-6 months

Both Guh et al. (2007) and Ingsathit et al. (2010) report that herbal products are associated with a small increased risk of developing CKD.[4,5] Tsai et al (2009) show herbal medicines are linked to a large increase in the risk of new cases of ESRD (crude OR = 6.26; 95% CI = 3.85-10.19).[7] Lai's study is the only article which specified the type of herbs involved and additionally, they found a dose related increase in risk of developing new cases of ESRD.[197]

In contrast, Lin et al. (2013) and Hsieh et al. (2012) report no association between Chinese herbal use, or prescribed Chinese herbal medicine, and new cases of CKD.[6,198] Despite occasional use of non-prescribed Chinese herbal medicine related to CKD, there is no clear pattern to this relationship.

4.1.2 Renal adverse effects of dietary supplements

Few studies have reported dietary supplements being associated with nephrotoxicity, see Table 4.3.[199-201] Creatine supplements, L-glutamine, ascorbic acid and cranberry have all been shown to be related to kidney problems. Three case reports, together with a clinical trial, report creatine supplements resulted in a deterioration of renal function.[202-205] L-glutamine decreased eGFR[200], whilst ascorbic acid increased 20% and 33% of urinary oxalate in normal subjects and kidney stone formers, respectively.[201] Finally, cranberry increased amounts of calcium oxalate in urine.[199]

Table 4.3 Dietary supplements related to nephrotoxicity

Authors	Study design	Number of participants	Intervention	Outcomes	Results
Gualano et al. 2008[203]	12-week, double blind, randomised, placebo-controlled trial	18 healthy men	0.3 g of creatine supplements/kg/day for 1st week and then 0.15 g/day/kg for the next 11 weeks	Scr	Increase in Scr among creatine group
Gualano et al. (2010)[202]	Case report	20-year-old-man having a single kidney	20 g/day of creatine monohydrate for 5 days and then took 5 g/day for the next 30 days	Scr	Scr increased from 1.03 to 1.27 ml/min
Pritchard and Kara (1998)[204]	Case report	25-year-old man with focal segmental glomerulosclerosis	Creatine of 5 g tid per week and then a maintenance dose of 2 g/day for 7 weeks	eGFR	Decrease in eGFR
Thorsteinsdottir et al. (2006)[205]	Case report	24-year-man	5 g of creatine monohydrate 3 times per week	Renal biopsy	He had acute interstitial nephritis
Galera et al. (2010)[200]	Controlled, randomised, double-blind, crossover study	30 residents of a long-term-care institution	• 0.5 g of L-glutamine/kg/day for 14 days • 0.5 g of calcium caseinate/kg/day (control group)	eGFR	Decrease of 13.3% in eGFR among group of L-glutamine
Traxer et al. (2003)[201]	Randomised, double-blind, crossover study	12 normal subjects and 12 stone formers*	• Ascorbic acid 1 g twice a day for 6 days • Placebo containing excipient twice a day	• Scr • urinary oxalate	• No differences of Scr in both groups • Increase in urinary oxalate in both groups, compared with placebo phrase
Terris et al. (2001)[199]	Clinical trial	5 healthy volunteers	A cranberry tablet twice a day for a week	UA	Increase in 50% of amounts of calcium oxalate in urine

Abbreviation: g = gram, kg = kilogram, Scr = Serum creatinine, tid = three times a day, UA = urinalysis, eGFR= estimated glomerular filtration rate, * = participants having the history of kidney stones

4.1.3 Herbal and dietary supplements related to complications of CKD

Some HDS leads to worsening complications focused on hyperkalemia and hyperphosphatemia, because HDS may directly induce more severe complications or HDS may contain large amounts of potassium and phosphate. For instance, taking herbal diuretics, such as alfalfa, dandelion, horsetail, milkweed and nettle, may result in hyperkalemia.[163] Several HDS containing high amounts of potassium, such as Noni juice, Lamp wick herb, Herba ecliptae, Rice paper plant pith, Red stem wormwood, Cyathula root and Cardamon, St. John's Wort and psyllium, can lead to worsening hyperkalemia.[30,206-208] Likewise, liquorice and multivitamin supplements consist of large amounts of phosphate, so they may induce deteriorating hyperphosphatemia. However, such information has been reported based upon low level evidence, such as case reports, or theoretical information[30,206,208,209] and there is a lack of evidence regarding the association between HDS and CKD complications.

4.1.4 Adulteration of herbal products

Not only can the active ingredients in HDS damage the kidneys, but so can contaminants. Heavy metals, adulteration of conventional medicines, fake herbs and excessive levels of microorganisms are the principal contaminants associated with renal failure.[210-212] Some herbal products contain lead, cadmium and mercury, which may lead to the loss of renal function.[213,214] An example of adulteration with conventional medications are Tung Shueh pills, a Taiwanese herbal product, which was contaminated with mefenamic acid, known to cause drug-induced nephropathy.[210] There have also been cases of fake herbs. Chan (2003) reports that a slimming herbal product contained *Aristolochia fangchi* rather than *Stephania tetrandra*; and as a result, a large number of people taking it suffered from renal failure.[212]

A report on national quality surveillance of dietary products by the Thai Food and Drug Administration (FDA) in 2012, shows that 18% of herbal medicines, such as turmeric products, or Thai folk remedies were contaminated with steroids, excessive levels of bacteria or heavy metals, and 2% of imported Chinese herbal medicines were contaminated with arsenic and microorganisms.[215] Three samples of mixed Chinese herbal medicines were contaminated with sildenafil and/or tadalafil, medications for sexual dysfunction and a contraindication for a person with renal insufficiency; these examples were reported by the Thai alert system for safety of health products.[216]

4.1.5 Herb and nutrient-drug interactions

Herb-drug interactions may cause renal effects, particularly in patients undergoing renal replacement therapy, such as dialysis or kidney transplant. A cross-sectional study amongst 114 patients receiving haemodialysis in Turkey reported four possible herb-drug interactions. These were: garlic - anticoagulant agents, garlic - NSAIDs, garlic – insulin, and liquorice - antihypertensive agents.[14] However, these interactions do not have negative or beneficial effects on renal function. A case report has revealed that three patients with kidney transplants took herbal tea with cyclosporin – an immunosuppressant agent, and had a decrease in the level of cyclosporin, which may lead them to reject their kidney graft.[217]

In general, reports on herb or dietary supplement-drug interactions are based on information from theoretical data, in vitro, animal studies, a few case reports and clinical trials. They focus on common HDS, such as garlic, ginkgo biloba, ginseng, St. John's Wort and liquorice.[218,219] These papers report adverse effects related to bleeding problems, neurological problems and hyper/hypotensive effects. Currently, herb or dietary supplement-drug interactions leading to the loss of renal function, or deteriorated complications of CKD are unknown.

4.2 Renal benefits from HDS

There is limited evidence of positive effects on chronic kidney disease from HDS use, particularly from clinical trials. Chinese herbal medicine is the most frequently researched treatment of CKD despite the small number of clinical trials and sample sizes.[220] Only three Chinese herbal medicines have proven effective on decreasing proteinuria caused by diabetes, nephrotic syndrome and IgA nephropathy. Such data are supported by work with cellular mechanisms, animal and human studies, involving *Astragalus* and its combination with *Angelica sinensis*, *Rheum* or its combination, and the decoction named 'Saireito' containing *Radix bupleuri*.[220,221] Other herbal medicines for CKD treatment have been mainly studied in vitro and in vivo experiments, such as *Cordyceps sinensis*, shallots, turmeric, and onion.[220,222-224]

Regarding other effects on kidneys, a systematic review has reported that only three herbal medicines have diuretic effects when used in human studies investigating increasing urinary volume and urinary excretion of sodium; the medicines involve *Equisetum bogotense*, *Phyllanthus amarus* and *Withania somnifera*.[225] However, each herbal medicine has been supported by only one small, non-randomised, non-controlled study. A small controlled trial in Thailand showed that roselle (*Hibiscus sabdariffa*) increased urinary excretion of uric acid in patients with renal stones.[226]

5. Aims and objectives

This thesis is comprised of two main studies: i) a survey of the prevalence, patterns and reasons for HDS usage in Thai patients with CKD and, ii) the association between HDS use, the fast progression of CKD and its complications. The main research question of this study was "Is HDS associated with the fast progression of CKD in Thai patients with stages 3 to 5 CKD?"

The primary aim of this thesis was to investigate any relationships between HDS use and the progression of CKD and its complications amongst Thai outpatients with stages 3 to 5 CKD. Specific objectives of each study are as follows.

The first study: A survey of the prevalence and patterns of HDS usage in Thai outpatients with CKD together with a qualitative study regarding reasons for HDS use

1. To determine the prevalence of HDS usage in the previous 12 months in outpatients with CKD at two teaching hospitals in Thailand.
2. To determine the types and patterns of HDS use amongst this population.
3. To identify the demographic characteristics of Thai patients with CKD who are using HDS, compared with non-users.
4. To determine the association between HDS use and a level of adherence to prescribed, conventional medication.
5. To determine the reasons for HDS use in this population.
6. To determine patients' experiences of the beneficial and adverse effects from using HDS.
7. To determine the rate of non-disclosure of HDS use to a doctor and its reasons.

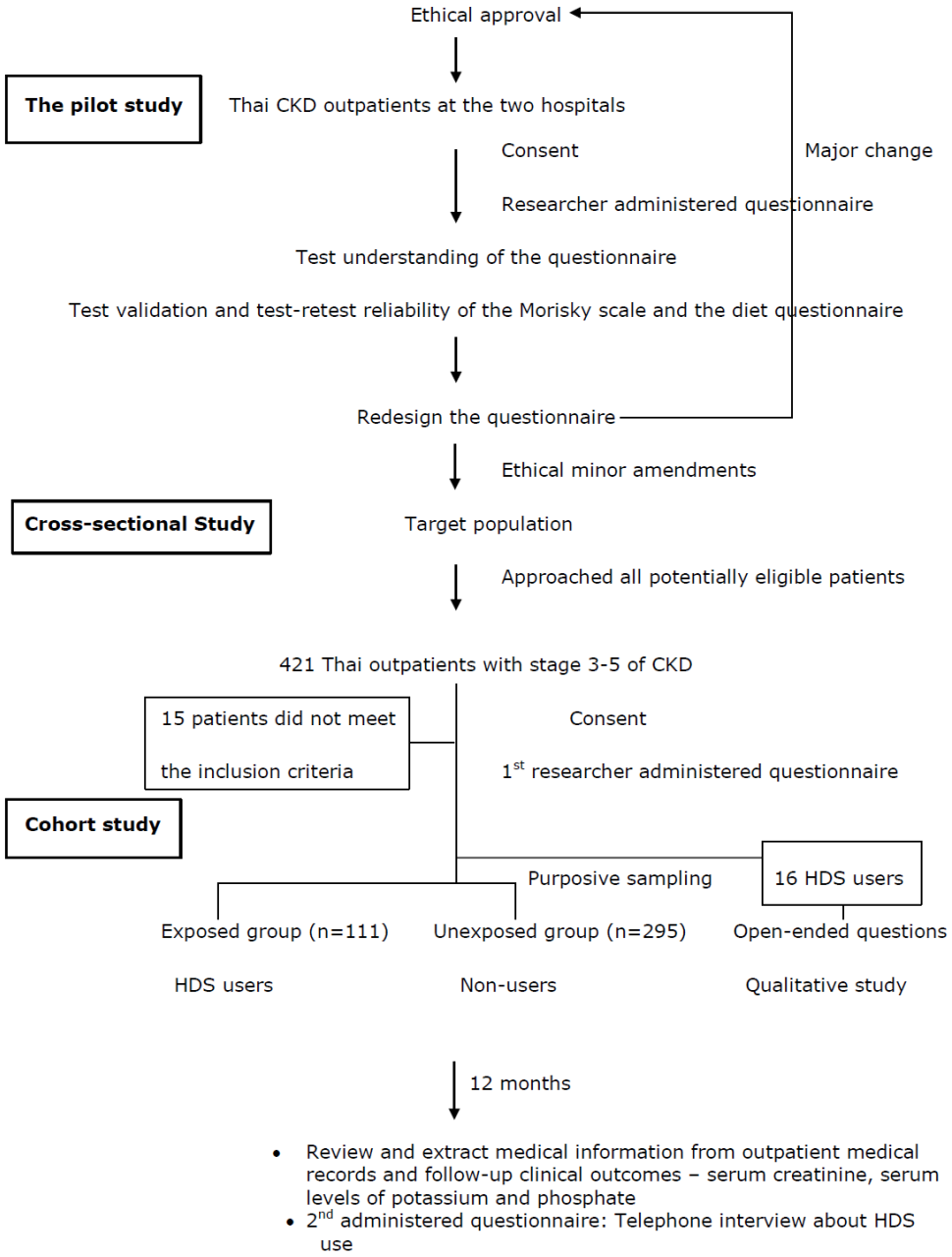
The second study: The association between HDS use, the fast progression of CKD and its complications amongst Thai outpatients with CKD in a prospective, cohort study

1. To determine any associations between HDS use and the fast progression of CKD.
2. To determine any associations between HDS use and CKD complications
3. To determine the patterns of any other risk factors of CKD progression and its complications.

6. Study methods

Details of study methods, settings for data collection, participant inclusion and exclusion criteria, sample size determination, ethical approval and funding are presented in this chapter. An overview of the study design and recruitment process of the two main studies is shown in Flowchart 6.1.

Flowchart 6.1 Schematic diagram of the study



6.1 Pilot study

The objectives of this pilot study were to i) develop and test questionnaires, ii) determine the completeness of routinely collected information in patient records in both hospitals, and iii) to test the suitability of the data extraction sheet from medical notes. Medical information from records were extracted and recorded on the form, see Appendix 5 and Chapter 7.

A researcher-administered questionnaire for the survey and cohort study, together with open-ended questions for the qualitative study, were developed and piloted from September to December 2011. The first questionnaire consisted of questions regarding demographic characteristics of HDS users, patterns of HDS usage, reasons for HDS use, sources of information and HDS products, and disclosure of HDS use to a doctor. This questionnaire also included the Thai version of the 8-item Morisky Medication Adherence Scale® (MMAS-8-Item®)[227,228], and the Restriction of Protein, Potassium, Phosphate and Salt diet (RPPPS) questionnaire for pre-dialysis patients.[229] The last two questionnaires were to measure potential factors related to the cohort study outcomes. This questionnaire was administered with samples of HDS and types of food pictures in order to assist respondents with understanding what HDS is. Also, each type of food restriction in patients with CKD, such as being aware of food rich in potassium, phosphate or salt, was explained, see Appendix 3. This pilot study tested understanding of the questions.

The Thai versions of the MMAS-8-Item® and the RPPPS questionnaire were tested for their validity and reliability, as the former questionnaire had not been tested for validity and reliability in Thai patients with CKD and the latter was modified from the dialysis diet and fluid non-adherence questionnaire (DDFQ).[229]

The eight open-ended questions gathered information about attitudes towards reasons for HDS use, which served as a qualitative study, tested for face validity, see Appendix 4.

The first pilot study tested the clarity of the questionnaire for the survey and cohort study and the validity and reliability of the Thai version of the 8-Item Morisky Medication Adherence Scale® (MMAS-8-Item®) and the Restriction of Protein, Potassium, Phosphate and Salt Diet questionnaire for pre-dialysis patients (RPPPS). The second pilot study tested the revised RPPPS questionnaire and patients' understanding of the researcher administered open-ended questions.

6.2 Survey of the prevalence and patterns of HDS use and qualitative study regarding reasons for HDS use

This study consisted of two parts - a survey and a qualitative study.

Part one: The cross-sectional survey was conducted using the first researcher-administered questionnaire, from January to June 2012, see Appendix 6. All outpatients with CKD, who attended one of two teaching hospitals in Thailand, were approached to take part and those who consented were interviewed.

Part two: To determine the reasons for HDS use, the qualitative study was conducted. Respondents who participated in the survey were recruited for this part using purposive sampling from both settings. They were interviewed face-to-face, using eight open-end questions which were audio recorded, see Appendix 4. The findings were used to better understand the responses to the questions.

6.3 Prospective, cohort study

This study was to determine any associations of HDS use, and the progression of CKD, or CKD complications. It consisted of two parts: the baseline data collection and follow-up data collection over one year.

Part one: Baseline information was provided by responses to the survey. Participants were identified as exposed or unexposed to HDS. The exposed group was defined as current, regular herbal users and/or dietary supplement users, who had taken herbs and/or dietary supplements at least three times a week during the previous month prior to the index date: the interview date in the survey. The unexposed group was defined as those who have never taken herbs or dietary supplements (non-users of HDS) or who have stopped using them in the previous month before the index date (former users of HDS) or who have taken them less than three times per week in the month before the index date (occasional or rare users of HDS).

From respondents' medical notes, data were extracted regarding their chronic illnesses, current medication use and laboratory results on the index date to form the baseline data, see Appendix 5.

Part two: These respondents were followed up regarding their HDS and over-the-counter medication use, and their laboratory results extracting from their medical notes over one year. Appendix 7 shows a data sheet for the telephone interview and a data extraction sheet for the medical notes for the follow-up study. Respondents were interviewed over the telephone regarding HDS usage, reasons for continuing or stopping using HDS and use of over-the-counter medicines during a 12 month period after the index date. Information was extracted from patients' medical notes over one year in the same as the baseline data was established.

Regarding outcomes of this study, progression of CKD was identified by a change of mean estimated glomerular filtration rate (eGFR) over one year. The outcome was compared between the exposed and unexposed groups. CKD complications were also measured, i.e. serum potassium levels and serum phosphate levels in order to classify uncontrolled hyperkalemia and hyperphosphatemia. These parameters were compared between exposed and unexposed groups.

6.4 Inclusion criteria

1. Patients who were diagnosed as having chronic kidney disease and who had eGFR levels of less than 60 ml/min/1.73 m^2 at baseline calculated by the Thai Modification of Diet in Renal Disease equation.[183]
2. Patients aged 18 years or over.
3. Outpatients attending a kidney clinic.
4. Patients who could verbally communicate and were able to give informed consent.

Outpatients were selected to be recruited in this study as their kidney function was more likely to be stable than inpatients, reflecting valid kidney function rather than in an emergency state.

6.5 Exclusion criteria

1. Patients receiving dialysis or kidney transplant at baseline
2. Patients who could not remember most of their information, especially regarding herbal products and dietary supplements.

Patients receiving dialysis or kidney transplant at baseline, were excluded because they have different outcomes of their treatment and different factors related to their outcomes, compared to pre-dialysis patients. For instance, the main therapeutic outcome amongst these patients is to slow the progression of

CKD, whilst dialysis patients require supportive treatment for their complications, such as water and sodium retention. Amongst kidney transplant recipients, poor adherence to immunosuppressant drugs affects kidney function.

6.6 Settings

The study settings were the outpatient kidney clinic in King Chulalongkorn Memorial Hospital, which is also known as 'the hospital of Chulalongkorn University (CU)', in Bangkok, and the HRH Princess Maha Chakri Sirindhorn Medical Center, which is also known as 'the hospital of Srinakharinwirot University (SWU)', in Nakhon-Nayok province. These settings were purposively selected as they are tertiary hospitals, which provide health services for complicated diseases, such as CKD and cancer. The target population is referred to these hospitals by their GP under the Thai National Health System and they are the primary source of CKD health care in Thailand. These are two out of the 12 medical school hospitals in Thailand. Bangkok has the highest prevalence of CKD (24%), compared with other regions of Thailand.[5] The CU hospital serves an urban population, whereas the SWU hospital serves a rural population.

6.7 Recruitment process

The principal investigator (MT) approached all Thai patients with CKD who met the inclusion criteria and informed them about the purpose, methods and potential benefits of the study and provided each prospective candidate with a participant information sheet and consent form, see Appendices 8 and 9. It was explained to the patients that entry into the study was entirely voluntary and that their treatment and care would not be affected by their decision. It was also explained that they could withdraw at any time but attempts were made to avoid this occurrence. Their information was regarded as confidential. Patients providing consent were recruited for the survey and cohort study.

Some respondents who reported using HDS in the survey, and seemed able to provide more information about reasons for HDS use, were invited to be interviewed using the researcher administered open-ended questions about their attitudes to HDS use. This was for the qualitative study, which was audio recorded with permission. Those who consented to participate in the qualitative study were recruited.

6.8 Sample size determination

The cohort study was to serve the primary objective of this thesis, so sample size determination was based on this study.

The null hypothesis was the absence of a relationship between HDS and the fast progression of CKD. The sample size was calculated to ensure that this study had sufficient power to detect the effect size, which was a difference in a decline in eGFR of at least 5 ml/min/1.73m^2/year between exposed and unexposed groups. A decline in eGFR of at least 5 ml/min/1.73m^2/year defined the fast progression of CKD in this study, which was a dependent variable.[145] Sample size was calculated to compare two means using the formula from Kirkwood and Sterne.[230] Ong-Ajyooth et al. (2009) reported 78.9 ml/min of mean eGFR and 0.3 standard error of eGFR in Thai residents. Therefore, the standard deviation of eGFR in Thai patients with CKD was 16.75.[146] Drop out was estimated to be 5%, as a previous study using face-to-face interviews with a similar population reported a 2% drop out rate.[29] The study was designed for a two-tailed hypothesis. The statistically significant level and the power were 5% and 80%, respectively. The allocation ratio between exposed and unexposed groups was 1:2 because 33% of Thai people have reported using herbs.[5] Kirkwood and Sterne have recommended an adjustment factor for use to compare unequal sized groups. If a ratio of larger to smaller group is 2, ¾ is the adjustment to the sample size of the smaller group.[230] The estimated sample size of this study was

140 in the exposed group and 280 in the unexposed group. Therefore, at least 420 patients were aimed to be recruited in this study.

After completing the follow-up period, 8% of participants initiated dialysis therapy, which was likely to be due to the fast progression of CKD. As a result, the dependent variable was newly defined as either a decline in eGFR of at least 5 ml/min/1.73m^2/year[11,145] or initiated renal replacement therapy during the follow-up period. This was a dichotomous variable defined as having the fast progression of CKD or no fast progression. Post hoc determination of the sample size for non-parametric statistical analyses, using the comparison of two proportions of the fast progression of CKD,[230,231] suggested that this cohort study required a sample size at least 72 and 144 numbers of the exposed and unexposed groups, respectively.

6.9 Ethical approval and funding

Ethical approval was obtained from the Institutional Review Board for Research in Human Subjects at the Faculty of Medicine, Chulalongkorn University (CUIRB No. 297/54) and Srinakharinwirot University (SWUEC/Ex No. 43/2554), Thailand, and the Medical School Research Ethics Committee, University of Nottingham, UK for the pilot study and the main study in September 2011 (reference No. CHS22082011), see Appendix 10.

The Royal Thai government funded MT's PhD study.

7. Pilot study

The first pilot study tested the clarity of the questionnaire and the validity and reliability of the Thai version of the 8-Item Morisky Medication Adherence Scale® (MMAS-8-Item®) and the Restriction of Protein, Potassium, Phosphate and Salt Diet questionnaire for pre-dialysis patients (RPPPS).

The second pilot study tested the revised RPPPS questionnaire and the respondents' understanding of the researcher administered open-ended questions in the qualitative study, regarding the attitudes towards reasons for HDS use.

7.1 Objectives

The primary objectives of the pilot study were to test the validity and reliability of the Thai version of the 8-Item Morisky Medication Adherence Scale® (MMAS-8-Item®) and the Restriction of Protein, Potassium, Phosphate and Salt diet questionnaire for pre-dialysis patients (RPPPS). Additionally, self-designed researcher administered open-ended questions about attitudes towards reasons for herbal and dietary supplement use were tested for face validity.

The second objective was to test the clarity of the questions in the questionnaire, the feasibility of the recruitment process and to measure the number of patients attending the kidney clinics. The data extraction sheet for the outpatient records was also tested regarding the completeness of routinely collected information in patient records in both hospitals.

7.2 Development of the questionnaire

The questionnaire for the survey was adapted from Kuo's questionnaire,[98] with some added questions in order to achieve the objectives of this study. The new

questions asked about reasons for HDS use, experiences of positive and negative effects from using HDS, and non-disclosure of HDS use to a doctor, see Appendix 3. Kuo's questionnaire was well suited to the present survey as it consisted of demographics, patterns of herbal use, people's recommendations for their use, and information sources for herbal medicine, see Appendix 11.

The Thai-version of the 8-Item Morisky Medication Adherence Scale® (MMAS-8-Item®) was chosen to measure adherence to conventional medication in the present survey, as it is relatively short and has been validated in many countries around the world, including Thailand and is widely used.[227,232-234] The main focus of this study was not adherence and therefore a simple method that gave a broad measure of adherence was wanted. Other questionnaires that measure adherence included the Simplified Medication Adherence Questionnaire (SMAQ), which has been used for dialysis patients; however, it is developed from the Morisky scale[235] and does not have a validated Thai version. A number of measures are specific to individual diseases, such as the Medication Adherence Rating Scale (MARS), which is appropriate for patients with psychiatric illnesses[236], or the Hill-Bone compliance questionnaire which is a specific measure of adherence for patients with hypertension.[237] Other measures focus on a particular aspect of adherence, such as the Adherence Estimator which measures intentional non-adherence[238]; whereas the present study aimed to measure both intentional and non-intentional non-adherence. The Brief Medication Questionnaire (BMQ) does have a Thai version, but shows lower sensitivity and specificity compared with the original, which may be due to cultural differences in understanding of questions about medication adherence.[239] It was decided to use a questionnaire in order to measure adherence to conventional medication rather than other tools, such as pill counts and electronic monitoring systems, as it would form part of a larger questionnaire and therefore be convenient, inexpensive and practical for use in

the study. However, there are some disadvantages of using a questionnaire to measure adherence, including recall and social desirability bias, and patients overestimating their adherence.[240]

To measure the degree of protein, potassium and phosphate intake, the dialysis diet and fluid non-adherence questionnaire (DDFQ)[229] was the only validated questionnaire which seemed to be relevant to the objectives of the present study, see Appendix 12. This questionnaire was adapted and some questions were added in order to achieve the desired outcomes of the present study, which was named the Restriction of Protein, Potassium, Phosphate and Salt Diet questionnaire (RPPPS), see Appendix 3. Dietary intake assessed by a food frequency questionnaire is commonly used in epidemiological research, due to such a tool being convenient and feasible. However, such an approach may involve small inaccuracies in the estimate amount of food for an individual, compared with other tools, such as 24-hour dietary recall and food diaries.[241]

Both Kuo's questionnaire and the DDFQ were translated from English into Thai by MT who is fluent in both languages, and then these were developed into Thai language. The process of backward translation of these questionnaires was not performed as the questions in both instruments were straightforward.

The researcher administered open-ended questions about attitudes towards the reasons for HDS use amongst pre-dialysis patients, see Appendix 4. These questions were developed in the Thai language by the author, based on the literature[89,242] in order to achieve the objective of this study.

The Thai version of the researcher administered questionnaire in the present survey and open-ended questions in the present qualitative study is the original. This thesis also presented the English version of such questionnaires, in Appendices 3 and 4 in order to communicate to international readers.

7.3 Method

7.3.1 The first pilot study

The first pilot study was conducted between 28 September and 26 October 2011. Forty-two patients, who met the inclusion criteria and provided their consent, were recruited and interviewed face-to-face, using the researcher administered questionnaire, together with samples of HDS and types of food pictures, see Appendix 3. The patients were recruited from each hospital; 20 to 50 are accepted as the general numbers of respondents appropriate for the pilot trial of a questionnaire.[243] The reason why patients from both hospitals were recruited for the pilot study was that the populations in each hospital are different and it was important that the questionnaire was shown to be suitable for both sites.

Validity test

Validity assessment of the MMAS-8-Item® and the RPPPS questionnaire, see Appendix 3, was required, as the former was only validated in Thai patients with diabetes[227], so needed validation for a different group of patients: namely those with CKD.[244] The RPPPS questionnaire also needed to be validated as it is adapted from the dialysis diet and fluid non-adherence questionnaire[229] and was translated from English into Thai. The MMAS-8-Item® classifies conventional medication adherence into three categories, i.e. a low, medium or high levels of adherence to prescribed, conventional medication, whilst the RPPPS questionnaire classifies degrees of consumption of protein, potassium, phosphate and salt diets into two categories: low or high level of diet intake. Concurrent validation, which is the subtype of criterion validity and the validity between the new questionnaire and an existing criterion measure at the same time, was conducted on both questionnaires as the two scales have indirect criterion measurements.[244] Estimated GFR levels are the criterion measurement of the

MMAS-8-Item®, because if patients adhere to their prescribed, conventional medication regime, particularly angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), they will slow the progression of CKD.[245-247] Therefore, if patients have a decrease in a difference of mean eGFR during 3 months, compared with those with either an increase, or no change, it indicates non-adherence to their conventional medication regime. However, an increase in an eGFR level may be caused by other factors, such as high protein consumption and taking nephrotoxic agents.

The indirect criterion measurement of the RPPPS questionnaire is a serum level of potassium and phosphate, and level of blood pressure. This is because diet is the main factor influencing the serum levels of potassium and phosphate in patients with CKD, due to the decreased elimination of potassium and phosphate[165,248], whilst a high salt diet can result in uncontrolled high blood pressure.[249] If these levels are outside the target of treatment, it could be that the patients with CKD consume high potassium, phosphate and salt diets. The target treatment of blood pressure, and a serum potassium level, is equal to or less than 130/80 mm/Hg and 5 mEq/L (mmol/l), respectively.[185] The target of a serum phosphate level is equal to or less than, 4.6 and 5.5 mg/dl (1.5 and 1.7 mmol/l) for stages 3 to 4 CKD and stage 5 CKD, respectively.[186]

Next, the outcomes of the two criterion measurements were classified into a dichotomous scale. Non-adherence to prescribed, conventional medications was defined as a decrease in a difference of mean eGFR during 3 months, whereas adherence was an increase or no change of mean eGFR in the same period. High potassium, phosphate and salt consumption were defined as higher mean levels of potassium, phosphate or blood pressure, respectively than the goal of their therapy. Correlation between the existing measurements and the questionnaires was analysed using Chi-squared test.

Reliability test

The Thai version of the MMAS-8-Item® was tested for internal consistency using Cronbach's alpha, because this questionnaire consists of 8 items, which measure one outcome, that of conventional medication adherence. Due to this, the questionnaire needs to be tested for correlations between each item and the outcome.[230] Additionally, test-retest reliability of the two questionnaires, which measures the agreement between repeated measurements taken at different times, was conducted.[230] Respondents were interviewed at the entry into the pilot study in September 2011 and then 2 weeks later, as the RPPPS questionnaire was designed to explore the previous 14-day dietary intake. Moreover, the periods between the first and the second measurement should be 2 to 14 days.[244] The second interview was conducted over the telephone. The intraclass correlation coefficient (ICC), which measures the agreement of numerical variables[230], was calculated using two-way mixed effects model[250], and was calculated for the Thai version of MMAS-8-Item®, because this questionnaire classifies the degree of conventional medication adherence using a numerical scale. The interpretation of the ICC is that an ICC $\geq$ 0.75 is an excellent agreement; 0.4 $\leq$ ICC < 0.75 is a fair to good agreement and an ICC < 0.4 is a poor agreement.[251] The Kappa coefficient, which tests the proportion of responses in the agreement of a dichotomous scale, was used for the RPPPS questionnaire, because it classifies either a low level of dietary intake, or a moderate to high level of dietary intake. From 0.81 to 1.00 of Kappa coefficient represents very good agreement; 0.61 and 0.80 indicates good agreement; between 0.41 and 0.60 shows moderate agreement; between 0.21 and 0.40 shows fair agreement, whilst a Kappa coefficient under 0.20 shows poor agreement.[252]

7.3.2 The second pilot study

The second pilot study was conducted in December 2011 and recruited 21 patients in order to assess the test-retest reliability of the revised RPPPS

questionnaire. This instrument was designed to measure the degree of dietary consumption in the last 14 days, as the first pilot study was found to have poor reliability, particularly regarding the measurement of protein and phosphate consumption. This may be because the questions did not specify types of protein or phosphate diets and respondents may change their diet behaviour during the 14-day period. Therefore, the RPPPS questionnaire was revised, see Appendix 6. The period between the first and the second measurement was 7 days due to i) the limited time of the study and ii) the researcher being concerned that respondents may change their diet if their diet is measured far from the first measurement.

Face validity of researcher administered open-ended questions about reasons for HDS use

After the respondents who used HDS had participated in the survey, they were invited to be interviewed regarding their attitudes towards the reasons for HDS use. These sessions were to be audio-recorded. If they consented, they were recruited. This face to face interview was to test the clarity of the questions. The audio recordings were transcribed and translated from Thai into English based on meaning.[253] The transcripts were analysed by a brief inductive thematic analysis in order to assess the findings to some extent and to fulfil the research objective. Key words, which seemed to be related to reasons for HDS use from all transcripts, were coded and grouped based on the same meaning in each group, and then a title of each group indicated their theme. Therefore, such themes were built up from the data.

7.4 Results of the first pilot study

Fifty five patients in two hospitals were recruited, although 13 patients (25%) were then excluded. Three had received hemodialysis, eight had stage 1 or 2 CKD and two patients had communication problems. Therefore, the total number

of respondents was 42, of which 22 were recruited from CU hospital and 20 were recruited from SWU hospital. The rate of recruitment was 10 patients per week.

7.4.1 Characteristics of respondents

The 42 respondents had a mean age of 66 years (SD 12, range 25-86) and 43% were men. The characteristics of respondents are shown in Table 7.1.

Table 7.1 Characteristics of respondents (n=42)

Characteristics	Number of respondents	Percent	Missing data (%)
Age (> 60 years)	31	73.8	-
Education levels			-
Uneducated	1	2.4	
Primary school	21	50.0	
Secondary school	6	14.3	
Vocational degree	5	11.9	
Undergraduate degree	8	19.0	
Higher than undergraduate degree	1	2.4	
Household income (baht per month)			20 (47.6%)
< 10,000 (£200/month)	24	57.1	
10,000-50,000 (£200-1000/month)	17	40.5	
> 50,000 (£1000/month)	1	2.4	
Occupation			-
Unemployed	2	4.8	
Retired	24	57.1	
Housewife	6	14.3	
Employee	6	14.3	
Farmer	2	4.8	
Business owner	1	2.4	
Priest	1	2.4	
Smoking status			-
Never	34	81.0	
Former smoker	8	19.0	
Alcoholic consumption			-
Never	34	81.0	
Current consumer	6	14.3	
Former consumer	2	4.8	
BMI (kg/m^2)			1 (2.4%)
< 18.5	3	7.3	
18.5 – 26.9 in men or 18.5 – 24.9 in women	21	51.2	
$\geq$ 27 in men or $\geq$ 25 in women	17	41.5	

Percent was calculated using an absolute number of respondents, which was not included a number of missing data.

Twenty respondents (48%) did not provide household income because some could not estimate their income and others refused to disclose this information. The number of respondents who had never smoked (81%) or consumed alcoholic beverages (81%) was high because the interviewer asked all respondents "Do you smoke or drink alcoholic beverages?" and most of them said "no". Seventeen respondents (42%) were obese, whilst three respondents were underweight defined as less than 18.5 kg/m^2 of BMI.[254] Table 7.2 shows severity of CKD, CKD complications, co-morbidity and the follow-up appointment time.

Table 7.2 Stages of chronic kidney disease and co-morbid conditions (n=42)

Types	Number of respondents	Percent	Unknown data (%)
Stages of CKD			-
3	26	61.9	
4	15	35.7	
5	1	2.4	
Hyperkalemia	16	39.0	2 (4.8%)*
Hyperphosphatemia	11	32.3	8 (19.0%)*
Hypertension	41	97.6	-
Peripheral oedema	7	20.0	7 (16.7%)*
Diabetes	32	76.2	-
Heart diseases	8	19.0	-
Dyslipidaemia	34	81.0	-
Existing proteinuria	19	48.7	3 (7.1%)*
Proteinuria tests			
1. Random urine protein and urine creatinine ratio	17	43.6	
2. Total protein (24 hr urine collection)	3	7.7	
3. The dipstick protein measurement	19	48.7	
Follow-up of physician's appointment			1 (2.4%)
$\leq$ 3 months	40	97.6	
> 3 months	1	2.4	

* = no record of a test or physical examination of oedema in medical notes

Percent was calculated using an absolute number of respondents, which was not included a number of unknown data.

Other co-morbid conditions were gout (6, 14%) and cancer (3, 7%). Most respondents (n=40, 98%) were monitored by a doctor at least every 3 months, so medical records could be followed and assessed over time. Regarding laboratory examinations in the year prior to the index date, 98% of respondents had a serum level tested for creatinine at least 3 times per year; whereas 78% provided at least 3 values of serum potassium levels per year. Sixteen respondents (47%) had at least 3 values of serum phosphate levels per year whilst 18 respondents (53%) provided only 1 or 2 values. There was unknown data about CKD complications - hyperkalemia (n=2), hyperphosphatemia (n=8), peripheral oedema (n=7) and existing proteinuria (n=3) because a doctor at SWU hospital did not examine peripheral oedema and did not order patients to be tested for serum levels of potassium, phosphate and urinary protein tested.

This study found patients received on average 8 prescribed, conventional medications. Fifty-seven percent received renoprotective agents, i.e. ACEIs or ARBs. Erythropoietin, folic acid, ferrous compounds and vitamin $B_{1\text{-}6\text{-}12}$ were used for supportive treatment of anemia, see Table 7.3. Calcium polystyrene sulfonate and phosphate binders were used for hyperkalemia and hyperphosphatemia, respectively. Sodamint was used for treatment of metabolic acidosis.

Table 7.3 Medicines prescribed for respondents (n=42)

Types of medications	Number of respondents	Percent
Erythropoietin	11	26.2
Folic acid	24	57.1
Ferrous compounds	13	31.0
Vitamin $B_{1\text{-}6\text{-}12}$	7	16.7
Diuretics	13	31.0
Calcium polystyrene sulfonate	14	33.3
Phosphate binders	11	26.2
Sodamint	11	26.2
Antihypertensive agents	41	97.6
Dyslipidemic agents	34	81.0
Hypoglycemic agents	19	45.2
Antihyperuricemic agents	14	33.3
Aspirin	17	40.5

Thirteen respondents (31%) were current, regular HDS users and 29 (69%) were non-users, see Table 7.4.

Table 7.4 Patients reported use of alternative medicines including HDS (n=42)

Types of alternative medicines	Number of respondents	Percent	Missing data
Herbal and dietary supplement use			-
Current, regular users[a]	13	31.0	
Non-users			
Never used[b]	14	33.3	
Former users[c]	10	23.8	
Occasional users[d]	5	11.9	
Other alternative medicines			1 (2.4%)
No	33	80.5	
Yes	8	19.5	
Meditation	4	9.8	
Massage	4	9.8	

a = current, regular users were defined as patients taking herbal medicine or dietary supplements at least three times a week in the month prior to the interview date

b = patients had never used HDS was defined as patients who did not use HDS prior to the interview date

c = former users were defined as patients who had stopped using HDS before the month prior to the interview date

d = occasional users were defined as patients who had taken HDS less than three times a week in the month prior to the interview date

Percent was calculated using an absolute number of respondents, which was not included a number of missing data.

There was the same proportion of HDS users and non-users between CU and SWU hospitals. Twenty percent of respondents reported using other alternative medicines, i.e. meditation and massage.

Table 7.5 shows types and number of HDS used by in current, occasional or former users (n=28). Two respondents in one hospital did not report to the interviewer that they used HDS; however they had informed their doctor about using HDS, as this was recorded in their medical notes. One was a former user and another was a current, regular user. This disparity may be because the interviewer had met respondents for the first time, so they may not have trusted the interviewer. It also highlights one difficulty when conducting face to face research.

Table 7.5 Types and number of HDS used (n=28)

Patterns of HDS use	Number of respondents	Percent	Missing data
Type of HDS used			-
Herbal products	12	42.8	
Dietary supplements	12	42.8	
Both	4	14.4	
Number of different HDS used			1 (3.6%)
1	19	70.4	
2	4	14.8	
3	2	7.4	
4	2	7.4	
Total number of HDS used	41	100	

Percent was calculated using an absolute number of respondents, which was not included a number of missing data.

The total number of HDS used was 41, see Table 7.5. Oral capsules or tablets were the most frequently used formulation of HDS in current, occasional or former users (66%), see Table 7.6. Some respondents used fresh herbal medicines, such as leaves or stems (11%). Missing data on the dosage form, duration and frequency of HDS use in Table 7.6 may be because respondents could not remember details of their HDS use, due to their using many types of HDS.

Table 7.6 Patterns of HDS used (total number of HDS used=41)

	Number of HDS usage*	Percent	Missing data
Dosage form of HDS used			3 (7.3%)
Oral capsules or tablets	25	65.8	
Liquid form	6	15.8	
Raw material	4	10.5	
Powder	3	7.9	
Duration of HDS use			10 (24.4%)
Less than 1 year	23	74.2	
1-2 year(s)	6	19.3	
3-4 years	0	0	
More than 5 years	2	6.5	
Frequency of HDS use			7 (17.1%)
Daily	25	73.5	
Once a week	5	14.7	
2-3 times a week	2	5.9	
Few times a year	2	5.9	

* Respondents reported for each product they used so these total more than 28

Percent was calculated using an absolute number of respondents, which was not included a number of missing data.

Maintenance of well-being was the most common indication for using dietary supplement reported by respondents (50%), whilst more than a third of herbal products were taken for treatment of disorders (41%), see Table 7.7. Some respondents used herbs for relieving symptoms such as flatulence, pain, peripheral oedema and loss of libido. Some used HDS for treatment of their chronic diseases, such as diabetes and dyslipidaemia.

Table 7.7 Reported indications for herbal products and dietary supplements used (n=28)

	Number of HDS usage*	Percent	Missing data
Indications of herbal use			1 (3.6%)
Well-being	8	29.6	
Symptom relief	4	14.8	
Treatment of other chronic diseases	4	14.8	
CKD treatment	3	10.1	
Indications of DS use			4 (14.3%)
Well-being	12	50.0	
Symptom relief	1	4.2	
Treatment of other chronic diseases	3	12.5	
CKD treatment	1	4.2	

* Respondents reported for each product they used and one product may have been reported more than one indication

Percent was calculated using an absolute number of respondents, which was not included a number of missing data.

Eighteen respondents (72%) reported one reason for HDS use, whilst the remaining respondents provided 2 or 3 reasons. Sixty-eight percent of HDS users reported family members and friends influencing their HDS use, see Table 7.8. Other reasons (20%) were that some respondents believed in superstition and some heard about benefits of HDS from radio or television.

Table 7.8 Reasons why respondents use HDS (n=28)

Reasons for using HDS	Number*	Percent
Family/friend's recommendation	17	68.0
Belief that HDS will work	4	16.0
Decided to use HDS by themselves	3	12.0
Other	5	20.0
Wanted to try	2	8.0
Safer than conventional medicines	2	8.0
Health care provider's recommendation	1	4.0

* Respondents were able to report more than one reason, missing data = 3 (10.7%)

Percent was calculated using an absolute number of respondents, which was not included a number of missing data.

Over two-thirds did not inform their doctor about using HDS because they were not asked (10, 59%), see Table 7.9.

Table 7.9 Reporting to their doctor about HDS use (n=28) and reasons for not reporting (n=17)

Categories	Number of respondents	Percent
Informed about HDS use*		
Yes	8	32
No	17	68
Reasons	Number of reasons**	Percent
Doctor did not ask about HDS use	10	58.8
There is no need to inform the doctor	5	29.4
Doctors will blame patients for using	4	23.5

* Percent was calculated using an absolute number of respondents, which was not included a number of missing data. Missing data was 3 (10.7%).

** Respondents were able to report more than one reason.

Table 7.10 reports the name of the HDS used and their indications. Respondents used 22 different HDS. Six respondents could not remember the ingredients of the HDS they took (21%).

Table 7.10 Types of HDS used by respondents (the total number of HDS used=41)

Types of HDS use	Number*	Indications reported by respondents
Herbal products		
Chinese herbs	4	Promotion for well-being and treatment of chronic diseases, including CKD
Turmeric (*Curcuma Longa*)	2	Flatulance
Thai herbs	2	Treatment of chronic diseases, including CKD
Holy mushroom (*Garnoderma lucidum*)	1	Well-being
Boesenbergia (*Boesenbergia spp.*)	1	Well-being
Horse radish tree (*Moringa spp.*)	1	Well-being
Butea Superba (*Mucuna collettii*)	1	Increasing libido
Curcuma xanthorrhiza	1	Diuretic
Traditional mixed herb powder	1	Prevent fainting
Kariyat (*Andrographis paniculata*)	1	Treatment of the common cold
Dietary supplements		
Rice germ	3	Well-being (2) Treatment of CKD and diabetes (1)
Rice bran oil	3	Well-being (2), to relieve pain (1)
Multivitamins	2	Well-being
Evening primrose oil	1	Well-being
Mixed vegetable and fruit beverage	1	Treatment of diabetes
Fish oil	1	Well-being
Co-Q10	1	Treatment of heart diseases
Glucosamine	1	Treatment of osteoarthritis
Pollen	1	Treatment of diabetes
Protein supplements	1	Well-being
Vitamin C	1	Well-being
Spirulina	1	Well-being

* Respondents were able to report more than one product so these total more than 28.

Missing data = 9 products that patients could not remember the ingredients of the HDS they took

Most HDS users (19, 68%) thought that they gained benefit from taking HDS, see Table 7.11. Two perceived that their diabetes had improved and one reported improved dyslipidaemia. Five respondents reported that they had had side effects from HDS. Three experienced increased serum levels of lipid profiles, blood sugar levels or body weight, whilst another one perceived it worsening of her chronic disease. One thought that HDS was unsafe but did not report experiencing any specific side effects.

Table 7.11 Perception of benefits and adverse events of HDS reported by respondents (n=28)

Benefits and adverse effects	Number of benefits and adverse events	Percent	Missing data
Benefits of HDS used			-
No	6	21.4	
Yes	19	67.9	
Do not know	3	10.7	
Types of the benefit			-
Relieving symptoms	9	47.4	
Well-being	6	31.6	
Treatment of diabetes or dyslipidaemia	3	15.8	
Treatment of chronic diseases	1	5.2	
Adverse effects of HDS used			3 (10.7%)
No	20	80	
Yes	5	20	

Percent was calculated using an absolute number of respondents, which was not included a number of missing data.

7.4.2 Validity and reliability

The Thai version of the 8-Item Morisky Medication Adherence Scale® (MMAS-8-Item®)

Respondents having a low level of adherence to prescribed, conventional medication seemed to have a decrease in mean eGFR greater than those with a medium or high level of medication adherence, see Table 7.12. It would appear that this relates to the hypothesis that if patients do not adhere well to conventional medications, their renal function would decrease. However, the total number of respondents was not sufficient to estimate the relationship with a statistical significance of less than 0.05 level.

The present study yielded a Cronbach's alpha score of 0.67, meaning moderate internal consistency (n=42) for the Thai version of the MMAS-8-Item®. Regarding test-retest reliability, the ICC of MMAS-8-Item® was 0.73 (95%CI 0.52-0.85, $p < 0.01$) (n=34, missing data = 8), meaning this questionnaire had fair to good agreement. Due to severe flooding in Bangkok at the time of this study, eight respondents could not be contacted by phone in order to be interviewed the second time.

Table 7.12 The association between the degree of conventional medication adherence and change in mean eGFR over 3 months (n=42)

MMAS-8-Item®	Increased mean eGFR	Decreased mean eGFR
Low medication adherence	5 (41.7%)	7 (58.3%)
Medium medication adherence	9 (56.3%)	7 (43.7%)
High medication adherence	7 (50.0%)	7 (50.0%)

- Chi-squared tested the association between low, medium or high medication adherence and increased or decreased mean eGFR within 3 months.
- $\chi^2 = 0.58$, p-value = 0.75

The Restriction of Protein, Potassium, Phosphate and Salt diet questionnaire for pre-dialysis patients (RPPPS)

There were the expected trends in associations between the degree of protein, potassium, phosphate and salt consumption and their target treatments, i.e. respondents consuming low protein, potassium, phosphate and salt diet seemed more able to meet the targets for their condition, than those with moderate to high consumption of protein, potassium, phosphate and salt diet, see Table 7.13. Statistically significant associations between low potassium intake and controlled mean level of serum potassium were found (p-value < 0.05). However, the total number of respondents is not sufficient to estimate other associations with a statistical significance of less than 0.05 level.

Table 7.13 Correlation between degree of protein, potassium, phosphate and salt consumption and their clinical outcomes (n=42)

Degree of food consumption	Clinical outcomes		χ^2	*p*-value	Missing data
Protein	Decreased mean eGFR	Increased mean eGFR	0.43	0.51	4 (9.5%)
Low consumption	7 (43.7%)	9 (56.3%)			
Moderate to high consumption	12 (54.5%)	10 (45.5%)			
Potassium	Uncontrolled mean serum potassium levels	Controlled mean serum potassium levels	5.51	0.02	7 (16.7%)
Low consumption	0 (0%)	17 (100%)			
Moderate to high consumption	5 (27.8%)	13 (72.2%)			
Phosphate	Uncontrolled mean serum phosphate levels	Controlled mean serum phosphate levels	0.368	0.54	10 (23.8%)
Low consumption	1 (6.2%)	15 (93.8%)			
Moderate to high consumption	2 (12.5%)	14 (87.5%)			
Salt	Uncontrolled blood pressure	Controlled blood pressure	3.79	0.05	-
Low consumption	5 (29.4%)	12 (70.6%)			
Moderate to high consumption	15 (60%)	10 (40%)			

The test-retest reliability of the RPPPS questionnaire was tested using Kappa. The reliability of the questionnaire evaluating the degree of potassium and salt consumption had good agreement (Kappa = 0.79 and 0.76, respectively), see Table 7.14. However, the reliability of the questionnaire assessing the degree of protein and phosphate consumption had only fair agreement (Kappa = 0.32 and 0.27, respectively). The missing data resulted from both interviews was a result of respondents who were unable to answer the questions.

Table 7.14 Test-retest reliability between the first and the second interview regarding protein, potassium, phosphate and salt consumption (n=42)

First interview	Second interview		Kappa	*p*-value	Missing
Degree of food intake	Low intake	High take			data
Protein			0.32	0.07	12 (28.6%)
Low intake	7 (23.3%)	7 (23.3%)			
High intake	3 (10.0%)	13 (43.4%)			
Potassium			0.79	<0.01	13 (31.0%)
Low intake	11 (37.9%)	2 (6.9%)			
High intake	1 (3.5%)	15 (51.7%)			
Phosphate			0.27	0.09	12 (28.6%)
Low intake	13 (43.3%)	2 (6.7%)			
High intake	9 (30.0%)	6 (20.0%)			
Salt			0.76	< 0.01	8 (19.0%)
Low intake	12 (35.3%)	1 (3.0%)			
High intake	3 (8.8%)	18 (52.9%)			

High intake = Moderate to high intake

7.5 Results of the second pilot study

There was poor reliability of the RPPPS questionnaire in the first pilot study, so this questionnaire was revised and tested for test-retest reliability again, see Appendix 6. The duration between the first and second interviews was 7 days. The reliability of this questionnaire, designed to evaluate the degree of phosphate and salt consumption, had very good agreement, respectively (Kappa = 0.81 and 0.81), see Table 7.15. The reliability of the questionnaire assessing

the degree of protein and potassium consumption also had good agreement (Kappa = 0.69 and 0.74, respectively).

Table 7.15 Test-retest reliability of the revised RPPPS questionnaire between the first and the second interviews regarding protein, potassium, phosphate and salt consumption (n=21)

First interview	Second interview		Kappa	*p*-value
Degree of food intake	Low intake	High intake		
Protein			0.69	0.01
Low intake	6 (28.6%)	2 (9.5%)		
High intake	1 (4.8%)	12 (57.1%)		
Potassium			0.74	0.01
Low intake	4 (19.0%)	1 (4.8%)		
High intake	1 (4.8%)	15 (71.4%)		
Phosphate			0.81	< 0.01
Low intake	10 (47.6%)	0 (0.0%)		
High intake	2 (9.5%)	9 (42.9%)		
Salt			0.81	< 0.01
Low intake	8 (38.1%)	1 (4.8%)		
High intake	1 (4.8%)	11 (52.4%)		

High intake = Moderate to high intake

This pilot study assessed the understanding of the researcher administered open-ended questions about attitudes towards the reasons for HDS use in patients with CKD; this particular research instrument being designed by the author, see Appendix 4. All respondents understood and answered the questions fully (n=6). Six respondents using HDS currently and regularly were interviewed; each interview lasting between 5 to 10 minutes. Five were audio-recorded and the other did not give permission to be recorded. Two relatives of the patients who had decided that the patients used HDS, were also interviewed. Half of the interviewees were women and most respondents attended the kidney clinic at CU hospital (n=5). There were four themes about their attitudes towards the reasons for HDS use, which were ‘finding out about HDS’, ‘reasons for HDS use’, ‘attitudes towards the benefits of HDS’, and ‘concerns about HDS’.

Finding out about HDS

Patients found out about HDS in a variety of ways. Two patients and one relative took HDS based upon recommendations from their friends' or family. Additionally, patient A and a daughter of patient F, who had decided her mother should use HDS, searched for HDS information by themselves via HDS conferences at the School of Pharmacy, Mahidol University, or via the internet. Another patient found out about HDS from television, friends who sold HDS, and a nurse.

Reasons for HDS use

There were several reasons for HDS use amongst the respondents. One patient was used to taking HDS.

> *I was using HDS when I was young because my parents provided HDS for me when I was ill*, said patient A

Three patients said they took them as they needed to treat their diseases or symptoms, i.e. CKD, diabetes, immunocompromised disorder, or dyspepsia, or their friends or family members recommended.

> *My wife wanted me to try them even though I did not want to use them*, said patient E
>
> *I was not well, so I wanted to have well-being by using HDS*, said patient B
>
> *Other people told me that HDS was good*, said patient C

Other factors related to HDS use were that HDS is natural and has information about benefits.

> *HDS did not contain chemical substances*, said patient A
>
> *Some HDS were supported by scientific evidence and some doctors produced HDS products and my friend recommended me to use it. However, I wanted to ask a doctor or an expert on HDS before doing so*, said patient B.

Attitudes towards the benefits of HDS

Attitudes towards the positive effects of HDS were that three patients and one relative thought that they gained benefits from HDS.

> *I used HDS because my kidneys did not work hard and tried to avoid or limit the use of conventional medicines, such as pain killers*, said patient A

One patient did not know whether or not he gained benefits from using HDS, but continued using it.

> *I could not assess the benefits of HDS*, said patient B

However, one relative thought that a patient did not gain benefits from using HDS.

> *My husband did not gain any benefits from HDS*, said wife of patient E

Regarding the comparison of the benefits between HDS and CM, some patients thought that they could not compare them.

> *I have never compared the benefits between HDS and CM*, said patient B

> *The benefits between HDS and CM are not possible to compare*, said patient C

> *HDS and CM have different benefits*, said the relative of patient F

Some could compare different benefits between HDS and CM, which found that CM was superior to HDS.

> *CM prescribed by a doctor was more beneficial than HDS*, said patient E

Two patients with CKD thought that they gained more benefit from HDS than what they had expected.

> *I did not expect any benefits of HDS*, said patient B

Concerns about HDS

Two patients and two relatives did not have any concerns about HDS; whereas they were concerned that CM may accumulate in the body; as a result, CM may cause harm.

> *My kidneys may have to work harder if I used high numbers of CM*, said patient A
>
> *Dietary supplements are safe because they supplemented diet and were not medications*, said patient C

On the contrary, one patient was concerned about both HDS and CM and another one was worried about HDS as his friends had warned him about side effects of HDS.

> *I had different concerns about HDS and CM, and wanted to ask a doctor whether I could use HDS or not*, said patient B
>
> *High consumption of HDS may not be good so I use HDS only occasionally*, said patient D

Regarding warnings about HDS use from health professionals or other people, two respondents said no one had warned them about using HDS, as they knew how to use it safely.

> *My relatives did not have HDS knowledge*, said patient B
>
> *I knew how to use HDS*, said patient A

In contrast, two patients were warned by their doctor not to use HDS. One had stopped using them whilst the other did not. However, patient C did not obtain any warning from her doctor, although she did inform her doctor about her use of HDS.

It would appear that the patients using HDS had two characteristics. Firstly, some patients trusted in the benefits from HDS and had no concerns about them, as they thought that HDS did not contain chemical substances or were dietary. Secondly, others wanted to try HDS as their friends and family had

recommended them; however, some respondents questioned the efficacy and safety of HDS and some wanted to consult their doctor.

7.6 Discussion

The two pilot studies tested the study instruments and methods which were largely acceptable, although some issues arose during the testing. Regarding information about household income, 48% were not able to provide household income because some did not know this information and others refused to disclose this information. As a result, this question was deleted from the questionnaire. The number of respondents who had never smoked or consumed alcoholic beverages was high: the interviewer asked all respondents “Do you smoke or drink alcoholic beverages?” and the majority said “no”. Then the interviewer improved the question to “Have you ever smoked or drunk alcoholic beverages?” This question seemed to provide a more accurate answer than the original question. Therefore, the new question was used in the main study.

The pattern of HDS use amongst Thai patients with CKD, in this pilot study, was similar to the trends found in the bus stop survey, see Appendix 1, which was conducted in the general population in Bangkok. The bus stop survey found that the equal proportion (40%) between the use herbal medicine and dietary supplement; the main purpose of herbal medicine use was the treatment of illnesses, whilst dietary supplements were used for maintaining well-being. There is the same proportion of respondents using herbal products and dietary supplements with the same pattern of usage in both the bus stop survey and the pilot study.

Regarding whether there are adequate numbers of laboratory results in patients’ notes for determining clinical outcomes, i.e. serum levels of creatinine, potassium and phosphate, were recorded, approximately 80% had at least 3 values of serum levels of serum creatinine and potassium in the previous year,

prior to the index date. Half had at least 3 values of serum levels of phosphate. Therefore, the main study would have adequate information about the study outcomes.

Recruitment rate was 10 respondents per week in the first pilot study, when only the principal investigator approached and interviewed respondents. The sample size determination was at least 420 patients for the cohort study. This rate was too low; therefore the recruitment process may have taken at least 11 months to achieve the required sample size for the baseline data. Given that there is a planned 12 months follow-up, the cohort study would then have taken at least 2 years, which is not possible within the scope of 3-year PhD programme. To improve the recruitment rate, in the second pilot study, the main investigator (MT) and two research assistants trained by MT, approached and interviewed patients, so the recruitment rate was nearly doubled (15-20 respondents per week). Therefore, the sample size of at least 420 patients could be recruited within 6-7 months and this process was used in the main study.

The Thai version of the MMAS-8-Item® had already been tested for validity and reliability in Thai diabetic patients by Sakthong et al. (2009).[227] They found 0.61 of Cronbach's alpha and 0.83 of ICC. In the present study, the Thai version of MMAS-8-Item® was tested for concurrent validity, internal consistency and test-retest reliability amongst CKD patients. Respondents with a low level of adherence to prescribed, conventional medication had decreased mean eGFR scores greater than those with medium or high medication adherence. However, the association between the degree of medication adherence and the change of mean eGFR was not statistically significant due to the small number of respondents. Regarding reliability, the present study found 0.668 for Cronbach's alpha and 0.728 for ICC, meaning there was acceptable reliability. Internal consistency in the present study was close to the previous study, whilst the ICC

value in the present study was slightly lower than the value from Sakthong's study. Therefore, the MMAS-8-Item® was used in the main study.

The RPPPS questionnaire was adapted from the dialysis diet and fluid adherence questionnaire (DDFQ).[229] For the first pilot study, the RPPPS questionnaire was developed in order to assess dietary adherence, see Appendix 13; however the majority of respondents (17, 77.3%) found the question about "To what degree did you deviate from such recommendation?" was difficult and hesitated for a moment in order to answer this question. Therefore, this question was revised to "How much did you comply with your doctor's recommendation?" when respondents could not answer the original question immediately.

Most respondents (19, 86.4%) found it difficult to answer the question "How many days during the past 14 days didn't you follow recommendation of your food restriction?". None of the respondents could answer the question about estimating the change of their diet after they were neither diagnosed with CKD; nor could they accurately recall the amount of each type of food eaten, such as from a high-protein diet, a high-potassium diet and a high-phosphate diet. Therefore, these questions were deleted and new questions based on the questionnaire of Vlaminck et al. (2001) were developed and used in the remaining period of the pilot study, see Appendix 3.

The RPPPS questionnaire classified the degree of food consumption into low and high food consumption. Respondents answering 'no' or 'very small amounts' were classified as low food consumption; meanwhile those with moderate or large amounts of consumption were high consumption. Patients with complications of CKD, i.e. hyperkalemia, hyperphosphatemia and hypertension, have to restrict the amount of protein, potassium, phosphate and salt they eat. Although these patients consumed a moderate amount of these nutrients in their diet, they may consume more than their dietary recommendations. Therefore, it

would seem that they reported eating moderate amounts, meaning they were exceeding the recommendations for their dietary intake.

Regarding the validity of the RPPPS questionnaire, respondents with low protein consumption had increased mean eGFR, as compared to those with high protein consumption. Likewise, those with low potassium, phosphate and salt consumption had controlled serum levels of potassium and phosphate, and controlled blood pressure, compared to those with high potassium, phosphate and salt consumption. A statistically significant association was found between low potassium consumption and controlled serum potassium levels. However, other correlations were not statistically significant, due to the small number of respondents. Other factors played their part influencing these correlations, such as the severity of CKD and prescribed, conventional medicine for treatment of hyperkalemia, hyperphosphatemia or hypertension.

Vlaminck et al. (2001), who developed the DDFQ, had one question: “To what degree did you deviate from your diet guidelines?” which measured the degree of dietary non-adherence, which is potassium and phosphate intake. They conducted criterion validity of the DDFQ in order to evaluate the correlation between the degree of dietary non-adherence and serum levels of potassium and phosphate. They found a positive correlation between the degree of dietary non-adherence and serum levels of phosphate, but not with potassium. It would seem therefore, that the RPPPS questionnaire directly measures the degree of potassium and phosphate consumption, rather than the DDFQ doing so.

The test–retest reliability of the RPPPS questionnaire assessing the degree of potassium and salt consumption had good agreement (Kappa= 0.79 and 0.76, respectively), meaning acceptable reliability. Therefore, these questions were used in the main study. In contrast, the reliability of the questions assessing the degree of protein and phosphate consumption had only fair agreement (Kappa = 0.32 and 0.27, respectively). This may be because the questions were not

specific; at least a quarter of respondents were not able to assess the degree of protein and phosphate in their diet. High protein and phosphate diets consist of several types of food: for instance, high phosphate foods are cereal, milk, chocolate, yogurt, ice-cream, etc. High protein diets contain pork, chicken, egg white, fish, etc. Therefore, only one question assessing the degree of protein and phosphate consumption may not be suitable. These aspects of diet should have more questions; for example, the questions about high protein diet, 'How often have you eaten pork in the last 14 days?', 'How often have you eaten chicken in the last 14 days?', and 'How often have you eaten egg white in the last 14 days?', etc. Additionally, doctor's advice about food restrictions influenced a change in food consumption in respondents. Therefore, these questions were revised, see Appendix 6 and the new questions were piloted again in December 2011. Additionally, the poor reliability of the RPPPS questionnaire in the first pilot study may result from a change of respondents' diet behaviour under observation, which is known as the Hawthorne effect.

Some respondents found it difficult to estimate their food consumption, so the interviewer had to estimate the food consumption based on the respondent's information. To measure the degree of food consumption accurately, the definition of the degree of food consumption needed to be put forward. The degree of food consumption was classified into 5 levels: no, low, moderate, high and very high, see Table 7.16.[255]

Table 7.16 Definition of degree of food consumption

Degree of food consumption	Definition
No	No food consumed at all
Low	Eating 1-2 days per week
Medium	Eating 3-4 days per week
High	Eating 5-6 days per week
Very high	Eating daily

Kappa values of test-retest reliability of the revised RPPPS questionnaire in the second pilot study were acceptable. This may be because the questions in the second pilot study were more specific and there was the short period (7 days) between the first and second interviews, so that respondents may not have changed their diet behaviour. The reliability of assessing protein, potassium, phosphate and salt consumption was improved (Kappa = 0.69, 0.74, 0.81 and 0.81, respectively). Appendix 6 shows the final version of the questionnaire employed for the survey.

Regarding the researcher administered open-ended questions, about attitudes towards the reasons for HDS use amongst patients with CKD, see Appendix 4, these questions were used in the qualitative study because all respondents in the second pilot study understood the questions fully and the findings seemed to relate to reasons for HDS use, which was the objective of this qualitative study. Reasons for HDS use were perceptions of benefits and safety of HDS. Sources of information influencing decision making of HDS use were family members, friends and the media supported by the literature.[51,55,90]

7.7 Conclusion

The researcher administered questionnaire in the survey and the researcher administered open-ended questions about attitudes towards the reasons for HDS use, in the qualitative study, were developed and piloted, and finally acceptable results were obtained. Both the Thai version of the MMAS-8-Item® and the RPPPS questionnaire were tested for criterion validity and test-retest reliability, and found to have acceptable validity and reliability. The final version of this questionnaire, which includes the RPPPS questionnaire, is shown in Appendix 6.

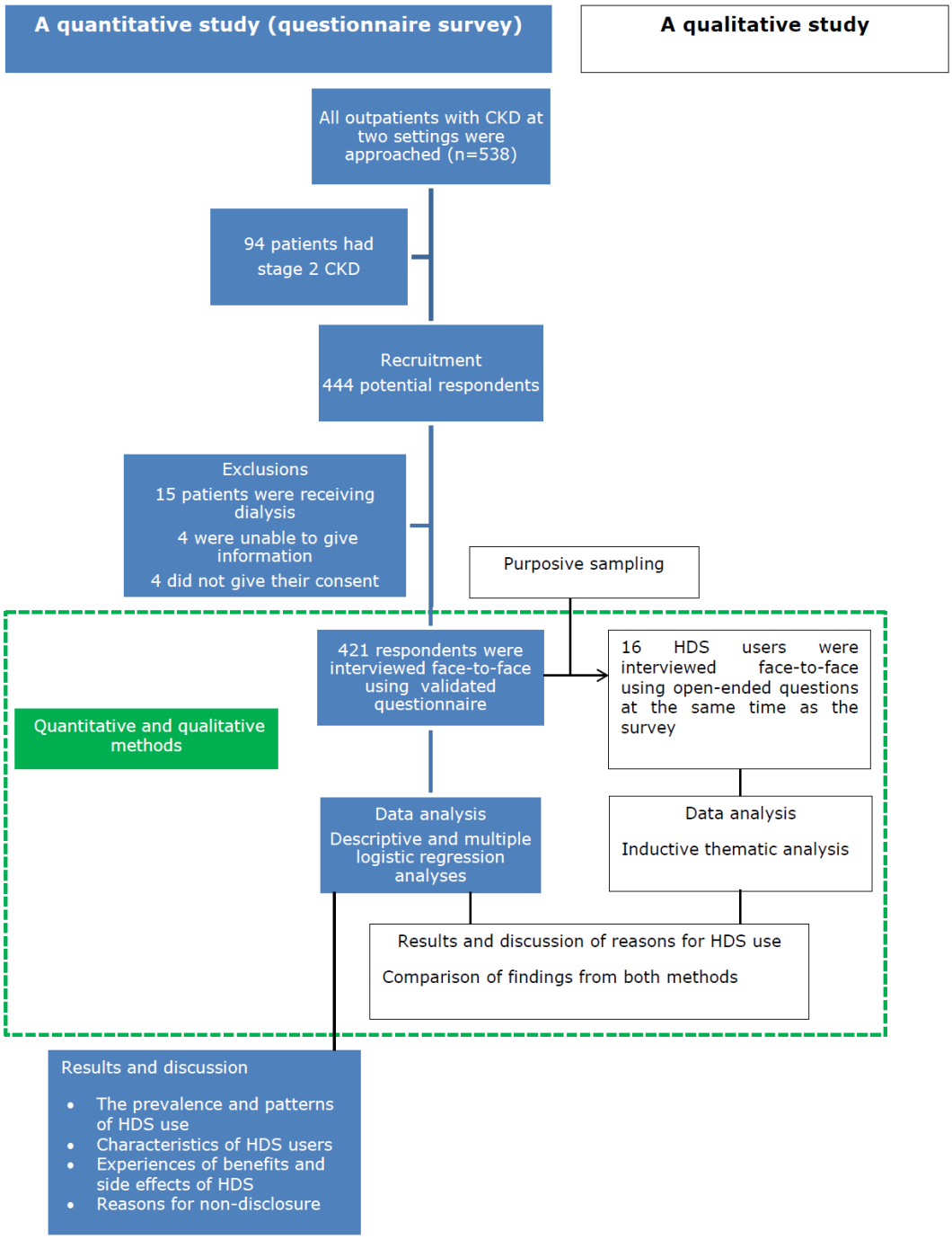
8. The prevalence, patterns and reasons for HDS use

The objectives of this study were to determine 1) the prevalence and patterns of HDS use in Thai patients with CKD; 2) the types and patterns of HDS use amongst this population; 3) the demographic characteristics relating to HDS use, compared with the non-users; 4) the association between HDS use and a level of adherence to prescribed, conventional medication; 5) the reasons why Thai CKD patients use HDS; 6) respondents' experiences of benefits and adverse effects from using HDS; and 7) the rate of non-disclosure of HDS use to a doctor and its reasons.

8.1 Methods

A survey was performed in order to serve objectives 1, 2, 3, 4, 6 and 7 whilst the fifth objective was achieved using quantitative and qualitative methods, where quantitative and qualitative data were collected in parallel, analysed independently, and then compared, see Flowchart 8.1.[256]

Flowchart 8.1 Diagram of study methods



8.1.1 Choice of method

The survey collected data using a questionnaire, because extracting data from medical notes alone was considered unlikely to provide complete information, particularly in relation to HDS use. In addition, the literature shows that patients using HDS were unlikely to disclose their use to their doctor.[15,16,51,58] Despite the high costs of an interview method, compared to a postal survey, there are many advantages of face-to-face interviewing: a high response rate, the ability to ensure all questions are answered, questions can be clarified by the interviewer to ensure informants understand the questions, the ability to probe for responses and sessions are not limited to those with sufficient reading ability to answer the questions.

This survey was planned to collect data for 6 months, as most patients had to visit their doctor every three months, so they all had an equal chance of being recruited during the six-month period.

The third objective: 'reasons why Thai CKD patients use HDS', was designed to collect data using a qualitative method in order to gain a greater insight than would be obtained from using the survey data alone.

8.1.2 Definition of HDS use

Herbal and dietary supplement use was defined as use of products containing plant-derived material, either raw or processed ingredients, from one or more plants or containing dietary ingredients, such as vitamins, minerals, amino acids and substances, such as, enzymes, organ tissues, glands and metabolites.[31,32] This definition was used in this study because it is sufficiently wide to capture use in Thailand and an acceptable definition for comparison with the literature. Additionally, the prevalence of HDS use was defined as its use in the previous 12 months, as most studies which ascertain prevalence have used this period and it

is commonly used in prevalence studies[10,25,36,40,42,43,45,46], thereby allowing comparisons to be made.

The inclusion of both herbal medicine and dietary supplements in this study was because 1) both are frequently used; and 2) their definition overlaps in the literature. For example, raw ginkgo can be defined as a herbal medicine, particularly in Asian studies, whilst its extracts are commonly defined as dietary supplements, particularly in US studies; 3) the term 'dietary supplements' is more likely to be used in the US, and this sometimes includes herbal products,[10] whilst the terms 'natural products' or 'natural herbs' include both herbal medicines and dietary supplements in the literature.[15,28]

This study focused on HDS use for the treatment of illnesses or health promotion, rather than consumption as daily food intake or cosmetic purposes, which may affect the study outcomes. If the present survey included all purposes of HDS use, the prevalence in Thailand may be overestimated, compared with prevalence in Western populations, as some of the herbs are used in flavouring food in Thailand and are less likely to be used as frequently for this purpose in Western population. This assumption is supported by the bus stop survey of the prevalence of HDS use in Thai general population, where the definition of HDS use included the use of HDS for treatment, dietary and cosmetic purposes, see Appendix 1. Moreover, the definition of HDS usage in the present survey did not include prescribed conventional medications, such as calcium supplements, folic acid, vitamin B complex, iron supplements or Senokot®, which are commonly prescribed for supportive treatment of CKD complications.

8.1.3 Questionnaire survey

A cross-sectional survey was recruited Thai outpatients with stages 3 to 5 CKD at two teaching hospitals from January to June 2012.

The five parts of the final version of the questionnaire consisted of demographic characteristics, HDS use, experiences of benefits and adverse effects from the HDS use, the Thai version of MMAS-8-Item® and the RPPPS, see Appendix 6. Demographic characteristics included age, sex, current address, education, occupation, smoking status and alcohol consumption. HDS usage included types, medical purposes, dosage forms, doses and duration of HDS use, the reasons why respondents use HDS, their information sources and how they obtained the HDS. The RPPPS questionnaire measured the degree of dietary intake for the cohort study, see Chapter 9.

All patients who met the inclusion criteria were approached in order to determine their willingness to participate in this survey. If they consented, the questionnaire, with pictures of HDS samples and diets, was administered in face-to-face interviews, see Appendix 6.

The principal investigator (MT) and two research assistants - Ms. Panjit Chaiyasanit and Mr. Piya Kaewkrachang interviewed respondents. The assistants were trained to conduct the interviews by MT and the first respondent interviewed by them was observed by MT in order to ensure the standardisation and conformity of the interview procedures.

Data were coded and entered into the IBM SPSS software version 19.0. This database was checked to ensure accuracy and completeness of data entry. Ten per cent of questionnaires (n = 42) were randomly selected using Microsoft Excel software and these questionnaires were checked against the database. The questionnaire contained 28 questions and 103 variables. A total of 3 errors were found in 1,176 questions (4,326 variables). These errors were rectified. To check

consistency of the database, issues related to other variables were checked; for example, the total number of HDS used and the number of herbal medicines and dietary supplements used. Such errors (1%) found were rectified.

Data analysis consisted of simple frequencies with percentages, which were used to determine the prevalence of HDS use and descriptive results. Chi-squared tests were performed to determine the factors related to HDS use and any associations between HDS use and conventional medication adherence. Multiple logistic regression analysis was undertaken to determine associations between HDS users and conventional medication adherence, adjusted for demographic characteristics. Tests were 2-tailed, and a p-value < 0.05 was considered statistically significant. IBM SPSS software version 19.0 was used for the statistical analyses.

8.1.4 Qualitative study

HDS users from the questionnaire survey, in both settings, who were willing to participate in the qualitative study were recruited. Additionally, participants who reported using HDS and provided reasons why they used HDS were chosen, as they were likely to have positive attitudes towards HDS use. Respondents were interviewed face-to-face by MT, using eight open-ended questions about their reasons for HDS use, see Appendix 4, until the data was saturated. Therefore, 16 respondents were recruited. The interviews lasted approximately 5-10 minutes and were audio recorded.

Open-ended questions were used in the qualitative study and were audio recorded, as this method permitted informants to provide detailed answers and minimised the extent to which these answers were influenced by the interviewers' own perspectives.[257] An advantage of audio recording is that complete and verbatim data collection could be obtained, in comparison with writing notes, although some informants may feel slightly uncomfortable in being

recorded. Also, this method lacks data regarding non-verbal aspects of communication, such as body language and facial expressions.

The audio recordings were transcribed verbatim and the Thai transcripts were twice checked for accuracy against the records, before starting the process of forward translation. Meaning-based translation from Thai language to English language was performed and English transcripts were twice checked with the Thai transcripts.[253] Then five out of sixteen transcripts were back translated by Dr. Charoen Treesak, who is fluent in both languages. This process was performed in order to validate the transcripts. One error out of five transcriptions was found. The error was rectified.

Despite the fact that the interviewer did not ask about their reasons for non-disclosure of HDS use to a doctor, six respondents in the qualitative study provided this information. One respondent mentioned disclosure of HDS use to her doctor by herself.

The transcripts were analysed by the inductive thematic approach, with line-by-line coding; the Weft QDA-a software programme, for qualitative data analysis, was used for assisting in the organisation of the transcripts.[258,259] MT coded key words related to reasons for HDS use from all transcripts, and then grouped them under the same theme. Next, these were searched for characteristics which were shared between the themes until there was consistency and themes emerging from the information were identified. Comparing these themes with the transcripts again enabled new themes to emerge, which were not included in the previous analyses. Finally, such processes were performed until the themes were consistent.

8.2 Results

The survey presents demographic characteristics of respondents and HDS users, the prevalence and patterns of HDS use, sources of information and HDS, experiences of benefits and adverse effects from using HDS, disclosure of HDS use and reasons for non-users.

Reasons for HDS use were supported by both the survey (n=189) and the qualitative study (n=16). Six respondents who participated in the qualitative study provided more information about reasons for the non-disclosure of HDS use to their doctor and some explained the reasons for the disclosure. Reasons for non-adherence to conventional medication emerged from qualitative analysis. As there was overlap in the topics for the researcher administered questionnaire both in the survey and the open-ended questions in the qualitative study, the results are presented together.

8.2.1 Description of respondents

The total number of potential respondents, who were approached to take part in the survey, was 538. Patients at SWU hospital did not have eGFR calculated by the Thai MDRD equation and they were approached based on an increase in serum creatinine levels. Subsequently after calculating eGFR, 94 respondents were excluded as they had stage 2 CKD. This left a total of 444 patients of which 23 (5.2%) were excluded because they were receiving dialysis (n=15), were unable to provide information due to illnesses (n=4), or did not give their consent (n=4). Thus, 421 patients were recruited to the study. Demographic characteristics are shown in Table 8.1. Some patient information (n=60) was provided by relatives as the patients could not provide the information due to their illness. Respondents had a mean age of 66 years with a standard deviation (SD) of 13, and 54% were women. More than half of respondents had less than

a secondary school education (56%), were retired (68%), were non-smokers (64%) and non-drinkers (57%), see Table 8.1. The majority of respondents had stage 3 CKD (71%) and reported moderate to high levels of prescribed, conventional medicine adherence (74%).

Table 8.1 Demographics of respondents (n=421)

Demographics	Frequency	Percent	Missing data
Respondents from each hospital			-
CU hospital	238	56.5	
SWU hospital	183	43.5	
Interviewers			-
Main investigator	349	82.9	
Research assistants	72	17.1	
Information providers			1
Respondents	329	78.3	
Patient's relatives	60	14.3	
Both	31	7.4	
Mean age and SD	66 $\pm$ 13 years		-
Sex			-
Male	194	46.1	
Female	227	53.9	
Current address			-
Bangkok	148	35.2	
Rural areas	273	64.8	
Education			1
Less than secondary school	234	55.7	
Secondary school	67	16.0	
Vocational degree	29	6.9	
Undergraduate degree	69	16.4	
Higher degree	21	5.0	
Occupation			-
Retired	286	67.9	
Employed	41	9.7	
Self-employed/ business	39	9.3	
Housewife/ house husband	19	4.5	
Professional	13	3.1	
Unemployed	11	2.6	
Farmer	7	1.7	
Priest	4	1.0	
Student	1	0.2	

Table 8.1 (continued)

Demographics	Frequency	Percent	Missing data
Smoking status			-
Never smoked	269	63.9	
Former smoker	131	31.1	
Current smoker	21	5.0	
Alcohol consumption			2
Never	240	57.3	
Former drinker	156	37.2	
Current drinker	23	5.5	
Stage of CKD			-
3	297	70.6	
4	107	25.4	
5	17	4.0	
Prescribed medication adherence*			-
Low	108	25.7	
Medium	201	47.7	
High	112	26.6	

Percent was calculated using an absolute number of respondents, which was not included a number of missing data.

* Medication adherence was measured using the Thai version of the 8-Item Morisky Medication Adherence Scale® [227,228]. Low, medium and high adherence was defined as MMAS $\leq$ 6, 6 < MMAS < 8, MMAS =8, respectively.

8.2.2 Demographic variables associated with herbal and dietary supplement use

The prevalence of herbal and dietary supplement (HDS) use in the previous 12 months amongst Thai patients with CKD was 45% (n=189, 95%CI 40%-50%). Almost all HDS users combined these supplements with their prescribed, conventional medicines (n=187, 99%). However, two (1%) of the HDS users had stopped using their prescribed medicines and had relied on HDS alone to relieve their symptoms. Additionally, almost one third of the respondents used other complementary and alternative medicines (CAM), of which massage was the main type of CAM use, reported by respondents (50%), see Table 8.2.

Table 8.2 The use of CAM (n=421)

	Frequency	Percent	Missing data
CAM users			7
Yes	127	30.7	
No	287	69.3	
Types of CAM used (n=204)*			-
Massage	103	50.5	
Meditation	57	27.9	
Acupuncture	36	17.6	
Yoga	5	2.5	
Tai-chi	3	1.5	

* Some respondents reported more than one type of CAM used

Percent was calculated using an absolute number of respondents, which was not included a number of missing data.

Respondents who used HDS were more likely to use other CAMs ($\chi 2 = 24.9$, $p < 0.01$), see Table 8.3.

Table 8.3 Relationship between HDS and CAM use (n=421)

	HDS users (n=189)	Non-users (n=232)	χ^2 *p*-value
CAM users	81 (43.1%)	46 (20.4%)	< 0.01*
Non-users	107 (56.9%)	180 (79.6%)	
Missing data	1	6	

* Statistically significant at *p*-value < 0.05.

HDS users were more likely to have low adherence with prescribed, conventional medicines, compared with non-users ($\chi 2 = 8.46$, $p = 0.015$), see Table 8.4. There were no differences between HDS users and non-users regarding age, sex, education levels, current address, smoking status, and the severity of CKD.

Table 8.4 Univariate analysis of factors associated with HDS use in patients with CKD (n=421)

Factors	HDS user (n=189)	Non user (n=232)	X^2 *p*-value
Age			0.334
≤ 60	62 (32.8%)	66 (28.4%)	
> 60	127 (67.2%)	166 (71.6%)	
Sex			0.708
Male	89 (47.1%)	105 (45.3%)	
Female	100 (52.9%)	127 (54.7%)	
Education			0.862
Less than secondary school	104 (55.3%)	130 (56.0%)	
Secondary school	27 (14.4%)	40 (17.2%)	
Vocational degree	14 (7.4%)	15 (6.5%)	
Undergraduate degree	34 (18.1%)	35 (15.1%)	
Higher than undergraduate degree	9 (4.8%)	12 (5.2%)	
Address			0.186
Bangkok	60 (31.7%)	88 (37.9%)	
Rural areas	129 (68.3%)	144 (62.1%)	
Smoking status			0.812
Never	122 (64.6%)	147 (63.4%)	
Former	59 (31.2%)	72 (31.0%)	
Current	8 (4.2%)	13 (5.6%)	
Alcoholic consumption			0.080
Never	119 (63.3%)	121 (52.4%)	
Former	60 (31.9%)	96 (41.5%)	
Current	9 (4.8%)	14 (6.1%)	
Stages of CKD			0.936
3	133 (70.4%)	164 (70.7%)	
4	49 (25.9%)	58 (25.0%)	
5	7 (3.7%)	10 (4.3%)	
Medication adherence**			0.015*
Low	61 (32.3%)	47 (20.2%)	
Medium	79 (41.8%)	122 (52.6%)	
High	49 (25.9%)	63 (27.2%)	

* Statistically significant at $p < 0.05$

** Medication adherence was measured using the Thai version of the 8-Item Morisky Medication Adherence Scale® [227,228]

The multiple logistic regression analysis included all potential independent variables. Former drinkers (adjusted odds ratio (OR) 0.43, 95% CI 0.25-0.75) and respondents having medium adherence to prescribed, conventional medicines (adjusted OR 0.53, 95% CI 0.32-0.87) were more likely to use HDS. No other statistically significant associations with HDS use were found (see Table 8.5).

Table 8.5 Multiple logistic regression analysis of the association between HDS use and demographics amongst patients with CKD (n=421)

Factors	Adjusted odds ratio*	95% CI
Age		
≤ 60	1.00	
> 60	0.84	0.52-1.36
Sex		
Male	1.00	
Female	0.77	0.47-1.29
Education		
Less than secondary school	1.00	
Secondary school	0.77	0.43-1.40
Vocational degree	1.11	0.48-2.52
Undergraduate degree	1.16	0.64-2.11
Higher than undergraduate degree	0.88	0.33-2.36
Current address		
Bangkok	1.00	
Rural address	1.38	0.90-2.12
Smoking status		
Never smoked	1.00	
Former smoker	1.57	0.85-2.89
Current smoker	0.90	0.33-2.47
Alcohol consumption		
Never	1.00	
Former drinker	0.43	0.25-0.75
Current drinker	0.52	0.20-1.33
Stages of CKD		
3	1.00	
4	1.02	0.64-1.64
5	0.92	0.32-2.63
Prescribed, conventional medication adherence**		
Low	1.00	
Medium	0.53	0.32-0.87
High	0.68	0.39-1.20

* OR adjusted for all other variables listed in the table

** Medication adherence was measured using the Thai version of the 8-Item Morisky Medication Adherence Scale® [227,228]

With respect to qualitative results, in terms of the reasons for poor adherence to conventional medication (CM) amongst HDS users, only two respondents raised this issue. They either decreased doses of CM, or stopped using CM, as they were either concerned about taking high numbers of CM, or had experiences of side effects from using CM.

> *I worry whether or not I've taken too many medications... If I've taken too many and feel it is wrong, I'll try to decrease the doses of the medications.* (R12, m age 75)

> *I had lots of side effects from conventional medicines, so I turned my thoughts to herbal use and used it... I'm normal at the moment although I don't take my conventional medicines.* (R5, m age 43)

Four out of six interviewees who had negative attitudes towards CM had poor adherence to CM, as measured by the MMAS-8-Item®. Their negative attitudes towards CM appeared to explain their poor adherence to CM. On the other hand, eight out of nine respondents who had moderate or high levels of adherence did not raise any concerns about using CM and trusted their doctor.

8.2.3 Herbal and dietary supplement usage

Of the respondents using HDS (n=189), more than half of the respondents reported herbal use (64%, n=138), whilst 36% (n=77) used dietary supplements; of those 14% used both (see Table 8.6). The mean number of different HDS used was 1.6 (SD $\pm$ 0.9) products. The total number of different HDS used was 304, see Table 8.6.

Table 8.6 Patterns of HDS use (n=189)

Patterns	Frequency	Percent
Types of HDS used		
Herbal products	112	59.3
Dietary supplements	51	27.0
Both	26	13.7
The number of different HDS used		
1	112	59.2
2	56	29.6
3	10	5.3
4	7	3.7
5	2	1.1
6	2	1.1
Total number of HDS used	304	100

Amongst 304 different HDS used, capsules or tablets were the usual oral dosage forms (51%, n=154) of which 11% (n=17) were traditional Thai or Chinese pills called 'Luke Klon', which are a black round pill (see Table 8.7). Nearly 10% (n=22) reported using unprocessed herbs, of which 64% were collected from the respondent's garden. Additionally, most HDS products (71%, n = 213) were used daily and around half of the products (52%, n = 153) had been used for less than one year.

Table 8.7 Pharmaceutical forms, frequency and duration of HDS use (total number of HDS used=304)*

Patterns	Frequency	Percent	Missing data
Oral dosage forms			1
Capsules or tablets	154	50.8	
Liquid forms	94	31.0	
Powder	33	10.9	
Unprocessed herbs	22	7.3	
Frequency of use			4
Daily	213	71.0	
Weekly	47	15.7	
Few times a month	24	8.0	
Few times a year	16	5.3	
Duration of use			9
Less than 1 year	153	51.9	
1-2 year(s)	67	22.7	
3-5 years	37	12.5	
More than 5 years	38	12.9	

* Respondents reported for each product they used so these total more than the 189 respondents who used HDS

Percent was calculated using an absolute number of respondents, which was not included a number of missing data.

The purposes of using HDS were for maintaining well-being (61%), followed by the treatment of other chronic diseases (40%), minor ailments (33%), and kidney diseases (30%). Illnesses, including chronic disease, kidney disease, minor ailments and leg oedema, were the main purposes for using herbs (92%, n=171), whist most dietary supplements were used for well-being (40%, n=74), see Table 8.8. Herbs used for kidney stones (n=2) and diuretic effect (n=1) were categorised as being taken to treat kidney diseases, and others were used for CKD (n=46). Chronic diseases treated with herbs included diabetes, hypertension, dyslipidaemia, cardiovascular diseases, gout, allergy, thyroid, and cancer. However, nine cases of HDS use reported using HDS for chronic disease, but the diseases were not specified. Minor ailments treated with herbs included gastrointestinal symptoms (such as dyspepsia, flatulence, constipation), fever, common cold, pain, migraine and haemorrhoids. In Thai culture, maintaining well-being was reported using various phrases, such as body detoxification,

relieving fatigue or anxiety, increasing appetite, maintaining or balancing their body function and having a good night's sleep.

Table 8.8 Medical purposes of HDS use (n=189)*

	Frequency**	Percent	Missing data
Purposes of herbal use			3
Chronic disease	64	34.4	
Minor ailment	56	30.1	
Kidney disease	49	26.3	
Well-being	42	22.6	
Leg oedema	2	1.1	
Unknown	1	0.5	
Purposes of DS use			5
Well-being	74	40.2	
Chronic disease	12	6.5	
Supplement	8	4.3	
Kidney disease	7	3.8	
Minor ailment	6	3.3	

* Respondent reported using more than one herbal medicine and/or dietary supplements

** Respondents reported using more than one medical purpose per product

Percent was calculated using an absolute number of respondents, which was not included a number of missing data.

8.2.4 Reasons for and influences on herbal and dietary supplement usage

Most frequently reported reasons for HDS use in the survey were family or friends' recommendations, followed by the expectation of gaining benefits from using HDS and a willingness to try HDS, see Table 8.9. This was similar to the findings from the qualitative study. Meanwhile, the safety of HDS and experiences of adverse effects of CM in the survey were reported by 5% of respondents. The qualitative study supported this finding from the survey, that patients who were concerned about side effects from using HDS were more likely to use them with caution, such as taking lower doses than recommended, see Table 8.9.

Table 8.9 Reasons for HDS use from both quantitative (n=189) and qualitative (n=16) studies

Quantitative results		Qualitative results
Question	Frequency (%)	
Reasons why HDS used*		
Family/friend's recommendation	111 (58.7)	Influenced by their social network who were health care professionals or teachers (n=9)
HDS will work	71 (37.6)	Perception of their benefits (n=11)
Willing to try anything that helps	61 (32.3)	• Health care needs (n=7)
Prefer to use HDS	34 (18.0)	• Willing to try (n=4)
		• Intention to use (n=2)
Health care provider's recommendation	21 (11.1)	No mention
Safer than CM	9 (4.8)	Perception of their safety (n=5)
		• Their characteristics
		• No or little side effects
		• Safer than CM
		Concerns about side effects of HDS (n=3)
		• Patients used HDS with caution
Easy access	5 (2.6)	No mention
Recommended by traditional practitioners or HDS sellers	2 (1.1)	Their family recommended and then consulted Chinese herbal medicine practitioners (n=1)
Experienced adverse effects from conventional medicines	2 (1.1)	Had experiences or concerns about adverse effects of CM (n=2)
Recommended by fellow patients	1 (0.5)	Influenced by their social network (n=9)

* Respondents reported more than one reason, so these total more than 189

Most respondents who participated in the qualitative study were female and living in rural areas, see Table 8.10.

Table 8.10 Demographic characteristics of respondents in the qualitative study (n=16)

Demographics	Frequency (%)
Respondents from each hospital	
CU hospital	11 (68.8)
SWU hospital	5 (31.2)
Mean age and SD	62.5 + 12.3 years
Sex	
Male	6 (37.5)
Female	10 (62.5)
Current address	
Bangkok	6 (37.5)
Rural areas	10 (62.5)
Education	
Primary or secondary school	8 (50.0)
Higher education	8 (50.0)

The most frequently reported information sources of HDS in the survey were family and friends, and the media, e.g. television, radio, internet, books and leaflets, see Table 8.11. These seemed to influence decision-making regarding respondents using HDS. These findings were supported by the qualitative study. The five themes given as reasons for HDS use were: 1) health care need, 2) perception of benefits and 3) safety of HDS, 4) willingness to try HDS and 5) side effects of CM, see Figure 8.1. Additionally, two further themes, recommendations via a respondent's social network and from the media, were also reported as influencing their HDS use. This figure also shows the links between the themes.

Figure 8.1 Themes from the qualitative study with 16 respondents about their reasons for using HDS

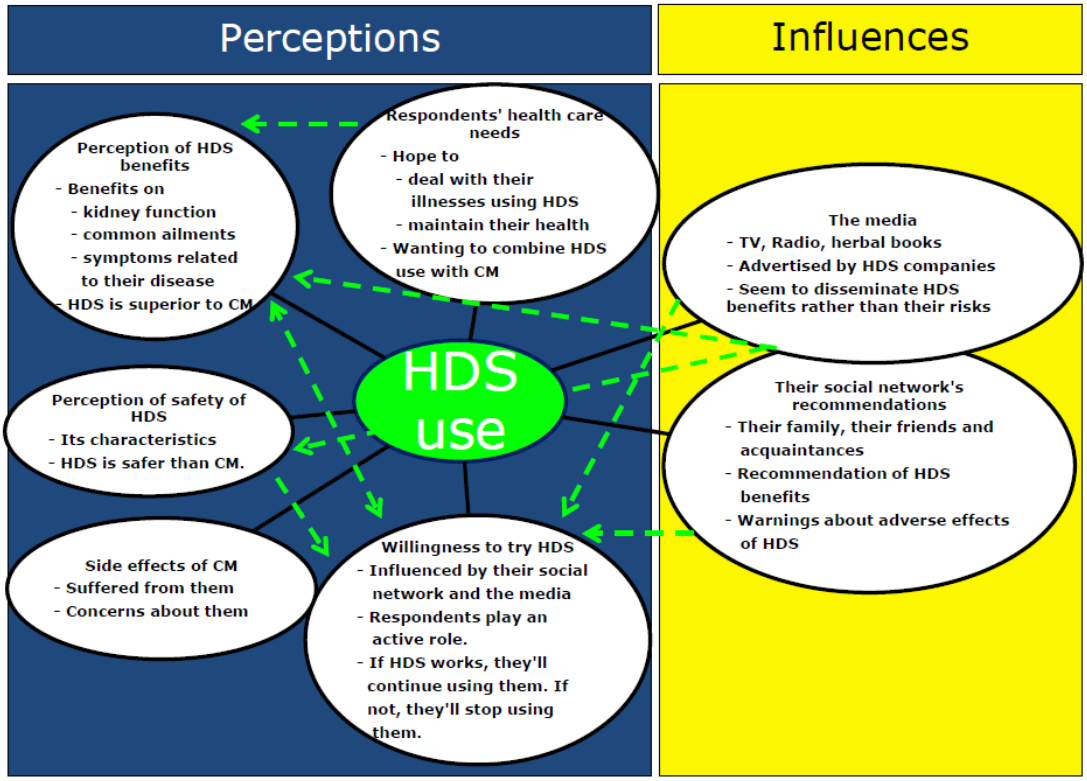


Table 8.11 Reported information sources about HDS and how they obtain HDS (n=189)

	Frequency*	Percent	Missing data
Information sources			1
Family and friends	115	61.2	
TV	20	10.6	
Radio	18	9.6	
Internet	12	6.4	
Health care providers	12	6.4	
Books	11	5.9	
Traditional practitioners	8	4.3	
HDS companies	7	3.7	
Leaflets from HDS companies	7	3.7	
Own knowledge of HDS	7	3.7	
Other patients with CKD	2	1.1	
Scientific evidence	2	1.1	
Newspapers	1	0.5	
HDS sources			-
Bought in**	128	67.7	
Pharmacies, herbal or Dietary supplement shops	56	43.8	
Direct sale companies	41	32.0	
Markets or stores	25	19.5	
Hospitals	11	8.6	
A temple	1	0.8	
Bought from abroad	1	0.8	
Provided by family and friends	54	28.6	
Collected from own garden	19	10.1	

* Respondents reported more than one source, so these total more than 189

** Respondents reported more than one place they bought HDS, so these total more than 128

Percent was calculated using an absolute number of respondents, which was not included a number of missing data.

8.2.4.1 The influence of family and friends' recommendations

In the survey, family or friends were reported as important factors influencing HDS use (59%), see Table 8.9. It would appear that they provided not only HDS information (61%), but also HDS products (29%), see Table 8.11. This finding was consistent with the qualitative results, where family and friends were reported as providing information about the benefits and safety of HDS. Additionally, interviewees were willing to try HDS recommended by their friends, family members or fellow patients who experienced the benefits and safety of HDS, see Figure 8.1. It would appear that friends or family members who had positive attitudes towards HDS influenced respondents to use HDS. Respondents also seemed to respect their educated family members, friends or acquaintances, such as doctors, nurses, and teachers.

> *My younger brother confirmed that it is good and cleans the blood vessels so blood circulation is improved. He said "You should take it" "It is no harm".* (R4, f age 56)

> *He [my older brother who has a wife working as a nurse and whose brother-in-law is a doctor] said "You should eat these herbs, which are good".* (R13, m age 70)

8.2.4.2 Desire to gain benefit from HDS

The second most frequent reason for HDS use was that, according to the survey, respondents expected to gain benefit from HDS (38%). This result was similar to respondents' health care needs, as reported in the qualitative study, and was related to their perception of HDS benefits, see Figure 8.1. This seemed to strongly influence HDS use in patients with CKD. It appears that some respondents felt hopeless and wanted to use any therapy which might help them. Some used HDS because they hoped to maintain their health in order to be able to live their normal daily life, such as being able to walk and cook.

Although others perceived that CM was more effective than HDS, they wanted to use HDS. Thus, they concurrently used HDS and CM.

> *I'm afraid of receiving dialysis... I want to use everything, which helps me to avoid receiving dialysis*. (R8, m age 67)

> *Conventional medicines are more effective than any herb. Herbs supplement conventional medicines.* (R12, m age 75)

However, one respondent did not expect to gain any benefit from trying HDS, when she used them the first time. She merely wanted to try HDS due to being desperate to try anything that might work.

8.2.4.3 Willingness to try HDS

Nearly one third of the reasons given for HDS use were reported as willingness to try HDS in the survey. This was similar to the qualitative results. The qualitative study found that HDS users were mainly influenced by their social network and the media, see Figure 8.1. Some respondents perceived that HDS did no harm, so they were willing to try HDS. Some actively sought HDS information, particularly about their benefits, and decided to use HDS by themselves.

> *I have to learn about herbal information by myself and know about them from my colleagues' or friends' experience of using herbs... I have to think whether or not herbs suit me and decide to use them by myself.* (R11, f age 44)

Respondents reported experimenting with HDS and monitoring their effects. Where they noticed positive effects from using HDS, they would continue using them and, if no improvement, they would stop using them.

> *I wanted to try them. After trying them, they were good. Thus, I continue to use them.* (R1, f age 59)

However, one respondent did not want to try HDS, but he felt he needed to use everything which might help him avoid dialysis; as a result, he used it.

8.2.4.4 Perception of the safety of HDS

Although 5% of the reasons for using HDS were reported as HDS being safer than CM in the survey, the qualitative study found respondents perceived HDS as safe: in particular, the absence of negative effects of HDS, or having little concern about adverse effects resulting from HDS as compared with CM. HDS were perceived by respondents as part of their diet or natural. Additionally, respondents were influenced by their social network and the media, which tended to provide information about positive effects of HDS, rather than their adverse effects.

> *I don't see their negative effects.* (R12, m age 75)

> *... herbs are natural and not chemicals. I think herbs are less accumulated in my body, compared to conventional medicines.* (R5, m age 43)

The qualitative study found that some respondents were concerned, or small numbers of them, had received warnings about renal adverse effects of HDS from their social network, the media or their doctor and this may explain why warning information was rarely given as an answer. As a result, they tended to use HDS with caution and would consult with their health care providers.

> *If I take too many herbs, I'm afraid of worsening liver and kidney function.* (R7, m age 67)

> *...my friend said you should not eat "Hem" [Coscinium fenestratum] too much because another person who used it died, and had his body cut open and they found his stomach was dark yellow. Thus, I don't want to eat it at all.* (R12, m age 75)

> *You know, there is marked lack of warning about taking herbs.* (R11, f age 44)

It would seem that the positive perception of HDS benefits may not have the same attitude as the safety of HDS. Although the majority of HDS users had positive attitudes towards benefits of HDS, it does not mean that they thought that HDS are safe.

8.2.4.5 Experiences with side effects from using CM

A few respondents reported experiences of adverse effects from using CM, as a reason for HDS use in the survey. This was supported by the qualitative study, in which some reported using HDS due to dissatisfaction with CM, or because they had negative attitudes towards CM.

> *I had lots of side effects from conventional medicines, so I turned my thoughts to herbal use and used it.* (R5, m age 43)

> *I'm afraid of worsening kidney function. If I take lots of prescribed medicines, whether they will affect kidneys or not?* (R9, f age 46)

8.2.4.6 The media influence on HDS use

The media, that is television, radio, internet, books, leaflets, newspapers and medical journals, were the second most frequently reported source of HDS information (38%) in the survey. From the qualitative study participants reported the media disseminating information about the benefits of HDS use, rather than the adverse effects. Additionally, HDS companies advertised benefits and safety of their products via the media by indicating that "the product is approved by the Thai FDA".

> *I wonder whether I should try it or not because I listened on the radio and they said "It was good".Thus, I tried it. They also said "It is to treat kidney disease".* (R3, f age 67)

> *... a herbal company advertises on television that the product is approved by the Thai FDA for dietary supplement... A herbal company advertises "This herb is the best sale product" "It is useful" "You would not be disappointed".* (R13, m age 70)

8.2.4.7 HDS practitioners and health care providers influence on HDS use

From the survey, it would seem that herbal practitioners in Thailand have a minor impact on respondents' decision-making regarding whether or not to use HDS amongst patients with CKD. Only one respondent reported that he used HDS recommended by a traditional practitioner, and only 4% of information about HDS was provided by such practitioners (see Tables 8.11). This is consistent with the small number of respondents reporting that it was health care providers who recommended HDS use (11%) or provided HDS information (6%). The qualitative study suggests that whilst patients are largely influenced by non-health care professionals, some did consult them before using HDS.

8.2.4.8 Availability of HDS

Easy access to HDS was reported by fewer than 5% as a reason for using HDS in the survey. Respondents reported that most HDS products were bought from pharmacies, or herbal or dietary supplement shops (44%), see Table 8.11. Thirty percent of HDS products were directly bought from their companies, which advertised their products on satellite television or radio, and respondents bought them by telephoning the company. Some respondents reported that the HDS company salesman visited their house in order to advertise and sell their products. One respondent reported obtaining their HDS at a temple in Thailand. Some priests are herbal practitioners and will provide herbal products for people consulting them.

8.2.5 Types of HDS used

Amongst 304 different reports of HDS being used, 199 herbal medicines (see Table 8.12) and 105 dietary supplements used (see Table 8.13), 58 different herbal products and 18 dietary supplement products were identified. Herbal products used (n=58) were as either a single herb (n=38) or a herbal combination (n=20), including Thai herbal combinations (n=15), Chinese herbal combinations (n=4), and a mixed botanical extract (n=1). However, for 51 (17%) of the HDS products reported, the ingredients were unknown as respondents did not either know or remember their details. This group comprised of six Chinese herbs, nine Thai herbal combinations, 23 single Thai herbs and 13 dietary supplement products. Kariyat (12%), turmeric (10%) and horse radish tree (8%) were the three most frequently reported herbs used, see Table 8.12.

Table 8.12 Types of herbs used, their purpose and adverse effects reported by respondents (total number of herbal medicines used=199)*

Types of herb used	Frequency (%)	Main purpose as reported by respondents	Adverse effects reported by respondents
Kariyat (*Andrographis paniculata*)	23 (11.6)	Common cold, fever, sore throat, diabetes	Increased SCr
Turmeric (*Curcuma longa*)	19 (9.5)	Gastrointestinal symptoms**, constipation, CKD	-
Horse radish tree (*Moringa oleifera*)	16 (8.0)	Diabetes, hypertension, constipation	Unable to stop bleeding
Mixed botanical extract or fruit drink	12 (6.0)	CKD, diabetes, well-being	-
Ginseng (*Panax spp.*)	7 (3.5)	Well-being	-
Holy mushroom (*Garnoderma lucidum*)	5 (2.5)	CKD	Oedema
River spiderwort (*Tradescantia fluminensis*)	4 (2.0)	CKD	Increased SCr, fatigue
Babbler's Bill Leaf (*Thunbergia laurifolia*)	3 (1.5)	Detoxification, diabetes	-
Senna (*Senna alexandrina*)	3 (1.5)	Constipation	-
Ginkgo (*Ginkgo biloba*)	3 (1.5)	Improved brain function	-
Boesenbergia (*Boesenbergia rotunda*)	3 (1.5)	CKD	-
Garlic	3 (1.5)	Dyslipidaemia	-
Mixed Thai traditional herbs called 'Ya Hom'	3 (1.5)	Well-being, fainting, dizziness	-
Heart-leaved moonseed (*Tinospora cripa*)	3 (1.5)	Diabetes,well-being	-
Coix seed (*Semen Coicis*)	3 (1.5)	CKD, well-being, diabetes	-
Vap Ca (*Houttuynia cordata*)	2 (1.0)	Kidney stones, CKD	-
Aloe (*Aloe vera*)	2 (1.0)	Diuretic effects, well-being	-
Blue Pea (*Clitoria ternatea*)	2 (1.0)	CKD	-
Mixed 3 or 6 types of mushrooms	2 (1.0)	CKD	-
Shiitake mushroom (*Lentinus edodes*)	2 (1.0)	CKD, well-being	-
Cinnamon (Cinnamomum verum)	2 (1.0)	Diabetes	-

* Respondents reported using more than one type of herb; ** Flatulance, dyspepsia and peptic ulcers; SCr = Serum creatinine

Table 8.12 (continued)

Types of herb used	Frequency (%)	Main purpose as reported by respondents	Adverse effects reported by respondents
Mixed Thai traditional herbs called 'Ya Khom'	2 (1.0)	Fever	-
Mixed Thai traditional herbs called 'Ka Sai'	2 (1.0)	Constipation, well-being	-
Jujube (*Zizyphus mauritiana*) and Roselle (*Hibiscus sabdariffa*)	2 (1.0)	CKD, dyslipidaemia	-
Spirulina	2 (1.0)	Detoxification, diabetes	-
Lemongrass	1 (0.5)	Dyslipidaemia and CKD	-
Boesenbergia, sweet basil, honey and lime juice	1 (0.5)	CKD	Fainting
Boesenbergia, mint, ginger, galangal, lemongrass, kaffir lime leaves and shallots	1 (0.5)	CKD	-
Spring bitter cucumber (M*omordica cochinchinensis*)	1 (0.5)	CKD	-
Chinese folk remedy - Cordyceps, Lovage (*Angelica sinensis*), deer antler velvet, cinnamon and Schisandra berry (*Schisandra chinensis*)	1 (0.5)	CKD	-
Lime	1 (0.5)	Kidney stones	-
Chinese folk remedy - Cordyceps, Lovage (*Angelica sinensis*), deer antler velvet, cinnamon and Schisandra berry (*Schisandra chinensis*)	1 (0.5)	CKD	-
Paragrass roots (*Brachiaria mutica*) and pomegranate leaves (*Punica granatum*)	1 (0.5)	CKD	-
Leaves of *Clerodendrum petasites*	1 (0.5)	CKD	-
Java tea	1 (0.5)	Diuretic effects	-

Respondents reported a variety of uses for herbs: kariyat was used for common colds, including fever, sore throats, and diabetes; turmeric was used for flatulence, dyspepsia, peptic ulcer and constipation; horse radish tree was to treat diabetes, hypertension and to alleviate constipation.

Vitamins and minerals were common types of dietary supplements (DS) reported (16%, n=17), of which vitamin C (n=6) and calcium supplement (n=4) were the most commonly reported (see Table 8.13), followed by essence of chicken drink (13%, n=14) and germ oil (12%, n=13). All of these were used for maintaining well-being.

The thirty-one different types of herbs and seven different DS used were reported once, see Appendix 14.

Table 8.13 Types of dietary supplements used, their purpose and adverse effects reported by respondents (total number of DS used=105)*

Types of dietary supplement used	Frequency (%)	Purposes reported by respondents	Adverse effects reported by respondents
Vitamins and minerals	17 (16.2)	Well-being	Weight gain
Essence of chicken drink	14 (13.3)	Well-being	Increased blood sugar
Germ oil	13 (12.4)	Well-being	-
Rice Bran oil	9 (8.6)	Well-being, CKD, diabetes	-
Fish oil	8 (7.6)	Well-being, cardiovascular diseases	-
Protein	7 (6.7)	Well-being	Proteinuria
Chlorophyll	6 (5.7)	Well-being, CKD, diabetes, hypertension	-
Swiftlet's nest drink	5 (4.8)	Well-being	-
Bee pollen	2 (1.9)	Well-being	-
Wheatgrass	2 (1.9)	Well-being	Increased SCr
Fibre	2 (1.9)	Constipation	-
Coconut oil	1 (0.9)	Well-being	Diarrhoea

* Respondents reported more than one type of dietary supplement used; SCr = Serum creatinine

8.2.6 Perception of beneficial and detrimental effects from HDS reported by respondents

The perception of benefits from using HDS, based on data from both the survey and the qualitative study are presented.

Benefits from HDS were reported for around three quarters of the HDS used, see Table 8.14. The most frequently reported types of perceived benefits were the alleviation of minor ailments, followed by enhanced well-being and slowed progression of CKD. In the qualitative study, some respondents reported benefits to kidney function based on their laboratory results and some reported increased urine output as a benefit. It appears that they perceived benefits based on medical evidence. Some reported that the efficacy of HDS is superior to conventional medication.

> *My creatinine level wasn't increased. Now, I don't take it [herbal medicine]; my creatinine level increased, which is 1.6.* (R14, f age 51)

> *... they are more effective than conventional medications.* (R6, f age 57)

The survey found that 71% of respondents who perceived benefits from HDS continued using HDS. Amongst those reporting "don't know about HDS benefits" (n=31), see Table 8.14, six respondents seemed to hope that HDS might provide benefits in the future, despite not experiencing any at the moment. Another reason offered by the remaining respondents was that they concurrently took both HDS and conventional medication so they could not identify effects resulting from either HDS or CM.

> *Because I've taken the dietary supplement and prescribed medicines together, I don't know which one gives the benefit.* (R14, f age 51)

Table 8.14 Benefit and adverse effects reported by patients from their HDS use (n=189)

	Frequency	Percent	Missing data
Benefit experienced from HDS use[a]			2
Yes	147	78.6	
No	15	8.0	
Just started using HDS and not sufficient time to gain benefits	7	3.7	
Don't know	31	16.6	
Types of benefit (n= 147)[b]			-
Alleviated minor ailments	54	36.7	
Enhanced well-being	45	30.6	
Slowed the progression of CKD	15	10.2	
Treatment of chronic disease (unspecified)	13	8.8	
Reduced blood sugar	12	8.2	
Desired diuretic effect	10	6.8	
Reduced blood pressure	5	3.4	
Increased appetite	4	2.7	
Reduced serum lipid levels	2	1.4	
Adverse effects experienced from HDS use			-
Yes	19	10.0	
No	169	89.5	
Don't know	1	0.5	
Type of adverse effect (n=19)			-
Progression of CKD	7	36.9	
Gastrointestinal symptoms[c]	3	15.7	
Neurological symptoms[d]	3	15.7	
Oedema	2	10.5	
Raised blood sugar	1	5.3	
Rash	1	5.3	
Weight gain	1	5.3	
Unable to stop bleeding	1	5.3	

Percent was calculated using an absolute number of respondents, which was not included a number of missing data.

[a] Respondents reported more than one benefit, so these total more than 189

[b] Respondents reported more than one type of benefit, so these total more than 147

[c] abdominal pain, diarrhoea or vomiting

[d] dizziness, fainting, or fatigue

From the survey, the main benefits from HDS use were reported as alleviation of minor ailments (n=54, 37%), such as constipation (24%, n=13), musculoskeletal pain (18.5%, n=10) and flatulence (14.8%, n=8). Respondents reported using several different types of HDS for constipation, many of which contain fibre; for example, senna, turmeric, horse radish tree, Thai folk remedies 'Tri pala' and 'Ka sai', dietary supplements containing fibre and a mixed fruit drink. Of ten products used to alleviate musculoskeletal pain, five were Thai (n=4) or Chinese (n=1) folk remedies where the ingredients were unknown; others were Boesenbergia, a mixture of 23 botanical extracts, a mixed fruit drink, a calcium supplement, and a Chinese herbal combination - holy mushroom, Cordyceps, ginseng and Chinese Wolfberry. Amongst the eight HDS products used for flatulence, turmeric was the most frequently reported active ingredient (n=5).

The effect of their HDS use on the progression of their CKD was reported, with around 10% (n=15) of respondents reporting that their CKD progress had slowed. Of these four were using herbs with unknown ingredients (see Table 8.14). There were nine different HDS reported to provide this benefit: Holy mushrooms (n=3), a herbal combination – Boesenbergia, mint, ginger, galangal, lemongrass, kaffir lime leaves and shallots (n=1), a herbal combination - Boesenbergia, onion, galangal, lemongrass, kaffir lime leaves, lime leaves and mint (n=1), turmeric (n=1), Spring bitter cucumber (n=1), a Chinese folk remedy - Cordyceps, *Angelica sinensis*, Chinese Wolfberry, Astragalus (*Astragalus membranaceus*), *Eucommia ulmoides*, *Codonopsis pilosula* and deer antler velvet (n=1), Jujube, Roselle, Boesenbergia and mixed 3 types of mushrooms (n=1), spirulina (n=1) and mangosteen peel juice (n=1).

Ten percent of respondents (n=19) reported problems with HDS use, of which the progression of CKD was the most frequently reported adverse effect (37%, n=7), see Table 8.14. Types of HDS and patients' reports of their adverse effects

are shown in Tables 8.12 and 8.13. Kariyat, river spiderwort, a protein product, and wheatgrass were reported as being related to worsening CKD. However, eight adverse effects were reported, i.e. increased serum creatinine (n=3), leg oedema, stomach ache, vomiting, rash and dizziness, were all related to HDS with unknown ingredients.

8.2.7 Disclosure of HDS use to doctors

The survey presented the rate of non-disclosure of HDS use to their doctor and the reasons why HDS users did not inform them. Some respondents in the qualitative study provided reasons for the non-disclosure and disclosure of HDS use to their doctor.

Most respondents reported that they did not inform their doctor about HDS use (72%, n=145), and almost half reported that this was because their doctors did not ask them (49%, n=66), see Table 8.15. A number of the reasons given seemed to reflect respondents preferring not to discuss HDS use with their doctor (31%, n=42). They worried that their doctor would disapprove of HDS use, did not see a need to inform their doctor about HDS use, or did not want to tell their doctor. These reasons were supported by some participants in the qualitative research. One respondent did not want to tell their doctor about HDS use, although the doctor asked, as the patient was worried about a negative response from their doctor.

> *He [their doctor] doesn't ask and these herbs are vegetables.* (R16, f age 73)

> *Even though my doctor asks me about using herbs, I'm afraid of telling him... I'm afraid that he may blame me [for any deterioration in my condition]* (R8, m age 67)

There was a statistically significant difference in non-disclosure of HDS use between two settings ($\chi 2 = 14.37$, $p < 0.01$), see Table 8.16. There was a difference in health care service between the CU and SWU hospitals. In the CU kidney clinic, CKD patients were taken care of by members of a health care

team, i.e. doctors, pharmacists and dietitians, whilst the patients in the SWU hospital were mainly serviced by a doctor. The CU hospital (approximately 10 nephrologists) had a higher number of nephrologists than the SWU hospital (approximately 5). Respondents who attended the SWU hospital were less likely to disclose their HDS use, compared with those who attended the CU hospital. At the SWU hospital, 75 patients (55%) did not inform their doctor, compared with 61 patients (45%) at the CU hospital.

Table 8.15 Informed doctors about using HDS and reasons (n=189)

	Frequency	Percent	Missing data
Whether HDS users informed their doctor about their HDS use			-
Yes	53	28.0	
No	136	72.0	
Reasons for not reporting about HDS use to their health care providers (n= 136)*			1
Health care providers don't ask	66	48.9	
Patients worried that their doctor will disapprove of HDS use	22	16.3	
Short-term or occasional use	19	14.1	
No need to inform their practitioner	18	13.3	
Didn't see their doctor during the period of HDS use	8	5.9	
Just started using HDS and no opportunity	4	3.0	
Stopping or planning to stop using HDS	3	2.2	
Don't want to tell them	2	1.5	
HDS are safe	1	0.7	
Doesn't influence their disease (s)	1	0.7	

* Respondents reported more than one reason

Percent was calculated using an absolute number of respondents, which was not included a number of missing data.

Table 8.16 Association of disclosure of HDS use amongst both settings

	Don't inform (n=136)	Inform (n=53)	X^2 *p*-value
CU hospital	61 (44.8%)	40 (75.5%)	< 0.01*
SWU hospital	75 (55.2%)	13 (24.5%)	

* Statistically significant at $p < 0.05$

With respect to the reasons for the disclosure of HDS use to their doctor in the qualitative study, one respondent had had a positive experience with their doctor who had explained whether or not the HDS could be used and why. It appears that a respondent discloses their HDS use to their doctor when they are confident that their doctor would not disapprove of their use.

> *After that [using HDS] my doctor said "My creatinine level was reduced". I was glad and asked my doctor can I take these herbs? He said "They are fine" and told me "If you want to take any herbal and dietary supplements ..., you should tell me before taking them" ... I'll not take herbs that my doctor tells me "I should not take because they will worsen your kidney function"* (R6, f age 57)

8.2.8 Reasons for not using HDS

Amongst the non-HDS users (n=232), 87% reported that they were not planning to use HDS in next 12 months (n=202) and gave their reasons (see Table 8.17). It would seem that non-users' reasons reflected not only their positive attitudes towards conventional medicines (59%), but also their negative attitudes towards HDS (25%). The former attitudes were that respondents trusted their doctor (n=24) or trusted/needed to use conventional medicines (n=47), followed by their doctor's recommendation (n=43) and those CM users perceived that the benefits of conventional medicines were superior to HDS (n=5). The latter attitudes were that respondents worried about harm from HDS (n=29), doubts about benefits from using HDS (n=12), and that they had previously tried HDS but had not gained any benefit (n=6), or had suffered from harm (n=2). However, 27 (12%) respondents were not able to decide whether they will use HDS or not. Three respondents (1%) are planning to start using HDS because they either expect to gain benefits from HDS or can obtain HDS from their family.

Table 8.17 Reasons given for not planning to use HDS (n=202)[a]

Reasons	Frequency	Percent
• Patients trusted their doctor or trusted/needed to use conventional medicines	71	35.1
• Health care providers[b] advised that the patient should not use HDS	44	21.8
• Concerns about harm from HDS[c]	29	14.3
• Don't want to use HDS	16	7.9
• Doubt about benefits of HDS	12	5.9
• Taking a high number of conventional medicines	11	5.4
• Don't know enough information about HDS[d]	9	4.5
• Had renal insufficiency, so patients concerned about harm from HDS	7	3.5
• Previously tried and experienced no benefits from HDS	6	3.0
• Benefits of conventional medicines are superior to HDS	5	2.5
• Patient's relatives recommended that they should not use HDS	5	2.5
• HDS are expensive	4	2.0
• They perceived that they are well	3	1.5
• HDS are not available in their area	2	1.0
• Previously experienced a decrease in renal function or other adverse effect from HDS	2	1.0
• Had many chronic diseases, so patients concerned about harm from HDS	2	1.0
• A book about kidney diseases indicated that CKD patients should not use HDS	1	0.5
• A patient need not use HDS if (s)he adheres to medication and dietary recommendations for CKD patients	1	0.5

[a] Respondents reported more than one reason; [b] Doctors or Pharmacists

[c] Adverse effects of HDS, contaminated HDS, or HDS-conventional medicine interactions

[d] Indications, doses, benefits, or risks of HDS

8.3 Discussion

8.3.1 Key findings

The prevalence of HDS use amongst CKD patients in Thailand was 45% (95%CI 40%-50%). There is no clear pattern of HDS usage with only a medium level of adherence to conventional medicines and being a former alcohol consumer associated with HDS use. Herbal products used to treat illnesses were more frequently reported than dietary supplements, which were more frequently used for well-being. The majority of respondents did not disclose using HDS to their doctor; the most frequently reported reason being that their doctor did not ask them about their HDS use. Kariyat, turmeric, horse radish tree, vitamins and minerals were the most commonly reported HDS. Most respondents reported gaining benefit from HDS, whilst one-tenth reported adverse effects. From the survey and the qualitative study, the main reason why HDS were used by patients with CKD was an expectation of beneficial effects of HDS; an expectation which was influenced by respondents' social network and the media. Thus, they were willing to try HDS and when they did, if they perceived benefits, they would continue using them.

8.3.2 Comparison of the prevalence of HDS use between patients with CKD and the general population

After comparing demographics between the population in this survey and the Thai general population, there were no differences regarding sex, education levels, living in urban or rural areas, smoking and drinking status.[260] However, respondents in the present survey were older (mean $\pm$ SD 66 $\pm$ 13) than those in a study of the CKD patients in the Thai general population (mean $\pm$ SD 57 $\pm$ 15).[146] This may be because Ong-Ajyooth's study screened people aged 15 or over, whilst in practice younger people with asymptomatic CKD do not seek a

diagnosis within the Thai National Health System. The mean age in the present study, and in a survey of the prevalence of HDS use amongst patients with CKD in Canada, were similar (HDS users 64 ± 12; non-users 60 ± 15).[16] This may be because people who suffered from CKD will go to see a doctor when they have symptoms, and such patients are more likely to be older. Therefore, it would seem that there is no difference in age between these two countries. This indicates that the sample in the present study is likely to represent Thai patients with CKD.

The prevalence of HDS use amongst Thai patients with CKD was 45%. This supports Spanner and Duncan's survey (2005) in Canada (45%), which studied the prevalence of dietary supplement (DS) use, including botanical extracts in outpatients with CKD.[16] However, the researchers used a slightly different definition of HDS use, i.e. current daily intake. Although the prevalence in the current study cannot be directly compared with previous surveys of HDS use in Thailand, due to the different definitions of HDS use and the different populations, the obtained prevalence is consistent with a survey of HDS use in Thai patients with chronic diseases (45%).[27] The prevalence amongst patients with advanced CKD, in the present survey, was higher compared with a Thai general population survey (33%).[5] However, the prevalence of HDS use amongst patients with CKD (29%)[15] was lower than the general population (52 to 73%) in the US.[10,35]

8.3.3 Comparison of characteristics between HDS users and non-users

There were no differences in demographic characteristics between HDS users and non-users regarding age, sex, smoking status or education. This is consistent with Spanner and Duncan's survey (2005), although the two surveys have different ethnic distributions in the population.[16] There was no association

between the severity of CKD and HDS use. This differs from Spanner and Duncan's survey, which reported that patients at an early stage of CKD were more likely to use DS; however, the survey did not compare the severity of CKD between Canadian HDS users and non-users.

Although almost all HDS users combined HDS with their conventional medicines, there is a significant association between HDS use and adherence to conventional medication. Respondents having a medium level of adherence to conventional medication were less likely to use HDS, compared with those with poor adherence (OR 0.53, 95%CI 0.32-0.87). This result is consistent with Krousel-Wood et al. (2010)[17] and Gohar et al. (2008)[19] who conducted a study of patients with hypertension. The reason for this association, supported by the present qualitative study, was due to the fact that some HDS users had had experiences, or concerns, regarding adverse effects from using conventional medication, so they decreased their doses of conventional medications or stopped using them. Rifkin et al. found that side effects of CM were a barrier to adherence to CM in patients with CKD.[261] Additionally, the current qualitative study found that four HDS users, who had negative attitudes towards CM, had poor adherence to CM. However, the reasons why HDS users had poor adherence needs to be further investigated before firm conclusions can be made.

In contrast, there was no relationship between HDS use and high adherence to conventional medication in the current survey. The present qualitative study showed that HDS users who reported that they trusted their doctor, and did not have concerns about side effects of CM, had a moderate or high level of medication adherence. This is supported by a previous study, which also established the doctor-patient relationship as an important factor in adherence to conventional medicines.[262]

Former alcohol drinkers were less likely to use HDS. However, there is a lack of literature describing the association between HDS use and drinking in patients

with chronic diseases. This finding in the present survey contrasts with the US national surveys of complementary and alternative medicine (CAM) users amongst young adults in 2000, where it was found former drinkers were more likely to use CAM.[28] This could be due to the differing ages of the populations. Further studies are required to examine this association in patients with other chronic diseases, before firm conclusion can be made.

8.3.4 Patterns and medical purposes of HDS use in patients with CKD

The majority of the respondents in this current research reported using HDS daily and around one-fifth using them long-term. This may raise concerns about interactions between conventional medication and HDS. Well-being was a frequently reported reason for using HDS in patients with CKD, particularly DS use. This is consistent with Spanner and Duncan's survey[16]; however, they did not specify how many of their patients used DS for CKD. The present survey found that the treatment of their CKD was not a frequently reported reason for using HDS. This is similar to Yeh's (2006) research, which reported that the main purposes of herbal use in patients with cardiovascular diseases were musculoskeletal illnesses rather than their cardiovascular disease.[58]

8.3.5 Perception of benefits and side effects from using HDS

Most HDS users perceived that they gained benefit from using HDS, whilst 10% reported adverse effects. This is consistent with Spanner and Duncan's survey.[16] It would seem that HDS users are more interested in positive effects rather than negative effects.[57] Furthermore, HDS users who perceived benefits from using HDS were more likely to continue using them. Nine different HDS were reported to have improved kidney function, although there are limited clinical trials to demonstrate their efficacy. *Astragalus membranaceus* has been the only herb

which has been tested in clinical trials[263,264] and which can slow the progression of diabetic nephropathy and CKD. However, these trials involved small numbers of people and were not blinded. Ginger, onion, turmeric, cordyceps and *Codonopsis pilosula* have been trialled in animal models to test potential for slowing the progression of either diabetic nephropathy or CKD;[222,223,265-267] it was found that they had renoprotective effects via a decrease in lipid peroxidation (ginger and onion)[223,265], renal triglyceride accumulation (turmeric)[222], and inhibition of the proinflammatory cytokine TNF-α release (*Codonopsis pilosula*).[266] Although some herbs have been reported as suitable for CKD, supported by clinical trials or animal models, their main effect is in slowing the progression of diabetic nephropathy, which is only one cause of CKD. Therefore, their efficacy to treat CKD resulting from other causes, such as glomerulonephritis and hypertension, is unknown.

Most of the HDS, reported as being used to treat CKD, have no scientific evidence in either human or animal models to support their efficacy. Supplements include holy mushrooms, boesenbergia, spring bitter cucumber, jujube, roselle. Some respondents used roselle for treating CKD; however, this is a diuretic and there is no evidence of any effect on CKD.[225] Health care providers need to ensure they provide factual information for patients about the lack of evidence of benefits to their CKD, from using some HDS.

Regarding renal adverse effects reported by respondents, proteinuria, which indicates worsening kidney function, was reported as resulting from using protein supplements. A high protein intake is related to a decrease in renal function and this is likely to be why the protein supplements caused this adverse effect.[268] River spiderwort, kariyat and wheatgrass were reported by respondents to increase serum creatinine. To date, there is no evidence in the literature to support this reported effect. The Thai National List of Essential Medicines (2011) suggests that, for patients with CKD, senna, java tea, roselle, Ya Hom and Ka sai

are not recommended[119]; however, the present survey found some patients reported using them. Additionally, turmeric, ginger and lemongrass could potentially harm kidneys if the patients take them at high doses or long term. This is because they inhibit cyclooxygenase-2, which increases blood pressure in glomerulus and leads to kidney injury[269-272], although no patients reported this adverse effect in the current study. Both health care providers and patients with CKD should be aware of the benefits and risks of using HDS and report any adverse effects to the Health Product Vigilance Center in Thailand, in order to establish rigorous evidence. Further trials of the efficacy and safety of HDS are required.

8.3.6 Reasons for, and influences on HDS use

From both the survey and qualitative study, the most frequently cited reason for HDS use in Thai patients with CKD was family and friends' recommendations, followed by the desire to gain benefit from using HDS, a willingness to try HDS, safety of HDS and experiences of adverse effects from CM. Respondents' social network and the media were most frequently reported as an important influence on their HDS use.

Family and friends influencing patients' decision-making, regarding HDS use amongst Asian populations, is similar to other studies of CAM use in patients with chronic diseases in Thailand, Malaysia, Japan and Turkey.[14,50,51,54,57,61] This is also consistent with CAM use amongst the general population in South Korea.[45] Such behaviour could be a result of the close knit family culture in Asian countries. In Western countries, both patients with chronic illnesses and the general population used HDS, as their health care providers suggested it.[16,25,58] This may be why high numbers of HDS users with CKD in Western countries inform their health care providers about using HDS (55 to 67%).[15,16]

The second reason for using HDS was that HDS was perceived as supporting respondents' health care needs, such as avoiding dialysis treatment. Such usage is because they felt hopeless, used HDS as a last resort, and expected that HDS would solve their health concerns, as suggested in the qualitative study. This is consistent with the literature.[63,90,93,96] Using HDS as a last resort, and due to feelings of hopelessness, were more frequently reported in patients with chronic diseases than the general population.[87,96]

Wanting to try HDS was a frequently reported reason for using HDS, which has been reported in the current survey and other surveys of CAM use amongst patients with chronic illnesses, in both Asian and Western countries.[58,61,99] Studies have suggested that the personality trait of "having an open mind" is linked to patients being willing to try HDS.[61,99] Some respondents wanted to try HDS as they perceived that HDS was safe and they hoped to gain benefit as reported in the qualitative study. It should be emphasised that although patients want to try HDS, they would also monitor any HDS effects. If they perceived a benefit, they would continue using them; if not, they would stop using them. Moreover, such patients are more likely to actively search for information from several sources, such as the media and their social network, to decide whether or not to use HDS by themselves; a conclusion supported by data from the present qualitative study, and also supported by the literature.[97]

Both the current survey and qualitative study found that the perception of HDS safety was less likely to influence decision-making regarding HDS use, compared to the perception of their benefits amongst patients with CKD. This may be because respondents were concerned about adverse effects of HDS. This is consistent with the literature.[16,56,57,66,93,98] In the present qualitative study, patients with CKD, who were concerned about adverse effects of HDS, seemed to want to have consultations with their health care providers.

Both the survey and qualitative study found that some respondents experienced adverse effects from using CM, so this drove them to use HDS. This situation is similar to that cited in the literature, which explained that some patients were likely to use HDS, as they either had side effects from CM or wanted to decrease them.[61,66]

Both the survey and qualitative study reported that the media, such as television, radio, etc. was a second influence on decision-making regarding HDS use, after family and friends' recommendations. The qualitative study also showed that the media was likely to report benefits of HDS, rather than warn about their adverse effects, and that HDS companies used the media in order to advertise their products in terms of their benefits, rather than mentioning anything about their possible adverse effects. This is consistent with Bubela et al. (2008) who found that 90% of newspapers in Western countries reported the benefits of herbal medicine.[107] In addition, a systematic review showed that the mass media reported positive effects of CAM, rather than any of their negative effects.[108] This may explain why a large number of Thai respondents buy HDS products from HDS companies.

8.3.7 Reasons for non-users

Respondents who either trusted their doctor, or were advised by their doctor to avoid using HDS, were less likely to use HDS. It would seem that the doctor-patient relationship influences decision-making regarding non-HDS use amongst Thai patients with CKD. The remaining reasons for non-use were that non-users were sceptical about the benefit of HDS, as well as being concerned about their adverse effects. This is consistent with the reasons for non-use of herbal medicine or CAM, based on the literature: products are ineffective, patients worry about their side effects and there is a lack of information about them.[55,57,60]

8.3.8 The non-disclosure of HDS use to their doctor

Most HDS users in the present survey did not disclose HDS use to their doctor (72%). This contrasted with Western patients with CKD, where most informed their doctor about their HDS use (55 to 67%).[15,16] This high amount of non-disclosure found in the current survey has also been found in other Asian populations.[98,110,111] Most frequently reported reasons of non-disclosure were that their doctor did not enquire, concern that the doctor may disapprove of their HDS use or they felt the doctor did not need to know about HDS use. These findings are consistent with a previous systematic review of the disclosure of CAM use to health care providers.[273]

The qualitative study showed that although doctors asked patients about HDS use, one patient reported he did not want to tell his doctor about his HDS use because he worried about a negative response from that doctor. Another respondent, who had experienced such a response from his doctor in the past, refused to disclose HDS use to his doctor in the future. Therefore, it would seem that health care providers' communication is an important factor influencing whether patients would disclose their HDS use to those providers.[53,109] This is also supported by reasons for the disclosure of HDS use to a doctor; respondents were willing to inform their doctor about their use where they experienced a positive response from their doctor or were confident that their HDS use would not be disapproved of.

To compare reasons for non-disclosure of HDS use between SWU and CU hospitals, 53% (n=40) of respondents attending the SWU hospital reported a reason – 'their doctor did not ask' - more than respondents at the CU kidney clinic (43 %, n=26) (p-value < 0.01). This could be because the former hospital had a small number of kidney consultants, so their patients were less likely to be asked about HDS use than the latter; where a health care team service consisted

of a kidney consultant, a pharmacist and a dietician, therefore, giving more opportunities to be asked or discuss HDS use.

8.3.9 HDS availability in Thailand

Pharmacies were frequently reported as places selling HDS; a finding similar to Grabe and Garrison's study (2004) in the US, so pharmacists should be aware that CKD could be a contraindication for some HDS. It is important to note that direct sale companies were frequently reported as a place for selling HDS in Thailand. There are limited reports about such companies selling HDS in previous studies in other countries.[14,15] It would be a problem in HDS distribution in Thailand if those companies provided inaccurate information about benefits and risks of HDS. The Thai Health Body should closely monitor their advertising and enforce the medicine advertising law if companies violate that law.

8.4 Strengths and weaknesses

8.4.1 Strengths

This survey is the first survey of HDS use amongst Thai patients with advanced CKD and therefore provides, to some extent, fundamental knowledge about prevalence, patterns and reasons for HDS use. Both quantitative and qualitative methods provide more understanding of the reasons why these patients used HDS. There was the large sample size in the current survey (n=421), compared with former surveys amongst patients with CKD (n=100-250).[15,16] Advantages of the researcher-administered questionnaire were a high response rate (98%) and a low rate of missing data (less than 5%).

The sample in this survey represented an Asian population, so this finding can be generalised to such populations. This is due to the fact that Asian countries share their self-care behaviour, particularly that people are more likely to use herbal

medicines, and their attitudes to health management. Several findings in the current survey were similar to the literature in Asian countries. For example, friends and family members were the main influence on HDS use.[54,57,61] Also, the high amount of non-disclosure in the present survey was similar to the literature in other Asian populations.[98,110,111]

8.4.2 Weaknesses

The sample population in this survey was not randomly selected from patients with advanced CKD across Thailand, but was recruited at two hospitals for six months. This may mean that the sample is not representative of the general CKD patient population. However, demographic characteristics of the sample in this survey were similar to the Thai census in 2007 [260] and the literature.[16] Most patients with CKD in the two settings were likely to visit their doctor every 3 months, so this period seemed to be sufficient time to approach almost all of the target population.

Information about HDS use in this study relied on self-report so this approach may be subject to social desirability bias, such as patients not disclosing their HDS use as they felt it might be disapproved of.

The use of three people to collect data may have led to differences in the way questions were asked; however, the assistant researchers were trained by the main researcher (MT) who observed the collection of their first data to ensure consistency.

A cross-sectional study cannot determine the incidence of HDS use, compared with a cohort study.

8.5 Conclusions and implications

The prevalence of HDS use in Thai patients with CKD was 45% (95%CI 40%-50%), which is greater than the general population. This is similar to Western populations. Although there was no clear pattern of associations between HDS use and conventional medication adherence, respondents with poor adherence were more likely to use HDS. This may be because they had experiences of adverse effects from using CM. The most frequently reported reason for using HDS was to maintain well-being rather than treatment of CKD. However, most HDS reported as being used for CKD, other than *Astragalus membranaceus*, have no scientific evidence to support their efficacy from clinical trials. Furthermore, river spiderwort, kariyat and wheatgrass were reported to increase serum creatinine, but there is no literature to indicate their adverse effects. Therefore, further studies are needed to investigate both efficacy and adverse effects of HDS on renal function.

In Thailand, the patient's social network and the media seem to influence their decision making regarding HDS use, rather than HDS practitioners or health care providers. Most reasons for HDS use in patients with CKD were based on hoping to gain benefits from using HDS, and did not involve concern about HDS safety. Although the patients were willing to try HDS, they were likely to evaluate their benefits. If they did not gain any benefit, they would stop using them.

The doctor-patient relationship appears to be a crucial factor related to non-use of HDS. Frequently reported reasons of the non-disclosure about HDS use were that their doctor did not ask about HDS use, or that HDS users were concerned about a negative response from their doctor. Additionally, pharmacies were involved in HDS distribution. Thus, health care providers should acknowledge the high prevalence of HDS use in patients with CKD, and therefore should always

ask them about HDS use, recommend and discuss whether they should use HDS, or not, when the patients go to see a doctor or buy HDS at pharmacies.

9. The association of HDS, the progression of CKD and its complications

The primary and secondary objectives of this study were to determine any associations between HDS use and the fast progression of CKD, and any associations between HDS use and CKD's complications, i.e. uncontrolled hyperkalemia and hyperphosphatemia. Another objective was to determine patterns of any other risk factors influencing CKD progression.

9.1 Method

9.1.1 Choice of method

A prospective, cohort study was designed in order to determine any associations between exposure to HDS and the primary outcome of this study, i.e. the fast progression of CKD measured by a decline in estimated glomerular filtration rate (eGFR) over 12 months. The measurement of this outcome requires at least 3 months.[145] The present study was designed to follow this outcome over 12 months, as the longer the follow-up period in which eGFR is measured, the more valid the data.[11] The length of follow-up was limited by the scope of this 3-year PhD programme. There are advantages of this method, compared with a case-control study; data about exposure is collected before the measurement of outcome and therefore is less likely to be subject to recall bias, compared with a case-control study.[274] However, the cohort study is costly, time-consuming and has a high rate of loss to follow-up, as participants need to be followed up over long time periods.

The target population in this cohort study was defined as Thai outpatients with stages 3 to 5 CKD. This study recruited from entire samples in the selected settings, at baseline, as these settings might not have been able to provide a

sufficient number of the target population, based on sample size determination, if samples were randomly selected.

9.1.2 Study design

The prospective cohort study was conducted from January 2012 to July 2013. In the recruitment process, 421 Thai adult outpatients with CKD, at kidney clinics in two teaching hospitals, were approached and consented to be research participants, see Chapter 8. However, it was found that three patients had received dialysis prior to the recruitment, and 12 patients had stage 2 CKD (approximately eGFR of 60-65 ml/min/1.73m^2) at baseline. These patients (n=15) did not meet the inclusion criteria; therefore, 406 patients were enrolled for this one-year follow-up study, see Flowchart 9.1.

9.1.3 Definition of variables and outcomes

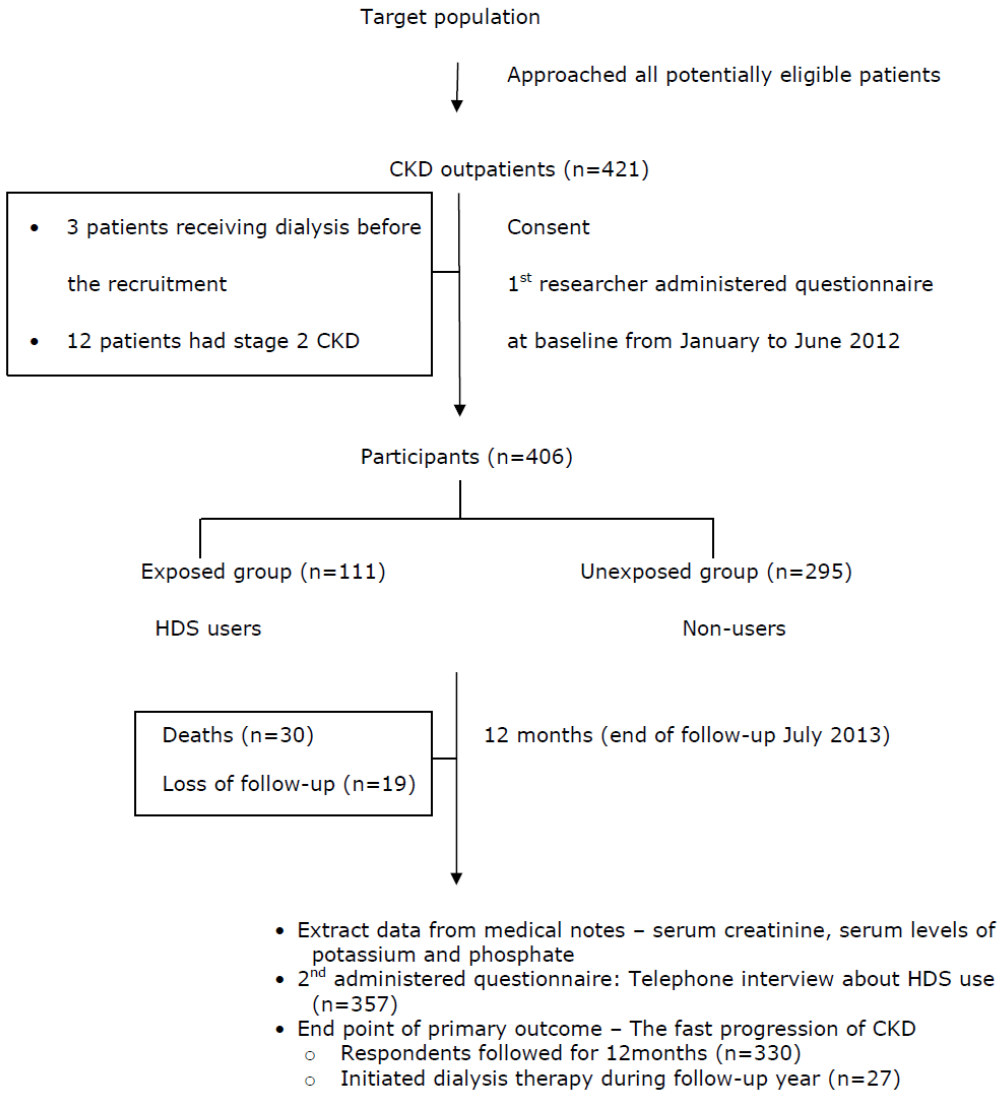
Exposure and non-exposure to HDS

The index date was defined as the day that the survey took place. The exposed group was defined as current, regular herbal users and/or dietary supplement users, i.e. patients taking herbs and/or dietary supplements at least three times a week in the last month before the index date. There was no literature defining how the frequency of exposure is linked to a decline in kidney function, so this definition was adapted from literature on conventional medication-induced nephropathy, where non-steroidal anti-inflammatory drugs lead to end-stage renal disease.[275,276] The exposed group included the use of all types of HDS, rather than specific ones, due to the limited number of patients in the exposed group and the limited evidence regarding which Thai herbal medicines may affect kidney function.

The unexposed group was defined as those who had never taken herbs and/or dietary supplements (non-users of herbal and dietary supplements), or who had

stopped using them before the month prior to the index date (former users of herbal and dietary supplements), or who had taken them less than three times per week in the previous month prior to the index date (occasional or rare users of herbal and dietary supplements).

Flowchart 9.1 Schematic diagram of the cohort study



The primary outcome

The primary outcome of this study, the dependent variable, was classified as 'fast progression of CKD'. Fast progression of CKD was defined as either a decline in eGFR of at least 5 ml/min/1.73m^2/year[11,145] or initiated renal replacement therapy during the follow-up period. Dichotomous variables of the dependent variable were 'yes' meaning patients having the fast progression of CKD and 'no'. This definition differed from the first definition in sample size determination, see Chapter 6, because the initiation of renal replacement therapy during the follow-up is likely to be due to the fast progression of CKD.

There are various definitions of 'fast progression' in clinical practice and literature[11,158,161,184], which related to, and were based upon, -3, -4 or -5 ml/min/1.73 m^2/year. To test the robustness of the results, sensitivity analyses regarding various cut-off points of a decline in eGFR over a year were performed.

An eGFR level was calculated from serum creatinine using the Thai Modification of Diet in Renal Disease (MDRD) equation, including the Thai coefficient, which is 1.129.[183] This equation was 375.5 X serum creatinine$^{(-0.848)}$ X Age$^{(-0.364)}$ X 0.712 (if female). This equation estimated eGFR has been recommended by the National Kidney Disease Education Program in the US, the NICE guideline for CKD in the UK and the Thai guidelines for CKD.[12,145,181] The level of serum creatinine related to acute kidney injury, as reported by a doctor, was excluded as the MDRD equation precisely estimates GFR under stable kidney function. This equation should be used with caution when patients are aged over 70, due to underestimate GFR.

Measurement of serum creatinine in the current study was part of the normal care of CKD patients, and was analysed by the hospital laboratory service as usual. The testing was therefore subject to the normal quality standards in the hospitals and can be considered valid measures of the outcome.

A rate of decline in eGFR over 12 months, for an individual, was estimated using a slope of a best fit linear regression line, which was plotted on a graph, i.e. eGFR levels and time, for each respondent as recommended by the KDOQI guideline (2002).[158] At least three measures of eGFR over a year, for each respondent, were plotted in order to minimise imprecise rates of decline in eGFR.[145,158]

The secondary outcomes

Uncontrolled hyperkalemia and hyperphosphatemia were the secondary outcomes in this study. These outcomes were chosen as some HDS contains potassium or phosphate, which may cause such complications. Uncontrolled hyperkalemia was defined as patients having more than 5.0 mEq/L (mmol/l) of mean level of serum potassium over a year.[277] A cut-off point of uncontrolled hyperphosphatemia is shown in Table 9.1.[186] A mean of this level over a year, which was more than such values in this table, was defined as uncontrolled hyperphosphatemia.

Table 9.1 Definition of uncontrolled hyperphosphatemia

Stages of CKD	Serum levels of phosphate
3-4	> 4.6 mg/dL (0.87-1.49 mmol/L)
5	> 5.5 mg/dL (1.13-1.78 mmol/L)

Variables known to influence the progression of CKD and the secondary outcomes

Known risk factors for the progression of CKD are: being male, obesity, smoking, existing proteinuria, uncontrolled blood pressure, hypertension, diabetes, hyperlipidaemia, high protein consumption, and taking nephrotoxic agents, such as nonsteroidal anti-inflammatory drugs (NSAIDs), cyclo-oxygenase-2 inhibitors (COX-2 inhibitors), and aspirin.[157,158,167] Factors related to uncontrolled hyperkalemia and hyperphosphatemia are: high potassium and phosphate

intake, or received treatment of hyperkalemia and hyperphosphatemia, together with their associated medication-induced complications, such as angiotensin-converting enzyme inhibitors (ACEIs) and/or angiotensin II receptor antagonists (ARBs) related to hyperkalemia.[278] These variables are defined below.

Age was defined as aged 60 years and over. This cut-off point influences a susceptibility to CKD, because people aged 60 years and older have a decrease in renal function compared to those aged less than 60 years.[279]

Obesity at baseline was defined in the Thai population as 27 kg/m^2 of body mass index (BMI), or over, in men and 25 kg/m^2 of BMI, or over, in women[280] in the last 3 months before the index date. This definition differs from the cut-off values for obesity in Caucasian populations, which is defined as 30 kg/m^2 or more.[281] This is because the Thai population has a different body fat distribution compared with Western populations.

Smoking status at baseline was classified as current, former or non-smokers. Current smoking was defined as a person who had smoked in the last 5 years before the index date; meanwhile former smoking was defined as a person who had quit more than 5 years before the index date.[282] A non-smoker was a person who had never smoked. These criteria were chosen because Yacoub's study defined current smoking as above and found it associated with CKD.[282]

Existing proteinuria at baseline was defined based on the Thai guideline for CKD management in 2009 and the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI^{TM}) in 2002 and 2007 as follows.[12,187,283] A person who has one of these criteria is defined as having proteinuria.

1. 24-hour urinary protein excretion rate over 300 mg/ 24 hour in the last 3-6 months before the index date.[12]
2. A protein and creatinine ratio (PCR) more than 500 mg/g creatinine in the last 3-6 months before the index date.[12]

3. An albumin and creatinine ratio (ACR) more than 300 mg/g.[12,187]
4. At least 2+ urine dipstick protein measurements for diabetic patients in the last 3-6 months before the index date or at least 1+ of urine dipstick protein measurement for non-diabetic patients in the last 3-6 months before the index date.[12,283]

The Thai guideline for CKD management has recommended testing proteinuria every 6 months for patients with stage 3 CKD and every 3 months for patients with stages 4 to 5 CKD.[12] The measurement of proteinuria using a dipstick test, recommended by the NKF-KDOQI™ in 2002 and the Thai guideline for CKD management in 2009, differs from the NICE guideline for CKD in 2008 which preferred using the albumin-to-creatinine ratio (ACR).[145] This is because the Thai guideline was established based on medical facilities in Thailand, evidence of cost-effectiveness and clinical outcomes.

Uncontrolled blood pressure at baseline was defined as patients having blood pressure of more than 130/80 mmHg in the last 3 months before the index date.[12,284] Hypertension was defined as either hypertension diagnosed by a doctor or receiving antihypertensive agents.

Dyslipidaemia or diabetes was defined as patients who have been diagnosed with dyslipidaemia or diabetes. Uncontrolled low-density lipoprotein (LDL) cholesterol was defined as more than 100 mg/dl (2.59 mmol/l) of a LDL cholesterol level, which related to the progression of CKD. Likewise, more than 7% of glycated haemoglobin (A1C) is associated with CKD progression.[11] A level of A1C and LDL cholesterol at baseline were defined as such levels measured in the last 3 - 6 months before the index date because these levels are measured every 6 months, as recommended by the Thai guideline for CKD (2009).[12]

Moderate to high protein consumption at baseline was defined as patients taking a moderate to high protein diet, as measured in the last 14 days before the

index date, by using the Restriction of Protein, Potassium, Phosphate and Salt diet questionnaire in pre-dialysis patients (RPPPS). This approach yielded a measurement of moderate to high potassium and phosphate consumption at baseline, which were factors related to the secondary outcomes.

Exposure and non-exposure to nephrotoxic agents at baseline, i.e. NSAIDs, COX-2 inhibitors or aspirin, was defined as follows. The exposed group was defined as a person taking them in the last month before the index date (current users)[276]; whilst the unexposed group were defined as those taking 20 tablets or less during their lifetime (non-users), or those who stopped taking them for at least a month before the index date (former users).[285,286]

The use of loop diuretics, ACEIs or ARBs at baseline, was defined as a person who had been prescribed such medicines in the last 3 months before the index date. These medications are likely to be prescribed for patients with CKD and may induce hypokalemia or hyperkalemia. Receiving treatment for hyperkalemia at baseline was defined as those who had received prescribed sodium or calcium polystyrene sulfonate in the last 3 months before the index date. Receiving treatment for hyperphosphatemia, at baseline, was defined as those who had received prescribed phosphate binders in the last 3 months before the index date.

9.1.4 Data collection

At baseline, risk factors related to the outcomes and the outcome data were collected by surveying and extracting data from medical notes using the researcher-administered questionnaire and data extraction sheet, see Appendices 5 and 6. Independent variables, including the exposure, tested for a relationship with the progression of CKD and its complications are: age, sex, obesity, smoking status, history of diabetes, and hypertension, existing proteinuria, NSAIDs, COX-2 inhibitors, and aspirin, blood pressure, A1C, and LDL

cholesterol levels, degree of protein, potassium, and phosphate intake, use of loop diuretics, ACEIs, or ARBs, and treatment of hyperkalemia, and hyperphosphatemia. The outcomes of this study, i.e. eGFR levels, serum levels of potassium and phosphate, were extracted from medical notes.

In the follow-up period, data of the outcomes were extracted from medical notes over a year using a structured questionnaire, see Appendix 7. All respondents were interviewed over the telephone regarding their HDS use in the twelfth month of their involvement, using a questionnaire, see Appendix 7. This information was to support the results of any associations between HDS use and the progression of CKD. Telephone interviews were used, as they were more convenient, cheaper and took less time than face-to-face interviews. Telephone interviews are suitable for short questions on non-sensitive subjects.[287] In this case, the respondents had already taken part in the baseline data collection and had completed a shortened version of the questionnaire, which asked about their HDS use since the baseline survey. The respondents had supplied their telephone numbers for the purpose of further contact.

Data was coded and entered into IBM SPSS software version 19.0. To validate this process, frequencies of categorical variables were performed and checked in order to identify inaccurate codes. A total of 5 errors were found in 16,422 variables (46 variables and 357 respondents) and these errors were rectified. Numerical variables were checked according to their range. Some numbers fell outside the expected range, which were checked against the original records, and no errors were found. Ten percent of the questionnaires (n = 33) were randomly selected using Microsoft Excel software and these questionnaires were checked against the database in the IBM SPSS software version 19.0. This database had 100 variables per respondent. A total of 17 errors were found in 35,700 variables (0.05%). These errors were rectified.

Regarding consistency checks, variables related to other variables were checked for their consistency. For instance, body mass index and obesity. Sixteen errors (0.12%) were found in 12,852 variables (36 variables and 357 respondents) and were rectified.

9.1.5 Statistical analyses

Descriptive analyses were performed and presented as frequencies and percentages. Potential confounding factors related to the exposure or the primary outcome – the fast progression of CKD based on literature, step one: univariate analyses between the exposure and the potential confounding factors at baseline were tested using Chi-squared tests in order to ascertain any associations between the exposure and the potential confounding factors. These factors at baseline were age, sex, smoking status, obesity, proteinuria, degree of protein intake, hypertension, diabetes, dyslipidaemia, severity of CKD, controlled blood pressure, A1C, LDL cholesterol, use of NSAIDs, aspirin or COX-2 inhibitors, and the level of adherence to prescribed conventional medication.

Step two, univariate analyses between the exposure at baseline, including the potential confounding factors and the dependent variable – the fast progression of CKD at the end point were performed using Chi-squared tests and calculating unadjusted odds ratios. Tests were 2-tailed and a p-value < 0.05 was considered statistically significant. This step aimed to identify the potential confounding factors related to the dependent variable.

The final step, that of multiple logistic regression analysis, was included the exposure and the statistically significant confounding factors from the step one and two in order to select the potential confounding factors. This step is presented as adjusted odds ratio of the exposure after controlling each potential confounding factor from step one and two. If a difference between the unadjusted odds ratio of the exposure associated with the outcome from step

two and the adjusted odds ratio from multiple logistic regression analysis is at least 10%, this means that such factors are likely to be confounding factors in the association between the exposure and the outcome. As a result, that factor was included in building the model of association between the exposure and the outcome in order to control the confounding factor.[288]

If the dataset, a decline in eGFR over 12 months, had normal distribution, a comparison of mean decline in eGFR amongst variables using a t-test was performed in respondents who had not received dialysis during the follow-up period. Those with initiated renal replacement therapy could not be tested on this outcome as their eGFR did not represent their kidney function.

The secondary outcomes, i.e. uncontrolled hyperkalemia and hyperphosphatemia, were analysed only amongst respondents who did not initiate dialysis therapy as this therapy increases excretion of potassium and phosphate from the body. Univariate analyses tested any associations between the exposure and dichotomous dependent variables – controlled and uncontrolled hyperkalemia and hyperphosphatemia - using Chi-squared tests. Potential confounding factors related to these dependent variables were tested using Chi-squared tests and unadjusted odds ratios. Factors related to worsening hyperkalemia, based on the literature, were moderate to high potassium intake, treatment of hyperkalemia, use of loop diuretics and use of ACEIs or ARBs. Factors related to worsening hyperphosphatemia, based on literature, were moderate to high phosphate intake and treatment of hyperphosphatemia.

Multiple logistic regression analyses of association between the exposure and the secondary outcomes included the exposure and all potential confounding factors, based on the literature as above, in order to explore effects of each factor. The unadjusted and adjusted odds ratios of the exposure related to the outcomes were compared. If they have a difference of at least 10%, this means that such

factors are confounding factors of the associations between the exposure and the outcomes.

Multiple sensitivity analyses were performed in order to test the robustness of the association between HDS and the primary outcome. Firstly, four cut-off points of a decline in eGFR over a year, defined as 'fast progression of CKD' were classified based on literature and the nature of the dataset in this study, which were mean plus a quarter of the standard deviation (SD), mean plus a half of the SD, and mean plus the SD. Univariate analyses between variables and these cut-off points were performed by Chi-squared tests and were compared. Secondly, different causes of CKD influenced the various rates of a decline in eGFR over a year.[158] For example CKD resulting from glomerular diseases, HIV, cirrhosis and cancer had a different rate of a decline in eGFR over a year, compared with CKD caused by diabetes and hypertension. This may affect the primary outcome – the fast progression of CKD. Associations of the fast progression of CKD with the exposure between all respondents and those who did not have glomerular diseases, HIV, cirrhosis and cancer were analysed using Chi-squared tests and compared.

Finally, both exposed and unexposed groups may have changed their HDS use during the follow-up period, so whether there was consistent exposure or non-exposure to HDS over a year needed to be explored, together with their association with the primary outcome, compared with both groups at baseline. The telephone interview in the twelfth month collected data about the use of HDS during the follow-up, and information was then classified into consistent exposure and non-exposure to HDS. Consistent exposure was defined as respondents exposed to HDS at least three times a week at baseline and over 12 months. Consistent non-exposure was defined as the non-users, former HDS users or the occasional users of HDS at baseline and over 12 months.

Associations of the fast progression of CKD between the consistent exposure and non-exposure were performed using Chi-squared tests and compared.

9.2 Results

9.2.1 Demographic characteristics

Four hundred and six patients were enrolled in this one-year follow-up study. Forty-nine patients (12%) left the study: 30 (7.4%) due to deaths; 16 (3.9%) loss to follow-up and 3 (0.7%) being referred to another hospital. Reasons for death were unknown. Three-hundred and fifty-seven patients were followed-up over 12 months and 27 patients (8%) started to receive dialysis during the follow-up period. Respondents had a mean age of 66 years with a standard deviation (SD) of 13, and 55% were women, see Table 9.2. Mean BMI and mean eGFR at baseline were 25.0 $\pm$ 4.9 kg/m^2 and 39 $\pm$ 12 ml/min/1.73 m^2. Thirty-two respondents aged over 70 years (8%) had eGFR at baseline of 50 – 59 ml/min/1.73m^2, which may be underestimated due to a limitation of the MDRD equation. At least 60% had diabetes and hypertension. Seventeen percent (n=62) had glomerular disease. A small number of the patients had polycystic kidney disease (n=7, 1.9%), cirrhosis (n=7, 1.9%) or human immunodeficiency virus (HIV) infection (n=4, 1.1%).

Table 9.2 Characteristics of respondents at baseline (n=357)

Characteristics	Frequency	Percent	Missing data
Age			-
≤ 60	114	31.9	
> 60	243	68.1	
Male	162	45.4	-
Smoking			-
Never smoked	233	65.3	
Former smoker	106	29.7	
Current smoker	18	5.0	
Alcohol consumption			1 (0.3%)
Never	207	58.1	
Former drinker	130	36.5	
Current drinker	19	5.3	
Obesity[a]	139	40.6	15 (4.2%)
Stage of CKD[b]			-
3 a (eGFR = 45-59)	125	35.0	
3 b (eGFR = 30-44)	138	38.7	
4 (eGFR = 15-29)	85	23.8	
5 (eGFR < 15)	9	2.5	
Comorbidities			-
Hypertension	333	93.3	
Dyslipidaemia	313	87.7	
Diabetes	213	59.7	
Heart disease	100	28.0	
Cancer	31	8.7	
Existing proteinuria	163	52.1	44[c] (12.3%)
Degree of protein intake[d]			-
Low	203	56.9	
Medium	129	36.1	
High	25	7.0	

Percent was calculated using an absolute number of respondents, which was not included a number of missing data.

[a] Obesity was defined in the Thai population as 27 kg/m2 of body mass index (BMI) or over in men and 25 kg/m2 of BMI or over in women.[280]

[b] Stage of CKD was defined based on the KDIGO guideline 2012[11] and the NICE guideline for CKD 2008.[145]

[c] Respondents were not measured.

[d] Protein intake was assessed using the Restriction of Protein, Potassium, Phosphate and Salt diet questionnaire

At baseline, patients were taking an average of 8 ± 3 prescribed, conventional medications (range 2-20). At least half of the patients received both anti-diabetic medications and lipid-lowering drugs, whilst at least a quarter took ACEIs and/or

ARBs, which can slow the progression of CKD, particularly in diabetic nephropathy and kidney diseases with proteinuria, see Table 9.3. Regarding the use of nephrotoxic agents, a small number of patients took NSAIDs (6%) or COX-2 inhibitors (3%). Only one patient regularly and currently took NSAIDs (0.3%), whilst 6% reported intermittent use. Forty percent received aspirin for cardiovascular diseases and most of them took aspirin 81 mg daily (89%), which is available in Thailand.

There were three patterns of HDS use in the present study. Firstly, respondents who have always taken HDS; this study shows 17% of all patients (n=62) continued to regularly take HDS during the follow-up. Secondly, 50% (n=177) did not take them at all. Finally, some respondents took HDS on and off. Twenty-nine percent of respondents currently and regularly took HDS at baseline, which was the exposed group (n=102). Of this group, 26 patients (25%) stopped using supplements during the follow-up period. Amongst the unexposed group (n=255), 10 patients (4%) started using HDS regularly during the follow-up period.

Table 9.3 HDS and medication use at baseline (n=357)

The use	Frequency	Percent
HDS use		
Non-use	191	53.5
Current and regular use	102	28.6
Current and occasional use	34	9.5
Former use	30	8.4
The use of NSAIDs		
Non-use	298	83.5
Current use	21	5.9
Former use	38	10.6
The use of COX-2 inhibitors		
Non-use	330	92.4
Current use	11	3.1
Former use	16	4.5
Aspirin use		
Non-use	207	58.0
Current use	141	39.5
Former use	9	2.5
Prescribed medication adherence*		
Low	89	24.9
Medium	172	48.2
High	96	26.9
Use of prescribed medications related to CKD management and its complications		
ACEIs	86	24.1
ARBs	125	35.0
Lipid-lowering drugs	278	77.9
Anti-diabetic medications	175	49.0
Erythropoietin	73	20.4
Iron supplement	114	31.9
Folic acid	159	44.5
Vitamin B 1-6-12	66	18.5
Loop diuretics	97	27.2
Kayexalate or calcium polystyrene sulfonate	70	19.6
Phosphate binders	112	31.4
Sodamint	86	24.1
Hypouricemic agents	113	31.7

* Medication adherence was measured using the Thai version of the 8-Item Morisky Medication Adherence Scale® [227,228]

Amongst the 330 respondents who were not initiated into dialysis therapy during the follow-up period, the median number of eGFR measurement over a year was 5 times (range 3-12) and the median follow-up period was 12 months (range 9-16). Mean decline in eGFR and SD was 2.09±7.58 ml/min/1.73m^2/year, see Figure 9.1. The distribution of change in eGFR over 12 months was not normal as tested by Kolmogorov-Smirnov analysis (*p*-value < 0.01), so comparison of mean change in eGFR over one year, between the exposed and unexposed groups, was not performed. Median change in eGFR over one year, between the exposed and unexposed groups, was -2.32 and -1.86 ml/min/1.73 m^2/year, respectively. There was no difference in these median between two groups (*p*-value = 0.72) tested by Mann Whitney *U* test.

Figure 9.1 The distribution of change in eGFR over a year (n=330)

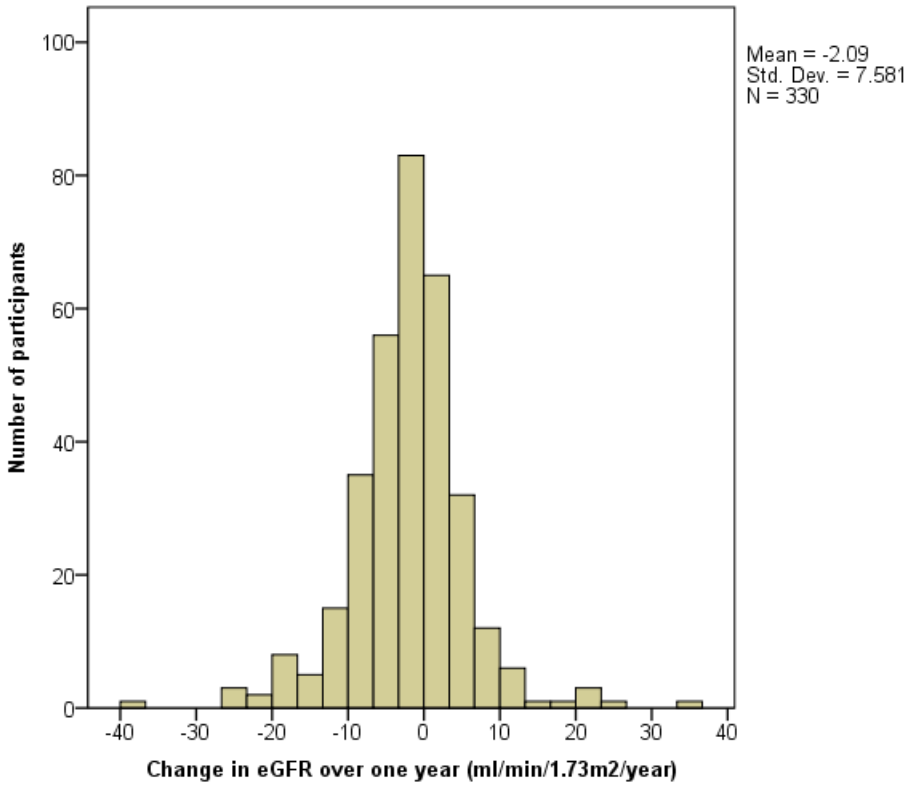


Table 9.4 Distribution of changes in rates of eGFR over a year (n=330)

Changes in rates of eGFR over a year (ml/min/1.73m^2/year)	Frequency	Percent
> -10	31	9.4
-6 to -10	59	17.9
-1 to -5	107	32.4
0	28	8.5
1 to 5	73	22.1
6 to 10	20	6.1
> 10	12	3.6

Table 9.5 Laboratory results at baseline (n=357)

Laboratory results at baseline	Frequency	Percent	Non-measurement
Controlled blood pressure (BP $\leq$ 130/80)	114	32.2	3* (0.9%)
A1C**			142 (39.8%)
$\leq$ 7%	117	54.4	
> 7%	98	45.6	
LDL cholesterol**			43 (12.0%)
< 100 mg/dl	155	49.4	
$\geq$ 100 mg/dl	159	44.5	
Hyperkalemia	61	17.7	12 (3.4%)
Hyperphosphatemia	18	7.0	100 (28.0%)

Percent was calculated using an absolute number of respondents, which was not included a number of missing data.

* missing data

** The cut-off point based on KDIGO guideline 2012[11]

Less than half of the patients achieved their target of blood pressure and low-density lipoprotein (LDL) cholesterol at baseline, see Table 9.5. Less than 20% had hyperkalemia or hyperphosphatemia at baseline. There was a high number of the non-measurement of serum levels of phosphate at baseline (28%): 60 (18%) respondents had the non- measurement of such electrolytes over one year. The total number of respondents regarding such measurement over one year was 330, as dialysis influences excretion of potassium and phosphate. As a result, patients receiving dialysis had invalid serum levels of potassium and phosphate and these patients were not included in the analyses of the secondary

outcomes of this study, uncontrolled hyperkalemia and hyperphosphatemia. Comparing between the exposure and the non-measurement of serum levels of potassium and phosphate tested by Chi-squared tests is shown in Tables 9.6 and 9.7.

Table 9.6 Comparison between the exposure and the non-measurement of serum levels of potassium

Exposure to HDS	The non-measurement of serum levels of potassium at baseline (n=357)		X^2 value	*p*-value
	Yes	No		
Yes	8 (66.7%)	94 (27.2%)	8.83	< 0.01*
No	4 (33.3%)	251 (72.8%)		
	The non-measurement of serum levels of potassium over one year (n=330)			
	Yes	No		
Yes	1 (50.0%)	97 (29.6%)	0.40	0.53
No	1 (50.0%)	231 (70.4%)		

* Statistical significance at *p*-value < 0.05

The exposed group had a higher number of the non-measurement of serum potassium levels at baseline (67%) than the unexposed group (33%) (*p*-value < 0.01); however, there was no difference in such data over one year, see Table 9.6.

Table 9.7 Comparison between the exposure and the non-measurement of serum levels of phosphate

Exposure to HDS	The non-measurement of serum levels of phosphate at baseline (n=357)		X^2 value	*p*-value
	Yes	No		
Yes	30 (30%)	72 (28%)	0.14	0.71
No	70 (70%)	185 (72%)		
	The non-measurement of serum levels of phosphate over one year (n=330)			
	Yes	No		
Yes	18 (30%)	80 (29.6%)	0.003	0.96
No	42 (70.0%)	190 (70.4%)		

There was no difference in the non-measurement of serum phosphate levels between the exposed and unexposed groups at baseline and over one year, see Table 9.7.

There were 65 different types of HDS amongst the exposed group, see Tables 9.8 and 9.9. Ten respondents in the exposed group (10%) did not remember or know the ingredients of their HDS. The three most frequently used HDS were turmeric, a mixture of botanical extracts, and horse radish tree. Regarding the dosage regimen of HDS, senna was used in the recommended dose for a general population, as well as the two Thai folk remedies: 'Ka sai' and 'Ya hom'. One patient used a high dose vitamin C and others used 250-500 mg/day of vitamin C.

Table 9.8 Types of herbal medicine used in the exposed group (n=102)

Name of HDS	Frequency
Turmeric (*Curcuma longa*)	12
A mixture of botanical extracts*	9
Horse radish tree (*Moringa oleifera*)	8
Ginseng or coffee contained ginseng	6
Boesenbergia (*Boesenbergia rotunda*)	5
Different types of mushrooms, such as holy or shiitake mushrooms	4
Garlic	4
River spiderwort (*Tradescantia fluminensis*)	4
Mixed Thai traditional herbs called 'Ka sai'	3
Tea for diuretic effects, such as java tea, babbler's bill leaves	3
Tinospora crispa	3
Aloe vera	2
Bamboo grass (*Tiliacora triandra*)	2
A mixture of Jujube and roselle	2
Mixed Thai traditional herbs called 'Ya hom'	2
A mixture of Boesenbergia, ocimum and honey	1
Cinnamon	1
Veld grape (*Cissus quadrangularis*)	1
Clerodendrum petasites	1
Echinochloa spp.	1
Gynura procumbens	1
Kaffir lime	1
Lemongrass	1
Blue plea (*Clitoria ternatea*)	1
Malva nut (*Scaphium scaphigerum*)	1
A mixture of bamboo grass, blue plea and pandanus palm	1
Mixed Thai traditional herbs called 'Ya khom'	1
Spirulina	1
Senna	1
Gac fruit (*Momordica cochinchinensis*)	1
Chinese folk remedy - Cordyceps, *Angelica sinesis*, deer antler velvet, five flavour berry (*Schisandra chinensis*) and cinnamon	1
Chinese folk remedy - Holy mushroom, cordyceps, ginseng, goji berry	1
Helicteres isora	1
Kariyat (*Andrographis paniculata*)	1
Lotus seed	1
Ivy gourd (*Coccinia grandis*)	1
A mixture of boesenbergia, mint, galanga, onion, lemongrass, kaffir lime leaves and lime leaves	1
Lemongrass, kaffir lime leaves, mango, yardlong bean, carrot, wildbetal leafbush (*Piper sarmentosum*) and pomelo	1
Thai folk remedy called 'Tri pala' – *Phyllanthus emblica*, *Terminalia belerica* and *Terminalia chebula*	1

* some products contained cereal

Table 9.9 Types of dietary supplement used in the exposed group (n=102)

Name of dietary supplements	Frequency	Name of dietary supplements	Frequency
Fish oil	7	Calcium supplement	2
Protein supplement	7	Vitamin B	2
Germ oil	6	Beta - glucan	1
Essence of chicken drink	5	Bee pollen	1
Rice bran oil	5	Chlorophyll	1
Vitamin C	5	Cod liver oil	1
Gingko	4	Chondroitin	1
Multiple vitamin	3	CoQ10	1
Swiftlet's nest drink	3	Glucosamine	1
Vitamin E	3	Omega-3	1
Wheatgrass	3	Lecithin	1
Virgin cold pressed coconut oil	2	Zinc	1
A product contained vitamins, minerals and botanical extracts	3	A product contained vitamins, minerals and cereal	1

To compare the demographics between the included group and the group of drop-out, including deaths, the group of drop-out controlled their blood pressure better than the included group (p-value < 0.05), see Table 9.10. Any differences of other factors, in either group, were not found.

Table 9.10 Similarities and differences of demographics at baseline between the included group and the group of drop-out (n=406)

Variables	The included group (n=357)	The group of drop-out (n=49)	X^2 value	*p*-value
Exposure to HDS			2.26	0.13
Yes	102 (28.6%)	9 (18.4%)		
No	255 (71.4%)	40 (81.6%)		
Age			3.75	0.05
≤ 60	114 (31.9%)	9 (18.4%)		
> 60	243 (68.1%)	40 (81.6%)		
Sex			0.22	0.63
Male	162 (45.4%)	24 (49.0%)		
Female	195 (54.6%)	25 (51.0%)		
Current smoking			0.10	0.75
No	339 (95.0%)	46 (93.9%)		
Yes	18 (5.0%)	3 (6.1%)		
Obesity	(n=342)	(n=44)	1.27	0.26
No	203 (59.4%)	30 (68.2%)		
Yes	139 (40.6%)	14 (31.8%)		
Existing proteinuria	(n=313)	(n=38)	0.30	0.58
No	150 (47.9%)	20 (52.6%)		
Yes	163 (52.1%)	18 (47.4%)		
Degree of protein intake			2.78	0.09
Low	203 (56.9%)	34 (69.4%)		
Moderate to high	154 (43.1%)	15 (30.6%)		
Hypertension			0.79	0.37
No	24 (6.7%)	5 (10.2%)		
Yes	333 (93.3%)	44 (89.8%)		
Diabetes			0.04	0.83
No	144 (40.3%)	19 (38.8%)		
Yes	213 (59.7%)	30 (61.2%)		
Dyslipidaemia			0.18	0.67
No	44 (12.3%)	5 (10.2%)		
Yes	313 (87.7%)	44 (89.8%)		
eGFR (ml/min)			2.88	0.41
45-59	125 (35.0%)	21 (42.9%)		
30-44	138 (38.6%)	13 (26.5%)		
15-29	85 (23.8%)	14 (28.6%)		
< 15	9 (2.6%)	1 (2.0%)		
Controlled blood pressure	(n=354)	(n=49)	5.48	0.02*
No	234 (66.1%)	24 (49.0%)		
Yes	120 (33.9%)	25 (51.0%)		

Table 9.10 (continued)

Variables	The included group (n=357)	The group of drop-out (n=49)	X^2 value	*p*-value
A1C	(n=215)	(n=34)	0.23	0.63
≤ 7	117 (54.4%)	20 (58.8%)		
> 7	98 (45.6%)	14 (28.6%)		
LDL cholesterol	(n=314)	(n=48)	0.79	0.37
< 100	155 (49.4%)	27 (56.3%)		
≥ 100	159 (50.6%)	21 (43.7%)		
Current use of NSAIDs or COX-2 inhibitors			0.26	0.61
Yes	21 (5.9%)	2 (4.1%)		
No	336 (94.1%)	47 (95.9%)		
Current use of aspirin			1.61	0.20
Yes	141 (39.5%)	24 (49.0%)		
No	216 (60.5%)	25 (51.0%)		
Prescribed, conventional medication adherence**			0.30	0.58
Low	89 (24.9%)	14 (28.6%)		
Medium to high	268 (75.1%)	35 (71.4%)		

* Statistical significance at *p*-value < 0.05

** Medication adherence was measured using the Thai version of the 8-Item Morisky Medication Adherence Scale® [227,228]

Use of the ©MMAS is protected by US copyright laws. Permission for use is required. A license agreement is available from: Donald E. Morisky, ScD, ScM, MSPH, Professor, Department of Community Health Sciences, UCLA School of Public Health, 650 Charles E. Young Drive South, Los Angeles, CA 90095-1772.

9.2.2 The association between risk factors and the progression of CKD

To test the potential confounding factors at baseline related to the exposure using Chi-squared tests, indicated there were no differences in the factors between people exposed and unexposed to HDS at baseline, with two exceptions: the use of NSAIDs or COX-2 inhibitors, and adherence to prescribed, conventional medication, see Table 9.11. The exposed group was more likely to take NSAIDs or COX-2 inhibitors (unadjusted OR 3.64, 95%CI 1.49-8.94) and have a low level of prescribed medication adherence, as compared to the unexposed group (unadjusted OR 1.7, 95%CI 1.02-2.83).

Table 9.11 Comparison of demographics and factors related to the progression of CKD between exposed and unexposed groups at baseline (n=357)

Variables at baseline	Exposure to HDS (n=102)	Non-exposure (n=255)	X^2 value	*p*-value
Age			0.74	0.39
≤ 60	36 (35.3%)	78 (30.6%)		
> 60	66 (64.7%)	177 (69.4%)		
Sex			< 0.01	0.95
Male	46 (45.1%)	116 (45.5%)		
Female	56 (54.9%)	139 (54.5%)		
Current smoking			0.21	0.65
No	96 (94.1%)	243 (95.3%)		
Yes	6 (5.9%)	12 (4.7%)		
Obesity	(n=99)	(n=243)	0.83	0.36
No	55 (55.6%)	148 (60.9%)		
Yes	44 (44.4%)	95 (39.1%)		
Existing proteinuria	(n=84)	(n=229)	1.47	0.23
No	45 (53.6%)	105 (45.9%)		
Yes	39 (46.4%)	124 (54.1%)		
Degree of protein intake			0.50	0.48
Low	55 (53.9%)	148 (58.0%)		
Moderate to high	47 (46.1%)	107 (42.0%)		
Hypertension			3.26	0.07
No	3 (2.9%)	21 (8.2%)		
Yes	99 (97.1%)	234 (91.8%)		
Diabetes			< 0.01	0.97
No	41 (40.2%)	103 (40.4%)		
Yes	61 (59.8%)	152 (59.6%)		
Dyslipidaemia			0.31	0.57
No	11 (10.8%)	33 (12.9%)		
Yes	91 (89.2%)	222 (87.1%)		
eGFR (ml/min)			1.88	0.59
45-59	40 (39.2%)	85 (33.3%)		
30-44	39 (38.2%)	99 (38.8%)		
15-29	20 (19.6%)	65 (25.5%)		
< 15	3 (3.0%)	6 (2.4%)		
Controlled blood pressure	(n=101)	(n=253)	0.65	0.42
No	70 (69.3%)	164 (64.8%)		
Yes	31 (30.7%)	89 (35.2%)		
A1C	(n=64)	(n=151)	0.42	0.51
≤ 7	37 (57.8%)	80 (53.0%)		
> 7	27 (42.2%)	71 (47.0%)		
LDL cholesterol	(n=86)	(n=228)	0.02	0.89
< 100	43 (50.0%)	112 (49.1%)		
≥ 100	43 (50.0%)	116 (50.9%)		

Table 9.11 (continued)

Variables at baseline	Exposure to HDS (n=102)	Non-exposure (n=255)	X^2 value	*p*-value
Current use of NSAIDs or COX-2 inhibitors			8.92	< 0.01*
Yes	12 (11.8%)	9 (3.5%)		
No	90 (88.2%)	246 (96.5%)		
Current use of aspirin			0.03	0.86
Yes	41 (40.2%)	100 (39.2%)		
No	61 (59.8%)	155 (60.8%)		
Prescribed, conventional medication adherence**			4.20	0.04*
Low	33 (32.4%)	56 (22.0%)		
Medium to high	69 (67.6%)	199 (78.0%)		

* Statistical significance at *p*-value < 0.05

** Medication adherence was measured using the Thai version of the 8-Item Morisky Medication Adherence Scale® [227,228]

Use of the ©MMAS is protected by US copyright laws. Permission for use is required. A license agreement is available from: Donald E. Morisky, ScD, ScM, MSPH, Professor, Department of Community Health Sciences, UCLA School of Public Health, 650 Charles E. Young Drive South, Los Angeles, CA 90095-1772.

Analysing associations between the exposure, including the potential confounding factors at baseline and the fast progression of CKD at the end point, which was the dependent variable and defined as either a decline in eGFR of at least -5 ml/min/1.73m^2/year or receipt of dialysis therapy were performed using a Chi-squared test and calculating unadjusted OR, see Tables 9.12 and 9.13. No association was found between the exposure to HDS and the fast progression of CKD (unadjusted OR 0.81, 95%CI 0.50 – 1.32).

To explore associations between other factors at baseline, and the fast progression of CKD at the end point, there were positive associations between this dependent variable and being a younger age (risk ratio 1.69, 95% CI 1.29 – 2.20), being male (risk ratio 1.42, 95% CI 1.08 – 1.87), having existing proteinuria (risk ratio 2.64, 95% CI 1.87 – 3.72), or having poor adherence to prescribed medication (risk ratio 1.42, 95% CI 1.08 – 1.88), see Table 9.12. No associations between this outcome and other variables were found, including the use of NSAIDs, aspirin or COX-2 inhibitors.

Table 9.12 Univariate analyses of the fast progression of CKD at the end point and variables at baseline (n=357)

Variables at baseline	Fast progression (n=131)	Slow progression (n=226)	X^2 value	*p*-value
HDS use			0.69	0.40
Exposure	34 (26.0%)	68 (30.1%)		
Non-exposure	97 (74.0%)	158 (69.9%)		
Age			14.50	< 0.01*
≤ 60	58 (44.3%)	56 (24.8%)		
> 60	73 (55.7%)	170 (75.2%)		
Sex			6.49	0.01*
Male	71 (54.2%)	91 (40.3%)		
Female	60 (45.8%)	135 (59.7%)		
Current smoking			0.04	0.84
Yes	7 (5.3%)	11 (4.9%)		
No	124 (94.7%)	215 (95.1%)		
Obesity	(n=124)	(n=218)	0.13	0.71
Yes	52 (41.9%)	87 (39.9%)		
No	72 (58.1%)	131 (60.1%)		
Severity of CKD			2.63	0.11
Stage 4-5	41 (31.3%)	53 (23.5%)		
Stage 3	90 (68.7%)	173 (76.5%)		
Existing proteinuria	(n=120)	(n=193)	38.05	<0.01*
Yes	89 (74.2%)	74 (38.3%)		
No	31 (25.8%)	119 (61.7%)		
Degree of protein intake			0.59	0.44
Moderate to high	60 (45.8%)	94 (41.6%)		
Low	71 (54.2%)	132 (58.4%)		
Hypertension			0.63	0.43
Yes	124 (94.7%)	209 (92.5%)		
No	7 (5.3%)	17 (7.5%)		
Diabetes			0.87	0.35
Yes	74 (56.5%)	139 (61.5%)		
No	57 (43.5%)	87 (38.5%)		
Dyslipidaemia			0.91	0.34
Yes	112 (85.5%)	201 (88.9%)		
No	19 (14.5%)	25 (11.1%)		
Controlled blood pressure	(n=129)	(n=225)	3.25	0.07
No	93 (72.1%)	141 (62.7%)		
Yes	36 (27.9%)	84 (37.3%)		
A1C (%)	(n=73)	(n=142)	0.04	0.83
> 7	34 (46.6%)	64 (45.1%)		
≤ 7	39 (53.4%)	78 (54.9%)		

Table 9.12 (continued)

Variables at baseline	Fast progression (n=131)	Slow progression (n=226)	X^2 value	*p*-value
LDL cholesterol (mg/dl)	(n=109)	(n=205)	3.42	0.06
≥ 100	63 (57.8%)	96 (46.8%)		
< 100	46 (42.2%)	109 (53.2%)		
Current use of NSAIDs or COX-2 inhibitors			0.02	0.89
Yes	8 (6.1%)	13 (5.8%)		
No	123 (93.9%)	213 (94.2%)		
Current use of aspirin			3.85	0.05
Yes	43 (32.8%)	98 (43.4%)		
No	88 (67.2%)	128 (56.6%)		
Prescribed, conventional medication adherence**			5.62	0.02*
Low	42 (32.1%)	47 (20.8%)		
Medium to high	89 (67.9%)	179 (79.2%)		

* Statistical significance at *p*-value < 0.05

** Medication adherence was measured using the Thai version of the 8-Item Morisky Medication Adherence Scale® [227,228]

Use of the ©MMAS is protected by US copyright laws. Permission for use is required. A license agreement is available from: Donald E. Morisky, ScD, ScM, MSPH, Professor, Department of Community Health Sciences, UCLA School of Public Health, 650 Charles E. Young Drive South, Los Angeles, CA 90095-1772.

Table 9.13 The association of the fast progression of CKD at the end point and the independent variables at baseline (n=357)

Variables	Unadjusted OR	95% Confidence interval
HDS use		
Exposure	0.81	0.50 – 1.32
Non-exposure	1.00	
Age		
≤ 60	2.41	1.53 – 3.81
> 60	1.00	
Sex		
Male	1.76	1.14 – 2.71
Female	1.00	
Current smoking		
Yes	1.10	0.42 – 2.92
No	1.00	
Obesity		
Yes	1.09	0.70 – 1.70
No	1.00	
Severity of CKD		
Stage 4-5	1.49	0.92 - 2.41
Stage 3	1.00	
Existing proteinuria		
Yes	4.62	2.80 – 7.62
No	1.00	
Protein intake		
Moderate to high	1.19	0.77 – 1.83
Low	1.00	
Hypertension		
Yes	1.44	0.58 – 3.57
No	1.00	
Diabetes		
Yes	0.81	0.53 – 1.26
No	1.00	
Dyslipidaemia		
Yes	0.73	0.39 – 1.39
No	1.00	
Controlled blood pressure		
No	1.54	0.96 – 2.46
Yes	1.00	
A1C (%)		
> 7	1.06	0.60 – 1.87
≤ 7	1.00	

Table 9.13 (continued)

Variables at baseline	Unadjusted OR	95% Confidence interval
LDL cholesterol (mg/dl)		
≥ 100	1.56	0.97 – 2.49
< 100	1.00	
Current use of NSAIDs or COX-2 inhibitors		
Yes	1.07	0.43 – 2.64
No	1.00	
Current use of aspirin		
Yes	0.64	0.41 -1.00
No	1.00	
Prescribed, conventional medication adherence**		
Low	1.80	1.10 – 2.93
Moderate to high	1.00	

** Medication adherence was measured using the Thai version of the 8-Item Morisky Medication Adherence Scale® [227,228]

Use of the ©MMAS is protected by US copyright laws. Permission for use is required. A license agreement is available from: Donald E. Morisky, ScD, ScM, MSPH, Professor, Department of Community Health Sciences, UCLA School of Public Health, 650 Charles E. Young Drive South, Los Angeles, CA 90095-1772.

To identify the confounding factors related to the association between exposure and the primary outcome, multiple logistic regression analysis was performed. Comparing unadjusted OR of the association between the exposure and the outcome (unadjusted OR 0.81, 95%CI 0.50 -1.32) with its adjusted OR, resulting from multiple logistic regression analysis, found only proteinuria as a confounding factor related to this association. This was because there was more than 10% of the difference between unadjusted and adjusted OR of such relationship (adjusted $OR_{proteinuria}$ 1.21, 95%CI 0.70 – 2.10). Age, sex, medication adherence and the use of NSAIDs or COX-2 inhibitors were not confounding factors as less than 10% of the differences in unadjusted and adjusted OR of the association between the exposure and the outcome (adjusted OR_{age} 0.77, 95%CI 0.47 – 1.27; adjusted OR_{sex} 0.81, 95%CI 0.50 – 1.32; adjusted $OR_{medication\ adherence}$ 0.76, 95%CI 0.46 – 1.24; adjusted $OR_{use\ of\ NSAIDs\ or\ COX\text{-}2\ inhibitors}$ 0.81, 95%CI 0.49 – 1.32).

Therefore, the model of the association between the exposure and to the fast progression of CKD was step by step included each of the factor: the exposure, age, sex, and proteinuria based on this order, see Table 9.14. The finding indicated that the association between the exposure and the outcome was not found (adjusted OR 1.16, 95%CI 0.66 – 2.03). In contrast, existing proteinuria at baseline and younger age were associated with the fast progression of CKD (adjusted odds ratio (OR) 4.22, 95% CI 2.52 – 7.05; adjusted OR 1.91, 95% CI 1.14 – 3.18, respectively), see Table 9.14. The total number of multiple logistic regression analysis was 313, as 44 respondents were not measured for proteinuria.

Table 9.14 Multiple logistic regression analysis of the fast progression of CKD and variables at baseline (total number of analysis= 313)

Variables	Adjusted odds ratio*	95% Confidence interval
HDS use		
Non-exposure	1.00	
Exposure	1.16	0.66 – 2.03
Age		
> 60	1.00	
≤ 60	1.91	1.14 – 3.18
Sex		
Female	1.00	
Male	1.57	0.96 – 2.58
Existing proteinuria		
No	1.00	
Yes	4.22	2.52 – 7.05

* OR adjusted for all other variables listed in the table

9.2.3 Patients experiencing renal adverse effects and benefits from HDS and analgesic use

Medical notes amongst the exposed group were reviewed in order to examine HDS induced acute kidney injury (AKI) reported by a doctor. Reported renal adverse effects in the medical notes showed that two patients, who were using herbal medicine, suffered from AKI in addition to CKD, as diagnosed by a doctor.

The incidence of herbal medicine-induced AKI was 0.6% in this cohort study. After the concerned patients stopped using the medicine, their eGFR improved. The first patient used a mixture of 10 unknown Chinese herbal medicines and his eGFR improved from 26 to 41 ml/min/1.72m^2 (serum creatinine changed from 4.15 to 2.45 mg/dl) after stopping them. The second patient took both river spiderwort and diclofenac; after stopping both the herbal medicine and the NSAID, his eGFR increased from 18 to 25 ml/min/1.72m^2 (serum creatinine changed from 8.36 to 5.64 mg/dl). These patients exposed such herbal medicines within one month before worsening their kidney function, a situation which is likely to associate with the onset of herbal medicine-induced AKI. After they stopped using suspected herbal medicines and NSAID, their kidney function returned to their baseline of kidney function within 3 months. Additionally, other factors, which may be related to worsening kidney function, were less likely to change during this period. This was the process of assessing causality of these suspected adverse events, using World Health Organisation's Uppsala Monitoring Centre causality categories[289] analysed by MT. Therefore, AKI were likely to be related to such herbal medicines, and both the herbal medicine and the NSAID could be associated with AKI in the second patient.

Medical notes of all respondents who used NSAIDs or COX-2 inhibitors during the study were reviewed to collect data regarding a report of these medications related to AKI diagnosed by a doctor. Sixteen patients (4.8%) had AKI, in addition to CKD, due to taking NSAIDs, COX-2 inhibitors or an analgesic dose of aspirin; their renal function was improved by between 8% to 36%, after stopping them.

Regarding benefits of HDS use, 8 patients out of 62 patients, who regularly used HDS for 12 months (13%), reported that their kidney function did not worsen, which was related to their rate of decline in eGFR per year. Most of them were

not obese, or had proteinuria, and could control their blood pressure, which are main factors-related to the progression of CKD, see Table 9.15.

Table 9.15 Patients reported gaining benefit from HDS use and their risk factors

Patient no.	HDS use	Age	Stages of CKD	Co-morbidities	Obesity	Analgesic or aspirin use	Proteinuria	Controlled BP	Controlled A1C	Controlled LDL
1	Spring bitter cucumber (*Momordica cochinchinensis*)	67	4	Diabetes, HTN	Yes	Aspirin 81 mg	Yes	Yes	No	Yes
2	Jujube combined with roselle, boesenbergia's juice and a mixture of three types of mushrooms' juice	57	4	HIV, HBV	No	No	No	No	-	No
3	A Chinese folk remedy - Cordyceps, *Angelica sinensis*, deer antler velvet, five flavour berry (*Schisandra chinensis*) and cinnamon	67	3a	HTN	No	NSAID use	No	Yes	Yes	No
4	Unknown Chinese folk remedy for CKD	42	3a	HTN	No	Aspirin 81 mg	No	Yes	-	Yes
5	Boesenbergia's juice and unknown Chinese folk remedy for CKD	43	3b	Chronic glomerulonephritis	No	No	Yes	No	-	No
6	A herbal combination – Boesenbergia, mint, ginger, galangal, lemongrass, kaffir lime leaves and shallots	79	4	Diabetes, HTN	No	Aspirin 81 mg	No	Yes	Yes	Yes
7	Wheatgrass and a mixture of 60 botanical agents	54	4	Diabetes, HTN	No	Aspirin 81 mg	No	Yes	Uncontrolled FBS	No
8	Turmeric (Curcuma longa)	64	4	Diabetes, HTN	No	Aspirin 81 mg	No	No	Yes	Yes

Note: BP = Blood pressure; HTN = Hypertension; FBS = Fasting blood sugar

9.2.4 The association between exposure to HDS and CKD complications

Three-hundred and thirty patients who did not receive dialysis during the follow-up study were analysed to ascertain any correlations of uncontrolled hyperkalemia and hyperphophatemia between exposed and unexposed groups. Only two patients had over 5.5 mEq/l of a mean serum level of potassium over one year. There was a statistically significant association between uncontrolled hyperphosphatemia and exposure to HDS (risk ratio 3.05, 95% CI 1.18 – 7.92), whilst an association between uncontrolled hyperkalemia and exposure was not found (risk ratio 0.62, 95% CI 0.29 – 1.29), see Table 9.16.

There were no differences in numbers of the non-measurement of serum levels of potassium or phosphate over one year in each independent variable at baseline, except the non-measurement of serum levels of phosphate between respondents receiving treatment of hyperphosphatemia and those who did not receive it (X^2 value 14.67, p-value < 0.01) and such non-measurement between CKD stage 3 and stages 4 to 5 (X^2 value 12.48, p-value < 0.01). Fifty-four respondents (90%) who were not treated for hyperphosphatemia had the non-measurement of serum levels of phosphate over one year, compared with those receiving treatment of hyperphosphatemia (6 respondents, 10%). Respondents with stage 3 CKD had the non-measurement of such electrolyte (57 respondents, 95%), rather more than those with stages 4 to 5 CKD (3 respondents, 5%).

Table 9.16 Univariate analyses between the secondary outcomes, exposure to HDS and related factors at baseline (n=330)

Variables at baseline	Uncontrolled hyperkalemia over one year		Missing data	X^2 value	*p*-value	Unadjusted OR (95%CI)
	Yes (n=39)	No (n=289)	(n=2)			
HDS use				1.75	0.19	0.58 (0.26 - 1.31)
Exposure	8 (20.5%)	89 (30.8%)	1 (50.0%)			
Non-exposure	31 (79.5%)	200 (69.2%)	1 (50.0%)			
Age				0.38	0.54	0.79 (0.37 - 1.69)
≤ 60	10 (25.6%)	88 (30.4%)	0 (0.0%)			
> 60	29 (74.4%)	201 (69.6%)	2 (100.0%)			
Sex				0.82	0.37	1.36 (0.70 - 2.66)
Male	20 (51.3%)	126 (43.6%)	1 (50.0%)			
Female	19 (48.7%)	163 (56.4%)	1 (50.0%)			
Severity of CKD				4.76	0.03*	2.18 (1.07 – 4.46)
Stage 4-5	14 (35.9%)	59 (20.4%)	0 (0.0%)			
Stage 3	25 (64.1%)	230 (79.6%)	2 (100.0%)			
Degree of high potassium intake**				0.77	0.38	0.73 (0.36 - 1.48)
Moderate to high	25 (64.1%)	205 (70.9%)	2 (100.0%)			
Low	14 (35.9%)	84 (29.1%)	0 (0.0%)			
Treatment of hyperkalemia***				10.57	< 0.01*	3.14 (1.53 - 6.42)
Yes	15 (38.5%)	48 (16.6%)	0 (0.0%)			
No	24 (61.5%)	241 (83.4%)	2 (100.0%)			
Use of loop diuretics				1.46	0.23	0.59 (0.25 - 1.40)
Yes	7 (17.9%)	78 (27.0%)	0 (0.0%)			
No	32 (82.1%)	211 (73.0%)	2 (100.0%)			
Use of ACEIs or ARBs				0.01	0.92	1.04 (0.53 - 2.04)
Yes	23 (59.0%)	168 (58.1%)	1 (50.0%)			
No	16 (41.0%)	121 (41.9%)	1 (50.0%)			
Prescribed, conventional medication adherence				3.18	0.08	1.89 (0.93 – 3.85)
Low	14 (35.9%)	66 (22.8%)	1 (50.0%)			
Medium to high	25 (64.1%)	223 (77.2%)	1 (50.0%)			

Table 9.16 (continued)

Variables at baseline	Uncontrolled hyperphosphatemia over one year		Missing data	X^2 value	*p*-value	Unadjusted OR (95%CI)
	Yes (n=16)	No (n=254)	(n=60)			
HDS use				5.78	0.02*	3.31 (1.19 - 9.24)
Exposure	9 (56.3%)	71 (28.0%)	18 (30.0%)			
Non-exposure	7 (43.7%)	183 (72.0%)	42 (70.0%)			
Age				3.54	0.06	2.58 (0.93 – 7.13)
≤ 60	8 (50.0%)	71 (28.0%)	19 (31.7%)			
> 60	8 (50.0%)	183 (72.0%)	41 (68.3%)			
Sex				1.70	0.19	0.49 (0.17 – 1.46)
Male	5 (31.2%)	122 (48.0%)	20 (33.3%)			
Female	11 (68.8%)	132 (52.0%)	40 (66.7%)			
Severity of CKD				2.81	0.09	2.36 (0.84 – 6.59)
Stage 4-5	7 (43.8%)	63 (24.8%)	3 (5.0%)			
Stage 3	9 (56.3%)	191 (75.2%)	57 (95.0%)			
Degree of high phosphate intake**				1.63	0.20	0.44 (0.12 - 1.60)
Moderate to high	3 (18.8%)	87 (34.3%)	19 (31.7%)			
Low	13 (81.2%)	167 (65.7%)	41 (68.3%)			
Treatment of hyperphosphatemia				0.12	0.73	0.83 (0.28 - 2.46)
Yes	5 (31.3%)	90 (35.4%)	6 (10.0%)			
No	11 (68.7%)	164 (64.6%)	54 (90%)			
Prescribed, conventional medication adherence				0.03	0.87	1.10 (0.34 – 3.54)
Low	4 (25.0%)	59 (23.2%)	18 (30.0%)			
Medium to high	12 (75.0%)	195 (76.8%)	42 (70.0%)			

Missing data = the non-measurement of serum levels of potassium or phosphate over one year, * Statistical significance at *p*-value < 0.05

** measured by the restriction of protein, potassium, phosphate and salt diet questionnaire, *** received sodium or calcium polystyrene sulfonate

Multiple logistic regression analysis included exposure and all independent variables of hyperkalemia or hyperphosphatemia in order to examine the effect of each variable on the dependent variable – uncontrolled hyperkalemia or hyperphosphatemia. Based on the literature, independent variables which may be related to uncontrolled hyperkalemia were the degree of high potassium intake, treatment of hyperkalemia, the use of loop diuretics, ACEIs or ARBs. Independent variables related to hyperphosphatemia, based on the literature, were the degree of high phosphate intake and treatment of hyperphosphatemia. Age, sex, the severity of CKD and prescribed, conventional medication adherence were also included in the multiple logistic regression analysis, as these variables may influence the dependent variables.

Comparing unadjusted and adjusted OR of the relationship between HDS and the secondary outcomes, in order to examine potential confounding factors, found no differences in both outcomes (unadjusted OR of uncontrolled hyperkalemia 0.58, 95%CI 0.26 – 1.31; its adjusted OR 0.59, 95%CI 0.25 – 1.38; unadjusted OR of uncontrolled hyperphosphatemia 3.31, 95%CI 1.19 – 9.24; and its adjusted OR 3.53, 95%CI 1.20 – 10.43), see Tables 9.16-9.17. Examining potential confounding factors related to the association between HDS and uncontrolled hyperkalemia, i.e. age, sex, the severity of CKD and treatment of hyperkalemia, found no differences between unadjusted and adjusted OR when controlling such factors (unadjusted OR 0.58, 95%CI 0.26 – 1.31; adjusted OR_{age} 0.59, 95%CI 0.26 – 1.33; adjusted OR_{sex} 0.58, 95%CI 0.26 – 1.32; adjusted $OR_{severity\ of\ CKD}$ 0.59, 95%CI 0.26 – 1.34; and adjusted $OR_{treatment\ of\ hyperkalemia}$ 0.63, 95%CI 0.28 – 1.44). Likewise, there was no difference in the association between HDS and uncontrolled hyperphosphatemia after controlling for age or sex (unadjusted OR 3.31, 95%CI 1.19 – 9.24; adjusted OR_{age} 3.33, 95%CI 1.19 – 9.38; and adjusted OR_{sex} 3.49, 95%CI 1.24 – 9.82).

. .

Table 9.17 Multiple logistic regression analyses between the secondary outcomes over one year, exposed group and other factors at baseline

Variables at baseline	Adjusted OR*	95% CI
Uncontrolled hyperkalemia over one year (n=328)		
HDS use		
Non-exposure	1.00	
Exposure	0.59	0.25 - 1.38
Age		
> 60	1.00	
≤ 60	0.59	0.26 – 1.37
Sex		
Female	1.00	
Male	1.72	0.83 – 3.57
Severity of CKD		
Stage 3	1.00	
Stage 4-5	2.90	1.28 – 6.55
Degree of potassium intake		
Low	1.00	
Moderate to high	0.84	0.40 - 1.77
Treatment of hyperkalemia		
No	1.00	
Yes	3.02	1.43 - 6.40
Use of loop diuretics		
No	1.00	
Yes	0.41	0.16 – 1.05
Use of ACEIs or ARBs		
No	1.00	
Yes	1.14	0.54 – 2.41
Prescribed, conventional medication adherence		
Medium to high	1.00	
Low	2.16	1.00 – 4.70

* OR adjusted for all other variables listed in the table

Table 9.17 (continued)

Variables at baseline	Adjusted OR*	95% CI
Uncontrolled hyperphosphatemia over one year (n=270)		
HDS use		
Non-exposure	1.00	
Exposure	3.53	1.20 – 10.43
Age		
> 60	1.00	
≤ 60	3.01	0.99 – 9.13
Sex		
Female	1.00	
Male	0.59	0.18 – 1.88
Severity of CKD		
Stage 3	1.00	
Stage 4-5	2.22	0.71 – 6.91
Degree of phosphate intake		
Low	1.00	
Moderate to high	0.43	0.11 – 1.64
Treatment of hyperphosphatemia		
No	1.00	
Yes	1.11	0.32 – 3.80
Prescribed, conventional medication adherence		
Medium to high	1.00	
Low	0.78	0.22 – 2.77

* OR adjusted for all other variables listed in the table

Stages 4 to 5 CKD was associated with uncontrolled hyperkalemia or hyperphosphatemia, compared with stage 3 CKD (adjusted OR of uncontrolled hyperkalemia 2.90, 95%CI 1.28 – 6.55; adjusted OR of uncontrolled hyperphosphatemia 2.22, 95%CI 0.71 – 6.91). Patients receiving treatment for hyperkalemia or hyperphosphatemia at baseline still had uncontrolled hyperkalemia or hyperphosphatemia at the end point (adjusted OR of uncontrolled hyperkalemia 3.02, 95%CI 1.43 – 6.40; adjusted OR of uncontrolled hyperphosphatemia 1.11, 95%CI 0.32 – 3.80), see Table 9.17. Regarding controlling medication adherence, those receiving treatment of

hyperkalemia or hyperphosphatemia and having poor adherence were more likely to be uncontrolled hyperkalemia or hyperphosphatemia than those with moderate to high adherence (adjusted $OR_{medication\ adherence}$ of uncontrolled hyperkalemia 2.63, 95%CI 0.79-8.77; adjusted $OR_{medication\ adherence}$ of uncontrolled hyperphosphatemia 1.64, 95%CI 0.26 – 10.40). It would seem that patients receiving the treatment still had uncontrolled hyperkalemia or hyperphosphatemia due to poor medication adherence.

Patients who had moderate to high potassium or phosphate intake at baseline were likely to control their serum levels of potassium or phosphate over one year, compared with those with low intake (adjusted OR of uncontrolled hyperkalemia 0.84, 95%CI 0.40 – 1.77; adjusted OR of uncontrolled hyperphosphatemia 0.43, 95%CI 0.11 – 1.64). This could be influenced by standard practice for patients with uncontrolled hyperkalemia or hyperphosphatemia. Health care providers i.e. doctors, pharmacists or dieticians advised the patients to avoid consuming high potassium or phosphate intake when they had uncontrolled hyperkalemia or hyperphosphatemia.

Poor conventional medication adherence seemed to be associated with uncontrolled hyperkalemia (adjusted OR 2.16, 95%CI 1.00 – 4.70). In contrast, patients with poor adherence were able to control their serum levels of phosphate over one year (adjusted OR 0.78, 95%CI 0.22 – 2.77). Regarding controlling phosphate intake, patients with poor adherence and low phosphate intake controlled hyperphosphatemia more than those with poor adherence and moderate to high phosphate intake (adjusted $OR_{phosphate\ intake}$ 0.37, 95%CI 0.05 – 2.87). It would appear that patients with poor adherence had controlled hyperphosphatemia as they controlled their phosphate intake.

9.2.5 Sensitivity analyses

To test the robustness of the association between exposure to HDS and the fast progression of CKD, multiple sensitivity analyses were performed. The first analysis was to compare the associations between various classifications of cut-off points for the fast progression of CKD and related factors. Secondly, there were analyses of any associations between risk factors and this outcome between all patients, and those with glomerular disease, cancer, hepatitis, cirrhosis or HIV - related to various rates of the progression, compared with those with diabetes or hypertension. Finally, there was the investigation of such associations between consistent exposed and unexposed groups over one year, which were excluded patients who stopped using HDS, and those who started using HDS during the follow-up period, see Appendix 15.

Of the 330 patients who did not start receiving dialysis during the follow-up period, four cut-off points of decline in eGFR per year were: at least -5 ml/min/1.72m^2/year based on literature; at least -4 ml/min/1.72m^2/year based on mean decline in eGFR in this study and plus a quarter of SD; at least -6 ml/min/1.72m^2/year based on such mean plus half SD; and at least -10 ml/min/1.72m^2/year based on such mean plus SD. Univariate analyses were performed at these cut-off points and results were as follows.

An association between the exposure to HDS and the outcome was not found at any of the cut-off points. However, there were statistically significant associations between this outcome and being younger, having existing proteinuria, uncontrolled LDL cholesterol, or having poor adherence to prescribed conventional medication at all cut-off points. These factors are known as risk factors in the fast progression of CKD. There were inconsistent associations between sex and this outcome at some cut-off points. This outcome at -5 and -6 cut-off points was related to gender, but not at -4 and -10.

Causes of CKD affect the rate of CKD progression. For example, polycystic kidney disease and glomerulonephritis have faster rates of progression. The rate of CKD progression amongst patients with HIV, cirrhosis and cancer differs from patients with diabetes or hypertension. To test whether or not these confounding factors influenced the outcome, patients with glomerular diseases, HIV, cirrhosis or cancer were excluded. Then univariate analyses between variables and the progression of CKD were performed. As a result, there was no difference between all respondents and those who did not have such diseases.

The exposed and unexposed groups at baseline changed their exposure to HDS during the follow-up period, so this may have affected the findings. Sixty-two patients continued regularly taking HDS for 12 months and were defined as the exposed group, whilst 177 patients did not take them at all, i.e. the unexposed group. These groups were analysed to establish the effects on the CKD outcomes, and it was found that there was no difference from the originally defined groups.

9.3 Discussion

9.3.1 Key findings

Three-hundred and fifty-seven Thai patients with CKD were followed for 12 months and less than 10% died or received dialysis therapy. Mean age and SD in this cohort study was 66 and 13, and 55% of the participants were female. At least 60% of the research population had comorbid diabetes and hypertension. Mean BMI in this study was 25 kg/m^2 at baseline. Mean eGFR (SD) at baseline was 39 (12) ml/min and 74% had stage 3 CKD. Twenty-nine percent regularly used HDS at baseline.

There were no differences in demographic characteristics between exposed and unexposed groups, except that the exposed group was more likely to use

NSAIDs or COX-2 inhibitors; levels of adherence to prescribed, conventional medication were lower in the exposed group. A relationship between HDS use and the fast progression of CKD in Thai patients with CKD was not found (adjusted OR 1.16, 95%CI 0.66 – 2.03). There were associations between the fast progression of CKD, and existing proteinuria (adjusted OR 4.22, 95%CI 2.52 – 7.05) and younger age (adjusted OR 1.91, 95%CI 1.14 – 3.18).

In the 330 patients who did not initiate dialysis therapy, there was a statistically significant association between HDS use and uncontrolled hyperphosphatemia (adjusted OR 3.53, 95%CI 1.20 – 10.43). However, no association between HDS use and uncontrolled hyperkalemia was found (adjusted OR 0.59, 95% CI 0.25 – 1.38).

9.3.2 Characteristics of respondents

There was no difference in the mean age (66) in the present study and the stages 2 to 4 CKD population in Thailand (65).[290] The proportion of women in the present study was higher than men (55%), which is inconsistent with Chartsrisak's study in Thailand, where 44% of the population were female.[290] A small number of respondents aged over 70 years may have underestimated GFR at baseline due to a limitation of the MDRD equation (n=32, 8%).

Patients in the present study showed no difference in a prevalence of hypertension (93%) and diabetes (60%), compared to the Thai CKD population (91% and 56%, respectively).

The high number with hypertension in the current study may be due to this dataset including both the history of hypertension, and hypertension caused by CKD, in the definition of hypertension, as this was not separately identified in the medical notes. The sample in this study represented CKD resulting from hypertension and diabetes. Nine percent had cancer and registered a decline in

kidney function[156] in the present study, and this does not differ greatly from Goeij's study (2011) in the Netherlands (11%).[172]

The number of current smokers (5%) and mean BMI (25 kg/m^2) in the present study were lower than other cohort studies amongst patients with stages 3 to 5 CKD in European countries (current smoking 13-56%, mean BMI 26-27 kg/m^2).[172,291,292] However, these patients in both Thai and Western populations are overweight, which is defined as at least 23 kg/m^2 of BMI in a Thai population[293] and at least 25 kg/m^2 of BMI in a Western population.[281] Smoking status in the current study (5%) is also lower than Thai patients with CKD in the Thai national health survey (26%)[146], whilst the mean BMI in the present study was not different, compared to the Thai CKD population (25 kg/m^2) [290] and cohort studies in Japan (23-24 kg/m^2).[150,294] There was a different proportion of smoking status between the current study and data from the literature, due to the different populations. The Thai national health survey recruited people aged 15 or over and who were not diagnosed with CKD at recruitment, whilst the current study recruited patients diagnosed with CKD. Patients with CKD were more likely to have stopped smoking, compared with the general population.

A mortality rate (7%), and patients who reached end-stage renal disease (8%) in the present study, are consistent with Landray's study in the UK (6% and 12%) and Nicola's study in Italy (6% and 8%).[171,292] It would seem that respondents in the current study had less severe CKD than those patients cited in other studies[170,171,291,292,294] as most of them had stage 3 CKD (74%). The mean eGFR at baseline in the current study (39 ml/min/1.73m^2/year) was higher than other studies (range 22-31 ml/min/1.73m^2/year).[170,171,291,292,294] The proportion of patients with controlled blood pressure ($\leq$ 130/80 mmHg) in the current study (35%) was lower than Muntner's study in the US (47%)[295], but it is higher than Nicola's study in Italy (13%)[171] and Martinez-Castelao's study in Spain (17.4%).[151] Less than 35% received ACEIs or ARBs in the current study,

which is lower than other studies in Western countries (at least 60%).[44,291] However, this is not greatly different from a cohort study in Japan (ACEIs 21% and ARBs 40%).[294]

Regarding the proportion of existing proteinuria (52%), and hyperphosphatemia at baseline (7%), data are consistent with the CKD population in Western countries (60% and 9-11%, respectively)[151,171] and the Thai CKD population (hyperphosphatemia 8%).[290] There was a very small number of respondents that were currently using NSAIDs or COX-2 inhibitors (less than 10%), which is lower than Kuo's study amongst CKD patients in Taiwan (NSAIDs 19% and COX-2 inhibitors 1%)[174] and Ingsathit's survey in the Thai general population (NSAIDs 45%).[5]

It would appear therefore that respondents in the current study represent Thai patients with CKD stages 3 to 5, despite having less severe CKD than Western populations. The population in the present study had low rates of smoking and use of NSAIDs or COX2-inhibitors.

9.3.3 The association between risk factors and the progression of CKD

To compare demographic characteristics between the drop-out group (death and lost to follow-up) and the included groups, there were no differences between the groups, except control of blood pressure. The included group was less likely to have controlled blood pressure than the drop-out group (p-value < 0.05). This was unlikely to affect the primary outcome in this study as the drop-out group did not intentionally leave the study based on faster progression of CKD, compared with the included group.

There were no differences in demographic characteristics between exposed and unexposed groups. The only difference between these groups was the use of NSAIDs or COX-2 inhibitors, and the degree of adherence to prescribed,

conventional medication. Exposure to HDS was more likely to result in a low level of prescribed conventional medication adherence (unadjusted OR 1.7, 95%CI 1.02-2.83), which was discussed in Chapter 8. However, these factors did not influence the association between HDS use and the fast progression of CKD. Only existing proteinuria was a confounding factor in this association.

There was no association between the fast progression of CKD over a year and HDS use, as analysed by univariate and multiple variate analyses, which was also tested for robustness using sensitivity analyses. No differences were found. This may be because HDS, used by Thai patients with CKD, were more likely to be dietary, such as mushrooms, garlic, cinnamon, lemongrass, kaffir lime leaves, jujube and dietary supplements. There was also no report of renal adverse effects from the HDS used by respondents, i.e. turmeric, ginseng, garlic, veld grape, senna, kariyat and gingko. This finding is supported by the Thai Health Product Vigilance Center database from 2000 to 2008.[128]

Despite limited case reports on the renal adverse effects of many herbal medicines, used by the Thai population in the present study, there are several animal studies of acute and sub-chronic toxicity. Most studies, in rats, report no acute and/or sub-chronic renal toxicity from consuming *Moringa oleifera*[296], Thai folk remedy – 'Ka sai'[297], *Tiliacora triandra*[298], *Cissus quadrangularis*[299], *Gynura procumbens*[300], Cordyceps[301] or *Coccinia gradis*.[302]

However, some patients (n=11) in the present study used HDS, which should be avoided i.e. aloe, senna, ginseng and 'Ya hom'; avoidance recommended by the National Kidney Foundation in the US and the Thai National List of Essential Medicines.[119,194,208] Both aloe and senna contain anthraquinones, which could accumulate in renal tissues and induce electrolyte imbalance.[303] Ginseng could lead to an increase in blood pressure.[208] The Thai folk remedy – 'Ya hom' caused renal failure and death in a 2-year-old girl, as it contained *Magnolia officinalis* which can cause renal failure.[196]

There was one case report, and several animal studies (n=5), in which spirulina, *Tinospora crispa* and 'Tri pala' were found to be related to renal toxicity. A dose (1 g/day) of spirulina induced acute rhabdomyolysis in a 28-year-old man, which could have led to acute renal failure.[304] Prolonged high doses of *Tinospora crispa* can induce renal toxicity in rats.[305] A high dose 'Tri pala' in rats caused nephrocalcinosis, chronic pyelonephritis and renal hydrocalyx because it contains tannin, which is metabolised into gallic acid, resulting in renal toxicity.[306] Therefore, patients with CKD should avoid these herbal medicines.

The finding of 'no relationship' between HDS and the fast progression of CKD in the present study is inconsistent with cross-sectional studies in Thailand and Taiwan[4,5], which found herbal medicines were related to CKD and a case-control study in Taiwan[7] indicated an association between Chinese herbal medicine and end-stage renal disease.

There are several reasons to support the present finding, as follows. Firstly, the Thai population in the present study might have used different types of herbal medicine compared with the participants in the above studies; a small number of them were using Chinese herbal medicine (n=5), compared with studies in Taiwan. However, such previous studies did not provide the types of herbal medicine used, and populations in two out of three of the studies used Chinese herbal medicines, which are likely to induce nephrotoxic effects.[307] Secondly, all previous studies speculated about negative effects of herbal medicines based on evidence, despite unknown types of herbal medicines being included. Finally, the study in Thailand[5] showed a weak association between herbal medicine and CKD (adjusted OR 1.2, 95% CI 1.02-1.42), whilst the case control study in Taiwan found a strong association between Chinese herbal medicine and end-stage renal disease (crude OR 6.26, 95% CI 3.85-10.19).[7] These findings suggest that Thai herbal medicine may be less likely to be associated with adverse effects on kidney function than Chinese herbal medicine, due to the fact that Chinese

herbal medicine is likely to be contaminated with NSAIDs related to acute kidney injury.[7]

No association between HDS use and the fast progression of CKD may be because the effect size in this study was smaller than the expected effect on kidney function, when calculating sample size determination. As a result, the number of participants may not be sufficient to detect the effect. However, this study was the first study to determine this association, so the finding in the present study will inform further research.

Medical notes in the present study showed two respondents, who were using herbal medicine, suffered from acute kidney injury in addition to their CKD (0.6%). Unfortunately, the first person did not know ingredients in the Chinese herbal medicine he used; the other used river spiderwort combined with diclofenac. These herbal medicines were likely to be related to AKI; a conclusion reached when they were assessed using World Health Organisation's Uppsala Monitoring Centre causality categories.[289] There is no evidence to support whether or not river spiderwort is related to AKI. However, this incidence indicated an example of the infrequent, albeit serious, adverse effects of herbal medicine on worsening kidney function.[308] It is reasonable to conclude that health care providers should be aware of herbal medicine use amongst Thai patients with CKD, particularly Chinese herbal medicine and river spiderwort, and therefore that they should closely monitor adverse effects of herbal medicine. Further studies are required to explore what type of Thai herbal medicine leads to AKI amongst patients with CKD.

There was no association between NSAIDs, COX-2 inhibitors or aspirin and the fast progression of CKD, analysed by univariate and multivariate analyses in the current study. This is inconsistent with Kuo's study (2010) in Taiwan, which found that the use of these medications was related to end stage renal disease.[174] There are several reasons to explain the finding in the current study.

A small number of respondents took NSAIDs (6%) or COX-2 inhibitors (3%) in the present study, compared to Kuo's study (19%, 1%, respectively) and those taking aspirin took a lower dose (median dose 81 mg/day), compared to Kuo's study (median dose 113 mg/day). These are inconsistent associations between low doses of aspirin and the progression of CKD. Perneger et al. (1994) found no association between aspirin and the development of end stage renal disease[190], whilst Evans et al. in 2009 found slower progression of CKD in a group of aspirin users, compared with non-users.[191] Sixteen patients using NSAIDs, COX-2 inhibitors or aspirin in the present study suffered from AKI, in addition to CKD. After stopping them taking the herbal medicines their kidney function improved, so this may have interfered with the primary outcome of the present study. This result may reflect that health care providers in the two teaching hospitals advised their patients to avoid using NSAIDs and COX-2 inhibitors.

Proteinuria and younger age were associated with the fast progression of CKD (adjusted OR 4.22, 95%CI 2.52 – 7.05 and adjusted OR 1.91, 95%CI 1.14 – 3.18). This is consistent with the literature, which shows existing proteinuria is associated with the fast progression of CKD.[157,169-171,173]

The association between moderate to high protein, potassium and phosphate intake, and the fast progression of CKD, uncontrolled hyperkalemia and uncontrolled hyperphosphatemia was not found in the present study. This is inconsistent with theoretical knowledge.[157] There are several reasons to explain this result. Firstly, there are many factors related to these outcomes. High protein intake has a weak association with CKD progression[176] whilst proteinuria is strongly related to this progression.[169-171] At least 20% of the patients received loop diuretics, a treatment of hyperkalemia and hyperphosphatemia, so these may have interfered with the associations between high potassium and phosphate intake, and uncontrolled hyperkalemia and hyperphosphatemia.

Secondly, respondents may have changed the degree of such dietary intake, after visiting their doctor during the follow-up period.

Assessment of the degree of such dietary intake was measured by the Restriction of Protein, Potassium, Phosphate and Salt Diet (RPPPS) questionnaire in pre-dialysis patients, which was adapted from Vlaminck's study[229], and piloted for validity in the present study. The validity of this questionnaire had a tendency related to the progression of CKD, uncontrolled hyperkalemia and uncontrolled hyperphosphatemia, but there was no statistical significance due to the limited sample size (n=42). This was a limitation of using this questionnaire and it is strongly suggested re-validation of this questionnaire is required for further studies.

Sensitivity analyses determined the effects of two confounding factors on the primary outcome, which were causes of CKD and inconsistent exposure, or non-exposure, to HDS during the follow-up period. There was no difference between HDS use and the primary outcome.

9.3.4 The association between HDS and CKD complications

This is the first study to report on the association between HDS and uncontrolled hyperkalemia and hyperphosphatemia. Amongst patients who did not receive dialysis therapy, HDS use was associated with uncontrolled hyperphosphatemia (adjusted OR 3.53, 95% CI 1.20 – 10.43). This may be because some of the HDS used contained phosphate, such as bee pollen, multivitamins, swiftlet's nest drink, and some products which contained cereal or coffee, that are rich sources of phosphate, as well as wheatgrass.[165] Moreover, some dietary supplements contained vitamin D which increases absorption of phosphate in gastrointestinal tract and can lead to hyperphosphatemia in patients with CKD[165], i.e. multivitamins, rice bran oil, cod liver oil, bee pollen, and a product containing vitamins, minerals and botanical extracts. Uncontrolled hyperphosphatemia,

combined with calcium in the blood, can lead to the calcification of soft tissue and vascular tissue in patients with CKD.[162]

An association between HDS and uncontrolled hyperkalemia was not found (adjusted OR 0.59, 95% CI 0.25 – 1.38) as the HDS used may have contained only small amounts of potassium and some HDS may even increase excretion of potassium, such as tea for diuretic effects.

The non-measurement of serum levels of potassium (n=2) or phosphate (n=60) over one year did not affect the association of HDS use with uncontrolled hyperkalemia or hyperphosphatemia, as no differences in numbers of the non-measurement of such electrolytes, between the exposed and unexposed groups, were found. Further studies are required to examine such associations before any conclusions can be made, because there were small numbers of patients with hyperkalemia or hyperphosphatemia in the current study.

A limitation of the current study is that uncontrolled hyperkalemia was defined as over 5.0 mEq/l of a serum level of potassium, in order to create early detection of this problem. However, in practice hyperkalemia is defined as over 5.5 mEq/l of a serum level of potassium[185] and only two patients in the current study had over 5.5 mEq/l of a serum level of potassium. Therefore, the finding regarding association between HDS use and uncontrolled hyperkalemia, in the present study, should be used with caution. This issue needs to be investigated by involving a high number of participants when using a definition of hyperkalemia which is clinically significant.

Peripheral oedema, one of the CKD complications which may be affected by HDS containing sodium, was not examined, as a measure of oedema in clinical practice is inconsistent and relies on subjective data.

9.3.5 Methodological considerations

Sample size determination was calculated by the comparison of two means because this was the best way to analyse a continuous variable of the primary outcome in the present study, i.e. a decline in eGFR over a year. However the distribution of change in eGFR over a year was not normal, so a comparison of the two means cannot be made, as it violates the assumption of a t-test. Despite the fact that a t-test was not performed, it would appear that there was no difference in median change in eGFR over 12 months between exposed (-2.32 ml/min/1.73m^2/year) and unexposed groups (-1.86 ml/min/1.73m^2/year) (*p*-value = 0.72 tested by Mann Whitney *U* test).

This outcome was amended based on the dataset which found that the distribution of change in eGFR over a year was not normal and some respondents had initiated renal replacement therapy, which was likely to represent the fast progression of CKD. The primary outcome, the effect size, was thus newly defined as either at least -5 ml/min/1.73m^2/year of eGFR, or having reached renal replacement therapy. The dichotomous outcomes were defined as having fast progression of CKD and no fast progression. The finding showed that there was no association between the exposure of HDS and the fast progression of CKD when analysed by Chi-squared test, which was similar to comparing the median change in eGFR, over 12 months, between exposed and unexposed groups.

Therefore, univariate analyses between the exposure and the fast progression of CKD were conducted using Chi-squared tests and multiple logistic regression analysis in order to control for confounding factors. Post hoc determination of the sample size for non-parametric statistical analyses, using the comparison of two proportions of the fast progression of CKD,[230,231] indicated at least 72 and 144 numbers of the exposed and unexposed groups, respectively. Therefore,

numbers of respondents in the present study were a sufficient sample size in this study for the analysis which took place.

9.4 Strengths and weaknesses

9.4.1 Strengths

This is the first prospective, cohort study to ascertain the association between exposure to HDS and the fast progression of CKD, and its complications, amongst Thai patients with CKD stages 3 to 5. Advantages of a prospective cohort study are to determine a causal relationship and to minimise the recall bias of exposure, as the respondents were interviewed about their current HDS use. In contrast, a retrospective study collects data in the past, such as last year, so this may increase recall bias. There was a low rate of loss to follow-up (5%) in this study and no significant differences in demographic characteristics between the included group and the group of drop-outs. Objective data were collected for the outcomes in the present study and the quantity of exposure to HDS was measured, which prevented information and misclassification bias. There was unlikely to be selection bias as clinical characteristics between exposed and unexposed groups were not significantly different, such as age, sex, severity of CKD, comorbidities and uncontrolled blood pressure, A1C and LDL cholesterol. The sample in the present study seemed to represent the population of patients with CKD, stages 3 to 5, as there were no significant differences in demographic characteristics between the present study and those cited in the literature.

The findings in this study can be generalised to Asian patients with CKD, who tend to use the same types of herbal medicines as those identified in the present study, because the demographic characteristics of respondents in this study are consistent with the Asian population as a whole.[294] Some types of tropical herbal

medicine in the current study are shared across Asian countries, particularly in Southeast Asian countries, such as Gac fruit, Ivy ground and *Gynura procumbens* and some herbal medicines used in the present study are influenced by India, China or Japan, such as Shiitake mushrooms.

9.4.2 Weaknesses

Exposure to HDS was defined as the use of all types of HDS. This may have diluted the effects on kidney function, as each HDS may have a positive or negative influence on kidney function or no effect at all. Therefore, this study was likely to indicate only a crude association between HDS and the fast progression of CKD. Additionally, this research has examined the short-term effects (a year) of HDS on kidney function. This period may not be sufficient to examine or identify any long-term effects of HDS on kidney function.

Further studies are required to examine effects of specific herbal medicines on kidney function. The present findings suggest that river spiderwort and Chinese herbal medicines should be investigated for any detrimental effects on kidneys. A cohort study of the association between HDS and the progression of CKD should be followed up for more than a year, in order to investigate long-term effects on kidney function.

Of concern are the multiple confounding factors. Data for the large number of variables related to the primary outcome was collected, such as age, obesity, smoking status, degree of protein intake, uncontrolled blood pressure, A1C and LDL cholesterol, exposure to NSAIDs or COX-2 inhibitors, and prescribed, conventional medication adherence. Confounding effects were examined using multiple logistic regressions and it was found that existing proteinuria was a confounding factor in the present study.

Medical notes were not always comprehensive, with some biometric data not recorded. This is likely to have been because the clinician did not consider the tests necessary, rather than they were done but not recorded. However, there was sufficient sample size of such variables to analyse the findings.

9.5 Conclusions and implications

Despite no association between HDS and the fast progression of CKD amongst Thai patients with CKD evident from the present cohort study, a small number of patients suffered from acute kidney injury, which may be related to using river spiderwort combined with diclofenac or unknown Chinese herbal medicines. This does not mean that HDS can be safely used amongst patients with CKD, because some patients with CKD, in the present study, used HDS, which should be avoided; as noted in case reports or animal studies of renal toxicity, i.e. aloe, senna, ginseng, 'Ya Hom', 'Tripala', *Tinospora crispa* and spirulina. Moreover, there was a significant association between HDS use and uncontrolled hyperphosphatemia, although no relationship between HDS and uncontrolled hyperkalemia was found.

These findings provide scientific evidence of HDSs' effects on kidney function, and uncontrolled hyperkalemia and hyperphosphatemia amongst Thai patients with CKD stages 3 to 5 in order to inform health care providers who take care of CKD patients who plan to use HDS. Health care providers in Thailand should acknowledge these findings, and closely monitor kidney function and electrolytes amongst patients using HDS.

10. Thesis discussion

This final chapter summarises the findings presented in the previous chapters, in order to demonstrate how this work achieved the objectives of this thesis. Regarding the cohort study (presented in Chapter 9), the first objective was to determine any associations between HDS use and the progression of CKD. The second objective was to determine any association between HDS use and CKD complications, i.e. uncontrolled hyperkalemia or uncontrolled hyperphosphatemia and the final objective was to determine patterns of any other risk factors of CKD progression and its complications. Regarding the survey and qualitative study (presented in Chapter 8), the objectives were to determine 1) the prevalence, types and patterns of HDS use in Thai patients with CKD; 2) the demographic characteristics of Thai patients with CKD using HDS, compared with the non-users; 3) the association between HDS use and a level of adherence to prescribed, conventional medication; 4) the reasons why Thai outpatients with CKD use HDS; 5) patients' experiences of the beneficial and adverse effects from using HDS; and 6) the rate of non-disclosure of HDS use to a doctor and its reasons.

A survey provided background information regarding HDS use in Thai patients with CKD. The reasons for HDS use in patients with CKD were explored by both a survey and qualitative study, due to limited prior published evidence in this area amongst patients with CKD. The prospective, cohort study determined any association between HDS use and the fast progression of CKD in Thai patients, including any associations with uncontrolled hyperkalemia or hyperphosphatemia.

Key findings are now presented, together with an overview of the research results from the survey, the qualitative study and the prospective, cohort study. A summary of this discussion will show that the findings are robust, when

compared with previous literature. Finally implications for practice and policy and recommendations for further research are discussed.

10.1 Key findings

Respondents in both the survey and the prospective, cohort study were from the same sample and their demographic characteristics were as follows. Mean age (SD) was 66 (13) and the ratio between male and female was 0.8. There were a small number of current smokers (5%), and drinkers (5%). At least 60% of the respondents had diabetes and hypertension. Approximately 70% of the respondents had stage 3 CKD. At baseline, patients were taking an average of 8 $\pm$ 3 prescribed, conventional medications, which were anti-hypertensive agents (ACEIs 24%; ARBs 35%), anti-diabetic medicines (49%), lipid-lowering drugs (78%), low dose aspirin (40%), and medications for CKD complications (at least 20%). Less than 10% took NSAIDs or COX-2 inhibitors. A quarter had a low level of adherence to prescribed, conventional medication. Almost all HDS users combined them with their prescribed, conventional medicine (99%). The prospective, cohort study, over one year, found a 7% rate of death and that 8% initiated dialysis therapy.

The prevalence of herbal and dietary supplement (HDS) use over 12 months amongst Thai patients with stages 3 to 5 CKD was 45% (95%CI 40%-50%). In the survey, former alcohol drinking (adjusted OR 0.43, 95% CI 0.25-0.75) or those with a medium level of conventional medicine adherence (adjusted OR 0.53, 95% CI 0.32-0.87) were less likely to use HDS, compared with non-drinking or those with poor adherence to prescribed, conventional medication. However, there was inconsistency in associations between the degree of medication adherence and HDS use. In the cohort study, current and regular HDS users, i.e. the exposed group, were more likely to have a low level of

adherence (unadjusted OR 1.7, 95%CI 1.02-2.83) compared to the unexposed group.

The most frequently reported purposes for using HDS were to maintain well-being (61%), whilst HDS use for kidney diseases was also reported (30%). Thai patients with CKD used various types of HDS (304 and 65 different HDS used in the survey and the cohort study, respectively). The most frequently reported HDS used in both the survey and the cohort study were kariyat, turmeric, horse radish tree, mixed botanical extracts, vitamins and minerals, essence of chicken drink, germ oil, fish oil, protein supplement, and rice bran oil. Pharmacies and the media were frequently reported as sources of HDS and its information, respectively.

Most frequently reported influences on HDS use, from both the survey and the qualitative study, were family members and friends' recommendations, followed by a perception of HDS benefits and a willingness to try them. Almost three quarters reported non-disclosure of their HDS use to their doctor; reasons for secrecy being that their doctor did not ask (49%), or the patient had concerns about disapproval of HDS use from their doctor (16%).

The survey showed that nearly 80% of respondents reported perceived benefit from HDS, such as alleviating minor ailments (37%), maintaining well-being (31%), and slowing the progression of CKD (10%). However, one-tenth reported experiencing adverse events from HDS use, such as progression of CKD (37%), gastrointestinal symptoms (16%) and neurological symptoms (16%). Kariyat, river spiderwort and wheatgrass were reported by respondents to increase serum creatinine in the survey. Reviewing medical notes amongst the exposed group revealed two respondents had developed acute kidney injury, on top of their CKD, which may be related to the use of unknown Chinese herbal medicines, or river spiderwort combined with diclofenac diagnosed by a doctor. However, the cohort study did not find an association between current and

regular HDS use, and the fast progression of CKD, when defined as either a decline in eGFR of at least 5 ml/min/1.73m^2/year or reaching end-stage renal disease over one year (adjusted OR 1.16, 95%CI 0.66 - 2.03). Proteinuria showed the highest risk for the fast progression of CKD (adjusted OR 4.22, 95% CI 2.52 – 7.05), followed by younger age (adjusted OR 1.91, 95% CI 1.14 – 3.18). Existing proteinuria was found to be a confounding factor related to the association between HDS use and the fast progression of CKD.

Regarding HDS being related to CKD complications, the cohort study found an association between HDS use and uncontrolled hyperphosphatemia (adjusted OR 3.53, 95%CI 1.20 - 10.43). This may be because some HDS used in the exposed group contain phosphate or vitamin D, such as multivitamins, cod liver oil, bee pollen, rice brand oil, wheatgrass, botanical extracts and swiftlet's nest drink. Meanwhile there was no relationship between HDS use and uncontrolled hyperkalemia (adjusted OR 0.59, 95% CI 0.25 – 1.38).

10.2 Comparison with the literature

Demographic characteristics of the sample in the survey and the cohort study represent the population of Thai patients with CKD, as there were no differences in the proportions by sex, education levels, living in urban or rural areas, smoking and drinking status between respondents in the present study and the Thai general population in the Thai National census (2007).[260] There was no difference in the mean age and sex between the present study and the Thai CKD population.[290]

The prevalence of HDS use over 12 months, amongst Thai patients with CKD in the present survey (45%), is consistent with patients with CKD in Canada (45%)[16], and higher than reported in the Thai general population survey (33%).[5] Former drinking and medium adherence to prescribed, conventional medication were less likely to use HDS, compared with non-drinking and poor adherence.

However, there were no clear patterns for these factors and only limited evidence to support these associations.

There were no differences in the reasons for HDS use between the present studies and literature.[63,87,90,93,96] However, friends and family members were the most frequently reported influence on HDS use amongst Thai patients in the present studies; data which is consistent with the literature concerning other Asian populations, such as Malaysia and Japan.[54,57,61] In contrast, Western populations are more likely to use HDS which have been suggested by their health care providers.[16,25,58] Most Thai HDS users in the present survey reported non-disclosure of their use to their doctor (72%), which is consistent with other Asian populations.[98,110,111] On the other hand, Western populations are more likely to inform their doctor (55-67%).[15,16]

There are a lack of clinical trials to identify which types of HDS, reported to be used for kidney diseases in the present survey, are effective. Reported renal adverse effects from HDS in the present survey and the cohort study, also had only limited scientific evidence to support them.

An association between HDS use and the fast progression of CKD was not found in the present cohort study. This is inconsistent with previous surveys and a case-control study in Thailand and Taiwan[4,5,7], which found that herbal medicine, is related to CKD or end-stage renal disease. However, the respondents in the Taiwanese studies mainly used Chinese herbal medicine, which was likely to be contaminated with NSAIDs[7], whilst one survey in Thailand found a weak association between herbal medicine and CKD. Another reason for there being no association between HDS use and the fast progression of CKD in the current study may be due to the limited sample size to detect the small effect size of HDS use.

Various types of HDS were used amongst Thai patients with CKD in the present cohort study, and therefore such an equivocal situation challenges a researcher to investigate renal effects from a specific type of HDS, whilst simultaneously achieving a sufficient sample size to determine such association.

Existing proteinuria and younger age were associated with the fast progression of CKD in the present cohort study, which are known risk factors.[157,169-171,173]

There is a significant association between HDS and uncontrolled hyperphosphatemia; the first time this link has been found. This may be due to the use of several HDS products containing phosphate or vitamin D, such as multivitamins, cod liver oil, bee pollen, rice brand oil, wheatgrass, botanical extracts and swiftlet's nest drink. However, an association between HDS use and uncontrolled hyperkalemia was not found in the present cohort study. There are several reasons to support this finding; HDS may contain a small amount of potassium; and some HDS, such as tea for diuretic effects may increase excretion of potassium.

10.3 Strengths and weaknesses

Strengths

There are several strengths of this thesis. First of all, this is the first prospective cohort study to investigate any causal relationship between HDS and the fast progression of CKD in Thai patients with advanced CKD, including the associations with the complications of CKD. The findings from both the survey and the qualitative study also provide the comprehensive information about HDS use amongst Thai patients with advanced CKD. This study had a high response rate to the survey, as well as only small numbers of missing data in the survey, since information was gathered using face-to-face interviews. There was also a low rate of drop out in the cohort study, although interviews can result in social

desirability bias. The validity and reliability of the questionnaire in this thesis was acceptable, and helped to minimise information bias. Objective data was measured for the outcome in the cohort study, whilst the quantity of exposure to HDS was measured. Therefore, these procedures could prevent information and misclassification bias. Finally, sensitivity analyses were performed for the primary outcome of the cohort study; they revealed the same findings as the original results. This could contribute to the robust findings.

Weaknesses

Limitations of this thesis are that all types of HDS use were defined as 'the exposure' so this may have resulted in the inconclusive findings, because each HDS may have either different effects on the renal system or no effect. However, as the types of HDS used are unknown, this seems to be a sensible way to achieve the primary aim of this thesis. If only one type of HDS was defined as the exposure, then it is likely a larger sample size would be needed, which was not feasible within the scope of a 3-year PhD programme. Also it was unknown which HDS would be an appropriate choice to study, as the different types of HDS used by patients with advanced CKD were unknown. The findings in the present study provide suitable individual herbal medicines, into which further research would be valuable in order to understand their effects on CKD progression. If findings were to show a strong association between HDS use and the progression of CKD, individual ingredients should be investigated to determine which is responsible for the effect on CKD progression. Similarly, if any were suspected of being beneficial in slowing the progression of CKD, these would also be worthy of further investigation. Whilst no HDS were found to be implicated in the fast progression of CKD, the findings do suggest that river spiderwort should be examined for its potential negative effect in terms of acute kidney injury. HDS use in this study was self-reported, so some patients may not

disclose their HDS use; therefore the findings related to this issue should be used with caution.

Selecting two teaching hospitals for the recruitment may have resulted in selection bias and doubts as to whether the sample can be generalised. However, the demographics of respondents in this study, i.e. gender, education levels and living in urban or rural areas, and smoking and drinking status, are consistent with the Thai general population. The mean age of respondents in this study was also similar to the CKD general population in Thailand.

Despite the determination of sample size in this study calculated by a comparison of the means of the outcome, eGFR over one year, between two groups, Chi-squared tests and multiple logistic regressions were performed as the distribution of the outcome was not normal. Additionally, during the follow-up period some patients initiated dialysis, which seemed to indicate the fast progression of CKD. Therefore, the definition of the dependent variable was newly defined as either having or not having fast progression of CKD over one year - a dichotomous variable. The fast progression of CKD was defined as either a decline in eGFR of at least 5 ml/min/1.73m^2/year or initiated dialysis over one year. However, post hoc determination of the sample size, for non-parametric statistics, confirmed there was sufficient sample size in this study for the analysis to be conducted.

There were three investigators who interviewed respondents, which can lead to differences in responses and recording of data. To ensure consistency in data collection, the investigators were trained how to ask respondents the questions in a standardised way. The main researcher (MT), by observing the conduct of their first interview, confirmed the data collection procedure was consistent.

Extracting information from medical notes can result in missing data, as data may not have been recorded, or some parts of the medical notes may have been

misplaced or used for another purpose. However, there were little missing data in this study.

To examine potentially confounding factors in the cohort study, such factors, such as demographics, were tested using Chi-squared tests and multiple logistic regressions in order to identify whether such factors related to an association between the exposure and the outcomes. This found that existing proteinuria was a confounding factor in the association between HDS use and the fast progression of CKD. Therefore, this variable was included in the multiple logistic regression analysis to control for it.

10.4 Implications for practice and policy

The findings suggest that health care providers, particularly in Thailand, should acknowledge that almost half of their Thai patients with CKD stages 3 to 5 are likely to use HDS and they may not inform their doctor about this use. They should also be aware that patients with a medium level of adherence to prescribed, conventional medication are less likely to use HDS than those with poor adherence. However, there was an inconsistent association between HDS use and the degree of medication adherence. Thus, doctors and other health care professionals should regularly inquire about HDS use, as standard practice for managing CKD in Thailand. Pharmacists, in particular, should further study the relationship between HDS use and the degree of medication adherence before standard practice can be employed.

To date there is limited scientific evidence to provide information for health care providers, upon which to base decisions about which type of HDS should be avoided by patients with CKD. The findings in the present cohort study aimed to establish such knowledge. Even though an association between HDS and the fast progression of CKD was not found in the short-term, it would appear that unknown Chinese herbal medicine or river spiderwort combined with diclofenac

may be related to acute kidney injury, as reported by a doctor in patients' medical notes. HDS use was also associated with uncontrolled hyperphosphatemia in the current cohort study. This may be because some HDS used in this study contain phosphate or vitamin D. Thus, health care providers should closely monitor their patients using such products.

There are many modified risk factors related to the progression of CKD, such as obesity, smoking, proteinuria, uncontrolled blood pressure, raised blood sugar and raised lipid levels, based on evidence in the relevant literature. Given the findings from the present cohort study, it can be seen that existing proteinuria is more likely to be associated with the fast progression of CKD than other factors in Thai patients, which is consistent with findings presented in previous literature. Controlling for this factor should be the main priority for the prevention of fast progression of CKD. It would appear that this factor is more strongly associated with worsening kidney function than HDS use.

Most frequently reported as a supply source of HDS are pharmacies. Community pharmacists should therefore play an important role in educating their customers how to properly use HDS. They should also monitor any adverse effects of HDS, particularly in people with kidney insufficiency.

The Thai Health Product Vigilance Center has intensively monitored eight herbal medicines on the Thai National List of Essential Medicines, including Kariyat and turmeric[125] and has established, since 1997, a spontaneous reporting system in order to monitor adverse effects from other HDS products in Thailand.[126] Under this surveillance there has been limited evidence to provide information regarding the safety of HDS use in patients with CKD. Some HDS used in the present studies are not on the list, such as river spiderwort. Wheatgrass products have been registered as a food so they have not been restricted, nor has their safety been monitored under post-marketing surveillance, the same as medicines. River spiderwort was reported by a doctor to be related to acute

kidney injury in the medical note and wheatgrass was reported by a patient in the present survey to increase serum creatinine. These issues should be intensively monitored by Thai Health Product Vigilance Center. This center should also encourage health care providers and consumers in Thailand to report adverse events, particularly in patients with CKD, who are more vulnerable to adverse effects on their kidneys. Further studies of the HDS safety profile, in patients with CKD, need to be carried out by government bodies, researchers, and manufacturers of herbal or dietary supplement products.

The research findings showed that the media, such as television and radio, plays an important part in disseminating HDS information and influencing patients to use HDS. The Thai Food and Drug Administration should inspect HDS advertising in order to ensure that HDS companies provide proper information, due to the reported HDS use for unproven indications in the present survey. This body should provide a fact sheet of HDS information for consumers, in order to prevent unnecessary or inappropriate use of HDS.

10.5 Recommendations for further study

There has been a scarcity of safety information about HDS use in patients with CKD so research, particularly phase I clinical trials, in this field needs to be conducted in order to provide safety profiles of HDS. This is because many HDS have been registered as a diet, so they are not required to be studied for toxicity in humans. The association between HDS and the fast progression of CKD needs to be investigated for its long-term effects on kidney function and renal adverse effects, according to the specific herbal medicine used, such as river spiderwort. No association between HDS use and the fast progression of CKD was found in the present cohort study, due to limited sample size, so a population-based cohort study needs to confirm this finding before a conclusion can be made. It would seem that small numbers of herbal medicines may be related to acute

kidney injury (AKI) in Thai patients with stages 3 to 5 CKD as found in the results. Therefore, the causes of AKI apparently related to HDS use amongst patients diagnosed as acute renal failure, need to be examined.

The present studies were not aimed at investigating beneficial effects of HDS on kidney function and there is a significant lack of scientific evidence in this area, which needs to be examined. Some HDS used in this study appear to have beneficial effects on kidney function, in both animal and human models, such as spring bitter cucumber, a mixture of boesenbergia, mint, ginger, galangal, lemongrass, kaffir lime leaves and shallots, and holy mushrooms. This potentially beneficial association needs further investigation. Almost all patients reported using HDS together with prescribed, conventional medicine in the present survey. This raises the question of how to integrate HDS use with conventional medicines, in order to use them more effectively and safely in patients with CKD. This matter needs to be investigated, with particular focus on the effects of HDS-drug interaction.

The research results show an inconsistent association between HDS use and degree of adherence to prescribed, conventional medication. This should be further examined before any firm conclusions can be made. This could assist in understanding this relationship and guide health care providers in dealing with this issue.

The finding that there is a high amount of non-disclosure of HDS use to their doctors in Thai patients with CKD, requires qualitative studies to ascertain the root causes of this problem, and what strategies could be employed to resolve it.

10.6 Thesis conclusion

Almost half of Thai patients with CKD stages 3 to 5 in the current survey were likely to use HDS together with prescribed, conventional medication, although

there is limited scientific evidence to support their beneficial effects on kidney function and their safety. The findings in the present cohort study seem to provide safety information for using HDS in Thai patients with CKD. No association between HDS use and the fast progression of CKD in Thai patents with stages 3 to 5 CKD was found, due to limited sample size to detect the small effect size of using HDS. It would appear that proteinuria is likely to influence the fast progression of CKD more than HDS use. HDS use was also associated with uncontrolled hyperphosphatemia in the present cohort study. Health care providers should closely monitor patients who are using Chinese herbal medicine or river spiderwort which, as cases suggest, may be related to acute kidney injury in patients with stages 3 to 5 CKD. They should also monitor serum levels of phosphate amongst patients using products containing phosphate or vitamin D. Further studies are needed to investigate the association between HDS use and the fast progression of CKD, greater than one year, and to identify any beneficial and/or detrimental effects of specific herbal medicines on kidney function.

References

1. World Health Organization. *WHO traditional medicine strategy 2002-2005*. Geneva: World Health Organization, 2002.
2. Jha V. Herbal medicines and chronic kidney disease. *Nephrology* 2010;15(Suppl S2):10-17.
3. Luyckx VA. Nephrotoxicity of alternative medicine practice. *Adv Chronic Kidney Dis* 2012;19(3):129-41.
4. Guh JY, Chen HC, Tsai JF, Chuang LY. Herbal therapy is associated with the risk of CKD in adults not using analgesics in Taiwan. *Am J Kidney Dis* 2007;49(5):626-33.
5. Ingsathit A, Thakkinstian A, Chaiprasert A, Sangthawan P, Gojaseni P, Kiattisunthorn K, et al. Prevalence and risk factors of chronic kidney disease in the Thai adult population: Thai SEEK study. *Nephrol Dial Transplant* 2010;25(5):1567-75.
6. Hsieh CF, Huang SL, Chen CL, Chen WT, Chang HC, Wu ML, et al. Increased risk of chronic kidney disease among users of non-prescribed Chinese herbal medicine in Taiwan. *Prev Med* 2012;55(2):155-59.
7. Tsai SY, Tseng HF, Tan HF, Chien YS, Chang CC. End-stage renal disease in Taiwan: a case-control study. *J Epidemiol* 2009;19(4):169-76.
8. De Smet P. Health risks of herbal remedies: an update. *Clin Pharmacol Ther* 2004;76(1):1-17.
9. Kozyrskyj A. Herbal products in Canada: How safe are they? *Can Fam Physician* 1997;43:697-702.
10. Timbo BB, Ross MP, McCarthy PV, Lin C-TJ. Dietary supplements in a national survey: prevalence of use and reports of adverse events. *J Am Diet Assoc* 2006;106(12):1966-74.
11. Kidney Disease: Improving Global Outcome (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* 2012;3(1):1-150.
12. The Nephrology Society of Thailand. *Clinical practice guidelines for pre-dialysis patients in 2009*. 1st ed. Bangkok: The Nephrology Society of Thailand, 2009.
13. Wen CP, Cheng TYD, Tsai MK, Chang YC, Chan HT, Tsai SP, et al. All-cause mortality attributable to chronic kidney disease: a prospective cohort study based on 462293 adults in Taiwan. *Lancet* 2008;371(9631):2173-82.
14. Kara B. Herbal product use in a sample of Turkish patients undergoing haemodialysis. *J Clin Nurs* 2009;18(15):2197-205.
15. Grabe DW, Garrison GD. Comparison of natural product use between primary care and nephrology patients. *Ann Pharmacother* 2004;38(7):1169-72.
16. Spanner ED, Duncan AM. Prevalence of dietary supplement use in adults with chronic renal insufficiency. *J Ren Nutr* 2005;15(2):204-10.
17. Krousel-Wood MA, Muntner P, Joyce CJ, Islam T, Stanley E, Holt EW, et al. Adverse effects of complementary and alternative medicine on antihypertensive medication adherence: findings from the cohort study of medication adherence among older adults. *J Am Geriatr Soc* 2010;58(1):54-61.
18. Weizman AV, Ahn E, Thanabalan R, Leung W, Croitoru K, Silverberg MS, et al. Characterisation of complementary and alternative medicine use and its impact on medication adherence in inflammatory bowel disease. *Aliment Pharmacol Ther* 2012;35(3):342-49.

19. Gohar F, Greenfield SM, Beevers DG, Lip GYH, Jolly K. Self-care and adherence to medication: a survey in the hypertension outpatient clinic. *BMC Complement Altern Med* 2008;8(8):4-12.
20. Caspi O, Sechrest L, HC P, CL M, IR B, M N. On the definition of complementary, alternative, and integrative medicine: societal mega-stereotypes vs. the patients' perspectives. *Altern Ther Health Med* 2003;9(6):58-62.
21. Payyappallimana U. Role of traditional medicine in primary health care: an overview of perspectives and challenges. *Yokohama J Soc Sci* 2010;14(6):57-77.
22. National Center for Complementary and Alternative Medicine. What is complementary and alternative medicine? 2010. http://nccam.nih.gov/sites/nccam.nih.gov/files/D347_05-25-2012.pdf (accessed 12 October 2010).
23. House of Lords. Complementary and alternative medicine: science and technology, sixth report. 2000. http://www.publications.parliament.uk/pa/ld199900/ldselect/ldsctech/123/12301.htm (accessed 11 October 2010).
24. Ministry of Public Health. Traditional medicine in Kingdom of Thailand. 2013. http://herbalnet.healthrepository.org/bitstream/123456789/2288/10/09-p.97-120.pdf (accessed 26th March 2013).
25. Barnes PM, Powell-Griner E, McFann K, Nahin RL. Complementary and alternative medicine use among adults: United States, 2002. *Advance Data* 2004;343:1-19.
26. The Role of Thai traditional medicine in health promotion. 6GCHP Bangkok Thailand 2005; 2005; Bangkok, Thailand.
27. Jiaranaikajorn T, Panthawangkul J, Thamlikitkul V. Use of alternative medicines among medical patients at Siriraj hospital. *Siriraj Medical Journal* 2002;54(10):603-10.
28. Gardiner P, Kemper KJ, Legedza A, Phillips RS. Factors associated with herb and dietary supplement use by young adults in the United States. *BMC Complement Altern Med* 2007;7:39.
29. Kennedy J. Herb and supplement use in the US adult population. *Clin Ther* 2005;27(11):1847-58.
30. Laliberte M-C, Normandeau M, Lord A, Lamarre D, Cantin I, Berbiche D, et al. Use of over-the-counter medications and natural products in patients with moderate and severe chronic renal insufficiency. *Am J Kidney Dis* 2007;49(2):245-56.
31. World Health Organization. General guidelines for methodologies on research and evaluation of traditional medicine. 2000. http://whqlibdoc.who.int/hq/2000/WHO_EDM_TRM_2000.1.pdf (accessed 11 October 2010).
32. U.S. Food and Drug Administration. Q&A on dietary supplements. 2009. http://www.fda.gov/Food/DietarySupplements/QADietarySupplements/default.htm#what_is (accessed 25 October 2010).
33. Ministry of Public Health. Public health law. 2014. http://www.moph.go.th/ops/minister_06/laws.htm (accessed 21st April 2014).
34. Stys T, Stys A, Kelly P, Lawson W. Trends in use of herbal and nutritional supplements in cardiovascular patients. *Clin Cardiol* 2004;27(2):87-90.
35. Radimer K, Bindewald B, Hughes J, Ervin B, Swanson C, Picciano MF. Dietary supplement use by US adults: data from the National Health and Nutrition Examination Survey, 1999-2000. *Am J Epidemiol* 2004;160(4):339-49.
36. Aydin S, Bozkaya AO, Mazicioglu M, Gemalmaz A, Ozcakir A, Ozturk A. What influences herbal medicine use?- Prevalence and related factors. *Turk J Med Sci* 2008;38(5):455-63.

37. Guo X, Willows N, Kuhle S, Jhangri G, Veugelers PJ. Use of vitamin and mineral supplements among Canadian adults. *Can J Public Health* 2009;100(4):357-60.
38. Hess S, De Geest S, Halter K, Dickenmann M, Denhaerynck K. Prevalence and correlates of selected alternative and complementary medicine adult renal transplant patients. *Clin Transplant* 2009;23(1):56-62.
39. Nowack R, Balle C, Birnkammer F, Koch W, Sessler R, Birck R. Complementary and alternative medications consumed by renal patients in Southern Germany. *J Ren Nutr* 2009;19(3):211-19.
40. Al-Windi A, Elmfeldt D, Svardsudd K. The relationship between age, gender, well-being and symptoms, and the use of pharmaceuticals, herbal medicines and self-care products in a Swedish municipality. *Eur J Clin Pharmacol* 2000;56(4):311-17.
41. Balluz LS, Kieszak SM, Philen RM, Mulinare J. Vitamin and mineral supplement use in the United States: results from the Third National Health and Nutrition Examination Survey. *Arch Fam Med* 2000;9(3):258-62.
42. Singh V, Raidoo DM, Harries CS. The prevalence, patterns of usage and people's attitude towards complementary and alternative medicine (CAM) among the Indian community in Chatsworth, South Africa. *BMC Complement Altern Med* 2004;4:3.
43. Xue CC, Zhang AL, Lin V, Da Costa C, Story DF. Complementary and alternative medicine use in Australia: a national population-based survey. *J Altern Complement Med* 2007;13(6):643-50.
44. Marques-Vidal P, Pecoud A, Hayoz D, Paccaud F, Mooser V, Waeber G, et al. Prevalence and characteristics of vitamin or dietary supplement users in Lausanne, Switzerland: the CoLaus study. *Eur J Clin Nutr* 2009;63(2):273-81.
45. Ock SM, Choi JY, Cha YS, Lee J, Chun MS, Huh CH, et al. The use of complementary and alternative medicine in a general population in South Korea: results from a national survey in 2006. *J Korean Med Sci* 2009;24(1):1-6.
46. Aziz Z, Tey NP. Herbal medicines: prevalence and predictors of use among Malaysian adults. *Complement Ther Med* 2009;17(1):44-50.
47. Hunt KJ, Coelho HF, Wider B, Perry R, Hung SK, Terry R, et al. Complementary and alternative medicine use in England: results from a national survey. *Int J Clin Pract* 2010;64(11):1496-502.
48. Thomson P, Jones J, Evans JM, Leslie SJ. Factors influencing the use of complementary and alternative medicine and whether patients inform their primary care physician. *Complement Ther Med* 2012;20(1-2):45-53.
49. Matthees BJ, Anantachoti P, Kreitzer MJ, Savik K, Hertz MI, Gross CR. Use of complementary therapies, adherence, and quality of life in lung transplant recipients. *Heart Lung* 2001;30(4):258-68.
50. Moolasarn S, Sripa S, Kuesirikiet V, Sutawee K, Huasary J, Chaisila C, et al. Usage of alternative medicine in cancer patients. *Siriraj Medical Journal* 2003;55(6):307-23.
51. Moolasarn S, Sripa S, Kuessirikiet V, Sutawee K, Huasary J, Chaisila C, et al. Usage of and cost of complementary/alternative medicine in diabetic patients. *J Med Assoc Thai* 2005;88(11):1630-37.
52. Lee G, Charn T, Ng T. Complementary and alternative medicine use in patients with chronic diseases in primary care is associated with perceived quality of care and cultural beliefs. *Fam Pract* 2004;21(6):654-60.
53. Barraco D, Valencia G, Riba AL, Nareddy S, Draus CBSN, Schwartz SM. Complementary and alternative medicine (CAM) use patterns and disclosure to physicians in acute coronary syndromes patients. *Complement Ther Med* 2005;13(1):34-40.

54. Hyodo I, Amano N, Eguchi K, Narabayashi M, Imanishi J, Hirai M, et al. Nationwide survey on complementary and alternative medicine in cancer patients in Japan. *J Clin Oncol* 2005;23(12):2645-54.
55. Molassiotis A, Fernadez-Ortega P, Pud D, Ozden G, Scott JA, Panteli V, et al. Use of complementary and alternative medicine in cancer patients: a European survey. *Ann Oncol* 2005;16(4):655-63.
56. Kumar D, Bajaj S, Mehrotra R. Knowledge, attitude and practice of complementary and alternative medicines for diabetes. *Public Health* 2006;120(8):705-11.
57. Saw JT, Bahari MB, Ang HH, Lim YH. Herbal use amongst multiethnic medical patients in Penang hospital: pattern and perceptions. *Med J Malaysia* 2006;61(4):422-32.
58. Yeh GY, Davis RB, Phillips RS. Use of complementary therapies in patients with cardiovascular disease. *Am J Cardiol* 2006;98(5):673-80.
59. Hori S, Mihaylov I, Vasconcelos JC, McCoubrie M. Pattern of complementary and alternative medicine use amongst outpatients in Tokyo, Japan. *BMC Complement Altern Med* 2008;8:14.
60. Rossi P, Torelli P, Lorenzo CD, Sances G, Manzoni GC, Tassorelli C, et al. Use of complementary and alternative medicine by patients with cluster headache: results of a multi-centre headache clinic survey. *Complement Ther Med* 2008;16(4):220-27.
61. Hasan SS, Ahmed SI, Bukhari NI, Loon WCW. Use of complementary and alternative medicine among patients with chronic diseases at outpatient clinics. *Complement Ther Clin Pract* 2009;15(3):152-57.
62. Wilkinson JM, Jelinek H. Complementary medicine use among attendees at a rural health screening clinic. *Complement Ther Clin Pract* 2009;15(2):80-84.
63. Lambert TD, Morrison KE, Edwards J, Clarke CE. The use of complementary and alternative medicine by patients attending a UK headache clinic. *Complement Ther Med* 2010;18(3-4):128-34.
64. Ogbera AO, Dada O, Adeleye F, Jewo PI. Complementary and alternative medicine use in diabetes mellitus. *West Afr J Med* 2010;29(3):158-62.
65. Braun LA, Cohen M. Use of complementary medicines by cardiac surgery patients; undisclosed and undetected. *Heart Lung Circ* 2011;20(5):305-11.
66. Ali-Shtayeh MS, Jamous RM, Jamous RM. Complementary and alternative medicine use amongst Palestinian diabetic patients. *Complement Ther Clin Pract* 2012;18(1):16-21.
67. Shorofi SA, Arbon P. Complementary and alternative medicine (CAM) among hospitalised patients: an Australian study. *Complement Ther Clin Pract* 2010;16(2):86-91.
68. Strejilevich SA, Sarmiento MJ, Scapola M, Gil L, Martino DJ, Gil JF, et al. Complementary and alternative medicines usage in bipolar patients from Argentina and Colombia: associations with satisfaction and adherence to treatment. *J Affect Disord* 2013;149(1-3):393-7.
69. Satyapan N, Patarakitvanit S, Temboonkiet S, Vudhironarit T, Tankanitlert J. Herbal medicine: affecting factors and prevalence of use among Thai population in Bangkok. *J Med Assoc Thai* 2010;93(Suppl. 6):S139-44.
70. Barnes J, Ernst E. Complementary medicine. *Brit J Gen Pract* 1997;4(418):329.
71. Zollman C, Vickers A. What is complementary medicine? *Br Med J* 1999;319(7211):693-96.
72. Eisenberg DM, Kessler RC, Foster C, Norlock FE, Calkins DR, Delbanco TL. Unconventional medicine in the United States - prevalence, costs, and patterns of use. *N Engl J Med* 1993;328(4):246-52.

73. Ernst E, Resch KL, Mills S, Hill R, Mitchell A, Willoughby M, et al. Complementary medicine - a definition. *Br J Gen Pract* 1995;45(398):506.
74. Cheung CK, Wyman JF, Halcon LL. Use of complementary and alternative therapies in community-dwelling older adults. *J Altern Complement Med* 2007;13(9):997-1006.
75. Qato DM, Alexander C, Conti RM, Johnson M, Schumm P, Lindau ST. Use of prescription and over-the-counter medications and dietary supplements among older adults in the United States. *JAMA* 2008;300(24):2867-78.
76. Levine MAH, Xu S, Gaebel K, Brazier N, Bedard M, Brazil K, et al. Self-reported use of natural health products: a cross-sectional telephone survey in older Ontarians. *J Geriatr Pharmacother* 2009;7(6):383-92.
77. Gunther S, Patterson RE, Kristal AR, Stratton KL, White E. Demographic and health-related correlates of herbal and specialty supplement use. *J Am Diet Assoc* 2004;104(1):27-34.
78. Honda K, Jacobson JS. Use of complementary and alternative medicine among United States adults: the influences of personality, coping strategies, and social support. *Prev Med* 2005;40(1):46-53.
79. Araz A, Harlak H, Mese G. Factors related to regular use of complementary/alternative medicine in Turkey. *Complement Ther Med* 2009;17(5-6):309-15.
80. Imai T, Nakamura M, Ando F, Shimokata H. Dietary supplement use by community-living population in Japan: data from the National Institute for Longevity Sciences Longitudinal Study of Aging (NILS-LSA). *J Epidemiol* 2006;16(6):249-60.
81. Lee JS, Kim J. Factors affecting the use of dietary supplements by Korean adults: data from the Korean National Health and Nutrition Examination Survey III. *J Am Diet Assoc* 2009;109(9):1599-605.
82. Chung VCH, Ma PHX, Tang TSK, Lau CH, Kim JH, Griffiths SM. Do patients tell their clinicians they are using both prescribed and over the counter allopathic and traditional medicines? *Eur J Integr Med* 2011;3(4):e289-98.
83. Conner M, Kirk SF, Cade JE, Barrett JH. Why do women use dietary supplements? The use of the theory of planned behaviour to explore beliefs about their use. *Soc Sci Med* 2001;52(4):621-33.
84. Bruno JJ, Ellis JJ. Herbal use among US elderly: 2002 National Health Interview Survey. *Ann Pharmacother* 2005;39(4):643-48.
85. McFadden KL, Hernandez TD, Ito TA. Attitudes toward complementary and alternative medicine influence its use. *Explore* 2010;6(6):380-88.
86. Smith BW, Dalen J, Wiggins KT, Christopher PJ, Bernard JF, Shelley BM. Who is willing to use complementary and alternative medicine. *Explore* 2008;4(6):359-67.
87. Vickers KA, Jolly KB, Greenfield SM. Herbal medicine: women's views, knowledge and interaction with doctors: a qualitative study. *BMC Complement Altern Med* 2006;6:40.
88. Thomas K, Coleman P. Use of complementary or alternative medicine in a general population in Great Britain. results from the National Omnibus Survey. *J Public Health* 2004;26(2):152-57.
89. Astin JA. Why patients use alternative medicine: results of a national study. *JAMA* 1998;279(19):1548-53.
90. Yu H, Wang S, Liu J, Lewith G. Why do cancer patients use Chinese medicine? - a qualitative interview. *Eur J Integr Med* 2012;4(2):e197-203.
91. Rausch SM, Winegardner F, Kruk KM, Phatak V, Wahner-Roedler DL, Bauer B, et al. Complementary and alternative medicine: use and disclosure in radiation oncology community practice. *Support Care Cancer* 2011;19(4):521-29.

92. Sewitch MJ, Yaffe M, Maisonneuve J, Prchal J, Ciampi A. Use of complementary and alternative medicine by cancer patients at a Montreal hospital. *Integr Cancer Ther* 2011;10(4):305-11.
93. Verhoef MJ, Balneaves LG, Boon HS, Vroegindewey A. Reasons for and characteristics associated with complementary and alternative medicine use among adult cancer patients: a systematic review. *Integr Cancer Ther* 2005;4(4):274-86.
94. Wilkinson S, Gomella LG, Smith JA, Brawer MK, Dawson NA, Wajsman Z, et al. Attitudes and use of complementary medicine in men with prostate cancer. *J Urol* 2002;168(6):2505-09.
95. Chen W-T, Shiu C-S, Simoni J, Fredriksen-Goldsen K, Zhang F, Starks H, et al. Attitudes toward antiretroviral therapy and complementary and alternative medicine in Chinese patients infected with HIV. *J Assoc Nurses AIDS Care* 2009;20(3):203-17.
96. Rawsthorne P, Shanahan F, Cronin NC, Anton PA, Lofberg R, Bohman L, et al. An international survey of the use and attitudes regarding alternative medicine by patients with inflammatory bowel disease. *Am J Gastroenterol* 1999;94(5):1298-303.
97. Bishop FL, Yardley L, Lewith GT. A systematic review of beliefs involved in the use of complementary and alternative medicine. *J Health Psychol* 2007;12(6):851-67.
98. Kuo GM, Hawley ST, Todd WL, Balkrishnan R, Volk RJ. Factors associated with herbal use among urban multiethnic primary care patients: a cross-sectional survey. *BMC Complement Altern Med* 2004;4:18.
99. Sirois FM, Gick ML. An investigation of the health beliefs and motivations of complementary medicine clients. *Soc Sci Med* 2002;55(6):1025-37.
100. Klepser TB, Doucette WR, Horton MR, Buys LM, Ernst ME, Ford JK, et al. Assessment of patients' perceptions and beliefs regarding herbal therapies. *Pharmacotherapy* 2000;20(1):83-87.
101. Kappauf H, Leykauf-Ammon D, Bruntsch U, Horneber M, Kaiser G, Buschel G, et al. Use of and attitudes held towards unconventional medicine by patients in a department of internal medicine / oncology and haematology. *Support Care Cancer* 2000;8(4):314-22.
102. Eisenberg DM, Kessler RC, Van Rompay MI, Kaptchunk TJ, Wilkey SA, Appel S, et al. Perceptions about complementary therapies relative to conventional therapies among adults who use both: results from a national survey. *Ann Intern Med* 2001;135(5):344-51.
103. McCrea CE, Pritchard ME. Concurrent herb-prescription medication use and health care provider disclosure among university students. *Complement Ther Med* 2011;19(1):32-36.
104. Alkhateeb FM, Doucette WR, Ganther-Urmie JM. Influences on consumer spending for herbal products. *Res Social Adm Pharm* 2006;2(2):254-65.
105. Ryan A, Wilson S, Taylor A, Greenfield S. Factors associated with self-care activities among adults in the United Kingdom: a systematic review. *BMC Public Health* 2009;9:96-106.
106. Howell L, Kochhar K, Saywell R, Zollinger T, Koehler J, Mandzuk C, et al. Use of herbal remedies by Hispanic patients: Do they inform their physician? *J Am Board Fam Med* 2006;19(6):566-78.
107. Bubela T, Boon H, Caulfield T. Herbal remedy clinical trials in the media: a comparison with the coverage of conventional pharmaceuticals. *BMC Medicine* 2008;6:35.
108. Weeks LC, Strudsholm T. A scoping review of research on complementary and alternative medicine (CAM) and the mass media: looking back, moving forward. *BMC Complement Altern Med* 2008;8:43.
109. Farooqui M, Hassali MA, Shatar AKA, Shafie AA, Farooqui MA, Saleem F, et al. Complementary and alternative medicines (CAM) disclosure to the

health care providers: a qualitative insight from Malaysian cancer patients. *Complement Ther Clin Pract* 2012;18(4):252-56.
110. Chao MT, Wade C, Kronenberg F. Disclosure of complementary and alternative medicine to conventional medical providers: variation by race/ethnicity and type of CAM. *J Natl Med Assoc* 2008;100(11):1341-49.
111. Mehta DH, Gardiner PM, Phillips RS, McCarthy EP. Herbal and dietary supplement disclosure to health care providers by individuals with chronic conditions. *J Altern Complement Med* 2008;14(10):1263-69.
112. Peltzer K, Preez NF-d, Ramlagan S, Fomundam H, Anderson J. Traditional complementary and alternative medicine and antiretroviral treatment adherence among HIV patients in Kwazulu-Natal, South Africa. *Afr J Trad CAM* 2010;7(2):125-37.
113. Cherniack EP. Complementary medicine use is not associated with non-adherence to conventional medication in the elderly: a retrospective study. *Complement Ther Clin Pract* 2011;17(4):206-08.
114. Bailey GR, Barner JC, Weems JK, Leckbee G, Solis R, Montemayor D, et al. Assessing barriers to medication adherence in underserved patients with diabetes in Texas. *Diabetes Educ* 2012;38(2):271-79.
115. Jiratchariyakul W, Mahady GB. Overview of botanical status in EU, USA, and Thailand. *Evid Based Complement Alternat Med* 2013;21:480128.
116. Chuthaputti A. National traditional system of medicine recognized by the Thai government, 2007.
117. The Institute of Thai Traditional Medicine. Missions of the Institute of Thai Traditional Medicine. 2013. http://ittm.dtam.moph.go.th/index.php?option=com_content&view=featured&Itemid=152 (accessed 17th February 2014).
118. Medicinal Plant Research Institute. Missions of Medicinal Plant Research Institute. 2013. http://dmsc2.dmsc.moph.go.th/webroot/Plant/Mpri2013/index.shtm (accessed 17th February 2014).
119. National Drug Committee. *National list of herbal medicine products*. 1st ed. Bangkok: Ministry of Public Health Thailand, 2011.
120. Thai Food and Drug Administration. The food and medicine law. 2010. www2.fda.moph.go.th/law (accessed 8 October 2010).
121. Thai Bureau of Food. Rules of registration of dietary supplements. 2010. http://newsser.fda.moph.go.th/food/ (accessed 9th January 2013).
122. Gulati OP, Ottaway PB. Legislation relating to nutraceuticals in the European Union with a particular focus on botanical-sources products. *Toxicology* 2006;221(1):75-87.
123. European Food Safety Authority. Guidance on safety assessment of botanicals and botanical preparations intended for use as ingredients in food supplements. *EFSA Journal* 2009;7(9):1249-67.
124. National Drug Committee. *Lists of herbal medicinal products A.D. 2006*. 1st ed. Bangkok: Ministry of Public Health Thailand, 2006.
125. Oppamayun Y, Rungapirumnan W, Suwanakaesawong W, Uerchaikul C. Recent study on safety monitoring herbal medicines of Thai National Essential Drug List (NEDL). *Planta Med* 2009;75:26.
126. Biswas P. Pharmacovigilance in Asia. *JPP* 2013;4(Suppl 1):S7-19.
127. Intrasook J. Regulation of food supplements (vitamins and minerals) in EU, US, and Thailand: a comparative study. Wageningen University, 2013.
128. Saokaew S, Suwankesawong W, Permsuwan U, Chaiyakunapruk N. Safety of herbal products in Thailand: an analysis of reports in the Thai health product vigilance center database from 2000 to 2008. *Drug Saf* 2011;34(4):339-50.
129. Thai Food and Drug Administration. The declaration of health products. 2010. http://www.fda.moph.go.th/www_fda/newweb/index.php (accessed 9 November 2010).

130. Ministry of Public Health. Thailand health profile (2001-2004). In: Wilbulpolprasert S, editor. Bangkok: Printing Press, Express Transportation Organisation, 2005.
131. Vongprajan T, editor. Situations and problems of prescribed herbal medicines in public hospitals. The 5th Annual Northeast Pharmacy Research Conference of 2013 "Pharmacy Profession: Moving Forward to ASEAN Harmonization"; 2013; Thailand.
132. Institute of Thai Traditional Medicine. Research on Thai Traditional Medicines. 2008. http://ittm.dtam.moph.go.th (accessed 27 October 2010).
133. Department of Herbal Database Mahidol University. Med plant. 2010. http://www.medplant.mahidol.ac.th/index.asp (accessed 8 November 2010).
134. Chuengsamarn S, Rattanamongkolgul S, Luechapudiporn R, Phisalaphong C, Jirawatnotai S. Curcumin extract for prevention of type 2 diabetes. *Diabetes Care* 2012;35(11):2121-27.
135. Sangsuwan C, Udompanthurak S, Vannasaeng S, Thamlikitkul V. Randomized controlled trial of *Tinospora crispa* for additional therapy in patients with type 2 diabetes mellitus. *J Med Assoc Thai* 2004;87(5):543-46.
136. Cherdshewasart W, Nimsakul N. Clinical trial of *Butea superba*, an alternative herbal treatment for erectile dysfunction. *Asian J Androl* 2003;5(3):243-46.
137. Samappito S, Srichaikul B, Viroj J, Bakker G. Comparative study of double blind clinical trial in side-effects among *Areca catechu* l.,Thai traditional herbal formula and mebendazole. *Trop Parasitol* 2012;2(2):116-18.
138. Limkul N, Aramwit P, Chaiprasert A. Efficacy and safety of senna tablets for treatment of chronic constipation in patients with end-stage renal disease. *Thai Pharm Health Sci J* 2010;5(1):31-36.
139. Palaniswamy UR, editor. *Cassia siamea* induced hepatitis, a case report of phytomedicine side effect. The 3rd World Congress on Medicinal and Aramatic Plants: traditional medicine and nutraceuticals; 2003; Thiland. International Society for Horticultural Science.
140. Thailand Library Integrated System. Thai digital collection. 2010. http://tdc.thailis.or.th/tdc/ (accessed 13 December 2010).
141. Pylypa J. Healing herbs and dangerous doctors: "fruit fever" and community conflicts with biomedical cre in Northeast Thailand. *Med Anthropol Q* 2007;21(4):349-68.
142. Sanguansak A. Media exposure, knowledge and attitude towards Thai herbs among people in Bangkok. Thammasat University, 2004.
143. Srisupakwong S. Factory worker attitude towards consuming Thai's herbs in Mueang district, Samut Sakhon province. Chiang Mai University, 2003.
144. National Kidney Foundation. Definition and classification of stages of chronic kidney disease. *Am J Kidney Dis* 2002;39(2 Suppl 1):S46-75.
145. The National Collaborating Centre for Chronic Conditions (Great Britain). *Chronic kidney disease: national clinical guideline for early identification and management in adults in primary and secondary care*. 1st ed. London: Royal College of Physicians, 2008.
146. Ong-Ajyooth L, Vareesangthip K, Khonputsa P, Aekplakorn W. Prevalence of chronic kidney disease in Thai adults: a national health survey. *BMC Nephrol* 2009;10:35.
147. Perkovic V, Cass A, Patel AA, Suriyawongpaisal P, Barzi F, Chadban S, et al. High prevalence of chronic kidney disease in Thailand. *Kidney Int* 2008;73(4):473-79.
148. Zhang QL, Rothenbacher D. Prevalence of chronic kidney disease in population-based studies: systematic review. *BMC Public Health* 2008;11(8):117-30.

149. Zhang L, Wang F, Wang L, Wang W, Liu B, Liu J, et al. Prevalence of chronic kidney disease in China: a cross-sectional survey. *Lancet* 2012;379(9818):815-22.
150. Imai E, Matsuo S, Makino H, Watanabe T, Akizawa T, Nitta K, et al. Chronic kidney disease Japan cohort study: baseline characteristics and factors associated with causative diseases and renal function. *Clin Exp Nephrol* 2010;14(6):558-70.
151. Martinez-Castelao A, Gorriz JL, Portoles JM, de Alvaro F, Cases A, Luno J, et al. Baseline characteristics of patients with chronic kidney disease stage 3 and stage 4 in Spain: the MERENA observational cohort study. *BMC Nephrol* 2011;12:53.
152. Jha V, Garcia-Garcia G, Iseki K, Li Z, Naicker S, Plattner B, et al. Chronic kidney disease: global dimension and perspectives. *Lancet* 2013;382(9888):260-72.
153. Nilwarangkur S, Nimmannit S, Chaovakul V, Susaengrat W, Ong-Ajyooth S, Vasuvattakul S, et al. Endemic primary distal renal tubular acidosis in Thailand. *Q J Med* 1990;74(275):289-301.
154. Gupta SK, Eustace JA, Winston JA, Boydstun II, Ahuja TS, Rodriguez RA, et al. Guidelines for the management of chronic kidney disease in HIV-infected patients: recommendations of the HIV medicine association of the Infectious Diseases Society of America. *Clin Infect Dis* 2005;40(11):1559-85.
155. Remuzzi G, Benigni A, Finkelstein FO, Grunfeld JP, Joly D, Katz I, et al. Kidney failure: aims for the next 10 years and barriers to success. *Lancet* 2013;382(9889):353-62.
156. Stengel B. Chronic kidney disease and cancer: a troubling connection. *J Nephrol* 2010;23(3):253-62.
157. Greenberg A, editor. *Primer on kidney diseases*. 5th ed. Philadelphia: Saundes Elsevier, 2009.
158. National Kidney Foundation. Stratification of risk for progression of kidney disease and development of cardiovascular disease. *Am J Kidney Dis* 2002;39(2 Suppl1):S170-S212.
159. Campbell LJ, Ibrahim F, Fisher M, Holt SG, Hendry BM, Post FA. Spectrum of chronic kidney disease in HIV-infected patients. *HIV Med* 2009;10(6):329-36.
160. National Kidney Foundation. About chronic kidney disease. 2013. http://www.kidney.org/kidneydisease/aboutckd.cfm#symptoms (accessed 17th January 2013).
161. Levey AS, Coresh J. Chronic kidney disease. *Lancet* 2012;379(14):165-80.
162. National Kidney Foundation. Association of level of GFR with complications in adults. *Am J Kidney Dis* 2002;39(2 Suppl 1):S111-69.
163. Nyirenda MJ, Tang JI, Padfield PL, Seckl JR. Hyperkalaemia. *Br Med J* 2009;339.
164. Sarafidis PA, Blacklock R, Wood E, Rumjon A, Simmonds S, Fletcher-Rogers J, et al. Prevalence and factors associated with hyperkalemia in predialysis patients followed in a low-clearance clinic. *Clin J Am Soc Nephrol* 2012;7(8):1234-41.
165. Uribarri J. Phosphorus homeostasis in normal health and in chronic kidney disease patients with special emphasis on dietary phospharus intake. *Semin Dialysis* 2007;20(4):295-301.
166. Kidney Disease: Improving Global Outcome (KDIGO). Diagnosis of CKD-MBD: biochemical abnormalities. *Kidney Int* 2009;76(Suppl 113):S22-S49.
167. Taal MW, Brenner BM. Predicting initiation and progression of chronic kidney disease: developing renal risk scores. *Kidney Int* 2006;70(10):1694-705.

168. Chittinandana A, Chailimpamontree W, Chaloeiphap P. Prevalence of chronic kidney disease in Thai adult population. *J Med Assoc Thai* 2006;89(Suppl 2):S112-20.
169. Levin A, Djurdjev O, Beaulieu M, Er L. Variability and risk factors for kidney disease progression and death following attainment of stage 4 CKD in a referred cohort. *Am J Kidney Dis* 2008;52(4):661-71.
170. Obi Y, Kimura T, Nagasawa Y, Yamamoto R, Yasuda K, Sasaki K, et al. Impact of age and overt proteinuria on outcomes of stage 3 to 5 chronic kidney disase in a referred cohort. *Clin J Am Soc Nephrol* 2010;5(9):1558-65.
171. Nicola LD, Chiodini P, Zoccali C, Borrelli S, Cianciaruso B, Lorio BD, et al. Prognosis of CKD patients receiving outptient nephrology care in Italy. *Clin J Am Soc Nephrol* 2011;6(10):2421-28.
172. Goeij MCd, Voormolen N, Halbesma N, Jager DJd, Boeschoten EW, Sijpkens YW, et al. Association of blood pressure with decline in renal function and time until the start of renal replacement therapy in pre-dialysis patients: a cohort study. *BMC Nephrol* 2011;12:38.
173. Eriksen B, Ingebretsen O. The progression of chronic kidney disease: a 10-year population-based study of the effects of gender and age. *Kidney Int* 2006;69(2):375-82.
174. Kuo HW, Tsai SS, Tiao MM, Liu YC, Lee IM. Analgesic use and the risk for progression of chronic kidney disease. *Pharmacoepidemiol Drug Saf* 2010;19(7):745-51.
175. Samuelsson O, Mulec H, Knight-Gibson C, Attman PO, Kron B, Larsson R, et al. Lipoprotein abnormalities are associated with increased rate of progression of human chronic renal insufficiency. *Nephrol Dial Transplant* 1997;12(9):1908-15.
176. Klahr S, Levey AS, Beck GJ, Caggiula AW, Hunsicker L, Kusek JW, et al. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. *N Engl J Med* 1994;330(13):877-84.
177. Aljadhey H, Tu WZ, Hansen RA, Blalock S, Brater C, Murray MD. Risk of hyperkalemia associated with selective COX-2 inhibitors. *Pharmacoepidemiol Drug Saf* 2010;19(11):1194-98.
178. Weir MR, Rolfe M. Potassium homeostasis and renin-angiotensin-aldosterone system inhibitors. *Clin J Am Soc Nephrol* 2010;5(3):531-48.
179. Gutierrez OM, Wolf M. Dietary phosphorus restriction in advanced chronic kidney disease: merits, challenges, and emerging strategies. *Semin. Dial.* 2010;23(4):401-06.
180. Korgaonkar S, Tilea A, Gillespie BW, Kiser M, Eisele G, Finkelstein F, et al. Serum potassium and outcomes in CKD: insights from the RRI-CKD cohort study. *Clin J Am Soc Nephrol* 2010;5(5):762-69.
181. National Kidney Disease Education Program. Estimating GFR. 2013. http://nkdep.nih.gov/lab-evaluation/gfr/estimating.shtml (accessed 21st January 2013).
182. Ma YC, Zuo L, Chen JH, Luo Q, Yu XQ, Li Y, et al. Modified glomerular filtration rate estimating equation for Chinese patients with chronic kidney disease. *J Am Soc Nephrol* 2006;17(10):2937-44.
183. Praditpornsilpa K, Townamchai N, Chawatanarat T, Tiranathanagul K, Katawatin P, Susantitaphong P, et al. The need for robust validation for MDRD-based glomerular filtration rate estimation in various CKD populations. *Nephrol Dial Transplant* 2011;26(9):2780-85.
184. Chonchol M, Shlipak MG, Katz R, Sarnak MJ, Newman AB, Siscovick DS, et al. Relationship of uric acid with progression of kidney disease. *Am J Kidney Dis* 2007;50(2):239-47.
185. Dipiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM. Chronic kidney disease: management of complications. In: 8th, editor.

Pharmacotherapy: a pathophysiologic approach. stamford: Appleton & Lange, 2011.
186. National Kidney Disease. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis* 2003;42(4 Suppl 3):S1-201.
187. National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI). Clinical practice guidelines and clinical practice recommendations for diabetes and chronic kidney disease. *Am J Kidney Dis* 2007;49(2):S42.
188. Fouque D, M L. Low protein diets for chonic kidney disease in non diabetic adults. *Cochrane Database Syst Rev* 2009;8(3):CD001892.
189. Fored CM, Ejerblad E, Lindblad P, Fryzek J, Dickman PW, Signorello LB, et al. Acetaminophen, aspirin, and chronic renal failure. *N Engl J Med* 2001;345(25):1801-08.
190. Perneger TV, Whelton PK, Klag MJ. Risk of kidney failure associated with the use of acetaminophen, aspirin, and nonsteroidal antiinflammatory drugs. *N Engl J Med* 1994;331(25):1675-79.
191. Evans M, Fored CM, Bellocco R, Fitzmaurice G, Fryzek JP, McLaughlin JK, et al. Acetaminophen, aspirin and progression of advanced chronic kidney disease. *Nephrol Dial Transplant* 2009;24(6):1908-18.
192. National Toxicology Program. CAS registry number: 76-22-2 toxicity effects. 2013. http://ntp.niehs.nih.gov/?objectid=E882C9CF-BDB5-82F8-F4949C8A2D8C8B01 (accessed 6th February 2014).
193. Department of Medical Sciences. Warning about *Aristolochia* contained a carcinogenic agent. 2013. http://www.moph.go.th/show_hotnew.php?idHot_new=52540 (accessed 26th February 2014).
194. National Kidney Foundation. Use of herbal supplements in chronic kidney disease. 2013. http://www.kidney.org/atoz/content/herbalsupp.cfm (accessed 17th December 2013).
195. Wechwithan S, Sriphiromya P, Suwankesawong W. Report of potential signals from Thaivigibase during year 2007-2008. *Drug Saf* 2010;33(10):954.
196. WHO collaborating centre for international drug monitoring. National drug monitoring centres - drug safety issues. *Adverse Reaction Newsletter*. Uppsala, 1999:4.
197. Lai MN, Lai JN, Chen PC, Hsieh SC, Hu FC, Wang JD. Risks of kidney failure associated with consumption of herbal products containing Mu Tong or Fangchi: a population-based case-control study. *Am J Kidney Dis* 2010;55(3):507-18.
198. Lin MY, Chiu YW, Lee CH, Yu HY, Chen HC, Wu MT, et al. Factors associated with CKD in the elderly and nonelderly population. *Clin J Am Soc Nephrol* 2013;8(1):33-40.
199. Terris MK, Issa MM, Tacker JR. Dietary supplementation with cranberry concentrate tablets may increase the risk of nephrolothiasis. *Urology* 2001;57(1):26-29.
200. Galera SC, Fechine FV, Teixeira MJ, Coelho ZCB, de Vasconcelos RC, de Vasconcelos PRL. The safety of oral use of L-glutamine in middle-aged and elderly individuals. *Nutrition* 2010;26(4):375-81.
201. Traxer O, Huet B, Poindexter J, Pak CYC, Pearle MS. Effect of ascorbic acid consumption on urinary stone risk factors. *J Urol* 2003;170(2 Pt 1):397-401.
202. Gualano B, Ferreira DC, Sapienza MT, Seguro AC, Lancha AH. Effect of short-term high-dose creatine supplementation on measured GFR in a young man with a single kidney. *Am J Kidney Dis* 2010;55(3):e7-9.
203. Gualano B, Ugrinowitsch C, Novaes RB, Artioli GG, Shimizu MH, Seguro AC, et al. Effects of creatine supplementation on renal function: a

randomized, double-blind, placebo-controlled clinical trial. *Eur J Appl Physiol* 2008;103(1):33-40.
204. Pritchard NR, Kalra PA. Renal dysfunction accompanying oral creatine supplements. *Lancet* 1998;351(9111):1252-53.
205. Thorsteinsdottir B, Grande JP, Garovic VD. Acute renal failure in a young weight lifter taking multiple food supplements, including creatine monohydrate. *J Ren Nutr* 2006;16(4):341-45.
206. Mueller BA, Scott MK, Sowinski KM, Prag KA. Noni juice (*Morinda citrifolia*): hidden potential for hyperkalemia? *Am J Kidney Dis* 2000;35(2):310-12.
207. Kolasani A, Xu H, Millikan M. Evaluation of mineral content of Chinese medicinal herbs used to improve kidney function with chemometrics. *Food Chem* 2011;127(4):1465-71.
208. Cooke J. Pratical aspects of herbal supplement use in chronic kidney disease. *J Renal Nutr* 2004;14(1):e1-4.
209. Johns C. Glycyrrhizic acid toxicity caused by consumption of licorice candy cigars. *CJEM* 2009;11(1):94-96.
210. Abt AB, Oh JY, Huntington RA, Burkhart KK. Chinese herbal medicine induced acute renal failure. *Arch Intern Med* 1995;115(2):211-12.
211. Braithwaite R. Heavy metals and herbal medicines. In: Watson RR, Preedy VR, editors. *Botanical Medicine in Clinical Practice*. Trowbridge: Cromwellpress, 2008:851-57.
212. Chan K. Some aspects of toxic contaminants in herbal medicines. *Chemosphere* 2003;52(9):1361-71.
213. Yu CC, Lin JL, Lin-Tan DT. Environmental exposure to lead and progression of chronic renal diseases: a four-year prospective longitudinal study. *J Am Soc Nephrol* 2004;15(4):1016-22.
214. Kosalec I, Cvek J, Tomic S. Contaminations of medicinal herbs and herbal products. *Arh Hig Rada Toksikol* 2009;60(4):485-501.
215. Thai Food and Drug Administration. Summary report on the surveillance of health products in 2012. Bangkok: Thai Food and Drug Administration 2013:17-18.
216. Department of Medical Sciences. A report on herbal products contaminated with conventional medicine. 2013. http://tumdee.org/alert/ (accessed 10th February 2014).
217. Nowack R, Nowak B. Herbal teas interfere with cyclosporin levels in renal transplant patients. *Nephrol Dial Transplant* 2005;20(11):2554-56.
218. Hu Z, Yang X, Ho PCL, Chan SY, Heng PWS, Chan E, et al. Herb-drug interactions. *Drugs* 2005;65(9):1239-82.
219. Chavez ML, Jordan MA, Chavez PI. Evidence-based drug-herbal interactions. *Life Sci* 2006;78(18):2146-57.
220. Zhong Y, Deng Y, Chen Y, Chuang PY, He JC. Therapeutic use of traditional Chinese herbal medications for chronic kidney diseases. *Kidney Int* 2013;84(6):1108-18.
221. Li X, Wang H. Chinese herbal medicine in the treatment of chronic kidney disease. *Adv Chronic Kidney Dis* 2005;12(3):276-81.
222. Soetikno V, Sari FR, Sukumaran V, Lakshmanan AP, Harima M, Suzuki K, et al. Curcumin decreases renal triglyceride accumulation through AMPK-SREBP signaling pathway in streptozotocin-induced type 1 diabetic rats. *J Nutr Biochem* 2013;24(5):796-802.
223. Babu PS, Srinivasan K. Renal lesions in streptozotocin-induced diabetic rats maintained on onion and capsaicin containing diets. *J Nutr Biochem* 1999;10(8):477-83.
224. Patten GS, Abeywardena MY, Head RJ, Bennette LE. Processed dietary plants demonstrate broad capacity for angiotensin converting enzyme and angiotensin II receptor binding inhibition in vitro. *J Funct Foods* 2012;4(4):851-63.

225. Wright CI, Van-Buren L, Kroner CI, Koning MMG. Herbal medicines as diuretics: a review of the scientific evidence. *J Ethnopharmacol* 2007;114(1):1-31.
226. Prasongwatana V, Woottisin S, Sriboonlue P, Kukongviriyapan V. Uricosuric effect of Roselle (*Hibiscus sabdariffa*) in normal and renal-stone former subjects. *J Ethnopharmacol* 2008;117(3):491-95.
227. Sakthong P, Chabunthom R, Charoenvisuthiwongs R. Psychometric properties of the Thai version of the 8-item Morisky medication adherence scale in patients with type 2 diabetes. *Ann Pharmacother* 2009;43(5):950-57.
228. Morisky DE, Ang A, Krousel-Wood M, Ward HJ. Predictive validity of a medication adherence measure in an outpatient setting. *J Clin Hypertens* 2008;10(5):348-54.
229. Vlaminck H, Jacobs A, Reyntjens S, Evers G. The dialysis diet and fluid non-adherence questionnaire: validity testing of a self-report instrument for clinical practice. *J Clin Nurs* 2001;10(5):707-15.
230. Kirkwood BR, Sterne JAC. *Essential medical statistics*. 2nd ed. Oxford: Blackwell Science, 2003.
231. Fleiss JL. *Statistical Methods for Rates and Proportions* New York: John Wiley, 1981.
232. Cohen HW, Shmukler C, Ullman R, Rivera CM, Walker EA. Education and psychological aspects measurements of medication adherence in diabetic patients with poorly controlled HbA1C. *Diabet Med* 2010;27(2):210-16.
233. Gabriel A, Violato C. Knowledge of and attitudes towards depression and adherence to treatment: the Antidepressant Adherence Scale (AAS). *J Affect Disord* 2010;126(3):388-94.
234. Knobel H, Alonso J, Casado JL, Collazos J, Gonzalez J, Ruiz I, et al. Validation of a simplified medication adherence questionnaire in a large cohort of HIV-infected patients: the GEEMA study. *AIDS* 2002;16(4):605-13.
235. Arenas MD, Malek T, Gil MT, Moledous A, Alvarez-Ude F, Reig-Ferrer A. Challenge of phosphorus control in hemodialysis patients: a problem of adherence? *J Nephrol* 2010;23(5):525-34.
236. Thompson K, Kulkarni J, Sergejew AA. Reliability and validity of a new Medication Adherence Rating Scale (MARS) for the psychoses. *Schizophr Res* 2000;42(3):241-47.
237. Kim MT, Hill MN, Bone LR, Levine DM. Development and testing of the Hill-Bone compliance to high blood pressure therapy scale. *Prog Cardiovasc Nurs* 2000;15(3):90-96.
238. McHorney CA. The adherence estimator: a brief, proximal screener for patient propensity to adhere to prescription medications for chronic disease. *Curr Med Res Opin* 2009;25(1):215-38.
239. Sriwarakorn S, Krittiyanunt S, Sakulbumrungsil R. Sensitivity and specificity of Thai-Version brief medication questionnaire. *J Health Res* 2010;24(3):129-34.
240. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med* 2005;353(5):487-97.
241. Bross R, Noori N, Kovesdy CP, Murali SB, Benner D, Block G, et al. Dietary assessment of individuals with chronic kidney disease. *Semin Dialysis* 2010;23(4):359-64.
242. Caspi O, Koithan M, Criddle MW. Alternative medicine or "alternative" patients: a qualitative study of patient-oriented decision-making processes with respect to complementary and alternative medicine. *Med Decis Making* 2004;24(1):64-79.
243. Bradburn NM, Sudman S, Wansink B. *Asking questions: the definitive guide to questionnaire design - for market research, political polls, and social*

and health questionnaires, revised edition. San Francisco: A Wiley Imprint, 2004.
244. Streiner DL, Norman GR. *Health measurement scales: a practical guide to their development and use*. Fourth ed. Oxford: Oxford University Press, 2008.
245. Cinotti GA, Zucchelli PC. Effect of lisinopril on the progression of renal insufficiency in mild proteinuric non-diabetic nephropathies. *Nephrol Dial Transplant* 2001;16(5):961-66.
246. Ruggenenti P, Perna A, Gherardi G, Garini G, Zoccali C, Salvadori M, et al. Renoprotective properties of ACE-inhibition in non-diabetic nephropathies with non-nephrotic proteinuria. *Lancet* 1999;354(9176):359-64.
247. Chan JCN, Wat NMS, So WY, Lam KSL, Chua CT, Wong KS, et al. Renin angiotensin aldosterone system blockade and renal disease in patients with type 2 diabetes. *Diabetes Care* 2004;27(4):874-79.
248. Clausen T. Hormonal and pharmacological modification of plasma potassium homeostasis. *Fundam Clin Pharmacol* 2010;24(5):595-605.
249. Wright JA, Cavanaugh KL. Dietary sodium in chronic kidney disease: a comprehensive approach. *Semin Dialysis* 2010;23(4):415-21.
250. Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. *Psychol Bull* 1979;86(2):420-28.
251. Rosner B. *Fundamentals of biostatistics*. Fifth ed. Pacific Grove: Duxbury Thomson Learning, 2000.
252. Brennan P, Silman A. Statistical methods for assessing observer variability in clinical measures. *Br Med J* 1992;304(6):1491-94.
253. Larson ML. *Meaning-based translation: a guide to cross-language equivalence*. 2nd ed. Oxford: University Press of America, 1998.
254. WHO expert consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet* 2004;363(9403):157-63.
255. Nutritionquest. Food questionnaire - dialysis. 2005. www.nutritionquest.com (accessed 20 January 2011).
256. Creswell JW, Clark VLP. *Designing and conducting mixed methods research*. London: SAGE Publications, 2011.
257. Sim J, Wright C. *Research in health care: concepts, designs and methods*. 1st ed. Cheltenham: Nelson Thornes Ltd, 2000.
258. Guest G, MacQueen KM, Namey EE. *Applied thematic analysis*. 1st ed. California: SAGE Publications, 2012.
259. Braun V, Clarke V. Using thematic analysis in psychology. *Qual Res Psychol* 2006;3(2):77-101.
260. National Statistical Office. Population and society. 2007. http://web.nso.go.th/en/stat_theme_socpop.htm (accessed 27th March 2013).
261. Rifkin DE, Laws MB, Rao M, Balakrishnan V, Sarnak MJ, Wilson IB. Medication adherence behavior and priorities among older adults with CKD: a semi-structured interview study. *Am J Kidney Dis* 2010;56(3):439-46.
262. Stavropoulou C. Non-adherence to medication and doctor-patient relationship: evidence from a European survey. *Patient Educ Couns* 2011;83(1):7-13.
263. Li M, Wang W, Xue J, Gu Y, Lin S. Meta-analysis of the clinical value of *Astragalus membranaceus* in diabetic nephropathy. *J Ethnopharmacol* 2011;133(2):412-19.
264. Okuda M, Horikoshi S, Matsumoto M, Tanimoto M, Yasui H, Tomino Y. Beneficial effect of *Astragalus membranaceus* on estimated glomerular filtration rate in patients with progressive chronic kidney disease. *Hong Kong J Nephrol* 2012;14(1):17-23.

265. Afshari AT, Shirpoor A, Farshid A, Saadatian R, Rasmi Y, Saboory E, et al. The effect of ginger on diabetic nephropathy, plasma antioxidant capacity and lipid peroxidation in rats. *Food Chem* 2007;101(1):148-53.
266. Li Z, Zhu L, Zhang H, Yang J, Zhao J, Du D, et al. Protective effect of a polysaccharide from stem of *Codonopsis pilosula* against renal ischemia/reperfusion injury in rats. *Carbohydr Polym* 2012;90(4):1739-43.
267. Wang Y, Yin H, Lv X, Wang Y, Gao H, Wang M. Protection of chronic renal failure by a polysaccharide from *Cordyceps sinensis*. *Fitoterapia* 2010;81(5):397-402.
268. Knight EL, Stampfer MJ, Hankinson SE, Spiegelman D, Curhan GC. The impact of protein intake on renal function decline in women with normal renal function or mild renal insufficiency. *Ann Intern Med* 2003;138(6):460-67.
269. Shakibaei M, John T, Schulze-Tanzil G, Lehmann I, Mobasheri A. Suppression of NF-kB activation by curcumin leads to inhibitions of expression of cyclo-oxygenase-2 and matrix metalloproteinase-9 in human articular chondrocytes: implications for the treatment of osteoarthritis. *Biochem Pharmacol* 2007;73(9):1434-45.
270. van Breemen RB, Tao Y, Li W. Cyclooxygenase-2 inhibitors in ginger (*Zingiber officinale*). *Fitoterapia* 2011;82(1):38-43.
271. Katsukawa M, Nakata R, Takizawa Y, Hori K, Takahashi S, Inoue H. Citral, a component of lemongrass oil, activates PPARα and γ and suppress COX-2 expression. *Biochim Biophys Acta* 2010;1801(11):1214-20.
272. Rios A, Vargas-Robles H, Gamez-Mendez AM, Escalante B. Cyclooxygenase-2 and kidney failure. *Prostaglandins Other Lipid Mediat* 2012;98(3-4):86-90.
273. Robinson A, McGrail MR. Disclosure of CAM use to medical practitioners: a review of qualitative and quantitative studies. *Complement Ther Med* 2004;12(2-3):90-98.
274. Friis RH, Sellers TA. *Epidemiology for public health practice*. 3rd ed. Massachusetts: Jones and Bartlett Publishers, 2009.
275. Ibanez L, Morlans M, Vidal X, Martinez MJ, Laporte JR. Case-control study of regular analgesic and nonsteroidal anti-inflammatory use and end-stage renal disease. *Kidney Int* 2005;67(6):2393-98.
276. Plantinga L, Grubbs V, Sarkar U, Hsu C-y, Hedgeman E, Robinson B, et al. Nonsteroidal anti-inflammatory drug use among persons with chronic kidney disease in the United States. *Ann Fam Med* 2011;9(5):423-30.
277. Brophy DF, Gehr TW. Disorders of potassium and magnesium homeostasis. In: Dipiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, editors. *Pharmacotherapy: a pathophysiologic approach*. 7th ed. New York: The McGraw-Hill Companies, 2008:877.
278. Einhorn LM, Zhan M, Hsu VD, Walker LD, Moen MF, Seliger SL, et al. The frequency of hyperkalemia and its significance in chronic kideny disease. *Arch Intern Med* 2009;169(12):1156-62.
279. Lash JP, Go AS, Appel LJ, He J, Ojo A, Rahman M, et al. Chronic Renal Insufficiency Cohort (CRIC) study: baseline characteristics and associations with kidney function. *Clin J Am Soc Nephrol* 2009;4(8):1302-11.
280. Pongchaiyakul C, Nguyen T, Kosulwat V, Rojroongwasinkul N, Charoenkiatkul S, Pongchaiyakul C, et al. Defining obesity by body mass index in the Thai population: an epidemiologic study. *Asia Pac J Clin Nutr* 2006;15(3):293-99.
281. World Health Organization. Obesity: Preventing and Managing the Global Epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser* 2000;894:1-253.

282. Yacoub R, Habib H, Lahdo A, Al Ali R, Varjabedian L, Atalla G, et al. Association between smoking and chronic kidney disease: a case control study. *BMC Public Health* 2010;25(10):731-36.
283. National Kidney Foundation. Evaluation of laboratory measurements for clinical assessment of kidney disease. *Am J Kidney Dis* 2002;39(2 Suppl 1):S76-S110.
284. Kidney Disease: Improving Global Outcome (KDIGO). KDIGO clinical practice guideline for the management of blood pressure in chronic kidney disease. *Kidney Int Suppl* 2012;2(5):340-97.
285. Fored CM, Ejerblad E, Lindblad P, Fryzek JP, Dickman PW, Signorello LB, et al. Acetaminophen, aspirin, and chronic renal failure. *N Engl J Med* 2001;345(25):1801-08.
286. Gooch K, Culleton BF, Manns BJ, Zhang J, Alfonso H, Tonelli M, et al. NSAID use and progression of chronic kidney disease. *Am J Med* 2007;120(3):280.e1-7.
287. Powell R. Surveys. In: Walker DM, editor. *An introduction to health services research*. London: SAGE, 2014:189.
288. Greenland S, Rothman KJ. Introduction to stratified analysis. In: Rothman KJ, Greenland S, Lash TL, editors. *Modern epidemiology*. Philadelphia: Lippincott Williams & Wilkins, 2008:260-63.
289. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. *Lancet* 2000;356(9237):1255-59.
290. Chartsrisak K, Vipattawat K, Assanatham M, Nongnuch A, Ingsathit A, Domrongkitchaiporn S, et al. Mineral metabolism and outcomes in chronic kidney disease stage 2-4 patients. *BMC Nephrol* 2013;14:14.
291. Hoefield RA, Kalra PA, Baker P, Lane B, New JP, O'Donoghue DJ, et al. Factors associated with kidney disease progression and mortality in a referred CKD population. *Am J Kidney Dis* 2010;56(6):1072-81.
292. Landray MJ, Emberson JR, Blackwell L, Dasgupta T, Zakeri R, Morgan MD, et al. Prediction of ESRD and death among people with CKD: the Chronic Renal Impairment in Birmingham (CRIB) prospective cohort study. *Am J Kidney Dis* 2010;56(6):1082-94.
293. Thaikruea L, Seetamanotch W, Seetamanotch S. Appropriate cut-off level of BMI for screening in Thai adults. *J Med Assoc Thai* 2006;89(12):2123-8.
294. Yamashita T, Yoshida T, Ogawa T, Tsuchiya K, Nitta K. Clinical outcomes in patients with chronic kidney disease: a 5-year retrospective cohort study at a University hospital in Japan. *Clin Exp Nephrol* 2011;15(6):831-40.
295. Muntner P, Anderson A, Charleston J, Chen Z, Ford V, Makos G, et al. Hypertension awareness, treatment, and control in adults with CKD: results from the Chronic Renal Insufficiency Cohort (CRIC) study. *Am J Kidney Dis* 2010;55(3):441-51.
296. Asare GA, Gyan B, Bugyei K, Adjei S, Mahama R, Addo P, et al. Toxicity potentials of the nutraceutical *Moringa oleifera* at supra-supplementation levels. *J Ethnopharmacol* 2012;139(1):265-72.
297. Sireeratawong S, Nanna U, Vannasiri S, Chiruntanat N, Srithiwong S, Subcharoen P, et al. Acute and subchronic toxicity study of Tud-Rak-Ka-Sai-Puu recipe in rats. *Afr J Tradit Complement Altern Med* 2013;10(1):142-48.
298. Sireeratawong S, Lertprasertsuke N, Srisawat U, Thuppia A, Ngamjariyawat A, Suwanlikhid N, et al. Acute and subchronic toxicity study of the water extract from *Tiliacora triandra* (Colebr.) Diels in rats. *Songklanakarin J Sci Technol* 2008;30(5):611-19.
299. Kothari SC, Shivarudraiah P, Venkataramaiah SB, Koppolu KP, Gavara S, Jairam R, et al. Safety assessment of *Cissus quadrangularis* extract (CQR-300): subchronic toxicity and mutagenicity studies. *Food Chem Toxicol* 2011;49(12):3343-57.

300. Rosidah, Yam MF, Sadikun A, Ahmad M, Akowuah GA, Asmawi MZ. Toxicology evaluation of standardized methanol extract of *Gynura procumbens*. *J Ethnopharmacol* 2009;123(2):244-49.
301. Meena H, Singh KP, Negi PS, Ahmed Z. Sub-acute toxicity of cultured mycelia of Himalayan entomogenous fungus *Cordyceps sinensis* (Berk.) Sacc. in rats. *Indian J Exp Biol* 2013;51(5):381-87.
302. Attanayake AP, Jayatilaka K, Pathirana C, Kumari L, Mudduwa B. Efficacy and toxicological evaluation of *Coccinia grandis* (Cucurbitaceae) extract in male wistar rats. *Asian Pac J Trop Dis* 2013;3(6):460-66.
303. Foote J, Cohen B. Medicinal herb use and the renal patient. *J Ren Nutr* 1998;8(1):40-42.
304. Mazokopakis EE, Karefilakis CM, Tsartsalis AN, Milkas AN, Ganotakis ES. Acute rhabdomyolysis caused by spirulina (*Arthrospira platensis*). *Phytomedicine* 2008;15(6-7):525-27.
305. Chavalittumrong P, Attawish A, Chuthaputti A, Chuntapet P. Toxicological study of crude extract of *Tinospora crispa* Mier ex Hook F.&Thoms. *Thai J Pharm Sci* 1997;21(4):199-210.
306. Chavalittumrong P, Attawish A, Rugsamon P, Chuntapet P. Subacute toxicity of traditional medicinal Tripala. *Bull Dept Med Sci* 1996;38(3):169-91.
307. Colson CRD, De Broe ME. Kidney injury from alternative medicines. *Adv Chronic Kidney Dis* 2005;12(3):261-75.
308. The Uppsala Monitoring Centre. Glossary of terms used in pharmacovigilance. 2011. http://who-umc.org/Graphics/24729.pdf (accessed 16th December 2013).

Appendices

Appendix 1: Bus stop survey

DE GRUYTER J Complement Integr Med. 2014; 11(3): 203–211

Mayuree Tangkiatkumjai*, Helen Boardman and Dawn-Marie Walker

Herbal and dietary supplement use in Bangkok: a survey

Abstract

Background: People living in Asian countries including Thailand are likely to use herbal and dietary supplements (HDS). However, there is limited evidence of their usage in Thailand. The objectives of this study were to determine (1) the prevalence of HDS usage amongst a general population in Bangkok; (2) patterns of HDS use; (3) reasons why Bangkok residents use HDS.

Methods: This cross-sectional survey recruited 400 Thai people aged 15 years or over at busy bus stops in Bangkok, Thailand, using convenience sampling. Data were collected via an interview regarding demographics, HDS usage and reasons of using HDS. Descriptive statistics, such as frequencies and percentages, were used to analyse the prevalence and the patterns of HDS use.

Results: The prevalence of HDS usage in the previous 6 months was 52%. The majority of people who took herbs used them to treat illnesses (58%), whereas the majority of people who took dietary supplements used them to promote well-being (65%). Respondents reported using HDS due to their efficacy (28%), wanting to try them (26%) and safety concerns with conventional medicines (15%).

Conclusions: Health care providers should be aware of HDS use amongst Thai residents in Bangkok. Policy makers should educate people about appropriate HDS use.

Keywords: dietary supplements, herbal medicine, prevalence, Thailand

DOI 10.1515/jcim-2013-0016
Received May 5, 2013; accepted April 10, 2014; previously published online June 7, 2014

***Corresponding author: Mayuree Tangkiatkumjai,** Division of Primary Care, School of Medicine, University of Nottingham, QMC, Nottingham NG7 2UH, UK, E-mail: mayureet@g.swu.ac.th
Helen Boardman, Division of Social Research in Medicines and Health, School of Pharmacy, University of Nottingham, Nottingham, UK
Dawn-Marie Walker, Division of Primary Care, School of Medicine, University of Nottingham, QMC, Nottingham NG7 2UH, UK

Introduction

The use of herbal and dietary supplements (HDS) is widespread, particularly in Asian countries. More than three quarters of the population in some Asian countries use traditional medicine for primary health care [1]. Definitions vary across studies and there is considerable variation in the proportion of people who use HDS across the world where studies have considered both herbs and dietary supplements. The prevalence of HDS usage in the general population ranges from 19% in Korea to 73% in the United States [2–4]. Studies of the prevalence of herb use in Taiwan, Malaysia and Thailand found it to be 22%, 34% and 33%, respectively [5–7]. Finally, studies in the United States, Japan, Korea and Switzerland have found between 22% and 61% of people report taking dietary supplements [8–11]. Regarding the range of time periods used to determine the prevalence, the majority of studies defined the time periods of HDS usage as the previous 12 months. Guh et al. [5], Ingsathit et al. [7], Satyapan et al. [12] and Marques-Vidal et al. [11] did not define the time periods, whereas Radimer et al. [8] defined the period as within the past a month. It is likely that some of the variation in prevalence is related to the wide range of definitions used for herbal and/or dietary supplements, and the range of time periods used to determine prevalence.

Many studies report the characteristics of complementary and alternative medicine (CAM) users, as on average middle-aged, female and affluent [4, 13–15]. This is inconsistent with demographics amongst HDS users, particularly in Asian countries. Previous studies in Europe and Malaysia found users of herbal products or dietary supplements were more likely to be older, female and educated to a higher level [6, 11, 16]. However, Lee and Kim [10] in Korea found no association between age and use of dietary supplements.

The use of herbal medicines not only results from traditional beliefs but also the Thai government's promotion of their use in 1999 to reduce the population's reliance on imported medicines from Western countries [17]. Expenditure on herbal products was approximately 47,520 million bahts (1,485 million USD) in 2005 [17], whilst dietary supplement spending was lower at 18,000 million bahts (562.5 million USD) in 2008 [18].

Additionally, the Thai Health Product Vigilance Center has monitored side effects of herbal medicines using spontaneous and intensive reporting systems since 2000. Seventy-one items of Thai herbal medicines, such as *Andrographis paniculata* and *Curcuma Longa*, are in the National List of Essential Medicines (2011) in order to promote herbal use amongst Thai residents and to provide appropriate dosage regimens and indications for these products as guidance for their safe and effective use [19]. There are limited studies of the prevalence and types of HDS use in Thailand. Two studies conducted by Ingsathit et al. [7] and Satyapan et al. [12] found that the prevalence of herbal use in Thailand and Bangkok was 33% and 28.6%, respectively. The main objective of Ingsathit's study was to determine risk factors influencing chronic kidney disease (CKD) and found that herb users were more likely to have CKD than non-users (adjusted odd ratio 1.2, 95% confidence interval 1.0–1.4). Although Satyapan's study was to determine the prevalence of herbal use in Bangkok, they recruited respondents from Thai people attending or working at the Phramongkutklao hospital in Bangkok [12]. Therefore, this may not represent the general population in Bangkok. Moreover, neither study described the characteristics of HDS users nor the patterns and types of HDS use, and reasons for using HDS, so these remain unknown.

There is no readily available comprehensive way to recruit a general population in Bangkok as, for example, residents do not register with a doctor in the same way as Western countries. Thus recruitment of a general population at public places, such as a bus stop or pedestrian pavements, is a reasonable alternative. This idea is supported by Aziz's study, which recruited the general population from busy pedestrian walkways in Malaysia [6]. Additionally, the majority of Bangkok residents, except extremely affluent citizens use public transport, such as a bus or a train in order to travel from their house to their workplace as part of their daily routine all the year round.

This study aimed to determine the prevalence and characteristics of HDS use in the general population in Bangkok; patterns of and indications of HDS use; and reasons why Bangkok residents use HDS. These findings will provide a basic knowledge regarding herbal and dietary supplement use in Bangkok in order to assist health professionals to identify patients who are more likely to use HDS and may therefore need additional information about their safe use. Additionally, indications of HDS use would reveal whether Bangkok residents appropriately use HDS or not. The findings regarding common HDS use would guide health care providers and policy makers through monitoring adverse effects.

Methods

A cross-sectional survey of the general population aged 15 or over using bus stops in Bangkok, specifically Victory Monument bus stop and Rangsit bus stop, was conducted from December 2010 to February 2011. The two bus stops are the main bus stops in Bangkok – the first bus stop is in the central Bangkok and the second in a Bangkok suburb. Therefore, this recruitment process would ensure a valid representation of Bangkok residents. A sample size calculation based on the Bangkok population size of 5.7 million [20] suggested that 400 respondents would be sufficient to estimate the prevalence of HDS use with a standard error of 5% [21]. The inclusion criteria were Thai people who were aged 15 years or over and were willing to participate in the study at either bus stop. Respondents who could not provide information were excluded. The questionnaire was administered via face-to-face interviews with people waiting at these bus stops during the daytime as the majority of Bangkok residents use these bus stops during this period. The interviews took approximately 5 min per person. The questionnaire was adapted from a survey used by Kuo et al. [22], with added questions in order to achieve the research outcomes. The study was approved by the Ethical Review Committee for Research in Human Subjects, Faculty of Pharmacy, Srinakharinwirot University, Thailand.

The prevalence of HDS usage was defined as use within the previous 6 months. HDS were defined as products containing plant-derived material which may be raw or processed ingredients from one or more plants, or containing dietary ingredients, such as vitamins, minerals, amino acids and substances, for example, enzymes, organ tissues, glands and metabolites [23, 24].

Data analysis consisted of simple frequencies with percentages which were used to determine the prevalence and patterns of HDS use and demographic characteristics of respondents. Cross-tabulations of demographic variables and HDS use and Chi-square tests were performed to determine if there were any associations between the variables. Tests were 2-tailed, and a p-value<0.05 was considered statistically significant.

Results

Participants

Four hundred and forty people were approached and total number of 400 participants agreed to be interviewed

(response rate 90%). Non-responses were mainly due to a lack of time. However, characteristics of non-respondents were not reported. Respondents had a mean age of 41 – SD 16 years (range 16–94 years) and 64% were women. Regarding the proportion between aged 35 or less and aged over 35 in this survey was (43.5% and 56.5%) similar to the population in National Statistical Office Bangkok survey (42.6% and 57.4%) [25]. However, female in this study was more than the general population in Bangkok which is 54% [25].

The prevalence of herbal and dietary supplement use in the previous 6 months was 52% (n = 206). Demographic characteristics are shown in Table 1. HDS users were more likely to be educated to university level compared with non-users ($\chi^2 = 6.534$, $p = 0.011$) (Table 2). We did not find any other statistically significant associations between demographic variables and the use of HDS.

Table 1 Demographic characteristics of respondents (n = 400).

Demographics	Number of respondents	Percentage
Age (n = 400)		
15–25	86	21.5
26–35	88	22.0
36–45	73	18.3
46–55	73	18.3
56–65	51	12.7
>65	29	7.2
Gender (n = 398)		
Male	145	36.4
Female	253	63.6
Education (n = 398)		
Less than high school	101	25.4
High school	89	22.4
Vocational degree	23	5.8
Undergraduate degree	151	37.9
Higher than undergraduate degree	34	8.5
Occupation (n = 396)		
Employed	178	44.9
Self-employed/business	103	26.0
Students	45	11.4
Unemployed	32	8.1
Housewife	20	5.0
Professional	15	3.8
Farmer	2	0.5
Other	1	0.3
Address (n = 396)		
The outskirts of Bangkok	215	54.3
Bangkok	178	44.9
Rural areas	3	0.8

Table 2 HDS use by demographic variables (n = 400).

Characteristics	HDS users, n (%) (n = 206)	Non-users, n (%) (n = 194)	p Value[a]
Age (n = 400)			0.745
≤35	88 (42.7)	86 (44.3)	
>35	118 (57.3)	108 (55.7)	
Gender (n = 398)			0.127
Male	67 (32.8)	78 (40.2)	
Female	137 (67.2)	116 (59.8)	
Education (n = 398)			0.011
Less than higher education	97 (47.3)	116 (60.1)	
Higher education	108 (52.7)	77 (39.9)	
Occupation (n = 396)			0.120
Employed	87 (42.8)	91 (47.2)	
Self-employed/business	62 (30.5)	41 (21.2)	
Students	25 (12.3)	20 (10.4)	
Unemployed	14 (6.9)	18 (9.3)	
Housewife	6 (3.0)	14 (7.3)	
Professional	8 (4.0)	7 (3.6)	
Farmer	0 (0.0)	2 (1.0)	
Other	1 (0.5)	0 (0.0)	
Address (n = 396)			0.723
The outskirts of Bangkok	114 (55.6)	101 (52.9)	
Bangkok	90 (43.9)	88 (46.1)	
Rural areas	1 (0.5)	2 (1.0)	

[a] χ^2 test.

Patterns, purposes and reasons of herbal and dietary supplement usage

Amongst HDS users, 62% (n = 127) used herbal products and 60% (n = 124) used dietary supplements, of whom 22% (n = 45) used both (Table 3). More than half of the users (56%, n = 116) consumed a single product; however, there were a small number of respondents (6%, n = 12) who reported using four or more HDS products. Around half of the HDS (53%, n = 111) were used daily and most respondents had used the product less than 2 years (71%, n = 146).

The majority of herbal product use (58%) was to treat illness; whilst the main purpose of dietary supplement use was to maintain good health (65%), see Table 4. Women (23%) were more likely to use HDS for cosmetic purposes compared with men (10%). However, no reported purposes for the use of 24 products were given. Respondents were asked why they chose to use HDS products. The top three reasons were positive effects of HDS, wanting to try HDS and safety of HDS (28%, 26% and 15%, respectively), see Table 5.

Table 3 Patterns of HDS use in the previous 6 months.

	Number	Percentage
Types of HDS used (n = 206)		
Herbal products	82	39.8
Dietary supplements	79	38.4
Both	45	21.8
The number of different HDS used (n = 206)		
1	116	56.3
2	55	26.7
3	23	11.2
4	5	2.4
5	4	1.9
>5	3	1.5
Duration of HDS use (n = 207)[a]		
Less than 1 year	73	35.3
1–2 year(s)	73	35.3
3–5 years	31	15.0
More than 5 years	30	14.4
Frequency of HDS use (n = 211)[a]		
Daily	111	52.6
Few times a week	27	12.8
Few times a month	30	14.2
Few times a year	43	20.4

[a]Respondents were able to report more than one option so these total more than 206.

Table 4 Reported purposes of using herbal products and dietary supplements.

	Number, n (%)[a]	Missing data
Purposes of herbal use (n = 154)		20 (11.5%)
Medical conditions	90 (58.4)	
Well-being	32 (20.8)	
Cosmetic	23 (14.9)	
Other	2 (1.3)	
Don't know	7 (4.6)	
Purposes of DS use (n = 184)		3 (1.6%)
Medical conditions	11 (6.0)	
Well-being	120 (65.3)	
Cosmetic	36 (19.5)	
Don't know	17 (9.2)	

[a]Respondents were able to report more than one option.

Types of and purpose for herbal and dietary supplement use

Respondents reported using 61 different herbal products and 27 different dietary supplements. Kariyat was the most frequently used herbal product (19%), followed by turmeric (16%) and horseradish tree (10%), see Table 6. The most common purpose of using kariyat and horseradish tree was to relieve fever, whilst turmeric was used for flatulence and for peptic ulcers. Herbal diuretics used were safflower, kidney tea plant, and Indian marsh fleabane. Additionally, herbal or fruit juices which contained Ye ju hua, ginger, roselle, Pandanus palm or passion fruit were used. No reported purpose for the use of Ye ju hua or ginger juices were given. Roselle (*Hibiscus sabdariffa*) was used for improving lipid profiles, whilst Pandanus palm or passion fruit was used for the promotion of well-being. A liquid form of dietary supplements were reported to be used for tiredness or health promotion, these included collagen, 23 botanical extracts and swiftlet's nest. Collagen tablets were also reported for strengthening bones. Topical herbal products were Phai (*Zingiber cassumunar*) balm or cream, or capsicum gel for relieving muscle pain, or lemon grass oil as a mosquito repellent, balm containing *Barleria lupulina* for relieving symptoms caused by insect bites, or soap nut tree shampoo for fungal infection on the scalp. Cosmetic herbal products were tamarind lotion for whitening the skin, mangosteen lotion for good skin health, blue pea (*Clitoria ternatea*) shampoo for good hair health, kaffir lime shampoo for hair loss, or Siamese rough bush (*Streblus asper*) for relieving dental problems.

Table 5 Reasons why respondents use HDS (n = 224).

Reasons for utilizing HDS	Number, n[a]	Percentages
HDS will work	63	28.1
Wanting to try	59	26.3
Safer than conventional medicines	33	14.7
Family/friend's recommendation	24	10.7
Other	19	8.5
Easy access	10	4.5
Supplements	7	3.1
Conventional medicines don't work	3	1.3
Physician's recommendation	3	1.3
Scientific evidence	2	1.0
Cheaper than conventional medicine	1	0.5

[a]Respondents reported more than one reason, so these total more than 206.

Other herbal medicines and their purpose are as follows. (1) Hoan-Ngoc (*Pseuderanthemum palatiferum*) for cancer; (2) "Ya Hom" – a Thai folk remedy for relieving dizziness; (3) "Ya That" – a Thai folk remedy for flatulence; (4) a pill of *Glycyrrhiza glabra* and *Phyllanthus emblica* for sore throat; (5) Devil's fig pill (*Solanum torvum*) for sore throat and cough; (6) a capsule of *Schefflera leucantha* for cough; (7) holy mushroom

Table 6 Types of HDS used.

Types of HDS use	Number of the use, n (%)	Indications reported by respondents	Missing data
Herbal products (n = 154)			20 (11.5%)
Kariyat (*Andrographis paniculata*)	29 (18.8)	Fever, sore throat	
Turmeric (*Curcuma Longa*)	24 (15.6)	Antiflatulence, peptic ulcer, good skin health	
Horseradish tree (*Moringa spp.*)	15 (9.7)	Fever, diuretics, decreased cholesterol	
Herbal or fruit juice	9 (5.8)	Promotion for well-being	
Ginseng (*Panax spp.*)	8 (5.2)	Promotion for well-being	
Topical herbal products	7 (4.6)	Various indications	
Aloe (*Aloe vera*)	6 (3.9)	Burning skin, good skin health	
Herbal diuretics	6 (3.9)	Diuretics	
Cosmetic herbal products	6 (3.9)	Cosmetic purposes	
Boesenbergia (*Boesenbergia spp.*)	5 (3.2)	Antiflatulence	
Other	32 (20.8)	Various indications	
Don't know	7 (4.6)		
Dietary supplements (n = 184)			3 (1.6%)
Vitamins and minerals	75 (40.8)	Promotion for well-being, cosmetic purposes	
Protein	24 (13.0)	Promotion for well-being	
Liquid dietary supplements	19 (10.3)	Promotion for well-being, cosmetic purposes	
A combination of fish oil and cod liver oil	17 (9.2)	Promotion for well-being, treatment of dyslipidaemia	
Evening primrose oil	6 (3.3)	Good skin health	
Rice bran oil	5 (2.7)	Promotion for well-being	
Other	21 (11.4)	Various indications	
Don't know	17 (9.3)		

(*Ganoderma lucidum*) for kidney stones; (8) hoary basil seeds (*Ocimum basilicum*) as a laxative; (9) senna as a laxative; (10) bitter cucumber (*Momordica charantia*) for diabetes; (11) *Cissus quadrangularis* for haemorrhoid; (12) black pepper (*Piper nigrum*) for treatment of dyslipidaemia; (13) swamp eel (*Eurycoma longifolia Jack*) for tiredness; (14) *Tiliacora triandra* for treating hypertension; (15) Asiatic pennywort (*Centella asiatica*) for benign prostatic hyperplasia; (16) jewel vine (*Derris scandens*) for pain; (17) heart-leaved moonseed (*Tinospora crispa*) for decreased blood sugar; (18) Chinese angelica (*Angelica sinensis*) for dysmenorrhoea; (19) *Plumula Nelumbinis* for treating hypertension; and (20) eagle wood (*Aquilaria agallocha*) for diarrhoea.

Nearly half of the dietary supplement use was vitamins and minerals, followed by protein supplements (13%). Vitamin C (32%), multivitamins (21%), and calcium supplements (19%) were the most commonly used vitamins and minerals. Other dietary supplements were brewer's yeast for the prevention of hair loss, coenzyme Q10 for anti-oxidants, glucomannan and L-carnitine for weight loss, glucosamine for relieving knee pain, glutathione for good skin health, lecithin for improving memory and probiotics for constipation.

Discussion

Our study found the prevalence of HDS use within the previous 6 months to be 52% amongst people using Bangkok bus stops. This result is difficult to directly compare with other studies in Thailand, which reported a range of prevalence of 28–33% for use because they did not define the time periods of herbal use prior to recruitment and their definition of herbal medicine was different from the one used by the present study [7, 12]. However, if we consider only respondents who reported using HDS to treat a symptom (rather than for general health), our prevalence would be 31%, which was close to the prevalence of herbal use in Ingsathit's study which was 33% [7].

Our respondents were equally likely to report either herbal or dietary supplement use (about 60% reported using each type). This contrasts with a study in Sweden where respondents used high numbers of dietary supplements when compared with herbal products [26]. Previous studies in a range of Asian and Western countries suggest that herbal product use is more common in Asian countries [2, 4, 27].

Previous studies have found herbal products or dietary supplements are more likely to be used by women,

older people and those with a higher level of education [6, 11, 16]. We only found a positive correlation between a higher education and HDS use. Therefore, health care professionals in Bangkok should acknowledge that their better-educated patients are more likely to use HDS.

Bangkok residents principally used herbal products to relieve symptoms or treat illnesses, whereas dietary supplements were mainly used to promote good health. A study in the United States reported 29% people used HDS to maintain well-being; however, they did not report herbal product and dietary supplement data separately [28], so it is not possible to directly compare that study with our findings. Reasons for using HDS in the present study were similar to those found in other studies with efficacy, wanting to try the product and safety being the most frequently cited reasons [2, 6, 27].

The respondents reported using a wide variety of HDS. Kariyat and turmeric were the most commonly used in the present study similar to Satyapan's study [12]. Consistent with earlier studies, vitamins and minerals, such as vitamin C, multivitamins and calcium supplements, were the most frequently used dietary supplements [8, 9, 11]. Additionally, liquid dietary supplements are commonly consumed in Asian countries, especially in Japan [9]. These products have been imported into Thailand and were used by around 11% of the respondents.

Most of the herbal products reported by respondents have been approved by the Thai Food and Drug Administration (FDA) and were used for the recommended indications – kariyat for relieving fever and sore throat, and turmeric for flatulence and good skin health, aloe for the treatment of burning skin and good skin health, safflower/kidney tea plant and Indian marsh fleabane for diuretic effects and flatulence, all topical or cosmetic herbal products, except tamarind lotion for whitening skin care and kaffir lime shampoo for hair loss, have no scientific evidence to support their use [29]. Likewise, all herbal products reported for relieving dizziness, antiflatulence, sore throat, cough, constipation, haemorrhoid, or pain have been approved by Thai FDA, which are Ya Hom, Ya That, boesenbergia, a pill of *Glycyrrhiza glabra* and *Phyllanthus emblica*, *Solanum torvum*, *Schefflera leucantha*, hoary basil seeds, senna, *Cissus quadrangularis*, and jewel vine [19, 29].

However, there is no literature and no Thai FDA approval for some herbal products and the reported indications – *Ganoderma lucidum* for kidney stones, black pepper for treatment of dyslipidaemia [30], *Eurycoma longifolia Jack* for tiredness [31], *Centella asiatica* for benign prostatic hyperplasia [32], *Plumula Nelumbinis* for treatment of hypertension, and *Aquilaria agallocha* for diarrhoea. *Angelica sinensis* for dysmenorrhoea has little or no evidence to support this indication [33]. Moreover, *Tinospora crispa* has no effect on decreasing blood sugar in diabetes patients supported by controlled trials [34, 35].

People were also using herbal products for other indications some of which have been studied in animal models or in vitro but for which no human evidence exists, such as turmeric for healing peptic ulcers [36, 37], horseradish tree to reduce cholesterol, fever and excrete urine, and Hoan-Ngoc for cancer [38–41]. There is little evidence to support the use of *Momordica charantia* for diabetes [42]. Further studies are needed to determine whether the products are efficacious and/or harmful.

With respect to the appropriate use of dietary supplements regarding their purposes, most dietary supplements were used properly – vitamins, minerals, protein supplements, and liquid dietary supplements were to promote good health. Fish oil was used for treating dyslipidaemia supported by Chan and Cho [43]. An oral preparation of coenzyme Q10 has an antioxidant effect supported by Kumar et al. [44] similar to glucomannan for weight loss amongst obese people supported by Walsh et al. [45].

There is insufficient evidence to support efficacy of some dietary supplements – the use of oral collagen for strengthened bones, the use of oral evening primrose oil for good skin health, or L-carnitine for weight loss [46–48]. People who consume sufficient amounts of diet need not use rice bran oil [49], so this is inappropriate for healthy people to use. Brewer's yeast is used for hair loss caused by protein and micronutrient deficiency rather than the prevention of hair loss [50]. Glucosamine for relieving knee pain has been reported by literature, but there is lack of robust evidence [51]. Glutathione for good skin health has no scientific evidence to support, although it has antioxidant effects [52]. The effectiveness of lecithin for improving memory is questionable amongst older adults without serious degenerative neural disease [53]. Finally, there is inconsistent evidence of efficacy of the use of probiotics for constipation due to bacteria strains. Weichselbaum [54] reported that probiotic failed to relieve constipation in adults whilst Chmielewska and Szajewska [55] found it effective in a study participated by a small number of patients.

Therefore, it indicates that some HDS were inappropriately used amongst Thai residents in Bangkok, which should be acknowledged by health care providers

and national health authorities. As a result, policy makers should educate these residents about appropriate HDS use.

Kariyat and turmeric have been included in the Thai National List of Essential Medicines in 2006, so their adverse effects have been intensively monitored by the Thai Health Product Vigilance Center [56] and argued to be safe [57]. Given the relatively high levels of use in this study, the safety of the horseradish tree should also be monitored under this surveillance system.

The strength of the present study was that the survey used a broad definition of HDS and also recorded types, frequency and duration of HDS usage and for what indications they were taken for. However, there are some limitations. Firstly, respondents in this survey may not represent the general population in Thailand. Recruitment was via convenience sampling at bus stops in Bangkok, meaning that the sample is likely to have fewer affluent people, and does not represent people living outside the city. Secondly, the time period of HDS use prior to recruitment was defined as within the previous 6 months to increase the likelihood of remembering the name of HDS, dosage regimens and for what indications they were used. This differs from other studies, which have defined HDS use within the past 12 months [2, 4, 6, 9, 16, 27]. Therefore, the prevalence in this study is difficult to directly compare with others. Finally, our study did not gather some characteristics which may influence HDS use, such as household income, smoking, alcohol consumption, medical problems, or self-perception of health status. This was due to the time limitations imposed when conducting interviews at bus stops.

However, our findings suggest that health care providers in Bangkok should be aware that many of their patients will use HDS and this need to be taken into consideration when treating them. The government should also educate Thai residents about appropriate use of HDS. Further research should investigate the side effects of HDS amongst the general population, particularly in those with renal and liver impairments because they may be especially vulnerable to any adverse effects of HDS.

Conclusions

This survey found around half respondents in Bangkok reported HDS usage in the previous 6 months with various HDS being used for treatment of common illnesses and for the maintenance of good health. Kariyat, turmeric and vitamins and minerals were the most frequently reported HDS used. The findings showed that some HDS were inappropriately used for some purposes. Health care providers and national health authorities should educate people about guideline of proper use of HDS. Further studies should examine the safety of HDS in the general population.

Conflict of interest statement

Authors' conflict of interest disclosure: The authors stated that there are no conflicts of interest regarding the publication of this article.
Research funding: The Royal Thai Government.
Employment or leadership: None declared.
Honorarium: None declared.

References

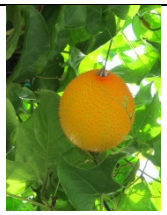
1. World Health Organization. WHO traditional medicine strategy 2002–2005. Geneva: World Health Organization, 2002.
2. Kennedy J. Herb and supplement use in the US adult population. Clin Ther 2005;27:1847–58.
3. Timbo BB, Ross MP, McCarthy PV, Lin C-T. Dietary supplements in a national survey: prevalence of use and reports of adverse events. J Am Diet Assoc 2006;106:1966–74.
4. Ock SM, Choi JY, Cha YS, Lee J, Chun MS, Huh CH, et al. The use of complementary and alternative medicine in a general population in South Korea: results from a national survey in 2006. J Korean Med Sci 2009;24:1–6.
5. Guh JY, Chen HC, Tsai JF, Chuang LY. Herbal therapy is associated with the risk of CKD in adults not using analgesics in Taiwan. Am J Kidney Dis 2007;49:626–33.
6. Aziz Z, Tey NP. Herbal medicines: prevalence and predictors of use among Malaysian adults. Complement Ther Med 2009;17:44–50.
7. Ingsathit A, Thakkinstian A, Chaiprasert A, Sangthawan P, Gojaseni P, Kiattisunthorn K, et al. Prevalence and risk factors of chronic kidney disease in the Thai adult population: Thai SEEK study. Nephrol Dial Transplant 2010;25:1567–75.
8. Radimer K, Bindewald B, Hughes J, Ervin B, Swanson C, Picciano MF. Dietary supplement use by US adults: data from the national health and nutrition examination survey, 1999–2000. Am J Epidemiol 2004;160:339–49.
9. Imai T, Nakamura M, Ando F, Shimokata H. Dietary supplement use by community-living population in Japan: data from the national institute for longevity sciences longitudinal study of aging (NILS-LSA). J Epidemiol 2006;16:249–60.
10. Lee JS, Kim J. Factors affecting the use of dietary supplements by Korean adults: data from the Korean national health and nutrition examination survey III. J Am Diet Assoc 2009;109:1599–605.

11. Marques-Vidal P, Pecoud A, Hayoz D, Paccaud F, Mooser V, Waeber G, et al. Prevalence and characteristics of vitamin or dietary supplement users in Lausanne, Switzerland: the CoLAUS study. Eur J Clin Nutr 2009;63:273–81.
12. Satyapan N, Patarakitvanit S, Temboonkiet S, Vudhironarit T, Tankanitlert J. Herbal medicine: affecting factors and prevalence of use among Thai population in Bangkok. J Med Assoc Thai 2010;93:S139–44.
13. Barnes PM, Powell-Griner E, McFann K, Nahin RL. Complementary and alternative medicine use among adults: United States, 2002. Advance Data 2004;343:1–19.
14. Ryan A, Wilson S, Taylor A, Greenfield S. Factors associated with self-care activities among adults in the United Kingdom: a systematic review. BMC Public Health 2009;9:96–106.
15. Hunt KJ, Coelho HF, Wider B, Perry R, Hung SK, Terry R, et al. Complementary and alternative medicine use in England: results from a national survey. Int J Clin Pract 2010;64:1496–502.
16. Al-Windi A, Elmfeldt D, Svardsudd K. The relationship between age, gender, well-being and symptoms, and the use of pharmaceuticals, herbal medicines and self-care products in a Swedish municipality. Eur J Clin Pharmacol 2000;56:311–17.
17. Chuthaputti A. National traditional system of medicine recognized by the Thai government, 2007.
18. National Food Institute in Thailand. Dietary supplement manufacturers, 2008.
19. National Drug Committee. National list of herbal medicine products, 1st ed. Bangkok: Ministry of Public Health Thailand, 2011.
20. Department of Provincial Administration. The number of population in Thailand, 2011.
21. Yamane T. Statistics: an introductory analysis, 2nd ed. London: Harper and Row, 1967.
22. Kuo GM, Hawley ST, Todd WL, Balkrishnan R, Volk RJ. Factors associated with herbal use among urban multiethnic primary care patients: a cross-sectional survey. BMC Complement Altern Med 2004;4:18.
23. World Health Organization. General guidelines for methodologies on research and evaluation of traditional medicine, 2000.
24. U.S. Food and Drug Administration. Overview of dietary supplements, 2009.
25. National Statistical Office. Population and society, 2007.
26. Messerer M, Johansson SE, Wolk A. Sociodemographic and health behaviour factors among dietary supplement and natural remedy users. Eur J Clin Nutr 2001;55:1104–10.
27. Aydin S, Bozkaya AO, Mazicioglu M, Gemalmaz A, Ozcakir A, Ozturk A. What influences herbal medicine use?-Prevalence and related factors. Turk J Med Sci 2008;38:455–63.
28. Mehta DH, Gardiner PM, Phillips RS, McCarthy EP. Herbal and dietary supplement disclosure to health care providers by individuals with chronic conditions. J Altern Complement Med 2008;14:1263–9.
29. Department of Herbal Database Mahidol University. Med Plant, 2010.
30. Ahmad N, Fazal H, Abbasi BH, Farooq S, Ali M, Khan MA. Biological role of Piper nigrum L. (Black pepper): a review. Asian Pac J Trop Biomed 2012;2:S1945–53.
31. Bhat R, Karim AA. Tongkat Ali (Eurycoma longifolia jack): a review on its ethnobotany and pharmacological importance. Fitoterapia 2010;81:669–79.
32. Zheng CJ, Qin LP. Chemical components of Centella asiatica and their bioactivities. J Chin Integr Med 2007;5:348–51.
33. Dantas SM. Menopausal symptoms and alternative medicine. Prim Care Update OB/GYNS 1999;6:212–20.
34. Klangjareonchai T, Roongpisuthipong C. The effect of Tinospora crispa on serum glucose and insulin levels in patients with type 2 diabetes mellitus. J Biomed Biotechnol 2012;2012:808762.
35. Sangsuwan C, Udompanthurak S, Vannasaeng S, Thamlikitkul V. Randomized controlled trial of Tinospora crispa for additional therapy in patients with type 2 diabetes mellitus. J Med Assoc Thai 2004;87:543–6.
36. Mahattanadul S, Nakamura T, Panichayupakaranant P, Phdoongsombut N, Tungsinmunkong K, Bouking P. Comparative antiulcer effect of bisdemethoxycurcumin and curcumin in a gastric ulcer model system. Phytomedicine 2009;16:342–51.
37. Tuorkey M, Karollin K. Anti-ulcer activity of curcumin on experimental gastric ulcer in rats and its effect on oxidative stress/antioxidant, IL-6 and enzyme activities. Biomed Environ Sci 2009;22:488–95.
38. Ghasi S, Nwobodo E, Ofili JO. Hypocholesterolemic effects of crude extract of leaf of Moringa oleifera Lam in high-fat diet fed Wistar rats. J Ethnopharmacol 2000;69:21–5.
39. Mehta LK, Balaraman R, Amin AH, Bafna PA, Gulati OD. Effect of fruits of Moringa oleifera on the lipid profile of normal and hypercholesterolaemic rabbits. J Ethnopharmacol 2003;86:191–5.
40. Caceres A, Saravia A, Rizzo S, Zabala L, De Leon E, Nave F. Pharmacologic properties of Moringa oleifera. 2: screening for antispasmodic, antiinflammatory and diuretic activity. J Ethnopharmacol 1992;36:233–7.
41. Vo TN, Nguyen PL, Tuong LT, Vo PN, Nguyen KP, Nguyen NS. Constituents of the leaves of Pseuderanthemum carruthersii (Seem.) Guill. var. Atropurpureum (Bull.) Fosb. Phytochem lett 2012;5:673–6.
42. Basch WE, Gabardi S, Ulbricht C. Bitter melon (Momordica charantia): a review of efficacy and safety. Am J Health Syst Pharm 2003;60:356–9.
43. Chan EJ, Cho L. What can we expect from omega-3 fatty acids? Clev Clin J Med 2009;76:245–51.
44. Kumar A, Kaur H, Devi P, Mohan V. Role of coenzyme Q10 (CoQ10) in cardiac disease, hypertension and meniere-like syndrome. Pharmacol Ther 2009;124:259–68.
45. Walsh DE, Yaghoubian V, Behforooz A. Effect of glucomannan on obese patients: a clinical study. Int J Obes 1983;8:289–93.
46. Dyck DJ. Dietary fat intake, supplements, and weight loss. Can J Appl Physiol 2000;25:495–523.
47. Bayles B, Usatine R. Evening primrose oil. Am Fam Physician 2009;80:1405–8.
48. Abou Neel EA, Bozec L, Knowles JC, Syed O, Mudera V, Day R, et al. Collagen – emerging collagen based therapies hit the patient. Adv Drug Deliv Rev 2013;65:429–65.
49. Ryan EP. Bioactive food components and health properties of rice bran. J Am Vet Med Assoc 2011;235:593–600.
50. Goldberg LJ, Lenzy Y. Nutrition and hair. Clin Dermatol 2010;28:412–19.

51. Burdett N, McNeil JD. Difficulties with assessing the benefit of glucosamine sulphate as a treatment for osteoarthritis. Int J Evid Based Healthc 2012;10:222–6.
52. Samaranayaka AG, Li-Chan EC. Food-derived peptidic antioxidants: a review of their production, assessment, and potential applications. J Funct Foods 2011;3:229–54.
53. McDaniel MA, Maier SF, Einstein GO. "Brain-specific" nutrients: a memory cure? Nutrition 2003;19:957–75.
54. Weichselbaum E. Potential benefits of probiotics – main findings of an in-depth review. Br J Community Nurs 2010;15:110–14.
55. Chmielewska A, Szajewska H. Systematic review of randomised controlled trials: probiotics for functional constipation. World J Gastroenterol 2010;16:69–75.
56. National Drug Committee. Lists of herbal medicinal products A. D. 2006, 1st ed. Bangkok: Ministry of Public Health Thailand, 2006.
57. Saokaew S, Suwankesawong W, Permsuwan U, Chaiyakunapruk N. Safety of herbal products in Thailand: an analysis of reports in the Thai health product vigilance center database from 2000 to 2008. Drug Saf 2011;34:339–50.

Appendix 2: Common use of herbal medicines in Thailand

Types of herbal medicine	Picture	Part of the tree for herbal medicine use	Medical purposes*
Kariyat (*Andrographis paniculata*)		Leaf	Common cold
Turmeric (*Curcuma longa)*		Rhizome	Flatulence
Horse radish tree (*Moringa spp.*)		Leaf	Insomnia Laxative and diuretic effects
River spiderwort (*Tradescantia fluminensis*)		All parts	No evidence
Babbler's Bill Leaf (Thunbergia laurifolia)	-	Leaf	Fever
Boesenbergia (*Boesenbergia rotunda*)		Rhizome	Flatulence and diarrhoea
Heart-leaved moonseed (*Tinospora cripa*)	-	Stem	Fever, expectorant and muscle pain
Vap Ca (*Houttuynia cordata*)		Leaf	Diuretic effect and cough
Blue Pea (*Clitoria ternatea*)		Flower	Topical use: hair loss and good hair health

Types of herbal medicine	Picture	Part of the tree for herbal medicine use	Medical purposes*
Roselle (*Hibiscus sabdariffa*)		Flower	Diuretic effect
Spring bitter cucumber (*Momordica cochinchinensis*)		Fruit	No evidence
Java tea		Leaf	Diuretic effect
Types of Thai folk remedy	**Picture**	**Main ingredients**	**Medical purposes***
'Ya hom'		Licorice, nutmeg, clove, cinnamon, Indian small civet, saffron, camphor, aglia, *Magnolia officinalis*	Faint
'Ka sai'	-	Rhubarb, senna, asafetida, aloe, Garcinia hanburyi	Constipation
'Ya khom'	-	Turmeric, *Tinospora cripa*, *Aristolochia*, *Gymnopetalum cochinchinense*	fever

Reference: National Drug Committee. *National list of herbal medicine products*. 1st ed. Bangkok: Ministry of Public Health Thailand, 2011.

Department of Herbal Database Mahidol University. Med plant, 2010.

* Approved by Thai FDA

Appendix 3: Questionnaire

Translation version

Questionnaire for patients with chronic kidney disease

The purpose of this interview is to gather information about the use of herbal and dietary supplements amongst pre-dialysis patients in order to provide information regarding them for patients with chronic kidney disease (CKD).

CU / SWU Hospital

Participant number..... Date of data collection...../...../.....

Information provider ☐ Patient (0) ☐ Care giver (1)

Ht.....cm.

Demographic data

1. Gender ☐ Male (0) ☐ Female (1)

2. Current address ☐ Bangkok (0)

   ☐ Rural area (1) City.....Province.....

3. Education

   ☐ None (0) ☐ Primary school (1) ☐ Secondary School (2)

   ☐ Vocational degree (3) ☐ Bachelor's degree (4) ☐ Higher degree (5)

4. Household income .....baht/month

5. Occupation

   ☐ Unemployed (0) ☐ Retired (1) ☐ Housewife (2) ☐ Business owner(3)

   ☐ Employee (4) ☐ Farmer (5) ☐ Professional (6) ☐ Other (specify) (7).....

6. Smoking status

   ☐ Never (0) ☐ Former smoker (1) ☐ Current smoker (2)

   Date stopped..... Amount.....cigarettes, packs/day

7. Alcoholic consumption

   ☐ Never (0) ☐ Former consumer (1) Date stopped.....

   ☐ Current consumer (2): Types .....Amount.....glasses,cans,bottles per day/week

The use of herbal and dietary supplements

8. Did you use herbal or dietary supplements in the last month? (excluding herbal or dietary supplement use for daily food intake or cosmetic purposes)

   ☐ Never (0) (go to question no. 19)

   ☐ Former use (1) Stop date...../...../.....(go to question no. 19)

   ☐ Yes (2) (go to question no.9-18): ☐ Herbs (0) ☐ Dietary supplements (1) ☐ Both (2)

9. How many herbal and dietary products do you use if any? Herbs..... Dietary supplements.....

☐ Cannot remember (999)

10. What are the products? What purposes do you use them? How do you use them? How much do you use them? How often do you use them? How long do you use them? (please fill in the table)

Name of medications and HDS	Indication[a]	Dosage form[b]	How do you use[c]	Dose (per day)	How often (per day/ week)	How long[d] (month/year)
Paracetamol						
NSAIDs						

Note: HDS = Herbal and dietary supplements, Missing data = Participants cannot remember (999)
(a) Treatment of CKD (1), Well-being (2), Long life expectancy (3), others (4)
(b) Pills, capsules, tablets, powder, solution, crude herbs
(c) Swallow (1), Topical use (2), Make into a drink/food using hot water (3), other (4)
(d) How long have you used them?

11. Why do you use them? Please rank the top three of reasons (can tick more than 1 answer)

.....I wanted to try them (1) .....I hope they will work (2)

.....They are safer than modern medicines (3) .....Modern medicines don't work (4)

.....They are cheaper than modern medicines (5) .....They are easily accessed (6)

.....Health care providers recommended them (7) .....My family and friends recommended them (8)

.....Used by themselves (9) .....Other (specify) (10).....

12. From what sources did you receive information about herbal and dietary supplements? (can tick more than 1 answer)

☐ Radio (1) ☐ Television (2) ☐ Newspaper (3) ☐ Leaflet (4)

☐ Internet (5) ☐ Family or friend (6) ☐ Other (specify) (7).....

13. How did you obtain herbal and dietary supplements? (can tick more than 1 answer)

☐ Buy (1) from ☐ Drug store (1) ☐ Folk remedy shop (2) ☐ Health food store(3)

☐ Hospital (4) ☐ Direct sale (5)

☐ Provided by their family/ friends (2) ☐ Collecting them from their garden (3)

☐ Other (specify) (4).....

14. Did you inform your health care providers that you use them?

☐ No (0) because ☐ They don't ask (1) ☐ No need to inform (2) ☐ Other (specify) (3).....

☐ Yes (1) : Doctor/nurse/pharmacist/ other (specify).....

15. Have you had any positive effects from herbal and dietary supplements?

☐ No (0)

☐ Yes (1) What are benefits?..... Name of HDS.....

☐ Unsure (2) ☐ Don't know (3)

16. Have you had any problems after taking herbal and dietary supplements?

☐ No (0) (go to question no. 18)

☐ Yes (1) What are problems?..... (go to question no.17)

Name of HDS.....

☐ Unsure (2) ☐ don't know (3)

17. Do you stop using them when you have such problems?

☐ No (1) because.....

☐ Yes (0)

18. How long will you continue to use the HDS? .....months/years

Because.....

☐ Unsure (1) ☐ don't know (2)

19. Do you use other alternative medicines, such as meditation, acupuncture, yoga, etc.?

☐ No (0) ☐ Yes (1) (can answer more than 1 answer, please fill in the table):

	Period per time minute/hour	Frequency.....time(s)per day/week/month	Duration day/month/year
Meditation (1)			
Acupuncture (2)			
Yoga (3)			
Tai-chi (4)			
Other (specific) (5).....			

20. Do you plan to use them within this year? (for participants who have not taken them)

☐ No (0) because.....

☐ Yes (1) because.....

☐ Unsure (2) ☐ don't know (3)

Medication history

21. I have your medication list from the chart. Have you used any other medicines in the last month, such as OTC medications?

☐ No (0) ☐ Yes (1) (specify in the table page 2)

22. Thai-version of 8-item Morisky medication adherence questionnaire

©Morisky Medication Adherence Scale (MMAS-8-Item). This is a generic adherence scale and the name of the health concern can be substituted in each question item.

You indicated that you are taking medication for your kidneys. Individuals have identified several issues regarding their medication-taking behavior and we are interested in your experiences. There is no right or wrong answer. Please answer each question based on your personal experience with your kidney medication.

(Please circle the correct number)

	No=1	**Yes=0**
1. Do you sometimes forget to take your kidney pills?.....		
2. People sometimes miss taking their medications for reasons other than forgetting. Thinking over the past two weeks, were there any days when you did not take your kidney medicine?.....		
3. Have you ever cut back or stopped taking your medication without telling your doctor, because you felt worse when you took it?.....		
4. When you travel or leave home, do you sometimes forget to bring along your [health concern] medication?.....		
5. Did you take your kidney medicine yesterday?.....		
6. When you feel like your kidney is under control, do you sometimes stop taking your medicine?.....		
7. Taking medication everyday is a real inconvenience for some people. Do you ever feel hassled about sticking to your kidney treatment plan?.....		

8. How often do you have difficulty remembering to take all your medications?
(Please circle the correct number)

Never/Rarely.....4

Once in a while.....3

Sometimes.....2

Usually.....1

All the time.....0

23. What medications do you most often forget? .....

4

The Restriction of Protein, Potassium, Phosphate and Salt diet questionnaire for pre-dialysis patients (RPPPS)

It can be difficult to stick to the dietary requirements for CKD and we want to know how you manage with your diet.

Individuals have identified several issues regarding their diet behaviour and we are interested in your experiences. There is no right or wrong answer. Please answer each question based on your own personal experience of your diet.

24. Did you receive dietary recommendations from doctors or dieticians?

☐ No (0) (go to question no. 26) ☐ Yes (1) (go to question no. 25)

25. The Modification of dialysis diet and fluid non-adherence questionnaire (DDFQ)

1. How much did you comply with a doctor's recommendation for your protein-rich food restriction in the last 14 days?

No	Low	Moderate	High	Very high
0	1	2	3	4

2. To what degree did you deviate from such recommendation?

No	Low	Moderate	High	Very high
0	1	2	3	4

3. To what degree did you comply with a doctor's recommendation for your phosphate-rich food restriction in the last 14 days?

No	Low	Moderate	High	Very high
0	1	2	3	4

4. To what degree did you comply with a doctor's recommendation for your salt-rich food restriction in the last 14 days?

No	Low	Moderate	High	Very high
0	1	2	3	4

End of questions

Thank you

26. The Modification of dialysis diet and fluid non-adherence questionnaire (DDFQ) for respondents who did not receive a doctor's or a dietician's advice about food restriction

1. How much did you eat protein-rich food in the last 14 days?

No	Low	Moderate	High	Very high
0	1	2	3	4

2. How much did you eat potassium-rich food, such as fruit and vegetable in the last 14 days?

No	Low	Moderate	High	Very high
0	1	2	3	4

3. How much did you eat phosphate-rich food in the last 14 days?

No	Low	Moderate	High	Very high
0	1	2	3	4

4. How much did you eat salt-rich food in the last 14 days?

No	Low	Moderate	High	Very high
0	1	2	3	4

End of questions

Thank you

Herbal medicines






Dietary supplements

Types of dietary intake





The original version of questionnaire

แบบสัมภาษณ์ผู้เข้าร่วมโครงการวิจัย

แบบสัมภาษณ์นี้มีวัตถุประสงค์เพื่อ รวบรวมข้อมูลเกี่ยวกับการใช้สมุนไพรและผลิตภัณฑ์เสริมอาหารในผู้ป่วยโรคไตเรื้อรัง ซึ่งจะเป็นข้อมูลในการศึกษาการใช้สมุนไพรและผลิตภัณฑ์เสริมอาหารในผู้ป่วยกลุ่มนี้

รพ.จุฬาฯ/ศูนย์การแพทย์สมเด็จพระเทพฯ

ผู้ป่วยคนที่…….. วันที่เก็บข้อมูล ……../……/……

ผู้ให้ข้อมูล ☐ ผู้ป่วย (0) ☐ ญาติผู้ป่วย (1)…….

ส่วนสูง……cm.

ข้อมูลทั่วไปของผู้ป่วย

1. เพศ ☐ ชาย (0) ☐ หญิง (1)
2. ที่อยู่ปัจจุบัน ☐ กทม (0)

   ☐ ต่างจังหวัด (1) อำเภอ……จังหวัด……
3. ระดับการศึกษา

   ☐ ไม่ได้เรียนหนังสือ (0) ☐ ประถมศึกษา (1) ☐ มัธยมต้น/ มัธยมปลาย (2) ☐ ปวช/ปวส.(3)

   ☐ ปริญญาตรี (4) ☐ สูงกว่าปริญญาตรี (5)
4. รายได้ของครอบครัวโดยประมาณ……บาท/เดือน
5. อาชีพ

   ☐ ผู้ว่างงาน (0) ☐ ผู้เกษียณอายุ (1) ☐ แม่บ้าน/พ่อบ้าน (2) ☐ ประกอบธุรกิจส่วนตัว (3)

   ☐ ลูกจ้าง (ข้าราชการทั่วไป พนักงานบริษัท ช่างต่างๆ) (4) ☐ เกษตรกร (5)

   ☐ วิชาชีพ เช่น ครู แพทย์ พยาบาล เภสัชกร วิศวกร สถาปนิก ฯลฯ (6)

   ☐ อื่นๆ (7)……
6. คุณเคยสูบบุหรี่หรือไม่

   ☐ ไม่เคยสูบ (0) ☐ เคยสูบบุหรี่แต่ปัจจุบันเลิกสูบแล้ว (1) วัน/เดือน/ปี ที่หยุดสูบ……..

   ☐ สูบบุหรี่ (2) ปริมาณ……..มวน/ห่อ ต่อวัน
7. คุณเคยดื่มเครื่องดื่มที่มีแอลกอออล์หรือไม่

   ☐ ไม่เคยดื่ม (0) ☐ เคยดื่มแต่ปัจจุบันเลิกแล้ว (1) วัน/เดือน/ปี ที่หยุดดื่ม……..

   ☐ ดื่ม (2) ประเภท…… ปริมาณ……..แก้ว/กระป๋อง/ขวด ต่อวัน/สัปดาห์

การใช้สมุนไพรและผลิตภัณฑ์เสริมอาหาร

8. คุณเคยใช้สมุนไพรและ/หรือผลิตภัณฑ์เสริมอาหารเมื่อเดือนที่แล้วหรือไม่

   สมุนไพรในที่นี้หมายถึงผลิตภัณฑ์ที่มีส่วนประกอบของสมุนไพร, หรือพืชสมุนไพรที่ยังไม่ได้แปรรูป หรือสารสำคัญที่ได้จากสัตว์ **ไม่หมายรวมถึงสมุนไพรที่ใส่ในอาหาร เพื่อรับประทานในชีวิตประจำวัน เช่น ตะไคร้ในต้มยำ และสมุนไพรในเครื่องสำอาง**

   ☐ ไม่เคยใช้ (0) (ตอบคำถามข้อ 19)

   ☐ เคยใช้แต่ปัจจุบันเลิกใช้แล้ว (1) วัน/เดือน/ปี ที่หยุดใช้..... (ตอบคำถามข้อ 19)

   ☐ ใช้ (2) (ตอบคำถามข้อ 9-18): ☐ สมุนไพร (0) ☐ ผลิตภัณฑ์เสริมอาหาร (1) ☐ ใช้ทั้ง 2 อย่าง (2)

9. คุณใช้สมุนไพรและ/หรือผลิตภัณฑ์เสริมอาหารจำนวนกี่ชนิด

   สมุนไพรจำนวน.....ชนิด ผลิตภัณฑ์เสริมอาหารจำนวน.....ชนิด

   ☐ จำไม่ได้ (999)

10. คุณใช้สมุนไพรและ/หรือผลิตภัณฑ์เสริมอาหารอะไรบ้าง ใช้เพื่อวัตถุประสงค์ใด มีวิธีใช้อย่างไร ขนาดเท่าใด ใช้มานานหรือยัง (กรุณากรอกข้อมูลในตาราง)

ชื่อยา หรือ สมุนไพรหรือ ผลิตภัณฑ์เสริมอาหาร	ข้อบ่งใช้[a]	รูปแบบยา[b]	วิธีใช้[c]	ขนาดยา (ต่อวัน)	ความถี่ของการใช้ (ต่อวัน/เดือน)	ระยะเวลาที่ใช้ (เดือน/ปี)
Paracetamol						
NSAIDs						

Note: (a) รักษาโรคไตเรื้อรัง (1), เพื่อให้สุขภาพดี (2), เพื่อช่วยให้อายุยืน (3), อื่นๆ (4)

(b) ลูกกลอน เม็ด แคปซูล ผง ยาน้ำ หรือ สมุนไพรที่ยังไม่ได้แปรรูป (c) รับประทาน (1), ใช้ภายนอก (2), ต้มน้ำดื่ม (3), อื่นๆ (4)

หมายเหตุ: Missing data = จำไม่ได้ (999)

11. เพราะเหตุใดคุณถึงใช้สมุนไพรหรือผลิตภัณฑ์เสริมอาหาร (ตอบได้มากกว่า 1 ข้อ)

.....อยากลองใช้ (1) .....หวังว่าสมุนไพรหรือผลิตภัณฑ์เสริมอาหารจะมีประสิทธิภาพ (2)

.....เชื่อว่าสมุนไพรหรือผลิตภัณฑ์เสริมอาหารปลอดภัยกว่ายาแผนปัจจุบัน (3)

.....ยาแผนปัจจุบันไม่มีประสิทธิภาพ (4) .....สมุนไพรหรือผลิตภัณฑ์เสริมอาหารถูกกว่ายาแผนปัจจุบัน (5)

.....หาซื้อได้ง่าย สะดวก (6) .....บุคลากรทางการแพทย์แนะนำให้ใช้ (7)

.....ครอบครัวและเพื่อนแนะนำ (8) .....ตัดสินใจใช้ด้วยตัวเอง (9)

.....อื่นๆ (10).....

12. คุณเคยได้รับข้อมูลเกี่ยวกับสมุนไพรหรือผลิตภัณฑ์เสริมอาหารจากแหล่งข้อมูลใด (ตอบได้มากกว่า 1 ข้อ)

☐ วิทยุ (1) ☐ โทรทัศน์ (2) ☐ หนังสือพิมพ์ (3) ☐ แผ่นพับ (4)

☐ อินเทอร์เนต (5) ☐ ครอบครัว หรือเพื่อน (6) ☐ อื่นๆ (โปรดระบุ) (7).....

13. คุณได้รับสมุนไพรหรือผลิตภัณฑ์เสริมอาหารด้วยวิธีใด (ตอบได้มากกว่า 1 ข้อ)

☐ ซื้อ (1) จาก ☐ ร้านยาแผนปัจจุบัน (1) ☐ ร้านยาแผนโบราณ/ร้านขายสมุนไพร (2)

☐ ร้านขายผลิตภัณฑ์เสริมอาหาร (3) ☐ โรงพยาบาล (4) ☐ เซลล์ขายตรง (5)

☐ ญาติหรือเพื่อนหามาให้ (2) ☐ เก็บจากสวนที่บ้าน (3) ☐ อื่นๆ (โปรดระบุ) (4) .....

14. คุณได้บอกบุคลากรทางการแพทย์หรือไม่ ว่าคุณใช้สมุนไพรหรือผลิตภัณฑ์เสริมอาหาร

☐ ไม่ได้บอก (0) เพราะ

☐ บุคลากรทางการแพทย์ไม่ได้ถาม (1) ☐ ไม่จำเป็นต้องบอก (2)

☐ อื่นๆ (3).....

☐ บอก (1): แพทย์/พยาบาล/เภสัชกร

15. คุณได้รับประโยชน์จากการใช้สมุนไพรหรือผลิตภัณฑ์เสริมอาหารหรือไม่

☐ ไม่ได้ประโยชน์ (0) ☐ ได้ประโยชน์ (1) คือ.....

☐ ไม่แน่ใจ (2) ☐ ไม่รู้ (3)

16. คุณมีปัญหาเกี่ยวกับสุขภาพจากการใช้สมุนไพรหรือผลิตภัณฑ์เสริมอาหารหรือไม่

☐ ไม่มีปัญหา (0) (ตอบคำถามข้อ 18) ☐ มี (1) ปัญหาคือ.....

จากผลิตภัณฑ์ชื่อ.....(ตอบคำถามข้อ 17)

☐ ไม่แน่ใจ (2) ☐ ไม่รู้ (3)

17. คุณหยุดใช้สมุนไพรหรือผลิตภัณฑ์เสริมอาหารหรือไม่ เมื่อมีปัญหา

☐ หยุดใช้ (0)

☐ ใช้ต่อไป (1) เพราะ.....

18. คุณคิดว่าจะใช้สมุนไพรหรือผลิตภัณฑ์เสริมอาหารอีกนานเท่าใด .....เดือน/ปี

เพราะ.....

☐ ไม่แน่ใจ (1) ☐ ไม่รู้ (2)

19. คุณเคยใช่หรือกำลังใช้การแพทย์ทางเลือกอื่นหรือไม่ เช่น นั่งสมาธิ ฝังเข็ม เล่นโยคะ รำไทเก๊ก

☐ ไม่ (0) ☐ ใช้ (1) (ตอบได้มากกว่า 1 ข้อ กรุณากรอกข้อมูลในตาราง)

ประเภทการแพทย์ทางเลือก	ระยะเวลาที่ใช้ต่อครั้ง นาที/ชม.	จำนวนครั้งที่ทำต่อ วัน/ อาทิตย์/ เดือน	เป็นระยะเวลา วัน/ เดือน/ ปี
นั่งสมาธิ (1)			
ฝังเข็ม (2)			
เล่นโยคะ (3)			
รำไทเก๊ก (4)			
อื่นๆ (5).....			

20. คุณคิดว่าคุณจะใช้สมุนไพรหรือผลิตภัณฑ์เสริมอาหาร ภายในปีนี้หรือไม่ (สำหรับผู้ที่ตอบว่าไม่ใช้สมุนไพรหรือผลิตภัณฑ์เสริมอาหาร)

☐ ไม่ (0) เพราะ.....

☐ ใช้ (1) เพราะ.....

☐ ไม่แน่อาจจะใช้ (2) ☐ ไม่รู้ (3)

ประวัติการใช้ยา

21. คุณซื้อยามาใช้เองหรือไม่ เมื่อเดือนที่แล้ว

☐ ไม่ (0) ☐ ใช่ (1) (ระบุในตารางหน้า 3)

22. แบบประเมินความร่วมมือในการใช้ยาที่แพทย์สั่ง: Morisky Medication Adherence Scale (MMAS)

คำชี้แจง : กรุณากาเครื่องหมาย ✓ลงในกล่อง ❒ ในคำถามต่อไปนี้ให้ตรงกับความเป็นจริง

1. มีบางครั้งที่คุณลืมรับประทานยาใช่หรือไม่	❒ ใช่	❒ ไม่ใช่
2. บางคนไม่ได้รับประทานยาด้วยเหตุผลต่างๆ นอกเหนือจากลืม คุณคิดทบทวนว่าในช่วง 2 สัปดาห์ที่ผ่านมา มีบางวันที่คุณไม่ได้รับประทานยา	❒ ใช่	❒ ไม่ใช่
3. คุณเคยลดขนาดยาหรือหยุดยา เนื่องจากรู้สึกแย่เวลารับประทานยา โดยที่ไม่ได้บอกแพทย์	❒ ใช่	❒ ไม่ใช่
4. เมื่อคุณออกจากบ้านหรือเดินทางไกล มีบางครั้งที่คุณลืมพกยาติดตัวไปด้วย	❒ ใช่	❒ ไม่ใช่
5. เมื่อวานนี้ คุณรับประทานยาครบ ใช่หรือไม่	❒ ใช่	❒ ไม่ใช่
6. เมื่อคุณรู้สึกว่าอาการของโรคที่คุณเป็นควบคุมได้แล้ว บางครั้งคุณหยุดรับประทานยา	❒ ใช่	❒ ไม่ใช่
7. การรับประทานยาทุกวันอาจไม่สะดวกสำหรับบางคน คุณเคยรู้สึกอึดอัดที่ต้องรับประทานยาอย่างเคร่งครัดหรือเข้มงวด ใช่หรือไม่	❒ ใช่	❒ ไม่ใช่
8. คุณรู้สึกว่ามีความยุ่งยากบ่อยเพียงใด ในการจดจำยาทั้งหมดที่ต้องรับประทาน (กาเครื่องหมาย ✓ลงในกล่อง ❒ **โดยเลือกเพียง 1 ข้อเท่านั้น**)		
❒8.1) ไม่รู้สึกหรือแทบจะไม่รู้สึกว่ามีความยุ่งยากในการจดจำยาที่ใช้ (หรือมี 0 ถึง 1 ครั้งต่อสัปดาห์ที่จำไม่ได้ว่ายาตัวไหนทานอย่างไร)		
❒ 8.2) รู้สึกว่ายุ่งยากบ้างเล็กน้อย ในการจดจำวิธีทานยาแต่ละอย่างให้ถูกต้อง (หรือมี 1 ถึง 2 ครั้งต่อสัปดาห์ที่จำไม่ได้ว่ายาตัวไหนทานอย่างไร)		
❒ 8.3) รู้สึกว่ายุ่งยากปานกลาง ในการจดจำวิธีทานยาแต่ละอย่างให้ถูกต้อง (หรือมี 3 ถึง 4 ครั้งต่อสัปดาห์ที่จำไม่ได้ว่ายาตัวไหนทานอย่างไร)		
❒ 8.4) รู้สึกว่ายุ่งยากเป็นประจำ ในการจดจำวิธีทานยาแต่ละอย่างให้ถูกต้อง (หรือมี 5 ถึง 6 ครั้งต่อสัปดาห์ที่จำไม่ได้ว่ายาตัวไหนทานอย่างไร)		
❒ 8.5) รู้สึกว่ายุ่งยากทุกครั้งหรือตลอดเวลา ในการจดจำวิธีทานยาแต่ละอย่างให้ถูกต้อง (มีความยุ่งยากทุกวัน จำไม่ได้ว่ายาตัวไหนทานอย่างไร)		

23. สำหรับยาที่แพทย์สั่ง ยาอะไรที่คุณมักลืมรับประทาน

.....

แบบสอบถามการควบคุมอาหารที่มีส่วนประกอบของโปรตีน โพแทสเซียม ฟอสเฟต และเกลือ สำหรับผู้ป่วยโรคไตเรื้อรังที่ยังไม่ได้ฟอกเลือด

เป็นการยากที่จะควบคุมการรับประทานอาหารสำหรับผู้ป่วยโรคไตเรื้อรัง และผู้วิจัยต้องการทราบว่าคุณมีการจัดการเกี่ยวกับการควบคุมอาหารของคุณอย่างไร

ผู้ป่วยแต่ละรายมีหลายปัญหาในการควบคุมอาหารขึ้นกับพฤติกรรมการบริโภคของแต่ละคน และผู้วิจัยสนใจที่จะเรียนรู้จากประสบการณ์ของคุณ การตอบคำถามต่อไปนี้ ไม่มีคำตอบที่ถูกหรือผิด กรุณาตอบคำถามแต่ละข้อตามประสบการณ์การรับประทานอาหารของคุณ

24. คุณได้รับคำแนะนำในการควบคุมอาหารสำหรับผู้ป่วยโรคไตเรื้อรังจากแพทย์/นักโภชนาการหรือไม่
    ☐ ไม่ (0) (ตอบคำถามข้อ 26) ☐ ใช่ (1) (ตอบคำถามข้อ 25)
25. แบบสอบถามดัดแปลงจาก dialysis diet and fluid non-adherence questionnaire (DDFQ)
    1) คุณปฏิบัติตามคำแนะนำการรับประทานอาหารที่มีโปรตีนสูงมากหรือน้อย เมื่อ 2 อาทิตย์ที่แล้ว

ไม่มี	น้อย	ปานกลาง	มาก	มากที่สุด
0	1	2	3	4

    2) คุณปฏิบัติตามคำแนะนำการรับประทานอาหารที่มีโพแทสเซียมสูงมากหรือน้อย เมื่อ 2 อาทิตย์ที่แล้ว

ไม่มี	น้อย	ปานกลาง	มาก	มากที่สุด
0	1	2	3	4

    3) คุณปฏิบัติตามคำแนะนำการรับประทานอาหารที่มีฟอสเฟตสูงมากหรือน้อย เมื่อ 2 อาทิตย์ที่แล้ว

ไม่มี	น้อย	ปานกลาง	มาก	มากที่สุด
0	1	2	3	4

    4) คุณปฏิบัติตามคำแนะนำการควบคุมอาหารที่มีรสเค็มมากหรือน้อย เมื่อ 2 อาทิตย์ที่แล้ว

ไม่มี	น้อย	ปานกลาง	มาก	มากที่สุด
0	1	2	3	4

จบการตอบแบบสอบถาม

ขอบคุณคะ

26. แบบสอบถามดัดแปลงจาก dialysis diet and fluid non-adherence questionnaire (DDFQ) สำหรับผู้ป่วยที่ไม่ได้รับคำแนะนำเรื่องการควบคุมอาหาร

1) คุณทานอาหารที่มีโปรตีนสูงปริมาณมากน้อยเท่าไหร่ เมื่อ 2 อาทิตย์ที่แล้ว

ไม่มี	น้อย	ปานกลาง	มาก	มากที่สุด
0	1	2	3	4

2) คุณทานผลไม้ หรือผักปริมาณมากน้อยเท่าไหร่ เมื่อ 2 อาทิตย์ที่แล้ว

ไม่มี	น้อย	ปานกลาง	มาก	มากที่สุด
0	1	2	3	4

3) คุณทานอาหารที่มีฟอสเฟตสูงปริมาณมากน้อยเท่าไหร่ เมื่อ 2 อาทิตย์ที่แล้ว

ไม่มี	น้อย	ปานกลาง	มาก	มากที่สุด
0	1	2	3	4

4) คุณทานอาหารที่มีรสเค็มปริมาณมากน้อยเท่าไหร่ เมื่อ 2 อาทิตย์ที่แล้ว

ไม่มี	น้อย	ปานกลาง	มาก	มากที่สุด
0	1	2	3	4

จบการตอบแบบสอบถาม

ขอบคุณคะ

สมุนไพร






ผลิตภัณฑ์เสริมอาหาร

ประเภทอาหารที่รับประทาน



















Appendix 4: Open-ended questions about attitudes towards the reasons for HDS use

Translation version

This questionnaire is to gather information about reasons for HDS use in pre-dialysis patients in order to understand HDS users.

CU / SWU Hospital

Participant number……....

Date of data collection……/……/…….

Information provider ☐ Patient (0) ☐ Care giver (1)

1. How and when were you introduced to HDS?
2. Why do you use HDS?
3. What led you to start using HDS?
4. Did anything influence you to start using HDS, e.g. advice from friends, doctor, news reports, etc?
5. Are there benefits of HDS compared with conventional medicines? Please explain why you think this.
6. What did you hope taking HDS would achieve?
7. Do you have any concerns about using HDS? If yes, what? Then please compare with conventional medicines.
8. Have you had any warnings about taking the HDS such as from doctors, friends? If yes, has it influenced your use in anyway?

The original version of open-ended questions

แบบสัมภาษณ์ทัศนคติต่อเหตุผลการใช้สมุนไพรหรือผลิตภัณฑ์เสริมอาหาร

แบบสอบถามนี้ สำหรับรวบรวมข้อมูลเกี่ยวกับเหตุผลการใช้สมุนไพร หรือผลิตภัณฑ์เสริมอาหารในผู้ป่วยโรคไตเรื้อรังที่ยังไม่ได้รับการฟอกเลือด เพื่อทำความเข้าใจเกี่ยวกับการใช้สมุนไพร หรือผลิตภัณฑ์เสริมอาหาร

รพ.จุฬาฯ/ศูนย์การแพทย์สมเด็จพระเทพฯ

ผู้ป่วยคนที่…….. วันที่เก็บข้อมูล ……../……../……

ผู้ให้ข้อมูล ☐ ผู้ป่วย (0) ☐ ญาติผู้ป่วย (1)……

1. คุณรู้จักสมุนไพร หรือผลิตภัณฑ์เสริมอาหารอย่างไร และตั้งแต่เมื่อไหร่
2. ทำไมคุณถึงใช้สมุนไพร หรือผลิตภัณฑ์เสริมอาหาร
3. ปัญหาอะไร ที่ทำให้คุณเริ่มใช้สมุนไพร หรือผลิตภัณฑ์เสริมอาหาร
4. มีปัจจัยอะไร ที่ทำให้คุณเริ่มใช้สมุนไพรหรือผลิตภัณฑ์เสริมอาหาร เช่น ได้รับคำแนะนำจากเพื่อน แพทย์ ได้รับข้อมูลจากหนังสือพิมพ์ วิทยุ โทรทัศน์ แผ่นพับ และอื่นๆ
5. คุณได้ประโยชน์จากการกินสมุนไพรหรือผลิตภัณฑ์เสริมอาหาร หรือไม่ เมื่อเปรียบเทียบกับยาแผนปัจจุบัน

   กรุณาอธิบายว่าเพราะเหตุใด

6. ผลอะไร ที่คุณคาดหวังว่าจะได้รับจากการกินสมุนไพรหรือผลิตภัณฑ์เสริมอาหาร
7. คุณมีข้อกังวลใจเกี่ยวกับการใช้สมุนไพรหรือผลิตภัณฑ์เสริมอาหารหรือไม่ ถ้ามี คืออะไร

   กรุณาเปรียบเทียบข้อกังวลใจของการใช้สมุนไพรหรือผลิตภัณฑ์เสริมอาหาร กับการใช้ยาแผนปัจจุบัน
8. คุณเคยได้รับคำเตือนเกี่ยวกับการใช้สมุนไพรหรือผลิตภัณฑ์เสริมอาหารหรือไม่ เช่นจากแพทย์ จากพยาบาล จากเภสัชกร หรือจากเพื่อน ถ้ามี คำเตือนดังกล่าวมีผลต่อการใช้สมุนไพรหรือผลิตภัณฑ์เสริมอาหารของคุณหรือไม่อย่างไร

Appendix 5: Data extraction sheet for outpatient notes

Translation version

Data extraction sheet for an outpatient note

Hospital ..... Date of data collection.....

Participant No.....

Demographic data

1. Date of Birth.....
2. Date of diagnosis chronic kidney disease (CKD).....
3. Other illnesses/ conditions

☐ Hypertension (1) ☐ Diabetic mellitus (2) ☐ Cardiovascular diseases (3)

☐ Dyslipidemia (4) ☐ Others (5).....

4. Health care system

☐ National health system (1) ☐ Officer's welfare (2) ☐ Health insurance (3)

☐ Paying for care from personal money (4)

5. Current medication list

Date / Medication	Name of medication						
		Dose					
Erythropoietin							
Fe compounds							
Folic acid							
Vit B1-6-12							
Ca compounds							
Al compounds							
Calcitriol							
Kayexalate							
Kalimate							
Sodamint							
ACEIs							
ARBs							
Furosemide							
HCTZ							
CCBs							
BBs							
Aspirin							
SU							
Metformin							
Insulin							
Statins							
Fibrates							

Notes: ACEIs = Angiotensin converting enzyme inhibitors

ARBs = Angiotensin receptor blockers, HCTZ = Hydrochlorothiazide

CCBs = Calcium channel blockers, BBs = Beta blockers

SU = Sulfonyl ureas

2

6. Laboratory results

Date / Lab tests									
Fasting plasma glusoce (mg/dl)									
HbA1C									
BUN (mg/dl)									
Scr (mg/dl)									
Clcr (24 hr. urine)									
Na (mEq/L)									
K (mEq/L)									
Cl (mEq/L)									
HCO_3 (mEq/L)									
Ca (mg/dl)									
Albumin (mg/dl)									
PO_4 (mg/dl)									
PTH (pg/ml)									
Hct (%)									
Hg (mg/dl)									
TC (mg/dl)									
TG (mg/dl)									
HDL (mg/dl)									
LDL (mg/dl)									
Uric acid (mg/dl)									
BP (mmHg)									
PR (beats/min)									
BW (kg)									

3

Date / Lab tests									
U/A: Protein Blood/RBC									
24-hour urinary protein excretion rate									
PCR									
ACR									
Pitting oedema									

PCR = A protein and creatinine ratio; ACR = An albumin and creatinine ratio

The original version of data extraction sheet for outpatient notes

แบบเก็บข้อมูลจากเวชระเบียนผู้ป่วยนอก

โรงพยาบาลจุฬาฯ / ศูนย์การแพทย์สมเด็จพระเทพฯ

ผู้ป่วยคนที่..... วันที่เก็บข้อมูล ...../...../.....

ข้อมูลทั่วไปของผู้ป่วย

1. วันเดือนปีเกิด ...../...../.....
2. วันที่ได้รับการวินิจฉัยว่าเป็นโรคไตเรื้อรัง ...../...../.....
3. โรคประจำตัว

   ☐ ความดันโลหิตสูง (1) ☐ เบาหวาน (2) ☐ โรคหัวใจ (3) ☐ ไขมันในเลือดสูง (4)

   ☐ อื่นๆ (5) .....

4. สิทธิการรักษา ☐ ระบบสุขภาพดีถ้วนหน้า (1) ☐ สวัสดิการข้าราชการ (2)

   ☐ ระบบประกันสุขภาพ (3) ☐ จ่ายค่ารักษาพยาบาลด้วยตนเอง (4)

5. รายการยาที่ผู้ป่วยใช้ในปัจจุบัน

วันที่ / ยา	ชื่อยา						
		ขนาดยา					
Erythropoietin							
Fe compounds							
Folic acid							
Vit B1-6-12							
Ca compounds							
Al compounds							
Calcitriol							
Kayexalate							
Kalimate							
Sodamint							
ACEIs							
ARBs							
Furosemide							
HCTZ							
CCBs							
BBs							
Aspirin							
SU							
Metformin							
Insulin							
Statins							
Fibrates							

Notes: ACEIs = Angiotensin converting enzyme inhibitors,

ARBs = Angiotensin receptor blockers, HCTZ = Hydrochlorothiazide

CCBs = Calcium channel blockers, BBs = Beta blockers

SU = Sulfonyl ureas

6. ผลการตรวจทางห้องปฏิบัติการ

วันที่ / Lab tests									
Fasting plasma glusoce (mg/dl)									
HbA1C									
BUN (mg/dl)									
Scr (mg/dl)									
Clcr (24 hr. urine)									
Na (mEq/L)									
K (mEq/L)									
Cl (mEq/L)									
HCO_3 (mEq/L)									
Ca (mg/dl)									
Albumin (mg/dl)									
PO_4 (mg/dl)									
PTH (pg/ml)									
Hct (%)									
Hg (mg/dl)									
TC (mg/dl)									
TG (mg/dl)									
HDL (mg/dl)									
LDL (mg/dl)									
Uric acid (mg/dl)									
BP (mmHg)									
PR (beats/min)									
BW (kg)									
U/A: Protein Blood/RBC									
24-hour urinary protein excretion rate									
PCR									
ACR									
Pitting oedema									

PCR = A protein and creatinine ratio; ACR = An albumin and creatinine ratio

3

Appendix 6: Final version of questionnaire

Translation version

Questionnaire for patients with chronic kidney disease

The purpose of this interview is to gather information about the use of herbal and dietary supplements amongst pre-dialysis patients in order to provide information regarding them for patients with chronic kidney disease (CKD).

CU / SWU Hospital

Participant number..... Date of data collection...../...../.....

Information provider ☐ Patient (0) ☐ Care giver (1)

Ht.....cm.

Demographic data

1. Gender ☐ Male (0) ☐ Female (1)

2. Current address ☐ Bangkok (0)

   ☐ Rural area (1) City.....Province.....

3. Education

   ☐ None (0) ☐ Primary school (1) ☐ Secondary School (2)

   ☐ Vocational degree (3) ☐ Bachelor's degree (4) ☐ Higher degree (5)

4. Occupation

   ☐ Unemployed (0) ☐ Retired (1) ☐ Housewife (2) ☐ Business owner(3)

   ☐ Employee (4) ☐ Farmer (5) ☐ Professional (6) ☐ Other (specify) (7).....

5. Smoking status

   ☐ Never (0) ☐ Former smoker (1) ☐ Current smoker (2)

   Date stopped..... Amount.....cigarettes, packs/day

6. Alcoholic consumption

   ☐ Never (0) ☐ Former consumer (1) Date stopped.....

   ☐ Current consumer (2): Types .....Amount.....glasses,cans,bottles per day/week

The use of herbal and dietary supplements

7. Did you use herbal or dietary supplements in the last month? (excluding herbal or dietary supplement use for daily food intake or cosmetic purposes)

   ☐ Never (0) (go to question no. 18)

   ☐ Former use (1) Stop date...../...../.....(go to question no. 18)

   ☐ Yes (2) (go to question no.8-17): ☐ Herbs (0) ☐ Dietary supplements (1) ☐ Both (2)

8. How many herbal and dietary products do you use if any? Herbs..... Dietary supplements.....

☐ Cannot remember (999)

9. What are the products? What purposes do you use them? How do you use them? How much do you use them? How often do you use them? How long do you use them? (please fill in the table)

Name of medications and HDS	Indication[(a)]	Dosage form[(b)]	How do you use[(c)]	Dose (per day)	How often (per day/ week)	How long[(d)] (month/year)
				……tablet(s)/time	………time(s)/day	• Current use……month(s)/year(s) • Stop using……month(s)/year(s) Duration of former use……month(s)/year(s)
				……tablet(s)/time	………time(s)/day	• Current use……month(s)/year(s) • Stop using……month(s)/year(s) Duration of former use……month(s)/year(s)
				……tablet(s)/time	………time(s)/day	• Current use……month(s)/year(s) • Stop using……month(s)/year(s) Duration of former use……month(s)/year(s)
				……tablet(s)/time	………time(s)/day	• Current use……month(s)/year(s) • Stop using……month(s)/year(s) Duration of former use……month(s)/year(s)

Note: HDS = Herbal and dietary supplements, Missing data = Participants cannot remember (999)
(a) Treatment of CKD (1), Well-being (2), Long life expectancy (3), others (4)
(b) Pills, capsules, tablets, powder, solution, crude herbs
(c) Swallow (1), Topical use (2), Make into a drink/food using hot water (3), other (4)
(d) How long have you used them?

10. Why do you use them? Please rank the top three of reasons (can tick more than 1 answer)

……I wanted to try them (1) ……I hope they will work (2)

……They are safer than modern medicines (3) ……Modern medicines don't work (4)

……They are cheaper than modern medicines (5) ……They are easily accessed (6)

……Health care providers recommended them (7) ……My family and friends recommended them (8)

……Used by themselves (9) ……Other (specify) (10)……………………………

11. From what sources did you receive information about herbal and dietary supplements? (can tick more than 1 answer)

☐ Radio (1) ☐ Television (2) ☐ Newspaper (3) ☐ Leaflet (4)

☐ Internet (5) ☐ Family or friend (6) ☐ Other (specify) (7)…………………………....

12. How did you obtain herbal and dietary supplements? (can tick more than 1 answer)

☐ Buy (1) from ☐ Drug store (1) ☐ Folk remedy shop (2) ☐ Health food store(3)

☐ Hospital (4) ☐ Direct sale (5)

☐ Provided by their family/ friends (2) ☐ Collecting them from their garden (3)

☐ Other (specify) (4)……………………………………………………………………

2

13. Did you inform your health care providers that you use them?

☐ No (0) because ☐ They don't ask (1) ☐ No need to inform (2) ☐ Other (specify) (3).....

☐ Yes (1) : Doctor/nurse/pharmacist/ other (specify).....

14. Have you had any positive effects from herbal and dietary supplements?

☐ No (0)

☐ Yes (1) What are benefits?..... Name of HDS.....

☐ Unsure (2) ☐ Don't know (3)

15. Have you had any problems after taking herbal and dietary supplements?

☐ No (0) (go to question no. 17)

☐ Yes (1) What are problems?..... (go to question no.16)

Name of HDS.....

☐ Unsure (2) ☐ don't know (3)

16. Do you stop using them when you have such problems?

☐ No (1) because.....

☐ Yes (0)

17. How long will you continue to use the HDS? .....months/years

Because.....

☐ Unsure (1) ☐ don't know (2)

18. Do you use other alternative medicines, such as meditation, acupuncture, yoga, etc.?

☐ No (0) ☐ Yes (1) (can tick more than 1 answer):

	Period per time minute/hour	Frequency.....time(s)per day/week/month	Duration day/month/year
Meditation (1)			
Acupuncture (2)			
Yoga (3)			
Tai-chi (4)			
Massage (5)			
Other (specific) (6).....			

19. Do you plan to use them within this year? (for participants who have not taken them)

☐ No (0) because.....

☐ Yes (1) because.....

☐ Unsure (2) ☐ don't know (3)

Medication history

20. I have your medication list from the chart. Have you used any other medicines in the last month, such as OTC medications?

☐ No (0) ☐ Yes (1) (specify in table)

Name	Dose	How often	How long (month/year)
Paracetamol	.....tablet(s)/time	.....time(s)/week ..... time(s)/month ..... time(s)/year	• Current use.....month/year • Stop using..... month/year Duration of former use..... month/year
NSAIDs	.....tablet(s)/time	.....time(s)/week ..... time(s)/month ..... time(s)/year	• Current use.....month/year • Stop using..... month/year Duration of former use..... month/year

21. Thai-version of 8-item Morisky medication adherence questionnaire

©Morisky Medication Adherence Scale (MMAS-8-Item). This is a generic adherence scale and the name of the health concern can be substituted in each question item.

You indicated that you are taking medication for your kidneys. Individuals have identified several issues regarding their medication-taking behavior and we are interested in your experiences. There is no right or wrong answer. Please answer each question based on your personal experience with your kidney medication.

(Please circle the correct number)

	No=1	**Yes=0**
1. Do you sometimes forget to take your kidney pills?.....		
2. People sometimes miss taking their medications for reasons other than forgetting. Thinking over the past two weeks, were there any days when you did not take your kidney medicine?.....		
3. Have you ever cut back or stopped taking your medication without telling your doctor, because you felt worse when you took it?.....		
4. When you travel or leave home, do you sometimes forget to bring along your [health concern] medication?.....		
5. Did you take your kidney medicine yesterday?.....		
6. When you feel like your kidney is under control, do you sometimes stop taking your medicine?.....		
7. Taking medication everyday is a real inconvenience for some people. Do you ever feel hassled about sticking to your kidney treatment plan?.....		

8. How often do you have difficulty remembering to take all your medications?
(Please circle the correct number)

Never/Rarely.....4

Once in a while.....3

Sometimes.....2

Usually.....1

All the time.....0

22. What medications do you most often forget? .....

5

The Restriction of Protein, Potassium, Phosphate and Salt diet questionnaire for pre-dialysis patients (RPPPS)

It can be difficult to stick to the dietary requirements for CKD and we want to know how you manage with your diet.

Individuals have identified several issues regarding their diet behaviour and we are interested in your experiences. There is no right or wrong answer. Please answer each question based on your own personal experience of your diet.

23. Did you receive dietary recommendations from doctors or dieticians?

☐ No (0) (go to question no. 25) ☐ Yes (1) (go to question no. 24)

24. The Modification of dialysis diet and fluid non-adherence questionnaire (DDFQ)

1. To what degree did you comply with a doctor's recommendation for your protein-rich food restriction in the last 14 days?

No	Low	Moderate	High	Very high
0	1	2	3	4

2. To what degree did you comply with a doctor's recommendation for your potassium-rich food restriction in the last 14 days?

No	Low	Moderate	High	Very high
0	1	2	3	4

3. To what degree did you comply with a doctor's recommendation for your phosphate-rich food restriction in the last 14 days?

No	Low	Moderate	High	Very high
0	1	2	3	4

4. To what degree did you comply with a doctor's recommendation for your salt-rich food restriction in the last 14 days?

No	Low	Moderate	High	Very high
0	1	2	3	4

End of questions

Thank you

25. The Modification of dialysis diet and fluid non-adherence questionnaire (DDFQ) for respondents who did not receive a doctor's or a dietician's advice about food restriction

1. How much did you eat protein-rich food in the last 14 days?
   1.1 Pork.....times/week

No	Low	Moderate	High	Very high
0	1	2	3	4

1.2 Chicken.....times/week

No	Low	Moderate	High	Very high
0	1	2	3	4

1.3 Fish.....times/week and/or egg white.....times/week

No	Low	Moderate	High	Very high
0	1	2	3	4

2. How much did you eat potassium-rich food in the last 14 days?

   Fruit .....times/week Vegetable .....times/week

No	Low	Moderate	High	Very high
0	1	2	3	4

3. How much did you eat phosphate-rich food in the last 14 days?
   3.1 Milk .....times/week, yogurt .....times/week, butter .....times/week, coffee .....times/week

   Cocoa .....times/week

No	Low	Moderate	High	Very high
0	1	2	3	4

3.2 Cereals.....times/week, beans.....times/week, soy beans.....times/week, bread.....times/week

No	Low	Moderate	High	Very high
0	1	2	3	4

3.3 Ice cream.....times/week, chocolate.....times/week, coke .....times/week

No	Low	Moderate	High	Very high
0	1	2	3	4

4. How much did you eat salt-rich food in the last 14 days?

No	Low	Moderate	High	Very high
0	1	2	3	4

End of questions

Thank you

Definition of degree of food consumption for question no. 25

Degree of food consumption classified into five levels – no, low, moderate, high and very high, see Table.

Degree of food consumption	Definition
No	No food consumed at all
Low	Eating 1-2 days per week
Medium	Eating 3-4 days per week
High	Eating 5-6 days per week
Very high	Eating daily

Reference: Nutritionquest. 2005. *Food Questionnaire - Dialysis* [Online]. Available: www.nutritionquest.com [Accessed 20 January 2011].

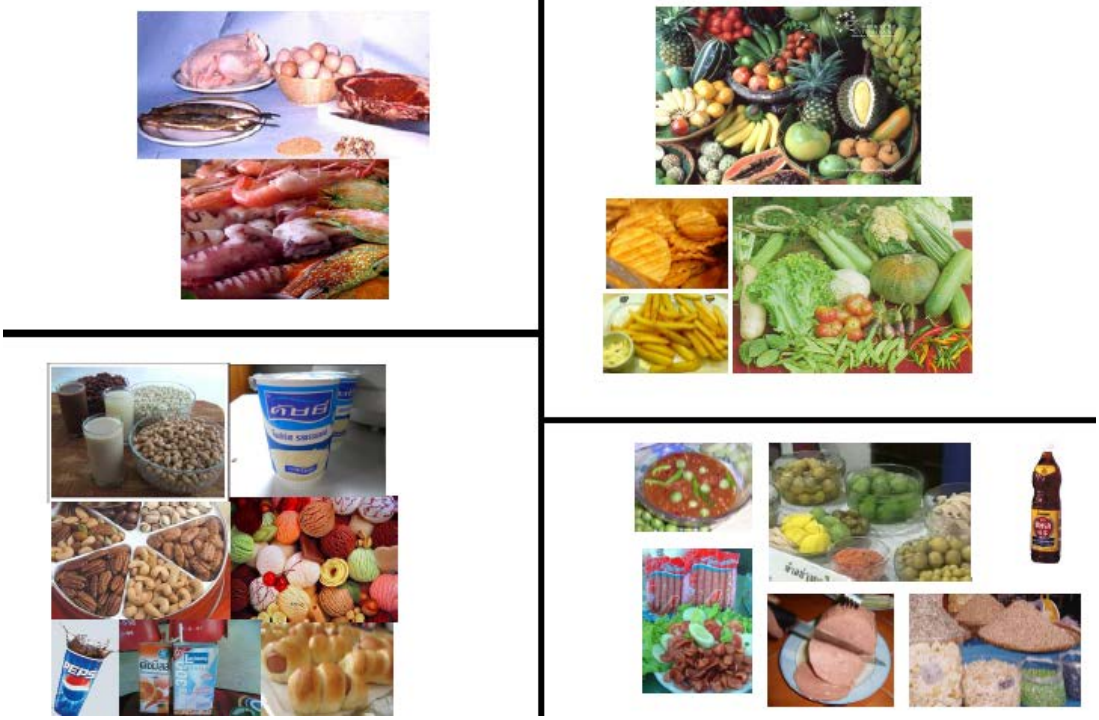
Classification of degree of diet intake for dietary questionnaire

There are two categories of the degree of diet intake – low diet intake and moderate to high diet intake. Respondents who do not take such types of diets or take low amounts of food (score 0-1) are defined as low diet intake whilst those with moderate to very high diet intake (score 2-4) are defined as moderate to high diet intake.

Herbal medicines

Dietary supplements

Types of dietary intake



The original final version of questionnaire

แบบสัมภาษณ์ผู้เข้าร่วมโครงการวิจัย

แบบสัมภาษณ์นี้มีวัตถุประสงค์เพื่อ รวบรวมข้อมูลเกี่ยวกับการใช้สมุนไพรและผลิตภัณฑ์เสริมอาหารในผู้ป่วยโรคไตเรื้อรัง ซึ่งจะเป็นข้อมูลในการศึกษาการใช้สมุนไพรและผลิตภัณฑ์เสริมอาหารในผู้ป่วยกลุ่มนี้

รพ.จุฬาฯ/ศูนย์การแพทย์สมเด็จพระเทพฯ

ผู้ป่วยคนที่..... วันที่เก็บข้อมูล ...../...../.....

ผู้ให้ข้อมูล ☐ ผู้ป่วย (0) ☐ ญาติผู้ป่วย (1).....

ส่วนสูง.....cm.

ข้อมูลทั่วไปของผู้ป่วย

1. เพศ ☐ ชาย (0) ☐ หญิง (1)
2. ที่อยู่ปัจจุบัน ☐ กทม (0)
   ☐ ต่างจังหวัด (1) อำเภอ.....จังหวัด.....
3. ระดับการศึกษา
   ☐ ไม่ได้เรียนหนังสือ (0) ☐ ประถมศึกษา (1) ☐ มัธยมต้น/ มัธยมปลาย (2) ☐ ปวช/ปวส.(3)
   ☐ ปริญญาตรี (4) ☐ สูงกว่าปริญญาตรี (5)
4. อาชีพ
   ☐ ผู้ว่างงาน (0) ☐ ผู้เกษียณอายุ (1) ☐ แม่บ้าน/พ่อบ้าน (2) ☐ ประกอบธุรกิจส่วนตัว (3)
   ☐ ลูกจ้าง (ข้าราชการทั่วไป พนักงานบริษัท ช่างต่างๆ) (4) ☐ เกษตรกร (5)
   ☐ วิชาชีพ เช่น ครู แพทย์ พยาบาล เภสัชกร วิศวกร สถาปนิก ฯลฯ (6)
   ☐ อื่นๆ (7).....
5. คุณเคยสูบบุหรี่หรือไม่
   ☐ ไม่เคยสูบ (0) ☐ เคยสูบบุหรี่แต่ปัจจุบันเลิกสูบแล้ว (1) วัน/เดือน/ปี ที่หยุดสูบ.....
   ☐ สูบบุหรี่ (2) ปริมาณ.....มวน/ห่อ ต่อวัน
6. คุณเคยดื่มเครื่องดื่มที่มีแอลกอออล์หรือไม่
   ☐ ไม่เคยดื่ม (0) ☐ เคยดื่มแต่ปัจจุบันเลิกแล้ว (1) วัน/เดือน/ปี ที่หยุดดื่ม.....
   ☐ ดื่ม (2) ประเภท..... ปริมาณ.....แก้ว/กระป๋อง/ขวด ต่อวัน/สัปดาห์

การใช้สมุนไพรและผลิตภัณฑ์เสริมอาหาร

7. คุณเคยใช้สมุนไพรและ/หรือผลิตภัณฑ์เสริมอาหารเมื่อเดือนที่แล้วหรือไม่

   สมุนไพรในที่นี้หมายถึงผลิตภัณฑ์ที่มีส่วนประกอบของสมุนไพร, หรือพืชสมุนไพรที่ยังไม่ได้แปรรูป หรือสารสำคัญที่ได้จากสัตว์ **ไม่หมายรวมถึงสมุนไพรที่ใส่ในอาหาร เพื่อรับประทานในชีวิตประจำวัน เช่น ตะไคร้ในต้มยำ และสมุนไพรในเครื่องสำอาง**

   ☐ ไม่เคยใช้ (0) (ตอบคำถามข้อ 18)

   ☐ เคยใช้แต่ปัจจุบันเลิกใช้แล้ว (1) วัน/เดือน/ปี ที่หยุดใช้..... (ตอบคำถามข้อ 18)

   ☐ ใช้ (2) (ตอบคำถามข้อ 8-17): ☐ สมุนไพร (0) ☐ ผลิตภัณฑ์เสริมอาหาร (1) ☐ ใช้ทั้ง 2 อย่าง (2)

8. คุณใช้สมุนไพรและ/หรือผลิตภัณฑ์เสริมอาหารจำนวนกี่ชนิด

   สมุนไพรจำนวน.....ชนิด ผลิตภัณฑ์เสริมอาหารจำนวน.....ชนิด

   ☐ จำไม่ได้ (999)

9. คุณใช้สมุนไพรและ/หรือผลิตภัณฑ์เสริมอาหารอะไรบ้าง ใช้เพื่อวัตถุประสงค์ใด มีวิธีใช้อย่างไร ขนาดเท่าใด ใช้มานานหรือยัง (กรุณากรอกข้อมูลในตาราง)

ชื่อสมุนไพรหรือ ผลิตภัณฑ์เสริมอาหาร	ข้อบ่งใช้[a]	รูปแบบยา[b]	วิธีใช้[c]	ขนาดยา (ต่อวัน)	ความถี่ของการใช้ (ต่อวัน/เดือน)	ระยะเวลาที่ใช้ (เดือน/ปี)
				......เม็ด/ครั้ง	.........ครั้ง/วัน ....ครั้ง/สัปดาห์	• ใช้อยู่..........เดือน/ปี • หยุดใช้........เดือน/ปี - ช่วงที่เคยใช้ ใช้ ติดต่อกัน..........เดือน/ปี
				......เม็ด/ครั้ง	.........ครั้ง/วัน ....ครั้ง/สัปดาห์	• ใช้อยู่..........เดือน/ปี • หยุดใช้........เดือน/ปี - ช่วงที่เคยใช้ ใช้ ติดต่อกัน..........เดือน/ปี
				......เม็ด/ครั้ง	.........ครั้ง/วัน ....ครั้ง/สัปดาห์	• ใช้อยู่..........เดือน/ปี • หยุดใช้........เดือน/ปี - ช่วงที่เคยใช้ ใช้ ติดต่อกัน..........เดือน/ปี
				......เม็ด/ครั้ง	.........ครั้ง/วัน ....ครั้ง/สัปดาห์	• ใช้อยู่..........เดือน/ปี • หยุดใช้........เดือน/ปี - ช่วงที่เคยใช้ ใช้ ติดต่อกัน..........เดือน/ปี
				......เม็ด/ครั้ง	.........ครั้ง/วัน ....ครั้ง/สัปดาห์	• ใช้อยู่..........เดือน/ปี • หยุดใช้........เดือน/ปี - ช่วงที่เคยใช้ ใช้ ติดต่อกัน..........เดือน/ปี

Note:(a) รักษาโรคไตเรื้อรัง (1), เพื่อให้สุขภาพดี (2), เพื่อช่วยให้อายุยืน (3), อื่นๆ (4)

(b) ลูกกลอน เม็ด แคปซูล ผง ยาน้ำ หรือ สมุนไพรที่ยังไม่ได้แปรรูป (c) รับประทาน (1), ใช้ภายนอก (2), ต้มน้ำดื่ม (3), อื่นๆ (4)

หมายเหตุ: Missing data = จำไม่ได้ (999)

3

10. เพราะเหตุใดคุณถึงใช้สมุนไพรหรือผลิตภัณฑ์เสริมอาหาร (ตอบได้มากกว่า 1 ข้อ)

.....อยากลองใช้ (1) .....หวังว่าสมุนไพรหรือผลิตภัณฑ์เสริมอาหารจะมีประสิทธิภาพ (2)

.....เชื่อว่าสมุนไพรหรือผลิตภัณฑ์เสริมอาหารปลอดภัยกว่ายาแผนปัจจุบัน (3)

.....ยาแผนปัจจุบันไม่มีประสิทธิภาพ (4) .....สมุนไพรหรือผลิตภัณฑ์เสริมอาหารถูกกว่ายาแผนปัจจุบัน (5)

.....หาซื้อได้ง่าย สะดวก (6) .....บุคลากรทางการแพทย์แนะนำให้ใช้ (7)

.....ครอบครัวและเพื่อนแนะนำ (8) .....ตัดสินใจใช้ด้วยตัวเอง (9)

.....อื่นๆ (10).....

11. คุณเคยได้รับข้อมูลเกี่ยวกับสมุนไพรหรือผลิตภัณฑ์เสริมอาหารจากแหล่งข้อมูลใด (ตอบได้มากกว่า 1 ข้อ)

☐ วิทยุ (1) ☐ โทรทัศน์ (2) ☐ หนังสือพิมพ์ (3) ☐ แผ่นพับ (4)

☐ อินเทอร์เนต (5) ☐ ครอบครัว หรือเพื่อน (6) ☐ อื่นๆ (โปรดระบุ) (7).....

12. คุณได้รับสมุนไพรหรือผลิตภัณฑ์เสริมอาหารด้วยวิธีใด (ตอบได้มากกว่า 1 ข้อ)

☐ ซื้อ (1) จาก ☐ ร้านยาแผนปัจจุบัน (1) ☐ ร้านยาแผนโบราณ/ร้านขายสมุนไพร (2)

☐ ร้านขายผลิตภัณฑ์เสริมอาหาร (3) ☐ โรงพยาบาล (4) ☐ เซลล์ขายตรง (5)

☐ ญาติหรือเพื่อนหามาให้ (2) ☐ เก็บจากสวนที่บ้าน (3) ☐ อื่นๆ (โปรดระบุ) (4) .....

13. คุณได้บอกบุคลากรทางการแพทย์หรือไม่ ว่าคุณใช้สมุนไพรหรือผลิตภัณฑ์เสริมอาหาร

☐ ไม่ได้บอก (0) เพราะ

☐ บุคลากรทางการแพทย์ไม่ได้ถาม (1) ☐ ไม่จำเป็นต้องบอก (2)

☐ อื่นๆ (3).....

☐ บอก (1): แพทย์/พยาบาล/เภสัชกร

14. คุณได้รับประโยชน์จากการใช้สมุนไพรหรือผลิตภัณฑ์เสริมอาหารหรือไม่

☐ ไม่ได้ประโยชน์ (0) ☐ ได้ประโยชน์ (1) คือ.....

☐ ไม่แน่ใจ (2) ☐ ไม่รู้ (3)

15. คุณมีปัญหาเกี่ยวกับสุขภาพจากการใช้สมุนไพรหรือผลิตภัณฑ์เสริมอาหารหรือไม่

☐ ไม่มีปัญหา (0) (ตอบคำถามข้อ 17) ☐ มี (1) ปัญหาคือ.....

จากผลิตภัณฑ์.....(ตอบคำถามข้อ 16)

☐ ไม่แน่ใจ (2) ☐ ไม่รู้ (3)

16. คุณหยุดใช้สมุนไพรหรือผลิตภัณฑ์เสริมอาหารหรือไม่ เมื่อมีปัญหา

☐ หยุดใช้ (0)

☐ ใช้ต่อไป (1) เพราะ.....

17. คุณคิดว่าจะใช้สมุนไพรหรือผลิตภัณฑ์เสริมอาหารอีกนานเท่าใด .....เดือน/ปี

เพราะ.....

☐ ไม่แน่ใจ (1) ☐ ไม่รู้ (2)

18. คุณเคยใช่หรือกำลังใช้การแพทย์ทางเลือกอื่นหรือไม่ เช่น นั่งสมาธิ ฝังเข็ม เล่นโยคะ รำไทเก๊ก

☐ ไม่ (0) ☐ ใช้ (1) (ตอบได้มากกว่า 1 ข้อ กรุณากรอกข้อมูลในตาราง)

ประเภทการแพทย์ทางเลือก	ระยะเวลาที่ใช้ต่อครั้ง นาที/ชม.	จำนวนครั้งที่ทำต่อ วัน/ อาทิตย์/ เดือน	เป็นระยะเวลา วัน/ เดือน/ ปี
นั่งสมาธิ (1)			
ฝังเข็ม (2)			
เล่นโยคะ (3)			
รำไทเก๊ก (4)			
นวด (5)			
อื่นๆ (6).....			

19. คุณคิดว่าคุณจะใช้สมุนไพรหรือผลิตภัณฑ์เสริมอาหาร ภายในปีนี้หรือไม่ (สำหรับผู้ที่ตอบว่าไม่ใช้สมุนไพรหรือผลิตภัณฑ์เสริมอาหาร)

☐ ไม่ (0) เพราะ.....

☐ ใช้ (1) เพราะ.....

☐ ไม่แน่อาจจะใช้ (2) ☐ ไม่รู้ (3)

ประวัติการใช้ยา

20. คุณซื้อยามาใช้เองหรือไม่ เมื่อเดือนที่แล้ว

☐ ไม่ (0) ☐ ใช่ (1) (ระบุในตาราง)

ชื่อยา	ขนาดยา	ความถี่ของการใช้	ระยะเวลาที่ใช้ (เดือน/ปี)
Paracetamol	.....เม็ด/ครั้ง	.....ครั้ง/สัปดาห์ .....ครั้ง/เดือน .....ครั้ง/ปี	• ใช้อยู่.....เดือน/ปี • หยุดใช้.....เดือน/ปี - ช่วงที่เคยใช้ ใช้ ติดต่อกัน.....เดือน/ปี
NSAIDs (ยาแก้ปวดข้อ)	.....เม็ด/ครั้ง	.....ครั้ง/สัปดาห์ .....ครั้ง/เดือน .....ครั้ง/ปี	• ใช้อยู่.....เดือน/ปี • หยุดใช้.....เดือน/ปี - ช่วงที่เคยใช้ ใช้ ติดต่อกัน.....เดือน/ปี

21. แบบประเมินความร่วมมือในการใช้ยาที่แพทย์สั่ง: Morisky Medication Adherence Scale (MMAS)

คำชี้แจง : กรุณากาเครื่องหมาย ✓ลงในกล่อง ❒ ในคำถามต่อไปนี้ให้ตรงกับความเป็นจริง

1. มีบางครั้งที่คุณลืมรับประทานยาใช่หรือไม่	❒ ใช่	❒ ไม่ใช่
2. บางคนไม่ได้รับประทานยาด้วยเหตุผลต่างๆ นอกเหนือจากลืม คุณคิดทบทวนว่าในช่วง 2 สัปดาห์ที่ผ่านมา มีบางวันที่คุณไม่ได้รับประทานยา	❒ ใช่	❒ ไม่ใช่
3. คุณเคยลดขนาดยาหรือหยุดยา เนื่องจากรู้สึกแย่เวลารับประทานยา โดยที่ไม่ได้บอกแพทย์	❒ ใช่	❒ ไม่ใช่
4. เมื่อคุณออกจากบ้านหรือเดินทางไกล มีบางครั้งที่คุณลืมพกยาติดตัวไปด้วย	❒ ใช่	❒ ไม่ใช่
5. เมื่อวานนี้ คุณรับประทานยาครบ ใช่หรือไม่	❒ ใช่	❒ ไม่ใช่
6. เมื่อคุณรู้สึกว่าอาการของโรคที่คุณเป็นควบคุมได้แล้ว บางครั้งคุณหยุดรับประทานยา	❒ ใช่	❒ ไม่ใช่
7. การรับประทานยาทุกวันอาจไม่สะดวกสำหรับบางคน คุณเคยรู้สึกอึดอัดที่ต้องรับประทานยาอย่างเคร่งครัดหรือเข้มงวด ใช่หรือไม่	❒ ใช่	❒ ไม่ใช่
8. คุณรู้สึกว่ามีความยุ่งยากบ่อยเพียงใด ในการจดจำยาทั้งหมดที่ต้องรับประทาน (กาเครื่องหมาย ✓ลงในกล่อง ❒ **โดยเลือกเพียง 1 ข้อเท่านั้น**)		
❒8.1) ไม่รู้สึกหรือแทบจะไม่รู้สึกว่ามีความยุ่งยากในการจดจำยาที่ใช้ (หรือมี 0 ถึง 1 ครั้งต่อสัปดาห์ที่จำไม่ได้ว่ายาตัวไหนทานอย่างไร)		
❒ 8.2) รู้สึกว่ายุ่งยากบ้างเล็กน้อย ในการจดจำวิธีทานยาแต่ละอย่างให้ถูกต้อง (หรือมี 1 ถึง 2 ครั้งต่อสัปดาห์ที่จำไม่ได้ว่ายาตัวไหนทานอย่างไร)		
❒ 8.3) รู้สึกว่ายุ่งยากปานกลาง ในการจดจำวิธีทานยาแต่ละอย่างให้ถูกต้อง (หรือมี 3 ถึง 4 ครั้งต่อสัปดาห์ที่จำไม่ได้ว่ายาตัวไหนทานอย่างไร)		
❒ 8.4) รู้สึกว่ายุ่งยากเป็นประจำ ในการจดจำวิธีทานยาแต่ละอย่างให้ถูกต้อง (หรือมี 5 ถึง 6 ครั้งต่อสัปดาห์ที่จำไม่ได้ว่ายาตัวไหนทานอย่างไร)		
❒ 8.5) รู้สึกว่ายุ่งยากทุกครั้งหรือตลอดเวลา ในการจดจำวิธีทานยาแต่ละอย่างให้ถูกต้อง (มีความยุ่งยากทุกวัน จำไม่ได้ว่ายาตัวไหนทานอย่างไร)		

22. สำหรับยาที่แพทย์สั่ง ยาอะไรที่คุณมักลืมรับประทาน

.....

แบบสอบถามการควบคุมอาหารที่มีส่วนประกอบของโปรตีน โพแทสเซียม ฟอสเฟต และเกลือ สำหรับผู้ป่วยโรคไตเรื้อรังที่ยังไม่ได้ฟอกเลือด

เป็นการยากที่จะควบคุมการรับประทานอาหารสำหรับผู้ป่วยโรคไตเรื้อรัง และผู้วิจัยต้องการทราบว่าคุณมีการจัดการเกี่ยวกับการควบคุมอาหารของคุณอย่างไร

ผู้ป่วยแต่ละรายมีหลายปัญหาในการควบคุมอาหารขึ้นกับพฤติกรรมการบริโภคของแต่ละคน และผู้วิจัยสนใจที่จะเรียนรู้จากประสบการณ์ของคุณ การตอบคำถามต่อไปนี้ ไม่มีคำตอบที่ถูกหรือผิด กรุณาตอบคำถามแต่ละข้อตามประสบการณ์การรับประทานอาหารของคุณ

23. คุณได้รับคำแนะนำในการควบคุมอาหารสำหรับผู้ป่วยโรคไตเรื้อรังจากแพทย์/นักโภชนาการหรือไม่
    ☐ ไม่ (0) (ตอบคำถามข้อ 25) ☐ ใช่ (1) (ตอบคำถามข้อ 24)
24. แบบสอบถามดัดแปลงจาก dialysis diet and fluid non-adherence questionnaire (DDFQ)
    1) คุณปฏิบัติตามคำแนะนำการรับประทานอาหารที่มีโปรตีนสูงมากหรือน้อย เมื่อ 2 อาทิตย์ที่แล้ว

ไม่มี	น้อย	ปานกลาง	มาก	มากที่สุด
0	1	2	3	4

    2) คุณปฏิบัติตามคำแนะนำการรับประทานอาหารที่มีโพแทสเซียมสูงมากหรือน้อย เมื่อ 2 อาทิตย์ที่แล้ว

ไม่มี	น้อย	ปานกลาง	มาก	มากที่สุด
0	1	2	3	4

    3) คุณปฏิบัติตามคำแนะนำการรับประทานอาหารที่มีฟอสเฟตสูงมากหรือน้อย เมื่อ 2 อาทิตย์ที่แล้ว

ไม่มี	น้อย	ปานกลาง	มาก	มากที่สุด
0	1	2	3	4

    4) คุณปฏิบัติตามคำแนะนำการควบคุมอาหารที่มีรสเค็มมากหรือน้อย เมื่อ 2 อาทิตย์ที่แล้ว

ไม่มี	น้อย	ปานกลาง	มาก	มากที่สุด
0	1	2	3	4

จบการตอบแบบสอบถาม

ขอบคุณคะ

25. แบบสอบถามดัดแปลงจาก dialysis diet and fluid non-adherence questionnaire (DDFQ) สำหรับผู้ป่วยที่ไม่ได้รับคำแนะนำเรื่องการควบคุมอาหาร

1) คุณทานอาหารที่มีโปรตีนสูงมากหรือน้อย เมื่อ 2 อาทิตย์ที่แล้ว

1.1 หมู .....ครั้ง/สัปดาห์

ไม่มี	น้อย	ปานกลาง	มาก	มากที่สุด
0	1	2	3	4

1.2 ไก่ .....ครั้ง/สัปดาห์

ไม่มี	น้อย	ปานกลาง	มาก	มากที่สุด
0	1	2	3	4

1.3 ปลา .....ครั้ง/สัปดาห์ ไข่ขาว .....ครั้ง/สัปดาห์

ไม่มี	น้อย	ปานกลาง	มาก	มากที่สุด
0	1	2	3	4

2) คุณทานผลไม้ หรือผักมากหรือน้อย เมื่อ 2 อาทิตย์ที่แล้ว

ผลไม้.....ครั้ง/สัปดาห์ ผัก.....ครั้ง/สัปดาห์

ไม่มี	น้อย	ปานกลาง	มาก	มากที่สุด
0	1	2	3	4

3) คุณทานอาหารที่มีฟอสเฟตสูงมากหรือน้อย เมื่อ 2 อาทิตย์ที่แล้ว

3.1 นม โยเกิร์ต เนย

.....ครั้ง/สัปดาห์ .....ครั้ง/สัปดาห์ .....ครั้ง/สัปดาห์

กาแฟ โอวัลติน

.....ครั้ง/สัปดาห์ .....ครั้ง/สัปดาห์

ไม่มี	น้อย	ปานกลาง	มาก	มากที่สุด
0	1	2	3	4

3.2 ธัญพืช ถั่ว ข้าวกล้อง ขนมปัง

.....ครั้ง/สัปดาห์ .....ครั้ง/สัปดาห์ .....ครั้ง/สัปดาห์ .....ครั้ง/สัปดาห์

นมถั่วเหลือง (น้ำเต้าหู้) เต้าหู้

.....ครั้ง/สัปดาห์ .....ครั้ง/สัปดาห์ หรือเดือน

ไม่มี	น้อย	ปานกลาง	มาก	มากที่สุด
0	1	2	3	4

3.3 ไอศรีม ช็อคโกแลต โค้ก

.....ครั้ง/สัปดาห์ .....ครั้ง/สัปดาห์ .....ครั้ง/สัปดาห์

ไม่มี	น้อย	ปานกลาง	มาก	มากที่สุด
0	1	2	3	4

4) คุณทานอาหารที่มีรสเค็มมากหรือน้อย เมื่อ 2 อาทิตย์ที่แล้ว

ไม่มี	น้อย	ปานกลาง	มาก	มากที่สุด
0	1	2	3	4

จบการตอบแบบสอบถาม

ขอบคุณคะ

คำจำกัดความของการประเมินปริมาณอาหารที่รับประทานสำหรับแบบสอบถามข้อ 25

การประเมินปริมาณอาหารที่รับประทานแบ่งเป็น 5 ระดับ ได้แก่ ไม่ได้รับประทานอาหาร, รับประทานอาหารน้อย, ปานกลาง, มาก และมากที่สุด เกณฑ์การประเมินตามตารางด้านล่าง

ปริมาณการรับประทานอาหาร	คำจำกัดความ
ไม่ได้รับประทาน	ไม่ได้รับประทานอาหารเลย
รับประทานน้อย	รับประทาน 1-2 วันต่อสัปดาห์
รับประทานปานกลาง	รับประทาน 3-4 วันต่อสัปดาห์
รับประทานมาก	รับประทาน 5-6 วันต่อสัปดาห์
รับประทานมากที่สุด	รับประทานทุกวัน

เอกสารอ้างอิง: Nutritionquest. 2005. *Food Questionnaire - Dialysis* [Online]. Available: www.nutritionquest.com [Accessed 20 January 2011].

การแบ่งประเภทของปริมาณการรับประทานอาหาร สำหรับแบบสอบถามการรับประทานอาหาร

ปริมาณการรับประทานอาหารแบ่งเป็น 2 ประเภท คือ การรับประทานอาหารน้อย และการรับประทานอาหารปานกลางถึงมาก ผู้ตอบแบบสอบถามที่ตอบว่าไม่ได้รับประทานอาหารหรือรับประทานอาหารน้อย (คะแนน 0-1) จัดเป็นการรับประทานอาหารน้อย สำหรับผู้ตอบแบบสอบถามที่ตอบว่ารับประทานอาหารปานกลางถึงมากที่สุด (คะแนน 2-4) จัดเป็นการรับประทานอาหารปานกลางถึงมาก

สมุนไพร






ผลิตภัณฑ์เสริมอาหาร

ประเภทอาหารที่รับประทาน






Appendix 7: Data sheet for telephone interview and data extraction sheet for the follow-up study

Translation version

Interview over the telephone for follow-up study

CU hospital / SWU hospital

Participant number..... Date of interview ...../...../.....

Information provider ☐ Patient (0) ☐ Care giver (1)

The use of herbal and dietary supplements for one year (after recruitment)

1. Did you use herbal or dietary supplements during the last year?

☐ No (0) ☐ Yes (1), which ☐ Herbs (0) ☐ Dietary supplements (1) ☐ Both (2)

☐ Current user (1) due to

☐ Achieving benefits from using HDS (1)

☐ Hope to achieve their benefits (2)

☐ HDS provided by my family and friends (3)

☐ Other (specify) .....

Types of HDS used

Name of HDS	Indication	How long (months in the last year)

☐ Former use (used in last year but now stopped)(0) Stop date...../...../.....

Reasons for stopped using HDS

☐ Cannot afford (1) ☐ Fail to achieve benefits from using HDS (2)

☐ Experienced adverse effects from using HDS (3)

Types of adverse events.....

☐ Other (specify) .....

Types of HDS used

Name of HDS	Indication	How long (months in the last year)

1

2. Did you use paracetamol or pain killers in the last year? If so, how often and how long had you used them? (please fill in the table)

☐ No (0) ☐ Yes (1)

OTC medications	How often	How long (weeks, months in the last year)
Paracetamol		
NSAIDs		

Data extraction sheet from outpatient notes: follow-up study

CU hospital / SWU hospital

Participant number..... Date of data collection ...../...../.....

1. Medication list for one year after recruitment

Date / Medication	Name of medication						
		Dose					
Erythropoietin							
Fe compounds							
Folic acid							
Vit B1-6-12							
Ca compounds							
Al compounds							
Calcitriol							
Kayexalate							
Kalimate							
Sodamint							
ACEIs							
ARBs							
Furosemide							
HCTZ							
CCBs							
BBs							
Aspirin							
SU							
Metformin							
Insulin							
Statins							
Fibrates							

Notes: ACEIs = Angiotensin converting enzyme inhibitors

ARBs = Angiotensin receptor blockers, HCTZ = Hydrochlorothiazide

CCBs = Calcium channel blockers, BBs = Beta blockers, SU = Sulfonyl ureas

3

2. Laboratory results for one year after recruitment

Date / Lab tests									
Fasting plasma glusoce (mg/dl)									
HbA1C									
BUN (mg/dl)									
Scr (mg/dl)									
Clcr (24 hr. urine)									
Na (mEq/L)									
K (mEq/L)									
Cl (mEq/L)									
HCO_3 (mEq/L)									
Ca (mg/dl)									
Albumin (mg/dl)									
PO_4 (mg/dl)									
PTH (pg/ml)									
Hct (%)									
Hg (mg/dl)									
TC (mg/dl)									
TG (mg/dl)									
HDL (mg/dl)									
LDL (mg/dl)									
Uric acid (mg/dl)									
BP (mmHg)									
PR (beats/min)									
BW (kg)									

Date / Lab tests									
U/A: Protein Blood/RBC									
24-hour urinary protein excretion rate									
PCR									
ACR									
Pitting oedema									

PCR = A protein and creatinine ratio; ACR = An albumin and creatinine ratio

The original version of data sheet for the follow-up study

แบบสัมภาษณ์ทางโทรศัพท์ สำหรับติดตามการใช้สมุนไพรและผลิตภัณฑ์เสริมอาหารเป็นระยะเวลา 1 ปี

รพ.จุฬาฯ/ศูนย์การแพทย์สมเด็จพระเทพฯ

ผู้ป่วยคนที่..... วันที่สัมภาษณ์...../...../.....

ผู้ให้ข้อมูล ☐ ผู้ป่วย (0) ☐ ผู้ดูแลผู้ป่วย (1)

การใช้สมุนไพรและผลิตภัณฑ์เสริมอาหารเป็นระยะเวลา 1 ปี หลังจากคัดเลือกผู้ป่วยเข้าการศึกษา

1. คุณใช้สมุนไพร และ/ หรือ ผลิตภัณฑ์เสริมอาหารในระยะเวลา 1 ปีที่ผ่านมาหรือไม่

☐ ไม่ได้ใช้ (0) ☐ ใช้ (1) ได้แก่ ☐ สมุนไพร (0) ☐ ผลิตภัณฑ์เสริมอาหาร (1) ☐ ทั้งสองอย่าง (2)

☐ ปัจจุบันยังใช้สมุนไพรและ/หรือผลิตภัณฑ์เสริมอาหารอยู่ (1) เนื่องจาก

☐ ได้ประโยชน์จากการใช้ (1) คือ.....

☐ คาดหวังว่าจะได้ประโยชน์ (2) คือ.....

☐ ญาติหรือเพื่อนหามาให้ใช้ (3)

☐ อื่นๆ (โปรดระบุ) (4) .....

ชื่อสมุนไพรและ/หรือผลิตภัณฑ์เสริมอาหาร	ข้อบ่งใช้	ระยะเวลาที่ใช้นับจากปีที่แล้ว (เดือน)

☐ คนที่เคยใช้สมุนไพรและ/หรือผลิตภัณฑ์เสริมอาหารเมื่อปีที่แล้ว แต่ปัจจุบันหยุดใช้แล้ว (0)

วันที่ที่หยุดใช้ ...../...../..... เนื่องจาก

☐ ราคาแพง หรือไม่มีเงินซื้อมาใช้ (1) ☐ ไม่ได้รับประโยชน์จากการใช้ (2)

☐ เกิดอาการข้างเคียงจากการใช้ (3) ได้แก่.....

☐ อื่นๆ (โปรดระบุ) (4) .....

ชื่อสมุนไพรและ/หรือผลิตภัณฑ์เสริมอาหาร	ข้อบ่งใช้	ระยะเวลาที่ใช้นับจากปีที่แล้ว (เดือน)

1

2. คุณได้ซื้อพาราเซตามอล หรือยาแก้ไข้ แก้ปวดเมื่อย มาใช้หรือไม่ เมื่อปีที่แล้ว

☐ ไม่ได้ซื้อมาใช้เอง (0) ☐ ใช่ (1)

ชื่อยา	ความถี่ของการใช้	ระยะเวลาที่ใช้ (สัปดาห์, เดือน)
Paracetamol		
NSAIDs		

แบบเก็บข้อมูลจากเวชระเบียนผู้ป่วยนอก ติดตามการใช้ยาและผลการตรวจทางห้องปฏิบัติการเป็นเวลา 1 ปี

โรงพยาบาลจุฬาฯ / ศูนย์การแพทย์สมเด็จพระเทพฯ

ผู้ป่วยคนที่..... วันที่สัมภาษณ์ผู้ป่วย ...../...../.....

1. ยาที่ผู้ป่วยใช้ (บันทึกชื่อยาและขนาดยาทุกชนิดเป็นระยะเวลา 1 ปี นับจากวันที่สัมภาษณ์ผู้ป่วย)

วันที่ / ยา	ชื่อยา						
		ขนาดยา					
Erythropoietin							
Fe compounds							
Folic acid							
Vit B1-6-12							
Ca compounds							
Al compounds							
Calcitriol							
Kayexalate							
Kalimate							
Sodamint							
ACEIs							
ARBs							
Furosemide							
HCTZ							
CCBs							
BBs							
Aspirin							
SU							
Metformin							
Insulin							
Statins							
Fibrates							

1

2. ผลการตรวจทางห้องปฏิบัติการ (บันทึกเป็นระยะเวลา 1 ปี นับจากวันที่สัมภาษณ์ผู้ป่วย)

วันที่ / Lab tests									
Fasting plasma glusoce (mg/dl)									
HbA1C									
BUN (mg/dl)									
Scr (mg/dl)									
Clcr (24 hr. urine)									
Na (mEq/L)									
K (mEq/L)									
Cl (mEq/L)									
HCO_3 (mEq/L)									
Ca (mg/dl)									
Albumin (mg/dl)									
PO_4 (mg/dl)									
PTH (pg/ml)									
Hct (%)									
Hg (mg/dl)									
TC (mg/dl)									
TG (mg/dl)									
HDL (mg/dl)									
LDL (mg/dl)									
Uric acid (mg/dl)									
BP (mmHg)									
PR (beats/min)									
BW (kg)									
U/A: Protein Blood/RBC									
Urine protein (24 hr)									
PCR									
ACR									
Pitting edema									

PCR = A protein and creatinine ratio; ACR = An albumin and creatinine ratio

2

Appendix 8: Information sheet for research participant

Information Sheet for Research Participant

Title: The association between herbal and dietary supplement use and the progression of chronic kidney disease (CKD) and its complications among patients with chronic kidney disease in Thailand

Principal investigator: Mayuree Tangkiatkumjai

Division of Primary Care, School of Community Health Sciences

University of Nottingham, Nottingham, NG7 2RD

Phone: 074-0177-7803, Email: mcxmt3@nottingham.ac.uk

We would like to invite you to take part in a research study. Before you decide you need to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully. Talk to others about the study if you wish. This information sheet tells you the purpose of this study and what will happen to you if you take part. Please ask us if there is anything that is not clear or if you would like more information and take time to decide whether or not you wish to take part.

The aim of this study is to investigate any relationship between herbal and dietary supplements, and the progression of chronic kidney disease (CKD) and its complications in Thailand. We are interested in studying of the use of herbal and dietary supplements amongst patients with chronic kidney disease in order to provide safety evidence for the patients taking them. We will interview 690 patients. You are being invited to take part in this research because you have been diagnosed with CKD and are attending the kidney clinic. Your information helps us to provide information for health care providers who take care of the CKD patients taking herbal and dietary supplements.

You will be asked to be interviewed 2 times. Firstly, the investigator will interview you for 10-15 minutes taking note of your background data, medication information, dietary intake, such as types and amounts of food daily, alcohol consumption, education, personal income and the use of herbal and dietary supplements. Twelve months later, you will be interviewed on the telephone for 5 minutes about your use of herbal and dietary supplements over the past 12 months. Your medical information in outpatient medical records will be extracted up to be telephone interview.

All information which is collected about you during the course of the research will be kept strictly confidential and will be used for research purposes only. Your information regarding your use of herbal and dietary supplements will not be disclosed to their health care providers. Any information about you which is

published will have your name and telephone number removed so that you cannot be recognised from it.

We hope that you feel able to help us with this study. If at any time you decide that you do not want to continue to take part in the study, you are free to withdraw without your medical care or legal rights being affected.

If you would like to discuss anything further, please contact me at the above email address or telephone number.

If you would like to have a complaint, please contact research affairs at Chulalongkorn University on 0-2256-4455 ext. 14 or 15 or Srinakharinwirot university on 0-2664-1000 ext. 60428.

Thank you for reading this information sheet.
Please don't hesitate to ask me any questions if you need to.

Appendix 9: Consent form

The University of Nottingham

CONSENT FORM

Title of Study: The association between herbal and dietary supplement use and the progression of chronic kidney disease (CKD) and its complications among patients with chronic kidney disease in Thailand

Name of Researcher: Mayuree Tangkiatkumjai

Name of Participant: **Please initial box**

1. I confirm that I have read and understand the information sheet version number ……dated..... for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected. I understand that should I withdraw then the information collected so far cannot be erased and that this information may still be used in the project analysis. ☐

3. I understand that relevant sections of my medical notes and data collected in the study may be looked at by authorised individuals from the University of Nottingham, the research group and regulatory authorities where it is relevant to my taking part in this study. I give permission for these individuals to have access to these records and to collect, store, analyse and publish information obtained from my participation in this study. I understand that my personal details will be kept confidential. ☐

4. I agree to take part in the above study. ☐

Name of Participant	Date	Signature
Name of Principal Investigator	Date	Signature

2 copies: 1 for participant and 1 for the project notes

Appendix 10: Ethics approvals

COA No. 589/2011
IRB No. 297/54

INSTITUTIONAL REVIEW BOARD
Faculty of Medicine, Chulalongkorn University
1873 Rama 4 Road, Patumwan, Bangkok 10330, Thailand, Tel 662-256-4455 ext 14, 15

Certificate of Approval

The Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, has approved the following study which is to be carried out in compliance with the International guidelines for human research protection as Declaration of Helsinki, The Belmont Report, CIOMS Guideline and International Conference on Harmonization in Good Clinical Practice (ICH-GCP)

Study Title : The association between herbal and dietary supplement use and the progression of chronic kidney disease (CKD) and its complications among patients with chronic kidney disease in Thailand.

Study Code : -

Study Center : Faculty of Pharmacy, Srinakharinwirot University.

Principal Investigator : Miss Mayuree Tangkiatkumjai

Review Method : Full board

Document Reviewed :

1. Protocol Version 2.0/ 22 August 2011
2. Protocol Synopsis Version 1.0 / 23 May 2011
3. Information sheet for research participant Version 2.0/ 22 August 2011
4. Consent Form Version 2.0 / 22 August 2011
5. Interviews with trial participants Version 1.0 / 23 May 2011
6. The data from patient medical records Version 1.0 / 23 May 2011

Signature:..... Signature:.....

(Emeritus Professor Tada Sueblinvong MD)
Chairperson of
The Institutional Review Board

(Kanyalak Vithessonthi MD)
Committee and Assistant Secretary, Acting
Secretary of The Institutional Review Board

Date of Approval : September 15, 2011

Approval Expire Date : September 14, 2012

Approval granted is subject to the following conditions: (see back of this Certificate)

Protocol Number 297/54

INSTITUTIONAL REVIEW BOARD

Faculty of Medicine, Chulalongkorn University
1873 Rama 4 Road, Patumwan, Bangkok 10330, Thailand, Tel 662-256-4455 ext 14, 15

Approval of Documents related to Study Protocol

The Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, has approved the following study which is to be carried out in compliance with the International guidelines for human research protection as Declaration of Helsinki, The Belmont Report, CIOMS Guideline and International Conference on Harmonization in Good Clinical Practice (ICH-GCP)

Study Title : The association between herbal and dietary supplement use and the progression of chronic kidney disease (CKD) and its complications among patients with chronic kidney disease in Thailand

Study Code : -

Principal Investigator : Miss Mayuree Tangkiatkumjai

Study Center : Faculty of Pharmacy, Srinakharinwirot University

Document Approval :
1. Questionnaire Version 2.0 date 11/Jan/2012

Signature .....
(Associate Professor Unnop Jaisamrarn MD, MHS)
Vice-Chairman, Acting Chairman
The Institutional Review Board

Signature .....
(Kanyalak Vithessonthi MD)
Member and Assistant Secretary,Acting
Secretary The Institutional Review Board

Date of Approval : January 24, 2012

Approval granted is subject to the following conditions: (see back of this Certificate)

COA No. 416/2012
IRB No. 297/54

INSTITUTIONAL REVIEW BOARD
Faculty of Medicine, Chulalongkorn University

1873 Rama 4 Road, Patumwan, Bangkok 10330, Thailand, Tel 662-256-4455 ext 14, 15

Certificate of Approval

The Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, has approved the following study which is to be carried out in compliance with the International guidelines for human research protection as Declaration of Helsinki, The Belmont Report, CIOMS Guideline and International Conference on Harmonization in Good Clinical Practice (ICH-GCP)

Study Title : The association between herbal and dietary supplement use and the progression of chronic kidney disease (CKD) and its complications among patients with chronic kidney disease in Thailand.

Study Code : -

Principal Investigator : Assist.Prof.Mayuree Tangkiatkumjai

Study Center : Faculty of Pharmacy, Srinakharinwirot University.

Document Reviewed :

1. Continuing Review Report
2. Protocol Version 2.0/ 22 August 2011
3. Protocol Synopsis Version 1.0 / 23 May 2011
4. Information sheet for research participant Version 2.0/ 22 August 2011
5. Consent Form Version 2.0 / 22 August 2011
6. Interviews with trial participants Version 1.0 / 23 May 2011
7. The data from patient medical records Version 1.0 / 23 May 2011
8. Questionnaire Version 2.0 date 11/Jan/2012

Signature:..... **Signature:**.....

(Emeritus Professor Tada Sueblinvong MD)
Chairperson
The Institutional Review Board

(Assistant Professor Prapapan Rajatapiti MD, PhD)
Member and Assistant Secretary, Acting
Secretary The Institutional Review Board

Date of Approval : September 15, 2012 (First Extension)

Approval Expire Date : September 14, 2013

Approval granted is subject to the following conditions: (see back of this Certificate)

62 หมู่ 7 อำเภอองครักษ์
จังหวัดนครนายก 26120
โทร.0-3739-5085-6 ต่อ 60428

เอกสารรับรองโครงการวิจัย

โดย

คณะกรรมการจริยธรรมสำหรับการพิจารณาโครงการวิจัยที่ทำในมนุษย์แบบเร่งพิเศษ

(Expedited Review)

SWUEC/EX เลขที่หนังสือรับรอง 43/2554

ชื่อโครงการ	ความสัมพันธ์ระหว่างการใช้สมุนไพรและผลิตภัณฑ์เสริมอาหารกับการดำเนินไปและภาวะแทรกซ้อนของโรคไตเรื้อรังในผู้ป่วยโรคไตเรื้อรังในประเทศไทย
ชื่อหัวหน้าโครงการ / หน่วยงานที่สังกัด	อาจารย์มยุรี ตั้งเกียรติกำจาย / คณะเภสัชศาสตร์ มหาวิทยาลัยศรีนครินทรวิโรฒ
SWUEC รหัสโครงการ	SWUEC/Ex
เอกสารรับรอง	- ข้อเสนอโครงการวิจัยฉบับลงวันที่ 5 พฤษภาคม 2554 - เอกสารชี้แจง/ตอบคำถาม ลงวันที่ 8 สิงหาคม 2554 - หนังสือให้ความยินยอมเข้าร่วมโครงการวิจัย - แบบสัมภาษณ์ - แบบเก็บข้อมูลจากเวชระเบียนผู้ป่วยนอก
รับรองโดย	คณะกรรมการจริยธรรมสำหรับการพิจารณาโครงการวิจัยที่ทำในมนุษย์ (Ex)
วันที่รับรอง	9 สิงหาคม 2554
วันหมดอายุ	8 สิงหาคม 2555

หนังสือรับรองฉบับนี้ออกโดยความเห็นชอบในการพิจารณาจากคณะกรรมการจริยธรรมสำหรับพิจารณาโครงการวิจัยที่ทำในมนุษย์ คณะแพทยศาสตร์ มหาวิทยาลัยศรีนครินทรวิโรฒ ตามประกาศเฮลซิงกิ

(ศาสตราจารย์ นายแพทย์ชัยรัตน์ นิรันตรัตน์)
ประธานคณะกรรมการจริยธรรมฯ

ลงนาม.....
(ศาสตราจารย์ นายแพทย์วุฒิชัย ธนาพงศธร)
คณบดีคณะแพทยศาสตร์

Translation version

62 Mu 7 Ongkharak

Nakhon-Nayok 26120

Tel. 0-3739-5085-6 ext. 60428

Certificate of Approval by Institutional Review Board

(Expedited Review)

Faculty of Medicine, Srinakharinwirot University

SWUEC/EX IRB No. 43/2554

Study Title	The association between herbal and dietary supplement use and the progression of chronic kidney disease (CKD) and its complications among patients with chronic kidney disease in Thailand
Principal Investigator Institution	Miss Mayuree Tangkiatkumjai Faculty of Pharmacy, Srinakharinwirot University
SWUEC code	SWUEC/Ex
Document Reviewed	1. Protocol version 5 May 2011 2. The document of questions answering on 8 August 2011 3. Consent form 4. Structured questionnaire 5. The data from patient medical records
Approval by	Institutional Review Board (Ex)
Date of Approval	9 August 2011
Approval Expire Date	8 August 2012

The Institutional Review Board of the Faculty of Medicine, Srinakharinwirot University has approved this study which is to be carried out in compliance with the International guidelines for human research protection as Declaration of Helsinki.

62 หมู่ 7 อำเภอองครักษ์
จังหวัดนครนายก 26120
โทร.0-3739-5451-5 ต่อ 60428-9

เอกสารรับรองโครงการวิจัย
โดย
คณะกรรมการจริยธรรมสำหรับการพิจารณาโครงการวิจัยที่ทำในมนุษย์แบบเร่งพิเศษ
(Expedited Review)

SWUEC/EX **เลขที่หนังสือรับรอง** 43/2555(**ต่อใบอนุญาตครั้งที่** 1)

ชื่อโครงการ	ความสัมพันธ์ระหว่างการใช้สมุนไพรและผลิตภัณฑ์เสริมอาหารกับการดำเนินไปและภาวะแทรกซ้อนของโรคไตเรื้อรังในผู้ป่วยโรคไตเรื้อรังในประเทศไทย
ชื่อหัวหน้าโครงการ / หน่วยงานที่สังกัด	ผศ. มยุรี ตั้งเกียรติกำจาย / คณะเภสัชศาสตร์ มหาวิทยาลัยศรีนครินทรวิโรฒ
SWUEC **รหัสโครงการ**	SWUEC/Ex 43/2555
เอกสารรับรอง	- เอกสารโครงการวิทยานิพนธ์ ฉบับย่อ(ขอต่อใบอนุญาต) - แบบสำเนาหนังสือรับรอง เลขที่ SWUEC/EX 43/2554
รับรองโดย	คณะกรรมการจริยธรรมสำหรับการพิจารณาโครงการวิจัยที่ทำในมนุษย์ (Ex)
วันที่รับรอง	9 สิงหาคม 2555
วันหมดอายุ	8 สิงหาคม 2556

หนังสือรับรองฉบับนี้ออกโดยความเห็นชอบในการพิจารณาจากคณะกรรมการจริยธรรมสำหรับพิจารณาโครงการวิจัยที่ทำในมนุษย์ คณะแพทยศาสตร์ มหาวิทยาลัยศรีนครินทรวิโรฒ ตามประกาศเฮลซิงกิ

ลงนาม.....
(ศาสตราจารย์ นายแพทย์ชัยรัตน์ นิรันตรัตน์)
ประธานคณะกรรมการจริยธรรมฯ

ลงนาม.....
(ศาสตราจารย์ นายแพทย์วุฒิชัย ธนาพงศธร)
คณบดีคณะแพทยศาสตร์

Translation version

62 Mu 7 Ongkharak

Nakhon-Nayok 26120

Tel. 0-3739-5085-6 ext. 60428

Certificate of Approval by Institutional Review Board

(Expedited Review)

Faculty of Medicine, Srinakharinwirot University

SWUEC/EX IRB No. 43/2555 (First extension)

Study Title	The association between herbal and dietary supplement use and the progression of chronic kidney disease (CKD) and its complications among patients with chronic kidney disease in Thailand
Principal Investigator Institution	Assist. Prof. Mayuree Tangkiatkumjai Faculty of Pharmacy, Srinakharinwirot University
SWUEC code	SWUEC/Ex 43/2555
Document Reviewed	1. Protocol version 5 May 2011 2. Certificate of ethics approval SWUEC/EX 43/2554
Approval by	Institutional Review Board (Ex)
Date of Approval	9 August 2012
Approval Expire Date	8 August 2013

The Institutional Review Board of the Faculty of Medicine, Srinakharinwirot University has approved this study which is to be carried out in compliance with the International guidelines for human research protection as Declaration of Helsinki.

Direct line/e-mail
+44 (0) 115 8231063
Louise.Sabir@nottingham.ac.uk

The University of Nottingham
Faculty of Medicine and Health Sciences

Medical School Research Ethics Committee
Division of Therapeutics & Molecular Medicine
D Floor, South Block
Queen's Medical Centre
Nottingham
NG7 2UH

Tel: +44 (0) 115 8231063
Fax: +44 (0) 115 8231059

14th September 2011

Mayuree Tangkiatkumjai
PhD Student
Division of Primary Care
School of Community Health Sciences
D1421, D Floor
The Medical School
QMC Campus
Nottingham University Hospitals
NG7 2UH

Dear Mayuree

Ethics reference No: **CHS22082011 – please use this number on all correspondence**
Title of Project: The association between herbal and dietary supplement use and the progression of chronic kidney disease and its complications among patients with chronic kidney disease in Thailand.
Lead Investigator/Supervisors: Dr Dawn-Marie Walker, Principal Supervisor, Division of Primary Care, School of Community Health Sciences and Dr Helen Boardman, Lecturer, Division of Social Research in Medicines and Health, School of Pharmacy, University of Nottingham
PhD Student investigator: Mayuree Tangkiatkumjai, Division of Primary Care, School of Community Health Sciences.

Thank you for submitting the above application which was considered by the Medical School Research Ethics Committee and the following documents were reviewed:

- Application form of ethical committee_Mayuree V 3.0, 23/08/2011.doc
- Study Protocol_Mayuree v 7.0/28th March 2011 for in house approval 23/08/2011.doc
- Ethical approval in Thailand 23/08/2011.docx
- Consent form for SWU hospital 23/08/2011.docx
- consent form_CU hospital 23/08/2011.doc
- Information Sheet for Research Participant for SWU hospital 23/08/2011.docx
- information sheet_CU hospital Version 1.0/23 May 2011 23/08/2011.doc;
- Questionnaire for patients with chronic kidney disease v 4.0 23/08/2011.docx;
- Form of data collection from outpatient charts v 2.0 23/08/2011.docx

The Study was approved.

- Please can you submit copies of the Ethics approval letters from the King Chulalongkorn Memorial Hospital and HRH Princess Maha Chakri Sirindhorn Medical Center.

Approval is given on the understanding that the Conditions of Approval set out below are followed.

Conditions of Approval

You must follow the protocol agreed and any changes to the protocol will require prior Ethics Committee approval.

This study is approved for the period of active recruitment requested. The Committee also provides a further 5 year approval for any necessary work to be performed on the study which may arise in the process of publication and peer review.

You promptly inform the Chairman of the Ethics Committee of

(i) Deviations from or changes to the protocol which are made to eliminate immediate hazards to the research subjects.

(ii) Any changes that increase the risk to subjects and/or affect significantly the conduct of the research.

(iii) All adverse drug reactions that are both serious and unexpected.

(iv) New information that may affect adversely the safety of the subjects or the conduct of the study.

(v) The attached End of Project Progress Report is completed and returned when the study has finished.

Yours sincerely

Dr Clodagh Dugdale
Chair, Nottingham University Medical School Research Ethics Committee

Appendix 11: Kuo's questionnaire

Harris County Hospital District
Baylor College of Medicine
Kelsey-Seybold Clinics
Healthcare for the Homeless-Houston

Herbal Use Survey - 2

Thank you for agreeing to complete this Herbal Use Survey; it will help healthcare professionals know better how to provide herb-related information to you. Please provide any additional information at the end of the survey. Thanks for your participation!

1. **How old are you?**
   □ <20 □ 20-29 □ 30-39 □ 40-49 □ 50-59 □ ≥ 60
2. **Gender**
   □ Male □ Female
3. **Race**
   □ White (non-Hispanic) □ White (Hispanic) □ Black/African American
   □ Asian □ Native Hawaiian/Pacific Islander □ American Indian/Alaskan Native
   □ Arab/West Asian □ Indian/South Asian □ Other (specify) _____
4. **Are your family members immigrants to the United States?** □ Yes □ No
5. **Do you speak another language other than English?** □ Yes, specify_____ □ No
6. **Education**
   □ Less than high school □ High School □ College □ Grad School
7. **Do you agree/disagree with the following statements?**
   a. You think using both prescribed medications and herbs are better than using either alone. □ Agree □ Disagree □ Neither
   b. You think herbs are superior to prescribed medications. □ Agree □ Disagree □ Neither
8. **Do you use any of the following? Please check all that apply.**
   □ Herbs/herbal products or natural medicine (e.g., Echinacea, St. John's wort, ginseng, gingko, soy supplement) □ Vitamins □ Minerals □ Folk Medicine or Home Remedy □ None

   c. If you answer "None", what is/are your reason(s)?
      - o I'm not interested in herbal medicines.
      - o I'm interested; but I don't know enough about herbs.
      - o Herbal medicines are unscientific.
      - o I have not thought about using herbal medicines.
      - o I'm satisfied with my prescribed medication so I don't need herbal medicines.
      - o Herbal medicines are not covered by my insurance and I cannot afford it.
      - o Other _____

*** PLEASE GO TO QUESTION #20"

d. If you use herbs, vitamins, minerals, or folk medicine, what is/are your reason(s)?

- o They will work and achieve faster resolution of symptoms.
- o I want to be able to use my own methods to take care of my health.
- o I want to try all the alternatives.
- o I am not being helped by my physician's treatments.
- o My problem is not serious enough to involve my physician's care.
- o Western medicine cannot meet my needs because of the modalities it uses (e.g., pills or surgery).
- o Other _____

9. What specific health problems do you use herbal medicines for?

10. Do you take prescribed medications for the same health problems that you take herbs for? □ Yes □ No

11. Do you tell your physician or pharmacist about your use of herbs? □ Yes □ No

e. If not, please check all that apply:

- o It wasn't important for my physician or pharmacist to know.
- o My physician or pharmacist never asked.
- o My physician or pharmacist would not understand.
- o My physician or pharmacist would disapprove.
- o My physician or pharmacist would discourage me.
- o My physician or pharmacist might not continue to provide care for me.
- o Other_____

12. What specific herbs are you using?

13. How often do you use herbal products?

□ Daily □ Frequently (few times/month) □ Occasionally (few times/year)

14. How long have you been using herbal products for?

- o < 1 year
- o 1-2 year(s)
- o 3-5 years
- o > 5 years

15. How much do you usually spend on herbal products per month?

□ <$50 □ $50-99 □ $100-500 □ >$500

16. How do you pay for herbs?
- o Out-of-pocket
- o Insurance
- o Paid by someone else (free)
- o Manufacturer promotions/samples (free)
- o Other_____

17. Who first recommended /suggested herbs to you?
- o Self
- o Family
- o Friends
- o Family physician
- o Internist
- o Nurse/Nurse practitioner
- o Pharmacist
- o Other_____

18. Did you ever experience a bad reaction from herbs you took? □ Yes □ No

19. If you answered "Yes" to Question #18, did you tell your doctor about it? □ Yes □ No

20. From which of these sources do you get information about herbal use?
- o None
- o Family/relatives
- o Magazines
- o Newspapers
- o Television
- o Internet
- o Books
- o Physician
- o Nurse
- o Pharmacist
- o Store recommendations
- o Other_____

21. Do other members of your family use herbs? □ Yes □ No □ Don't know

22. What kind of herbal information would you like to get from your physician or pharmacist?
- o Effectiveness
- o Side-effects
- o Interactions with prescribed medications
- o Other_____

23. How would you like your doctor or pharmacist to get this information to you?
- o Handout / Brochure
- o Website
- o Consultation by appointment
- o Other_____

Additional Comments:

*****Thank you for your participation, you have completed this survey. *****

Appendix 12: Vlaminck's questionnaire

1.1. How many days during the past 14 days didn't you follow your diet guidelines? …….

1.2. To what degree did you deviate from your diet guidelines?

No deviation	Mild	Moderate	Severe	Very Severe
0	1	2	3	4

2.1. How many days during the past 14 days didn't you follow your fluid guidelines?
……

2.2. To what degree did you deviate from your fluid guidelines?

No deviation	Mild	Moderate	Severe	Very Severe
0	1	2	3	4

Appendix 13: First version of dietary questionnaire

Translation version

Restriction of protein, potassium, phosphate and salt diet (RPPPS) questionnaire for pre-dialysis patients

It can be difficult to stick to the dietary requirements for CKD and we want to know how you manage with your diet.

Individuals have identified several issues regarding their diet behaviour and we are interested in your experiences. There is no right or wrong answer. Please answer each question based on your own personal experience of your diet.

24. Do you receive dietary recommendations from doctors or dieticians?

☐ No (0) (go to question no. 26) ☐ Yes (1) (go to question no. 25)

25. The Modification of dialysis diet and fluid non-adherence questionnaire (DDFQ)

1. How many days during the past 14 days didn't you follow recommendation of your protein-rich food restriction?

.....

2. To what degree did you deviate from such recommendation?

No deviation	Mild	Moderate	Severe	Very Severe
0	1	2	3	4

3. How many days during the past 14 days didn't you follow recommendation of your potassium-rich food restriction?

.....

4. To what degree did you deviate from such recommendation?

No deviation	Mild	Moderate	Severe	Very Severe
0	1	2	3	4

1

5. How many days during the past 14 days didn't you follow recommendation of your phosphorus-rich food restriction?

   …….

6. To what degree did you deviate from such recommendation?

No deviation	Mild	Moderate	Severe	Very Severe
0	1	2	3	4

7. How many days during the past 14 days didn't you follow recommendation of your salt restriction?

   …….

8. To what degree did you deviate from such recommendation?

No deviation	Mild	Moderate	Severe	Very Severe
0	1	2	3	4

26. Has your diet changed since you were diagnosed with kidney problems?

☐ No (0) (go to question no.28 to 30) ☐ Yes (1) (go to question no. 27)

27. Please explain how your diet has changed within the previous 14 days.

……

……

……..……

……

……..……

28. What kinds of food do you eat in the past 14 days, i.e. fruits, vegetables, dairy products, meats and ready meals or preserved food? Please rank the most preference until the least.

Types of food	How much[a] (per meal)	How often (per day)
1.		
2.		
3.		
4.		
5.		

a = Patients will be asked to approximate percentage of amount of food for each type of food, compared with total amount of food.

29. Do you always add salt or fish sauces when you eat food in the past 14 days?

☐ No (0) ☐ Yes (1)

30. How often do you add them per day in the past 14 days? .....times/day

The original first version of dietary questionnaire

แบบสอบถามการควบคุมอาหารที่มีส่วนประกอบของโปรตีน โพแทสเซียม ฟอสเฟต และเกลือ สำหรับผู้ป่วยโรคไตเรื้อรังที่ยังไม่ได้ฟอกเลือด

เป็นการยากที่จะควบคุมการรับประทานอาหารสำหรับผู้ป่วยโรคไตเรื้อรัง และผู้วิจัยต้องการทราบว่าคุณมีการจัดการเกี่ยวกับการควบคุมอาหารของคุณอย่างไร

ผู้ป่วยแต่ละรายมีหลายปัญหาในการควบคุมอาหารขึ้นกับพฤติกรรมการบริโภคของแต่ละคน และผู้วิจัยสนใจที่จะเรียนรู้จากประสบการณ์ของคุณ การตอบคำถามต่อไปนี้ ไม่มีคำตอบที่ถูกหรือผิด กรุณาตอบคำถามแต่ละข้อตามประสบการณ์การรับประทานอาหารของคุณ

24. คุณได้รับคำแนะนำในการควบคุมอาหารสำหรับผู้ป่วยโรคไตเรื้อรังจากแพทย์/นักโภชนาการหรือไม่
    ☐ ไม่ (0) (ตอบคำถามข้อ 26) ☐ ใช่ (1) (ตอบคำถามข้อ 25)
25. แบบสอบถามดัดแปลงจาก dialysis diet and fluid non-adherence questionnaire (DDFQ)
    1) เมื่อ 14 วันที่แล้ว มีกี่วันที่คุณไม่ได้ปฏิบัติตามคำแนะนำการรับประทานอาหารที่มีโปรตีนสูง เช่น หมู ไก่ ปลา อาหารทะเล .....วัน
    2) คุณไม่ปฏิบัติตามคำแนะนำการรับประทานอาหารที่มีโปรตีนสูงมากหรือน้อย

ไม่มี	น้อย	ปานกลาง	มาก	มากที่สุด
0	1	2	3	4

    3) เมื่อ 14 วันที่แล้ว มีกี่วันที่คุณไม่ได้ปฏิบัติตามคำแนะนำการรับประทานอาหารที่มีโพแทสเซียมสูง เช่น ผลไม้ ผัก .....วัน
    4) คุณไม่ปฏิบัติตามคำแนะนำการรับประทานอาหารที่มีโพแทสเซียมสูงมากหรือน้อย

ไม่มี	น้อย	ปานกลาง	มาก	มากที่สุด
0	1	2	3	4

    5) เมื่อ 14 วันที่แล้ว มีกี่วันที่คุณไม่ได้ปฏิบัติตามคำแนะนำการรับประทานอาหารที่มีฟอสเฟตสูง เช่น ธัญญพืช ผลิตภัณฑ์จากนม .....วัน
    6) คุณไม่ปฏิบัติตามคำแนะนำการรับประทานอาหารที่มีฟอสเฟตสูงมากหรือน้อย

ไม่มี	น้อย	ปานกลาง	มาก	มากที่สุด
0	1	2	3	4

    7) เมื่อ 14 วันที่แล้ว มีกี่วันที่คุณไม่ได้ปฏิบัติตามคำแนะนำการควบคุมอาหารที่มีรสเค็ม .....วัน

1

8) คุณไม่ปฏิบัติตามคำแนะนำการควบคุมอาหารที่มีรสเค็มมากหรือน้อย

ไม่มี	น้อย	ปานกลาง	มาก	มากที่สุด
0	1	2	3	4

26. คุณเปลี่ยนแปลงชนิดอาหารและปริมาณอาหารที่คุณรับประทานหรือไม่ หลังจากคุณได้รับการวินิจฉัยว่าเป็นโรคไตเรื้อรัง

☐ ไม่ (0) (ตอบคำถามข้อ 28-30) ☐ ใช่ (1) (ตอบคำถามข้อ 27)

27. กรุณาอธิบายว่าคุณมีการเปลี่ยนแปลงชนิดอาหารและปริมาณอาหารที่คุณรับประทานอย่างไร เมื่อ 14 วันที่ผ่านมา

.....

.....

.....

28. ชนิดอาหารต่อไปนี้ ผลไม้ ผัก ผลิตภัณฑ์จากนม ธัญญพืช หมู ไก่ ปลา อาหารทะเล อาหารสำเร็จรูป หรือ อาหารหมักดอง ที่คุณรับประทานเมื่อ 14 วันที่ผ่านมา คุณรับประทานอาหารประเภทใดมากที่สุด ให้เรียงลำดับจากมากไปหาน้อย

ประเภทอาหาร	ปริมาณที่รับประทานต่อมื้อ[a] (%)	ความถี่ในการรับประทานต่อวัน
1.		
2.		
3.		
4.		
5.		

a = ประมาณการปริมาณอาหารแต่ละประเภทที่รับประทานเป็นเปอร์เซ็นต์ โดยเปรียบเทียบกับอาหารทั้งหมดที่รับประทานต่อมื้อ

29. เมื่อ 14 วันที่แล้ว คุณมักจะเติมเกลือหรือน้ำปลาเวลารับประทานอาหารเป็นประจำ

☐ ไม่ (0) ☐ ใช่ (1)

30. เมื่อ 14 วันที่แล้ว คุณเติมเกลือหรือน้ำปลาเวลารับประทานอาหารบ่อยแค่ไหนต่อวัน.....ครั้ง/วัน

Appendix 14: Different HDS used in the present survey reported by one respondent

Thirty-one different types of herbal medicines and seven different dietary supplements used were reported once, see table below.

Types of HDS used	
Black galingale (*Kaempferia parviflora*)	Roselle juice
Lemongrass	Lime
An herbal combination – Boesenbergia, sweet basil, honey and lime juice	Spring bitter cucumber (M*omordica cochinchinensis*)
An herbal combination – Boesenbergia, mint, ginger, galangal, lemongrass, kaffir lime leaves and shallots	Lotus (*Nelumbo nucifera*)
An herbal combination - Boesenbergia, sweet basil, honey, lime juice and Asiatic Pennywort (*Centella asiatica*)	Ivy gourd leaves (*Coccinia grandis*)
An herbal combination – Boesenbergia and Asiatic Pennywort	Bamboo grass leaves (*Tiliacora triandra*)
Sweet basil and pineapple	Alfafa
An herbal combination - Boesenbergia, onion, galangal, lemongrass, kaffir lime leaves, lime leaves and mint	An herbal combination – paragrass roots (*Brachiaria mutica*) and pomegranate leaves (*Punica granatum*)
A Chinese folk remedy – holy mushroom, Cordyceps (*Cordyceps sinessis*), ginseng and Chinese Wolfberry (*Lycium Chinese*)	A Chinese folk remedy - Cordyceps, Lovage (*Angelica sinensis*), deer antle velvet, cinnamon and Schisandra berry (*Schisandra chinensis.*)
Java tea (*Orthosiphon aristatus*)	*Mimosa pudica*
An herbal combination – garlic, leaves of Cassod tree (*Cassia siamea*), piper and aloe vera	An herbal combination - green tea, pepper and garcinia.
A stem from *Coscinium fenestratum*	*Echinochloa spp.*
Leaves of Palmae (*Corypha lecomtei*)	Algae

Types of HDS used	
Leaves of *Clerodendrum petasites*	*Gynura procumbens*
A Thai folk remedy called "Tri Pla" – Chebulic myrobalans (*Terminalia chebula*), Beleric myrobalan (*Terminalia bellirica*) and Emblic myrablan (*Phyllanthus emblica*)	A Chinese folk remedy - Cordyceps, *Angelica sinensis*, Chinese Wolfberry, Astragalus (*Astragali radix*), *Eucommia ulmoides*, *Codonopsis pilosula* and deer antler velvet
C*issus quadrangularis*	Sesame oil
Coconut oil	Collagen
Glucosamine	Chondroitin sulphate
Lecithin	A soy bean extract and beta-glucan

Appendix 15: Sensitivity analyses

Table 1: Univariate analyses of the progression of CKD at the cut-off point of a decline in eGFR over a year at least 5 ml/min/1.73m^2/year and variables (n=330)

Variables	Fast progression (n=104)	Slow progression (n=226)	X^2 value	*p*-value
HDS use			0.05	0.82
Exposure	30 (30.6%)	68 (69.4%)		
Non-exposure	74 (31.9%)	158 (68.1%)		
Age			8.31	< 0.01*
≤ 60	42 (40.4%)	56 (24.8%)		
> 60	62 (59.6%)	170 (75.2%)		
Sex			5.32	0.02*
Male	56 (53.8%)	91 (40.3%)		
Female	48 (46.2%)	135 (59.7%)		
Current smoking			< 0.01	0.98
Yes	5 (4.8%)	11 (4.9 %)		
No	99 (95.2%)	215 (95.1%)		
Obesity	(n=98)	(n=218)	0.69	0.40
Yes	44 (44.9%)	87 (39.9%)		
No	54 (55.1%)	131 (60.1%)		
Existing proteinuria	(n=98)	(n=193)	25.07	< 0.01*
Yes	68 (69.4%)	74 (38.3%)		
No	30 (30.6%)	119 (61.7%)		
Degree of protein intake			1.22	0.27
Moderate to high	50 (48.1%)	94 (41.6%)		
Low	54 (51.9%)	132 (58.4%)		
Hypertension			0.84	0.36
Yes	99 (95.2%)	209 (92.5%)		
No	5 (4.8%)	17 (7.5%)		
Diabetes			0.68	0.41
Yes	59 (56.7%)	139 (61.5%)		
No	45 (43.3%)	87 (38.5%)		
Dyslipidaemia			0.02	0.89
Yes	92 (88.5%)	201 (88.9%)		
No	12 (11.5%)	25 (11.1%)		
Controlled blood pressure	(n=102)	(n=225)	1.94	0.16
No	72 (70.6%)	141 (62.7%)		
Yes	30 (29.4%)	84 (37.3%)		
A1C (%)	(n=59)	(n=142)	0.28	0.59
> 7	29 (49.2%)	64 (45.1%)		
≤ 7	30 (50.8%)	78 (54.9%)		

Table 1: (continued)

Variables	Fast progression (n=104)	Slow progression (n=226)	X^2 value	*p*-value
LDL cholesterol (mg/dl)	(n=88)	(n=205)	6.05	0.01*
≥ 100	55 (62.5%)	96 (46.8%)		
< 100	33 (37.5%)	109 (53.2%)		
Current use of NSAIDs or COX-2 inhibitors			0.45	0.50
Yes	8 (7.7%)	13 (5.8%)		
No	96 (92.3%)	213 (94.2%)		
Current use of aspirin			2.79	0.09
Yes	35 (33.7%)	98 (43.4%)		
No	69 (66.3%)	128 (56.6%)		
Prescribed, conventional medication adherence**			5.44	0.02*
Low	34 (32.7%)	47 (20.8%)		
Medium to high	70 (67.3%)	179 (79.2%)		

* Statistical significance at *p*-value < 0.05

** Medication adherence was measured using the Thai version of 8-Item Morisky Medication Adherence Scale® [227,228]

Table 2: Univariate analyses of the progression of CKD at the cut-off point of a decline in eGFR over a year at least 4 ml/min/1.73m^2/year and variables (n=330)

Variables	Fast progression (n=121)	Slow progression (n=209)	X^2 value	*p*-value
HDS use			< 0.01	0.99
Exposure	36 (29.8%)	62 (29.7%)		
Non-exposure	85 (70.2%)	147 (70.3%)		
Age			7.65	< 0.01*
≤ 60	47 (38.8%)	51 (24.4%)		
> 60	74 (61.2%)	158 (75.6%)		
Sex			3.47	0.06
Male	62 (51.2%)	85 (40.7%)		
Female	59 (48.8%)	124 (59.3%)		
Current smoking			< 0.01	0.94
Yes	6 (5.0%)	10 (4.8%)		
No	115 (95.0%)	199 (95.2%)		
Obesity	(n=115)	(n=201)	0.62	0.43
Yes	51 (44.3%)	80 (39.8%)		
No	64 (55.7%)	121 (60.2%)		
Existing proteinuria	(n=113)	(n=178)	25.19	< 0.01*
Yes	76 (67.3%)	66 (37.1%)		
No	37 (32.7%)	112 (62.9%)		
Degree of protein intake			1.43	0.23
Moderate to high	58 (47.9%)	86 (41.1%)		
Low	63 (52.1%)	123 (58.9%)		
Hypertension			< 0.01	0.98
Yes	113 (93.4%)	195 (93.3%)		
No	8 (6.6%)	14 (6.7%)		
Diabetes			0.14	0.71
Yes	71 (58.7%)	127 (60.8%)		
No	50 (41.3%)	82 (39.2%)		
Dyslipidaemia			0.78	0.38
Yes	105 (86.8%)	188 (90.0%)		
No	16 (13.2%)	21 (10.0%)		
Controlled blood pressure	(n=119)	(n=208)	1.75	0.19
No	83 (69.7%)	130 (62.5%)		
Yes	36 (30.3%)	78 (37.5%)		
A1C (%)	(n=71)	(n=130)	0.40	0.52
> 7	35 (49.3%)	58 (44.6%)		
≤ 7	36 (50.7%)	72 (55.4%)		
LDL cholesterol (mg/dl)	(n=105)	(n=188)	5.81	0.02*
≥ 100	64 (61.0%)	87 (46.3%)		
< 100	41 (39.0%)	101 (53.7%)		

Table 2: (continued)

Variables	Fast progression (n=121)	Slow progression (n=209)	X^2 value	*p*-value
Current use of NSAIDs or COX-2 inhibitors			1.16	0.28
Yes	10 (8.3%)	11 (5.3%)		
No	111 (91.7%)	198 (94.7%)		
Current use of aspirin			1.23	0.27
Yes	44 (36.4%)	89 (42.6%)		
No	77 (63.6%)	120 (57.4%)		
Prescribed, conventional medication adherence**			6.09	0.01*
Low	39 (32.2%)	42 (20.1%)		
Medium to high	82 (67.8%)	167 (79.9%)		

* Statistical significance at *p*-value < 0.05

** Medication adherence was measured using the Thai version of 8-Item Morisky Medication Adherence Scale® [227,228]

Table 3: Univariate analyses of the progression of CKD at the cut-off point of a decline in eGFR over a year at least 6 ml/min/1.73m^2/year and variables (n=330)

Variables	Fast progression (n=90)	Slow progression (n=240)	X^2 value	*p*-value
HDS use			< 0.01	0.94
Exposure	27 (29.3%)	71 (29.6%)		
Non-exposure	63 (70.7%)	169 (70.4%)		
Age			7.72	< 0.01*
≤ 60	37 (41.1%)	61 (25.4%)		
> 60	53 (58.9%)	179 (74.6%)		
Sex			7.36	< 0.01*
Male	51 (56.7%)	96 (40.0%)		
Female	39 (43.3%)	144 (60.0%)		
Current smoking			0.13	0.71
Yes	5 (5.6%)	11 (4.6%)		
No	85 (94.4%)	229 (95.4%)		
Obesity	(n=85)	(n=231)	0.94	0.33
Yes	39 (45.9%)	92 (39.8%)		
No	46 (54.1%)	139 (60.2%)		
Existing proteinuria	(n=86)	(n=205)	23.93	< 0.01*
Yes	61 (70.9%)	81 (39.5%)		
No	25 (29.1%)	124 (60.5%)		
Degree of protein intake			0.03	0.86
Moderate to high	40 (44.4%)	104 (43.3%)		
Low	50 (55.6%)	136 (56.7%)		
Hypertension			0.98	0.32
Yes	86 (95.6%)	222 (92.5%)		
No	4 (4.4%)	18 (7.5%)		
Diabetes			1.02	0.31
Yes	50 (55.6%)	148 (61.7%)		
No	40 (44.4%)	92 (38.3%)		
Dyslipidaemia			0.13	0.72
Yes	79 (87.8%)	214 (89.2%)		
No	11 (12.2%)	26 (10.8%)		
Controlled blood pressure	(n=88)	(n=239)	0.93	0.34
No	61 (69.3%)	152 (63.6%)		
Yes	27 (30.7%)	87 (36.4%)		
A1C (%)	(n=51)	(n=150)	0.21	0.65
> 7	25 (49.0%)	68 (45.3%)		
≤ 7	26 (51.0%)	82 (54.7%)		
LDL cholesterol (mg/dl)	(n=75)	(n=218)	10.94	< 0.01*
≥ 100	51 (68.0%)	100 (45.9%)		
< 100	24 (32.0%)	118 (54.1%)		

Table 3: (continued)

Variables	Fast progression (n=90)	Slow progression (n=240)	X^2 value	*p*-value
Current use of NSAIDs or COX-2 inhibitors			0.41	0.52
Yes	7 (7.8%)	14 (5.8%)		
No	83 (92.2%)	226 (94.2%)		
Current use of aspirin			2.49	0.11
Yes	30 (33.3%)	103 (42.9%)		
No	60 (66.7%)	137 (57.1%)		
Prescribed, conventional medication adherence**			9.82	< 0.01*
Low	33 (36.7%)	48 (20.0%)		
Medium to high	57 (63.3%)	192 (80.0%)		

* Statistical significance at *p*-value < 0.05

** Medication adherence was measured using the Thai version of 8-Item Morisky Medication Adherence Scale® [227,228]

Table 4: Univariate analyses of the progression of CKD at the cut-off point of a decline in eGFR over a year at least 10 ml/min/1.73m^2/year and variables (n=330)

Variables	Fast progression (n=40)	Slow progression (n=290)	X^2 value	*p*-value
HDS use			2.05	0.15
Exposure	8 (20.0%)	90 (31.0%)		
Non-exposure	32 (80.0%)	200 (69.0%)		
Age			8.99	< 0.01*
≤ 60	20 (50.0%)	78 (26.9%)		
> 60	20 (50.0%)	212 (73.1%)		
Sex			3.09	0.08
Male	23 (57.5%)	124 (42.8%)		
Female	17 (42.5%)	166 (57.2%)		
Current smoking			2.62	0.11
Yes	4 (10.0%)	12 (4.1%)		
No	36 (90.0%)	278 (95.9%)		
Obesity	(n=36)	(n=280)	0.11	0.74
Yes	14 (38.9%)	117 (41.8%)		
No	22 (61.1%)	163 (58.2%)		
Existing proteinuria	(n=40)	(n=251)	12.74	< 0.01*
Yes	30 (75.0%)	112 (44.6%)		
No	10 (25.0%)	139 (55.4%)		
Degree of protein intake			1.38	0.24
Moderate to high	14 (35.0%)	130 (44.8%)		
Low	26 (65.0%)	160 (55.2%)		
Hypertension			0.05	0.82
Yes	37 (92.5%)	271 (93.4%)		
No	3 (7.5%)	19 (6.6%)		
Diabetes			0.12	0.73
Yes	23 (57.5%)	175 (60.3%)		
No	17 (42.5%)	115 (39.7%)		
Dyslipidaemia			0.08	0.78
Yes	35 (87.5%)	258 (89.0%)		
No	5 (12.5%)	32 (11.0%)		
Controlled blood pressure	(n=38)	(n=289)	2.37	0.12
No	29 (76.3%)	184 (63.7%)		
Yes	9 (23.7%)	105 (36.3%)		
A1C (%)	(n=23)	(n=178)	1.09	0.29
> 7	13 (56.5%)	80 (44.9%)		
≤ 7	10 (43.5%)	98 (55.1%)		
LDL cholesterol (mg/dl)	(n=36)	(n=257)	9.05	< 0.01*
≥ 100	27 (75.0%)	124 (48.2%)		
< 100	9 (25.0%)	133 (51.8%)		

Table 4: (continued)

Variables	Fast progression (n=40)	Slow progression (n=290)	X^2 value	*p*-value
Current use of NSAIDs or COX-2 inhibitors			1.01	0.31
Yes	4 (10.0%)	17 (5.9%)		
No	36 (90.0%)	273 (94.1%)		
Current use of aspirin			2.01	0.16
Yes	12 (30.0%)	121 (41.7%)		
No	28 (70.0%)	169 (58.3%)		
Prescribed, conventional medication adherence**			7.92	< 0.01*
Low	17 (42.5%)	64 (22.1%)		
Medium to high	23 (57.5%)	226 (77.9%)		

* Statistical significance at *p*-value < 0.05

** Medication adherence was measured using the Thai version of 8-Item Morisky Medication Adherence Scale® [227,228]

Table 5: Univariate analyses of the fast progression of CKD and variables amongst respondents who did not have glomerular diseases, cancer, HIV, and cirrhosis (n=258)

Variables	Fast progression (n=84)	Slow progression (n=174)	X^2 value	*p*-value
HDS use			< 0.01	0.98
Exposure	24 (28.6%)	50 (28.7%)		
Non-exposure	60 (71.4%)	124 (71.3%)		
Age			6.07	0.01*
≤ 60	27 (32.1%)	32 (18.4%)		
> 60	57 (67.9%)	142 (81.6%)		
Sex			5.24	0.02*
Male	47 (56.0%)	71 (40.8%)		
Female	37 (44.0%)	103 (59.2%)		
Current smoking			2.05	0.15
Yes	7 (8.3%)	7 (4.0%)		
No	77 (91.7%)	167 (96.0%)		
Obesity	(n=78)	(n=166)	0.59	0.44
Yes	37 (47.4%)	70 (42.2%)		
No	41 (52.6%)	96 (57.8%)		
Existing proteinuria	(n=75)	(n=144)	22.94	< 0.01*
Yes	51 (68.0%)	49 (34.0%)		
No	24 (32.0%)	95 (66.0%)		
Degree of protein intake			0.88	0.35
Moderate to high	37 (44.0%)	66 (37.9%)		
Low	47 (56.0%)	108 (62.1%)		
Hypertension			0.45	0.50
Yes	82 (97.6%)	167 (96.0%)		
No	2 (2.4%)	7 (4.0%)		
Diabetes			0.14	0.70
Yes	54 (64.3%)	116 (66.7%)		
No	30 (35.7%)	58 (33.3%)		
Dyslipidaemia			< 0.01	0.94
Yes	77 (91.7%)	159 (91.4%)		
No	7 (8.3%)	15 (8.6%)		
Controlled blood pressure	(n=83)	(n=173)	0.01	0.91
No	56 (67.5%)	118 (68.2%)		
Yes	27 (32.5%)	55 (31.8%)		
A1C (%)	(n=57)	(n=118)	< 0.01	0.93
> 7	26 (45.6%)	53 (44.9%)		
≤ 7	31 (54.4%)	65 (55.1%)		
LDL cholesterol (mg/dl)	(n=75)	(n=164)	5.27	0.02*
≥ 100	44 (58.7%)	70 (42.7%)		
< 100	31 (41.3%)	94 (57.3%)		

Table 5: (continued)

Variables	Fast progression (n=84)	Slow progression (n=174)	X^2 value	*p*-value
Current use of NSAIDs or COX-2 inhibitors			0.35	0.55
Yes	7 (8.3%)	11 (6.3%)		
No	77 (91.7%)	163 (93.7%)		
Current use of aspirin			0.97	0.33
Yes	37 (44.0%)	88 (50.6%)		
No	47 (56.0%)	86 (49.4%)		
Prescribed, conventional medication adherence**			6.27	0.01*
Low	26 (31.0%)	30 (17.2%)		
Medium to high	58 (69.0%)	144 (82.8%)		

* Statistical significance at *p*-value < 0.05

** Medication adherence was measured using the Thai version of 8-Item Morisky Medication Adherence Scale® [227,228]

Use of the ©MMAS is protected by US copyright laws. Permission for use is required. A license agreement is available from: Donald E. Morisky, ScD, ScM, MSPH, Professor, Department of Community Health Sciences, UCLA School of Public Health, 650 Charles E. Young Drive South, Los Angeles, CA 90095-1772.

Table 6: Univariate analysis of the fast progression of CKD between the exposed group who currently and regularly used HDS at baseline and during the follow-up period (n=62) and the unexposed group who was non-users, former users or occasional users at baseline and during the follow-up period (n=177)

Variables	Fast progression (n=85)	Slow progression (n=154)	X^2 value	*p*-value
HDS use			2.42	0.12
Exposure	17 (20.0%)	45 (29.2%)		
Non-exposure	68 (80.0%)	109 (70.8%)		