Usage and Safety of Herbal Medicines in Patients Attending Primary and Secondary Care Clinics in Abu Dhabi, UAE.

By

Fatima Ali Al Braik

This thesis is submitted in partial fulfilment of the requirements for the award of the degree of Doctor of Philosophy of the University of Portsmouth

In collaboration with

- Ministry of Health, UAE
- Faculty of Medicine and Health Science (FMHS), UAE University

September 2009

Abstract

Introduction: herbal medicines (HMs) are popular and have become increasingly used in the prevention, diagnosis, and treatment of minor medical conditions and life-threatening illnesses. Patients are reluctant to link herbs with a risk of adverse effects. Adverse drug reactions (ADRs) are a common cause of hospital admission and make a significant contribution to healthcare costs. ADRs resulting from herb-drug interactions have been identified as significant factors responsible for patient morbidity and mortality.

Research aim: there was a limited pool of information on HM safety and no studies of the context of use, for example alone or in combination with other herbs or allopathic medicines, in the UAE. The present research sought to address this.

Methods: in order to quantify usage of HMs in a primary care setting in the UAE, the attitudes and beliefs of UAE Nationals visiting the Al Rowda Clinic, one of biggest Primary Healthcare settings in Abu Dhabi city were sought through a questionnaire. The research was then extended to a three-month, prospective study of secondary care patients attending the Nephrology Clinic in Sheikh Khalifa Medical City (SKMC), Abu Dhabi. Data was obtained from several sources besides the patient interview, including medical notes, drug charts and the patients' doctors. Potential links between HM use and ADRs were assessed by a consensus panel of investigators using the Naranjo algorithm.

Results: in primary care, the use of HMs was widespread; three quarters of the sample had experience of HM use; with a point-prevalence of current HM use of 38%. A wide range of herbs was used to treat a large number of disorders. Most herbal remedies were in the crude form, often used in mixtures and frequently obtained from unregulated sources. A large majority of users considered the HMs they were taking to be effective, natural and therefore safe; but an appreciable proportion (11%) cited adverse reactions which they thought were due to the HMs they were taking. Most of herb users were recommended by users' family or friends.

The use of herbs was again widespread among patients visiting the nephrology clinic in SKMC, with 468 of 688 patients (68%) reporting use at the time of interview. Over 100 different HMs, many of them mixtures, were being used. More patients in this setting were also taking prescription medicines (PMs) (70% vs 39%) and 323 (69.0%) were taking three or more herbal preparations. Approximately 70% of patients in both studies had not informed their doctors that they were using HMs.

Interestingly, 28 ADRs to HMs were identified in 26 patients (5.6%); 13 (46.4%) were judged to be probably related and 15 (53.6%) possibly related to the HM. Seven (25%) involved HMs alone and 21 involved a HM / PM interaction. Even though an association was judged to be present in 28 cases (in 26 patients) it was still often difficult to determine which, of the range of HMs taken by the patient, was the culprit. In three cases HMs contributed to existing renal disease.

Conclusions: HMs contain a myriad of pharmacologically active compounds that, when used by people with or without chronic concomitant disease, may be hazardous. Both the primary and secondary care studies contribute information on the widespread use and popularity of HMs in the UAE and show that use is not without risk. The reluctance of subjects to inform their healthcare professionals about current HM use lead the author to recommend that thorough drug histories should be taken on clinic visits or admission to ensure that the attending clinician is aware of all potentially harmful preparations being taken by the patient. Pharmacists may have an important role to play in this process

As the pharmacovigilance scheme to be adopted in UAE is developed, HM safety should be monitored alongside that of PMs.

CONTENTS

CONTENTS continued	Page

CONTENTS continued

DECLARATION

The research described in this thesis was undertaken by the author. The work was carried out between 2003 and 2009 in Abu Dhabi, United Arab Emirates, supervised by Professor David Brown (University of Portsmouth), Dr Paul Rutter (University of Wolverhampton) and Professor Mohamed Yousef Hasan (UAE University).

Whilst registered as a PhD candidate at the University of Portsmouth, I have not been registered for any other research award. The results and conclusions embodied in this thesis are the work of the named candidate (Fatima Ali Al Braik) and have not been submitted for any other academic award.

Signed, Fatima Ali Al Braik: Fatima Ali

LIST OF TABLES

LIST OF FIGURES

Page

Abbreviation List

ADR / ADRs	Adverse drug reaction(s)
AED /Dhs	UAE Currency (Dirham)
AIDS	Acquired immunodeficiency syndrome
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMI	Acute myocardial infarction
ASA	American Society of Anaesthesiologists
AST	Aspartate aminotransferase
CAM	Complementary and alternative medicines
CD	Controlled Drugs
CKD	Chronic kidney disease
CM	Conventional Medicine
CYP	Cytochrome P450
DCD	Drug control department
DHA	Dubai Health Authority
DHCC	Dubai Healthcare City
DM	Diabetes mellitus
DOHMS	Department of Health and Medical Services
DRCD	Drug Registration and Control Department
ED	Emergency Department
EMEA	European Medicines Agency
FDA	Food and Drug Administration
GAHS	General Abu Dhabi Health Service
GAPs	Good agricultural practices
GCC	Cooperation Council for the Arab States of the Gulf
GDP	Gross Domestic Product
GFR	Glomerular filtration rate
GMPs	Good manufacturing practices
GPs	General practitioners
GSLS	General Sale List for Supermarket
GSPs	General Sale Products

HAAD	Health Authority of Abu Dhabi
HCP	Healthcare Professional
HCT	Higher Colleges of Technology
HCTs	Hospital healthcare trusts
HM	Herbal Medicine
INCB	International Narcotic Control Bureau
INR	International normalised ratio
IRB	Institutional Review Board
MHRA	Medicines and Healthcare products Regulatory Agency
MoH	Ministry of Health
NHS	National Health Service
NMC	New Medicine Centre hospital
NSAID	Non-steroidal anti-inflammatory drug
OTC	Over the counter
P	Pharmacy Medicines
PCP	Primary care physician
PCT	Primary care trust
PHC	Primary healthcare centre
PM	Prescription medicine
POM	Prescription only medicine
PV	Pharmacovigilance
SEHA	Abu Dhabi Health Services Company
SJW	St John's wort
SKMC	Sheikh Khalifa Medical City
TAIM	Arabic traditional herbal medicine (TAIM)
TCAM	Traditional complementary and alternative medicines
TCC	Transitional cell carcimoma
TCM	Traditional Chinese medicine
TGA	Therapeutic Goods Administration
THM	Traditional herbal medicine
UAE	United Arab Emirates
UAEU	United Arab Emirates University
UK	United Kingdom

UMC	Uppsala Monitoring Centre
UN	United Nations
US / USA	United States of America
WHO	World Health Organisation
WM	Western medicine
ZU	Zayed University

Acknowledgements

First and foremost I would like to express my sincere gratitude to my supervisors, Prof. David Brown - my director of studies and Dr. Paul Rutter - my supervisor for their immense knowledge, patience, guidance, motivation, understanding and continuous support of my PhD research. I would also like to express my special thanks to Prof. Mohamed Hasan Bani Yas, Medicine & Health Sciences, UAE University - my local supervisor in UAE, for his patient, continuous support and advice on the planning and development of my PhD research.

I am very thankful to the following people, all of whom contributed valuable support:

- Prof. Nico Nagelkerke, Department of Community Medicine, Faculty of Medicines and Health Sciences, United Arab Emirates University.
- Prof. Abdu Adem, Department of Pharmacology and Therapeutics, Faculty of Medicines and Health Sciences, United Arab Emirates University.
- Dr. AbdelKarim Saleh , Head of Nephrology Division , physicians and nurses of Nephrology Division, as well as the patients who participated in the questionnaire study SKMC hospital.
- Administration and Management of SKMC hospital and staff of Medical Record Department of SKMC hospital, Abu Dhabi
- Physicians and nurses, as well as the patients who participated in the questionnaire study of Rowdha Clinic, Abu Dhabi
- My colleagues at Drug Registration and Control Department, Ministry of Health; Dr. Khalid Nashat, K.M AbdSamed and Tariq Rida.

Finally I would like to thank all of those close to me, for providing me with a friendly and supportive atmosphere, and who have been very loving and patient through all these years and I would particularly thank all my family members especially Mom, sisters and brother who have stood by my side always, as well as being my closest friends.

Dissemination

Phase 1 of the research was published as a full paper in the following:

Al-Braik, F.A., Rutter, P.M., Brown,D.

A cross-sectional survey of herbal remedy taking by United Arab Emirate (UAE) citizens in Abu Dhabi.

Pharmacoepidemiology and Drug Safety 2008; 17: 725-732.

A synopsis of the ADR section of Phase 2 of the research was presented as a poster at the 2009, International Society of Pharmacovigilance meeting in Reims, 7-9th September, and published in the proceedings:

Al-Braik,F.A., Rutter,P.M., Hasan,M.Y., Brown,D.

Potential adverse drug reactions from herbal products in UAE patients with kidney disease.

Drug Safety 2009; 32(10): 887.

Chapter One: Introduction

1.1 The UAE – A General Overview

The United Arab Emirates (UAE) is a young country, only established on 2nd December 1971. It is unique in terms of political structure and diversity of population. The country flourished for more than 30 years under its first president, Sheikh Zayed Bin Sultan Al Nahyan, who died in November 2004. The current president is his son, Sheikh Khalifa bin Zayed Al-Nahyan.[1] The constitution of the UAE is outlined in Section 1.3.

The UAE is part of the Arabian Peninsula and lies to the east of the Arabian Gulf. It is bordered by Saudi Arabia to the west and south, and by Oman to the east. In the north, the UAE has a short frontier with Qatar. Its climate is very dry, with little rain, vegetation and animal life, with average summer temperatures of 40°C, but reaching 48°C. In winter, average temperatures are approximately 18°C.

Most of the UAE is an arid desert land particularly in the inner western region. There are many famous oases in that desert region such as Al-Ain and Liwa oases. UAE territorial water is generally shallow, which is a feature of the Arabian Gulf coastline. The UAE territorial water is fringed with coral reefs and is rich in pearl oyster, which was traditionally a major source of revenue for the UAE. There are many islands and small sandy islets, including 200 islands for the emirate of Abu Dhabi, the most important of which is the island of Sir Bani Yass which was made into a natural refuge for rare animals.

UAE is not particularly hilly with mountains taking up only a few percent of the total territory, most of which is in the emirate of Fujairah. These mountains form part of World Wide Fund for Nature's Arabian Highland Woodlands and Shrublands Ecoregion and are an officially protected zone (as of June 2008).

1.1.1 UAE Population

In 2004, the total estimated population of the UAE was 4.25 million; however, the UAE population is predicted to hit 5 million by 2010.[2] The population has risen dramatically in recent years due to an influx of male foreign workers and their dependants; for example the total labour force rose from 1.2 million in 1995 to 2 million in 2002.[2] National UAE citizens account for approximately 25% of the population. The remaining 75% come primarily from

the Indian sub-continent (50%), the Arab nations, notably Egypt (10%), and Iran (15%). There are also small minorities from Europe and the Philippines.

The labour force has seen commensurate increases, mimicking the immigration of workers, but also the number of women in work has also increased, rising from 19% in 1995 to 28% in 2003.[3] The population of the UAE is concentrated primarily in the major cities along both coasts, although the interior oasis settlement of Al-'Ain has grown into a major population centre.

The official language of the UAE is Arabic, but English, Urdu, Hindi and Farsi are also spoken.

1.2 A Brief History of the UAE

The UAE and Oman share much of their ancient history and cannot be separated from the greater history of Oman and the Arabian Gulf, which stretches back for thousands of years. However, its more recent history is influenced by the British dating back to the mid-18th century, as British naval power began to dominate the Gulf. At this time, two important tribal confederations dominated the coast; the Qawasim and the Al-Busaids (who are now the ruling family of Oman). In 1798 the British signed a treaty with the Al-Busaids. This was seen by the Qawasim as the British allying themselves with their enemy and they began to attack the British. The British interpreted this as simple piracy and dubbed the west coast of the present day UAE as the 'pirate coast'. Attacks on the British continued until 1819 when the British decided to resolve the situation by destroying and capturing the Qawasim ships. This led to a maritime truce in 1835 that later became known as the 'Treaty of Peace in Perpetuity' thus giving the British responsibility for arbitrating disputes among the sheikhs. What is now the UAE became known as the Trucial coast. In 1968, Britain announced it would leave the Gulf by the end of 1971. The British began work on forming a single state consisting of Bahrain, Qatar and the Trucial coast. This proposal failed and Bahrain and Qatar formed independent states. Finally, in July 1971, six of the Trucial emirs (Abu Dhabi, Dubai, Sharjah, Umm al Qiween, Ajman and Fujairah) agreed on a federal Constitution for achieving independence as the UAE. The emirs agreed to a formula under which Abu Dhabi and Dubai would carry the most weight in the federation but each emir would remain largely autonomous.

The new country came into existence on 2nd December 1971. The remaining sheikhs of Ras Al Khaimah joined the UAE in February 1972. On achieving state-hood, Shiekh Zayed took

office as the first President of the UAE. On the 6th of December 1971 the UAE became the eighteenth member of the League of Arab States and on the 9th of December 1971 it became the 132nd member of United Nations. The UAE was an original member of the Cooperation Council for the Arab States of the Gulf (GCC) founded in May 1981. The GCC remit is to achieve greater political and economic integration between Gulf countries.

1.3 Current UAE Structure

The UAE is comprised of a federation of the seven states of Abu Dhabi, Dubai, Sharjah, Ajman, Umm Al Qiween, Ras Al Khaimah and Fujairah. Key statistics are shown in Table 1.1

Emirate	**Estimated population (2007)**	**Area (km^2)**	**% of UAE landmass *(Excluding the islands)***	**Ruler**
Abu Dhabi	1.85 million	67,340	86.7	Sheikh Khalifa bin Zayed Bin Sultan Al Nahyan
Dubai	1.4 million	3,885	5.0	Sheikh Mohammed bin Rashid Al Maktoum
Sharjah	750,000	2,590	3.3	Sheikh Sultan Bin Muhammad al-Qasimi
Ajman	275,000	259	0.3	Sheikh Humaid bin Rashid Al-Nuaimi.
Ras Al-Khaimah	230,000	1,680	2.2	Sheikh Saqr bin Muhammad Al-Qasimi
Fujairah	130,000	1,165	1.5	Sheikh Hamad bin Muhammad Al-Sharqi
Umm-Al-Qiween	75,000	777	1.0	Su'aod Bin Rashid Al Mu'alla

Table 1.1: Key statistics for the UAE. [4,5]

1.4 UAE Government Structure and Constitution

Over the course of 2007, major reform of the government structure occurred, at both federal and local level. These steps were designed to make it both more responsive to the needs of the country's population and to ensure that it was better equipped to cope with the challenges of development. The most important development during 2007 was the formal launching of a UAE government strategy for the years ahead in six areas: social development, economic, public sector, justice, safety, infrastructure and rural areas.

1.4.1 Federal and Local Government

In parallel with the federal institutions, each of the emirates has its own local government. All have expanded significantly as a result of the country's growth, though they differ in complexity from emirate to emirate, depending on factors such as population, geographical size and degree of development. The powers of the various federal institutions and their relationship with the separate local institutions have evolved since the establishment of the state. Under the terms of the constitution, rulers may relinquish certain areas of authority to the federal government.

The highest federal authority in the UAE is the Supreme Council of Rulers, which comprises the hereditary rulers of the seven emirates. It elects the President and Vice-President from among its members; both appointments are elected for five-year terms. The President appoints a Prime Minister and a Council of Ministers. Proposals submitted to the Council require the approval of at least five of the Rulers, which must include those of Abu Dhabi and Dubai. The Council is responsible for general policy matters involving communications, education, defence, foreign affairs and development, and for ratifying federal laws. Reporting directly to the supreme council is the Federal National Council. This council, formed under the Constitution, is composed of 40 members appointed by each emirate (eight each from Abu Dhabi and Dubai, six each from Sharjah and Ras al-Khaimah, and four each from Ajman, Fujairah and Umm al-Qiween) who each serve a two year term. The Council review laws proposed by the Council of Ministers and has authority to reject, amend and initiate those laws.

1.4.2 Justice and Security

The constitution calls for a legal code based on Shari'ah (Islamic) law. In practice, the judiciary blends Western and Islamic legal principles. At the federal level, the judicial branch consists of a supreme court and several lower courts: the former deals with emirate-federal or inter-emirate disputes and crimes against the state, and the latter cover administrative, commercial, and civil disputes between individuals and the federal government; other legal matters are left to local judicial bodies.

1.5 Religion

The cultural traditions of the UAE are rooted in Islam and identify with the wider Arab world. Islam is the official religion in the UAE; although other faiths are respected and practiced, including Christianity. The majority of nationals are Sunni Muslims with a minority of Shi'I Muslims. Strong cultural ties are maintained with the neighbouring Arabic Gulf states and tribal identities remain fairly strong, despite urbanisation; the family is still considered the strongest and most cohesive social unit.

1.6 Economy of the UAE

The official currency of the currency is the Dirham (AED) which is currently equal to $3.68 and £6.125 (day of exchange rate quoted is June 22nd 2009). The UAE nominal GDP (gross domestic product) in 2006 was 600 billion AED according to the UAE Central Bank.[2] Key factors are the continued oil market, establishment of a number of major developments and infrastructure projects and further expansion of free zones. Oil and gas, primarily from Abu Dhabi, contribute approximately 37% to GDP. The remainder of GDP is derived mainly from the manufacturing and construction industries, real estate and government services.

Trade has long been important to the UAE. Even before the discovery of oil, Dubai's prosperity was assured by its role as the Arabian Gulf's leading city due to its location and safe port facilities. For centuries Dubai was known as 'the city of the merchants'. Today the UAE has over 20 ports, although the three main ports are located in Dubai, Abu Dhabi, and Sharjah.

Oil was first discovered in Abu Dhabi in 1958 and commercial export started in 1962. Under the leadership of Sheikh Zayed, the emirate set up the Abu Dhabi National Oil Company through which it nationalised concession agreements in the 1970s. The Dubai emirate also struck oil in 1966 with production beginning in 1969. Although oil has been found in other emirates, (e.g. Al-Sharjah and Ras al-Khaimah) Abu Dhabi and Dubai account for the overwhelming majority of production. Indeed, Abu Dhabi is the third largest oil producer in the Gulf, after Saudi Arabia and Kuwait.

The UAE has attempted to diversify its economy to avoid complete dependence on oil. Significant natural gas reserves have been discovered and Abu Dhabi has begun to extract this for both local use and export. Additionally, tourism has been a major area of economic growth in the UAE, with Dubai becoming a holiday destination and major airline hub between Europe and South East Asia. This success is now being replicated in Abu Dhabi. As part of the UAEs diversification away from oil dependence the UAEs manufacturing base now includes cement, ceramics, textiles, pharmaceuticals, gold and jewellery. The UAEs strategic location and transportation infrastructure has also helped to attract foreign investors to set up headquarters. Important factors in attracting companies to invest in the UAE are the existence of numerous free zones where conditions for operating business enterprises are highly attractive.

Agriculture production is centered largely in the emirates of Ras Al-Khaimah and Al-Fujairah. The enclaves of Ajman and the oasis area of Al-Ain have expanded considerably through increasing use of wells and pumps to provide water for irrigation. Dates are a major crop, as are tomatoes, cucumbers, and aubergines. The country is reliant on imports for certain foodstuffs, most notably grains, but now produces enough eggs, poultry, fish, and dairy products to meet its own needs. Commercial fishing is concentrated in the emirate of Umm Al Qiween.

Exports are dominated by oil, shipped primarily to Japan, the United States, and Western Europe, who are also UAE's main trading partners, as well as Australia, Singapore and neighbouring Gulf countries. Main imports, apart from foodstuffs include machinery and transport equipment, chemicals, and crude minerals.

1.7 Education

The rapid rise in population has necessitated considerable investment in education. Today, the UAE offers comprehensive education to all; from kindergarten to university. Education for the country's citizens is free at all levels. Much has been achieved since the early 1970s but efforts are now being made to improve the educational environment for all pupils, in line with a re-evaluation of the role of government.

The educational system of the UAE is broadly similar to that of the UK. The existing structure is a four-tier system:

- 4 to 5 year-olds attend kindergarten;
- 6 to 11 year-olds attend primary schools;
- 12 to 14 year-olds attend preparatory schools; and,
- 15 to 17 year-olds attend secondary schools.[2]

Over 40% of pupils attend private schools. Some of these offer foreign language education geared towards expatriate communities, usually preserving the culture and following the curriculums of the students' countries of origin.

Ninety-five per cent of women and 80% of men who are enrolled in the final year of secondary school apply for admission to a higher education institution in the UAE or study abroad. The Al Ain-based United Arab Emirates University (UAEU) continues to be the country's flagship national institution of higher education, whilst newer institutions such as Zayed University, which has campuses in Abu Dhabi and Dubai, were established in 1998 by the Federal Government, to educate national women and prepare them to actively participate in society. In addition to university education there are 12 Higher Colleges of Technology (HCT) that offer a more technically oriented education. Besides UAE institutions, there are a number of private institutions, including the American Universities of Sharjah and Dubai, Sharjah University and the Ajman University of Science and Technology.

The country has also established schools for adult UAE citizens to overcome illiteracy. Students can enrol in public higher institutes and universities after they have attained their high school certificate. Consequently, four-fifths of the UAE population is now literate with the female literacy rate exceeding that of males.

1. 8 The UAE Healthcare System

At the time of the country's formation, the UAE health infrastructure was limited to seven hospitals and 12 primary healthcare centres (PHCs) throughout the country.[6] By 2000, The World Health Organisation (WHO) ranked the UAE healthcare system 27th best out of 191 countries,[7] and by 2006, government statistics showed that:

- in the northern regions there were 13 hospitals and 61 PHCs;[8]
- in Abu Dhabi, there were seven hospitals and 45 PHCs;[9] and,
- in Dubai, there were three hospitals and 18 PHCs.[10]

In addition, there are three government dental clinic centres in Abu Dhabi and six in the northern emirates. This increase in healthcare provision has seen increasingly complex and diverse management of the healthcare sector, currently managed by a mix of federal and local government.

1.8.1 Federal Healthcare System

The Federal Ministry of Health (MoH) manages government-run hospitals and PHCs, including their private counterparts, in all emirates except Abu Dhabi and Dubai, which have their own local healthcare arrangements.

1.8.2 Local Healthcare Systems

These arrangements apply to the emirates of Abu Dhabi and Dubai. Dubai established a Department of Health and Medical Services (DOHMS), now called the Dubai Health Authority (DHA). In Abu Dhabi the General Abu Dhabi Health Service (GAHS) was established in 2001;[11] this oversaw the running of all Abu Dhabi's hospitals and PHCs, and additionally regulated the private pharmacy sector, which includes community pharmacies and medical stores. GAHS was replaced in 2007 by two organisations, the Health Authority of Abu Dhabi (HAAD) and Abu Dhabi Health Services Company (SEHA).[9]

1.8.3 Private Healthcare System

1.8.3.1 Dubai Healthcare City

The Government of Dubai is developing Dubai Healthcare City (DHCC), with the goal of creating a regional centre of excellence for medical services, medical education, and life

science research and development in the Middle East. DHCC has links with internationally respected institutions in healthcare delivery, education, and research and development and is organised into four divisions: Dubai Healthcare City Free zone; Centre for Healthcare Planning and Quality; Harvard Medical School Dubai Centre and Dubai Harvard Foundation for Medical Research.[12]

DHCC has two complementary communities; the medical community and the wellness community. The medical community focuses on clinical services for disease treatment and prevention, whilst the wellness community encompasses hospitals, outpatient clinics and luxury spa resorts.

1.8.3.2 Health Insurance

Up until May 2003, all residents regardless of nationality were entitled to free treatment and healthcare services. However, a supreme cabinet resolution declared that free healthcare services would stop due to financial considerations. Since then non-GCC nationals have had to pay a pre-determined sum for each service used.

Currently, the MoH is studying the implementation of a health insurance system to cover healthcare costs for non-UAE and non-GCC nationals in both government and privately run healthcare sectors.

In September 2005, it became law for employers and business owners in Abu Dhabi to provide compulsory health insurance cover for their expatriate employees and their families. Daman was the first specialised national health insurance company to be formed in the UAE.[13] This venture represented a milestone in the history of healthcare for the Emirate of Abu Dhabi.

The new (mid 2008) health insurance programme "thiqa" (or "trust") entitles UAE nationals to a comprehensive range of healthcare services at all public and private sector healthcare facilities in the thiqa Network. Enrolment in thiqa is free of charge and is for UAE nationals of all ages. Thiqa is managed by a health insurance company, Daman, and supported by the Health Authorities HAAD and SEHA.[14] In 2008, HAAD and SEHA started to offer "Weqaya" (or "protection") health checks to protect UAE nationals who have risk factors for developing hypertension, diabetes and hypercholesterolaemia. UAE nationals over the age of 18 can complete their Weqaya health check at the same time as enrolment into thiqa. Free Weqaya health checks are offered every two years. The government of Abu Dhabi will pay the cost of

these health services if it is listed within the Daman scheme. Non-UAE nationals can approach public hospitals and clinics of SEHA in the Abu Dhabi Emirate through their Daman Health cards. Recently Daman and HAAD declared that they would pay half the cost of the dental healthcare services and medicines supplied by the private healthcare sector for UAE nationals.[15]

In 2008, the MoH established a new department for health insurance, responsible for regulating health insurance and implementing the health insurance systems throughout the country. Public healthcare providers such as SEHA and DHA have already implemented their own health insurance systems in their hospitals and PHCs.[16] A drafted federal law on health insurance has been submitted to the UAE Ministers' Cabinet for further discussion and approval. It is expected that the new health insurance law will be ratified by the end of 2009.

1.9 Comparison of the Healthcare Systems in the UAE and UK

1.9.1 Overview of the UK Healthcare System

The UK National Health Service (NHS) was established by the then Health Minister Aneurin Bevan in 1948 to provide comprehensive care for everyone, based on a person's clinical need, not their ability to pay. This central tenet still holds true today.[17] The NHS is split into various tiers of management responsibility known as Trusts, either in primary care, known as primary care trusts (PCTs) or in secondary care, known as hospital healthcare trusts (HCTs). These take responsibility for running the different NHS services in four local regions of the UK: Scotland, England, Wales and Northern Ireland.

1.9.1.1 Primary Care Trusts

Primary care is the care provided to patients when they first have a health problem. These health needs are met by PCTs (and now as PCTs merge, strategic health authorities) and are responsible for managing health services in a specified local area in the UK.[18] They work with local authorities and other agencies that provide health and social care to make sure the community's needs are being met. Healthcare may be delivered by a range of providers, including doctors, dentists, nurses, opticians and pharmacists. NHS Walk-in Centres, and the phone line service NHS Direct, are also part of primary care services. PCTs receive 75% of the total NHS budget and are responsible for all health services provided.

1.9.1.2 Hospital Healthcare Trusts

If a health problem cannot be managed by primary care, or if an emergency exists, patient care is managed by HCTs. Patients are usually referred to the hospital by a doctor based in primary care, except in emergencies.[19]

1.9.2 The UAE Healthcare System

The UAE healthcare system has many similarities to the UK system, in that there is a network of primary care outlets (e.g. doctors, dentists and pharmacists) managing the day-to-day welfare of patients, and secondary care services in hospitals that look after the more complex problems or acute medical emergencies. The range of staff and services offered is comparable to the UK; however the way in which a patient would access these services differs. In the UAE the patient is free to choose one of three treatment plans described below.

1.9.2.1 Treatment Plan A

This plan is most similar to UK practice. A patient would visit a PHC to seek help, advice and treatment on illness and disease ranging from acute self-limiting conditions to the management of long-term chronic conditions. The general practitioners (GPs) in the PHC would diagnose the disease and prescribe essential medicines for the patient. However, unlike the UK, if the patient is not satisfied with the GP's treatment plan, he or she may follow treatment plan B or C independently of the GP's knowledge or recommendation. If the patient were a new patient or not registered with a secondary care healthcare institution, then they would require a referral from the GP at the PHC or a doctor from an accident and emergency department.

1.9.2.2. Treatment Plan B

In Plan B, the patient would go directly to hospital without the doctor's knowledge whether for acute illness or serious/chronic disease. They will be seen by either doctors solely working at the hospital or by GPs who still spend time in secondary healthcare institutions. Here they would receive treatment regardless of the type of disease even though they may have a minor illness. If the patient feels that the prescribed treatment was ineffective, they may return to the same hospital or they could choose to go to another government hospital, see a GP in a PHC or follow treatment plan C.

1.9.2.3. Treatment Plan C

The patient would chose to see any doctor, either a GP or specialist, for minor illness or major disease in a private medical centre or hospital, without referral from any doctor from a government run primary or secondary healthcare institution. The patient would pay all costs for services provided to him or her in the private sector, unless it is covered by health insurance.

There are no links or co-ordination between doctors who work for government and private institutions, in primary or secondary care. Thus there is no sharing of patient notes or any other patient information between government and private healthcare providers.

1.9.3 The Lay Healthcare System in the UAE

A variety of non-prescription products are available to patients through a number of retail routes. Pharmacies, as in the UK, provide patients with access to medication and advice. Pharmacies are regulated by the MoH and therefore provide certain standards of quality. This is not the case if patients chose non-pharmacy outlets to get their remedies and treatment. These routes are uncontrolled and non-regulated by the MoH. Many of the practitioners and healers working from such outlets have inadequate education and experience to allow them to deal with healthcare problems, and their treatment. Traditional healers are found throughout the country; most of them are not licensed by MoH.

Access to non-Western medicines and practitioners is common in the UAE and people visit traditional healers either at their homes or at special centres. Traditional healers will prescribe treatment and prepare the remedy for them. Although still widely used, this traditional way of obtaining medicines is becoming less common in the UAE. Alternatively, the public may visit special shops known as condimental shops, health food shops, alternative medicine and herbal centres, supermarkets and even gym clubs. Pharmacy establishments are considered by the MoH to be the only conventional route to purchase medicines.

1.9.4 Regulation of Pharmacies in the UAE

Pharmacies are regulated and licensed according to the UAE Federal Law No. 4 (1983) for the pharmaceutical profession, which states that:

- no person is permitted to practice the pharmaceutical profession without obtaining a licence according to the provisions of UAE Pharmacy law. (Articles 1, 2); and,
- no person is permitted to open a pharmacy before obtaining a licence from the ministerial pharmaceutical licence committee according to the provisions of pharmacy law (Article 18).[20]

These laws do not stipulate that medicines can only be found, sold and supplied to the public through pharmacies.

1.9.4.1 Community Pharmacies in the UAE

There are approximately 1,300 community pharmacies in the UAE. (Drug Registration and Control Department - Ministry of Health statistics for October 2008). Their distribution is shown in Table 1.2.

UAE Region	No. of pharmacies	% of Pharmacies	No. of Pharmacists	% of Pharmacists	No. of Pharmacy Technicians	% of Pharmacy Technicians
Abu Dhabi	433	32.8	748	29.7	326	27.7
Dubai	421	31.9	931	36.9	473	40.2
Sharjah	274	20.8	489	19.4	240	20.4
Ajman	84	6.4	146	5.8	64	5.4
Um Al Qiween	14	1.1	26	1.0	10	0.9
Fujairah	29	2.2	45	1.8	24	2.0
Ras Al Khaimah	65	4.9	135	5.4	39	3.3
Total	**1320**	**100**	**2520**	**100**	**1176**	**100**

Table 1.2: Numbers and Distribution of Community Pharmacies in the UAE

1.9.4.2 Role of Community Pharmacies in UAE

The UAE Federal Law No. 4 (1983) for the pharmaceutical profession and institutions does not clearly specify the roles and responsibilities of the pharmacist; however it does state that the pharmacist should carry out his or her duties in conformity with regulations and guidelines of the pharmacy profession as per article 16:

- the pharmacist shall not conduct any practices against the honour of the profession;
- the pharmacist shall keep confidential the disease, which he may come to know through the medical prescription presented to him or through any means related to his or her practicing work; and,
- the pharmacist shall abide by the laws and regulations of the profession.

The Drug Registration and Control Department (DRCD) of the UAE MoH has issued minimum good pharmacy practice guidelines for the pharmacy profession in 2003, which highlighted the basic rules for dispensing prescriptions and controlled medicines.[21]

The minimum service standards of pharmacy in UAE are concerned mainly with dispensing medicines and selling pharmaceutical products to the public. Currently, there is a limited role for pharmacists in advising the public on medicines compared to pharmacists in the UK. This is primarily due to a lack in interest and knowledge among pharmacists practicing in the UAE.[22] In addition, commercial pressures on community pharmacists and a lack of enforcement of the regulations governing pharmacy practice contribute to the problem.

1.9.5 Non-Pharmacy Outlets

These shops sell pharmaceutical products or products which may have pharmacological actions similar to conventional pharmaceutical products. Some of these non-pharmacy outlets are regulated by local government departments (municipalities) of each emirate that are mainly responsible for regulating food and health products.[23]

1.9.5.1 Condimental Shops

These are shops licensed and regulated by the municipality of each emirate except Abu Dhabi where they are regulated by the Abu Dhabi Food Control Authority. Condimental shops are shops that sell foodstuffs, cereals and condiments, e.g. spices, flavours and edible herbs. These shops are very common in the UAE and represent the culture of the

traditional community. Sellers, with no formal training, will recommend and sell products to treat a wide range of medical conditions. According to UAE economic data there are approximately 2000 condimental shops in the UAE.

1.9.5.2 Herbal Centres

Herbal centres are licensed and regulated by the MoH as a medical clinic for traditional complementary and alternative medicines (CAM). Healers, working in such centres, should be licensed by the MoH for specific CAM therapy e.g. Ayurvedic, Unani, Sida or Chinese herbal medicines. All medicines used by those practitioners on their patients should be registered and licensed by the MoH. No medicines can be sold in these centres but healers or CAM practitioners can issue prescriptions for herbal medicines for patients, which must be supplied through pharmacies.

1.9.5.3 Alternative Therapy Centres

Similarly to herbal centres, these centres are regulated by the MoH and the healers and practitioners are licensed by the MoH. They mainly offer types of CAM therapy other than herbal medicines e.g. homoeopathy and reflexology. In this context, a healer is licensed by the MoH to practice traditional medicine, but practitioners are licensed to practice according to specific alternative/complementary systems of treatment.

1.9.5.4 Health Food Shops

Health food shops are licensed and regulated by the municipalities within each emirate. They are allowed to sell some products registered by the MoH, which are mainly dietary and herbal supplements e.g. vitamins, minerals, amino acids and herbal teas. Medicated cosmetics and herbal medicines that are registered by the MoH as over the counter products can be sold in such shops after obtaining the necessary approval. Sellers in these shops are not licensed in any way. The majority, are unqualified sellers or traders without any background in nutrition.

Many health food shops sell unlicensed herbal medicines. Herbal medicines are classified in UAE as medicinal products and treated as other conventional medicines, hence they are evaluated according to their risk level. High risk herbal products have the same status as prescription only medicines, moderate risk as pharmacy medicines and low risk as general sale products.

1.9.5.5 Supermarkets

These are licensed by municipalities and are allowed to sell food and home products to the public. No medicines should be offered for sale unless the MoH has given authorisation (Law No. (4) For 1983 of Pharmacy & Pharmaceutical Institutions). In practice, supermarkets openly ignore this requirement and sell a range of unlicensed herbal and general sale products which are imported via municipalities.

1.9.5.6 Gyms and Spa Clubs

These are regulated and licensed by the respective municipalities and no medicinal products are permitted to be sold; although anecdotally, this appears to be frequently ignored. Muscle pain balms for massage, and aromatherapy products can be used inside such clubs but cannot be sold. Practitioners, operating from these premises are not regulated by the MoH but this is currently under review.

1.10 Medicines Legislation in the UAE

The DRCD is the main government agency responsible for enforcing the regulations of medicines in UAE; it is supported by a number of committees that play an important role in the regulation of different classes of medicines. The main legislation governing medicines in the UAE is the Federal Pharmacy Law no 4 (1983), which established a national system of control for medicines.

In addition, a number of ministerial Decrees also regulate the registration and pricing of products,[24,25] the dispensing of controlled medicines and the licensing requirements for pharmaceutical establishments.[26,27]

1.10.1 Definition of Conventional Medicines

Within UAE law a conventional medicine is technically defined as a drug used in or in connection with:

1. preventing, diagnosing, curing or alleviating a disease, ailment, defect or injury; or
2. influencing, inhibiting or modifying a physiological process; or
3. testing the susceptibility of persons to a disease or ailment; or
4. influencing, controlling or preventing conception; or
5. testing for pregnancy; or
6. the replacement or modification of parts of the anatomy.

Medicinal products in the UAE generally belong to one of six dispensing categories:[26]

1. General Sale List for Supermarket (GSLS)
2. Pharmacy Medicines (P)
3. Prescription Only Medicines (POM)
4. Controlled Drugs – Control Drug Class B (CD- B)
5. Controlled Drugs – Control Drug Class A (CD- A)
6. Controlled Drugs – Narcotics

GSLS – these contain substances in pack sizes that do not require a prescription e.g. cold and mild fever medicines containing drugs such as paracetamol. This group also contains products such as toothpaste, shampoo and antiseptics. GSLS items are freely sold in pharmacies and some large supermarkets.[27]

Pharmacy Medicines (P) these are preparations sold or supplied by a pharmacist for therapeutic use, which are substantially safe in use but where advice or counselling is available if necessary. Products that can be prescribed by pharmacists include antacids, vitamins, mild analgesics, some cold preparations and eye wash lotions.

Prescription only medicines (POMs) - must only be sold/supplied with a medical prescription and include such products as injectable preparations, antibiotics, and anti-inflammatories. However, it is common practice within the UAE for pharmacists and their staff to breach this law and sell such products over-the-counter.

CD-B medicines - these include anti-depressants, anti-convulsants, some sleep inducers, anti-psychotics and other non-habit inducing medicines. They are sold only with a "Special Control" white medical prescription, which is valid for 30 days.

CD-A medicines - these medicines are sold only with a 'CD-A' medical prescription, which is valid for 30 days. Benzodiazepines, some appetite suppressants and other habit-inducing controlled medicines are examples of CD A medicines.

Narcotics Medicines - These are International Narcotic Control Bureau (INCB) controlled medicines and are most tightly controlled. Sale/supply is only through hospitals and prescriptions must be written on a Narcotic Medical Prescription Form. The prescription is valid for 28 days and must be issued by a consultant physician. Amphetamines and other

stimulants (such as methylphenidate), opioids (such as morphine and oxycodone) and other strong habit-forming controlled medicines are designated as narcotic medicines.

1.10.1.1 Licensing, Inspection and Enforcement of Medicine Supply

The DRCD regulates a wide range of materials from medicines and medical devices to blood and therapeutic products/services; one of the main activities of the DRCD is licensing and enforcement. The objectives being to ensure that the import, manufacture, sale, supply, management, and use of pharmaceuticals, cosmetics and healthcare products comply with UAE standards. The DRCD ensures this by:

- enforcing legislation through various UAE laws;
- following international convention, e.g. implementing INCB provisions on psychotropic substances;
- licensing regulations to ensure the import, storage, sale and supply are carried out by qualified or fit persons;
- controlling narcotics, pyschotropics and precursor chemicals for legitimate use;
- controlling medicine advertising;
- inspection at entry points to ensure drugs, cosmetics and chemicals are imported by legitimate importers; and,
- inspection of premises of license holders and professionals, including pharmacists to ensure compliance with the law and regulations.

The DRCD is also responsible for ensuring the quality of medicines and pharmaceutical products. Samples are sent for testing in quality control laboratories via registration, surveillance or enforcement activities.

1.10.2 Definition of General Sale Products (GSPs)

GSPs are pharmaceutical preparations containing non-prescription ingredients but which have health or medical claims. These are described below:

1. Dietary supplements and health foods

In the UAE a dietary supplement is defined as any product containing a dietary ingredient manufactured in a pharmaceutical dosage form, including natural ingredients, or composed from partially synthesised elements, or both, with exact doses of vitamins and/or mineral

salts, proteins, carbohydrates or fats intended for human use. Dietary supplements include the following:

- dietary ingredients allocated for some conditions connected with malnourishment, such as diets for diabetes patients; high or low calorie containing diets or diets containing low quantities of sodium, gluten, or lactose content diets;

- special dietary ingredients specifically used for certain disease states, such as: hypertension, hypercholesterolaemia and hyperallergic conditions due to certain foods; herbal teas and artificial sweeteners used as sucrose alternatives; and,

- dietary ingredients used at periods characterised by physiological changes, such as reinforced and special diets for suckling babies and weaning children; elderly and geriatric diets; royal jelly products; milk formulas having health or medical claims in certain diseases; and diets for athletes.

2. Medicated Cosmetics

Medicated cosmetics are defined as topical preparations intended to treat and/or prevent diseases, or otherwise affect the structure or functions of the human body.

3. Antiseptics

Antiseptic preparations are defined as preparations for external use intended for local application on the human body to eradicate microbial contamination.

4. Other pharmaceutical products

These include natural extracts, anti-lice products, herbal lozenges and volatile oils e.g. menthol, camphor, and eucalyptus oil preparations for topical use.

1.10.2.1 Registration Rules for GSPs

A number of rules control GSPs. For example, it is prohibited to sell products either manufactured locally or imported, before registration by the MoH. The registration of the product can be cancelled if:

- it is proved that the submitted registration documents are forged;
- the manufacturer is listed among boycotted companies;

- the manufacturer repeats violations or fails to adhere to good manufacturing practice;
- the product proves to be toxic or having serious side effects;
- the manufacturing, registration, or marketing of the product is terminated or suspended in the country of origin.

1.11 The Place of CAM in the UAE Healthcare System

Widespread systems of traditional medicine and CAM are practised within the UAE; these have been classified by the WHO as follows:[28]

1.11.1 Ayurveda

Ayurveda originated in the 10th century BC, but its current form took shape between the 5th century BC and the 5th century AD. In Sanskrit, ayurveda means "science of life". Ayurvedic philosophy is attached to sacred texts, the Vedas, and based on the theory of Panchmahabhutas "all objects and living bodies are composed of the five basic elements: earth, water, fire, air, and sky". Similarly, there is a fundamental harmony between the environment and individuals, which is perceived as a macrocosm and microcosm relationship. As such, acting on one influences the other. Ayurveda is not only a system of medicine, but also a way of living. It is used to both prevent and cure diseases. Ayurvedic medicine includes herbal medicines and medicinal baths. It is widely practised in South Asia, especially in Bangladesh, India, Nepal, Pakistan, and Sri Lanka.

1.11.2 Traditional Chinese Medicine (TCM)

The earliest records of traditional Chinese medicine date back to the 8th century BC. Diagnosis and treatment are based on a holistic view of the patient and the patient's symptoms, expressed in terms of the balance of yin and yang. Yin represents the earth, cold, and femininity. Yang represents the sky, heat, and masculinity. Traditional Chinese medicine encompasses a range of practices, including acupuncture, herbal medicines, manual therapies, exercises, breathing techniques and diets. Surgery is rarely used. Chinese medicine, particularly acupuncture, is the most widely used traditional medicine.

1.11.3 Chiropractic

Chiropractic was founded at the end of the 19th century in Iowa, USA. Chiropractic is based on an association between the spine and the nervous system and on the self-healing properties of the human body.

1.11.4 Homoeopathy

Homoeopathy was first mentioned by Hippocrates (462–377 BC), but it was a German physician, Hahnemann (1755–1843), who established its basic principles: law of similarity, direction of cure, principle of single remedy, the theory of minimum diluted dose, and the theory of chronic disease. In homoeopathy, diseases are treated with remedies that in a healthy person would produce symptoms similar to those of the disease. Rather than fighting the disease directly, medicines are intended to stimulate the body to fight the disease.

1.11.5 Unani

Unani is based on Hippocrates' (462–377 BC) theory of the four bodily humours: blood, phlegm, yellow bile, and black bile. Galen (131–210 AD), Rhazes (850–925 AD), and Avicenna (980–1037 AD) heavily influenced unani's foundation and formed its structure. Unani draws from the traditional systems of medicine of China, Egypt, India, Iraq, Persia, and the Syrian Arab Republic.

1.11.6 Herbal Medicine

Herbal medicine can be broadly classified into four basic systems: traditional Chinese herbalism, Ayurvedic herbalism, Western herbalism (which originally came from Greece and Rome to Europe and then spread to North and South America) and Arab traditional medicine, which forms the basis for alternative and herbal medicine in use today.[29]

Herbal medicines, according to the WHO, are preparations or finished herbal products that contain as active ingredients, parts of plants, or other plant materials, or combinations. Terminology associated with herbal medicines includes:

Herbs: crude plant material such as leaves, flowers, fruit, seed, stems, wood, bark, roots, rhizomes or other plant parts, which may be entire, fragmented or powdered.

Herbal materials: these are found in the following forms; fresh juices, gums, fixed oils, essential oils, resins and dry powders of herbs. In some countries, these materials may be processed by various local procedures, such as steaming, roasting, or stir-baking with honey, alcoholic beverages or other materials.

Herbal preparations: are the bases for finished herbal products and may include comminuted or powdered herbal materials, extracts, tinctures and fatty oils of herbal materials. They are produced by extraction, fractionation, purification, concentration, or other physical or biological processes. They also include preparations made by steeping or heating herbal materials in alcoholic beverages and/or honey, or in other materials.

Finished herbal products: are herbal preparations made from one or more herbs. If more than one herb is used, the term herbal product mixture can also be used. Finished herbal products and herbal product mixtures may contain excipients in addition to the active ingredients. However, finished products or mixed products to which chemically defined active substances have been added, including synthetic compounds and/or isolated constituents from herbal materials, are not considered to be herbal.

Traditional use of herbal medicines: refers to the long historical use of these medicines. Their use is well established and widely acknowledged to be safe and effective, and may be accepted by national authorities.

Active ingredients of herbal medicines: refer to ingredients of herbal medicines with therapeutic activity. In herbal medicines where the active ingredients have been identified, the preparation of these medicines should be standardised to contain a defined amount of the active ingredients, if adequate analytical methods are available. In cases where it is not possible to identify the active ingredients, the whole herbal medicine may be considered as one active ingredient.

1.12 The Uptake and Use of Herbal Medicines

The use of herbs for medical benefit has played an important role in nearly every culture on earth. Herbal medicine has been practiced by ancient cultures in Asia, Africa, Europe and the Americas.

Herbal medicines are widely used in the prevention, diagnosis, and treatment of diseases. According to a WHO report, one-third of the world's population and over half of the

populations of the poorest parts of Asia and Africa do not have regular access to essential (conventional) medicines,[30] and it is reported that more than 60% of the world's population use herbal medicines.[31] In rural areas, cultural beliefs and practices often lead to self-care, home remedies or consultation with traditional healers.

Herbal medicines constitute a major part of some cultures healthcare; for example China, where TCM still accounts for around 40% of all healthcare delivered. In India, 65% of the population in rural areas use Ayurveda and medicinal plants and in some African countries, e.g. Ghana, Mali, Nigeria and Zambia, herbal medicines have been shown to be first-line treatment for children with high fever.[32]

Herbal medicine has also been used in the treatment and care of such life-threatening illnesses as malaria and HIV/AIDS. Studies in Africa and North America have shown that up to 75% of people living with HIV/AIDS use traditional medicine alone or in combination with other medicines for various symptoms or conditions.[33] Over the last 20 years, herbal medicine has become increasingly used;[34] for example herbal usage in United States (US) has increased by 380% between 1990 and 1997,[35] and in 2002 roughly two-thirds of US adults were reported as using herbal medicines.[36]

Prevalence data according to the WHO also suggest widespread use in other Western countries. Studies have reported use on at least one occasion, prevalence rates of 48% in Australia, 31% in Belgium, 70% in Canada, and 49% in France.[33] Furthermore a US national health survey in 2002 involving 30,617 adults showed that 5,787 (19%) took herbal medicines in the previous 12 months, and of those, 3,315 (57%) used herbal medicines to treat a specific health condition.[36]

Other data from the US has shown that 46% of adolescents had used dietary supplements and herbal medicines in their lifetime, with almost 29% using such a therapy in the previous month and 9% reported concurrent use of supplements and conventional prescription medication.[37]

In Australia, Foster *et al* [38] found that the use of herbal supplements in pregnant women was relatively high; 36% (n=588) took at least one herbal supplement, the most common being raspberry leaf (14%), ginger (12%) and chamomile (11%).

The increased use by Western society of herbal medicine has made them an important economic commodity. Within the European Community, herbal medicines represent annual

sales of US$7 billion and in the US, the sale of herbal products has risen from $200 million in 1988 to $3.3 billion in 1997. Such widespread use throughout the world has raised serious questions concerning the quality, safety and efficacy of these products.[30]

The recent rise in popularity of herbal medicines in Western culture has been attributed to the belief that herbal medicine can provide some benefit over and above conventional Western medicine.[39] Consequently, there have been numerous studies looking at specific disease states and people's use of herbal medicines. As this thesis concerns mainly the safety of use of such products in a UAE context, this aspect is not considered further here.

1.12.1 Middle Eastern Perspective

The historical importance of Arab medicine has been well documented in the literature. Historical and current studies indicate that the Eastern region of the Mediterranean and the near east has been endowed throughout the generations with a rich inventory of medicinal herbs. Indigenous Arab medicine has contributed greatly to the development of modern medicine in Europe and remains one of the closest forms of original European medicine. Several surveys and studies reveal that 200-250 herbs are used in treating human disease.[40]

There are a number of papers from various countries showing the strong use of herbal medicines by people from this region. In Pakistan, substantial use of folk remedies for different medical conditions has been documented.[41] Herbs commonly used included cinnamon, ginger, cloves, cardamom, sesame oil, poppy seeds and honey and lemon that are used to treat minor medical conditions such as the common cold, cough and flu through to more serious conditions such as asthma, jaundice and heat stroke.

In Jordan, Afifi *et al* [42] interviewed over 100 inhabitants from seven villages in 2006. Results showed over 20 plant species were used to treat at least 18 different ailments. Five herbs were used by more than 50% of the interviewees; these were golden chamomile, wormwood, thyme, Syrian marjoram and sage. Interestingly, the results showed that over half the inhabitants practiced folk medicine without referring to anyone with relevant qualifications, and half (57%) grew or collected the medicinal plants themselves.

In Egypt, El Mahalli *et al* [43] conducted a 2004 survey with 337 households comprising of 1480 people. Twenty-five percent of people used complementary medicine, of which herbal medicine was the most popular. A further study in 2003 by Abdel Hady *et al* [44] looked at

patient knowledge, attitude and use of traditional remedies. This showed that 36% of respondents had used complementary medicine. Again, herbal remedies were used most frequently. It was also found that three-quarters of the respondents did not consult any conventional health care professionals before using these remedies.

In Iran, knowledge, attitudes, and practice of complementary medicine were investigated by Sadighi and Ziai amongst 4,123 people.[31] Results showed that 76% of respondents had some knowledge of herbal therapy and over half had used herbal medicine at least once. Commonly, herbal medicines were used to help relieve problems associated with gastro-intestinal, respiratory and nervous system diseases and most reported treatment to be very effective. Married women and the elderly were the most frequent users and the majority did not refer to physicians before using treatment.

A further Iranian study [45] was conducted to estimate the prevalence of herbal medicine use amongst 447 pregnant women. Overwhelmingly (92%), respondents had positive attitudes toward the use of herbal medicines during pregnancy and over half (52%) reported using them during pregnancy. The most commonly reported uses were for common cold (29%), abdominal pain (17%) and induction of labour (12%). Of those who had used herbal medicines 56% had not reported use to their doctor. Common reasons for non-disclosure were the belief that herbal medicines were natural and safe (39%) and that doctors never asked about them (35%). Family and relatives were the main source of information on the herbs they used.

A Turkish survey in 2004 [46] determined that 76% of 19,022 respondents had used herbal medication at least once. Herbal medicines were used to treat a wide range of problems including hair loss, haemorrhoids, skin problems, peptic ulcer, gastritis and infertility. Products most commonly used were nettle, St. John's wort, rosemary, sage and hawthorn. In addition, ginger was observed to be frequently used in Ayurvedic therapy in a Turkish population.[47]

Traditional and folk medicine continue to be used in many developing countries, including the Kingdom of Saudi Arabia.[48,49] Studies in the Arabian Gulf countries also show high use of herbal medicines. A 2003 survey (published in 2008)[50] conducted amongst 1,408 Saudi Arabian residents showed that 68% of the respondents had used alternative medicines; the Holy Quran as a therapy (e.g. prayer) was the most frequently used (50%), however herbal medicines were also commonly used, for example, black seed (39%) and myrrh (35%). A further study[51] that interviewed 300 diabetic patients in four hospitals in Riyadh in 1999

reported that 51 people (17%) used some form of herbal medicine. The commonest herbs used were myrrh, black seed, helteet, fenugreek and aloe. Almost three-quarters (73%) of herb users did not inform their doctor.

Al Saeedi *et al* [49] also interviewed 1,039 diabetic patients about their beliefs in traditional herbal remedies. Findings showed that one-third of patients were using traditional remedies, 16% believed they were safe and effective and 26% thought they were beneficial. Similarly, a 2004 Bahrain study by Nasser *et al* [52] was conducted on 300 people with diabetes. Data showed that 44% of patients had or were using herbal medicines over the previous year; more than 30% did not know the names of the herbs they were using and over 60% obtained their herbs from friends or relatives.

Studies from other Arab nations e.g. Tunisia and Morocco, have shown that herbal medicine use is popular.[53-55] For example, a study by Eddouks *et al* [55] for example, sought opinion from 700 people, including diabetic patients, patients with hypertension and cardiac disorders and traditional herbal healers from different areas of Eastern Morocco. The results indicated that 80% of people interviewed used medicinal plants to treat their conditions as they believed that herbal medicines were cheaper (58%), more efficient (40%) and better (65%) than modern medicine.

1.13 Herbal Medicine Safety

Herbal remedies often contain highly active pharmacological compounds and are therapeutic at one dose and toxic at another. With increasing use it is important for public safety that herbal medicines are scrutinised as carefully as conventional medicines. The perception that herbal remedies are natural and therefore safe is widespread among users.[56] However, toxicity related to herbal medicines is becoming more widely recognised as these remedies become more popular and examples of serious iatrogenic disease involving herbs have been reported.[57,58] Most reports of adverse effects are associated with hepatotoxicity although reports of toxic effects in other systems including kidney, nervous system, blood, cardiovascular, skin, and mutagenicity and carcinogenicity have also been published.[59,60]

Recent concern over reports of serious hepatotoxicity attributed to the herb kava kava in several European countries is a case in point;[61] this led the German authorities to legislate for the move of products containing the herb from general sale to prescription only status. Further examples include recurrent health warnings on the use of St John's wort with certain allopathic medicines due to serious drug interactions [62,63] and the withdrawal of aristolochia

preparations due to serious renal effects, including cancer.[64] Serious psychiatric and neurological adverse effects with fatalities have also been recorded.[65]

Adverse reactions may be caused by improper use, toxicity of the herbal ingredients themselves, and herb/conventional drug interactions but also due to ingredients introduced as contaminants or deliberate adulteration. Such occurrences raise serious quality control as well as safety issues.[65]

1.13.1 Adulteration of Herbal Products

Heavy metal contamination, adulteration with Western pharmaceuticals and inclusion of prohibited animal and plant ingredients are regularly reported in herbal medicines.[65-67]

This can affect the efficacy and/or safety of the herbal products being used. Current product quality ranges from very high to very low due to intrinsic, extrinsic, and regulatory factors. Intrinsically, species differences, organ specificity and diurnal and seasonal variations can affect the qualitative and quantitative accumulation of active chemical constituents in the source medicinal plants. Extrinsically, environmental factors such as field collection methods; cultivation, harvest, post-harvest transport and storage; manufacturing practices; inadvertent contamination and substitution; and intentional adulteration are contributing factors to the quality of herbal medicinal products. Source plant materials that are contaminated with microbes, microbial toxins, environmental pollutants, heavy metals or finished products that are adulterated with foreign toxic plants or synthetic pharmaceutical agents can lead to adverse events. Substandard source materials or finished products will yield therapeutically less effective agents.

Herbal medicine quality can also be attributed to regulatory practices. In a number of countries, herbal medicines are unregulated, which has led to product quality differences. Product quality improvement may be achieved by implementing control measures from the point of medicinal plant procurement under good agricultural practices (GAPs) and the manufacture of the finished botanical products under good manufacturing practices (GMPs), plus post-marketing quality assurance surveillance.[68]

Adulterations with conventional or synthetic drugs are common problems with herbal medicine, and many serious adverse events reported relate to problems of contamination or adulteration.[69,70] For example, contamination or adulteration of Chinese star anise (Illicium verum Hook), with Japanese star anise (Illicium religiosum) resulted in the poisoning of one

child.[71] Japanese star anise is a neurotoxic plant as it contains sesquiterpenic lactones which led to the poisoning. It has also been reported that adulteration of Chinese herbal medicines with inferior species is on the increase.[72]

Ensuring the quality of expensive products such as ginseng is important as adulteration with cheaper substances is tempting and traditional means of authentication via smell, taste or physical appearance are unreliable.[73] It is therefore important to determine the presence of contamination in herbal medicines to ensure patient safety.[74]

Within the UAE, the MoH has a duty to ensure medicines are not adulterated and Table 1.3 highlights those herbal medicines that have been found to contain substances that should not be present. The data show a wide range of products, often unlabelled, from a wide variety of sources and containing a variety of potent prescription medicines (e.g. sildenafil and hypoglycaemic agents) or poisons (e.g. mercury).

Because of the widespread use of herbal medicines, the MoH has warned consumers about the potential health risks involved in using unregistered medicines. This came after the finding from one MoH study that 37 unregistered herbal medicines were being sold through pharmacies, where supply is supposed to be controlled.[75]

Also, the Health Authority of Abu Dhabi (HAAD) has cautioned the public not to use an unbranded natural product promoted for use in diabetes as it could pose health risks.[76] Further to this, medical officials in the emirate of Ras Al Khaimah issued a warning against the use of herbal medicines to treat diabetes in children. This follows instances of certain shops in the emirate claiming that these medications were the only effective remedy.[77]

Product Name	Origin if known	Adulterated substances	Product Name	Origin if known	Adulterated substances
Unknown samples A&B	-	glibenclamide	Furunbao	China	tadalafil
Sandhivat tablets	-	phenylbutazone, salicylamide	Titanic K-2	India	sildenafil
Satibo capsules	China	sildenafil in capsule-shell	Tongkat Ali Power Plus	Malaysia	sildenafil
Unknown capsules	-	sildenafil	Golden Bull capsules	Swiss	sildenafil
WellLong capsules	China	tadalafil, caffeine	Unknown powder	-	sildenafil
Unknown tablets	-	glibenclamide , iron	Unknown tablets	-	glibenclamide, metformin
YongGang tablets	China	tadalafil	Unknown capsules (2 cases)	-	caffeine
King's capsules	China	tadalafil	Unknown tablets (3 cases)	-	chromium picolinate
Unknown capsules	-	sildenafil	Unknown capsules and tablets + Reductil capsules	-	chromium picolinate, caffeine
Unknown tablets	-	glibenclamide	Royal Herbs capsules	China	tadalafil
An Fu tablets	China	tadalafil	Unknown tablets and capsules	-	Tablets : chromium & capsules: herbs
Titanic-K-2 capsules	India	sildenafil	Dragon 1 (unknown)	China	tadalafil
Satibo capsules	China	sildenafil	Dia tech 2000 capsules	Canada	metformin
Trex	China	sildenafil	Amira Magic cream	KSA	mercury (Hg) positive
Dongfang chaoneng tablets	China	tadalafil	Rose Cream For Spots & acne	Lebanon	Hg positive
Royal Honey	Malaysia	tadalafil	Unknown cream	-	Hg positive
Ginseng Kianpi pil	China	cyproheptadine, dexamethasone	Argussy Whitening Cream	Thailand	Hg positive
Phyto-Andro capsules	Canada	sildenafil	Diana cream	Lebanon	Hg positive

Table 1.3: Identification of adulterated herbal products and GSPs by Quality Control Laboratories in UAE Ministry of Health (2001-2008).

Product Name	Origin if known	Adulterated substances	Product Name	Origin if known	Adulterated substances
Stillmans cream	USA	Hg positive	Unknown tablets. (glibenclamide)	-	glibenclamide
YOKO Herbal cream	Thailand	Hg positive	Ideal cream-30ml Jar	Lebanon	Hg positive
YOKO Herbal Fruty cream	Thailand	Hg positive	Unknown Pills (black)	-	metformin, glibenclamide
YOKO Whitening cream	Thailand	Hg positive	Unknown pills	-	metformin, glibenclamide, iron
Zang bion bio capsules	-	sildenafil	Unknown black pills	-	metformin & iron,
Ginseng Kianpi Pil capsules	China	dexamethasone, cyproheptadine	Hair strengthener spray (2 cases)	Lebanon	minoxidil
Unknown (Herbal) powder	-	Counterfeit with anti rheumatic product	Tonic Liquid	Lebanon	minoxidil
Unknown (Herbal) powder	-	metformin, iron	Satibo capsule	-	sildenafil (Viagra) or sildenafil derivatives
Unknown (Nairuz) cream	-	mercury, hydroquinone	Yonggang capsule	-	tadalafil (Cialis)
Ideal cream	Lebanon	Hg positive	Ginseng Kianpi pill	-	Cyproheptadine, ,dexamethasone
Ideal FAIR cream	Lebanon	Hg positive	Phytoshape	-	sibutramine (Reductil)
Phytoshape capsules (2 cases)	Malaysia	sibutramine	Golden Bull	-	sildenafil (Viagra)
Abeer beauty salon Hanna cream	UAE	Hg positive	Tongkat Ali capsule	-	sildenafil (Viagra) or sildenafil derivatives
Unknown tablets. (glibenclamide)	-	glibenclamide	Power capsule	-	sildenafil (Viagra) or sildenafil derivatives
Phyto shape capsules (4 cases)	Malaysia	sibutramine	Herbal pills	-	Iron, metformin, glibenclamide
Abeer beauty salon Hanna cream	UAE	Hg positive	Zein Herbal Tonic liquid	Lebanon	minoxidil (Regain)

Table 1.3 continued: Identification of adulterated herbal products and GSPs by Quality Control Laboratories in UAE Ministry of Health (2001-2008).

1.14 Herbal Medicine Use in the UAE

Like other Arab countries, the UAE has a long history of using herbal medicine. The MoH has a duty to regulate and control their use and therefore has created its own set of definitions surrounding herbal medicines along WHO lines.[25]

A **herbal medicine** is defined as a finished, labelled medicinal product that contains as active ingredients, aerial or underground parts of plants, or other plant materials or combinations thereof, whether in the crude state or as plant preparations intended for prophylactic or therapeutic or other human health benefits.

A **traditional herbal medicine** (THM) is defined as a finished medicinal product intended for self-medication that contains, as the active principle(s), herbal ingredients that have received relatively little attention in the world scientific literature, but for which traditional or folkloric use is well-documented.

A **medicinal plant** is defined as a plant, either cultivated or growing wild, used for its medicinal value.

The term **plant origin** excludes all synthetic and semi-synthetic active ingredients. Such products should be evaluated and registered in accordance with the current legislation on pharmaceuticals.

Plant materials are either the whole plants or parts of medicinal plants in the crude state.

Plant preparations are defined as herbal ingredients present in a form other than the crude medicinal plant material, including powdered plant material, balsams, dried and fluid extracts, tinctures, essential, oils, fatty oils, gums and resins and expressed juices, prepared from plant material, and plant preparations obtained by fractionation, purification or concentration, without chemically defined isolated constituents and regardless of whether or not its therapeutically active constituents have been identified.

Medicinal (active) ingredients are those herbs or their constituents that are responsible for the therapeutic action of the product. All medicinal ingredients should contribute to the intended effect(s) indicated on the product label. The actions of similarly acting herbs (e.g. sedatives) are considered additive in nature, and some herbs, although present in small

amounts, will be considered medicinal ingredients if, according to the supporting references, they contribute to the overall effect of the THM product.

The MoH has advised that combinations of medicinal herbs should be rational such that different herbs do not exert different effects that form an illogical or contradictory combination.

1.14.1 Herbal Medicine Regulation in the UAE

Registration of herbal medicines is only granted to topical, oral or rectal formulations.[78] Three main principles guide herbal product regulation:

- single ingredient herbal products are preferable and more acceptable for registration in the UAE;
- labels for herbal medicines should enable the consumer to judge the purpose of a product and use it wisely; and,
- the presentation of the herbal medicines should not encourage false belief that they are foods or that, because of their herbal source, they are innocuous or in any way better than allopathic medicines.

For a company to gain registration of its herbal product, the applicant must submit two files. The first details the quality control laboratory features, such as the manufacturing method, composition and quality control of the finished product, stability studies and the quality of raw materials. The second file includes information about the mode of action of the product, indications, toxicity and expected side-effects and interactions.

1.14.2 Sources of Herbal Medicines

Herbal medicines are generally sold from pharmacies as prescription and over-the-counter medicines and in special outlets (e.g. condimental shops). However, many herbal products and food supplements are also imported under special permits from the municipalities and sold in health food outlets. A new national committee, chaired by the MoH, was formed in late 2008 to regulate herbal medicines and General Sale Products through the municipalities and local health authorities.

1.14.3 Main Uses of Herbal Medicines in the UAE

The number of herbal medicines and their uses within the UAE are not constrained by modern day land boundaries. Medicinal herbal plants span the Arabic gulf countries.[56] Table 1.4 and Appendix 1 highlight the main (known) herbal medicines used.

Disease	Number of plants used	Examples
Skin diseases	40	*Alchemilla vulgaris, Anchusa strigosa, Calotropis procera*
Kidney and urinary system	27	*Ammi visnaga, Brassica napus, Glycyrrhiza glabra*
Diabetes	26	*Achillea millefolium, Allium cepa*
Digestive system	23	*Ceratonia siliqua, Foeniculum vulgare, Micromeria myrtifolia*
Liver disease	22	*Allium cepa, Asparagus officinalis, Cynara scolymus*
Respiratory system	16	*Anchusa strigosa, Brassica oleracea*
Cancer	13	*Allium cepa, Arum palaestinum, Brassica oleracea*

Table 1.4: Medicinal herbs and their uses to treat various diseases according to Arab medicine.[56]

It is known that the number of crude herbs, herbal medicines and dietary supplements imported into the country far exceeds the number of conventional medicines. The MoH, has registered 2,000 dietary supplements and herbal products compared to 5,200 conventional products; but roughly 30,000 dietary supplements and general sale items are freely imported into the country which are unregistered. Those that are registered and therefore regulated (and therefore available on prescription or through a pharmacy) have set costs, with the exception of dietary supplements and medicated cosmetics; those which are not controlled have no fixed price.

1.14.4 Herbal Medicine Use by UAE Citizens

Herbal medicines are widely used by UAE citizens yet very little research has been conducted in this area. In 2000, Hassan *et al*,[79] investigated alternative medicine taking amongst students, doctors and their friends and relatives. They found that almost 73% of students indicated personal use of herbal medicine and 76% reported use by a friend or relative. Two further studies looked at particular groups. Al-Mazroui *et al*,[80] found 51% of the

221 mothers interviewed had fed their babies local herbal drinks. Another study by Al Attia and Bakir [81] found that 26% of educated diabetic patients believed in the superiority of herbal medicine over the conventional hypoglycemic agents as compared to the uneducated (10%). Although not a herb, it is interesting to note that nearly 30% of all patients believed in honey as a useful remedy for diabetes regardless of their level of education. There are no specific data on the use of herbal medicines, alone or in combination, with conventional medicines, by the UAE community. The first stage of this research sought to address this information gap.

1.15 Monitoring the Safety of Medicines

Drug safety is a major public health priority. During the last few decades, it has been demonstrated that medicine-related morbidity and mortality is one of the major health problems.[82]It has been estimated that adverse effects from medicines are one of the leading causes of mortality in some countries,[83] and the percentage of hospital admissions due to such reactions has been reported to be between 10 and 20%.[84] Consequently, there is a high economic impact on health care services, with some countries spending upward of 20% of their healthcare budget on drug-related problems.[85]

Many of these risks are identified in pre-market testing and can be managed as "expected" or "tolerable" side effects that are outweighed by the product's benefits. However, once a product is made available on the market, new unexpected or undesirable adverse drug reactions (ADRs), are sometimes discovered when the product is used in "real world" conditions. ADRs may occur even when a product is being used within its licensed indications. A reaction may occur within minutes after exposure or it can take years to develop. Reactions can range from minor irritations, like a skin rash, to serious and life threatening reactions, such as a heart attack or liver damage. Most often, the magnitude of an adverse reaction is unknown and is not necessarily mentioned in the product literature.

Many regulatory authorities have a legal duty to protect their populations from harm, and usually have statutory functions to ensure new products brought to the market have been assessed for quality, efficacy and safety. These data inform the authorities to issue licences for products and allows the licensing authority to amend, suspend or revoke a license if new information on the product comes to light after it has entered the market.

A well-organised drug safety management service is therefore a prerequisite for the early detection of the risks of drugs, prevention of ADRs and aiding health professionals and

patients to make the best benefit/risk assessment for safe and effective pharmacotherapy. Medicine induced morbidity and mortality can be substantially reduced through an integrated strategy for drug safety monitoring which includes:[84]

- education and training of health care professionals on benefit/risk assessment and rational use of drugs;
- behaviour change amongst patients and healthcare workers to decrease unnecessary and irrational use of drugs; and,
- establishing pharmacovigilance services.

Pharmacovigilance is the science of collecting, monitoring, researching, assessing and evaluating information from healthcare providers and patients on the adverse effects of medications, biological products and traditional medicines with a view to:

- identifying new information about hazards associated with medicines; and,
- preventing harm to patients.[86]

1.15.1 ADR Reporting

The greatest ADR disaster was the thalidomide tragedy of 1961-1962. Thalidomide had been introduced as a safe and effective hypnotic and anti-emetic drug; it rapidly became popular for the treatment of nausea and vomiting in early pregnancy. Tragically, the drug proved to be a potent human teratogen that caused major birth defects in children in the countries in which it was used in pregnant women.[87]

The thalidomide disaster led to the establishment of the drug regulatory-mechanisms of today. These programmes require that new drugs should be subject to a benefit versus risk assessment by the well-established regulatory authorities before being granted a marketing authorisation (licence) and introduced into clinical usage.[88,89] This, it might be thought, would have made medicines safe, or at least acceptably so. However, no drug which is pharmacologically effective is without hazard; furthermore, not all hazards can be known before a drug is marketed. All these factors led to the development of the concept of pharmacovigilance.[90]

The WHO set up a programme for international drug monitoring in 1968 after the thalidomide disaster. Since 1978, the Uppsala Monitoring Centre (UMC) – a WHO Collaborating Centre for International Drug Monitoring, has carried out this work. As of 2004, it had a membership

of 94 countries and 28 associate members.[91,92] To participate in this programme, each member country must have its own national pharmacovigilance centre. The UMC receives records from these countries and centrally processes them via a WHO database. This subsequently informs all member countries on drug safety issues.

International regulatory authorities e.g. the Food and Drug Administration (FDA) in the US, Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK, European Medicines Agency (EMEA) for countries in the European Union and Therapeutic Goods Administration (TGA) in Australia, continue to monitor the safety, effectiveness and quality of health products after they reach the marketplace. These organisations routinely evaluate adverse reaction reports and selected foreign reports, from manufacturers, health professionals and consumers.

Pharmacovigilance is needed in every country because there are differences between countries (and even regions within countries) in the occurrence of ADRs and other drug-related problems. This may be due to differences in drug production, distribution, use (indications, dose), genetics, diet and traditions of the people.[93]

These evaluations may include a comprehensive reassessment of the benefit-risk profile of a product. If a safety issue is identified, perhaps by noting an unexpected/increased number of reports of a particular event (a signal) appropriate action is taken. Such actions range from distributing new product safety information to the public and/or the health care community, to recommending changes to the product's labelling or requesting the removal of the product from the market.

1.15.2 Current state of ADR Reporting

ADRs are a significant cause of morbidity and mortality and contribute to increased healthcare costs. Healthcare providers need to understand their role and responsibilities in the detection, management, documentation, and reporting of ADRs; all essential activities for optimising patient safety.[83]

Centres are more likely to receive reports from healthcare professionals on serious or rare ADRs and ADRs associated with newly marketed drugs yet under-reporting is a common phenomenon.[94-96] There is significant and widespread under-reporting of ADRs to spontaneous reporting systems including serious or severe ADRs.[97] Issues identified that affect the decision to report or not to report by healthcare professionals are whether the

reaction was considered well-known or not, the severity of the reaction, hesitance to report only on suspicion, lack of confidence in recognising ADRs, knowledge of existing rules, excessive workload and lack of time to report ADRs.[98]

Correcting for under-reporting is difficult as the extent is unknown and very variable. Several countries that have participated for many years in the WHO Drug Monitoring Programme receive 200 or more adverse reactions per million inhabitants annually, but even at established centres the reported proportion of serious reactions may not be more than 10%.[93] In many other countries the reporting rates are much lower.[99,100]

In the last ten years, pharmacovigilance of herbal products has become a priority with several organisations due to increasing concern over the quality and safety of herbal medicines.[92] This has led to a growing interest in developing spontaneous reporting systems for herbal medicines by organisations such as the WHO and individual countries, including the UK and Germany.[101,102]

1.15.3 Pharmacovigilance in the UAE

A national pharmacovigilance committee has only very recently (late 2008) been formed in the UAE. At present, ADR monitoring is in its infancy. An ADR form has been developed and distributed to hospitals, clinics and pharmacies in the private and public sectors. Reporting is voluntary and the MoH has received few reports from practitioners.

According to the DRCD, the current vision toward development of a medicines safety system in the UAE is to establish an independent federal medicines monitoring centre and to become a partner of the WHO-UMC. To realise this vision the DRCD has identified a number of objectives that need to be met for the UAE to have a national programme:

- to organise the monitoring for domestic ADRs, including collection, analysis, supervision and communication of suspicious case reports on ADRs;
- to liaise and coordinate with WHO regarding ADR case reports;
- to offer drug information services to healthcare providers and exchange of data and information of ADRs.

This latter service will be tasked with:

- distributing ADR forms;
- sending ADR reports to the reporting centre of ADRs at WHO;
- providing an effective way to collect and assess ADR information to share with regional and international centres;
- alerting health professionals, manufacturers and public in case of risk;
- advising healthcare providers on how to deal with cases of drug interactions with drug, herbs, food, additives and medical devices;
- integrating with regulatory affairs decisions on the marketing of suspicious products and interactions of drugs;
- promoting educational and training courses for coordinators and healthcare professionals;
- providing drug safety assessments

1.16 Conclusion and research plan

There is a growing global trend for greater use of herbal medicines to treat acute and chronic conditions, yet there is a limited pool of information on their safety. This has promoted some countries to put mechanisms in place to identify potential problems associated with herbal medicines. However, in the context of Middle Eastern countries (and in particular countries such as the UAE) where Western medicine is playing a growing part in healthcare provision alongside traditional use of herbal medicines, no data is known on uptake, usage and safety.

The use of herbs as medicines remains high in the UAE. They are available from a variety of outlets subject to varying degrees of control and there have been no systematic studies of the context of use, for example alone or in combination with other herbs or allopathic medicines or indeed the safety of such use. The aims of the present research were firstly to look at the extent and nature of herbal use within the Abu Dhabi population in general (Chapter 2) and then investigate a method of studying herbal ADRs in a more focussed, secondary care setting at a nephrology clinic (Chapter 3). An overall discussion of the findings and recommendations on herbal ADR monitoring in the UAE appears in Chapter 4.

Chapter Two:

Uptake and use of herbal medicines in a sample of primary care clinic patients in Abu Dhabi.

As indicated in Chapter 1, at the time of conducting this research, there were no data relating to the uptake, usage or safety of herbal medicines from within the UAE. In a country such as the UAE, where herbal usage appears to be common, the need for accurate, current information on uptake and safety is of national importance. The initial stage of this research explored herbal use by a cross-section of UAE citizens and their attitudes to this type of medicine.

2.1 Aim and objectives

The aim of this phase of this study was to gain baseline data on the incidence of herbal medicines (HMs) used by UAE nationals. The research had the following objectives.

- To determine UAE nationals' views and beliefs on safety, quality and efficacy of HMs.
- To determine where nationals purchase HMs.
- To identify their reasons and influencing factors over purchasing or obtaining HMs.
- To gain their views on the relative benefits of HMs compared to conventional medicines.

2.2 Methodology

2.2.1 Background

The plan of investigation for the first stage of the research was to conduct a cross sectional survey of nationals residing in Abu Dhabi. Abu Dhabi Emirate was chosen as population statistics for the Emirate were reflective of National figures.

The sampling frame was to be drawn from an electoral register and randomly selected with sample size determined by an appropriate power calculation.

A number of sampling options were investigated. Most of the available data sources lacked the basic requirement of people's names and addresses and were abandoned

as avenues from which to draw the sample. The following options were investigated and reasons for their de-selection are given.

1. *Using an electoral register*

An electoral register was considered the most obvious listing of people to initially pursue. Unfortunately, at the time of this research, the UAE government did not keep such a list for UAE nationals.

2. *Telephone listings*

Directories of telephone numbers were explored for lists of nationals. However, very few nationals had their numbers listed. This was probably due to UAE culture, where privacy is considered so important that most of the national families do not register their home phone numbers.

3. *Post offices lists*

The post offices in Abu Dhabi were approached to obtain postal addresses of UAE nationals. Unfortunately, the post office management refused to disclose this information for confidentiality and privacy reasons.

4. *Federal Ministry of Planning*

It was discovered that the Federal Ministry of Planning had a database of the UAE citizens, generated for a UN report in 1999. However, the sample contained no private postal addresses and telephone numbers were obsolete due to a change in digit length.

5. *Local department of planning for Abu Dhabi*

In 2001 a census of 1000 households was undertaken. This collected limited information such as name and age but postal addresses were absent.

6. *Abu Dhabi Water and Electricity Distribution Company and Etisalat*

As with the post office, these companies refused to provide details of Abu Dhabi nationals for confidentiality reasons.

7. *Health Card Registration Centre for public hospitals and PHC clinics of Abu Dhabi*

This body is responsible for issuing health cards for Abu Dhabi residents and nationals but most available data derived from 1998 and up-to-date information on UAE citizen postal addresses was unreliable.

8. *Health Card Database in the IT Department of the Ministry of Health*

The department had very old data but was too incomplete to be considered reliable.

9. *Ministry of the Interior*

The Ministry of the Interior was approached for information; however access was refused for security and confidentiality reasons.

10. *Commercial mailing lists*

No mailing lists could be obtained from commercial firms that were reliable enough to be used in this study.

As a result of the above, an alternative sampling methodology was sought; primarily by opportunity sampling from a public space or by targeting a PHC. After consultation between the researcher, a Ministry of Planning statistician, the UAE MoH and the author's supervisors, it was decided that recruitment at one of the main PHCs in Abu Dhabi City, was the most pragmatic and reliable solution; it was felt that the demographic profile of attendees would be similar to that of the population as a whole. A structured interview was considered the most direct and useful method of data collection.

2.2.2 Survey development

From January to March 2004, themes were identified initially by the researcher and her supervisors. Themes were categorised in six broad areas:

- demographic information;
- details of herbal medicines taken by respondents;
- subjects' views on why they took herbal medicines;
- information on where subjects bought them from and what influenced their purchasing decisions;
- views on the relative benefits of herbal and conventional medicines; and,
- attitudes toward healthcare providers.

Following identification of the themes, survey items for each theme were developed by the researcher and reviewed by an advisory panel of three plus the author's local supervisor. The advisory panel members were employed at the Drug Regulatory Department in MoH. One member was in charge of regulating herbal products; the second was in charge of regulating dietary supplements and general sale products; and the third was a pharmacy advisor to the Department.

The final survey, which was produced in English, was agreed in May 2004 before being translated into Arabic. It was then reviewed again by two of the advisory panel members and the local supervisor (all native Arabic speakers) to ensure the survey questions had not lost their meaning.

An English version of the final survey and associated cover note are shown in Appendix 2.

2.2.3 Description of survey questions

The survey contained 45 questions; they were a mixture of open, closed, single and multiple items. The survey was accompanied with a covering letter. The letter explained the aim of the research, provided instructions on completion, contact details of the researcher and defined some terms used in the survey in lay language. The questions within the six themes on the survey were as follows.

1. *Demographic information (questions 1 to 12)*

These included questions on gender, age, living area, educational, marital and income status and occupation.

2. *Herbal Medicine Use (questions 13 to 22)*

Respondents were asked for details of herbal medicines they took. Questions included the number and types used; perceived effectiveness and incidence of side-effects experienced.

3. *Reasons for taking and frequency of use (questions 23-25)*

It was important to gain an insight into why respondents took herbal remedies and also the extent of their exposure.

4. *Purchasing patterns and disclosure (questions 26 to 36)*

This section of the survey explored respondent views on where they bought herbal medicines and what influenced their purchasing decisions from specific outlets, and if they discussed this with their doctor.

5. *Views on herbal medicines (questions 37 to 43)*

Respondents' views of herbal medicines were sought ranging from efficacy to safety, and a comparison with conventional medicines was explored.

6. *Attitudes toward different healthcare providers (questions 44-45)*

These questions were asked to evaluate respondents' views on the practitioners from which they received their medicines.

2.2.4 Research setting and sample size

The Al Rawdha Primary Healthcare Clinic, Abu Dhabi was eventually selected for the survey setting. This PHC was the largest in Abu Dhabi and only provided services to UAE nationals. The centre offered a wide range of services, including, general medicine, mother and child healthcare, emergency medicine, immunisation, diabetes care and dental services.

Taking advice from a statistician from the Ministry of Planning using the Abu Dhabi Statistics Data on nationals, it was determined that 300-400 subjects would constitute a sufficient sample size for the survey.

The exclusion criteria were as follows:

1. any non-UAE national;
2. patients unable to communicate in Arabic;
3. patients with severe communication problems such as deafness;
4. patients with obvious mental impairment or other diseases preventing clear communication; and,
5. patients less than 15 years old.

2.2.5 Ethics approval

University of Portsmouth Biosciences Research Ethics Committee approval was obtained for this study in March 2004. Approval was also obtained from the UAE MoH Health Ethics Review Committee (ref 200/2004) on 28th March 2004. To facilitate the researcher's work in a PHC in Abu Dhabi, a letter (ref 120/2004, dated 22/304) was issued by the Director of Primary Healthcare and Motherhood & Childhood Department from the MoH to the Directors of PHCs in Abu Dhabi, advising them of the research work and requesting their co-operation.

2.2.6 Informed consent and data confidentiality

Patients had the choice not to participate in the survey, and were not coerced into agreeing to take part. Patient confidentiality was maintained by each person being assigned a unique number, only known to the researcher, which was used to identify individual data. Data were stored securely and patient identity was obscured in all reports and databases.

2.2.7 Pilot Work

Before commencing the survey, the author visited the clinic to talk with medical staff and determine the most acceptable way of conducting it with minimal disruption to day-to-day operations of the PHC.

The clinic building was divided in to two; one section for men and another for women. Patients were split by gender and treated separately because of UAE cultural customs. The clinic operated from 7.30 am till 11.30 pm in two shifts. It was closed at weekends, except for emergency cases. On average, the number of patients visiting the clinic daily included 150 females, 70 males and 60 children.

In May and June 2004 pilot work was conducted. Patients were recruited by opportunity sampling and most were interviewed by the researcher in a dedicated room. The clinic nurses called each patient to the room in turn as they arose. The questionnaire was piloted in 35 patients. Fifty-one patients were approached; 40 female patients were asked to be interviewed, of which 23 agreed, seven self-completed and 10 refused because they were either in a hurry, waiting to see a GP or were in pain. Eleven male patients were asked to be interviewed; only two agreed,

three insisted on filling in the survey by themselves and 6 refused because they were in hurry or waiting to see a GP.

A number of barriers were identified which hindered the recruitment of people to participate in the survey.

1. Patients were reluctant to be seen in a separate room as they liked to wait at the doctor's door; some people refused to come for interview as they were afraid they would miss their turn to see the doctor.

2. Male subject participation was very low. It was apparent that men did not want to be interviewed by the female lead researcher for cultural reasons.

3. Some people did not want to complete the survey face-to-face with the researcher. Time was quoted as a factor in non-participation.

As a result of the above, a number of changes were proposed to the logistics of recruiting people to the study, these are described below.

1. The possibility of using a trained male investigator to help the lead researcher recruit male patients was considered; however, at the time this proved impossible. This problem was discussed with the director of the clinic and nurse in charge and it was agreed that approaches to men would also be made by nursing and medical staff. This necessitated people recruited in this way to self-complete the survey, either at the clinic or at home; in the latter case returning it by pre-paid mail. The approach of offering self-completion would hopefully also accommodate those people that had declined to be involved due to time commitments.

2. The lead investigator was advised to wear a white coat instead of casual dress to enhance patient perception of the researcher and hopefully increase participant recruitment.

3. Some subjects who were reluctant to be interviewed in a separate room were approached in the waiting areas.

4. A small number of survey items were reworded to simplify the Arabic phrases.

2.2.8 Main study conduct

Subjects were recruited over a 4 month period (August to December 2004). A sampling frame was constructed over this time to ensure that people were recruited on all working days (except the weekends – the clinic was closed) and opening hours of the medical practice to reduce sampling bias. Opportunity sampling was employed.

Two approaches to recruitment were conducted. Female patients were approached by the researcher or clinic nurse whilst they were sitting in the waiting area; for males the doctors and nurses requested patients to complete the survey whilst waiting for their appointment. For those subjects that were interviewed by the lead researcher the process took approximately 15 minutes. Interviews and written surveys were conducted in Arabic.

2.2.9 Data analysis

Each completed survey was given a unique identifying number and entered into an SPSS database (Version 11). Two research assistants, both pharmacists, helped the lead researcher in coding and data entry. Assistants were fully trained on how to use SPSS and enter the data. The author reviewed the whole database before analysis was performed. The majority of data was analysed using descriptive statistics. Where necessary, more sophisticated techniques used an acceptable level of statistical significance of $p<0.05$.

2.3 Results

2.3.1 Response rate

A total of 560 surveys were distributed to the target population; 374 surveys were completed or returned, yielding a response rate of 66.8% (n=374/560). However, 44 were unusable due to being incomplete, therefore 330 surveys were analysed (usable response rate of 330/560, 59%). A breakdown of how the 330 surveys were collected is as follows:

- 132 (40%) via doctor and nurse support;
- 90 (27%) by direct interview by the researcher;
- 54 (16%) self-completed at the PHC; and,
- 54 (16%) self-completed and returned via post.

2.3.2 Demographic characteristics of respondents

The demographic profile of participants is shown in Table 2.1. Subjects were predominantly female (70%) and came from a wide age range that was skewed towards a younger age profile; over half who gave their age were aged 25 years or younger. Approximately 75% of those who indicated their place of residence lived in urban surroundings. Of the 328 respondents who indicated their marital status, 150 (46%) were married, 172 (52%) single and 6 (2%) were divorced or widowed. Of the 100 married females, 36 were either pregnant or breastfeeding. The majority of participants (74%, n=237/322) belonged to family units of between 4 and 12 people and most were educated to at least high school level (84%, n=273/324).

Nearly half were employed in a full time job working in the government sector (44%, n=145/328), although the sample did contain a high proportion of students (39%, n=127/328). Income analysis revealed that 46% (n=136/296) of participants had an average monthly income of between 8,000 and 13,999 Dhs.

When compared to national statistics (Table 2.2) significant differences (at the $p<0.05$ level) were found in respect to all variables where comparable data were available, namely gender (increased proportion of females), age range (a skew to more younger subjects), residence (a greater proportion of urban dwellers), marital status (a greater proportion of single subjects), education (better educated) and occupation (more employed and more students).

From 329 respondents who identified their health status during the last month, 85%, (n=279/329) said that their health was either excellent or good; only 5% (n=14/329) declared that their health was weak or very weak.

Parameter	Basic Description (n and % values)
Gender (n= 330)	
Male	98 (29.7%)
Female	232 (70.3%)
Age Distribution (n=276)	
15 - 25 years	158 (57%)
26 - 35 years	79 (28.6%)
36 - 45 years	29 (10.5%)
46 - 55 years	6 (2.2%)
56 - 65 years	4 (1.5%)
Location Distribution (n=232)	
Urban	175 (75.4%)
Rural	57 (24.6%)
Marital Status of respondent (n=328)	
Single	172 (52.4%)
Married	150 (45.7%)
Divorced or widow	6 (1.8%)
Status of Married Female (n=100)	
Pregnant	14 (14%)
Lactating	22 (22%)
Neither	64 (64%)
Total number of family members (n=322)	
1-3	33 (10.3%)
4-6	79 (24.5%)
7-9	79 (24.5%)
10-12	79 (24.5%)
More than 12	52 (16.2%)
Education status (n=324)	
Cannot read nor write	3 (0.9%)
Can read and write only	9 (2.8%)
Less than high school	39 (12%)
High school	121(37.3%)
Undergraduate	146 (45.1%)
Graduate (high)	6 (1.9%)
Employment of respondent (n=328)	
Work in Government sector	145 (44.2%)
Private business	1 (0.3%)
Unemployed	6 (1.8%)
House wife	38 (11.6%)
Retired	8 (2.4%)
Student	127 (38.7%)
Work in government and private sector	2 (0.6%)
Other	1(0.3%)
Monthly income of family in UAE currency Dhs* (n=296)	
< 5000	20 (6.8%)
5000-7999	71 (24%)
8000-10999	89 (30.1%)
11000-13999	47 (15.9%)
14000-16999	21(7.1%)
17000-19000	16 (5.4%)
> 20000	32 (10.8%)

Table 2.1: Demographic characteristics of respondents

*1 Pound=7.3 Dhs; 1$=3.6 Dhs; 1 Euro=5.4 Dhs.

Data	Survey Findings		Abu Dhabi National Statistics	
Parameter	**Frequency**	**Valid Percent (%)**	**frequency**	**Valid Percent (%)**
Gender				
Male	98	29.7	175178	50.4
Female	232	70.3	172293	49.6
Total	330	100	347471	100
Age				
15 - 25 years	158	57.2	100174	49.1
26 - 35 years	79	28.6	52514	25.8
36 - 45 years	29	10.5	27135	13.3
46 - 55 years	6	2.2	15804	7.7
56 - 65 years	4	1.5	8307	4.1
Total of Age	276	100	203934	100
Location				
Urban	175	75.4	167939	51.7
Rural	57	24.6	157149	48.3
Total	232	100	325088	100
Marital status				
Single	172	52.4	89305	42.5
Married	150	45.7	110648	52.7
Divorced or widow	6	1.8	10169	4.8
Total of Marital Status	328	100	210122	100
Family Size				
No comparable data				
Education Level				
Cannot read nor write	3	0.9	20986	8.3
Can read and write only	9	2.8	23265	9.2
Less than High school	39	12	93058	36.8
Got high school	121	37.3	88651	35
Undergraduate	146	45.1	24131	9.5
Graduate (high)	6	1.9	3008	1.2
Total of Education	324	100	253099	100
Employment				
Work full time (government)	145	44.2	70902	34.5
Private business	1	0.3	5096	2.5
Unemployed	6	1.8	4309	2.1
house wife	38	11.6	49054	23.9
Retired	8	2.4	5871	2.9
Student	127	38.7	61925	30.2
Do not want to work	N/A	N/A	4509	2.2
Unable to work	N/A	N/A	3576	1.7
work Full time + Private full time	2	0.6	N/A	N/A
Total of employment	328	99.6	205242	100

Table 2.2: Comparison of demographic results to Demographic Data for UAE Nationals in Abu Dhabi Emirate*

2.3.3 Use of herbal medicines

Three quarters of respondents (76%, n=250/330; 95%CI: 70.8–80.2%) had previously used herbal remedies with 38% (n=94/248; CI: 31.8–44.3%) currently taking some form of herb. Those from rural areas were more likely to be or have been, taking HMs (Chi^2=5.455; p=0.02). Most herbal remedies were not Western 'off the shelf' or proprietary herbal products (18%, n=44/241; CI: 13.6–23.7%) but herbs in the crude form (63%, n=152/241; CI: 56.6–69.2%) or as compounded/mixed forms (36%, n=87/241; CI: 30.0–42.5%). Liquids (58%, n=138/240; CI: 51.0–63.8%) and herbal teas (55%, n=131/240; CI: 48.1–61.0%) were the most common ways of taking the herb. A wide range of herbs was used (Table 2.3) for a large number of complaints (Table 2.4); two hundred and three reported taking 65 different types of herbs to treat 48 different conditions.

Herb	**Frequency (n=463)*** **N (%; 95%CI)**
Thyme	73 (15.8%; 12.6–19.4%)
Senna	48 (10.4%; 7.7–13.5%)
Black seed (n=32) and black seed with honey (n=10)	42 (9.1%; 6.6–12.1%)
Ginger	31 (6.7%; 4.6–9.4%)
Chamomile	30 (6.5%; 4.4–9.1%)
Sage	22 (4.8%; 3.0–7.1%)
Anise	17 (3.7%; 2.2–5.8%)
Unnamed herbal products	16 (3.5%; 2.0–5.5%)
Aloe	16 (3.5%; 2.0–5.5%)
Fenugreek	15 (3.2%; 1.8–5.3%)
Myrrh	15 (3.2%; 1.8–5.3%)
Peppermint	11 (2.4%; 1.2–4.2%)
Green tea	10 (2.2%; 1.0–3.9%)
Other products (values less than 1.5%)	117 (25.2%; 21.4–29.5%)

Table 2.3. Herbs taken by respondents
* Some respondents mentioned more than one herb

Condition	Frequency (n=463)* N (%;95%CI)
Abdominal problems	72 (15.5%; 12.4–19.2%)
Cold/flu/throat infection	64 (13.7%; 10.8–17.3%)
Constipation	46 (9.9%; 7.4–13.0%)
Cough	39 (8.4%; 6.1–11.3%)
Dysmenorrhoea	31 (6.7%; 4.6–9.4%)
General health	26 (5.6%; 3.7–8.1%)
Slimming	24 (5.2%; 3.4–7.6%)
Anti-flatulent	22 (4.7%; 3.0–7.1%)
Asthma	12 (2.6%; 1.4–4.5%)
Dermatological problems	12 (2.6%; 1.4–4.5%)
Relaxation	11 (2.4%; 1.2–4.2%)
Dermatological cosmetics	9 (1.9%; 0.9–3.7%)
Hair tonic	9 (1.9%; 0.9–3.7%)
Acne	6 (1.3%; 0.4–2.8%)
Diarrhoea	6 (1.3%; 0.4–2.8%)
Headache	6 (1.3%; 0.4–2.8%)
Eye problems	5 (1.1%; 0.4–2.5%)
Hyperacidity/ulcer	5 (1.1%; 0.4–2.5%)
Other conditions (with values less than 1%)	61 (13.1%; 10.2–16.6%)

Table 2.4 Conditions which correspondents were treating with herbs
* Some respondents mentioned more than one condition

When asked about the effectiveness a large majority of respondents (88%, n=198/225; CI: 83.0–92.0%) thought that the last herbal remedy they had used was either effective or very effective. Respondents who were currently taking HMs (n=94) were asked how many types they were consuming. Most (n=38, 40%) were taking only one HM, but 35 (37%) were taking two or three, 9 (10%) between four and five different HMs and 12 (13%) were taking five or more.

Respondents tended to store their HMs in one place (n=217, 92%), with storage in cupboards (n=108, 42%) being the most common; although a fifth (n=55, 21%) kept them in a fridge.

Self-reported rates for adverse events associated with herbs was 11% (n=27/240). Twenty people went on to describe the nature of the adverse event. Ten people experienced gastrointestinal effects (e.g. nausea/vomiting, diarrhoea, abdominal pain and constipation). Other adverse events reported included allergic reactions (2), kidney pain (1), fever (1), spasm (2), anaemia (1), acne (1) and decreased breast milk production (2). Interestingly, this latter effect was observed in both cases with people taking thyme. Figure 2.1 details what action they took on experiencing an adverse event.

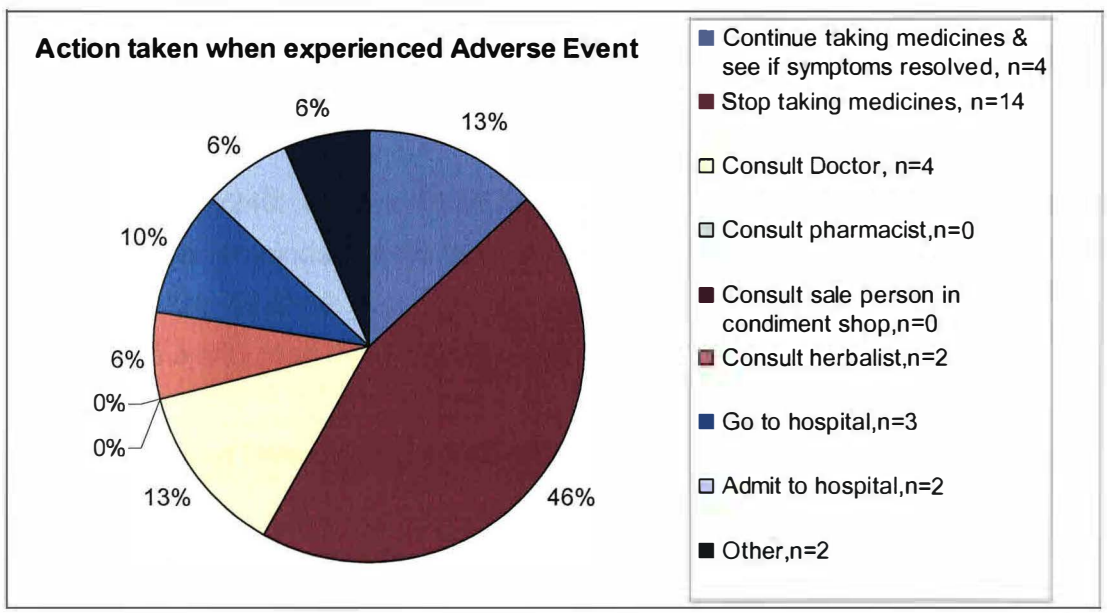


Figure 2.1: Respondent action taken when adverse events experienced.

Thirty-seven people (37, 39%) were taking herbal medicines concurrently with Western medicine. Multiple herbal use was common; 132 products were cited by these 37 people. In addition, the majority of these respondents (28, 76%) were taking herbal medicines for the same condition being treated with Western medicine. Of these, at least five cases involved chronic conditions: diabetes (2), obesity (2) and chronic cough (1).

2.3.4 Reasons for taking herbal medicines and frequency of use

Those respondents who said they took HMs were asked to state why they did so. Some of the 275 responses received contained more than one reason; but three main reasons emerged:

- they thought they were effective (n=99, 36.0%);
- safe (n=94, 34.2%); and,
- from natural sources (n=82, 30.0%).

Other less frequently cited reasons included 'heritage' (n=20), ease of availability (n=13), had trust in them (n=11) and a 'prophet' medicine (n=7).

Only 9% (n=22/240; CI: 5.8–13.6%) stated they took herbs every day with the majority of the remainder taking them on an occasional / when needed basis (75%, n=181/240; CI: 69.5–80.1%). Where herbal medicines were used as a finished product, a majority read the associated label information (82%, n=156/190).

2.3.5 Sources of HMs obtained by respondents

Respondents most frequently bought herbal medicines from condimental shops (58%, n=141/243), followed by supermarkets/grocery stores (33%, n=80/243), and herbal medical centres (22%, n=54/243). Pharmacies (17%, n=40/243) and health food shops (15%, n=37/243) were less frequently cited sources. Other outlets such as the internet were very rarely used (1.6%, n=4/243). Repeat purchasing patterns reflected the respondents' preferences for particular outlets (see Table 2.5). However, no clear pattern emerged from the frequency of purchasing, although it appears that respondents were more frequent repeat buyers from grocery shops and supermarkets compared to other outlets.

	Number of visits made over the last 12 months					
	1	2	3	4	5	> 5
Herbal Medical centre	29	18	9	1	0	7
(n=64)	(45.3%)	(28.1%)	(14.1%)	(1.6%)	(0%)	(10.9%)
Health food shops	18	7	10	1	2	2
(n=40)	(45%)	(17.5%)	(25%)	(2.5%)	(5%)	(5%)
Condimental shops	44	28	14	11	4	11
(n=112)	(39.3%)	(25%)	(12.5%)	(9.8%)	(3.6%)	(9.8%)
Pharmacy	29	23	8	4	3	9
(n=76)	(38.2%)	(30.3%)	(10.5%)	(5.3%)	(3.9%)	(11.8%)
Grocery/ supermarket	17	25	15	5	6	26
(n=94)	(18.1%)	(26.6%)	(16%)	(5.3%)	(6.4%)	(27.7%)
Gym club	6	2	1	2	0	6
(n=17)	(35.3%)	(11.8%)	(5.9%)	(11.8%)	(0%)	(35.3%)
Other places	6	2	7	1	1	0
(n=17)	(35.3%)	(11.8%)	(41.2%)	(5.9%)	(5.9%)	(0%)

Table 2.5. Frequency of visits to purchase herbal medicines

Almost three-quarters of respondents stated that they received advice from the seller on how to take the medicine (74%, n=176/238). A number of further questions were posed that explored participants' purchasing patterns and responses are summarised in Table 2.6. The two primary reasons people chose a particular outlet were because it had an experienced herbal practitioner present (42%, n=98/232) and had a wide choice of herbal remedies (41%, n=95/232). Other factors which shaped their decisions were closeness to home (22%, n=51/232) and proximity to other stores (18%, n=41/232). Price (9%, n=20/232), customer friendly attitude of staff (8%, n=18/232), obtaining free samples (4%, n=9/232) and appearance of the store (3%, n=6/232) appeared to be minor influences.

Respondents were then asked to select from a list what influenced their purchasing decisions. Recommendations by family or friends (76%, n=182/240) were clearly the most influential; but reading articles in magazines (28%, n=67/240) or through other reading such as books, leaflets and posters (23%, n=55/240) and radio and TV advertising (22%, n=53/240) were also cited; although the internet was less used (10%, n=25/240). Over twice as many respondents said they gained information from

herbal practitioners (19%, n=46/240) as from health care professionals (9%, n= 22/240).

Statement	Basic Description (n and % values)
Reasons for buying from that particular outlet (n=232), responses n=360*	
There is an experienced herbal practitioner	98 (42.2%)
The shop is big & has various types of H.M	95 (40.9%)
It is close to my home	51 (22.0%)
The shop is located in big shopping centre / food market	41 (17.7%)
Other reasons	22 (9.5%)
The prices are cheaper than other places	20 (8.6%)
The sale person in that shop is kind to me	18 (7.8%)
I got free samples when I buy	9 (3.9%)
It is tidy and elegant	6 (2.6%)

Table 2.6. Influences on purchasing patterns

* % greater than 100% as responders could chose more than 1 response

When respondents were asked how they choose between herbal products when there was more than one choice (see Table 2.7), recommendation from family and friends was again the most important (50%, n=116/232). This is in stark contrast to recommendations by staff (12%, n=27/232). This reliance on using family and friends is not unsurprising given that 64% (n=195/303) of respondents stated that they knew some of their family members used herbal medicines. Decisions on which to purchase were also driven by media exposure (seen or heard most about, 42%, n=97/232) and what they thought to be the most effective product (21%, n=48/232). Interestingly, more respondents would choose a stronger version (40%, n=93/232) over brand confidence (13%, n=29) or those which required less doses a day to be taken (14%, n=32/232).

A substantial minority of respondents (34%, n=90/263; CI: 28.5–40.3%) had visited a herbal practitioner at some time. It was also found that those people who lived in rural areas as opposed to urban areas were significantly more likely to visit a herbalist (Chi^2=10.904, p=0.001). Seventy-eight went on to say where they saw them (see Table 2.8). The most visited places were condimental shops and herbal medical

centres (69%, n=54/101), followed by a government hospital (14%, n=11/101); while the least visited place was the herbal practitioner's home (8%, n= 6/101).

How respondents chose between HMs (n=232), responses = 515*	
It has been recommended by a friend/ family	116 (50%)
It is the product which I have seen / heard most about	97(41.8%)
It is the strongest version available	93(40.1%)
It is the one I believe to be most effective	48 (20.7%)
It has the most informative label	38(16.4%)
The one which requires least doses per day	32(13.8%)
It has the brand name which inspires the most confidence	29(12.5%)
It has been recommended by staff	27(11.6%)
Other reason	14 (6%)
Because of flavour	11(4.7%)
The one which comes in largest quantity	8(3.4%)
The cheapest	2(0.9%)
It has the most attractive label	0(0%)

Table 2.7: Influences on choice when more than one product available
* % greater than 100% as responders could chose more than 1 response

Where do you meet the Herbal Practitioner? (n=78), responses = 101	
Condimental shop	27 (34.6%)
Herbal centre	27 (34.6%)
Government hospital	11 (14.1%)
Pharmacy	8 (10.3%)
Patient's home	8 (10.3%)
Private hospital/clinic	7 (9.0%)
Health food shop	7 (9.0%)
Herbal practitioner's home	6 (7.7%)

Table 2.8: Places where respondents saw herbal practitioners
* % greater than 100% as responders could chose more than 1 response

2.3.6. Respondents' views on HM compared to Western (conventional) medicine

Eighty-four percent (n=260/311) of respondents had taken conventional medicines to treat previous illnesses, and most (82%, n=213/259) said that treatment using conventional medicine was effective or very effective. Yet over three-quarters (78%, n=258/330) of respondents had taken herbal medicines concurrently with conventional medicines. The range of conditions that were reported to be treated with conventional medicines is shown in Table 2.9. The most common symptoms / illness treated concurrently were coughs and colds (26%, n=32/124), headache/migraine (10%, n=12/124) and fever (7.2%, n=9/124). This is reflected in the listed names of Western medicines the respondents were able to recall. Fifty-three respondents were able to give details of 95 medicines that they took. Medicines taken ranged from corticosteroids to appetite suppressants but analgesics (27%, n=26/95; paracetamol (n=17) and NSAIDs (n=9), antibiotics (17%, n=16/95), acne and cough preparations (both 7%, n=7/95) were the most commonly taken medicines.

Disease Category (n=124)	n (%)
Respiratory Tract	45 (36.3%)
Central Nervous System	21 (16.9%)
Gastrointestinal	15 (12.1%)
Endocrinology	9 (7.3%)
ENT	8 (6.5%)
Infection	8 (5.6%)
Skin	5 (4.0%)
Joint and Musculoskeletal	7 (4.0%)
Cardiovascular	3 (2.4%)
Nutrition and Blood	2 (1.6%)
Gynaecological	1(0.8%)

Table 2.9: Conditions (per BNF category) being treated with conventional medicines.

Respondents were also asked a series of nine statements that encouraged the comparison between herbal and Western medicine; these are summarised in Table 2.10.

Statement	Agree and strongly agree (%)	No opinion (%)	Disagree and strongly disagree (%)
a) I have more confidence in herbal medicine than conventional medicine. (n=299)	60	24	16
b) Herbal medicines are safer to use than conventional medicines. (n=307)	75	16	9
c) Herbal medicines are more effective than conventional medicines. (n=301)	48	37	15
d) Herbal medicines work as quickly and effectively as conventional medicines. (n=300)	39	36	25
e) There are no problems taking herbal medicines with conventional medicines. (n=291)	42	38	20
f) Herbal medicines have no place in modern medicine. (n=292)	21	22	57
g) Herbal medicines have been more useful for me when treating a previous ailment than conventional medicines. (n=292)	55	29	16
h) Herbal medicines treat the whole body to make a person better, not just a problem. (n=304)	59	33	8
i) Herbal medicines should contain a leaflet of similar information to conventional medicines. (n=300)	87	10	3

Table 2.10: Responses to statements comparing herbal to Western medicine.

Statements a to e and statement g (Table 2.10) directly compared HM to Western medicine. Statements a, b, c and g showed respondents to be strongly in support of herbal medicines; Statements d and e, relating to onset of action and potential for

interactions, although more positive toward herbal medicines, did have large neutral values. For statements that were not direct comparisons (f, h and i) these too were positive toward herbal medicines.

Further statements explored respondents' views on HMs with respect to safety. Respondents were asked to choose a preference between HM and Western medicine (Table 2.11).

Statement	Herbal medicines (HMs)	Western medicines (WMs)	Both (HMs & WMs)
a. Safe to use. (n=288)	231(80.2%)	51 (17.7%)	6 (2.1%)
b. Processed Chemical Manufacturing. (n=245)	28 (11.4%)	216 (88.2%)	1 (0.4%)
c. Has no side effects. (n=267)	227 (85%)	33 (12.4%)	7 (2.6%)
d. Cannot get addicted. (n=254)	218 (85.8%)	34 (13.4%)	2 (0.8%)
e. Can prevent a person from getting sick. (n=270)	162 (60%)	85 (31.5%)	23 (8.5%)
f. Can improve and maintain a person's health. (n=273)	197 (72.2%)	57 (20.9%)	19 (7%)
g. Is safe to be given to pregnant women. (n=250)	195 (78%)	50 (20%)	5 (2%)
h. Is safe to be given to breastfeeding mothers (n=243)	193 (79.4%)	44 (18.1%)	6 (2.5%)
I. Is safe to be given to children below 12 years old (n=263)	176 (66.9%)	72 (27.4%)	15 (5.7%)

Table 2.11: Respondents' perceptions of comparative safety between herbal and Western medicines.

Respondents were much more inclined to favour HM over Western medicine for all statements. In particular, approximately 80% or more of respondents favoured HM in relation to their overall safety (statement a), having no side effects (c) and being safe to give whilst either pregnant or breastfeeding (g, h). Interestingly, sub-analysis showed that more women than men thought HM was safer (Chi^2=8.420, p=0.004) and had no side effects (Chi^2=9.409, p=0.002). Additionally, almost all women (n=24/25) who were currently pregnant or breastfeeding would continue taking HM.

The majority of respondents (77%, n=160/207) also stated that HM would be their treatment of choice.

Those respondents that took HMs (76%, n=250/330) were asked if they consulted a doctor first before taking them. The majority, (69%, n=164/238) said they did not inform a doctor; reasons for not doing so are shown in Table 2.12.

Statement	**n=147**
Did not think to mention it to the doctor.	60 (40.8%)
Don't think my doctor believes in herbal medicines so would not take me seriously.	46 (31.3%)
Don't think my doctor needs to know about medications I take unless it's medication that they prescribed for me.	44 (29.9%)
Other reasons: (variable answers, although 5 respondents mentioned they were safe and therefore the doctor did not need to know).	34 (23.1%)

Table 2.12 Reasons why respondents did not disclose HM taking to their doctors.

It is clear from those who disclosed their reasons that many (41%) had not thought to talk to their doctor, although approximately 30% thought that they would not be taken seriously or believed it was not for the doctor to know about as they had not prescribed the medicine. For those people that took HM and did speak to their doctor first (n=74, 31.1%) seventy went on to state why. The commonest reasons for disclosure was they believed their doctor should be fully aware of all medicines they took (n=45/70, 64.3%) and that they wanted to discuss any new medication with their doctor before taking it (n=29/70, 41.4%).

Respondents were also asked to state whether herbal medicine or conventional medicine would be their first choice treatment for a range of conditions. Responses are shown in Table 2.13.

Condition (n=respondents expressing an opinion)	Herbal medicine (%)	Western medicine (%)
Herbal medicine preferred		
Weight loss (n=260)	74	26
General well being (n=263)	73	27
Weight gain (n=255)	73	27
Stomach/digestive disorders (n=261)	66	34
Opinion equally divided		
Colds and flu (n=270)	56	44
Fatigue (n=261)	51	49
Insomnia (n=262)	50	50
Sexual disorders (n=234)	47	53
Western medicine preferred		
Anxiety/depression (n=254)	43	57
Immunity/nutrients disorders (n=253)	43	57
Diabetes (n=255)	41	59
Bruises/injuries (n=268)	40	60
Back/neck pain (n=274)	39	61
Skin disorders (n=253)	37	63
Infertility (n=233)	37	63
High cholesterol (n=253)	36	64
Arthritis (n=254)	34	66
Asthma/lung disorders (n=255)	33	68
High blood pressure (n=259)	33	67
Headache/migraine (n=274)	28	72
Cancer (n=232)	21	79

Table 2.13: Respondents' preferred choices for treating specific conditions

From the 21 conditions listed, herbal medicine was only strongly preferred in four conditions:

- Weight loss;
- General well being;
- Weight gain;
- Stomach/digestive disorders; and,

In comparison, conventional medicines were strongly preferred in thirteen conditions:

- Diabetes;
- Bruises/injuries;
- Back/neck pain;
- Skin disorders;
- Infertility;
- High cholesterol;
- Arthritis;
- Asthma/lung disorders;
- High blood pressure;
- Headache/migraine;
- Cancer;
- Anxiety and depression;
- Immunity and nutrient disorders.

No significant differences were found in those conditions in which opinion was equally divided.

2.3.7 Views on Health Professionals and others who sell / supply herbal medicines

A series of questions was asked of the respondents regarding herbal practitioners, doctors and other healthcare providers. Table 2.14 highlights statements comparing respondents' views between herbal practitioners and doctors. The responses showed very few polarised viewpoints, with most statements having large neutral responses.

The final series of questions looked at whether respondents had been recommended, prescribed or given advice on HMs, as well as referral on to a herbal practitioner. The results are summarised in Table 2.15.

Statements comparing Herbal Practitioner to Physician	Agree or strongly Agree	No Opinion	Disagree or strongly disagree
Visit to Herbal Practitioner is cheaper than to a Physician. (n=301)	115 (38%)	119 (40%)	67(22%)
Herbal Practitioner shows more counselling skills than Physician. (n=303)	97 (32%)	139 (46 %)	67(22%)
Herbal Practitioner offers more promises of cure than Physician. (n=297)	148 (50%)	107 (36 %)	42(14%)
Medications given by Herbal Practitioner are never out of stock. (n=296)	176 (59%)	80 (27 %)	40 (14%)
Medications given in Healthcare centres/ hospital is often out of stock. (n=290)	90 (31%)	70 (24%)	130 (45%)
Herbal Practitioner discourages me from visiting a Physician. (n=289)	55 (19%)	108 (37%)	126 (44%)
Physician discourages me from visiting a Herbal Practitioner. (n=294)	81(28%)	99 (34%)	114 (39%)
Physician discourages me from taking HM. (n=296)	72 (24%)	88 (30%)	136 (46%)
Herbal Practitioner discourages me from taking. CM (n=298)	72 (24%)	107 (36 %)	119 (40%)

Table 2.14: Respondents' comparisons of Herbal Practitioners and Doctors.

Advising person	Suggest to use HM (n=318)	Suggest to see Herbal Practitioner (n=205)	Have prescribed an HM (n=288)	Have given advice on how to take HM (n=289)
Doctor (n=78)	25 (8%)	10 (5%)	22 (8%)	21 (7%)
Pharmacist (n=50)	15 (5%)	6 (3%)	13 (5%)	16 (6%)
Dentist (n=11)	5 (2%)	2 (1%)	2 (0.7%)	2 (0.7%)
Nurse (n=19)	4 (1%)	5 (2%)	5 (2%)	5 (2%)
Herbal Practitioner (n=188)	44 (14%)	n/a	79 (27%)	65 (23%)
Sale person in condiment shop (n=167)	40 (13%)	44 (22%)	42 (15%)	41 (14%)
Sale person in health food shops (n=55)	15 (5%)	15 (7%)	10 (4%)	15 (5%)
Other* (family and friends) (n=532)	170 (54%)	123 (60%)	115 (40%)**	124 (43%)

Table 2.15: Respondents Response to Recommendations and referrals relating to HMs from other people.

* On analysis, 'other' was primarily friends and family and is reported as such.

** in this context, the author interprets prescribe as 'given'

Results from Table 2.15 show that the respondent's family and friends was the majority group suggesting that the respondents use HM (54%, n=170/318); this is far higher than any other group, with herbal practitioners (14%,n=44/318) ranked second and sales people in condimental shops being third (13%, n=40/318). Likewise, family and friends suggested visiting a herbal practitioner more than any other group (60%, n=123 /205); referrals by healthcare professionals was very low (physician, 5%, n=10/205; pharmacist 3%, n=6/205; nurse, 2%, n=5/205; and dentist, 1%, n= 2/205).

Predictably, herbal practitioners were the group to have prescribed HM to respondents the most (27%, n=79/288); yet a high proportion of family and friends appear to have 'given' HMs to respondents (40%, n=115 /288). Yet again, when it came to advice on administration, family and friends were the most influential (43%, n=124/289).

2.4 Discussion

This phase of the work has shown that the majority of UAE nationals rely heavily on herbal medicines to treat both acute and chronic conditions. The prevalence rate seen in this data is much higher than those studies conducted in Western countries.[23,32,33,35,36,103,104,105]

This is further underlined by these findings being purely based on herbal use whereas most Western studies have used umbrella terms such as 'complementary' or 'alternative' medicine, that encompass other forms of treatment such as massage, homoeopathy, spiritual healing and acupuncture, to name but a few. In Western studies where prevalence rates for herbal remedy taking are specified, then rates are much lower, ranging between 10 and 20%.[103,106,107] This was partly expected due to the different cultures of UAE and Western countries. As stated previously, the UAE is an emerging nation which is embracing Western approaches to health care but it is steeped in traditional healing using herbal products. Prevalence studies from other African and Middle Eastern countries support high HM taking. Ogur *et al* [46] and Eddouks et al [55] reported similarly high rates to these findings (between 75 and 80%), whilst other reports from Iran [31] and Bahrain [52] also described prevalence rates of approximately 50%. In addition, other ethnopharmacological surveys in Morocco, Israel and Egypt show that traditional herbal medicines available for people to buy are extensive.[105-110]

Crude formulations sold from traditional 'condimental' stores that were then made into infusions and teas were most popular. No control over the quality of these products exists in the UAE. This raises questions over the safety of such products. Adulteration of herbs is a real concern and a number of cases have been reported to and investigated by the UAE MoH (see Chapter 1, section 1.13.1). In addition to adulteration, the lack of standardisation of crude herbs also increases the likelihood that patients will experience ill effects or reduced efficacy from them.

Faith in herbal remedies was strong, both from the standpoint of effectiveness and safety. This faith is probably a product of heritage. Generation after generation have used these products, with no attributed harm and a perception of much good. The cultural mindset is reinforced by family and friends being the main influences on respondents' purchasing patterns. This, however, is not culturally unique as others have shown that relatives are also instrumental in shaping decisions regarding the purchase of medicines.[111]

The range of herbal medicines taken was large. The most frequently cited herbal medicines were those which have been used in healing for many centuries, for example thyme, sage, aloe, senna and fenugreek. This is in contrast to Western herbal medicine taking where products such as echinacea, ginkgo and garlic supplements have gained much media attention regarding their purported effects and are now frequently used. [106] It appears because of respondents' confidence in herbal medicine, that they infrequently inform their medical practitioner and use remedies for a wide range of conditions. However, herbal remedies are not without unwanted effects and possible interactions. An appreciable proportion of people (11%) reported an adverse event whilst taking a herbal product. However, because most took multiple remedies and the survey relied on recall, it is almost impossible to establish causality. Two cases involved thyme and a reduction in breast milk although this appears not to be a documented adverse event. The natural medicines comprehensive database states *'there is insufficient reliable information available about the safety of thyme when used in medicinal amounts during pregnancy and breast feeding'*.[112] From these study findings further investigation seems prudent.

Reports of herb usage during pregnancy are scarce. Nordeng and Havnenan [113] surveyed 400 postpartum women at a Norwegian University Hospital about herbal product use. Over a third (36%) reported using herbs during pregnancy, often combining several preparations; use increased progressively from the first to the third trimester. The authors considered a significant proportion (39%) to be potentially harmful or lacking supporting safety information and concluded that more safety data are required. A further Iranian study conducted amongst 447 pregnant women reported 52% of women took herbal medicines whilst pregnant.[45] A recent review of the safety of traditional Arab herbal medicine recognised the lack of safety data on many preparations in common use and the need for further investigation using

modern techniques including cell culture.[59] These study findings together with this data suggest that further investigation is required.

The Arab world has always made extensive use of herbs as medicines, drawn from a rich inventory of indigenous natural ingredients; indeed, traditional Arab medicine has contributed much to the development of modern European medicine. It is estimated that 200–250 plant species are still in use.40,56 The cultural beliefs and attitudes to herbal medicines have a long history and still influence choices for self-care, often reinforced by consultation with traditional healers, particularly in rural areas; even for illnesses such as infertility, impotence, obesity, epilepsy and psychomotor disorders. The findings in this work that 21% of respondents indicated a preference for herbal over Western medicine for treating cancer is of concern. This may be an illustration of the prevalent trust in traditional medicines discussed above. As discussed above, the high prevalence of herbal medicine taking in the UAE is not an isolated occurrence with other Arab countries reporting similar rates. This has important health implications, as over-reliance on ineffective herbal remedies could lead to deferral of more effective chemotherapy.

As Azaizeh *et al* [40] point out, herbal remedies in this region are prescribed by 'ethnopharmacologists', often based solely on signs and symptoms rather than with a full understanding of the disease. Many herbalists are not trained in the field of herbal medicine beyond the knowledge passed down from their predecessors and they may miss important diagnoses because of this (see Chapter 1, section 1.9.5.1).

The number of people taking herbal and Western medicines together was high. The potential for interactions with Western medicines is therefore high. Unfortunately, the documentation of herbal / Western medicine interactions is limited and most interactions are based on pharmacological action rather than clinical case reports. Furthermore, many subjects were self-medicating with herbal medicines for the same problem being treated with Western medicine. If the findings of this study are taken as being a true picture of UAE citizen behaviour, then these issues need to be recognised by practitioners of Western medicine to ensure patients are not putting themselves in unnecessary danger. It could be argued that as Abu Dhabi is very prosperous, and in many ways westernised, that patients in this area are more likely to use a mixture of traditional herbal medicine and Western medicine compared to the less developed rural parts of the UAE. As such, Abu Dhabi and other areas with similar population demographics such as Dubai, may present the greatest challenges

of prescribing Western medicine against a background of herbal medicine consumption. Certainly, Western medicine was generally preferred to herbal medicines when respondents were forced to choose between them. This was especially true for chronic disease states, although this may reflect the nature of the sample as the Rawdha Clinic supplies services are based on Western medicine.

2.4.1 Study limitations

This phase of the work did have its limitations. Firstly, the sample did not reflect national statistics. However, this is in part due to the make-up of the UAE. Abu-Dhabi is one of seven geographical regions, and along with Dubai, is responsible for most of the country's wealth, when compared to some of the more remote regions such as Um Al Qiween and Ras Al khaimah. Abu Dhabi therefore attracts younger, better educated people with better employment prospects, which accounts for the demographic differences between our sample and national statistics.

Secondly, the clinic used also served as a mother and child centre which probably contributed to the higher number of women being sampled. The study suffered from a cultural phenomenon, in that the lead researcher was female and this had a negative influence on recruiting men to the study. A change in sampling technique failed to address the disparity adequately. It is recognised that the absence of a disproportionately high number of men might influence the prevalence rates for herbal medicine usage—both type and indication. Future studies in this and other countries in the region might avoid this problem by using a male interviewer.

Children were excluded from the present study; however, it would be interesting to extend the investigation to include them. HM use is prevalent among pregnant and breastfeeding women too, and the effects of HMs on neonates, infants and children has not been studied extensively.

This study was limited to UAE citizens, which are actually a minority in the country due to high in-migration of foreign citizens, guest workers and nomadic peoples. These too would contribute to the overall picture of herbal use in the UAE, but lay outside our study.

Although aimed primarily at determining herbal use prevalence, side effects were noted in this study. Respondents volunteered little specific detail but the severity prompted one respondent to seek medical attention. Herbal remedies are widely considered to be safe and inexpensive but this is often not the case.

2.4.2 Conclusions

The major findings from this study are summarised below.

- 85% (n=279/329) of respondents said they were in good or excellent health;
- 76% (n=250/330) of respondents had, at some time, taken HMs;
- 38% (n=94/248) of respondents were currently taking HMs, with 65 different HMs being taken to treat 48 conditions;
- 88% (n=198/225) of respondents stated the last HM taken was either effective or very effective;
- 75% (n=181/240) of respondents took HMs on a when needed basis;
- 78% (n=258/330) of respondents stated that they had at some time taken a HM and Western medicine concurrently yet only 37 respondents (11%) stated they were currently taking HM and Western medicine together;
- 11% (n=27/240) reported suffering from an ADR;
- family and friends were by far the greatest influence on respondents in respect to purchasing decisions and seeking advice from herbal practitioners;
- respondents living in rural areas were more likely to use HM and visit a herbal practitioner than those from urban areas.
- disclosure to a doctor about taking HM was uncommon.

- respondents had confidence in HMs and preferred them to Western medicine on the grounds of effectiveness and safety, yet when given a choice between the two for certain conditions then Western medicine was preferred.

This chapter has shown that UAE citizens are very frequent users of herbal medicines. The lack of control on product quality, respondent faith in their usefulness, together with the wide prevalence of taking prescribed Western medicines whilst self medicating with herbal products, raises questions over patient safety.

2.4.3 Further work

Prevalence of HM taking within the study population has been established as being high. Safety concerns have been raised over their widespread use with little medical input or knowledge that people are taking such products. Chapter 3 describes a more focussed study of these issues in a secondary care setting.

Chapter Three:

A study of potential ADRs to herbs in patients with renal disease, visiting a hospital nephrology clinic in Sheikh Khalifa Medical City (SKMC), Abu Dhabi.

3.1 Introduction

As mentioned in Chapter 1, herbal medicines (HMs) are popular therapies across various communities. Coming from nature, people are still reluctant to link them with the risk of adverse effects. Many of these products do not require a prescription; thus their use and any potential risks may easily escape the physician's or pharmacist's attention. Increasing recognition that herbs can cause adverse effects or treatment failure, often through interaction with synthetic drugs, has stimulated interest in herbal medicine safety.[114,115]

ADRs are a common cause of hospital admission and make a significant contribution to healthcare costs. [116,117] ADRs resulting from herb-drug interactions have been identified as significant factors responsible for patient morbidity and mortality. [118]

With the exception of the findings in Chapter 2, information on the prevalence of subjectively experienced ADRs to HMs and their subsequent burden in the general population is mostly lacking in a Middle Eastern setting. In one Swedish study, a cross-sectional mail survey of self-reported ADRs occurring during a 2-week period of using prescription, over-the-counter (OTC), or HMs in a random national sample aged 18-84 years was conducted. ADRs were reported by 6.4% of the total study sample, 10.2% of the 2,851 users of prescription drugs, 1.0% of the 2,862 users of OTC drugs, and 0.1% of the 1,352 users of herbal drugs.[119]

A study conducting face-to-face interviews with 515 users of herbal remedies to determine the reporting of ADRs to HMs and conventional OTC medicines showed that HM consumers would act differently with regard to reporting an ADR (serious or minor) to their GP depending on whether it was associated with a HM or a conventional OTC medicine.[120] One hundred and fifty six (30.3%) respondents said they would consult their GP irrespective of whether the ADR was associated with the use of a herbal remedy or conventional OTC medicine, whereas 221 respondents (42.9%) would not consult their GP for a serious ADR associated with either type of preparation. One hundred and thirty-four respondents (26.0%) would consult their GP for a

serious ADR to a conventional OTC medicine, but not for a similar ADR to a herbal remedy. This study indicates that even when HMs cause problems, at least some patients may be reluctant to report them to their carers.

3.1.1 Potential of HMs to cause serious harm

Constituents of herbal medicines can be toxic and numerous examples of liver, kidney or other organ damage are on record.[121] All herbal medicines contain a range of pharmacologically active constituents, and users of herbal medicines often combine herbal medicines with prescribed drugs; thus herb-drug interactions are a real possibility.[114,115,118] While HMs under MoH control are firmly regulated, HMs and dietary supplements imported by the municipalities in their thousands, are not submitted to stringent regulation and control. Thus unreliable quality can be a problem. In particular, this poses a risk when herbal medicines are contaminated (e.g. with heavy metals) or adulterated (e.g. with prescription drugs).[121]

Cuzzolin *et al* [122] found that among 1,044 women interviewed during a 5-month period in the outpatient department of an urban university general hospital, 491 (47%) reported taking at least one herbal compound in the last year; of these, 272 (55.4%) consumed only HMs while 219 (44.6%) also took conventional drugs. Seventy three different herbal products were used. Forty seven of the 491 patients (9.6%) reported side-effects: 22 (4.5%) after taking only HMs and 25 (5.1%) in combination with conventional medicines. ADRs to HMs reported included gastrointestinal upset after dandelion, propolis or fennel; cardiovascular problems after liquorice, ginseng, and green tea; dermatological eruptions after propolis, thyme, arnica, and passionflower; and neurological disorders after guarana and liquorice. Drugs taken in association with the HM and potentially involved in adverse reactions were NSAIDs, antibiotics, benzodiazepines, antihypertensives and oral contraceptives. In 29 of 47 of cases (61.7%), the adverse reaction was not communicated to the doctor; however in five cases, side-effects were serious enough to cause hospital admission.

The potential for serious interactions between conventional medicines and HMs is discussed elsewhere in this thesis (see Section 1.13); however several cases resulting in hospitalisation are discussed below.

An increasing number of cancer patients are using complementary and alternative medicines (CAM) in combination with their conventional chemotherapy. A range of HMs has been reported to interact with anticancer drugs, including St. John's wort with irinotecan and imatinib.[123] Induction of drug-metabolizing enzymes leading to therapeutic failure is a probable mechanism; although this might go unrecognised because treatment failure is common in cancer treatment. Wu *et al* [124] report the case of a 67 year-old woman who developed severe pancytopenia with initial presentations of vomiting, diarrhoea, oral ulcers and fever about one week after taking a 5-day course of *Cantharanthus roseus.* Bone marrow biopsy showed autolysis, which indicated massive necrosis of the haematopoietic cells. There was no malignant cell infiltration. The patient also had severe gastrointestinal disturbances, bacteraemia, urinary tract infection, and impaired renal and liver function. The authors imply that the effects were due to an interaction with the HM resulting in reduced clearance of vinca alkaloid chemotherapy.

The use of herbal supplements by cancer patients in the perioperative period is common and consistent with the substantial increase in the use of alternative medical therapies. Different HMs or phytomedicine supplements are reported to possess antiplatelet activity, adversely interact with corticosteroids and central nervous system depressant drugs, have gastrointestinal manifestations, produce hepatotoxicity and nephrotoxicity, and produce additive effects when used with opioid analgesics.[125]

An 87-year-old African-American patient with a history of stage IV-A follicular non-Hodgkin's lymphoma, atrial fibrillation, and hypertension and long-term drug therapy consisting of warfarin, felodopine, lisinopril-hydrochlorothiazide, controlled-release diltiazem, potassium chloride, and oxycodone presented at the accident and emergency department with haematuria and an international normalised ratio (INR) of 6.9. After ruling out poor patient compliance and dietary changes, the authors discovered that the patient had started taking royal jelly one week previously. They stated that the most probable explanation for the patient's elevated INR and subsequent bleeding was an interaction between royal jelly and warfarin.[126]

Seak and Lin [127] report a case of unintentional poisoning from Ruta graveolens, a HM used for 'heart protection' in a 78-year-old woman in Taiwan. The patient developed bradycardia, acute renal failure with hyperkalaemia, and coagulopathy after three days of consuming a decoction made from the herb. She required haemodialysis in the emergency department; after which

symptoms gradually resolved. The authors suggested that Ruta caused multiple pathologies in their patient.

Chang *et al* [128] assessed the prevalence of adrenal dysfunction and any relation to prior HM use in a Taiwanese hospital emergency department. Thirty adult patients with sepsis or acute myocardial infarction (AMI) were eligible for the study; 23 (77%) were suffering from severe sepsis and the other seven (23%) had an AMI. Thirteen of the 30 patients (43%) had serum cortisol levels of <15micrograms/dL, consistent with adrenal insufficiency: nine with severe sepsis and four with an AMI. Eight (62%) of the 13 patients with low cortisol levels reported using HMs, while only two (12%) of the 17 with normal cortisol levels reported taking them. Only two (15%) of the patients with low cortisol levels failed their corticotropin stimulation test, suggestive of true adrenocortical insufficiency. Both reported using herbal preparations. The authors concluded that while adrenal dysfunction was common among critically ill patients seen in the emergency department, the use of HMs was high in patients with low serum cortisol.

HMs have been associated with serious end-organ damage resulting in hospitalisation;[129-133] indeed, several traditional HMs, notably kava [129,134] are banned in most countries because of this. Never-the-less, new reports involving novel HMs keep emerging. Rifai *et al* [135] reported the case of a 58-year-old male patient who was admitted because of developing severe acute hepatitis caused by ingestion of a *Chelidonium* (celandine)-containing preparation, which was thought to be responsible for the hepatitis. This was corroborated by resolution of liver function tests upon de-challenge. Savvidou *et al* [136] reported two cases of *Teucrium polium* (golden remander)-induced hepatitis in two Greek female patients, who used the plant extract to control cholesterol levels. Both patients presented with very high aminotransferases after consuming tea made from the herb for two or three months. One patient also developed jaundice. Histological examination of liver biopsies showed hepatitis with moderate or severe necro-inflammatory activity. Discontinuation of the herbal remedy resulted in normalisation of the liver enzymes in both patients. A similar reaction to this herb in a 70 year-old farmer using it as a hypoglycaemic aid, was also reported by Starakis *et al*.[137]

In summary, the use of HMs is not without risk. They can cause serious ADRs when used alone but also have considerable potential for important drug interactions. Most evidence is anecdotal and there is little pharmacoepidemiological information on the extent of the problem. Chapter 2 has shown that UAE citizens routinely use HMs alongside modern medicine. There is no data at the present on the safety of such herbal medicines taken by the public irrespective of whether

they are patients or healthy individuals. Phase two of this research attempted to explore the extent of the perceived problem in the context of patients visiting a single clinic at the hospital where the author was employed as a researcher.

3.1.2 Research aim

The aim of this research was to conduct a pilot study of adverse reactions to herbal medicines within the controlled environment of a tertiary clinic in the Abu Dhabi Emirate Sheikh Khalifa Medical City (SKMC).

3.1.3 Research objectives

1. To provide qualitative and quantitative data on the safety of herbal medicines in SKMC patients and to determine the health risks involved with their use.

2. To identify herbal ingredients, interactions, and outcomes of their use or misuse.

3.1.4 Subsidiary Study Questions

1. To describe the different types and causes of herbal ADRs

2. To estimate the risks anticipated from taking herbal medicines with and without Western medicines.

3. To identify risk factors which predispose an individual to herbal adverse reactions.

4. To estimate the incidence rate and magnitude of health risk associated with herbal use in the study population.

3.2 Methodology

3.2.1 Introduction

Several options were considered for this stage of the research; alternatives are discussed in Chapter 4 under 'Suggestions for future work'. The final choice of method was a pragmatic one, based on availability, proximity and what the author was permitted to do at the time of the study. The main sector chosen for the study was secondary care. It was hoped that studying patients

either on admission or visiting the outpatient departments might yield quality information on herbal use and potential risks, because the author would have access to full patient records and be in a position to develop her interviews, used in Phase 1 of the research, to question subjects in-depth about their use of and attitudes to HMs.

An initial thought was to approach a private hospital, the New Medical Centre (NMC) in Abu Dhabi. The latter is one of the busiest private hospitals in Abu Dhabi. Choice was based on its size (seeing over 2,000 outpatients per day) and the fact that it employed over 100 physicians who might be recruited to assist with the study. In April 2006, a meeting was held between the author, the Head of Research and Medical Director of NMC to explore these possibilities. Unfortunately it was decided not to progress the research at NMC for the following reasons:

1. NMC hospital did not have a computerised information system for medical records;
2. there was no formalised system for reporting ADRs; and,
3. most emergency cases were referred to public hospitals (such as SKMC which is the biggest public hospital in Abu Dhabi City).

To circumvent most of the problems described above, the focus of the research then turned to the largest public hospital in Abu Dhabi: the Sheikh Khalifa Medical City.

3.2.2 The Sheikh Khalifa Medical City (SKMC)

SKMC receives the highest number of public patients in Abu Dhabi City and provides a comprehensive network of health care facilities and services. The overall strategy of SKMC is to improve the current status of healthcare delivery by expanding its services and technology, upgrading and improving the physical condition of its existing facilities, combining its health care resources for a more efficient model of healthcare delivery, increasing its current bed capacity to accommodate the needs of its patients, and creating a system for health care professionals to work as one team within SKMC, under the guidance of the Abu Dhabi Health Authority. SKMC employs approximately 4,000 staff with an overall capacity of 520 beds. The centre was inaugurated officially in March 2,000 and identified as the most frequently used specialist centre in the country for major, complicated cases and critical emergencies. SKMC has a wide range of

specialist departments, including cardiology, renal and hepatic units and a busy accident and emergency department.

3.2.3 Establishing the project at SKMC

In August 2006, a letter outlining the research scope and objectives was sent to SKMC; subsequently, a meeting was held between the author, the SKMC Medical Director and Chair of the Medicine Department. Provisional support for the study was obtained, subject to the following conditions:

1. The project would require ethics approval and scrutiny by the SKMC Institutional Review Board (IRB).

2. A co-investigator should be appointed who is a member of the consulting staff at SKMC; subsequently, the Head of the Nephrology Clinic was appointed as co-investigator for this study.

3. Consent forms for the patient participation portion of the study should be vetted.

4. The Department of Medicine would arrange the appropriate physician contacts.

5. Access to medical records and research space in the Medical Records Department would be arranged.

From the meeting with the Medical Director, it was emphasised that:

- although prescribing HMs was not integrated in clinical practice at SKMC, patients would be questioned about their herbal use from other prescribers or self treatment and if they experienced any ADR to a HM.

- patient files were not fully integrated electronically, and most of the patient information and case details were not available online; however patient files could be checked manually. Laboratory results were accessible electronically.

- informed consent and confidentiality of patient data would be rigorously pursued.

- it was recommended that the nephrology division might be a suitable environment for the study.

The latter point was agreed between the author and her project supervisors and the Head of the Nephrology Division was approached by the author and the project proposal introduced, in May 2007. This met with an enthusiastic response and a further meeting was arranged with other physicians in the Division to again, outline the project, including a summary of the results from Phase 1 (see Chapter 2).

3.2.3.1 The SKMC Nephrology Division

At the time of the study, the Nephrology Division at SKMC received approximately 500 outpatient clinic visits per month in addition to regular visits from chronic dialysis patients (over 200 patients on haemodialysis and 20 patients on peritoneal dialysis). The Nephrology outpatient clinic employed 3 nurses and usually 2-3 physicians in each shift (9am -12 noon and 1 pm -5 pm) to see patients from Sunday to Wednesday each week. The Division was a busy but friendly environment in which to conduct the research, with ample opportunity to interview patients as well as access their records.

3.2.3.2 Nurse recruitment

The author met with the nurse in charge of the nephrology outpatient clinic and a group of nurses employed within the nephrology division, to discuss the project aims and methodology and seek their support in providing access to interview patients. The nursing staff helped by providing a visit schedule and a private, quiet room for conducting interviews. Recent patient attendance records were useful in determining the logistics for the investigation. The author also met with the nurse in charge of the dialysis unit where an estimate of patient numbers for the study was made.

3.2.3.3 Interviewer assistant recruitment

Due to the work involved, it was decided to recruit assistants to help with interviewing patients, medical review and data entry. Assistants were already employees at SKMC and were trained for two weeks prior to study entry to conduct the interviews and collect data to the same standard as the author. The author ensured that these assistants were aware of the aims, objectives, methodology and ethical issues of the project and were under her direct supervision.

A total of six assistants were used: three qualified pharmacists and three final year pharmacy students who all spoke English and Arabic.

3.2.4 Data capture form

A data capture form was designed for the study and piloted in the first five subjects. The form contained an adapted version of the ADR form proposed for use, but not yet implemented by the UAE Ministry of Health for recording ADRs to conventional medicines. The data capture went through several iterations and formed part of the ethics application. A final version of the form, together with covering information and consent sheets, is included in Appendix 3.1. Space was provided for patient demographic detail and recording their primary diagnoses, conventional and herbal medicines taken and supporting laboratory data, if available. A data validation form was incorporated to complete when checking the patient's medical notes.

3.2.5 Ethical Issues

The study was approved by SKMC institutional review board (IRB) on Feb. 28, 2007. The application included a full protocol for the study and a patient, informed consent form written in English and Arabic languages. This indicated that patients had the choice to participate in the survey and that they could withdraw at any time without prejudice.

Patients were required to sign the informed consent form prior to interview and accessing their medical records. The consent form was to be retained by the author for at least six years from the end of the study.

Confidentiality was assured by assigning a unique, anonymous study number to each patient, which was used to identify individual data sets. Data was stored securely either in a locked cabinet within a locked room or in the case of computerised data on a password protected desktop computer at the same location. Only the author and her supervisors had access to the coded data.

3.2.6 Study Design

A prospective, 3-month, cohort study followed all patients presenting at the SKMC nephrology department either as outpatients or for renal dialysis.

Inclusion criteria were:

1. UAE Nationals or residents, capable of understanding English or Arabic and responding to questioning;

2. patients aged 13 years or over. Younger patients attended a separate Paediatric Clinic.

Exclusion criteria were:

1. non-nationals/ non-residents who were on a short visit visa;
2. persons incapable of understanding English or Arabic;
3. children aged below 13 years.

3.2.7 Details of Methodology

The principal investigator (the author) or one of her assistants approached all patients visiting the clinic to assess suitability for inclusion in the study (see above). Nurses in charge provided daily lists of patients attending the clinic and dialysis units to the author. The list included age, gender, nationality details and patients' SKMC record numbers.

Included patients were approached for informed consent and once consented, were surveyed using a structured questionnaire described in Section 3.2.8.1 (see also Appendix 3.1). Interviews took place in a private room in the outpatient clinic; or by the patient's bed on the dialysis ward. The questionnaire was administered in Arabic or English according to preference. Specific questions were asked about whether the patient had experienced any ADRs and whether they felt they were related to the HM they were taking (if any). A list was compiled of the prescription medicines (PMs) and HMs that each patient was taking or had recently taken (in effect, a conventional drug history).

If necessary, when an ADR (herbal or otherwise) was identified, the author contacted the medical team to facilitate completing an ADR report using the form shown in Appendix 3.1.

3.2.7.1 Assessing ADR causality

Once a suspected ADR was detected, the author prepared a case study, including all the information on that particular patient, background published information on the pharmacological action(s) of each medicine taken (both PM and HM) and any previous reports of toxicity.

An assessment of causality was through consensus of a panel, consisting of the author, a professor of pharmacology and therapeutics and a nephrologist teaching physician based in the Faculty of Medicines and Health Sciences, UAE University.

Decisions were assisted by use of the algorithm developed by Naranjo *et al*.[138] This is widely used in research involving ADRs with conventional medicines,[139-145] and has been applied to the assessment of herb-drug interactions.[146] The elements of the original Naranjo and a modified version also used by the author are shown in Table 3.1.

Original Questions	Modified Questions
1. Are there previous conclusive reports on this reaction? *Yes (+1) No (0) Do not know or not done (0)* 2. Did the adverse event appear after the suspected drug was given? *Yes (+2) No (-1) Do not know or not done (0)* *3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given? *Yes (+1) No (0) Do not know or not done (0)* *4. Did the adverse reaction appear when the drug was re-administered? *Yes (+2) No (-1) Do not know or not done (0)* 5. Are there alternative causes that could have caused the reaction? *Yes (-1) No (+2) Do not know or not done (0)* *6. Did the reaction reappear when a placebo was given? *Yes (-1) No (+1) Do not know or not done (0)* *7. Was the drug detected in any body fluid in toxic concentrations? *Yes (+1) No (0) Do not know or not done (0)* *8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased? *Yes (+1) No (0) Do not know or not done (0)* *9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure? *Yes (+1) No (0) Do not know or not done (0)* • *9 = definite ADR; 5-8 = probable ADR; 1-4 = possible ADR; 0 = doubtful ADR*	1. Are there previous conclusive reports on this reaction? *Yes (+1) No (0) Do not know or not done (0)* 2. Did the adverse event appear after the suspected drug was given? *Yes (+2) No (-1) Do not know or not done (0)* 3. Are there alternative causes that could have caused the reaction? *Yes (-1) No (+2) Do not know or not done (0)* *Modified score (suggested by researcher)* • *5 = definite ADR* • *3-4 = probable ADR* • *1-2 = possible ADR* • *0 = doubtful ADR* *These questions in the original Naranjo algorithm would all have scored zero in the present study due to its nature. They were therefore omitted from the modified scoring system used by the author.

Table 3.1 Key elements of the Naranjo causality assessment algorithm and the modified algorithm used by the author.

3.2.7.2 Pilot study

The author conducted a pilot study of 15 subjects (5 females and 10 males) in the outpatient nephrology clinic at the start of the main study, to ensure that the questions and method of surveying were appropriate and understandable and whether patient identification and follow-up were practical. The interview took approximately 10 minutes to administer with most patients although some took up to 20 minutes. With the exception of having to include more space on the data collection form to record patient medicines, few problems were encountered with the methodology and these 15 patients were included in the main study.

3.2.8 Main study methodology

3.2.8.1 Interview schedule

Patients were recruited and interviewed over 13 weeks between June 17th and September 13th, 2007. The strategy for the patient interviews is detailed below.

1. The investigator checked the patients' schedule of visits with the nurses to find out how many patients were attending.

2. The nurse or investigator invited the selected patient to the interview room.

3. The investigator introduced herself and the project, then explained the focus on individual HM and PM use (if any).

4. The investigator assured the patient that what they said would not affect their medical care treatment plan and that the project was general research into the topic.

5. The investigator then asked for signed informed consent.

6. Once consent was obtained, the investigator started by asking the patient about their herb use and whether they were currently taking any. Also whether they had used HMs before becoming ill, how often and what for. Patients were also asked the same questions about any PMs they were taking.

7. The investigator then asked if the patient had ever experienced any discomfort or adverse drug event during their use of HMs or PMs. If taking HMs, the patient was asked if they had told their doctor that they were taking them.

8. After the investigator had finished the interview, she thanked the patient for their time, and in her capacity as a pharmacist explained the importance of checking with their doctor and pharmacist before taking any non-prescribed medicines or herbal supplements.

9. All data was recorded on the data collection form shown in Appendix 3.1.

10. Patients were also asked for any herbal samples, e.g. empty bottles or packs, to record the preparation and ingredients from the label. This was important for data validation and assessment of ingredients and their quality.

11. As this was a longitudinal study, the investigator cross-checked the identity of each interviewee between the outpatient and dialysis unit patient lists to ensure that no patient was interviewed twice.

3.2.8.2 Medical Review

After the interview stage a review of the patient's medical records, drug charts and laboratory data was conducted. All were traced using the patient's unique hospital record number. Medical review with the patient's attending doctor was conducted for every tenth record to validate the methodology.

The following procedure was used by the investigator when reviewing medical records.

1. The author gave the list of SKMC file numbers for review to the officer of the Medical Records Department.

2. The patient survey list, medical file numbers, patient name and signed consent form were cross-checked for consistency.

3. Details collected during the patient interview were validated and supplemented with that in the medical record including, where applicable, the patient's diagnosis(es), PMs and HMs taken (if recorded).

4. Results of laboratory tests were also recorded.

5. All available information sources were cross-checked, including physicians' notes, and drug charts from nephrologists / other physicians, regardless of specialty.

6. Details of possible ADRs were noted.

7. The author signed and dated the survey cover sheet and made a record of the numbers of all SKMC files reviewed.

3.2.8.3 Data Entry and Analysis

All data were coded as a series of variables matching the fields of the data collection form and manipulated and analysed using SPSS version 16. All data were validated by the author after entry and before analysis.

Appropriate statistical analyses were conducted after advice from the author's local supervisor, Prof. Mohamed Bani Yas, Vice Dean of the Faculty of Medicine and Health Science (FMHS) at UAE University. The data were also discussed with Prof. Nico Nagelkerke, Professor of Statistics, also of FHMS. Various analyses were conducted using a variety of statistical tests, depending on the level and distribution of the data. Tests used are detailed in appropriate sections of the results.

The strength of ADR causality was assessed by the Naranjo algorithm.[138]

3.2.9 Quality Assessment of the Outputs

Where a potential ADR to a HM was identified, corroboration was sought using systematic literature searches of standard world medical literature, including Medline, PubMed, and the WHO-EMRO database. Experts in the field were contacted from the UAE Ministry of Health, SKMC, and the Faculty of Medicine and Health Sciences (FMHS), UAE University.

3.3 Results

Five hundred and eight patients were interviewed in the outpatient clinic and 180 in the dialysis unit were included in the study (n=688). An additional 42 patients were excluded (15 outpatients and 27 on dialysis) because they could not understand either English or Arabic, were very sick, unconscious, had mental illness or were extremely confused. An additional 13 patients declined to participate in the study (10 outpatients and 3 on dialysis).

3.3.1 Demographics of Participants

The demographic profile of participants is shown in Table 3.2. Subjects were grouped into male (58.9%, n=405/ 688) and female (41.1%, n=283/688). All age groups over 12 years old were represented with fewer by proportion, less than thirty or greater than 70 years old. Over half of patients were UAE nationals.

The demographic profile of participants who said they were currently using herbs was similar to that of those who were not in terms of gender (Chi^2=3.646, p=0.056) and age distribution (Chi^2=4.057, p=0.669). However, there was a significant difference in terms of Nationality (Chi^2=18.9, p<0.001) where there were more Nationals in the herb-using sample.

Parameter	**Total Sample (n and % values) (n=688)**	**Current herb users (n and % values) (n=468)**
Gender		
Male	405 (58.9%)	264 (56.4%)
Female	283 (41.1%)	204 (43.6%)
Age Distribution (years)		
Less than 18	24 (3.5%)	18 (3.8%)
19-29	69 (10%)	45 (9.6%)
30-39	113 (16.4%)	80 (17.1%)
40-49	118 (17.2%)	75 (16%)
50-59	195 (28.4%)	140 (30%)
60-69	108 (15.7%)	71(15.2%)
Above 70	60 (8.7%)	39 (8.3%)
No reply	1 (0.1%)	
Nationalities		
UAE Nationals	402 (58.6%)	291 (62.2%)
Arab Nationalities	182 (26.5%)	126 (26.9%)
Asian Nationalities	95 (13.8%)	44 (9.4%)
Western Nationalities	7 (1.0%)	7 (1.5%)
No reply	2 (0.3%)	

Table 3.2 Demographics of patients in the study.

3.3.2 HM - taking Practices of Participants

The HM taking practices of patients are shown in Table 3.3.

The sample could be divided into those who had taken herbs at some time (80.7%, n=555/688) and non-herb users (19.3%, n=133/688).

Four hundred and sixty-eight patients (68.1%, n=468/687) said they were currently taking herbal medicines; 499 from the total sample (72.6%, n=499/687) said they had used herbs before they became ill, while 439 patients currently taking herbs (93.8%, n=439/468) said they used them before they got sick.

Three hundred and sixty-five (65.8%, n=365/555) patients exposed to herbs at any time had used HMs while taking prescription medicines, while 329 patients (70.3%, n=329/468) were currently using HMs while taking prescription medicines.

Question	Total sample (n and % values) (n=688)	Current herb users (n and % values) (n=468)
Patient taking herbal medicines, either now or in the past.		
Yes	555(80.7%)	468 (100%)
No	133 (19.3%)	
Is the patient currently using herbs?		
Yes	468 (68.1%)	468 (100%)
No	204 (29.7%)	
No answer	16 (2.3%)	
Did patients use herbs before they became ill?		
Yes	499 (72.6%)	439 (93.8%)
No	171 (24.9%)	24 (5.1%)
No answer	18 (2.6%)	5 (1.1%)
Patients using herbal medicines whilst taking prescription medicines		
Yes	365 (53.1%)	329 (70.3%)
No	99 (14.4%)	66 (14.1%)
Patients don't take HM	133 (19.3%)	0 (0%)
No answer	91 (13.2%)	73 (15.6%)

Table 3.3 Herb taking practices of participants.

Over two thirds of patients who were either taking or had used HMs in the past (69%, n=383/555) said that they did not inform their doctor or pharmacist that they were using herbal medicines, while 66 patients (11.9%, n=66/555) claimed they did. Of those patients currently taking herbs, 327 (69.9%, n=327/468) said they had not informed their doctor or pharmacist while 57 patients (12.2%, n=57/468) claimed they did.

Of the total sample, 16.6% (n=114/688) said they had visited a herbal centre recently, while in the patients currently taking herbs, this rose to 20.3% (n=95/468). Also, in the total sample, 17% (n=117/688) said they had taken HMs with OTC medicines; which was mirrored In the cohort currently taking HMs (17.7%; n=83/468).

Of the total sample, 62.6% (n=431/688) said they were currently visiting hospitals other than SKMC, while 64.1% (n=300/468) of those currently taking HMs did the same. In addition, 27.1% of the total sample (n=187/688) said they were visiting clinics other than the nephrology clinic, within SKMC and receiving medicines from them. In comparison, 29.7% (n=139/468) of those currently taking HMs were visiting other clinics within SKMC.

3.3.3 Diseases suffered by study participants.

3.3.3.1 Most common diseases other than renal.

Table 3.4 summarises the most common conditions suffered by the total sample of patients (n=688) and in those currently taking herbs (n=468).

Most common diseases	In total sample (n=688)*	In sample currently taking herbs (n=468)*
Hypertension	341 (49.6%)	283 (60.5%)
Diabetes	217 (31.5%)	179 (38.2%)
Dyslipidemia	105 (15.3%)	93 (19.9%)
Anaemia	47 (6.8%)	41 (8.8 %)

Table 3.4 Most common diseases other than renal, suffered by patients in the study.

*Totals add up to greater than n because some patients had more than one disease.

3.3.3.2 Most common renal diseases suffered

The specific renal diseases suffered by patients who were currently taking herbs (n=468) is shown in Table 3.5.

Renal condition	Current herb users (n=468)
Renal transplant	121 (25.9%)
Receiving dialysis	102 (21.8%)
Other nephrological diagnoses	245 (52.4%)*
Chronic kidney disease	81 (17.3%)
End stage renal disease	71 (15.2%)
Proteinuria	64 (28.2%)
Nephropathy	37 (7.9%)
Renal Failure	18 (3.8%)
Microalbuminuria	17 (2.6%)
Haematuria	12 (5.2%)
Renal Impairment	8 (1.7%)
Renal Stones	8 (1.7%)
Urinary tract infection	6 (1.3%)
Nephrotic syndrome	5 (1.1%)
Polycystic kidney disease	3 (0.6%)
Systemic lupus erythematosus	3 (0.6%)

Table 3.5 Renal diseases suffered by patients currently taking herbal medicines.

*Other nephrological diseases total more than 245 because some patients had more than one condition.

Patients suffered from a range of diseases (Table 3.4) in addition to their kidney-related diagnoses (Table 3.5). Some patients had multiple co-morbidities. The distribution of major morbidities did not change appreciably between those not currently taking herbs and those currently taking them (Chi^2=2.616; p=0.455). No association between the diseases listed and

HM use is implied from this data, but it serves to illustrate that a wide range of herbs were being used in a wide range of conditions. Suspected ADRs to HMs are discussed in Section 3.3.6.

3.3.4 Medicine taking characteristics of study patients.

3.3.4.1 Herbal medicines taken

More than 100 different herbal preparations were mentioned by the study patients. A list of the most commonly cited by five or more subjects is shown in Table 3.6 for the 468 who were currently taking herbs and the 555 who were taking or who had taken HMs – referred to as the all-time herb user group.

The first 16 herbs ranked the same between the two groups; there were minor differences in ranking thereafter. Some respondents said they were taking a 'mixture of herbs' and some patients were taking two 'mixtures of herbs' (52 in the all-time user groups and 4 in the current user group, making total numbers of herbal mixtures of 219 and 147 respectively). Fifty-nine of 167 (35.3%) subjects from the all-time herb group and 50 of 143 (35%) subjects currently taking herbs could not identify any of the ingredients of these mixtures by name. The identifications that were possible are shown in Table 3.7. This shows the wide variety of herbs taken in mixture form and in over one third of cases, the subject's lack of knowledge about their exact content.

Table 3.8 shows the varying numbers of herbal preparations taken by subjects. The mode was three preparations, but there was a wide range with 224 (47.9%) of those who said they were currently taking herbs, taking four or more preparations.

When validating reported herb use against the patient medical records, just two patients had anything about herbs written by their doctors. Only one recorded the patient taking an OTC medication. There were no records of patients having visited a herbal centre or experienced any discomfort or reaction to a herbal preparation.

Herb	Common herbs for all-time herb users (n = 555)*	Herb	Common herbs for current herb users (n = 468)*
Ginger	270 (48.6%)	Ginger	238 (50.9%)
Thyme	207 (37.3%)	Thyme	179 (38.2%)
Peppermint	198 (35.7%)	Peppermint	177 (37.8%)
Mixture of herbs	167 (30.1%)	Mixture of herbs	143 (30.6%)
Fenugreek	161 (29.0%)	Fenugreek	143 (30.6%)
Black seeds	136 (24.5%)	Black seeds	118 (25.2%)
Senna	113 (20.4%)	Senna	90 (19.2%)
Cardamom	72 (13.0%)	Cardamom	67(14.3%)
Anise	56 (10.1%)	Anise	52 (11.1%)
Sage	56 (10.1%)	Sage	49 (10.5%)
Chamomile	52 (9.4%)	Chamomile	47 (10.0%)
Karkadeeh (Hibiscus)	50 (9.0%)	Karkadeeh	45 (9.6%)
Herbal tea	46 (8.3%)	Herbal tea	36 (7.7%)
Cinnamon	31 (5.6%)	Cinnamon	26 (5.6%)
Teucrium	26 (4.7%)	Teucrium	19 (4.1%)
Asafetida	18 (3.2%)	Asafetida	16 (3.4%)
Red seeds	18 (3.2%)	Parsley	15 (3.2%)
Aloe	16 (2.9%)	Red seeds	14 (3.0%)
Cumin	16 (2.9%)	Cumin	13 (2.8%)
Parsley	16 (2.9%)	Aloe	10 (2.1%)
Myrrh	12 (2.2%)	Myrrh	10 (2.1%)
Arabic gum	10 (1.8%)	Saffron	10 (2.1%)
Saffron	10 (1.8%)	Arabic gum	8 (1.7%)
Ayurvedic	8 (1.4%)	Curcumin	6 (1.3%)
Herbal medicine	7 (1.3%)	Fennel	6 (1.3%)
Fennel	6 (1.1%)	Garlic	5 (1.1%)
Curcumin	5 (0.9%)		
Curry	5 (0.9%)		
Garlic	5 (0.9%)		
Moringa paregrina	5 (0.9%)		
Red pepper	5 (0.9%)		

Table 3.6 Herbs taken by five or more patients in the study.

*Total citations are greater than the number of patients because many patients were taking several HMs.

Patient identification of main ingredients in 'mixtures of herbs' taken.	All-time herb users (n = 555) From 219 total mixtures	Current herb users (n = 468) From 143 total mixtures
Unidentified	59 (26.9%)	53 (37.1%)
Mixture of herbs containing black seed	26 (11.9%)	19 (13.3%)
Mixture of herbs containing fenugreek	26 (11.9%)	21 (14.7%)
Mixture of herbs containing ginger	18 (8.2%)	11 (7.7%)
Mixture of herbs containing honey	14 (6.4%)	11 (7.7%)
Mixture of herbs containing peppermint	14 (6.4%)	7 (4.9%)
Mixture of herbs containing thyme	12 (5.5%)	8 (5.6%)
Mixture of herbs containing senna	12 (5.5%)	10 (7.0%)
Mixture of herbs containing anise	7 (3.2%)	3 (2.1%)

Table 3.7 Patient identification of main ingredients in 'mixtures of herbs' taken.

Number of herbal medicines taken by an individual	All-time herb users (n = 555)	Current herb users (n= 468)
1 herb	79 (14.2%)	60 (12.8%)
2 herbs	95 (17.1%)	80 (17.1%)
3 herbs	113 (20.4%)	99 (21.2%)
4 herbs	93 (16.8%)	76 (16.2%)
5 herbs	74 (13.3%)	67 (14.3%)
6 herbs	58 (10.5%)	52 (11.1%)
7 herbs	14 (2.5%)	13 (2.8%)
8 herbs	15 (2.7%)	12 (2.6%)
9 herbs	2 (0.4%)	2 (0.4%)
10 herbs	0 (0%)	0 (0%)
11 herbs	1 (0.2%)	1 (0.2%)
12 herbs	1 (0.2%)	1(0.2%)
Not determined	10 (1.8%)	5 (1.0%)

Table 3.8 Numbers of herbal medicines taken by individual patients.

3.3.4.2 Prescription medicines taken.

Patients were taking a wide range of PMs; the numbers of PMs taken by individual patients is summarised in Table 3.9. The mode was seven medicines, but there was a wide range, with 153 (32.7%) patients currently taking herbs, taking more than seven PMs.

Approximately half (52.5%, n=246/468) the current HM users could not remember the names of any of the PMs they were taking, but approximately one third (35%, n=164/468) could remember all their PM names. Thirty-nine (8.3%) could remember some of the names of their PMs. In contrast, almost all of the patients currently taking herbs could recall all the names of their individual HMs (95.1%, n=445/468) with the remainder (4.9%, n=23/468) having partial recall.

Number of prescription medicines taken by an individual	**All-time herb users (n = 555)**	**Current herb users (n= 468)**
1 PM	34(6.1%)	28 (6.0%)
2 PMs	49(8.8%)	45(9.6%)
3 PMs	35(6.3%)	27(5.9%)
4 PMs	35(6.3%)	31(6.6%)
5 PMs	48(8.6%)	45(9.5%)
6 PMs	49(8.8%)	46(9.8%)
7 PMs	61(11.0%)	51(10.9%)
8 PMs	47(8.5%)	42(9.0%)
9 PMs	45(8.1%)	36(7.7%)
10 PMs	35(6.3%)	30(6.4%)
11 PMs	28(5.0%)	26(5.6%)
12 PMs	10(1.8%)	7(1.5%)
13 PMs	8(1.4%)	7(1.5%)
14 PMs	7(1.3%)	5(1.1%)
Not determined	64 (11.5%)	42 (7.6%)

Table 3.9 Numbers of prescription medicines taken by individual patients.

3.3.5 Biochemical measurements in patients taking HMs.

It was of interest to characterise the biochemistry of patients currently taking HMs in the sample. This is shown in Table 3.10, where patients are classified as having high, low or normal levels of the parameter in question. Normal ranges are quoted from the SKMC biochemistry laboratory manual, current at the time of the investigation.

As expected for these patients, many showed signs of their kidney disease in terms of raised serum creatinine, urea, bilirubin and uric acid levels. Further evidence of kidney function deterioration was implied by reduced serum albumin and haemoglobin and decreased creatinine clearance. Markers for related diseases such as dislipidaemia (high cholesterol) and diabetes (raised fasting blood glucose) were also apparent.

When comparing the glomerular filtration rates of patients, classified according to renal impairment stage, based on the National Kidney Foundation criteria,[147] some interesting differences between those taking herbs and those not taking herbs were observed (see Table 3.11).

Laboratory parameter	**Current herb users (n and % values) n=468**	**All-time herb users (n and % values) n=555**
Serum creatinine	**(n=429)***	**(n=512)**
Low	14 (3.3%)	17(3.3%)
Normal (53-106 µmol/l)	121 (28.2%)	136 (26.6%)
High	294 (68.5%)	359 (70.1%)
Creatinine clearance	**(n=54)**	**(n=62)**
Low	32 (59.2%)	37 (59.7%)
Normal (85-125 ml/min)	11 (20.4%)	14 (22.6%)
High	11 (20.4%)	11 (17.7%)
Blood urea	**(n=431)**	**(n=512)**
Low	11 (2.5%)	11 (2.1%)
Normal (2.5-6.5 mmol/l)	152 (35.3%)	172 (33.6%)
High	268 (62.2%)	329 (64.3%)
Serum albumin	**(n=356)**	**(n=427)**
Low	161 (45.2%)	205 (48%)
Normal (35-50 g/l)	195 (54.8%)	222 (52%)
High	0 (0%)	0 (0%)

Serum bilirubin	**(n=308)**	**(n=376)**
Low	0 (0%)	0 (0%)
Normal (5-21 µmol/l)	287 (93.2%)	352 (93.6%)
High	21 (6.8%)	24 (6.4%)
Haemoglobin	**(n=415)**	**(n=492)**
Low	151(36.4%)	190 (38.6%)
Normal (115-155 g/l)	244(58.8%)	281 (57.1%)
High	20(4.8%)	21 (4.3%)
Cholesterol	**(n=311)**	**(n=363)**
Low	33 (10.6%)	42 (11.6%)
Normal (3- 5.2 mmol/l)	211 (67.8%)	249 (68.6%)
High	67 (21.5%)	72 (19.8%)
Glucose (fasting)	**(n=364)**	**(n=421)**
Low	7 (1.9%)	7 (1.3%)
Normal (3.9-6 nmol/l)	192 (52.7%)	358 (85%)
High	165 (45.4%)	60 (14.3%)
Uric Acid	**(n=227)**	**(n=257)**
Low	6 (2.6%)	7 (2.7%)
Normal (200- 415 mmol/l)	142 (62.6%)	159 (61.9%)
High	79 (34.8%)	91 (35.4%)
ALP	**(n=320)**	**(n=390)**
Low	6 (1.9%)	7 (1.8%)
Normal (35-120 IU/l)	265 (82.8%)	318 (81.5%)
High	49 (15.3%)	65 (16.7%)
AST	**(n=316)**	**(n=384)**
Low	38 (12%)	49 (12.8%)
Normal (13-35 IU/l)	248 (78.5%)	300 (78.1%)
High	30 (9.5%)	35 (9.1%)
ALT	**(n=319)**	**(n=387)**
Low	5 (1.6%)	6 (1.5%)
Normal (7-35 IU/l)	270 (84.6%)	327 (84.5%)
High	44 (13.8%)	54 (14%)

Table 3.10 Biochemical values for patients currently taking HMs.

* n= number of patients where data was available in their medical records; percentages are derived from these values. Values are point prevalence values taken from the patients' notes.

ALP = alkaline phosphatase; AST = aspartate aminotransferase; ALT = alanine aminotransferase

GFR stage *	Current herb takers (n=468)	All-time HM takers (n=555)	Non- herb taking group (n= 133)
Stage 1 (GFR = ≥90 ml/min)	68 (14.5%)	74 (13.3%)	11 (8.2%)
Stage 2 (GFR = 60-89)	80 (17.1%)	90 (16.2%)	23 (17.3%)
Stage 3 (GFR = 30-59)	101(21.6%)	116 (20.9%)	26 (19.5%)
Stage 4 (GFR = 15-29)	41(8.8%)	49 (8.8%)	13 (9.8%)
Stage 5 (GFR = Less than 15)	127(27.1%)	172 (31.0%)	51 (38.3%)
Data not available	51 (10.9%)	49 (8.8%)	9 (6.8%)

Table 3.11 Comparison of GFR stages between current herb, all-time herb and non-herb taking patients.

*GFR calculated using the Modification of Diet in Renal Disease (MDRD) Study equation.[147]

The distribution of patients between the various glomerular filtration rate (GFR) stages was not statistically significantly different when comparing current herb users with non-herb users (chi^2=7.42, df=4, p=0.115) or comparing all-time users with non-herb users (chi^2=4.108, df=4, p=0.392).

It was possible to calculate the mean GFR for patients at each renal disease stage. There was no statistically significant difference between the distribution of means for all-time herb users and non-herb users (p=0.12, Mann-Whitney, see Table 3.12); however, when current herb users were compared with non-herb users, a statistically significant difference emerged in favour of herb users (p=0.02, Mann-Whitney, see Table 3.13).

GFR stage	All-time herb user	N	Mean	Std. Deviation	Std. Error Mean
GFR stage 1	Yes	74	125.5	113.2	13.2
	No	11	111.9	11.4	3.4
GFR stage 2	Yes	90	72.4	8.4	0.9
	No	23	70.6	8.1	1.7
GFR stage 3	Yes	116	45.1	9.2	0.9
	No	26	44.7	8.6	1.7
GFR stage 4	Yes	49	21.1	5.0	0.7
	No	13	23.0	4.1	1.1
GFR stage 5	Yes	172	6.6	3.0	0.2
	No	51	6.9	3.2	0.4

Table 3.12 Comparison of GFR means (ml/min) within stages between all-time herb and non-herb users.

No significant difference; p=0.12, Mann-Whitney

GFR stage	Current herb user	N	Mean	Std. Deviation	Std. Error Mean
GFR stage 1	Yes	68	109.4	17.9	2.2
	No	11	111.9	11.4	3.4
GFR stage 2	Yes	80	72.2	8.4	0.9
	No	23	70.7	8.2	1.7
GFR stage 3	Yes	101	45.2	9.1	0.9
	No	26	44.7	8.6	1.7
GFR stage 4	Yes	41	21.0	4.8	0.7
	No	13	23.0	4.1	1.1
GFR stage 5	Yes	127	6.8	3.1	0.3
	No	51	6.9	3.2	0.5

Table 3.13 Comparison of GFR means (ml/min) within stages between current and non-herb users. (Significant difference; p=0.02, Mann-Whitney)

The apparent improved kidney function in those patients currently taking herbs compared with those who had not was supported by the differences found in other measures of kidney function. These are displayed in Table 3.14 and the results of the independent t-tests are shown in Table 3.15.

Biochemical parameter		N*	Mean	Std. Deviation	Std. Error Mean
Creatinine (µmol/l)	Yes	429	338.1	364.1	17.6
	No	129	416.4	396.9	35.0
Creatinine Clearance (ml/min)	Yes	54	79.2	53.1	7.2
	No	23	52.8	50.4	10.5
Tests of Urine Collection for 24 hr (L)	Yes	14	1.9	0.7	0.2
	No	5	1.1	0.4	0.2
Cholesterol (mmol/L)	Yes	311	4.5	1.4	0.1
	No	93	4.0	1.1	0.1
GFR (ml/min)	Yes	419	46.6	37.5	1.8
	No	124	37.7	34.1	3.1

Table 3.14 Comparison of mean values for selected biochemical measurements for current herb users and non-herb users.

Yes=patients currently using herbs (n=468); No=patients not using herbs (n=133).

*N = number of patients for which biochemical data could be retrieved.

Lab Test	t-test for equality of means						
	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
						Lower	Upper
Creatinine (µmol/l)	-2.00	197.2	0.05*	-78.3	39.1	-155.5	-1.2
Creatinine Clearance (ml/min)	2.07	43.7	0.05	26.4	12.8	0.7	52.1
Tests of urine Collection for 24 hr (L)	3.2	13.4	0.02	0.8	0.3	0.3	1.4
Cholesterol (mmol/L)	3.1	195.7	0.01	0.4	0.1	0.2	0.7
GFR (ml/min)	2.5	218.6	0.02	9.0	3.6	1.9	16.0

Table 3.15 Results of independent samples t-tests of means for biochemical measurements for current and non-herb using groups, reflecting some differences in renal function.

*Non-equal variances were assumed in this analysis due to a significant p value (0.02) for Levene's test.

These analyses indicate that in the herb taking group, the mean serum creatinine was lower (borderline significance), but 24-hour urine collection and GFR were higher. The differences in serum creatinine and creatinine clearance was borderline significant. The only other statistically significant difference in means was serum cholesterol, which was higher in herb-taking patients than in non-herb taking patients. The herb-taking group would appear to have healthier renal function than non-herb users; however the reasons for this are obscure. It may be that these patients have healthier function by chance and that herbs play no part in this. It was not possible to associate any one herb (or herbal mixture) as being responsible due to wide variation in nature and numbers of herbs taken by the study sample.

3.3.5.1 Other biochemical findings of interest - correlations.

Significant findings from cross-tabulation of biochemical variables and common herbs used by current-herb users using Pearson correlation gave the significant correlations shown in Table 3.16. No corroborating evidence for any of these associations could be found in the literature.

Biochemical parameter	Herb	df	Pearson Chi-Square value
Potassium	Thyme	40	0.035
	Anise	40	0.041
Serum albumin	Herbal Tea	38	0.011
Bilirubin	Chamomile	28	0.001
Haemoglobin	Thyme	92	0.045
	Herbal Tea	92	0.043
Cholesterol	Karkadeeh	58	0.028
AST	Peppermint	50	0.049
	Karkadeeh	50	0.025

Table 3.16 Significant correlations between herb use and biochemical variables (total n=468).

AST = aspartate aminotransferase

Common herbs and results of laboratory tests were analysed using the bivariate correlation method against the followings variables in SPSS:

- demographic variables : gender , age , age group;
- herbs: ginger, thyme, peppermint, mixture of herbs, fenugreek, black seeds, senna, cardamom, anise, sage, chamomile, karkadeeh, herbal tea;
- renal disease classes and most common disease: transplant, dialysis, anaemia, hyperlipidemia, dyslipidemia + hyperlipidemia, dyslipidemia, diabetes, hypertension, end stage renal disease, chronic kidney disease, proteinuria;
- most common medicines taken by patients: amlodipine, omeprazole, calcium, atorvastatin, prednisolone, acetylsalicylic acid, folic acid, vitamins, ciclosporin, atenolol, insulin, mycophenolate, iron, paracetamol, vitamin D, losartan, lisinopril, furosemide, irbesartan, gliclazide, candesartan;
- renal function lab tests: creatinine, creatinine clearance, 24-hour urine collection, urea, sodium, calcium, magnesium, potassium, phosphate, uric acid, albumin, micro albumin, bilirubin, total protein, haemoglobin, cholesterol, glucose, ALP, AST, ALT, GFR, GFR stage;

Significant correlations are shown in Table 3.17.

Biochemical parameter	Herb	Pearson correlation coefficient	Sig. (2-tailed)
Serum creatinine (n=429)	Thyme n=159[+]	-0.1182	0.0143
	Mixture of herbs n=103	-0.0980	0.0424
Calcium (n=354)	Anise n=39	+0.1513	0.0043
	Chamomile n=34	+0.1633	0.0021
Potassium (n=423)	Mixture of herbs n=101	+0.0971	0.0046
Uric acid (n=227)	Mixture of herbs n=59	-0.1436	0.0306
Microalbumin (n=75)	Ginger n=49	-0.2875	0.0124
	Sage n=8	+0.2453	0.0339
	Herbal tea n=4	+0.4020	0.0004
	Karkadeeh n=8	+0.2643	0.0219
Haemoglobin (n=415)	Thyme n=155	-0.0988	0.0443

Albumin (n=356)	Karkadeeh n=39	+0.1038	0.0346
	Senna n=72	+0.1137	0.0361
	Sage n=34	-0.1310	0.0157
Bilirubin (n=308)	Black seeds n=78	-0.1211	0.0336
ALT (n=319)	Karkadeeh n=28	+0.1444	0.0098
	Ginger n=217	+0.1078	0.0273
GFR (n=419)	Sage n=46	+0.1678	0.0006
	Chamomile n=38	+0.1283	0.0085
GFR stage* (n=419)	Sage n=46	-0.1516	0.0019
	Chamomile n=38	-0.1048	0.0320

Table 3.17 Significant correlations between individual herbs and biochemical variables for patients currently taking herbs, using bivariate correlation.

- = a negative correlation exists; + = a positive correlation exists.

* a negative correlation here actually signifies a negative correlation with increasing stages of renal impairment.

* n = the numbers of patients taking a particular herb for which data on the relevant biochemical variable was available.

The data in Table 3.17 tell us that while these correlations are statistically significant, the strength of the correlation, as indicated by the Pearson correlation coefficient is weak, never exceeding 0.402 (for herbal tea and microalbumin). Such weak associations are probably a function of the diversity of herbs and numbers of preparations taken by this cohort. Relationships are discussed further in Section 3.4.

3.3.6 Adverse reactions to herbal medicines.

ADRs were reported by 42 patients in the group currently using herbs (9.0%, n=42/468); this figure rose to 49 patients (8.8%, n=49/555) when all those who had taken or were taking HMs were considered. Just three patients from the current HM user group (7.1%, n=3/42) said that they had mentioned the reaction to their carers; five from the total HM user group (10.2%, n=5/49) said they had informed their carers.

On deeper investigation, 23 of the 49 patients were deemed by the expert panel to be unassessable or have a highly doubtful relationship to any medicine the patient was taking, due to lack of sufficient data on which to base a judgement. Key data for the remaining 26 patients (all taking herbs, with a total of 28 ADRs) appear in Table 3.18. Case details are shown in Appendix 3.2. All subjects were presenting for routine outpatient appointments at the Nephrology Clinic.

Parameter	Basic Description (n, %)
Gender	**(n=26)**
Females	12 (46.2%)
Males	14 (53.8%)
Age	**(n=26)**
Less than 18 years	1 (3.8%)
19-29 years	1 (3.8%)
30-39 years	3 (11.5%)
40-49 years	6 (23.1%)
50-59 years	10 (38.5%)
60-69 years	4 (15.4%)
70 years and above	1 (3.8%)
Type of Products involved in ADR	**(n= 28*)**
Herbs alone	7 cases (25.0%)
Herbs / PM combination	21 cases (75.0%)

Table 3.18 Key findings of herbal ADRs reported in the study.

PM= prescription medicine

*Two patients presented with two suspected ADRs each.

3.3.6.1 Assessment of herbal ADR causality

The scores allocated to each case using the author's modified Naranjo algorithm are shown in Table 3.19. Each case was also rated using the original Naranjo algorithm.[138]

A comparison of the conclusions of the two methods is summarised in Table 3.20; see Appendix 3.2 for case details.

Case number	Are there previous conclusive reports on the reaction? (yes =+1; no=0; do not know or not recorded=0)	Did the adverse reaction appear after the suspected drug was given? (yes =+2; no=-1; do not know or not recorded=0)	Are there alternative causes for the reaction? (yes =-1; no=+2; do not know or not recorded=0)	Total score (relationship)
2	1	2	-1	2 (possible)
6	1	2	-1	2 (possible)
8	1	2	2	5 (definitely)
9	1	2	2	5 (definitely)
10	1	2	2	5 (definitely)
11	1	2	2	5 (definitely)
13	1	2	2	5 (definitely)
14	1	2	2	5 (definitely)
15	1	2	2	5 (definitely)
15a	1	2	2	5 (definitely)
16	1	0	2	3 (probable)
17	1	1	-1	1 (possible)
19	1	2	-1	2 (possible)
21	1	2	-1	2 (possible)
22	0	0	2	2 (possible)
23	1	2	2	5 (definitely)

24	1	2	-1	2 (possible)
24a	1	2	-1	2 (possible)
25	1	2	2	5 (definitely)
26	0	2	2	4 (probable)
27	0	2	-1	1 (possible)
31	0	2	-1	1 (possible)
34	1	0	2	3 (probable)
35	1	2	-1	2 (possible)
36	1	2	2	5 (definitely)
37	1	2	2	5 (definitely)
40	1	2	2	5 (definitely)
48	1	1	0	2 (possible)

Table 3.19 Results of applying the author's modified causality algorithm to the ADR reports gathered in the study (n=28).

* Case numbers represent the case number used in the original sample of 49 suspected ADRs and are used here to facilitate cross-reference to the original research records. Two cases (15 and 24) showed two ADRs each.

Strength of association	Original Naranjo Scale (n=28)	Modified Naranjo Scale (n=28)
Definite	0 (0%)	13 (46.4%)
Probable	12 (42.9%)	3 (10.7%)
Possible	16 (57.1%)	12 (42.9%)

Table 3.20 Summary of strength of causality assessments for the 28 ADR cases, applying the original Naranjo scale[138] and the author's modified scale.

There was almost 100% agreement (with one exception, Case 37, see Appendix 3.2) between the outcome of applying the Naranjo algorithm and the panel consensus; whereas the author's modified Naranjo method overestimated the strength of association compared to the panel consensus in some cases (n=16). Therefore, the original Naranjo algorithm was taken as giving a more robust assessment of the true causality. There were no definite associations. This aspect is discussed further in the discussion section.

The agents involved and the strength of the association are summarised in Table 3.21. Herbal medicines alone were possibly or probably implicated in 7 cases (25%); or in combination with prescribed medicines in the form of a drug interaction in another 21 (75%).

Suspected agent (s)	Association (after consensus and using original Naranjo algorithm)		
	Possible	**Probable**	**Total**
Herb	3	4	7
Herb / prescription medicine	12	9	21
Total	15	13	28

Table 3.21 Strength of association within agent groups after panel consensus and using the original Naranjo algorithm.[138]

3.3.6.2 Specific herbal ADR associations

Reported ADRs ranged in type and severity. The original case study reports are shown in Appendix 3.2. A summary is provided in Table 3.22. The reader will note that in over half the cases (17), it was not possible to say exactly which herb, from the range taken by the patient, contributed to the ADR. Results of a supplementary literature search after study completion are shown in Appendix 3.3. This revealed no striking associations between herb use and ADRs based on the published toxicities of these products.

Agent	Nature of ADR (main herb involved)	Case number*
Herb (n=7)	Malaise (ginger)	34
	Severe asthma (multiple)	35
	Colon inflammation (sage)	40
	Diarrhoea (senna)	2
	Stomach acidity and blood in the stools (multiple)	8
	Itch (fenugreek)	10
	Abortion (multiple)	23
Herb / prescription medicine interaction (n=21)	Renal failure (all multiple)	22,26,31
	Finger numbness (cardamom)	27
	Weakness (multiple)	36
	Tiredness (senna,senna)	14,24a
	Stomach pain (both multiple)	37,48
	Abdominal pain (multiple, multiple, multiple)	6,16,24b
	Low blood pressure (multiple)	9
	Raised blood pressure (multiple)	17
	Dizziness (multiple)	13
	Stomach acidity (cinnamon, multiple)	11,15b
	Itch (fenugreek)	15a
	Nausea and vomiting (garlic, multiple, senna)	19,21,25

Table 3.22 Nature of the ADRs seen in this study.

Full details can be found in Appendix 3.2.

Cases 15 and 24 exhibited two ADRs each.

Multiple = the actual herb responsible could not be identified from the range taken by the patient.

3.4 Discussion

Herbal medicines contain a myriad of pharmacologically active compounds that, when used by people with kidney disease, may be hazardous and harmful. Little information is available about herbs and dietary supplement use in the kidney disease population.[148] Two examples shown to be of clinical significance in the dialysis population are noni juice, which should be avoided because of its high potassium content, and bulk-forming laxatives such as flaxseed which should be used with caution because of the need for increased fluid intake.

3.4.1 Evidence of harm to the kidney caused by herbal medicines.

There are numerous reports of herbal medicines contributing to the development of renal disease. Chang *et al* [149] studied 1,537 patients receiving chronic haemodialysis and observed a high incidence of chronic tubulo-interstitial nephritis related to the use of Chinese herbs or compound analgesics, which may contribute to transitional cell carcinomas (TCCs). The same team [150] noted a strong relationship between rapidly progressive interstitial renal fibrosis and the consumption of Chinese herbs. TCC is the predominant malignancy in Chinese renal transplant recipients. Female sex, the Chinese herb containing aristolochic acid and immunosuppression are markedly associated with the development of TCC.[151] Aristolochia has been associated with progressive renal fibrosis,[152,153] tubular atrophy and interstitial fibrosis leading to severe renal functional impairment and end-stage renal failure,[152] urothelial carcinomas,[153] and Fanconi's syndrome.[154,155] It is interesting to note that renal failure due to ingestion of Aristolochia was widely reported in China and other countries while no such toxicity was recorded in traditional Chinese herbal texts.[156] This illustrates an important point, relevant to the present research. Use of uncontrolled unlicensed herbal medicines and supplements may not be safe simply because no evidence of toxicity is written down. Absence of evidence is not evidence of absence as far as ADRs are concerned. More thorough study and documentation of suspected ADRs should help to ensure safer use of such traditional medicines. Aristolochia is now banned in most countries and no evidence of use of this herb was found in the present study.

The American National Kidney Foundation has cautioned against the use of HMs and supplements by patients with chronic kidney disease (CKD) and has published a list of hazardous herbs (see Table 3.23).[157] Herbal supplements may be unsafe for CKD patients

simply because clearance is reduced allowing accumulation to toxic levels. Some herbs that have diuretic properties may also cause further damage to an already diseased kidney; these include bucha leaves and juniper berries.[157]

Category 1: Herbs that may be toxic to the kidneys	
Artemisia absinthium (wormwood plant)	Periwinkle
Autumn crocus	Sassafras
Chuifong tuokuwan (Black Pearl)	Tung shueh
Horse chestnut	*Vandelia cordifolia*

Category 2: Herbs that may be harmful in chronic kidney disease				
Alfalfa	Buckthorn	Ginger	Nettle	Vervain
Aloe	Capsicum	Ginseng	Noni juice	
Bayberry	Cascara	Horsetail	Panax	
Blue Cohosh	Coltsfoot	Licorice	Rhubarb	
Broom	Dandelion	Mate	Senna	

Table 3.23 List of herbs cited as being unsafe to use in chronic kidney disease by the American National Kidney Foundation. [157]

Table 3.6 and Appendix 3.2 show that some of the above were being used by patients in the present study, although no Category 1 herbs were being used.

3.4.2 Herbal medicine – prescription medicine interactions.

Herb - prescription medicine interactions may also be clinical important.[66,158,159] Barone *et al* [160] report how two renal transplant recipients started self-medicating with St. John's wort (SJW), resulting in subtherapeutic ciclosporin levels. One patient developed acute graft rejection as a result. Renal patients consuming herbal drugs are at risk from herb-drug interactions by various mechanisms. In transplant recipients, toxicity and underdosage of calcineurin inhibitor-based immunosuppression have been linked to phytochemically triggered activity changes of cytochrome P-450 isoenzyme CYP3A4 metabolism and drug transport proteins. This type of

interaction might be triggered by many other plant products besides SJW, less well-known for this risk, producing significant interactions with antidiabetics, anticoagulants and antihypertensives. [161]

In an extensive review, Fugh-Berman[159] refers to studies that have shown possible interactions between specific herbal medicines (ginkgo, SJW, ginseng, garlic, echinacea, saw palmetto and kava) and prescribed drugs; 41 case reports or case series and 17 clinical trials were identified. The results indicated that SJW lowers blood concentrations of ciclosporin, amitriptyline, digoxin, indinavir, warfarin, phenprocoumon and theophylline; furthermore it causes intermenstrual bleeding, delirium or mild serotonin syndrome, respectively, when used concomitantly with oral contraceptives (ethinylestradiol/desogestrel), loperamide or selective serotonin-reuptake inhibitors (sertaline, paroxetine). Ginkgo interactions include bleeding when combined with warfarin, raised blood pressure when combined with a thiazide diuretic and coma when combined with trazodone. Ginseng lowers blood concentrations of alcohol and warfarin, and induces mania if used concomitantly with phenelzine. Garlic changes pharmacokinetic variables of paracetamol, decreases blood concentrations of warfarin and produces hypoglycaemia when taken with chlorpropamide. Kava increases 'off' periods in Parkinson patients taking levodopa and can cause a semicomatose state when given concomitantly with alprazolam. No interactions were found for echinacea or saw palmetto.

Some herbs, including garlic, ginkgo, ginseng, and SJW, can have a significant influence on concurrently administered drugs. Herbal medicines may mimic, decrease, or increase the action of prescribed drugs. This can be especially important for drugs with narrow therapeutic windows and in sensitive patient populations such as older adults, the chronically ill, including those with renal disease, and those with compromised immune systems.

Three quarters of the ADRs identified in the present research were thought to involve pharmacodynamic interactions with concurrent conventional medicines. For example the gastrointestinal symptoms seen in Case 6, 15, 16,19, 24 and 25 (see Appendix 3.2); a few were thought to have some interplay with the underlying renal disease (e.g. cases 26 and 31).

3.4.3 Non-disclosure of herb use by patients.

There have been calls for dialysis practitioners to include specific questions about herbs and dietary supplement use in medical and nutrition histories, and to increase their knowledge about these products in order to advise patients appropriately.[148] However, this study has revealed that there are significant barriers to them doing the former effectively. Not least of which is the lack of information offered by patients.

Of those currently taking HMs in this study, approximately one fifth said they had visited a herbal centre recently and one fifth said they were taking OTC medicines as well. Almost 70% said they had not informed their doctor or pharmacist that they were taking HMs. A majority said they were also visiting other hospital departments for treatment. These data (see Section 3.3.2) illustrate the complex nature of care received by some of the subjects in this study. It is likely that in addition to obtaining herbal medicines from a herbal centre and OTC medicines from a pharmacy, some subjects would have received additional prescription medicines from other clinics they attended, either at other hospitals or within SKMC. What is clear is that even with obvious opportunities to do so, a minority of patients informed their carers that they were taking HMs.

These observations are supported by the fact that when validating reported herb use against the patient medical records, just two patients had anything about herbs written by their doctors. Only one recorded the patient taking an OTC medication. There were no records of patients having visited a herbal centre or experienced any discomfort or reaction to a herbal preparation.

This could lead to inappropriate prescribing of conventional medicines with the potential to interact adversely. The phenomenon of non-disclosure has been observed previously. Saw *et al* [162] investigated potential drug-herb interactions with antiplatelet / anticoagulant drugs among 250 patients attending medical wards; 106 (42.4%) were taking herbs with 76 of these (71.7%) having used herbs for the previous 12 months. Twenty-three patients were taking one or more of ginseng, garlic, and ginkgo which are thought to interact with antiplatelet or anticoagulant therapy. More than 90% of herb-takers did not disclose the use of herbal medicine to their health professionals.

In the present study, many patients currently taking HMs were taking multiple herbal preparations, often in mixture form. In the case of the latter, over a third of patients could not name the ingredients in the compound herbal mixtures they were taking.

In this sample, it appears that patients were better able to recall the names of their HMs than the names of the PMs they were taking. This may reflect a greater familiarity with HMs compared to PMs; perhaps because patients had been taking them for longer, perhaps because the names were more familiar and in everyday use, or perhaps because patients did not feel the need to remember the names of their PMs, trusting that the prescriber would prescribe what they required without expecting them to remember details for identification.

3.4.4 Herbal medicines and biochemical measurements

Use of herbal and alternative medicines may significantly alter biochemical test results. This may indicate the emergence of a disease caused by the herbal medicine, but may also lead to misinterpretation of biochemical or other results due simply to interference by the herb. Hence communication among pathologists, clinical laboratory scientists, pharmacists and physicians providing care to the patient is important in interpretation. In the context of the present research, interest is focussed on the emergence of abnormal laboratory results owing to altered pathophysiology.

In this study, there appeared to be a slightly raised GFR associated with current herb use compared to no herb use at all, although this was variable within GFR stages. This is an interesting observation, but the picture is complicated; as shown earlier, herb-taking patients were consuming a wide variety and number of preparations; it was not possible to demonstrate that any single preparation was responsible for this difference. These comments also apply to the apparent decreased serum creatinine (but also raised serum cholesterol) observed in current compared to non-herb users and also to the rather weak correlations between use of herbs and some biochemical variables.

One could for example postulate that there is a weak positive correlation between the use of ginger, sage and chamomile and GFR and that these herbs are actually promoting improved kidney function. This is further supported by a negative association between use of sage and chamomile and reducing GFR stage and the observation that in general, herb users had better

renal function than non-herb users; moreover, the most common herb used by current herb users was sage. Nothing could be found in the literature to support this however.

The results of bivariate analysis shown in Table 3.17 revealed several interesting correlations between herbs taken by current herb users and laboratory measurements. It is stressed that while all the correlations were statistically significant, overall, they were weak and in many cases, the numbers of patients taking a particular herb were small. For example:

1. microalbumin level showed a significant negative correlation with ginger and positive correlations with sage, herbal tea and karkadeeh;
2. creatinine level showed significant negative correlations with thyme and mixtures of herbs; and
3. haemoglobin level showed a negative correlation with thyme but a positive correlation with karkadeeh.

Little supporting evidence for any of these observations could be found in the literature. Jadayil *et al* [163] studied the bioavailability of iron from local plants (black cumin seeds, milk thistle seeds, sesame seeds and thyme leaves) when incorporated into the diet of rats serum haemoglobin concentrations increased significantly ($p<0.05$) in the groups fed milk thistle seed and black cumin seed diets, but decreased for the group of rats fed thyme.

In a study [164] conducted to evaluate the effects of *Hibiscus sabdariffa* L. (karkadeeh) calyx extract on some haematological parameters (haemoglobin, haematocrit, total white blood cells and differentials) in rats for 14 days, significant elevations were observed in haematocrit ($p=0.03$) and haemoglobin ($p=0.004$) in the groups of animals given doses of 200 mg and 400 mg per kg; however groups given high doses revealed significant reductions.

3.4.5 Adverse effects to herbs seen in this study.

As indicated earlier, consensus on all possible and probable reactions was reached using the original Naranjo algorithm rather than the author's modified technique. The latter produced several 'definite' associations which, in retrospect would not be reached in practice due to the absence of objective evidence. In some cases, the author was reliant on patient recall with little written evidence to aid the decision; so the original Naranjo algorithm [138] was adopted for further analysis. Even then, it is worth emphasising that in a study like the present one, key data that

would strengthen the association is missing. For example, no re-challenge was conducted, there was no measurement of active herbal principles in plasma and the patients were not studied for long enough to see if stopping the drug led to improvement in the adverse effect.

In 17 of the 28 ADRs noted, it was not possible to identify the actual herb responsible due to the range of HMs being taken by the patient. Twelve of the ADRs produced gastrointestinal effects, most of which were the results of interactions with other medicines the patient was taking (see Appendix 3.2). In many cases, it was not possible to match the effects seen with anything in the published literature (see also Appendix 3.3 where a more detailed literature search was conducted after completion of the study); however some corroborating evidence was found.

Chamomile herbal tea has been used traditionally for medicinal purposes. Chamomile has moderate antioxidant and antimicrobial activities, and significant antiplatelet activity in vitro. Adverse reactions to chamomile, consumed as a beverage or applied topically, have been reported among subjects with allergies to other plants in the daisy family, i.e. Asteraceae or Compositae.[165] This may have been a factor in case 15.

Garlic is traditionally used for cardiovascular health and relief of cough, colds, and rhinitis. Adverse effects commonly include gastrointestinal disturbances, change in body odour through the sweat and breath, and rarely allergic reactions or hypoglycemia.[166] Garlic may well have had a role in the severe nausea and vomiting experienced by the patient described in case 19.

Venderperren *et al* [167] report the case of a 52-year-old woman who had ingested large amounts of senna herbal tea for more than 3 years. The patient developed severe hepatotoxicity and renal impairment requiring intensive care therapy. Renal impairment was consistent with proximal tubular acidosis, presenting with marked polyuria refractory to vasopressin administration. The chronic abuse of senna herbal tea may be associated with serious manifestations, including fluid and electrolyte loss, with chronic diarrhoea. Severe hepatotoxicity is unusual, but could be explained by the exposure of the liver to unusual amounts of toxic metabolites of anthraquinone glycosides (sennosides). An objective causality assessment suggested that hepatotoxicity was possibly related to senna laxative abuse. The finding of high urinary concentrations of cadmium suggested contamination of the herbal tea by metals. While the use of senna was associated with expected side effects such as diarrhoea and abdominal pain (e.g. cases 21 and 24), it was also being taken (along with other herbs) by one patient who

developed renal impairment (case 31). It is noteworthy that senna was the seventh most common herb taken by current herb users in this study, all of whom it should be remembered, were attending a nephrology clinic.

3.4.6 Lack of physicians' knowledge on herbal medicines.

Even assuming patients tell their doctors that they are taking herbal medicines, physicians often lack the knowledge base to effectively counsel patients regarding adverse effects and potential herb-drug interactions.[168,169] To prevent clinically important drug interactions it is important that the patient's carers have a thorough grasp of the pharmacocolgy of all the medicines the patient is taking and to realise the potential for significant interactions. It is recommended that on admission, a healthcare professional reviews all prescription, OTC and herbal medicines, and dietary supplements when taking a medication history.[170]

In addition, patient education about the potential interactions should be a routine component of preoperative assessment. The American Society of Anesthesiologists (ASA) recommends that all herbal medications should be discontinued 2-3 weeks prior to an elective surgical procedure. If the patient is not sure of the contents of the herbal medicine, he/she should be urged to bring the container so that an attempt can be made to review the contents of the preparation.[171] In a similar vein, a study of psychiatrists in Australia and New Zealand who regularly managed patients taking SJW still reported an appreciable number of side-effects and drug interactions involving the herb, leading to the recommendation that psychiatrists should routinely enquire about their patients' use of alternative treatments, be mindful of possible side-effects and in particular be aware of the dangers of combining SJW with other psychotropics. [172]

Improving pharmacovigilance of herbal ADRs might help expand the knowledge base and provide more robust advice on drug / herb combinations to avoid or expand the list of diseases where the herb is judged to be unsafe to use. In a Canadian study, just 19% of a sample of 132 community pharmacists surveyed, said they had previously reported an adverse event to Health Canada, the National pharmacovigilance scheme. When asked specifically about herbal medicine interactions, 47% of pharmacists stated that they had identified a potential interaction; however, only 2 of these reported it. The study showed that while pharmacists encounter reportable herbal-drug interactions, they rarely choose to report them.[173] The problem is by no means field-specific; Smith [174] observes that healthcare providers have little scientific evidence

on which to base recommendations about use of herbal supplements with chemotherapy. Lack of product standardisation and definitive knowledge about herb interaction with chemotherapy may expose patients with cancer to potentially serious side effects.

The findings of a relatively low level of reporting of ADRs to herbal preparations in the present study was compared to other studies. Cuzzolin *et al* [122] interviewed 1,420 consumers about their herbal medicines use. Almost three quarters (71.8%) reported taking conventional medicines along with natural products; 3.9% referred to having experienced adverse effects to herbal remedies in the previous year. Herbal products were largely taken on a self-treatment basis by respondents; 73 different herbal products were used and 32 were consumed in association with traditional drugs. Forty-seven of 491 (9.6%) reported side-effects, 22 after taking only herbal medicines (8.1%) and 25 in combination with conventional drugs (11.4%). The observed adverse manifestations included the following: gastrointestinal after dandelion, propolis or fennel; cardiovascular after liquorice, ginseng, and green tea; dermatological after propolis, thyme, arnica, and passionflower; and neurological after guarana and liquorice. Conventional drugs taken in association and potentially involved in adverse reactions were NSAIDs, antibiotics, benzodiazepines, antihypertensives and oral contraceptives. In some cases (n=5), side-effects were serious enough to justify admission to the hospital. In 29 of the 47 ADRs (61.7%), the adverse reaction was not communicated to the doctor. Bush *et al* [175] reported a study where 804 patients were surveyed, and 122 (15%) used herbal medicines. Eighty-five potential adverse herb-drug interactions were found in 49 patients (40% of herbal medicine users). Twelve possible adverse herb-drug interactions in 8 patients (7% of herbal medicine users) were observed. In all 12 cases, the severity scores were rated as mild, including 8 cases of hypoglycemia in diabetics taking nopal (prickly pear cactus).

As the author's study revealed, nephrologists rarely recorded herbal drugs used by their patient's in the medical records. Other studies have also shown that the use of herbal medicines is seldom documented in medical records and that health professionals often overlook patients' use of them. One small study noted that eight out of 58 patients in Sahlgrenska University Hospital, Sweden used herbal drugs regularly before admission, six of whom used regular prescribed drugs simultaneously; just one patient had this use written in their clinical record.[176] Rivera *et al* [177] discovered that no record of herbal use was documented in a retrospective chart review of hospital inpatients; however, when an additional 60 patients were interviewed prospectively, 42% reported using herbal medicines for the treatment of asthma. Ten patients

reported taking a herbal medicine that could potentially exacerbate their asthma and 18 patients reported using a herbal medicine that could interact with other medications or cause other types of adverse events. The authors recommended that use of herbal medicines should be routinely explored when taking a medication history.

3.4.7 Chapter overview and conclusions

The key findings from this study are listed below:

The percentage of patients studied at the nephrology clinic who reported taking herbal medicines currently was higher (68%) than that found in the general population study described in Chapter 2 (38%).

HM use was widespread in this sample, even in those with multiple pathologies.

Little published information was available to indicate that the most frequently taken herbs (see Table 3.6) were particularly toxic, although several had the potential to cause problems in individual cases (see Appendix 3.3).

Few patients mentioned their use of herbal medicines to either a doctor or pharmacist in this secondary care setting. A large majority (70%) did not.

Very few had the use of HMs documented in their medical records.

A small percentage of patients currently taking herbs mentioned a suspected adverse reaction to HM, either alone or as an interaction with prescription medicine 9.0% (n=42/468). Of these, 28 in 26 patients (5.6%), were deemed by consensus to be possibly or probably related to the HMs taken.

The use of alternative remedies derived from plants and animals is increasing worldwide. Their source and composition varies depending on the prevalent local practices. The majority remain untested for efficacy and safety; often, their ingredients are unknown and the dosage and route of administration are not standardised. Potentially toxic chemicals may be added to them to increase their potency and mistaken identity has led to the use of toxic plants instead of the

originally intended herb. Kidneys play a vital role in the metabolism and excretion of these substances and acute kidney injury is a common and important manifestation of their toxicity. The most usual renal lesions include acute tubular necrosis, cortical necrosis, and interstitial nephritis. Patients often present late to hospitals with multi-organ involvement. The diagnosis may be missed if the history is not sought specifically. These factors culminate in high mortality rates. Comprehensive study of this subject is difficult because of the remoteness of the rural areas, unfamiliarity with local cultures, and mystery and secrecy surrounding the natural medicines used. Physicians need to be aware of these factors to make a timely diagnosis and provide appropriate management. Public awareness and regulation of the use of these medicines are required to eradicate this entity from the community.[178]

Interactions between herbal medicines and synthetic drugs exist and can have serious clinical consequences. Healthcare professionals should ask their patients about the use of herbal products and consider the possibility of herb-drug interactions. Interactions between herbal medicines and prescribed drugs can occur and may lead to serious clinical consequences. There are other theoretical interactions indicated by preclinical data. Both pharmacokinetic and/or pharmacodynamic mechanisms have been considered to play a role in these interactions, although the underlying mechanisms for the altered drug effects and/or concentrations by concomitant herbal medicines are yet to be determined. The clinical importance of herb-drug interactions depends on many factors associated with the particular herb, drug and patient. Herbs should be appropriately labelled to alert consumers to potential interactions when concomitantly used with drugs, and to recommend a consultation with their general practitioners and other medical carers.

Many reports of herb-drug interactions are sketchy and lack laboratory analysis of suspect preparations. Healthcare practitioners should caution patients against mixing herbs and prescribed medicines.

The finding, as in the present study, that a high proportion of subjects did not consult their GP or pharmacist following a herbal ADR is also of concern.[120]

Due to inherent toxicity, some herbal remedies should not be used under any circumstance. In addition, because nearly all herbal remedies contain multiple, biologically active constituents,

interaction with conventional drugs is a concern. It is incumbent upon clinicians to be aware of those herbs that can cause intoxication, and to be cognisant of potential herb-drug interactions.

Laboratory technology can help to evaluate potential drug interactions when drugs are prescribed concurrently. Increasing knowledge of inter-individual variation in drug breakdown capacity and recent findings concerning the influence of environment, diet, nutrients, and herbal products can be used to reduce ADRs and iatrogenic diseases.[118]

Physicians, should have a detailed knowledge and understanding of the potential risks and purported benefits of herbal medicines and should thoroughly inquire about patient's use of herbal products. In addition, the education of each patient regarding the serious, potential drug-herb interactions should be a routine component of preoperative assessment. The American Society of Anesthesiologists (ASA) suggests that all herbal medications should be discontinued 2 to 3 weeks before an elective surgical procedure.[179] Dermatologists should be aware of herbal products likely to be used by their patients. Many of these products prescribed by alternative medicine physicians or purchased over the counter should be discontinued prior to dermatologic surgery to minimise the risk of surgical complications.[180] With the increasing use of herbal supplements by cancer patients, surgical staffs need to screen patients pre-surgically for use of these supplements.[125]

Potential herb-prescription drug interactions are not just limited to SJW. Inquiries regarding the usage of herbal supplements should be an integral component of a transplant recipient's medication history. Clinicians should be proactive and repeatedly provide education regarding the potential dangers of herbal medicines taken with conventional drugs. Interdisciplinary communication among medical herbalists, medical doctors, pharmacists and dietetic experts needs to be improved and encouraged.

If the patient is not sure of the contents of the herbal medicine, he or she should be urged to bring the container to the consultation so that the doctor or pharmacist can review its contents. Although this idea holds some promise in the outpatient clinic setting, care in emergency settings should be based on thorough drug history taking from the patient or a relative.

So, before patients take any herbal supplement, they must be recommended:

- to check with their physicians, dietician, pharmacist and/or product manufacturer regarding safety, dosage, duration of use and interactions with prescription drugs.
- to use only standardised herbal extracts made by licensed and authenticated companies.
- Not to take more than the recommended dosage, or for longer than recommended.
- not to use herbal remedies for serious illness.
- not to use herbs if considering pregnancy.

Physicians should be made aware of the need to take a herbal as well as a drug history, and the clinical laboratory has a role in helping understanding of how herbal products may affect laboratory tests and in suggesting relevant lines of investigation in patients whose symptoms may be linked to the use of herbal products.

Herbal medicines are not as safe as frequently claimed. Therefore, it can be harmful to take herbal medicines without being aware of their potential adverse effects. A comprehensive surveillance system for monitoring the adverse effects of herbal medicines is now essential.

3.4.8 Study Limitations

The study was of limited size and restricted to patients attending a single speciality within a single, albeit very large hospital in Abu Dhabi. Specific limitations are discussed below.

Missed ADRs

Other herbal ADRs or herb-drug interactions might have occurred during the study that were overlooked either by the patient (who in some circumstances was relying on recall) or the author and collaborators when analysing the case study data. Every effort was made to gather sufficient information to make an objective decision on the reported ADRs; but in some cases, clinical notes were incomplete or patients did not provide answers to the interviewer's questions.

Sample size

The sample of non-herbal users (control group) was much smaller than the current herb user group. This may have skewed some of the findings. Certainly, the numbers taking individual herbs were relatively small, hampering a robust co-relational analysis.

Data retrieval from medical notes

Details of the patients' disease profiles and laboratory findings were missing from some medical records; the illegible handwriting of some nephrologists also hampered data retrieval.

Patient availability

Some patients in the dialysis units could not participate in the study as they were unconscious, very sick or could not talk. Also, patients who were less than 13 years old and who could not speak English or Arabic languages were excluded from the study. In all these cases, valuable information on herb use might have been obtained through alternative approaches.

3.4.9 Suggestions for future work

Additional research strategies

The National pharmacovigilance centres in many countries are responsible for monitoring pharmacovigilance activities. At the outset of this research, this was not applicable to the UAE; accordingly, several alternatives were considered.

Firstly, to approaching alternative medicine practitioners in Herbal Clinics to report herbal ADRs encountered in the course of their practice. This would involve surveying the herbal practitioners via emails, specifically herbal practitioners in herbal medical centres who are prescribing herbal medicine, whether in crude or processed form. This idea was not explored further, as many of these practitioners were unlicensed and would be difficult to identify.

Secondly, approaching Health Food shops in shopping centres to survey customers about their experiences of HM use, including adverse effects.

Both strategies may have provided useful data, but the author would not have been able to corroborate what the subjects reported with their medical notes.

Extending the methodology used in the author's renal clinic study to other specialities such as cardiovascular, rheumatology, dermatology, surgical and emergency departments would be feasible and would perhaps provide additional information on the safety (or otherwise) of HM use in patients with a range of underlying diseases.

Establishing a pharmacovigilance centre in UAE Ministry of Health:

The initial idea of surveying the safety of HMs in the UAE, was through developing a national pharmacovigilance centre in the Drug Control Department (DCD) of the UAE MoH and extending its activities to cover HMs; however this was not feasible when the present research began, due to the acute shortage of human and financial resources, lack of technical assistance and lack of co-ordination between the MoH and other local healthcare authorities and municipalities.

A National Pharmacovigilance Committee has formed at the end of 2008 between the MoH, local health authorities and the Medical Faculty of UAE University with the objective of establishing a national pharmacovigilance scheme. While this is still in its infancy, the author's involvement in gathering safety data through this scheme would be a logical extension to this research, perhaps using a modified version of the data capture form used in Stage 2 of the research.

In addition Abu Dhabi's Health Authority (HAAD) has established its own local poison and drug information centre and produces a periodic news letter to educate practitioners to report ADRs. The author might have input to this and could study the effect of raised awareness of HM effects on frequency of reporting.

Tighter regulation of HM use

The MoH, local health authorities and municipalities have established a National Committee to regulate HMs and dietary supplements in the country, but this too is at an early stage of development. The MoH has also established a medical advertisement department to control the advertisements of all medical products including HMs and dietary supplements. The author might make a contribution to both these initiatives.

Chapter 4: Overall Discussion and Conclusions

4.1 Overall discussion

Chapter 1 indicated that in common with many other countries in the region, herbal medicines (HMs) are an important part of self-treatment strategies in the UAE. The country is in an interesting position, where Western medicine is being more widely embraced against a background of traditional HM use, stretching back for centuries. This use is more prominent in rural areas where cultural beliefs and practices often lead to self-care, home remedies or consultation with traditional healers; however, as Chapter 2 shows, use in towns and cities such as Abu Dhabi is extremely common.

Unlike conventional pharmaceutical products, many HMs are marketed without evaluation for quality, safety and efficacy and as a consequence, there is growing concern about the risk to patients from inappropriate use, inaccurate dosages, drug-herb and herb-herb interactions. Chapter 1 provided some stunning examples of the potential for deliberate or unintentional contamination of HMs discovered by the UAE MoH (see Table 1.3). A brief review of published evidence of the potential for harm was also provided. The perception that herbal remedies are natural and therefore safe is widespread among users, but incorrect.[59]

Herbal remedies often contain highly active pharmacological compounds and are therapeutic at one dose and toxic at another. With increasing widespread use, it is important for public safety that HMs are examined and regulated as carefully as conventional medicines. The lack of pharmacological and clinical data on the majority of HMs is a major impediment to the integration of herbal medicines into conventional medical practices.[68] No-where is this more important than in the UAE. For valid integration, pharmacological and especially, clinical studies, must be conducted on those plants lacking such data. Adverse events, including drug-herb interactions must also be monitored to promote safe integration of efficacious HMs into conventional medical practice. In addition to the quality of the medicines themselves, other major concerns impinging on safety include herbal practitioner's licensure, scope of practice, and malpractice. Whilst the MoH regulates the quality, efficacy and safety of licensed herbal products and dietary supplements which are mainly available from pharmacies, control in local municipalities is less strict. Thousands of HM products are available from unlicensed,

uncontrolled sources such as health food and condimental shops in the UAE, which contributes to potential safety problems.

At the time of conducting this research, there were no data relating to the usage of HMs in the UAE. The initial stage of the author's research attempted to quantify this and in addition, determine the attitudes and beliefs of users who were UAE Nationals. The results are discussed fully in Chapter 2. The Al Rowda Clinic was selected for the survey as it was considered the biggest PHC in Abu Dhabi and only provided services to UAE Nationals. Results confirmed the author's suspicions that the use of HMs was widespread – three quarters of the sample had experience of HM use – with a point-prevalence of current HM use of 38%. A wide range of herbs were used to treat a large number of disorders. Most herbal remedies were not Western 'off the shelf' or proprietary herbal products, but herbs in the crude form, often used in mixtures, frequently obtained from unregulated sources, and most frequently recommended by a family member or a friend. In keeping with other studies,[49] a large majority of users considered the HMs they were taking to be effective, natural and therefore safe; but an appreciable proportion (11%) cited adverse reactions which they thought were due to the HM(s) they were taking.

In general, there was a disinclination by the patients to inform their GPs about HM use with less than a third of subjects doing so; those not informing their GPs had either not thought to mention it, thought their GP did not need to know or thought their GP did not believe in HM and that they would not be taken seriously. This has important implications for future pharmacovigilance of HMs. If GPs are to be encouraged to report them, patients must first be encouraged to inform their GPs of all the medicines they are taking. This is compounded by the fact that, as the research from Chapter 3 shows, patients appear not to be able or willing to report adverse drug reactions themselves.

The objective of phase two of the research was to provide qualitative and quantitative data on the safety of HM use in a tighter group of patients where access to medical notes could be guaranteed. Chapter 3 explains that the choice of studying patients with renal disease, visiting a hospital nephrology clinic in Sheikh Khalifa Medical City Abu Dhabi, was based on reasons of access, etiquette and clinical relevance. Ways of extending the study are discussed below under 'suggestions for future work'. Despite these limitations, the study revealed some important new data. Patients in the sample, by definition, had moderate to serious kidney disease, yet concurrent use of HMs was approximately twice as high in this sample as it was in

the primary care sample studied in Phase 1 (68 vs 38%). Furthermore, a minority of patients mentioned their use of HMs to their attending Doctors; almost 70% said they had not informed their doctor or pharmacist that they were taking HMs. When validating reported herb use against the patient medical records, just two patients had anything about herbs written by their doctors. A smaller percentage in this sample reported an adverse reaction to the herbs they were taking (5.6% vs 11%) but the phase two study allowed sufficient clinical detail to be obtained to assess causality and to some extent, severity.

Over a third of patients taking compound herbal remedies could not identify the main active ingredient. Twenty-eight adverse reactions, described in 26 patients were deemed to be possibly or probably related to HM use but the actual herb involved could not be identified because the patient was taking multiple HMs in half the cases. Under such circumstances, there would be little benefit in applying standard pharmacovigilance techniques to this data, as building up a picture of ADR incidence, and thus generating a safety signal, would be impossible without the name of the herb (mixture or otherwise) involved.

There are potentially significant health risks posed by the concomitant use of HMs in patients taking conventional therapies. Phase 2 research showed that 7 (25%) of the adverse reactions involved HMs alone and 21 involved a HM / PM interaction. It is therefore important that if these are to be prevented, a full list of PMs and HMs taken should be available to the patient's attending healthcare professionals.

4.1.1 Suggestions for improving ADR reporting to HMs

The UAE is not unique in currently having little means of accessing, reporting and monitoring ADRs to conventional or any other types of medicines used by its citizens. The following are suggestions for some concrete steps that could lead to the support of a pharmacovigilance system in the HM field.

1. *Generating a safety and efficacy database.*

HM products have evolved against widely different ethnological, cultural, climatic, geographical and even philosophical backgrounds;[181] nevertheless they face many regulatory challenges in ensuring their safety and efficacy. There are very few drug regulatory authority bodies that

evaluate the safety and efficacy of herbs on the basis of clinical trials. Current herbal reference texts do not contain sufficient information for the assessment and management of adverse health effects of many botanical therapies.[182]

Large-scale clinical trials are needed to assess the public health potential of HMs and to establish indications and dosage recommendations. As a starting point, a searchable database could be constructed, containing licensed HM product details; this could then be expanded as new products, including crude herbal formulations imported through the municipalities and available through health food grocery and condimental shops, are investigated against established quality, efficacy and safety standards.

2. *Improving labelling and control of HMs*

It is clear from the results of this study that patients took a wide range of HMs about which little was known. Many were obtained from unlicensed suppliers and came in unlabelled containers, or with little indication of the main active ingredient, batch number or expiry date. There needs to be tighter legislation on the manufacture and supply of such products to protect patients from taking the same herb in two or more different forms and those overdosing themselves. Crude herbals are commonly formulated as a mixture, so that their ingredients may be ambiguous and even contain harmful contaminants; because nearly all herbal remedies contain multiple, biologically active constituents, interaction with conventional drugs is a concern. Thus there is a need for the MoH to insist on the licensing of all herbal products making a medicinal claim, especially those authorised for marketing by the municipalities, and the withdrawal from the market of clearly dubious HMs with no clear labelling or content. Source or manufacturer and batch number should also appear on the label, in addition to clear warnings against inappropriate use, for example during pregnancy.

If resources could be found, municipalities might be encouraged to build their own quality control laboratories to test HMs approved locally and investigate reports of adulterated or mis-labelled products.

There is also a need for improved communication between the MoH, local health authorities, municipalities, approved manufacturers and customs to detect substandard or counterfeit HM products.

3. *Licensing of HM manufacturers*

As with conventional Western medicines, manufacturers of HMs and dietary supplements approved by the municipalities should be subject to inspection against a minimum standard of good manufacturing practice and if successful, issued with a licence for production of specified HMs. Manufacturing processes should be subject to regular inspection and products produced under licence should be subject to quality control. Licences might be revoked if standards are not maintained.

Consideration should also be given to licensing the facilities where HMs and dietary supplements are kept and in which they are transported, particularly in the municipalities.

4. *Licensing of HM practitioners*

Consideration needs to be given to effective regulation of HM practitioners, who should be governed by a professional code of practice and have agreed standards of training and competency.

5. *Promotion of HMs*

The promotion of HMs as natural safe alternatives neglects the possibility of adverse reactions. Legislation to improve public health protection and promote only fully substantiated marketing claims for HM products is required. Promotion and advertisements of these products in media and journals should be regulated and subject to regular scrutiny. While the UAE has such a system for conventional medicines, little is known about its effectiveness in controlling HM advertising, particularly that reaching the country from the surrounding area.

6. *Patient education*

Most herbal products do not require a prescription in the UAE. Thus, their use and any potential risks may easily escape the physician's and pharmacist's attention. One strategy to address this is for an information leaflet to accompany every HM at point of sale or supply, containing vital

information such as the names of the ingredients, indications and dosage, in addition to contraindications, warnings and precautions, interactions with other medicines and potential side effects. Patients should be encouraged though the leaflet, and by their attending healthcare professionals, to report untoward effects to their doctor or pharmacist and to seek advice on potential drug interactions for taking a HM. Bi-lingual presentation (at least Arabic and English) would also be an advantage.

7. Healthcare professional education

This study has shown that patients are at risk of adverse reactions or interactions involving HMs, yet most practicing physicians have little knowledge of herbal remedies or their effects. Most healthcare professionals are not adequately prepared educationally to meet patients' requests for information on herbal products and dietary supplements. Perhaps this is why so few bothered to mention HM use to their carers. In the UAE, physicians' and pharmacists' knowledge of both herbs and adverse event reporting is poor and they are unaware that such events, particularly serious ones, should be reported.

To optimise patient care, healthcare professionals have a responsibility to educate themselves about herbal therapies in order to help patients, who clearly use HMs a lot, discern the facts from the fiction, avoid harm, and gain what benefits may be available. In order for this to happen, some requirement for training in this area might be injected into undergraduate and postgraduate curriculums, not just for doctors and pharmacists, but also for nurses.

8. Healthcare provider – patient communication

One outstanding finding from this study is the apparent reluctance of patients to involve their carers in the decision to use HMs. In addition to educating patients to disclose all the medicines they are taking it is essential that HCPs take a thorough drug history on first patient contact, be it in the GP surgery, the admissions ward of a hospital or in a speciality clinic, to ensure that the attending clinician is aware of all potentially harmful preparations taken by the patient. The history should include questions regarding the taking both herbal and over-the-counter medications. Furthermore, the history should be accurately transcribed into the patient's notes and updates with each visit. Recent studies have shown that suitably trained pharmacists are capable of taking accurate drug histories of high quality[183] and that drug histories can help

prevent ADRs.[184] This may be a role which UAE pharmacists could embrace when adopting a more clinical role. If so, the data collection tool developed by the author for phase 2 might well prove useful.

9. Integration of patient data

A recent MoH strategy to integrate patient information and share the patient's medical record through all UAE public healthcare settings will certainly facilitate the monitoring of HM use, but this will only be useful in this context if the patient tells the healthcare provider what they are taking and the provider enters the information in the patient's notes. Hospital and community pharmacies should be included in this process.

10. Encourage pharmacovigilance

ADR reporting is the main method of monitoring the safety of medicines. Encouraging spontaneous reporting can contribute to improved awareness among health personnel and patients about the benefit-harm profile. Reporting of suspected ADRs associated with HMs, whether licensed or unlicensed, and including physicians and community pharmacists as recognised reporters, are steps in the right direction. Ultimately, patients themselves might be encouraged to report, although at the moment, they seem reluctant to do so.

Such a pharmacovigilance scheme might also prove useful in detecting false claims and substandard medicines and devising risk management plans for suspect products. As mentioned previously, at time of writing, the UAE MoH, pharmacovigilance scheme is in its infancy; but there seems to the author to be no reason why this should not be expanded to HMs, with immediate effect and she strongly recommends this approach.

4. 2 Conclusions and suggestions for future work

Use of HMs for health maintenance, treatment or prevention of minor conditions, and also for serious, chronic illnesses is popular in UAE.

HM regulation seeks to protect the public health by ensuring the necessary guarantees of quality, safety and efficacy. Good communication between regulators, practitioners, patients and the public is necessary so that those who choose to take HMs can do so with acceptable safety.

This research has provided the first evidence of the extent of HM use in primary care and has focussed on use in just one secondary care setting. Future research might take the following lines.

1. Interview HCPs to gain their views on the use of HMs in their patients and what they would like their patients to tell them.

2. Interview HCPs to obtain a better idea of their level of knowledge about HMs, the information sources they use to educate themselves about HMs, and their training requirements.

3. Evaluate the power of drug history taking to discover the extent of HM use in patients admitted to hospital and the potential for avoiding harm from ADRs or herb-drug interactions during their hospital stay.

4. Apply the author's data collection form in the above and in other clinical settings where the potential for prescription of large numbers of PMs is high, for example the rheumatology, mental health, gastroenterology or cardiology clinics.

5. Introduce pilot pharmacovigilance programmes in the above. Covering both HMs and PMs using a spontaneous reporting system similar to that used in the US and UK as described in Chapter 1.

6. Review all HM product claims against the evidence base for safety and efficacy and produce a register of approved ingredients and their indications, and make inclusion on the list a pre-requisite for marketing and supply in the UAE.

5. REFERENCES

1. UAE interact. Sheikh Zayed Bin Sultan Al Nahyan. 2005. Available from: http://www.uaeinteract.com/uaeint_misc/pdf_2005/zayed_tribute/zayed.pdf. (cited 3/8/09)

2. UAE NMC. UAE Yearbook 2008. The National Media Council (previously the UAE Ministry of Information and Culture). Available from: http://viewer.zmags.co.uk/showmag.php?mid=stfrs&preview=1&_x=1#/page0/. (cited 3/8/09)

3. UAE Yearbook 2007.Ministry of Information and Culture. UAE. Available from: http://www.uaeinteract.com/uaeint_misc/pdf_2007/index.asp. (cited 3/8/09)

4. Ministry of Economy, UAE; 2009.
Ministry of Economy UAE estimates of population by nationality (citizens/non-citizens), sex and emirate, 2006-2009.
http://www.economy.ae/English/EconomicAndStatisticReports/StatisticReports/StatisticAbstract/Pages/sa2007.aspx. (cited 3/8/09)

5. UAE Government. UAE Government: Seven Emirates 2005. Available from: http://www.uae.gov.ae/Government/emirates1.htm. (cited 3/8/09)

6. UAE MoH. Ministry Of Health Statistics 2001. Available from: http://www.moh.gov.ae/AdminCP/AssetsManager/Files/Statistics/Statistics_2001/english_version/stat_moh.htm. (cited 31/1/09)

7. WHO 2000. World Health Organization assesses the world's health systems. 2000 Available from :http://www.who.int/whr/2000/media_centre/press_release/en/index.html. (cited 3/9/09)

8. Ministry of Health, UAE. Statistics of health Institutions in Ministry of Health, 2007. Available from:http://www.moh.gov.ae/en/Page_342.aspx. (cited 3/9/09)

9. SEHA Abu Dhabi Health Services Company. Services, Hospitals, PHCs 2008. Available from:http://www.seha.ae/en/index.htm. (cited 3/9/09)

10. DOHMS. Statistics of Hospitals and Clinics. 2008. Available from: http://www.dohms.gov.ae/default. (cited 31/1/09)

11. HAAD. Health Authority - Abu Dhabi. 2008; Available from: http://www.haad.ae/haad/tabid/36/Default.aspx. (cited 3/9/09)

12. (DHCC) DHC. About DHCC. 2008. Available from: http://www.dhcc.ae/EN/AboutDHCC/Pages/AboutDHCC.aspx. (cited 31/1/09)

13. (DAMAN) NHIC. Formation of DAMAN 2008; Available from: http://www.damanhealth.ae/formation.aspx. (cited 31/1/09)

14. HAAD. Thiqa and Wiqaya, 2008. Available from: http://www.haad.ae/haad/tabid/345/Default.aspx. (cited 31/1/09)

15. Emirates News Agency W. HAAD announces Thiqa Health Insurance Program for UAE nationals - posted on 12/02/2009. Emirates News Agency, WAM 2009. http://www.uaeinteract.com/russian/news/default.asp?ID=339 (cited 3/8/09)

16. DHA. DHA Insurance. 2008. Available from: http://www.dha.gov.ae/files/DHA_Insurance_email.pdf. (cited 31/1/09)

17. UK NHS. About NHS Services, 2008. Available from: http://www.nhs.uk/aboutNHSChoices/Pages/AboutNHSChoices.aspx. (cited 31/1/09)

18. UK NHS. Primary care trusts, 2008. Available from: http://www.nhs.uk/aboutnhs/howtheNHSworks/authoritiesandtrusts/Pages/Authoritiesandtrusts.aspx. (cited 31/1/09)

19. UK NHS. Acute Healthcare Trusts, 2008. Available from: http://www.nhs.uk/aboutnhs/howtheNHSworks/authoritiesandtrusts/Pages/Authoritiesandtrusts.aspx#q01. (cited 31/1/09)

20. UAE MoH. Federal Law No. 4 of Pharmacy Profession and Pharmaceutical Establishments. 1983. http://www.moh.gov.ae/admincp/assetsmanager/Files/Pharmacusts/Pharmacy_Federal_law_in_English.pdf (cited 3/8/09)

21. Drug Control Department MoH, UAE. Guidelines and minimum standards for Good Pharmacy Practice (GPP) in UAE Pharmacies. UAE 2003. http://www.moh.gov.ae/admincp/assetsmanager/Files/Pharmacusts/gpp.pdf (cited 3/8/09).

22. Abduelkarem A, Sackville M. Changes of some health indicators in patients with type 2 diabetes: a prospective study in three community pharmacies in Sharjah, United Arab Emirates. *Libyan J Med* 2008, 15 April 2008.

23. WHO. Eastern Mediterranean region medicines situation on traditional medicines. 2005. Available from: http://www.emro.who.int/emp/medicines_country_traditional_uae.htm. (cited 31/1/09)

24. Ministry of Health UAE. Ministerial Decree No. 840 for 2008 on registration of conventional products, companies and pricing. In: Registration and Drug Control; Ministry of Health UAE; 2008.

25. Ministry of Health UAE. Ministerial Decree No. 1072 for 2008 on Registration of herbal and general sale products and companies. In: Registration and Drug Control; Ministry of Health UAE; 2008.

26. Ministry of Health UAE. Ministerial Decree No 90 for 1992 on dispensing of Controlled Medicines. MoH, UAE, 1992.

27. Ministry of Health UAE. Ministerial Decree No 1752 for 1986 on dispensing of pharmaceutical products in supermarket and general markets. MoH, UAE,1986.

28. WHO. Legal status of traditional medicine and complementary/alternative medicine: a worldwide review, 2001. Available from: http://whqlibdoc.who.int/hq/2001/WHO_EDM_TRM_2001.2.pdf. (cited 31/1/09)

29. Azaizeh H, Saad B, Cooper E, Said O. Traditional Arabic and Islamic medicine, a re-emerging health aid. *Evidence-based Complementary and Alternative Medicine* (eCAM) June 13, 2008:nen039.

30. Mahady GB. Global Harmonization of herbal health claims. *J Nutr* 2001; 131(3):1120S-3.

31. Sadighi JM, Ziai, SA. Herbal medicine: knowledge, attitude and practice in Tehran. *J Med Plants* 2005;4(13):60-7.

32. WHO. WHO traditional medicine strategy 2002-2005. WHO, Geneva, 2002. http://whqlibdoc.who.int/hq/2002/WHO_EDM_TRM_2002.1.pdf, (cited 3/8/09)

33. WHO. Traditional Medicine - Fifty-sixth world health assembly A56/18 Provisional agenda item 14.10. WHO, Geneva, 2003. http://apps.who.int/gb/archive/pdf_files/WHA56/ea5618.pdf (cited 3/8/09)

34. 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.

35. Eisenberg DM, Davis RB, Ettner SL, Appel S, Wilkey S, Van Rompay M. Trends in alternative medicine use in the United States, 1990-1997: Results of a Follow-up National Survey. *JAMA* 1998;280(18):1569-75.

36. Bardia A, Nisly NL, Zimmerman MB, Gryzlak BM, Wallace RB. Use of herbs among adults based on evidence-based indications: findings from the National Health Interview Survey. *Mayo Clin Proc* 2007;82(5):561-6.

37. Wilson KM, Klein JD, Sesslberg TS, Yussman SM, Markow DB, Green AE, West JC, Gray NJ. Use of complementary medicine and dietary supplements among US adolescents. *J Adolesc Health* 2006;38(4):385-94.

38. Forster DA, Denning A, Wills G, Bolger M, McCarthy E. Herbal medicine use during pregnancy in a group of Australian women. *BMC Pregnancy Childbirth* 2006:6:21.

39. Wargovich MJ, Woods C, Hollis DM, Zander ME. Herbals, cancer prevention and health. *J Nutr* 2001;1:3034S-6S.

40. Azaizeh H, Saad B, Khalil K, Said O. The state of the art of traditional Arab herbal medicine in the eastern region of the Mediterranean: A Review. *Evidence-based Complementary and Alternative Medicine* (eCAM) 2006; 3(2):229-235.

41. Qidwai WA, Salman Raza, Dhanani, Raheem H, Jehangir, Sana, Nasrullah Aysha, Raza, Ammara. Use of folk remedies among patients in Karachi Pakistan. *J Ayub Med Coll - Abbotabade - Pak* 2003;15(2):31-3.

42. Afifi FUN, Rinad A, Abu I, Barakat E. Folk utilization of traditional medicinal plants among rural population in Wadi Mujib - Jordan. *Jordan Med J* 2006;40(4):232-40.

43. El Mahalli A, Aki O. Access to conventional and complementary medicine in a squatter area in Alexandria. *Bull High Inst Public Health* 2004;34(4):925-40.

44. Abdel Hady A, Rizk M, Kassem M, Baraka Y, Khalifa H. Community perception towards traditional medicine in Nasr - City [Cairo]. *Al-Azhar Med J* 2004;33(2):157-166.

45. Sereshty MA, Azari P, Rafiean M, Kheiri S. Use of herbal medicines by pregnant women in Shahr-e-Kord. *Med J Reprod Infertil* 2006;7(2):125-31.

46. Ogur RK, Ahmet BB. Herbal treatment usage frequency, types and preferences in Turkey. *Middle East J Fam Med* 2006;4(3):38-44.

47. Erdemir AD. The application of Ayurvedic therapies in Turkey and the importance of ginger use from the point of view of Ayurvedic principles. *J Int Soc Hist Islam Med* 2003; 2(4):58-60.

48. Al-Awamy BH. Evaluation of commonly used tribal and traditional remedies in Saudi Arabia. *Saudi Medical Journal* 2001;22(12):1065-8.

49. Al Saeedi M, El Zubier A, Bahnassi A, Al Dawood K. Patterns of belief and use of traditional remedies by diabetic patients in Mecca, Saudi Arabia. *East Mediter Health J* 2003; 9(1-2):99-107.

50. Al-Faris E, Al-Rowais N, Mohamed A, Al-Rukban M, Al-Kurdi A, Balla Al-Noor M, Al Harby S, Sheikh A. Prevalence and pattern of alternative medicine use: the results of a household survey. *Ann Saudi Med* 2008;28(1):4-10.

51. Al-Rowais NA. Herbal medicine in the treatment of diabetes mellitus. *Saudi Medical Journal* 2002;23(11):1327-31.

52. Nasser JG, Roger M. The use of herbs among people with diabetes in the Kingdom of Bahrain. *J Bahrain Med Soc* 2006;18(2):82-7.

53. Ben Rhouma F, Zeglaoui F, Kamoun M. Medecines alternatives et dermatologie. *Tunisie Med* 2005;83(1):6-12.

54. Rguibi MB, Belahsen R. Fattening practices among Moroccan Saharawi women. *East Mediterr Health J* 2006;12(5):619-24.

55. Eddouks M, Maghrani M, Lemhadri A, Ouahidi ML, Jouad H. Ethnopharmacological survey of medicinal plants used for the treatment of diabetes mellitus, hypertension and cardiac diseases in the south-east region of Morocco (Tafilalet) *J Ethnopharmacol* 2002;82(2-3):97-103.

56. Saad B, Azaizeh H, Said O. Tradition and perspectives of Arab herbal medicine: a review. *Evidence Based Compliment Alternative Med* 2005;2(4):475-479.

57. Beckman SE, Sommi RW, Switzer J. Consumer use of St. John's Wort: a survey on effectiveness, safety, and tolerability. *Pharmacotherapy* 2000;20(5):569-74.

58. Shaw D, Leon C, Kolev S, Murray V. Traditional remedies and food supplements. A 5-year toxicological study (1991-1995). *Drug Saf* 1997;17(5):342-56.

59. Saad B, Azaizeh H, Abu-Hijleh G, Said O. Safety of traditional Arab herbal medicine. *Evidence Based Compliment Alternative Med* 2006;3(4):433-9.

60. El-Nahhal Y. Contamination and safety status of plant food in Arab countries. *J Appl Sci* 2004;4(3):411-7.

61. Russmann S, Lauterburg BH, Helbling A. Kava hepatotoxicity. *Ann Intern Med* 2001; 135(1):68-69.

62. MCA. Reminder: St John's Wort (Hypericum perforatum) interactions. Current Problems in Pharmacovigilance: 2000;26:6-7. Available from: http://www.mhra.gov.uk/Publications/Safetyguidance/CurrentProblemsinPharmacovigilance/CON007461. (cited 31/1/09)

63. Schulz V. Incidence and clinical relevance of the interactions and side effects of Hypericum preparations. *Phytomedicine* 2001;8(2):152-60.

64. Arlt VM, Stiborova M, Schmeiser HH. Aristolochic acid as a probable human cancer hazard in herbal remedies: a review. *Mutagenesis* 2002;17(4):265-77.

65. Ernst E. Serious psychiatric and neurological adverse effects of herbal medicines - a systematic review. *Acta Psychiatr Scand* 2003;108(2):83-91.

66. Corns CM. Herbal remedies and clinical biochemistry. *Ann Clin Biochem* 2003;40(5):489-507.

67. Pittler MH, Ernst E. Systematic review: hepatotoxic events associated with herbal medicinal products. *Aliment Pharmacol Ther* 2003;18(5):451-71.

68. Fong HH. Integration of herbal medicine into modern medical practices: issues and prospects. *Integr Cancer Ther* 2002;1(3):287-93.

69. Pinn G. Adverse effects associated with herbal medicine. *Aust Fam Physician* 2001; 30(11):1070-5.

70. Drew AK, Myers SP. Safety issues in herbal medicine: implications for the health professions. *Med J Aust* 1997;166(10):538-41.

71. Minodier P, Pommier P, Moulene E, Retornaz K, Prost N, Deharo L. Star anise poisoning in infants. *Arch Pediatr* 2003;10(7):619-21.

72. Chen J, Wang Q, Cheng C, Liu Z, Zhan Y, Chen K. [Analysis of tendency of false and inferior species from Chinese medicinal materials markets]. *Zhong Yao* Cai 2001; 24(11):825-7. (Eng. Transl.)

73. Yap KY, Chan SY, Lim CS. Authentication of traditional Chinese medicine using infrared spectroscopy: distinguishing between ginseng and its morphological fakes. *J Biomed Sci* 2007;14(2):265-73.

74. Lau AJ, Holmes MJ, Woo SO, Koh HL. Analysis of adulterants in a traditional herbal medicinal products using liquid chromatography-mass spectrometry-mass spectrometry. *J Pharm Biomed Anal* 2003;31(2):401-6.

75. UAE Ministry of Health. UAE MoH warns warning on unbranded natural products. 2007 Available from: http://www.zawya.com/prinstory.cfm?storyid=ZAWYA20071214065750&1=065700071214 (cited 5/8/09)

76. UAE Ministry of Health. UAE warns over herbal medicine use. 2002 Available from: http://www.nutraingredients.com/Regulation/UAE-warns-over-herbal-medicine-use. (cited 7/2/09)

77. UAE Ministry of Health, Herbal medicine warning. 2008; Available from: http://www.ameinfo.com/172132.html. (cited 7/2/09)

78. Government U. Federal Law No: 20 for 1995 for Products Derived from Natural Sources.
http://www.moh.gov.ae/admincp/assetsmanager/Files/Pharmacusts/2.Medicines%20and%20Products%20Derived%20from%20Natural%20Sources%20Federal%20Law.pdf (cited 3/8/09)

79. Hasan M, Das M, Behjat S. Alternative medicine and the medical profession: views of medical students and general practitioners. *East Mediter Health J* 2000;6(1):25-33.

80. Al-Mazroui MJ, Oyejide CO, Bener A, Cheema MY. Breastfeeding and supplemental feeding for neonates in Al-Ain, United Arab Emirates. *J Tropical Pediatr* 1997;43(5):304-6.

81. Al Attia H, Bakir A. The influence of gender and level of education on the knowledge of adult diabetics on disease related issues and patients self care: the Abu Dhabi experience. *Clin Diabetes* 2006;5(2):86-8.

82. Palaian S, Mishra P, Shankar PR, Dubey AK, Bista D, Almeida R. Safety monitoring of drugs--where do we stand? *Kathmandu Univ Med J* 2006;4(1):119-27.

83. Zolezzi M, Parsotam N. Adverse drug reaction reporting in New Zealand: implications for pharmacists. *Ther Clin Risk Manag* 2005;1(3):181-8.

84. WHO. Safety of Medicines: A guide to detecting and reporting adverse drug reactions. In: Essential Drugs and Medicines Policy WHO, Geneva, 2002.

85. National Agency for Food and drug Administration and Control. Programme NP. Nigeria Pharmacovigilance Programme, Nigeria, 2002.
http://www.nafdacnigeria.org/pharmacovigilance.html, (cited 3/8/09)

86. WHO. The Importance of Pharmacovigilance - Safety Monitoring of Medicinal Products. WHO, Geneva, 2002.
http://apps.who.int/medicinedocs/en/d/Js4893e/4.html, (cited 3/8/09)

87. Waller PC. Making the most of spontaneous adverse drug reaction reporting. *Basic Clin Pharmacol Toxicol* 2006;98(3):320-3.

88. Mariani L, Minora T, Ventresca G. Drug surveillance and adverse reactions to drugs. The literature and importance of historical data. *Clin Ther* 1996;147(12):653-72.

89. Wallander MA. The way towards adverse event monitoring in clinical trials. *Drug Saf* 1993;8(3):251-62.

90. Mann RD, Andrews EB. Preface, In: Pharmacovigilance, 2002, J Wiley and Sons Ltd, Chichester, 2002.

91. WHO. WHO Programme for International Drug Monitoring, 2008. Available from: http://www.who-umc.org/DynPage.aspx?id=13140&mn=1514#1. (cited 31/3/09)

92. WHO. WHO guidelines on, safety monitoring of herbal medicines in pharmacovigilance systems, 2004. Available from:
http://www.whoindia.org/LinkFiles/Traditional_Medicine_WHO_Guideline_on_Safety_Monitoring_of_Herbal_Medicines_in_Pharmacovigilance_System.pdf. (cited 31/3/09)

93. WHO Uppsala Monitoring Center. Safety Monitoring of Medicinal Products: Guidelines for Setting up and Running a Pharmacovigilance Centre. WHO, Uppsala, 2002. http://apps.who.int/medicinedocs/en/d/Jh2934e/2.html, (cited 3/8/09)

94. Wysowski DK, Swartz L. Adverse drug event surveillance and drug withdrawals in the United States, 1969-2002: the importance of reporting suspected reactions. *Arch Intern Med* 2005;165(12):1363-9.

95. Motola D, Vargiu A, Leone R, Conforti A, Moretti U, Vaccheri A, Velo G, Montanaro N. Influence of regulatory measures on the rate of spontaneous adverse drug reaction reporting in Italy. *Drug Saf* 2008;31(7):609-16.

96. Schade CP, Hannah K, Ruddick P, Starling C, Brehm J. Improving self-reporting of adverse drug events in a West Virginia hospital. *Am J Med Qual* 2006;21(5):335-41.

97. Hazell L, Shakir SA. Under-reporting of adverse drug reactions: a systematic review. *Drug Saf* 2006;29(5):385-96.

98. Backstrom M, Mjorndal T, Dahlqvist R, Nordkvist-Olsson T. Attitudes to reporting adverse drug reactions in northern Sweden. *Eur J Clin Pharmacol* 2000;56(9-10):729-32.

99. Hughes ML, Whittlesea CM, Luscombe DK. Review of national spontaneous reporting schemes. Strengths and weaknesses. *Adverse Drug React Toxicol Rev* 2002; 21(4):231-41.

100. Williams D, Feely J. Underreporting of adverse drug reactions: attitudes of Irish doctors. *Ir J Med Sci* 1999;168(4):257-61.

101. Barnes J, Aggarawal, AM. Spontaneous reporting of ADRs associated with herbal medicines: final results of a cross-sectional survey of national pharmacovigilance centres. *Drug Saf* 2006;29(4):359.

102. Barnes J. Pharmacovigilance of herbal medicines: a UK perspective. *Drug Saf* 2003; 26(12):829-51.

103. MacLennan AH, Wilson DH, Taylor AW. The escalating cost and prevalence of alternative medicine. *Prev Med* 2002; 35(2):166-173.

104. Harris P, Rees R. The prevalence of complementary and alternative medicine use among the general population: a systematic review of the literature. *Complement Ther Med* 2000;8:88-96.

105. Thomas KJ, Nicholl JP, Coleman P. Use and expenditure on complementary medicine in England: a population-based survey. *Complement Ther Med* 2001; 9(1): 2-11.

106. Kennedy J. Herb and supplement use in the US adult population. *Clin Ther* 2005;27(11):1847-58.

107. Gray C, Tan A, Pronk NP, O'Connor PJ. Complementary and alternative medicine use among health plan members: A cross sectional survey. *Eff Clin Pract* 2002; 5: 17-22.

108. Lev E, Amar Z. Ethnopharmacological survey of traditional drugs sold in Israel at the end of the 20th century. *J Ethnopharmacol.* 2000;72(1-2):191-205. DOI: 10.1016/s0378-8741(00)00230-0

109. Lev E, Amar Z. Ethnopharmacological survey of traditional drugs sold in the Kingdom of Jordan. *J Ethnopharmacol*. 2002;82(2-3):131-45. DOI: 10.1016/s0378-8741(02)00182-4

110. Said O, Khalil K, Fulder S, Azaizeh H. Ethnopharmacological survey of medicinal herbs in Israel, the Golan Heights and the West Bank region. *J Ethnopharmacol*. 2002;83(3):251-65. DOI: 10.1016/s0378-8714(02)00253-2

111. Valente TW. Social networks and mass media: the 'diffusion' of CAM. In *Complementary and alternative medicine-challenge and change*. Kelner M, Wellman B, Pescosolido B, Saks M (eds). Routledge: London, 2003; 131-142.

112. The Natural Medicines Comprehensive Database. Therapeutic Research Faculty, Stockton, CA. Available at: ttp://www.naturaldatabase.com/(S(qepb0rznlrwfg0bmex0pj045))/nd/Search.aspx?cs=&s=ND&pt=9&Product=thyme (date accessed 26/8/09).

113. Nordeng H., Havnenen GC. The use of herbal drugs in pregnancy: a survey among 400 Norwegian women. *Pharamcoepidemiol Drug Saf* 2004;13(6):371-380.

114. Miller LG. Herbal medicinals: selected clinical considerations focusing on known or potential drug-herb interactions. *Arch Intern Med* 1998;158(20):2200-11.

115. Skalli S, Zaid A, Soulaymani R. Drug interactions with herbal medicines. Ther Drug Mon 2007;29(6):679-86.

116. Pirmohamed M., James S., Meakin S. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18,820 patients. *BMJ* 2004;329:15-19.

117. Kongkaew,C, Noyce,PR, Ashcroft,DM. Hospital admissions associated with adverse drug reactions: a systematic review of prospective observational studies. *Ann Pharmacol* 2008;42:1017-1025.

118. Sorensen JM. Herb-drug, food-drug, nutrient-drug, and drug-drug interactions: mechanisms involved and their medical implications. *J Alt Complement Med* 2002; 8(3):293-308.

119. Isacson D, Johansson L, Bingefors K. Nationwide survey of subjectively reported adverse drug reactions in Sweden. *Ann Pharmacother* 2008;42(3):347-53.

120. Barnes J, Mills SY, Abbot NC, Willoughby M, Ernst E. Different standards for reporting ADRs to herbal remedies and conventional OTC medicines: face-to-face interviews with 515 users of herbal remedies. *Br J Clin Pharmacol* 1998; 45(5):496-500.

121. Ernst E. Risks of herbal medicinal products. *Pharmacoepidemiol Drug Saf* 2004; 13(11):767-71.

122. Cuzzolin L, Zaffani S, Benoni G. Safety implications regarding use of phytomedicines. *Eur J Clin Pharmacol* 2006;62(1):37-42.

123. Meijerman I, Beijnen JH, Schellens JH. Herb-drug interactions in oncology: focus on mechanisms of induction. *Oncologist* 2006;11(7):742-52.

124. Wu ML, Deng JF, Wu JC, Fan FS, Yang CF. Severe bone marrow depression induced by an anticancer herb Cantharanthus roseus. *J Toxicol Clin Toxicol* 2004;42(5):667-71.

125. Kumar NB, Allen K, Bell H. Perioperative herbal supplement use in cancer patients: potential implications and recommendations for presurgical screening. *Cancer Control* 2001;12(3):149-57.

126. Lee NJ, Fermo JD. Warfarin and royal jelly interaction. *Pharmacotherapy* 2006; 26(4):583-6.

127. Seak CJ, Lin CC. Ruta Graveolens intoxication. *Clin Toxicol (Phila)* 2007;45(2):173-5.

128. Chang SS, Liaw SJ, Bullard MJ, Chiu TF, Chen JC, Liao HC. Adrenal insufficiency in critically ill emergency department patients: a Taiwan preliminary study. *Acad Emerg Med* 2001;8(7):761-4.

129. Schoepfer AM, Engel A, Fattinger K, Marbet UA, Criblez D, Reichen J. Herbal does not mean innocuous: ten cases of severe hepatotoxicity associated with dietary supplements from Herbalife products. *J Hepatol* 2007;47(4):521-6.

130. Zhou SF, Xue CC, Yu XQ, Wang G. Metabolic activation of herbal and dietary constituents and its clinical and toxicological implications: an update. *Curr Drug Metab* 2007;8(6):526-53.

131. Wai CT, Tan BH, Chan CL, Sutedja DS, Lee YM, Khor C, et al. Drug-induced liver injury at an Asian center: a prospective study. *Liver Int* 2007;27(4):465-74.

132. Bruguera M, Herrera S, Lazaro E, Madurga M, Navarro M, de Abajo FJ. Acute hepatitis associated with Colpachi intake. Apropros of 5 cases. *Gastroenterol Hepatol* 2007;30(2):66-8.

133. Cardenas A, Restrepo JC, Sierra F, Correa G. Acute hepatitis due to shen-min: a herbal product derived from Polygonum multiflorum. *J Clin Gastroenterol* 2006;40(7):629-32.

134. Singh YN. Potential for interaction of kava and St. John's wort with drugs. *J Ethnopharmacol* 2005;100(1-2):108-13.

135. Rifai K, Flemming P, Manns MP, Trautwein C. [Severe drug hepatitis caused by Chelidonium]. *Internist* (Berl) 2006;47(7):749-51.

136. Savvidou S, Goulis J, Giavazis I, Patsiaoura K, Hytiroglou P, Arvanitakis C. Herb-induced hepatitis by Teucrium polium L.: report of two cases and review of the literature. *Eur J Gastroenterol Hepatol* 2007;19(6):507-11.

137. Starakis I, Siagris D, Leonidou L, Mazokopakis E, Tsamandas A, Karatza C. Hepatitis caused by the herbal remedy Teucrium polium L. *Eur J Gastroenterol Hepatol* 2006;18(6):681-3.

138. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981 30(2):239-45.

139. Arulmani R, Rajendran SD, Suresh B. Adverse drug reaction monitoring in a secondary care hospital in South India. *Br J Clin Pharmacol* 2008;65(2):210-6.

140. Beltrami GC, Menegolli GP, Corra L, Weber U, Longobardi A, Albiero A, et al. [Drug adverse effects in the elderly hospitalized with acute pathologies]. *Clin Ther* 2000;151(1):19-23.

141. Franceschi M, Scarcelli C, Niro V, Seripa D, Pazienza AM, Pepe G, et al. Prevalence, clinical features and avoidability of adverse drug reactions as cause of admission to a geriatric unit: a prospective study of 1756 patients. *Drug Saf* 2008;31(6):545-56.

142. Ganeva M, Gancheva T, Lazarova R, Tzvetanova Y, Hristakieva E. A prospective study of adverse drug reactions in a dermatology department. Methods *Find Exp Clin Pharmacol* 2007;29(2):107-12.

143. Garcia-Cortes M, Lucena MI, Pachkoria K, Borraz Y, Hidalgo R, Andrade RJ. Evaluation of naranjo adverse drug reactions probability scale in causality assessment of drug-induced liver injury. *Aliment Pharmacol Ther* 2008;27(9):780-9.

144. Hafner JW, Jr., Belknap SM, Squillante MD, Bucheit KA. Adverse drug events in emergency department patients. *Ann Emerg Med* 2002;39(3):258-67.

145. Tulner LR, Frankfort SV, Gijsen GJ, van Campen JP, Koks CH, Beijnen JH. Drug-drug interactions in a geriatric outpatient cohort: prevalence and relevance. *Drugs Aging* 2008;25(4):343-55.

146. Lambert JP, Cormier J. Potential interaction between warfarin and boldo-fenugreek. *Pharmacotherapy* 2001;21(4):509-12.

147. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med.* 1999 130(6):461–70.

148. Burrowes JD, Van Houten G. Use of alternative medicine by patients with stage 5 chronic kidney disease. *Adv Chronic Kidney Dis* 2005;12(3):312-25.

149. Chang CH, Yang CM, Yang AH. Renal diagnosis of chronic hemodialysis patients with urinary tract transitional cell carcinoma in Taiwan. *Cancer* 2007; 15;109(8):1487-92.

150. Chang CH, Wang YM, Yang AH, Chiang SS. Rapidly progressive interstitial renal fibrosis associated with Chinese herbal medications. *Am J Nephrol* 2001;21(6):441-8.

151. Li XB, Xing NZ, Wang Y, Hu XP, Yin H, Zhang XD. Transitional cell carcinoma in renal transplant recipients: a single center experience. *Int J Urol* 2008;15(1):53-7.

152. Debelle F, Nortier J. [Nephropathy caused by Chinese plants and aristolochic acids: from clinical observation to experimental model]. *Bull Mem Acad R Med Belg* 2006;161(5):327-33.

153. Debelle FD, Vanherweghem JL, Nortier JL. Aristolochic acid nephropathy: a worldwide problem. *Kidney Int* 2008;74(2):158-69.

154. Lee S, Lee T, Lee B, Choi H, Yang M, Ihm CG, et al. Fanconi's syndrome and subsequent progressive renal failure caused by a Chinese herb containing aristolochic acid. *Nephrology* 2004;9(3):126-9.

155. Hong YT, Fu LS, Chung LH, Hung SC, Huang YT, Chi CS. Fanconi's syndrome, interstitial fibrosis and renal failure by aristolochic acid in Chinese herbs. *Pediatr Nephrol* 2006;21(4):577-9.

156. Zhu YP. Toxicity of the Chinese herb mu tong (Aristolochia manshuriensis). What history tells us. *Adverse Drug React Toxicol Rev* 2002;21(4):171-7.

157. American National Kidney Foundation. Use of Herbal Supplements in Chronic Kidney Disease 2009 [cited 2009 April 5]; Available from: http://www.kidney.org/ATOZ/atozItem.cfm?id=123.

158. Izzo AA, Ernst E. Interactions between herbal medicines and prescribed drugs: a systematic review. *Drugs* 2001;61(15):2163-75.

159. Fugh-Berman A. Herb-drug interactions. *Lance*t 2000;355(9198):134-8.

160. Barone GW, Gurley BJ, Ketel BL, Abul-Ezz SR. Herbal supplements: a potential for drug interactions in transplant recipients. *Transplantation* 2001;27;71(2):239-41.

161. Nowack R. Herb-drug interactions in nephrology: documented and theoretical. *Clin Nephrol* 2008;69(5):319-25.

162. Saw JT, Bahari MB, Ang HH, Lim YH. Potential drug-herb interaction with antiplatelet/anticoagulant drugs. *Complement Ther Clin Prac*t 2006;12(4):236-41.

163. Jadayil SA, Tukan SK, Takruri HR. Bioavailability of iron from four different local food plants in Jordan. *Plant Foods Hum Nutr* 1999;54(4):285-94.

164. Adigun MO, Ogundipe OD, Anetor JI, Odetunde AO. Dose-dependent changes in some haematological parameters during short-term administration of Hibiscus sabdariffa Calyx aqueous extract (Zobo) in Wistar albino rats. *Afr J Med Sci* 2006 Mar;35(1):73-7.

165. McKay DL, Blumberg JB. A review of the bioactivity and potential health benefits of chamomile tea (Matricaria recutita L.). *Phytother Res* 2006;20(7):519-30.

166. Bielory L. Complementary and alternative interventions in asthma, allergy, and immunology. *Ann Allergy Asthma Immunol* 2004;93(2 Suppl 1):S45-54.

167. Vanderperren B, Rizzo M, Angenot L, Haufroid V, Jadoul M, Hantson P. Acute liver failure with renal impairment related to the abuse of senna anthraquinone glycosides. *Ann Pharmacother* 2005;39(7-8):1353-7.

168. Villegas JF, Barabe DN, Stein RA, Lazar E. Adverse effects of herbal treatment of cardiovascular disease: what the physician must know. Heart Dis 2001;3(3):169-75.

169. Piscitelli S. Preventing dangerous drug interactions. *J Am Pharm Assoc (Wash)* 2000;40(5 Suppl 1):S44-5.

170. Suchard JR, Suchard MA, Steinfeldt JL. Physician knowledge of herbal toxicities and adverse herb-drug interactions. *Eur J Emerg Med* 2004;11(4):193-7.

171. Frost EA. Herbal medicines and interactions with anesthetic agents. *Middle East J Anesthesiol* 2006;18(5):851-78.

172. Walter G, Rey JM, Harding A. Psychiatrists' experience and views regarding St John's Wort and 'alternative' treatments. *Aust N Z J Psychiatry* 2000; 34(6):992-6.

173. Charrois TL, Hill RL, Vu D, Foster BC, Boon HS, Cramer K, et al. Community identification of natural health product-drug interactions. *Ann Pharmacother* 2007;41(7):1124-9.

174. Smith AM. Opening the dialogue: Herbal supplementation and chemotherapy. *Clin J Oncol Nurs* 2005;9(4):447-50.

175. Bush TM, Rayburn KS, Holloway SW, Sanchez-Yamamoto DS, Allen BL, Lam T, et al. Adverse interactions between herbal and dietary substances and prescription medications: a clinical survey. *Altern Ther Health Med* 2007;13(2):30-5.

176. Wallerstedt SM, Skrtic S. [Use of natural remedies is seldom documented in medical records. There is a risk of overlooked interactions and adverse effects, as a point prevalence study shows]. *Lakartidningen* 2005;102(44):3220-2.

177. Rivera JO, Hughes HW, Stuart AG. Herbals and asthma: usage patterns among a border population. *Ann Pharmacother* 2004;38(2):220-5.

178. Jha V, Rathi M. Natural medicines causing acute kidney injury. *Semin Nephrol* 2008;28(4):416-28.

179. Kaye AD, Kucera I, Sabar R. Perioperative anesthesia clinical considerations of alternative medicines. *Anesthesiol Clin North America* 2004;22(1):125-39.

180. Chang LK, Whitaker DC. The impact of herbal medicines on dermatologic surgery. *Dermatol Surg* 2001;27(8):759-63.

181. Kumar V A, Latha R, Sneha M, Singh PN, Ahmad S, Ansari SH, Porchezhian E. Towards rational regulation and legislation of herbal medicines. *Saudi Pharm J* 2002;10(4): 208-10.

182. Haller C A, Anderson IB. An evaluation of selected herbal reference texts and comparison to published reports of adverse herbal events. *Adverse Drug React Toxicol Rev* 2002;21(3): 143-50.

183. Kwan Y, Fernandes OA, Nagge JJ, Wong GG, Huh J, Hurn DA, Pond GR, Bajcar JM. Pharmacist medication assessments in a surgical preadmission clinic *Arch Intern Med.* 2007;167(10):1034-1040.

184. Badowski SA, Rosenbloom D, Dawson PH. Clinical importance of pharmacist-obtained medication histories using a validated questionnaire. *Am J Hosp Pharm* 1984;41:731–2.

Appendix 1.

Names of common herbs and their main uses in the UAE

Appendix 1: Names of common herbs and their main uses in the UAE

Herb	Arabic Name	Synonyms	Species (Family)	Herbal Use
Aloe	صبار - صبر	Aloe vera	(i) *Aloe barbadensis* (*Liliaceae*). (ii) *Aloe ferox* and its hybrids with *Aloe africana* and *Aloe spicata*.	Recommended for the treatment of atonic constipation and suppressed menstruation.
Anise	يانسون	Anise, Aniseed, Anisi Fructus, Anisum	*Pimpinella anisum* L. (*Apiaceae/umbelliferae*)	Expectorant, antispasmodic, carminative and parasiticide. Traditionally, it has been used for bronchial catarrh, pertussis, spasmodic cough, flatulent colic; topically for pediculosis and scabies; its most specific use is for bronchitis, tracheitis with persistent cough, and as an aromatic adjuvant to prevent colic following the use of cathartics. It has been used as an oestrogenic agent. It has been reputed to increase milk secretion, promote menstruation, facilitate birth, alleviate symptoms of the male climacteric and increase libido.
Asafetida	الخيل - الحلتيت	Asafetida, Asant, Devil's Dung, Gum Asafetida	(i) *Ferula assafoetida* L. (*Ferula rubricaulis Boiss*) (ii) *Ferula foetida* (*Apiaceae/Umbelliferae*)	Carminative, antispasmodic and expectorant. It has been used for chronic bronchitis, pertussis, laryngismus stridulus, hysteria and specifically for intestinal flatulent colic.
Black seed	الحبة السوداء - حبة البركة	Nutmeg flower	*Nigella Sativa*	It is used internally for difficulty in urination, dysmenorrhoea, indigestion, colds, asthma and for impotence. It has also been used as an antiflatulent and as an anthelmintic. And it is used externally for skin inflammations and for muscle and joint pain.

Appendix 1: Names of common herbs and their main uses in the UAE

Herb	Arabic Name	Synonyms	Species (Family)	Herbal Use
Aloe	صبار - صبر	Aloe vera	(i) *Aloe barbadensis* (*Liliaceae*). (ii) *Aloe ferox* and its hybrids with *Aloe africana* and *Aloe spicata.*	Recommended for the treatment of atonic constipation and suppressed menstruation.
Anise	يانسون	Anise, Aniseed, Anisi Fructus, Anisum	*Pimpinella anisum* L. (*Apiaceae/umbelliferae*)	Expectorant, antispasmodic, carminative and parasiticide. Traditionally, it has been used for bronchial catarrh, pertussis, spasmodic cough, flatulent colic; topically for pediculosis and scabies; its most specific use is for bronchitis, tracheitis with persistent cough, and as an aromatic adjuvant to prevent colic following the use of cathartics. It has been used as an oestrogenic agent. It has been reputed to increase milk secretion, promote menstruation, facilitate birth, alleviate symptoms of the male climacteric and increase libido.
Asafetida	الخيل - الحلتيت	Asafetida, Asant, Devil's Dung, Gum Asafetida	(i) *Ferula assafoetida* L. (*Ferula rubricaulis Boiss*) (ii) *Ferula foetida* (*Apiaceae/Umbelliferae*)	Carminative, antispasmodic and expectorant. It has been used for chronic bronchitis, pertussis, laryngismus stridulus, hysteria and specifically for intestinal flatulent colic.
Black seed	الحبة السوداء - حبة البركة	Nutmeg flower	*Nigella Sativa*	It is used internally for difficulty in urination, dysmenorrhoea, indigestion, colds, asthma and for impotence. It has also been used as an antiflatulent and as an anthelmintic. And it is used externally for skin inflammations and for muscle and joint pain.

Appendix 1 continued: Names of common herbs and their main uses in UAE

Chamomile	بابونج	Chamomilla recutita (L.) Rauschert, Hungarian Chamomile, Matricaria chamomilla L., Matricaria Flowers, Sweet False Chamomile, Wild Chamomile	*Matricaria recutita* L. (*Asteraceae*/*Compositae*)	Carminative, antispasmodic, mild sedative, anti-inflammatory, antiseptic and anticatarrhal. It has been used for flatulent nervous dyspepsia, travel sickness, nasal catarrh, nervous diarrhoea, restlessness and specifically for gastrointestinal disturbance with associated nervous irritability in children. It has been used topically for haemorrhoids, mastitis and leg ulcers. Also used for gastrointestinal spasms and inflammatory diseases of the gastrointestinal tract and externally for skin and mucous membrane inflammation and bacterial skin diseases including oral cavity and gums. It is also approved for inflammation and irritation of the respiratory tract (by inhalation) and ano-genital inflammation (baths and irrigation).
Cinnamon	قرفة - دارسين	(i) Ceylon Cinnamon, True Cinnamon (ii) Saigon Cinnamon (iii) Batavia Cassia, Batavia Cinnamon, Padang-Cassia, Panang Cinnamon	(i) *Cinnamomum zeylanicum* Bl. (*Lauraceae*) (ii) *Cinnamomum loureirii Nees* (iii) *Cinnamomum burmanii* (*Nees*) Bl.	Antispasmodic, carminative, antidiarrhoeal, antimicrobial, cooling agent and anthelmintic. It has been used for anorexia, intestinal colic, infantile diarrhoea, common cold, influenza, and specifically for flatulent colic, and dyspepsia with nausea. Cinnamon bark is also stated to be astringent, and cinnamon oil is reported to possess carminative and antiseptic properties.

Appendix 1 continued: Names of common herbs and their main uses in UAE

Clove	قرنفل	Caryophyllus aromaticus, Eugenia aromatica, Eugenia caryophyllata, Eugenia caryophyllus.	*Syzygium aromaticum* (*Myrtaceae*)	Carminative, anti-emetic, toothache remedy and counter-irritant.
Fenugreek	حلبة	Bockshornsame	*Trigonella foenum-graecum* L. (*Leguminosae*)	Possess mucilaginous demulcent, laxative, nutritive, expectorant and appetite stimulant properties, and has been used topically as an emollient. Traditionally, it has been used in the treatment of anorexia, dyspepsia, gastritis and convalescence, and topically for furunculosis, myalgia, lymphadenitis, gout, wounds and leg ulcers.
Ginger	زنجبيل	Zingiber	*Zingiber officinale Roscoe* (*Zingiberaceae*)	Possess carminative, diaphoretic and antispasmodic properties. Traditionally, it has been used for colic, flatulent dyspepsia, and specifically for flatulent intestinal colic. Modern interest in ginger is focused on its use in the prevention of nausea and vomiting, particularly motion sickness, as a digestive aid, and as an adjunctive treatment for inflammatory conditions, such as osteoarthritis and rheumatoid arthritis.
Harmal	حرمل		*Rhazya stricta*	Plant decoction is used for the treatment of diabetes mellitus, fever, stomach ulcers and as an anthelmintic. Inhalation of smoke from the leaves can be used for the treatment of nasal allergy.

Appendix 1 continued: Names of common herbs and their main uses in UAE

Myrrh	مر	(i) African Myrrh, Balsamodendron Myrrha, Commiphora, Commiphora myrrha (Nees) Engl., Somali Myrrh (ii) Arabian Myrrh, Yemen Myrrh	(i) *Commiphora molmol* (*Bursuraceae*) (ii) *Commiphora abyssinica* (iii) Other *Commiphora* species	Possess antimicrobial, astringent, carminative, expectorant, anticatarrhal and antiseptic properties. Traditionally, it has been used for aphthous ulcers, pharyngitis, respiratory catarrh, common cold, furunculosis, wounds and abrasions, and specifically for mouth ulcers, gingivitis and pharyngitis. Also used topically for mild inflammation of the oral and pharyngeal mucosa.
Parsley	بقدونس	Apium petroselinum L., Carum petroselinum (L.) Benth., Petroselinum sativum Hoffm.	*Petroselinum crispum* (*Apiaceae/Umbelliferae*)	Parsley is stated to possess carminative, antispasmodic, diuretic, expectorant, antirheumatic and antimicrobial properties. Traditionally, it has been used for flatulent dyspepsia, colic, cystitis, dysuria, bronchitic cough in the elderly, dysmenorrhoea, functional amenorrhoea, myalgia and flatulent dyspepsia with intestinal colic.
Red seed	الحبة الحمراء - الرشاد		*Lepidium sativum*	Seeds and green leaves are used, which are rich in vitamins and minerals. Used as a tonic, appetizer and with other herbs, to enhance sexual performance. Indicated medically in the treatment of mouth and throat infections. In the UAE it is used for cleaning the womb and stomach after delivery.

Appendix 1 continued: Names of common herbs and their main uses in UAE

Sage	ميرامية - القصعين	Dalmatian Sage, Garden Sage, True Sage Red Sage refers to Salvia haematodes Wall. Greek Sage refers to Salvia triloba Spanish Sage refers to Salvia lavundaefolia	*Salvia officinalis* L. (*Labiatae*)	Sage is stated to possess carminative, antispasmodic, antiseptic and astringent properties. Traditionally, it has been used to treat flatulent dyspepsia, pharyngitis, uvuitis, stomatitis, gingivitis, glossitis (internally or as a gargle/mouthwash), hyperhidrosis, and galactorrhoea. Also used internally for dyspeptic symptoms and excessive perspiration, and externally for inflammation of mucous membranes of mouth and throat.
Seder	السدر		*Ziziphus*	Fruits are rich in nutrients and have a beneficial effect in respiratory tract diseases. Decoction of the leaves is used for gastrointestinal disturbances, diabetes mellitus, menstrual bleeding, diarrhoea, fever and toothache. It is also used as an anthelmintic

Appendix 1 continued: Names of common herbs and their main uses in UAE

Senna	السنامكي - الحلول	(i) Alexandrian Senna, Cassia acutifolia Delite, Khartoum Senna (ii) Indian Senna, Tinnevelly Senna	(i) *Cassia senna* L. (ii) *Cassia angustifolia* (*Leguminosae*)	Senna is stated to possess cathartic properties (leaf greater than fruit) and has been used traditionally for constipation. Senna is also used in combination with ispaghula for constipation. The Committee on Proprietary Medicinal Products (CPMP) has adopted core SPCs (Summary of Product Characteristics) for senna leaf and senna fruit (C. angustifolia and C. acutifolia) with indications for short-term use in cases of occasional constipation.
Terminalia	هليليج - هليلة		*Terminalia chebula*	Used for constipation, dyspepsia, duodenal ulcer and hyperlipidaemia.
Teucrium	جعدة		*Teucrium* Sp.	Plant decoction or emulsion is used as an appetizer, for the treatment of diabetes, intestinal problems, lymph problems, liver malfunction, acute pneumonia, flu, rheumatism, malaria, fever and also to ease menstrual symptoms.
Thyme	زعتر	Common Thyme, French Thyme, Garden Thyme, Rubbed Thyme	*Thymus vulgaris* L., *Thymus zygis* L. (*Labiatae*)	It is stated to possess carminative, antispasmodic, antitussive, expectorant, bactericidal, anthelmintic and astringent properties. Traditionally, it has been used for dyspepsia, chronic gastritis, asthma, diarrhoea in children, enuresis in children, laryngitis, tonsillitis (as a gargle), and specifically for pertussis and bronchitis.

Appendix 2

Cover letter and questionnaire for Phase One of the study (English translations).

Only for UAE Nationals

Dear Sir / Madam

Attached is a survey which has been approved by the Ministry of Health to screen the UAE nationals in all districts, to study the safety of herbal medicines taken by patients, whether you are using herbs alone or along with prescribed medicines.

We would like to know your opinions regarding herbal medicines or medicinal herbs, whether you are using them or not. In case you are using / were using any herb(s), we would like to know the names of those herbs which have been of benefit in treating your disease to recommend them to others, and to know the names of the herbs that harm you; in order to warn others not to use them.

Also, we would like to inform you that taking some common herbs e.g. thyme, chamomile, ginger, senna, mixture of herbs, black seed, aloe, myrrh, anise etc are considered herbal medicines, therefore kindly make sure to answer question **(12) with "Yes " if you have ever been treated with herbs and complete the survey.**

We would like to assure you that the information given by you will be confidential and secured and will not be disclosed to others, and we promise to use your data to follow-up your condition and evaluate the healthcare services and medicines given to you.

Here are some definitions of terms used in the survey:

1. **Prescription / Conventional medicines**: Modern medicines of chemical nature prescribed in hospitals, clinics or pharmacies.

2. **Treatment with herbs: of 3 types**:

A. **Medicinal plants/ crude herbs (not chemically processed)**: are dried plants, either mashed,complete or in powdered form , sold in condimental shops or herbs selling shops e.g. thyme ,ginger , mixture of herbs , aloe , myrrh , senna , fenugreek, black seed, Gum, fennel, ..etc.

Continued.....

B. **Compounded herbs / Mixtures of herbs**: are crude herbs prepared by a herbal practitioner or traditional healers; they includes crude herbs or herbs mixed with honey, herbal oils, or herbs mixed with water or other liquids; also creams or pastes prepared in herbal shops or homes.

C. **Herbal medicines (chemically processed):** herbs or herbal medicines in pharmaceutical form (e.g. capsules, pills, liquids or creams) which look like a conventional medicine in its finished pack. These can be obtained from pharmacies, health food shops or natural product shops, organic shops or alternative medicines centres.

3. **Herbal practitioner** : a person who provides consultation or prescribes or dispenses herbs or treats with herbal medicines.

4. **Condimental shops**: shops where herbs or medicinal plants are sold - popular in old souks or traditional shops.

5. **Health food shops**: shops or centres that sell manufactured or processed herbal medicinal or dietary supplements; located mainly in modern shopping centres.

Kindly complete the survey and return it back to the nurse in the clinic / or put it in its envelope (pre-paid post) and send it to the address displayed on the outside of the envelope.

If you have any questions, please call: 02-6117421 or 02-6334958 or email: fabdallah@moh.gov.ae

SECTION ONE: GENERAL INFORMATION

Post ☐ Interview ☐

S.No _____ Health card No. (_____)

Please help us by answering the following questions on the information about your background:

1. Gender:
   a) Male..... ☐
   b) Female..... ☐

2. Age.....years old.

3. Where do you live?
   Emirate.....
   City .....
   Street or Area.....

4. Marital Status
   a) Single..... ☐
   b) Married..... ☐
   c) Divorced / Widow..... ☐

5. If you are married female, then are you?
   a) Pregnant ..... ☐
   b) Breastfeeding mother..... ☐
   c) non of the above ..... ☐

6. How many family members are living with you in the house?
   a) 1-3..... ☐
   b) 4-6..... ☐
   c) 7-9..... ☐
   d) 10-12..... ☐
   e) More than 12..... ☐

7. What is your education level?
   a) Cannot read nor write ..... ☐
   b) Read and write only..... ☐
   c) Less than high school..... ☐
   d) High school only..... ☐
   e) Graduate of College or University..... ☐
   f) Postgraduate (Master or Doctorate)..... ☐

8. Occupation
   a) In full time paid employment..... ☐
   b) Self-employed..... ☐
   c) Unemployed ..... ☐
   d) House wife ..... ☐
   e) Retired..... ☐
   f) Full time student..... ☐
   g) Other, please state.....

   If you are in employment; what is your occupation? .....
   .....

9. What is your total household monthly income (in Dirham)?
   a) Less than 5,000..... ☐
   b) 5,000-9,999..... ☐
   c) 10,000-14,999..... ☐
   d) 15,000-19,999..... ☐
   e) 20,000-24,999..... ☐
   f) 25,000 and above..... ☐

10. In general, how would you say your health was over last month?
    a) Excellent..... ☐
    b) Good..... ☐
    c) Fair..... ☐
    d) Poor..... ☐
    e) Very poor..... ☐

11. Have you ever been to see a herbal practitioner? ☐ Yes ☐ No

12. Have you ever tried treatment using herbs e.g. thyme, black cumin, chamomile, Aloe, ginger, senna, or herbs to treat diabetes, hypertension, stomach ulcer, reduce weight, cold and flu, headache; etc.? ☐ Yes ☐ No

If the answer to question *(12)* was *No*, please turn to section Five on page (5) to answer question (37), If the answer was *Yes*, please continue with this questionnaire.

SECTION TWO: WHAT HERBAL MEDICINES YOU TAKE

For this section, we would like to know *what* are the herbal medicine (s) you are taking or have taken. Only answer this section if you have ever taken, or are currently taking any herbal medicine.
(For the following questions, tick *any* that apply)

13. Which type of herbs have you used before or are using now? (Tick *all* that applies to you).

a) Medicinal plants or crude herbs..... ☐
b) Compounded herbs..... ☐
c) Herbal medicines (In pharmaceutical form). ☐
d) Other, Please state .....

14. Please list the herbal medicines you are taking now, or have taken in the last few months; providing a brief reason why (if you remember) *e.g. Senna to relive constipation.*

No.	Name of Herbal medicine	Reason for taking
1		
2		
3		
4		
5		

15. How effective was the last herbal medicine you used?

☐ Very effective ☐ Effective ☐ Not sure ☐ Not effective ☐ Made me feel worse

16. How many herbal medicines are you taking now?

a) 0..... ☐
b) 1..... ☐
c) 2-3..... ☐
d) 4-5..... ☐
e) More than 5..... ☐

17. How do you use herbal medicines? (Tick *all* that applies to you).

a) Oral solid;(tablet, capsule, powder)..... ☐
b) Oral Liquids;(syrup, oil)..... ☐
c) Herbal teas..... ☐
d) Topically applied on skin;(cream, ointment, gel, solution, oils, patches)... ☐
e) Other, please state.....

18. Where do you store herbal medicines?

a) I store them in the cupboard or cabinet ☐
b) I store them at room temperature ☐
c) I store them in the fridge..... ☐
d) Other, please state.....

19. Have you experienced any side effect or adverse effect from using herbal medicine? ☐ Yes ☐ No

20. If yes to the above question, then what were the symptoms of the side effect?

.....
.....
.....
.....
.....
.....

21. When you experienced this side effect, did you :(Please tick *all* that applies to you).

a) Continue taking medicine and see if the symptoms revolved..... ☐
b) Stop taking medicine immediately..... ☐
c) Consult your doctor..... ☐
d) Consult your pharmacist..... ☐
e) Consult the sale person in the health food shop ☐
f) Consult the sale person in the condimental shop ☐
g) Consult your herbal practitioner..... ☐
h) Go to the hospital as an emergency case..... ☐
i) Admit to the hospital..... ☐
j) Other, Please State..... ☐

22. Name all medications you were taking when you experienced the side effect including the conventional medications.

.....

.....

.....

SECTION THREE: WHY AND WHEN YOU TAKE HERBAL MEDICINES

In this section, we would like to know *why* you take herbal medicines and *when* you are taking or have taken herbal medicines.

23. Please state your reasons for choosing to take herbal medicines. e.g. I prefer to use herbal medicines because they have been obtained from natural sources.

1.
2.
3.

24. Approximately how often do you take herbal medicines?

a) I take them every day..... ☐
b) I take them very often..... ☐
c) I take them sometimes..... ☐
d) I take them only when I need them ☐
e) I rarely take them..... ☐
f) Other, Please state.....

25. Do you read information on the pack or leaflet before taking herbal medicines? ☐ Yes ☐ No

SECTION FOUR: WHERE AND HOW YOU BUY HERBAL MEDICINES?

In this section, we would like to know about *where* you buy your herbal medicines from and *how* you chose them. Again, only answer this section if you have ever taken, or are currently taking any herbal medicines.

26. From where do you normally obtain your herbal medicines? (Please tick *all* that applies to you).

a. Health food shop..... ☐
b. Herbal medical center..... ☐
c. Supermarket or grocery..... ☐
d. Health Spa or gym club..... ☐
e. Pharmacy..... ☐
f. Internet..... ☐
g. Condimental shop..... ☐
h. Other (please state) .....

27. When you buy your herbal medicine, do you normally receive any advice from the salesperson on how to take them? ☐ Yes ☐ No

28. Please state why you buy herbal medicines from the places you have chosen in question 26 (Please tick *all* that applies to you).

a. The shop is close to my home..... ☐
b. The shop is tidy and elegant ..... ☐
c. The shop is big and has various types of herbal medicines..... ☐
d. The shop located in big shopping center/ food market..... ☐
e. The sale person in the shop is kind to me ☐
f. The prices are cheaper than other places ☐
g. There is an experienced herbal practitioner ☐
h. I get free herbal samples when I buy from the shop..... ☐
i. Other, please state .....

29. How do you know that herbal medicines are useful for your conditions or ailments? (Please tick *all* that applies to you)?

a. From my experience in medicines or herbs (physician, pharmacist, Medical technician, and nurse, employee in the health care department, condimental shop, or health food shop)..... ☐
b. I have been recommended to use herbal medicines by herbal practitioner..... ☐
c. I have been recommended to use herbal medicines by family / friend..... ☐
d. I have been recommended to use herbal medicines by a physician, dentist, pharmacist or nurse..... ☐
e. I have attended lecture/workshop/conference that recommended using herbal medicines..... ☐
f. I have read a recommendation to use herbal medicines in an article of Magazine / Journal... ☐
g. I saw/ listened to show on TV or Radio which recommended using herbal medicines..... ☐
h. I read recommendation to use herbal medicines on the internet..... ☐
i. I read recommendation to use herbal medicines in Textbooks/ books & drug leaflets /posters ☐
j. Other, please state.....

30. If there is more than one choice of herbal medicine to treat your condition, how do you decide which one to choose? Please tick all that applies to you

a. The cheapest..... ☐
b. The most informative label..... ☐
c. The strongest version available..... ☐
d. The one you believe to be the most effective... ☐
e. The one, which comes in the largest quantity... ☐
f. The brand name, which inspires the most confidence..... ☐
g. The one, which requires least number of doses per day..... ☐
h. Flavor (if this is an option)..... ☐
i. The product you have seen/heard of the most ☐
j. Recommended by family/friend..... ☐
k. The most attractive label..... ☐
l. Recommended by staff..... ☐
m. Other (please state)..... ☐

31. During the last12 months approximately where and how many visits did you make to buy or obtain herbal medicine from the list below?

	Number of visits in last 12 months						
	0	1	2	3	4	5	more than 5
a) Herbal medical center.....	☐	☐	☐	☐	☐	☐	☐
b) Health food shops.....	☐	☐	☐	☐	☐	☐	☐
c) Condimental shops.....	☐	☐	☐	☐	☐	☐	☐
d) Pharmacy.....	☐	☐	☐	☐	☐	☐	☐
e) Grocery or supermarket.....	☐	☐	☐	☐	☐	☐	☐
f) Sport or gym club.....	☐	☐	☐	☐	☐	☐	☐
g) Other, please state.....	☐	☐	☐	☐	☐	☐	☐

32. Where did your meet the herbal practitioner?

a) Never been to herbal practitioner..... ☐
b) Government Hospital..... ☐
c) Private Hospital/ private clinic..... ☐
d) Health food shop..... ☐
e) Pharmacy..... ☐
f) Herbal/ Health medical center..... ☐
g) His home..... ☐
h) Condimental shop..... ☐
i) Your home..... ☐
j) Other, please state.....

33. Did you see a doctor and a herbal practitioner at the same time for the same reason? ☐ Yes ☐ No

34. Do you consult your doctor before taking any herbal medicine? ☐ Yes ☐ No

35. Please answer either section" a" or "b", whichever applies to you:

a. If the answer to question (34) was *yes*, why do you consult them? (Please tick all that applies).
   i. I always discuss any possible new medication with my doctor..... ☐
   ii. I feel my doctor should be fully aware about all the medication I take..... ☐
   iii. Any other reason? _

b. If the answer to question (34) was *no*, why don't you consult them? (Please tick all that applies).
   i. I don't think my doctor needs to know about any medication I take unless It's medication that they prescribed for me..... ☐
   ii. I didn't think to mention it to them..... ☐
   iii. I didn't want to trouble the doctor; they're busy enough as it is..... ☐
   iv. I don't think my doctor believes in herbal medicines so wouldn't take me seriously ☐
   v. Any other reason?

36. Do you think you will continue using herbal medicine(s) as treatment of your choice for your condition?
☐ Yes ☐ No

SECTION FIVE: YOUR VIEWS ABOUT HERBAL AND CONVENTIONAL MEDICINES

For this section we would like to know your *views on herbal medicines* and, if you chose to use them. Also your views about *conventional medicines* compared to herbal ones.

37. Please tick the appropriate box to show your opinion on the following statements:

	Strongly agree	*Agree*	*No opinion*	*Disagree*	*Strongly disagree*
a) I have more confidence in herbal medicines than conventional ones	☐	☐	☐	☐	☐
b) Herbal medicines are safer than conventional medicines.....	☐	☐	☐	☐	☐
c) Herbal medicines are more effective than conventional medicines....	☐	☐	☐	☐	☐
d) Herbal medicines work as quickly as conventional medicines to.....	☐	☐	☐	☐	☐
treat a problem.....	☐	☐	☐	☐	☐
e) There are no problems taking herbal medicines with conventional medicines from a doctor or pharmacy	☐	☐	☐	☐	☐
f) Herbal medicines have no place in modern medicine.....	☐	☐	☐	☐	☐
g) I Have experienced more useful and benefit for a previous ailment using herbal medicines than conventional ones.....	☐	☐	☐	☐	☐
h) Herbal medicines treat the whole body to make a person better, not just the problem.....	☐	☐	☐	☐	☐
i) Herbal medicines should contain a leaflet of similar standard and content to conventional medicines.....	☐	☐	☐	☐	☐

38. From the list below, please state your reasons for choosing to take herbal and / or conventional medicines. (Please tick *all* that applies to you).

	Herbal	Conv
a. Is safe to use?.....	☐	☐
b. Processed chemical manufacturing	☐	☐
c. Have no side effects.....	☐	☐
d. Cannot get addicted.....	☐	☐
e. Can prevent a person from getting sick	☐	☐
f. Can improve & maintain a person health...	☐	☐
g. Is safe to be given to pregnant women.....	☐	☐
h. Is safe to be given to breastfeeding mothers	☐	☐
i. Is safe to be given to children below 12 years old.....	☐	☐

39. Have you ever taken a conventional medicine to treat your conditions? ☐ Yes ☐ No

40. If yes to the above question, how effective was the treatment of your conditions using conventional medicines?

☐ Very effective ☐ Effective ☐ Not sure ☐ Not effective ☐ Made me feel worse

41. While you were taking any of the herbal medicines that you listed; were you also taking any conventional medications either prescribed or recommended by a doctor, dentist, and pharmacist?

☐ Yes ☐ No

If you chose yes, please continue; if you chose No please move to question (42).

What condition(s) was it treating?

Can you name the conventional medication(s)

42. For the following conditions, please state which would be your first choice of medication for treating condition:

The condition	*Herbal*	*Conventional*	*The condition*	*Herbal*	*Conventional*
a. Bruises and / or Injuries.	☐	☐	l. High cholesterol.....	☐	☐
b. Back pain and / or neck pain.....	☐	☐	m. Sexual disorders.....	☐	☐
c. Anxiety and / or depression.....	☐	☐	n. Infertility.....	☐	☐
d. Insomnia.....	☐	☐	o. Stomach and / or digestive disorders.	☐	☐
e. Diabetes.....	☐	☐	p. Skin disorders.....	☐	☐
f. Cold and flu.....	☐	☐	q. Weight loss.....	☐	☐
g. Asthma and /or lung disorders.....	☐	☐	r. Weight gain.....	☐	☐
h. Headache and / or migraine.....	☐	☐	s. Immunity and nutrients disorders.....	☐	☐
i. Fatigue.....	☐	☐	t. Cancer.....	☐	☐
j. Arthritis / joint pain.....	☐	☐	u. General well being for health & body..		☐
k. High blood pressure.....	☐	☐	v. Other (s) please state.....	☐	

43. Do you know if any of your family members use herbal medicines? ☐ Yes ☐ No

If yes, how many female members?.....; number of children..... number of adults.....

How many male members?.....; number of children..... number of adults.....

SECTION SIX: YOUR VIEWS ABOUT HEALTH PROFESSIONALS

In this final section, we would like to know about your *views to different health care professionals* and if you ever seek advice from them regarding your health or clinical condition (s).

44. Please tick the appropriate box to show your opinion on the following statements:

	Strongly agree	Agree	No opinion	Disagree	Strongly disagree
a. A visit to herbal practitioner is cheaper than doctor.....	☐	☐	☐	☐	☐
b. Herbal practitioner shows more counselling skills than doctor.....	☐	☐	☐	☐	☐
c. Herbal practitioner offers many promises of cure for chronic or medical condition(s) than doctor.....	☐	☐	☐	☐	☐
d. Medicines given by herbal practitioner is never out of stock	☐	☐	☐	☐	☐
e. Medicines given in the health centre/hospital is often out of stock	☐	☐	☐	☐	☐
f. Your herbal practitioner discourage you from visiting a doctor.....	☐	☐	☐	☐	☐
g. Your doctor discourages you from visiting herbal practitioner.....	☐	☐	☐	☐	☐
h. Your doctor discourages you from taking any herbal medicine (s)...	☐	☐	☐	☐	☐
i. Your herbal practitioner discourage you from taking any conventional medicine.....	☐	☐	☐	☐	☐

45. From the classified health care professionals and others listed in the following table, (please tick (√) all that applies to you):

Statement	1 Physician	2 Pharmacist	3 Dentist	4 Nurse	5 Herbal Practitioner	6 Sale person in condimental shops	7 Sale person in Health food shops	8 Other, Please state
A- Have suggested to you the use of herbal medicines?								
B-Have ever suggested to you to see the herbal practitioner?								
C- Have Prescribed to you an herbal medicine?								
D- Have advised you on what, when, how to use herbal medicine before you purchased your last herbal medicine?								

46. Would you like to leave your phone number to call you if it's necessary? ☐ Yes ☐ No

The contact number ----------

Remarks (if you would like to add anything to this Interview).

"Thank you for taking your time and being constructive and beneficial"

Appendix 3.1

Patient information and consent sheets, and data capture form used in Phase 2 of the research.

Information Sheet

This survey has been approved by SKMC for investigating the safety of herbs used by patients taking them with or without medicines prescribed by their Doctor.
It is very important for us to know the herbs that cause adverse events or reactions, as this will help to warn others as well.
Before we start, we would like you to read the informed consent information below.

- Participation in this survey is voluntary for individuals who would like to take part in this study.The survey will be completely anonymous and voluntary. We will not give your personal details to others.
- This survey will help us to determine the safety of your medicines and herbs you have taken or plan to take in the future.

If you have any questions please ask the investigator before you proceed.

Informed Consent

1. You must be of 13 years or older to participate in this survey.
2. There are no risks involved in completing the survey.
3. This survey is used to collect information on your health, medicines, and it will not interfere with your medical treatment.
4. The survey may take about **15-30 minutes** to complete.
5. Participation is entirely voluntary; you may at any time withdraw from participation.
6. All data obtained from this survey will be ***strictly confidential***. Data will be kept anonymously and will not be shared with any other parties under any circumstance.
7. This study and survey have been approved by the SKMC and your physician.

After reading the consent items, please proceed to the questionnaire on the next page to get started with the survey.
You may leave the survey at any time with nurse or at reception.

معلومات عامة

أمامك استمارة بحث تمت الموافقة علية من مستشفى الشيخ خليفة الطبي بهدف اجراء مسح شامل للمرضى للتأكد من سلامة استخدام الادوية العشبية سواء أكنت تستعملها مع الأدوية الكيميائية أو بدونها.

يهمنا معرفة الأعشاب أو الأدوية العشبية التي سببت لك ازعاجا أو ضررا حتى يتم تحذير الاخرون بعدم استخدامها.

لذا يرجى الاطلاع على البنود الأتية قبل الموافقة بالاشتراك في هذا الاستبيان.

- ان الموافقة بالاشتراك في هذا الاستبيان هي موافقة اختيارية للافراد الذين يرغبون بالاشتراك في هذا البحث كما اننا لن لن نكشف عن هويتك أو معلوماتك الشخصية و بياناتك التعريفية للاخرين.
- سيتم اطلاعك على أهداف و مزايا اجراء هذا الاستبيان للتعرف أكثر على سلامة أدويتك والأعشاب التي تناولتها أو تنوي تناولها.

لذا يرجى الاستفسار من الباحث عن أي ملاحظة أو سؤال لديك , وسيقوم الباحث بالاجابة عليك أثناء تواجده.

الموافقة البحثية

1. يشترط ان يكون عمر المتقدم لاجراء هذا الاستبيان 13 سنة على الاقل.
2. لن يكون هناك اي صعوبة أو مجازفة في ملئ هذا الاستبيان.
3. ان هذا الاستبيان مخصص لجمع المعلومات الطبية و الدوائية فقط. ولن يتدخل بطرق علاجك مع الطبيب.
4. سيتغرق هذا البحث مدة **15 – 30 دقيقة** فقط لانهائه و هذا سيكون خلال انتظارك للممرضة أو الطبيب.
5. ان المشاركة في اجراء هذا الاستبيان اختيارية وليست اجبارية و يمكنك الانسحاب عنها في أي لحظة.
6. سيتم التكتم بالمعلومات التي سنحصل عليها ***بسرية تامة*** ولن تكون هناك طريقة للتعرف عليك أو على بياناتك كما لن يتم اعطاء معلوماتك للاخرين أو مشاركتها مع جهات أخرى في جميع الأحوال.
7. أن هذة الدراسة والاستبيان تمت الموافقة عليه من مدينةالشيخ خليفة الطبية و طبيبك.

يرجى الان الاطلاع على بنود الموافقة في الصفحة الاتية للبدء في ملئ الاستبيان.
كما يمكنك ترك الاستبيان عند الممرضة أو مكتب تسجيل المواعيد للعيادة.

Sheikh Khalifa Medical City (SKMC)

Patient Code #_____

Name of Subject:
File Number:

Consent Form

Title of Project: ***Safety of Herbal Medicines in the UAE***

Name of Researcher: Fatima A. Abdulla
Telephone #.....

- I confirm that I have read and understood the information sheet for the above study.
- I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.
- I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and that this will not affect my medical care or legal rights.
- I understand that relevant sections of any of my medical notes and data collected during the study may be looked at by the responsible investigators where it is relevant to my taking part in this research. I give permission for these investigators to have access to my records.
- I agree to take part in the above research study.

➢ **Signature of Person**.....

Date.....
Time.....

➢ **Signature of Investigator**

Date.....
Time.....

مدينة الشيخ خليفة الطبية

الرقم السري للاستمارة._____

الاسم الاول للمشارك_____

رقم الملف_____

استمارة بالموافقة على الاشتراك بالبحث

عنوان البحث: ***سلامة الادوية العشبية في دولة الامارات العربية المتحدة.***

اسم الباحث الرئيسي : فاطمة علي عبدالله
رقم الهاتف.....

- لقد تم اطلاعي و معرفتي عن المعلومات العامة بالمشاركة في هذا الاستبيان والبحث.
- لقد توفرت لي الفرصة لفهم المعلومات عن هدف الاستبيان و للاجابة عن استفساراتي بشكل مرضي و جيد.
- أنا اعرف أن مشاركتي في هذا الاستبيان اختيارية و أنه يمكنني الانسحاب عن المشاركة في أي لحظة دون ابداء أي أسباب , كما أنه لن يؤثر ذلك على حقوقي أو رعايتي الصحية في المستشفى.
- انا موافق بأن يقوم الباحث بالاطلاع على بياناتي الصحية ذات العلاقة بالبحث خلال فترة اجراء الدراسة ولا أمانع باطلاع الباحث على ملفي بالمستشفى.
- انا موافق على الاشتراك بهذا الاستبيان.

➢ **توقيع المشارك**.....

التاريخ .....
الوقت.....

➢ **توقيع الباحث**.....

التاريخ .....
الوقت.....

Patient History Notes

Patient's First Name.....Gender:☐ M ☐ F Age..... SKMC File No: .....

Patient History

1. **What is your current health status "diseases"?**.....
.....
.....
2. **When did your health status "diseases" start, diseases history?**..... .....
.....
.....

Other history details .....
.....
.....
.....
.....

Herbal Medicines (HM):

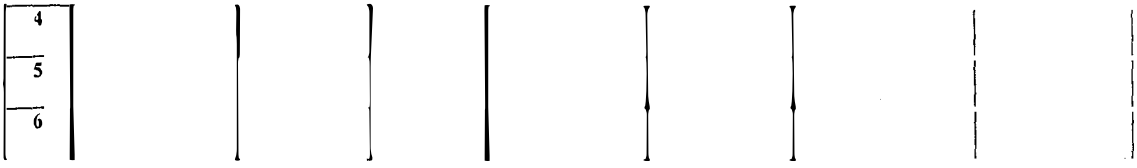
1. Have you used herbs in the past? ☐Yes ☐ No , if yes, then fill the table
2. Are you using any herbs right now? ☐Yes ☐ No , if yes, then fill the table
3. Have you used herbs before got your current health condition "disease"? ☐Yes ☐ No, if yes, then fill the table

No.	What were they	Why did you take it	How did you take it?	What form you use it?	How often did you use it?	Where did you obtain it?	When was last time you had / taking it?	Prescribed by?
1								
2								
3								
4								
5								
6								

4. Have you used any herbs while taking prescription medicines? ☐Yes, ☐ No
5. Patient claim that he / she did not used herb's" while they have used? ☐Yes, ☐ No
6. Have you informed your physician or pharmacist about using / taking herbs? ☐Yes, ☐ No
7. Have you experienced any discomfort or ADR during herb intake?☐Yes, ☐ No, ***if yes, then fill the ADR form.***
8. Have you informed your physician or pharmacist about this ADR?☐Yes, ☐ No
9. Patients have visited a herbal center? ☐Yes, ☐ No,
   if yes then name of Herbal Center .....
   and fill in the previous table the HM's that patient had, What for and how long?

Conventional Medicines (CM)

No.	Name of CM	Strength	Dosage form?	Dosage regimen?	How long have you used it?	Indications & reason for use	Prescribed by?
1							
2							
3							



Statements on CM	Yes or No	If yes then, what were/are they?	What for?
1. Are you taking any OTC medications?	☐Yes, ☐ No		
2. Are you visiting other clinic or hospital?	☐Yes, ☐ No		
3. Are you taking other medicines prescribed outside the nephrology clinic?	☐Yes, ☐ No		

S.N .....

SUSPECTED HERBAL ADVERSE DRUG REACTIONS (Confidential)

If you are suspicious that an adverse reaction may be related to a Herb (s) or combination of herb-drugs please complete this form.

Report suspected adverse reactions for:

Medically significant case, Patient discomfort and irrritability , Fatal , Life threatening , Involves or prolongs inpatient hospitalisation, Involves persistent or significant disability or incapacity, Congenital abnormality, Other improtant reactions.

PATIENT DETAILS:

Patient's First name(optional) : Sex: M / F Weight if known (kg):

Age (at time of reaction): .....Hospital or Health centre:.....File Number:

Marital status .....Pregnant / Lactating (if woman) Yes☐ No ☐

If pregnant woman consuming the herb(s)), the trimester is : **1 / 2 / 3**

If person consuming the herb(s) is an infant, the substance administered:
Directly ☐ or Breast Feeding Mother ☐

Reaction Type

Herbal Product (s) ☐ **Herb -Drug** ☐ **Herb-Nutrients** ☐ **Herb-Food** ☐ **Others**

SUSPECTED Herb (S) Give the Brand name

Brand Name	Active Ingredient	Form	Route	Dose	Date drug started	Date drug stopped	Source	Prescribed for

Suspected Reaction (s) Please describe the reaction(s) and any treatment given:

Please describe the reaction (s) , symptoms and any treatment given:

Outcome (Tick)

Recovered ☐ Recovering ☐

Hospitalized ☐ Continuing ☐

Day (s).....

Other ☐

Date started: If stopped, give date:

Was the reaction serious?

Yes ☐ No ☐ *If yes,* please indicate why the reaction is considered to be serious (please tick all that apply):

Patient died due to reaction ☐ Congenital abnormality ☐ Involved persistent or significant disability or incapacity ☐

Life threatening ☐ Caused involved or prolonged inpatient hospitalisation ☐

Medically significant ☐ Please give details:

OTHER HERBS / DRUGS / Ingredients (including self-medication & herbal remedies)	Did the patient take any other drugs in the last 3 months prior to the reaction? Yes☐ No ☐ If yes: **Item (Brand name if possible)** | **Route** | **Dose** | **Date started** | **Date stopped** | **Prescribed for:**
Medical History and Additional relevant information	**Other Medical Problems:** e.g. Medical history, test results, known allergies, rechallenge (if performed) suspected drug interactions. For congenital abnormalities please state all other herbs /drugs taken during pregnancy and the last menstrual period. .... **Other Health Factors:** ☐ **Obesity** ☐ **Smoking** ☐ **Others** ..... **Lab Tests/Liver Function/Other Blood Tests?** ..... **Significant Recent Stresses or Life Changes?** ..... Was the Drug information service/Physisian consulted about the reaction or before the drug(s) used? Yes☐ No ☐
Details of Reporter	Name (optional) **Profession** Department: Date Dr ☐ Parmacist ☐ Nurse☐ Patient ☐ Other .....
Return Form	**Kindly return the form after filling nesessary information to Dr. Fatima Ali on :** Fax :02-6313742 or call 02-6334958 (Day Timing) , or send an email to collect forms on: Albraiki2@yahoo.com

Data Validation and Clinical Assessment

Survey No.....

Patient First Name ..... **SKMC File No**.....

Describe General Patient Details

.....

.....

.....

.....

Describe Patient Renal Diseases

.....

.....

.....

Patient is : ☐ **General (Unspecified)** ☐ **Renal transplanted** ☐ **on Dialysis** ☐ **Other , to specify** .....

		History note Patient's file	Nephrologis t's Note
1.	Has patient used herbs in the past?	☐Yes ☐ No	☐Yes ☐ No
2.	Has patient taken any herbs in the present?	☐Yes ☐ No	☐Yes ☐ No
3.	Has patient informed the physician about taking herbs?	☐Yes ☐ No	☐Yes ☐ No
4.	Patient claim in interview that he / she ***Taking herb*** (s) ?	☐Yes ☐ No	☐Yes ☐ No
5.	Patient claim in interview that he / she ***Not Taking*** any herb?	☐Yes ☐ No	☐Yes ☐ No
6.	Has the Patient experienced any discomfort or ADR during herb intake, *if yes, then fill the ADR form.*	☐Yes ☐ No	☐Yes ☐ No
7.	Has patient had an adverse reaction to a herb, then takes it again and has the same reaction again?	☐Yes ☐ No ☐ unknown	☐Yes ☐ No ☐ unknown
8.	Patients has visited a herbal center? , if yes then name of Herbal Center ..... & fill in the previous table the HM's that patient had	☐Yes ☐ No	☐Yes ☐ No
9.	Patient has been admitted for emergency reason? if yes then what for?.....	☐Yes ☐ No	☐Yes ☐ No
10.	Patient has been seen in unscheduled appointment? if yes then what for?.....	☐Yes ☐ No	☐Yes ☐ No
11.	Has patient had an adverse reaction to a herb, then takes it again and has the same reaction again? *if yes, then fill the ADR form.*	☐Yes ☐ No	☐Yes ☐ No

12. Patient taking OTC medications? If yes then what medicines?.....What for?..... ... ☐Yes ☐ No ☐Yes ☐ No

13. Patient visiting other clinic or hospital? If yes then what clinic.....What for..... ☐Yes ☐ No ☐Yes ☐ No

14. Patient visiting other clinic in SKMC? If yes then what clinic.....What for..... ☐Yes ☐ No ☐Yes ☐ No

Remarks

.....
.....
.....
.....

Herbs taken by Patient (If different than Information given during Interview)

No.	What were they	Why did pt take it	How did pt take it?	What form pt use it?	How often pt use it?	Where did pt obtain it?	When was last time pt had it?	Prescribed by?	History note Patient's file	Nephrologist's Note
1									☐Yes ☐ No	☐Yes ☐ No
2									☐Yes ☐ No	☐Yes ☐ No
3									☐Yes ☐ No	☐Yes ☐ No
4									☐Yes ☐ No	☐Yes ☐ No
5									☐Yes ☐ No	☐Yes ☐ No
6									☐Yes ☐ No	☐Yes ☐ No

Conventional Medicines taken by Patient & Prescribed by Nephrologists

No.	Name of CM	Strength	Form	Dosage regimen	Duration of Use	Indications	Prescribed by
1							
2							
3							

4								
5								
6								
7								
8								

Naranjo causality scale for ADR

Question/ Scoring Yes/No/Do not know or unavailable	Yes	No	Do not know or unavailable
1. Are there previous conclusive reports on this reaction?	1	0	0
2. Did the adverse event appear after the suspected drug was given?	2	-1	0
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	1	0	0
4. Did the adverse reaction appear when the drug was re-administered?	2	-1	0
5. Are there alternative causes that could have caused the reaction?	-1	2	0
6. Did the reaction reappear when a placebo was given?	-1	1	0
7. Was the drug detected in any body fluid in toxic concentrations?	1	0	0
8. Was the reaction more severe when the dose was increased/increasing or less severe when the dose was decreased?	1	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	1	0	0
Total			

Scoring: 9 = Definite ADR, **(5-8)** =Probable ADR, **(1-4)** =Possible ADR, **0** =Doubtful ADR

Survey ID:..... ..... SKMC #.....

Name of Patient:..... .....Age .....Nationality.....

S.N	Test	Result	Report date / Remarks
1	Creatinine		
2	Creatinine Level		
3	Cr. Clearance		
4	Cr.Cl. Level		
5	GFR		
6	Urine 24 hr		
7	Urea		
8	Urea level		
9	Na		
10	Ca		
11	Mg		
12	K		
13	PO4		
14	Uric acid		
15	Albumin		
16	Albumin Level		
17	Total Albumin		
18	Mic. Albumin		
19	Billirubin		
20	Billirubin Level		
21	Total Protein		
22	Protein		
23	Protein Level		
24	Hb		
25	Hb Level		
26	Cholesterol		
27	Cholesterol Level		
28	Glucose		
29	Glucose Level		
30	Tacrolimus		
31	Tacrolimus Level		
32	Enzymes		
33	Enzymes Level		
34	Correlated.CCT		

Appendix 3.2

Case studies of patients reporting ADRs to herbal medicines in the Phase 2 study.

Summary of ADR Cases

Case numbers represent the case number used in the original sample of 49 suspected ADRs.

The 26 cases assigned possibly or probably related to herbs are presented here.

Case number	**2**		
Reporter details	**Patient** √	**Patient's doctor**	**Other**
Patient details	**Age (years)**	**Gender**	**Reason for Attendance at SKMC**
	15	Female	➢ Follow up visit at Nephrology Clinic
Case Type	**Retrospective** √		**Prospective**
Description of Suspected ADR	**Sign and symptoms** Diarrhoea **Lab tests (N:Normal , L: Low , H; High)** creatinine (N), urea (N),Na (N), Mg (N), K (N), PO4 (N),uric acid (N),albumin (N),bilirubin (N),total protein (N),HB (N),cholesterol 6 (H),glucose (N),ALP (N),AST(N), ALT(N),GFR 68 (L) **Other** Severe diarrhoea after senna intake		
Type	**Herbal ADR**		
List of Herbal Medicines taken	anise, thyme, senna, cinnamon		
List of Conventional Medicines taken	Niferex, alendronate, vit D, Ca, paracetamol,		
Sources of data	**Patient notes** √	**Conversation with patient** √	**Patient's doctor**
Possible cause(s)	Senna		
Author's conclusion	**Justification – brief summary** Niferex (multivitamins and iron) has diarrhoea[1] as a side effect, alendronate side effect is diarrhoea, senna causes diarrhoea[2] and possibly enhances this side effect of the PMs taken. **Naranjo score / modified Naranjo score** 1 (**possible**) / 1 (possible)		
Consensus conclusion	This relationship is possible. Most of the drugs listed are associated with diarrhoea.		

[1] http://www.drugs.com/sfx/niferex-side-effects.html (accessed 9/07/09)

[2] http://www.drugs.com/mtm/senna.html (accessed 9/07/09)

Case number	6		
Reporter details	**Patient** √	**Patient's doctor**	**Other**
Patient details	**Age (years)** 55	**Gender** **Female**	**Reason for Attendance at SKMC** ➢ Follow up visit at Nephrology Clinic
Case Type	**Retrospective** √		**Prospective**
Description of Suspected ADR	**Sign and symptoms** Abdominal pain **Lab tests (N:Normal , L: Low , H; High)** creatinine 104 (N),urea 8 (H),Na134 (L),Mg 1 (N), K 4 (L),PO4 2 (H),uric acid 428 (H),albumin 37 (N),bilirubin 15 (N),total protein 66 (N),HB 121 (N),cholesterol 6 (H),glucose 6 (N),ALP 70 (N),AST 15 (N),ALT 17 (N), CCT 97 (N),GFR 71 (L) **Other** Abdominal pain when patient had senna or thyme.		
Type	**Herb- Drug Interaction resulting in ADR**		
List of Herbal Medicines taken	senna, thyme, karkadeh, ginger, fenugreek		
List of Conventional Medicines taken	emla cream (lidocaine), lactulose, aspirin, losartan, amlodipine, folic acid, 'renal' multivitamin supplement, omeprazole, moxonidine, atorvastatin, ca-acetate, sevelamer (for hyperphosphatemia), gabapentin		
Sources of data	**Patient notes** √	**Conversation with patient** √	**Patient's doctor**
Possible cause(s)	Senna, thyme and lactulose **Justification – brief summary**		
Author's conclusion	Interactions between senna herbs & lactulose, atorvastatin side effect is stomach pain[3]. Senna may cause mild abdominal discomfort such as colic or cramps.[3] Toxic symptoms of volatile oil of thyme (thymol) documented for causing gastric pain[3] **Naranjo score / modified Naranjo score** 2 (**possible**) / 2 (possible)		
Consensus conclusion	This case is a possible ADR.		

[3]Herbal Medicine: A Guide for Health Care Professionals by Joanne Barnes, Linda A. Anderson, J. David Phillipson, and Joanne Barnes, 2002. Pharmaceutical Press.

Case number	**8**		
Reporter details	**Patient** √	**Patient's doctor**	**Other**
Patient details	**Age (years)**	**Gender**	**Reason for Attendance at SKMC**
	59	Male	➢ Follow up visit at Nephrology Clinic
Case Type	**Retrospective** √		**Prospective**
Description of Suspected ADR	**Sign and symptoms** Increase stomach acidity and presence of blood in stool after herbs intake **Lab tests (N:Normal , L: Low , H; High)** creatinine (N),urea (N), Na (N),Mg (N), K (N), PO4 (N),uric acid (N),albumin (N),bilirubin (N),total protein (N),cholesterol (N),ALP (N),AST (N),ALT (N),GFR =73 (L) **Other**		
Type	**Herbal ADR**		
List of Herbal Medicines taken	Peppermint, ginger, Arabic gum, thyme, fenugreek		
List of Conventional Medicines taken	amlodipine, paracetamol, allopurinol, ca-supplements, diclofenac sodium gel, multivitamins, hydroxyzine		
Sources of data	**Patient notes** √	**Conversation with patient** √	**Patient's doctor**
Possible cause(s)	Patient had increase in acidity after ginger intake , and blood in stool after thyme intake		
Author's (Fatima's) conclusion	**Justification – brief summary** Side effect of paracetamol is occasionally bleeding[4], rarely blood disorders (e.g thrombocytopenia , leucopenia , neutropenia)[5]. Ginger has inhibition of platelet activity [6], toxic symptoms of volatile oil of thyme (thymol) documented for causing gastric pain, nausea, vomiting[6].		
Consensus conclusion	**Naranjo score / modified Naranjo score** 5 (**probable**) / 5 (Definite) This case has a strong association. One or more herbs (thyme and/ or ginger) may have been associated with the patient's complaint. Diclofenac is an NSAID commonly associated with increased GI discomfort and sometimes blood in the stools, but in this case, in gel form so the risk will be a lot lower than with the oral form.		

[4] http://www.drugs.com/cons/tylenol-drops.html (accessed 9/07/09)

[5] British National Formulary (BNF) edition No.56 -September 2008

[6] Herbal Medicine: A Guide for Health Care Professionals by Joanne Barnes, Linda A. Anderson, J. David Phillipson, and Joanne Barnes, 2002. Pharmaceutical Press.

Case number	**9**		
Reporter details	**Patient** √	**Patient's doctor**	**Other**
Patient details	**Age (years)** **70**	**Gender** Female	**Reason for Attendance at SKMC** ➢ Follow up visit at Nephrology Clinic
Case Type	**Retrospective**		**Prospective** √
Description of Suspected ADR	**Sign and symptoms** Patient complained of low blood pressure after herbs intake.		
	Lab tests (N:Normal , L: Low , H; High) creatinine 108 (H),urea 9 (H),Na 138 (N),Mg 1 (N), K 4 (N),PO4 1 (N),uric acid 190 (L),albumin 34 (L),bilirubin 12 (N),total protein 74 (N),HB 111 (L),glucose 10 (H),ALP 88 (N),AST 21 (N),ALT 29 (N),GFR 65 (L)		
	Other		
Type	**Herb- Drug Interaction resulting in ADR**		
List of Herbal Medicines taken	senna, thyme, fenugreek, black seed, cardamom		
List of Conventional Medicines taken	Ca-acetate, aspirin, atorvastatin, omeprazole, isosorbide mononitrate, cetirizine		
Sources of data	**Patient notes** √	**Conversation with patient** √	**Patient's doctor**
Possible cause(s)	Thyme, fenugreek, black seeds		
Author's conclusion	**Justification – brief summary** Nitrate drugs (Imdur) may interact with thyme[7] and fenugreek[7]which also have hypotensive activity. Black seeds have hypotensive effect[7]		
	Naranjo score / modified Naranjo score 5 (**probable**) / 5 (definite)		
Consensus conclusion	This case has strong (probable) interaction.		

[7] Herbal Medicine: A Guide for Health Care Professionals by Joanne Barnes, Linda A. Anderson, J. David Phillipson, and Joanne Barnes, 2002. Pharmaceutical Press.

Case number	**10**		
Reporter details	**Patient** √	**Patient's doctor**	**Other**
Patient details	**Age (years)**	**Gender**	**Reason for Attendance at SKMC**
	63	Male	➢ Follow up visit at Nephrology Clinic
Case Type	**Retrospective** √		**Prospective**
Description of Suspected ADR	**Sign and symptoms** Patient complained of itching after herb intake. **Lab tests (N:Normal , L: Low , H; High)** creatinine 55 (N),urea 4 (N),Na 137 (N),Mg 1 (N), K 4 (N),PO4 1 (N),uric acid 180 (L),bilirubin 36 (H),HB 110 (L),cholesterol 4 (N),glucose 7 (H),GFR 107 (N) **Other** Itching after fenugreek intake		
Type	**Herbal ADR**		
List of Herbal Medicines taken	fenugreek		
List of Conventional Medicines taken	amlodipine, Ca-acetate, folic acid, 'renal' vitamin supplement, lactulose, Na docusate, omeprazole, hydralazine, metoprolol		
Sources of data	**Patient notes** √	**Conversation with patient** √	**Patient's doctor**
Possible cause(s)	Fenugreek		
Author's conclusion	**Justification – brief summary** Documented signs of an allergic reaction due to fenugreek are: an unexplained rash, hives, itching, unexplained swelling, wheezing, difficulty breathing or swallowing [8,9,10,11] **Naranjo score / modified Naranjo score** 5 (**probable**) / 5 (definite)		
Consensus conclusion	This case has strong or high probability.		

[8] http://nccam.nih.gov/health/fenugreek/#cautions (accessed 9/07/09)

[9] http://nccam.nih.gov/health/fenugreek/index.htm (accessed 9/07/09)

[10] http://www.ncbi.nlm.nih.gov/pubmed/18930518?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DiscoveryPanel.Pubmed_Discovery_RA&linkpos=1&log$=relatedarticles&logdbfrom=pubmed (accessed 9/07/09)

[11] http://www.ncbi.nlm.nih.gov/pubmed/9087156?ordinalpos=3&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum (accessed 9/07/09)

Case number	**11**		
Reporter details	**Patient** √	**Patient's doctor**	**Other**
Patient details	**Age (years)** 42	**Gender** Female	**Reason for Attendance at SKMC** ➢ Follow up visit at Nephrology Clinic
Case Type	**Retrospective**		**Prospective** √
Description of Suspected ADR	**Sign and symptoms** Acidity of stomach		
	Lab tests (N:Normal , L: Low , H; High) creatinine 338 (H),urea 39 (H*),Na 131 (L), K 6 (H), PO4 2 (H),albumin 30 (L),bilirubin 7 (N),total protein 79 (N),HB 108 (L),cholesterol 2 (L),glucose 12 (H),ALP 107 (N),AST 12 (L),ALT 8 (N), GFR 12 (L)		
	Other		
Type **List of Herbal Medicines taken**	**Herb- Drug Interaction resulting in ADR** ginger, cinnamon, cardamom, red chilli		
List of Conventional Medicines taken	losartan, atorvastatin, allopurinol, aspirin		
Sources of data	**Patient notes** √	**Conversation with patient**	**Patient's doctor**
Possible cause(s)	Cinnamon and possibly other herbs		
Author's (Fatima's) conclusion	**Justification – brief summary** Cinnamon is an irritant to mucous membranes[12], aspirin[13,14] and atorvastatin[15,16]side effects include stomach pain and heartburn.		
	Naranjo score / modified Naranjo score 5 (**probable**) / 5 (definite)		
Consensus conclusion	This case is of high probability. GI symptoms may also be associated with diabetic nephropathy and chronic renal failure.		

[12] Herbal Medicine: A Guide for Health Care Professionals by Joanne Barnes, Linda A. Anderson, J. David Phillipson, and Joanne Barnes, 2002. Pharmaceutical Press

[13] http://www.drugs.com/cdi/aspirin.html (accessed 9/07/09)

[14] http://www.drugs.com/sfx/aspirin-side-effects.html (accessed 9/07/09)

[15] http://www.drugs.com/lipitor.html (accessed 9/07/09)

[16] British National Formulary (BNF) edition No.56 -September 2008

Case number	**13**		
Reporter details	**Patient** √	**Patient's doctor**	**Other**
Patient details	**Age (years)** 51	**Gender** Female	**Reason for Attendance at SKMC** ➢ Follow up visit at Nephrology Clinic
Case Type	**Retrospective** √		**Prospective**
Description of Suspected ADR	**Sign and symptoms** Dizziness (and diarrhoea)		
	Lab tests (N:Normal , L: Low , H; High) creatinine 186 (H),urea 10 (H),Na 140 (N), Mg 1 (N), K 5 (N), PO4 1 (N),mic albumin 5 (N),HB 133 (N),cholesterol 4 (N),glucose 7 (H),GFR 35 (L)		
	Other herbs caused diarrhoea and dizziness		
Type	**Herb- Drug Interaction resulting in ADR**		
List of Herbal Medicines taken	mix (black seed, fenugreek, anise, oat), ginger, thyme		
List of Conventional Medicines taken	insulin, ASA, mycophenolate mofetil, Ca, atorvastatin, losartan, prednisolone,ciclosporin, amlodipine, metoprolol, moxonidine		
Sources of data	**Patient notes** √	**Conversation with patient** √	**Patient's doctor**
Possible cause(s)	Herbal mixture, ginger, thyme and PMs		
Author's conclusion	**Justification – brief summary** **Dizziness:** insulin interacts with herbal ingredients with hypoglycaemic activity (fenugreek[17]+ ginger[17]), leading to dizziness. Calcium channel blocking drugs (amlodipine) interact with herbal ingredients with hypotensive activity (ginger+ fenugreek+ thyme)[17], amlodipine drug side effect is dizziness.[18] Antihypertensive drugs (losartan) interact with herbal ingredients with hypotensive activity (ginger+ fenugreek+ thyme) to cause potentiation[17]. Mycophenolate mofetil side effect is diarhoea[18], omeprazole side effect is diarrhoea and dizziness[18], atorvastatin side effect is diarrhoea and dizziness[19], ASA side effects is dizziness and diarrhoea.[19] Losartan drug side effects is diarrhoea and dizziness.[20] Toxic symptoms of volatile oil of thyme (thymol) documented for causing dizziness[17]. **Diarrhoea:** none of the herbs listed are associated with diarrhoea.		
	Naranjo score / modified Naranjo score 5 (**probable**) / 5 (definite)		
Consensus conclusion	High possibility (probability) of herb – PM interactions linked to dizziness.		

[17] Herbal Medicine: A Guide for Health Care Professionals by Joanne Barnes, Linda A. Anderson, J. David Phillipson, and Joanne Barnes, 2002. Pharmaceutical Press

[18] British National Formulary (BNF) edition No.56 -September 2008.

[19] http://www.drugs.com/sfx/aspirin-side-effects.html (accessed 9/07/09)

[20] British National Formulary (BNF) edition No.56 -September 2008.

Case number	**14**		
Reporter details	**Patient** √	**Patient's doctor**	**Other**
Patient details	**Age (years)**	**Gender**	**Reason for Attendance at SKMC**
	34	Male	➢ Follow up visit at Nephrology Clinic
Case Type	**Retrospective** √		**Prospective**
Description of Suspected ADR	**Sign and symptoms** tiredness. **Lab tests (N:Normal , L: Low , H; High)** creatinine 144 (H),urea 10 (H),Na 141 (N), Mg 1 (N), K 5 (N), PO4 1 (N),uric acid 441 (H),albumin 38 (N),mic albumin 109 (H*),bilirubin 10 (N),total protein 65 (N),HB 134 (N),cholesterol 4 (N),glucose 9 (H) ,ALP 82 (N),AST 24 (N),ALT 32 (N),GFR 49 (L) **Other** senna causes tiredness		
Type	**Herb- Drug Interaction resulting in ADR**		
List of Herbal Medicines taken	senna, Phytoshape slimming brand		
List of Conventional Medicines taken	lisinopril		
Sources of data	**Patient notes** √	**Conversation with patient** √	**Patient's doctor**
Possible cause(s)			
Author's conclusion	**Justification – brief summary** Lisinopril listed drug side effect is fatigue and malaise[21] Phytoshape contains counterfeit sibutramine, which has weakness and fatigue[21] as side effects.		
Consensus conclusion	**Naranjo score / modified Naranjo score** 5 (**probable**) / 5 (definite) This case is of high possibility. High probability of drug interaction between drugs and herbs.		

[21] British National Formulary (BNF) edition No.56 -September 2008

Case number	15		
Reporter details	Patient √	Patient's doctor	Other
Patient details	Age (years) 39	Gender Female	Reason for Attendance at SKMC ➢ Follow up visit at Nephrology Clinic
Case Type	Retrospective √		Prospective
Description of Suspected ADR	**Sign and symptoms** 1 Itching, 2: vomiting, stomach acidity **Lab tests (N:Normal , L: Low , H; High)** creatinine 475 (H),urea 23 (H),Na 144 (N), Mg 1 (N), K 5 (N), PO4 2 (H),albumin 34 (L),bilirubin 11 (N), total protein 63 (N),HB 117 (N),cholesterol 4 (N),glucose 5 (N),ALP 57 (N),AST 6 (L),ALT 9 (N), GFR 10 (L) **Other** fenugreek caused itching , mixtures of herbs caused vomiting and heartburn		
Type	**Herb- Drug Interaction resulting in ADR**		
List of Herbal Medicines taken	mixture of herbs, fenugreek, arabic gum, chamomile, thyme, peppermint, senna, sage		
List of Conventional Medicines taken	Methyldopa		
Sources of data	Patient notes √	Conversation with patient √	Patient's doctor
Possible cause(s)	Herbs with methydopa		
Author's conclusion	**Justification – brief summary** **Itching:** methyldopa side effect is allergic (hypersensitivity) reaction[22]; signs of an allergic reaction due to fenugreek are: unexplained rash, hives, itching, unexplained swelling, wheezing, difficulty breathing or swallowing[23]. Chamomile can cause allergic skin reactions[24]. **Vomiting and stomach acidity:** herbal ingredients with local GI irritant activity include sage.[25] Toxic symptoms of volatile oil of thyme (thymol) documented for causing gastric pain, nausea, vomiting[26]. **Naranjo score / modified Naranjo score** 5 (**probable**) / 5 (definite)		
Consensus conclusion	This association is of high possibility. High probability of interaction between drugs and herbs especially in this case of end stage kidney disease.		

[22] British National Formulary (BNF) edition No.56 -September 2008

[23] http://diabetes.emedtv.com/fenugreek/fenugreek-side-effects.html (accessed 9/07/09)

[24] Herbal Medicine: A Guide for Health Care Professionals by Joanne Barnes, Linda A. Anderson, J. David Phillipson, and Joanne Barnes, 2002. Pharmaceutical Press.

[25] http://www.drugs.com/npp/sage.html (accessed 9/07/09)

[26] http://www.druginfosys.com/Drug.aspx?drugCode=1254&drugName=Thymol&type=7 (accessed 9/07/09)

Case number	**16**		
Reporter details	**Patient** √	**Patient's doctor**	**Other**
Patient details	**Age (years)**	**Gender**	**Reason for Attendance at SKMC**
	59	Male	➢ Follow up visit at Nephrology Clinic
Case Type	**Retrospective**		**Prospective** √
Description of Suspected ADR	**Sign and symptoms** Abdominal pain **Lab tests (N:Normal , L: Low , H; High)** creatinine 117 (H),urea 5 (N),Na138 (N),Mg 1 (N), K 4 (N),PO4 1 (N),uric acid 305 (N),albumin 39 (N),bilirubin 14 (N),total protein 67 (N),cholesterol 4 (N),glucose 5 (N),ALP 127 (H),AST 17 (N),ALT 18 (N),GFR 64 (L) **Other** abdominal pain when patient took herbs for constipation		
Type	**Herb- Drug Interaction resulting in ADR**		
List of Herbal Medicines taken	Mixture of herbs, thyme		
List of Conventional Medicines taken	sildenafil, paracetamol, diclofenac gel, amlodipine, gliclazide, losartan, aspirin, atorvastatin, ranitidine, docusate sodium.		
Sources of data	**Patient notes** √	**Conversation with patient** √	**Patient's doctor**
Possible cause(s)	Mixture of ingredients may have contributed to the ADR		
Author's conclusion	**Justification – brief summary** Laxative herbs e.g. senna can cause abdominal spasms and pain[27]; amlodipine drug side effect is nausea, stomach pain[28]; gliclazide side effect is stomach pain[29]. Toxic symptoms of volatile oil of thyme (thymol) include gastric pain.[27]		
Consensus conclusion	**Naranjo score / modified Naranjo score** 3 (**possible**) / 3 (probable) Possible association. Diabetic nephropathy may also contribute.		

[27] Herbal Medicine: A Guide for Health Care Professionals by Joanne Barnes, Linda A. Anderson, J. David Phillipson, and Joanne Barnes, 2002. Pharmaceutical Press.

[28] http://www.mayoclinic.com/health/drug-information/DR602957/DSECTION=side-effects (accessed 9/07/09)

[29] http://www.medicinenet.com/gliclazide-oral_tablet/article.htm (accessed 9/07/09)

Case number	**17**		
Reporter details	**Patient** √	**Patient's doctor**	**Other**
Patient details	**Age (years)** **54**	**Gender** Male	**Reason for Attendance at SKMC** ➢ Follow up visit at Nephrology Clinic
Case Type	**Retrospective** √		**Prospective**
Description of Suspected ADR	**Sign and symptoms** Raised blood pressure.		
	Lab tests (N:Normal , L: Low , H; High) creatinine 187 (H),urea 10 (H),Na141 (N),Mg 1 (N), K 3 (L),PO4 2 (H),albumin 34 (N),mic albumin 18 (N) ,total protein 72 (N),HB 83 (L),cholesterol 4 (N),glucose 5 (N),ALP 93 (N),AST 17 N),ALT 13 (N),Correlated CCT 11 (N)		
	Other ginseng may cause increased blood pressure.		
Type	**Herb- Drug Interaction resulting in ADR**		
List of Herbal Medicines taken	ginseng, thyme, fenugreek, ginger, herbal vitamin supplementation		
List of Conventional Medicines taken	darbepoetin, allopurinol, multivitamins with iron; sevelamer (for hyperphosphatemia) losartan, vitamin D, $NaHCO_3$, tamsulosin hydrochloride		
Sources of data	**Patient notes** √	**Conversation with patient** √	**Patient's doctor**
Possible cause(s)	Ginger and ginseng plus PM **Justification – brief summary**		
Author's conclusion	Tamsulosin may cause irregular heartbeat (tachycardia) and palpitations[30]. Animal studies have reported that ginger and ginseng have hypertensive activity[31]. **Naranjo score / modified Naranjo score** 1 (**possible**) / 1 (possible)		
Consensus conclusion	ADR linked to a possible drug interaction (antagonistic) with one or more PMs. Hypertension associated with renal impairment may have been a feature in this patient.		

[30] British National Formulary (BNF) edition No.56 -September 2008

[31] Herbal Medicine: A Guide for Health Care Professionals by Joanne Barnes, Linda A. Anderson, J. David Phillipson, and Joanne Barnes, 2002. Pharmaceutical Press.

Case number	**19**		
Reporter details	**Patient** √	**Patient's doctor**	**Other**
Patient details	**Age (years)** 19	**Gender** Female	**Reason for Attendance at SKMC** ➢ Follow up visit at Nephrology Clinic
Case Type	**Retrospective** √		**Prospective**
Description of Suspected ADR	**Sign and symptoms** Severe nausea & vomiting **Lab tests (N:Normal , L: Low , H; High)** creatinine 984 (H*),urea 16 (H),Na 135 (N), Mg 1 (N), K 5 (N), PO4 2 (H),albumin 35 (N),billirubin 13 (N),total protein 65 (N),HB 117 (N),ALP 65 (N),AST 15 (N),ALT 11 (N),GFR 4 (L) **Other** herbs caused nausea and vomiting		
Type	**Herb- Drug Interaction resulting in ADR**		
List of Herbal Medicines taken	Garlic		
List of Conventional Medicines taken	Omeprazole, Niferex (polysaccharide complex), darbepoietin, mycophenolate		
Sources of data	**Patient notes** √	**Conversation with patient** √	**Patient's doctor**
Possible cause(s)	Herb / PM / underlying disease interaction		
Author's conclusion	**Justification – brief summary** omeprazole interacts with irritant herbal ingredients (garlic) to cause exacerbation of side-effects of omeprazole[32], omeprazole side effects include nausea and vomiting[33], Niferex (iron supplements) side effects are stomach upset, vomiting & nausea,[34] darbepoetin side effects include vomiting, nausea and stomach pain[35], mycophenolic acid side effects include severe nausea and vomiting.[36] **Naranjo score / modified Naranjo score** 2 (**possible**) / 2 (possible)		
Consensus conclusion	Possible causal association due to herb / PM interaction. May be associated with existing chronic uraemia inducing severe nausea and vomiting in this end stage kidney failure patient. Any additional herbs and drugs may exacerbate the symptoms. This is a very possible interaction.		

[32] Herbal Medicine: A Guide for Health Care Professionals by Joanne Barnes, Linda A. Anderson, J. David Phillipson, and Joanne Barnes, 2002. Pharmaceutical Press.

[33] http://www.mayoclinic.com/health/drug-information/DR601471/DSECTION=side-effects (accessed 9/07/09)

[34] http://www.mayoclinic.com/health/drug-information/DR602285/DSECTION=side-effects (accessed 9/07/09)

[35] http://www.mayoclinic.com/health/drug-information/DR601793/DSECTION=side-effects (accessed 9/07/09)

[36] http://www.mayoclinic.com/health/drug-information/DR601823/DSECTION=side-effects (accessed 9/07/09)

Case number	**21**		
Reporter details	**Patient** √	**Patient's doctor**	**Other**
Patient details	**Age (years)**	**Gender**	**Reason for Attendance at SKMC**
	64	Female	➢ Follow up visit at Nephrology Clinic
Case Type	**Retrospective** √		**Prospective**
Description of Suspected ADR	**Sign and symptoms** Abdominal pain , vomiting **Lab tests (N:Normal , L: Low , H; High)** No abnormal lab tests in the patient's record **Other** Senna and / or thyme caused abdominal pain and vomiting		
Type	**Herb- Drug Interaction resulting in ADR**		
List of Herbal Medicines taken	cumin, senna, fenugreek, ginger, thyme, sage		
List of Conventional Medicines taken	meloxicam, omeprazole		
Sources of data	**Patient notes** √	**Conversation with patient** √	**Patient's doctor**
Possible cause(s)	Herbs interacting with PM		
Author's conclusion	**Justification – brief summary** Omeprazole interacts with irritant herbal ingredients (sage+ thyme) to cause exacerbation of side-effects[37], omeprazole side effects include abdominal pain[38], meloxicam side effects include heartburn, nausea, stomach upset and severe vomiting[38] Toxic symptoms of volatile oil of thyme (thymol) documented for causing gastric pain, nausea, vomiting.[37] **Naranjo score / modified Naranjo score** 2 (**possible**) / 2 (possible)		
Consensus conclusion	Possible Interaction of the herbs with the drugs used.		

[37] Herbal Medicine: A Guide for Health Care Professionals by Joanne Barnes, Linda A. Anderson, J. David Phillipson, and Joanne Barnes, 2002. Pharmaceutical Press

[38] British National Formulary (BNF) edition No.56 -September 2008

Case number	**22**		
Reporter details	**Patient** √	**Patient's doctor**	**Other**
Patient details	**Age (years)** **43**	**Gender** Male	**Reason for Attendance at SKMC** ➢ Follow up visit at Nephrology Clinic
Case Type	**Retrospective** √		**Prospective**
Description of Suspected ADR	**Sign and symptoms** Patient suspected herbs caused renal failure **Lab tests (N:Normal , L: Low , H; High)** creatinine 111 (H),GFR 52 (L) **Other** herbs caused renal failure		
Type	**Herb- Drug Interaction resulting in ADR**		
List of Herbal Medicines taken	mixture of herbs, thyme		
List of Conventional Medicines taken	amoxicillin/clavulanate, paracetamol, orphenadrine		
Sources of data	**Patient notes** √	**Conversation with patient** √	**Patient's doctor**
Possible cause(s)	Herbs interacting with orphenadrine.		
Author's conclusion	**Justification – brief summary** Orphenadrine should be used with caution in hypertension and renal impairment[39] .Orphenadrine may be interacting with herbal preparations to exacerbate kidney disease.		
	Naranjo score / modified Naranjo score 2 (**possible**) / 2 (possible) Possible Interaction.		
Consensus conclusion	Orphenadrine does in itself exacerbate renal failure in somebody who already has kidney insufficiency. It is possible that these herbs worsen the renal situation.		

[39] British National Formulary (BNF) edition No.56 -September 2008.

Case number	**23**		
Reporter details	**Patient** √	**Patient's doctor**	**Other**
Patient details	**Age (years)**	**Gender**	**Reason for Attendance at SKMC**
	43	Female	➢ Follow up visit at Nephrology Clinic
Case Type	**Retrospective** √		**Prospective**
Description of Suspected ADR	**Sign and symptoms** Patient complained that herbs caused her abortion in 2nd trimester. **Lab tests (N:Normal , L: Low , H; High)** creatinine 191 (H),urea 7 (H),Na 135 (N), Mg 1 (N), K 5 (N), PO4 1 (N),uric acid 432 (H),albumin 26 (L),bilirubin 9 (N), total protein 58 (L),HB 99 (L),glucose 5 (N),ALP 70 (N),AST 16 (N),ALT 10 (N), GFR 27 (L) **Other** peppermint oil, fenugreek, chamomile or sage caused abortion		
Type	**Herbal ADR**		
List of Herbal Medicines taken	fenugreek, anise, chamomile, cumin, fennel, ginger, black seed, red seed, peppermint oil.		
List of Conventional Medicines taken	atenolol, indapamide		
Sources of data	**Patient notes** √	**Conversation with patient** √	**Patient's doctor**
Possible cause(s)			
Author's conclusion	**Justification – brief summary** Chamomile[40,41] is known to be uterotonic (excessive use of chamomile during pregnancy and lactation should be avoided)[41] . Sage is contra-indicated during pregnancy. Traditionally, it is reputed to be an abortifacient and to affect the menstrual cycle. The volatile oil contains a high proportion of α- and β-thujones, which are known to be abortifacient and emmenagogic[41]. Peppermint oil should be avoided during pregnancy due to insufficient safety information and a potential for toxicity.[42] Fenugreek is reputed to be oxytocic and in-vitro has uterine stimulant activity has been documented[41]. Use of fenugreek during pregnancy and lactation in doses greatly exceeding those normally encountered is not advisable. Sage is contraindicated during pregnancy and is reputed to be an abortificient. Chamomile is reputed to be abortificient[43] **Naranjo score / modified Naranjo score** 5 (**probable**) / 5 (definite)		
Consensus conclusion	High probability of herb-induced abortion.		

[40] http://www.nlm.nih.gov/medlineplus/druginfo/natural/patient-chamomile.html (accessed 9/07/09)

[41] Herbal Medicine: A Guide for Health Care Professionals by Joanne Barnes, Linda A. Anderson, J. David Phillipson, and Joanne Barnes, 2002. Pharmaceutical Press.

[42] http://www.nlm.nih.gov/medlineplus/druginfo/natural/patient-peppermint.html (accessed 9/07/09)

[43] Herbal Medicine: A Guide for Health Care Professionals by Joanne Barnes, Linda A. Anderson, J. David Phillipson, and Joanne Barnes, 2002. Pharmaceutical press.

Case number	**24**		
Reporter details	**Patient** √	**Patient's doctor**	**Other**
Patient details	**Age (years)** **52**	**Gender** **Female**	**Reason for Attendance at SKMC** ➢ Follow up visit at Nephrology Clinic
Case Type	**Retrospective** √		**Prospective**
Description of Suspected ADR	**Sign and symptoms** 1: tiredness 2: nausea, abdominal pain		
	Lab tests (N:Normal , L: Low , H; High) No abnormal lab tests in patient's record		
	Other senna caused nausea and abdominal pain, mixture of herbs caused stomach pain and tiredness		
Type	**Herb- Drug Interaction resulting in ADR**		
List of Herbal Medicines taken	mix (black seeds, garlic, herbs), ginger, senna, fenugreek, senna, mixture of herbs		
List of Conventional Medicines taken	irbesartan		
Sources of data	**Patient notes** √	**Conversation with patient** √	**Patient's doctor**
Possible cause(s)	Interaction between ginger, fenugreek and irbesartan. Interaction between senna and irbesartan.		
Author's conclusion	**Justification – brief summary** **Tiredness:** antihypertensive drugs (irbesartan) interact with herbal ingredients with hypotensive effect (ginger, fenugreek). **Nausea and abdominal pain:** irbesartan side effects are nausea and stomach pain (dyspepsia and chest pain)[44], senna may cause mild abdominal discomfort such as colic or cramps. Prolonged use or overdosage can result in diarrhoea with excessive loss of potassium, albuminuria and haematuria[45] **Naranjo score / modified Naranjo score** 2 (**possible**) / 2 (possible)		
Consensus conclusion	Very possible interaction.		

[44] British National Formulary (BNF) edition No.56 -September 2008.

[45] Herbal Medicine: A Guide for Health Care Professionals by Joanne Barnes, Linda A. Anderson, J. David Phillipson, and Joanne Barnes, 2002. Pharmaceutical Press.

Case number	**25**		
Reporter details	**Patient** √	**Patient's doctor**	**Other**
Patient details	**Age (years)** **48**	**Gender** **Female**	**Reason for Attendance at SKMC** ➢ Follow up visit at Nephrology Clinic
Case Type	**Retrospective** √		**Prospective**
Description of Suspected ADR	**Sign and symptoms** Nausea (and dizziness)		
	Lab tests (N:Normal , L: Low , H; High) creatinine 660 (H),urea 13 (H),Na 132 (L), Mg 1 (N), K 5 (N), PO4 1 (N),albumin 29 (L),bilirubin 11 (N) ,total protein 69 (N),HB 105 (L),glucose 7 (H),ALP 54 (N),AST 17 (N), ALT 9 (N),GFR 7 (L)		
	Other senna caused nausea (and dizziness)		
Type	**Herb- Drug Interaction resulting in ADR**		
List of Herbal Medicines taken	mix (fenugreek, aloe), senna, aloe, stinkweed, myrrh		
List of Conventional Medicines taken	valganciclovir, prednisolone, sirolimus, omeprazole, co-trimoxazole, amlodipine, ASA, atorvastatin, tacrolimus, trimetazidine		
Sources of data	**Patient notes** √	**Conversation with patient** √	**Patient's doctor**
Possible cause(s)	Herbs interacting with PMs to produce nausea and possibly dizziness due to hypoglycaemia.		
Author's conclusion	**Justification – brief summary** Sirolimus side effects include nausea, vomiting and dizziness,[46] prednisolone side effects include nausea and vomiting)[47] and stomach pain[48]. Omeprazole side effects include stomach pain, nausea, vomiting and dizziness[49]; amlodipine side effects include nausea, dizziness and stomach pain[50], ASA side effects include heartburn, nausea and stomach upset[51], atorvastatin side effects include stomach upset[52]; senna is known to cause nausea[53].		
	Naranjo score / modified Naranjo score 5 (**probable**) / 5 (definite)		
Consensus conclusion	Strong possibility (probable). Probable kidney graft failure (GFR = 7). Herbal drugs are highly likely to interact with immunosuppressive and anti hypertensive drugs in view of virtually no renal excretion.		

[46] http://www.mayoclinic.com/health/drug-information/DR601827/DSECTION=side-effects(accessed 9/07/09)

[47] http://www.mayoclinic.com/health/drug-information/DR602329/DSECTION=side-effects (accessed 9/07/09)

[48] British National Formulary (BNF) edition No.56 -September 2008

[49] http://www.mayoclinic.com/health/drug-information/DR601471/DSECTION=side-effects (accessed 9/07/09)

[50] http://www.mayoclinic.com/health/drug-information/DR602957/DSECTION=side-effects (accessed 9/07/09)

[51] http://www.drugs.com/sfx/aspirin-side-effects.html (accessed 9/07/09)

[52] http://www.mayoclinic.com/health/drug-information/DR601517/DSECTION=side-effects (accessed 9/07/09)

[53] http://www.nlm.nih.gov/medlineplus/druginfo/meds/a601112.html (accessed 9/07/09)

Case number	**26**		
Reporter details	**Patient** √	**Patient's doctor**	**Other**
Patient details	**Age (years)** **49**	**Gender** Male	**Reason for Attendance at SKMC** ➢ Follow up visit at Nephrology Clinic
Case Type	**Retrospective** √		**Prospective**
Description of Suspected ADR	**Sign and symptoms** Renal failure **Lab tests (N:Normal , L: Low , H; High)** No available data **Other** patient took mixture of herbs to improve sex drive but it caused kidney failure		
Type	**Herb- Drug Interaction resulting in ADR**		
List of Herbal Medicines taken	mixture of herbs (identity unknown)		
List of Conventional Medicines taken	calcitriol, ramipril, candesartan, amlodipine, folic acid,$NaHCO_3$,darbepoetin		
Sources of data	**Patient notes** √	**Conversation with patient** √	**Patient's doctor**
Possible cause(s)	Interaction between herbal mixture and PMs		
Author's conclusion	**Justification – brief summary** Candesartan interacts with herbal preparations and dietary supplements[54], drug should be used with caution in renal artery stenosis[55]. Darbepoetin interacts with herbal preparations.[56] **Naranjo score / modified Naranjo score** 4 (**possible**) / 4 (probable)		
Consensus conclusion	Possible interaction.		

[54] http://www.umm.edu/altmed/drugs/candesartan-020625.htm (accessed 9/07/09)

[55] British National Formulary (BNF) edition No.56 -September 2008

[56] http://www.drugs.com/cdi/darbepoetin-alfa-albumin.html (accessed 9/07/09)

Case number	**27**		
Reporter details	**Patient** √	**Patient's doctor**	**Other**
Patient details	**Age (years)** **45**	**Gender** Male	**Reason for Attendance at SKMC** ➢ Follow up visit at Nephrology Clinic
Case Type	**Retrospective** √		**Prospective**
Description of Suspected ADR	**Sign and symptoms** Finger numbness		
	Lab tests (N:Normal , L: Low , H; High) creatinine 134 (H),urea 7 (H),Na 140 (N), Mg 1 (N), K 5 (N), PO4 1 (N),uric acid 349 (N),albumin 40 (N), total protein 67 (N),HB 162 (H),glucose 9 (H),GFR 50 (L)		
	Other cardamom caused numbness in fingers		
Type	**Herb- Drug Interaction resulting in ADR**		
List of Herbal Medicines taken	cardamom		
List of Conventional Medicines taken	prednisolone, ciclosporin, mycophenolate, losartan, amlodipine, carvedilol, atorvastatin, clonidine, insulin		
Sources of data	**Patient notes** √	**Conversation with patient** √	**Patient's doctor**
Possible cause(s)	Interaction of cardamom with PMs		
Author's conclusion	**Justification – brief summary** Ciclosporin[57,58], pednisolone[57], amlodipine[57], carvedilol[57,59,60]interact with herbal preparations. Carvedilol side effect is numbness or tingling of hands or feet.[61] This reaction could be an interaction of cardamom and conventional medicines taken by patient e.g. ciclosporin [62]		
	Naranjo score / modified Naranjo score 1 (**possible**) / 1 (possible)		
Consensus conclusion	Very weak possibility. Evidence for drug – drug interaction is strong. Whereas drug herb interaction in this patient with probable renal transplant insufficiency is very weak.		

[57] Herbal Medicine: A Guide for Health Care Professionals by Joanne Barnes, Linda A. Anderson, J. David Phillipson, and Joanne Barnes, 2002. Pharmaceutical Press

[58] http://www.drugs.com/pro/cyclosporine-capsules.html (accessed 9/07/09)

[59] http://www.drugs.com/pro/carvedilol.html (accessed 9/07/09)

[60] http://www.herbs2000.com/medica/carvedilol.htm (accessed 9/07/09)

[61] http://www.mayoclinic.com/health/drug-information/DR601665/DSECTION=side-effects (accessed 9/07/09)

[62] http://www.healthline.com/natstandardcontent/cardamom/2#H8 (accessed 9/07/09)

Case number	**31**		
Reporter details	**Patient** √	**Patient's doctor**	**Other**
Patient details	**Age (years)** 38	**Gender** Male	**Reason for Attendance at SKMC** ➢ Follow up visit at Nephrology Clinic
Case Type	**Retrospective** √		**Prospective**
Description of Suspected ADR	**Sign and symptoms** Patient suspected herbs causes renal failure		
	Lab tests (N:Normal , L: Low , H; High) creatinine 115 (H),urea 7 (H),Na 140 (N), Mg 1 (N), K 6 (H), PO4 1 (N),uric acid 432 (H), albumin 41 (N),bilirubin 12 (N), total protein 69 (N),HB 108 (L),cholesterol 4 (N),glucose 5 (N), GFR 71 (L)		
	Other		
Type	**Herb- Drug Interaction resulting in ADR**		
List of Herbal Medicines taken	Mixture(containing black seeds, cinnamon, moringa, paregrina, myrrh), senna, ginger, thyme, fenugreek		
List of Conventional Medicines taken	pioglitazone, gliclazide, ASA, ciclosporin, mycophenolate, prednisolone, lisinopril, amlodipine, omeprazole, atorvastatin		
Sources of data	**Patient notes** √	**Conversation with patient** √	**Patient's doctor**
Possible cause(s)	Herbs may interact with PMs used		
Author's conclusion	**Justification – brief summary** Ciclosporin interacts with prednisolone[63]; patients may not be able to use ciclosporin if they have kidney disease; ciclosporin may cause high BP or kidney problems, the risk is increased with high dose or prolonged use.[64] Ciclosporin may interact with herbal preparations.		
	Naranjo score / modified Naranjo score 1 (**possible**) / 1 (possible)		
Consensus conclusion	Very weak possibility for interaction of the herbs with the drugs. The immunosuppressant drugs in themselves could be nephrotoxic if their blood levels are not correct in a renal transplant patient such as this.		

[63] http://www.drugs.com/drug-interactions/prednisone_d00350_cyclosporine_d00079.html (accessed 9/07/09)

[64] http://www.drugs.com/cdi/cyclosporine-capsules.html (accessed 9/07/09)

Case number	**34**		
Reporter details	**Patient** √	**Patient's doctor**	**Other**
Patient details	**Age (years)** **53**	**Gender** Male	**Reason for Attendance at SKMC** ➢ Follow up visit at Nephrology Clinic
Case Type	**Retrospective** √		**Prospective**
Description of Suspected ADR	**Sign and symptoms** patient complained of loss of activity, malaise		
	Lab tests (N:Normal , L: Low , H; High) creatinine 413 (H),urea 21 (H),Na132 (L),Mg 1 (N), K 5 (N),PO4 1 (N),albumin 37 (N),billirubin 11 (N) ,total protein 76 (N),HB 144 (N),glucose 4 (N),ALP 107 (N),AST 10 (L),ALT 24 (N),GFR 14 (L)		
	Other loss of activity and malaise		
Type	**Herbal ADR**		
List of Herbal Medicines taken	senna, ginger, fenugreek, black seeds, chamomile, green tea		
List of Conventional Medicines taken	prednisolone, ciclosporin, allopurinol, amlodipine		
Sources of data	**Patient notes** √	**Conversation with patient** √	**Patient's doctor**
Possible cause(s)	**Justification – brief summary** Ginger side effect is unusual drowsiness, [65] All medicines of amlodipine[66],allopurinol[67], ciclosporin[68],prednisolone [69], side effects are to cause unusual tiredness or weakness; but the main effect appears to be ginger.		
Author's conclusion	**Naranjo score / modified Naranjo score** 3 (**possible**) / 3 (probable)		
Consensus conclusion	Possible interaction. In addition to the effect of the possible transplant rejection in this patient which itself can cause malaise and generalized fatigue there might be a possible contribution to this situation by the herbs.		

[65] http://www.drugs.com/cdi/ginger.html (accessed 9/07/09)

[66] http://www.mayoclinic.com/health/drug-information/DR600107/DSECTION=side-effects (accessed 9/07/09)

[67] http://www.mayoclinic.com/health/drug-information/DR601763/DSECTION=side-effects (accessed 9/07/09)

[68] http://www.mayoclinic.com/health/drug-information/DR601591/DSECTION=side-effects (accessed 9/07/09)

[69] http://www.mayoclinic.com/health/drug-information/DR602333/DSECTION=side-effects (accessed 9/07/09)

Case number	**35**		
Reporter details	**Patient** √	**Patient's doctor**	**Other**
Patient details	**Age (years)**	**Gender**	**Reason for Attendance at SKMC**
	62	Male	➢ Follow up visit at Nephrology Clinic
Case Type	**Retrospective** √		**Prospective**
Description of Suspected ADR	**Sign and symptoms** severe asthma attack **Lab tests (N:Normal , L: Low , H; High)** creatinine 424 (H),urea 26 (H),Na 137 (N),Mg 1 (N), K 3 (L),PO4 2 (H),uric acid 400 (N),albumin 37 (N),total protein 71 (N),HB 89 (L),cholesterol 5 (N),glucose 6 (N) **Other** ginger and mixture of herbs worsen the respiratory system and had severe asthma attack		
Type	**Herbal ADR**		
List of Herbal Medicines taken	Mixture of herbs, thyme, ginger, senna, sweet basil		
List of Conventional Medicines taken	valsartan, amlodipine, prednisolone, omeprazole, candesartan, budesonide with formoterol, salbutamol, tiotropium, azithromycin		
Sources of data	**Patient notes** √	**Conversation with patient** √	**Patient's doctor**
Possible cause(s)	Herbs used worsen respiratory function		
Author's (Fatima's) conclusion	**Justification – brief summary** Ginger and mixture of herbs may worsen the respiratory function in this asthmatic patient. There is good temporal association but no supportive evidence from the literature.		
	Naranjo score / modified Naranjo score 2 (**possible**) / 2 (possible)		
Consensus conclusion	Weak possibility.		

Case number	**36**		
Reporter details	**Patient** √	**Patient's doctor**	**Other**
Patient details	**Age (years)**	**Gender**	**Reason for Attendance at SKMC**
	57	Male	➢ Follow up visit at Nephrology Clinic
Case Type	**Retrospective** √		**Prospective**
Description of Suspected ADR	**Sign and symptoms** weakness		
	Lab tests (N:Normal , L: Low , H; High) creatinine 355 (H),urea 11 (H),Na134 (L),Mg 1 (N), K 4 (N),PO4 1 (N),uric acid 269 (N),albumin 20 (L),bilirubin 9 (N),total protein 49 (L),HB 92 (L),cholesterol 3 (N),glucose 16 (H),ALP 113 (N),AST 23 (N),ALT 20 (N),GFR 17 (L)		
Type	**Other** **Herb- Drug Interaction resulting in ADR**		
List of Herbal Medicines taken	mix of herbs (myrrh, stinkweed), ginger, fenugreek, red seeds		
List of Conventional Medicines taken	valganciclovir, prednisolone, ciclosporin, sirolimus, co-trimoxazole, omeprazole, valsartan, atorvastatin, amlodipine, gliclazide, Mg, phosphate, lactulose, insulin.		
Sources of data	**Patient notes** √	**Conversation with patient** √	**Patient's doctor**
Possible cause(s)			
Author's (Fatima's) conclusion	**Justification – brief summary** Valganciclovir side effects include weakness or tiredness[70], amlodipine can cause weakness[71]; atorvastatin side effects include weakness, muscle pain and tenderness[72], antidiabetic drugs (gliclazide) interact with herbal ingredients with hypoglycemic effect (ginger, fenugreek and myrrh)[73] **Naranjo score / modified Naranjo score** 5 (**probable**) / 5 (definite)		
Consensus conclusion	Possible interaction.		

[70] http://www.mayoclinic.com/health/drug-information/DR601413/DSECTION=side-effects (accessed 9/07/09)

[71] http://www.mayoclinic.com/health/drug-information/DR600107/DSECTION=side-effects (accessed 9/07/09)

[72] http://www.mayoclinic.com/health/drug-information/DR601517/DSECTION=side-effects (accessed 9/07/09)

[73] Herbal Medicine: A Guide for Health Care Professionals by Joanne Barnes, Linda A. Anderson, J. David Phillipson, and Joanne Barnes, 2002. Pharmaceutical Press.

Case number	37		
Reporter details	Patient √	Patient's doctor	Other
Patient details	Age (years) 68	Gender Male	Reason for Attendance at SKMC Follow up visit at Nephrology Clinic
Case Type	Retrospective		Prospective √
Description of Suspected ADR	Sign and symptoms stomach pain (peptic ulcer) Lab tests (N:Normal , L: Low , H; High) creatinine 91 (N),urea 4 (N),Na 142 (N),Mg 2 (H), K 4 (N),PO4 1 (N),uric acid 315 (N),mic albumin 22 (H),HB 165 (H),cholesterol 4 (N),glucose 6 (N),GFR 78 (L)		
Type	Other *ginger* caused stomach pain and acidity Herb- Drug Interaction resulting in ADR		
List of Herbal Medicines taken	thyme, ginger, senna		
List of Conventional Medicines taken	diclofenac sodium gel, paracetamol, amlodipine, insulin glargine, hydrochlorothiazide, lisinopril, ASA, atorvastatin, gliclazide, ezetimibe, rosiglitazone, sildenafil		
Sources of data	Patient notes √	Conversation with patient √	Patient's doctor
Author's conclusion	**Justification – brief summary** Paracetamol side effects include nausea, stomach pain and ulcer[74], amlodipine side effects include stomach pain[75], rosiglitazone side effects include stomach pain and nausea[78], hydrochlorothiazide side effects include severe nausea or stomach pain[77], lisinopril side effects include nausea and stomach pain[78], ASA side effects include heartburn, nausea, upset stomach, severe stomach pain[79], atorvastatin side effects include severe stomach pain,[80] sildenafil side effects include stomach upset and discomfort[81]. Toxic symptoms of volatile oil of thyme (thymol) documented to cause gastric pain[82]. Senna may cause mild abdominal discomfort such as colic or cramps.[83]		
Consensus conclusion	**Naranjo score / modified Naranjo score** 5 (**probable**) / 5 (definite) High possibility (probable). In addition to the different drugs which have stomach pain as side effect, the herbs might contribute to the situation.		

[74] http://www.mayoclinic.com/health/drug-information/DR601885/DSECTION=side-effects (accessed 9/07/09)

[75] http://www.mayoclinic.com/health/drug-information/DR602957/DSECTION=side-effects (accessed 9/07/09)

[76] http://www.mayoclinic.com/health/drug-information/DR602003/DSECTION=side-effects (accessed 9/07/09)

[77] http://www.mayoclinic.com/health/drug-information/DR602673/DSECTION=side-effects (accessed 9/07/09)

[78] http://www.mayoclinic.com/health/drug-information/DR602023/DSECTION=side-effects (accessed 9/07/09)

[79] http://www.drugs.com/sfx/aspirin-side-effects.html (accessed 9/07/09)

[80] http://www.mayoclinic.com/health/drug-information/DR601517/DSECTION=side-effects (accessed 9/07/09)

[81] http://www.mayoclinic.com/health/drug-information/DR601513/DSECTION=side-effects (accessed 9/07/09)

[82] Herbal Medicine: A Guide for Health Care Professionals by Joanne Barnes, Linda A. Anderson, J. David Phillipson, and Joanne Barnes, 2002. Pharmaceutical press

[83] Herbal Medicine: A Guide for Health Care Professionals by Joanne Barnes, Linda A. Anderson, J. David Phillipson, and Joanne Barnes, 2002. Pharmaceutical press.

Case number	**40**		
Reporter details	**Patient** √	**Patient's doctor**	**Other**
Patient details	**Age (years)** **58**	**Gender** Female	**Reason for Attendance at SKMC** ➢ Follow up visit at Nephrology Clinic
Case Type	**Retrospective** √		**Prospective**
Description of Suspected ADR	**Sign and symptoms** Colon inflammation		
	Lab tests (N:Normal , L: Low , H; High) creatinine 90 (N),urea 4 (N),Na140 (N),Mg 1 (N), K 4 (N),PO4 1 (N),albumin 40 (N),bilirubin 12 (N),total protein 68 (N),HB 133 (N),cholesterol 4 (N),ALP 113 (N),AST 37 (H),ALT 62 (H),GFR 91 (L)		
	Other sage caused colon inflammation		
Type	**Herbal ADR**		
List of Herbal Medicines taken	sage, parsley, ginger		
List of Conventional Medicines taken	None recorded in patient's medical file.		
Sources of data	**Patient notes** √	**Conversation with patient** √	**Patient's doctor**
Possible cause(s)			
Author's conclusion	**Justification – brief summary** sage and parsley are considered to be irritant herbal ingredients. **Naranjo score / modified Naranjo score** 5 (**probable**) / 5 (definite)		
Consensus conclusion	High possibility (probable).		

Case number	**48**		
Reporter details	**Patient** √	**Patient's doctor**	**Other**
Patient details	**Age (years)** 53	**Gender** Male	**Reason for Attendance at SKMC** ➢ Follow up visit at Nephrology Clinic
Case Type	**Retrospective** √		**Prospective**
Description of Suspected ADR	**Sign and symptoms** Stomach pain **Lab tests (N:Normal , L: Low , H; High)** creatinine 73 (N),urea 7 (H),Na 142 (N), K 4 (N),albumin 38 (N),mic albumin 57 (H),billirubin 12 (N) ,total protein 64 (N),HB 112 (L),cholesterol 4 (N),glucose 5 (N),ALP 53 (N),AST 21 (N),ALT 22 (N),GFR 74 (L) **Other** Chinese herbs caused stomach pain		
Type	**Herb- Drug Interaction resulting in ADR**		
List of Herbal Medicines taken	Chinese herbs		
List of Conventional Medicines taken	aspirin, omeprazole		
Sources of data	**Patient notes** √	**Conversation with patient** √	**Patient's doctor**
Possible cause(s)			
Author's conclusion	**Justification – brief summary** Aspirin side effects include upset stomach, severe or persistent stomach pain[84], omeprazole drug side effects include stomach pain[85]; but Chinese herbs were also strongly suspected in this case.		
Consensus conclusion	**Naranjo score / modified Naranjo score** 2 (**possible**) / 2 (possible) Highly possible.		

[84] http://www.drugs.com/sfx/aspirin-side-effects.html (accessed 9/07/09)

[85] http://www.mayoclinic.com/health/drug-information/DR601471/DSECTION=side-effects (accessed 9/07/09)

Appendix 3.3

Supplementary information on toxicity of herbs identified in Phase 2 of the research.

In both phases of the research, HM taking by subjects was widespread. In an attempt to gauge the potential harm of such use, a literature search was conducted to retrieve any relevant published reports of harm.

Method

The following sources were of particular interest:

Medline, and the journals: Phytochemistry; the Journal of Ethnopharmacology; and the Journal of Pharmacology and Toxicology. In addition, the reference textbook by Barnes et al.[1] was consulted.

The search terms used were: toxicity, side effects, adverse event, adverse reaction, adverse drug reaction, toxicology, linked to the name of herb (see below), from 1/1/1999 to the 28/12/09. Searches were carried out through the medical library of the Faculty of Medicine and Health Sciences in UAE University library. Other journals were also investigated where secondary references pointed to potentially relevant information.

Searches were conducted using the top ten herb names listed in Table 3.6, page 93 ('mixture of herbs' could not be identified further) and identified as being implicated in the adverse reactions described in Table 3.22, Page 111.

Findings are discussed below, both in the contexts of the presence of the herb in Table 3.6 and of the ADRs described in Table 3.22. Only relevant pharmacology and toxicology are discussed.

Results and discussion

With reference to Table 3.6 (Herbs taken by five or more patients in the study.), no links to ADRs with cardamom and anise were discovered, implicating that these herbs were unlikely to have caused problems in the 14.3% and 11.1% respectively of patients taking them. Indeed, very few reports of actual harm in humans were found for any of the herbs studied. In Middle Eastern societies, many of the herbs might have a dual purpose of a medicine in one context but a foodstuff in another. As foodstuffs, one would not expect to see excessive toxicity or if it occurred, that it would be identified as such by the user. However, all the herbs listed by the research subjects were identified as being taken by them for a medicinal purpose, which may have heightened their awareness of potential adverse effects. The following comments apply to the eight remaining herbs in the top 10 in Table 3.6, in descending order. Supporting references are listed at the end of this Appendix.

Ginger (used by 50.9% of patients in Phase 2)

Pharmacology

According to Barnes *et al*. [1], ginger has been shown to have both hyper- and hypotensive, hypocholesterolaemic, anti-inflammatory and hypoglycaemic properties *in vivo*. An anticoagulant activity, through inhibition of platelet activity, has also been observed *in vitro*. Ginger is reputed to be an abortifacient and uterotonic activity has been documented for a related species. *'The clinical significance of these findings, if any, is unclear'*.[1] Ginger may also help with motion sickness through a local action on the gastrointestinal tract and clinical studies have focused mainly on the effects of ginger in the prevention of nausea and vomiting.

Toxicity

Antiplatelet activity may have contributed to GI bleeding, leading to blood in the stools seen in Case 8, although other herbs were also implicated (hence the designation 'multiple'). Hypoglycaemic activity may have contributed to dizziness in Case 13, 'tiredness' in Case 24 and 'weakness' in Case 36, although other herbs were also implicated. Doses of ginger that greatly exceed the amounts used in foods should not be taken during pregnancy or lactation; but it was taken, along with eight other herbs by the patient in Case 23 and could have contributed to abortion. No relevant primary references for these toxicities were discovered.

Thyme (used by 38.2% of patients in Phase 2)

Pharmacology

Thyme is reported to have hypotensive, respiratory stimulant and antispasmodic effects *in vivo*.[1] *In vitro* antispasmodic activity of thyme and related Thymus species has been associated with the phenolic components of the volatile oil and with the flavonoid constituents; their mode of action is thought to involve calcium-channel blockage.[1]

Toxicity

Toxic symptoms documented for thymol include nausea, vomiting, gastric pain, headache and dizziness (as perhaps seen in Case 13).[1]Thymol is irritant to the gastrointestinal tract and may have contributed to the gastrointestinal symptoms seen in Cases 6, 8, 15, 16, 21 and 37; although all of these were described as having 'multiple' origins. No relevant primary references for these toxicities were discovered.

Peppermint (used by 37.8% of patients in Phase 2)

Pharmacology

Peppermint oil contains a range of aromatic compounds (e.g. menthol, menthone, cineole and menthofuran) which are reported to relax gastrointestinal smooth muscle, thus relieving flatulence and cholic.[2]

Toxicity

Peppermint is traditionally associated with a carminative action. However two reports of adverse gastrointestinal effects were located: one of heartburn and perianal irritation,[3] and one of abdominal distension and increased flatulence. [4] Peppermint use might have contributed to the symptoms described in Cases 8 and 15, but both were described as having 'multiple' causes.

Fenugreek (used by 30.6% of patients in Phase 2)

Pharmacology

Hypocholesterolaemic and hypoglycaemic actions have been documented for fenugreek in both laboratory animals and humans; this is of potential relevance to Case 13.[1] Hypoglycaemic activity in healthy individuals has been reported for whole seed extracts, with slightly lesser activity exhibited by gum isolate, extracted seeds and cooked seeds.

Proposed theories of action include a reduction in carbohydrate absorption by the mucilaginous fibre.

A stimulant action on the isolated guinea pig uterus, especially during late pregnancy, has been noted for both aqueous and alcoholic extracts.[1] This is of potential relevance to Case 23.

Toxicity

There is limited evidence from preclinical and preliminary clinical studies that fenugreek has hypoglycaemic activity and may therefore have contributed to the 'tiredness' mentioned in Case 24. The absorption of drugs taken concomitantly with fenugreek may be affected due to its high mucilaginous fibre content; but this was not thought to be a contributory interaction in the cases in this research.

Fenugreek is reputed to be oxytocic and *in vitro* uterine stimulant activity has been documented.[1] Fenugreek was taken by the patient in Case 23 and may have contributed to her abortion. As Barnes *et al*. observe: '*The use of fenugreek during pregnancy and lactation in doses greatly exceeding those normally encountered in foods is not advisable*.'[1]

Two primary references provided evidence for the involvement of fenugreek in other cases. Izzo *et al.* [5] noted the potential for fenugreek to cause GI symptoms (relevant to Cases 6, 8, 13, 15, 21, 24 and 25). Faeste *et al.* [6] observed that fenugreek seed powder contains several potential allergens and an allergic response to ingestion was observed in human subjects (of possible relevance to Cases 10 and 15).

Black seeds (*Nigella sativa*) (used by 25.2% of patients in Phase 2)

Pharmacology

Little is known of the pharmacology of black seed compounds. Traditional internal uses include urination difficulty, dysmenorrhoea, indigestion, asthma and impotence.

Toxicity

Four separate reports of the *in vivo* (animal) hypotensive and diuretic effects of black seed ingredients were located. [7-10] This hypotensive effect may be relevant to Case 9 although the contribution to the drug interaction is described as 'multiple'. No reports were located of such effects in man.

Senna (used by 19.2% of patients in Phase 2)

Pharmacology

The cathartic action of hydroxyanthracene, one of the constituents of senna, is well recognised and senna praparations have been used as laxatives for many years.[1] It is thought that hydroxyanthracene glycosides are absorbed from the gastrointestinal tract, the aglycones liberated during metabolism and excreted into the colon resulting in stimulation and an increase in peristalsis. However, it has also been suggested that the purgative action of senna is due to the action of intestinal bacteria. Using human intestinal flora, it was found that sennoside A is reduced to 8-glucosyl rheinanthrone, hydrolysed to rheinanthrone and oxidised to sennidin A. The active principle causing peristaltic movements of the large intestine was thought to be rheinanthrone.[1]

Toxicity

Senna may cause mild abdominal discomfort such as colic or cramps as seen in Cases 6, 21 and 24; although nausea was associated with senna use in Case 25. Prolonged use or overdosage can result in diarrhoea with excessive loss of potassium, albuminuria and haematuria, and dehydration.[1] Diarrhoea was noted in Case 2. No recent published case studies were found, perhaps because these affects are so well known. Potassium deficiency may lead to disorders of the heart and muscular weakness; 'tiredness' was noted as a symptom in Cases 14 and 24 and both subjects were senna users. Again, no corroborating case studies were found in the literature search.

Cardamom (used by 14.3% of patients in Phase 2)

No reports of toxicity were located.

Anise (used by 11.1% of patients in Phase 2)

No reports of toxicity were located.

Sage (used by 10.5% of patients in Phase 2)

Pharmacology

Sage is stated to possess carminative, antispasmodic, antiseptic and astringent properties.[1] Traditionally, it has been used to treat flatulent dyspepsia, pharyngitis, uvulitis, stomatitis, gingivitis, glossitis (internally or as a gargle/mouthwash), hyperhidrosis, and galactorrhoea.[1] A spasmogenic action exhibited by low doses of sage oil has been attributed to the pinene content. Antispasmodic activity *in vivo* (in guinea-pigs) has been reported for sage oil administered intravenously, which relieved contraction of Oddi's sphincter induced by intravenous morphine.[1]

Toxicity

A case of human poisoning has been documented following ingestion of sage oil for acne. Convulsant activity in humans (and animals) has been documented for sage oil. Sage oil is reported to be a moderate skin irritant. Barnes *et al.*[1] warn that sage oil is toxic (due to the thujone content) and should not be ingested in large amounts. The irritant effects might have contributed to the symptoms of Case 40.

Sage is widely contraindicated during pregnancy. The volatile oil contains a high proportion of a- and b-thujones, which are known to be abortifacient.[1] The herb was used by Case 23 who experienced an abortion, although the subject was taking a range of herbs at the time.

Chamomile (used by 10.0% of patients in Phase 2)

Pharmacology

The allergenic properties documented for chamomile have been attributed to anthecotulid, a sesquiterpene lactone present in low concentrations, and to matricarin, a proazulene which has produced positive patch tests in patients with an existing sesquiterpene lactone hypersensitivity.[1]

Toxicity

Reports of allergic reactions to chamomile are common, although in the majority of cases the plant species is not specified.[1] Patients with an existing hypersensitivity to chamomile have demonstrated cross-sensitivities to other members of the family Asteraceae/Compositae. The symptoms experienced included abdominal cramps, thickness of the tongue and a tight sensation in the throat, angioedema of the lips and eyes, diffuse pruritus, a full sensation of the ears, generalised urticaria, upper airway obstruction, and pharyngeal oedema.

Allergic skin reactions have been documented following external contact with chamomile. Consumption of chamomile tea may exacerbate existing allergic conditions and the use of a chamomile enema has been documented to cause asthma and urticaria.[1] Itching was experienced by Case 15, but this was thought to be more likely to be associated with fenugreek.

Chamomile is reputed to be a uterine stimulant when used excessively and use during pregnancy is widely contraindicated.[1] The herb was used, along with a multitude of others, by Case 23, who experienced an abortion.

References

1. Barnes J, Anderson LA, Phillipson JD. Herbal Medicines 3rd Edn. Pharmaceutical Press, London, 2007.
2. Sweetman SC (Ed.). Martindale: the Complete Drug Reference (34th Edn.) Pharmaceutical Press, London, 2005.
3. Grigoleit HG, Grigoleit P. Peppermint oil in irritable bowel syndrome. *Phytomedicine* 2005 ; 12(8):601-6.
4. Hiki N, Kurosaka H, tatsutomi Y, Shimoyama S, Tsuji E, Kojima J, Shimuzu N, Ono H. Peppermint oil reduces gastric spasm during upper endoscopy: a randomized, double-blind, double-dummy controlled trial. *Gastrointest Endosc* 2003;57(4):475-82.
5. Izzo AA, Di Carlo G, Borrelli F, Ernst E. Cardiovascular pharmacotherapy and herbal medicines: the risk of drug interaction. Int J Cardiol 2005;98(1):1-14.
6. Faeste CK, Namork E, Lindvik H. Allergenicity and antigenicity of fenugreek (Trigonella foenum-graecum) proteins in foods. *J Allergy Clin Immunol* 2009;123(1):187-94.
7. Zaoui A, Cherrah, Y, Lacaille-Dubois M, Settaf A, Amarouch H, Hassar M. Diuretic and hypotensive effects of Nigella sativa in the spontaneously hypertensive rat. *Therapie* 2000;55:379–382.
8. Zaoui A. Effects of Nigella sativa fixed oil on blood homeostasis in rats. *J Ethnopharmacol* 2002;79(1):23-6.
9. Salem ML. Immunomodulatory and therapeutic properties of the Nigella sativa L. seed. *Int Immunopharmacol* 2005;5(13-14):1749-70.
10. Le PM, Benhaddou-Andaloussi A,Elimadi A, Settaf A, Cherrah Y, Haddad PS. The petroleum ether extract of Nigella sativa exerts lipid-lowering and insulin-sensitizing actions in the rat. *J Ethnopharmacol* 2004;94(2-3):251-9.