Potential adverse reactions to herbal medicines in patients attending a nephrology clinic in Abu Dhabi, United Arab Emirates

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ABSTRACT

الأهداف: استعراض البيانات الطبية المُتعلقة باستخدام الأعشاب الطبية، ودراسة مدى سلامتها وتأثيرها على المرضى.

الطريقة: أُجريت هذه الدراسة الاستطلاعية خلال 3 أشهر وذلك من يونيو إلى سبتمبر 2007م، وشملت جميع المرضى الذين كانوا يراجعون عيادة الكلى في مركز الشيخ خليفة، أبوظبي، الإمارات العربية المتحدة. لقد قمنا باستخدام الاستبيان الهيكلي من أجل تحديد الأعشاب الطبية التي استعملها المرضى في الفترة الماضية والحالية، ووصف التفاعلات العكسية لهذه الأعشاب والآثار الجانبية التي تصاحبها. بالإضافة إلى ذلك فقد تم البحث عن الدليل المساند في السجلات الطبية الخاصة بالمرضى. وتم تقييم مسببات التفاعلات العكسية لهذه الأعشاب الطبية بطريقة الإجماع من قبل لجنة خبراء وباستخدام استبيان نارانجو اللوغارتمي.

النتائج: أشارت النتائج إلى أن استخدام الأعشاب الطبية كان متفشياً بين المرضى (468 مريضاً من أصل 688 مريضاً، 68%)، حيث تبين أن أكثر من ثلثي المرضى (69%) قام باستخدام 3 أو أكثر من الأعشاب الطبية في الوقت الحاضر. وأظهرت التقارير استخدام المرضى لأكثر من 100 نوع مختلف من المستحضرات العشبية، ولم يتمكن 35% من هؤلاء المرضى من معرفة مكون واحد من مكونات تلك المستحضرات، فيما لم يخبر 70% من المرضى أطبائهم عن استخدامهم لهذه المستحضرات. وقد بين السجل الطبي لمريضين فقط حقيقة استخدامهم للمستحضرات العشبية. تم الكشف عن 28 حالة من التفاعلات العكسية في 26 مريض (5.6%). وكانت أسباب هذه التفاعلات العكسية مُحتملة في 12 حالة، وممكنة في 16 حالة وذلك اعتماداً على استبيان نارانجو اللوغارتمي، كما أن 7 من هذه الحالات كان سببها المباشر هو استخدام الأعشاب الطبية فقط، و21 منها كانت نتيجةً للتفاعلات بين الأدوية الكيميائية التي تُصرف بالوصفة الطبية والأعشاب الطبية.

خاتمة: أثبتت هذه الدراسة انتشار استخدام الأعشاب الطبية بين المرضى المصابين بأمراض الكلى وقد يساهم ذلك في تفاقم الحالة المرضية لهؤلاء المرضى، ويمكن أن يحدث ذلك عند تناول المريض للأعشاب الطبية فقط أو عند تناولها مع الأدوية الكيميائية التي تُصرف بالوصفة الطبية. إن تردد المرضى في الإبلاغ عن استخدامهم للأعشاب الطبية يؤكد وجوب التدقيق والسؤال عن تاريخهم الطبي وإذا ما كانوا قد قاموا باستخدام الأعشاب الطبية أم لا، وتسجيل كل ذلك في سجلاتهم الطبية.

Objectives: To provide data on herbal medicine (HM) use and safety in patients attending a nephrology clinic at Sheikh Khalifa Medical City (SKMC), Abu Dhabi, United Arab Emirates (UAE).

Methods: A prospective, 3-month study between June and September 2007, investigated all patients presenting to the Nephrology Clinic of the Sheikh Khalifa Medical center (SKMC) in Abu Dhabi, UAE. A structured questionnaire determined previous and current HM use, and descriptions of associated adverse reactions. Corroborating evidence was sought from the patient's medical records. Causality was assessed by consensus from an expert panel using the Naranjo algorithm.

Results: The HM use was widespread (468 of 688; 68%). Over two-thirds (69%) reported currently taking 3 or more herbal preparations. Patients reported using over 100 different HMs, many of them compounded mixtures; 35% could not identify a single ingredient of these mixtures, and 70% had not informed the clinic doctors that they were taking HMs. Just 2 patients had HM use recorded in their medical record. Twenty-eight HM-related adverse reactions were identified in 26 (5.6%) patients; 12 probably and 16 possibly related to HMs. Seven involved HMs alone and 21, a HM/prescription medication (PM) interaction.

Conclusion: The use of HMs in patients with underlying kidney problems was extensive and contributed additional pathology to the underlying renal disease, either alone or in combination with PMs. The reluctance of patients to inform their healthcare providers of concurrent use highlights a need to take a thorough drug history on clinic registration.

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Herbal medicines (HMs) are popular in many communities, including Middle Eastern countries, and patients are reluctant to link them with risks of adverse effects.[1] Many herbal preparations are poorly controlled and do not require a prescription; hence their use and potential risks may escape the physician's or pharmacist's attention. Increasing recognition that herbs can cause adverse effects,[2,3] or treatment failure through interaction with conventional prescription medicines (PMs)[4,5] has stimulated interest in HM quality and safety. Many HMs are derived from poorly controlled sources and may be contaminated with heavy metals or adulterated with prescription drugs, raising further concerns regarding their use.[2] Adverse drug reactions (ADRs) are a common cause of hospital admission and make a significant contribution to healthcare costs.[6,7] While the contribution of HMs is largely unknown, ADRs resulting from herb-drug interactions have been identified as significant factors responsible for patient morbidity and mortality.[8] 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. We previously reported a study of HM use among United Arab Emirates (UAE) Nationals attending a large Primary Care clinic in Abu Dhabi providing services to UAE Nationals.[9] The use of HMs was widespread among patients (76%); the point-prevalence of current HM use was 38%. A wide range of herbs was 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. In keeping with other studies,[2,10] 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. The current study explored the extent of HM use and potential harm in patients visiting a secondary care clinic in Abu Dhabi.

Methods. A prospective, 3-month study between June and September 2007, using opportunity sampling, investigated all patients presenting to the Nephrology Clinic of the Sheikh Khalifa Medical Center (SKMC) in Abu Dhabi, UAE with a range of kidney-related problems. The SKMC receives the highest number of public patients in Abu Dhabi city, and provides a comprehensive network of healthcare services. The choice of the latter as a base for the study was pragmatic, based on accessibility to patients, high patient throughput (many visiting on an outpatient basis), potential for detecting HM end-organ damage, a system of standard and accessible medical records, and the enthusiasm of the management and staff. Ethics approval for the study was granted by the SKMC Institutional Review Board. For inclusion in the study, patients had to be over 13 years of age, UAE nationals or residents, and capable of understanding and responding to questioning in English or Arabic. Specific exclusion criteria were those patients that could not understand English nor Arabic, were too ill to participate, had incapacitating mental illness, or were extremely confused. All eligible patients visiting the Nephrology Clinic were invited to take part by informed consent. They were interviewed in a dedicated room, either in the outpatient clinic or dialysis unit, by trained interviewers using a piloted, structured questionnaire. This was administered in English or Arabic according to patient preference and sought information on demographics, the identity of all HMs taken by the patient, reasons for taking them, whether they had informed their doctor of current HM use, whether the subject had experienced any adverse reactions, and whether they felt it related to any HM(s) they were currently taking. Post-interview, 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. A medical review with the patient's attending doctor was conducted to validate the methodology and confirm the diagnosis. Medical records were used to obtain relevant laboratory data and a comprehensive list of PMs being taken, and to attempt to corroborate the names of the HMs cited by the patient. If an adverse reaction were identified by the patient, the chief investigator prepared a case study, compiling all relevant information such as: HMs and PMs taken, symptoms, corroborating biochemistry, and primary and secondary diagnoses. Information on the known pharmacology of the agents taken and previous published reports of toxicity were sought using systematic searches of standard literature obtained through Medline, PubMed, and the World Health Organization-Regional Office for the Eastern Mediterranean (WHO-EMRO) database. Assessment of causality was made through consensus from a panel consisting of the lead investigator, a Professor of Pharmacology and Therapeutics, and a Nephrologist Teaching Physician based in the Faculty of Medicine and Health Sciences, UAE University. Decisions were assisted using the Naranjo et al Algorithm;[11] a standard, validated causality algorithm that has been used to assess ADRs to conventional medicines, as well as herb-

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drug interactions. Each assessor first used the algorithm independently and then reached a final decision by consensus.

All relevant data were coded, processed, and analyzed using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) version 16. Data were mainly analyzed using descriptive statistics. Categorical data were analyzed using the Chi-squared test, taking $p<0.05$ to imply statistical significance.

Results. A total of 743 patients were approached; 42 (15 outpatients and 27 on dialysis) were excluded as they did not meet the inclusion criteria and a further 13 declined to participate (10 outpatients and 3 on dialysis) leaving 688 subjects. Most participants (508; 74%) were interviewed in the outpatient clinic; the remainder (180; 26%) were attending the Nephrology Clinic for dialysis. Of 688, 468 (68%) stated they were currently taking HMs. The demographic profile of these participants (**Table 1**) was similar to that of those who were not taking HMs 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 UAE nationals in the herb-using sample. Further analyses focused on the current herb users in this study (n=468). Some patients had multiple co-morbidities; these included: hypertension (283; 60.5%), diabetes (179; 38.2%), dyslipidemia (93; 19.9%), and anemia (41; 8.8%). 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. Four hundred and thirty-nine patients currently taking herbs (93.8%) said they used them before their current renal problems began, and 329 patients (70.3%) currently using HMs were also taking PMs. A large proportion (327, 69.9%) said they had not informed their current healthcare providers that they were taking HMs, while just 57 (12.2%) said they had; the remainder (17.9%) could not remember. Ninety-five (20.3%) said they had visited a herbal center

Table 1 - Demographics for Nephrology Clinic patients.

Parameter	Total sample N=688	Current herb users N=468
	n (%)	
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 (10.0)	45 (9.6)
30-39	113 (16.4)	80 (17.1)
40-49	118 (17.2)	75 (16.0)
50-59	195 (28.4)	140 (30.0)
60-69	108 (15.7)	71 (15.2)
Above 70	60 (8.7)	39 (8.3)
No age given	1 (0.1)	
Nationality		
UAE	402 (58.4)	291 (62.2)
Arab	182 (26.5)	126 (26.9)
Asian	95 (13.8)	44 (9.4)
Western	7 (1.0)	7 (1.5)
Nationality not given	2 (0.3)	

Table 2 - Herbs taken by 5 or more patients in the study.

Herb	Common herbs for current herb users (n=468)*
	n (%)
Ginger†	238 (50.9)
Thyme	179 (38.2)
Peppermint	177 (37.8)
Mixture of herbs	143 (30.6)
Fenugreek	143 (30.6)
Black seeds	118 (25.2)
Senna†	90 (19.2)
Cardamom	67 (14.3)
Anise	52 (11.1)
Sage	49 (10.5)
Chamomile	47 (10.0)
Karkadeeh	45 (9.6)
Herbal tea	36 (7.7)
Cinnamon	26 (5.6)
Teucrium	19 (4.1)
Asafetida	16 (3.4)
Parsley	15 (3.2)
Red seeds	14 (3.0)
Cumin	13 (2.8)
Aloe†	10 (2.1)
Myrrh	10 (2.1)
Saffron	10 (2.1)
Arabic gum	8 (1.7)
Curcumin	6 (1.3)
Fennel	6 (1.3)
Garlic	5 (1.1)

*total citations are greater than the number of patients as many patients were taking several herbal medicines, †appears in the US National Kidney Foundation list of herbs that may be harmful in chronic kidney disease[20]

Table 3 - Identification of ingredients in herbal mixtures currently being taken.

Main ingredients in mixtures of herbs taken	Total mixtures n=143
	n (%)
Unidentified	53 (37.1)
Black seed	19 (13.3)
Fenugreek	21 (14.7)
Ginger*	11 (7.7)
Honey†	11 (7.7)
Peppermint	7 (4.9)
Thyme	8 (5.6)
Senna†	10 (7.0)
Anise	3 (2.1)

*main ingredient in their herbal mixtures in a small number of cases, †appears in the US National Kidney Foundation list of herbs that may be harmful in chronic kidney disease[20]

recently, and 83 (17.7%) said they were also taking over the counter medicines. Three hundred (64.1%) reported currently visiting other hospital clinics outside of SKMC, and 139 (29.7%) were attending clinics within SKMC for other conditions. The study patients mentioned more than 100 different herbal preparations. Those cited as being taken by 5 or more patients are shown in **Table 2** in descending frequency order. Fifty-three of 143 (37.1%) patients currently taking herbal mixtures could not identify any of the ingredients. The identity of the main ingredient in the remainder of the herbal mixtures is shown in **Table 3**. Sixty (12.8%) patients said they were currently taking a single HM, 80 (17.1%) were taking 2 HMs, while 323 (69.0%) said they were taking 3 or more HMs concurrent with their therapy. It is noteworthy that despite this heavy use of HMs, just 2 patients had anything regarding HM use documented in their medical notes. Patients were taking a wide range of PMs not detailed further in this paper. Approximately half the patients currently taking HMs (246, 52.5%) could not identify a single PM that they were taking, despite 204 (43.6%) patients having 7 or more PMs written in the current medication section of their medical notes. Approximately one third (35%, n=164/468) could remember all their PM names. Of those currently taking HMs, 42 (9%) reported some form of adverse reaction to the herbs they were taking; just 3 patients said they had mentioned the reaction to their carers, however no record of this was found in a subsequent search of the medical record. On case presentation, 14 of the 42 reactions were deemed by the expert panel to have a highly doubtful relationship to any medicine the patient was taking, due to lack of sufficient data on which to base a judgement. Of the remaining 28 potential reactions, involving 26 patients (2 patients presented with 2 suspected reactions each), 7 cases involved HMs alone (25%), with the remainder (n=21) involving HMs in combination with a PM. Both genders were fairly equally represented (14 men, 12 women), although almost two-thirds (n=15, 58%) occurred in people older than 50 years of age. Causality assessments for the 28 cases are shown in **Table 4**, and the nature of these cases highlighted in **Table 5**. In 17 of 30 cases (56.7%), it was not possible to say exactly, which HM from the range taken by the patient contributed to the reaction.

Table 4 - Strength of association within medicine groups after panel consensus and using the Naranjo algorithm.[11]

Suspected agent(s)	Association*		
	Possible	Probable	Total
Herb	3	4	7
Herb/prescription medicine	12	9	21
Total	**15**	**13**	**28**

*after consensus and using the Naranjo algorithm

Discussion. In cultures such as the UAE, there is a long history of HM use to treat many illnesses, and consequently HM use is high.[9] In the present study, the prevalence of current HM taking was equally high and the incidence of patients informing their healthcare providers that they were taking HMs was low; only 2 patients had herbal medicines documented in the medical record. These high rates of prevalence and low rates of disclosure are consistent with other studies

Table 5 - Nature of the herbal medicine-related reactions found in this study.

Medicine	Nature of reaction	Herbs involved	n
Herb, n=7	Malaise	Ginger	34
	Severe asthma	Multiple	35
	Colon inflammation	Sage	40
	Diarrhea	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	Multiple	22,26,31
	Finger numbness	Cardamom	27
	Weakness	Multiple	36
	Tiredness	Senna	14,24[a]
	Stomach pain	Multiple	37,48
	Abdominal pain	Multiple	6,16,24[b]
	Low blood pressure	Multiple	9
	Raised blood pressure	Multiple	17
	Dizziness	Multiple	13
	Stomach acidity	Cinnamon, multiple	11,15[b]
	Itch	Fenugreek	15[a]
	Nausea and vomiting	Garlic, multiple, senna	19,21,25

Cases 15 and 24 exhibited 2 reactions each, multiple - the actual herb responsible could not be identified from the range taken by the patient, [a]first adverse reaction,[b]second adverse reaction

involving broad populations,[12-15] and more specific patient groups, for example, those with liver disease,[16-19] or taking specific medicines,[20] despite patients having obvious opportunities to inform carers.

Of those currently taking HMs in this study, approximately one-fifth had visited an herbal center recently, and just under one fifth were taking non-prescription medicines. Most was also simultaneously visiting other hospital departments for treatment. These data illustrate the complex nature of care provided in the UAE for some patients, and highlight lost opportunities to document HM taking, and the urgent need for improved history taking and documentation. With HM taking disclosure being low it is difficult to estimate the incidence of adverse reactions to HMs. In our previous study in primary care the incidence was 11%,[9] and in the present study, 9% of patients believed HMs were responsible for an adverse reaction, although expert consensus concluded that adverse reactions possibly or probably involved HM in 5.6% of patients. This higher self-reported figure of 9% is consistent with other authors such as Cuzzolin et al,[3] where 9.6% of patients stated they had experienced an adverse reaction whilst taking HMs. Levels of reporting are possibly also linked to patient perception. Barnes et al[1] observed that many patients acted differently with regard to reporting an adverse reaction to their doctors depending on whether it was associated with a HM or a conventional medicine. In a study of 515 HM users,[1] approximately one-quarter (26%) said they would report a serious reaction to a conventional medicine, but not for a similar reaction to a HM. This study and our own indicate that when HMs cause problems, at least some patients may be reluctant to report them.

Looking specifically at the HM reactions reported from this study, many were classified as mild in nature, but 5 were rated as serious: asthma (1), abortion (1), and renal impairment (3). While the use of specific HMs, notably containing the now-banned ingredient aristolochic acid are notorious,[21] the use of uncontrolled, unlicensed HMs may not be safe and there may be yet more to learn regarding HM use in patients with kidney disease.[22,23] Concern over HM taking is not confined to patients with kidney disease. In a 2008 report of a US study, approximately 10% cases of drug-induced liver injury were attributed to HMs or dietary supplements that were not regulated.[24] The American National Kidney Foundation has recently cautioned against the use of HMs by patients with chronic kidney disease,[25] and has published a list of particularly hazardous herbs, 3 of which (senna, ginger, aloe) were commonly used by patients in our study. This body has called for dialysis practitioners to include specific questions regarding herb and dietary supplement use when taking medical and nutritional histories. Similar pleas to remember HMs when taking drug histories have come from the fields of emergency medicine,[26] psychiatry,[27] anesthesiology,[28] cancer care,[29] and transplant surgery.[30]

Further investigations of the HM-specific reactions noted in our study were hampered by the inability to identify the actual herb responsible from the range taken by the patient. This highlights the difficulties of pinpointing a culprit in a patient sample such as ours, where most patients were taking not only a variety of named HMs, but also un-labelled HM mixtures where, in some cases, the patient could not identify the contents. In addition, adulteration of HMs, as seen in other settings,[31] has been detected in the UAE, and could potentially be a confounding factor. Unfortunately, determination of content of HMs was not part of this study. Our study was of limited size and restricted to patients attending a single care setting, albeit in a major hospital in Abu Dhabi. Extrapolation of the results to other care settings and specialities is therefore, difficult, but we suspect that based on the results, those from our earlier study in primary care, and from the literature,[12-20] one would find a similar incidence of herb use and potentially, herb-induced adverse reactions. Other herb reactions might have been detected in our study if patients who did not meet the inclusion criteria due to extreme illness or communication problems had been followed up over time and interviewed on recovery; our protocol did not allow for this, and the reported incidence of 5.6% may be an underestimate.

Three quarters of the adverse reactions involving HMs noted in the study were thought to involve pharmacodynamic interactions with PMs taken concurrently by the patients; for example, the gastrointestinal (GI) symptoms seen in 6 cases. In such cases, concurrent PMs were known to cause GI problems, but the timing and patient identification of the HM they took were persuasive in concluding that the HM had enhanced the effects of the PM. Fugh-Berman[32] pointed out that HM-PM interactions 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. This emphasizes the need to document and monitor the use of all HMs particularly carefully in such patients.

In conclusion, over two-thirds of Nephrology Clinic patients in our study were using HMs, however, there was a disinclination by the patients to inform their healthcare providers of HM use and even when they did, these were rarely documented in the patients' notes. Adverse reactions, possibly or probably related to HM use were identified in 5.6% of patients with no record in the patients' notes. This has important implications for future pharmacovigilance of HMs in the UAE.

If doctors and pharmacists are to be encouraged to report adverse reactions to HMs, patients must first be encouraged to divulge all the medicines they are taking during thorough drug history taking. Future studies could be directed to interview healthcare professionals to obtain better idea of their level of knowledge regarding HMs, the information sources they use to educate themselves regarding HMs, and their training requirements. In addition, it would be a challenge to 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. Finally, it is recommended to conduct research in other clinical settings where the potential for prescription of large numbers of PMs is high such as rheumatology, mental health, gastroenterology, or cardiology clinics.

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