

Herbal Supplement Use and Herb–drug Interactions among Patients with Kidney Disease

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INTRODUCTION

Chronic kidney disease (CKD) is a global public health problem with an increasing incidence and a lot of economic burden for treatment. Kidney failure may lead to a variety of complications such as cardiovascular disease, renal osteodystrophy, and renal anemia. According to the National Kidney Foundation classification, end-stage renal disease (ESRD) is called when the glomerular filtration rate is <15 ml/min/1.73 m², and in this case,

dialysis and transplantation are the substitution choices.^[1] In Iran, more than 24000 patients with ESRD are under treatment, and this number has increased over recent years.^[2] According to the 2012 National Health Interview Survey which was a comprehensive survey regarding the use of complementary and alternative medicine (CAM)

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ABSTRACT

Objective: The prevalence of herb–drug interactions and herb's adverse effects may be serious in susceptible population such as patients with chronic kidney disease (CKD). In this study, we planned to determine the usage prevalence of herbal products and herb–drug interactions in CKD patients.

Methods: A cross-sectional prospective study was conducted on CKD and posttransplant patients with a history of using herbal supplements in Isfahan, Iran. The patients were subjected to a validated checklist, containing demographic and clinical information. The knowledge of herbal use, side effects, and herb–drug interactions was assessed based on patients' responses. Data were reported as prevalence (percent) of the occurrence. **Findings:** The prevalence of herbal supplement usage among CKD patients was 18.6% in this study. The study included 400 patients (261 males and 139 females). The majority of the study population were in the age range of 50–70 years (61.5%). Hypertension (34.36%) was the most common cause of kidney failure, while diabetes mellitus (21.80%) took the second place. The most frequently used unformulated medicinal herb was *Echium* (*Echium amoenum*) (15.27%), and the most commonly used formulated herbal products were anticough and mucolytic based on *Thymus vulgaris* (24.27%). Eighteen patients (4.5%) used herbal mix with unknown entity and sources. In this study, ginseng has the most possible interactions with prescription drugs (18 interactions), while this interaction (with clopidogrel, warfarin, and heparin) was severe in six cases. **Conclusion:** The present study provided the information on possible herb–drug interactions in CKD patients on herbal usage. Since the issue of using herbal products may be arbitrarily in the majority of the patients, and considering the importance of adverse reactions or major interactions, health-care providers should play an active role to identify these cases and inform the patients regarding herbal product safety, adverse effects, and possible interactions.

KEYWORDS: Complementary medicine, herbal products, herb–drug interaction, kidney disease

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within American population, about 17.7% of American adult population had used a natural product where the vitamins and minerals were not included. Between natural products, fish oil was the most frequently used product.^[3]

Complementary medicine is a combination of a variety of medical therapies that may be used alongside conventional medicine in the treatment of disease. Alternative medicine is defined as the use of such alternative methods instead of conventional medicine. In majority of traditional medicine sources, CAM is classified as an alternative medicine system such as Ayurveda and Unani; mind–body interventions such as yoga; biologically based therapies such as herbal and dietary supplement therapy; manipulative and body-based methods such as massage therapy; and energy therapy such as reiki. Biologically treatments are based mostly on natural products which are not proven. However, a large number of these therapies have been shown that they are not safe and can be harmful due to their interactions with other drugs which are used contemporaneously.^[4]

An important marker to assess the efficacy of selected treatment and also to predict undesirable outcomes risk is health-related quality of life. In the population of dialysis patients, impaired quality of life is well-defined, although data are far less in CKD patients.^[1]

Patients with CKD turn to use different modalities of CAM to treat a variety of complications because of chronic nature of the disease, and the poor quality of life, but yet there is a lack of data on CKD patients' usage of CAM.^[5] In general, physicians and health-care providers are not aware of using CAM modalities by the patients.^[6,7] Only 50% of dialysis patients discussed about their CAM usage to physicians.^[8] In a Turkish study of CKD population, only 12.5% reported the herbal consumption to physicians.^[9] About 2.9% of the patients with CKD had a history of CAM usage before renal failure, whereas 25.2% of them had used CAM after disease occurred.^[7] A study showed that 63% of patients with CKD were willing to use some type of CAM therapies.^[10] Another study demonstrated that CAM usage is common among dialysis (57%) and transplant patients (49%); while 28.1% of CKD patients used herbals after kidney failure, 13.2% were currently continuing herbals.^[9] The prevalence of medication interactions with CAM products (mainly healthy food) was reported to be about 40% for CKD patients using this type of CAM modality.^[8]

The high rate of herb–drug interactions is reported, but yet the mechanism to explain them is unknown.

The chance of herb–drug interactions is more likely than drug–drug interactions, and this is related to various bioactive entities provided in herbals.^[11] Supplement usage can also affect CKD and transplant patients due to electrolyte changes, pharmacokinetic interactions, and effect on immune system or producing toxic metabolites.^[12] CKD patients may use a vast of medications due to the chronic nature of their disease, while most patients do not inform health-care providers about their herbal product usage which leads to the risk of herbal's adverse effects and interactions.^[6-8] This clarifies the positive role of health-care team to alert the patients about these side effects and avoid life-threatening interactions. A dynamic role of health-care team and specially nephrologists to educate patients taking CAM and supplements may help to prevent possible interactions and adverse effect.^[13,14]

In this study, we planned to determine the usage prevalence of herbal products and herb–drug interactions in patients with kidney diseases. These findings may highlight the main issues for health-care professionals to care about herbal product usage in CKD patients.

METHODS

A cross-sectional study was conducted in the nephrology units and clinics of Alzahra and Noor educational hospitals affiliated to Isfahan University of Medical Sciences in Isfahan, Iran, for a period of 8 months between February and October 2018. The determination of sample size was based on the previously reported prevalence of complementary medicine use in the literature;^[15] accordingly, the study was continued to recruit 400 CKD and posttransplant patients who had been using medicinal herbs and herbal products during their kidney disease. In this study, CKD was defined as having any kind of kidney diseases for more than 3 months,^[16] and the time span of positive history of herbal medicine use was from the diagnosis of the patient's kidney disease.

After obtaining institutional ethics committee approval (project number and ethics code: 294155) from the university research affairs, patients' demographic information (sex, age, educational status, occupational status, and marital status) were collected from patients' hospital records or by direct interviewing of patients and filled in a specially designed form for this study. The educational status was categorized as follows: illiterate, primary school education (school education till 8 years), high school education (12 years), postdiploma education (14 years), Master of Science (16 years), and PhD level. The occupational status had the following categorization: Without financial income

(without job, homemaker, and student) and with financial income (recruitment job and retired). The occupational status was finally interpreted regarding financial income. Marital status was categorized as single or married.

A 3-item newly researcher-designed checklist was applied. The first section consisted of the patients' demographic information, the second section was about disease-related information, including cause of renal failure, other comorbidities, and drug history in the past 2 months, while the third part consisted of herbal and supplemental usage by the patient, route of administration, how to advise it, where to buy from, and evaluation of herbal effects by the patient her- or himself.

The first question to start interview was asked to clear if the patient had herbal usage or not. If the answer was yes, questions were continued to find the type of the herbs as well as other chemical medications which were being used in order to detect any possible drug-herb interactions, according to the reliable references.^[17-19] The information on possible herb-drug interactions were obtained from different references which are declared following each interaction [Table 1]. Each interview took 10–20 min to complete.

Data were tabulated and expressed as descriptive statistics. To determine the influence of age, gender, comorbidities, educational status, and occupational status on the tendency to herbal usage, the Chi-square test was utilized to assess the influence. $P < 0.05$ was considered statistically significant.

RESULTS

A total of 2153 CKD and posttransplant patients have been interviewed upon study objectives; of these, 400 patients who declared to be CAM users were included. Accordingly, the prevalence of herbal supplement use among the study patients was about 18.6%. This population consisted of 261 males and 139 females, with the majority in the age range of 50–70 years (61.5%). Regarding CAM nonusers, the majority were in the age group of 20–60 years with the male/female ratio of 73/27 percent. Table 2 shows the demographic characteristics of the study population. Regarding causes of renal failure, hypertension (34.4%) was the most common cause of failure, and diabetes mellitus (21.8%) was the second most. It is notable that 11.89% of the patients had hypertension and diabetes contemporaneously. The others (13.23%) consisted of congenital kidney disease, polycystic kidney disease, drug-induced renal failure, and acute kidney injury. As shown in Table 2, among demographic characteristics, age, sex, and the status of financial income were the

influential parameters which determined the tendency of patients to herbal usage. With this regard, female patients more than 60 years old and patients with no financial income had more tendency to use herbal supplements.

As illustrated in Table 3, the most frequently used unformulated herb was *Echium* (*Echium amoenum*) (15.27%), while the most commonly used formulated herbal products were anticough and mucolytic based on *Thymus vulgaris* (24.27%).

Eighteen patients used herbal mix with unknown sources involving that they did not know what kind of herb they were using; however, the most common reason they were using these unknown herbs was for controlling obesity (50%). Other top most used herbs, whether formulated or unformulated herbal products, are depicted in Table 3.

The most common reason for which these CKD patients used herbal products was for common cold and respiratory symptoms (32.58%), followed by 19.13% for gastrointestinal problems and 11.69% for kidney and urinary disorders. Herb-drug interactions are depicted in Table 1.

Ginseng was found to have most interactions with prescription drugs (18 interactions). The interaction was severe in 6 cases (with clopidogrel, warfarin, and heparin), while the most possible interaction mechanism was found to be the effect on coagulation process.

One important interaction was found between *Hypericum perforatum* and cyclosporine which may lead to reduce the effectiveness of cyclosporine.

DISCUSSION

The present study was conducted in the nephrology clinics and included data of 400 CKD and posttransplant patients undergoing herbal product use. The majority of the patients identified as herbal users were in the age range of 50–70 years, and herbal usage prevalence was high among this age range. This finding was similar to Birdee *et al.*'s study,^[25] which reported that the trend was more prevalent among middle-aged (50–64) patients compared to other age groups. The CKD occurrence in this age range was more due to diabetes and hypertension. Different factors may affect herbal supplement usage, such as age, sex, geographic region, duration of disease, race, and socioeconomic status.

In our study, we evaluate the trend to herbal usage regarding age, gender, occupational status, marital status, educational status, duration of chronic disease, or years passed transplant. Demographic factors such as gender, age, and the status of financial income had a significant

Table 1: Possible herb-drug interactions among the study population

Scientific (common) name of herb or herbal supplement (total frequency of herb interaction)*	Drug name (frequency of this drug-herb interaction)	Mechanism of interaction	Significance of interaction**	Reference (s)	
<i>Hypericum perforatum</i> (St John's wort) (10 interactions)	Omeprazole (1)	Reduction of omeprazole AUC and Cmax	Low	[17]	
	Carbamazepine (1)	Reduction of serum concentration of carbamazepine due to CYP3A4 induction	High	[17]	
	Sertraline (2)	Increasing the risk of SSRIs' serotonin syndrome	High	[20]	
	Fluoxetine (1)	Increasing the risk of SSRIs' serotonin syndrome	High	[20]	
	Alprazolam (1)	Reduction of alprazolam serum concentration	Low	[20]	
	Atorvastatin (3)	Reduction of atorvastatin concentration	Moderate	[17,20,21]	
	Cyclosporine (1)	Reduction of cyclosporine AUC and Cmax	High	[17,18]	
<i>Ginkgo biloba</i> (ginkgo) (15 interactions)	Aspirin (7)	Increasing the risk of bleeding	Low	[18,22]	
	Heparin (1)	Increasing the risk of bleeding	Moderate	[7]	
	Clopidogrel (2)	Increasing the risk of bleeding	Moderate	[7]	
	Warfarin (2)	Increasing the risk of bleeding	Moderate	[18,21,22]	
	Enoxaparin (1)	Increasing the risk of bleeding	Moderate	[7]	
	Nifedipine (1)	Interaction with nifedipine metabolism	Low	[17,21]	
	Omeprazole (1)	Reduction of omeprazole effects	Low	[17,21]	
	Aspirin (8)	Possible synergic interaction with aspirin and increasing the risk of bleeding	Moderate	[18,23]	
	<i>Panax ginseng</i> (ginseng) (18 interactions)	Furosemide (3)	Increasing the risk of diuretic resistance	Low	[18,23]
Metformin (1)		Increasing the risk of hypoglycemia	Low	[7]	
Clopidogrel (4)		Increasing the risk of bleeding	High	[7]	
Warfarin (1)		Reduction in INR	High	[18,21,23]	
Heparin (1)		Reduction in heparin effects	High	[18]	
Heparin (1)		Increasing effect of heparin	High	[18]	
Aspirin (1)		Increasing effect of aspirin	Low	[18]	
<i>Oenothera biennis</i> (evening primrose) (3 interactions)	Carbamazepine (1)	Increasing the risk of seizure due to reduction in carbamazepine concentration	High	[18]	
	<i>Valeriana officinalis</i> (valerian) (3 interactions)	Clonazepam (2)	Synergist effect; increasing sedation	Low	[18]
		Lorazepam (1)	Synergist effect; increasing sedation	Low	[18]
<i>Aloe barbadensis</i> (aloe vera) (3 interactions)	Mycophenolate (3)	<i>Aloe vera</i> potentiates the immune system and decreases mycophenolate effect	Moderate	[18]	
<i>Piper nigrum</i> (black pepper) (2 interactions)	Enalapril (2)	Increasing the risk of cough	Low	[24]	
<i>Serenoa repens</i> (saw palmetto) (2 interactions)	Aspirin (2)	Increasing effect of aspirin; increasing the risk of bleeding	Low	[18]	
<i>Corynanthe yohimbe</i> (yohimbe) (1 interaction)	Clonazepam (1)	Yohimbine decreases the sedation effect of clonazepam	Low	[19]	
<i>Silybum marianum</i> (milk thistle) (5 interactions)	Losartan (5)	Increasing losartan AUC and effect; increasing risk of hypotension	Low	[17]	
	<i>Echinacea angustifolia</i> (echinacea) (3 interactions)	Cyclosporine (2)	<i>Echinacea</i> potentiates the immune system and decreases cyclosporine effect	High	[17,18]
Mycophenolate (1)		<i>Echinacea</i> potentiates the immune system and decreases mycophenolate effect	Moderate	[17,18]	
<i>Harpagophytum procumbens</i> (devil's claw) (1 interaction)	Warfarin (1)	Increasing effect of warfarin; increasing the risk of bleeding	Moderate	[18,21,23]	
<i>Glycyrrhiza glabra</i> (licorice) (1 interaction)	Sotalol (1)	Increasing blood pressure by licorice and decreasing the effect of sotalol	Moderate	[19]	
<i>Mentha piperita</i> (peppermint) (2 interactions)	Aspirin (2)	Increasing the risk of gastrointestinal mucosa injury	Low	[19]	

*Total frequency of herb interaction" shows the number of patients who used the herb and drug concomitantly in the study population,

**The significance of drug-herb interactions is not classified in the relevant references, nor the literature; data in this column are presented according to the authors' interpretation. AUC=Area under the (concentration-time) curve, Cmax=Maximum plasma concentration, CYP=Cytochrome P isoenzyme, INR=International normalized ratio, SSRIs=Selective serotonin reuptake inhibitors

Table 2: Demographic characteristics of the study population (n=2153)

Patients' characteristics	Number of CAM users (n=400), n (%)	Number of CAM non-users (n=1753), n (%)	P*
Sex			0.012
Male	261 (65)	1279 (73)	
Female	139 (35)	474 (27)	
Age group (years)			<0.001
0-20	19 (5)	175 (10)	
20-60	256 (64)	1270 (72.5)	
>60	125 (31)	308 (17.5)	
Marital status			0.331
Single	70 (17.5)	284 (16.2)	
Married	330 (82.5)	1469 (83.8)	
Educational status			0.079
Illiterate	69 (17.3)	315 (18)	
Primary school education	42 (10.5)	179 (10.2)	
High school education	103 (25.7)	361 (20.6)	
Postdiploma education	151 (37.8)	748 (42.7)	
Master of science	32 (8)	126 (7.2)	
PhD	3 (0.7)	24 (1.3)	
Occupational status**			<0.001
Without job	48 (12)	187 (10.7)	
Homeworker	82 (20.5)	158 (9)	
Student	17 (4.2)	102 (5.8)	
Recruitment job	84 (21)	750 (42.8)	
Retired	169 (42.3)	556 (31.7)	

*Chi-square test was used to assess the influence of each parameter on the tendency to herbal usage, **The occupational status was interpreted regarding financial income: without financial income (without job, homeworker, and student) and with financial income (recruitment job and retired). CAM=Complementary and alternative medicine, mainly herbal products

impact on herbal usage, while comorbidities and duration of disease were found to be the most highlighted reason for herbal supplement usage. Differences in the study population and their geographic location lead to different results achieved in studies on herbal usage. There is a fact that patients using CAM were hesitant to inform the physicians about it. Physicians' disapproval is one reason for CAM users not to disclose to the physicians about their CAM consumption.^[25,26]

Iranian borage (*E. amoenum*) as unformulated and anticough syrups as formulated herbal products were the most used ones in our study population, while common cold and respiratory problems were determined to be the main indications for this trend.

Iranian borage, native to the northern part of Iran and Caucasus, is one of the important medicinal herbs in Iranian traditional medicine mainly being used for variety of effects such as demulcent, anti-inflammatory, antioxidant, analgesic, and sedative, especially for treating common cold and anxiety. This herb has no serious side effects in usual doses applied for its therapeutic effects.^[27] In the study performed by Roozbeh *et al.* in 2013, *Cichorium intybus* was introduced as the most used herbal product for gastrointestinal disorders.^[14] Garlic was reported as the most commonly used herb in a Turkish study.^[9]

Panax ginseng appeared to have the most possible drug-herb interactions mainly with anticoagulant agents. This herb is used mostly for boosting immune system as well as sexual power enhancement. The most serious possible interaction was between *Panax ginseng* and warfarin which is a powerful anticoagulant agent usually used after heart attack. This interaction leads international normalized ratio (INR) to be reduced, and the possibility of coagulation may be increased in clinical setting.^[28] In this study population, dangerous interactions found where the posttransplant patients take their immunosuppressive regimen and also use *H. perforatum* or *Echinacea*, which both finally could lead to kidney graft rejection. *H. perforatum* could inhibit the reuptake of several neurotransmitters. In our study, *Hypericum* had shown a life-threatening interaction with cyclosporin, an immunosuppressive agent which uses after kidney transplant. This serious interaction decreases cyclosporine's serum level (with possible rejection in some cases) by inducing CYP3A4 enzyme. In the study performed by Borrelli and Izzo in 2009, the interaction between *H. perforatum* and cyclosporine was mentioned as the most well-documented herb-drug interactions among patients of renal and liver transplant.^[29] These interactions are common since CKD patients use many drugs for various conditions at the same time. The

Table 3: Top 10 formulated herbal products and unformulated medicinal herbs used by the study patients

	Frequency (%)
Herbal products' brand or common name (Scientific name)	
Anticough and mucolytic (<i>Thymus vulgaris</i>)	24.27
C-lax®, senna (<i>Cassia angustifolia</i>)	10.52
Prostatan® (<i>Pimpinella anisum</i> , <i>Tribulus terrestris</i> , <i>Cucurbita pepo</i> , and <i>Urtica dioica</i>)	7.79
Ginseng (<i>Panax ginseng</i>)	6.06
Livergol®, Liver support® (<i>Silybum marianum</i>)	4.15
Ginkgo (<i>Ginkgo Biloba</i>)	4.15
Sankol® (<i>Zea mays</i> , <i>Tribulus terrestris</i> , <i>Cerasus avium</i> , and <i>Foeniculum vulgare</i>)	4.04
Neuragol® (<i>Valeriana officinalis</i>)	2.12
Afrodit® (<i>Tribulus terrestris</i> , <i>Cinnamomum zeylanicum</i> , <i>Crocus sativus</i> , and <i>Zingiber officinale</i>)	2.12
Echinacea (<i>Echinacea angustifolia</i>)	1.92
Unformulated medicinal herbs' common name (Scientific name)	
Iranian borage, Echium (<i>Echium amoenum</i>)	15.27
Corn silk (<i>Zea mays</i>)	6.67
Valerian (<i>Valeriana officinalis</i>)	5.81
Damask rose (<i>Rosa damascena</i>)	5.81
Hedge mustard (<i>Sisymbrium officinale</i>)	4.73
Ginger (<i>Zingiber officinale</i>)	4.09
Unknown mixed herbs	3.87
Wild cherry (<i>Prunus avium</i>)	3.66
Horsetail (<i>Equisetum arvense</i>)	3.44
Green tea (<i>Camellia thea</i>)	2.80

usage of herbal products could be harmful for CKD patients because of nephrotoxicity or changes in kidney hemodynamic. Furthermore, electrolyte abnormalities by herbs could change the kidney performance.^[12] In our study, we have found that 26 patients use green tea which may have unwilling effects on kidney hemodynamic and 110 patients use senna which leads to electrolyte abnormalities including hypokalemia.^[18,19]

The fact that most patients do not inform health-care providers about their herbal product usage which leads to the risk of herbal's adverse effects and interactions.^[6-8] Furthermore, a study by Kelak *et al.* in 2018 showed that the attitude of patients toward herbal drug usage is an important factor to inform the health-care team about their consumption.^[30] This clarifies the positive role of health-care team to alert the patients about these side effects and avoid life-threatening interactions.

Our study has highlighted the main issues for health-care professionals to care about herbal product usage in CKD patients. More researches in other CKD and posttransplant populations may clarify more possible interactions between herbal products and prescribed medications.

The present study provided useful information on possible herb–drug interactions in CKD patients using medicinal herbs concomitant with conventional drug regimen. Ginseng was found to be the herb which may mostly have an interaction with prescribed medications. Age and educational status were determinative factors which may influence on herbal product usage. The majority of the patients were using herbal products to treat or relieve symptoms of common cold and respiratory disorders. Due to the possibility of important interactions, health-care team should play an active role to inform the patient about herbal product safety, adverse effects, and possible interactions. Discussing about herbal usage by physicians to the CKD and post-transplant patients, need more encourage by health-care providers which can be achieved by more efficacious education on risks and benefits of herbal therapy.

AUTHORS' CONTRIBUTION

All authors contributed the idea of research, design of study, data analysis and manuscript preparation.

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Conflicts of interest

There are no conflicts of interest.

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