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Review Article

EXISTING EVIDENCE FOR SAFE USE OF HERBAL MEDICINES IN CHRONIC KINEY DISEASE

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ABSTRACT

There has been a widespread use of herbal medicines in the last two decades, despite a lack of scientific evidence for their efficacy and safety. Health care professionals have expressed growing concerns about safety issues relating to use herbal medicine, particularly in patients with renal or liver insufficiency. This review will propose how to use existing evidence to suggest the safe use of herbal medicines in patients with renal insufficiency, as well as transferring toxicity findings of herbal medicines from animal studies to use in humans.

Safety information from postmarketing surveillance and case reports is likely to be the main information sources. However, there is little data relating to herbal medicines used by patients with chronic kidney disease. When human studies are lacking, animal studies can be seen as a substitute source of reliable information. An animal dose related to renal toxicity is used to calculate a theoretical human equivalent dose in order to estimate the toxicity in humans. However, this information should be used with caution. When herbal medicines used by people with renal insufficiency have, as yet, yielded no evidence of nephropathy, health care providers should regularly monitor kidney function of such people, together with their electrolytes. Observational studies are required to examine the renal adverse effects of herbal medicines.

Keywords: Herbal medicine, Nephrotoxicity, Evidence.

INTRODUCTION

The use of herbal medicine has been increasing worldwide over the last two decades, particularly by patients with chronic diseases and who are from Asian populations [1-3]. Prevalence of herbal use in patients with chronic kidney disease (CKD) ranges from 28-57% [4-7]. Although research in this field has been increasing [8], there is a lack of studies about safety issues regarding herbal use. Findings from in vitro and in vivo are likely to be the main information sources of the efficacy and safety of herbal medicine due to limited clinical trials and few epidemiological studies. This may be because regulation of herbal medicines in many Asian and Western countries has classified these products as dietary supplements or traditional herbal medicines. As a result, their registration has not required information from clinical trials, compared with conventional medicine [9-12]. This paper will propose how to use existing evidence to suggest safe use of herbal medicines in patients with renal insufficiency, and transfer toxicity findings of herbal medicines from animal studies to use in humans.

What available evidence is there for the safe use of herbal medicine?

Due to a lack of clinical trials regarding information about the safety of herbal medicines (15% of published randomized controlled trials in herbal medicine, compared with conventional medicines)[13], a prospective cohort study seems to offer rigorous evidence, see fig. 1. However, there are a few cohort studies in patients with CKD. One such study reported that Chinese herbal medicines were associated with developing CKD, see table 1 [14]. A case-control study is further evidence for the need for concern over safety issues relating to herbal medicines. There are a small number of these studies. For instance, only three case-control studies of herbal medicines related to either developing CKD or end-stage renal disease [15-17]. Likewise, there are limited cross-sectional studies of renal adverse effects from using herbal medicines. Only three cross-sectional studies reported that herbal medicines were associated with developing CKD [18-20].

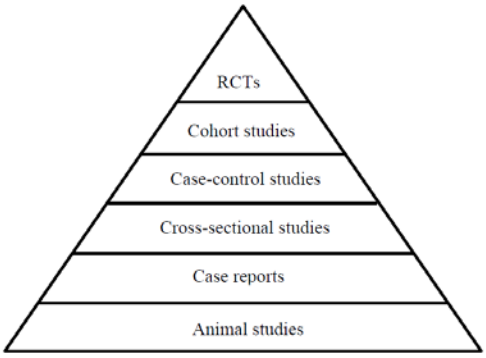

Fig. 1: Evidence hierarchy

Adapted from Ho PM, Peterson PN, Masoudi FA. Evaluating the evidence: Is there a rigid hierarchy? Circulation 2008;118(16):1675-84. [21] RCTs = randomised controlled trials.

Most of these observational studies did not specify a particular type of herbal medicine. They also reported herbal medicines as a whole, such as 'Chinese herbal medicine' or 'traditional herbal medicine'. Additionally, the studies were only conducted in Taiwan and

Thailand. Therefore, safety information regarding the use of herbal medicines seems to be based on postmarketing surveillance or case reports. These reports have provided the information from several regions, such as Europe, the US and Africa (tables 1-2).

Safety information from post-marketing surveillance and case reports

Several countries have established databases from their post-marketing surveillance systems, such as the U. S. FDA Adverse Event Reporting System, Canada Vigilance Adverse Reaction Online Database, the Therapeutic Goods Administration (TGA) Database of Adverse Event Notifications in Australia, and the WHO International Drug Monitoring Programme. In addition, data from poison centers provide further evidence of herbal medicine being related to serious adverse events. For instance, the U.S. FDA Center for Food Safety and Nutrition reported that eight patients were admitted to hospital due to dietary supplement use. One death from stroke resulted from the use of dietary supplements that contained caffeine and yohimbe [26].

As known, a voluntary reporting system of adverse events is under-reported [27], so there are only a limited number of reports on adverse effects, particularly herbal medicines as the culprit. From 1971 to 2012, a database of adverse events in Australia reported only 0.67% of adverse events related to herbal medicines [28]. Thus, intensive surveillance of the products, particularly in Asian populations, is needed to build up information on the safety of product use. This information would support developing a guideline for the rational use of herbal medicine.

A case report of herbal medicine related to adverse events is likely to be sufficient evidence to indicate whether or not people should avoid them. Forty-four case reports showed that herbal medicines or dietary supplements were associated with nephrotoxicity worldwide, see table 2 [29-32]. Existing literature reported that most herbal medicines were related to acute kidney injury [29]. Meanwhile, there is a lack of evidence regarding herbal medicines associated with the progression of chronic kidney disease in patients with CKD. The severity of adverse events in case reports is classified into three levels [33]: a severe adverse event is defined as death; moderate and mild adverse events are defined as life-threatening and non-life-threatening adverse events, respectively. Herbal medicines related to either severe or moderate adverse events supported by a case report should be avoided.

However, some herbal medicines, such as river spiderwort used by patients with CKD, have no reports on renal adverse effects [4]. Therefore, findings from animal studies are likely to be carefully evaluated in order to decide whether or not patients should avoid this medicine.

Table 1: Examples of herbal medicines or dietary supplements related to severe adverse effects

Information sources	Herbal medicines or dietary supplements	Adverse effects
U. S. FDA Adverse Event Reporting System (FAERS) [22]	Oxy Elite Pro®	Liver failure
Canada Vigilance Adverse Reaction Online Database [23]	Propolis	Acute renal failure
Thaivigibase during 2007-2008 [24]	Houttuynia cordata	Acute renal failure
Malaysia adverse drugs reaction advisory committee [25]	Ya-Hom Powder Five Pagodas Brand	Death
A prospective cohort study in Taiwan [14]	Chinese herbal medicines	Developing CKD (OR 1.20, 95%CI 1.16-1.24)
Three case-control study in Taiwan [15-17]	Chinese herbal medicines or MuTong	Developing CKD or end-stage renal disease
A cross-sectional study in Taiwan [18]	Chinese herbal medicines	Developing CKD (adjusted OR 1.39, 95%CI 1.20-1.70)
A cross-sectional study in Thailand [20]	Herbal medicines	Developing CKD (adjusted OR 1.20, 95%CI 1.02-1.42)

OR = Odds ratio, CI = Confidence interval

Table 2: Case reports on nephropathy related to herbal medicines or dietary supplements [29-32, 34]

Country	Herbal medicine	Adverse effect
Turkey	Anatolian hawthorn (Crataegus orientalis)	Acute interstitial nephritis
Japan	Bee pollen	Acute interstitial nephritis
South Africa	Cape aloe (Aloe capensis)	Acute tubular necrosis
Peru	Cat's claw (Uncaria tomentosa)	Acute interstitial nephritis
US, Mexico	Chaparral (Larrea tridentata)	Renal cysts
US	CKLS (kidney, liver, spleen purifier contains Aloe vera, Cascara sagrada, Larrea tridentata, and Arctostaphyos uva-ursi)	Acute interstitial nephritis
Australia, US	Cone flower (Echinacea)	Acute kidney injury
US	Creatine	Acute interstitial nephritis
Malaysia	Djenkol beans, jering (Pithecolobium lobatum)	Acute tubular necrosis
South Korea	Gongjin-dan (Moschus moschiferus, Cervus elaphus, Angelica gigas, Cornus officinalis)	Focal tubulointerstitial nephritis
Italy, US	Hemlock (Conium maculatum)	Acute tubular necrosis
Ireland	Horse chestnut seed extract (Aesculus hippocastanum)	Hemorrhage from renal amgiomyolipoma
US, Germany	Noni juice (Morinda citrifolia)	Hyperkalemia
Taiwan	Pien Tze Huang (Panax notoginseng, snake's gall bladder, dried cattle gall bladder stones, musk)	Acute kidney injury
Brazil, Taiwan	Propolis	Acute interstitial nephritis
Hong Kong, Taiwan	Star fruit (Averrhoa carambola)	Oxalate nephropathy
US, Europe	Wormwood oil (Artemisia absinthium)	Acute tubular necrosis
US, West Africa	Yohimbe (Pausinystalia yohimbe)	Acute kidney injury

Table 3: Conversion of body surface area to body weight

Species	Body weight (kg)	K_m factor
Human		
Adult	60	37
Child	20	25
Rabbit	1.8	12
Guinea pig	0.4	8
Rat	0.15	6
Hamster	0.08	5
Mouse	0.02	3

Adapted from Reagan-Shaw S, Nihal M, Ahmad N. Dose translation from animal to human studies revisited. *FASEB J* 2008;22(3):659-61.

How to transfer toxicity informaion from animal studies to humans

In the case of no reports on adverse effects of herbal medicines on humans, findings from animal studies seem to be crucial evidence to support a decision on herbal use in human beings. Several animal studies showed a toxic dose of herbal medicines leading to renal or liver toxicity.[35-37] This information is transferred to use in human by calculating a human equivalent dose from an animal dose.

Table 4: Six classes of acute toxic effects

Class	Severity of toxicity	A lethal dose in 50% of the population (LD_{50})
1	Extreme toxicity	<1 mg/kg
2	High toxicity	1-50 mg/kg
3	Moderate toxicity	50-500 mg/kg
4	Low toxicity	500-5,000 mg/kg
5	Practically non-toxic	5,000-15,000 mg/kg
6	Relatively harmless	>15,000 mg/kg

Theoretical human equivalent dose (mg/kg) =

$$\text{Animal dose (mg/kg)} \times [\frac{\text{Animal Km}}{\text{Human Km}}]$$, see table 3 [38].

Severity of acute toxic effects from animal studies has been classified into 6 categories based on a lethal dose in 50% of the population (LD_{50}) determination in rats, see table 4 [33].

The following is an example of calculating a theoretical human equivalent dose from an animal dose: Yacon leaves for anti-diabetic agents in Brazil were experimented in rats. Nephrotoxicity was caused by 100 mg/kg of an aqueous extract from Yacon leaves [35]. 1.8 grams of aqueous extract were prepared from 20 grams of dried leaves. From this information, the theoretical human equivalent dose of the Yacon extract was 16.2 mg/kg, which was equal to 180 mg of Yacon dried leaves per body weight (kg). It would appear that this dose is higher than a common dose of Yacon that people used for diabetes. LD_{50} of this herbal medicine is 5,000 mg/kg meaning low toxicity [39]. However, a Yacon water extract contains sesquiterpene lactones, which are likely to damage kidneys [35]. Therefore, Yacon should be used with caution, particularly by people with renal insufficiency.

Recommendation for herbal use based on theoretical knowledge

If there is no evidence of renal adverse effects in both human and animal studies, theoretical knowledge about adverse effects of herbal medicines is likely to be used, as a last resort, to provide guidance on the safe use of herbal medicines. For instance, the National Kidney Foundation and the National Lists of herbal medicinal products in Thailand have recommended avoiding certain herbal medicines, such as senna, rhubarb, based on theoretical knowledge [40, 41]. The side effects of senna are water and electrolyte loss, which may cause dehydration when people use either a high dose or take it long term. Consequently, it may induce acute kidney injury, especially in patients with CKD. One case report showed that a woman aged 52 years took a high dose of senna for 3 years and had renal and liver failure [42].

Existing evidence showed inconsistency with rhubarb-induced kidney damage. Albersmeyer et al. (2012) reported that a patient with diabetes type 1 used 500 mg/day of rhubarb for a month and oxalate nephropathy was found [43]. Meanwhile, Khan et al. (2014) conducted randomized controlled trials in 160 patients with stages 3 and 4 CKD, who received rhubarb of 750 mg/day with conventional therapy for 3 months [44]. They found no difference in adverse effects between the treatment and control groups. The rhubarb group also showed the slower progression of CKD. Therefore, further studies are required in order to prove validate safety information based on theoretical knowledge.

When the herbal medicines or dietary supplements used by patients with CKD have no any evidence on renal adverse effects, it is advisable as a precautionary measure that health care providers should regularly monitor such users' kidney function and electrolytes.

Summary

Existing evidence on renal adverse events, which have been precipitated by the use of herbal medicines, is supported by post-marketing surveillance and case reports. Due to a lack of information from human studies, animal studies seems to be a reliable source of information about renal and liver toxicity emanating from herbal medicines. Observational studies, such as case-control or cohort studies, are required to fill a gap in knowledge about the safety issues relating to herbal medicines.

CONFLICT OF INTERESTS

The author declares no conflict of interests.

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