



Review Article

AN UPDATE ON HERB INDUCED CHRONIC KIDNEY DISEASES

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ABSTRACT

The use of herbs as medicine has grown in popularity in this country over the past decade, contributing to a \$4.1 billion supplement industry. The popularity of herbs is due to several factors: they can be purchased without a prescription, a belief that "natural" products are safer and the knowledge that many of our modern drugs are derived from herbs. Toxicity can occur when a herb with unknown toxicity is consumed, incorrect identification leads to substitution of an innocuous herb with a toxic one, preparations are contaminated with toxic non-herbal compounds or when a herb potentiates the nephrotoxic effect of a conventional therapy. Renal injury has been reported in association with several herbs. The best known herb induced chronic kidney disease (CKD) is aristolochic acid nephropathy.

Keywords: Medicine, supplement industry, herbs, Toxicity.

INTRODUCTION

The use of plants, parts of plants and isolated photochemical for the prevention and treatment of various health ailments has been in practice from time immemorial. It is estimated that about 25% of the drugs prescribed worldwide are derived from plants and 121 such active compounds are in use. Of the total 252 drugs in WHO's essential medicine list, 11% is exclusively of plant origin [1]. Nearly 80% of African and Asian population depends on traditional medicines for their primary healthcare [2]. In India, about 80% of the rural population uses medicinal herbs or indigenous systems of medicine [3]. About 960 plant species are used by the Indian herbal industry [4]. Indian herbal market is registering a significant growth and is likely to reach Rs 145,000 million by 2012 and exports to Rs 90,000 million. The use of botanical medicine is ancient, and plant chemicals are still the

backbone of our pharmacopoeia because more than 50% of drugs used in Western pharmacopoeia are isolated from herbs or derived from modification of chemicals first found in plants [5,6]. Several factors, such as active uptake by tubular cells and high concentration in the medullary interstitial, make the kidneys particularly vulnerable to toxic insults [7]. Therefore, herbal medicine may be the source of kidney injury.

GENERAL OVERVIEW OF HAZARDS RELATED TO HERBAL MEDICINE:

Herbal toxicity can develop in any of the following situations: [8,10]

- (i) Consumption of an herb with unknown toxicity;
- (ii) Incorrect identification leading to substitution of an innocuous herb with a toxic one;

- (iii) Deliberate or inadvertent contamination with nephrotoxic non-herbal drugs (e.g. non-steroidal anti-inflammatory agents), pesticides or chemicals (e.g. heavy metal contamination from soil or water);
- (iv) Potentiation of the toxic effect of a conventional drug due to interaction with a compound present in the herb; and
- (v) Consumption of meat from an animal that has grazed on toxic plants (e.g. hemlock).

glycyrrhizic acid-induced hypertension and hypokalaemia, alfalfa or noni juice (*Morinda citrifolia*)-induced hyperkalaemia, star fruit (*Averrhoa carambola*)-induced encephalopathy and cranberry juice-induced nephrolithiasis.

The inherent toxicity of herbs

Aristolochic acid nephropathy (AAN) -

The best known example of herbal supplements resulting in renal failure is AAN (Chinese herbs nephropathy).

Table 1: Chronic kidney injury has been described in association with ingestion of several botanicals as follows:

Plant species	Common name	Toxic compound	Manifestation
<i>Aristolochia</i> sp.	-----	Aristolochic acid	Chronic interstitial nephritis, Renal tubular defects urothelial malignancies
<i>Larrea tridentate</i>	Chappara	Nordihydro guaiareti acid	Renal cysts, renal cell carcinoma
<i>Ephedra sinica</i>	Ma-Huang, Ephedra	Ephedrine	Nephrolithiasis, obstructive nephropathy
<i>Pithecolobium lobatum</i> ,	Djengkol	Djenkolic acid	Nephrolithiasis, obstructive nephropathy
<i>Averrhoa Carambola</i>	Star fruit	Oxalic acid	Nephrolithiasis, obstructive nephropathy
<i>Vaccinium Macrocarpon</i>	Cranberry	Oxalic acid	Nephrolithiasis, obstructive nephropathy
<i>Glycyrrhiza Glabra</i>	Licqorice	Glycyrrhizin	Hypokalaemic nephropathy
<i>Salix daphnoides</i>	Willow bark	Salicin	Renal papillary necrosis
<i>Pausinystalia Yohimbe</i>	Yohimbe	Yohimbine	Lupus nephritis
<i>Fucus Vesiculosus</i>	Bladder wrack	Heavy metals (contaminant)	Chronic interstitial nephritis
<i>Rhizoma Rhei</i>	Rhubarb	Anthraquinone	Chronic interstitial nephritis
<i>Echinacea</i> spp.	Coneflower	Arabinogalactan	Renal tubular acidosis

Renal involvement associated with the use of traditional medicinal products can take several forms,^[9,11,12] including acute kidney injury, tubular function defects, dyselectrolytaemias, Systemic hypertension, chronic kidney disease (CKD), renal papillary necrosis, urolithiasis and urothelial cancer. Patients with pre-existing CKD can develop complications due to herbal medicine use; some examples are *Ginkgo biloba*-induced haemorrhagic complications,

AAN became known to Western practitioners in early 1992 when Vanherweghem et al ^[27] discovered two similar cases of rapidly progressive fibrosing interstitial nephritis in young women. It was later found that one herb in a weight-reducing formula (*Stephania tetrandra*) had been inadvertently replaced^[27] by *Aristolochia fangchi* by the suppliers^[27]. *A. fangchi* contains AA, a plant alkaloid that is nephrotoxic and carcinogenic in humans and animals^[28]. The pathology of

AAN is characterized by extensive renal interstitial fibrosis and tubular atrophy, which generally decreases in intensity from the outer to the inner cortex. The glomeruli are usually spared, and immune deposits are not a feature. Endothelial cell swelling is often apparent with consequent thickening of interlobular and afferent arterioles. Uroepithelial malignancies are common, especially in those with a total Cumulative dose of *A. fangchi* in excess of 200 g. Furthermore, there is some concern that AA can cause acquired Fanconi syndrome in persons of susceptible race [30].

Balkan endemic nephropathy:

Balkan endemic nephropathy (BEN) occurs in certain areas of Romania, Croatia, Bosnia, Serbia and Bulgaria along the Danube river basin. According to some estimates, 25 000 people have proven or suspected BEN, with the number of people at risk being over 100 000 [32]. Characteristic findings include mild proteinuria, proximal tubular dysfunction, sterile pyuria, anaemia out of proportion to the degree of renal failure and small smooth kidneys [33]. Histology shows prominent interstitial fibrosis and tubular atrophy, with little cellular infiltration and mild glomerular damage. Urothelial malignancies are also characteristically associated with BEN [32].

Aristolochic acid is found in roots, stems, leaves and fruits of the plants of *Aristolochia* and *Asarum* genera.

CHRONIC KIDNEY DISEASES OF UNKNOWN AETIOLOGY

The impact of herbs on kidney disease elsewhere is probably underappreciated. DeBelle *et al.* compiled a list of botanical agents known to contain AA [36]. Despite a ban in many countries, products containing AA continue to be widely available. Inappropriate nomenclature and imprecise labeling are other confounding issues. Cheung *et al.* [39] found AA in a number of Chinese raw herbs and manufactured herbal products, many of which were due to the complexity of nomenclature leading to mistaken identification. It is also possible that more nephrotoxic plants still remain unidentified. The possibility of plants being responsible for CKD in other parts of the world has been suggested. A large proportion of CKD patients in the Indian subcontinent present with a relatively short history, advanced renal failure, little or no oedema, mild hypertension and small smooth kidneys.

CONCLUSION

The use of herbal remedies is common in large parts of the developing world, especially amongst the rural population. The true incidence of CKD due to nephrotoxic herbs remains uncertain. The structural and functional abnormalities are non-specific and may be overlooked. AA, present in a number of commonly used plants has been proved to cause chronic interstitial nephritis and urothelial malignancy. Clinical inquiry should be extended to include the possibility of use of herbal medicine when investigating a case of unexplained kidney disease or urothelial carcinoma. Regulatory control is essential to prevent toxicity due to misuse of herbs.

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