Review Article

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Renal Failure Associated with Plant Toxins

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Abstract

After cardiovascular disease, renal failure is a frequent cause of morbidity and mortality in the population worldwide. Humans are exposed to numerous plant toxins that cause deterioration of renal function with noticeable histopathological changes. Despite of extensive studies in past, recently only few articles have reported with an integrated approach to their nephrotoxic effects. In this article, we present plants which are involved in nephrotoxicity.

Keywords: Plant; Poisoning; Nephrotoxicity; Renal failure; Acute tubular necrosis.

Introduction

Plants contain various toxic substances that pose a serious risk of illness or death to humans or animals by causing systemic toxicity [1-3]. Nephrotoxic plants are commonly encountered both as common edible and medicinal plants [4]. More often, mistaken identification of these medicinal herbs and use of their toxic substitutes frequently lead to renal disease [5,6]. Herbal and traditional folk medicine nephropathy is common reported in China and Africa [7,8]. Several factors alter the physiology and histology of the kidney resulting in deterioration of the renal function and notable histopathological changes. These plant toxins may cause injury to the renal tubules at the transport site directly or by inducing renal ischemia, hemoglobinuria or myoglobinuria. Acute renal failure as a consequence of acute tubular necrosis and acute interstitial nephritis is most commonly reported [9]. In this paper, we conducted a comprehensive search using PubMed, ProQuest, ClinicalKey, Scopemed and Google Scholar from the year 1990 to 2018. All articles included were focused mostly on nephrotoxic effects on human. This paper attempted to appraise the importance of clinical toxicology by describing various plants that have been documented in the literature as causing nephrotoxicity.

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Literature

There are various plants which demonstrated the nephrotoxic effect. The results of review are presented in Table 1.

Aristolochiac lematitis (birthwort), *Magnolia officinalis* (magnolia bark) and *Stephania tetrandra* constitutes aristolochic acid, a carcinogenic compound derived from the seeds, demonstrated tubulointerstitial fibrosis associated with tubular atrophy and glomerular sclerosis on renal biopsy [10,11]. Tuber of *Callilepis laureola* (impila, ox-eye daisy) contains nephrotoxic principle atractyloside or carboxyatractyloside which causes renal tubular necrosis [12]. Irritant chemicals in the sap/ latex of the plant, *Euphorbia paralias* and *Euphorbia matabelensis* (spurge), a shrub showed focal segmental glomerulosclerosis associated with an acute tubular injury [13]. Active principles are methyl esters, diterpene polyesters and terpene compounds. Ingestion of *Archidendron pauciflorum* or *Pithecellobium lobatum* or *Pithecellobium jeringa* (djenkol or jenkol or jering bean) results in acute tubular necrosis with glomerular cell necrosis [14,15]. Active metabolite is djenkolic acid.

Table 1: List of plants manifesting nephrotoxicity

Common name	Region	Latin name	Active molecule	Renal pathology
Birthwort	Europe	*Aristolochia clematitis*	Aristolochic acid	Tubulointerstitial fibrosis, tubular atrophy, glomerular sclerosis,
Han Fang Ji	China, Taiwan	*Stephania tetrandra*		
Mognolia bark	China	*Magnolia officinalis*		
Ox-eye daisy Impila Black-eyed susan	South Africa	*Callilepis laureola*	Atractylosidecarboxyatractyloside	Renal tubular necrosis
Spurge	Europe, North Africa, Western Asia	*Euphorbia paralias, Euphorbia matabelensis*	Methyl esters, diterpene polyesters, Terpene compounds	Focal segmental glomerulosclerosis, acute tubular injury
Djenkol bean	Southeast Asia	*Archidendron pauciflorum*	Djenkolic acid	Acute tubular necrosis, glomerular cell necrosis
Rhubarb	China Tibet	*Rheum palmatum*	Emodin, aloe-emodin, oxalic acid, anthraquinone compounds	Interstitial fibrosis, kidney stones
Senna	Egypt	*Cassia acutifolia/ Senna alexandrina*	Anthraquinone glycosides (sennosides)	Renal tubular necrosis
Cascara buckthorn, sagrada	Northern America	*Rhamnus purshiana*	Hydroxyanthracene glycosides (cascarosides)	Acute tubulointerstitial nephritis
Buckthorn	Europe, Northern Africa, Western Asia	*Rhamnus frangula*	Anthraquinone compounds	Acute tubulointerstitial nephritis
Cape aloes, burn plant lily of desert	Asia, Africa	*Aloe capensis*	Aloins, aloinosides	Acute tubular necrosis, parenchymatous nephritis
Khat	Africa, Arabian peninsula	*Catha edulis*	Cathinone (S-cathionone, norephedrine, D-norpseudoephedrine)	Fat droplets in the upper cortical tubules, acute tubular necrosis
Autumn crocus, meadow saffron	Europe	*Colchicum autumnale*	Colchicine	Acute tubular necrosis
Liquorice	Southern Europe, parts of Asia	*Glycyrrhiza glabra*	Glycyrrhetinic acid/ glycyrrhetic acid	Acute tubular necrosis
Yam	Asia, Africa, America	*Dioscorea quinqueloba*	Diosgenin	Acute tubular necrosis, cortical necrosis, interstitial nephritis.
Chaparral, greasewood, creosote bush	North America	*Larrea tridentate*	Nordihydroguaiaretic acid	Tubular necrosis, renal cysts, renal cell carcinoma
Violet tree, wild wisteria	Africa	*Securidaca longipedunculata*	Alkaloid saponins, securinine, LD50 of Methylsalicylate, Gaultherin	Acute tubular necrosis, interstitial and glomerular haemorrhage
Marking nut tree	India	*Semecarpus anacardium*	Phenolic compounds (semicarpol)	Renal cortical necrosis
Broad bean	North Africa	*Vicis favus/ Vicis faba*	Divicine, isouramil	Acute renal failure
Tree cotton	India, Pakistan, East Africa	*Gossypium arboreum*	Gossypol (Phenolic compounds)	Distal renal tubular acidosis
Wormwood	Eurasia, Northern Africa, Northern America	*Artemisia absinthium*	Terpene	Acute renal failure with tubular casts
Cat's claw	South and central America	*Uncaria tomentosa*	Quinic acid, oxindole alkaloids and flavonols	Acute allergic interstitial nephritis
Bird flower, devil bean, rattle weed	Asia, Africa, Australia	*Crotalaria laburnifolia,Crotalaria retusa*	Pyrrolizidine alkaloids	Acute tubular necrosis
Cone flower	North America	*Echinacea purpurea*		Acute renal failure
Spearmint, lamb mint, mackerel mint, garden mint	Europe, Asia, Northern and western Africa, North and South America	*Mentha spicata*	Pulegone, menthofuran	Hydropic degeneration of tubular epithelial cells, atrophy of tubules and glomerules
Pennyroyal	Europe, North Africa, America	*Mentha pulegium, Hedeoma pulegioides*	Pulegone, menthofuran	Edematous hemorrhagic kidneys and acute tubular necrosis
Yohimbe Tree	Western and central Africa	*Pausinystalia yohimbe/ Corynanthe yohibi*	Yohimbine	Lupus nephritis and acute renal failure

Common name	Region	Latin name	Active molecule	Renal pathology
Cancer bush, balloon pea	Southern Africa	*Sutherlandia frutescens*	Canavanine, cycloartane glycosides, saponins, flavonoid	Renal tubular necrisis
Yellow wood	Australia	*Terminalia oblongata*	Terminalin	Avascular renal necrosis
Oduvan	India	*Cleistanthus collinus*	Arylnaphthalenelignan lactones, dyphyllin and its glycosides cleistanthin A, B and collinusin	Acute tubular necrosis
Thunder God Vine	China	*Tripterygium wilfordii*	Triptolide	Acute tubular necrosis
Mourning cypress	China, Vietnam	*Cupressus funebris*	Flavonoid	Acute tubular necrosis and interstitial nephritis
Easter lilies	Japan	*Lilium longiflorum*		Tubular nephrosis, interstitial edema
Jimson weed, devil's weed	North America, Australia	*Datura stramonium*	Tropane alkaloids such as scopolamine, hyoscyamine, and atropine	Acute tubular necrosis
Thorn apple	India, North America	*Datura innoxia*		
Chinese yew	China	*Taxus celebica*	Flavonoid (sciadopitysin)	Acute tubular necrosis, acute interstitial nephritis
Hemlock	Europe, North Africa	*Conium maculatum*	Cicutoxin, coniine	Acute tubular necrosis
Ma huang	China, Russia	*Ephedra sinica*	Ephedrine, norephedrine and pseudoephedrine	Nephrolithiasis, acute kidney injury
Star fruit	Southeast Asia, India	*Averrhoa carambola*	Ephedrine, oxalic acid	Oxalate nephropathy, tubular obstruction
Ting Kung Teng	Taiwan	*Erycibe henryi*	Cholinergic tropane alkaloids	Acute kidney injury
Yellow oleander	Mexico, Central America	*Thevetia peruviana/ Cascabela thevetia*	Cardiac glycosides (thevetin, oleandrin)	Acute tubular necrosis, glomerular vacuolation
Bladderwrack	Europe, North Russia, North America	*Fucus vesiculosus*	Arsenic	Tubular atrophy, heavy metal nephropathy
Willow bark	Europe	*Salix daphnoides*	Salicylate	Papillary necrosis
Cranberry, bearberry	North America	*Vaccinium macrocarpon*	Oxalic acid	Nephrolithiasis, obstructive nephropathy
Castor	Africa, India	*Ricinus communis*	Ricin	Acute tubular necrosis
Deathcap	Europe	*Amanita phalloides*	Cyclopeptides, (phallotoxins, amatoxins)	Acute interstitial nephritis and tubular necrosis
Deadly webcap	Europe, Australia	*Cortinarius speciosissimus*	Orellanine, orellin, orellinin and Cortinarin	Tubular necrosis with interstitial nephritis

Anthraquinone compounds are found in rhubarb, senna, cascara sagrada, aloe and buckthorn. Emodin, aloe-emodin, oxalic acid and related anthraquinone compounds are the active ingredients of Rhizoma Rhei (root) of *Rheum palmatum* Linne or *Rheum officinale (rhubarb)* cause diffuse interstitial fibrosis and kidney stones [16]. Toxic metabolites of anthraquinone glycosides, sennosides from *Cassia acutifolia* (senna) and angustifolia plants (leaf and pod) cause renal impairment with renal tubular cells necrosis [17]. *Rhamnuspurshiana* (cascara sagrada) containing hydroxyanthracene glycosides (cascarosides), and *Frangulae cortex/ Rhamni cathartics ftuctus/ Rhamnus frangula/* Frangulaalnus (buckthorn bark/berry) results in acute tubulointerstitial nephritis [18]. *Aloe capensis* (cape aloes) contains aloins and aloinosides which causes renal failure with acute tubular necrosis and parenchymatous nephritis [19].

Chewing of *Catha edulis* (khat) leaf revealed fat droplets in the upper cortical tubules and acute tubular necrosis on histology. The main metabolites are norephedrine, S-cathiononeand D-norpseudoephedrine [20]. *Colchicum autumnale* (meadow saffron, autumn crocus) constitutes colchicine which causes nephrotoxicity with acute tubular necrosis [21]. The active component glycyrrhetinic acid (glycyrrhetic acid) of *Glycyrrhiza glabra* (liquorice) induces acute tubular necrosis [22]. Dioscorea species like *Dioscorea quinqueloba* (yam) are tuberous plants results in acute tubular necrosis, cortical necrosis and interstitial nephritis [23]. It contains diosgenin, aglycone of saponoindioscin. Nordihydro-guaiaretic acid present in *Larrea tridentate* (Chaparral) reported to cause tubular necrosis, renal cysts and renal cell carcinoma[24]. The root of *Securidaca longipedunculata* (violet tree, wild wisteria) contains alkaloid saponins, LD 50 of

methyl salicylate and securinine. It also contains gaultherin, an amorphous steroid glucoside which cause the histopathologic changes of kidney including acute tubular necrosis with diffuse interstitial and glomerular haemorrhage [25,26]. Phenolic compounds (semicarpol, bhilawanol) in the sap of *Semecarpus anacardium*, the marking-nut tree of India, cause renal failure with renal cortical necrosis following prolonged exposure to the sap. Divicine and isouramil, active molecules in *Vicisfavus or faba*, broad bean can trigger hemolysis in certain subjects with Glucose-6 Phosphate Dehydrogenase deficiency, resulting in reversible acute renal failure. Gossypol, the principal ingredient of cotton seed oil, *Gossypium arboreum* could cause distal renal tubular acidosis [26]. *Artemisia absinthium* (wormwood essential oil) containing terpene result in acute renal failure with tubular casts [27].

Uncaria tomentosa, (cat's claw) documented acute renal failure with acute allergic interstitial nephritis contains quinic acid, oxindole alkaloids and flavonols [28]. *Crotalaria laburnifolia* (bird flower) and *Crotalaria retusa* contains pyrrolizidine alkaloids also been associated with renal damage with acute tubular necrosis [29]. Pyrrolizidine alkaloid contaminants is also present in *Echinacea purpurea* (cone flower) that cause acute renal failure [30]. *Mentha spicata* (garden mint) reported to cause hydropic degeneration of tubular epithelial cells along with some atrophic tubules and glomerules in experimental rat models [30]. Pennyroyal, an herb consisting of the leaves of either *Mentha pulegium* and *Hedeoma pulegioides* cause edematous hemorrhagic kidneys and acute tubular necrosis [32]. Mentha species constitutes containing pulegone and menthofuran. Yohimbine, indole alkaloid derived from the bark of *Pausinystalia yohimbe* or *corynanthe yohimbe (*yohimbe tree) reported to causelupus nephritis and acute renal failure [33]. *Sutherlandia frutescens* (cancer bush) contains canavanine, cycloartane glycosides, saponins and flavonoid, the extract possessed the potential to promote apoptosis, and alter the integrity of mitochondrial membranes in the renal tubules [34]. *Terminalia oblongata* (yellow wood) contains an unidentified nephrotoxic substance that causes avascular renal necrosis in mice and ruminants [35].

Toxic constituents of *Cleistanthus collinus* (oduvan) are arylnaphthalenelignan lactones, dyphyllin and its glycosides cleistanthin A, cleistanthin B and collinusin. Toxicity result in renal failure with acute tubular necrosis [36]. *Tripterygium wilfordii* hook F (Thunder God Vine) constitutes active molecule triptolide. It resulted in deterioration of renal function with acute tubular necrosis [37]. *Cupressus funebris* Endl (mourning cypress) possessing flavonoid exhibited acute tubular necrosis and interstitial nephritis [38]. Lilium species like *Lilium longiflorum* (easter lilies) have been documented to cause toxicosis in cats like interstitial edema and tubular nephrosis, characterized by epithelial cell necrosis in proximal tubule and exfoliation [39]. Leaves and flower of *Datura stramonium* (jimson weed) and *Datura innoxia* (thorn apple) produces ischemic acute tubular necrosis. In the renal cortex, there was shrinkage of the glomerulus with shrinkage of glomerulus in cortex. It contains tropane alkaloids such as scopolamine, hyoscyamine and atropine [40]. *Taxus celebica* (chinese yew) constitutes flavonoid, sciadopitysin reported acute tubular necrosis and acute interstitial nephritis [41]. The active components cicutoxin and coniinein *Conium maculatum* (hemlock) cause acute tubular necrosis [42]. *Ephedra sinica* (Ma huang) constitutes ephedrine, norephedrine and pseudoephedrine which revealed nephrolithiasis, acute kidney injury secondary to rhabdomyolysis [43]. *Averrhoa carambola (*star fruit) contain ephedrine and oxalic acid cause oxalate nephropathy and tubular obstruction [44]. Cholinergic tropane alkaloids in *Erycibe henryi* (Ting Kung Teng) cause acute kidney injury [45]. *Thevetia peruviana* (yellow oleander) has toxic metabolites cardiac glycosides. It reported to cause acute tubular necrosis and glomerular vacuolation [46]. *Vaccinium macrocarpon* (cranberry) contains oxalic acid which result in nephrolithiasis and obstructive nephropathy [47]. *Ricinus communis* (castor bean) containing active molecule ricin reported to cause acute tubular necrosis in sheeps [48]. *Salix daphnoides* (willow bark) containing salicylate cause renal dysfunction leading to papillary necrosis. *Fucus vesiculosus* (Bladder wrack), brown seaweed constitutes arsenic (from growth of plant in contaminated water) caused tubular atrophy and 'heavy metal nephropathy [49].

Propolis, a resinous substance collected by honey bees from various plants caused acute renal failure [50]. Acute renal failure with interstitial nephritis is even noticed in nutritional supplement containing bee pollen [51]. Wild mushrooms, *Amanita phalloides* (death cap) contain toxic agent cyclo peptides with components phallotoxins and the amatoxins. Renal pathology reported acute interstitial nephritis and tubular necrosis. Other species include *Amanita*

smithiana and *Amanita proxima* [52]. *Cortinarius speciosissimus* which possess the toxin orellanine exhibited tubular necrosis with interstitial nephritis [53]. Other mushroom like Galerina species also causes renal toxicity. Fava beans, poisonous mushrooms also causes acute kidney injury with acute tubular necrosis [53].

Conclusion

This systematic review provides details of various plants manifesting nephrotoxicity and enables the health care providers to diagnose and prevent the morbidity and mortality due to renal failure. We hope this review will stimulate the researchers for establishing the specific nephrotoxic principles.

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Ethical clearance

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