Expert Opinion on Drug Metabolism & Toxicology

ISSN: 1742-5255 (Print) 1744-7607 (Online) Journal homepage: http://www.tandfonline.com/loi/iemt20

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To cite this article: Xi-Lin Xu, Lin-Jiang Yang & Jian-Guo Jiang (2015): Renal toxic ingredients and their toxicology from traditional Chinese medicine, Expert Opinion on Drug Metabolism & Toxicology, DOI: 10.1517/17425255.2016.1132306

To link to this article: http://dx.doi.org/10.1517/17425255.2016.1132306

Accepted author version posted online: 15 Dec 2015.

Publisher: Taylor & Francis

Journal: *Expert Opinion on Drug Metabolism & Toxicology*

DOI: 10.1517/17425255.2016.1132306

Renal toxic ingredients and their toxicology from traditional Chinese medicine

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Abstract

Introduction: There have been increasing concerns regarding adverse reactions and toxicity incidents caused by traditional Chinese medicines (TCMs), among which the nephrotoxicity is particularly worrying.

Areas covered: This review summarizes the ingredients with renal toxicity from some TCMs through searching the relevant literature published over the past two decades. Renal toxicity components from TCMs include aristolochic acids (AAS), alkaloids, anthraquinones and others. TCM renal toxicity is most commonly caused by AAS and some alkaloids. AAS mainly come from *Aristolochia contorta* Bunge, *Aristolochia manshuriensis* Kom, *Clematis Chinensis* Osbeck, *Aristolochia cathcartii* Hook. Some renal toxic alkaloids are derived from *Tripterygium regelii* Sprague *et* Takeda, *Stephania tetrandra* S. Moore, *Strychnos nux-vomica* Linn. and *Aconitum carmichaeli* Debx. A few kinds of anthraquinones, flavonoids, and glycosides from TCMs also cause renal toxicity. All of these renal toxicity components and their associated renal toxicity, structures and toxic mechanism are introduced in detail in this review.

Expert opinion: Given the complexity of the toxic components, a lot of work needs to be done to analyze the specific modes of action of toxic components *in vivo* and *in vitro*, in particular, to elucidate the molecular mechanism of toxicity, in order to reduce the occurrence of renal toxicity of

TCM.

Keywords: AAS, alkaloids, renal toxicity, toxicology, Traditional Chinese medicines

Article highlights box

• With the extensive usage of TCMs, many drug-induced renal injury incidents have occurred in recent years, the renal toxic ingredients of TCMs and their toxicology have received wide attention.

• The renal toxic TCMs are mainly derived from *A. manshuriensis, A. cathcartii, S. nux-vomica, A. carmichaeli, Ricinus communis* Linn., *Rheum officinale* Baill.

• The poisonous components contain AAS, alkaloids, glycosides, anthraquinones.

• High dose of renal toxic TCMs can cause immediate degeneration and necrosis of renal tubular epithelial cells. Long term drug using often result in chronic renal interstitial fibrosis, leading to acute/chronic renal damage.

• A lot of work still needs to be done to analyze the nephropathy mechanism of some AAS, alkaloids and other TCMs components.

1 Introduction

Although the mechanism of most traditional Chinese medicine (TCM) is not clear, a lot of TCMs are effective in the clinic [1-3]. Previously, it is usually believed that TCMs are natural and therefore safe for the control of diseases. With the increasing cases of adverse drug reactions (ADRs), the ADRs induced by TCM are becoming more widely recognized [4, 5]. TCMs are the common remedy to treat major diseases in China, while it is considered as a complementary and alternative medicine in Western [2]. TCMs are regulated as a dietary supplement under the Dietary Supplement Health and Education Act in the United States, natural health products under the Natural Health Products Regulations in Canada [6]. Directive 2004/24/EC, which introduced and implemented a simplified registration procedure for TCM products, has played an important role in promoting TCM products harmonization in the EU [7]. However, TCMs are loosely regulated in comparison with other drugs. There are many kinds of TCMs, the total number is about eight thousand species besides seven hundred common used herbs. But, many of them have similar names and shapes, and some of their efficacy and safety dose are still not very clear [8].

In fact, some TCMs can cause damages on nervous, respiratory and reproductive systems, and liver and kidney injuries. Among the TCM-induced toxic effects, nephrotoxicity is one of the major concerns. The kidney plays a pivotal role in intermediary metabolism, the excretion of metabolic waste, and the acid-base balance. The severity of drug-induced kidney injury can range from nephritis to fatal kidney failure [9].

It is reported that many women in Belgium who had taken Chinese herbal capsules containing AAs for weight loss, more than 100 of them suffered from urinary tract cancer or renal failure finally [10]. Belgium's research report confirmed that the Chinese herb called *Stephania tetrandra* S. Moore was, in fact, inadvertently replaced by another Chinese herb, namely *A. fangchi* [11]. Misusing *A. fangchi* is a major cause of the cases of extensive interstitial fibrosis of the kidneys. After that Japan and the United States also reported about patients with kidney failure after using TCM [12]. The US FDA published two notices indicating that products containing aristolochic acid is a potential carcinogen, and have renal toxicity in 2000 [13]. Latest research has shown that exposure to aristolochia species contributes significantly to the incidence of upper urothelial cancer (UUC) in Taiwan [14]. According to these facts, Belgium, UK, Canada, Australia and Germany

have banned the use of these herbs [15].

The main renal toxicity components from TCMs are AAS and some alkaloids. AAS mainly comes from *Aristolochia contorta* Bunge, *Aristolochia manshuriensis* Kom, *Clematis Chinensis* Osbeck, and *Aristolochia cathcartii* Hook. Some renal toxic alkaloids are derived from *Tripterygium regelii* Sprague *et* Takeda, *Stephania tetrandra* S. Moore, *Strychnos nux-vomica* Linn., and *Aconitum carmichaeli* Debx. A few kinds of anthraquinones, flavonoids, and glycosides from TCMs also have renal toxicity. This review summarizes the research on kidney toxicity caused by TCM in the past twenty years, and focuses on the main components inducing kidney damage and their action pathways.

2 Aristolochic acids

AAS with a phenanthrene chromophore are small group of compounds mainly found in the Aristolochiaceae and 4,5-dioxoaporphines [16]. The main components of AAS are 8-methoxy-6-nitro-phenanthro-(3,4-d)-1,3-dioxolo-5-carboxylic acid (AAI) and 6-nitro-phenanthro -(3,4-d)-1,3-dioxolo-5-carboxylic acid (AAII) (Fig.1), and both AAI and AAII have been confirmed to lead to direct damage to renal tubular cells [15]. However, AAI is often the main ingredient in Chinese medicine pills [16].

A large number of reports have indicated that Aristolochic acid I (AAI) has toxicities to multiple organs, including glomerular, renal tubular and stomach [17]. Fig.2 shows the damages caused by AAI on kidney and its mechanism. Long-term exposure to high-dose AAI can cause chronic renal failure, tubulointerstitial fibrosis, tubular epithelial cell death, DNA damage and urothelial cancer (Table 1) [18,19]. More and more animal and clinical studies have suggested that AAI is a potent carcinogen having highly renal toxic [20].

Excessive intake of AAS is a major cause of aristolochic acid nephropathy (AAN). And the clinical manifestations and pathological features of AAN and Balkan nephropathy (BN) are very similar. There are several hypothesis assumes that BN in interaction with multiple environmental factors. But, the cause of Balkan nephropathy (BN) remains the major unanswered question. Therefore, the research about renal toxicity of TCMs maybe provide a good clue to determine the precise risk for BN.

2.1 Endoplasmic reticulum stress

Endoplasmic reticulum stress response is one of theories that AAS induce nephrotoxicity. Endoplasmic reticulum stress response is a self protective mechanism of cells. Moderate endoplasmic reticulum stress can restore homeostasis of the endoplasmic reticulum and maintain cell activity. But too strong or too long endoplasmic reticulum stress can induce the release a large amount of cytokines and ultimately lead to apoptosis [21].

It was found that, when AAS entered in tubular epithelial cells, it would enhance the phosphorylation of eukaryotic translating promotor -2α (eIF2a), increase XBP1 mRNA splicing, and up-regulate the GRP78/CHOP gene expression[22]. Retreatment with 4-sodium phenylbutyrate (4-PBA) could significantly inhibit apoptosis caused by aristolochic acids, which suggested the importance of endoplasmic reticulum stress in aristolochic acid-induced apoptosis.

Further studies have shown that pre-treatment with NAC or GSH can significantly reduce the content of related stress proteins in the endoplasmic reticulum and decrease the death of cells. Based on the results, it is concluded that AAS may induce apoptosis through the endoplasmic reticulum stress, which provides a new experimental evidence for renal toxicology of AAS [22].

2.2 Oxidative stress reaction

Oxidative stress response is related to the occurrence of various diseases. When oxidative stress occurs, if the body can not timely clear the increased reactive oxygen species, it will make lipid peroxidation increased, cause DNA oxidative damage and apoptosis [23]. Using 20 mg/ml AAS to stimulate HK-2 cells for 48 hours, and compared to the control group, HK-2 cells activity of the AAS group was significantly inhibited, the proportion of cell apoptosis increased, and SOD, GSH-PX activity decreased significantly [24], suggesting that the HK-2 apoptosis is related to oxidative stress injury.

Li et al. used the Comet Assay to detect the extent of DNA breakage in kidney tissues and immunohistochemistry to check the expression of 8-oxo–deoxyguanosine (8-oxo-dG) [25]. The results showed that TCM containing AAS can increase kidney tissue reactive oxygen species, thereby cause oxidative damage of DNA. Therefore, oxidative stress reaction may be one of the pathogenesis of aristolochic acid nephropathy.

2.3 Immune inflammatory mechanism

In aristolochic acid nephropathy (AAN), the characteristics of pathological changes in kidney represent in the interstitial cellular infiltration fibrosis [26]. It has been reported that inflammatory cell infiltration were found in rats with AAN, which suggests that inflammatory reaction is one of the symptoms of AAN. Therefore, it is speculated that the immune response may be one of the pathogenesis of AAN [27]. Sun established a mice model of AAN utilizing large doses of AAS, which displayed a acute kidney injury in early stage [28], and then developed into a tubulointerstitial fibrosis. A rat model was established on AAN and confirmed that there were monocytes/macrophages and T lymphocytes infiltrating in proximal tubular necrosis area [29]. These studies indicated that immune inflammatory mechanisms may be involved in the occurrence and development of AAN.

2.4 Renal tubular epithelial cell transdifferentiation

Activation of transforming growth factor (TGF)–β pathway is one of the important mechanisms of renal interstitial fibrosis caused by AAS, and tubular epithelial cells will lead to the secretion of a large amounts of TGF-β, promot the expressions of plasminogen activator inhibitor-1 and metal matrix proteins tissue inhibitors -1mRNA, eventually resulting in interstitial fibrosis [30]. A study found that 50 ng/ml of AAS acting on the renal tubular epithelial cells can cause increased expression of Smad2, 300 ng/ml of AAS entering into the tubular epithelial cells can cause decreased expression of Smad7. Using specific TGF-β1 receptor antagonists can reduce renal tubular epithelial cell transdifferentiation induced by AAS, which further demonstrated that the TGF-β1 signaling pathway participated in the transdifferentiation process of epithelial cells-induced by AAS [31].

Similar reports also could be seen in clinical experiments, Yang et al. found that the expressions of TGF-α, connective tissue growth factor, and extracellular matrix components increased in the biopsy specimens of patients with renal pathology AAS nephropathy [32, 33]. This hinted that transdifferentiation of renal tubular epithelial cells may be an important mechanism of renal interstitial fibrosis caused by AAS. Niu et al. considered that AAS inhibited the expression of MMP-7 mRNA, decreased the regeneration capacity of renal tubulars, and impaired renal function seriously [34, 35]. Therefore, to clear tubular epithelial cell transdifferentiation would provide a new therapeutic target for clinical treating aristolochic acid nephropathy.

3 Alkaloids

Alkaloids are a large class of basic nitrogen compounds widely distributed in nature. Most of them have a complex structure of heterocyclic, which is the active ingredient of many medicinal plants with a wide range of physiological activity [36]. Although alkaloids are distributed in various parts of herbs, most of them are concentrated in a particular organ [37]. Though referencing literatures in recent decades, toxic components, the renal toxicity, and the toxic mechanism of some alkaloid-induced nephropathy were listed in Table 2, and their structures are shown in figure 3.

3.1 Aconitine

Aconitine, existing in some medicinal plants like *A. carmichaeli* and *A. tanguticum*, is a kind of highly toxic alkaloid [38]. Aconite is a drug for resuscitation, and also a famous toxic TCM. Fresh aconite must be processed by frying, steaming or cooking to reduce its toxicity for the purpose of oral administration. It has been shown that 1.46 mg/kg of aconitine administered to mice will lead to denaturation of part of tubular epithelial cells and renal tubular epithelial cell apoptosis [39]. Toxic effects of aconitine can inhibit the TCA cycle of cardiac muscle and the oxidative phosphorylation of respiratory chain, resulting in myocardial aerobic dysbolism and cardiac dysfunction [40], which will lead to renal ischemia and hypoxia, destroy the redox dynamic equilibrium, and form a severe oxidative stress status. As a result, the pro-apoptotic genes are activated, and apoptosis of renal cells occurs [41].

3.2 Strychnine

Strychnine is the major toxic components of *S. nux-vomica*. When it reaches the toxic doses, the renal tubular epithelial cell will be impaired, which will lead to acute renal failure or uremia finally [25].

Strychnine can cause the damage and apoptosis of renal tubular epithelial cell [17], showing a significant cytotoxicity to tubular epithelial cells, which will lead to a significant injury in cell ultrastructure including somatic nucleus, hyper chromatic nuclear chromatin, nucleus missing, and mitochondrial swelling [42]. In vitro experiments discovered that 20 ~ 40 μg/ ml concentration of strychnine can inhibit cell proliferation of the human proximal tubular epithelial [17], higher concentrations of strychnine (40 μg/ml) significantly stimulate cell apoptosis, and 80 ~ 160 mg/ml

of strychnine have significant cytotoxicity to HK-2 cells [43].

3.3 Tripterygium alkaloids

Tripterygium alkaloids is one of the major toxic components of *T. regelii Sprague* [44]. Animal toxicity test showed that tripterygium alkaloids (9.97mg/g) Chronically administered to SD male rats for four weeks, will make tubular epithelial cell necrosis. Rat sub-chronic toxicity experiments showed that tripterygium alkaloids can make the glomerular stratified epithelial mild hyperplasia in most of rats, at the same time, it was found that glomerular began to be damaged and decreased in volume in poisoning death. Therefore, the damage caused by tripterygium alkaloids on kidney may be one of the main reasons that mice die in subchronic toxicity [45].

3.4 Brucine

Transporter is a class of functional proteins transporting various of endogenous and exogenous compounds through the cell membrane (Fig.4). The major function of organic anion transporters(OATs) is transporting organic anions from blood to proximal tubular epithelial cells. And when the kidney function is damaged [46], OATs transfer function will be abnormal. What's more, OATs' substrates are numerous, so they play an irreplaceable role in the process of excreting internal/external toxicants, drugs and metabolic wastes. Once OATs function is inhibited by drugs or poisons, normal physiological activities of the body will be disrupted or even be hurt [47].

Research found that brucine, aconite alkaloids, AAS inhibit OTA1, OTA3 function causing kidney damage. Therefore, TCMs inhibiting organic anion transporter may be one of the mechanisms leading to the kidney damage.

4 Others

In addition to AAS, alkaloids, and some other individual components including anthraquinone, flavonoids, and glycosides from TCMs have renal toxicity (Table 3), and their structures are shown in figure 5.

4.1 Flavonoid or Anthraquinone compounds

Partial proximal tubular epithelial cells cloudy swelling and partial proximal convoluted tubule autolyzed were observed in SD mice feeding with high doses of Chamaejasme flavonoids [48]. Excessive exposure to *Cassia angustifolia* Vahi will lead to a massive myoglobin and hemoglobin

obstructing tubular accompanied by proteinuria and hematuria, and tubular epithelial cells were seriously damaged [49]. Similar renal toxicity was also found in *Cassia obtusifolia* L. *Rheum officinale* Baill.and *Brucea mollis* Wall. (Table 3)

4.2 Esculentoside A

Zhou et al. used MTT assay to investigate the toxicity of Esculentoside A on HK-2 cells (Human renal tubular epithelial cells) through detecting cell morphological changes, activities of LDH, SOD and MDA in the cells, and cell apoptosis [50]. The results showed that Esculentoside A could inhibit HK-2 cells viability dependently on time and dose (IC50: 149.11ug/mL), Esculentoside A could increase the activity of LDH in HK-2 cells supernatant, reduce SOD activity and increase MDA content in HK-2 cells, cause cell apoptosis and necrosis and damage nephrocyte structure. Inducing cell apoptosis and oxidative damage are the major cause that esculentoside A has renal toxicity. Other species including *Gardenia jasminoides* Ellis., Cottonseed and *Camellia oleifera* Abel have similar renal toxicology which are listed in table 3.

4.3 *Leonurus tataricus Linn.*

Research showed that majority of kidney damages caused by *L. tataricus* are reversible, which would return to normal in a short time in addition to interstitial fibrosis. After 30 days being successive administrated with *L. tataricus* water decoction (16g/kg.d), SD rats urine NAG, urine THP, urine β2MG were significantly increased, the renal tubules, renal interstitial were damaged, or angiotelectasis [51]. Renal pathology showed that there were infiltration of inflammatory cells and fibrous tissue in renal interstitial, and renal tubular epithelial cell appeared vacuolar degeneration [52].

6 Expert opinions

The special characteristics of TCMs and their medicinal use make the post-marketing safety monitoring an important issue for drug safety evaluation. Pharmacovigilance system should cover some potential therapeutic approaches to attenuate TCM nephrotoxicity. To improve the current monitoring system, further pharmacovigilance procedures dedicated to TCMs should be established, in accordance with all their particularities, which require devising specific guidelines [53].

It is difficult to develop a standardized pharmacovigilance system for herbals in worldwide.

Herbal medicines come from all traditions including Chinese, Indian, African, north and south American and European systems. This diversity adds to the difficulties of herbal pharmacovigilance including basic questions such as defining the most appropriate herb naming system and validation of the botanical identity of the herbal ingredients [54]. A lot more work is still required to introduce pharmacovigilance systems into the monitoring and evaluation system of herbal medicines on the international market [55].

In Asia, AAI is always prescribed in adjunct with other herbs including *Scutellaria baicalensis Georgi*, *Glycyrrhiza uralensis Fisch.* and *Silene yunnanensis Franch.* by herbalists [56, 57]. Human CYP1A1 and CYP1A2 are the most important enzymes involved in the biotransformation of AAI to AAIa [58, 59]. Using angiotensin converting enzyme inhibitor (ACEI) or angiotensin II receptor I antagonist in the early poisoning stage can prevent or reduce the formation of interstitial fibrosis. Patients who enter the end stage of renal disease renal function were damaged significantly. It is necessary to be treated with replacement therapy, that is, dialysis or kidney transplantation [60]. It is still necessary for healthcare providers to minimize the usage of herbal medicines containing renal toxicity components [61].

A large part of the toxic events of TCM is the renal toxicity, and aristolochic acid is the main component of nephrotoxicity Up till now, 187 aristolochic acid and its derivatives have been isolated from natural sources. Because the ingredients of TCM is very complex, it has been found in recent years that some alkaloids and other ingredients also have renal toxicity, and more toxic ingredients are constantly identified from TCMs [62].

Currently, it has been confirmed that epithelial cells of the proximal tubules, distal tubules and collecting tubules are the sensitive targets of renal toxicity ingredients in TCMs [63]. According to animal experiments, it has been demonstrated that high dose of renal toxic TCMs can cause immediate degeneration and necrosis of renal tubular epithelial cells. Long term drug using often result in chronic renal interstitial fibrosis, leading to acute/chronic renal damage, or even renal failure if effective measures were not taken.

TCMs have complex component and often have similar name and appearance, leading to misuse or abuse of TCMs. Despite the renal toxicity, some of these TCMs are effective in treating certain diseases [64, 65]. Therefore, in clinical it is necessary to detoxicate the toxicity of these

drugs, which means to reduce and relieve toxicity [66].

In order to effectively reduce the toxicity events of TCM, Drug system of TCM needs further improvement. Although this work has been carried out, for example, the medicinal standard of *Aristolochia debilis*, *Aristolochia manshuriensis* and *Aristolochiae fangchi* were abolished several years ago, and the species containing AA was strictly restricted, more work still needs to continue. China Pharmacopoeia need to emphasize and consummate the safety of TCM, for example, China Pharmacopoeia lack of the restriction on alkaloids in most monographs, some toxic alkaloids and their potential threats to human health are overlooked, which needs to be paid enough attention in the future.

Although more and more constituents with renal toxicity have been identified from different TCMs, the nephropathy mechanism of most of the components is still not clear. Considering the complexity of the toxic components and the diversity of their acting pathway, a lot of work needs to do on pharmacovigilance, "Omics" technologies, and administration of mixtures alleviating toxicities. Pharmacovigilance methods can be used for monitoring kidney toxicity TCMs safety. "Omics" technologies have the potential for the development of molecular markers hopefully allowing for detection of early changes in toxic kidney injury with high sensitivity and specificity. These researches may help us to deeply learn the mechanism of TCM renal toxicity at the molecular and gene level.

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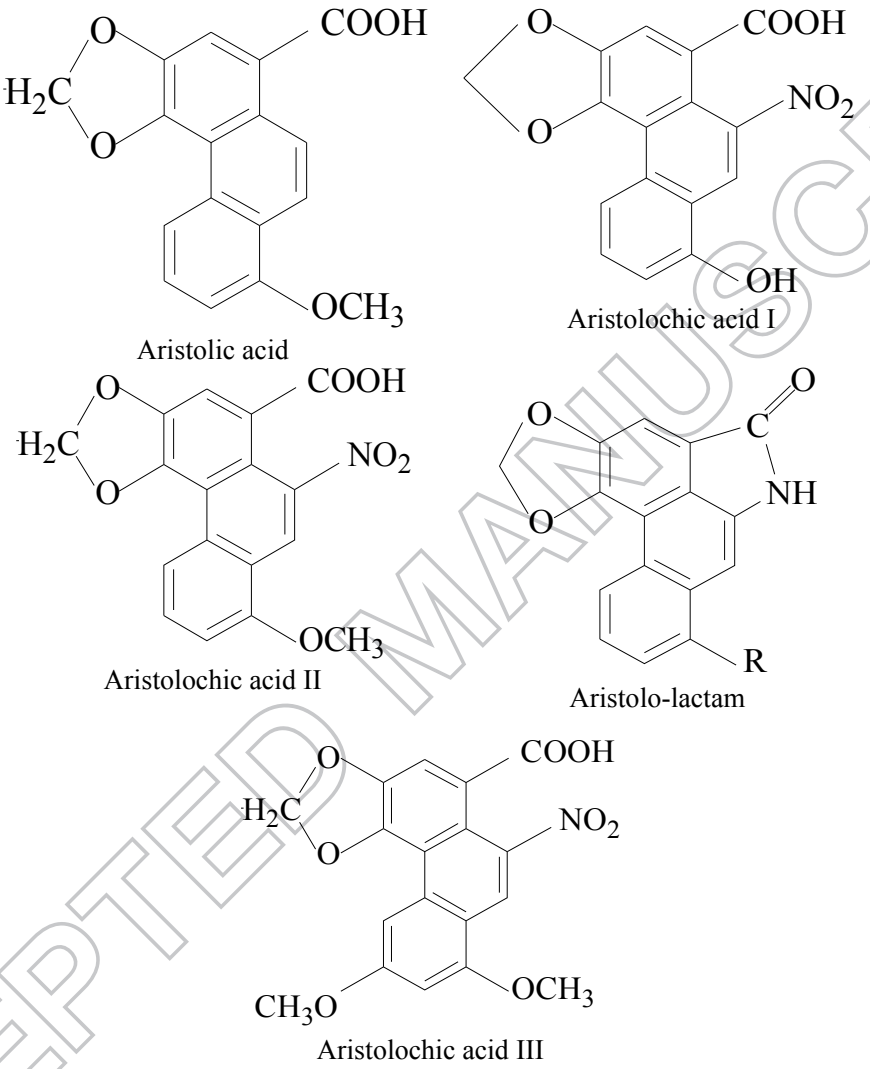


Fig. 1 Chemical structures of Aristolochic acid analogues

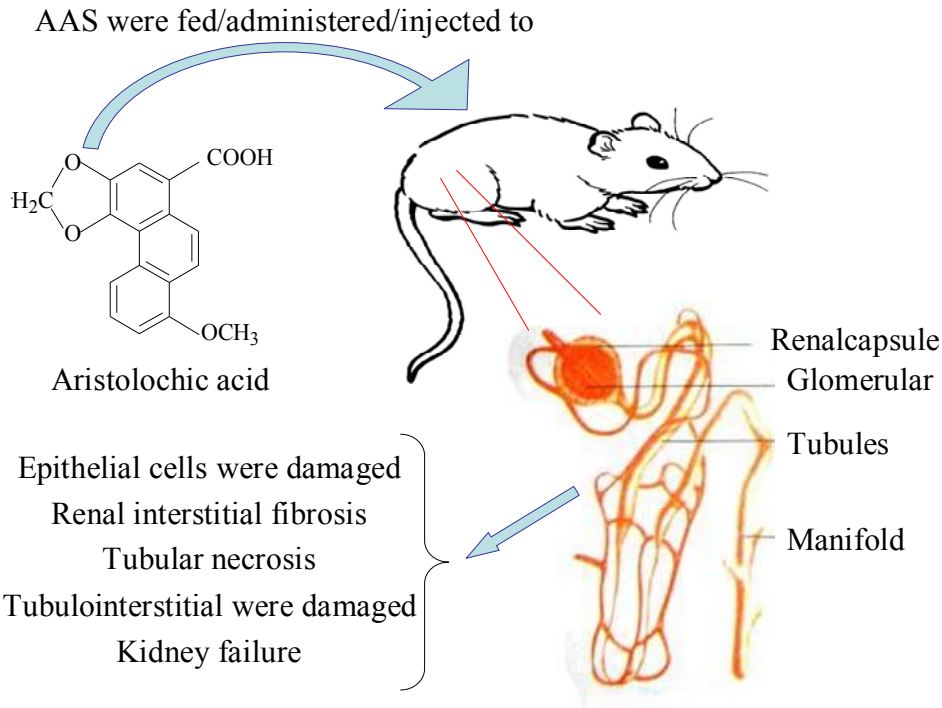
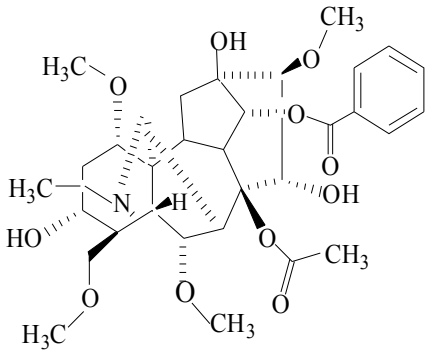
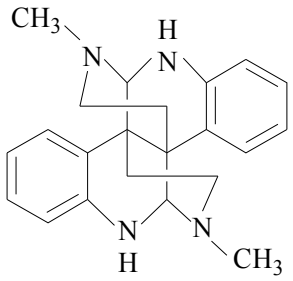


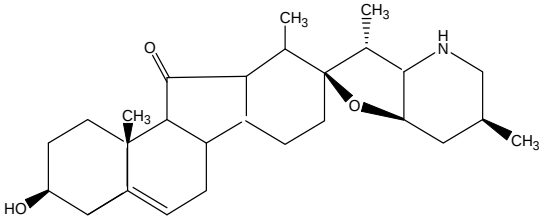
Fig. 2 Aristolochic acid renal toxicity mechanism on mice.



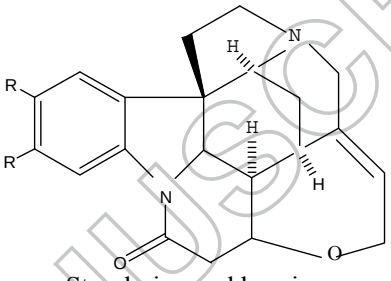
Aconitine



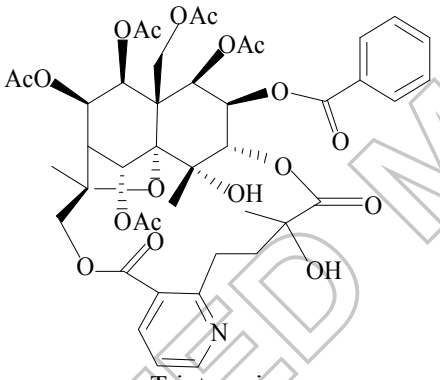
Calycanthine



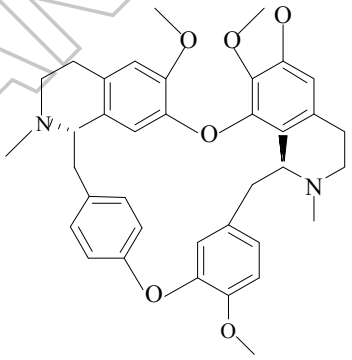
Jervine



Strychnine and brucine



Tripterygine



Tetrandrine

Fig. 3 Chemical structures of some alkaloids from TCM

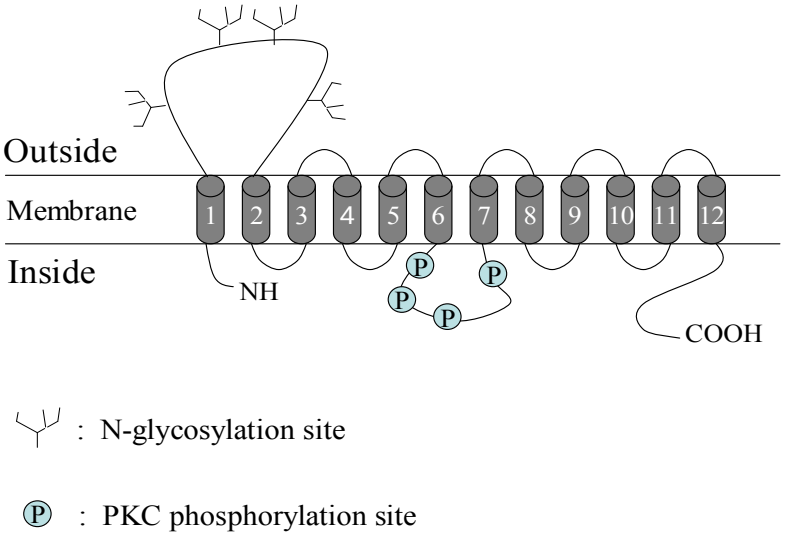


Fig.4 Organic anion transporter (OATs) function structure diagram (refer to [67], Modified)

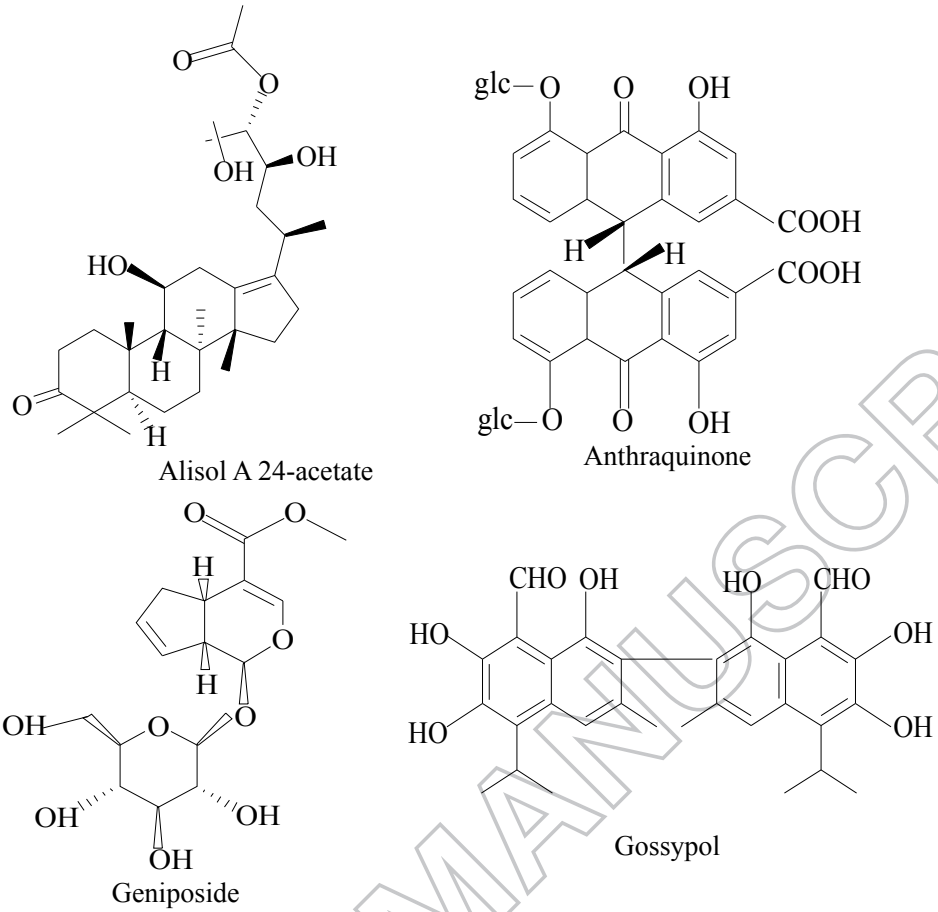


Fig. 5 Chemical structures of other renal toxicity components from TCMs.

Table 1 the effect and its mechanism on nephropathy induced by AAS from TCM

Active Ingredients	Source (Latin name/English name/Pinyin)	Methods	Toxicity	Mechanism	References
Aristolochic acid	*Aristolochiaceae* /Aristolochic/Ma douling	SD mices were administered with with aristolochic (0.2~25 mg/kg.d) for 4 weeks.	Causing hematuria, creatinine increase, kidney failure.	Tubular epithelial cell swelling, degeneration and necrosis	[68]
		Six patients who have used *Aristolochiaceae* for a long time.	Renal function was impaired	The number of tubules, interstitial fibrosis were reduced	[69]
		Injected into the vein of male mice (20mg/kg~60mg/kg).	Kidney failure. LD_{50}: 38.4mg/kg.	Tubular necrosis	[70]
Aristolochic acid	*Aristolochia debilis* Sieb. et Zucc./Radix Aristolochiae/Qing muxiang	Patients who has used radix aristolochiae for a long time.	Tubule interstitial lesions	renal tubular necrotizing Irreversibly	[71]
		water decoction were chronically administered to male wistar rats for 4d (166.85~128.55g/kg).	Renal interstitial fibrosis LD_{50}: 146.45g/kg	Tubulointerstitial was damaged	[72]
Aristolochic acid	*Aristolochia obliqua* S. M. Hwang/Fangchi/Guang fangji	Drugs were chronically fed to SPF male rats.	Tubular epithelial cell swelling, glomerular structural was damaged. LD_{50}: 55.9mg/kg	Influencing excretion functions of renal tubular	[73]
		water decoction were administered chronically to SD mices for 4 weeks (8.1g/kg.d).	Epithelial cells of proximal tubule were damaged slightly	Causing a damage of renal tubules and renal medullary	[74]
Aristolochic acid	*Aristolochia manshuriensis* Kom/Manshuriensis/Guan mutong	Drugs were chronically fed to SPF male rats for 12h.	Tubular necrosis	Interstitial fibrosis and the tubular were destroyed.	[75,76]
		Detecting the content of urine protein and urine NAG mildew after wistar rats have been gavaged the water decoction (15g/kg.d) for eight weeks	The NAG enzyme and urinary protein were reduced significantly.	Tubule interstitial fibrosis	[77]
		Mice were injected intraperitoneally.	Kidney failure. LD_{50} : 19.4g/kg	Glomerular filtration rate decreased and hematuria increased	[78]

Aristolochic acid	*Aristolochia cinnabarina* C. Y. Cheng et J. L. Wu/Root of Kaempfer Dutchmanspipe/Zhu shalian	Detecting renal activity on a middle-aged man who has taken root of Kaempfer Dutchman--spipe for a long time.	Acute aristolochic acid nephropathy	Tubules became necrotic	[79]
		A middle-aged man who has taken 100g of root of Kaempfer Dutchmanspipe in a day.	Renal Failure in a short time	Glomerular filtration rate decreased	[79]
Aristolochic acid A	*Aristolochia mollissima* Hance /Aristolochia /Xun gufeng	aristolochia water decoction were administered to female wistar rats (2.7g/kg.d).	Renal function was impaired	Tubules shrivelled	[80]
Aristolochic acid	*Clematis Chinensis* Osbeck/ radix clematidis/Wei lingxian	water decoction were chronically administered to female wistar rats for 3months (6.75g/kg·d).	Tubules and renal interstitial were damaged	Tubules shrinked significantly	[81]
Aristolochic acid -I	*Asarum heterotropoides* Fr. Schmidt var. mandshuricum (Maxim.) Kitag. /Asarum sieboldii/Xixin	Administered to female wistar rats.	Renal function was impaired. LD_{50} :4.8g/kg	Unclear	[82]
Aristolochic acid	*Aristolochia cathcartii* Hook./ Aristolochia / fangji	water decoction were administered to SD male rats for 4 weeks (8.1g/kg.d).	Glomerular and tubular became harden	Renal tubules were damaged	[74]

Table 2 The effect and mechanism on nephropathy induced by alkaloids from TCM

Active Ingredients	Source (Latin name/English name/Pinyin)	Methods	Toxicity	Mechanism	References
Tripterygine	*Tripterygium regelii* Sprague et Takeda/Tripterygium/Lei gongteng	Administered to SD male rats for 90d.	Renal function was impaired	Glomerular were damaged	[83]
		Injected into the abdominal cavity of mices.	Renal function was impaired	Papillae renales were damaged	[84]
Calycanthine	*Chimonanthus praecox* (Linn.) Link/Chimonanthus/La meigen	Injected into the vein of mices.	Causing hematuria. LD_{50}: 43.79±1.89mg /kg	Unclear	[85]
Tetrandrine	*Stephania tetrandra* S. Moore/Tetrandra/Fen fangji	3ml tetrandra were chronically administered to SD male rats for 60d.	Tubulointerstitial were damaged.	Tubular epithelial cells were damaged.	[86]
		(9.97mg/g) Chronically administered to SD male rats for four weeks.	The structure of glomerular was destroyed significantly	Tubular epithelial cell became necrosis	[74]
Dauricine	*Menispermum dauricum* DC /Menispermi/Bei dougen	Water extraction of Menispermi were administered to wistar rats.	Glomerular and tubular became wastage to varying degrees.	Unclear	[87]
Brucine	*Strychnos nux-vomica* Linn. /Strychnos/Ma qianzi	Strychnos were administered to mice	Leading to acute renal failure. LD_{50}: 3.27 mg/kg	Tubular epithelial cells were damaged.	[25]
Strychnine	*Strychnos nux-vomica* Linn. /Strychnos/Ma qianzi	Strychnos were administered to mice	Leading to acute renal failure	Tubular epithelial cells were damaged.	[88]
Veratrine	*Leucothoe griffithiana* C.B. Clarke /Wood Veratry//Mu lilu	Fed to mice	The kidney was slightly damaged	Inhibit the kidney to absorpt oxygen	[89]
Aconitine	*Aconitum carmichaeli* Debx. /Aconitum//Wutou	(1.46mg/kg) Aconitine were administered to mice.	Leading to denaturation of part of tubular epithelial cells. LD_{50}:0.25mg/kg.	Inducing apoptosis of tubular epithelial cells.	[39]
Pyrrolizidine alkaloids	*Senecio scandens* Buch-Ham/Groundsel/Qian liguang	Extract of Pyrrolizidine alkaloids were administered to SD rat.	Slightly impaired kidney	Unclear	[90]
Aconitine	*Aconitum tanguticum* (Maxim.) Stapf/Monkshood/Fuzi	Metabolomice was employed in wistar rat studies.	Renal tubular function was greatly affected.	Unclear	[91]

Table 3 the effect and its mechanism on nephropathy Induced by some other renal toxicity components from TCMs.

Active Ingredients	Source (Latin name/English name/Pinyin)	Methods	Toxicity	Mechanism	References
croton oil	*Croton caudatus* Geisel.*Croton*/Croton/Ba dou	Croton oil were administered to wistar rat.	Causing kidney damaged and hematuria. LD_{50}: 506mg/kg	Lead to necrosis of part of tubular epithelial cells.	[92]
Toadstool polypeptide	Toadstool/Duqun	Administered to Kunming mice.	Acute renal failure	Causing renal interstitial fibrosis and acute tubular necrosis	[93]
Anthraquinone compounds	*Cassia obtusifolia* L./Cassia/Jue mingzi	Cassia extract were fed to wistar rat for 90d.	Appearance of the kidney became dim.	That led to pigment of cassia deposition in the tubules.	[94]
Anthraquinone compounds	*Cassia angustifolia* Vahi/Folium senne/Fa xieye	Administered to Kunming mice.	Tubular necrosis. LD_{50}: 1.414g/kg.	Renal vasoconstriction. A large number of myoglobin and hemoglobin tubular obstruction	[95]
Anthraquinone compounds	*Rheum officinale* Baill/Rhubarb / Da huang	Administered to SD rat.	Lead to renal insufficiency.	Lead to necrosis of tubular epithelial cells.	[96]
Chamaejasme flavonoids	*Euphorbia fischeriana* Steud/Stellera chamaejasme/Lang du	Chamaejasme flavonoid was administered to SD rat.	Tubules structure is unclear.	Unclear	[97]
Podophyllotoxin	*Dysosma versipellis* (Hance) M. *Cheng ex Ying*/Dysosma/Ba jiaolian	Dysosma were administered to SD rat.	Tubular epithelial cells were Seriously damaged. LD_{50}: 0.493 g/kg.	Renal proximal tubule epithelial cells became swollen.	[98]
Alisol A 24-acetate	*Alisma plantago-aquatica* Linn/Alisma/Zexie	Alisma were fed to SD rat for 60d.	Lead to renal tubular damage.	unclear	[99]
Brucea alcohol	*Brucea mollis Wall*/Brucea /Ya danzi	Long-term toxicity experiments on SD rat.	Renal function of rats.	Deserve further research	[100]
Bakuchiol	*Psoralea corylifolia* Linn./Psoralen/Bu guzhi	Administered to mice	Glomerulonephritis.	Deserve further research	[101]
Geniposide	*Gardenia jasminoides* Ellis/Gardenia/Zhizi	Aqueous extract of Gardenia were administered to SD mice	Slightly enlarged kidneys was ebony.	Tubules became necrotic.	[102]
Gossypol	Cottonseed/Mianzi	5 Patients who ate cottonseed oil	Tubular function were damaged.	Renal potassium increased, leading to hypokalemia.	[103]

Sasanquasaponin (SQS)	*Camellia oleifera* Abel/oil-tea camellia/Youcha	Different doses of SQS were orally or administered given to Mices.	Renal Hemorrhage, Oral LD50: 1999.3mg·kg^{-}. administration LD50: 36.525mg·kg^{-}	unclear	[104]
Esculentoside A	*Phytolacca acinosa* Roxb./ pokeberry root/Shanglu	MTT assay was used to test the cell viability	cause damage of nephrocyte structure. IC_{50}: 149.11 ug/mL.	cellular oxidative damage and cell apoptosis	[50]