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Herbal Medicines for Acute Kidney Injury: Evidence, Gaps and Frontiers

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ABSTRACT

Acute kidney injury (AKI) is a major health threat worldwide. The literature on herbal intervention in AKI was searched from English and Chinese databases and reports were critically analyzed in terms of preventing AKI, promoting repair and regeneration, enhancing extrarenal clearance of uremic toxins, and preventing progression to chronic kidney disease (CKD). Altogether, 16 herbal formulae and a few extracts derived from individual herbs were reported to prevent or mitigate AKI in animal models induced by renal ischemia/reperfusion, cisplastin, gentamicin, glycerol, adenine, sepsis or physical exhaustion. Four formulae and six individual herbs were reported to accelerate recovery and/or to prevent CKD in established AKI animal models. Intrarectal herbal medicines, with or without simultaneous oral administration, were reported in six clinical trials and in an animal model to increase extrarenal clearance of uremic toxins. Additional 13 clinical trials reported oral or intravenous herbal interventions in AKI of different etiologies. Despite recurring problems, notably poor compliance with good practice guidelines for clinical trials and for authentication, naming and quality control of herbal materials, accumulating experimental data on the preventive effects of herbal medicines in AKI look encouraging and urge for better, definitive trials to guide clinical practice. Herbal enemas promoting extrarenal clearance of uremic toxins seem cost-effective, but better clinical evidence is certainly needed before any affirmative recommendation be made for AKI patients without access to dialysis. New frontiers, however, lie in those herbal remedies that promote repair/regeneration and prevent chronicity after AKI. Recent experimental data suggest that this may be possible.

Key words: Acute renal failure, renoprotective, traditional Chinese medicine, herbal medicinal products, traditional medicine

Abbreviations: AKI: acute kidney injury; AKIN: Acute Kidney Injury Network; αSMA: α smooth muscle actin; ARF: acute renal failure; ATN: acute tubular necrosis; BUN: blood urea nitrogen; CAT: catalase; CKD: chronic kidney disease; CXCL12: chemokine C-X-C motif ligand 12; CXCR4: chemokine C-X-C motif receptor 4; CLP: cecal ligation and puncture; Cu-Zn-SOD: copper-zinc superoxide dismutase; ECM: extracellular matrix; eGFR: estimated glomerular filtration rate; EMT: epithelial-to-mesenchymal transition; ESWL: extracorporeal shock wave lithotripsy; FSP: fibroblast-specific protein 1; GSH: glutathione; GSH-Px: glutathione peroxidase; HMP: herbal medicinal product; HO-1: heme oxygenase 1; ICAM-1: intercellular adhesion molecule-1; ICU: intensive care unit; IFN-γ: interferon-γ; IL: interleukin; iNOS: inducible nitric oxide synthase; i.p.: intraperitoneally or intraperitoneal; I/R: ischemia/reperfusion; i.v.: intravenous or intravenously; JNK: c-Jun N-terminal kinase; KDIGO: Kidney Disease Improving Global Outcomes; KIM-1: kidney injury molecule 1; LPS: lipopolysaccharides; MCP-1: monocyte chemotactic protein 1; MDA: malondialdehyde; MMP9: matrix metalloproteinase 9; Mn-SOD: manganese superoxide dismutase; NF-κB: nuclear factor κB; NGAL: neutrophil gelatinase-associated lipocalin; NO: nitric oxide; PCI: percutaneous coronary intervention; PCNA: proliferating cell nuclear antigen; p.o.: *per os* (oral administration); pRIFLE: modified RIFLE guideline for pediatric use; RCT: randomized controlled clinical trial; ROS/RNS: reactive oxygen/nitrogen species; RIFLE: Risk, Injury, Failure, Loss, and End-stage renal disease; RPTECs: renal proximal tubular epithelial cells; Scr: serum creatinine; TCM: traditional Chinese medicine; TGF-β: transforming growth factor β; TIMP1: tissue inhibitor of metalloproteinase 1; TNF-α: tumor necrosis factor-α; UUO: unilateral ureteral obstruction.

INTRODUCTION

Acute kidney injury (AKI), an abrupt renal damage and sudden decline of kidney functions, notably results in rapid increase in serum creatinine (Scr), blood urea nitrogen (BUN) and dysregulation of extracellular volume and electrolytes in a short term. Although AKI is also known as "kidney attack", an analogy to heart attack that mainly results from coronary atherosclerotic heart disease[1, 2], the causes of AKI are much more complex, including renal ischemia reperfusion (I/R), nephrotoxicity, infection, glomerular and interstitial nephritides, obstructive nephropathy, to mention a few. AKI may manifest an entire spectrum of severity, ranging from minor changes in urinary enzymes and Scr to severe cases needing dialysis and other renal replacement therapy. The latter severe scenario is also known as acute renal failure (ARF)[3].

On 14th March 2013, the 8th World Kidney Day was celebrated worldwide to alert the public of an increasing prevalence of AKI. Recent hospital studies in the developed world report AKI in 3.2–9.6% of admissions, with overall in-hospital mortality around 20%, and up to 50% in intensive care unit (ICU). ARF requiring dialysis treatment occurs in

5–6% of ICU patients, with an extremely high in-hospital mortality rate of 60%. The take-home message of the World Kidney Day was that AKI is very common, extremely harmful, and largely preventable[4].

In conventional medicine, however, strategies towards AKI are essentially preventive and supportive — avoidance of nephrotoxic agents is advised to patients, preconditioning is considered before exposure to a known AKI inducer, and dialysis is offered if indicated. Little evidence has so far supported any drug that specifically attenuates AKI or expedites recovery. If patients survive their illness and do not present premorbid chronic kidney disease (CKD), they typically recover to dialysis independence. However, evidence suggests that patients who have suffered an AKI are at increased risk of subsequent CKD[5]. Indeed, although AKI and CKD were once believed to be distinct disease entities, they are now increasingly regarded as closely interconnected syndromes, which are risk factors to each other and are both risk factors for cardiovascular disease and all-cause mortality[6].

For renal diseases, traditional medicines may have both contraindications, yielding or reinforcing nephrotoxicity, and indications, addressing medical needs unmet in AKI and CKD prevention and treatment — just like the "double-edged sword" effects of botanicals that we recently highlighted in the more general context of fibrotic diseases[7]. On one hand, some botanicals used in traditional medicine or ethnic cuisine are known to induce or exacerbate AKI, retard AKI recovery and/or promote AKI progression to CKD. These should be administered with caution, if at all, and prohibited in AKI; such nephrotoxic botanicals have raised major clinical concerns and their avoidance or controlled use has already an acknowledged place in worldwide renoprotective strategies[8–16]. On the other hand, some herbal medicines might have therapeutic values for the prevention and treatment of AKI. For example, silymarin is a lipophilic extract of the seeds of *Silybum marianum* (L.) Gaertn., the whole plant of which is also used in traditional Chinese medicine (TCM) as Shuǐ Fēi Jì (Herba Silybi). The herbal extract comprises three isomers of flavonolignans (silybin, silydianin and silychristin) and two flavonoids (taxifolin and quercetin) and its potential renoprotective effects in AKI/CKD were recently reviewed by Dashti-Khavidaki et al[17]. In line with this timely review, the present paper aims to critically examine the experimental and clinical evidence suggesting potential therapeutic values for herbal medicines, especially those used in TCM in the context of AKI.

TCM is a function-oriented, syndrome differentiation-based medical system that emphasizes Yin-Yang balance and interrelation between different organs. The concept of the functional organ shèn largely covers the functions of the kidney in modern medicine and AKI is often diagnosed as xū láo (vacuity taxation, fatigue), shuǐ zhǒng (water swelling, edema), lóng bì (dribbling urinary block, auria), yuē nì (vomiting, nausea), guān gé (block and repulsion, auria/vomiting), and/or niào dú (uremia)[18]. Thus, herbal remedies aiming at tonifying shèn, protecting the kidney, and dealing with imbalance and functional disorders are prescribed according to TCM theory and/or experiences of TCM practitioners.

In this review, we aim to enlist emerging evidence on efficacy, effectiveness and mechanisms of action of herbal medicines in the prevention and treatment of AKI, by focusing on four potential aspects: (i) preventing or mitigating induction of AKI; (ii) promoting repair or regeneration; (iii) promoting extrarenal clearance of uremic toxins; and (iv) preventing AKI progression to CKD (Fig. 1).

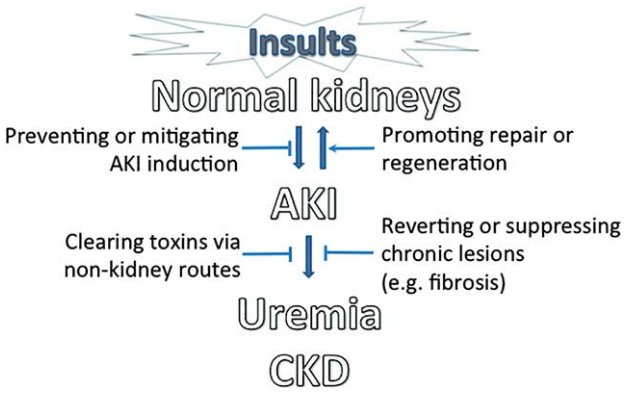

Figure 1. Four possible therapeutic effects of herbal remedies in prevention and treatment of AKI.

METHODS

To review the *in vitro*, *in vivo* and clinical renoprotective studies of botanicals possibly relevant to the prevention and treatment of AKI, PubMed and Scopus databases were screened by searching ("Acute Kidney Injury" [Mesh] or Acute-kidney-failure or Acute-renal-failure or Acute-kidney-insufficiency or Acute-renal-insufficiency) AND ("Drugs, Chinese Herbal" [Mesh] OR "Herbal Medicine" [Mesh]). In order to retrieve those randomized clinical studies and experimental studies published in Chinese, especially those on TCM, the China National Knowledge Infrastructure (www.global.cnki.net) and the Wanfang Data (www.wanfangdata.com) were accessed. The strategy used to search Chinese databases was (急性肾功能不全 OR 急性肾衰 OR 急性肾功能衰竭 OR 急性肾损伤 OR 急性肾损) AND (中药 OR 中医 OR 中西医 OR 汤 OR 方 OR 法 OR 治则 OR 草药 OR 回药 OR 蒙药 OR 藏药 OR 滇药) AND (治疗 OR 预防 OR 干预). Three reviewers independently scrutinized the titles and abstracts. Full manuscripts likely relevant to herbal medicines for the prevention and treatment of AKI were obtained and analyzed by at least two reviewers. Final decisions on addition and inclusion were made on examination of the full manuscripts, including brief communications, based on the relevance to the focus of this search. As we cannot exclude the possibility that a paper poorly written may have important contents of value to inspire future quality studies, we have not excluded any paper on the grounds of poor quality; instead, we introduce papers with higher quality with more details, while only briefly mentioning those with poorer quality. Meanwhile, we have pointed out common problems, as well as specific

weaknesses of each paper as far as we can in related texts and tables. Nonetheless, interested readers are invited to read any cited papers themselves to make their own judgements. To facilitate access to Chinese literature not cited by Pubmed, we have included corresponding Wanfang Data web links to these papers in the REFERENCES section.

Throughout this manuscript, scientific names and authority names of medicinal plants will only be shown when authentication of an herb was reported in the original publication[19]. Wherever information on authentication is unavailable, herbs used in TCM are referred to as accented Chinese pinyin names followed by, in brackets, the English pharmaceutical names retrieved from http://dict.paradigm-pubs.com/test31.htm.

BOTANICALS FOR AKI: EXPERIMENTAL STUDIES

1. Preventing and alleviating AKI

1.1 Ischemia/reperfusion (I/R) kidney injury

I/R is one of the most common causes of AKI and herbal entities have been reported effective in preventing I/R-induced AKI in animal models.

In TCM, two or more herbs are often used together as herbal formulae. Those formulae reportedly preventing I/R-induced AKI are shown in Table 1. We summarize reports on the preventive effects of herbal formulae, individual herbs and pure compounds of an herbal origin, as follows.

A preventive effect on I/R-induced AKI in rats has been reported for the formula Dang Gui Bu Xue Tang (DGBXT), comprising huáng qí (Astragali Radix) and dāng guī (Angelicae Sinensis Radix). DGBXT (2 ml, by gavage, once daily) administered for 3 days before clamping and then continued for another 3 days significantly repressed the rise of Scr 24h and 48h after reperfusion, as compared with the control group, which were given distilled water instead of DGBXT. DGBXT also significantly increased the percentage of tubular cells expressing proliferating cell nuclear antigen (PCNA) and increased renal c-Jun N-terminal kinase (JNK) activity[20].

Wen-Pi-Tang administered by gavage for 30 days was also reported to prevent I/R-induced AKI in rats, preventing the rise of Scr and BUN and reducing apoptosis in the kidney[21]. In a renal tubular epithelial cell line, Wen-Pi-Tang, as well as three of its ingredients, dà huáng (Rhei Radix et Rhizoma; *Rheum officinale* Baillon), gān cǎo (Glycyrrhizae Radix; *Glycyrrhiza glabra* Linn. var. *glandulifera* Regel et Herder) and rén shēn (Ginseng Radix; *Panax ginseng* C.A. Meyer), but not the other two ingredients, were shown to reduce cellular malondialdehyde (MDA) contents and prevent cell death induced by hypoxia-reoxygenation. Epicatechin 3-O-gallate and licochalcone A, major polyphenols of dà huáng and gān cǎo respectively, also showed similar protective effects in this *in vitro* model[22].

In an I/R-induced AKI mouse model, Wen-Pi-Tang-Hab-Wu-Ling-San, administered orally for 14 days prior to I/R until the end of the study, prevented I/R-induced Scr rise and renal tubular injury, while preserving the renal activities of copper-zinc (Cu-Zn-SOD) and manganese superoxide dismutases (Mn-SOD) and reducing lipid peroxidation and hydrogen peroxide production[23].

Shenhua Tablet (also known as Fufang Shenhua Tablet or Compound Shenhua Tablet), given to rats by gavage 7 days prior to I/R intervention, reduced Scr, serum interleukin-8 (IL-8), serum interferon-γ (IFN-γ) and renal expression of Toll-like receptor (TLR)-2 and -4[24]. The pretreatment reduced Na^+-K^+-ATPase relocalization from the apical to the basal membrane of tubular epithelial cells, suggesting that it protected the renal tubules from I/R-induced depolarity[32].

Cordyceps sinensis (Berk.) Sacc. is a fungus that parasites caterpillars and its fruiting body is used in TCM as dōng chóng xià cǎo (Cordyceps) for tonifying shèn, which may be positive for AKI patients (as detailed later in Section 4). Modern research validated a renoprotective activity mediated by enhancement of antioxidative defenses[25]. In an I/R-induced AKI model in rats, Shahed et al. reported that i.p. injection of a *Cordyceps sinensis* extract 1 h before renal I/R procedure significantly repressed Scr rise, suppressed the mRNA expression of monocyte chemotactic protein 1 (MCP-1), tumor necrosis factor α (TNF-α), heme oxygenase 1 (HO-1), inducible nitric oxide synthase (iNOS), Fas and Fas ligand, as well as caspase 3 activity in the I/R kidney, indicating a likely down-regulation of apoptotic and pro-inflammatory signalling[26]. Renoprotective effects of *Cordyceps sinensis* were also reported by Wang et al., who showed that Scr of rats orally receiving a commercialized fermented *Cordyceps sinensis* extract (Corbrin capsule, Bailing Jiaonang, Bailing capsule or Bailing granule) for 2 days before I/R recovered faster. The authors attributed this effect to an induction of chemokine C-X-C motif ligand 12/chemokine C-X-C motif receptor 4 (CXCL12/CXCR4) signaling and alleviation of senescence[27].

Dān shēn (Salviae Miltiorrhizae Radix; *Salvia miltiorrhiza* Bunge (Labiatae)), an herb commonly used in TCM for its acknowledged capacity of promoting blood circulation and removing blood stasis, was also reported to have protective effects in I/R-induced AKI. Rats orally administered an ethanolic extract of the herb for 20 days had blunted rises in Scr, BUN, circulating IL-6, IL-8, TNF-α and renal MDA, and increased renal SOD, catalase (CAT), glutathione (GSH) and glutathione peroxidase (GSH-Px)[28]. It was proposed that the renoprotective effects of the herb was at least in part attributable to its capacity to repress excessive nitric oxide (NO) production and its subsequent transformation into the pro-oxidant peroxynitrite ($ONOO^-$); indeed *S. miltiorrhiza* aqueous extract and isolated compounds (caffeic acid and its oligomers, rosmarinic acid, lithospermic acid, lithospermic acid B and magnesium lithospermate B) dose-dependently reduced NO production from activated macrophages[29].

Picroliv, a mixture of iridoid glycosides extracted from Hú húang lián (Picrorhizae Rhizoma; *Picrorhiza kurrooa* Royle ex Benth-unresolved botanical name, consulted on 6th June 2015, www.theplantlist.org), was suggested of beneficial effects in a rat model of I/R-induced AKI. Although renal functional parameters (e.g. Scr and BUN) were not reported, daily oral administration of picroliv for a week improved

Table 1. Formulae for preventing I/R-induced AKI.

Formula	Ingredients	References
Dang Gui Bu Xue Tang	**2 herbs:** huáng qí (Astragali Radix) and dāng guī (Angelicae Sinensis Radix)	[20]
Wen-Pi-Tang	**5 authenticated herbs:** dà huáng (Rhei Radix et Rhizoma; *Rheum officinale* Baillon), rén shēn (Ginseng Radix; *Panax ginseng* C.A. Meyer), gān cǎo (Glycyrrhizae Radix; *Glycyrrhiza glabra* Linn. var. *glandulifera* Regel et Herder), gān jiāng (Zingiberis Rhizoma; *Zingiber officinale* Roscoe), and fù zǐ (Aconiti Radix Lateralis Praeparata; *Aconitum japonicum* Thunberg)	[21, 22]
Wen-Pi-Tang-Hab-Wu-Ling-San	**14 authenticated herbs:** dǎng shēn (Codonopsis Radix; *Codonopsis pilosula* (Fr.) Nannf), dān shēn (Salviae Miltiorrhizae Radix; *Salvia miltiorrhiza* Bunge), bàn xià (Pinelliae Rhizoma; *Pinellia ternata* (Thunb.) Makino), huáng lián (Coptidis Rhizoma; *Coptis chinensis* Franch.), yín yáng huò (Epimedii Herba; *Epimedium koreanum* Nakai), dà huáng (Rhei Radix et Rhizoma; *Rheum palmatum* L.), zǐ sū yè (Perillae Folium; *Perilla frutescens* (L.) Britton), gān cǎo (Glycyrrhizae Radix; *Glycyrrhiza uralensis* Fisch), yīn chén hāo (Artemisiae Capillaris Herba; *Artemisia capillaris* Thunb.), zé xiè (Alismatis Rhizoma; *Alisma plantago-aquatica* L.), fú líng (Poria; *Wolfiporia cocos* (Schw.) Ryv. & Gibn – the authors used its old Latin name *Poria cocos* Schw.), bái zhú (Atractylodis Macrocephalae Rhizoma; *Atractylodes macrocephala* Koidz.), zhū líng (Polyporus; *Polyporus umbellatus* (Pers.) Fries), and guì zhī (Cinnamomi Ramulus; *Cinnamomum cassia* (L.) J.Presl).	[23, 79]
Shenhua Tablet	**7 herbs**: Huáng qí (Astragali Radix), nǚ zhēn zǐ (Ligustri Lucidi Fructus), sān léng (Sparganii Rhizoma), bái zhú (Atractylodis Macrocephalae Rhizoma), é zhú (Curcumae Rhizoma), jīn yín huā (Lonicerae Flos), sháo yào (Paeoniae Radix).	[24]

renal GSH, GSH-Px and SOD, and reduced renal MDA, intercellular adhesion molecule-1 (ICAM-1) and apoptosis, suggesting antioxidative, anti-inflammatory, and renoprotective potentials[30].

Ligustrazine, also known as tetramethylpyrazine, is a compound purified from chuān xiōng (Chuanxiong Rhizoma; *Ligusticum striatum* DC.). In unilaterally nephrectomised mice subjected to renal I/R, intraperitoneal (i.p.) injection of ligustrazine 30 min before the I/R procedure significantly blunted rises in Scr and BUN, while increasing renal Bcl-2 and SOD, suppressing renal tubular necrosis and apoptosis, and reducing renal MDA and ICAM-1[31].

Oral administration of astragaloside IV, a triterpenoid glycoside isolated from *Astragalus membranaceus* (Fisch.) Bunge, was also reported to prevent I/R-induced AKI in rats, repressing BUN, Scr, serum IL-8 and IFN-γ, reducing renal TLR-2 and TLR-4 and kidney injury molecule 1 (KIM-1) expression, while preventing the loss of renal Na^+-K^+-ATPase[32]. In another independent report of I/R-induced AKI in rats, astragaloside IV pretreatment for a week reduced BUN, Scr, serum cystatin C, neutrophil gelatinase-associated lipocalin (NGAL) and urinary KIM-1, reduced oxidative stress and tubular cell apoptosis, while increasing Bcl-2 expression, reducing p38 mitogen-activated protein kinase phosphorylation, and Bax expression[33].

Notoginsenoside R1 is a triterpenoid saponin extracted from sān qī (Notoginseng Radix; *Panax notoginseng* (Burkill) F. H. Chen), an herb with a long history of traditional use for the treatment of various cardiovascular diseases in China, Korea, and Japan. The compound has antioxidant, anti-inflammatory, anti-apoptotic and immune-stimulatory properties and was recently reported to accelerate structural and functional recovery of I/R-injured kidneys in rats. I.p. injection of the compound 1 h before I/R procedure did not affect the peak of Scr rise 24h after I/R, but significantly reduced Scr at 72h after I/R. It notably promoted Bcl2 expression, suppressed renal myeloperoxidase, TNF-α, p38 mitogen-activated protein kinase and nuclear factor κ B (NF-κ B), and reduced tubular apoptosis[34]

1.2 AKI induced by nephrotoxicants

Nephrotoxicants, notably some antibiotics, anti-cancer drugs and contrast agents, are another major causes of AKI. Nine herbal formulae (Table 2), a number of multi-component herbal extracts and pure herbal compounds reportedly prevented and/or mitigated experimental AKI induced by different nephrotoxicants.

Cisplatin-induced AKI Cisplatin is an effective and commonly used chemotherapy drug against many cancers and its nephrotoxicity is a major dose-limiting side effect. Gao et al. reported that pretreatment for three days with a "Recipe for nourishing kidney and activating blood" followed by three more days of treatment after cisplatin injection in mice significantly reduced cisplatin-induced rise of Scr and ameliorated acute tubular necrosis (ATN)[35].

When orally administered in rats once daily for 23 days before and 5 days after cisplatin injection, an aqueous extract of hóng shēn (Ginseng Radix Rubra; steamed roots of *Panax ginseng* C.A. Meyer) reduced cisplatin-induced renal expression of inflammatory cytokines and renal oxidative stress, mitigated renal apoptosis and AKI renal pathology, and attenuated Scr and BUN rises[36]. Furthermore, a Korean-Chinese collaboration reported a new type of hóng shēn, known as Sun Ginseng, which is processed at higher temperature and pressure and contains much higher

Table 2. Formulae for preventing nephrotoxicant-induced AKI.

Formula	Ingredients	Types of AKI (Reference)
Recipe for nourishing kidney and activating blood	**12 ingredients:** shēng huáng qí (Astragali Radix Cruda), wǔ wèi zī (Schisandrae Fructus), dān shēn (Salviae Miltiorrhizae Radix), chuān xiōng (Chuanxiong Rhizoma), dà huáng (Rhei Radix et Rhizoma), dà huáng tàn (Rhei Radix et Rhizoma Charred), bàn zhī lián (Scutellariae Barbatae Herba), yīn chén hāo (Artemisiae Scopariae Herba),qīng hāo (Artemisiae Annuae Herba), cǎo jué míng (Cassiae Semen), pú huáng tàn (Typhae Pollen Carbonisatum), wǔ líng zhī (Trogopteri Faeces), etc.	Cisplatin-induced AKI [35]
Gujingdan	**10 herbs**: Huáng qí (Astragali Radix), yì zhì rén (Alpiniae Oxyphyllae Fructus), shān yào (Dioscoreae Rhizoma), dān shēn (Salviae Miltiorrhizae Radix), yín yáng huò (Epimedii Herba), tài zǐ shēn (Pseudostellariae Radix), dù zhòng (Eucommiae Cortex), qiàn shí (Euryales Semen), dāng guī (Angelicae Sinensis Radix), and jī nèi jīn (Galli Gigeriae Endothelium Corneum).	Gentamicin-induced AKI [44].
Shenkangning	**8 herbs**: Huáng qí (Astragali Radix), dàn fù piàn (Aconiti Radix Lateralis Insalsa), yì mǔ cǎo (Leonuri Herba), suǒ yáng (Cynomorii Herba), dān shēn (Salviae Miltiorrhizae Radix), fú líng (Poria), zé xiè (Alismatis Rhizoma), and shān yào (Dioscoreae Rhizoma).	Gentamicin-induced AKI [44]
Zhibai Dihuang Wan	**8 authenticated herbs:** shān zhū yú (Corni Fructus; *Cornus officinalis* Siebold & Zucc), shú dì huáng (Rehmanniae Radix Praeparata; *Rehmannia glutinosa* (Gaertn.) DC.), shān yào (Dioscoreae Rhizoma; *Dioscorea oppositifolia* L.), guān huáng bǎi (Phellodendri Cortex & Orientalis; *Phellodendron amurense* Rupr.), zhī mǔ (Anemarrhenae Rhizoma; *Anemarrhena asphodeloides* Bunge), mǔ dān pí (Moutan Cortex; *Paeonia suffruticosa* Andrews), zé xiè (Alismatis Rhizoma; *Alisma plantago-aquatica* L.), and fú líng (Poria; *Wolfiporia cocos* (Schw.) Ryv. & Gibn – the authors used one of its older Latin names *Poria cocos* (Schw.) Wolf)	Gentamicin-induced AKI [45]
VI-28	**8 herbs:** rén shēn (Ginseng Radix), lù róng (Cervi Cornu Pantotrichum), dōng chóng xià cǎo (Cordyceps), dān shēn (Salviae Miltiorrhizae Radix), jiǔ cài zī (Allii Tuberosi Semen), shé chuáng zǐ (Cnidii Fructus), wú zhū yú (Evodiae Fructus), and shān nài (Kaempferiae Rhizoma)	Gentamicin-induced AKI [46]
WH30+	**7 ingredients**: Dà huáng (Rhei Radix et Rhizoma), dān shēn (Salviae Miltiorrhizae Radix), dōng chóng xià cǎo (Cordyceps), yì mǔ cǎo (Leonuri Herba), yín yáng huò (Epimedii Herba), huáng qí (Astragali Radix), and dǎng shēn (Codonopsis Radix).	Glycerol-induced AKI [52]
Shenshuai Mixture (aka Shenshuai Compound Medicine)	**10 ingredients (only seven disclosed)**: Shēng dì (Rehmanniae Radix (Exsiccata seu Recens)), dà huáng (Rhei Radix et Rhizoma), chì sháo (Paeoniae Radix Rubra), huáng lián (Coptidis Rhizoma), dān pí (Moutan Cortex), zé xiè (Alismatis Rhizoma), and huá shí (Talcum).	Glycerol-induced AKI. [53].[54]
Shensheng fang	**4 ingredients**: Huáng qí (Astragali Radix), yín yáng huò (Epimedii Herba), shuǐ zhì (Hirudo), shān zhā (Crataegi Fructus), etc.	Glycerol-induced AKI [55]
Ermiao San	**9 constituents**: Cāng zhú (Atractylodis Rhizoma), huáng bǎi (Phellodendri Cortex), dà huáng (Rhei Radix et Rhizoma), yì mǔ cǎo (Leonuri Herba), bái huā shé shé cǎo (Oldenlandiae Herba), zhū líng (Polyporus), Huáng qí (Astragali Radix), niú xī (Achyranthis Bidentatae Radix), guāng cí gū (Tulipae Edulis Tuber), etc.	Adenine and ethambutol hydrochloride-induced AKI [56]
Fufang Xi Xian Cao Capsule	**8 ingredients**: Xī xiān cǎo (Siegesbeckiae Herba), jīn qián cǎo (Lysimachiae Herba), qín jiāo (Gentianae Macrophyllae Radix), fáng jǐ (Stephaniae Tetrandrae Radix), zhū líng (Polyporus), zé xiè (Alismatis Rhizoma), chē qián cǎo (Plantaginis Herba), niú xī (Achyranthis Bidentatae Radix), etc.	Adenine and oteracil potassium-induced AKI [57]

concentrations of the ginsenosides unique to hóng shēn. They found that a Sun Ginseng extract reduced cisplatin-induced LLC-PK1 cell death more effectively than non-processed ginseng. An activity-guided fractionation and isolation identified ginsenosides Rh4 and Rk3 as the compounds responsible for this cytoprotective activity[37].

Emodin, a naturally occurring anthraquinone derivative isolated from dà huáng (Rhei Radix et Rhizoma; *Rheum officinale* Baillon), has been reported to alleviate cisplatin-induced nephrotoxicity in rats. Emodin treatment for 4 days prior to and 5 days after cisplatin administration increased renal GSH content, reduced oxidative stress and mitigated cisplatin-induced tubular necrosis and rises of Scr and BUN[38].

Líng Zhī, the fruiting body of the fungus *Ganoderma lucidum* (Curtis ex Fr.) P. Karst., has been used traditionally for extending patient's life span and promoting good health[39]. The major bioactive constituents of *Ganoderma* are polysaccharides and triterpenes: more than 140 triterpenoids have been reported, of which 50 are unique to *G. lucidum*[39]. These triterpenoids have demonstrated a beneficial activity towards cisplatin-induced oxidative stress in mice: a triterpene extract (100 mg/kg body weight) prevented the renal failure in preserving antioxidant enzymes (SOD, CAT and GSH-Px) and restoring GSH concentrations[40].

Gān cǎo (Glycyrrhizae Radix; *Glycyrrhiza glabra* Linn. var. *glandulifera* Regel et Herder) is well known for its detoxicating effects in TCM and is often used in herbal formulae for the prevention of AKI. In a mouse model of cisplatin-induced AKI, the protective effects of a gān cǎo-derived compound, glycyrrhizic acid, and its metabolite 18β-glycyrrhetinic acid, were investigated. Oral administration of either compound six days before and two days after cisplatin treatment significantly reduced cisplatin-induced increases of BUN, Scr, and serum lactate dehydrogenase three days after cisplatin treament. Renal histopathological studies indicated that either compound delayed the progression of renal injury, including tubular necrosis, hyaline casts, and tubular degeneration in response to cisplatin exposure. The compounds reduced renal MDA, increased renal SOD, CAT, GSH, GSH-Px, and HO-1 levels, and restored redox status and inflammatory responses in cisplatin-treated mice to almost normal levels. These protective effects are associated with upregulation of nuclear factor E2-related protein and downregulation of NF-κB in the kidney. The two compounds also rendered renal tissue resistant to cisplatin-induced cytoplasmic translocation of high mobility group box 1[41].

Dāng guī (Angelicae Sinensis Radix; *Angelica sinensis* (Oliv.) Diels (Apiaceae)) is often used in herbal formulae for AKI. A methanolic extract of the herb was reported to reduce apoptosis, increase survival and enhance proliferation and migration of HK-2 human kidney proximal tubular cells exposed to cisplatin[42].

Wǔ wèi zǐ (Schisandrae Fructus; *Schisandra chinensis* (Turcz.) Baill.) is also used in some herbal formulae for the prevention of AKI. Schizandrin and schizandrin B, compounds isolated from wǔ wèi zǐ, have been reported to alleviate apoptosis, reduce collagen accumulation and enhance regeneration capacities in HK-2 human proximal tubular cells exposed to cisplatin[43].

Gentamicin-induced AKI Gentamicin is a potent antibiotic but its nephrotoxicity remains a major clinical concern.

Daily gavage of Gujingdan or Shenkangning, either starting from one week before the first gentamicin injection or after each gentamicin treatment, has been reported to prevent gentamicin-induced AKI in rats. Both herbal remedies reduced Scr, BUN, urinary N-acetyl-beta-D-glucosaminidase (NAG), renal cortical MDA, and increased renal cortical SOD, Na^+-K^+-ATPase, Ca^{2+}-ATPase and Mg^{2+}-ATPase[44].

Oral administration of an extract of the classic Shèn-tonic formula Zhibai Dihuang Wan before each gentamicin injection for 10 days was also reported to significantly attenuate gentamicin-induced apoptosis of renal tubular cells and prevented rises of BUN and Scr in mice[45]. This renoprotective effect was supported by *in vitro* data that the Zhibai Dihuang Wan extract and two constituent herbs of the formula, guān huáng bǎi (Phellodendri Cortex & Orientalis; *Phellodendron amurense* Rupr.) and zhī mǔ (Anemarrhenae Rhizoma; *Anemarrhena asphodeloides* Bunge), attenuated gentamicin-induced Bcl2 repression, caspase-3 activation and apoptosis in NRK-52E rat kidney epithelial cells[45].

Pretreatment for two days, followed by 10 days of co-treatment with VI-28 (by gavage), has been reported to prevent gentamicin-induced rises in Scr and BUN, and to enhance the renal mitochondrial antioxidant system in rats, as indicated by dose-dependent increases in the level/activities of reduced GSH, Mn-SOD, Se-GSH-px GSH reductase and GSH-S-transferases[46].

Dōng chóng xià cǎo (Cordyceps; *Cordyceps sinensis* (Berk.) Sacc.) was reported to ameliorate gentamicin-induced nephrotoxicity in rats, as evident from the less prominent increment of BUN, Scr, sodium excretion, urinary NAG and less severe histopathological changes in the Cordyceps treatment group[47].

An aqueous extract of hóng shēn (Ginseng Radix Rubra; steamed roots of *Panax ginseng* C.A. Meyer), was reported to significantly reduce gentamicin-induced rises in Scr, BUN, proteinuria, urinary excretion of 8-hydroxy-2'-deoxyguanosine, renal Bax and cytochrome-c, renal caspase-9 and caspase-3 activation, and renal tubular cell apoptosis, while restoring Bcl-2 expression and increasing GSH in renal cortex in a mouse model of gentamicin-induced AKI; it also prevented gentamicin-induced apoptosis and oxidative stress in NRK-52E rat renal tubular cells[48].

Ligustrazine, which was reported effective in preventing I/R-induced AKI in mice[31], was also reported to abrogate gentamicin-induced apoptosis of renal tubular cells in rats[49]. In cultured NRK-52E rat kidney tubular cells, ligustrazine pretreatment protected against gentamicin-induced apoptosis and, dose-dependently, repressed gentamicin-induced generation of reactive oxygen species, reduced caspase-3, caspase-8 and caspase-9 activities, prevented

cytochrome c release, TNF-α excretion and NF-κB activity, increased Bcl-xL expression[50].

Schizandrin B, a derivative from wǔ wèi zǐ discussed previously for its protection of HK-2 human proximal tubular cells exposed to cisplatin, also ameliorated the oxidative stress in renal mitochondria of rats exposed to gentamicin. The protection was attributed to an enhanced antioxidant status (as observed via GSH and α-tocopherol levels and Mn-SOD activity), leading to an improvement in mitochondrial structure and function (highlighted by ATP, MDA levels, Ca^{2+} loading and cytochrome c release). As a result, the kidney structure and function were preserved and normal Scr and BUN levels were restored[51].

Glycerol-induced AKI Pretreatment with WH30+, a 7-herb TCM formula, for 10 days has been reported to attentuate glycerol-induced AKI in rats, preventing rises of Scr and BUN[52]. Treatment with Shenshuai Mixture ("Shenshuai Compound Medicine"), a 10-herb TCM formula (by gavage, twice daily for 5 days), immediately after intramuscular injection of glycerol in rats was also reported to significantly reduce plasma endothelin-1 and serum TNF-α, increase serum NO, enhance PCNA expression in renal tubular cells, and significantly attentuate rises of Scr and BUN[53, 54]. In another report, six days of Shenshengfang pretreatment attenuated a similar AKI model, increasing the urinary output and reducing serum potassium 24 h after glycerol injection, and reducing Scr and BUN at 24 h and 72 h[55].

Adenine-induced AKI AKI and/or CKD can be induced by adenine due to hyperuricemia, tubular obstruction and tubulointerstial nephritis. Ermiao San was reported to prevent AKI induced by adenine and ethambutol hydrochloride in rats when administered by daily gavage from day 1 of the nephrotoxic treatment. The herbal extract significantly suppressed the rises of BUN and Scr on days 7, 14 and 21, and significantly reduced serum uric acid on days 14 and 21[56].

When administered daily along with adenine and oteracil potassium in rats, Fufang Xi Xian Cao Capsules were reported to alleviate AKI induced by adenine and oteracil potassium, preventing rises of serum uric acid, BUN and Scr on days 7, 14 and 21[57].

A decoction of dì yú (Sanguisorbae Radix; *Sanguisorba officinalis* L.) was reported to alleviate AKI induced by adenine and yeast extract in rats. Administered daily by gavage along with the nephrotoxic treatment for 6 weeks, the decoction dose-dependently increased urinary excretion and reduced serum concentration of uric acid without affecting serum xanthine oxidase activity; the herbal decoction dose-dependently reduced BUN and Scr, reduced tubular dilation, cast formation, ATN, dilation of the Bowman's capsule and reduced mortality (6.25%, 18.75% in high- and low-dose decoction treatment groups vs 37.50% in non-treated group)[58].

AKI induced by contrast agents Breviscapine, an extract from dēng zhǎn xì xīn (Erigerontis Herba; *Erigeron breviscapus* (Vaniot) Hand.-Mazz.) principally enriched in the glycoflavone scutellarin, was found effective to prevent AKI induced by a single intravenous injection of iopromide (Ultravist 370). Daily peritoneal injections for three days, starting from the day of intravenous injection of the contrast medium, significantly reduced Scr and serum cystatin C, and prevented the reduction of renal Na^+/K^+-ATPase activity 3 days after injection of the contrast medium[59].

Oral administration of astragaloside IV for a week prior to injection of iopamidol was reported to alleviate the contrast agent-induced AKI and preserved renal function; histological examinations revealed reduced ATN, which was correlated with reductions of BUN, Scr, serum cystatin C and NGAL, as well as urinary KIM-1. In the astragaloside IV treatment group, the renal oxidative stress was reduced, with notably decreased MDA and increased CAT and SOD activities; decreased Bax and increased Bcl2 renal expression, reduced caspase-3 activation and apoptosis were also observed[33].

AKI induced by chromium, mercury, iron or lead. Chromium intoxication can induce both AKI and CKD. An extract of total tannins, but not anthraquinones, of dà huáng (Rhei Radix et Rhizoma; *Rheum officinale* Baill.) was reported to prevent chromium-induced AKI in rats[60].

Mercuric chloride causes oxidant AKI that affects mainly proximal tubules. In rats, schizandrin B pretreatment (oral administration for 9 days) ameliorated i.p. mercury-induced tubular and mitochondrial damage, reduced heat shock proteins in the renal cortex, increased cytochrome c oxidase and restored eNOS and nNOS in glomeruli[61].

I.p. injection of nephrotoxic doses of iron dextran for 2 weeks or lead for 10 days induces AKI in mice. I.p. administration of Danshen injection (an aqueous extract of dān shēn (Salviae Miltiorrhizae Radix), 4 hours before each nephrotoxic injection led to significant improvements of body weight and decreased iron or lead levels in the kidney. In both AKI models, Danshen injection reduced BUN, Scr and renal MDA, and enhanced renal SOD and GSH-Px activities[62, 63]

AKI/CKD induced by organic xenobiotics A single administration of a nephrotoxic dose of absolute ethanol to fasted mice produces extensive AKI. A líng zhī (Ganoderma; *Ganoderma lucidum* (Curtis ex Fr.) P. Karst.) aqueous decoction was reported to dose-dependently exert antioxidative effect on kidney lipid peroxidation and alleviate ethanol-induced nephrotoxicity in a mouse model[64]. Oral pretreatment with ligustrazine, at least in part, prevented ethanol-induced AKI due to its superoxide scavenging effect[65].

Schizandrin B was reported to ameliorate cyclosporine A-induced AKI in mice, attenuating histopathological changes and alleviating the rises in BUN and Scr. Schizandrin B also decreased renal MDA and increased GSH levels in cyclosporine A-treated mice. Furthermore, in cyclosporine A-treated HK-2 cells, schizandrin B reduced apoptosis, increased intracellular GSH and ATP levels and attenuated the generation of reactive oxygen species[66].

An aqueous extract of máo shǔ (Dioscoreae Alatae Tuber; *Dioscorea alata* L.) was reported to alleviate AKI induced by

acetaminophen in rats, partially preventing rises in Scr, BUN and serum uric acid[67].

Aflatoxin B1 is a potent hepatotoxic and hepatocarcinogenic mycotoxin that can also induce AKI. Marked increases in lipid peroxide levels in kidneys and liver and a concomitant decrease in antioxidant enzymes levels (SOD, catalase, GSH transferase, etc) were observed in aflatoxin B1-intoxicated rats, while picroliv and silymarin treatments both reversed the conditions to almost normal level[68].

1.3 AKI induced by sepsis, endotoxin or over-exercise

Sepsis, infection and harsh exercise (such as extreme physical exercise) are also important causes of AKI. Table 3 summarizes the various herbal formulae and remedies reported to prevent AKI induced by these causes.

In rats, an i.p. injection of Xuebijing, a proprietary extract mainly containing five herbs, significantly reduced the rises of Scr, BUN, serum β2-microglobulin and renal IL-6 observed after sepsis induction by cecal ligation and puncture (CLP)[69]. A post-CLP intravenous injection of an extract of huáng qí (Astragali Radix) significantly reduced serum cystatin C and suppressed renal IL-1β and TNF-α expression and decreased renal NFκB activity 8 and 24 hours after CLP[70]. In rats, upon CLP, an i.p. injection of an extract of kǔ mǎi cài (Ixeris Denticulatae Herba; *Ixeris sonchifolia* (Bunge) Hance) significantly prevented rises of Scr and renal MDA and increased renal SOD after 3, 6 and 24 hours[71].

Lipopolysaccharides (LPS) can also induce AKI in mice. 1 h before i.p. injection of LPS, an i.p. injection of ginseng panaxadiol saponins extracted from rén shēn (Ginseng Radix; Panax ginseng C. A. Meyer) reduced Scr, renal iNOS, NO and MDS, increased renal SOD and reduced apoptosis in the kidney[72].

Exhaustingly exercised rats developed AKI within 8 weeks, which is more pronounced under conditions of high temperature, high humidity and bearing weight, etc. Yishen Huanji Decoction treatment prevented rises in Scr, BUN, urinary albumin and NAG excretion, and preserved renal Na+-K+-ATPase activity in these models[73,74].

2. Promoting repair and regeneration, increasing extrarenal uremic toxin removal and preventing chronic lesions after AKI

Most published experimental investigations focused on prevention and mitigation of AKI through herbal pretreatment or simultaneous use of herbal medicines with inducers of AKI. Nevertheless, some emerging evidence supports a potential for herbal formulae (Table 4), extracts of individual herbs and pure herbal compounds in promoting repair and regeneration, increasing extrarenal uremic toxin removal and preventing chronic lesions in AKI, either by starting treatment in the early stages of AKI or when AKI is already established.

Promoting repair and regeneration after AKI As recently reviewed by Wang et al[75], a possibility exists that herbal medicines exert actions through prohealing progenitor cells. Direct evidence for botanicals having therapeutic effects on AKI through such cells is however scarce. Interestingly, it was recently reported that exposure of human adipose-derived mesenchymal stem cells to astragaloside IV increased stem cell migration to cisplatin-damaged renal tubular epithelial cells, suppressed proinflammatory cytokine and chemokine expression and increased erythropoietin and insulin-like growth factor 1 expression[76]. In addition, in *in vitro* and *in vivo* AKI models, herbal remedies have been reported to promote proliferation of tubular epithelial cells[27,53,77,78].

Increasing extrarenal removal of uremic toxins after AKI In a rat model with established gentamicin-induced AKI, both a decoction of *Huanghuai Wendan Recipe*, administered by gavage, and the *Shenshuaikang enema*, administered intrarectally, significantly reduced Scr and BUN and reduced the histology of tubular injury[18].

Preventing chronic lesions Effects of herbal medicines on long-term outcomes in AKI have been rarely studied. Nonetheless, some emerging evidence suggests that herbal medicines could repress chronic renal lesions in AKI induced by I/R, aristolochic acid-containing herb or cisplatin.

Wen-Pi-Tang-Hab-Wu-Ling-San, when administered to mice for 12 days starting from 2 days after renal I/R, was reported to prevent I/R-induced decrease of renal SOD activities, reduce lipid peroxidation and hydrogen peroxide production, attenuate renal phosphorylation of mitogen-activated protein kinases and activation of NF-κB and, importantly, prevented renal fibrosis[79].

Aristolochic acid-containing herbs are known to induce both AKI and CKD. Rats fed simultaneously with Wen Yang Huo Xue Fang and guān mù tōng (Aristolochiae Manshurensis Caulis; *Aristolochia manshuriensis* Kom.) decoctions for 20

Table 3. Formulae for preventing AKI induced by sepsis or over-exercise.

Formula	Ingredients	Type of AKI (Reference)
Xuebijing	**5 herbs:** Hóng huā (Carthami Flos), chì sháo (Paeoniae Radix Rubra), chuān xiōng (Chuanxiong Rhizoma), dān shēn (Salviae Miltiorrhizae Radix), dāng guī (Angelicae Sinensis Radix).	Sepsis-induced AKI [69]
Yishen Huanji Decoction	**10 herbs:** dǎng shēn (Codonopsis Radix), zhì huáng qí (Astragali Radix cum Liquido Fricta), hóng jīng tiān (Rhodiolae Herba), yín yáng huò (Epimedii Herba), xiān hè cǎo (Agrimoniae Herba), gōng láo yè (Mahoniae Folium), qiān nián jiàn (Homalomenae Rhizoma), wǔ jiā pí (Acanthopanacis Cortex), xià kū cǎo (Prunellae Spica), zhī zǐ (Gardeniae Fructus).	Over-exercise induced AKI [73, 74]

Table 4. Formulae for treatment of established AKI.

Formula	Ingredients	Type of AKI (Reference)
Huanghuai Wendan Recipe	**10 herbs:** Bàn xià (Pinelliae Rhizoma), chén pí (Citri Reticulatae Pericarpium), fú ling (Poria), zhú rú (Bumbusae Caulis in Taenia), zhì dà huáng (Rhei Radix et Rhizoma Preparata), shēng huái huā (Sophorae Flos Crudus), bái huā shé shé cǎo (Oldenlandiae Herba), gān cǎo (Glycyrrhizae Radix), shēng jiāng (Zingiberis Rhizoma Recens), dà zǎo (Jujubae Fructus).	Gentamicin-induced AKI [18]
Shenshuaikang enema	**4 herbs:** Tài zī shēn (Pseudostellariae Radix), dà huáng (Rhei Radix et Rhizoma), hóng huā (Carthami Flos), gān cǎo (Glycyrrhizae Radix).	Gentamicin-induced AKI [18]
Wen-Pi-Tang-Hab-Wu-Ling-San	**14 herbs** (Same as Table 1) : dǎng shēn (Codonopsis Radix; *Codonopsis pilosula* (Fr.) Nannf), dān shēn (Salviae Miltiorrhizae Radix; *Salvia miltiorrhiza* Bunge), bàn xià (Pinelliae Rhizoma; *Pinellia ternata* (Thunb.) Makino), huáng lián (Coptidis Rhizoma; *Coptis chinensis* Franch.), yín yáng huò (Epimedii Herba; *Epimedium koreanum* Nakai), dà huáng (Rhei Radix et Rhizoma; *Rheum palmatum* L.), zī sū yè (Perillae Folium; *Perilla frutescens* (L.) Britton), gān cǎo (Glycyrrhizae Radix; *Glycyrrhiza uralensis* Fisch), yīn chén hāo (Artemisiae Capillaris Herba; *Artemisia capillaris* Thunb.), zé xiè (Alismatis Rhizoma; *Alisma plantago-aquatica* L.), fú líng (Poria; *Wolfiporia cocos* (Schw.) Ryv. & Gibn – the authors used its old Latin name *Poria cocos* Schw.), bái zhú (Atractylodis Macrocephalae Rhizoma; *Atractylodes macrocephala* Koidz.), zhū líng (Polyporus; *Polyporus umbellatus* (Pers.) Fries), and guì zhī (Cinnamomi Ramulus; *Cinnamomum cassia* (L.) J.Presl).	I/R-induced AKI [79]
Wen Yang Huo Xue Fang	**5 herbs:** Táo rén (Persicae Semen), hóng huā (Carthami Flos), ròu cōng róng (Cistanches Herba), xiān líng pí (Epimedii Herba) and dān pí (Moutan Cortex).	Aristolochic acid-induced AKI/CKD[80]

weeks presented significantly reduced Scr, BUN and urinary excretion of proteins, β2-microglobulin and NAG as well as improved anemia. Thus, when administered early, this decoction attenuated the long-term chronic damage of the disease model[80].

In HK-2 human kidney proximal tubular cells, a methanolic extract of dāng guī (Angelicae Sinensis Radix; *Angelica sinensis*) did not alleviate oxidative stress but reduced collagen production upon cisplatin exposure. This coincided with reduced activation of the β-catenin pathway, which is involved in epithelial-to-mensenchymal transition (EMT) and fibrosis. Deeper investigation on major bioactive compounds of the herb (ferulic acid, Z-ligustilide and E-ligustilide) identified ferulic acid as the most potent protectant; in a cisplatin-mediated toxicity model using HK-2 cells, it not only reduced apoptosis, but also reduced collagen accumulation and prevented activation of the β-catenin pathway[42,78]. Thus, whether such favorable effects can be translated into *in vivo*, and whether *Angelica sinensis* compounds reduce long-term chronic lesions in AKI deserve further studies. Similarly, some herbal medicines, such as dān shēn (*Salviae Miltiorrhizae* Radix; Salvia miltiorrhiza Bunge (Labiatae), huáng qí (Astragali Radix; *Astragalus membranaceus* (Fisch.) Bunge), dōng chóng xià cAo (Cordyceps; *Cordyceps sinensis* (Berk.) Sacc.), and líng zhī (Ganoderma; *Ganoderma lucidum* (Curtis ex Fr.) P. Karst.), have demonstrated favorable effects in preventing and mitigating AKI, and also have promising anti-fibrotic effects[7, 81, 82]. Thus, it awaits further investigations to find out whether use of these herbs affects long-term outcomes in AKI patients.

BOTANICALS FOR AKI: CLINICAL STUDIES

Clinical diagnosis of AKI has long been mainly based on acute changes of Scr and urinary volume, but the detailed criteria, dominated by expert opinions, differed internationally. This started to change in the new millennium. Using both evidence and consensus, international collaborations have gained pace in standardizing the clinical definition of the different stages of AKI, leading to publications of the Risk, Injury, Failure, Loss, and End-stage renal disease (RIFLE) guideline, the modified RIFLE guideline for pediatric use (pRIFLE), and the AKI Network (AKIN) guidelines in 2004 and 2007. The RIFLE and AKIN guidelines were then merged in 2012 to form the Kidney Disease Improving Global Outcomes (KDIGO) guideline[83]. It was recommended by a group of experts commissioned by the UK National Institute of Health and Care Excellence that KDIGO and pRIFLE guidelines be used for diagnosing adult and pediatric AKI patients, respectively[83]. In view of the above evolving clinical definition of AKI, it is not surprising that published clinical studies have used a variety of criteria for AKI diagnosis, as summarized in Tables 5 and 6.

There were altogether 19 randomized clinical trials on herbal prevention and treatment of AKI: common weaknesses of these trials included lack of reporting authentication and quality control of the herbal products (a problem shared

by *in vitro* and *in vivo* studies, as reported in the preceding section), small trial sizes, blank controls, and non-blinded designs. Five randomized controlled trials (two published in English and three in Chinese) were retrieved from the Pubmed database — they were otherwise compliant with the CONSORT guidelines (http://www.consort-statement.org/), except for the aforementioned weaknesses (Table 5). The remaining 14 were not indexed in Pubmed and were retrieved from Chinese databases. They were all published in Chinese (only five have titles and abstracts in English) by authors from hospitals in counties (2/14) or small-to-medium-sized cities (11/14), where medical resources and resources for clinical trial training are generally limited; their quality, as judged by the CONSORT guidelines, is thus unsurprisingly poor (Table 6). These abstracts or brief reports (0.5–2.5 pages) share weaknesses with those cited in the Pubmed database. In addition, these papers hardly report methodology of randomization, ethical approval and consent, and rarely provide details of the baseline comparison between treated and control groups. We describe Pubmed-cited reports and also cover the reports cited only in Chinese database (except one which is too confused for analysis), not as conclusive evidence, but rather as possible sources of experience, knowledge or information, which we hope will promote future high-quality developments.

1. Pubmed-cited reports (Table 5)

Fermented dōng chóng xià cǎo (Cordyceps) for prevention of contrast medium-induced AKI The preventive effects of Corbrin Capsules, a commercially available fermented Cordyceps powder, on contrast medium-induced AKI were studied in patients with stable angina pectoris. 103 inpatients were randomly divided into two groups: blank control treatment (n=51) and Cordyceps treatment (n=52). Corbrin Capsules (3 g, p.o., thrice daily), were given to the Cordyceps group 3 days before angioplasty using low-osmolarity non-ionic contrast media (iopamidol, i.v.) and 3 days after angioplasty. Scr was assessed at the time of hospital admission and 1, 2, and 3 days after angioplasty. Urinary KIM-1, NGAL and IL-18 were examined before angioplasty and 1 day after angioplasty. The prevalence of contrast medium-induced nephropathy was 5.77% in the Cordyceps group and 11.76% in the blank control group (the difference was not statistically significant). The post-procedure mean peak of Scr, post-procedure increase in Scr levels from baseline, and urinary KIM-1, NGAL and IL-18 after the procedure in the Cordyceps group were significantly lower than those in the control group[84].

Danhong Injection for prevention of contrast medium-induced AKI The preventive effects of Danhong Injection, a commercial product comprising extracts of dān shēn (Salviae Miltiorrhizae Radix) and hóng huā (Carthami Flos), were studied on contrast medium-induced renal impairment after percutaneous coronary intervention (PCI) using the contrast medium ioperamide. Eighty patients were randomly assigned to a blank control group and the Danhong treatment group, n = 40/group. All patients received routine medicines such as enteric-coated aspirin and metoprolol, as well as routine rehydration therapy. For patients in the treatment group, 20 ml Danhong Injection was intravenously dripped by adding in 250 ml normal saline from 2-3 days before PCI to 3 days afterwards, once daily. Scr, serum cystatin C, urinary albumin, and β2-microglobulin were measured before and 24, 48, 72 h after PCI. 5 (12.5%) patients in the control group and 2 (5.0%) in the treatment group had contrast medium-induced nephropathy (the difference was not statistically significant). However, the treatment group had significantly lower Scr, serum cystatin C and urinary β2-microglobulin 24h after PCI, had significantly lower serum cystatin C, urinary β2-microglobulin and albumin 48h after PCI and had significantly lower urinary albumin 72h after PCI[85].

Qishen Huoxue Granule as an auxiliary treatment of AKI in an intensive care unit The effects of Qishen Huoxue Granule, a commercial product comprising extracts of 6 herbs, on AKI in ICU patients were studied in 52 AKI patients randomly assigned to two groups: a blank control group (n = 27) treated only by hemofiltration therapy and the treatment group (n = 25) treated with Qishen Huoxue Granule (10 g, by gavage, thrice daily) for 2 weeks in addition to hemofiltration therapy. Mechanical ventilation and vasoactive drugs were administered when necessary. It took 8.00 ± 1.02 days for urinary output to recover (>0.5 ml/kg/h) in the treatment group, a significantly shorter time compared to the blank control group (13.00 ± 0.95 days). Supporting accelerated recovery of renal function, serum cystatin C was lower in the treatment group at days 10 and 14. The needs for mechanical ventilation and vasoactive drugs were significantly lower in the treatment group, which tended to have lower 28-day mortality (12% vs 29.6%) and fewer days of ICU stay (19.25 ± 2.15 vs 21.00 ± 2.57), but the differences were not statistically significant[86].

An 11-herb decoction for AKI induced by extracorporeal shock wave lithotripsy (ESWL) 60 patients with renal calculus to be treated by ESWL were randomly assigned to treatment and blank control groups. Post-ESWL plasma NO, endothelin-1 (ET-1), MDA and serum TNF-α significantly increased in the control group, but not in the treatment group. The difference between the groups was statistically significant. 72 h after ESWL, the levels of plasma SOD decreased in the control but not in the treatment group; the plasma NO and urinary β2-microglobulin were significantly lower in the treatment group[87].

Chongcao Shenkang Capsules for preventing and treating AKI due to epidemic hemorrhagic fever 150 AKI patients with epidemic hemorrhagic fever were randomly assigned to the treatment group (n = 76) and the blank control group (n = 74). All patients were given ribavirin and supporting treatment to maintain electrolyte and water homeostasis and the treatment group received Chongcao Shenkang

Table 5. Herbal medicine prevention and treatment of AKI: Analysis of the five randomized controlled trials indexed in Pubmed.

Authors	Total subject No. (control, treatment)	Randomization methodology	Herbal medicines	Route	Control	Blind design and concealment of allocation	Consent and ethical approval	Baseline comparability	AKI diagnosis criteria
Zhao et al [84].	103 (51, 52)	Random number table	**Corbrin Capsules**, a fermented dōng chóng xià cǎo (Cordyceps) power.	p.o.	Blank control	None	Yes	Yes	Contrast medium-induced nephropathy was defined as Scr rise ≥0.5 mg/dl or ≥25% of basal level within 3 days after exposure to contrast medium, excluding other etiology
Wang et al [85]	80 (40, 40)	Random number table	**Danhong Injection**, a commercial product comprising extracts of dān shēn (Salviae Miltiorrhizae Radix) and hóng huā (Carthami Flos).	i.v.	Blank control	None	Not described	Yes	Contrast medium-induced renal impairment was defined as Scr rise >44.2 μM or >25% of basal level within 3 days after exposure to contrast medium, excluding other etiology
Yu et al [86]	52 (27, 25)	Random number table	**Qishen Huoxue Granule**, a commercial product comprising extracts of huáng qí (Astragali Radix), dān shēn (Salviae Miltiorrhizae Radix), chì sháo (Paeoniae Radix Rubra), chuān xiōng (Chuanxiong Rhizoma), hóng huā (Carthami Flos), dāng guī (Angelicae Sinensis Radix).	By gavage	Blank control	None	Not described	Yes	RIFLE criteria
Sheng et al [87]	60 (30, 30)	Not described	**A decoction of 11 herbs**, including shān yào (Dioscoreae Rhizoma), shēng dì (Rehmanniae Radix), shān zhū yú (Corni Fructus), zé xiè (Alismatis Rhizoma), fú líng (Poria), mǔ dān pí (Moutan Cortex), huáng qí (Astragali Radix), chē qián cǎo (Plantaginis Herba), bái máo gēn (Imperatae Rhizoma), jīn qián cǎo (Lysimachiae Herba), hǎi jīn shā (Lygodii Spora).	p.o.	Blank control	None	Yes	Yes	Rise in urinary NAG, γ-GT and β2-microglobulin
Fu et al [88]	150 (76, 74)	Not described	**Chongcao Shenkang Capsules**, a commercial product mainly comprising dān shēn (Salviae Miltiorrhizae Radix), huáng qí (Astragali Radix) and dōng chóng xià cǎo (Cordyceps).	p.o. or by gavage	Blank control	None	Not described	Yes	1985 national criteria for diagnosing hemorrhagic fever with renal syndrome.

Capsules (2.7 g, p.o. or by gavage, thrice daily) till the end of polyuric phase. Patients in the treatment group had significantly shorter oliguric and polyuric periods than those in the control group. Proteinuria and Scr in the treatment group returned to normal ranges within significantly shorter time than the control group. Furthermore, serum and urinary β2-microglobulin levels of the treatment group were significantly lower than those of the control group on the fifth and tenth days after treatment. The treatment group also had significantly lower incidence of severe complications[88].

2. Reports indexed in Chinese database (Table 6)

Bailing Capsule for established AKI in ICU patients with acutely exacerbating chronic obstructive pulmonary disease 40 patients treated by routine therapy, including control of infection, non-invasive ventilation, treatment of asthma and improving homeostasis, were compared with 42 patients treated by routine therapy plus oral or gavage administration of Bailing Capsule, a proprietary fermented dōng chóng xià cǎo (Cordyceps). After 12 days, the treatment group presented significantly reduced BUN and Scr, with higher estimated glomerular filtration rate (eGFR) and urinary output[89].

Jinshuibao Capsule for prevention of AKI in patients with severe brain injury 53 patients treated by routine therapy (preventing brain edema, hemorrhage, spasm of brain blood vessels and protecting gastric mucosa) were compared with 54 patients treated by routine therapy plus oral or gavage administration of Jinshuibao Capsule, a proprietary fermented dōng chóng xià cǎo (Cordyceps) powder for 5-10 days. The Jinshuibao Capsule treatment group presented significantly lower Scr and less AKI severity according to the RIFLE criteria[90].

"Shennong 33", a five-herb formula, used for the treatment of AKI caused by a variety of etiologies 30 patients treated by routine therapy, including removal of etiology, control of infection, maintaining water and electrolyte homeostasis, supply of nutrients, correction of acidosis, blood transfusion, expectant and supporting treatment (including hemodialysis), were compared with 34 patients treated by routine therapy plus injections of "Shenong 33". The treatment group needed fewer hemodialysis, had significantly shorter period of anuria and oliguria, and took significantly shorter time for BUN, Scr and urinary protein excretion to recover to normal ranges[91].

An alkalinized four-herb retention enema ("rectal dialysis") for pediatric AKI due to acute glomerulonephritis or nephrosis In a study of pediatric AKI (2–12 years old), 16 patients treated by routine therapy, including control of infection, diuretics, antihypertensives, steroid hormones, water, electrolyte and acid-base homeostasis, were compared with 22 patients treated by routine therapy plus rectal treatment with a four-herb aqueous decoction plus 18 ml 5% sodium bicarbonate, up to 8 times per day until renal function recovered. The treatment significantly accelerated decline of BUN, recovery of urinary volume and clinical cure of the primary glomerular diseases[92].

A three-ingredient retention enema for treatment of AKI complication due to epidemic hemorrhagic fever 30 patients treated by 20% mannitol (125 ml, p.o., twice daily) and metoclopramide, (20 mg, i.m., twice daily) were compared with 30 patients treated by rectal administration of a three-ingredient decoction, twice daily. All patients were offered routine therapy, including water intake restriction, diuretics and expectant treatment. Both treatments were equally effective in terms of declining BUN, recovering urinary volume and urinary protein level and clinical cure of epidemic hemorrhagic fever[93].

Gavage and retention enema of a five-ingredient decoction for AKI in patients with cerebral hemorrhage 25 patients treated by "Western medicine" routine therapy (including water intake restriction and diuretics) were compared with 25 patients treated by routine therapy plus gavage (50 ml) and rectal administration (100 ml) of a five-ingredient decoction, thrice daily. The gavage and enema treatment significantly reduced Scr and increased urine volume[94].

Gavage and retention enema of a five-ingredient decoction for AKI in patients after cranial surgery 25 patients treated by routine therapy (including reducing cranial pressure, anti-inflammatory agents, and expectant treatments; use of diuretics not stated) were compared with 25 patients treated by routine therapy plus diuretics and gavage (50 ml) and rectal administration (100 ml) of a five-ingredient decoction, thrice daily. The diuretics, gavage and enema treatment group significantly reduced Scr and increased urine volume[95].

Retention enema of a seven-ingredient decoction for mannitol-induced AKI in patients with cerebral hemorrhage, infarction or subarachnoid hemorrhage Rectal administration of a seven-ingredient decoction, once daily, was reported to be more effective to recover Scr and BUN in 2–5 days than 20–100 mg/day furosemide i.m. or i.v. or a diuretic mixture (regilin, dopamine & furosemide), i.v., 10 patients/group[96].

Retention enema of a five-herb decoction for pediatric AKI of unspecified etiology: 22 patients treated by routine therapy, including water and sodium intake restriction, low protein diet, treatment of disorders of acid-base and metabolite homeostasis, diuretics, vasodilatating agents, antihypertensives and antibiotics were compared with 26 patients treated by routine therapy plus rectal administration of a 5-herb decoction. The enema treatment group was found to present significantly lower BUN and Scr[97].

Jiushentang, a nine-herb formula, for oliguric AKI of a variety of etiologies, excluding urinary obstruction and pre-renal oliguria: 32 patients treated by routine therapy, including

Table 6. Herbal medicine prevention and treatment of AKI: Analysis of the 14 randomized controlled trials indexed in Chinese databases but not in Pubmed.

Authors	Total subject No. (control, treatment)	Rando-mization method	Herbal medicines	Route	Control	Blind design & concealment of allocation	Consent and ethical approval	Baseline compar-ability	AKI diagnosis criteria and other notes
Pan et al. [89]	82 (40, 42)	Not described (ND)	**Bailing Granule**, mainly comprisng fermented dōng chóng xià cǎo (Cordyceps).	p.o. or by gavage	Blank control	None	ND	Yes	2006 AKI National Criteria of China, which were based on the AKIN criteria: Scr rise of >26.5 μM or >50% Scr rise from baseline within 48 h, or urinary output <0.5 ml/kg/h for more than 6 h.
Tang et al [102]	435 in title, 436 in abstract, 36 if adding number for each group	ND	**Bailing Granule**, mainly comprisng fermented dōng chóng xià cǎo (Cordyceps).	p.o.	Blank control	None	ND	Yes	AKI criteria in a paper published in a Chinese medical journal in 2004. ***The research and subject number are so confusing that this report has to be excluded from review.
Pan et al. [90]	107 (53, 54)	Tossing coin	**Jinshuibao Capsule**, mainly comprisng fermented dōng chóng xià cǎo (Cordyceps).	p.o. or by gavage	Blank control	None	ND	Yes	RIFLE AKI criteria.
Sun et al. [91]	64 (30, 34)	ND	**"Shennong 33"**, comprising Hóng huā (Carthami Flos), chuān xiōng (Chuanxiong Rhizoma), chì sháo (Paeoniae Radix Rubra), dān shēn (Salviae Miltiorrhizae Radix), dāng guī (Angelicae Sinensis Radix).	i.v.	Blank control	None	ND	ND	1992 National AKI criteria, not clearly described.
Yan [92]	38 (16, 22)	ND	**An alkalinized four-herb retention enema**, comparising Dà huáng (Rhei Radix et Rhizoma), huáng qí (Astragali Radix), dān shēn (Salviae Miltiorrhizae Radix), hóng huā (Carthami Flos) plus 18 ml 5% sodium bicarbonate.	Rectal administration	Blank control	None	ND	ND	Not clearly defined.
Qian [93]	60 (30, 30)	ND	**A three-ingredient retention enema** comprising Dà huáng	Rectal administration	20% mannitol 125 ml, p.o., twice daily;	None	ND	Yes	1986 Nanjing criteria for the prevention and treatment of

Table 6. (Continued)

Authors	Total subject No. (control, treatment)	Randomization method	Herbal medicines	Route	Control	Blind design & concealment of allocation	Consent and ethical approval	Baseline comparability	AKI diagnosis criteria and other notes
			(Rhei Radix et Rhizoma), máng xiāo (Natrii Sulfas), mǔ lì (Ostreae Concha).		metoclopramide, 20mg, i.m., twice daily				epidemic hemorrhagic fever; not clearly defined.
Qian et al. [94]	50 (25, 25)	ND	**A five-ingredient decoction**, comprising Dà huáng (Rhei Radix et Rhizoma), duàn lóng gǔ (Mastodi Ossis Fossilia Calcinata), duàn mǔ lì (Ostreae Concha Calcinata), pú gōng yīng (Taraxaci Herba), yì mǔ cǎo (Leonuri Herba).	Gavage and rectal administration	Blank control	None	ND	Yes	Scr>176 μM, BUN>10.1 mM, lasting 5-6 days.
Ma et al. [95]	50 (25, 25)	ND	**A five-ingredient decoction**, comprising Dà huáng (Rhei Radix et Rhizoma), duàn lóng gǔ (Mastodi Ossis Fossilia Calcinata), duàn mǔ lì (Ostreae Concha Calcinata), pú gōng yīng (Taraxaci Herba), yì mǔ cǎo (Leonuri Herba).	Gavage and rectal administration	Blank control	None	ND	Yes	Anuria or oliguria 2-5 days after cranial operation, Scr >176 μ M.
Meng et al. [96]	20 (10, 10)	ND	**A seven-ingredient decoction**, comprising Dà huáng (Rhei Radix et Rhizoma), dān shēn (Salviae Miltiorrhizae Radix), pú gōng yīng (Taraxaci Herba), mǔ lì (Ostreae Concha), zhì fù zǐ (Aconiti Radix Lateralis Praeparata), tǔ fú ling (Smilacis Glabrae Rhizoma), huái mǐ (Sophorae Flos Immaturus).	Rectal administration	Furosemide i.m. or i.v. or regilin, dopamine & furosemide, i.v.	None	ND	ND	Oliguria, BUN 9.3-22.8 mM, Scr 186-442 μM 3-7 days after mannitol treatment.
	48 (22, 26)	ND			Blank control	None	ND	Yes	

Table 6. (Continued)

Authors	Total subject No. (control, treatment)	Randomization method	Herbal medicines	Route	Control	Blind design & concealment of allocation	Consent and ethical approval	Baseline comparability	AKI diagnosis criteria and other notes
Deng et al. [97]			**A five-ingredient decoction**, comprising Dà huáng (Rhei Radix et Rhizoma), huáng bǎi (Phellodendri Cortex), bái tóu wēng (Pulsatillae Radix), huái huā (Sophorae Flos), xì xīn (Asari Herba).	Rectal administration					National draft diagnosis criteria of pediatric AKI published in 1997.
Huang et al. [98]	67 (32, 35)	ND	**Jiushentang,** a decoction of nine herbs: dà huáng (Rhei Radix et Rhizoma), zhǐ shí (Aurantii Fructus Immaturus), hòu pò (Magnoliae Officinalis Cortex), qiāng huó (Notopterygii Rhizoma et Radix), huáng qí (Astragali Radix), dāng guī (Angelicae Sinensis Radix), zhì fù zǐ (Aconiti Radix Lateralis Praeparata), dān shēn (Salviae Miltiorrhizae Radix), chuān xiōng (Chuanxiong Rhizoma).	p.o.	Blank control	None	ND	Yes	Urinary output <400 ml/24h; Scr rise >88.4 μM or BUN rise >3.57 mM within 24 h; excluding urinary obstruction and pre-renal oliguria.
Xia et al. [99]	98 (48, 50)	ND	**Jiushen decoction,** decoctions with a core formula: shēng shí gāo (Gypsum Crudum), zhī mǔ (Anemarrhenae Rhizoma), xuán shēn (Scrophulariae Radix), shēng dì huáng (Rehmanniae Radix (Exsiccata seu Recens)), jīn yín huā(Lonicerae Flos), lián qiào (Forsythiae Fructus), shēng zhī zǐ (Gardeniae Fructus Crudus), huáng qín (Scutellariae Radix), dān	p.o.	Blank control	None	ND	Yes	Auria for 48-124 hours; therapeutic effects are classified based improved urinary output and decline of BUN and Scr as reported in a textbook (Shaoji Yang. Infectious diseases. Beijing: People's Health Publishing House. 2005; pp78)

Table 6. (Continued)

Authors	Total subject No. (control, treatment)	Randomization method	Herbal medicines	Route	Control	Blind design & concealment of allocation	Consent and ethical approval	Baseline comparability	AKI diagnosis criteria and other notes
			shēn (Salviae Miltiorrhizae Radix), chuān xiōng (Chuanxiong Rhizoma), chì sháo (Paeoniae Radix Rubra), which is modified according to TCM pattern differentiation by adding or subtracting herbs.						
Lin et al. [100]	49 (25, 24)	ND	**Sheshangliangxue mixture:** bàn biān lián (Lobeliae Chinensis Herba), bái máo gēn (Imperatae Rhizoma), chì sháo (Paeoniae Radix Rubra), mò hàn lián (Ecliptae Herba).	p.o.	Blank control	None	ND	Yes	2006 AKI National Criteria of China, which were consistent with the AKIN criteria.
Li et al. [101]	98 (49, 49)	ND	**A fourteen-ingredient decoction**, comprising Dà huáng (Rhei Radix et Rhizoma), má huáng (Ephedrae Herba), guǎng mù xiāng (Aucklandiae Radix), xìng rén (Armeniacae Semen), huò xiāng (Agastaches Herba), cāng zhú (Atractylodis Rhizoma), dà fù pí (Arecae Pericarpium), zhǐ shí (Aurantii Fructus Immaturus), chì sháo (Paeoniae Radix Rubra), táo rén (Persicae Semen), shuǐ zhì (Hirudo), zé xiè (Alismatis Rhizoma; zhū líng (Polyporus), wēi gān suì (Kansui Radix Tostum).	p.o. or by gavage	Blank control	None	ND	Yes	AKI criteria published in a Chinese internal medicine textbook published in 2004.

etiology and inciting factor treatment, hemodialysis, treatment of disorders of acid-base and metabolite homeostasis, nutritional support, control of infections and treatment of complications, were compared with 35 patients treated by routine therapy plus oral administration of Jiushentang. The author stated that Jiushentang was significantly more effective to reduce BUN and Scr and to induce clinical resolution of AKI, but the frequency and duration of hemodialysis were not discussed[98].

Jiushen Decoction, a formula mainly comprising 11 herbs, varied according to TCM diagnosis, for the treatment of anuric AKI in epidemic hemorrhagic fever 48 patients treated by routine therapy, including stabilizing homeostasis, improving microcirculation, improving renal blood flow, diuretics and expectant treatments were compared with 50 patients treated by routine therapy plus Jiushen decoctions, which had a core formula of 11 herbs and was modified according to TCM pattern differentiation by adding or subtracting herbs. The Jiushen Decoction group had significantly improved urinary output and reduced Scr and BUN; hematological parameters and liver function improved more rapidly in the Jiushen Decoction group[99].

Sheshangliangxue Mixture, a four-herb formula, for venomous snake bite-induced AKI 25 patients treated by routine therapy, including wound cleaning, local anesthesia, injection of anti-venom serum, furosemide, glucocorticoid hormones and dialysis (indicated when there was anuria for 24h or oliguria for 48h, Scr $\geq$ 354 μM or serum potassium > 6.5 mM), were compared with 24 patients treated by routine therapy plus Sheshangliangxue Mixture, 30 ml, p.o., thrice daily. The Sheshangliangxue Mixture group presented significantly shorter oliguric duration, fewer requirements for dialysis treatments and enhanced therapeutic effects[100].

A fourteen-ingredient formula, for AKI induced by a variety of etiology 49 patients treated by routine therapy, including expectant treatment, etiological treatment, hemodialysis, treatment of disorders of acid-base and metabolite homeostasis and nutritional support were compared with 49 patients treated by routine therapy plus oral or gavage administration of a 14-herb decotion. The author stated that the herbal medicine group was significantly more effective to reduce BUN and Scr and to induce clinical resolution of AKI, but the frequency of hemodialysis and the duration of inducing clinical cure of AKI were not shown[101].

CONCLUDING REMARKS AND OUTLOOK

As far as we know, this is the first comprehensive review on the potential therapeutic value of herbal medicines, especially Chinese herbal medicines, in the prevention and treatment of AKI. The hypotheses that herbal medicines could have potentials to (i) prevent or mitigate induction of AKI; (ii) promote repair or regeneration; (iii) promote extrarenal clearance of uremic toxins; and (iv) prevent AKI progression to CKD have each gained certain levels of support from experimental and/or clinical reports.

The potential value for herbal medicines in prevention of AKI has gained the most experimental support and is especially noteworthy, in view that many AKIs such as those induced by I/R, nephrotoxicants, sepsis, endotoxins and contrast agents should be largely preventable. Although most clinical trials reviewed in this study presented low-level evidence, the indicative value of the clinical and experimental reports should not be disregarded; major plants emerging from these studies certainly warrant further investigation. To encourage future research on these herbs for the prevention and treatment of AKI, we have listed in Table 7 the most reported ones, whether as single-herb remedies or as part of multi-herb formulae.

In particular, 30% clinical studies focused on the application of TCM-based enemas for promoting extrarenal clearance of uremic toxins, an approach with good affordability and likely suited for those with poor access to renal replacement therapies. Most of these enemas contained dà huáng (Rhei Radix et Rhizoma; *Rheum officinale* Baillon; contains anthracenic purgatives), but detailed formulation varied. Thus better-characterized formulations and better clinical trials of such enemas may support TCM use for AKI in developing regions. However, dilemma exists. On one hand, centers with poor access to dialysis facilities and thus most likely benefitting from enema therapies often lack training in randomized controlled clinical trials; on the other hand, centers with established clinical trial expertise most likely have access to dialysis facilities and less likely need such enema therapy. Collaborations between different types of centers and provision of rigorous training on good practices in designing and conducting clinical trials seem plausible solutions to yield quality data and to ensure that related ethical issues are not overlooked.

Experimental evidence has emerged to support probable therapeutic value for herbal medicines in promoting repair

Table 7. Fourteen herbs most commonly prescribed in herbal remedies for AKI (more than 5 citations in the reports summarised in Tables 1-6).

Herb	Number of citations in Tables 1-6
Dà huáng (Rhei Radix et Rhizoma)	16
Dān shēn (Salviae Miltiorrhizae Radix)	16
Huáng qí (Astragali Radix)	14
Sháo yào or chì sháo (Paeoniae Radix or Paeoniae Radix Rubra)	8
Zé xiè (Alismatis Rhizoma)	8
Dōng chóng xià cǎo (Cordyceps)	7
Hóng huā (Carthami Flos)	7
Yín yáng huò (Epimedii Herba)	7
Chuān xiōng (Chuanxiong Rhizoma	6
Dāng guī (Angelicae Sinensis Radix)	6
Fú líng (Poria)	6
Gān cǎo (gān cǎo (Glycyrrhizae Radix)	5
Yì mǔ cǎo (Leonuri Herba)	5
Zhū líng (Polyporus)	5

and regeneration through kidney resident and possibly pluripotent cells. This line of research represents a new frontier that deserves further investment.

Another new frontier is to prevent chronic lesions following AKI. Given that some herbal species with anti-fibrotic properties such as *Salvia miltiorrhiza*, *Astragalus membranaceus*, *Schizandra sinensis*, *Cordyceps sinensis*, and *Ganoderma lucidum* have shown *in vitro*, *in vivo* and/or clinical promises in AKI, research on herbal entities in preventing chronic fibrotic lesions seems rational.

However, the usefulness of herbal medicines ultimately depends on high-level quality control and clinical evidence. We specifically wish to point out two major areas for thorough improvements — quality control of herbal medicines and good practice in clinical trials — both necessary to support scientific integrity and reproducibility. Readers are encouraged to refer to guidelines on reporting herbal medicines (www.gp-tcm.org/links/#good-practice-guidelines) and clinical trials (www.consort-statement.org).

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