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Australian Journal *of* **Herbal** Medicine

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Evaluation of *Salvia miltiorrhiza* radix (Danshen) in the treatment of chronic kidney disease: a literature review

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Abstract

Chronic kidney disease (CKD) is a significant global public health issue with few treatments currently available that effectively reverse the disease or prevent its progression. Diabetes mellitus, cardiovascular disease, hypertension and acute kidney disease are the major contributors to CKD. These co-morbidities cause the destruction of glomeruli resulting in blood flow changes, activation of the renin-angiotensin-aldosterone system, systemic hypertension, proteinuria, inflammation and oxidative stress. Pharmaceutical interventions, including angiotensin converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers and diuretics, are used as mono- or combination therapies to achieve blood pressure control and improve the condition. However, combinations of pharmaceuticals increase the risk of adverse events and in many patients does not prevent progression to renal failure. *Salvia miltiorrhiza radix* (Danshen) is a traditional Chinese herb that shows considerable potential in ameliorating the effects of CKD. A computer-based search of Cinahl, The Cochrane Library, Embase, Medline and TRIP databases was performed to appraise the scientific literature on this herb. While there is little evidence for the use of Danshen in CKD and no human studies have been located, this review provides a summary of the research to date that may reveal a novel treatment for this disease.

Keywords: Chronic kidney disease, CKD, Danshen, *Salvia miltiorrhiza,* review.

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Conflicts of interest

The author has no conflicts of interest to declare.

Introduction

Kidney disease is a problem of worldwide significance with 8–16% of the global population affected.[1] In 2010, chronic kidney disease (CKD) was estimated to cause 7,350,000 deaths worldwide and was ranked 18th in the list of total death causes.[2]

According to the international organisation, Kidney Disease: Improving Global Outcomes, kidney disease is defined as the loss of renal function resulting in a decline in glomerular filtration rate (GFR) and reduced creatinine clearance.[3] CKD is diagnosed when GFR falls below 60mL/min/1.73m^2 for three months or more, or when the urinary albumin to creatinine ratio exceeds 30mg/g. It is classified into five stages that progress along a continuum of deteriorating function, culminating in end-stage renal failure where renal replacement therapies, including dialysis and kidney transplant, are the only currently available options.[3] CKD stages 1–3 are often asymptomatic, progressing undetected, until late in the disease when fewer therapeutic options exist.[3,4]

Epidemiology

With the current world population of over 7 billion, at a conservative prevalence of 10%,[1] some 700 million people worldwide are affected by CKD. In Australia, approximately 1.7 million adults have at least one clinical sign of CKD.[5] The incidence is higher in older age groups,[4,6] indigenous populations,[3,4] those in rural and remote areas,[5,7] and the economically disadvantaged.[8,9] Kidney disease co-morbidities further increase mortality risk and include cardiovascular disease, neuropathies, anaemia and bone diseases.[3] The 2015 AusDiab study of 6138 adults found that 11.3% had some indication of CKD; 6% were at stages 1 and 2, 5% were at stage 3 and 0.3% were at stages 4 and 5.[10] The mortality rate is

approximately 19.5% for patients at stage 2, 24.3% for stage 3 and 45.7% for stage 4.[11]

The cost of treating CKD in the USA was US$60 billion in 2007 and £1.44 billion in the UK in 2009–10.[1] In Australia, the estimated treatment cost of CKD in 2012 was $4.1 billion[10] and the cumulative cost of end-stage kidney disease from 2009 to 2020 is projected to be as high as $12.3 billion.[12]

Given the pervasiveness of the problem in Australia and worldwide and the significant attendant costs in terms of morbidity, mortality and health expenditure,[4,13] CKD has become a treatment priority for governments and public health authorities the world over.[14]

This literature review examines the aetiological and pathophysiological factors underlying CKD. Current classes of conventional medications are evaluated for efficacy and safety and a traditional Chinese herb, *Salvia miltiorrhiza* radix (Danshen), is presented as a potential treatment for this global challenge.

Methods

A computer-based search of Cinahl, The Cochrane Library, Embase, Medline and TRIP databases was performed from inception to June 2017.

The key search terms were: 'danshen', 'dan shen', 'danshensu', 'lithospermate', 'lithospermic', 'red sage', 'tan shen', 'salvia miltiorrhiza', 'salvianolate', 'salvianolic acid', 'tanshinone', 'angiotensin', 'blood pressure', 'ckd', 'diastolic', 'glomerular', 'hypertension', 'kidney', 'nephropathy', 'raas', 'renal', 'systolic', 'pathology', 'pathophysiology' and 'urinary'.

MeSH terms: hypertension — renal, kidney diseases, salvia miltiorrhiza.

References of retrieved articles were hand-searched for additional studies.

Studies were included if they: (1) investigated Danshen or any of its key constituents; (2) administered the supplement via any route using any dose; and (3) examined kidney disease or its antecedent events. While additional *a priori* inclusion criteria were for full text English language articles using Danshen monotherapy, the limited research retrieved required broadening the literature reviewed to include combination therapies and three abstracts of pertinent articles, the full texts of which were written in Chinese.

Pathophysiology

Fluid pressure within the kidney is normally controlled by the renin-angiotensin-aldosterone system (RAAS). RAAS maintains blood flow and renal perfusion through glomerular cells that secrete renin in response to declining glomerular afferent arteriole hydrostatic pressure. Renin cleaves angiotensinogen to produce angiotensin I. Angiotensin converting enzyme (ACE) then converts angiotensin I to angiotensin II.[15] The actions of angiotensin II include vasoconstriction, which maintains tissue perfusion by increasing blood pressure, and the release of aldosterone which instigates reabsorption of sodium and water in the kidney.[15,16]

The major conditions contributing to CKD are diabetes mellitus, cardiovascular disease, hypertension,[4,11,13] and acute kidney disease.[4,17] These conditions variously cause the most common underlying CKD pathologies of diabetic nephropathy, hypertensive nephrosclerosis and glomerulonephritis.[18] The initiating events leading to these pathologies follow a common path that cause the destruction of glomeruli and eventually entire nephrons.[15,19] Destruction of sufficient numbers of nephrons reduces renal mass, resulting in blood flow changes, activation of RAAS, systemic hypertension, proteinuria, inflammation and oxidative stress.[20-22]

With the reduction of kidney mass, remaining functional nephrons undergo compensatory hyperfiltration, hypertrophy and glomerular capillary hypertension in order to maintain a constant GFR.[19,23] Pre-glomerular arterioles dilate more than post-glomerular arterioles, increasing capillary pressure and filtrate volume.[23] This is a normal renal response, as the maintenance of GFR is necessary for the efficient removal of metabolic wastes.[24]

Increased systemic blood pressure is normally prevented from reaching the glomeruli by kidney auto-regulatory mechanisms to maintain a relatively constant renal flow and glomerular pressure. With prolonged systemic and glomerular hypertension, and glomerular hyperfiltration, injury to glomeruli progresses despite autoregulation,[25] leading to glomerular pressure injury, increased glomerular permeability and eventually proteinuria due to excessive filtration.[19,23] Progressive deterioration of the kidney vasculature causes further ischaemic loss of nephrons.[25,26] Once sufficient nephrons have been lost, these auto-regulatory mechanisms become disturbed, contributing to glomerular injury.[25]

The reduction of renal mass also causes increased release of renin, angiotensin II and aldosterone. Angiotensin II, as well as elevating systemic and glomerular blood pressure, reinforces glomerular filtration and stimulates the local release of cytokines that activate inflammatory pathways, which amplify glomerular hypertrophy and hyperfiltration.[15] Persistently high aldosterone results in increased sodium reabsorption, and consequently fluid retention, in the nephron. Glomerular hyperfiltration then promotes the movement of this sodium and fluid back into the systemic circulation, further increasing blood pressure.[15,23]

Excessive protein is toxic to renal tubules and stimulates inflammation as well as the production of pro-sclerotic proteins and collagen. This leads to glomerular scarring and tubular fibrosis. Over time, as increasing numbers of glomeruli and whole nephrons are destroyed, the remaining nephrons continue hyperfiltration and hypertrophy to maintain GFR, leading to a degenerative cycle.[15,21,22,24]

The combined and unrelenting progression of these events initiate ongoing injury, inflammation and oxidative stress.[22] Glomerular injury produces an inflammatory state through the up-regulation of cytokines, cell adhesion molecules and profibrotic growth factors. This creates abnormal cellular proliferation and augments adrenal production of aldosterone, a further contributor to pro-inflammatory cytokines.[23,24] Oxidative stress caused by the upregulation of angiotensin II produces nephrotoxic reactive oxygen species,[15,21] with increased oxidative stress seen in various stages of CKD.[27-29]

The interplay of these factors accelerates abnormal cellular proliferation, tubular inflammation, tissue remodelling, glomerulosclerosis, connective tissue fibrosis, apoptosis and an increased loss of kidney mass.[15,19-23] Eventually renal compensatory mechanisms can no longer keep pace with nephron loss, resulting in reduced GFR and the accumulation of nitrogenous wastes in the plasma, including creatinine and urea.[15,21] The result is CKD.

Pharmaceutical management of kidney disease

Research into pharmaceutical interventions for CKD has centred on hypertension and its precursor RAAS, with most research targeting angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs) and diuretics.

ACEi lower blood pressure by decreasing the production of angiotensin II and aldosterone, leading to reduced sodium and water retention.[21] This results in the normalisation of haemodynamic effects, the reduction in renal fibrosis and proteinuria,[15,24] and the prevention of renal injury.[24] In various studies, ACEi have been shown to ameliorate hypertension, reduce proteinuria and delay the progression of CKD.[15]

However, ACEi have been associated with adverse effects, the most common being the increased incidence of cough.[30-32] Indeed, one study found cough represented almost half (43%) of all reported adverse events, leading to withdrawal from treatment.[33] In addition, atrial flutter, oedema, rash and increased creatinine levels have been reported.[33]

ARBs control systemic and capillary hypertension, reduce proteinuria and microalbuminuria, and slow CKD progression.[15,34] This occurs through blocking the activation of angiotensin II and reducing the production of aldosterone,[25] leading to decreased blood volume and blood pressure.

ARBs have been linked to various cancers, though this finding is controversial, with one study suggesting an increased,[35] and another finding no increased,[36] level of risk. Some studies also show an increased risk of myocardial infarction with the use of ARBs,[37,38] yet others show no risk increase.[39] Other reported adverse effects of ARBs include dizziness, nausea, hypotension, palpitations, dyspnoea, headache, oedema, urticaria and macroalbuminuria.[33]

CCBs inhibit aldosterone production and downregulate myocardial contraction force, reducing blood pressure.[40] Their use decreases proteinuria and reduces glomerular permeability, providing renoprotection.[41]

CCBs have been found to reduce the risk of stroke, but increase the risk of congestive heart failure compared with ACEi, ARBs and diuretics.[38] However, one review challenges this finding as little evidence was found of an association between long-acting CCBs and cardiovascular events.[40]

Diuretics promote the excretion of sodium and fluid, thereby reducing blood pressure.[42] Research has found diuretics to be more effective at reducing hypertension than CCBs, and CCBs more effective than ACEi and ARBs.[30,38,43] When reviewing the safety of diuretics, controversy surrounds their use in patients with acute renal failure, with one study finding an increased risk of mortality or non-recovery of renal function,[42] and another finding no greater mortality risk.[44] A further study found diuretics led to hypokalaemia, increased uric acid levels and increased total cholesterol and triglycerides.[43]

Few pharmaceutical medications target multiple CKD pathophysiological pathways and are often required in combination to achieve effective results in blood pressure control and prevention of CKD progression.[15,41] Clinical trials have demonstrated the efficacy of combinations of ACEi/CCBs[45] and ACEi/ARBs.[46] A 2008 meta-analysis of 49 studies involving 6181 participants on the effect of mono- and combination pharmaceuticals on proteinuria found ACEi and ARBs to be more effective in combination that either drug alone.[47] However, adverse effects with these pharmaceutical combinations are frequently seen.

A 2016 meta-analysis of 65 randomised controlled trials with a total of 390,269 participants found ACEi, CCBs and diuretics led to significantly increased discontinuation of treatment due to adverse events over those occurring for placebo and ARBs, with incidence proportional to the number of medications used concomitantly.[48]

A 2008 meta-analysis of ACEi and ARBs found that only 33% of studies reported detailed adverse drug reactions causing treatment discontinuation with reactions including allergies, cough, dizziness, hyperkalaemia and hypertensive episodes.[47] Less frequently fatigue, headache, nausea, vomiting, hyperglycaemic episodes and hyperglycaemia were reported. The investigators concluded there was uncertainty about the benefits of these therapies to patients due to the risks of adverse effects.

Not all studies have found an increased risk of adverse effects from the use of pharmaceutical interventions however. A 2001 study found no difference in adverse effects between ACEi, CCBs, diuretics and placebo.[30]

This investigation was supported by industry sponsors.

A summary of additional adverse effects reported from the use of these pharmaceuticals is included in Table 1.

Given the increased risks of adverse effects of these treatments, there is a pressing need for safer alternatives that are efficacious in the treatment of CKD. Furthermore, while the mainstay of current treatments has targeted RAAS blockade, some researchers have challenged this, as an unacceptable number of patients on these medications continue to progress to end-stage renal failure. They posit the targeting of inflammation and fibrosis as more effective treatment strategies.[53]

Salvia miltiorrhiza radix (Danshen)

Salvia miltiorrhiza is a member of the Lamiaceae plant family and has been traditionally used in Asia to treat a number of conditions including coronary heart disease, hyperlipidaemia, cerebrovascular disease[54] and kidney disease.[55] It has been used in China for hundreds of years but more contemporary use in the 1970s was through intravenous infusions to treat heart disease and in the 1980s for angina pectoris.[56]

Danshen is the dried radix (root) containing approximately 50 chemical constituents isolated from aqueous extracts. These constituents fall into two classes, the lipophilic diterpene component of which 30 have been identified, and 15 phenolic acid compounds.[54] Among the most well studied of the diterpenes are tanshinone IIA and cryptotanshinone.[54,57] The key phenolic acids are salvianolic acid, of which 80–90% is magnesium lithospermate B,[54,57] danshensu, protocatechuic aldehyde and protocatechuic acid.[54] Other compounds identified from alcoholic and ethyl acetate extracts include baicalin, β-sitosterol, 5,3'-dihydroxy-7,4'-dimethoxyflavanone, vitamin E and tannin.[54]

The pharmacological actions of Danshen include ACE inhibition, vasodilation, microcirculatory stimulant,[54,55] inhibition of platelet aggregation,[54,55,58] anti-inflammatory and antioxidant.[59-61] These actions variously lead to decreased angiotensin II and aldosterone,[62] increased nitric oxide and arterial dilation,[59] reduced blood pressure,[62,63] decreased blood clotting,[54] reduced cardiac and renal hypertrophy,[54,60] and protection of tissues from ischaemic-reperfusion injury.[54]

No human trials using Danshen monotherapy in patients with CKD could be located. However there are numerous *in vitro* and *in vivo* investigations that support its use in kidney disease.

In vitro and *in vivo* studies

An *in vitro* investigation conducted by Kang *et al*. in 2003 on rodent thoracic aortae found administration of lithospermic acid B significantly inhibited ACE activity in a dose-dependent manner and reduced the production of angiotensin I.[63] The researchers concluded the anti-hypertensive effect of Danshen could be partly due to the ACE inhibiting effects of lithospermic acid B.

In 2010 Pan *et al*. found an extract of salvianolic acid B reversed fibrotic changes in human kidney proximal tubular epithelial cells and observed a return of these cells to normal morphology in a dose-dependent manner.[64] The authors hypothesised that salvianolic acid B could promote the repair of tubular epithelial structures and facilitate the regression of renal fibrosis in injured kidneys.

A 2002 *in vivo* study by Kang *et al.* on experimentally induced renovascular hypertension in rodents found administration of an aqueous extract of Danshen for three weeks significantly reduced systolic blood pressure compared with controls in a dose-dependent manner ($P<0.05$), inhibited ACE activity in a dose-dependent

Table 1: Adverse drug reactions: Summary of additional clinical research findings for ACEi and ARBs

Author(s) (year)	Study type (No. of subjects)	Adverse drug reactions	Reference
ACE inhibitors			
Jafar *et al.* (2003)	Meta-analysis (1860)	Potential for increased risk of CKD progression if SBP decreases <110mmHg	49
Cooper *et al.* (2006)	Retrospective cohort (29,507)	Major congenital malformations in neonates exposed during the first trimester	50
Bullo *et al.* (2012)	Systematic review of case reports/case series (186)	Congenital malformations in up to 48% of neonates exposed during the first trimester	51
Angiotensin receptor blockers			
Bullo *et al.* (2012)	Systematic review of case reports/case series (186)	Congenital malformations in 87% of neonates, with cerebral complications and death reported	51
Schuster *et al.* (2005)	Review	Hepatotoxicity of Tasosartan, drug withdrawn in 1998 due to unacceptable risks	52

manner (P<0.01) and reduced the production of angiotensin I, indicating an antihypertensive effect.[62]

In 2004 Kang *et al.* examined the effect of 40mg/kg/day lithospermic acid B for four days on renal functional parameters of experimentally induced acute renal failure in rodents. The results were a partial restoration of creatinine clearance, urinary sodium excretion, urinary osmolality and solute-free reabsorption, as well as amelioration of renal damage and preservation of kidney morphology, most likely due to antioxidant effects.[65]

A study on diabetic nephropathy induced in rodents conducted by Kim *et al.* in 2009 found 12 weeks of tanshinone IIA administration ameliorated renal hypertrophy and decreased 24-hour urinary protein excretion (P<0.05). The treatment reduced levels of advanced glycation end products, angiotensin II (both P<0.05), transforming growth factor β1 (TGF-β1), collagen IV (both P<0.01), and monocytes/macrophages.[66]

A 2010 study in rodents by Ahn *et al.* on renal insufficiency induced by partial nephrectomy found that, compared with controls, administration of tanshinone IIA for eight weeks significantly lowered serum creatinine (P<0.01) and reduced proteinuria, angiotensin II, TGF-β1 and collagen IV (all P<0.05), suggesting improved renal function associated with CKD.[67]

You *et al.,* in a study conducted in 2012, found Danshen significantly increased antioxidant activity and nitric oxide production (P<0.05) after four weeks when administered to rodents with experimentally induced kidney damage from toxic N(G)-nitro-d-arginine.[59] The waste products urea, creatinine and malondialdehyde were all significantly lower (P<0.05). The investigators concluded kidney damage induced by toxicity was likely due to oxidative stress and Danshen likely ameliorated the resulting nephrotoxicity by scavenging free radicals and upregulating nitric oxide synthase.

An aqueous extract of Danshen administered by Yin *et al.* to rodents with diabetic nephropathy for eight weeks in 2014 led to significantly decreased 24-hour urinary excretion (P<0.05), serum creatinine (P<0.01), blood urea nitrogen (P<0.05) and TGF-β1 compared with untreated controls. Treatment also increased levels of the antioxidants superoxide dismutase and glutathione peroxidase (both P<0.05).[60] Danshen alleviated glomerular hypertrophy, matrix expansion and fibrosis, and partially restored decreased megalin, which plays a role in the recapture of filtered molecules in the proximal kidney tubule, leading to improved renal reabsorptive function. Danshen provided renoprotection from hyperglycaemia-induced toxicities of oxidative stress, advanced glycation stress, cytokine secretion and

Table 2: Summary of additional *in vivo* studies using *S. miltiorrhiza* or constituents

Author(s) (year)	Condition (subjects)	Intervention	Outcomes	Reference
Chen *et al.* (2006)	Renal microcirculation and haemodynamics (rodents)	Magnesium lithospermate B intravenously	Increased renal cortical microperfusion, no change in renal blood flow or systemic haemodynamics, indicating improved renal microcirculation	70
Guan *et al.* (2009)	Ischaemia- reperfusion injury following renal transplant (rodents)	Danshen	Decreased inflammation and tubular damage and increased antioxidant status	71
Chan *et al.* (2011)	Hypertension (rodents)	Tanshinone IIA	Vasodilation and decreased SBP through decreased intracellular calcium ions in aortic smooth muscle	72
Liu *et al.* (2011)	Nephropathy (mice)	Tanshinone IIA sodium sulfonate	Improvement in renal lesions, regulation of oxidative stress and protein synthesis providing renoprotection	73
Lee *et al.* (2011)	Diabetic nephropathy (rodents)	*S.miltiorrhiza* aqueous extract	Reduced 24-hour urinary protein excretion, inflammation and collagen IV	74
Li *et al.* (2014)	Lead-induced nephrotoxicity (mice)	*S.miltiorrhiza* injection	Reduced renal lead levels, apoptosis and serum waste products, and increased antioxidant levels	75
Xu *et al.* (2016)	Ischaemia- reperfusion-induced renal injury (rodents)	Tanshinone IIA	Renoprotection provided by down-regulation of myeloperoxidase expression, inflammation. macrophage migration inhibitory factor, TNF-α and IL-6	76

megalin suppression was the conclusion drawn by the investigators.

In 2015, Xiaomei *et al.* investigated the use of Danshen over eight weeks in mice with renal injury induced by myocardial infarction.[68] While there were no significant decreases in serum creatinine, blood urea nitrogen, urinary albumin and 24-hour urinary protein excretion, Danshen demonstrated significant decreases in TGF-β1, collagen types I and III ($P<0.05$), malondialdehyde and reactive oxygen species (both $P<0.05$), and a significant increase in superoxide dismutase ($P<0.05$). The investigators concluded Danshen reduces renal fibrosis and provides renoprotective effects likely due to its antioxidant actions.

In the most recent 2017 study, Ma *et al.* examined the effect of salvianolic acid B on renal ischaemic-reperfusion injury after single nephrectomy in rodents. They found attenuation of oxidative stress and suppression of lipid peroxidation production with significantly lower creatinine and blood urea nitrogen compared with controls (both $P<0.01$). Inflammation was significantly decreased ($P<0.05$) and renoprotective effects were observed.[69]

Further *in vivo* studies using *S. miltiorrhiza* or its constituents are summarised in Table 2.

These pre-clinical studies demonstrate Danshen possesses significant potential for treating CKD in humans. When interpreting these studies caution is required as *in vitro* assessments may not accurately predict *in vivo* effects and metabolic differences between animal species make predictions in humans based on this research unreliable. Nonetheless, the demonstrated pre-clinical actions of Danshen in reducing blood pressure and inflammation, decreasing serum waste products, increasing antioxidants status, and promoting renal repair mechanisms give sufficient plausibility and justification to consider its use as a clinical therapeutic treatment option.

Clinical trials

Human clinical trials, mostly using combination formulae of herbs/pharmaceuticals, while not investigating CKD, nonetheless support the hypothesis that Danshen has a role to play in the treatment of kidney disease.

In a study conducted by Tian *et al.* in 2005, only the abstract of which is available in English, an injection of Danshen was used as an adjuvant with conventional treatment in 112 patients soon after renal transplantation.[77] Compared with 109 controls who received conventional treatment alone, the Danshen group had a significantly higher urinary volume and endogenous creatinine clearance rate ($P<0.05$). Serum creatinine, renal function recovery retardation, blood viscosity/resistance and platelet aggregation rate in graft were significantly lower than controls ($P<0.05$). Acute rejection reaction, however, did not differ between groups. The authors concluded Danshen is helpful for recovery of renal function after transplantation as it can improve microcirculation and decrease renal function recovery retardation.

In 2006 a placebo-controlled trial conducted by Pu *et al.*, only the abstract of which is available in English, three months' treatment with *S. miltiorrhiza* ameliorated oxidative stress and inflammation in 18 patients undergoing continuous haemodialysis.[61] Malondialdehyde and advanced oxidative protein products were significantly lower and superoxide dismutase was higher after one, two and three months treatment (all $P<0.01$). C-reactive protein was significantly lower after three months' treatment ($P<0.01$); however, there was no significant decrease in interleukin-6 and tumour necrosis factor-alpha.

Xu and colleagues in 2009 examined the use of Danshen, *Panax notoginseng* and *Dryobalanops camphor* in stroke patients and found significantly reduced C-reactive protein in the treatment group compared with controls ($P<0.05$); however, no difference in mortality or intracranial haemorrhage was detected.[78]

In 2011, Sheng *et al.* reported on 30 patients treated with a combination of 11 different herbs, including Danshen, and found reduced renal tubular damage induced by extracorporeal shock-wave lithotripsy for renal calculi.[79]

A systematic review and meta-analysis conducted by Zou *et al.* in 2012 incorporating five trials totalling 513 children with Henoch-Schonlein purpura and co-morbid renal disease concluded Danshen formulations may prevent the development of renal disease, but given the low quality of the trials there was insufficient evidence to recommend Danshen.[80]

In 2012, alprostadil (a pharmaceutical vasorelaxant) and reduced glutathione liquid were administered intravenously with and without salvianolate in 2 groups of patients with CKD stages 2 to 4 ($n=30$).[81] After four years there was no difference in serum albumin and electrolyte levels between groups; however, the number of patients reaching study termination decreased significantly in the salvianolate group (40%) compared with controls (93%) ($P<0.01$). The authors concluded regulated, integrated, traditional Chinese and Western medicine can effectively delay the deterioration of renal function in CKD patients. In the same year Yang *et al.* conducted a double-blind, placebo-controlled, randomised trial over 12 weeks with 55 hypertensive patients.[82] The investigators found significant reductions in blood pressure ($P<0.005$) and pulse rate ($P=0.027$) following administration of a formula containing extracts of Danshen, *Rhodiola rosea*, *Chrysanthemum* and *Peuraria*.

However, a 2015 trial by van Poppel *et al.* of 11 hyperlipidaemic and hypertensive patients found a high 3000mg/day aqueous extract (equivalent to 15,000mg/day *S. miltiorrhiza* root) had no effect on blood pressure.[83]

These clinical studies provide some, though not complete support, for the use of Danshen in conditions associated with kidney disease. The use of combination products and adjuvant treatments makes it difficult to distinguish the contribution Danshen makes to the treatment effect. This lack of clarity makes it imperative that further research be conducted using Danshen monotherapy in order to establish whether it can be considered a legitimate treatment option for this significant condition.

Danshen herb–drug interactions

Animal studies have shown that Danshen enhances the effect of warfarin and increases the risk of haemorrhage,[54,55,84-86] through inhibiting platelet aggregation, blockade of extrinsic blood coagulation and promotion of fibrinolytic activity.[85] Interactions with warfarin have also been described in case reports.[87,88] A controlled clinical trial of Danshen/warfarin co-administration for two weeks found significantly increased prothrombin time compared with controls,[88] increasing the risk of spontaneous bleeding. Co-administration of Danshen and warfarin is therefore contraindicated.

Danshen has been found to displace salicylate, thereby increasing free salicylate concentrations,[89] and may therefore be contraindicated in salicylate-sensitive individuals. It does not appear to interfere with digoxin,[90,91] but has been found to decrease concentrations and increase clearance of diazepam through induction of CYP450 isoforms.[92]

Danshen safety

Due to the dearth of human studies on Danshen there is little safety evidence in the literature and what data exists is conflicting, potentially due to dosing anomalies, requiring further research to determine appropriate dosage levels for both safety and efficacy.[93] The following presents the most recent evidence on the safety of Danshen in animal and human studies.

A post-market evaluation conducted in 2014 found a salt injection of Danshen administered to Beagle dogs at doses below 80mg/kg over the long term was safe.[93] Doses above 320mg/kg were toxic, with reactions including digestive disorders, erythrocyte malformations, mild haemolysis and mild hyperplasia in haemotopoietic tissue. The investigators concluded Danshen is a low-toxicity cardiovascular drug.

A 2005 review of *in vivo* and human trials investigating the pharmacology of Danshen concluded the herb was safe, with few adverse effects and no serious adverse events.[54] However, the investigators reported many of the reviewed trials lacked rigorous methodological quality.

A Cochrane review of six human trials in 2007 involving 494 acute ischaemic stroke patients using various Danshen agents concluded there was insufficient information and too few studies to determine Danshen's safety.[94] This conclusion was confirmed the following year when another Cochrane review of six human trials (n=2368) concluded that, although some adverse events have been reported, the safety of Danshen is unproven due to the small number of poor-quality studies.[95]

Lu *et al.* conducted a review of the spontaneous reporting system database of the Chinese national adverse drug reaction monitoring centre in 2013, only the abstract of which is available in English.[96] The investigators found parenterally administered salvianolate resulted in 739 case reports, 1310 events, 24 serious adverse drug reaction cases, but no deaths. The 10 most frequently reported reactions were rash, dizziness, itching, headache, chills, bad breath, nausea, palpitations, anaphylactic reactions and fever.

In 2014, a compound containing Danshen, *Panax notoginseng* and *Borneol* used to treat 367 patients, was compared with Di'ao Xinxuckang used to treat 366 patients. A statistically insignificant 3.54% adverse event rate was reported in the Danshen group compared with 1.64% for Di'ao Xinxuckang (P=0.105).[97] The six adverse events reported in the Danshen group were flatulence, heartburn, abnormal liver function parameters, positive urinary albumin levels and oral ulcer, all of which returned to baseline at the end of the trial. No serious adverse events were reported.

A study of hyperlipidaemic and hypertensive patients conducted in 2015 using a high dose of Danshen found adverse events including headache, dizziness, change in stool frequency and flatulence were most frequently observed. One serious adverse event, peripheral facial nerve paralysis (Bell's palsy), was reported.[83] Also in 2015 a double-blind, multi-centre, randomised trial of Danshen in combination with *Panax notoginseng* and Borneol reported no occurrence of clinically significant adverse effects and no significant difference in the rate of adverse events between groups (P=0.622).[98]

Further safety data can be found in Table 3.

The clinical and pre-clinical evidence on efficacy and safety, while encouraging, are not in complete agreement regarding Danshen's benefits for CKD. Further research is, therefore, necessary in order to fully explore its potential use. CKD is progressive and degenerative with no currently known therapy completely restoring kidney function. There is little research into efficacious, non-pharmaceutical interventions for CKD, therefore expanding the research into this domain is clinically significant. The development of an effective and safe therapeutic option that addresses the human and financial costs of CKD will have a substantial impact in reducing the burden of this condition worldwide.

Conclusion

In this review of kidney disease the global scale of the problem has been examined. The pathophysiology of CKD has been explored and current pharmaceutical interventions reviewed, along with their adverse effects.

There is a compelling need to develop alternatives that target multiple aetiological CKD pathways that are both efficacious and safe.

Within this context, the potential use of *Salvia miltiorrhiza* radix (Danshen) is presented. The therapeutic benefit of this herb has been evaluated for its ability to improve markers of CKD.

However, this review was hampered by the paucity of research on Danshen, the varied quality of the available research and the inability to review full texts not available in English.

To date, the pre-clinical research suggests that Danshen can increase antioxidant levels, reverse renal fibrosis and deliver reductions in angiotensin II, blood pressure, renal hypertrophy, creatinine, proteinuria and inflammation. While pre-clinical research shows promise for its use, results from non-human studies may not be applicable to humans. Clinical studies investigating Danshen in CKD are lacking and safety data show conflicting results.

Therefore, well-designed human trials involving CKD patients using authenticated Danshen products at therapeutic doses are warranted to establish whether the efficacious results seen in animals can be safely replicated in humans.

The magnitude of the problem presented by CKD is immense and the significance of establishing a safe, efficacious and relatively affordable intervention on human suffering, disease burden, mortality and health expenditure, both locally and internationally, will be profound.

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Table 3: Additional clinical studies reporting adverse effects of *S. miltiorrh*iza or constituents

Author(s) (year)	Condition treated (No. of subjects)	Intervention	Safety outcomes	Reference
Wong *et al.* (2004)	Healthy subjects (100)	Danshen and *Coriolus versicolor*	No serious adverse effects reported, liver function, renal function, bone profile, haematological parameters and clotting factors all normal and not significantly different compared with placebo (P>0.05)	99
Zhang *et al.* (2008)	Coronary heart disease, angina pectoris (480)	Lyophilised *Salvia* salt of Lithospermic Acid compared with Danshen injections	No serious adverse events after 14 days' treatment, dizziness and headache were reported, no abnormal laboratory parameters, no toxic reactions	100
Tam *et al.* (2009)	Coronary heart disease (100)	Danshen and *Pueraria lobata*	Fewer adverse events compared with placebo after 24 weeks	101
Yang *et al.* (2012)	Hypertension (55)	Danshen, *Rhodiola rosea, Chrysmanthemum, Pueraria lobata*	No difference in adverse events compared with placebo after 12 weeks, most frequently reported were diarrhoea, fatigue and common cold	82
Wang *et al.* (2013)	Acute pancreatitis (306)	Various combinations of *S. miltiorrhiza, somatostatin* and ulinastatin	Treatments well tolerated, no adverse events evident after 7 days' treatment.	102
Qian *et al.* (2015)	Diabetes and coronary artery disease (62)	*S. miltiorrhiza* root hydrophilic extract	No adverse effects, liver and renal function tests normal after 60 days' treatment	103
Rongrong *et al.* (2016)	Haemodialysisin CKD stage 4 or 5 (40)	*S. miltiorrhiza* iontopheric injections	No adverse effects after one month treatment	104

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