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Review Article

Medicinal herbal extracts – renal friend or foe? Part two: Herbal extracts with potential renal benefits

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SUMMARY: In this second of two articles regarding the renal toxicities or benefits of medicinal herbs, herbs are reported as being 'potentially beneficial' to the kidneys if there is strong *in vivo* evidence of renal protection from toxic substances or drugs; potent, specific renal anti-oxidant effects; *in vivo* cancer antiproliferative effects specific to the kidneys; or *in vivo* evidence of being beneficial in renal disease or failure. Among the herbs, polyherbal formulae and fungi with potential renal benefits are *Cordyceps sinensis*, Sairei-to, Rheum spp., *Salvia miltiorrhiza* and its component, magnesium lithospermate B and others.

KEY WORDS: **benefits, *Cordyceps sinensis*, Cordyceps, herbal medicine, Rheum, Sairei-to, *Salvia miltiorrhiza*.**

INTRODUCTION

In the last issue of *Nephrology*, we reviewed the renal toxicity associated with herbal therapies.[1] The goal of the current review is to present information about medicinal herbal and fungal extracts that may in the future be proven to be efficacious as complementary therapy in the prevention or treatment of renal disorders. Herbs are defined as 'potentially beneficial' to the kidneys if there is strong *in vivo* evidence of renal protection from toxic substances or drugs; potent, specific renal anti-oxidant effects; *in vivo* cancer antiproliferative effects specific to the kidneys; or *in vivo* evidence of being beneficial in renal disease or failure. Herbs that have evidence of being beneficial for reducing the quantity or size of nephrolithiasis, those with potential diuretic actions, and those that appeared to be beneficial in diabetic nephropathy because of their hypoglycaemic or antihyperglycaemic effects, have not been included. Among the herbs, polyherbal formulae and fungi considered potentially beneficial are *Cordyceps sinensis*, Sairei-to, *Rheum* spp., *Salvia miltiorrhiza* and its component, magnesium lithospermate B and others.

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CORDYCEPS (*Cordyceps sinensis*)

Cordyceps is the fungus that colonizes the larvae of moths. The parasitic complex of the fungus and the caterpillar is found in the soil at elevations of 3500–5000 m. The fungal fruiting body and the caterpillar host are chemically similar, have similar pharmacological properties and are traditionally dried and consumed together.[2] Cordyceps has been a valued medicine in China for 2000 years, being thought of as a kidney tonic, but used to aid in the treatment of multiple disorders.[3] Recent Western scientific evaluation of cordyceps has supported the use of this extract for hepatic protection,[4] immune enhancement,[5] cardiovascular and endocrine disorders[3] and renal protection and disease.

There have only been a few clinical trials on the use of cordyceps for kidney disorders and most of them have had serious methodological flaws, including the lack of controls, and/or the inclusion of other drugs in the treatment regimen. In a study without appropriate controls, Chen *et al.* found that treatment with fermented cordyceps significantly improved creatinine clearance and decreased blood urea nitrogen (BUN) and serum creatinine (SCr) in their 30 patients with chronic renal failure (CRF).[6] A combination supplement containing cordyceps (Jin Shui Bao) significantly reduced BUN and SCr, and decreased urinary proteins and blood pressure, but again appropriate controls were not used.[7] In a ran-

domized study, Lu investigated 61 patients with lupus nephritis unresponsive to corticosterone and cyclophosphamide.[7] The combination of 2–4 g of cordyceps powder and 0.6 g artemisinin (a sesquiterpene lactone from *Artemisia annua*) for 3 years protected the kidney function, as measured by creatinine clearance, and it was significantly better than another Chinese traditional regimen (tripterygiitotorium and/or Baoshekang tablets).

Clinical trials testing cordyceps for protection against iatrogenic nephrotoxicity have been of far better quality. Xu *et al.* aimed to determine whether cordyceps could reverse cyclosporin nephrotoxicity in kidney transplanted recipients.[8] At least 3 months after grafting, the 69 stable renal recipient patients were randomly divided into two groups, receiving placebo plus cyclosporin (5 mg/kg per day) or the same dose of cyclosporin plus 3 g/day cordyceps. Data collected after 5, 10 and 15 days revealed a linear increase in the benefits with the increased duration of cordyceps administration. The group receiving cordyceps developed less nephrotoxicity as evidenced by lower SCr, BUN and urinary N-acetyl-glucosaminidase.

Other double-blind, placebo-controlled clinical trials found less nephrotoxicity associated with amikacin sulphate administration in the group receiving cordyceps simultaneously,[9] and cordyceps protected against gentamicin nephrotoxicity in a population of 52 respiratory disease patients.[10] While none of these clinical studies had biopsies to support their serologically noted benefits, a study on rats has found regeneration of tubular cells in the cordyceps treated group receiving gentamicin.[11] Likewise, in a study by Zhao and Li, cotreatment with cordyceps in rats receiving cyclosporin A resulted in significantly less chronic interstitial oedema and fibrosis and tubular necrosis when compared to rats receiving only cyclosporin A.[12]

At least one of cordyceps' mechanisms of protection from iatrogenic nephrotoxic insult is thought to be its potent anti-oxidant actions.[13] Shahed *et al.* used a hot water extract of cordyceps powder to determine the effects on renal injury in a rat kidney ischaemia/reperfusion model.[14] The treated rats had significantly lower SCr and the expression of inflammatory genes, MCP-1 and TNF-α, was significantly inhibited. Cordyceps treatment had no effect on Bcl-2 and Bax expression, suggesting that its benefits were not via the apoptotic pathway. An anti-oxidant mechanism was proposed after vitamin E administration to rats undergoing reperfusion resulted in significant renal benefits.[15]

Contrary to the lack of apoptosis induced with aqueous cordyceps extracts, Yang *et al.* found that a purified, methanol soluble component of cordyceps, H1-A, did induce apoptosis in cultured human mesangial cells.[16] In an earlier experiment by that same group,[17] MRL lpr/lpr mice treated daily with H1-A had a progressive reduction in anti-dsDNA, decreased lymphadenopathy and a delayed progression of proteinuria. They suggested that H1-A may be beneficial in lupus nephritis. Inhibitory effects of cordyceps on mesangial cell proliferation were also found by Zhao-Long *et al.* when an ethanol extraction of the whole fruiting body of cordyceps was used in an *in vitro* study.[18] Further work directly comparing H1-A to whole extractions of the fruiting body of cordyceps is needed to evaluate the potential synergistic effects of components within cordyceps.

SAIREI-TO

Another promising extract is Sairei-to (ST), a combination of 12 herbs that has been traditionally used in Japan for renal diseases.[19] Sairei-to has been shown to ameliorate an animal model of gentamicin nephrotoxicity, in which rats consuming a diet containing 2.5% ST demonstrated reduced urinary N-acetyl-beta-D-glucosaminidase and protein excretion compared to the no treatment group.[20] These benefits were hypothesized to have been caused by the anti-oxidant actions of ST,[20] given that gentamicin has been shown to exert renal tubular toxicity via enhanced generation of superoxide anion and hydroxyl radical in renal cortical mitochondria.[21] Sairei-to has similarly proved to be beneficial in a subtotal nephrectomy model of CRF, whereby animals administered 2.5% ST in their food had lower blood pressure, reduced renal damage, decreased protein excretion and greater efferent arteriolar dilation when compared to the untreated rats.[19] However, Satoh *et al.* found no benefit of ST, alone or in combination with enalapril, on survival following subtotal renal ablation in male Wistar rats.[22]

Perhaps the most common use of ST in Japan has been in the treatment of glomerulonephritis. In a prospective, randomized, controlled study investigating the efficacy of ST in children with newly diagnosed IgA nephropathy, 101 patients received either ST or no treatment for 2 years.[23] Urinary abnormalities normalized in 46% of the patients in the ST group compared with only 10% in those untreated ($P < 0.001$). Blood pressure and creatinine clearance remained normal in all patients throughout the 2-year trial, except for one patient in the control group who developed CRF. Although the study had insufficient statistical power to assess hard clinical end-points, the normalization of urinary sediment abnormalities suggests the possibility that early intervention with ST may be efficacious in preventing the progression of IgA nephropathy.

Sairei-to may also have a role in the treatment of lupus nephritis. Administration of ST to MRL/lpr mice has been shown to shift Th1/Th2 balance, suppress B cell function, reduce proteinuria and BUN, and decrease the proportion of glomeruli with haematoxylin bodies.[24] Given that the haematoxylin body is regarded as one of the specific histological changes in severe lupus nephritis, the authors suggested that these histological benefits

induced by ST were responsible for the improvements of proteinuria and BUN, and hypothesized that ST would be beneficial in persons with lupus nephritis. Recent *in vitro* work suggests that ST also inhibits serum-induced proliferation and extracellular signal-regulated kinase (Raf-1/ERK) activation of mesangial cells, probably by activating cyclic adenosine monophosphate (cAMP).[25]

Sairei-to has also be shown to be effective in the treatment of puromycin aminonucleoside nephrosis[26] and monoclonal antibody 1-22-3-induced glomerulonephritis.[27]

There have been attempts to find similar benefits in mixtures with fewer herbs than are present in ST. In 1989, Hattori *et al.* reported the first in a series of animal experiments to test the efficacy of TJ-8014 (0.5–4 g/kg/day), a polyherbal formula based on ST.[28] Later, Li *et al.* found that the suppressive effect of ST on monoclonal antibody glomerulonephritis in rats was mainly caused by the *Bupleuum* sp. root.[29]

RHUBARB (Rheum spp., Rhie Rhizoma, Daio, Chinese Rhubarb)

There is some scientific evidence to support the traditional Chinese use of the roots of rhubarb for treatment of disorders involving inflammation, hypertension, hyperlipidaemia[30] and renal failure. In 1983, Yokozawa *et al.* began a series of experiments to test the efficacy of rhubarb extract on rats with adenine-induced renal failure.[31] Through those experiments, the group found that an aqueous extract of rhubarb administered orally to rats after the induction of renal failure lowered BUN, SCr, methylguanidine and guanidinosuccinic acid in a dose-dependent manner when compared to the controls. In 1991, the same group tested different tannins from rhubarb on rats with adenine-induced renal failure.[32] A decrease in SCr comparable to that observed after the administration of 270 mg rhubarb aqueous extract was found in rats given 5 and 10 mg of the rhubarb tannin (-)-epicatechin 3-O-gallate. Another rhubarb tannin, procyanidin C-13,3′,3′-tri-O-gallate, produced significant increases in BUN and SCr. Later, Zhang and el Nahas tested the efficacy of rhubarb in a subtotal nephrectomy model of CRF.[30] Those rats consuming rhubarb extract in their drinking water (750 mg/kg per day) had significantly less proteinuria and less glomerulosclerosis than those rats not treated.

Few clinical trials have been performed to determine the efficacy of rhubarb, and given the flaws in these studies, they can only be used to support further clinical trials. In a small study of patients with moderate to severe CRF ($n = 30$), Zhang *et al.* found the combination of Captopril (25 mg, three times daily) and rhubarb extract (6–9 g/day) induced a non-significant improvement in renal function by normalizing BUN and SCr ($P > 0.05$).[33] Kang *et al.* performed an uncontrolled observational study of 50 inpatients suffering from CRF.[34] While maintaining 'small doses of diuretics and hypertension pills' for 3 months, the main therapy was a decoction of 10 g rhubarb, 20 g dandelion (*Taraxacum officinale*), and 30 g oyster shell, administered orally or by retention enema. In the 1–3 years follow up, the BUN of 37 of the patients dropped from an average of 35 to 17.56 mmol/L, and pruritus and paraesthesia were significantly decreased. The 13 remaining cases needed to be switched to full conventional therapy; seven with successful dialysis treatment and six died from complications of renal failure. Diarrhoea in the initial treatment with rhubarb was not considered an adverse effect, as that action was considered one of the medicinal properties of the herb.[35] However, it is important to note that in most clinical trials with rhubarb, doses began at approximately 1 g/day and were increased gradually to the doses tolerable to the individual.

Salvia miltiorrhiza ROOT and MAGNESIUM LITHOSPERMATE B

In 1989, Yokozawa *et al.* isolated and identified some of the active compounds from the root of *Salvia miltiorrhiza*.[36] The compound, magnesium lithospermate B (MLB), a tetramer of caffeic acid, was found to be the most effective constituent isolated, the action at a dose of 20 mg/kg corresponding to that of the aqueous whole root extract at a dose of 300 mg/kg. A single i.p. dose administered to rats with adenine-induced renal failure significantly increased the glomerular filtration rate (GFR) in a dose-dependent manner. That same group had previously found that root extracts of *S. miltiorrhizae* (100 mg/kg per day) in rats with adenine-induced renal failure increased GFR by 50% and renal blood flow by 40% when compared to the rats with no treatment.[37]

In subsequent years, numerous studies on the compound MLB have been performed by the same group. Yokozawa *et al.* investigated the efficacy of MLB as a therapeutic agent in rats with subtotal nephrectomy.[38] Approximately 4 mg/kg per day MLB resulted in a significant reduction in extracapillary crescents and adhesions, tubular interstitial lesions and a significantly lower glomerular sclerosis index than the rats receiving no therapy. Furthermore, the MLB reversed the increase of BUN and SCr. In two other papers investigating the protective effect of MLB on cephaloride-induced renal injury,[39] and the mechanism by which MLB protects in renal failure,[40] that group found restoration of superoxide dismutase and catalase activities, concluding that MLB may act through inhibition of reactive oxygen species (ROS) generation. Lee *et al.* added evidence to this hypothesis, finding that MLB inhibited ROS generation when added to mesangial cells cultured under high glucose.[41] This subsequently led to protein kinase C activation and transforming growth factor *beta*-1 and

Table 1 Medicinal herbs with potential renal benefits (oral administration)

Herbal preparation (dose)	Subjects	Significant differences when compared to controls
Acanthopanax senticosus root (100 or 200 mg/kg per day)[42]	Rats	Lower nitric oxide, BUN, SCr and TBARS
Andrographis paniculata (100 mg/kg per day)[43]	Mice	Higher renal levels of GST, CAT, and DT-diaphorase
Black cumin (*Nigella sativa*) (50 and 100 mg/kg per day)[50]	Rats	Increased (normalized) renal CAT and lower BUN, SCr and DNA synthesis
Buckwheat (*Fagopyrum esculentum*) (100 or 200 mg/kg per day)[46]	Rats	Raised (restored) renal SOD and CAT
Ganoderma lucidum (a mushroom) (750–1100 mg/day)[47]	Humans	Combined therapy with vasodilators suppressed proteinuria in nephrosis with focal segmental glomerulosclerosis
Ginseng (*Panax ginseng*) saponins (25 mg/kg per day)[51]	Rat	Decreases in BUN, SCr, proteinuria, mesangial proliferation and severity of extratubular lesions and glomerular sclerotic lesions
Hachimi-jio-gan (1 g/kg, 5 days weekly)[48]	Mice	Suppressed development of glomerulonephritis, proteinurea, immune complexes and lymphadenopathy
Indian gooseberry (*Emilica officinalis*) (100 mg/kg per day)[45]	Mice	Higher renal glutathione and CAT activity and lower glutathione peroxidase and GST
Juglans sinensis (0.1 g/kg per day)[49]	Rabbits	Greater GFR and decreased SCr and lipid peroxidation
Perilla (*Perilla frutescens*) (50 or 500 mg/kg/day)[52]	Mice	Less proteinuria, serum IgA, IgG deposits and proliferation of glomerular cells
Phellinus rimosus sporocarps (25 or 50 mg/kg)[53]	Mice	Higher (normalized) renal SOD, CAT and GPX
Rhazya stricta (1 mg/kg per day)[54]	Rats	Lower SCr, BUN and TBARS; higher renal GSH and SOD (all were normalized)
Rosmarinic Acid (from perilla leaves) (100 mg/kg per day)[55]	Rats	Suppressed mesangial cell proliferation, glomerular depositions of fibronectin, type IV collagen and fibrin
Salvia sp. (species not stated) (0.1 g/kg per day)[56]	Rabbits	Increased GFR; lower renal lipid peroxidation and SCr levels
Shichimotsu-koka-to (1.5 g/kg per day)[57]	Rats	Prevented renal lesions; reduction of BUN and XOD; and increases in renal SOD (normalization)
Spirulina (*Spirulina fusiformis*) powder (1.5 g/kg per day)[58]	Rats	Higher renal SOD, CAT, reduced glutathione (all normalized)
Stinging nettle (*Urtica dioica*) (100 mg/kg per day)[60]	Mice	Increased renal SOD, CAT and GST
Striga orobanchioides (100 mg/kg per day)[59]	Rats	Higher renal CAT; decreased TBARS
Wen-Pi-Tang (62.5 or 125 mg/kg per day)[61]	Rats	Higher renal SOD, CAT, and GPX
Wild yam (*Dioscorea* spp.) (0.5 or 1 mg/kg)[44]	Rats	Decreased histological abnormalities in the glomeruli and convoluted tubule

Common name is provided when extract is commonly used in Australia. BUN, blood urea nitrogen; CAT, catalase; DT, di or tri; GFR, glomerular filtration rate; GPX, glutathione peroxidase; GSH, glutathione-S-hydrogenase; GST, glutathione-S-transferase; SCr, serum creatinine; TBARS, thiobarbituric acid reactive substances; SOD, superoxide dismutase; XOD, xanthine oxidase.

fibronectin upregulation by the increase in the profibrotic proteins in the *in vitro* experiments.

OTHER HERBS THAT MAY BE BENEFICIAL IN PATIENTS WITH RENAL DISEASE

Several other medicinal plants have been found to have potential benefits in renal disorders. Table 1 lists selected studies of herbs, which may be beneficial in the treatment of renal failure, tumours of the kidneys, and/or protection against oxidation damage. Because of the large number of studies that have found potential benefits, this table (Table 1) includes only those studies in which the extract was orally administered in a dose less than or equal to 1.5 g/kg per day. In cases of multiple studies on the same herb, the most recent work was chosen. Furthermore, Thatte *et al.* extensively reviewed the modulation of programmed cell death by medicinal plants, therefore Table 1 does not include the studies presented by that group.[62]

COMMENT AND CONCLUSIONS REGARDING THE RENAL BENEFITS OF HERBAL THERAPIES

There is increasing evidence that many medicinal herbal supplements have the potential to become valuable complementary therapy in the treatment of various renal disorders and in the protection against iatrogenic nephrotoxicity. The reader is reminded, however, that there

are potential toxicities associated with some herbal therapies[1] and many herbal therapies are only beginning to be properly investigated by Western scientific methods. Toxicity studies, preliminary *in vivo* studies and clinical trials are necessary to help decide on which combinations of herbal medicines (or their components) are most appropriate to be used as complementary therapy with pharmaceutical agents. Such experiments are currently being performed in our labs, and should be encouraged in the scientific community.

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