Review

Herbal treatments of glomerulonephritis and chronic renal failure: Review and recommendations for research

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Remissions of nephrotic syndrome due to membranous nephropathy (MN) induced by *Astragalus membranaceus* have drawn nephrologists attention to medicinal herbs as alternative treatments of glomerulonephritis. MN stands for a group of chronic glomerulonephritides that are routinely treated with corticosteroids and cytotoxic drugs, although treatment responses are unsatisfactory and the toxic burden significant. The investigational status of *Astragalus* and other medicinal herbs like *Angelica sinensis, Tripterygium wilfordii, Rheum palmatum, Ligusticum wallichii, Perilla frutescens, Salvia miltiorrhiza, Arctium lappa* with respect to their use as treatments of chronic renal disease and specifically of glomerulonephritis is reviewed. Most of these herbs are in current clinical use in China and appear to have promising constituents capable of modifying immune processes in glomerulonephritis. Nevertheless, their application in patients can still not be advocated as clinical studies meeting international quality standards have not been performed and toxic risks had not been excluded with adequate scrutiny.

Key words: Glomerulonephritis, medicinal herbs, triptolide, astragalus, perilla, rhubarb.

INTRODUCTION

Why are herbs investigated as treatments of glomerulonephritis?

''Will we ever have options other than steroids and cytotoxics to treat glomerulonephritis?'' lamented the authors of a recent review on glomerulonephritis (Basit and Quig, 2005). Glomerulonephritides are primary renal disorders or secondary to a systemic disease, characterized by inflammation within the renal glomerulus. Glomerulonephritides have an underlying autoimmune pathogenesis and are routinely treated with corticosteriods and various cytotoxic drugs. Although in many instances such therapies are successful, they are associated with significant morbidity; as such, alternatives are clearly warranted.

Some of the most common forms of chronic glomerulonephritis like membranous nephropathy (MN) and Immunoglobulin A-nephropathy (IgAN) simply lack effective treatment concepts. The response towards cytotoxic drugs is highly variable and not reliably predictable. Spontaneous improvements and even remissions of these entities occur and may feign drug effects. Thus, the risk of an unnecessary exposure to an ineffective, yet toxic treatment is imminent (Polanco et al., 2010; Dikow et al., 2009).

Cytotoxics like azathioprin, cyclosporin A, cyclophosphamide, chlorambucil, infliximab and rituximab (anti-CD 20) had all been administered in MN (Babacan et al., 2010; Ponticelli et al., 1995) with variable, but finally

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disappointing results. A combination of steroids and chlorambucil had been a standard treatment of MN for two decades following the publication of encouraging data in the late 1970s. When a later follow-up disclosed only marginally improved preservation of renal function, nephrologists discarded this regime; however, as the outcome of many patients with MN remains poor, the search for a better treatment of this glomerulonephritis should be intensified.

The situation for the Immunoglobulin A-Nephropathy (IgNA), the most prevalent glomerulonephritis worldwide, is much the same. Immunosuppressive regimes are currently re-investigated in larger clinical trials (Eitner et al., 2008), because short-term studies in smaller cohorts had variable outcomes. Routinely applied regimens are not well tolerated by patients for their rather high corticosteroid doses.

Recently, reported remissions of MN following treatment with a herbal drug prepared from *Astragalus membranaceus* nourished hopes and curiosity among patients and nephrologists. A generally increased interest into alternative treatments by nephrologists and a change of their traditionally reluctant attitude towards herbal drugs appears to be the consequence (Ahmed et al., 2007).

Patients had an interest into alternative treatments already before, primarily on behalf of superior tolerability. As they are not trained to evaluate scientific evidence and easily misled by case-stories and so called testimonials, their physician's competence is required to guide them. Thus, the present paper intends to provide a balanced view of herbal treatment of chronic glomerulonephritis in current use and investigation for physicians to enable them to counsel patients in this respect.

Astragalus membranaceus

A. membranaceus (Fisch. ex Link) Bunge
Astragalus mongholicus dahuricus (DC.) Podlech
Astragalus penduliflorus membranaceus Glehn
Astragalus mongolicus Bunge
Astragalus membranaceus Bge. var. *mongolicus* (Bge.) Hsiao
Family: *Fabaceae*
Drug: Huangqi (TCM), Radix astragali

Traditional use and constituents

A. membranaceus is native to temperate Asia. Its active components are flavonoids, polysaccharides, triterpene glycosides (e.g. astragalosides I-VII), saponins and amino acids (Zhang et al., 2001). Astragalus is widely used in China to treat diseases of presumed autoimmune pathogenesis, it has been studied in animal models of

renal disease and administered to patients with various renal diseases.

In vitro data and animal models

Pre-incubation of peripheral blood mononuclear cells obtained from patients with systemic lupus erythematosus (SLE) with *Astragalus* restored the reduced natural killer cell activity of these cell (Zhao, 1992). Elevated levels of interleukin (IL)-1, IL-6, IL- 8 and tumor necrosis factor (TNF-alpha) in childhood nephrotic syndrome were more efficiently reduced by prednisone in combination with *Astragalus* than by prednisone alone (measured by mRNA expression and production of these cytokines) (Yu et al., 2001).

Astragalus has been studied in animal models of renal disease for its effect on cytokines and reactive oxygen species, ischemia/reperfusion injury, and mechanisms of renal fibrosis. Quite different renal diseases share the pathogenetic mechanisms that lead to renal fibrosis in their final stage. *Astragalus* reduced proteinuria in animal models of immune complex nephritis and adriamycin-induced nephrotic syndrome (Su et al., 2000). In a rat model of chronic puromycin-induced nephrosis *Astragalus* in combination with *Angelica sinensis* retarded the progression of renal fibrosis as much as the ACE-inhibitor (ACEI) enalapril and *Astragalus* reduced the upregulated expression of type III and IV collagen, fibronectin and laminin in renal fibrosis (Wang et al., 2002; Wang et al., 2004). The *Astragalus/Angelica* combination was superior over enalapril to halt renal fibrosis in rat models of obstructive uropathy and puromycin nephrosis (Wojcikowski et al., 2010; Min et al., 2003; Yu et al., 2000).

Astragaloside IV, extracted from *Astragalus* increased T and B lymphocyte proliferation and antibody production *in vivo* and *in vitro*, but inhibited production of IL-1 and TNF-alpha of mice peritoneal macrophages (Wang et al., 2002b). *Astragalus*' nephro-protective effects in animal models of diabetic nephropathy have been critically reviewed (Zhang et al., 2009). Although the quality of studies was considered as generally poor, beneficial effects of *Astragalus* on fasting glucose, albuminuria, pathologic hyperfiltration state, and patho-histological parameters of diabetic nephropathy were unanimously reported from rats with streptozotozin induced diabetes.

Chronic renal ischemia and hypoxia in the renal tubulo-interstitium are important mechanisms of progressive renal failure. *Astragalus* attenuated the infiltration of inflammatory cells and promoted recovery from renal ischemia reperfusion injury in rats (Chen et al., 2000; Jang et al., 2003; Cai et al., 2001). *Astragalus* combined with *Angelica* accelerated functional and histological recovery after acute renal ischemia reperfusion injury, possibly by increasing the activity of c-Jun N-terminal kinase32 and inhibiting osteopontin expression (Wang et

al., 2004). In a remnant kidney model in rats (5/6 nephrectomy) the *Astragalus/Angelica* combination reduced proteinuria more efficiently than enalapril, suppressed extra-cellular matrix deposition and improved microvascular insufficiency (Song et al., 2009).

Decoctions of *A. membranaceus* together with *A. sinensis* had anti-fibrotic effects through multiple pathways in different animal models of renal disease, e.g. by interfering with transforming growth factor beta (TGF-ß) as a key regulator of the fibrogenic process (Border et al., 1990). Compared with controls the combination of *Astragalus* and either *Angelica* or the HMGCoA inhibitor pravastatin given for 10 weeks reduced deposition of renal extracellular matrix (ECM), including type III and IV collagen, fibronectin, laminin, as well as the expressions of mRNA and protein of TGF-ß in glomeruli and tubules in rats with puromycin-induced nephrotic syndrome (Ding et al., 1998). *Astragalus* also retarded the progression of renal fibrosis secondary to unilateral ureteral obstruction. The reno-protective effect of *Astragalus* had been attributed on the inhibition of myofibroblast activation and reduced TGF-beta1 expression (Zuo et al., 2009).

Clinical studies

Astragalus' effects on proteinuria in nephrotic syndrome had been studied in clinical trials performed in China. Injections of *Astragalus* (40 g/day for 3 weeks) to patients with different forms of chronic glomerulonephritis (n= 30) (mesangioproliferative glomerulonephritis (MGN) due to IgA nephropathy (IgAN) (n=21), focal and segmental glomerulosclerosis (FSGS) (n=8), and membranous nephropathy (MN) (n=1)) had reduced proteinuria from 2328 ± 3157 to 1017 ± 765 mg/day (Shi et al., 2002). Further studies with impressive counts of included patients (>100) found reduction of proteinuria in chronic glomerulonephritis by *Astragalus* alone (Chen, 2001; Bao et al., 2003; Shi et al., 2003) or in combination with *A. sinesis* or Ligustrazine (Xue et al., 2002). *Astragalus* also ameliorated the nephrotic syndrome related dyslipidemia in these trials (Wang et al., 2002a).

The successful treatment of nephrotic syndrome secondary to MN in a 77 year-old woman by *Astragalus* had received lots of attention, probably because it was reported from outside China. The patient had already received ACEI, angiotensin receptor blockers, cyclosporine A and mycophenolate mofetil without response for more than 2 years of unremitting nephrosis, when she promptly responded to an extract of *A. membranaceus* (15 g/day). The nephrotic syndrome recurred after temporary cessation of *Astragalus* therapy, with complete remission of nephrosis observed after its reintroduction (Ahmed et al., 2007).

The influence of parenteral *Astragalus (*32 g i.v. per day for 1 month) on disease progression had been studied in patients with chronic renal failure (serum creatinine 176

to 300 mmol/L; creatinine clearance 30 to 50 ml/min) (n=68) in a randomized study vs. saline. *Astragalus* improved renal function (s-creatinine decreased from 244 ± 51 to 162 ± 63 mmol/L; creatinin-clearance increased from 37.8 ± 6.2 to 53.4 ± 5.3 ml/min) as compared to the saline treated control group which was unchanged (Zhao et al., 2000). An even higher dose of parenteral *Astragalus* (40 g/day) had been as effective as the ACEI captopril (75 mg/day) to improve renal function in patients with chronic renal failure (Yang et al., 1997).

Toxicity

Information about potential hazards of *Astragalus* extracts is scarce. Toxicity data are required before these extracts can be considered as treatment of glomerulonephritis. *Astragalus* had been safe in therapeutic doses without any distinct toxicity and side effects when given to rats and dogs in short-term experiments. A safe dose range is reported as 5.7 to 39.9 g/kg for rats and 2.85 to 19.95 g/kg for beagle dogs, which exceed the respective doses recommended for humans (0.57 g/kg) (Yu et al., 2007). Astragaloside IV purified from *A. membranaceus* had been maternally toxic at 1.0 mg/kg in rats and fetotoxic at a dose higher than 0.5 mg/kg, but devoid of teratogenic effects in rats and rabbits. In light of these findings it seems prudent to advise caution to women who might use astragaloside IV during pregnancy (Jiangbo et al., 2009). The LD50 of *Astragalus* is approximately 40 g/kg when administered by intraperitoneal injection in rats, but there had been no adverse effects reported from rats receiving doses as high as 100 g/kg of the raw herb by gavage (Steven 1998).

Critical evaluation

Astragalus alone or combined with medicinal herbs like *Angelica* or *Ligusticum* could be considered as a potential treatment of some forms of active glomerulonephritis. The reported reduction of proteinuria by *Astragalus* is intriguing but needs to be confirmed in larger scale studies with patients of precise histological renal diagnosis. So far, clinical trials had studied heterogeneous populations of patients, had an open design and rather short observation periods as to draw firm conclusions from the results. For example, the reduction of proteinuria by *Astragalus* reported by Shi et al. (2002) appears to be irrelevant as the follow-up time did not exceed 3 weeks. Such studies are not powerful enough to find therapeutic principles that modify the long-term fate of renal patients, as considerable quantitative short-term fluctuations of proteinuria and renal function will interfere with results. Proteinuria is nevertheless a valuable end-point of studies as it is not only a marker of

renal damage but at the same time itself noxious to the renal tubulo-interstitial tissue.

There is encouraging evidence that Astragalus can modify the course of renal disease at their later stages by affecting fibrogenic mechanisms, e.g. those mediated by TGF-ß. Clinical studies focussing on renal function need long observation times and have to be performed against existing evidence based strategies like ACEI (Zhao et al., 2000).

Angelica sinensis

A. sinensis (Oliver) Diels
Family: Apiaceae
Drug: Radix Angelicae Sinensis, Dong quai, Dang gui, Female Ginseng.

Traditional use and constituents

A. sinensis is indigenous to China. The plant's phytochemicals are coumarins, phytosterols, phytoestrogens, polysaccharides, ferulate, and flavonoids. It is traditionally used to treat gynaecological disorders and hypertension.

Toxicity

Angelica has anticoagulant effects and may cause bleeding in combination with anticoagulants like warfarin. Cases of male gynaecomastia (due to estrogen-content) have been reported. Dong quai is traditionally viewed at as increasing the risk of miscarriage.

Critical evaluation

Angelica had been combined with Astragalus for treatment of renal disease. The database for this plant is too small to be evaluated separately.

Tripterygium wilfordii

T. wilfordii Hook F
Family: Celastraceae
Drug: Lei Gong Teng, Radix T. wilfordii

Traditional use and constituents

T. wilfordii has been used for centuries in China as an anti-inflammatory agent (Gu et al., 1995), specifically for the treatment of rheumatoid arthritis. Active constituents are diterpenoids like triptolide and tripdiolide, alkaloids,

glycosides, beta-sitosterol and tritoquinones (Gu et al., 1995; Ma et al., 1991; Kupchan et al., 1972). The diterpene triepoxide triptolide is considered the major active component. It has been explored for anti-inflammatory and immunosuppressant activities, e.g. in rheumatoid arthritis, but it is currently also investigated as an anti-cancer agent. The use of Tripterygium for the treatment of glomerulonephritis is rather recent in China.

In vitro data and animal models

Triptolide has been studied in vitro for its disease-modifying potency in rheumatoid arthritis. Triptolide blocked the lipopolysaccharide (LPS)-induced expression of macrophage genes encoding for pro-inflammatory cytokines and chemokines like TNF-alpha, IL-1beta, and IL-6 in a dose-dependent manner (Matta et al., 2009). Triptolide suppressed the production and gene expression of pro-matrix metalloproteinases 1 and 3 (proMMP) and augmented those of tissue inhibitors of metalloproteinases 1 and 2 (TIMP) in human synovial fibroblasts. The IL-1alpha-induced gene expression and production of TIMPs 1 and 2 were further augmented by triptolide in synovial cells. Triptolide also inhibited the IL-1alpha-induced production of PGE2 by selectively suppressing the gene expression and production of COX-2, but not of COX-1. In addition, triptolide suppressed the LPS-induced production of PGE2 in mouse macrophages. Gene expression of IL-1alpha, IL-1beta, TNFalpha, and IL-6, as well as the production of IL-1beta and IL-6 were inhibited by triptolide in LPS-treated mouse macrophages. Based on these findings, the therapeutic effects of Tripterygium in rheumatoid arthritis had been attributed to chondroprotective effects of triptolide through a suppression of proMMPs 1 and 3 production and the simultaneous up-regulation of TIMPs in IL-1-treated synovial fibroblasts (Lin et al., 2001). Further research from this group showed that triptolide reduced inflammation and cartilage destruction in a mouse model of collagen-induced arthritis and exerts chondroprotective and anti-inflammatory effects in RA (Lin et al., 2007). Triptolide's effect on gene expression of proinflammatory cytokines and cyclooxygenase 2 activity/prostaglandin E2 production have been confirmed by others (Tao et al., 1998). Tripterygium extracts and triptolide inhibited in vitro synthesis of prostaglandin E2 (PGE2) and reduced the expression of the cyclooxygenase isoforms COX-1 and COX-2 in various human cell types.

Research on triptolide as a treatment of renal diseases is rare. One report described successful treatment of anti-GBM disease in rats with a combination of triptolide and emodin (from Rhubarb) without providing details (Dai et al., 2000). The immunosuppressive profile of triptolide has been evaluated for its applicability in organ transplantation. Triptolide improved survival rate and survival time of rats following renal transplantation (Dong

et al., 1993) and modified important pathogenetic elements in transplant rejection. It induced apoptosis of activated lymphocytes (Yang et al., 1998), inhibited IL-2 production by T or B lymphocytes and attenuated the pro-inflammatory factor-induced over-expression of major histocompatibility complex and B-7 molecules in renal tubular epithelial cells and the activity of nuclear factor kappa B (Li et al., 2002). Triptolide strongly inhibited up-regulation of C3, CD40 and B-7 in human proximal tubular epithelial cells and was more potent than cyclosporine A and tacrolimus in inhibiting C3 expression (Hong et al., 2002).

Triptolide effectively reduced proteinuria in a model of podocyte injury by puromycin aminonucleosides. The antiproteinuric effect was associated with improvement in histological markers, e.g. of the foot-process effacement, and a decrease in podocyte injury marker desmin as well as with restoration of nephrin and podocin expression. Triptolide pre-treatment prevented the puromycin-induced disruption of the actin cytoskeleton and microfilament-associated synaptopodin while protecting nephrin and podocin expression in cultured mouse podocytes. Triptolide suppressed reactive oxygen species generation and p38 mitogen-activated protein kinase activation while restoring RhoA signaling activity (Zheng et al., 2008). Triptolide and tripdiolide ameliorated nephritis in a mouse model of lupus nephritis (NZB × NZW) F1 mice, reduced cytokine and chemokine production, and prolonged survival (Tao et al., 2008). Triptolide has also been investigated for its effects on adult polycystic kidney disease (ADPKD). ADPKD is an inherited kidney disease devoid of inflammatory or autoimmune pathogenesis that leads to end-stage renal failure. Misled kidney organogenesis causes renal cyst formation and loss of functional renal parenchyma, a process linked to an inherited defect of a calcium (Ca^{2+}) channel polycystin-2 (PC2) molecule. Loss or mutation of either PC2 or its regulatory protein polycystin-1 (PC1) results in ADPKD. Triptolide induced Ca^{2+} release by a PC2-dependent mechanism and furthermore, in a murine model of ADPKD, triptolide arrested cellular proliferation and attenuated overall cyst formation by restoring Ca^{2+} signaling in these cells. This induction of PC2-dependent calcium release by triptolide is considered a promising therapeutic strategy for ADPKD (Leuenroth et al., 2007).

Clinical studies

Triptolide, when administered at 2 mg/kg/day for 4 weeks had induced complete remission of nephrotic syndrome in 15/18 patients with nephrotic syndrome (8 IgAN, 4 MN, 6 minimal change glomerulonephritis (MGN)) and had reduced proteinuria from 2.34 ± 1.14 to 0.5 ± 0.59 g/day (Hu et al., 1997). Comparable reductions of proteinuria by triptolide were found in further smaller studies involving patients with mesangial proliferative glomerulonephritis

(IgNA?, possibly) (Rong et al., 1998), lupus nephritis (histologically not specified) (Qin et al., 1981) and IgAN (Wang et al.,1991). Prevention of renal allograft rejection was investigated by adding triptolide to a standard triple immunosuppression in a prospective clinical trial of 79 renal transplant recipients (Ji et al., 1998). After a follow-up of 12 months the frequency of acute allograft rejection had been lower in patients treated with prednisone, cyclosporine (CsA), azathioprine (AZA) and triptolide (1 or 2 mg/kg/day) than in patients treated with the standard medication alone.

Despite the good experimental evidence for chondroprotection by triptolide in animal models (Lin et al., 2007) the clinical evidence for *T. wilfordii* extract for effects in human RA still low. Only a limited number of randomized controlled trials (RCT), all of them of small sample size and with methodological problems had been performed. A recent RCT from Canada employing a topical extract (Cibere et al., 2003) had a follow-up of only 6 weeks, but a highly significant response was reported. Expanded larger trials need to be performed to confirm this finding.

Toxicity of *tripterygium* extracts and their isolated constituents

The narrow therapeutic range of the TCM-drug Lei Gong teng had been known already to the ancient. Adverse symptoms related to the drug are dizziness, palpitation, weakness, nausea, vomiting, stomach pain, diarrheoa, intestinal bleeding, respiration, liver failure and even death. It has been recommended that the daily dose should not exceed 12 to 15 g. Classic texts instructed users to peel and discard the root bark of the herb before decoction, and cook it for at least 60 min before the addition of other herbs. Lei gong teng has been regarded as contraindicated in pregnancy and cautious use was advised for geriatric and paediatric patients.

Modern research confirmed triptolide to be highly cell-toxic (Mak et al., 2009) and hepatotoxic and to have a narrow therapeutic window. It is investigated as anti-cancer agent and had been discussed as a male contraceptive for its documented effects on male reproductive fertility (Lue et al., 1998).

In renal patients (79 patients with histologically confirmed chronic kidney disease and normal renal function) treated with *Tripterygium* extracts temporal mild elevation of SGPT (25.3%), SGOT (6.3%), gastrointestinal symptoms (7.6%) and abnormal menstruation in female patients (8%) occurred after a median follow-up of 19.3 months (Rong et al., 1998).

Critical evaluation

Triptolide is potentially qualified as an immunosuppressant in autoimmune diseases and in

transplantation. The experimental data are impressive for RA, however, triptolide cannot be approved for use in humans since meaningful clinical studies have not been performed. Clinical data on triptolide in renal diseases are encouraging as impressive reductions of proteinuria have been reported. However, follow-up times of these studies have been still too short, and many studies lack methodological precision, e.g. when triptolide is administered for treatment of lupus nephritis irrespective of the precise histological diagnosis which should guide the intensity and choice of immunosuppression. Triptolide appears to have a narrow therapeutic range and a thorough safety assessment is necessary before its application in relative benign diseases like chronic glomerulonephritis can be approved.

Rhubarb

Rheum palmatum L. and *Rheum officinale* Baillon
Related species: *R. tanguticum* (Maximowicz ex Regel) Maximowicz ex Balfour.; *Rheum rhaponticum* L. (substitute for medicinal rhubarb, rarely used).
Family: *Polygonaceae*
Drug: Rhei rhizoma (dried root), Onpi-to, Dahuang

Traditional use and constituents

Indiginous to north-west China and Tibet, but cultivated in other parts of China, Korea, India and Pakistan. Both species (*R. palmatum, R. officinale* – their hybrids and mixtures of the drugs) are used for medicinal purposes. Rhubarb´s main traditional use in TCM is as a laxative. Anthraquinone-glycosides are the lead compounds of the roots. The best investigated anthraquinones are emodin (3- methyl-1,6,8-carboxyl-anthraquinone) and rhein (4,5-dihydroxyanthraquinone-2-carboxylic acid) (Li, 1996a). The tannin content of rhubarb has also been linked to effects in renal diseases.

In vitro data and animal studies

Rhubarbs influence on renal fibrosis has been studied in 5/6 nephrectomised rats, an animal model mimicking progressive renal failure. After 16 weeks of treatment 75% of Rhubarb-treated rats had survived, 71% of an enalapril treated group and 61 of the untreated group. Both Rhubarb and enalapril-treated animals had better renal function and less proteinuria than the control (Yang et al., 1994; Zhang and El Nahas, 1996). In a similar model of renal failure in rats orally administered rhubarb extract reduced proteinuria and the severity of glomerular scarring (glomerulosclerosis) in remnant kidneys (Zhang and El Nahas, 1996). Rhubarb-tannins had been reported to reduce uremic toxins in blood and improve glomerular

filtration rate in animal-models of subtotal nephrectomy and diabetic nephropathy (Yokozawa and Fujiko, 1991; Yokozawa et al., 1997).
Rhein antagonised the effect of TGF-ß1 in mesangial cells (Guo et al., 2001) and attenuated hypertrophy of renal tubular epithelial cells and accumulation of extracellular matrix (ECM) induced by TGF-ß1 (Guo et al., 2001; Zhu et al., 2003). Rhein had been protective on endothelial function by inhibiting overexpression of plasminogen activator inhibitor-1, related to the activity of mitogen-activated protein kinase (Zhu et al., 2003). Further *in vitro* studies suggest that emodin decreased the gluconeogenesis of tubular cells and the adenosine triphosphate content of epithelial mitochondria, and suppressed cytokine production in macrophages and human mesangial cells, as well as tubular and mesangial cell proliferation (Li, 1996b). The effects appeared to be mediated through suppressed gene expression of c-myc and retardation of cell cycles (Liu et al., 1996). These experimental studies suggest a renoprotective effect of emodin mediated by inhibition of TGF-ß activity and cellular metabolism of renal tubular and mesangial cells.

Rhein retarded the progression of diabetic nephropathy as much as the ACEI benazepril in the db/db mouse model of type 2 diabetes (Jia et al., 2007). Rhein´s protective effect on renal cells in diabetic nephropathy had been linked to an ameliorated hyperlipidaemia and suppression of TGF-beta1 production (Guo et al., 2001; Zhang et al., 1999). In rat mesangial cells rhein prevented key-features of mesangial expansion in DN like cellular hypertrophy, fibronectin synthesis, increased expression of extracellular matrix (ECM) components in response to high ambient glucose.

Clinical studies

Rhubarb-extracts have been administered to no less than 151 patients with chronic renal failure to retard disease progression. Patients with an initial s-creatinine of 328 ± 92 mmol/L had been randomised to receive Rhubarb alone or the ACEI captopril or the combination of both. End stage renal failure occurred in 54.3% of ACEI treated patients, 25.9% of Rhubarb-treated, and 13.1% of patients receiving the combined regime after a follow-up of 32.5 months (range, 15 to 62). Progression rate of renal failure calculated as 1/S-Creatinine versus time had been reduced in both the Rhubarb- and the Rhubarb plus captopril group. Thus, rhubarb had been more potent than the synthetic ACEI captopril to slow progression of renal failure in this trial, and the best protection of renal function had been provided by the combination of both treatments (Li, 1996; Yu et al., 1995). A similar clinical protocol had been applied in a study with less than 10 patients per group. These patients had been randomised to three groups, one treated with *Rheum*-extract, one with captopril and the third with the combination of both(Zhang

et al., 1990), showing benefits with retarded progression of CRF for both *Rheum*-treated groups.

Toxicity

An ingested overdose of Rhubarb may induce diarrhoea. The LD 50 of *R. rhaponticum* is more than 5 g/kg when administered by intravenous injection, and more than 10 g/kg when ingested (Steven, 1998). This information cannot be directly transferred to the closely related, but still different medicinal rhubarb. *R. rhaponticum* is not the drug in use.

Critical evaluation

Experimental research, particularly on diabetic nephropathy qualifies rhubarb and their isolated constituents as promising principles in retardation of chronic renal diseases. Rhubarb is not known to have immunosuppressive activity and is therefore probably not suitable for treatment of active glomerulonephritis. Its pharmacological profile in renal disease appears to come close to that of ACEI. As the latter are well established drugs for treatment of chronic renal failure, any study with rhubarb needs to be performed with ACEI or ARB in a parallel treatment group. One of the most impressive clinical studies lacks the information on the standardisation of the extract (Yu et al., 1995). Standardized extracts are required for all studies with rhubarb to allow reproduction of results in future applications.

Ligusticum wallichii

L. wallichii Franch. *Ligusticum chuanxiong*
Family: *Apiaceae*
Drug: Radix Ligustici; Chuanxiong

Traditional use and constituents

L. wallichii is used in TCM for treatment of ischemia, thrombosis and haematological disorders. It is also prescribed for headaches, abdominal pain, arthralgias, and menstrual disorders. *Ligusticum's* active ingredients include alkaloids, tetramethylpyrazine, ferulic acid (a phenolic compound), chrysophanol, sedanoic acid, and 1 to 2% of essential oils such as ligustilide and butylphthalide (Steven, 1998: Sun et al., 2002). Tetramethylpyrazine is also termed Ligustrazine. In Japan the source of the drug had been reported as *Cnidium officinale*. According to recent taxonomic literature this plant is conspecific with *L. wallichii*.

In vitro and animal research

Pre-treatment with oral tetramethylpyrazine (TMP) prevented renal failure induced by acute administration of absolute ethanol (10 ml/kg) in mice, which was attributed mainly on the constituent´s superoxide scavenging effect. Although interesting, the model is highly artificial and not representative for the majority of renal disease in humans (Liu et al., 2002a). Studies in 5/6 nephrectomised rats (Liu et al., 2002c) demonstrated sodium ferulate to reduce 24 h urinary protein excretion and ameliorate creatinine-clearance and renal histopathological changes. Reduction of proteinuria by sodium ferulate was also found in a rat model of adriamycin-induced nephritic syndrome (Liu et al., 2002b).

Sodium ferulate improved abnormal endothelial gene expression of nitric oxide synthase induced by TNF-ß (Wang et al., 2003) and inhibited expression of e-selectin and p-selectin in activated human umbilical vein endothelial cells (Zhao et al., 2003). Reduced production of renal TGF-ß1 and Smad7 was observed in 5/6 nephrectomised rats treated with sodium ferulate. In addition, *in vivo* studies demonstrated that ferulic acid has endothelin antagonistic activity (Wang et al., 1999). Reduction of proteinuria and improvement of renal function by *Ligusticum* had been linked to corrections of blood endothelial system disorders (Wang et al., 1999; Li et al., 2001). Preliminary data on its molecular mechanism suggested that sodium ferulate exerts its renoprotective effect by reducing renal TGF-ß production and inhibiting adhesion molecules expression (Zhao et al., 2003), and by endothelin-antagonistic activity (Wang et al., 1999).

Clinical studies

Ligustrazine had been administered to slow or halt progression of renal failure in Chinese patients (n=45) with biopsy proven renal mesangial cell proliferation (histological feature of IgNA). Patients had been randomized to receive steroids, cyclophosphamide, losartan and dipyridamole or ligustrazine in addition to this regime (80 mg twice a day i.v.) for three weeks. Patients receiving ligustrazine were reported as having higher urine volumes, serum albumin and creatinine-clearances as well as improved proteinuria and hematuria (Tang, 2003). In infants, ligustrazine had been administered for prevention of gentamycin renal toxicity (Yang and Ren, 1994). Ferulic acid, the supposed major active component of tang-kuei and one of the active components of chuanxiong, had beneficial effects in patients with diabetic nephropathy (Zheng et al., 2001).

The clinical effectiveness of *Ligusticum* on chronic renal failure had been evaluated in some smaller clinical trials. In 82 patients with chronic renal failure (Ren et al., 2001) *Ligusticum* and its active component sodium

ferulate improved patient's clinical condition and lowered blood levels of creatinine and urea nitrogen. Sodium ferulate added to an ACEI had been studied in further 67 patients with chronic renal failure versus the ACEI alone (Zhou and Yuan, 2003). During a follow-up time of 30 days, reductions of creatinine and blood urea nitrogen were observed only in the patients receiving the sodium ferulate regime.

Sodium ferulate has been administered as an add-on to prednisone in 120 patients with primary childhood NS. After a follow-up of 20 days, patients treated with sodium ferulate plus prednisone had lower levels of 24 h urinary protein excretion than those treated with prednisone alone (0.4 mg/kg/day) (Liu et al., 2001). Similar results had been obtained in adults with nephrotic syndrome (Liu et al., 2000).

Toxicity

Ligusticum is prescribed in traditional Chinese decoctions at doses of up to 9 g administered over several days (Steven, 1998). Overdose symptoms may include vomiting and dizziness.

Critical evaluation

Ligustrazine is apparently widely used to treat renal diseases, even in children. It is mandatory to obtain solid data about its efficacy and safety, published in peer-reviewed international journals. The pharmacological profile, as far as it has been characterized, differs from that of the other plants presented here by its endothelin-antagonistic activity.

Perilla frutescens

P. frutescens (L.) Britton
Family: Labiatae
Drug: Shiso, Sairei-To (TJ-114), Saiboku-to

Traditional use and active constituents

P. frutescens is a spice used in Korean and Japanese cuisine and a TCM-drug (Shiso). Decoctions of *Perilla* have been administered for centuries in Japanese herbal medicine (=Kampo Medicine) to treat kidney diseases. Perilla-oil contains perillaldehyde as major constituent, the seeds are rich in linolenic acid. Rosmarinic acid is another active ingredient. *Perilla* is an ingredient of popular herbal combinations in Japanese–Chinese herbal medicines, e.g. Sairei-to. TJ-114 (Tsumura Sairei-to) is a powdered extract prepared from 12 Chinese herbs including *Perilla*. Saiboku-to is another *Perilla*-based polyherbal Kampo formula. Sairei-to is traditionally administered to treat collagen disease and edema in nephrotic syndrome.

In vitro and animal research

Orally administered *Perilla*-decoction lowered serum IgA-levels and proteinuria and improved renal histology (proliferation of glomerular cells, IgA-deposition.) in a mouse model of mesangial IgA-deposition and high IgA serum-levels (high serum IgA (HIGA) mice) (Makino et al., 2003). The effect could be attributed mainly, but not exclusively to the *Perilla* constituent rosmarinic acid (Makino et al., 2002). Of note, the *Perilla*-extract was successful only in one specific strain of mice, and failed in another outbred strain. This reflects the pathogenetic heterogeneity of animal models of IgAN and is reminiscent of the human situation with extremely variable clinical courses and responsiveness towards drug treatments. Further studies with this mouse model proved sairei-to to inhibit platelet-derived growth factor (PDGF) receptor tyrosine kinase (which causes mesangial proliferation) as a potential anti-nephritic mechanism. These results suggest the anti-nephritic effects of sairei-to in HIGA mice to be partly due to inhibiton of PDGF tyrosine kinase by oroxylin A and isoliquiritigenin, both components of sairei-to (Hattori et al., 2007).

Saiboku-to had anti-proliferative effects on cultured murine mesangial cells (Ono et al., 1998, 2005). Mesangial proliferation is a histologic key-feature of mesangioproliferative glomerulonephritides (e.g. IgAN).

Sairei-to inhibited mesangial cell proliferation (Awazu et al., 2002) in rats, and reduced proteinuria in aminonucleoside nephritis of rats, probably by interference with prostaglandin metabolism (Suzuki et al., 1997). In another rat model of mesangioproliferative GN, sairei-to suppressed mesangial proliferation, supposedly by increasing anti-oxidative protection through stimulation of superoxide dismutase activity (Liu et al., 2004).

In a rat model of anti-glomerular basement membrane nephritis (anti-GBM disease) administration of sairei-to or saikosaponin D significantly suppressed the increase of urinary protein excretion and histopathological changes in adrenalectomized nephritic rats. Administration of sairei-to and saikosaponin D prevented an increase in IL-2 levels in the renal cortex of anti-GBM nephritic rats. (Hattori et al., 2008).

Clinical research

The Kampo formula TJ-96 had beneficial effects in patients with infection associated IgAN (Ono et al., 1992). Sairei-to was studied in a prospective but open controlled study in children with IgAN. 101 children with biopsy-

proven IgAN had been assigned to receive either Sairei-to for 2 years or to receive no intervention. At the study end 46% of the herb-treated children had normal urinary findings (no proteinuria/hematuria) as compared to only 10% of the untreated children (Yoshikawa et al., 1997).

Toxicity

Sairei-to had been reported as a cause of sterile cystitis in children. The clinical symptoms resolved after Sairei-to treatment had been withdrawn. Sairei-to-induced cystitis occurred mainly in children and developed 6 months or later after the treatment had been initiated. An allergic pathogenesis had been suggested as an eosinophilic cell infiltration found histopathologically. Altogether 9 cases have been described (Kano et al., 1997).

Critical evaluation

Rather solid data suggest efficacy of *Perilla* in experimental models of IgAN. A single clinical trial also suggests an extraordinary success. However, childhood IgAN is rare, usually it is a condition called Schönlein-Henoch purpura which has a low tendency to become chronic. Spontaneous remissions may therefore have accounted for the very positive reported results.

Salvia miltiorrhiza

S. miltiorrhiza Bunge
Family: *Lamiaceae*
Drug: Danshen-root (=the dried root of *Salvia miltiorrhiza*)

Traditional use and active constituents

S. miltiorrhiza is native to China and Japan. Danshen is used for treatment of various diseases, e.g. coronary and cerebrovascular disease, sleep disorders, hepatitis, cirrhosis, chronic renal failure, dysmenorrhea, amenorrhea, carbuncles and ulcers. Danshen has been used in China for at least thirty years to treat chronic renal failure. The chief active constituent of danshen is magnesium lithospermate (Yokozawa, 1989).

In vitro research and animal experiments

Lithospermate B and other constituents of Danshen root enhanced renal plasma flow and glomerular filtration rate in laboratory animals with renal failure. Rather weak evidence suggests that lithospermic acid B which has strong antioxidant activity ameliorates ischemia/reperfusion injury in rats, probably through scavenging of ROS (Kang et al., 2004). A study designed to investigate the effect of danshen on ischemia/reperfusion injury after experimental kidney transplantation in rats by preconditioning the donor- and recipient rats before surgery significantly reduced the ischemia/reperfusion injury and improved graft function (Guan et al., 2009).

Clinical studies

Peritoneal dialysis patients had been treated with *salvia*-injections, and an improvement of residual renal creatinine-, urea- and uric acid- clearances had been reported (Xu, 1993).

In China, *Salvia* had also been administered since the 1980s to transplant patients for prevention and treatment of organ rejection. Pharmacological studies appeared to support this application (Zhuang et al., 1988). A review of its use in renal transplant patients was published recently (Zhang et al., 2004). Claimed benefits include improvement in nearly all blood parameters that monitor renal function, improved recovery from transplantation surgery, and protection of the transplant. These data have only been published online, and apparently not in an international journal. Of 81 renal allograft recipients the control group received methylprednisolone pulse and the treatment group methylprednisolone pulse plus *salvia* (treated group) for 14 days. *Salvia* had been administered parenterally (30 ml of *salvia* extract in 5% glucose saline (250 ml)). The authors reported improvement of all measured renal parameters (including serum-creatinine) in both groups, but superior results for the group receiving the regimes that included salvia. No data on the number and severity of transplant rejections treated and the diagnostic criteria for rejections had been provided. The authors nevertheless concluded that *salvia* could enhance the curative effect of methylprednisolone impulse in controlling acute vascular rejection.

Toxicity

Like other *Salvia* species, e.g. *Salvia divinorum*, *S. miltiorrhiza* contains neurotoxic constituents. Overdose of danshen had caused complex neurological manifestations including convulsions, mental changes and dystonia syndromes (Wang and Yang, 2003).

Critical evaluation

Interesting experimental data suggest a role of *Salvia* in prevention of allograft rejections, and the drug is apparently already administered for that purpose in humans. They are yet available data on its clinical use lack important details and are not sufficient to establish

this drugs use on a wider scale.

Arctium lappa

A. lappa L.
Family: *Compositae*
Drug: *Fructus Arctii* Lappae

Traditional use and constituents

Arctium is traditionally used to treat inflammatory diseases and dermatosis/furunculosis. Antimicrobial and antifungal properties have been demonstrated *in vitro*. Active constituents are Arctiin, Arctigenin and essential oils. Arctigenin appears to be the main bioactive constituent with anti-inflammatory activities, isolated from dried seeds of *A. lappa*.

In vitro and animal research

Arctigenin suppressed lipopolysaccharide (LPS)-stimulated NO production and secretion of pro-inflammatory cytokines including TNF-alpha and IL-6 by macrophages. It downregulated the expression of iNOS and thus the overproduction of NO, whereas the expression of COX-2 and COX-2 enzymatic activity were not affected by arctigenin. These findings may explain the anti-inflammatory action of arctigenin (Zhao et al., 2009).

Arctiin had been studied in an experimental model of MN (induced by cationic bovine serum albumin in rats) for its effect on histological parameters of renal injury and on the production of pro-inflammatory cytokines (Interleukin-6 (IL-6), tumor necrosis factor (TNF-alpha), nuclear factor-kappaB p65 (NF-kappaB) and enhanced superoxide dismutase (SOD) activity. Arctiin had an ameliorating effect on all parameters including histological damage. The latter could virtually be reversed by arctiin. The beneficial effect of arctiin on glomerulonephritis was considered to be due to suppression of NF-kappaB activation and nuclear translocation and the decreases in the levels of these pro-inflammatory cytokines, while SOD is involved in the inhibitory pathway of NF-kappaB activation (Wu et al., 2009).

Clinical research

Currently, no clinical studies with Arctium are available.

Critical evaluation

Promising results from animal experiments, yet too preliminary to apply them in humans.

CONCLUSIONS AND RECOMMENDATIONS FOR RESEARCH

The investigational status of herbal products for renal diseases differs considerably, but is generally not advanced enough to advocate their application in patients with renal disease. This reservation extends also to those herbs that are currently used in China. The authors of this review regret this overall negative conclusion as several plant constituents have promising pharmacological profiles and could possibly evolve as innovative treatments of renal diseases, which are eagerly awaited by patients and nephrologists. This final paragraph deals with two general aspects of herbal research in renal diseases as the specific scientific evidence has already been discussed for each herb separately.

The randomized controlled trial (RCT) is the golden standard for the evaluation of any therapeutic principle. None of the herbal products discussed had been studied by RCT for its efficacy in renal disease, and it is unlikely that this will happen in the near future. Thus, as there is a demand for innovative treatments of renal diseases, even the second best category of clinical research cannot be discarded but should be scored for information. This is emphasised here as herbal treatment of renal diseases is a reality in China that should be taken advantage of to expand the scientific knowledge about these herbs.

The herbs in question have a long history of empiric symptom-oriented use in China, complemented in recent years by observations and studies in specific nosological entities, e.g. transplant rejections and glomerulonephritis. Observational studies with encouraging clinical responses towards herbs, e.g. remissions of nephrotic syndrome had been published, but inadequate design and documentation had cast doubt upon the validity of these findings. Improvement of the documentation of local herbal use for renal disease by meeting international scientific standards is a primary and attainable goal to reach. This encompasses a full and valid characterization of the administered herbal extract, a renal diagnosis based on internationally accepted histological classification, sufficient follow-up times of observation, assessment of efficacy by meaningful parameters as well as thorough monitoring of safety issues. The most valuable information will be obtained from cohorts of homogeneous histological entity rather than from case-mixes. Studies on dose-response-relationships of the herbal extracts should be encouraged to understand the potential therapeutic range. Studies fulfilling these basic quality criteria will be acknowledged by scientists worldwide and could be a starting point for the evolution of innovative treatments of renal diseases.

Toxicity aspects of the herbs need to be specifically addressed. There are obvious toxicity indices for all

plants included in this review. Herbs that modify the course of glomerulonephritis by affecting autoimmunity will compromise the immune competence of patients to fight infection and cancer. Overlooked toxicity even in herbs with a long traditional use is not exceptional as recent studies show (Wojcikowski et al., 2009).

Which is a promising screening strategy to finding herbs for renal diseases by ethnobotanic research and from herbal literature? Treatments of glomerulonephritides are more likely discovered among traditional herbal cures of rheumatism, arthritis and edema rather than among those for pelvic pain, dysuria or hematuria. The latter symptoms are closer linked to urinary infections and nephrolithiasis. Thus, asking for herbal cures of "painful urine discharge, burning sensation, inflammation and bleeding in the kidney, irritable condition of bladder, haemorrhage of kidney and removal of blocked urine and kidney stone" is neither sensitive nor specific to detect herbs against glomerulonephritis (Ballabh et al., 2008; Adams et al., 2009).

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