Medicinal plants with kidney-protecting effect in diabetic nephropathy

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Diabetic nephropathy (DN) is a progressive kidney disease, which may often lead to end-stage renal diseases. DN is becoming more prevalent due to the increase in the incidences of diabetes. Controlling blood glucose levels can inhibit DN, but a significant fraction of the diabetic population can develop DN despite glycemic control. Therefore, identification of new drug molecules that can prevent or ameliorate DN by directly acting on the kidney would be a breakthrough in its management. Medicinal plants offer a vast repository of potential therapeutic agents for several diseases, including diabetes and its complications. A good number of plants have been studied for their kidney-protecting effects on DN. This article summarizes the active compounds and mechanisms by which these plants protect the kidney in diabetic conditions. The majority of the studies are found for animal models. Clinical trials are available only for a few plants, which are also included in this article.

Keywords: Diabetic nephropathy, kidney, medicinal plants, renal diseases, therapeutic agents.

DIABETIC nephropathy, a progressive kidney disease, is a major cause of kidney failure. DN is characterized by hypertrophy of glomeruli, diffuse or nodular mesangial expansion, thickening of the basement membrane, and tubular and glomerular hyperfiltration[1,2]. DN is a global epidemic, and approximately 30% and 40% of individuals with type-1 (TTDM) and type-2 diabetes mellitus (T2DM) respectively, develop the disease[3]. The prevalence of DN in India is 34.4% (ref. 3). Increased albuminuria, hyperglycaemia, increasing oxidative stress, hypertension, dyslipidemia and obesity increase the risk of DN[3]. Lifestyle factors like smoking, an unhealthy diet with high fat and a sedentary lifestyle can also enhance the risk of this disease[4]. Age and prolonged duration of diabetes have been found to accelerate the progression of DN[5]. Genetic and epigenetic factors can also contribute to the development of DN[6] which may vary with ethnicity[5]. Management of DN includes intensive control of blood glucose, blood pressure and lipid. In addition to blood glucose-lowering drugs like metformin, the introduction of sodium-glucose cotransporter-2 (SGLT2) inhibitors that lower oxidative stress, inflammation and fibrosis has opened a new era in the treatment of DN[7]. Other new effective drugs include angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs)[8] and glucagon-like peptide-1 receptor agonists (GLP-1RA)[9]. A comprehensive approach to management, including lifestyle interventions by changing food habits with a balanced diet rich in grains, legumes, plant-based proteins and unsaturated fats, cessation of smoking, moderate physical exercise, etc. can bring down the incidence.

Despite this advanced approach to DN prevention and management, an estimated 10% of deaths in T2DM is attributed to kidney failure[4]. Further, prolonged use of synthetic drugs can cause adverse effects in the users, and may be too costly to afford for patients with low annual income. Therefore, there is growing interest among the users for herbal medicines that might have fewer toxic effects due to their natural origin and are being cheaper. Thus it is worth exploring the literature on medicinal plants and their molecules with kidney-protecting effects.

Medicinal plants constitute a rich source of therapeutic agents for several diseases. Plant-based traditional medicines serve approximately 65% of the world's population for primary health care[10]. An extraordinary number of plant species, including more than 400 species, are reported to have anti-diabetic activity[11]. This article includes research findings on medicinal plants with kidney-protective effects in diabetes, their active biomolecules and their mechanism of protection.

Methodology

There is vast literature on medicinal plant's potential role in diabetic kidney protection. The aim of this study was not to compile all these plants but to focus on those which have been more commonly studied, i.e. for which more than one independent study was found in the literature. The selected plants are distributed throughout different continents and not restricted to a specific region. Several studies tested the antioxidant and anti-inflammatory property of plant extracts with potential reno-protective effect, but did not include any histopathological observations. In this study, we have included articles that showed

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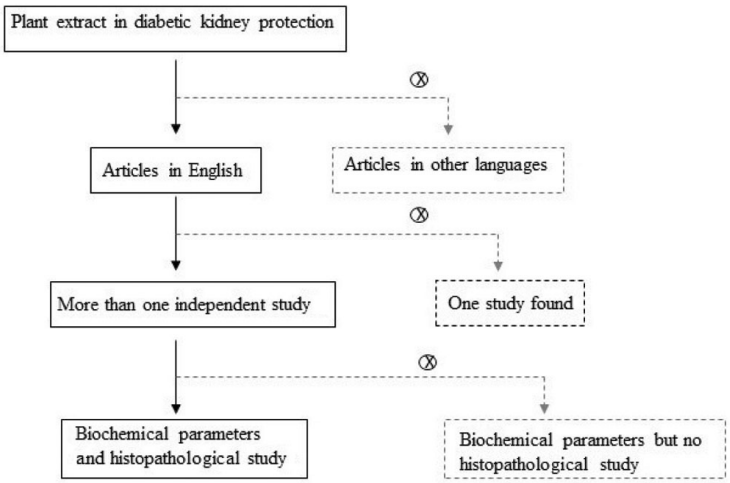

Figure 1. Flow chart showing the method of literature search.

histopathological changes in the kidney along with biochemical parameters. Most of these studies were carried out in model organisms; few were human clinical trials.

The literature was searched using the keywords 'plant extract in diabetic kidney protection'. Original articles written in English were included (Figure 1).

Plants with kidney-protecting effects

It is well established in the literature that inflammatory processes and oxidative stress play an important role in the progression of DN. Table 1 summarizes the effects of different plant extracts on renal oxidative stress markers, inflammatory markers and kidney morphology changes in diabetic model organisms. This table does not include routine biochemical markers for liver, pancreatic and kidney function tests. Figure 2 depicts the potential mechanisms by which plants could protect the kidney in DN. Table 2 shows the active biomolecules of the plants.

Abroma augusta L.

A. augusta, an evergreen shrub, is found in the tropical regions of the world. Different parts of this plant are used in treating a wide range of diseases, including diabetes in folk medicine.

Khanra *et al.*[12] found that treatment with *A. augusta* leaf extract restored an almost normal structure of glomerulus and renal tubule in rats. Nuclear factor kappa B (NF-κB) is a ubiquitous transcription factor responsible for high inflammatory and immune response in T2DM and is induced in renal tissues in the presence of oxidative stress that is increased in hyperglycemic conditions. The extract supplementation significantly reduced the levels of proinflammatory cytokines, e.g. interleukins IL-6, IL-1β and tumour necrosis factor TNF-α in the renal tissues. These cytokines are usually upregulated under the influence of NF-κB and play an instrumental role in developing nephropathy.

Signalling protein kinase C (PKC) and its isoforms (α, β, δ and ε), when activated, cause alterations in several transcription proteins in DN, and treatment with *A. augusta* leaf extract reduced their expression in diabetic rats[9]. Mir *et al.*[13] observed amelioration of degenerative changes in kidney cortex, subcapsular region, collecting tubules and tubular epithelium when treated with *A. augusta* extract.

Taraxerol, a stimulator of glycogen synthesis and glucose-transport activator, was identified in the phytochemical analysis of *A. augusta* leaf extract[12]. It can reverse insulin resistance and inflammation. The plant also contains antioxidants like flavonoids and phenolics that can reduce the risk of kidney damage[12]. Khanra *et al.*[14] demonstrated that taraxerol treatment regulated blood glucose levels and reduced proinflammatory cytokines.

Allium sativum L.

Aqueous extract of garlic *A. sativum*, a culinary herb with medicinal properties, has been shown to protect kidney tissues by its anti-inflammatory and antioxidant properties[15]. Nanoemulsified garlic was an oil blend (30%–50% diallyl disulphide, 10%–13% diallyl trisulphide and 5%–13% allyl sulphide) was found to inhibit progression to DN in T2DM, significantly reduced podocyte injury marker podocalyxin and two recently found markers for kidney injury, CD 36 and neutrophil gelatinase-associated lipocalin (NGAL)[16]. Podocytes are an integral part of the glomerular filtration barrier and are often damaged in diabetes leading to DN.

The major biologically active component of garlic is diallyl thiosulfinate or allicin, which may protect from DN by modulating the transforming growth factor-β1/extracellular signal-regulated kinase (TGF-β1/ERK)

Table 1. Medicinal plants with kidney-protective effects

Plant species	Plant part	Month of collection	Effective extract and dose (mg or ml/kg body wt)	Treatment and duration	Model organism (diabetes-inducing agent)	Mechanisms of kidney protection	Reference
Abroma augusta	Leaf	May	Methanolic extract (100 and 200 mg/kg)	Daily fed for 28 days	Wister rats (STZ-NAD)	Glomerular and renal tubule structure restored; resumed expression of NF-κB; PKC isoforms reduced; intrinsic apoptotic pathway attenuated; reduced oxidative stress and inflammatory markers.	12
	Leaf	–	Aqueous extract (2 ml/kg)	Twice daily fed for 21 days	New Zealand white rabbits (Allx)	Amelioration of histomorphological changes.	13
Allium sativum L.	Bulb clove	Purchased	Aqueaous extract (2 g/kg)	Fed for 33 days	Wistar rats (STZ)	General kidney structure was improved; kidney TNFα, NO decreased significantly; total oxidative stress decreased.	15
	Garlic oil blend	Purchased	Nanoemulsified in Tween 80 at 20 mg/kg	Fed daily for 5 months	Wistar rats (STZ)	Recovery from glomerular and tubular injury; reduction of renal NGAL, CD36, podocalyxin.	16
	Allicin injection	Purchased	15, 30 and 45 mg/kg	Fed daily for 12 weeks	Sprague–Dawley rats (STZ)	Glomerular hypertrophy, thickening of the GBM, increased collagen I expression and ECM accumulation reduced. Inhibited renal collagen accumulation, expression of collagen I, TGF-β1 and p-ERK1/2.	17
Asparagus racemosus	Root	Root purchased	Ethanolic extract (100 and 250 mg/kg)	Fed daily for 4 weeks	Wistar rats (STZ)	Significantly attenuated GBM thickening and mesangial proliferation.	21
	Not mentioned	Powder purchased	Powder (500 mg/kg)	Fed daily for 30 days	Albino rats (Allx)	Amelioration of histomorphological and functional changes	22
	Root	May	Ethanolic extract (400 mg/kg)	Fed daily for 90 days	Wistar rats (STZ-NAD)	Regeneration of tubular epithelium and reduced intertubularhaemorrhage.	23
Azadirachata indica	Leaves	June and July	Ethanolic extract 500 mg/kg	Fed daily for 50 days	Wistar rats (STZ)	No glomerular lesions.	25
Curcuma longa	Curcumin	Purchased	150 mg/kg	Fed daily for 12 weeks	Sprague–Dawley rats (STZ)	Renal hypertrophy ameliorated; inhibited FN and TGF-β1, AP-1, SphK1 in GMC.	29
	Curcumin	–	100 mg/kg	Fed daily for 20 weeks	Long–Evans rat (fatty)	Reduced glomerular hypertrophy, GBM thickness, fading of the podocyte foot processes; number of open slit pore increased.	30
	Curcumin	Purchased	200 mg/kg	Fed daily for 16 weeks	C57BL/KsJ mice (db/db)	Significantly reduced glomerular matrix expansion, collagen IV and FN; inhibited IL-1β production, cleaved caspase-1 and NLRP3 inflammasome activity.	31
	Curcumin	Purchased	100 mg/kg	Fed daily for 8 weeks	Sprague–Dawley rats (STZ)	Segmental sclerosis in glomeruli reduced; macrophage infiltration markedly reduced; reduced NF-κB, TNF-α and IL-1β.	32

(*Contd*)

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Plant species	Plant part	Month of collection	Effective extract and dose (mg or ml/kg body wt)	Treatment and duration	Model organism (diabetes-inducing agent)	Mechanisms of kidney protection	Reference
	Curcumin	Purchased	100 mg/kg	Fed daily for 8 weeks	Sprague–Dawley rats (STZ)	Prevented decrease in antioxidant enzyme GPx activity; PKC-α and-β1 expression reduced, inhibited phosphorylation of ERK1/2; attenuated expression of fibrotic factors like CTGF, osteopontin, p300, FN and type IV collagen; ameliorated hyperglycemic pro-angiogenic factors VEGF and VEGR II (flk-1); improved renal changes like hyaline casts, glomerular thickening and moderate interstitial fibrosis and arteriolopathy.	33
	Curcumin	Purchased	100 µl/100 g	Fed daily for 12 weeks	Wistar rats, STZ; mouse podocyte cell line	Renal fibrosis improved; glomerulosclerosis dramatically decreased; FN and collagen I reduced; MCP-1 and renal macrophage infiltration reduced; TLR4 activation inhibited by suppressing phosphorylation of cav-1; downregulation of inflammatory genes in podocytes (*in vitro*).	35
	Curcumin	Purchased	100 µl/100 g	Fed daily for 12 weeks	Wistar rats (STZ) mouse podocyte cell line	Prevented EMT suppressing cav-1 phosphorylation.	36
	Curcumin	Purchased	300 mg/kg	Fed daily for 8 weeks	Sprague–Dawley rats (STZ) conditionally immortalized mouse podocytes	Reduced glomerular atrophy, tubular dilatation and inflammatory cell infiltration; upregulated E-cadherin, downregulated vimentin and TWIST1 proteins (EMT factors); downregulated p62, p-mTOR, p-Akt and P13K proteins of autophagy.	37
	Curcumin	Purchased	200 mg/kg	Fed daily for 2 weeks	Wistar rats (STZ)	Integrin α3 increased, and miR-124 decreased.	38
Momordica charantia	Fruit	Purchased	Aqueous extract (50 mg/kg)	Fed daily for 10 days	Sprague–Dawley rats (STZ)	Resumed normal glomerular structure, reduced tissue necrosis.	40
	Fruit	Purchased	Crude polysaccharide fraction. 150 and 300 mg/kg	Fed daily for 8 weeks	Albino rats (STZ)	Dose-dependent increase in SOD activity and regulation of lipid peroxidation in kidney; increased dose-dependent expression of kidney HO-1 and Nrf2; Epithelial cell integrity improved; reduced focal fibrosis.	43
	Fruit	Purchased	Ethanolic extract (200 and 400 mg/kg)	Fed 6 days per week for 10 weeks	Sprague–Dawley rats (STZ)	Retained normal kidney structure without glomerular degeneration and inflammatory cellular infiltration.	44
Moringa oleifera	Green leaves	October	Methanolic extract (250 mg/kg) reconstructed by water	Fed daily for 6 weeks	Wistar rats (STZ)	TNF-α, IL-6 and oxidative stress reduced; significant reduction in DN.	49

(*Contd*)

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Plant species	Plant part	Month of collection	Effective extract and dose (mg or ml/kg body wt)	Treatment and duration	Model organism (diabetes-inducing agent)	Mechanisms of kidney protection	Reference
	Seed powder	–	Seed powder (50 and 100 mg/kg)	Fed daily for 4 weeks	Albino rats (STZ)	Reduced IL-6, lipid peroxidation; increased kidney antioxidant enzymes; resumed normal kidney histology.	50
Punica granatum	Leaves	January	Methanolic extract (100, 200 and 400 mg/kg)	Fed daily for 8 weeks	Sprague–Dawley rats (STZ)	Increased renal SOD, GSH and CAT; reduced vacuolar degeneration of tubules, reduced basement membrane thickening at 400 mg/kg.	54
	Seed oil	Purchased	Seed oil (0.4 and 0.8 ml/kg)	Fed daily for 3/4 weeks	Wistar rats (STZ)	Reduced irregular, widened glomerular capillaries, inflammatory cell infiltration.	55
Trigonella foenum-graecum	Seed	–	Reconstructed seed phytochemicals (50, 100, 200 mg/kg)	Fed daily for 30 days	Wistar rats (Allx)	Potent renoprotective in early nephropathy and moderately protective in late nephropathy.	56
	Seed	–	Fenugreek extract (100 mg/kg)	Four weeks orally every other day or daily or IP	Sprague–Dawley rats (STZ)	Did not protect kidney tissues.	57
	Oil	–	Oil at a dose of 10% in food	Fed daily for 4 weeks	Wistar rats (Alloxan)	Renal SOD, CAT, GPX, and GSH increased; tubular epithelial damage and fatty infiltration corrected.	58
	Seed	Purchased	Aqueous seed extract (9 g/kg)	Treated daily for 12 weeks	Sprague–Dawley rats (STZ)	Glomerular SOD, CAT, and GSH-PX activated; ECM accumulation in glomeruli inhibited; TGF-β1 and CTGF inhibited in glomeruli; prevented segmental thickening of GBM, widely fused foot processes of podocytes, and excessively deposited mesangial matrix; glomerular hypertrophy mitigated.	59
	Seed	Purchased	10% Fenugreek seed powder and/or 3% onion powder	Fed daily for 6 weeks	Wistar rats (STZ)	Renin–angiotensin system blocked; nearly normalized podocyte damage; shrunken glomeruli with mesangial matrix expansion.	60
	Seed	–	5% in powdered rat food	Fed daily for 12 weeks	Albino rates (Allx)	Antioxidant enzymes increased; IL-6 and inflammation attenuated; mesangial expansion reduced.	61
	Seed	Purchased	10% Aqueous solution	Fed daily for 8 weeks	Sprague–Dawley rats	Uneven thickening of glomerular base membrane ameliorated.	62
Vitis spp.	Whole grape powder	Acquired	5% (w/w) diet	Fed daily for 6 months	Obese ZSF1 rats; heat-sensitive mouse podocyte	Partial prevention of renal pathology, including lower glomerular atrophy, reduced mesangial expansion, fewer protein cast formation and less severe tubular dilation and atrophy; protected podocytes from H_2O_2-induced apoptosis.	64

(*Contd*)

Table 1. (*Contd*)

Plant species	Plant part	Month of collection	Effective extract and dose (mg or ml/kg body wt)	Treatment and duration	Model organism (diabetes-inducing agent)	Mechanisms of kidney protection	Reference
	Grape seed proantho-cyanidin extract	Purchased	125/250/500 mg/kg	Fed daily for 16 weeks	Sprague–Dawley rats (STZ)	MMP-9 upregulated, and TIMP-1; renal SOD, CAT increased; downregulated inflammatory cytokines MCP-1, ICAM-1, TNF-α.	65
	Procyanidin B2		30 mg/kg	Fed daily for 10 weeks	C57BL/KsJ mice (db/db)	Inhibited MFG-E8, along with ERK 1/2 Akt and GSK-3β signalling pathways.	66
Zingiber officinale	Rhizome	Purchased	Ethanolic extract (400 or 800 mg/kg)	Fed daily for 6 weeks	Wistar rats (STZ)	Reduced glomerular necrosis, interstitial hemorrhage, fibrotic and degenerative changes, inflammatory cell infiltration, endotheliosis and perivascular lymphocytic aggregates; renal GSH and CAT enzymes increased; decreased TNF-α, IL-1β and IL-6, cytochrome *c*, caspase-3 and apoptosis.	67
	Zingerone	Purchased	50 mg/kg	Injected daily for 10 weeks	C57BL/KsJ mice (db/db)	Atrophy and fragmentation of glomeruli, epithelial desquamation, degeneration, and necrosis of renal tubules ameliorated; reduced TNFα and IL-6; renal GSH increased; NOX4 decreased.	68

Allx, Aloxan; Cav-1, Caveolin-1; ECM, Extra cellular matrix; EMT, Epithelial–mesenchymal transition; FN, Fibronectin; GBM, Glomerular basement membrane; GMC, Glomerular mesangial cells; NAD, Nicotinamide; NGAL, Neutrophil gelatinase-associated lipocalin; NLRP 3, NOD-like receptor 3; NO, Nitric oxide; STZ, Streptozotocin.

signalling pathway[17]. ERK, a downstream protein of TGF-β1 plays an important role in epithelial–mesenchymal transition (EMT) that leads to renal fibrosis[17]. Hyperglycemia has been shown to induce EMT in renal proximal tubular cells[17]. Allicin was shown to reduce proinflammatory cytokines IL-β, IL-6, NF$\kappa\beta$ and TGF-β1 and increase inhibitor of NF$\kappa\beta$ (I$\kappa\beta$)[18].

Asparagus racemosus Willd.

Asparagus (Shatavari, Satamuli) is known as the 'queen of herbs' in Ayurveda. Among the several species found, *A. racemosus* is most commonly used as indigenous medicine in India[19]. *Asparagus* root extract is used to treat non-insulin-dependent diabetes mellitus (NIDDM) and its complications like retinopathy and microalbuminuria[20]. Treatment with ethanolic root extract effectively prevented glomerular basement membrane (GBM) thickening and mesangial cell proliferation in rats[21]. Wesam *et al.*[22] found that treatment with *A. racemosus* powder restored the structure and function of the kidney damage in diabetic rats. Histopathological observations in T2DM rats revealed that the extract could lead to regeneration of tubular epithelium and reduced intertubular haemorrhage[23].

The major constituents of *A. racemosus* are steroidal saponins. The other primary constituent, asparagine, is a strong diuretic[24]. Saponins can prevent the breaking of disaccharides into monosaccharides, increase glycogen storage and lower hepatic gluconeogenesis.

Azadirachta indica A. Juss.

Almost every part of the neem tree, *Azadirachta indica* (Meliaceae), has been is known for its therapeutic values since ancient times. It is indigenous to South Asia and most parts of the Indian subcontinent. Diabetic rats treated with ethanolic leaf extract of *A. indica* did not develop features of DN like nodular glomerulosclerosis and proximal tubule cell vacuolation, also known as the Armanni–Ebstein phenomenon[25]. The treatment also retained normal kidney function. Chloroform extract of *A. indica* was found to inhibit the formation of advanced glycation end-products (AGEs) that may lead to complications in diabetes, including nephropathy[26].

Six compounds, including quercetin, myricetin, kaempferol, rutin and their glycosides, were found to contribute to the hypoglycemic effect of *A. indica*[27].

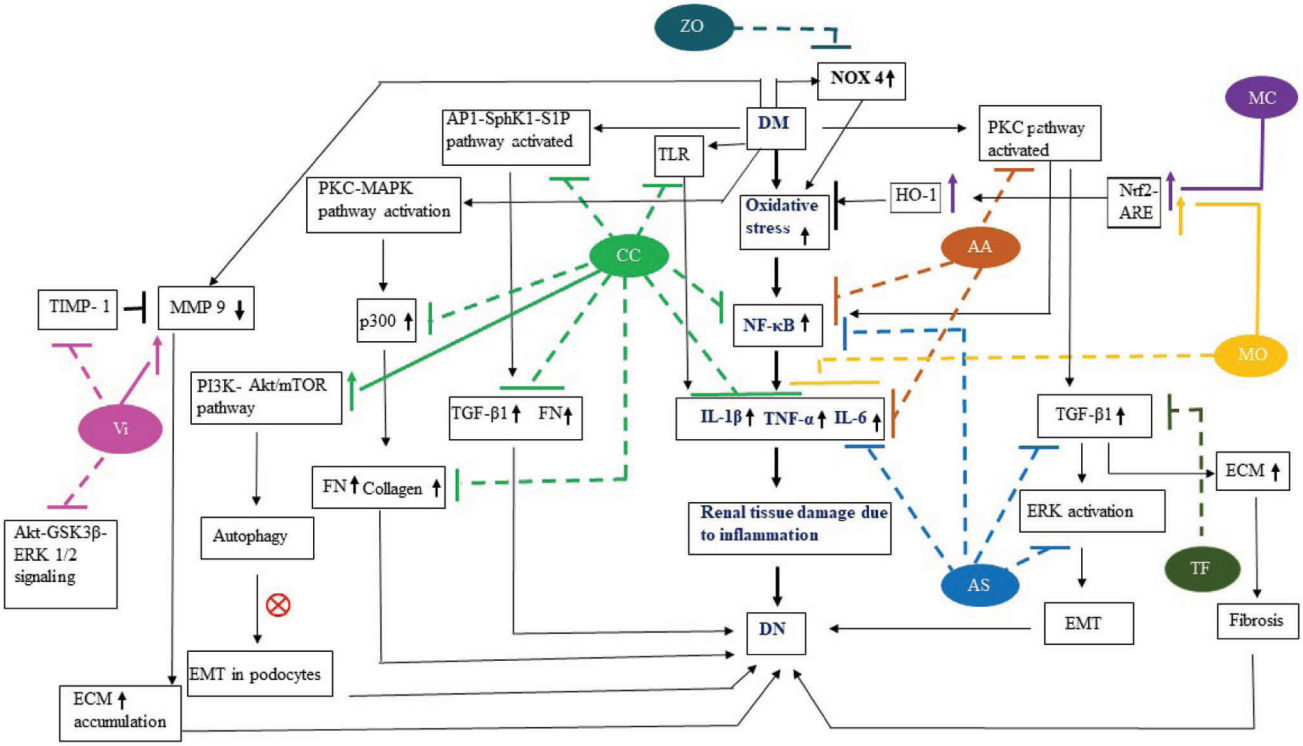

Figure 2. Effect of medicinal plant extracts on major signalling pathways involved in the development of diabetic nephropathy. AA, *Abroma augusta*; AS, *Allium sativum*; CC, Curcumin; DM, Diabetes mellitus; DN: Diabetic nephropathy; ECM, Extra cellular matrix; EMT, Epithelial-mesenchymal transition; FN, Fibronectin; HO-1, Heme-oxygenase 1; MC, *Momordica charantia*; MO, *Moringa oleifera*; SphK1-S1P, Sphingosine kinase 1-sphingosine 1-phosphate; TF, *Trigonelafoenum-graecum*; Vi, *Vitis* spp.; ZO, *Zingiber officinale*. Solid line from plant extract shows activation/upregulation.

Table 2. Plant active biomolecules with putative kidney-protecting effects

Plant	Active compounds
A. augusta	Taraxerol, flavonoids and phenolic components
A. sativum	Diallyl thiosulphnate or allicin
A. racemosus	Saponins, asparagine
C. longa	Curcumin
M. charantia	Saponin
M. oleifera	Quercetin, *Moringa* isothiocyanate
T. foenum-graecum	4-HI trigonelline
Vitis spp	Proanthocyanidin

Curcuma longa L.

The golden spice turmeric, *C. longa* has been known for its medicinal value since ancient times. Curcumin, a major component of the turmeric rhizome extract, is a highly pleiotropic molecule known for its antioxidant, anti-inflammatory and hypoglycemic activities[28].

Huang *et al.*[29] demonstrated that curcumin ameliorated DN by inhibiting the sphingosine kinase 1-sphingosine 1-phosphate (SphK1-S1P) signalling pathway, which has the potential to contribute to the progression of DN. As an intracellular second messenger, S1P activates TGF-β leading to renal fibrosis. Curcumin significantly downregulated SphK1 and S1P in the kidney of diabetic rats and also in glomerular mesangial cells exposed to high glucose concentration[29]. Further, it was demonstrated that activator protein-1 (AP-1), which mediates the expression of SphK1 was inhibited by curcumin[29]. Curcumin was also able to reduce degeneration of the podocyte foot processes. It increased the number of open-slit pores in diabetic rats[30]. Lu *et al.*[31] showed that curcumin reduced DN by suppressing NOD-like receptor 3 (NLRP3) inflammasome signalling in mice as well as in HK-2 cell lines. The NLRP3, when activated, leads to the maturation of proinflammatory cytokines such as IL-1β and may contribute to the development of DN[31].

Curcumin was shown to reduce hyperglycemia-induced macrophage infiltration by inhibiting NF-κB, TNF-α and IL-1β in the kidney of diabetic rats and inhibited the development of DN[32]. Hyperglycemia may induce microtubule-associated protein kinase (MAPK) activation resulting in increased production of cytokines, growth factors and a transcriptional co-activator p300. Also, p300 increases the expression of extracellular matrix (ECM) proteins, e.g. fibronectin and collagen. Soetikno *et al.*[33] found that curcumin reduced the expression of these signalling factors and p300, thus resulting in reduced production of ECM proteins. They also suggested that curcumin has an anti-fibrotic effect due to its strong antioxidant properties.

Toll like receptors (TLR), a component of the innate immune system, are known to induce inflammation and promote disease progression in high glucose environment[34]. Molecular silencing of TLR4 significantly attenuated high sugar-induced upregulation of IL-6 and TNF-α in podocytes[35]. Podocytes can undergo EMT following a chronic injury that may result in a defective glomerular filtration barrier and develop DN[36]. Curcumin was shown to prevent EMT in podocytes. It also increased P-cadherin and synaptopodin of slit diaphragm cell adhesion complexes[36]. PI3K-Akt/mTOR signalling pathway plays a crucial role in the regulation of autophagy in podocytes. It was shown that curcumin could alleviate DN by inhibiting EMT in podocytes by inducing autophagy via the PI3K/Akt/mTOR pathway *in vivo* and *in vitro*[37]. Curcumin also prevented podocyte adhesion damage by inhibiting microRNA miR-124 in hyperglycemic condition[38]. Curcumin-free spent turmeric was also found effective in the protection of diabetic kidney[39].

Momordica charantia L.

M. charantia or bitter gourd is a commonly consumed vegetable in the Indian subcontinent which is known for its antidiabetic properties[40]. Heme-oxygenase 1 (HO-1) enzyme that catabolizes heme also possesses antioxidant and cell protective activities[41,42]. It is regulated by cytoprotective Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) transcription factor[41]. Crude polysaccharide fraction of *M. charantia* fruit increased expression of both HO-1 and Nrf2 proteins in a dose-dependent manner in diabetic rats[43]. Offor *et al.*[44] found that adjuvant therapy of *M. charantia* and antiretroviral drug triplavar protected kidney architecture effectively in diabetic rats. Heparan sulphate (HS) is usually reduced in diabetic conditions and contributes to abnormal permeability. *M. charantia* powder was shown to protect against HS-related kidney injury in diabetic rats[45]. However, Mardani *et al.*[46] showed that long-term exposure to *M. charantia* extract in mice might have nephrotoxic effects.

The main active ingredient of *M. charantia*, which has an anti-diabetic effect, is saponin[47]. It may have a renoprotective effect through inhibition of the intrarenal renin-angiotensin-aldosterone system (RAAS)[48].

Moringa oleifera Lam.

M. oleifera (drumstick) is found in many tropical and subtropical regions around the world. Leaves, fruits, flowers and roots of this plant are used as food and in traditional medicine for various diseases, including diabetes.

Free radicals cause lipid peroxidation that may result in the disorientation of the cell membrane. Omodanisi *et al.*[49] found decreased lipid peroxidation, increased activities of antioxidant enzymes and reduced inflammation in diabetic rats treated with *M. oleifera* extract. Severe renal damage with interstitial nephritis at the kidney cortex and glomerular haemorrhage of diabetic rats were ameliorated by treatment with *Moringa* extract. Al-Malki and Rabey[50] tested the ameliorative effect of *Moringa* seed powder on DN rats with T1DM. The treatment significantly reduced lipid peroxidation and increased catalase, SOD and GSH antioxidant enzyme activity in serum as well as kidney tissue homogenate. It also reduced IL-6 in both serum and kidney homogenate.

High levels of total polyphenols, flavonols and flavonoids were found in *M. oleifera* methanolic extract which may reduce oxidative stress and cell damage[49]. Quercetin-3-glycoside, rutin, kaempferol and glycosides are potential polyphenols of *M. oleifera* leaves those may have potential to reduce blood glucose[51]. Quercetin was found to significantly attenuate renal dysfunction and oxidative stress in diabetic rats[52]. In a recent study, it was shown that *Moringa* isothiocyanate (MIC-1), the main active isothiocyanate of *M. oleifera*, strongly activated the Nrf2-ARE signalling pathway, which in turn suppressed inflammation, reduced oxidative stress and possibly transforming growth factor TGF-β1 signalling (overexpressed in the later stage of DN) in renal cells[53].

Punica granatum L.

Pomegranate *P. granatum*, a fruit native to the Middle East, has antioxidant and anti-inflammatory properties. Its leaf extract and seed oil have been shown to protect kidney architecture in diabetic rats[54,55]. Its polyphenolic compounds, including tannins and flavonoids, have antidiabetic properties, which may be responsible for their kidney protective effects[54].

Trigonella foenum-graecum L.

T. foenum-graecum dietary fenugreek seeds are a common spice rich in dietary fibre. Arora *et al.*[56] found that fenugreek seed phytochemical preparation was effectively renoprotective in early nephropathy and mildly protective in late nephropathy. The preparation partially prevented glomerular cellularity and matrix formation in rats with DN. On the other hand, fenugreek treatment with higher doses and longer duration was recommended for optimum protection of the kidney and other tissues in rats[57]. Fenugreek oil was found to have protective as well as therapeutic effects on diabetic kidney damage[58].

Connective tissue growth factor (CTGF) carries signals from TGF-β1 to induce ECM accumulation and cause fibrosis under oxidative stress in hyperglycemia leading to DN[59]. Jin *et al.*[59]observed that upregulation of TGF-β1 and CTGF in diabetic rats was inhibited by fenugreek treatment. Significant reduction in ECM accumulation and pathological alteration was also observed. Funugreek restored to

some extent of the mRNA level of podocyte- specific proteins, e.g. nephrin, podocalyxin and podocin, which are reduced in DN[60]. Funugreek reduced kidney injury molecule Kim-1 expression, which is found in increased amounts in the urine in DN. It was shown to have antioxidative and anti-inflammatory activity that could attenuate DN in diabetic rats, suggesting its therapeutic potential against DN[61]. Xue *et al*.[62] demonstrated that aqueous seed extract of funegreek could protect the kidney from morphological and functional injuries in diabetic rats by increasing the activities of antioxidant enzymes and inhibiting the accumulation of oxidized DNA in the organ.

It is proposed that alkaloid 4-HI trigonelline may be responsible for the renoprotective effect of *T. foenum-graecum* seed[56]. Trigocoumarin and trimecoumarine have also been reported to show anti-hyperglycemic action[63]. Low molecular weight galactomannan is another major active ingredient[59].

Grape (Vitis spp.)

Grapes, one of the most popular fruits, contain more than 1600 phytonutrients, including flavonoids, anthocyanins, flavonols, resveratrol, etc.[64]. It was shown that the progression of kidney disease could be prevented in obese diabetic ZSF1 rats when fed with 5% (w/w) whole grape powder mixed diet[64].

Grape seed proanthocyanidin (GSP) is a natural polyphenol extracted from grape seeds and skin, which has potent antioxidant and anti-inflammatory properties[65]. Matrix metalloproteinase MMP-9 plays an important role in ECM turnover in the kidney. MMP-9 directly degrades ECM components and its downregulation has been shown to be associated with diabetes in rats. Bao *et al*.[65] found that with increasing concentration of proanthocyanidin MMP-9 was upregulated, whereas tissue inhibitor of metalloproteinase-1 (TIMP-1) was downregulated. Zhang *et al*.[66] identified milk fat globule protein E-8 (MFG-E8), which was overexpressed in the kidney of diabetic mice. MFG-E8 accelerated diabetic kidney injury and acted by the activation of the extracellular signalling-regulated kinase (ERK 1/2), Akt and glycogen-synthase kinase-3 beta (GSK-3β) signalling pathway. Procyanidin B2 of grape seed is a powerful polyphenol with several pharmacological effects, including anti-inflammatory properties. This acted by inhibiting MFG-E8, along with ERK 1/2, Akt and GSK-3β signalling pathways[66].

Zingiber officinale Roscoe

Z. officinale, commonly known as ginger, is a spice used worldwide in cooking and for its medicinal value. It was shown to have renoprotective effects by reducing oxidative stress, inflammation and apoptosis in diabetic rats[67]. Cui *et al*.[68] demonstrated the kidney-protective effect of zingerone, a stable active component of the ginger rhizome. They showed that zingerone acted through downregulation of NADPH oxidase NOX 4 in human proximal tubular cells (HK-2 cells), increasing oxidative stress under hypoglycemia and leading to the development of DN.

Zingerone (4-(4-hydroxy-3-methoxyphenyl) butan-2-one), an active compound of ginger, exhibits anti-inflammatory, anti-apoptotic and antioxidant properties[68,69].

Clinical trials

In contrast to the above-discussed experiments in model organisms, there are only a handful of clinical trials on the medicinal value of plants for DN. In a clinical trial in patients with overt T2DM, it was demonstrated that short-term (two months) oral supplementation with turmeric (daily three capsules, each containing 22.1 mg of curcumin) could attenuate proteinuria[70]. In another clinical trial, Vanaie *et al*.[71] demonstrated that the effect of curcumin might appear after two months of therapy. Serum levels of TGF-β1 and IL-8 decreased significantly. Despite its medicinal values, good safety profile and long history of safe use, there are limited clinical trials on curcumin due to its poor water solubility, short half-life and low oral bioavailability[72]. A meta-analysis of clinical trials for *Astragalus membranaceus*, a medicinal plant used to treat diabetes in Chinese medicine and East Asian countries, suggested that *Astragalus* may have an enormous kidney protective effect in DN. However, its bioactive components are not known[73].

Conclusion and future perspectives

Plant-based remedy for diabetes and its complications is an age-old practice, which is particularly common in rural areas as there are limited medical facilities. It is becoming increasingly popular among the urban population, especially considering that plant-based drugs have fewer side-effects than synthetic drugs. While the efficacy of the plant-based drugs has been proven, issues related to their safety are often less studied. The plants discussed in this study seem to hold promise for kidney protection in DN in animal models. However, they should be assessed for efficacy in humans, associated toxicity, contraindications, etc.

Although all plants with hypoglycemic property may not be necessarily kidney-protective[74], some of them with strong anti-oxidant property can be explored for kidney-protecting effect as high level of oxidative stress is responsible for various complications of diabetes, including DN. Further, plants with anti-nephrotoxic activities associated with disorders other than diabetes can be studied for DN. For example, *Oroxylum indicum*, a deciduous tree distributed in the Indian subcontinent, is medicinally important for its free-radical scavenging activities. Whole plant extract of *O. indicum* was shown to protect the kidney in rats with experimentally induced acute nephrotoxicity[75].

Its active biomolecules, baicalein 1 and its aglycon baicalein 2, are considered to be responsible for kidney protection[76].

We explored medicinal plants with potential kidney-protecting effects in hyperglycemic conditions. This study has certain limitations. During the literature search, we found a few more plants having such effects, but they could not be accommodated in the study as only one published article was available for each of them. Further, some articles written in other languages and not in English could not be included. Whereas the plants included here have been extensively studied in different laboratories. We have also included the bioactive molecules of these plants and the underlying signalling pathways. This discussion compiles a baseline information for further studies. Multicentric studies involving biochemical, pharmaceutical and animal laboratories will enable us to establish their role and mechanisms of action. This will help identify and characterize new drug molecules of natural origin that can directly alleviate or prevent DN.

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ACKNOWLEDGEMENTS. This work was financially supported by the Himalayan Fellowship 2018–19, National Mission on Himalayan Studies, Grant Number GBPNI/NMHS-2018-19/HSF23-01/152.

Received 11 February 2022; revised accepted 7 May 2022

doi: 10.18520/cs/v123/i4/542-553