Medicinal plants with kidney protecting effect in diabetic nephropathy

Arundhati Bag\(^1\)*, Abhishek Byahut\(^1\), Bidita Khandelwal\(^2\)

\(^1\)Department of Medical Biotechnology, Sikkim Manipal University, 5\(^{th}\) Mile, Tadong, Gangtok, Sikkim 737102, India

\(^2\)Department of Medicine, Sikkim Manipal Institute of Medical Sciences, Sikkim Manipal University, 5\(^{th}\) Mile, Tadong, Gangtok, Sikkim 737102, India

*For correspondence. (e-mail: arundhatis5@rediffmail.com)
Diabetic nephropathy (DN) is a progressive kidney disease, which may often lead to end-stage renal diseases. DN is becoming more prevalent due to increase in the incidences of diabetes. Controlling blood glucose level can inhibit DN but a significant fraction of diabetic population can develop DN despite glycemic control. Therefore, identification of new drug molecule that can prevent or ameliorate DN by directly acting on kidney would be a major breakthrough in the management of DN. 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 in DN. This article summarizes the active compounds and mechanisms by which these plants protect kidney in diabetic condition. Majority of the studies are found for animal models. Clinical trials are available only for few plants which are also included in this article.

**Keywords:** Diabetes, diabetic nephropathy, kidney, medicinal plants
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 basement membrane, and tubular and glomerular hyperfiltration\(^1,2\). DN is a global epidemic, and approximately 30% and 40% of the individuals with type 1 and type 2 diabetes, respectively develop the disease\(^3\). India has 34.4% prevalence for DN\(^3\). Increased albuminuria, hyperglycemia increasing oxidative stress, hypertension, dyslipidemia, obesity increase the risk for DN\(^3\). Other than these, lifestyle factors like smoking, unhealthy diet with high fat, sedentary life-style 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\(^6\) that may vary with ethnicity\(^5\). Management of DN include intensive control of blood glucose, blood pressure and lipid. Other than blood glucose lowering drug like metformin, 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 newly entered effective drugs include angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs)\(^8\), Glucagon-like peptide-1 receptor agonists (GLP-1RA)\(^9\). A comprehensive approach of management including life-style interventions by changing food habit with balanced diet rich with grain, legumes, plant-based proteins and unsaturated fats, cessation of smoking, taking moderate physical exercise etc. can bring down the incidences.

Despite this advanced approach of DN prevention and management, an estimated 10% of death in T2DM is attributed to kidney failure\(^4\). Further prolonged use of the synthetic drugs can cause adverse effects in the users, and may be too costly to afford for the patients with low annual income. Therefore, there is growing interest among the users for herbal medicine which might have fewer toxic effects due to their natural origin and may be cheaper. Therefore, it is worth to explore the literature for the 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 population for primary health care\(^1\). And an extraordinary number of plant species including more than 400 species are reported to have anti-diabetic activity\(^1\). This review includes research findings on medicinal plants with kidney-protective effect in diabetes, their active biomolecules and mechanism of protection.

**Methodology**

There is a vast literature on medicinal plants having potential role in diabetic kidney protection. Aim of this review was not to compile all these plant names rather to focus on the plants which were more commonly studied, i.e., for which more than one independent study was found in literature. The selected plants are distributed throughout different continents and not restricted to a specific region. Many studies tested antioxidant property, anti-inflammatory property of plant extracts with potential reno-protective effect but did not include any histopathological observations. In our review we included those articles which showed histopathological changes in kidney along with biochemical parameters. Majority of these studies were carried out in model organisms; few were human clinical trials.

Literature was searched using key words “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 literature that inflammatory processes and oxidative stress play 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. Routine biochemical markers for liver, pancreatic and kidney function tests are not included in this table. Figure 2 depicts the potential mechanisms by which the plants could protect kidney in DN. Table 2 shows 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 to cure a wide range of diseases including diabetes in folk medicine.

Khanra *et al.*\(^{12}\) found that treatment with *A. augusta* leaf extract restored almost normal structure of glomerulus and renal tubule in rats. NF-κB is a ubiquitous transcription factor responsible for high inflammatory and immune response in T2DM and is induced in renal tissues in presence of oxidative stress that is increased in hyperglycemic condition. 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.

Signaling 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.

Presence of Taraxerol, a stimulator of glycogen synthesis and glucose-transport activator, was identified in phytochemical analysis of *A. augusta* leaf extract.\(^{12}\) It can reverse insulin resistance and inflammation. Other than taraxerol, the plant also contains flavonoids and phenolic components that are antioxidants and can reduce the risk of kidney damage.\(^{12}\) Khanra *et al.*\(^{14}\) demonstrated that taraxerol treatment regulated blood glucose level, reduced pro-inflammatory cytokines.

**Allium sativum** L.

Aqueous extract of garlic *A. sativum*, a culinary herb with medicinal properties, was shown to protect kidney tissues by its anti-inflammatory and antioxidant properties.\(^{15}\) Nanoemulsified garlic
oil blend (30–50% Diallyl disulfide, 10–13% Diallyl trisulfide and 5–13% Allyl Sulfide) was found to inhibit progression to DN in type 2 DM and significantly reduced podocyte injury marker podocalyxin and two recently found markers for kidney injury CD 36 and neutrophil gelatinase-associated lipocalin (NGAL). Podocytes are an integral part of glomerular filtration barrier and are often damaged in diabetes leading to DN.

The major biologically active component of garlic is diallyl thiosulfinate or allicin that may protect from DN by modulating the transforming growth factor-β1/extracellular signal-regulated kinase (TGF-β1/ERK) signaling pathway. ERK, a downstream protein of TGF-β1 plays an important role in epithelial-mesenchymal transition (EMT) that leads to renal fibrosis. Hyperglycemia has been shown to induce EMT in renal proximal tubular cells. Allicin was shown to reduce proinflammatory cytokines IL-β, IL-6, NFκβ, and TGF-β1 and increase inhibitor of NFκβ (Iκβ).

Asparagus racemosus Willd.

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

The major constituents of A. racemosus are steroidal saponins. Other primary constituent asparagine is a strong diuretic. Saponins can prevent breaking of disaccharides into monosaccharides, increased glycogen storage, lower hepatic gluconeogenesis.
Almost every part of a neem tree, *Azadirachta indica* (Meliaceae), is known for its therapeutic values since ancient times. It is indigenous to south Asia and in most parts of 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 Armanni-Ebstein phenomenon. The treatment also retained normal kidney function. Chloroform extract of *A. indica* was found to inhibit formation of advanced glycation end-products (AGEs) those may lead to complications in diabetes including nephropathy.

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

The golden spice turmeric *C. longa* is known for its medicinal value from a long past. Curcumin, a major component of turmeric rhizome extract, is a highly pleiotropic molecule and is known for its antioxidant, anti-inflammatory, hypoglycemic activities.

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

Curcumin was shown to reduce hyperglycemia-induced macrophage infiltration by inhibiting NF-κB, TNF-α and IL-1β in kidney of diabetic rat and inhibited development of DN\textsuperscript{32}. Hyperglycemia may induce microtubule associated protein kinase (MAPK) activation resulting in increased production of cytokines, growth factors and a transcriptional co-activator p300. The p300 increases expression of extracellular matrix (ECM) proteins, e.g., fibronectin and collagen. Soetikno \textit{et al.}\textsuperscript{33} found that curcumin reduced expression of these signaling factors and p300 thus resulting in reduced production of ECM proteins. They also suggested that curcumin plays its anti-fibrotic effect principally due to its strong anti-oxidant property.

Toll-like receptors (TLR), a component of innate immune system, is known to induce inflammation and promote disease progression in high glucose environment\textsuperscript{34}. Molecular silencing of TLR4 significantly attenuated high sugar-induced upregulation of IL-6 and TNF α in podocytes\textsuperscript{35}. Podocytes can undergo EMT following a chronic injury that may result in a defective glomerular filtration barrier and develop DN\textsuperscript{36}. Curcumin was shown to prevent EMT in podocytes. It also increased P-cadherin and synaptopodin, of slit diaphragm cell adhesion complexes\textsuperscript{36}. PI3K- Akt/mTOR signaling pathway plays crucial role in regulation of autophagy in podocytes. It was shown that curcumin could alleviate DN by inhibiting EMT in podocytes by inducing autophagy via PI3K/ Akt/mTOR pathway \textit{in vivo} and \textit{in vitro}\textsuperscript{37}. Curcumin also prevented podocyte adhesion damage by inhibiting microRNA miR-124 in hyperglycemic condition\textsuperscript{38}. Not only curcumin but curcumin-free spent turmeric was also found effective in protection of diabetic kidney\textsuperscript{39}.

\textit{Momordica charantia} L.

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

The main active ingredient of \textit{M. charantia} which has anti-diabetic effect is saponin\textsuperscript{47}. Saponin may have a renoprotective effect via the inhibition of the intrarenal RAAS\textsuperscript{48}.

\textit{Moringa oleifera} Lam.

\textit{M. oleifera} (drumstick), are 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 disorientation of cell membrane. Omodanisi \textit{et al.}\textsuperscript{49} found decreased lipid peroxidation, increased activities of antioxidant enzymes and reduced inflammation in diabetic rats treated with \textit{M. oleifera} extract. Severe renal damage with interstitial nephritis at the kidney cortex and glomerular haemorrhage of diabetic rats were ameliorated with the treatment of \textit{Moringa} extract. Al-Malki and Rabey\textsuperscript{50} tested ameliorative effect of \textit{Moringa} seed powder on DN rats with type I diabetes. 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 \textit{M. oleifera} methanolic extract\textsuperscript{49} that may reduce oxidative stress and cell damage. Quercetin-3-glycoside,
rutin, kaempferol and glycosides are potential polyphenols of *M. oleifera* leaves those may have potential to reduce blood glucose\(^5^1\). Quercetin was found to significantly attenuate renal dysfunction and oxidative stress in diabetic rats\(^5^2\). In a recent work, it was shown that Moringa isothiocyanate (MIC-1), the main active isothiocyanate of *M. oleifera*, strongly activated Nrf2-ARE signaling pathway, which in turn, suppressed inflammation, reduced oxidative stress and possibly transforming growth factor TGF-β1 signaling (overexpressed in later stage of DN) in renal cells\(^5^3\).

**Punica granatum** L.

Pomegranate *P. granatum*, a fruit native to Middle East, has antioxidant, anti-inflammatory property. Its leaf extract and seed oil were shown to protect kidney architecture in diabetic rats\(^5^4,5^5,5^6\). Its polyphenolic compounds including tannins and flavonoids have anti-diabetic property, which may be responsible for their kidney protective effects also\(^5^4\).

**Trigonella foenum-graecum** L.

*T. foenum-graecum* dietary fenugreek seeds are common spice and are rich in dietary fibre. Arora *et al.*\(^5^6\) 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 were recommended for the optimum protection of the kidneys and other tissues in rats\(^5^7\). Fenugreek oil was found to have protective as well as therapeutic effect from diabetic kidney damage\(^5^8\).

Connective tissue growth factor (CTGF) carries signal from TGF-β1 to induce ECM accumulation and cause fibrosis under oxidative stress in hyperglycemia leading to DN\(^5^9\). Jin *et al.*\(^5^9\) observed that up regulation of TGF-β1 and CTGF in diabetic rat was inhibited by fenugreek treatment. Significant reduction of ECM accumulation and pathological alteration was also
observed. Funegreek restored to some extent the mRNA level of podocyte-specific proteins, e.g., nephrin, podocalyxin, and podocin, which are reduced in DN\(^6\). Funegreek reduced kidney injury molecule Kim-1 expression which is found in increased amount in urine in DN. Funegreek was shown to have anti-oxidative, anti-inflammatory activity that could attenuate DN in diabetic rats suggesting\(^6\) its therapeutic potential against DN. Xue et al.\(^6\) also demonstrated that aqueous seed extract could protect kidneys from morphological and functional injuries in diabetic rats by increasing the activities of antioxidant enzymes and by inhibiting accumulation of oxidized DNA in the organ.

It is proposed that alkaloid 4-HI trigonelline may be responsible for renoprotective effect of \(T.\) foenum-graecum seed\(^5\). Other than trigonelline, trigocoumarin and trimecoumarine alkaloids have also been reported, which have antihyperglycem action\(^6\). Low molecular weight galactomannan is another major active ingredient\(^5\).

**Grape (Vitis spp.)**

Grapes, one of the most popularly taken fruits, contain more than 1600 phytonutrients including flavonoids, anthocyanins, flavonols, resveratrol etc.\(^6\) It was shown that progression of kidney disease was prevented in obese diabetic ZSF1 rats when fed with 5%, w/w whole grape powder mixed diet\(^6\). Grape seed proanthocyanidin (GSP) is a natural polyphenol extracted from grape seeds and skins and is a potent antioxidant, anti-inflammatory substance\(^5\). Matrix metalloproteinase MMP-9 plays important role in ECM turnover in kidneys. MMP-9 directly degrades ECM components and its downregulation has been shown to be associated with diabetes in rats. Bao et al.\(^5\) found that with increasing concentration of proanthocyanidin MMP-9 was upregulated whereas tissue inhibitor of metalloproteinase-1 (TIMP-1) was downregulated. In proteomic analysis Zhang et al.\(^6\) identified milk fat globule protein E-8 (MFG-E8), which was overexpressed in kidney of diabetic mice. MFG-E8 accelerated diabetic kidney injury and acted by activation of extracellular signal-
regulated kinase (ERK 1/2), Akt and glycogen- synthase kinase-3 beta (GSK-3β) signaling 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 signaling pathways. 

*Zingiber officinale* Roscoe

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

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

**Clinical trials**

In contrast to above discussed experiments in model organisms, there are only a handful of clinical trials on medicinal values of the plants for DN. In a clinical trial in patients with overt type 2 DN it was demonstrated that short term (2 months) oral supplementation with turmeric (daily 3 capsules each containing 22.1 mg of curcumin) could attenuate proteinuria. In another clinical trial Vanaie *et al.* demonstrated that the effect of curcumin may appear after 2 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. A meta- analysis on clinical trials for *Astragalus membranaceus*, a medicinal plant used to treat diabetes in Chinese medicine and
East Asian countries, suggested that *Astragalus* may have enormous kidney protective effect in DN. However, its bioactive components are not known.

Conclusion and future perspective

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. They are becoming increasingly popular in urban populations also, especially based on the belief that they would have fewer side-effects in comparison to the synthetic drugs. While efficacy of the plant-based drugs are proven several times, issues related to their safety are often less studied. The plants discussed in this article seem to be promising in 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, 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 also be studied for DN. For example, *Oroxylum indicum*, a deciduous tree distributed in Indian subcontinent, is a medicinally important tree for its free-radical scavenging activities. Whole plant extract of *O. indicum* was shown to protect kidney in rats with experimentally induced acute nephrotoxicity. Its active biomolecules baicalin 1 and its aglycon baicalein 2 are believed to be responsible for kidney protection.

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


Curcumin ameliorates macrophage infiltration by inhibiting NF-κB activation and proinflammatory cytokines in streptozotocin induced-diabetic nephropathy. *Nutr. Metab. (Lond)*, 2011, **8**(1), 35.


480  of saponin on a hypertension target organ in spontaneously hypertensive rats. *Exp. Ther.
482
483  49. Omodanisi, E. I., Aboua, Y. G. and Oguntibeju, O. O., Assessment of the anti-
484  hyperglycaemic, anti-inflammatory and antioxidant activities of the methanol extract of
485  *Moringa oleifera* in diabetes-induced nephrotoxic male Wistar Rats. *Molecules*, 2017,
486  22(4), 439.
487
489  oleifera* Lam. seeds on streptozotocin induced diabetes and diabetic nephropathy in male
491
495
496  52. Anjaneyulu, M. and Chopra, K., Quercetin, an anti-oxidant bioflavonoid, attenuates
498
500  isothiocyanate activates Nrf2: potential role in diabetic nephropathy. AAPS J.*, 2020, 21,
501  31.
502
504  nephropathy in streptozotocin-induced diabetic rats by *Punica granatum* Linn. leaves
506
507  55. Mollazadeh, H., Sadeghnia, H. R., Hoseini, A., Farzadnia, M. and Borouchaki, M. T.,
508  Effects of pomegranate seed oil on oxidative stress markers, serum biochemical
509  parameters and pathological findings in kidney and heart of streptozotocin-induced


63. Mowla, A., Alauddin., M, Rahman, M. A. and Ahmed, K., Antihyperglycemic effect of *Trigonella foenum-graecum* (fenugreek) seed extract in alloxan-induced diabetic rats and


ACKNOWLEDGEMENT. The work is financially supported by the Himalayan Fellowship 2018-19, National Mission on Himalayan Studies, Grant Number GBPNI/NMHS-2018-19/HSF23-01/152.
<table>
<thead>
<tr>
<th>Plant species</th>
<th>Plant part</th>
<th>Collection month</th>
<th>Effective extract and dose (mg or ml/kg body weight)</th>
<th>Treatment and duration</th>
<th>Model organism (diabetes inducing agent)</th>
<th>Mechanisms of kidney protection</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Abroma augusta</em></td>
<td>Leaf</td>
<td>May</td>
<td>Methanolic extract (100 and 200mg/kg)</td>
<td>Daily fed for 28 days</td>
<td>Wister rats (STZ-NAD)</td>
<td>Glomerular and renal tubule structure restored; resumed expression of NF-κB; PKC isoforms reduced; intrinsic apoptotic pathway attenuated; reduced oxidative stress and inflammatory markers</td>
<td>12</td>
</tr>
<tr>
<td><em>Allium sativum L.</em></td>
<td>Bulb clove</td>
<td>Purchased</td>
<td>Aqueous extract 2g/kg</td>
<td>Fed for 33 days</td>
<td>New Zealand white rabbits (Allx)</td>
<td>Amelioration of histomorphological changes General kidney structure was improved; Kidney TNFα, NO decreased significantly; total oxidative stress decreased</td>
<td>13</td>
</tr>
<tr>
<td>Garlic oil blend</td>
<td>Purchased</td>
<td>Nanoemulsified in Tween 80 at 20 mg/kg</td>
<td>Fed daily for 5 months</td>
<td>Wistar rats, STZ</td>
<td>Sprague–Dawley rats, STZ</td>
<td>Recovery from glomerular and tubular injury; reduction of renal NGAL, CD36, podocalyxin 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</td>
<td>16</td>
</tr>
<tr>
<td><em>Asparagus racemosus</em></td>
<td>Root</td>
<td>Root purchased</td>
<td>Ethanolic extract (100mg and 250mg/kg) Powder (500 mg/kg)</td>
<td>Daily fed for 4 weeks</td>
<td>Wistar rats (STZ)</td>
<td>Significantly attenuated GBM thickening and mesangial proliferation</td>
<td>17</td>
</tr>
<tr>
<td><em>Azadirachta indica</em></td>
<td>Leaves</td>
<td>June and July</td>
<td>Ethanolic extract (400mg/kg)</td>
<td>Fed for 90 days</td>
<td>Wistar rats (STZ-NAD)</td>
<td>Amelioration of histomorphological and functional changes Regeneration of tubular epithelium and reduced intertubular haemorrhage No glomerular lesions</td>
<td>20</td>
</tr>
<tr>
<td><em>Curcuma longa</em></td>
<td>Curcumin</td>
<td>Purchased</td>
<td>150mg/kg</td>
<td>Fed daily for 12 weeks</td>
<td>Sprague–Dawley rats, STZ</td>
<td>Renal hypertrophy ameliorated; inhibited FN and TGF-β1, AP-1, SphK1 in GMC Reduced glomerular hypertrophy, GBM thickness, fading of the podocyte foot processes;</td>
<td>21</td>
</tr>
<tr>
<td><em>Curcumin</em></td>
<td>-</td>
<td>100 mg/kg</td>
<td></td>
<td>Fed daily for 20 weeks</td>
<td>Long-Evans rat (fatty)</td>
<td></td>
<td>22</td>
</tr>
</tbody>
</table>

Reference numbers: 12, 13, 14, 15, 16, 17, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30.
Curcumin Purchased 200mg/kg Fed daily for 16 weeks C57BL/KsJ mice; (db/db) number of open slit pore increased Significantly reduced glomerular matrix expansion, collagen IV and FN; inhibited IL-1 \( \beta \) 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-\( \kappa \)B, TNF-\( \alpha \) and IL-1\( \beta \) 32

Curcumin Purchased 100 mg/kg Fed daily for 8 weeks Sprague–Dawley rats; STZ Prevented decrease in antioxidant enzyme GPx activity; PKC-\( \alpha \) and -\( \beta_1 \) 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 VEGFR II (flk-1); improved renal changes like hyaline casts, glomerular thickening and moderate interstitial fibrosis and arteriolopathy 33

Curcumin Purchased 100µl/100g 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 100µl/100g Fed daily for 12 weeks Wistar rats, STZ; mouse podocyte cell line Prevented EMT suppressing cav-1 phosphorylation 36

Curcumin Purchased 300mg/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); 37
<table>
<thead>
<tr>
<th>Plant</th>
<th>Part</th>
<th>Source</th>
<th>Dose/Concentration</th>
<th>Animal Model</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curcumin</td>
<td>Dried rhizome roots</td>
<td>Purchased</td>
<td>200mg/kg</td>
<td>Sprague-Dawley rats (STZ)</td>
<td>Reduced NOX, increased expression of cellular ATPase, improved kidney function</td>
</tr>
<tr>
<td>Momordica charantia</td>
<td>Fruit</td>
<td>Purchased</td>
<td>Aqueous extract (50 mg/kg)</td>
<td>Sprague-Dawley rats (STZ)</td>
<td>Reduced NOX, increased expression of cellular ATPase, improved kidney function</td>
</tr>
<tr>
<td>Fruit</td>
<td>Crude polysaccharide fraction, 150 and 300 mg/kg</td>
<td>Fed daily for 8 weeks</td>
<td>Wistar rats, STZ</td>
<td>Integrin α3 increased, and miR-124 decreased</td>
<td></td>
</tr>
<tr>
<td>Fruit</td>
<td>Ethanol extract; 200 and 400 mg/kg</td>
<td>Fed 6 days per week for 10 weeks</td>
<td>Sprague-Dawley rats (STZ)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moringa oleifera</td>
<td>Green leaves</td>
<td>October</td>
<td>Methanolic extract (250 mg/kg) reconstructed by water</td>
<td>Sprague-Dawley rats (STZ)</td>
<td>Reduced NOX, increased expression of cellular ATPase, improved kidney function</td>
</tr>
<tr>
<td>Seed powder</td>
<td>Seed powder (50 and 100 mg/kg)</td>
<td>Fed for 4 weeks</td>
<td>Albino rats (STZ)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Punica granatum</td>
<td>Leaves</td>
<td>January</td>
<td>Methanolic extract 100, 200 and 400mg/kg</td>
<td>Sprague-Dawley rats (STZ)</td>
<td>Reduced NOX, increased expression of cellular ATPase, improved kidney function</td>
</tr>
<tr>
<td>Seed oil</td>
<td>Seed oil 0.4 and 0.8ml/kg</td>
<td>Fed daily for 3/4 weeks</td>
<td>Wistar rats, STZ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trigonella foenum-graecum</td>
<td>Seed</td>
<td>Reconstructed seed phytochemicals; 50, 100, 200 mg/kg</td>
<td>Fed for 30 days</td>
<td>Sprague-Dawley rats (STZ)</td>
<td></td>
</tr>
<tr>
<td>Seed</td>
<td>Fenugreek extract 100 mg/kg</td>
<td>4 weeks orally every other day or daily or IP Fed for 4 weeks</td>
<td>Sprague-Dawley rats, STZ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seed</td>
<td>Aqueous seed extract 9g /kg</td>
<td>Treated daily for 12 weeks</td>
<td>Sprague-Dawley rats, STZ</td>
<td>Reduced NOX, increased expression of cellular ATPase, improved kidney function</td>
<td></td>
</tr>
<tr>
<td>Ingredient</td>
<td>Source</td>
<td>Type</td>
<td>Quantity/Dosage</td>
<td>Model/Conditions</td>
<td>Effects</td>
</tr>
<tr>
<td>------------</td>
<td>--------</td>
<td>------</td>
<td>----------------</td>
<td>-----------------</td>
<td>---------</td>
</tr>
<tr>
<td>Seed</td>
<td>Purchased</td>
<td>10% fenugreek seed powder and/or 3% onion powder</td>
<td>Fed for 6 weeks</td>
<td>Wistar rats, STZ</td>
<td>Prevented segmental thickening of GBM' widely fused foot processes podocytes, and excessively deposited mesangial matrix; glomerular hypertrophy mitigated.</td>
</tr>
<tr>
<td>Seed</td>
<td>-</td>
<td>5% in powdered rat food</td>
<td>Fed for 12 weeks</td>
<td>Albino rats, Allx</td>
<td>Renin-angiotensin system blocked; nearly normalized podocyte damage; shrunken glomeruli with mesangial matrix expansion.</td>
</tr>
<tr>
<td>Seed</td>
<td>Purchased</td>
<td>10% aqueous solution</td>
<td>Fed for 8 weeks</td>
<td>Sprague-Dawley rats</td>
<td>Antioxidant enzymes increased; IL-6 and inflammation attenuated; mesangial expansion reduced.</td>
</tr>
<tr>
<td>Vitis spp.</td>
<td>Whole Grape Powder</td>
<td>Acquired</td>
<td>5%, w/w diet</td>
<td>Fed daily for 6 months</td>
<td>Obese ZSF1 rats; heat-sensitive mouse podocyte</td>
</tr>
<tr>
<td>Grape seed proanthocyanidin extract</td>
<td>Purchased</td>
<td>125/250/500 mg/kg</td>
<td>Fed for 16 weeks</td>
<td>Sprague-Dawley rats; STZ</td>
<td>Uneven thickening of glomerular base membrane ameliorated.</td>
</tr>
<tr>
<td>Procyanidin B2</td>
<td></td>
<td>30mg/kg</td>
<td>Fed daily for 10 weeks</td>
<td>C57BL/KsJ mice; db/db</td>
<td>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 H2O2 induced apoptosis.</td>
</tr>
<tr>
<td>Zingiber officinale</td>
<td>Rhizome</td>
<td>Purchased</td>
<td>Ethanolic extract 400 or 800 mg/kg</td>
<td>Fed daily for 6 weeks</td>
<td>Wistar rats, STZ</td>
</tr>
<tr>
<td>Zingerone</td>
<td>Purchased</td>
<td>50 mg/kg</td>
<td>Injected daily for 10 weeks</td>
<td>C57BL/KsJ mice; db/db</td>
<td>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.</td>
</tr>
</tbody>
</table>
necrosis of renal tubules ameliorated; reduced TNFα and IL-6; renal GSH increased; NOX4 decreased

<table>
<thead>
<tr>
<th>Plant</th>
<th>Active compounds</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. augusta</td>
<td>Taraxerol, flavonoids and phenolic components</td>
</tr>
<tr>
<td>A. sativum</td>
<td>Diallyl thiosulfinate or allicin</td>
</tr>
<tr>
<td>A. racemosus</td>
<td>Saponins, asparagine</td>
</tr>
<tr>
<td>C. longa</td>
<td>Curcumin</td>
</tr>
<tr>
<td>M. charantia</td>
<td>Saponin</td>
</tr>
<tr>
<td>M. oleifera</td>
<td>Quercetin, Moringa isothiocyanate</td>
</tr>
<tr>
<td>T. foenum-graecum</td>
<td>4-HI trigonelline</td>
</tr>
<tr>
<td>Vitis spp</td>
<td>Proanthocyanidin</td>
</tr>
</tbody>
</table>
Figure legends

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

**Figure 2.** Effect of medicinal plant extracts on major signaling 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: *Trigonela foenum-graecum*; Vi: *Vitis* spp.; ZO: *Zingiber officinale*. Solid line from plant extract shows activation/upregulation
Figure 1.
Figure 2.