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Review

A comprehensive review of diabetic nephropathy and its management by Phytomedicine

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Abstract

Diabetic nephropathy (DN), the leading microvascular complication of diabetes mellitus, is the principal driver of cardiovascular morbidity and end-stage renal disease (ESRD) in this population. Epidemiological studies indicate that 25–40 % of people with diabetes will develop diabetic nephropathy. Chronic hyperglycemia induces oxidative stress via excessive generation of short-lived free radicals; although the radicals are transient, their downstream damage to lipids, proteins and DNA persists and serves as a measurable marker of oxidative burden. Persistent albuminuria together with a progressive decline in glomerular filtration rate (GFR) are the clinical hallmarks of diabetic nephropathy, yet phenotypic expression is heterogeneous. Here we summarize current evidence on botanical and conventional therapeutics that modulate the key signaling cascades implicated in diabetic nephropathy pathogenesis.

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Introduction: Diabetic nephropathy (DN) is the leading micro-vascular complication of diabetes mellitus and the commonest cause of end-stage renal disease (ESRD) worldwide [1,2]. DN is defined by persistent albuminuria (albuminuria excretion rate exceeding 300mg/d or 200µg/min) confirmed at least twice within three to six-month intervals, a progressive decline in glomerular filtration rate (GFR), frequently accompanied by elevated blood pressure ultimately resulting in end-stage renal disease (ESRD) [3]. Individuals with DN exhibit a 30-fold increased mortality rate from all causes compared to diabetics, and a significant percentage of these individuals may succumb to cardiovascular complications upon reaching end-stage renal disease [4]. Globally, 25–40 % of people with diabetes develop DN; pooled data from 2020–2024 show that the age-standardized incidence of ESRD attributable to diabetes rose from 42.6 to 53.1 cases per 100 000 diabetic population, with the steepest increase recorded in low- and middle-income countries [5–7]. In the United States, 50 600 diabetic patients initiated renal-replacement therapy in 2023, a 26 % increase compared with 2019 [8]. China now carries the largest national burden: an estimated 24.3 million people with diabetes have chronic kidney disease (CKD), and DN accounts for 42 % of incident dialysis cases. These epidemiological trends are mirrored in South Asia, the Middle East and North Africa, where diabetes prevalence is projected to double by 2045 [9]. DN is clinically defined as persistent albuminuria (≥ 30 mg g^{-1} creatinine in at least two of three spot urine samples) accompanied by a progressive decline in glomerular filtration rate (GFR) in the absence of other renal disease [10]. Once macro-albuminuria develops, the cumulative 10-year risk of ESRD exceeds 45 %, and cardiovascular mortality increases 6-fold. Current standard-of-care tight glycemic control combined with renin–angiotensin–aldosterone system (RAAS) blockade slows, but does not halt, disease progression, and 30–40 % of patients continue to lose renal function despite optimal therapy [11,12]. These limitations, together with the high cost of biological agents (e.g., SGLT-2 inhibitors, non-steroidal mineralocorticoid receptor antagonists), have re-ignited interest in complementary therapeutic strategies, including evidence-based phytomedicine. Recent study indicates that inflammatory mediators are significant in the initial phases of the disease [13]. Research studies indicates that the inflammatory response contributing to insulin resistance in diabetes is primarily driven by the accumulation of macrophages in tissue [14]. DN is augmented by a macrophage influx triggered by an increase in intercellular adhesion molecule-1 (ICAM-1) and monocyte chemotactic protein-1 (MCP-1) [15], the inhibition of macrophage inflow diminishes albuminuria, mitigates glomerular damage, and brakes the progression of renal disease [16].

Medicinal plants and their constituents have been utilized in the treatment of ailments since ancient times. Over the past decade, there has been a growing interest in employing a holistic and combinatorial strategy for the management of clinical illnesses such as hypertension, diabetes mellitus, cancer, renal dysfunctions, and cardiovascular disorders [17]. Phytomedicine is rapidly emerging as a crucial component of the expanding global health commerce. Extensive literature exists concerning the significance of these wellness-promoting substances [18,19]. Moreover, compelling data indicates that the consumption of foods abundant in phytochemicals may progressively diminish the risk of diabetes and cardiovascular diseases by gradually regulating immune-inflammatory indicators. The robust chemical defence mechanisms in these plants consistently attract and rejuvenate the interest of eager researchers aiming to discover novel medicines [20,21]. Phytomedicine, in conjunction with other health-care disciplines, has significantly transformed and fortified the foundation of the current health-care system and holds a substantial position in the industry. Global reports reveal that over 35,000 plant species are presently utilized in herbal medicines and recipes Series [22]. Research indicates that just 20% of the total proceeds to phytochemical analysis, whereas 10% advances to biological screening [23]. The remainder need further research utilising contemporary tools. The future of pharmaceuticals derived from medicinal plants appears to hold significant potential for the discovery of innovative therapeutic techniques and products [24]. Due to its safety and little side effects, about 80% of the global population utilises plant-derived medication as their primary healthcare option [25]. Herbal medications exist in multiple regulatory formats, including prescription drugs, traditional medicines, over-the-counter products, and nutritional supplements [26]. The study aims to summarize the medicinal plants and certain phytomedicine utilised in the treatment and management of diabetic nephropathy.

Pathophysiology of diabetic nephropathy: According to recent research, inflammatory biomarkers play an important role in the early stages of the disease [27]. The inflammatory response that leads to insulin resistance in diabetes and exacerbates it is largely caused by the accumulation of macrophages in tissue [28]. Furthermore, DN is supplemented by a macrophage influx in response to a rise (MCP-1) and (ICAM-1) [29,30]. Other chronic kidney diseases that have seen an increase in macrophages include anti-GBM nephritis and ANCA-associated pauci-immune crescentic glomerulonephritis [18,30]. DN is characterized by thickening of the glomerular basement membrane, mesangial expansion, and loss of podocytes. However, the cellular types and signaling pathways that contribute to disease development are not well understood [28]. Diabetic nephropathy is

classified into two levels based on urinary albumin excretion (UAE) levels: microalbuminuria and macroalbuminuria. DN has a distinct pathophysiology. Hyperfiltration of the glomerulus, endothelial dysfunction, and, subsequently, microalbuminuria develops. Nitric oxide transport is lost. Loss of afferent and efferent autoregulation results in a diminishing glomerular filtration capacity over time [31]. DN can cause renal failure if not managed. Early diagnosis and therapy are needed to slow disease progression [32]. Hemodynamics, reactive oxygen species (ROS), and renin-angiotensin system activation worsen DN. New disease pathways have been identified. More evidence shows that inflammation is crucial in diabetic nephropathy. Levels of cytokines and adhesion molecules in blood and urine relate to albuminuria in diabetic patients. Chemokines and growth factors in kidney tissue are also involved [33]. The filtration rate of the glomerulus can decrease by 2 to 20 mL/min per year, with an average decline of approximately 12 mL/min per year [4]. Chronic high blood sugar levels increase oxidative stress in biopolymers, including carbohydrates, lipids, nucleic acids, and proteins. oxidative stress inhibits the expression of DNA repair enzymes, leading to apoptosis and DNA damage [34,35]. High levels of advanced glycation end-products (AGEs) resulting from hyperglycemia activate the NF-κB and protein kinase C pathways. This activates DN transcription factors, promotes growth, and stimulates ECM production. Higher ROS levels during long-term high blood sugar play a major role in complications. Endogenous antioxidants can't keep up with mitochondria's ROS output [36]. Both type 1 and type 2 diabetics are affected by DN, but its causes are not fully understood [34,37].

Excessive O2 leakage and decreased ATP production in the kidneys make them particularly sensitive to hyperglycemia, leading to increased intracellular glucose flow and rapid mitochondrial O2 oxidative phosphorylation. Endogenous antioxidant production can be increased, or exogenous antioxidants can be utilized as a prophylactic treatment for patients suffering from diabetic nephropathy [38]. In an experiment, Hyperlipidemia plays a role in the development of diabetic kidney disease. Glomerular infiltration of LDL and other LDL alterations, such as oxidation, glycation, and the production of advanced glycation end products, causes glomerulosclerosis, whereas hypercholesterolemia exacerbates proinflammatory processes [39]. Figure.1 represents the pathophysiology of DN.

Traditional Chinese Medicine (TCM) in the management of Diabetic Nephropathy: Tangshen Decoction (TSD), a seven-herb formulation, reduced albuminuria and restored autophagy markers (Beclin-1, LC3-II) in streptozotocin (STZ)-induced diabetic rats; these effects were abolished when the AMPK/ULK1 pathway was pharmacologically inhibited, suggesting that TSD acts via AMPK-mediated podocyte autophagy [40]. In the same model, 8-week treatment with TSD (4 g kg^{-1} day^{-1}) lowered fasting blood glucose from 21.8 ± 2.1 mmol L^{-1} to 14.3 ± 1.7 mmol L^{-1} and decreased mesangial matrix expansion by 35 % compared with untreated diabetic controls [20,41]. Researchers found that intraperitoneal injections of Streptozotocin STZ resulted in considerable weight loss and a rise in blood sugar in the diabetic rat model employed in this research. A substantial drop in blood sugar and weight loss were seen over 8 weeks of treatment with TSJ medication [42]. Eefooton, a liquid preparation containing Astragalus membranaceus, Codonopsis pilosula, Ligustrum lucidum, Panax quinquefolius and Rhodiola sacra, has been evaluated in two small randomised trials conducted in China (total n = 156, follow-up 12 weeks).
In patients with early DN (urinary albumin–creatinine ratio 30–300 mg g^{-1}), add-on Eefooton (30 mL twice daily) reduced albuminuria by 28 % versus 7 % in the losartan-only arm ($p < 0.05$), while serum creatinine and estimated GFR remained stable [26,39]. Pre-clinical data in STZ rats showed parallel reductions in renal interstitial fibrosis and TGF-β1 expression, but human histological confirmation is still lacking [43].

Bushen Huoxue Formula (BSHXF) improved markers of renal function (↓ serum creatinine, ↓ 24-h urinary protein) in a multicentre, double-blind trial involving 210 patients with stage 3 CKD due to type 2 diabetes; however, the study was limited to 24 weeks and hard renal end-points were not assessed [44]. In vitro, BSHXF-rich fractions suppressed NLRP3 inflammasome activation in high-glucose-exposed HK-2 cells, corroborating the anti-inflammatory phenotype observed in animals [45]. Dolabi, a Herbo-mineral preparation containing *Acacia arabica*, *Eugenia jambolana* and zinc, restored renal SOD and GSH levels and lowered MDA in STZ mice after 27 days; these anti-oxidative effects were accompanied by a 25 % reduction in urinary albumin excretion. Antioxidant ratios in the kidneys of diabetic nephropathy rats, including lipid peroxidation, glutathione, and superoxide dismutase (SOD), were restored to normal levels after 27 days [40].

Phytomedicine in Management of Diabetic Nephropathy: Most of the plants having hypoglycemic effects come from their ability to either stimulate an increase in insulin synthesis, inhibit the absorption of glucose, or support metabolites in insulin-dependent processes. Natural compounds have hypoglycemic potency that operate through either insulin mimetic or secretagogue characteristics [46,47]. Figure 2 showing the management of DN by phytomedicine.
Natural sources are appealing for the discovery of new antidiabetics because they contain biological molecules that exhibit substitute and consistent effects on diabetes; several of these, such as compound preparations known as murakkabat and separate drugs

known as mufradat, have been used since antiquity and are described in our literary sources.Safoofe Ziabetus, Qurs Tabasheer, Safoofe Hindi, and Kachnar (*Bauhina variegata*), Tukhme Jamun (*Eugenia jambolana*), Tukhme Karela (*Momordica charantia)*, Satte Gilo (*Tinospora cordifolia*), Tukhme Methi (*Trigonella foenum-graecum)*, Kalonji *(Nigella sativa).* Table no 1 summarizes the medicinal plants having role in management of DN.

Conclusion: Diabetic nephropathy is not seen as a decently hemodynamic or metabolic ailment; inflammatory cytokines oxidative stress, mitochondrial dysfunction and epigenomics are now documented as equal contributors to cause podocyte loss, mesangial expansion and progressive fibrosis. The plant species and conventional herbal formulas studied here constantly inhibit one or more of these signaling pathways in pre-clinical models: inhibiting TGF-β/Smad-mediated fibrosis, down-regulating NF-κB/NLRP3 inflammasome Signaling, improving mitochondrial efficiency by restoring endogenous antioxidant enzymes (SOD, CAT, GPx), and, in parallel, lowering blood glucose, HbA1c and dyslipidemia. Several compounds: ginsenoside Rb1, resveratrol berberine, curcumin, EGCG, and jujuboside A have already entered early human trials and show analogous efficacy to standard-of-care renin–angiotensin drugs without significant adverse events. Taken together, the evidence supports the integration of evidence-based phytomedicine as an adjuvant to conventional glycemic and blood-pressure control in DN. Nevertheless, demanding pharmacokinetic profiling, standardization of medicinal herb extracts, large-scale randomized trials and safety data in progressive chronic kidney disease stages are still missing; closing these gaps will be essential before herbal therapy can be promoted from “promising” to “recommended” in international guidelines.

Conflict of Interest: The authors declare that there is no conflict of interest.

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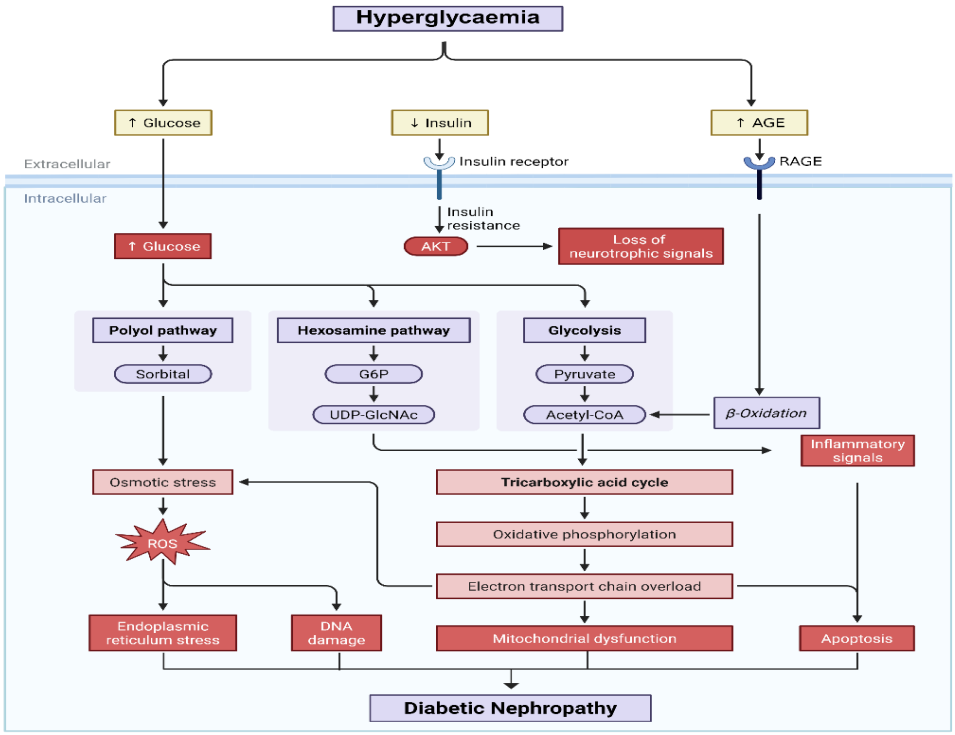

Fig 1. Pathophysiology of diabetic nephropathy

Fig 2. Showing the management of DN by Phytomedicine

Table 1. Medicinal Plants with mechanism having potential role in management of DN

Name of Herbs	Family	Chemical Constituent	Mechanism of Action	Reference
Allium sativum (Garlic)	Alliaceae	Diallyl thiosulfate (allicin)	Allicin decreases the cytokines like TNF-α, IL-1β, and IL-6, which are increased in diabetic conditions. It also can inhibit the production of fibrotic markers implicated in kidney fibrosis, such as connective tissue growth factor (CTGF) and transforming growth factor-β1 (TGF-β1).	[48,49]
Aloe barbadensis (Aloe vera)	Liliaceae	Aloe-emodin	Aloe-emodin targets Interferon regulatory factor 4 (IRF4), which is increased in diabetic nephropathy. It also decreases oxidative stress indicators like malondialdehyde (MDA) and increases production of antioxidant enzymes such as superoxide dismutase (SOD) and catalase in diabetic rats Aloe vera changed the representation of proteins involved in diabetic metabolic pathways, including fructose-bisphosphate aldolase A and cytochrome P450 2C23.	[50–52]

Astragalus membranous (Milk vetch root)	Fabaceae	Quercetin, Formononetin, Calycosin.	It lowers fibrosis markers such as TGF-β1, CTGF, collagen IV, Wnt4, and β-catenin, while elevate the anti-fibrosis marker BMP-7.	[53]
Avena sativa (Oats)	Poaceae	β-d-glucan, Avenanthramides	Reduce the rate of kidney fibrosis Decrease OS, HbA1c, and BGL indicators Reduced HbA1c and BSL in diabetic people.	[54]
Berberis vulgaris L. (Barberry)	Berberidaceae	Berberine Magnoflorine Reticuline Quercetin	Berberine (BBR) acts on the VEGFR2 protein. It is identified as the primary focus of diabetic nephropathy (DN) treatment. The binding BBR to VEGFR2 clashes with the PI3K/AKT/mTOR signaling pathway. This interference leads to the restriction of abnormal proliferation of mesangial cells.	[55]
Boerhavia diffusa (Punarnava)	Nyctaginaceae	Boerhavisterol, Liriodenine, Ursolic acid.	Regularization of serum sodium and potassium-maintained Na+ - K+ATPase activity in the plant extract treated rats. This provides proof that B. diffusa is an effective Reno protective agent in diabetic animals.	[56]
Bombax ceiba (Malabar silk)	Bombacaceae.	Mangiferine	Reduce the production of ROS and can also inhibit the expression of NOX4 in the kidneys of diabetic mice	[57]
Bauhinia variegate (Kanchanara)	Caesalpiniaceae	Hentriacontane, Octacosanol, Sitosterol, Stigmasterol, Lupeol.	It is proved that its extract can inhibit AGEs, which are toxic compounds that involves in diabetic nephropathy	[58]
Butea monosperma (Reetha)	Fabaceae	Isobutrin and butrin,	Butein shows notable Aldose Reductase (AR) inhibitory effect, which is beneficial in preventing diabetic nephropathy.	[59,60]
Camellia sinensis (Green tea)	Theaceae	Epigallocatechin-3-gallate (EGCG)	It inhibits the formation of inflammatory cytokines such as TNF-α and iNOS, reducing inflammation in renal tissues. TGF-β/Smad signaling pathway is restricted by green tea peptides, mitigating extracellular matrix protein accumulation and fibrosis in diabetic nephropathy. Activation of diacylglycerol kinase α (DGKα) by EGCG has been shown to improve albuminuria and protect podocytes from high glucose-induced damage.	[61,62]
Cinnamomum zeylanicum (Ceylon cinnamon)	Lauraceae	Cinnamaldehyde	Cinnamon can suppress AGE, and by diminishing urine albumin and creatinine level, its procyanidin-B2 fraction helps rats with diabetes-induced renal dysfunction.	[63]
Citrus paradisi (Graps)	Rutaceae	Obacunone (OB)	Obacunone inhibit GSK-3β signaling, enhancing Nrf2 activity and having a defensive effect against HG-induced cytotoxicity in NRK-52E cells by oxidative damage.	[64]
Cordyceps sinensis (Cordyceps)	Clavicipitaceae	Guanosine Inosine, Myriocin	CS stimulates the growth of renal proximal tubular cells and inhibits apoptosis, especially by the regulation of key proteins such as Caspase-3 and Bax and signaling pathways like AKT and ERK.	[65,66]
Calculus bovis (Cow bezoar)	Sulfur-containing amino acid	Taurine	Decreases the generation of MtROS, diminished the excessive synthesis of MDA, lowered the levels of antioxidant enzyme SOD, and enhanced mitochondrial oxidative stress triggered by ROS production.	[67]
Cucumis melo Linn (Muskmelon)	Cucurbitaceae.	Quercetin Gallic acid Trans-4-hydroxy-3-methoxy cinnamic acid.	The leaves of Cucumis melo lower down inflammatory markers such as TNF-α and IL-6 in diabetic rats. They also reduce oxidative stress markers like TBARS while enhancing activity of antioxidant enzyme, including catalase and superoxide dismutase (SOD).	[68–70]
Curcuma longa (Turmeric)	Zingiberaceae	Curcumin	Curcumin inhibits the expression of TGF-β afterwards targets such as plasminogen activator inhibitor-1 (PAI-1), α-smooth muscle actin (α-SMA), and collagen I, which play a significant role in the fibrotic process.	[71,72]

Erigeron breviscapus (Dengzhan Hua)	Asteraceae	Breviscapine	It mediates pyroptosis pathway by inhibiting the NF-κB/NLRP3-, which is essential in the pathogenesis of diabetic nephropathy by reducing renal podocyte injury.	[73]
Ganoderma lucidum (Reishi mushroom)	Ganodermatacea	Ganoderic acids	GLP stimulates the PI3K/Akt/mTOR pathway, enhancing autophagy and decreasing apoptosis and inflammation, which are crucial in relieving DN. GL inhibits TGFβ-1 and TLR-4/NFκB signaling pathways, lowers pro-inflammatory cytokines and fibrosis markers, Consequently, renal function is improved.	[74,75]
Ginkgo biloba (Maidenhair tree)	Ginkgoaceae	Genkwanin Apigenin, Rutin Quercetin, Ginkgolide B	Ginkgo biloba leaf extract (GBE) diminishes tissue transglutaminase (tTG) expression, which is built up in extracellular matrix in diabetic nephropathy, mostly caused by the accumulation of TGF-β.	[76,77]
Gymnemma sylvester (Gymnema)	Asclepiadaceae	Gymnemagenin	It Shows strong hindering effects on α-amylase and α-glucosidase, enzymes involved in carbohydrate digestion, thereby lowering postprandial blood glucose levels	[78]
Herniaria hirsute (Hairy rupturewort)	Caryophyllaceae	Gallic-acid Catechin. Hirudin, Medicagenic acid	Medicagenic acid lowers oxidative stress in renal tissues, which is a powerful impact in diabetic nephropathy	[79]
Hibiscus sabdariffa (Roselle)	Fabaceae	Anthocyanins	It inhibits toll-like receptor 4 (TLR4), which shows its Anti-inflammatory potential and improves renal function by decreasing serum creatinine and urea levels.	[80,81]
Juniperus communis (Juniper berries)	Cupressacea	α-Pinene	Juniper berries modify substantial metabolic pathways by activating peroxisome proliferator-activated receptors (PPARα and PPARγ) and liver X receptor (LXR), decreasing fat build-up and improving glucose uptake.	[82,83]
Ziziphus jujuba (Jujube)	Rhamnaceae	Jujuboside A (JuA)	It reduces O_2^- and H_2O_2 levels, control the expression of respiratory chain complexes, augment SOD, CAT, and GPx activity, diminish NOX4 expression, contribute in redox regulation, and reduced Mito and ER oxidative stress.	[84]
Lactuca sativa (Lettuce)	Asteraceae.	Lactucaxanthin carotene and vitamin C, vitamin E.	Lactucaxanthin inhibit α-amylase and α-glucosidase, thereby lowering post-prandial blood sugar level in diabetic models	[85]
Linum usitatissimum (Flaxseed)	Lineacea	Gamma linolenic acid	Gamma linolenic acid, a bio-active component of flaxseed, has been shown to inhibit the mediators of pro-inflammatory markers such as ICAM-1 and MCP-1 in diabetic nephropathy.	[86,87]
*Lonchocarpus **c yanescens*** (Yoruba Indigo)	Fabaceae	Rotenone	Lowered the GSSG/GSH ratio, reverse the low expression of antioxidant enzyme SOD2, inhibit the overexpression of superoxide dismutase, TCA, and OXPHOS.	[88]
Lycopus lucidus (Bugleweed)	Lamiaceae	Rosmarinic acid, Betulinic-acid Oleanolic acid.	Lycopus extracts inhibits TGF-β1 and Smad4 markers, which play a vital role in podocyte injury and renal fibrosis. The extracts also inhibit the phosphorylation of Smad2/3, ERK1/2, and p38, show significant role in reduction of inflammatory reactions related to DN.	[89]
Momordica charantia (Bitter gourd)	Cucurbitaceae	Momordicin Charantin Eleostearic acid Stearic acid.	Compounds like mcIRBP-9 have shown remarkable anti-inflammatory properties, altering the paths such as nuclear factor-κB (NF-κB) to reduce inflammatory responses in kidney tissues.	[90]
Nigella sativa (Black cumin)	Ranunculaceae	Thymoquinone (TQ), Trans-anethole, p-cymene, Alpha-pinene Limonene Carvone	TQ downregulate the enhancing growth factor activation-β1 (TGF-β1), a significant mediator in renal fibrosis, thus avoiding significant extracellular matrix deposition and podocyte injury.	[91]

Panax ginseng (Asian ginseng)	Araliaceae	Ginsenoside Rb1, Dencichine	Ginsenoside Rb1, reduces apoptosis and mitochondrial damage by blocking aldose reductase activity, which lessens podocyte damage. Dencichine, suppress the TGF-β1/Smad signaling pathway, lower down extracellular matrix accumulation and mesangial cell growth, which are crucial to the development of DN.	[92,93]
Panax notoginseng (Chinese ginseng)	Araliaceae	Ginsenoside Rb1	Ginsenoside Rb1 inhibits NOX4 expression to suppress ROS production.	[94]
Phyllanthus Emblica (Indian Gooseberry)	Euphorbiaceae	Emblicanin A and Emblicanin B.	The presence of multiple ascorbate biosynthesis pathways in P. emblica serves as powerful antioxidant activities, which are important in treating kidney tissues from oxidative damage. The anti-inflammatory effects function via the suppression of enzymes like 15-lipoxygenase, which play a role in inflammatory processes.	[95,96]
Pterocarpus marsupium (Indian Kino)	Fabaceae	Pterosupin Pterostilbene Marsupsin Epicatechin	Inhibit α-amylase and α-glucosidase enzymes, meanwhile increase insulin secretion, and sensitivity. By lowering oxidative damage, protect pancreatic cells.	[97,98]
Petroselinum crispum (Parsley)	Umbelliferae	Apiol Petroselinic Acid Phytol Myristicin	It downregulates the formation of angiotensin II, in the RAAS that excites vasoconstriction and inflammation, thereby decreasing renal issues.	[99,100]
Picrorhiza kurrooa (Picroliv)	Scrophulariaceae	Veronicoside Pikuroside Cucurbitacins, 4-hydroxy-3-methoxyacetophenone Siridoid Glycosides	Upgraded the mitochondrial dysfunction in DN by reducing total intracellular ROS and MtROS.	[101]
Polygonum cuspidatum (Japanese knotweed)	Polygonaceae	Polydatin	Upgraded the mitochondrial dysfunction in DN by reducing total intracellular ROS and MtROS.	[102,103]
Poria cocos (Rotten pine-tree fungus)	Polyporaceae	Triterpenes Pachyman Pachymaran DehydrotrametenOlic acid	Its emphasis on pathways like Notch1 signaling, Sirtuins, and the ACE2-Angiotensin-(1-7)-Mas receptor treatment targets for diabetic nephropathy.	[104]
Portucca oleracaea (Purslane)	Portulacaceae	Apigenin-4'-O-α-L-Rhamnopyranoside and caffeic acid.	Its Extracts inhibits pro-inflammatory markers like TNF-α and IL-6, while formating protective factors such as IL-10 and PPARγ.	[105,106]
Psidium guajava (Guava)	Myrtaceae	Triterpenoids	Reduces BGL and enhances insulin sensitivity index. Protects diabetic rats' kidney lesions Reduces BUN and SCr while improving kidney structural damage.	[107]
Pueraria lobata (Kudzu)	Fabaceae	Puerarin	Having antioxidant properties upregulate the expression levels of the SIRT1/FOXO1 signaling pathway, increasing the activity of Mn-SOD and CAT, and abolishing ROS.	[108]
Rehmannia glutinosa (Rehmannia)	Orobanchaceae	Catalpol Rehmannioside	R. glutinosa extract reduces the risk of renal failure by inhibiting angiotensin II and AT1 receptor marker and controlling TGF-β1 and type IV collagen expression	[109,110]
Rhizoma alismatis (Water plantain)	Labiatae/ Alismataceae	Sesquiterpenes Terpenoid Alismoxide, Orientalols A, B, and C.	It inhibits fibrosis markers such as TGF-β and collagen IV, thereby reducing renal fibrosis.	[111]
Rosa laevigata (Cherokee rose)	Rosaceae	Quercetin, Kaempferol, Rutin, Catechin.	Enhancing mitogen-activated protein kinase signaling pathways. Antioxidant, hypolipidemic activities can lower the inflammation.	[112,113]
Rosmarinus officinalis (Rosemary)	Labiatae	Rosmarinic acid Carnasol Carnosic acid Rosmaridiphenol Diterpene	It shows antioxidant and anti-inflammatory properties, NF-B inhibition, enhanced glutathione transferase activity, Anti-Bcl-2 activity, and peroxynitrite elimination	[111,114]

Solanum lycopersicum (Tomato)	Solanaceae	Lycopene	Lycopene raises HDL-C levels while simultaneously dramatically lowering TC, TG, and LDL-C levels. Antioxidant properties as well as lipid-lowering effect reduced the 24-hour urea protein, creatinine, and blood urea nitrogen levels as well as improving oxidative status and regulating p-Akt and CTGF.	115
Solidago canadensis (Goldenrod)	Asteraceae	Carotenes, and diterpenoids.	It inhibits pro-inflammatory mediators involved in DN, such as TGF-β and NF-κB. [142]. It also promotes glucose uptake in muscle cells, significantly improving insulin sensitivity and glucose metabolism. [143]	144,145
Salvia miltiorriza (Danshen)	Lamiaceae	DehydromiltironeSalvianolic acids	Dehydromiltirone downregulates the PI3K-AKT pathway, regulating mesangial cell activation and renal fibrosis. Salvianolic Acids focus on numerous pathways that are involved in oxidative stress, inflammation, and fibrosis.	116,117
Silybum marianum (Milk thistle)	Asteraceae	Flavonolignans, Silymarin, Silybin Silicristin Isosilibinin, Silidianin, Silibinin	It protects renal fibrosis by inhibiting the NF-κB signaling pathway, which is frequently triggered in diabetic nephropathy.	118
Spirulina platensis (Blue green algae)	Oscillatoriaceae	Phycocyanin and Phycocyanobilin	It regulates the levels of NAD(P)H oxidase. It also improves the function of antioxidant enzymes such as superoxide dismutase (SOD) and catalase. Facilitate the insulin release from pancreatic β-cells and stops dipeptidyl peptidase IV activity, which performs glucose metabolism.	119–121
Syzygium cumini (Eugenia jambolana)	Myrtaceae	Mycaminose.	It considerably inhibits the expression of RAGE and NF-κB, inhibiting their nuclear translocation and transcriptional activity, thereby downregulating inflammatory cytokines like IL-6 and TNF-α. The methanolic extract of Syzygium cumini improves insulin sensitivity by downregulating protein tyrosine phosphatase 1B (PTP1B) and upregulating insulin receptor substrate 1 (IRS1) and PKB signaling pathways.	68,122,123
Trianthema portulacastrum (Narma/Biskhapra)	Aizoaceae	Trianthemine Ecdysterone	Aqueous extract of Trianthema portulacastrum inhibits both alpha-amylase and alpha-glucosidase enzymes which reduces glucose absorption	124,125
Tinospora cordifolia (Gilo)	Menispermaceae	Gliquidone	It has been found that gliquidone suppresses the Notch/Snail signaling pathway, which prevents the renal interstitial fibrosis. 1,2,3,4,6-penta-O-galloyl-β-D-glucose (PGG), influence the MAPK/NF-κB and ERK/Nrf2/HO-1 pathways minimizing oxidative stress and inflammation in the tissue of the kidney.	126–128
Trigonella foenum-graecum (Fenugreek)	Fabaceae.	Trigonelline	Fenugreek has antidiabetic effects through mechanisms like improving GLUT4 translocation, downregulating enzymes, and modifying GLP-1 and AMPK. Fenugreek inhibits the progression of diabetic nephropathy in a rat model by decreasing oxidative stress, extracellular matrix accumulation, and expression of TGF-β1 and CTGF.	97,129
Veratrum grandiflorum (Mao ye li lu)	*Melanthiaceae*	Resveratrol (RSV)	RSV can reverse the reduction in Mn-SOD activity caused by tyrosine nitration in the kidneys	130,131
Vitis vinifera (European wine grape)	Vitaceae	Resveratrol and Pterostilbene	Lowers the expression of tissue inhibitor of metalloproteinase1, raises the activity of matrix metalloproteinase, improves renal function parameters, and lowers fasting BGL, serum insulin, HbA1c, and systolic blood pressure in diabetic rats. Additionally, it decreased CRP levels and the kidney's production of TNF-α, MCP-1, and ICAM-1 while increasing the activity of antioxidant enzymes.	132,133
Withania coagulans (Paneer Booti)	Solanaceae	Withanolides A	Withanolide A, show significant results with antidiabetic targets such as α-glucosidase and DPP-4	134

Withania somnifera (Ashwagandha)	Solanaceae	Withaferin-A, Withanolide-B, Withanolide A, Withanoside-IV	withaferin-A minimized oxidative and nitrosative stress induced by streptozotocin, along with decreased in pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6), in addition to decline in DNA fragmentation and apoptosis. These results validate the potential protective effect of withaferin-A for diabetes mellitus. withaferin-A and other bioactive components, can suppress dipeptidyl peptidase-4 (DPP-4), thus decreasing insulin resistance and cell dysfunction.	[135,136]
Xanthium strumarium L. (Chhotaghokru)	Asteraceae	Caffeoylquinic acid	Caffeoylquinic acid acts as strong inhibitors of α-glucosidase, which are involved in glucose metabolism, which shows its antidiabetic property.	[51]