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A Comprehensive Review on Plant derived Natural products for Diabetes and its complication as nephropathy

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ABSTRACT

Diabetic nephropathy is one of the most severe microangiopathies of diabetes taking heavy toll on human lives. Diabetic nephropathy is characterized by the accumulation of extracelluar matrix protein leading to irreversible decline in renal function and end stage renal disease. Incomplete knowledge about molecular mechanism underlying nephropathy limit the use of modern medicines to treat this clinical entity. Moreover, current standard of therapy for diabetic nephropathy mainly focus on reduction in hyperglycemia and hypertension. These therapies have limited effect on delaying nephropathy progression. A pressing need for novel therapies initiated studies targeting various molecular pathways involved in nephropathic changes. Herbal medicines with beneficial phytochemicals are reported to delay the progression of nephropathic changes in diabetes in various experimental studies. This review try to summarize various phytoconstituents proved to be effective in management of diabetic nephropathy. The goal is to identify promising phytoconstituents that can be translated into beneficial therapeutic options.

Keywords: Diabetic complications, Medicinal plants, Phytoconstituents, Oxidative stress.

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Introduction

Diabetes mellitus (DM) is emerging as a serious public health concern with major challenges to human health in 21st century. Type 2 diabetes has been considered as a global pandemic, extending from affluent industrialized countries to the developing nation of Asia, Latin America, and Africa[1]. The disease is known to affect 415 million people globally and this figure is likely to escalate to 642 million by the year 2040[2]. The reasons for the considerable increase in type 2 diabetes in emerging economics are rapid economic development, urbanization, nutrition transition and increase in sedentary lifestyle[3]. In India, a recent steep rise in the type 2 diabetes prevalence makes it considered as "diabetes capital of the world"[4].

DM is a chronic metabolic disorder characterized by impaired metabolism of carbohydrates, fats and proteins. The resulting hyperglycemia is due to decrease utilization of carbohydrate and excessive glycogenolysis and gluconeogenesis from amino acids and fatty acids[5]. As reported by previous studies, link between muscle insulin resistance and predisposition of type 2 diabetes has been well established[6]. The persistent uncontrolled hyperglycemia and oxidative stress can lead to serious life threatening diabetic complications accounting for significant morbidity and mortality[7]. At microvascular level, chronic hyperglycemia commonly induces nephropathy, neuropathy and retinopathy[8]. At macrovascular level, atherosclerosis is a common complication resulting in ischemic heart disease, cerebrovascular disease and peripheral vascular disease[9].

Diabetic nephropathy

Diabetic nephropathy (DN) has been identified as an important cause of chronic kidney disease. This devastating complication occurs in approximately 40% of patients suffering from diabetes. Diabetic nephropathy is typically characterized by increase in urinary albumin excretion (UAE) in the absence of other kidney diseases[10]. Albuminuria is followed by a gradual decline in glomerular filtration rate, podocyte loss, progressive glomerular sclerosis and finally tubulointerstitial fibrosis[11]. End stage renal disease (ESRD) is most recognizable consequence of DN with significant mortality resulting from cardiovascular diseases and infection[12]. The pathophysiology leading to development of DN results from diabetes induced disturbance in metabolic and hemodynamic pathways[13]. Polyol pathway, formation of advanced glycation end products (AGEs), hexosamine pathway, protein kinase C pathway, growth factors,

cytokines and free radicals, mitogen activated protein kinase (MAPK) activation and poly ADP ribose polymerase (PARP) activation have been identified as various pathways playing significant role in pathogenesis of DN[14]. In diabetes, excessive glucose influx activates these cellular signaling pathway which favors interaction of inflammatory factors. This lead to facilitation of inflammatory process and subsequently development of glomerulosclerosis[15]. Additionally, generation and circulation of AGEs, release of growth factors and hemodynamic and hormonal changes lead to release of reactive oxygen species(ROS) and inflammatory mediators. These changes lead to glomerular hypertension, glomerular hyperfiltration, altered glomerular composition and renal hypertrophy. Collectively all these renal pathological changes clinically manifested as albuminuria and hypertension[16].

In spite of newly developed effective treatment options, DN still remain continue to rise. This is because current clinical therapies mainly focus on control of hyperglycemia, hypertension and inhibition of renin-angiotensin system (RAS)[17]. Currently available drugs such as angiotensin-converting enzyme inhibitor (ACEI) and angiotensin II receptor blockers (ARB) are effective in protecting renal function of DN. However, these medicines are not sufficient to delay or retard the progression of diabetic nephropathy[18]. Hence, the prime culprit for DN i.e. baseline glycosylated heamoglobin remain relatively high. Moreover, high cost and associated side effects of modern medicines indicated requirement for search of alternative strategies for management of diabetes and its complications.

Role of medicinal plants in management of diabetic complications

Since ancient times natural compounds from plants are known to possess medicinal properties and used in treating various illnesses. These plants have a vast potential in the treatment of medical disorders due to presence of therapeutically important phytochemicals [19]. Plants such as *Allium sativum, Eugenia jambolana, Monordica charantia, Ocimum sanctum, Phyllanthus amarus, Pterocarpus marsupium, Tinospora cordifolia, Trigonella foenum graecum and Withania somnifera* are found to reduce ill effects of diabetes and its secondary complications[20]. Most of these plants enhance the performance of pancreatic tissues by increasing the insulin secretion or reducing the intestinal absorption of glucose[21]. Herbal medicines are cost-effective and exhibit improved therapeutic effects with lesser side effects. Medicinal plants enriched with flavonoids, alkaloids, phenolic compounds, saponins, terpenoids, tannins and phytosterol are reported to be effective in the management of diabetic complications. These secondary metabolites are known to ameliorate persistent hyperglycemia, oxidative stress and modulate various metabolic pathways leading to diabetic complications[7]. Although many medicinal plant have been reported for anti-diabetic potential only a small number of these are proved scientifically for their efficacy[22].

In current days, focus of experimental studies has been diverted towards identification of specific plant compound with therapeutic potential. Discovery of specific compound obtained from various parts of plant help to better understand their mechanism of action and future therapeutic potential[23]. Till date numerous plant phytoconstituents have been studies for their efficacy in management of DN. In this context, this review will provide newer insight on phytoconstituents which are natural antioxidant compounds and capable of reducing oxidative stress and subsequently classical signs of DN.

Phytoconstituents effective in diabetic nephropathy

Previously conducted studies investigated the effect of phytoconstituents on structural and functional changes occurring in DN. Different phytochemicals studied in animal models are found to exert significant renoprotective effect by targeting various molecular pathways. Experimental studies highlight the relevance of phytoconstituents as an alternative therapeutic option in management of DN. The present review provides detailed discussion on the effectiveness of scientifically evaluated phyoconstituents.

Curcumin

Curcumin, originally isolated from rhizomes of *Curcuma longa*, is widely used herbal remedy and spice. It is an active ingredient of turmeric and found to display potent anti-inflammatory properties[24].

Strong antifibrotic effect of curcumin was reported in diabetic nephropathy on db/db mice. Experimental animals receiving curcumin for 16 weeks exhibited diminished renal hypertrophy, reduced mesangial matrix expansion, and lower level of albuminuria. Moreover, curcumin administration inhibited the upregulated protein and mRNA expression of collagen IV and fibronectin in the renal cortices. Additionally, curcumin was associated with reduction in mature interleukin-1β and cleaved caspase-1. Major renoprotective effect was thought to promote by suppression of NOD-like receptor 3 (NLRP3) inflammasome. NLR3 are composed of the NLRP3 protein, caspase-1, and the adaptor protein apoptosis-associated speck-like protein containing a caspase-activating recruitment domain. These inflammasome play significant role in development and progression of DN[25].

In another experimental study curcumin was found more nephroprotective than metformin in attenuating oxidative stress in DN. Streptozotocin induced Wistar rats treated with curcumin showed regeneration in the form of reduction in necrotic and degenerative changes in the tubular and glomerular epithelium. Additionally, curcumin produced low tubular epithelial hypertrophy and inflammatory cells infiltration. Nephroprotective effect of curcumin is considered due to reduction in oxidative stress as exhibited by normalization of oxidative enzymes level[26]. These preclinical study results warrant further testing of curcumin in clinical setting as a treatment for DN.

Quercetin

Quercetin (3,5,7-trihydroxy-2-(3,4-dihydroxyphenyl)-4H-chromen-4-one) is potent dietary flavonoid frequently found in onion, apple, berries, nuts, seeds, barks, flowers, tea, brassica vegetables and leaves[27]. Quercetin shows a broad range of pharmacological activities and act as a potent antioxidant[28].

Treatment with quercetin in streptozotocin induced diabetic rats showed improvement in renal function over 12 weeks period. Administration of quercetin attenuated the overexpression of transforming growth factor-β1 (TGF-β1) and connective tissue growth factor (CTGF) involved in pathophysiological mechanism of DN[29].Renoprotective significance of quercetin was also demonstrated in DN associated with hypercholesterolemia. Another team of researchers studied effect of low-dose quercetin for 6 weeks in streptozotocin induced diabetic rat model where diabetes was associated with dyslipidemia. Quercetin was found to significantly reduce DN by inducing biochemical changes such as decrease in glucose and triglyceride serum levels and reduction of glomeruloscelrosis. Quercetin is known to

exhibit high antioxidant activity, long half-lives, high mitochondrial permeability, ability to suppress pro-oxidant enzymes and stimulation of antioxidant enzymes. All these qualities make quercetin as an ideal candidate for nephroprotection in DN[30].

Treatment with quercetin in a rat model of adenine-induced chronic kidney disease leads to improvement in renal function. This was accompanied with reduced oxidative stress factors, decreased renal inflammation and reduction in renal tubular damage. Quercetin treatment regulated the expression of fibroblast growth factor 23 (FGF23) and parathyroid hormone and subsequently regulated levels of calcium and phosphorus in the body[31].

Mangiferin

Mangiferin (2-β-D-glucopyranosyl-1,3,6,7-tetrahydroxy-9H-xanthen-9-one) is a xanthone derived from higher plants and mango fruits[32]. Several lines of investigation exhibited its pharmacological activities including antioxidant effects, anti-inflammatory, antidiabetic and immunomodulatory activities [33].

Nephroprotective effect of mangiferin was investigated in STZ induced diabetic nephropathy by inhibition of oxidative stress and protection of cells from apoptotic death. Magniferin treatment efficiently reduced the alterations in the markers of nephrotoxicity including serum urea, creatinine and uric acid level. Magniferin was found to improve the changes of diabetic renal injury such as reduction in the size of glomerulus and decrease in the hydropic changes in the proximal convoluted tubules. This renoprotective effect against oxidative injury was thought to be develop by modulating various pathways including ROS-induced PKCs, MAPKs, NF-kB and TGF-β1 mediated and TNFα related mitochondrial dependent apoptotic pathways[34].

Mangiferin was demonstrated to delay the progression of DN and protected podocyte in STZ-induced diabetic rats by modulating various pathways. Treatment with mangiferin in diabetic rats was found to significantly reduced albuminuria, inhibited glomerular extracellular matrix expansion and restored the expression of nephrin, a podocyte marker. Previous studies suggested role of podocyte injury in development of progressive proteinuria in DN. Podocytes are highly specialized, terminally differentiated cells in glomeruli. These cells are unable to differentiate and autophagy process maintains the structure and function of podocytes. Impairment in autophagy leads to podocyte loss and subsequently proteinuria in DN. Magniferin was found to promote autophagy as exhibited by the up-regulation of LC3 II and the down-regulation of p62 in both DN rats and podocytes. It is also noted that mangiferin increased the number of autophagosomes in the podocytes by up-regulating AMPK phosphorylation and p-ULK1 and down-regulation of mTOR phosphorylation[35].

Treatment with magniferin significantly ameliorated renal dysfunction as exhibited in another study. Magniferin efficiently reduced serum AGEs level, malondialdehyde (MDA) and 24 hours albuminuria in rat model. It significantly increased an activity of superoxide dismutase (SOD) and glutathione peroxidase (GSH) and creatinine clearance rate. Magnifierin inhibited glomerular extracellular matrix expansion and accumulation and reduced overexpression of TGF-β1 in glomeruli[36]. Similarly, beneficial renoprotective effect of magniferin was evaluated in a rat model by up-regulating glycoxalase 1 ,a detoxifying enzyme of methylglyoxal (a precursor of AGEs).In this study, magniferin was found to reduce levels of AGEs and mRNA expression of their receptor (RAGE) in the renal cortex of diabetic rat and ameliorated progression of DN. However, magniferin failed to produce reduction in blood glucose and body weight in experimental rats[37].

Berberine

Beberine (BBR) is the most active alkaloid belonging to the structural class of protoberberines. It has been commonly used as a non-prescription drug for management of diarrhea, dysentery, stomatitis and hepatitis[38]. BBR can be derived from plants such as *Coptis chinesis* (Coptis or Goldthread), *Hydrastis Canadensis* (Goldenseal), *Berberis aquifolium* (Oregon grape),*Berberis aristata* (Tree Turmeric), *Berberis vulgaris* (Barberry) and *Arcangelisia flava* [39].

Therapeutic potential of BBR was elucidated in DN in STZ induced diabetic rat model. Treatment with BBR significantly attenuated renal histological injuries due to inhibition of renal inflammation associated with inactivation of nuclear factor kappa-light-chain-enhancer of activated B-cell signaling. Subsequently, this blocked upregulation of pro-inflammatory cytokines (interleukin-1β, tumour necrosis factor-α) and chemokine (monocyte chemotactic protein-1). BBR administration was also found to inactivate TGF-β/Smad 3signalling and suppressed renal fibrosis, including expression of fibronectin, collagen I and collagen IV[40].

Potential application of berberine was proved in diabetic nephropathy in experimental model. Berberine administration in STZ induced DN rats attenuated the systemic and renal cortex inflammatory response and podocyte apoptosis. Machanistic analysis concluded the role of berberine in lowering HG-induced apoptosis of podocytes by inactivating TLR4/NF-kB pathway[41]. Similarly, in another study BBR improved renal function in diabetic rats by down-regulating inflammatory molecules. BBR significantly reduced diabetic-induced increase of TNF-α and II 6 and inhibited macrophage infiltration[42].

Beneficial role of BBR was also documented in inhibition of DN induced renal fibrosis. Treatment with BBR significantly reduced kidney injury and expression levels of TGF-β, vimentin and α-smooth muscle actin (α-SMA) suggesting importance of BBR in management of renal fibrosis[43]. Another study investigated the renoprotective mechanism of BBR by improvement in the abnormal changes in the matrix metalloproteinases/tissue inhibitor of matrix metalloproteinases (MMPs/TIMPs) system. Also BBR administration reduced TGF-β_1, fibrinectin and type IV collagen expression levels. All these collectively inhibited accumulation of extracellular matrix and ameliorated symptoms of DN[44].

Emodin

Emodin is an anthraquinone polyphenol present in medicinal herbs [45].It is commonly derived from Chinese medicinal herbs such as Rheum palmatum, Polygonum cuspidatum and Polygonum multiflorum[46].

Protective effect of emodin was recorded in high glucose (HG) induced podocyte epithelial-to-mesenchymal transition (EMT) pathway. Emodin was found to efficiently inhibit integrin-linked kinase inhibitor, reduce desmin expression and partially restored nephrin expression in HG-stimulated podocyte. Thus, emodine ameliorated HG induced EMT and correct podocyte dysfunction and albuminuria[47].

In another study emodine was demonstrated to control renal inflammation and modulate various pathways involved in DN pathogenesis in STZ induced diabetes. Emodine was found to efficiently inhibit inflammation-related factors and oxidative stress. Moreover, it suppressed the expression of

intercellular adhesion molecule 1(ICAM-1) and B-cell lymphoma 2-associated X protein (Bax).It also lead to activation of phosphorylated Akt and phosphorylated glucogen synthase kinase 3 (p-GSK-3β) expression[48].

Endoplasmic reticulum (ER) stress is cytotoxic and associated with podocyte apoptosis, thus play vital role in pathogenesis of DN. Emodin treatment in experimental mice decreased the expression of signaling pathways involved in ER stress including phosphorylated protein kinase RNA-like endoplasmic reticulum kinase (P-PERK) and phosphorylated eukaryotic initiation factor 2α (P-eIF2α) in both *in vivo* and *in vitro*. Thus emodin exert renoprotective action by inhibiting podocyte apotosis in DN[49].Furthermore, emodine efficiently provided protection in renal dysfunction by inhibiting expressions of phosphorylated mitogen activated protein kinase 38 (p38 MAPK) and downregulation of the expression of fibronectin. This decreased average kidney weight to body weight ratio, glomerular area and glomerular volume along with reduction in biochemical parameters[50].

Luteolin

Luteolin (2-[3,4-fihydroxyphenyl]-5,7-dihydroxy-4-chromenone) is a naturally occurring flavonoid present in fruits and vegetables [51].Edible plants such as pepper, celery, carrot and spinach are enriched with luteolin[52]. Plants enriched with luteolin form an important part of Chinese traditional medicine. It is well-known for its antioxidant or pro-oxidant function that produces multiple biological effects [53].

Wang et al in their experimental study concluded that luteolin administration prevented the morphological destruction of the kidney and regulated redox balance due to its direct antioxidant activity. Treatment with luteolin in STZ-induced diabetic rats showed improvement in clearance of blood urea and creatinine by kidney. Moreover, luteolin was found to reduce MDA level and increase SOD activity, suggesting its role in reducing oxidative stress in diabetes[54].

Luteolin was found to restore STZ-induced insulin resistance, dyslipidemia, hyperuricemia and renal inflammatory cell infiltration in experimental mice. This action was thought to be due to inhibition of RIP 140/NF-kB pathway and improvement in insulin signaling pathway.NF-kB is ubiquitous transcription factor responsible for regulating the expression of genes, which mediated production of inflammatory cytokines, chemokines and adhesion molecules. Lutolin induced inhibition of this pathways regulated inflammatory process in renal cells providing renoprotective effect[55].

Thymoquinone

Thymoquinone (TQ) is a monoterpene molecule, chemically known as 2-methyl-5-isopropyl-1,4-benzoquinone[56]. This bioactive compound is obtained from black seed (*Nigella sativa*) oil. It is a spice found in the Mediterranean region and in Western Asia countries including India, Pakistan and Afghanistan[57].

Kanter found that treatment with thymoquinone in STZ induced diabetic rat lead to renal morphological and functional improvement. Thymoquinone effectively reduced glomerular size, thickening of capsular, glomerular and tubular basement membranes. It increased amount of mesangial matrix and tubular dilation and renal function indicating its usefulness in DN[58].

Sayed investigated effect of thymoquinone and proanthocyanidin and combination of both in reducing oxidative stress in experimental model of DN. Both were found to efficiently reduced the elevated levels of IL-6,an inflammatory cytokines involved in thickening of glomerular basement membrane and proliferation of mesangial cells and increased endothelial permeability. Reduction in IL-6 subsequently lead to decrease in serum urea and creatinine level. Both were found to effectively increased levels of glutathione (GSH) and superoxide dismutase (SOD) activity with reduction in lipid peroxidation and NO level. This suggested potential antioxidant impact of thymoquinone in DN [59].

TQ found to offer protective effects in experimental DN by attenuating renal morphological and immunohistochemical changes in STZ-diabetic rats. TQ treatment reduced glomerular size, decreased thickening of capsular glomerular and tubular basement membranes and mesangial matrix and decreased tubular dilatation and cast formation. Immunohistochemical studies confirmed protective TQ effect by exhibiting moderate expression of ZO-1(an epithelial marker in glomeruli) and low or absent expression of FspI, desmin and MMP-17 (mesenchymal markers in glomeruli and tubules).These results suggested recovery of podocyte and tubular epithelial-mesenchymal transition (EMT) in diabetic rat with TQ treatment[60].

Trigonelline

Trigonelline (TRIG), chemically known as *N*-methylnicotinic acid ($C_7H_7NO_2$), is a major alkaloid component commonly derived from fenugreek (Trigonella foenum-graecum)[61]. This polar hydrophilic alkaloid can also be extracted from Allium sepapea, Coffea sp, Pissum sativum, Glycine max and Lycopersicon esculentum. It is well-known for its biological activities giving protection against hyperglycemia and hypercholesterolemia[62].

Role of trigonelline was investigated in diabetic hypertensive nephropathy in neonatal diabetic (nSTZ) rat model. Trigonelline was found to be effective in suppressing oxidative stress in kidney and reduced renal cell apoptosis. It improved renal function as indicated by reduction in serum creatinine and BUN levels and enhancement in glomerular filtration rate. The treatment group exhibited alleviation in the degenerative changes in kidney tissue and fibrosis[63].

Administration of trigonelline along with sitagliptin (SITA) in experimental rat model found to prevent structural kidney damage and development of DN. Concomitant administration of TRIG and SITA was found to reduce renal oxidative stress by reducing MDA content and increasing SOD and GSH concentration, suggesting development of defense mechanism against free radicles [64].

Naringenin

Naringenin is aglycone of naringin belong to series of citrus flavonoids[65]. This naturally occurring flavonone is mainly found in grapefruit and oranges. It exhibits diverse biological activities including antidiabetic, immunomodulatory, anti-inflammatory, DNA protective and antioxidant effects[66].

Nephroprotective effect of naringenin was found to be associated by ameliorating kidney injury via regulating let-7a/TGFBR1 signaling. Naringenin upregulated let-7a in mesangial cells affecting expression of Co14 and FN, thus inhibiting excessive mesangial cells proliferation.Additionally,let-7a is negatively regulated the expression of TGFBR1 which is required for downregulation of TGF-β1/smad signaling. Thus, naringenin inhibited TGF-β/smad signaling activation by upregulating let-7a[67].

Protective effect of naringenin was demonstrated in diabetic renal impairment by altering oxidative stress, modulating cytokines expression and apoptotic events. Naringenin administration in diabetic rat significantly lead to reduction

of MDA levels and increase of SOD, GSH and catalase levels in diabetic kidney. It also lead to reduction of apoptotic activity and expression of TGF-β1 and IL-1 that help to ameliorate structural alterations in the kidney tissues[68].

In diabetic mice, naringenin treatment dose-dependently reduced renal TNF-α level. It was effective in reducing production of IL-1β,Il-6 and monocyte chemoattractant protein-1.With increased dose, naringenin reduced production of type IV collagen, fibronectin and TGF-β1.It was effective in reducing protein kinase c activity, suppressed NF-kβ p65 activity, mRNA expression and protein production in kidney. Thus, naringenin exert renoprotective effect due to its anti-inflammatory and anti-fibrotic effects[69].

Hesperidin

Hesperidin is a member of flavanone group of flavonoids largely derived from citrus fruits[70]. It offers widespread health application due to its antioxidant and anti-inflammatory actions[71].

Jain et al found nephroprotective effect of hesperidin in early DN in experimental type 2 diabetic rats associated with antioxidant property. It was found to effectively revere creatinine clearance and attenuated hyperfiltration suggesting its role in prevention of progression of early DN. Moreover, it was found to be effective in restoring structural changes in kidney including thickening of basement membrane and mesangial expansion[72].Another study explored the renoprotective role of hesperidin by suppressing TGF-β1-ILK-Akt signaling pathway. Administration of hesperidin for 4 weeks regulated blood glucose level and impaired glucose tolerance ability in diabetic mice. It normalized pathological abnormalities in renal tissues including distortion in glomerular basement membrane and expanded mesangial regions. Also, it repaired podocyte function by increasing renal nephrin expression and decreasing renal alpha smooth muscle actin expression. This effect was considered due to hesperidin induced inhibition of expression of TGF-β1 and downstream effector integrin-linked kinase and Akt[73].

Aliskiren

Aliskiren is an orally active nonpeptide direct renin inhibitor, which plays pivotal role in DN by blocking renin-angiotensin-aldosterone system (RAAS)[74]. Chemically aliskiren is known as 2(S),4(S),5(S),7(S)-N-(2-carbamoyl-2-methylpropyl)-5-amino-4-hydroxy-2,7 diisopropyl-8-(4-methoxy-3-[3-methoxypropoxyl-]phenyl)-octanamide[75].

Renin is rate-limiting enzyme of the renin-angiotensin system (RAS).It generates angiotensin I and signals through the (pro)renin receptor (p)RR to exert angiotensin II-independent effects. This plays major role in damaging renal cells in DN. Aliskiren was found to effectively alleviated albuminuria and glomerulosclerosis. Morphologically, it was found to be effective in reducing thickening of the glomerular basement membrane and reduced podocyte loss. It ameliorates diabetic renal injury by compensatory increase in renin in the glomeruli due to blockage of the negative feedback loop and partially suppressed the intracellular signaling mediated via receptor (p)RR activated in hyperglycemia[76]. Clinically, renoprotective effect of both aliskiren monotherapy and in combination with pentoxifylline was demonstrated in patients with DN. Monotherapy with aliskiren showed significant antiproteinuric effect by reducing urinary albumin excretion (UAE).Effect is due to aliskiren induced inhibition of the rate-limiting step in the RAS (conversion of angiotensinogen to ANG I via renin).Thus, aliskiren is effective as renoprotective agent by blocking generation of angiotensin II completely and inhibiting effects produced via activation of (p)RR. Similarly, aliskiren found to reduce serum creatinine level by inducing complete blockage of Ang II generation and inhibition of (p)RR effects[77].

Renoprotective role of aliskiren was also recorded in another clinical study involving type 2 diabetic patients with insufficient blood pressure control. Administration of aliskiren (300 mg) in combination with losartan reduces albuminuria of DN independent of baseline blood pressure[78].

Myricetin

Myricetin is a plant derived flavonoid, well-known for its neutraceutical properties[79]. It is commonly consumed as a part of human diet through fruits, vegetables, tea, berries and red wine[80].

An experimental study found improvement in altered renal functions and restoration of renal activities in DN with myricetin treatment. Myricetin administration in STZ-induced diabetic rat efficiently decreased glomerulosclerosis and reduced BUN and proteinuria. It also found to improve creatinine clearance and restored altered renal activities of glutathione peroxidase (GPx) and xanthine oxidase (XO)[81]

Myricetin was found to produce remarkable nephroprotection in STZ-cadmium induced diabetic nephrotoxicity in rat model. Structurally, myricetin suppressed extracellular mesangial matrix expansion, glomerulosclerosis and interstitial fibrosis in nephrotoxic rats. It was demonstrated that myricetin suppressed sterol regulatory element binding protein-1a (SREBP-1a), SREBP-1c,SREBP-2, TGF-β_1 and vascular endothelial growth factor (VEGF). It also upr

egulated peroxisome proliferator-activated receptor alpha (PPAR-α) protein expression[82].

Apigenin

Apigenin (4′,5,7,-trihydroxyflavone) is a yellow crystalline powder belonging from flavone class[83].This bioactive flavonoid is widely investigated for antioxidant, anti-inflammatory and anticancer properties[84].

Apigenin was found to halt the development and progression of DN in experimental model by suppressing oxidative stress and fibrosis. When apigenin in dose of 20mg/kg was administered in STZ-induced diabetic rat, it attenuated renal dysfunction, oxidative stress and fibrosis by inhibiting MAPK pathways. Apigenin was recorded to reduce TGF-β1, fibronectin and type IV collagen. Apigenin prevented MAPK activation which subsequently inhibited inflammation by reducing TNF-α, IL-6 and NF-kB expression. Inhibition of MAPK lead to reduction in apoptosis by increasing expression of Bcl-2 and decreased Bax and caspase-3[85].Apigenin administration in diabetic rats normalized the deterioration in kidney by reversing swelled Bowman's capsule of kidneys, damaged glomeruli and nephritic cells[86].

Paeoniflorin

Paeoniflorin (PE) is the active component of *Paeonia lactiflora Pall* or *Paeonia veitchil* Lynch[87]. PE is monoterpene glycoside, the β-glucoside of paeoniflorigenin. It is commonly used in Chinese Traditional Medicine[88].

Investigational studies showed that PE prevented the progression of DN by modulating inflammatory process.PE was found to be efficient in normalizing urinary albumin creatinine ratio. Also, it significantly suppressed glomerular hypertrophy, expression of TGF-β, type IV collagen, intracellular adhesion molecule 1 and renal infiltration of macrophages[89]. Likewise, PE is noted to have therapeutic

potential for DN by mediating anti-inflammatory actions. Toll-like receptors (TLRs) are involved in pathogenesis of DN by promoting inflammation.12 weeks intraperitoneal injection of paeoniflorin efficiently reduced albuminuria with restoration of renal histopathology. Paeoniflorin was effective in reducing macrophage infiltration with reduced expression of TLR_2 signaling pathway biomarkers[90]. Similarly, anti-inflammatory and immuneregulatory mechanism of PE was evaluated in both *in vivo* and *in vitro* studies. In *vivo*, PE could reduce albuminuria and inhibited macrophage infiltration and activation through blockage of the $TLR_2/4$ signaling pathway. *In vitro*, PE reduced the AGEs-induced $TLR_2/4$ activation and subsequently controls inflammatory responses[91].

12 weeks treatment with paeoniflorin restored functional and histological damage to kidney. In this study, PE exerted renoprotective effect with reduction of macrophage infiltration and inflammatory factor expression. Additionally, PE was effective in suppressing Janus kinase (JAK)2/signal transducer (STAT)3 signaling pathway which regulates a broad range of biological effects including cell proliferation, differentiation, inflammation and apoptosis[92].

Table 1: Phytoconstituents with mechanism of action

S. No	Phytoconstituents	Targeted metabolic pathway/Mechanism of action	Ref
1	Curcumin	Suppression of NOD-like receptor 3 (NLRP3) inflammasome Reduction in oxidative stress	25 26
2	Quercetin	Attenuatation of overexpression of TGF-β1 and CTGF Exhibit high antioxidant activity	29 30
3	Mangiferin	Modulation of ROS-induced PKCs, MAPKs, NF-kB and TGF-β1 mediated and TNFα related mitochondrial dependent apoptotic pathways Promote autophagy by the up-regulation of LC3 II and the down-regulation of p62 and increase the number of autophagosomes in the podocytes by up-regulating AMPK phosphorylation and p-ULK1 and down-regulation of mTOR phosphorylation	34 35
4	Berberine	Inactivate TGF-β/Smad 3 signalling and suppressed renal fibrosis, including expression of fibronectin, collagen I and collagen IV Lowering of HG-induced apoptosis of podocytes by inactivating TLR4/NF-kB pathway	40 41
5	Emodin	Inhibit integrin-linked kinase inhibitor, reduce desmin expression and partially restored nephrin expression in HG-stimulated podocyte Suppression of the expression of ICAM-and Bax-protein, activation of phosphorylated Akt and p-GSK-3β expression	47 48
6	Luteolin	Reduction of oxidative stress Inhibition of RIP 140/NF-kB pathway and improvement in insulin signaling pathway	50 55
7	Thymoquinone	Reduction of oxidative stress Moderate expression of ZO-1and low or absent expression of FspI, desmin and MMP-17	59 60
8	Trigonelline	Suppression of oxidative stress	63
9	Naringenin	Inhibition of TGF-β/smad signaling activation by upregulating let-7a Reduction of oxidative stress	67 68
10	Hesperidin	Antioxidant property	72
11	Aliskiren	Blocking renin-angiotensin-aldosterone system	73
12	Myricetin	Restored altered renal activities of glutathione peroxidase (GPx) and xanthine oxidase (XO) Suppressed SREBP-1a,SREBP-1c,SREBP-2, TGF-β_1 and VEGF and upregulated PPAR-α protein expression	81 82
13	Apigenin	Prevented MAPK activation which subsequently inhibited inflammation by reducing TNF-α,IL-6 and NF-kB expression and reduction in apoptosis by increasing expression of Bcl-2 and decreased Bax and caspase-3	85
14	Paeoniflorin	Reduction in macrophage infiltration with reduced expression of TLR_2 signaling pathway biomarkers Reduction in AGEs-induced $TLR_2/4$ activation and control of inflammatory responses Suppression of Janus kinase (JAK)2/signal transducer (STAT)3 signaling pathway	90 91 92
15	Rutin	Reduction in expression of AGEs, collagen IV, laminin, TGF-β1,p-Smad 2/3 and CTGF Inhibition of expression of $ACTA_2$ and p38	96 97
16	Allicin	Inhibition of expression of collagen I,TGF-β1 and p-ERK ½	100

Rutin

Rutin, chemically known as 3,3′,4′,5,7-pentahydroxyflavone-3-rhamoglucoside,is a flavonoid abundantly present in plant kingdom[93]. This vital nutritional component of diet is commonly found in passion flower, buckwheat, tea and apple[94]. It offers diverse range of pharmacological application due to its significant antioxidant property[95].

Nephroprotective effect of rutin was proved in a clinical study involving patient with long-term diabetes mellitus. Administration of rutin supplementation tablets over period of 120 days decreased serum levels of urea and creatinine, which minimizes the risk of kidney damage and failure[34].

10 weeks oral administration of rutin prevented development of DN in STZ induced diabetic rats. Hers, rutin decreased the levels of FBG, serum creatinine, urine protein and BUN. It also reduced expression of AGEs, collagen IV, laminin, TGF-β1,p-Smad 2/3 and connective tissue growth factor (CTGF).Thus, rutin offered renoprotective effect by inhibiting proliferation of mesangial cells and decreased thickness of glomerular basement membrane[96]. Protective

effect of rutin was also proved on high-glucose-induced mesangial cell group. Actin,α2,smooth muscle, aorta ($ACTA_2$) is an important protein required for the contraction of vascular smooth muscle cell.p38 is a key component of mitogen-activated protein kinase-mediated signaling pathway involved in proliferation, apoptosis and inflammation. High glucose induced mesangial cells showed increased expression of both $ACTA_2$ and p38.Rutin administration significantly inhibited expression of both $ACTA_2$ and p38. It also inhibited glucose induced cell viability and ATP content and thus regulated cell cycle progression in mesangial cells[97].

Allicin

Allicin (allyl 2-propenethiosulfinate or diallylthiosulfinate) is the principle bioactive compound present in garlic (*Allium sativum* L.)[98]. It is produced during tissue damage from non-proteinogenic amino acid alliin (S-allylcysteine sulfoxide) in a reaction catalyzed by the enzyme alliinase. Presence of thiosulfinate makes allicin as a reactive sulfur species (RSS).It undergoes a radox-reaction with thiol groups in glutathione and protein which is responsible for diverse range of biological activities[99].

12 weeks treatment with allicin induced protective effect on renal damage in STZ diabetic rats. Allicin reduced altered biochemical parameter in DN including FBG, BUN, serum creatinine and albuminuria. It inhibited expression of collagen I, TGF-β1 and phosphorylated extracellular signal-regulated kinase ½ (p-ERK ½). These results were associated with recovery in morphological alterations of the kidney in DN with allicin treatment[100].

Conclusion

In summary, results obtained from various experimental studies revealed that use of phytoconstituents in DN improves biochemical markers and antidiabetic cellular mechanism. Our incipient understanding about beneficial effect of phytoconstituents in DN indicate requirement of further experimental studies exploring mechanism of action, effectiveness and safety in details.

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