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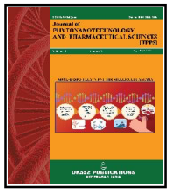

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Diabetic nephropathy: An outline on molecular mechanism and protective pathways of phytoconstituents

Mohd Hashim*, Badruddeen◆, Juber Akhtar*, Mohammad Irfan Khan*, Mohammad Ahmad*, Anas Islam*, Asad Ahmad* and Fatima Zahra**

** Faculty of Pharmacy, Integral University, Lucknow-226026, Uttar Pradesh, India*

*** Department of Pharmacology, Rameshwaram Institute of Technology and Management, Lucknow-227202, Uttar Pradesh, India*

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Abstract

Diabetic nephropathy is a debilitating complication of diabetes mellitus characterized by progressive kidney damage. This review provides a comprehensive overview of the molecular pathways underlying its pathogenesis and explores the protective mechanisms offered by various phytobioactives. The pathogenetic mechanisms of diabetic nephropathy are multifaceted, encompassing the activation of key pathways such as the rennin angiotensin-aldosterone system (RAAS), the polyol pathway, protein kinase C (PKC) pathway, hexosamine pathway, and the formation of advanced glycation end products (AGEs). Understanding these pathways is crucial for developing effective therapeutic strategies to combat diabetic nephropathy. In parallel, this review sheds light on the role of phytobioactives, including alkaloids, flavonoids, tannins, and stilbenes, in mitigating the progression of diabetic nephropathy. These natural compounds exhibit a spectrum of protective properties, including antioxidative and anti-inflammatory effects. Their ability to modulate the molecular pathways implicated in diabetic nephropathy offers promising avenues for novel therapeutic interventions. This review of the pathogenetic mechanisms and the protective potential of phytobioactives underscore the importance of considering natural compounds as adjunctive therapies in managing diabetic nephropathy, potentially improving patient outcomes and quality of life.

1. Introduction

Due to its rising frequency and incidence, diabetes mellitus (DM) poses a major risk to the health of all people. In 2019, there were 463 million persons worldwide who had DM. By 2045, the International Diabetes Federation (IDF) predicts that this number would have surpassed 700 million (IDF, 2023; Kumaraswamy *et al.,* 2022). A chronic metabolic condition known as diabetes mellitus (DM) causes higher than normal blood sugar levels (hyperglycemia) as a result of impaired insulin secretion, cellular resistance to insulin, or both (Punthakee *et al.,* 2018). There are two main varieties of diabetes: type 1, in which the pancreas cannot generate insulin, and type 2, in which the body cannot effectively use the insulin that is produced (Latha and Vijaykumar, 2019). Microvascular consequences caused by DM include diabetic nephropathy (DN), diabetic retinopathy, and diabetic neuropathy in addition to macrovascular issues such stroke, cardiovascular disease (CVDs), and peripheral vascular disease (Adapa and Sarangi, 2015; Okur *et al.,* 2017).

Diabetic nephropathy, also known as diabetic kidney disease, is a persistent renal ailment that has the potential to impact individuals diagnosed with either type 1 or type 2 diabetes. About 40% of all cases of diabetes are affected by DN, and projections indicate that by 2023, there will be 382 million cases of diabetes worldwide, or 8-10% of the world's population (Lim, 2014). Diabetic nephropathy (DN) is characterized by a plethora of clinical manifestations, including heightened arterial blood pressure, a compromised glomerular filtration rate (GFR), the presence of diabetic glomerular lesions, and escalated urine albumin excretion levels surpassing the threshold of 300 mg/day (Gheith *et al.,* 2016). High blood sugar damages renal blood vessels, which leads to kidney dysfunction and is the underlying cause of DN (Gajjala *et al.,* 2015). There are five stages of kidney degeneration associated with DN, and stage 4 is typically when symptoms first appear. It is advised that diabetics have annual renal problems screenings because symptoms do not manifest until later stages. The swelling of ankles, legs, and hands due to water retention, blood in the urine, exhaustion from low oxygen levels in the blood, and nausea are the defining characteristics of the fourth stage of DN. If left unaddressed, this can progress to end-stage renal disease (ESRD), which is the fifth and final stage, where dialysis or kidney transplantation are the only viable treatment options as the kidneys can no longer function to meet daily needs. The risk factors associated with developing DN include hypertension dyslipidemia, smoking and poor glycemic control. A person's genetic makeup also has a significant impact on developing DN because those with a family history of the condition are more likely to do so (Ahmad *et al.,* 2013). According to current reports, DN accounts for 30 - 40% of ESRD cases in the US and is one of the main causes of ESRD (Ghaderian *et al.,* 2015).

Corresponding author: Dr. Badruddeen

Professor, Faculty of Pharmacy, Integral University, Lucknow-226026, Uttar Pradesh, India

E-mail: badarmiracle@gmail.com

Tel.: +91-9918196188

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Email: ukaaz@yahoo.com; Website: www.ukaazpublications.com

2. Pathogenesis of DN

The etiology of diabetic nephropathy (DN) is multifactorial. The onset of hyperglycemia is a pivotal event that triggers structural and functional alterations in the renal system, such as glomerular hyperfiltration, hypertrophy of glomerular and tubular epithelium, and microalbuminuria. Eventually, thickening of the glomerular basement membrane, accumulation of mesangial matrix, overt proteinuria, glomerulosclerosis, and end-stage renal disease (ESRD) ensue. There are number of pathways involved in pathogenesis of DN (Figure 1).

2.1 Protein kinase C pathways

The pathogenesis of diabetic nephropathy (DN) has been associated with elevated flux of glucose through the hexosamine pathways, leading to an increase in TGF-β expression (Kolm-Litty *et al*., 1998). This occurs due to the glycosylation of transcription factor Sp1 by N-acetylglucosamine, causing fructose-6-phosphate from glycolysis to convert to glucosamine-6-phosphate, thereby promoting TGF-β transcription. The hexosamine pathway also upregulates the expression of upstream stimulatory factors (USFs), which activate the TGF 1 promoter (Weigert *et al*., 2004). Furthermore, intracellular glucose accumulation increases the de novo production of diacylglycerol (DAG) from glycolytic intermediates such as dihydroxyacetone phosphate (Haneda *et al*., 2003). Consequently, the activation of protein kinase C isoforms by DAG and inhibition of PKC, the main isoform generated by hyperglycemia in the kidney, reduces DN. Activation of PKC may also stimulate MAPKs, including Erk 1,2 and p38 MAPK, which have been implicated in DN signaling processes (Haneda *et al*., 2003). Additionally, ROS activation of MAPKs may lead to cross-talk between the various pathways (Heilig *et al*., 2001). Recent findings have demonstrated the significance of PKC in the development of various DN alterations, as albuminuria was found to be absent in diabetic PKC-α deficient mice, although PKC-α deficiency had no effect on glomerular hypertrophy or the up-regulation of TGF-β (Menne *et al*., 2004).

2.2 Advance glycation end products

In chronic hyperglycemia, the extra glucose reacts with tissue proteins or free amino acids. DN is created as a result of this glycosylation. Initial products of this process are reversible early glycosylation products, and later, AGE. Because of the rise in AGEs, the glomerular epithelial cells' matrix proteins accumulate, collagenase activity declines, and the tight connection between the cells becomes defective (Singh *et al.,* 1998).

2.3 Oxidative stress

The metabolic activity of the nephron generates a significant amount of reactive oxygen species, which are counterbalanced by numerous antioxidant enzymes and free radical scavenging systems. These reactive oxygen species are responsible for harmful biological effects, such as protein oxidation, renal vasoconstriction, and DNA damage. Unfortunately, hyperglycemia exacerbates the production of reactive oxygen species, primarily within the mitochondria (Nishikawa *et al*., 2007). Reactive oxygen species also contribute to the adverse pathways that glucose may take when hyperglycemia occurs, such as PKC activation and advanced glycation end product formation (Kiritoshi *et al*., 2003; Vasavada *et al*., 2005). Even prior to the onset of diabetes, hyperglycemia induces oxidative stress. In patients with more severe nephropathy (*i.e*., proteinuria versus microalbuminuria), there are higher levels of DNA damage indicators triggered by reactive oxygen species. Additionally, biopsies of human kidney specimens from individuals with diabetes have revealed glyco-oxidation products (*i.e.,* combined products of glycation and protein oxidation) and lipoxidation in the mesangial matrix and glomeruli, which are less prevalent in specimens from non-diabetic individuals (Suzuki *et al*., 1999).

2.4 Polyol pathways

The process of converting glucose to sorbitol through aldose reductase and subsequently to fructose by sorbitol dehydrogenase is observed within the polyol pathway. An increase in glucose uptake by the cell leads to a greater influx of glucose into the polyol pathway. The reduction of glucose to sorbitol necessitates the depletion of NADPH in cells, which is a vital substrate for the regeneration of glutathione. This, in turn, exacerbates intracellular oxidative stress. It is crucial to note that three deoxyglucone, an intermediate substance, serves as a precursor for AGEs (Haneda *et al.,* 2003; Bernobich *et al.,* 2004).

2.5 Renin angiotensin aldosterone system (RAAS)

Diabetic nephropathy is a serious complication of diabetes mellitus that arises due to a complex cascade of physiological processes. It begins with the activation of the renin angiotensin aldosterone system (RAAS). In response to various factors such as elevated blood sugar levels, the body increases the release of renin, an enzyme produced by the kidneys. Renin sets off a chain reaction, leading to the production of Angiotensin II, a potent vasoconstrictor. As Angiotensin II levels rise, it causes the blood vessels in the kidneys to constrict, resulting in increased pressure within the glomeruli, the tiny filtration units in the kidneys. This heightened pressure, over time, damages the delicate kidney cells, particularly those responsible for filtration. As a consequence of this damage, these cells become less effective at retaining essential proteins, such as albumin, within the bloodstream. The loss of albumin into the urine, known as albuminuria, is a hallmark sign of diabetic nephropathy. Over time, if left uncontrolled, this condition can progress to more severe kidney dysfunction, ultimately leading to end-stage renal disease (Rahimi, 2016; Sato *et al.,* 2003).

3. Phytochemicals

A plant-based diet's many health benefits are attributable to phytochemicals, which are organic compounds found in plants (Liu, 2013). Phytochemicals are classified into numerous classes according to their chemical composition, each of which has unique properties and potential health advantages. Phytochemical subgroups such as carotenoids, flavonoids, phenolic acids, alkaloids, and terpenoids are frequently found (Koche *et al.,* 2016). It has been shown that many phytochemicals have pharmacological action, which implies that they may interact with the body to produce benefits for the cardiovascular system, nervous system, anticancer, antiviral, and anti-hyperglycemic qualities (Hang *et al.,* 2018; Islam *et al.,* 2023). Because of their anti-inflammatory and nephroprotective properties, they are believed to have health benefits. There are number of reported phytochemicals having protective role DN (Table 1).

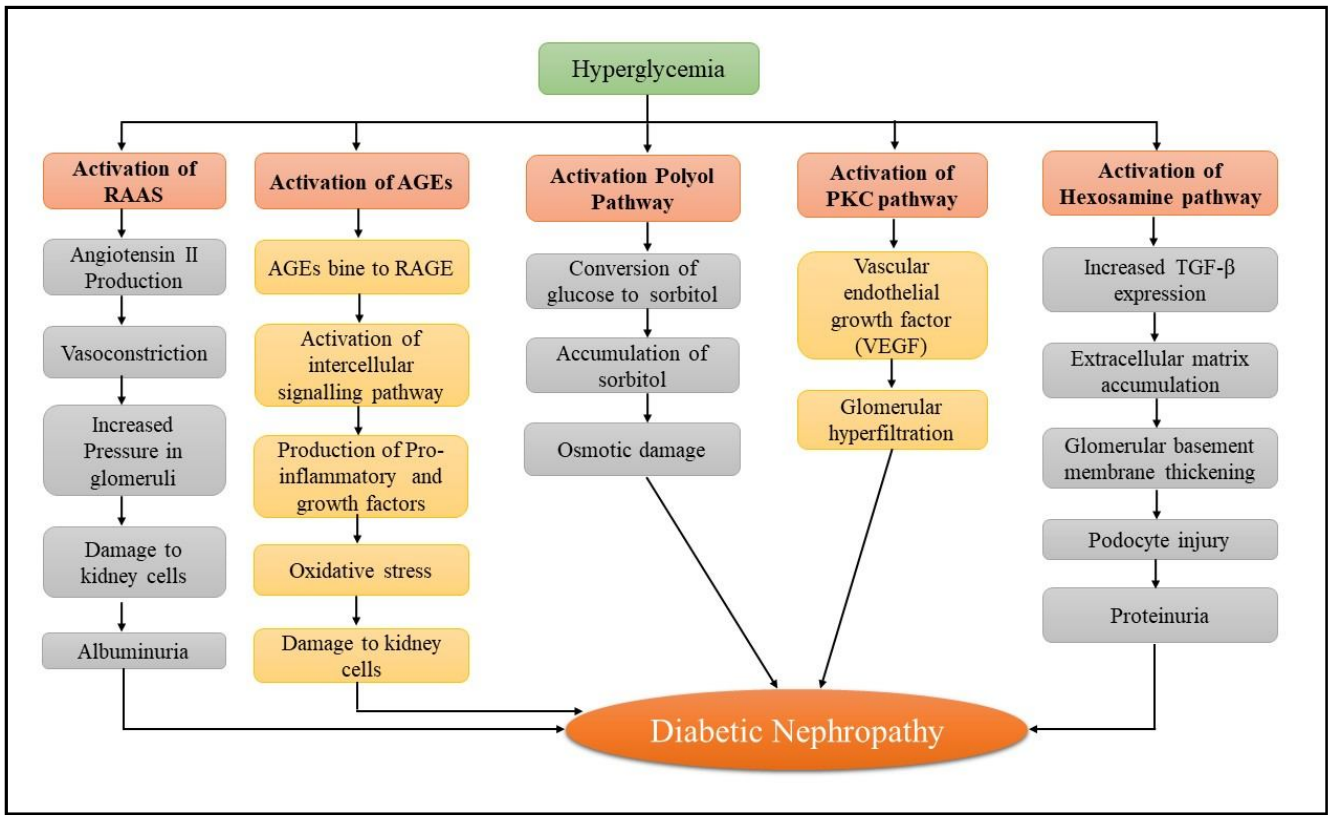

Figure 1: Different pathways of diabetic nephropathy.

3.1 Alkaloids

3.1.1 Berberine

In an animal model, berberine has proven to be an efficient diabetic nephropathy (DN) treatment. BUN, SCR, proteinuria, KI, IL-6, TNF-α, oxidative stress, and MDA are all indications of improved renal function, as are risk factors TG, TC, and LDL. Because of its antifibrotic, anti-inflammatory, and antioxidative stress capabilities, it has positive benefits (Hu *et al.,* 2022; Ni *et al.,* 2015). By deactivating the TLR4/NF-κB pathways, BBR lowers kidney damage, inflammation, and podocyte death in DN (Zhu *et al.,* 2018). By preventing the growth of the glomerular mesangial matrix through the activation of AMPK, HGSD, a novel berberine solution, enhances kidney function, decreases glomerular volume, activates autophagy, and guards against diabetic kidney disease (Zhang *et al.,* 2020). By suppressing the NLRP3 inflammasome, BBR can reduce tubulointerstitial fibrosis and epithelial-to-mesenchymal transition (EMT) in diabetic kidney disease (DKD) (Ma *et al.,* 2022). Berberine's potential as a DN treatment is suggested by the possibility that it may lessen renal fibrosis, decrease glomerular hypertrophy and mesangial matrix growth, decrease TGF-β and -SMA expression, and lessen kidney damage (Li *et al.,* 2017). Because it controls glucose uptake, inhibits the PI3K/Akt/AS160/GLUT1 signalling pathways, and stops abnormal glomerular mesangial cell (GMC) proliferation, berberine has the potential to treat DN-related renal pathology and glomerular dysfunction (Ni *et al.,* 2022). Berberine has the potential to treat DN by reducing tubulointerstitial fibrosis. It accomplishes this by promoting Nrf2 pathways, blocking TGF-β/Smad/EMT signalling, and lowering oxidative stress, which eventually results in kidney protection (Zhang *et al.,* 2016). The combination of metformin and berberine displays increased anti-diabetic nephropathy effects by reducing blood sugar, boosting insulin sensitivity, improving lipid metabolism, and lessening renal damage. This combination improves renal function by upregulating Trib1, downregulating C/EBP, inhibiting lipid synthesis proteins, and decreasing NF-κB signalling (Zhang *et al.,* 2021). Berberine has protective properties in streptozotocin-induced DN *via* modulating the G protein-adenylyl cyclase (AC)-cAMP signalling pathway, lowering glomerular mesangial cell (MC) proliferation, and alleviating renal damage (Tang *et al.,* 2013). Through inhibition of aldose reductase (AR) activity, reduction of oxidative stress, enhancement of extracellular matrix formation, and cell proliferation, berberine exhibits potential in the treatment of renal dysfunction in DN (Liu *et al.,* 2008).

3.1.2 Boldine

Due to its anti-inflammatory, antioxidant, and hypoglycemic properties, the alkaloid boldine from the boldo plant has therapeutic potential. Boldine reduced blood pressure, oxidative stress, elevated blood sugar, and protein leakage in diabetic rats. Additionally, it decreased kidney damage indicators and matrix protein changes (Hernández-Salinas *et al.,* 2013). In hypertension, boldine therapy decreased systolic blood pressure, oxidative stress, and kidney damage. Additionally, it prevented inflammation (ED-1, OPN) and kidney injury (-SMA, COM III) indicators in the 2K1C animals. Boldine stopped RAS mediators (ACE-1, TGF-β) from rising (Gomez *et al.*, 2018).

3.1.3 Trigonelline

Trigonelline, an alkaloid present in the extract of various plants such as *Trigonella foenum-graecum*, Coffea sp., *Glycine max*, and *Lycopersicon esculentum*, displays diverse biological effects, encompassing cancer treatment, hyperglycemia, high cholesterol, and hormonal imbalances (Mohamadi *et al*., 2018). Research studies have indicated that trigonelline greatly reduces the expression of FN and collagen IV in mesangial ECM in DKD rats, thereby significantly decreasing oxidative stress and pathological alterations in the kidneys (Shao *et al*., 2019). In the context of treating human mesangial cells (HMCs) activated by HG, trigonelline was found to dramatically decrease the levels of FN and collagen IV, as well as the hyperproliferation of HMCs. Further, trigonelline prevented the activation of the Wnt/β-catenin signaling pathway, thereby decreasing cell cycle progression and apoptosis (Chen *et al*., 2022). In DKD rats, trigonelline increased the expression of peroxisome proliferator-activated receptor-gamma (PPAR-γ) and glucose transporter type 4 (GLUT4) proteins, while suppressing the expression of leptin and tumor necrosis factor alpha (TNF-α) proteins, thus decreasing oxidative stress, inflammation, and kidney cell apoptosis (Li *et al*., 2019). Trigonelline has been found by (Chen *et al*., 2021) to upregulate the expression of miR-5189-5p, lower the amount of the inhibitor of hypoxia-inducible factor 1 subunit alpha (HIF1AN), activate the AMPK signaling pathway, increase the level of autophagy, and protect renal mesangial cells (Chen *et al*., 2021). The administration of trigonelline to mice at a dose of 50 mg/kg for 21 days did not cause any changes in the weight of the liver, kidney, thymus, thyroid, or adrenal gland (Zhou *et al*., 2012). Additionally, trigonelline has been found to enhance renal function by increasing apoptotic cell death in the kidney, decreasing oxidative stress, and reducing kidney tissue fibrosis and degenerative alterations, which suggests its potential in preventing kidney damage in diabetic rats (Ghule *et al*., 2012).

3.2 Flavonoids

3.2.1 Quercetin

In DN, quercetin has protective properties. Reduced polyuria, lower blood sugar, and normalised hypertriglyceridemia are the effects of quercetin therapy. Additionally, it lowers proteinuria, lowers creatinine levels, and guards against alterations to the structure of the kidneys (Gomes *et al.,* 2015). The blood glucose level was the only one that quercetin treatment did not improve in diabetic rats with raised kidney weight, urine albumin, serum creatine, blood urea nitrogen, and impaired creatinine clearance. Additionally, TGF-1 and CTGF expressions were elevated in diabetic rats, which quercetin reduced (Lai *et al.,* 2012; Gomes *et al.,* 2014; Elbe *et al.,* 2015). Quercetin dramatically improves renal indicators, lowering creatinine, blood urea nitrogen, urine protein, albumin, malondialdehyde, and interleukin-1 while raising the activity of superoxide dismutase and catalase (Hu *et al.,* 2022; Goswami *et al.,* 2023). The treatment of quercetin considerably reduced oxidative stress (lowered malondialdehyde while raising superoxide dismutase and catalase activity) and enhanced a number of renal function markers. By lowering levels of interleukin-1 (IL-1) and tumour necrosis factor-alpha (TNF-α), it also demonstrated anti-inflammatory effects (Feng *et al.,* 2022). Mesangial index, Scr, BUN, proteinuria, BG, and other indicators were decreased by quercetin, whereas HDL-C, SOD, GSH, and other markers were increased. By acting through pathways like PI3K/PKB, AMPK-P38 MAPK, Nrf2/HO-1, *etc*., quercetin improved kidney disease (Li *et al.,* 2022). Quercetin has potential therapeutic effects in cardiovascular and renal illnesses; however, it is unclear how it affects the growth of glomerular mesangial cells (MC) in early DN. The effect of quercetin on high glucose-induced MC proliferation in mice, which showed that it inhibited MC proliferation through activating the Hippo pathway (Lei *et al.,* 2019). In diabetic situations, quercetin reduces EMT and renal fibrosis, possibly through modifying mTORC1/p70S6K and certain transcription factors (Lu *et al.,* 2015). Early diabetic kidney damage is safely and effectively treated by quercetin, which may do so via enhancing lipid metabolism *via* the SCAP-SREBP2-LDLr signalling pathway (Jiang *et al.,* 2019). Early diabetic kidney damage is safely and effectively treated by quercetin, which may do so *via* enhancing lipid metabolism *via* the SCAP-SREBP2-LDLr signalling pathway (Liu *et al.,* 2022). According to studies, quercetin possesses substantial anti-diabetic properties that could lower blood sugar levels and improve insulin sensitivity. It affects important elements and signalling pathways, including TNF-α, NF-κB, AMPK, AKT, and Nrf2, that are involved in insulin resistance and the onset of type 2 diabetes. By focusing on the underlying mechanisms, quercetin has also shown promise in preventing and treating diabetes complications, including diabetic nephropathy (Yan *et al.,* 2022).

3.2.2 Curcumin

In diabetic rat kidneys and glomerular mesangial cells (GMCs) exposed to high glucose, curcumin lowered SphK1 expression, activity, and S1P synthesis, which in turn reduced FN and TGF-β1 overproduction. AP-1 DNA-binding activity was also decreased by curcumin, and c-Jun-siRNA restored the up-regulation of SphK1 brought on by HG (Huang *et al.,* 2013). The effects of curcumin treatment included decreased albuminuria, mesangial matrix expansion, and renal hypertrophy, as well as decreased collagen IV and fibronectin expression and levels of interleukin-1β, cleaved caspase-1, and NLRP3 protein. Curcumin may be used to treat diabetic nephropathy by inhibiting the NLRP3 inflammasome (Lu *et al.,* 2017). Curcumin significantly reduced the phosphorylated ERK1/2 and PKC-α and PKC-β1 activity caused by high hyperglycemia. Additionally, curcumin reduced the expression of ECM proteins such fibronectin and type IV collagen as well as TGF-β1, CTGF, osteopontin, and p300 (Soetikno *et al.,* 2011).

3.2.3 Kaempferol

Kaempferol (3,5,7-trihydroxy-2-[4-hydroxyphenyl]-4H-1-benzopyran-4-one) is a natural flavonoids compound. Various sources of this substance can be observed in conventional medicinal practices, including, ginkgo, Sophora japonica and galangal, as well as in consumables such as, cauliflower, gooseberry, cabbage, strawberries, grapes, tomatoes and tea (Burgos-Moron *et al.,* 2011). Kaempferol has anti-inflammatory (Crespo *et al.,* 2008), anti-oxidative stress (Suh *et al.,* 2009). antitumor (Mylonis *et al.,* 2010), anti-atherosclerotic (Feng *et al.,* 2021), hypoglycemic (Alkhalidy *et al.,* 2018), and hypolipidemic (Torres-Villarreal *et al.,* 2019) effects. Kaempferol treatment prevented weight loss, renal damage, and alterations in biochemical parameters. It also reduced inflammation markers, caspase-3, p38, and increased anti-apoptotic factors. Kaempferol improved glucose, insulin levels, reduced oxidative stress, and upregulated Nrf2/HO-1, suggesting its

antioxidant potential in preventing diabetic nephropathy (Alshehri, 2023). A study reported, based on in vitro tests using rat and human renal tubular epithelial cells, indicate that kaempferol inhibits RhoA activation, reduces oxidative stress, pro-inflammatory cytokines, and fibrosis-related markers (Sharma *et al.,* 2019). kaempferol treatment increased GLP-1 and insulin release, improved renal histology, reduced fibrosis, and downregulated key markers of DN (Sharma *et al.,* 2020). The potential of kaempferol as a therapeutic agent to mitigate inflammation. It reduced renal inflammation, fibrosis, and kidney dysfunction in diabetic mice by downregulating TRAF6. *In vitro*, KPF attenuated high glucose-induced inflammatory and fibrogenic responses in renal cells by downregulating TRAF6 (Luo *et al.,* 2021). Kaempferol shows protective action against DN by enhancing podocyte autophagy and reducing apoptosis, likely mediated through the AMPK/mTOR pathway (Sheng *et al.,* 2022). Kaempferol effects were associated with increased SIRT1 levels and activity, as well as enhanced acetylation of Nrf2 and NF-κB. The SIRT1 inhibitor, kaempferol alleviates DOX-induced nephropathy by upregulating and activating SIRT1 (Alagal *et al.,* 2022). Kaempferol treatment significantly attenuated kidney injury, and functional disturbances. It reduced oxidative stress, inflammation, and apoptotic markers while promoting antioxidant enzyme levels. Kaempferol's effects were associated with modulation of NF-κB p65 and Nrf2 pathways (Alshehri *et al.,* 2022). Kaempferol attenuated D-ribose-induced changes in mesangial cells, possibly by repairing autophagy and reducing AGE accumulation and ROS production (Zhang *et al.,* 2019).

3.2.4 Rutin

The preventive effect of Rutin on diabetic nephropathy (DN) is closely associated with oxidative stress and various signaling pathways, such as TGF-β1/Smad/ECM and TGF-β1/CTGF/ECM, thus highlighting its potential as a preventive treatment for DN in rats (Hao *et al*., 2012). Recent studies have revealed that Rutin administration effectively prevents the progression of diabetic nephropathy and cardiomyopathy by improving fibrosis and metabolic acidosis (Ganesan *et al*., 2020). Furthermore, the combined treatment of Rutin and Selenium significantly reduces the levels of IL-6, NF-κB, TNF-α, Jak-2, and p-Stat3, indicating a potential renoprotective effect against DN through the upregulation of Nrf-2/HO-1 and downregulation of Jak-2/Stat3 pathways (Zaghloul *et al*., 2022). The protective potential of Rutin against diabetic complications is attributed to its ability to decrease the formation of harmful substances associated with hyperglycemia, such as sorbitol, reactive oxygen species, advanced glycation end-products, and inflammatory cytokines (Ghorbani, 2017). Rutin was administered at various doses and found to inhibit high glucose-induced mesangial cell viability, ATP content, and expression of ACTA2 and p38. Furthermore, it improved the cell cycle progression of mesangial cells, thereby highlighting the potential of Rutin as a preventive and therapeutic agent for DN by inhibiting the expression of ACTA2 and p38 (Han *et al*., 2017). Combination therapy of Rutin and Ramipril successfully restored the antioxidant status, down-regulated endoplasmic reticulum stress markers, reversed gene expression changes, reduced oxidative stress and fibrosis, and lowered side effects (Ganesan *et al*., 2018). rutin treatment was found to prevent hyperpermeability and dysfunction of the tight junction, and this protective effect was associated with the activation of Nrf2, leading to a decrease in reactive oxygen species and inhibition of the RhoA/ROCK pathway (Wang *et al*., 2016). Furthermore, the combination of rutin and Vildagliptin was found to be more effective, leading to improved histological conditions and reduced damage of glomeruli and tubules (Tilethe *et al*., 2013). Rutin was found to reduce the G0/G1 cell phase percentages, inhibit Smad 2/3, laminin, type IV collagen, and TGF-β1 mRNA expression, and increase antioxidant capacity, S phase cell percentages, and Smad 7 expression (Tang *et al*., 2011). Lastly, Rutin effectively improves renal function in 5/6 nephrectomised rats, likely through antioxidation and inhibiting TGFβ1-Smad signaling (Han *et al*., 2015).

3.2.5 Fisetin

Fisetin, a flavonoid, showed positive outcomes in ameliorating DN. fisetin alleviate podocyte injury and DN by restoring the CDKN1B/P70S6K pathway, promoting autophagy, and inhibiting NLRP3 inflammasomes (Dong *et al.,* 2022). Fisetin enhanced antioxidative stress in DN through the Nrf2/HO-1/GPX4 pathway, attenuating podocyte injury and DN formation (Qian *et al.,* 2023). fisetin mitigated HFD-induced renal injury by regulating iRhom2/NF-κB and Nrf-2/HO-1 signaling pathways (Chenxu *et al.,* 2021). Fisetin reduced reactive oxygen species (ROS), advanced glycosylation end products (AGEs), inflammatory cytokines, and extracellular matrix accumulation in the kidney, by inhibiting the TGFβ/SMAD signaling pathway and regulating matrix metalloproteinases (MMPs), both *in vivo* and *in vitro* fisetin therapeutic effects on kidney fibrosis were mediated by inhibiting CD36 expression (Zou *et al.,* 2023). Fisetin treatment lowered extracellular matrix protein expression, reduced p300 expression, and increased MMP-2 expression (Liu *et al.,* 2014). Luteolin and fisetin on inflammatory responses in human monocytes exposed to high glucose levels. The combination treatment reduced NF-κB activity, cytokine release, and histone acetyltransferase activity, while activating SIRT1 and FOXO3a expressions (Kim *et al.,* 2017).

3.2.6 Silibinin

Silibinin improved the diabetic condition, leading to reduced body weight, HbA1c levels, and serum insulin levels. It prevented kidney injury, reduced oxidative stress, activated the AKT signaling pathway, and decreased the levels of p-GSK-3β, Bax, and cleaved caspase-3. Overall, silibinin showed potential in ameliorating diabetic nephropathy through the activation of the AKT signaling pathway (Liu *et al.,* 2019; Chu *et al.,* 2018; Islam *et al.,* 2021). Silibinin attenuate renal fibrosis *in vitro* and *in vivo via* inhibition of NF-κB (Liu *et al.,* 2019). Diabetic rats exhibited hyperglycemia, hyperlipidaemia, and kidney dysfunction, which were significantly improved with silibinin treatment. It had potential to prevent the progression of early diabetic nephropathy (Jain, 2015). Silibinin significantly increased the anti-fibrosis effect of valsartan in TGF-β1-treated HK-2 cells via inhibition of TGF-β1 signaling pathway (Liu *et al.,* 2020). The combination of Silibinin and MK-521 notably decreased the expression of fibrosis-related genes and proteins in cultured kidney cells (HK-2) exposed to TGF-β. In a high-fat diet-induced renal fibrosis mouse model, silibinin enhanced the anti-fibrotic effects of MK-521 (Ma *et al.,* 2020).

3.2.7 Luteolin

Luteolin lowered blood glucose and BUN levels in diabetic rats, raised serum sodium and chloride levels, and hindered glycoprotein deposition and collagen fiber production in kidney. It boosted kidney

antioxidant enzymes *via* Nrf2, reduced inflammatory cytokines *via* NF-κB down-regulation, inhibited PI3K/Akt pathway, and suppressed apoptosis-related proteins (Chen *et al.,* 2023; Mehtab *et al.,* 2021). A study showed luteolin protects against diabetic nephropathy by altering SOD, MDA, and HO-1 levels (Wang *et al.,* 2011). Luteolin has been observed to diminish diabetic nephropathy (DN) primarily through the suppression of inflammatory and oxidative responses. The potential target identified is the STAT3 pathway, which ultimately results in the reduction of renal fibrosis and a delay in the advancement of DN (Zhang *et al.* 2021; Xiong *et al.,* 2020). Luteolin hinder podocyte injury and activation of the NLRP3, making potential to treat diabetic nephropathy (Yu *et al.,* 2019). It restored insulin resistance, dyslipidemia, hyperuricemia, and renal inflammation, as well as inhibited the RIP140/NF-κB pathway and enhanced insulin signaling (Chen *et al.,* 2016).

3.2.8 Diosmin

Diosmin raised insulin, decreased blood sugar, and increased body weight. It improved the levels of antioxidants (SOD, CAT, GSH, and NO) and normalised the structure of the kidney tissue. Diosmin also supported the maintenance of renal function by reducing NF-κB levels (Ahmad *et al.,* 2016). When diosmin and crocin were combined, insulin resistance was improved, blood pressure, uric acid, and lipoproteins were decreased, and diabetic nephropathy indicators such albumin excretion rate were alleviated. Additionally, they improved filtration and decreased inflammation and oxidative stress, as shown by decreased serum TNF and inflammatory cells (El-Fawal *et al.,* 2018). Diosmin alleviated the HG-mediated endoplasmic reticulum stress injury in HK-2 *via* restraining the PI3K/AKT pathway (Deng *et al.,* 2022).

3.2.9 Catechin

By blocking AGEs and inflammatory pathways, catechin oral administration may reduce the problems associated with diabetes (Zhu *et al.,* 2014). In mice fed with catechin, circRNA.5549 and circRNA.4712 seem to have favourable effects, especially on the circRNA.5549/miR-29a-5P/Cd36 network. This suggests that a potential treatment strategy for diabetic nephropathy would involve targeting their ceRNA regulatory network (Chen *et al.,* 2022).

3.2.10 Apigenin

Apigenin, a natural flavonoid with anti-inflammatory and anti-fibrosis properties, has shown promise in DN. Apigenin downregulate inflammatory factors (IL-6, IFN-γ, TNF-α), inhibited renal fibrosis markers. apigenin's protective role in DN is mediated through the miR-423-5p-USF2 axis (Hou *et al.,* 2021). Apigenin taken orally decreased body weight, corrected HFD-induced hyperinsulinemia, hyperglycemia, hyperlipidemia, kidney impairment, and collagen deposition. While reducing MDA, TNF-α, IL-6, nuclear NF-κB p65, and the mRNA levels of TGF-β1, Bax, and caspase-3, apigenin raised the levels of Nrf2, as well as GSH, SOD, and CAT (Aldayel, 2022). Treatment with apigenin decreased renal dysfunction and oxidative stress. Type IV collagen, fibronectin, and TGF-1 levels decreased, indicating lessened fibrosis. Additionally, it prevented the activation of the mitogen-activated protein kinase (MAPK), reducing inflammation (Cavero and Holzgrefe, 2019; Malik and Arya, 2021). By lowering TGF-1, fibronectin, and type IV collagen, apigenin reduced oxidative stress, fibrosis, and renal failure. Additionally, it inhibited MAPK activation, which reduced inflammation (TNF-α, IL-6, and NF-B expression) and apoptosis (increased Bcl-2, decreased Bax, and raised caspase-3 (Malik *et al.,* 2017; Arya *et al.,* 2018). Both anti-inflammatory (inhibiting the release of inflammatory factors) and antioxidant activity (decreasing the formation of lipid peroxidation) were characteristics of apigenin. Apigenin showed protective effects, and the Nrf2/heme oxygenase-1/NF-B pathway may be responsible for these effects (Zhang *et al.,* 2019).

3.2.11 Genistein

Genistein, a phytoestrogen from soybean, shows potential in treating diabetic complications, as it reduces hyperglycemia, insulin resistance, and offers therapeutic benefits (Jiang *et al.,* 2023; Weng *et al.,* 2019). genistein alleviated diabetic nephropathy by inhibiting the MAPK/NF-κB pathway, enhancing mitochondrial function, and exerting anti-inflammatory effects (Li *et al.,* 2022). It shows promise in inhibiting ECM and TGF-β (Yuan *et al.,* 2009). Genistein influences inflammatory responses and reduces oxidative stress by acting on IL-1, IL-6β, TNF-α, SIRT1, NF-κB, and TGF-β1/smad targets. Improved podocyte autophagy, suppression of RAAS overactivity, and eventual alleviation from diabetic nephropathy result from these actions (Hu *et al.,* 2021). Genistein has the potential to prevent DN through regulating inflammation and oxidative stress, particularly in people with diabetes with medium-to-high blood sugar levels (Kim and Lim, 2013). In addition to increased levels of phospho-tyrosine and phospho-ERK/ERK ratio, diabetic mice displayed heightened levels of oxidative stress and apoptosis. These alterations were reversed by genistein administration, suggesting that its reno-protective impact in diabetes is connected to decreased oxidative stress, inflammatory response, and apoptosis (Elmarakby *et al.,* 2011). By lowering multiple risk variables connected to ovariectomy-induced renal impairment, genistein has the potential to protect kidney function. This entails enhancing insulin resistance, decreasing renal oxidative stress, lowering lipid buildup, and reducing extracellular matrix protein expression (Choi and Song, 2009).

3.2.12 Chrysin

Propolis and mushrooms contain a naturally occurring flavonoid called chrysin (5,7-dihydroxyflavone) that has anti-inflammatory, antioxidant, and anticancer activities. Proteinuria, glomerular ultrastructure, and slit diaphragm protein levels were all improved by chrysin treatment. Chrysin's efficiency in reducing diabetes-induced podocyte injury is associated with its focus on ER stress pathways (Kang *et al.,* 2017; Siddiqui *et al.*, 2022). Animal models of chrysin protective properties through controlling oxidative stress, inflammation, and apoptosis (Farkhondeh *et al.,* 2019; Siddiqui *et al.,* 2020). In DN mice, chrysin reduced obesity, insulin resistance, impaired renal function, and pathological damage. Additionally, it reduced inflammation and oxidative stress, both essential for the advancement of DN. Chrysin controlled lipid metabolism by altering downstream proteins including adenosine 52 monophosphate-activated protein kinase (AMPK). A study revealed that lipid metabolic modulation by way of activated AMPK plays a role in how chrysin improves DN (Zhou *et al.,* 2022). Chrysin controlled mesenchymal and epithelial markers, which prevented excessive hyperglycemia from causing EMT. Additionally, it affected the migration and integrity of tubular cells as well as collagen formation. Tight junction proteins were reconstituted by chrysin. This raises the possibility that chrysin can prevent the EMT-driven

tubulointerstitial fibrosis that results from diabetic nephropathy (Kang *et al.,* 2015). Chrysin targets glomerulosclerosis and fibrosis brought on by AGE to reduce the buildup of matrix protein in diabetic glomeruli (Lee *et al.,* 2018).

3.2.13 Hesperidin

Hesperidin improved serum, liver, and kidney parameters and fixed abnormalities in the kidneys. Hesperidin's protective actions in diabetic nephropathy may entail regulation of TGF-1-ILK-Akt signalling. It improved nephropathy-related alterations, restored podocyte function, and lowered TGF-1 signalling (Zhang *et al.,* 2018). Hesperidin dramatically reduced glucose levels, liver and kidney damage indicators, and NF-κB and SIRT1 levels while controlling oxidative stress and NF-κB levels (Iskender *et al.,* 2017). Hesperidin treatment dramatically reduced serum and renal tissue FGF-23 levels (Dokumacioglu *et al.,* 2019). Hesperidin decreased oxidative stress and renal dysfunction following I/R damage in diabetic rats, indicating its potential to lessen renal consequences in this situation (Kakadiya *et al.,* 2010).

3.3 Tannins

Resources that are naturally renewable are used to make tannins (Pizzi, 2008; Ramakrishnan and Krishnan, 1994). which phenolic compounds are subsequent to phenol in plants (Hagerman, 2002; Sharma, 2019). Galloyl esters and proanthocyanidins, which can be oligomeric or polymeric, are examples of tannins (Khanbabaee and Van Ree, 2001), generated by plants' secondary metabolism (Lewis and Yamamoto, 1998). produced by biogenetic processes. Tannins have a variety of pharmacological effects, including antioxidant, anti-inflammatory, anticancer, antinutritional, and free radical scavenging properties. They also seem to improve metabolic conditions and postpone the beginning of a number of oxidative stress-related disorders (Smeriglio *et al.,* 2017).

3.3.1 Epigallocatechin gallate

The ability of EGCG to stop apoptosis in rats with diabetic nephropathy brought on by a high-fat diet and STZ. The antiapoptotic properties of EGCG, reduction of TGF, improvement of kidney function, and reduction of diabetic nephropathy (Mohan *et al.,* 2017). Supplementing with EGCG prevented high glucose's effects on enhanced IGF-I and IGF-II production. Additionally, it enhanced arachidonic acid pathways, increased GSH content, and decreased lipid peroxide, which prevented mesangial cell failure (Han and Park, 2007). In diabetic nephropathy, EGCG decreased hyperglycemia, proteinuria, lipid peroxidation, as well as the buildup of advanced glycation end products and associated kidney disease. This suggests that EGCG has the ability to minimise the kidney damage brought on by oxidative stress associated with aberrant glucose metabolism (Yamabe *et al.,* 2006; Yoon *et al.,* 2014). Early-stage DN may benefit from EGCG's ability to activate the Nrf2/ARE pathway by raising nuclear Nrf2 while decreasing nuclear Keap1 (Mohan *et al.,* 2020).

3.3.2 Ellagic acid

Ellagic acid plus metformin may prevent type II diabetes-related nephropathy by regulating blood sugar levels, lowering oxidative stress and inflammation, and combating free radicals. This will eventually result in a reduction in the apoptosis of kidney tissue (Harakeh *et al.,* 2023). Ellagic acid protected against oxidative stress, apoptosis, inflammation, and kidney injury. Reduced NF-κB activity, elevated levels of antioxidant enzymes (GSH, GCL, SOD), and improved Nrf2 nuclear translocation were all associated with this. It also increased Akt and GS3K phosphorylation, decreased Fyn phosphorylation and nuclear accumulation, and inhibited keap1's expression in the cytoplasm and its interaction with Nrf2 (ALTamimi *et al*., 2021). Through suppression of the HMGB1-TLR4-NF-κB pathway, ellagic acid prevented oxidative renal damage brought on by STZ (Zhou *et al.,* 2019). Ellagic acid decreased oxidative stress and renal impairment. Along with lowering renal pathology and inhibiting NF-κB activation, it also reduced fibronectin and transforming growth factor-beta (TGF-β) expression. Ellagic acid also reduced IL-1β, IL-6, and TNF-α serum levels of pro-inflammatory cytokines (Ahad *et al.,* 2014).

3.4 Stilbenes

Both food and medicinal plants contain the wide group of secondary plant metabolites known as stilbenes, which are a member of the larger family of natural polyphenols (Su *et al.,* 2022; Khan *et al*., 2021). The most known and best characterized stilbene is resveratrol (Gambini *et al.,* 2015). Studies on the pharmacological effects of stilbenes also show that they possess a variety of qualities, such as effects that have anticancer, antimicrobial, anti-inflammatory, antioxidant, antidegenerative disorders, antidiabetic, neuroprotective, antiageing, and cardioprotective properties (Teka *et al.,* 2022).

3.4.1 Resveratrol

VEGF and Flk-1 expressions in cultured glomerular cells caused by high glucose were reduced by resveratrol, with effects mediated by Sirt1. Additionally, resveratrol prevented endothelial cells from becoming more permeable and rupturing their cellular junctions when VEGF was present. Resveratrol might lessen DN through controlling angiogenesis (Wen *et al.,* 2013). Resveratrol reduces oxidative stress by restoring normal Mn-SOD activity and glucose-lipid metabolism, which in turn reduces renal damage and increases mitochondrial biogenesis with Mn-SOD failure in the kidney. Resveratrol possesses antioxidative properties through a mechanism independent of AMPK and SIRT1 (Kitada *et al.,* 2011; Li *et al.,* 2021). In patients with DN, resveratrol may be a useful adjuvant to angiotensin receptor blockers (ARBs) for lowering urine albumin excretion (Sattarinezhad *et al.,* 2019). By lowering MDA levels and increasing SOD, CAT, GSH, and GPx activities, resveratrol displays antioxidant benefits. It has the potential to lower the pro-inflammatory cytokine IL-1β (Hu *et al.,* 2022). Resveratrol and Rosuvastatin normalised expression to TGF-1β, fibronectin, while decreasing antioxidant enzyme activity, raising MDA, and increasing MDA. NF-κB/p65. FoxO1, Nrf2, and Sirt1. Encourage preventing oxidative injury to the kidneys (Hussein and Mahfouz, 2016). Resveratrol prevents diabetes-related damage to renal tissue by obstructing the p38 MAPK/TGF-1β signalling pathway (Qiao *et al.,* 2017). Resveratrol up-regulates AMPK expression and activation, exhibits concurrent pro and anti-inflammatory activities, and protects against oxidative stress, all of which may contribute to its positive effects on the early stage of DN (Chang *et al.,* 2011). Expression of intracellular adhesion molecules-1 and resveratrol PAI-1 in diabetic renal cortex. Additionally, it reduced cell growth by inhibiting the Akt/NF-κB pathways (Xu *et al.,* 2014).

Table 1: Different phytochemicals and their protective mechanism of actions in DN

Phytochemicals		Mechanism of action	References
Alkaloids	Berberine	Improve renal function	Hu *et al.,* 2022
		Reduce inflammation, oxidative	Ni *et al.,* 2015
		Reduces renal injury, inflammation, and podocyte apoptosis in DN by inactivating the TLR4/NF-κB pathways	Zhu *et al.,* 2018
		Alleviate tubulointerstitial fibrosis and attenuate EMT in diabetic kidney disease (DKD) by supressing the NLRP3 inflammasome	Ma *et al.,* 2022
		Activating the Nrf2 pathways, supressing TGF-β/Smad/EMT signalling, and reducing oxidative stress	Zhang *et al.,* 2016
		Ameliorating renal dysfunction in DN by inhibiting aldose reductase	Liu *et al.,* 2008
		Reduces NF-κB signalling, leading to improved renal function	Zhang *et al.,* 2021
	Boldine	Reduced matrix protein alterations and renal damage markers	Hernández-Salinas *et al.,* 2013
		Decrease systolic blood pressure in hypertension	Gomez and Velarde, 2018
		Inhibited markers of kidney damage (α-SAM, COM III) and inflammation (ED-1, OPN) in the 2K1C rats	
	Trigonelline	Reduced oxidative stress, and increased apoptotic cell death in the	Ghule *et al.,* 2012
		kidney Alleviated degenerative changes and fibrosis in kidney tissue	
		Reduce inflammation, oxidative stress, and kidney cell apoptosis	Li *et al.,* 2019
		Increased peroxisome proliferator-activated receptor-gamma (PPARγ) and GLUT4 protein expression	
		Significantly alleviated the oxidative stress and pathological changes in the kidneys	Shao *et al.,* 2019
Flavonoids	Quercetin	Decreases creatinine levels, reduced proteinuria and protected against renal structure changes	Gomes *et al.,* 2015
		Attenuated TGF-β1 and CTGF expressions	Lai *et al.,* 2012; Gomes *et al.,* 2014; Elbe *et al.,* 2015
		Reduced creatinine clearance	
		Improved renal pathology and acts via pathways like PI3K/PKB, AMPK-P38 MAPK, Nrf2/HO-1	Li *et al.,* 2022
		Alleviated oxidative stress	Feng *et al.,* 2022
		Exhibited anti-inflammatory activity by TNF-α and IL-1β levels	
		Inhibited the EGFR signaling pathway by reducing phosphorylation of EGFR and ERK1/2	Liu *et al.,* 2022
	Curcumin	Decreased FN and TGF-β1 overproduction	Huang *et al.,* 2013
		Decreased interleukin-1β, cleaved caspase-1, and NLRP3 protein levels,	Lu *et al.,* 2017
		Attenuated the expression of TGF-β1, CTGF	Soetikno *et al.,* 2011
	Kaempferol	Reduced inflammation markers, caspase-3, p38, and increased anti-apoptotic factors	Alshehri, 2023
		Reduced renal inflammation, fibrosis, and kidney dysfunction in diabetic mice by downregulating TRAF6	Luo *et al.,* 2021
		Reduced oxidative stress, inflammation, and apoptotic markers while promoting antioxidant enzyme levels	Alshehri *et al.,* 2022
		Reducing AGE accumulation and ROS production	Zhang *et al.,* 2019

		Reduce apoptosis, likely mediated through the AMPK/mTOR pathway	Sheng *et al.,* 2022
		Improved renal histology, reduced fibrosis, and downregulated key markers of DN	Sharma *et al.,* 2020.
		Alleviates DOX-induced nephropathy by upregulating and activating SIRT1	Alagal *et al.,* 2022
	Rutin	Decrease in reactive oxygen species and inhibition of the RhoA/ROCK pathway	Wang *et al.,* 2016
		Reduced oxidative stress and fibrosis, down-regulated endoplasmic reticulum stress markers	Ganesan *et al.,* 2018
		Reduced levels of IL-6, NF-κB, TNF-α, Jak-2, and p-Stat3	Zaghloul *et al.,* 2022
	Fisetin	Enhanced antioxidative stress in DN mice through the Nrf2/HO-1/GPX4 pathway	Qian *et al.,* 2023
		Mitigated HFD-induced renal injury by regulating iRhom2/NF-κB and Nrf-2/HO-1 signaling pathways	Chenxu *et al.,* 2021
		Reduced ROS, AGEs, inflammatory cytokines	Zou *et al.,* 2023
		Inhibiting the TGF-β/SMAD signaling pathway	
		Reduced p300 expression, and increased MMP-2 expression	Liu *et al.,* 2014
		Reduced NF-κB activity	Kim *et al.,* 2017
		activating SIRT1 and FOXO3a expressions	
		Alleviate podocyte injury and DN by restoring the CDKN1B/P70S6K pathway	Dong *et al.,* 2022
		Enhanced antioxidative stress in DN through the Nrf2/HO-1 /GPX4 pathway	Qian *et al.,* 2023.
	Silibinin	Enhanced the anti-fibrotic effects of MK-521	Ma *et al.,* 2020
		Attenuate renal fibrosis *in vitro* and *in vivo via* inhibition of NF-κB	Liu *et al.,* 2019
	Luteolin	Reduced NF-kB levels, supporting renal function maintenance	Ahmad *et al.,* 2016
		Improved insulin resistance, lowered blood pressure, uric acid, and lipoproteins, and mitigated diabetic nephropathy markers	El-Fawal *et al.,* 2018
		Alleviated the HG-mediated endoplasmic reticulum stress injury in HK-2 *via* restraining the PI3K/AKT pathway	Deng *et al*., 2022
	Catechin	Inhibiting AGEs and inflammation pathways	Zhu *et al.,* 2014
	Apigenin	Inhibiting the release of Inflammatory factors	Zhang *et al.,* 2019
		Reducing lipid peroxidation production	
		Reducing TGF-β1, fibronectin, and type IV collagen	Malik *et al.,* 2001Arya *et al.,* 2018
		Decreased inflammation (TNF-α, IL-6, NF-κB expression	
		Inhibited Mitogen Activated Protein Kinase	Cavero and Holzgrefe, 2019
		Apigenin increased Nrf2 levels, along with GSH, SOD, and CAT,	Aldayel, 2022
		Decreasing MDA, TNF-alpha, IL-6, nuclear NF-κB p65,	
		and mRNA levels of TGF-beta1, Bax, and caspase-3	
		Downregulate inflammatory factors (IL-6, IFN-γ, TNF-α)	Hou *et al.,* 2021
	Genistein	Decreasing expression of extracellular matrix proteins	Choi and Song, 2009
		Decreased inflammation, oxidative stress, and apoptosis	Elmarakby *et al.,* 2011
		Improved podocyte autophagy, inhibition of RAAS overactivity	Hu *et al.,* 2021
		Inhibiting ECM and TGF-β	Yuan *et al.,* 2009
		Alleviate diabetic nephropathy by inhibiting the MAPK/NF-κB pathway	Li *et al.,* 2022

	Hesperidin	Suppression of TGF-β1-ILK-Akt signaling	Zhang *et al.,* 2018
		Decreased TGF-β1 signaling	
		Regulating oxidative stress and NF-κB levels, and decreasing SIRT1 levels	Iskender *et al.,* 2017
		Improved renal dysfunction and oxidative stress post I/R injury	Kakadiya *et al.,* 2010
	Chrysin	Mitigate matrix protein accumulation in diabetic glomeruli by targeting AGE-associated glomerulosclerosis	Lee *et al.,* 2018
		Improved of DN involves lipid metabolism regulation *via* activated AMPK	Zhou *et al.,* 2022
Tannins	Epigallocate chin gallate	Activates Nrf2/ARE pathway by reducing Keap1 and increasing nuclear Nrf2	Mohan *et al.,* 2020
		Decreasing advanced glycation end-product accumulation and related kidney pathology,	Yamabe *et al.,* 2006
	Ellagic Acid	Decreased serum levels of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α)	Ahad *et al.,* 2014
		Inhibited the cytoplasmic expression of keap1 and its interaction with Nrf2, boosted Akt and GS3Kβ phosphorylation	AL-Tamimi *et al.*, 2021
Stilbenes	Resveratrol	Reversed increase cell proliferation, through Akt/NF-κB pathways inhibition	Xu *et al.,* 2014
		Up-regulate AMPK expression and activation	Chang *et al.,* 2011
		Inhibiting the p38 MAPK/TGF β1 signaling pathway	Qiao *et al.,* 2017
		Decreasing MDA levels and enhancing SOD, CAT, GSH, and GPx activities	Hu *et al.,* 2022
		Reducing IL-1β, a pro-inflammatory cytokine	

4. Conclusion

In conclusion, diabetic nephropathy represents a complex and devastating complication of diabetes mellitus, driven by a network of intricate molecular pathways. Our exploration of the renin-angiotensin-aldosterone system (RAAS), polyol pathway, protein kinase C(PKC) pathway, hexosamine pathway, and advanced glycation end products (AGEs) reveals the multifaceted nature of its pathogenesis. Importantly, the protective potential of phytobio actives, including alkaloids, flavonoids, tannins, and stilbenes, offers a promising avenue for therapeutic intervention. These natural compounds exhibit diverse mechanisms of action, providing hope for the development of novel strategies to combat diabetic nephropathy. Incorporating phytobioactives into treatment regimens holds the potential to enhance patient outcomes and alleviate the burden of this debilitating condition.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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