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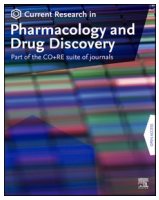

Molecular mechanisms and therapeutic potential of natural flavonoids in diabetic nephropathy: Modulation of intracellular developmental signaling pathways

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ABSTRACT

Recognized as a common microvascular complication of diabetes mellitus (DM), diabetic nephropathy (DN) is the principal cause of chronic end-stage renal disease (ESRD). Patients with diabetes have an approximately 25% risk of developing progressive renal disease. The underlying principles of DN control targets the dual outcomes of blood glucose regulation through sodium glucose cotransporter 2 (SGLT 2) blockade and hypertension management through renin-angiotensin-aldosterone inhibition. However, these treatments are ineffective in halting disease progression to kidney failure and cardiovascular comorbidities. Recently, the dysregulation of subcellular signaling pathways has been increasingly implicated in DN pathogenesis. Natural compounds are emerging as effective and side-effect-free therapeutic agents that target intracellular pathways. This narrative review synthesizes recent insights into the dysregulation of maintenance pathways in DN, drawing from animal and human studies. To compile this review, articles reporting DN signaling pathways and their treatment with natural flavonoids were collected from PubMed, Cochrane Library Web of Science, Google Scholar and EMBASE databases since 2000. As therapeutic interventions are frequently based on the results of clinical trials, a brief analysis of data from current phase II and III clinical trials on DN is discussed.

1. Introduction

Diabetic nephropathy (DN) is a major chronic complication of diabetes and a leading cause of renal failure (Kanwar et al., 2008). It is characterized by a sustained decline in the glomerular filtration rate (GFR), progressive renal fibrosis, and persistent albuminuria, which ultimately leads to end-stage renal disease (Raptis and Viberti, 2001). The pathogenesis of DN is complex and multifactorial in origin and involves a multitude of deregulated metabolic, hemodynamic, immunological, and molecular processes leading to structural and functional changes in the kidney (Cao and Cooper, 2011). Recently, several key maintenance signaling pathways, such as Wnt, Notch, and Hedgehog, and inflammatory pathways, such as the NRLP3 inflammasome, NFκB, and TGFβ pathways implicated in tissue fibrogenesis and repair, have been shown to be associated with disease pathogenesis (Wang et al., 2021). Despite enhanced knowledge about the disease, the arsenal of drugs used to treat this condition remains limited. Current strategies are primarily centered on tight glycemic and blood pressure control to slow disease progression (Elendu et al., 2023). However, these interventions are associated with the risk of frequent hypoglycaemia and hypotension (Rossing et al., 2022). Therefore, there exists a compelling need for innovative therapeutic approaches that target underlying molecular mechanisms of the disease to enhance clinical outcomes.

Interestingly, the advent of multifunctional small-molecule agents allows for the in-depth exploration of novel mechanism-based strategies to halt or reverse DN progression. Natural compounds derived from plants, animals, and microorganisms, which have been used in traditional medicine for centuries, show therapeutic promise for diseases such as diabetes and kidney diseases. Recent studies have highlighted the potential of flavonoids to modulate intracellular signaling pathways, targeting specific intermediates in DN pathogenesis (Yi et al., 2023). In animal models of DN, compounds such as resveratrol (from grapes), curcumin (from turmeric), and quercetin (from fruits/vegetables) exhibit renoprotective effects. Resveratrol, a polyphenolic compound found in grapes and red wine, reduces albuminuria and renal fibrosis in diabetic mice (Bhatti et al., 2022). In recent studies, curcumin, a yellow pigment obtained from turmeric, has been demonstrated to enhance renal function and to attenuate renal fibrosis in diabetic rats (Tu et al.,

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2019). Quercetin, a flavonoid present in fruits and vegetables, has also been found to block the NFκB pathway and to attenuate renal inflammation in diabetic rats (Chen et al., 2012). These studies suggest that natural compounds may be used to improve renal function and delay DN progression in animal models. The outcome of supplementation with these agents in randomized controlled trials corresponded well with findings from animal studies. In the case of curcumin, the latter included reduced urinary albumin excretion and an increase in eGFR (Zhu et al., 2022), while quercetin supplementation produced the same effects on both markers of renal function (Caro-Ordieres et al., 2020).

The emerging consensus in the literature indicates that the beneficial effects of natural flavonoids may be due to their modulatory effects on intracellular signaling pathways implicated in DN pathogenesis. Several natural compounds have been found to target the Wnt signaling pathway, which plays a critical role in the development of renal fibrosis (Wang et al., 2021). For example, resveratrol reverses the myofibroblastic phenotype in mouse kidneys by targeting fibroblast–myofibroblast differentiation (FMD) and epithelial–mesenchymal transition (EMT) during fibrosis by inhibiting the Wnt signaling pathway (Zhang et al., 2019a). Similarly, quercetin has also been found to inhibit fibroblast activation during kidney fibrosis via crosstalk with mTOR and β-catenin signaling (Ren et al., 2016). There is a general consensus that in addition to maintenance signaling pathways, dysregulation of inflammatory pathways such as the NLRP3 inflammasome and oxidative stress, also contribute substantially to DN development (Gao et al., 2021). As per consensus, high glucose and lipopolysaccharide levels activate the NLRP inflammasome through the ROS/TXNIP pathway in mesangial cells initiating disease pathogenesis (Hong et al., 2016). In turn, persistent oxidative stress in early DN can accelerate progression to end-stage renal disease (Yoshida et al., 2005), (Cheng et al., 2018). Thus, NLRP3 inflammasome exacerbates DN by promoting inflammation, fibrosis, and oxidative stress with the latter driving pathogenesis and progression. Targeting these two pathways may offer potential therapeutic strategies for disease management. Indeed, Luteolin suppresses the NLRP3 inflammasome pathway and interleukin1β secretion in response to high glucose levels in podocytes (Yu et al., 2019). Similarly, Fisetin suppresses the NLRP3 inflammasome by activating autophagosome formation in mouse podocytes (Dong et al., 2022). Attenuation of NLRP3 signaling and TXIP-mediated pyroptotic signaling has also been observed in calysocin-treated rat DN models (Yosri et al., 2022). Findings from the above animal models demonstrate that antioxidative-stress treatment strategies may efficaciously maintain normal renal function while halting or delaying DN progression.

The lack of effective DN therapies in parallel with rising social and economic burdens, have inspired the search for alternative therapies. Natural compounds are emerging as strong contenders suitable for DN therapy, but their protective effects, pharmacological activity, and possible intracellular mechanistic targets remain obscure. This review is structured into three parts whereby, the first part summarizes the molecular mechanisms in DN development, with emphasis of dysregulated intracellular signaling pathways especially the maintenance, inflammatory and oxidative stress pathways. The second part discusses the increasing potency of natural flavonoids as an emerging therapeutic agent in both animal and human models, along with their intracellular mechanistic action. Despite promising preclinical data, translational "bench to bedside" knowledge gaps present major hurdles that thwart the elevation of these compounds for DN treatment. Therefore, the third part presents a glimpse of future treatment with phase II and phase III intervention trial data from the ClinicalTrials.Gov directory.

2. Methods

2.1. Search strategies

This narrative review of flavonoids utilized in the treatment of diabetic nephropathy was edited based on research articles that were searched in PubMed, the Cochrane Library, Scopus and Web of Science databases and the EMBASE database. Studies that utilized flavonoids for intervention of DN and which discussed intracellular targets and signaling mechanisms in animals and humans were included and those that lacked scientific merit or displayed methodological errors were excluded. A total of articles on ~40 flavonoids as well as their use in the treatment of DN is discussed.

2.2. Occurrence and progression of DN

DN is a primary microvascular complication of DM, the exact pathogenesis of which remains to be determined. However, chronic hyperglycemia has been identified as the key initiating factor of DN. Hyperglycemia-induced oxidative stress and inflammation, are involved in the pathogenesis and progression of DN. Furthermore, the elevation of intraglomerular pressure within the kidneys directly induced by hyperglycemia damages the glomerular filtration barrier and subsequently promotes renal fibrosis. The occurrence of DN is related to the genetic susceptibility and inflammatory status of the body, as well as with the indirect relationship between DN and the associated insulin resistance and coagulation abnormality. It is also associated with the abnormal vascular endothelial cell function commonly observed in DN (Xu et al., 2022). Hyperglycemia results in the activation of angiotensin II via the ANgII/AT1R axis, subsequently promoting the inflammatory injury by the activation of the NF-κB pathway (Pandey et al., 2015). Therefore, effective glycemic control can profoundly impact these initiating events and the subsequent acceleration of the progression of DN to the end-stage renal disease. A summary of the ultrastructural changes that occur at different DN stages is presented in Table 1.

2.3. Stages of diabetic nephropathy and initiation of pathogenesis

Diabetic nephropathy (DN) is a complex disease characterized by specific kidney dysfunction indicators. The classical presentation is initially characterized by glomerular hyperfiltration and microalbuminuria, progressing to a sustained induction in oxidative stress, and to the subcellular pathways leading to the progressive deterioration of renal function. Hyperglycaemia induces subtle microvascular changes—e.g., vessel sprouting. Cell-to-cell cross-talk within the milieu—e.g., podocytes and endothelial cells from the filtration barrier—induces glomerular basement membrane (GBM) thickening or regulates mesangial matrix expansion, determining the progression of DN. Concurrently, renal tubular epithelial cells (TECs) injury precedes the glomerular lesions and impairs glomerular filtration. With the progression on DN, vascular endothelial cells and pericytes phenotypic switching leads to the fibroblast formation which induces apoptosis and atrophy of TECs. Recruitment of inflammatory cells during the process fuels DN progression. Table 1 summarizes the structural and functional changes that characterize the pathogenesis of DN.

2.4. Potential molecular alterations in diabetic nephropathy and the role of maintenance signaling pathways

As the pathogenesis of DN encompasses various molecular alterations involving multiple kidney cell types it is challenging to establish a hierarchy on the individual processes. Early lesions of DN are characterized by glomerular basement membrane (GBM) thickening and mesangial expansion. The disease rather commences with microalbuminuria, advances to macroalbuminuria, and an increased GFR, before culminating in end-stage renal disease (ESRD). Numerous cellular mechanisms have been associated with DN, for instance disrupted autophagy, increased oxidative stress, hypoxia-mediated processes, inflammatory responses and up-regulation of the RAAS have been implicated. In the past, the abnormalities of signaling pathways centered on mesangial cells and their reduced expression of matrix metalloproteinases. Recently, damage to other cell types has garnered

Table 1
Stages of diabetic nephropathy.

Stages	Molecular Changes	Functional Changes	Structural Changes	Ref
Early Stage	Hyperglycemia ROS Activation of PKC, polyol, hexosamine, AGEs, Inflammatory cytokine production (TNFa, IL1, 16,18, MCP1, MMP9, ICAM1), Gut microbiome changes	Glomerular hyperfiltration, hemodynamic changes, mild microalbuminuria, Altered cortical interstitial fraction volume (VvInt), estimated GFR (eGFR), albumin:creatinine ratio (ACR)	Microvascular dysfunction, loss of glycocalyx, GBM thickening, diffuse mesangial expansion, Tubulo-interstitial damage, followed by Glomerular lesions.	(Nair et al., 2018), (Tuttle et al., 2022a), (Zhang et al., 2023)
Middle Stage	Angiotensin II, Aldosterone, Endothelins, Fibrotic factors (TGFβ, Fibronectin, collagen1, CTGF)	Increased perfusion, activation of RAA system causing glomerular hypertension	ECM expansion and accumulation, fibrosis, Cellular hypertrophy and proliferation, cellular crosstalk between endothelial and mesangial cells	(Hartman et al., 2020), (Alicic et al., 2017), (Yu and Bonventre, 2018)
Late Stage	High albuminuria, Prolonged inflammation, NFkB, JAK-STAT pathway activation, Epigenetic alterations (histone methylation/ acetylation)	Kidney damage, low eGFR	Glomerulosclerosis Tubulointerstitial inflammation and fibrosis	(Alicic et al., 2018), (Pérez-Morales et al., 2019), (Hofherr et al., 2022)

Abbreviations: PKC -Protein kinase C; TGFβ- Transforming growth factor; TNF, tumor necrosis factor; ECM, extracellular matrix; MMP, matrix metalloproteinase; RAA -Renin-angiotensin-aldosterone; GBM -Glomerular basement membrane; NFkB, nuclear factor kappa B; JAK/STAT, Janus kinase/signal transducers and activators of transcription; GFR, glomerular filtration rate; ROS, reactive oxygen species; AGE- Advanced glycation end-products.

attention. It is now clear that podocyte damage and loss are early events in DN (Pagtalunan et al., 1997). Indeed, multiple pathways are dysregulated in podocytes during DN pathogenesis (Fig. 1). Renal podocyte injury is a complex process mediated by various molecular pathways including mitochondrial dynamics, biogenesis, mitophagy, oxidative phosphorylation, and mitochondrial protein quality control (Audzeyenka et al., 2022). These pathways are particularly relevant to podocytes, which are rich in mitochondria and are heavily dependent on mitochondrial energy. Disruption of these pathways can culminate in bioenergetics crisis, oxidative stress, inflammation, and podocyte demise, ultimately contributing to the pathogenesis of DKD.

2.5. Wnt pathway activation: podocyte injury and ultrastructural damage linked to oxidative stress

The genetic landscape of DN is complex. A recent meta-analysis of genome-wide linkage studies (GWLS) has implicated multiple genetic loci in several genes conferring predisposition to DN (Tziastoudi et al., 2020). Subsequent gene ontology (GO) analyses of the biological and functional roles of these genes have concluded that the core feature of DN pathogenesis is likely a perturbed Wnt and cadherin signaling pathway(s) (Tziastoudi et al., 2021). Upregulation of Wnt ligands in kidneys has been demonstrated in several studies of diabetes, and the canonical Wnt/β-catenin signaling pathway has been shown to play a role in podocyte dysfunction and renal injury. Its activation reduces podocyte-specific proteins which result in injury, and thus contributes to AKI progression (Zhou et al., 2019). GO studies have revealed an intersection between the Wnt and β-catenin pathways with the glycoprotein E-cadherin, which mediates cell-cell adhesion (Nelson and Nusse, 2004). High levels of urinary E-cadherin are reported in diabetic nephropathy (DN) early stages and correlate with rapid disease progression. Independent studies have documented early DN in gene enrichment and pathway analyses in human biopsies and animal models and demonstrated a marked increase in Wnt signaling and cytokine-cytokine receptor interaction. Animal models further illustrate the relationship between oxidative stress and podocyte damage.

Zhou et al. (2019) demonstrated higher podocyte damage in line with elevated oxidative stress in animal models of chronic kidney

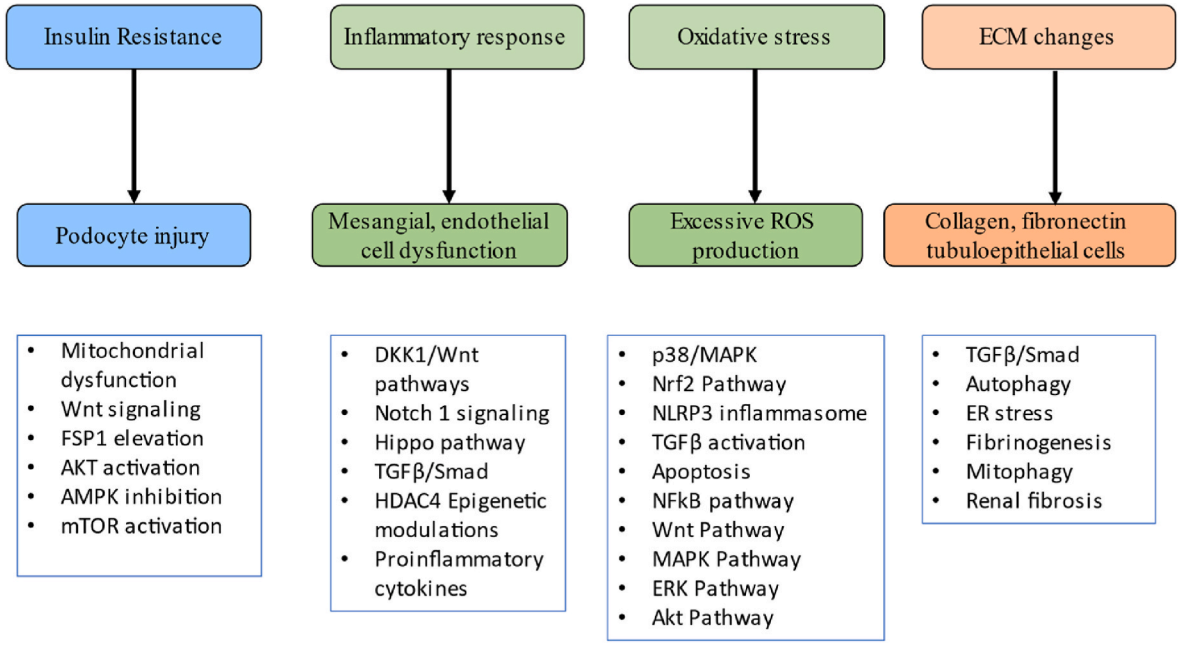

Fig. 1. Molecular alterations during initiation and progression of Diabetic nephropathy.

disease (Zhou et al., 2019). Chronic kidney disease increased serum advanced oxidation protein products (AOP), a marker of oxidative stress, and was associated with worse glomerular filtration, proteinuria, and serum Wnt 1 levels. AGEs released during persistent hyperglycemia increased Wnt1 and Wnt7a expression with activated β-catenin and loss of podocyte-selective marker expression in vitro and in vivo in mice (Liu et al., 2022a), (Zhou and Liu, 2015). Perhaps signal transduction through β-catenin is crucial for kidney injury, as conditional knockout mice of β-catenin exhibit protection against podocyte site injury and albuminuria, with upregulated fibronectin, desmin, MMP-9, and Snail 1 levels. Wnt/β-catenin action is dependent on receptor of advanced glycation end products (RAGE)-mediated NADPH oxidase induction, reactive oxygen species generation, and nuclear factor-κB activation. Similarly, increased WNT 1 protein expression is demonstrated by podocytes in both animal models and human kidney biopsies (Loeffler and Wolf, 2015). Interestingly, canonical Wnt signaling is also involved in other kidney diseases and in the apoptotic regulation of mesangial cells. However, the role of non-canonical Wnt signaling remains unclear. While some studies show that non-canonical Wnt is protective and represses β-catenin in podocytes (Zhou et al., 2022a), there is alternative data showing the Wnt 5a signaling leads to further metabolic inflammation through activation of the c-Jun N-terminal kinase (JNK) pathway in animal models (Li et al., 2021).

The Wnt signaling pathway is now evidently treated as a pathway connecting various pathways that lead to DN. High-throughput technology studies of gene network identification unraveled the interconnectedness of Wnt signaling pathways to MAPK signaling, extracellular matrix (ECM)-receptor interaction, angiogenesis, PI3-Akt signaling, Jak-STAT signaling, renin-angiotensin pathway, NFkB, TGFβ signaling pathways, and oxidative stress response also corroborated by biological data (Heinzel et al., 2015). Dysregulated dickkopf-1 (DKK1)/Wnt/β-catenin signaling pathways play a major role in the pathogenesis of diabetic glomerular injuries (Tung et al., 2018a). The Wnt pathway also works in concert with other pathways such as the receptor tyrosine kinase/Ras/mitogen-activated protein kinase (RTK/Ras/MAPK) pathway (Wang et al., 2021). Activation of the Wnt pathway is also observed during the terminal stages of nephron damage in DN. For example, the Wnt pathway is modulated by Dapper 1, activating Wnt1 to suppress Cyclin G2, thereby inhibiting tubulointerstitial fibrosis in diabetic nephropathy (Zhao et al., 2020). Similarly, studies have shown that matrix metalloproteinase-7 serves as a surrogate marker for predicting renal Wnt/β-catenin activity in chronic kidney disease (He et al., 2012). For a comprehensive review of this subject, we refer to (Tziastoudi et al., 2021).

2.6. Increased TGFβ, notch signaling: contribution of epithelial, mesangial, endothelial cells and epithelial-mesenchymal transition (EMT)

The ultrastructural pathological damage to the mesangium occur due to ECM accumulation leading to fibrosis within the interstitial spaces surrounding the tubules consequently to cause fibrosis (Kriz et al., 2023). This tubulointerstitial fibrosis is a critical event in the progression of DKD, which occurs as a result of excessive ECM secretion and fibrosis as a consequence of epithelial-to-mesenchymal transition (EMT). TGFβ1 signaling activation through phosphorylation of downstream effectors such as Smad 2 and Smad 3 plays a prominent role in EMT, leading to increased expression of cellular proteins such as alpha-smooth muscle actin (α-SMA) and decreased E-cadherin expression (Lan, 2012).

In Mesangial cells, dysregulation of dickkopf-1 (DKK1)/Wnt/β-catenin signaling pathway contributes to the pathogenesis of diabetic glomerular injuries (Tung et al., 2018a). High glucose-induced Ras/-Rac1-dependent superoxide formation inhibits Wnt signaling, and DKK1 binding to the Kremen-2 receptor increases ECM deposition in the mesangium. Notch 1 signaling reactivation is also implicated in podocytopathy and proteinuria (Tung et al., 2018b). Similarly, TGFβ1 activates the TGFβ1/Smad signaling pathway in glomerular mesangial cells, via which TGFβ1's downstream Smads are essential for upregulated collagen 1 expression and cell proliferation, both of which the ACE inhibitor fosinopril can partly suppress (Schnaper et al., 2003). In this context, Smad 3 is considered pathogenic, contributing to DN, while Smad 2 is protective, and its downstream signaling is mediated by several microRNAs, such as miR-29 and miR-200 (Lan, 2012).

Besides epithelial cells, endothelial cell dysfunction also links to fibrosis through EndoMT (endothelial-to-mesenchymal transition), which contributes to progression in kidney disease. Although the role of EndoMT in renal fibrosis is debated, it is often associated with endothelial dysfunction (Pohl and Schiessl, 2023). Recent studies utilizing time-course single-cell sequencing and genetic lineage tracing in transgenic mouse models have suggested that myofibroblast and fibroblast subgroups, rather than endothelial cells, contribute to fibrotic tissue scarring and remodelling (Kuppe et al., 2021). A detailed review on sequence of events that cause structural damage and functional impairment during renal fibrosis can be found here (Xiang et al., 2024).

2.7. Increased ROS production and inflammation-related NF-κB and JAK/STAT pathway activation

Elevated ROS production has been highlighted as mediators in the progression of DN. High glucose levels and ROS can induce signal transduction cascades, such as protein kinase C (PKC), mitogen-activated protein kinases (MAPKs), and JAK/STAT pathways (Lee et al., 2003). Subsequently, this can lead to the synthesis of transcription factors, including NF-κB, activated protein-1 (AP-1), and specificity protein 1 (SP1) that enhance the upregulation of TGF-β1 and ECM proteins. ROS is also pivotal to mitochondrial function, leading to apoptotic cell death and altered mitochondrial permeability that results in necrosis in diabetic kidney disease (Lindblom et al., 2015). Ultrastructural damage is also common due to accumulating oxidative stress mediated by various NADPH oxidases (NOXs) leading to glomerular injury, albuminuria, and tubular fibrosis (Jha et al., 2016). Finally, mitochondrial ROS production alters mitochondrial respiration and O2 consumption, which determine the coupling and other aspects of DN pathogenesis (Galvan et al., 2021).

2.8. The role of inflammasomes in DN pathogenesis

DN arises from inflammation. Numerous studies have shown dysfunction in inflammatory pathways. The presence of macrophages in the early stages of diabetic kidneys, as observed in human biopsies and animal models, has strengthened the view that DN is essentially an inflammatory disorder (Lim and Tesch, 2012). Tubular epithelial cells (TECs) recruit macrophages and initiate the inflammatory cascade by secreting proinflammatory cytokines, such as MCP-1, IL-6 and TNFα, which, in turn, enhances insulin resistance and advanced glycation end-product formation (Yang et al., 2018), (Bonacina et al., 2019). Hyperglycemia also decreases levels of the key intermediate proteins Nrf2 (nuclear factor-erythroid 2-related factor 2), an enhancer of the antioxidant response element (ARE), and its basal protein, HO-1 (heme oxygenase-1), and its "induced" protein, NQO 1 (NAD(P)H-quinone oxidoreductase 1), and thereby enhances oxidative stress (Lazaro et al., 2018). Furthermore, increased glucose levels amplify inflammation by activating the NLRP3 inflammasome (nucleotide binding and oligomerization domain-like receptor family pyrin domain-containing 3), resulting in the release of cytokines such as IL-18 and IL-1β (Zhu et al., 2020a).

3. Utility of flavonoids in targeting developmental pathways in diabetic nephropathy

In addition to prescribing hypoglycemic drugs, traditional methods of controlling DN include controlling weight, blood pressure, smoking,

and lipid and protein intakes. Despite these measures, progression to end-stage renal disease is variable and unpredictable in different patients owing to pharmacodynamic factors such as insufficient blood concentrations and non-targeted drug delivery, as well as their high clearance from the blood (Tuttle et al., 2022b). Developing a highly effective and low-cost intervention is a permanent challenge in DN treatment. Therefore, there is growing promise that dietary and pharmacological antioxidant/anti-inflammatory interventions could attenuate renal damage (Kalantar-Zadeh et al., 2021; Hu et al., 2022). A typical research flow that signifies the cycle of drug development in DN is shown in Fig. 2. Polyphenols are phenolic compounds that include anthocyanins and flavonoids and have been used as broad-spectrum antioxidants and potential therapeutic agents against many kidney diseases (Pani et al., 2022). They act by modulating the oxidative and inflammatory pathways at various levels.

3.1. Flavonoids targeting the Wnt pathway

Wnt β-catenin is a key pathway implicated in many kidney diseases, especially DN. Numerous studies have demonstrated that blocking the Wnt pathway prevents DN progression, including cell proliferation and ECM expression, mostly in human glomerular mesangial cells (HMCs). Both canonical and non-canonical pathways appear to be involved in DN pathogenesis. Few natural compounds have been evaluated for their role in Wnt pathway inhibition, and most studies have evaluated pathway modulations in mesangial cells. In a cellular DN model, trigonelline, the active component in fenugreek seeds, inhibited Wnt pathway activation and suppressed mesangial cell proliferation induced by high glucose as well as EMT expression of fibronectin and collagen IV (Chen et al., 2022). Likewise, Ginsenoside Rb1, a triterpene saponin, administered at a dose of 75 mg, has been shown to alleviate oxidative stress and reduce Wnt/β-catenin pathway activation by modulating miRNA expression levels of miR-3550 as well as downregulation of fibronectin and collagen IV in mesangial cells in DN (Shao et al., 2019). Scutellarin, a component of breviscapine, also improved mesangial matrix accumulation in vivo and ameliorated glomerular expansion, renal fibrosis, and podocyte injury via reduced expression levels of β-catenin, axin 2, and snail proteins (Huang et al., 2023). However, substantial crosstalk with the TGF-β pathway has been observed.

Few studies have reported the effects of natural compounds on Wnt pathway modulation in other kidney cells. Tripolide reversed Wnt3a/β-catenin pathway activation in high glucose-induced podocytes at low doses by concomitant reduction in EMT transition through upregulation of epithelial markers such as nephrin and podocin, and downregulation of mesenchymal markers desmin and collagen IV (Shi et al., 2018). Liu et al., reported that soybean isoflavones inhibit expression of Wnt4, β-catenin and TGFβ1 proteins in the renal interstitium and regulates renal interstitial fibrosis (Liu et al., 2018).

3.2. Flavonoids targeting the TGF-β pathway and crosstalk with notch and other pathways

Mesangial dilatation and renal fibrosis are key pathological features of DN progression. In diabetic nephropathy, glomerulosclerosis is primarily characterized by hyperproliferation of mesangial cells and accumulation of excess matrix proteins, including collagen III and fibronectin. Renal fibrosis consists of additional changes to the glomerulus and tubulointerstitium and is critically dependent on the elevated expression of TGFβ1. Overexpressing TGFβ1 facilitates fibrosis while inhibiting TGFβ1 or its downstream partners inhibit renal fibrosis. TGFβ1 signaling through its canonical pathway includes the downstream regulators SMAD2, SMAD3 and SMAD4, which form a complex to translocate into the nucleus to activate downstream protein expression. Interestingly, TGF-β exhibits crosstalk with several other pathways during DN progression.

In high-fat diet/streptozotocin-induced type 2 rats, baicalin also suppressed NF-κB activation and the subsequent expression of iNOS and TGFβ1 (Ahad et al., 2014). Kidney-targeted baicalin-lysozyme conjugates also showed reduced inflammation via NF-κB pathway regulation and prevention of ECM accumulation via the TGFβ/Smad pathways (Zheng et al., 2020a). A similar regulatory effect was observed in human mesangial cells following isoliquiritigenin treatment. As cited above, Huang et al., demonstrated that Scutellarin exhibits crosstalk between TGFβ, Erk and Wnt pathways in ameliorating mesangial matrix accumulation and renal fibrosis (Huang et al., 2023). Similarly, silibinin when administered alone significantly compounded the potent anti-fibrotic effect of valsartan in vitro in human proximal tubular epithelial cells (PTECs) and in vivo in high-fat diet (HFD) fed mice with renal fibrosis, through abrogation of the transforming growth factor (TGF) β1 pathway (Liu et al., 2020). Many in vivo experimental animal models have recently been utilized to demonstrate the protective role of flavonoids in attenuating inflammation-related cascades. For example, in HFD/streptozotocin-induced DN mice, hesperetin (Zhang et al., 2018) also suppressed the expression of TGFβ1 and its downstream effectors, integrin-linked kinase (ILK) and Akt. Likewise, Icariside II was shown to suppress oxidative stress and downregulate the TGFβ/Smad/CTGF

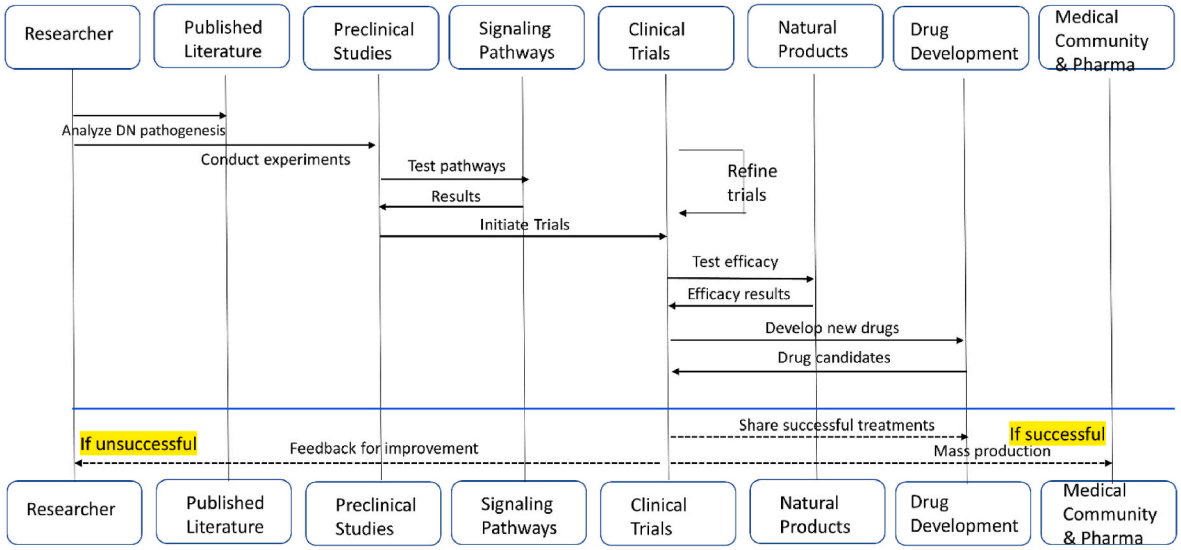

Fig. 2. Typical research flow during drug development in DN.

signaling pathway in the same model (Tian et al., 2015). Chen et al. demonstrated that silymarin downregulated inflammation-related cytokines and proteins, such as ICAM-1, via regulation of the JAK2/-STAT3/SOCS1 and TGFβ pathways, in mice with podocyte injury (Chen et al., 2021). Interestingly, administration of isoflavone calycosin resulted in marked improvement in renal glomerulosclerosis and interstitial fibrosis with modulation of the IL-1 cytokine family, IL33/ST2 signaling, and the TGFβ pathway (Elsherbiny et al., 2020).

In addition to inflammation pathways, natural compound treatment triggers cross talk between TGF-β pathways and apoptosis mediated pathways. Kaempferitrin treatment of glomerular mesangial cells resulted in suppression of the mitochondrial/cytochrome c-mediated apoptotic pathway. A related compound Kaempferol showed inactivation of hyperglycemia-induced RhoA activation in human renal tubular epithelial cells and TGFβ-mediated fibrosis. Researchers found that in mesangial cells, naringenin inhibits TGFβ1/smad signaling by up regulating a negative regulator of TGF-β receptor 1 (TGFβR1) let-7a (Sharma et al., 2019). Different studies have shown cross talk between the TGFβ and Notch pathways by inhibition of TGFβRII and Smad phosphorylation during epigallocatechin gallate (EGCG) of human embryonic kidney cells as evidenced by decreased fibronectin and Notch 1 levels (Zhu et al., 2020b). Very few studies have investigated the role of flavonoids in targeting the Hippo pathway in DN. Inactivation of the Hippo pathway seems to be an early event in DN pathogenesis, perhaps triggered by the high glucose milieu. Quercetin treatment protects the early stages of DN by reactivation of the Hippo pathway in the renal cortex of db/db mice (Lei et al., 2019).

3.3. Flavonoids targeting the NF-κB, MAPK, ERK, and Akt pathways

Several flavonoids inhibit glomerula basement membrane thickening and fibrosis by reducing oxidative stress and inflammation via regulation of PI3K/Akt signaling pathway in DN rats. Ferroptosis is an emerging key regulator of cell death in multiple organ disorders such as ischemia-reperfusion injury and cancer. Herein, excess intracellular iron level increases ROS production that eventually leads to cell death. Glabridin treatment in HFD-induced DN rats or HG-induced NRK-52E cells repressed ferroptosis and suppressed the levels of VEGF, phosphorylated Akt and p–ERK1/2 (Tan et al., 2022). Likewise, Quercetin treatment inhibited ferroptosis in renal tubular epithelial cell models and DN mice by inhibiting ferroptosis and activating the Nrf2/HO-1 pathway. As summarized in Table 2, quercetin also modulates IL6/STAT3 signaling in determining interstitial fibrosis as well as mTORC1/p7056K signaling, which mediates epithelial-mesenchymal transition via the expression of proteins such as Snail and Twist. Similarly, apoptosis activation and MAPK, Erk and Akt pathway inhibition have been reported when flavonoids Silibinin, Genistein, Hesperetin and Luteolin have been administered in HFD/STZ-induced animal models. In mouse glomerular mesangial cells MES13, Hyperoside inhibited glucose-induced proliferation without inducing apoptosis, but through inactivation of the ERK pathway and phosphorylation of its downstream transcriptional factor CREB (Zhang et al., 2020). Using the same model, Chen et al. showed that tangeretin alleviates oxidative stress via ERK pathway inactivation and decreases fibronectin and collagen levels (Chen et al., 2018a). However, in podocytes, chrysin was shown to restore high glucose-induced changes in vitro, while in vivo it restored glomerular ultrastructure in diabetic db/db mice kidneys to a great extent via ER stress responses (Kang et al., 2017).

3.4. Flavonoids targeting the Nrf2 and inflammasome pathways

Several flavonoids have been shown to exhibit significant cellular crosstalk among pathways while exerting their protective potential. This is particularly true for the Nrf2 and inflammasome pathways, which can trigger multiple cellular responses. Using spontaneous DN model rats, Ma et al. showed that baicalin (BA) exerted its renoprotective effects by reversing histopathological changes in rats and preventing immune infiltration by simultaneous activation of Nrf2 and inhibition of MAPK pathways (Ma et al., 2021). Inhibition of the AGE/RAGE axis has also been shown to influence the Nrf2 pathway during hesperetin action (Chen et al., 2019). In both in vitro and in vivo models of the renal tubular epithelium, quercetin was reported to inhibit ferroptosis and Nrf2/HO-1 pathway activation (Feng et al., 2023). Meanwhile, rutin supposedly influences crosstalk among several pathways, such as Nrf2/HO-1, Rhoa, and TGFβ1/Smad, to deliver its protection in STZ-induced rat DN models (Zaghloul et al., 2022). In a recent study, the flavonoid formononetin (FMN), which ameliorates renal fibrosis via oxidative stress, was shown to exert its effects through the Nrf2/ARE signaling pathway (Zhuang et al., 2020). Interestingly, multiple studies have demonstrated the inflammasome-suppressing effects of calycosin in the context of experimental DN by synergistic attenuation of the NLRP3, IL33/ST2 signaling, and Nrf2 pathways (Elsherbiny et al., 2020). Similarly, icariin, in addition to modulating the NFkB and TGFβ signaling pathways as cited above, increases sestrin2-induced mitophagy to inhibit the NLRP3 inflammasome (Ding et al., 2022). Both formononetin and isoliquiritigenin act via a common mechanism of action by modulating the expression of sirtuin 1 (SIRT1) during Nrf2 inactivation. Thus, the approach targeting the inflammatory response may be effective for DN therapy.

3.5. Impact of emerging technologies in natural products discovery

Recently, Zhou et al., reviewed the mechanism of action of flavonoids in general and their impact on Nrf2, NF-kB, TGFβ pathways, NLRP3 inflammasome, autophagy, glycolipid metabolism and ER stress. They proposed the need for a systematic analysis based on transcriptomic, proteomics, pathway inhibitor-based approaches to effectively decipher the global intracellular role of flavonoids (Zhou et al., 2022b). For example, the advanced single-cell RNA sequencing (scRNA-seq) allows characterization of complex cell-to-cell interaction by classifying cells into appropriate clusters at a proper resolution within the heterogenous kidney milieu. Such techniques have been used to identify the pathophysiologic role of hub genes in DKD mice with varying genetic backgrounds that further modulate the microenvironment. Like scRNA-seq, another technique that enables unbiased transcriptomic characterization of kidney cells to identify cell-type-specific changes in the disease state is the single-nucleus RNA-seq (snRNA-seq). Additionally, to better characterize the role of lipid soluble hormones such as mineralocorticoids in inducing nuclear gene expression, the single-nucleus assay for identifying transposase-accessible chromatin regions (snATAC-seq) have been utilized (Tsai et al., 2023). Interestingly, these techniques allow mapping the genetic response of an individual cell or group of cells during therapy (Zhou et al., 2022b). This approach can be extended to address monotherapy or combination therapies targeting different cell types in experimental models.

In recent times a growing nexus between the fields of omics-based discovery and AI-based computational drug design has also been noted (Mullowney et al., 2023). The advent of omics technologies has facilitated the discovery of newer class of natural products active on a genomic scale. For example, advanced machine learning techniques allow algorithm-based modelling of hitherto untested chemical structures catalogued in public databases to find potential protein targets, predict *in vivo* toxicity etc., leading to quicker molecular profiling. Similarly, AI-based approaches can now synthesize chemical compounds for selected molecular targets or predict plausible targets based on a molecules' chemical structure via docking and subsequently study their *in vitro* behaviour on the nano-to milli-second timescale (Bertoni et al., 2021). Both the approaches have greatly increased our understanding of the interplay between natural products and their intracellular targets. However, the field is still nascent with a high occurrence of false positives and false negatives and challenges surrounding the training of algorithms. Since a detailed discussion on the machine

Table 2
Natural flavonoids and their intracellular targets in diabetic nephropathy.

Compound Name	Model	Pathway targeted	Key Intermediate/pathway step targeted	Ref
Glabridin (Glab)	high-fat diet with streptozotocin induced-diabetic rat; High glucose-induced NRK-52E cells	ferroptosis and VEGF/Akt/ERK pathways	Glab repressed ferroptosis by increasing SOD and GSH activity, and GPX4, SLC7A11, and SLC3A2 expression. suppressed VEGF, p-AKT, p-ERK1/2 expression	Tan et al. (2022)
Baicalin	Spontaneous DN model rats	Increased downstream antioxidant enzymes (HO-1, NQO-1 expression. Inhibited levels of pro-inflammatory cytokines (IL-1β, IL-6, MCP-1 and TNFα)	Activated Nrf2 signaling, inhibition of MAPK family, such as Erk1/2, JNK and P38.	Ma et al. (2021)
baicalein (BAC)	high fat diet/streptozotocin induced type 2 diabetic Wistar rats	suppressed the activation of NF-κB, decreased expression of iNOS and TGF-β1,	Attenuation of NFkB	Ahad et al. (2014)
Kidney-targeted baicalin-lysozyme conjugate	STZ induced DN in SD rats	inhibiting inflammation via NFkB, inhibiting ECM accumulation via TGFβ/Smad and regulating cell proliferation via IGF-1/IGF-1 receptor/p38 (MAPK) pathway	Downregulated NFkB-p65, IL-1, IL-6, Smad 4, FN, COL 1 expression levels	(Zheng et al., 2020a)
Hesperetin	Streptozotocin-induced diabetic rats	inhibition of AGEs/RAGE axis and inflammation. increases in Nrf2 and p-Nrf2 levels and target gene, γ-glutamylcysteine synthetase upregulation	activating Nrf2/ARE/glyoxalase 1 pathway	(Chen et al., 2019)
Hesperetin	high-fat/streptozocin (STZ)-induced diabetic nephropathy mice	inhibited the expression of transforming growth factor-β1 (TGF-β1) and its downstream effectors integrin-linked kinase (ILK) and Akt.	suppressing TGF-β1-ILK-Akt signaling	(Zhang et al., 2018)
Scutellarin	streptozotocin-induced diabetic nephropathy	Ameliorates glomerular expansion, mesangial matrix accumulation, renal fibrosis, and podocyte injury. TGF-β1-Erk-Wnt/β-catenin pathway crosstalk	TGF-β1- Erk-Wnt signaling pathway crosstalk	(Huang et al., 2023)
Soybean isoflavones	DN rats	Decreases expression of Wnt4, β-catenin and TGF-β1	Wnt/β-catenin and the TGF-β1 signaling pathway	(Liu et al., 2018)
Trigonelline	High-glucose cellular DN model	Reverses proliferation, EMT expression and fibrosis of mesangial cells	Modulation of Wnt signaling pathway	Chen et al. (2022)
Triptolide	High-glucose immortalized podocytes in vitro	After treatment increased expression of epithelial markers nephrin, podocin and lowered mesenchymal markers desmin and collagen IV, lowered EMT mediator snail and reduced Wnt 3a/b-Cat expression in podocytes	Modulation of Wnt3a signaling	Shi et al. (2018)
Ginsenoside Rb1	Mesangial cells in STZ-induced DN rat model	Reduced oxidative stress, Wnt pathway intermediates and EMT expression of fibronectin and collagen IV	Inhibiting Wnt-β-catenin pathway via miR-3550	Shao et al. (2019)
Quercetin	DN mice and high glucose (HG)-incubated renal tubular epithelial cell models	increasing the levels of Nrf2 and HO-1	Inhibiting Ferroptosis via Activating Nrf2/HO-1 signaling Pathway	Feng et al. (2023)
Quercetin	High glc, renal tubular proximal epithelial cells (HK-2 and NRK-52E)	elevated expression of TFs,Snail and Twist	mTORC1/p70S6K signaling-mediated renal tubular epithelial-mesenchymal transition	Lu et al. (2015)
Quercetin	renal tubular epithelial cells (RTECs) of db/db mice and HG-cultured HK-2 cells	Via YY1 (Yin Yang 1), new pro-inflammatory mediator and became the important target of DN-related TIF (tubulointerstitial fibrosis)	Modulating IL-6/STAT-3 pathway	Yang et al. (2023)
Quercetin	high glucose-induced mouse glomerular MCs and in db/db mice	Decreased MST1 phosphorylation, and increased nuclear Lats1, YAP levels to promote target gene cyclin E expression	reactivated the Hippo pathway	Lei et al. (2019)
Quercetin	High glucose (HG)-induced human mesangial cell (HMC)	effects of quercetin maybe partially mediated by NF-κB signaling	suppression of NF-κB	Chen et al. (2012)
Quercetin	Leprdb/Leprdb (db/db) mice, a model of type 2 diabetes	down regulated expression of LDLr, HMGCR, SREBP-2, and SCAP	Lipid metabolism via SCAP-SREBP2-LDLr signaling pathway	Jiang et al. (2019)
Quercetin	HG-induced human mesangial cells (HMCs), serum of DN patients	downregulation of miR-485–5p and upregulation of YAP1	miR-485–5p/YAP1 axis	Wan et al. (2022)
metformin, canagliflozin, metformin + canagliflozin, and quercetin	preclinical rat model of DKD (STZ-NAD-N(ω)-Nitro-L-Arginine Methyl Ester (L-NAME) To induce DKD in Wistar Rats	Various pathway intermediates	inhibition of the NFκB pathway.	Corremans et al. (2023)
Silibinin	db/db mice model	decreased the levels of p-GSK-3β, Bax and cleaved caspase-3	activated AKT signaling pathway	Liu et al. (2019)
Silibinin + valsartan	Proximal tubular cells (HK-2); HFD-induced renal fibrosis mice model	silibinin markedly increased anti-fibrosis effect of valsartan in vitro and in vivo	inactivation of TGF-β1 signaling pathway	Liu et al. (2020)
Genistein	DN model in SD rats	NOX4, MAPK, p65 and p53 were downregulated; upregulated mnf2 levels	inhibiting MAPK/NFκB pathway	Li et al. (2022)
Genistein	streptozotocin-induced C57BL/6 diabetic mice	increased renal phospho-tyrosine expression and renal phospho-ERK/ERK ratio	ERK pathway	Elmarakby et al. (2011)
Rutin	STZ-induced diabetic nephropathy in SD rats	Elevated Sirt-1, Nrf-2 and HO-1 levels; reduced levels of NF-κB, TNF-α, Jak-2, and p-Stat3	downregulating Jak-2/Stat3 pathway and upregulating Nrf-2/HO-1 pathway	Zaghloul et al. (2022)
Rutin	High glc induced human renal glomerular endothelial cells	Via Nrf2. For eg., activation of RhoA/ROCK were significantly abolished with Nrf2 knockdown	Inhibiting the ROS/Rhoa/ROCK Signaling Pathway	Wang et al. (2016)

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Table 2 (*continued*)

Compound Name	Model	Pathway targeted	Key Intermediate/pathway step targeted	Ref
Rutin	STZ-induced diabetic nephropathy in SD rats	Inhibition of AGEs, collagen IV and laminin, TGF-β(1), p-Smad 2/3 and CTGF	TGF-β(1)/Smad/ECM and TGF-β(1)/CTGF/ECM signaling pathways	Hao et al. (2012)
Combination of rutin and ramipril	alloxan induced DN in rats	Decreased ACE, TGF-β1 and podocin levels and down-regulated endoplasmic reticulum stress markers GRP78 and CHOP	targeting various pathophysiological changes and stress pathways.	Ganesan et al. (2018)
Luteolin (Lut)	C57BL/6 J db/db and C57BL/6 J db/m mice	repressing the STAT3 activation	Inhibiting STAT3 Pathway	Zhang et al. (2021)
Luteolin	HG-induced MPC-5 cells	reduced NLRP3 inflammasome formation and subsequent interleukin-1β (IL-1β) secretion	suppressing NLRP3 inflammasome pathway	Yu et al. (2019)
Icariside II (ICA II)	streptozotocin-induced diabetic rats.	significantly downregulate the levels of malondialdehyde and TGF-β/Smad/CTGF signaling	TGF-β/Smad/CTGF) signaling	Tian et al. (2015)
Fisetin	high glucose (HG)-induced podocyte injury and streptozotocin (STZ)-induced DN in mice	suppressed the phosphorylation of P70S6K, a downstream target of CDKN1B, activated autophagosome formation, and inhibited Nod-like receptor protein 3 (NLRP3) inflammasomes	Inhibiting NLRP3 Inflammasome.	Dong et al. (2022)
Fisetin	streptozotocin (STZ)-induced diabetic atherosclerosis in low density lipoprotein receptor deficient (LDLR−/−) mice	Reduced ECM accumulation, inhibits VEGFA, fibronectin and collagen	inactivating transforming growth factor β (TGFβ)/SMAD family member 2/3 (Smad2/3) pathways	Zou et al. (2023)
Silymarin nanoliposomes	(STZ)-induced diabetic nephropathy model (DN) rats.	Suppressed expression of inflammatory cytokines IL-6, ICAM-1 and TNF-α	co-suppressing TGF-β/Smad and JAK2/STAT3/SOCS1 pathway	Chen et al. (2021)
Diosmetin	Streptozotocin (STZ)-Induced Diabetic Nephropathy Mice	Akt, NFkB reduction and iNOS increased expression	Attenuates Akt Signaling Pathway by Modulating Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells (NF-κB)/Inducible Nitric Oxide Synthase (iNOS)	Jiang et al. (2018a)
Formononetin	db/db (diabetic) mouse model	Sirt1	Activates the Nrf2/ARE Signaling Pathway	Zhuang et al. (2020)
Calycosin	Streptozotocin (STZ) DN rats	increased serum levels of IL-1β, renal NF-κBp65, NLRP3, TXNIP and MDA contents with declined levels of IL-10 and TAC and decreased Nrf2 expression.	Attenuates NLRP3 and TXNIP-mediated pyroptotic signaling	Yosri et al. (2022)
Calycosin	cultured mouse tubular epithelial cells (mTEC) and db/db mice	suppressing the phosphorylation of IKBa and NF-κB p65 in vitro and in vivo	inhibition of NFkB signaling pathway	Zhang et al. (2019b)
Calycosin	high fat diet-fed/STZ injected rats	Decreased renal levels of IL33/ST2 mRNA as well as increased renal NF-κBp65, TNF-α, IL-1β, MDA, and TGF-β and increased Nrf2 and TAC	IL-33/ST2 signaling	Elsherbiny et al. (2020)
Ombuin	high-sucrose and high-fat STZ- DN rats	downregulated the expressions of transforming growth factor beta1 (TGF-β1), connective tissue growth factor (CTGF), fibronectin (FN), p65, phosphorylated (p)-p65, Cleaved-Notch 1, and hairy and enhancer of split 1 (Hes 1). All effects through PPAR γ upregulation	Notch 1 and PPAR γ signaling pathways	Liu et al. (2022b)
Apigenin	streptozotocin-induced diabetic nephropathy rats	prevented MAPK activation, which inhibited inflammation (reduced TNF-α, IL-6, and NF-κB expression) and apoptosis (increased expression of Bcl-2 and decreased Bax and caspase-3	MAPK–NF–κB-TNF-α and TGF-β1-MAPK-fibronectin pathways.	Malik et al. (2017)
Apigenin	HG-induced Human renal epithelial cell HK-2	Apigenin suppressed oxidative stress and increased mRNA expressions of Nrf2 and HO-1	activation of the Nrf2 pathway	Zhang et al. (2019c)
Icariin	D2.BKS(D)-Leprdb/J (db/db) DN mice	Upregulated the Raf kinase inhibitor protein (RKIP), The MEK/ERK pathway suppression	AR/RKIP/MEK/ERK pathway	Yao et al. (2024)
Icariin	STZ-induced DN in rats and MPC-5 cells	increase Sesn2-induced mitophagy to inhibit NLRP3 inflammasome activation by the Keap1-Nrf2/HO-1 axis	Modulation of Keap1-Nrf2/HO-1 axis	Ding et al. (2022)
Icariin	STZ-induced DN	inhibited the expressions of TLR4, p–NF–κB p65, TNF-α and IL-6 remarkably in renal tissues	suppressing the TLR4/NF-κB signal pathway	Qi et al. (2021)
Icariin	icariin inhibited TGF-β canonical Smad signaling and extracellular signal-regulated kinase (ERK)1/2 signaling by decreasing Smad2/3 and ERK1/2 phosphorylation	Via G protein-couples estrogen receptor (GPER)	Decreasing transforming growth factor-β (TGF-β) and type IV collagen expression	Li et al. (2013)
Isoliquiritigenin	STZ-induced type 1 DN and in high glucose-induced NRK-52E cells	Via sirtuin 1 (SIRT1)	inhibition of MAPK activation, and the induction of Nrf-2 signaling	Huang et al. (2020)
Isoliquiritigenin (ISO)	STZ-induced SD rats and high glc-human renal HK-2 cells	down-regulated ROS content and up-regulated expression levels of GSH, SOD2, and GPX1, inhibit JAK2	inhibiting JAK2/STAT3 signaling pathways	Sun et al. (2021)
Isoliquiritigenin	High glucose-induced human mesangial cells (HRMC	suppressed induction of TGFβ RII and TGFβ RI with blunting their downstream SMAD signaling	TGFβ1-SMAD signaling reduction	Li et al. (2010)

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Table 2 (*continued*)

Compound Name	Model	Pathway targeted	Key Intermediate/pathway step targeted	Ref
Liquiritigenin	High glucose treated glomerular mesangial cells (HBZY-1)	Inhibits NFkB activation and NLRP3 inflammation along with ECM accumulation and oxidative stress	suppression of the NF-κB and NLRP3 inflammasome pathways	Zhu et al. (2018)
vitexin	obesity-induced DN in a high-fat diet (HFD)-fed experimental C57BL/6 mice model	alteration in renal NF-κB, IκBα, nephrin, AMPK, and ACC phosphorylation levels	modulation of NF-κB/IkBα and AMPK/ACC pathways	Zhou et al. (2021)
jaceosidin	db/db diabetic mice	Decreased VEGF-a (vascular endothelial growth factor-a)	upregulation of insulin receptor downstream pathways in the liver and skeletal muscles	Park et al. (2020)
puerarin (PR)	streptozotocin (STZ)-induced diabetic mice	SIRT1, forkhead box protein O1 (FOXO1) and PPAR gamma coactivator-1 (PGC-1α) up-regulated and NFkB downregulated	attenuating SIRT1/FOXO1 pathway	Xu et al. (2016)
Astragalin	streptozotocin (STZ)-induced diabetic mouse model.	modulated mitochondrial health, homeostasis and energy metabolism	AMPK-dependent PGC1α pathway.	Sun et al. (2023)
Diosmin	Alloxan-Induced Diabetic Nephropathy	Downregulation of NFkB	NF-kB Signal Transduction Pathways and Downregulation of Various Oxidative Stress Markers	Ahmed et al. (2016)
Diosmin	high glucose (HG)-induced HK-2 cell	Increased PTEN levels and decreased p-PI3K/PI3K and p-AKT/AKT after treatment	alleviating the PI3K/AKT pathway	Deng et al. (2022)
Dihydromyricetin	DN rat model and In vitro, NRK-52E cells	Increased autophagy and miR-155–5p levels and decreased PTEN	Inhibiting miR-155–5p/PTEN and PI3K/AkT/mTOR signaling	Guo et al. (2020a)
Genistein and MyD88	in vitro high glucose (HG)-treated podocyte model	induced expression of the autophagy activation marker LC3-II	inactivating mTOR signaling	Wang et al. (2018)
Hyperoside	High Glucose-Induced Proliferation of Mesangial Cells (MES-13 cells)	inhibited the activation of ERK pathway and phosphorylation of its downstream transcriptional factor CREB, as well as the miRNA-34a expression	Inhibition of the ERK/CREB/miRNA-34a Signaling Pathway	Zhang et al. (2020)
Kaempferitrin (KM)	AGE-induced damage in cultured glomerular mesangial cells (GMCs)	inhibited the expression of collagen IV and transforming growth factor-β1 (TGF-β1)	suppressed the mitochondrial/cytochrome c-mediated apoptosis pathway	Jiang et al. (2018b)
kaempferol	Rat (NRK-52E) and human renal tubular epithelial cells (RPTEC)	inhibits hyperglycemia-induced activation of RhoA and decreased oxidative stress, pro-inflammatory cytokines (TNF-α and IL-1β) and fibrosis (TGF-β1 expression, extracellular matrix protein expression	RhoA/Rho-associated coiled-coil forming protein serine/threonine kinase (ROCK) pathway	Sharma et al. (2019)
Kaempferol (KPF)	STZ-induced C57BL/6 mice and High glc-NRK-52E, a tubular epithelial cell line,	Reduced TRAF6 levels and NF-kB in vitro and in vivo.	TRAF6-NFkB regulation	Luo et al. (2021)
Chrysin	high glucose-exposed podocytes and in db/db mouse kidneys	up-regulation of PERK-eIF2α-ATF4-CHOP	Inhibition of ER stress	Kang et al. (2017)
Naringenin	high glucose-induced rat mesangial cell	Reduced levels of NLRP3, caspase-1, IL-1β, and IL-18	NLRP3-caspase-1-IL-1β/IL-18 signaling pathway	Chen et al. (2018b)
Naringenin	DN rats	NAR inhibited TGF-β1/smad signaling activation by upregulating let-7a	Let-7a/TGFβR1 Signaling	Yan et al. (2016)
Morin	High glucose-induced glomerular mesangial cells (MCs)	reversed HG-inhibited expression of p21Waf1/Cip1 and p27Kip1; suppressed HG-induced phosphorylation of p38 MAPK and JNK1/2	suppressing the activation of p38 MAPK and JNK signaling pathways	Ke et al. (2016)
Marein	Db/db mice and high glucose treated HK-2 cells	suppressing the pro-inflammatory factors interleukin-6 (IL-6) and monocyte chemotactic protein-1 (MCP-1), and expression of the extracellular matrix proteins, fibronectin (FN) and collagen 1 (COL1)	inhibiting renal SGLT2 and activating p-AMPK pathway	Guo et al. (2020b)
Isobavachalcone (ISO)	streptozotocin (STZ) – diabetic rats and high glc treated human renal glomerular endothelial cells in vitro	weak hypoglycaemic and notable anti-inflammatory effects	modulation of the NF-κB pathway	Dong et al. (2020)
Chalcones	mouse peritoneal macrophages and a streptozotocin-induced T1D mouse model.	decrease in the expression of pro-inflammatory cytokines and cell adhesion molecules	modulation of the MAPK/NF-κB pathway	Fang et al. (2015)
Tectorigenin (TEC)	Db.db mice	TEC partially restored the reduction in expression of adiponectin receptor 1/2 (AdipoR1/2), pi-LKB1, pi-AMPKα, and PPARα in vitro and in vivo	AdipoR1/2 pathway	Yang et al. (2020)
Wogonin	Streptozotocin (STZ)-induced diabetic mouse models and high glucose Glomerular mesangial cells SV40	Reduced expression of extracellular matrix (ECM), including fibronectin (FN), collagen IV (Col-IV), α-smooth muscle actin (α-SMA), and transforming growth factor-β1 (TGF-β1)	Inhibition of NFkB and TGF-β1/Smad 3 pathway	Zheng et al. (2020b)
Wogonin	STZ-induced diabetic mice and cultured high glucose Human tubular epithelial cells (HK-2)	Reduced pro-inflammatory cytokines and autophagic dysfunction in vivo and in vitro	PI3K/Akt/NF-κB signaling pathway-mediated autophagy and inflammation	Lei et al. (2021)
epigallocatechin gallate (EGCG)	human embryonic kidney cells	Inhibition of TGFβRII and Smad3 phosphorylation. Decreased fibronectin and Notch1 levels	Notch/TGFβRII/Smad3 pathway	Zhu et al. (2020b)

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Table 2 (*continued*)

Compound Name	Model	Pathway targeted	Key Intermediate/pathway step targeted	Ref
EGCG	STZ-induced C57BL/6 wild type (WT) and Nrf2 knockout mice, high glc mouse mesangial cells	inactivation of KEAP1 protein by EGCG may mediate EGCG function in activating NRF2	HRF2-Keap 1 signaling	Sun et al. (2017)
Epicatechin and metabolite 2,3-dihy-droxybenzoic acid (DHBA)	HG-induced renal proximal tubular NRK-52E cells	Decreased ICAM-1, p-ERK, p-JNK, VCAM-1 and p-p38 levels	P38 pathway	Álvarez Cilleros et al. (2020)
Ginkgetin	high glucose (HG)-induced glomerular mesangial cell	Decreased extracellular matrix (ECM) deposition, activating AMPk/mTOR-mediated autophagy pathway	activating AMPk/mTOR pathway	Wei et al. (2021)
Tangeretin	High glc human glomerular mesangial cells (MCs)	inhibits HG-induced cell proliferation, ROS, MDA levels and fibronectin expression in glomerular MC	inactivation of ERK signaling pathway	Chen et al. (2018a)
Hispidulin	High glc -induced murine podocytes	Pim1 inhibition was associated to RAB18, NRas, PARK7, and FIS1. Induces autophagy and inhibits apoptosis	Pim1-p21-mTOR signaling axis	Wu et al. (2018)
Vitexin	High fat diet-induced DN in C57BL/6J mice	alteration in renal NF-κB, IκBα, nephrin, AMPK, and ACC phosphorylation levels was effectively restored by vitexin	modulation of NF-κB/IkBα and AMPK/ ACC pathways	Zhou et al. (2021)
Cardomonin (CAD)	normal rat kidney tubular epithelial cells (NRK-52E); Streptozotocin (STZ) induced diabetes rat model	CAD repressed PI3K/AKT and JAK/STAT3 signaling in NRK-52E cells and in vivo kidney injury	Modulating PI3K/AKT and JAK/STAT signaling pathway	Gao et al. (2022)
Astilbin	HG-induced human proximal tubular epithelial cells (HK-2 cells)	attenuated HG-induced autophagy and apoptosis	PI3K/Akt pathway	Chen et al. (2018c)

Abbreviations: HG-induced – High glucose-induced, HFD – high fat diet.

learning algorithms and training models employed are beyond the scope of the current review, interested readers may consult a recent review on the subject here (Mullowney et al., 2023). These powerful technologies enable lucid molecular characterization of global transcriptional changes in cells and their microenvironment during the disease or its treatment with natural compounds allowing the construction of an atlas of snRNA-seq datasets that offers a glimpse into the cellular complexity of DN and different classes of therapy. The outcomes of these advancements are likely to have a huge socio-economic impact in altering the treatment landscape of DN in the near future.

4. Status of flavonoids as treatment compounds in phase 2 and 3 clinical trials on diabetic nephropathy

Early intervention of DN is often desirable because it can prevent several complications that are potentially irreversible (Lu et al., 2023). Since clinical trial data is the basis on which life-saving treatment decisions are made we performed a cross-sectional analysis according to STROBE (Strengthening the Reporting of Observational studies in Epidemiology) by searching the ClinicalTrials.Gov registry for trials that globally targeted DN. The data from the treatment interventions was organized in a spreadsheet for analysis. Descriptive statistics was performed using the standard methods because of the exploratory nature of the data. We looked at the study design, drugs tested as well as the comparators. After assessing these factors, studies that failed to satisfy the exclusion criteria such as absence of investigations on diabetic patients and/or an irrelevant intervention concerning diabetic kidney disease (DKD) were excluded. Clinical trials were characterized as completed, ongoing, non-recruiting, or terminated based on publicly available information. A total of 64 phase III clinical studies, 138 phase II and 42 phase I, were identified in ClinicalTrials.Gov registry. Of these, phase II and phase III clinical trials were chosen for further evaluation. Phase II involves testing drugs in a larger group of patients for optimal dosage and potential side effects, and phase III tests the drugs in larger populations to confirm their effectiveness in comparison with the current standard or a placebo.

Traditionally, blood pressure and blood glucose-lowering medications have been the cornerstones of diabetic nephropathy treatment. In summary, 138 and 64 clinical trials were registered in phases II and III, respectively, to treat diabetic nephropathy (Fig. 3). Of these, 7 studies were terminated in phase II and 11 in phase III. Interestingly, 62% of the trials in Phase II were completed compared to 52% in Phase III (Fig. 4).

Blood pressure-lowering drugs were the most represented class of drugs in all trials, comprising 20% of the experimental treatment options for DN (Fig. 5). However, the efficacy of these drugs used in isolation in reversing the decrease in GFR is unclear; they have been shown to reduce the risk of microalbuminuria when administered along with diuretics (Patel et al., 2007). Glucose metabolism regulators are the

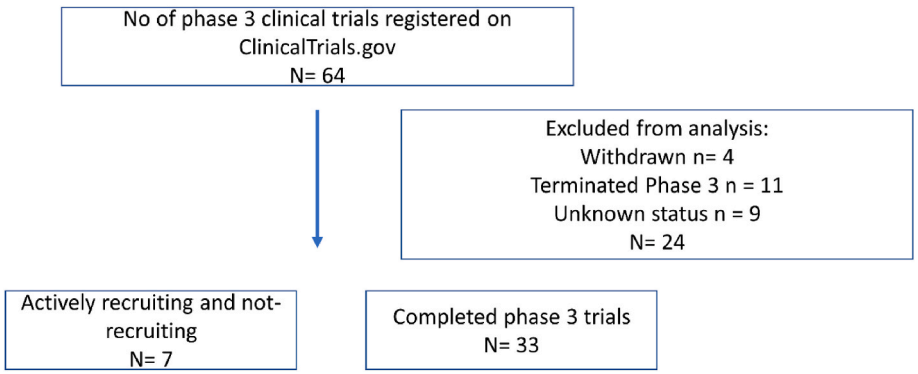

Fig. 3. Study flow diagram of phase 3 clinical trials on DN in the ClinicalTrials.gov registry.

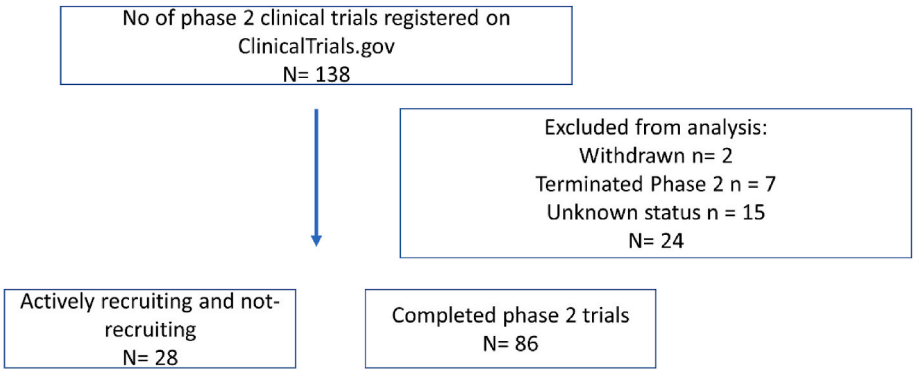

Fig. 4. Study flow diagram of phase 2 clinical trials on DN in the ClinicalTrials.gov registry.

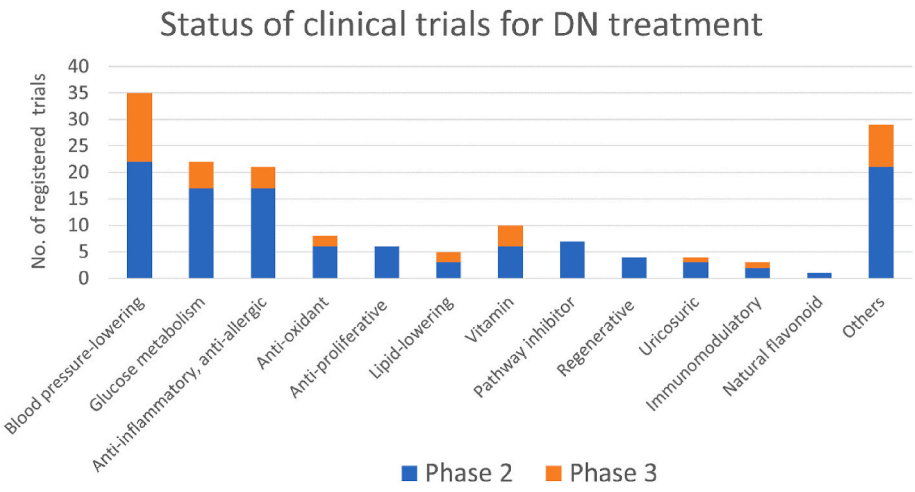

Fig. 5. Status of clinical trials in DN.

second preferred choice of DN treatment, understandably because diabetes control is already in place in these patients. Since these two interventions have been unable to treat proteinuria effectively, the search for alternative targets that mediate renal dysfunction has recently gained renewed attention. Accordingly, it could be seen that 25% of phase II trials target inflammation, oxidative stress and cellular proliferation in comparison to 15% of trials currently in phase III. Interestingly, none of the studies in phase III were currently aimed at evaluating pathway inhibitors, whereas in phase II, 7 studies were aimed at addressing their role. These include inhibitors of the NF-κB, MAPK, JAK, IGF-1, VEGF-B, Nrf2, and Notch pathways. In addition to these inhibitors, vitamins, uricosuric drugs, and treatment with the natural flavonoid fisetin have been characterized in phase II trials. However, the outcomes of many of the experimental drugs cited above have yet to be published. Additionally, our analysis of clinical trials was limited to the ClinicalTrials.Gov registry alone as well as published data from literature cited in Pubmed and Google scholar using the accepted methodology adopted by past studies in the field (Modafferi et al., 2019). Hence, our analysis of clinical trials is an attempt to provide status update regarding DN treatment.

5. Conclusion

In conclusion, as past phase III studies have reported, new investigative strategies are needed for improvements in diabetic patient care. Hence, we opted to expand our horizons, glimpsing at some of the emerging options for DN treatment as captured in phase 2 clinical trial data. Herein, we enumerated several new experimental agents (anti-inflammatory, antioxidant, pro-fibrotic signaling pathway inhibitors and especially natural flavonoids) that are currently under investigation in phase II and III clinical trial – their clinical therapeutic success having considerable value, as therapeutic outcomes in clinical trials often become the foundation stone for patient treatment decisions. As a group of compounds with potentially low toxicity and naturally occurring agents, these compounds could have exceptional promise in targeting DN. Nevertheless, as our survey of the landscape indicated, their adoption in phase II and III clinical trials is scarce despite identification of the plausible intracellular targets and mechanisms of action of these natural compounds. More trials targeting specific pathways in DN and systematic reviews discussing the effective doses of natural compounds are required to substantiate their potential. We hope that future research will effectively calibrate the utility of these compounds in multiple DN models facilitating increased recruitment into clinical trials, thereby expanding the treatment arsenal for DN.

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Mahaboob Khan Sulaiman: Conceptualization, Methodology, Data curation, Writing – review & editing, Visualization, Validation, Writing – review & editing.

Declaration of competing interest

The authors have nothing to declare.

Data availability

No data was used for the research described in the article.

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