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Role of Phytochemicals against Diabetic Nephropathy: An Insight into Molecular Receptors

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Abstract

Diabetic nephropathy is a growing disorder among diabetic patients. A multifactorial disorder affects various factors like elevated metabolism and hypertension and blocks various molecular pathways such as AGE (Advanced Glycation End Product), RAAS (Renin Angiotensin Aldosterone System), PKC (Protein Kinase C), Hexosomamine, and polyol. Individuals are temporarily relieved by available combined treatments like ACE inhibitors and calcium channel blockers for blood pressure control as well as for severe albuminuria conditions, but these therapies have significant adverse health consequences. Herbal preparations play a potential role in the cure of various ailments that come first in the mind for humans which have least or without side effects and are economically stable for consumption. Since these constituents are cost-effective and have minimal side effects, scientifically validated phytochemicals or combined formulations are significant against diabetic nephropathy. This review focuses on the mechanism of receptors and the genes involved in the disease and the potential phytochemicals effectiveness against it.

Keywords: Diabetic Nephropathy, Genetic Factors, Markers, Mechanism, Phytochemical, Receptors

1. Introduction

Diabetes mellitus is a significant health problem in today's society, and it is the main cause of mortality among ESRD patients[1]. Diabetic nephropathy occurs in many people within 20 years of the onset of diabetes (3 percent each year)[2]. It takes 15 years for small blood vessels in organs like the kidneys, eyes, and nerves to become damaged. In more than 20% to 40% of diabetic individuals, progressive kidney damage is predicted (CKD)[3,4]. According to the International Diabetic Federation, the incidence of diabetes among individuals aged 20 to 79 was 8.8% in 2015, impacting around 440 million people[5]. By 2035, it is predicted that this population will have climbed to about 550 million people[6].

Diabetes mellitus affects the glomerular microvasculature of the kidneys and is the primary source of problems. The prevalence of Diabetic Nephropathy (DN) is influenced by several factors, including genetic variability, lifestyle, nutrition, and healthcare systems. As a result, depending on the reason, the frequency of DN varies[6]. The Asian diabetic population is more vulnerable to DN than the Western diabetic population due to the prevalence of microalbuminuria or macroalbuminuria[7].

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Symptoms of glomeruli damage include pedal edema, difficulty breathing, albumin excretion in the urine, and low serum albumin. The estimated glomerular filtration rate may gradually decrease from a normal of more than 90 ml/min/1.73m^2 to less than 15, indicating End-Stage Renal Disease (ESRD). It usually progresses slowly over time[8].

Several clinical studies have revealed that patients with Type 1 diabetes develop ESRD sooner than those with type 2 diabetes. It is widely recognized as the most common diabetic consequence. Diabetic nephropathy is more common in ethnic minorities than in other groups[9]. Despite the availability of new medicines, there is no permanent cure. End-Stage Kidney Disease (ESKD) affects a considerable proportion of the population, necessitating renal replacement therapy such as kidney transplantation.

2. Pathogenesis of Diabetic Nephropathy

DN begins with poorly managed blood glucose levels that have been present for a long time. Multiple alterations occur in the kidney's filtration units, particularly in the nephrons[10,11]. Each adult kidney contains around 7,50,000-1.5 million nephrons. Initially, the efferent arterioles constrict, and the afferent arterioles dilate, resulting in glomerular capillary hypertension and hyper filtration, eventually leading to hyper filtration.

2.1 Changes in Hemodynamics

Diabetic Nephropathy directly dependent on the kidney's hemodynamic factors showing an increase in IGF-1, TGF-β, VEGF, PG, glucagon, ET-1, and SGLT2. The glomerulus regulates hemodynamics and blood pressure, and it plays a significant role in contracting afferent and efferent arterioles[4,13].

2.2 RAAS Activation

Renin Angiotensin Aldosterone System (RAAS) acts as greater impacts in control body fluids and blood pressure. however its abnormalities brings changes in haemodynamics that causes endothelial dysfunction. The important hormone called Angiotensin Coverting Enzyme (ACE) mainly found in kidney epithelial cells helps in coverting Angiotensin I into an octapeptide Angitensin II that further stimulates the hormone called aldosterone that ends in RAAS cascade. The electrolye flux pathways undergoes upregulation when Aldosterone binds to the mineralocorticoid receptor. Angiotensin-II

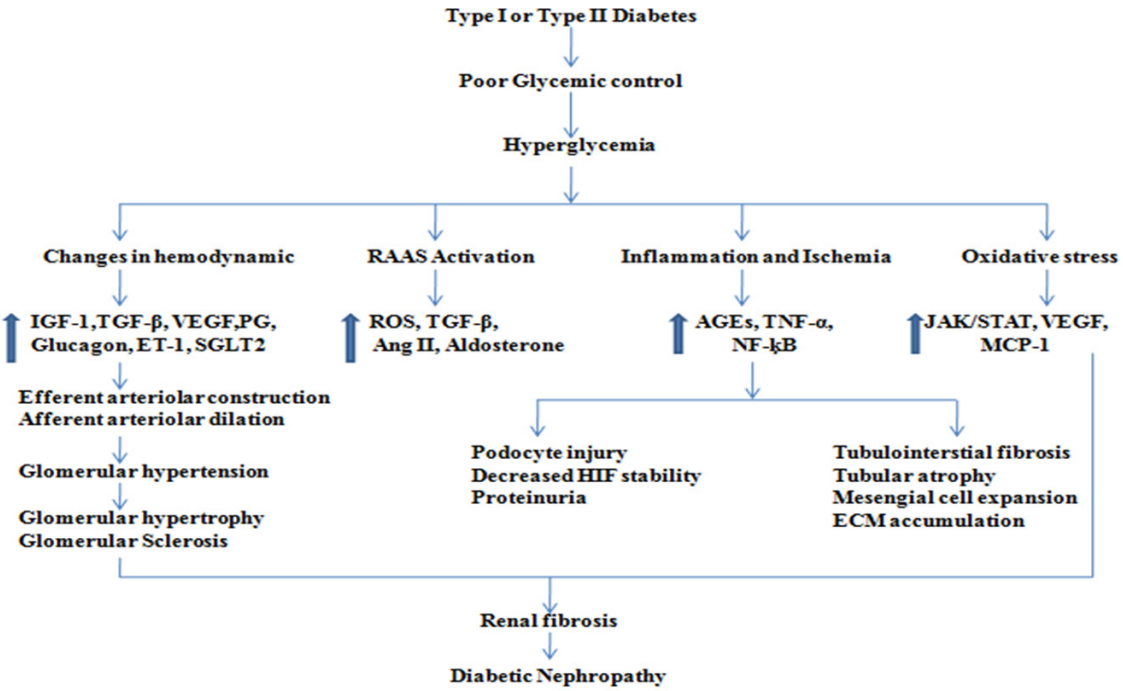


Figure 1. Pathophysiological changes in Diabetic nephropathy[12].

is also responsible for developing pancreatic β-cell integrtaed oxidative stress, inflammation, and apoptosis. It causes an increase in Reactive Oxygen Species (ROS), Tumour growth factor- β, Angiotensin II, and Aldosterone. Inhibitors of the renin-angiotensin pathway effectively lower proteinuria and system blood pressure[14].

2.3 Inflammation and Ischemia

TNF-ά, IL-1, IL-6, and IL-18 are inflammatory cytokines expressed in higher proportions in diabetic kidney models than in non-diabetic kidney controls[15,16]. Glomerular hypercellularity is caused by increased vascular endothelial cell permeability, and GBM thickening causes kidney cell apoptosis[17].

2.4 Oxidative Stress

The pathogenesis of diabetic nephropathy is aided by oxidative stress, caused by various factors such as AGEs and rennin-angiotensin system components. AT1 angiotensin receptor activation or AT2 angiotensin receptor activation causes these factors to be produced[18]. In the glomerulus, the basement membrane deepens, the podocyte slit membranes expand, and the amount among both mesangial and the mesangial matrix increases. Kimmelstiel-Wilson nodules are caused by damage to the mesangial matrix, which causes glomerular capillaries to rupture. The mesangial cells and matrix can effectively shut off filtration by extending and absorbing the whole glomerulus[20].

3. Role of Receptors in Diabetic Nephropathy

3.1 Nuclear Hormone Receptors

Nuclear hormone channels can influence the production of a wide variety of genes in several ways, for example, by regulating their expression level. The activity and quantity of ligands, the action of series resistance proteins, and post-translational changes like phosphorylation,

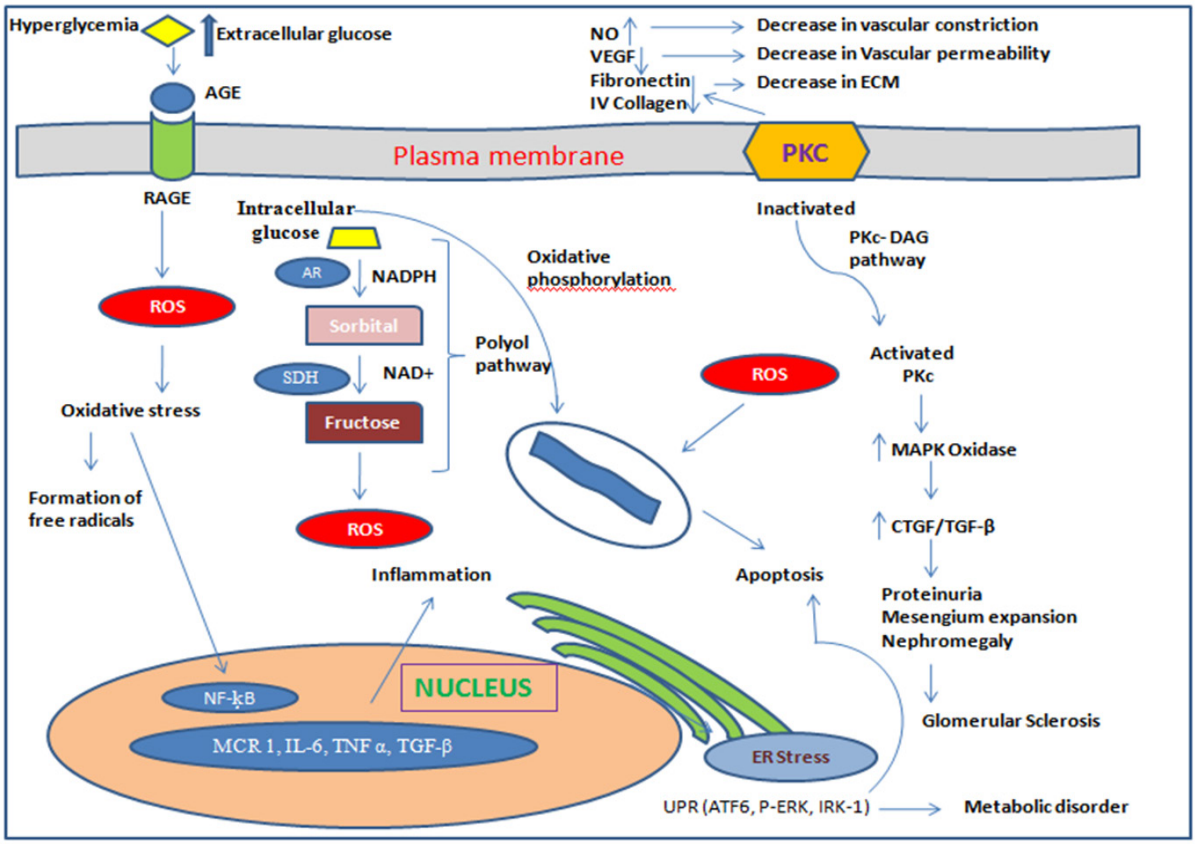


Figure 2. Pathways involved in Pathogenesis of Diabetic Nephropathy[19].

acetylation, and sumoylation always affect the function of nuclear hormone receptors.

3.1.1 Peroxisome-Proliferator-Associated Receptors (PPAR)

PPAR is predominantly expressed in the renal tubular and the ascending limb of nephron in the kidney. Initially, it was assumed that PPAR was only found in the distal nephron's medullary collecting duct; however, recent research has revealed that PPAR is also found in nephron and developed mesangial cells[19]. *In-vivo* ligand specificities, both PPAR and PPAR show a considerable sensitivity for naturally produced fats and steroid hormones secretion alkaline compounds. Endogenous PPAR ligands include lysophosphatidic acid, nitro linoleic acid, prostaglandin D2, and prostaglandin J2[20].

3.1.1.1 Peroxisome-Proliferator-Associated Receptor α

Renal PPAR regulates renal fatty-acid oxidation, which plays a crucial role in controlling energy use in the kidney. The renal PPAR response to dietary lipids[21] and the relevance of this function is demonstrated by the protective impact of PPAR versus hypoperfusion damage, in which diminished renal oxidative leads to fatty acid buildup and cellular toxicity, resulting in renal tubules cell death. Blood pressure control is also linked to the activity of the cytochrome P450 complex in the renal tubular. Although PPAR production in glomerular cells is modest, an increase in PPAR expression in rodent mesangial cells after lipopolysaccharide stimulus has been observed-a mechanism that might help to reduce lipopolysaccharide-induced inflammatory responses[22].

PPAR agonist had also been demonstrated to help people with diabetic nephropathy. In diabetic nephropathy, PPAR activation may have renal-specific effects, mediating nephroprotection. The capacity of PPAR to suppress the activation of Nuclear factor kappa B (NF-κB), an essential step in the manufacture of proinflammatory cytokines, and inducible nitric oxide synthase, a significant inducer of nitrosative stress, might explain its anti-inflammatory and anti-nitrosative actions in diabetic nephropathy animal models. It has not been investigated if PPAR has a function in decreasing oxidative stress caused by renal NADPH oxidase. The PPAR agonist fenofibrate inhibited leukocyte adherence to mesangial cells generated by high glucose levels. It lowered the production of Type I collagen, Type IV collagen, and TGF-ά in mesangial cells treated with high glucose levels, indicating that PPAR directly impacts the kidney. The evidence implies that PPAR agonists have therapeutic promise in delaying the development of diabetic nephropathy and their lipid-lowering benefits[23].

3.1.1.2 Peroxisome-Proliferator-Associated Receptor γ

PPAR agonists were shown to inhibit the development of renal disease in several trials. And over 15 years ago, glitazone therapy was reported to be obese Zucker rat model of Type 2 diabetes. Troglitazone reduced urine protein excretion and sugar levels, hypertension, plasma hormone, and circulating lipids in these mice. Since then, glitazones have been regularly shown to improve diabetic nephropathy in animal studies of Type 1 and Type 2 diabetes. Glitazones were found to reduce albuminuria while also reducing glomerular hyperfiltration and preventing glomerulosclerosis and proximal tubular fibrosis in many of these trials[24].

In animal studies, isolated glomeruli, and renal cell cultures, glitazones have been found to have direct effects on renal cells. PPAR agonists have antiproliferative, antifibrotic, and anti-inflammatory properties in mesangial and proximal tubule cells. In animal models of Type 2 diabetes, activation of PPARγ activation prevents renal endothelial cell dysfunction and podocyte injury. It inhibits activation of NFκB, the accumulation of reactive oxygen species, and the infiltration of macrophages in the kidney. As according to research in mesangial cells, PPAR may influence glomerular lipogenesis by stimulating the Liver X Receptor (LXR) to ATP-binding cassettes 1 system to promote cholesterol efflux, implying a plausible explanation for our more recent findings[25].

3.1.1.3 Peroxisome-Proliferator-Associated Receptor δ

PPAR enhances lipid degradation and may have a role in controlling insulin levels, glucose homeostasis, adipocyte, and exercise adaptation. In the Akita and the OVE26 mouse models of Type 1 diabetes, renal expression of PPARδ is significantly suppressed compared with wild-type mice. While subjected to degraded lipids, which are prevalently produced in the kidney tissue of model organisms of diabetic nephropathy, renal tubules cell of obese diabetic rats showed suppression of PPAR expression. These data suggest a potentially important role for PPARδ in diabetic nephropathy. In mouse models of ischemia-induced renal injury, administration of a synthetic PPARδ agonist was

associated with solid renoprotection and a reduction in medullary necrosis, apoptosis, and inflammation[26]. The role of PPARδ in alleviating inflammation and regulating lipid metabolism in animal models of diseases such as ischemia-induced injury suggests that PPARδ agonists may also confer renal protection in diabetic nephropathy.

3.1.2 Estrogen Receptors

The estrogen receptor α are found as predominant isoform than receptor β in the kidney which expressed in glomeruli as well as in isolated mesangial cells. The expression was found in podocytes through immunohistochemical studies. Additionally, estrogen receptors are also located in nucleus, plasma membrane and in cytoplasmic organelles, such as the mitochondria and the endoplasmic reticulum. The connectivity among estrogen-receptor activity with diabetic nephropathy is evidenced through reduction in levels of plasma estradiol and dysregulation of estrogen-receptor signaling in diabetic kidneys from clinical data[27]. Estrogen receptor activation in podocytes has been discovered by immunofluorescence. The oestrogen receptor is the most potent hormone sensor in terms of actions, as well as the kidney is one of the organs where oestrogen receptor effects are most noticeable[28].

Clinical and animal investigations have indicated lower levels of plasma estradiol and deregulation of estrogen-receptor signaling in diabetic kidneys, suggesting a link between estrogen-receptor activity and nephrotic syndrome[29]. Estrogen receptors have been implicated in the lack of female-sex nephroprotection in diabetic patients. Estrogen receptor signaling occurs in renal mesangial, endothelial, and podocytes in the kidney. Estrogen receptor activation suppresses cell proliferation, lowers TGF expression, lowers extracellular matrix buildup, enhances endothelial nitric oxide synthase activity, and raises VEGF expression in these cells[30].

3.1.3 Vitamin D Receptor (VDR)

The activity of 1,25(OH)2D3 is controlled by VDR, one of the earliest members of the human nuclear hormone receptor family. In complement to mineral homeostasis control, 1,25(OH)2D3–VDR has many physiologic and pathologic activities, including renal and cardiac function regulation[31]. Although VDR may not be involved since 1,25-(OH)2D3 may function swiftly even without it, the nongenomic route controlled by 1,25(OH)2D3 may engage the with a chromosomal pathway to alter VDR-dependent gene expression. The phosphorylation of important VDR co-activators is caused by nongenomic 1,25(OH)2D3 rapid activation of cytosolic kinases, culminating in VDR-dependent gene transcription regulation[32]. VDR might immediately affect the nuclei, producing p65-mediated gene transcription suppression by building compounds with the NFB p65 subunit. This suppression of gene expression has an anti-inflammatory impact.

3.1.4 Hepatocyte Nuclear Factor 4α

HNF4 interacts with DNA as dimers. Its activity may be modulated by the interaction of fatty acyl-CoA thioesters, given that it was previously thought to be an orphan receptor. HNF4 may be acetylated, phosphorylated, and connect with TGF-regulated Smad3 and Smad4, indicating that HNF4 activity is regulated in several ways[33]. HNF4 is only expressed in the liver, gastrointestinal system, pancreas, and kidneys in adults. There have been multiple putative HNF4 target genes found. These genes control various metabolic processes, including glucose, lipid, steroid, xenobiotic, and amino acid metabolism. Mutations within the gene that encodes human HNF4α result in the development of Maturity-Onset Diabetes of the Young (MODY)[34]. Using a Chromatin Immunoprecipitation (ChIP) experiment to find genes that HNF4 directly controls, the relevance of HNF4 in diabetic nephropathy has yet to be confirmed. The HNF4 genetic code TRPC1 (which codes the short transient receptor potential channel 1) was influential in modulating mesangial contraction, which affects glomerular function.

3.1.5 Farnesoid X Receptor

FXR is upregulated in the liver, gut, adrenal gland, and kidney, particularly with high kidney expression. The enterohepatic system relies heavily on FXR activation to maintain sugar, lipids, and bile salt balance. FXR was found in isolated nephrons in the mouse kidney. Glomeruli had 30 percent of the expression levels of proximal tubule cells. FXR is also found in cultured mouse mesangial cells as well as podocytes. Proteinuria, glomerulosclerosis, tubulointerstitial fibrosis, and macrophage infiltration improved in these illness models. Actions on adipogenesis, oxidative stress, and the generation of proinflammatory and myofibroblast growth factors are all involved in these nephroprotective effects[35].

3.1.6 Liver X Receptors

TRPC1 is involved in the control of mesangial contraction, which affects glomerular function. In the kidneys of Zucker rats with Type 2 diabetes and rat with streptozotocin induced diabetic, TRPC1 expression was lower than in non-diabetic rats. LXR is present primarily in the liver, gut, and kidney at low-to-moderate levels. TRPC1 is involved in the control of mesangial contraction, which affects glomerular function. In the kidneys of Zucker rats with type 2 diabetes and rat with stz - induced diabetic, TRPC1 expression was lower than in non-diabetic rats. LXR is present primarily in the liver, gut, and kidney at low-to-moderate levels.

3.2 Toll-Like Receptors

TLR1, TLR2, TLR3, TLR4, and TLR6 are expressed by renal tubular and mesangial cells in the kidney. The podocytes and Bowman's capsule have both been shown to express TLR4. TLR1, TLR2, TLR4, TLR5, and TLR6 are cell surface receptors, whereas TLR3, TLR7, TLR8, and TLR9 are intracellular receptors. The intracellular localization of distinct TLRs may be related to the molecules of their ligands to some extent[36]. Except for TLR3, which communicates through TIR domain-containing adaptor protein (TRIF), all TLRs employ the MyD88 route. Following the detection of specific ligands, one of two signaling pathways, either MyD88-dependent or MyD88-independent, can be used. TLRs recruit MyD88 by contact with their respective TIR domains in the first route, which leads to the activation of signal transduction cascades, including IRAKs (IL-1R-associated kinases), IKK [IB (inhibitor of NF-B) kinase], and NF-B. TRIF is required for the MyD88-independent pathway, exclusively found in TLR3 and TLR4. It stimulates IRF3 (IFN regulatory factor 3) and is involved in the late phase of NF-B activation, resulting in IFN production and expression of IFN-inducible genes. TLR4-mediated inflammatory cytokine production involves both the MyD88-dependent and MyD88-independent pathways, whereas TLR2 only uses the MyD88-dependent pathway. The Toll-Interleukin-1 Receptor (TIR) domain-containing adaptor protein (TIRAP) is necessary for TLR2 and TLR4's MyD88-dependent signal transduction pathways, but Toll Like Receptor Adaptor Molecule (TRAM) is essential for TLR4's MyD88-independent signal transduction route[37]. Ultimately, the signaling pathways culminate in the activation of NF-κB. NF-B is found in the cytoplasm of unstimulated cells. After activation, NF-B translocates into the nucleus to control the expression of several genes implicated in inflammation, including cytokines, chemokines, and other innate immune effectors. The NF-B transcription factor family members are p65 (REL-A), REL-B, cytoplasmic (c) REL, p50, and p52. TLRs activate NF-B by activating IB, allowing mostly p65 heterodimers to translocate to the nucleus[38].

The role of endogenous ligands in inducing TLR-mediated NF-κB activation has been established in several models of kidney disease[39]. NF-B has been demonstrated to be active in diabetic nephropathy patients' activated macrophages and triggered by high glucose levels. Proteinuria has also been identified as a causative component in NF-B activation in renal cells in diabetic nephropathy patients, suggesting that NF-B activation is a sign of renal damage progression[40]. Furthermore, that NF-B is activated in kidney proximal tubular cells in response to TLR2 and TLR4 stimulation in the condition of elevated glucose levels, and thus transcriptional regulation of proinflammatory cytokines, cell adhesion molecule proteins, inflammatory cytokines, and other molecules involved in exacerbating inflammatory responses in diabetic nephropathy[41].

3.2.1 Role of TLR2 and TLR4 in Diabetic Nephropathy

Li *et al*. discovered enhanced renal TLR2 tubular expression and the existence of signaling molecules HMGB1 and HSP70 and renal expression of MyD88 and MCP-1, NF-B activation, and macrophage infiltration in STZ-induced diabetic rats. TLR2 expression was also identified in significant concentrations in the nephrons of diabetic nephropathy biopsies. *In vitro*, severe hyperglycemia elevated TLR2 mRNA expression in NRK-52E cells, confirming their findings[42]. Furthermore, the diabetic TLR2-knockout animal regained nephrin, podocin, podocyte number, and effacement as compared wild-type mice. They also found that preserving podocyte number and normalizing microalbuminuria reduced incipient diabetic nephropathy. Consequently, even though TLR4 expression was present in the knockout diabetic animal, the lack of TLR2 expression lowered inflammatory markers. TLR2 agonists have been shown to inhibit fibrocyte development, which may be helpful in preventing renal collagen deposition in renal dysfunction[43].

When TLR4 expression or signaling was muted or repressed *in vitro*, NF-B activation and production of proinflammatory cytokines were reduced. On the other

hand, TLR2 siRNA did not influence NF-B transcriptional activity[44]. Cha *et al*. have discovered that TLR4 and NF-B p65 subunit transcription is elevated in the nephron of diabetic mice. TLR4 transcription and proinflammatory cytokine secretion were elevated in podocytes and adipocytes exposed to high glucose and NEFAs (non-esterified 'free' fatty acids) *in-vitro*, showing that TLR4 plays a crucial role in transmitting inflammation in the body[45]. Increased ceramide production was not required for TLR4-dependent inflammatory cytokine induction. Still, it was required for TLR4-dependent insulin resistance, suggesting that sphingolipids like ceramide may be essential components ultimately contributing to diabetes and its complications[46].

3.3 GPCRs in Diabetic Nephropathy

3.3.1 Prostaglandin E (EP) Receptor

EP1 is critical in hastening the progression of DN. EP1 expression was elevated in DN rats induced by Streptozocin (STZ)[47]. In terms of the TGF-b1 pathway, it has been suggested that urine Smad1 could be a new marker for DN, and that Bone Morphogenetic Protein 4 (BMP4) up-regulates Smad[48]. EP1-induced TGF-b1 activation could activate BMP4/Smad1 pathways, speeding up the buildup of ECM and therefore contributing to glomerulosclerosis, which is a critical factor in developing nephropathy. The findings showed that TGF-b1, TGF, and collagen expression increased dramatically in glomerular mesangial cells. GBM thickness, glomerular hypertrophy, and glomerulosclerosis were all aggravated due to increased inflammation and ECM deposition, all of which led to the development of DN[49]. In addition, a new study found that the EP1 receptor diminished DN-associated proteinuria via reducing Ang II-stimulated oxidative stress in podocytes[50]. The ability of ONO-8713 to inhibit nephrin mRNA downregulation and foot process effacement in podocytes represents a significant therapeutic target in DN[51].

3.3.2 Adenosine Receptor (AR)

Adenosine activates the G protein-coupled receptors that affect renal functions. Under terrible conditions like inflammation, diabetes, and hyperglycemia that give rise to extracellular adenosine levels were mainly raised in glomeruli. A2BAR has been the subject of the bulk of study, and there is substantial evidence that it plays a harmful role in mitigating the beginning stages of kidney hypertrophy and diabetes failure[52]. A2BAR stimulation can activate both the AC and the PLC via Gas and activates extracellular signal-regulated kinase 1/2 (ERK1/2)[53].

According to contrary data, the inhibition of VEGF did not improve early diabetic renal abnormalities in Type 2 diabetes[54]. Meanwhile, A2BAR activation activated the ERK1/2 pathway, which allowed TGF-b1 to be released via Smad3. The target gene transcription and mRNA expression are regulated due to the passageway. As a result, fibronectin, Type I, and IV collagen expression increases, resulting in a synergistic acceleration of mesangial cell proliferation and elevation of excessive ECM buildup[55]. TNF-a, MCP-1, fibronectin, and macrophage glomerular infiltration in podocytes, as well as albuminuria, podocyte foot process fusion, and rennin production in DN, may be reduced by A2AAR activation in conjunction with the C-Raf/ERK pathway[56].

3.3.3 Endothelin-1 (ET-1) Receptor

ET-1, a 21-amino-acid molecule, is considered a leading new diabetic treatment target. ET-1 stimulated 2 Endothelin Receptors (ETRs), ETAR and ETBR. The renal ET system is chronically stiwmulated in people with diabetes, as evidenced by raised flow peaks of ET-1 and enhanced renal ET-1 concentration levels, which would seem to be crucial for the pathophysiology of DN. ET1 is the main subtype exerting significant renal biological effects among the various ETs. ETBR is a useful transcription factor because it acts as a "clearance receptor" stopping ET-1 from stimulated ETAR and increasing endothelial secretion (NO). ETAR is a ligand-activated receptor associated with the proteins Gaq/11 and Ga12/13. When the Gaq/11 protein is activated in diabetes, it activates the PLC pathway, which other moderates PKC and Calcium ions+ movement via Inositol Triphosphate(IP3) and Diacylglycerol (DAG) signals. Meanwhile, energizing the Ga12/13 protein was shown to activate the RhoA/ROCK pathway. Shortly after, IkBa sumoylation was inhibited, and downstream target genes of NF-kB were activated[57]. Intercellular Adhesion Molecule-1 (ICAM-1), TNF-a, TGF-b1, VEGF, and nephrin are among the gene changes, which cause continuous and gradual inflammation, podocyte death, and proteinuria, facilitating the progression of DN[57-61].

3.3.4 Angiotensin II Receptor (ATR)

Angiotensin II is an essential RAS peptide and among the most valuable vasoactive peptides. Ang II is

generated in the vascular system and functional areas by connecting to 2 kinds of ATRs, Type 1 AT1R and Type 2 AT2R. AT1R also stimulates G protein-independent passageways via Gai/o, including b-arrestin-mediated ERK activation and the Jak/STAT system. The NF-kB pathway was activated after AT1R activation, associated with decreased insulin levels, enhanced RAS action, and improved ICAM-1 and VEGF creation. As a result, glomerular hyperfiltration was accelerated, and abnormal protein changes occurred, including lessened nephrin and increased desmin protein production. As a result of these changes, retinal inflammation, glomerular hypertrophy, and proteinuria exacerbate the DN debilitating process[62]. Growing evidence shows that AT1R blockers can be used therapeutically to prevent Ang II-induced involution.

3.3.5 Cannabinoid Receptor (CBR)

Cannabinoids, which are intrinsic fatty acid facilitators, initiate physical and metabolic impacts by stimulating 2 significant GPCRs, Cannabinoid Receptor 1 (CB1R) and receptor 2 (CB2R) (CB2R). CBRs dysfunction could play a part in the pathogenesis of DN by attempting to influence inflammation, hypertrophy, and the progression of nephropathy[63]. As per increasing evidence, the CB1R is often up-regulated in diabetic glomerular podocytes. When the CB1R is activated, it unites with the Gai/o protein. It decreases cAMP levels, activating the NF-kB, MAPKs, PI3K/Akt, Ras, and peroxisome proliferator-activated receptor g2 (PPARg2) signaling pathways, the further outcome in a wide range of abnormal changes in diabetes[64]. Downregulation of nephrin and podocin protein expression, increased ICAM-1 and VCAM-1 expression, increased insulin resistance, increased renal oxidative stress, and RAS activity contributes to podocyte death, renal inflammation, and fibrosis metabolic disturbances[65]. Glomerulosclerosis and proteinuria are the hallmarks of progressive DN, and the changes as mentioned earlier eventually lead to them.

CB1R could be a promising anti-diabetic therapy for the treatment of DN. Data shows that activating CB2R can lower cAMP levels and block PI3K/Akt pathways, which can lower MCP-1 receptor CCR2 levels and reduce podocyte protein deficiency such as nephrin and podocin as well as ECM components like fibronectin overexpression in experimental diabetes[66,67].

3.3.6 GLP-1 Receptor

The GLP-1 receptor is overexpressed in the glomeruli and proximal tubules of the nephron. GLP-1 agonists improve renoprotection in hyperglycaemic kidneys by increasing macromolecular expression levels. GLP-1 was shown to have antioxidant activities due to the stimulation of Foxo3a signaling pathway after up-regulation. The activation of Foxo3a leads to activation of antioxidant enzymes such as Superoxide Dismutase (SOD). GLP-1 increases plasma interleukin 1 receptor antagonist concentrations significantly. This would counteract IL-1's detrimental effect on the pancreatic β-cell, possibly increasing insulinogenesis and possibly extending cell life. Exenatide also reduced plasma levels of GF (Transforming Growth Factor), a cytokine involved in developing diabetic nephropathy[68-71]. GLP-1 antagonist reduces blood Angiotensin II levels, contributing to the observed increase in renal sodium wasting. This decrease in Angiotensin II levels after GLP-1 administration could be due to various factors. This decrease in Angiotensin II levels after GLP-1 administration could be attributed to increased blood pressure, increased sodium delivery to the macula densa, and decreased activity of the tissue renin-angiotensin-aldosterone system[72]. The Dipeptidyl Peptidase-4 (DPP4) inhibitors and GLP-1 receptor agonist causes enhanced activity in the kidney, resulting in the activation of protein kinase (A) by cAMP (cyclic AMP receptor). However, as hyperglycemia rises, the expression and function of Sodium-Glucose cotransporter (SGLT2) in the kidney's proximal tubule becomes maladaptive. As a result, glucose reabsorption in people with poorly managed diabetes could increase by 20%. SGLT2 is a glucose transport protein with a low affinity and high capacity that reabsorbs 90% of filtered glucose[73,74].

4. Diabetic Nephropathy-An Overview of Genetic Polymorphism

Several chromosomal regions have recently been detected via genome-wide linkage scans and genes linked to diabetic nephropathy susceptibility. In Figure 3, the complementary approaches have been depicted.

Diabetic nephropathy tends to be multifactorial, with genetic and environmental factors interacting. As seen in Figure 3, the genes mentioned have recently been linked to diabetic nephropathy, which plays a vital role in

lipid and glucose metabolism. The genetic roles of these genes make it easier to explore the genetic factors that already exist[76-86]. Proteinuria, or the existence of protein in urine, is used to track DN's progression. The amount of proteinuria depicts the extent of the problem toward any nephrons that are still functional. The serum creatinine level can be used to calculate the approximate Glomerular Filtration Rate (eGFR), representing the percentage of filtered glomeruli. Table 1 shows how early biomarkers for renal dysfunction can be defined based on the type of injury and pathogenesis.

5. Natural Remedies for Diabetic Nephropathy

Recently, the treatment has become more multifactorial, including preventing cardiovascular and renal risk factors such as hypertension, albuminuria, glycemic regulation, dyslipidemia, and obesity. Nausea, vomiting, hyponatremia, lactic acidosis, pernicious anemia, dyspepsia, joint pain, and other side effects are common with allopathic treatment. As a result, phytocompounds can be a safe option with little to no side effects[153]. In recent years, natural drug usage has

Table 1. Biomarkers of diabetic nephropathy

Pathogenesis/Injury Type	Biomarkers	Sample	Value Status
Glomerular[87-92]	Transferrin, Type IV collagen, Ceruloplasmin, Immunoglobulin G, Laminin, Glycosaminoglycans Fibronectin	Urine Urine/ Plasma	Increases
Tubular[87,93-121]	KIM1, NGAL, NAG, L-FABP, AIM, RBP, FLCs	Urine	Increases
Oxidative Stress[109, 122-141]	8-OHdG, AGA, Podocytes-podocalyxin Pentosidine	urine Urine/Serum	Increases
Inflammation[133,142-152]	TNF-α, IL-6, VEGF, Orosomucoid TNFR 1/2	Urine/serum Urine Urine	Increases

KIM1: Kidney injury molecule 1, NGAL: Neutrophil gelatinase-associated lipocalin; NAG: N-acetyl-bd-glucosaminidase; L-FABP: Liver type fatty acid-binding protein, AIM: α-1-microglobulin; 8-OHdG: 8-oxo-7,8-dihydro-2'-deoxyguanosine; AGA: α-1-acid glycoprotein; TNF-α: Tumour necrosis factor α; IL-6: Interleukin-6; VEGF: Vascular endothelial growth factor; TNFR 1/2: Tumour necrosis factor α receptors 1 and 2;

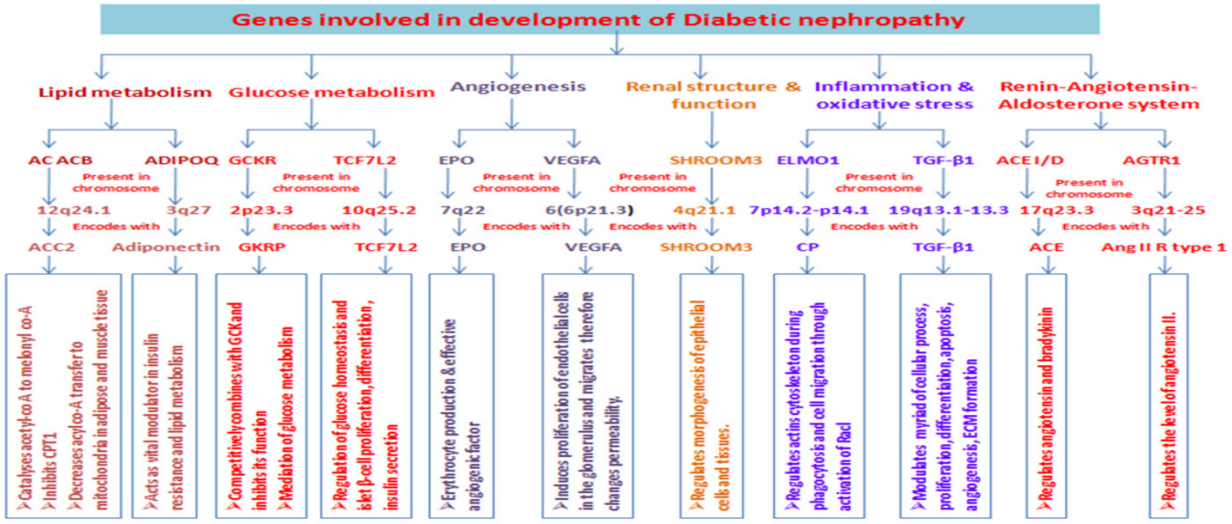


Figure 3. Genes involved in the development of Diabetic nephropathy through various mechanisms (ACACB - Acetyl Coenzyme A Carboxylase Beta, ADIPOQ-Adiponectin, GKRP-Glucokinase regulatory protein, TCF7L2-Transcription factor 7 like 2, EPO-Erythropoietin Promoter Gene, VEGFA-Vascular Endothelial Growth Factor-A, SHROOM3-, ELMO1-Engulfment and Cell Motility Protein 1, CP-Cytoplasmic protein, TGF-β1, ACE-Angiotensin Converting enzyme gene, AGTR1-Angiotensin II receptor Type 1)[75].



Figure 4. Mechanism of phytochemical compounds against diabetic nephropathy[135,154-163].

increased the prevalence of various diseases among the general population, not just due to their easy availability without a prescription, low cost, and proximity to health care professionals. Herbal therapy is an option that aids in the treatment of chronic diseases.

Phytoconstituents isolated from various sources, as shown in Figure 5, were crucial in reducing abnormalities of biomarkers operating on various pathways. Most active principles found in plant sources have been confirmed to have pancreatic cell regeneration, insulin resistance reduction, and insulin release properties. Plants were crucial in maintaining a balanced lifestyle. In India, about 20,000 medicinal plant species have been recognized. Populations employ around 500 common plant species to treat a variety of diseases[164].

6. Phytochemicals used in Treatment of Diabetic Nephropathy

Diabetic nephropathy is slowed by the interaction of Advanced Glycation End Products (AGEs), activated Protein Kinase C (PKC), and angiotensin II. The Renin Angiotensin Aldosterone System (RAAS), like renin-angiotensin-converting enzymes (AGEIs), can be targeted to delay disease development. The phytochemicals from different plants sources were listed in Table 2.

The phytoconstituents such as ellagic acid and gallic acid of seeds of Eugenia jambolana were studied against diabetic nephropathy by molecular docking studies using 108 A diabetic nephropathy protein. The findings revealed that the 108 A nephropathy protein had a bonding score of -8.05708 Kcl/mol and -6.67303 Kcl/mol, further confirming the possibility of an anti-diabetic impact[185]. Brain-Derived Neurotrophic Factor (BDNF) incorporated against the pathogenesis of Alzheimer's disease and depression, which co-exist with Type II diabetes. When compared to -carotene, the astaxanthin docking score is lower, indicating that it has a better affinity for the target proteins. As a result, it is utilized to reduce glucose levels[186]. Arguslab was used to determine whether the three proteins, Glucokinase, Insulin Receptor, and PPAR Gamma, had the best binding affinity. PPAR gamma protein had the lowest binding energy, followed by Glucokinase and insulin receptor, which had binding energies of > - 8.5 kcal/mol. As a result, the Camptothecin compound could be used as a lead molecule in developing anti-diabetic drugs[187].

Table 2. List of phytochemicals used for the treatment of diabetic nephropathy

S.No	Phytochemicals	Source of Phytochemicals	Biological Activity	References
1	Curcumin	Rhizomes of *Curcuma longa*	Glucose lowering activity, lipid reducing capacity, activity against Oxidative stress.	[165]
2	Catachins	Leaves of *Camellia sinensis*	Inhibition in insulin resistance, blocks glucose absorption in intestine	[166]
3	Alkaloids	All parts of *Boerhaavia diffusa*	Increase the production of insulin, increases glucose tolerance.	[167]
4	Salasol A and B, Slaquinones A and B	All parts of *Salacia oblongata*	Potential inhibitors of ȁ- glucosidose	[168]
5	saponin	*Tribulus terrestris*	Reduces fasting glucose level in diabetic patients	[169]
6	Morin	*Prunus dulcin, Chlorophora tinctoria, Psidium guajava*	ses insulin resistance, reduces the level of TNFȁ	[170]
7	Stevioside, rebaudioside diterpenes	*Stevia rebaudiana*	Antidiabetic activity	[171]
8	glycosides	*Glymnema sylvester, Jatropha curcus*	Reduces ȁ-amylase and lactate dehydrogenase level	[172]
9	kaempferol	Soyabean leaves	Reduces HbA/c level decreases fatty acid synthase in liver	[173]
10	alkaloids	*Catharanthus roseus*	Potent antidiabetic and antioxidant	[174]
11	kinenoside	*Anoectochilus roxburghii*	Showed significant hypoglyceamic activity, restored damaged β cells	[175]
12	Resveratrol	*Vitis vinifera*	Modulates the function of Sirterin – 1 ses HbA/c	[176]
13	Chamaemeloside 3 – hydroxyl-3-methylglutaric acid (HMG)	*Chamaemelum nobile* (L)	Decrease plasma glucose conceentration	[177]
14	Bacosine	*Bacopa monnieri* (L)	Antihypergeyceamic activity	[178]
15	Mangiferrin	*Mangifera indica* (L)	Reduces plasma glucose level, inhibits ȁ- amylase and ȁ-glucodidose activity	[179]
16	Berberine	*Berberis aristata*	Inhibits DPPIV, enhances GLP-1 regulates insulin receptor expression	[180]
17	Moracin M, Steppogenin- 4'-O-β-D-glucoside, mulberroside A	*Morus albo* L	Hypoglyceamic activity, reduces fasting blood glucose	[181]
18	Taraxearo	*Abroma augusta* (L)	Stimulates glucogen synthesis activates glucose transport	[182]
19	Procyanidin B2	Grape seed	Increases MMP-9 regulation, increases antioxidant enzyma	[183]
20	Carob polyphenols	*Ceratonia siliqua*	Defenses against nephrotoxicity	[184]

The mammalian Target of Rapamycin (mTOR) is a protein kinase that belongs to the phosphatidylinositol 3 kinase-related kinase family. It connects two separate protein complexes, mTOR complex 1 and mTOR complex 2, that regulate various cellular processes, including cell growth, motility, survival, protein synthesis, autophagy, and transcription. Pathogenic pathways have been identified as mTOR overactivation and decreased autophagy. Rapamycin is a selective mTOR inhibitor because no particular medications exist to treat diabetic nephropathy. Some natural chemicals, such as santalin-A, can be used as a lead compound. This was demonstrated using anin-silico molecular docking method[188]. Salacinol, Kotolanol, and mangiferin are phytocomponents found in Salacia reticulata. These compounds are promising alpha-glucosidase inhibitors in docking and SAR tests[189].

7. Conclusion

Diabetic nephropathy is a severe condition associated with diabetic complications, leading to chronic kidney disease and renal failure. While science has progressed, there is still no reliable specific approved medication for treating diabetic nephropathy and its complications. Modern treatment techniques provide sufferers with immediate symptomatic relief but still cause severe side effects without counteracting etiology. Phytopharmaceuticals have played a significant role in treating a variety of illnesses. This review has highlighted the beneficial role of phytomolecules with their mechanism of action in controlling the etiology of the disease-free of adverse effects and initiated the researchers to focus on alternative treatments in herbal combination for the early recovery from diabetic nephropathy.

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