Herbal Drugs Interventions In Diabetic Nephropathy

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Abstract
Chronic hyperglycemia, which arises from abnormal insulin secretion, function, or both, is a hallmark of a group of metabolic illnesses known as Diabetes mellitus.The kidney damage that strikes diabetics is referred to as diabetic nephropathy (DN), with glomerulus thickening being the first observable symptom of the condition. There are two stages of diabetic kidney disease (DN): microalbuminuria and macroalbuminuria, the conditions in which the kidney leaks more serum albumin than usual into the urine. As DN advances, more glomeruli are observed to be damaged by progressive nodular glomerulosclerosis, possibly by enhanced. The aetiology of DN has been linked to a number of signalling pathways, including increased production of reactive oxygen species (ROS), advanced glycation end products (AGEs), and protein kinase C (PKC) activation.Effective techniques to avoid the pathogenesis of diabetic nephropathy should be developed, as the number of diabetic patients with end-stage renal disease is still rising despite the effectiveness of therapeutic alternatives such as glycemic management, hypertension medication, antioxidants and hyperlipidemia in preventing DN. Herbal drugs present a great potential in the treatment and prevention of DN. In this article, we provide an overview of the many signalling pathways that are implicated in the development of DR. In the review, a variety of herbal medications for the treatment of DN have also been covered.

Keywords: Diabetes mellitus, Diabetic nephropathy, Pathogenesis, Herbal dugs, Antioxidants

INTRODUCTION

The most frequent cause of end-stage renal disease (ESRD) globally, diabetic nephropathy (DN), is responsible for the high death rate among diabetes patients [1]. The World Health Organisation (WHO) predicts that by 2030, there will be over 370 million more diabetic individuals globally [2]. Excessive extracellular matrix (ECM) deposition in the kidney causes tubulointerstitial fibrosis and glomerular mesangial enlargement in diabetic kidney disease (DN) [3-4]. According to some theories, there are five stages of DN: the first is called the early hypertrophy stage, which is marked by an increase in renal plasma flow and GFR; the second is called the silent stage; in this stage, morphological changes such as glomerular hypertrophy, tubulointerstitial expansion, and thickening of the glomerular basement membrane occur; the third stage is known as incipient DN, which is typified by microalbuminuria with the onset of hypertension [5-6]. ESRD with uremia is the fifth stage, which comes after the subsequent stage of overt DN, which is characterised by dipstick positive proteinuria [6]. It has been discovered that stringent blood pressure and glucose management greatly reduced the onset and progression of diabetic nephropathy in both type I and type II diabetes [7]. Numerous risk factors, such as race, genetic predisposition, smoking, dyslipidemia, high blood pressure, and raised blood sugar, have been linked to the development of DN [7-8]. The pathogenesis of DN is further complicated by a number of hyperglycemia-induced signalling mechanisms, such as increased formation of AGEs, enhanced ROS generation, PKC activation, upregulation of transforming growth factor-beta 1 (TGF-β1), polyol pathway, and renin-angiotensin system (RAS) [9-11]. The use of traditional herbs and extracts in the treatment of DN requires consideration, wherein some herbs and their extracts are believed to provide health benefits [12]. Alkaloids, polyphenols, and saponins have been found in plant extracts by phytochemical research, and these compounds are essential to offer health benefits by herbal drugs [12-13]. The present article has been aimed to discuss numerous strategies for the prevention and treatment of DN.

PATHOGENESIS OF DN

Hyperglycemia has been known to stimulate the renal cells, which release growth factors, cytokines, and humoral mediators leading to structural changes in the kidney, which forms a part of the DN pathophysiology [14]. Additionally, several hyperglycemia-induced metabolic and hemodynamic disturbances, including elevated AGE production, increased ROS generation and PKC activation, the polyol pathway, and RAS, have been involved in the development and progression of DN (Fig 1) [14-15].

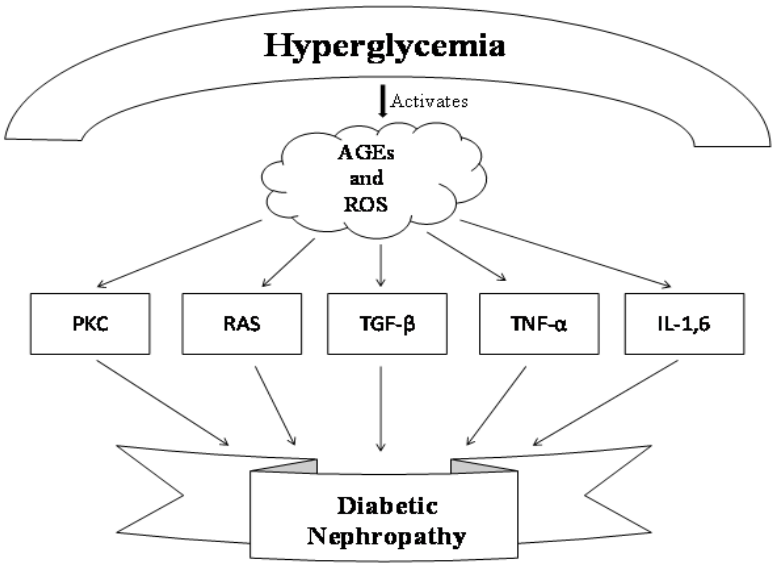

Figure 1: Diagram showing pathogenesis of DN

Under diabetic conditions, the generation and accumulation of AGEs have been observed to proceed more quickly. Furthermore, it has been observed that AGEs and the interaction between them and signal-transducing receptors cause oxidative stress, vascular inflammation, and thrombosis. As a result, they are crucial in the pathophysiology of vascular problems in diabetes [15-16]. Due to increased AGE synthesis and slower clearance in DN patients, diabetic patients with end-stage renal disease (ESRD) have around twice as much AGEs in their tissue as diabetic individuals without renal disease [17]. Additionally, it has been shown that AGEs increase the expression of monocyte chemoattractant protein-1 (MCP-1) in mesangial cells. This is linked to the infiltration of monocytes into mesangium and is seen during the early stages of DN [18]. Furthermore, AGEs promote mesangial cells' production of insulin-like growth factors I and II, platelet-derived growth factor (PDGF), and transforming growth factor-β (TGF-β), which has been linked to the development of glomerulosclerosis and tubulointerstitial fibrosis in diabetic kidney disease [19]. Additionally, a growing body of research indicates that the AGE-RAGE axis modulates the pathogenesis of DN, as supported by multiple animal studies that also highlight the critical role that RAGE plays in the onset and progression of DN [20]. Increased mitochondrial ROS generation brought on by hyperglycemia is thought to have a significant part in the pathophysiology of diabetic neuropathic pain (DN) and is regarded as a major mediator of vascular problems [21]. It has been observed that glucose auto-oxidation, metabolism, and AGE production cause hyperglycemia to produce ROS. Under hyperglycemia, it has been discovered that numerous renal cell types, including mesangial cells, endothelial cells, and tubular epithelial cells, create large amounts of reactive oxygen species (ROS) [15]. It has been observed that ROS activates a number of pro-inflammatory transcriptional factors, which in turn causes the kidney to become infected with inflammatory cells by producing cytokines, chemokines, and vascular adhesion molecules. Renal dysfunction, apoptosis, and ROS-mediated cell damage are all made worse by this development of ROS-mediated renal inflammation [22]. TGF-β1, a crucial regulator of extracellular matrix remodelling, is produced by ROS-induced mesangial expansion and tubular epithelial-mesenchymal transition, which results in tubule interstitial fibrosis. This indicates that ROS has a role in the development of DN [22-23]. Furthermore, it has been observed that ROS can activate many transcription factors, such as NF-κB and activated protein-1 (AP-1), which results in the overexpression of genes and proteins linked to the onset and advancement of DN [24]. Other factors likeobesity and the release of growth factors and proinflammatory factors have been shown to cause glomerular hyperfiltration by reducing the resistance of the afferent and efferent glomerular arterioles, which increases renal perfusion and appears to play a role in the pathogenesis of diabetic kidney disease (DN) [25-26]. Furthermore, there was proof that ET-1 had a role in the aetiology of DN since the plasma levels of this significant vasoconstrictor, endothelin 1 (ET-1), increased with time in the DN patients. It has been observed that albuminuria exacerbates diabetic neuropathic pain by initiating a number of inflammatory pathways via tubular cells [27]. Furthermore, the mechanical stress brought on by renal hyperperfusion triggers the release of growth factors (VEGF, TGF-β1), cholesterol, and local triglycerides, as well as cytokines (TNF-α) [9-10]. These factors further trigger the accumulation of extracellular matrix proteins, which results in glomerulosclerosis and mesangial expansion [9. Additionally, DN is associated with elevated levels of a number of circulating markers of inflammation, including TNF, CRP, and interleukin (IL)-1,6, and 18, whose levels are linked to the advancement of ESRD. Furthermore, free radicals, inflammatory cytokines, and proteases produced by macrophages cause tubular damage in DN patients, indicating a modulatory function in the onset and course of DN [22,28].

THERAPEUTIC AGENTS IN PREVENTION AND TREATMENT OF DN

It is widely acknowledged that, contingent upon the disease's severity and stage, same concepts apply to both prevention and therapy of DN [29]. On the other hand, the goal should be to slow down the onset or progression of DN and lower the death and morbidity rates of the patients. It seems that proteinuria and the pace at which creatinine doubles were reduced by ACE inhibitors and angiotensin receptor blockers (ARBs) [29-30]. Studies have been conducted recently to assess the advantages of strict glycemic management in sizable patient populations that have demonstrated protective effects against the onset and progression of albuminuria [4]. RAS blocking with ACE inhibitors or ARB provides an additional therapeutic option for the prevention and treatment of DN, as it improves renal function without lowering blood pressure [31]. Because these medications lower urine albumin excretion (UAE) and the rate at which microalbuminuria progresses to more advanced stages of DN, combining these medication classes has been suggested as an approach to treat DN [32]. Blocking aldosterone action is another strategy that has been suggested; adding spironolactone, an aldosterone antagonist, to ARBs or ACE inhibitors has been shown to reduce UAE and proteinuria in patients with type II diabetes who have chronic kidney disease more effectively than either medication alone [33]. Furthermore, individuals with DN demonstrated a higher reduction in proteinuria when the renin-angiotensin-aldosterone pathway was dual blocked with a direct renin inhibitor, aliskiren, and losartan at the maximum indicated dose. Additionally, it has been observed that glitazones and sulfonylureas are utilised in stages III-V chronic renal disease, confirming their potential as a therapeutic adjuvant in the management and prevention of DN [34]. Furthermore, dietary intervention is a viable option for the prevention and treatment of diabetic nephropathy (DN). This is supported by a meta-analysis of studies involving patients with type I and type II diabetes mellitus and clinical nephropathy, which found that dietary protein restriction slowed the progression of DN and thus validated the importance of dietary intervention in DN prevention and treatment [35].

HERBAL DRUGS IN PREVENTION AND TREATMENT OF DN

Diverse herbal drug extracts have been reported to have nephroprotective effect, albeit through diverse methods [36]. Certain plant-derived active ingredients have been shown to positively affect kidney function in individuals with diabetes mellitus [36-37]. Several naturally occurring antioxidants and therapeutic plant extracts have been investigated in DN animal models (Fig. 2).

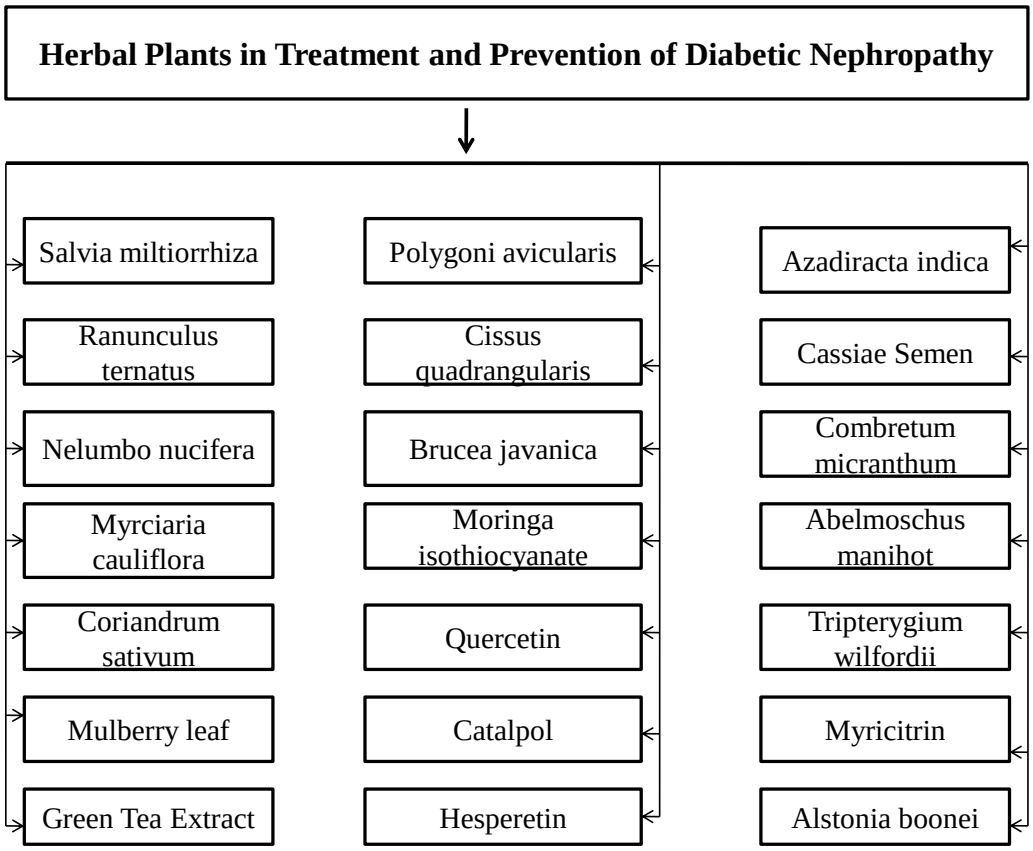

Figure 2: Diagram Showing Herbal Plants in Treatment and Prevention of DN.

The processes that underlie *Salvia miltiorrhiza's* (SM) ability to treat diabetic nephropathy (DN) were investigated. The results of the analysis showed that the administration of SM reduced the levels of AGEs, oxidative stress, inflammatory response, and immunological modulation. The work offers a reference for the widespread use of SM in therapeutically managing DN and identified the active ingredients and possible molecular therapeutic mechanisms of SM in DN.

[38].Further, the possible impact of extract from *Ranunculus ternatusThunb* (Ranunculaceae), or RTT, on diabetic nephropathy (DN) was studied. RTT extract primarily inhibited SMYD2 activation and protein expression to produce antifibrotic and anti-inflammatory actions in STZ-induced DN, which showed that RTT extract may be useful in treating high glucose-induced nephropathy [39].In a recent study, a rat model of type II diabetes was used to examine the renoprotective and antidiabetic effects of *Nelumbonucifera* leaf extract (NLE). NLE therapy has been shown in histological tests to block Bowman's capsule dilation, confirming its renoprotective effect in diabetes. In addition, NLE treatment reduced the expression of antioxidant enzymes in MES-13 cells, primarily due to quercetin-3-glucuronide. All things considered, these results suggest that NLE may prevent diabetes and protect the kidneys from HFD/STZ-induced diabetes through antioxidative mechanisms [40].Anthocyanin-rich *Myrciariacauliflora* is a functional food with anti-inflammatory and antioxidative qualities. According to a study, M. cauliflora extract (MCE) improved renal fibrosis-related proteins and Ras/PI3K/Akt, which in turn had positive effects on DN [41].In a study, chromatographic, spectroscopic, and spectrometric analysis were used to show the phytochemical composition of the petroleum ether extract of *Coriandrumsativum* (CPE) seeds. The potential contribution of CPE to DN mitigation in the STZ-nicotinamide (NAD) induced type 2 diabetes model was assessed. It was hypothesised using the STZ-NAD model that CPE's bioactive ingredients may slow down the course of DN and function as a possible adjuvant for antidiabetic medication [42]. Moreover, the potential advantages of *Mulberry leaf* extract (MLE) and neochlorogenic acid (nCGA), its main constituent, were investigated. MLE and nCGA both significantly inhibited the accumulation of glycosylated substances in glomeruli, regulated abnormalities in lipid metabolism, and modulated important signalling pathways associated with DN. Targeting lipid metabolism and important molecular pathways, the MLE and nCGA demonstrated considerable promise in treating DN brought on by glucolipotoxicity[43].In another study, patients with type II diabetes mellitus and DN were given green tea extract (GTE) to see how it affected their metabolic profile, renal function, and sRAGE concentrations. GTE administration showed its promise in the treatment of DN by increasing blood concentrations of sRAGE and GFR and decreasing those of fasting serum glucose and triacylglycerols [44]. In a recent study, the effects and mode of action of *Polygoniavicularis* (PA), which has been linked to DN in human renal mesangial cells and db/db mice, were investigated. Histopathologically, PA reduced tubular fibrosis and glomerular enlargement in db/db mice. Based on enhanced insulin resistance and the prevention of nephritis and fibrosis in DN, these findings imply that PA protects against renal impairment [45].An additional investigation was conducted to assess the potential antidiabetic properties of *Allium jesdianum* (A. jesdianum) ethanolic extract. Additionally, the effects were assessed with respect to oxidative stress markers, connective tissue growth factor (CTGF) expression, and RAGE gene expression in the kidney of rats with type I diabetes. When compared to the diabetic group, it was demonstrated that A. jesdianum dramatically reduced the kidney expression levels of CTGF and RAGE genes and improved oxidative stress in the kidney tissues. The study's findings demonstrated that giving A. jesdianum to diabetic rats had positive anti-diabetic and anti-nephropathic effects [46]. Furthermore, the fruit of the traditional Chinese medicine plant *Bruceajavanica* (L.) Merr. contains a naturally occurring quinoid chemical called "brucine A," which has a wide range of biological activity. Bruceine A was shown to be an undisclosed galectin-1 inhibitor that significantly protected against diabetic kidney damage and may offer new pharmacological treatments for the condition [47].A recent study was conducted to assess the potential therapeutic benefit of extract from *Azadiractaindica* (neem) leaves as a novel treatment for DN in rats that was neonatalized and induced by streptozotocin (STZ). In diabetic rats, there was a notable increase in oxidative stress markers. The promise of neem leaf extract in the treatment of diabetic neuropathy was confirmed by its ability to successfully ameliorate the histological, ultrastructural, and biochemical alterations caused by the disease[48]. In addition, investigations were conducted on the therapeutic effects and underlying mechanisms of the anti-diabetic, antioxidant, and anti-inflammatory activities of hesperetin (HES) and quercetin isolated from *Trifoliumalexandrinum* (TAE) and TAE in DN caused by STZ. The findings showed that the STZ-treated group had significantly higher levels of oxidative stress indicators as well as increases in urea, creatinine, total protein, albumin, and globulin when compared to the control group of rats. After administering HES, quercetin, and TAE to diabetic rats, the prior harmful changes were considerably lessened. Ultimately, the study showed that TAE, quercetin, and HES might be effective therapeutic agents to combat DN by having anti-inflammatory, antioxidant, and antidiabetic properties [49].Another study was investigated to determine whether the ethanolic extract of *Cissusquadrangularis* (EECQ) protected rats with DN caused by STZ and a high-fat diet. Elevated levels of creatinine, lipid profile, and insulin resistance were significantly reduced after receiving EECQ treatment. Furthermore, in rats with diabetic nephropathy, EECQ improved albuminuria, glomerular filtration rate, and creatinine clearance. Thus, the conclusion was drawn that EECQ exhibits a protective effect against DN based on the aforementioned findings [50].An investigation was conducted on the impact of catalpol on diabetic nephropathy in rats. Catalpol demonstrated potential benefits against experimental diabetes mellitus by drastically improving kidney function and pathological changes while lowering tissue levels of Ang II, TGF-β1, and CTGF. Restricting the expression of TGF-β1, CTGF, and Ang II may be one of the strategies involved in lowering the buildup of extracellular matrix [51]. Moreover, the primary active isothiocyanate of *Moringa oleifera*, a plant used in traditional herbal medicine and diet, is called Moringaisothiocyanate (MIC-1). Understanding MIC-1's Nrf2-ARE antioxidant activity and its potential in DN was the aim of one investigation. In high-glucose-stimulated renal cells, MIC-1 promoted Nrf2-ARE signalling, upregulated Nrf2 target gene expression, inhibited inflammation, and decreased oxidative stress. All things considered, it seems that Nrf2 activation is one possible therapeutic approach for treating DN that is now being developed in clinical settings [52]. In a recent study, this has been observed that Quercetin, a flavonoid with a wide range of biological activity, reduces kidney

damage in diabetic rats. In this case, the study's objective was to evaluate quercetin's impact on DN and provide an overview of potential processes. Renal index, serum/plasma creatinine (SCr), urine protein, urine albumin, and oxidative stress indicators were all markedly reduced by quercetin. In DN animal models, quercetin enhanced renal function and reduced renal oxidative stress and inflammatory response, confirming its potential in DN [53]. In addition, a traditional Chinese remedy uses Cassiae Semen, which is the dried seed of *Cassia obtusifolia* L. (Leguminosae). The study was to look into the potential renoprotective and anti-diabetic benefits of Cassiae Semen extract (CSE) in rats with STZ-induced diabetes. A notable improvement in body weight, glycemic control, oral glucose tolerance, and lipid metabolism were among the anti-diabetic effects of CSE. Moreover, the CSE demonstrated protective effects on renal functioning by lowering serum creatinine (Scr) levels, urine volume, urine protein, and the kidney/body weight ratio. In diabetic rats, it was discovered that CSE exhibited renoprotective as well as anti-diabetic properties[54]. Further, in rats with nicotinamide-induced STZ-induced DN nephropathy, the nephroprotective potential of a standardisedhydroalcoholic extract of *Combretummicranthum* was investigated. The renal biochemical markers and histological alterations brought on by diabetes mellitus were improved by treatment with CM extract, offering scientific evidence for the traditional application of *Combretummicranthum* in DN[55].In experimental DN, a combination of a high-fat diet, STZ following unilateral nephrectomy, and supplementation with *Abelmoschusmanihot* (AM) leaf extracts were tried. The diabetic kidney's glomerular and tubular architecture showed a marked alteration when stained with Periodic Acid Schiff and Sirius red, which was linked to podocyte loss and the buildup of fibrotic protein. In DN mice, treatment with AM extract reduced these alterations. By controlling autophagy and mitochondrial dynamics, AM extracts acted as a protective mechanism that markedly enhanced the expression of proteins. This may have protected the kidney and liver from collecting harmful proteins and malfunctioning mitochondria, slowing the onset of DN [56].In another study, the safety and effectiveness of low-dose *Tripterygiumwilfordii* Hook F (TWHF) in the treatment of DN were investigated. It was proposed that following a protracted course of treatment, low-dose TWHF has a beneficial effect on individuals with DN. Despite certain adverse effects, symptoms can go better after stopping a medication or receiving symptomatic treatment [57]. In a recent study, Myricitrin (Myr), a glycosyloxyflavone that is isolated from the bark of *Myricaesculenta*, was assessed for its potential as a treatment for DN. This was noted that Myr reduced oxidative stress by scavenging oxidative radicals and enhancing endogenous redox defence through Nrf-2 activation. It was also discovered that Myr reduced renal inflammation caused by diabetes by inhibiting NF-κB activation. The findings indicated that Myr might one day be used as a therapeutic agent in the patients presented with DN [58].

CONCLUSION

In affluent nations, DN is thought to be the primary cause of end-stage renal disease (ESRD), and its prevalence is steadily rising in poorer nations as well. Furthermore, since DN is a chronic DM consequence with an increasing prevalence, it is critical to comprehend it better in order to give preventive and management to stop DN from progressing. The number of diabetic individuals with end-stage renal disease (ESRD) is still rising in developed nations, despite the fact that the available treatment options are far from ideal. Although, herbal drugs and their extracts present a potential target in both experimental and clinical set up, this is immediately thought to be required to create novel therapeutic techniques that could specifically target DN.

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