RESEARCH PAPER

Herbal Extracts and Bioactive Phytoconstituents in the Management of Diabetic Nephropathy: Insights from STZ-Induced Experimental Rat Models – A Review

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ABSTRACT

Diabetic nephropathy (DN) is a major microvascular complication of diabetes mellitus (DM) and one of the leading causes of end-stage renal disease (ESRD) worldwide. Its progression is driven by sustained hyperglycemia, hemodynamic alterations, oxidative stress, inflammation, and fibrotic changes in renal tissue. Early stages are marked by microalbuminuria and glomerular hyperfiltration, while advanced stages present with proteinuria, declining glomerular filtration rate (GFR), and structural damage to mesangial cells, podocytes, and tubulointerstitial compartments. Streptozotocin (STZ)-induced diabetic rat models closely mimic the histopathological and biochemical features of human DN, providing a robust platform for preclinical evaluation of therapeutic agents. Medicinal plant leaf extracts—rich in bioactive constituents such as flavonoids, alkaloids, and phenolic acids—have demonstrated antihyperglycemic, antioxidant, anti-inflammatory, and renoprotective effects in STZ-induced DN models. This phototherapeutics significantly improve renal function markers, attenuate oxidative stress, and preserve kidney histoarchitecture. Enzyme-linked immunosorbent assay (ELISA) kits are integral to DN research, enabling the quantification of renal injury, inflammatory, fibrotic, and oxidative biomarkers. Collectively, integrating phytochemical interventions with advanced biomarker profiling may offer promising avenues for the prevention and management of DN.

Keyword: Diabetic nephropathy; Diabetes mellitus; Streptozotocin-induced rat model; Medicinal plant leaf extract; Oxidative stress; Inflammation; ELISA biomarkers; Renoprotective agents; End-stage renal disease; Phytotherapy.

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Hyperglycaemia, a hallmark of diabetes mellitus, results from either defective insulin secretion or diminished insulin sensitivity.[1] Diabetic nephropathy (DN) represents a major microvascular complication, contributing to approximately 30–47% of end-stage renal disease (ESRD) cases.[2] In both the United States and Europe, chronic hyperglycaemia remains the leading cause of ESRD.[3] The progression to ESRD involves multiple pathophysiological mechanisms, including hemodynamic disturbances, inflammatory processes, and sustained hyperglycaemia. If untreated, early-stage microalbuminuria can advance to overt proteinuria, exceeding 500 mg per 24 hours. In diabetic nephropathy (DN), the early stage is characterized by microalbuminuria, defined as urinary albumin excretion ranging from 30 to 299 mg over a 24-hour period.[4]

Chronic hyperglycaemia in diabetes mellitus significantly increases the risk of cardiovascular disease (CVD) and several long-term microvascular complications, including retinopathy, neuropathy, and nephropathy.[5] In the early stages of diabetes, the kidneys may undergo hypertrophy, accompanied by alterations in the glomerular filtration rate (GFR).[6] In diabetic nephropathy (DN), all renal cell types-including mesangial cells, podocytes, and tubulointerstitial cells-are susceptible to injury.[7] Renal impairment is reported in 20–30% of individuals with type 2 diabetes

mellitus (T2DM). In addition to hypoglycemia, diabetes can lead to hyperlipidemia, oxidative stress, polyuria, ketosis, neuropathy, nephropathy, and a range of cardiovascular disorders.[8]

Classification of Diabetes Mellitus

Diabetes mellitus (DM) is a heterogeneous metabolic disorder characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both. According to the American Diabetes Association (ADA) and the World Health Organization (WHO), DM is classified into the following major categories:[9]

Type 1 Diabetes Mellitus (T1DM):

An autoimmune-mediated or idiopathic form of diabetes, characterized by destruction of pancreatic β-cells, leading to absolute insulin deficiency. It is commonly diagnosed in childhood or adolescence but can occur at any age.[10]

Type 2 Diabetes Mellitus (T2DM):

The most prevalent form of diabetes, resulting from a combination of insulin resistance and relative insulin secretory deficiency. It is strongly associated with obesity, sedentary lifestyle, and genetic predisposition, and is typically diagnosed in adulthood, although its incidence in younger individuals is rising.[11]

Gestational Diabetes Mellitus (GDM):

Glucose intolerance of variable severity with onset or first recognition during pregnancy. It is associated with increased maternal and fetal complications and an elevated risk of developing T2DM later in life.[12]

Other Specific Types of Diabetes:

These include a variety of less common forms caused by genetic defects in β-cell function or insulin action, diseases of the exocrine pancreas, endocrinopathies, drug- or chemical-induced diabetes, and certain infections.[13] Examples include maturity-onset diabetes of the young (MODY), neonatal diabetes, and diabetes secondary to conditions such as cystic fibrosis or chronic pancreatitis.[14]

Diabetes Nephropathy

Diabetic Nephropathy (DN), another common complication of diabetes type 1 and type 2, is commonly linked to diabetes. At least 30% of people with diabetes have diabetic nephropathy (DN), the most common side effect of the disease, which puts a substantial expense to public health.[15] It is the primary cause of End-Stage Renal Failure (ESRD) globally and contributes significantly to morbidity and death patients with diabetes. Chronic kidney disease (DN) is the most prevalent cause of long-term kidney impairment in persons starting treatment for renal replacement.[16] In 1997, 40% of new patients with ESRD were identified due to diabetes-related nephropathy. Only a tiny percentage of individuals with type 2 diabetes develop end-stage renal disease (ESRD), while between 25 and 30 percent of people with both forms of diabetes have nephropathy symptoms.[17]

Patients with diabetes who have diabetes nephropathy exhibit a specific collection of structural and functional kidney problems. The functional alteration includes an early increase in glomerular with intraglomerular hypertension and a progressive decline in renal function. Therapeutic approaches such as strict blood pressure or glycaemic control can prevent the development and progression of diabetic nephropathy. Nonetheless, the number of diabetes individuals undergoing haemodialysis continues to increase.[18]

The streptozotocin-induced diabetic rat is the most widely used model for studying diabetic nephropathy in rats. The rat model of histological changes of diabetic nephropathy are quite similar to those of human illness. Since they detect renal impairment in subgroups of diabetics, micro-albuminuria tests and serum markers of glomerular filtration rate should also be used to screen for nephropathy in older diabetics.[19]

The American Diabetes Association (ADA) and the National Institutes of Health recommend monitoring the estimated Glomerular Filtration Rate (eGFR), which is generated from serum creatinine, at least once a year in order to identify renal impairment in all diabetics.[20] End-stage renal failure has become more common in type II diabetics in recent years, both in the United States and a little later, in several nations throughout Europe. Given that 30 to 40% of persons develop diabetic nephropathy, diabetes is the primary cause of ESRD. The two stages of diabetic nephropathy are macroalbuminuria (UAE>200 g/min)36 and microalbuminuria (UAE>20 g/min and UAE>199 g/min). Lately, the kidney's early stages in type 2 diabetes have drawn more attention.[21]

When it comes to renal morphology, kidney hemodynamics, or the progression of pre-existing diabetic nephropathy, type I and type II diabetes are not dramatically different. Despite the fact that DN has historically been generally considered a metabolic disease, there is growing evidence that the immune system plays a major part in the development of of this situation. The kidneys filter waste products and surplus fluids from the blood while keeping electrolyte levels balanced.[22]

In diabetic nephropathy, continuous exposure to high glucose levels causes structural and functional alterations in the kidneys, including:

Glomerular hypertrophy: In the early phase of diabetes, the glomeruli (the kidney's filtering structures) become enlarged. This occurs due to hyperfiltration and the increased functional demand placed on them.[23]

Thickening of the glomerular basement membrane (GBM): Persistent hyperglycemia leads to abnormal deposition of proteins, which causes the GBM to thicken. As a result, its filtration efficiency is reduced.[24]

Mesangial expansion: Excessive production and accumulation of extracellular matrix by mesangial cells result in mesangial expansion, which contributes to glomerulosclerosis.[25]

Podocyte injury: Damage to podocytes, the specialized cells that maintain the filtration barrier, allows proteins to leak into the urine and can progress to diabetic nephropathy. These structural alterations are further aggravated by haemodynamic changes, particularly the rise in intraglomerular pressure caused by hyperfiltration, ultimately accelerating renal dysfunction.[26]

Risk factor and Mechanism

The development and progression of diabetic nephropathy are influenced by a combination of genetic, metabolic, and hemodynamic factors:

1. **Genetic susceptibility**: The chance of getting diabetic nephropathy is increased by certain polymorphisms. These include alterations in genes linked to oxidative stress pathways, inflammatory mediators, and the renin-angiotensin-aldosterone system (RAAS).
2. **Hyperglycemia:** One of the main causes of DN is persistently elevated blood glucose levels.

When AGEs are produced in response to hyperglycemia, they attach to their receptors (RAGE) on kidney cells, causing fibrotic and inflammatory reactions.

3. **Hypertension:** By raising glomerular capillary pressure and encouraging vascular alterations, high blood pressure hastens kidney injury.
4. **Dyslipidemia:** Through oxidative stress and lipid deposition, abnormal lipid profiles, which are prevalent in diabetes, lead to kidney damage.
5. **Inflammation and Oxidative Stress**: Both chronic inflammation and oxidative stress are major contributors to the pathophysiology of DN, leading to fibrosis and cellular damage. [27,28]

Pathophysiology of Diabetic Nephropathy

Recent advances in research have clarified several mechanisms that contribute to the onset and progression of diabetic nephropathy.

1. Renin–angiotensin–aldosterone system (RAAS) activation: The RAAS plays a central role in regulating blood pressure and renal hemodynamics. Its overactivation in diabetes promotes vasoconstriction, sodium retention, and elevated intraglomerular pressure, all of which accelerate kidney injury.[29]

2. TGF-β1 signaling: Transforming growth factor-β1 (TGF-β1) is a potent profibrotic cytokine closely associated with renal fibrosis. Under hyperglycemic conditions, TGF-β1 activity increases, stimulating extracellular matrix accumulation and contributing to glomerulosclerosis.[30]

3. Podocyte injury: Podocytes are essential for maintaining the integrity of the glomerular filtration barrier. Their dysfunction or loss in diabetic nephropathy leads to proteinuria and progressive deterioration of renal function.[31]

4. Mitochondrial impairment: Mitochondrial dysfunction in renal cells results in reduced energy production and increased oxidative stress, which aggravates cellular injury and tissue damage.[32]

5. Urine investigations: Early detection of kidney damage often relies on measuring urinary albumin excretion. The persistence of microalbuminuria indicates early disease, while progression to macroalbuminuria reflects more advanced nephropathy.[33]

6. Blood investigations: Monitoring serum creatinine and estimating glomerular filtration rate (eGFR) are important for assessing renal function and determining the stage of chronic kidney disease.[34]

7. Renal biopsy: In selected cases, kidney biopsy may be performed to confirm the diagnosis, assess the extent of structural damage, and guide therapeutic decisions.[35]

Symptoms of Diabetic Nephropathy

The primary clinical manifestation of diabetic nephropathy (DN) is progressive albuminuria, reflecting a gradual decline in renal function. Poor glycemic control accelerates kidney damage, leading to both structural and functional impairment. Early symptoms may include elevated blood pressure, proteinuria, unintended weight loss, and increased serum levels of blood urea nitrogen (BUN) and creatinine. As the condition advances, patients may experience cognitive difficulties, anemia, and further deterioration of renal function, potentially progressing to end-stage renal disease (ESRD).[36]

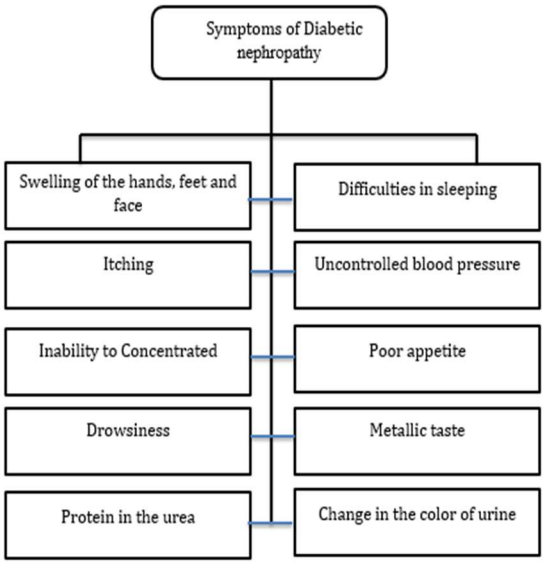

Fig 1: Symptoms of diabetes nephropathy

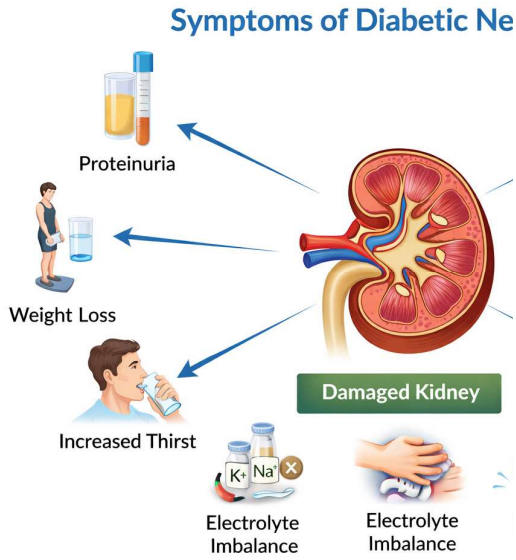

Fig 2: Symptoms of diabetic nephropathy

Pathogenesis of Diabetic Nephropathy

Diabetic nephropathy is a progressive kidney disease caused by long-standing diabetes mellitus. Its pathogenesis involves a complex interplay of metabolic, hemodynamic, and inflammatory mechanisms that lead to structural and functional changes in the kidneys.

- **Metabolic factors** – Chronic hyperglycemia induces non-enzymatic glycation of proteins, leading to the formation of advanced glycation end-products (AGEs). These AGEs alter the structure and function of the glomerular basement membrane, promote oxidative stress, and trigger pro-inflammatory pathways.[37]

- **Hemodynamic changes** – Persistent hyperglycemia and insulin resistance contribute to glomerular hyperfiltration through dilation of the afferent arteriole and constriction of the efferent arteriole. This increases intraglomerular pressure, causing mechanical stress and damage to the filtration barrier.[38]

- **Activation of intracellular signalling pathways** – Hyperglycemia stimulates pathways such as protein kinase C (PKC), transforming growth factor-β (TGF-β), and the renin-angiotensin-aldosterone system (RAAS). These promote mesangial cell proliferation, extracellular matrix accumulation, and fibrosis.[39]

- **Oxidative stress and inflammation** – High glucose levels and AGEs generate reactive oxygen species (ROS), which damage endothelial cells and podocytes. Inflammatory cytokines and chemokines further exacerbate injury, leading to glomerulosclerosis and interstitial fibrosis. [40]

- **Structural changes** – Over time, these processes cause thickening of the glomerular basement membrane, mesangial expansion, podocyte loss, and eventual glomerular sclerosis, resulting in a gradual decline in kidney function.[41]

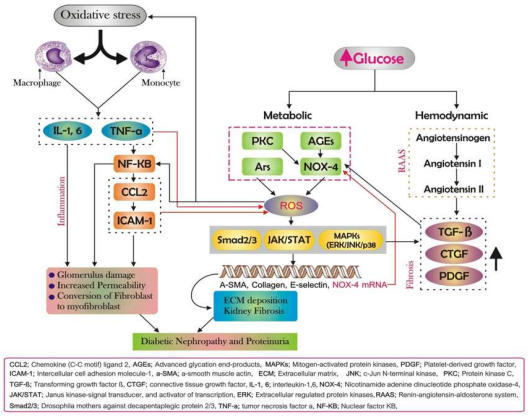

Fig 3: Pathogenesis of Diabetes Nephropathy

Medicinal Plant Leaf Extract Used in Cure Diabetes Nephropathy by STZ induced Rat Model:

Medicinal plant leaf extracts have been extensively investigated for their protective effects against diabetic nephropathy (DN) in streptozotocin (STZ)-induced rat models. These extracts, rich in bioactive

phytoconstituents such as flavonoids, phenolic acids, alkaloids, and terpenoids, exhibit antihyperglycemic, antioxidant, anti-inflammatory, and renoprotective properties. In experimental settings, STZ administration induces persistent hyperglycemia and renal damage resembling human DN, allowing evaluation of plant-based interventions. Leaf extracts from plants such as *Moringa oleifera*, *Azadirachta indica*, *Ocimum sanctum*, and *Camellia sinensis* have demonstrated the ability to reduce blood glucose levels, improve renal function markers (serum creatinine, BUN, urinary albumin), enhance antioxidant enzyme activities, and attenuate histopathological alterations in the kidney. [42]

Table 1: Various herbal plants leave extract in cure of diabetic nephropathy by 'streptozotocin-induced rats' model. [43,44,45]

Sr. No.	Medicinal Plant (Scientific name)	Family	Common name	Animal/ Cell model & STZ dose (mg/kg)	Parts used	Extraction method	Typical parameters studied for DN
1	Moringa oleifera	Moringaceae	Drumstick tree	Wistar/ Albino rat, STZ 50 mg/kg (single i.p.)	Leaves	Ethanolic / Aqueous	Blood glucose, serum creatinine, BUN, urinary albumin, kidney histology, SOD/CAT/GPx, MDA
2	Azadirachta indica	Meliaceae	Neem	Wistar/ Albino rat, STZ 50 – 55 mg/kg	Leaves	Aqueous / Methanolic	Blood glucose, proteinuria, creatinine, renal histopathology, inflammatory cytokines
3	Ocimum sanctum (Ocimum tenuiflorum)	Lamiaceae	Holy basil / Tulsi	Wistar rat, STZ 50 mg/kg	Leaves	Methanolic / Aqueous	Urinary albumin, creatinine clearance, antioxidant enzymes, histology

4	Camellia sinensis	Theaceae	Green tea	Wistar rat, STZ 45 – 50 mg/kg	Leaves	Hydroalcoholic / Aqueous	Serum creatinine/BUN, proteinuria, TNF-α, IL-6, renal histology
5	Gymnema sylvestre	Apocynaceae	Gurmar	Wistar rat, STZ 50 mg/kg	Leaves	Ethanolic	Blood glucose, urinary albumin, oxidative stress markers, kidney morphology
6	Andrographis paniculata	Acanthaceae	Kalmegh	Wistar/ Albino rat, STZ 50 – 55 mg/kg	Leaves	Ethanolic / Aqueous	Renal function tests, antioxidant status, histopathology
7	Allium sativum	Amaryllidaceae	Garlic	Albino rat, STZ 50 mg/kg	Bulb	Aqueous / Ethanolic	Serum creatinine/BUN, lipid profile, oxidative markers, proteinuria
8	Curcuma longa	Zingiberaceae	Turmeric	Wistar rat, STZ 45 – 60 mg/kg	Rhizome	Ethanolic / Aqueous	Blood glucose, TGF-β, fibrotic markers, kidney histology, oxidative stress
9	Phyllanthus niruri	Phyllanthaceae	Stonebreaker	Wistar rat, STZ 50 mg/kg	Leaves	Aqueous / Methanolic	Proteinuria, serum creatinine, antioxidant enzymes, histopathology

10	Centella asiatica	Apiaceae	Gotu kola	Wistar rat, STZ 50 mg/kg	Leaves	Methanolic / Aqueous	Renal function, histopathology, oxidative /inflammatory markers
11	Nigella sativa	Ranunculaceae	Black seed / Kalonji	Wistar rat, STZ 50 – 55 mg/kg	Seeds	Aqueous / Oil / Ethanolic	Urinary albumin, BUN /creatinine, antioxidant enzymes, renal histology
12	Aloe vera	Asphodelaceae	Aloe	Albino rat, STZ 50 mg/kg	Leaves (gel)	Aqueous / Hydroalcoholic	Blood glucose, proteinuria, creatinine, inflammatory markers
13	Boerhavia diffusa	Nyctaginaceae	Punarn ava	Wistar rat, STZ 50 mg/kg	Leaves/ roots	Ethanolic / Aqueous	Serum creatinine /BUN, histopathology, oxidative stress markers
14	Punica granatum	Lythraceae	Pomegranate	Wistar rat, STZ 50 mg/kg	Peel/ Seeds	Aqueous / Ethanolic	Proteinuria, creatinine, MDA, SOD, histology
15	Berberis aristata (or Berberis spp.)	Berberidaceae	Indian barberry	Wistar rat, STZ 50 mg/kg	Stem bark	Ethanolic / Aqueous	Blood glucose, renal function, inflammatory cytokines, histology
16	Zingiber officinale	Zingiberaceae	Ginger	Wistar/ Albino rat, STZ 50	Rhizome	Ethanolic / Aqueous	Serum creatinine /BUN, oxidative stress, histo

				mg/kg			pathology
17	Tribulus terrestris	Zygophyllaceae	Gokshura	Wistar rat, STZ 50 mg/kg	Leaves / Fruits	Ethanolic	Urinary protein, creatinine, antioxidant enzymes, kidney histology
18	Syzygium cumini	Myrtaceae	Jamun / Black plum	Wistar rat, STZ 50 mg/kg	Seeds / Leaves	Ethanolic	Blood glucose, renal function tests, urinary albumin, histology
19	Eclipta prostrata	Asteraceae	Bhringraj	Wistar rat, STZ 50 mg/kg	Whole plant / Leaves	Methanolic	Serum creatinine /BUN, oxidative stress, histopathology
20	Pterocarpus marsupium	Fabaceae	Indian kino tree	Wistar rat, STZ 50 – 55 mg/kg	Heart wood / Leaves	Methanolic	Blood glucose, renal markers, histology, antioxidant markers

Role of ELISA Kits in Diabetic Nephropathy

- Enzyme-linked immunosorbent assay (ELISA) kits play a critical role in the quantitative measurement of specific biomarkers associated with the onset and progression of diabetic nephropathy (DN). These assays offer high sensitivity, specificity, and reproducibility, making them suitable for both experimental research and clinical studies.
- In DN research, ELISA kits are employed to measure:
- Renal injury markers: Urinary albumin, kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), and cystatin C.
- Inflammatory mediators: Tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interleukin-1β (IL-1β), and monocyte chemoattractant protein-1 (MCP-1).
- Fibrosis-related proteins: Transforming growth factor-beta (TGF-β1), connective tissue growth factor (CTGF), and fibronectin.
- Oxidative stress markers: Advanced glycation end products (AGEs), 8-hydroxy-2'-deoxyguanosine (8-OHdG), and nitrotyrosine.
- Metabolic and hormonal parameters: Insulin, adiponectin, leptin, and renin-angiotensin system components.
- By enabling precise quantification of these biomarkers in serum, plasma, urine, or tissue homogenates, ELISA kits help in:

- Early diagnosis: Detecting microalbuminuria and subclinical inflammation before irreversible kidney damage.
- Monitoring disease progression: Tracking biomarker changes over time in STZ-induced animal models or patient cohorts.
- Evaluating therapeutic interventions: Assessing the efficacy of plant extracts, synthetic drugs, or combination therapies in experimental DN.

Common Parameters Used to Study Diabetic Nephropathy in STZ Models:

- **Biochemical markers:** Blood glucose, serum creatinine, blood urea nitrogen (BUN), uric acid, creatinine clearance, urinary albumin, urinary protein.
- **Oxidative stress markers:** Superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), malondialdehyde (MDA).
- **Inflammatory markers:** Tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), transforming growth factor-beta (TGF-β).
- **Histopathological evaluation:** Glomerular basement membrane thickening, mesangial expansion, tubular degeneration, interstitial fibrosis.
- **Morphometric parameters:** Kidney weight, kidney-to-body weight ratio.

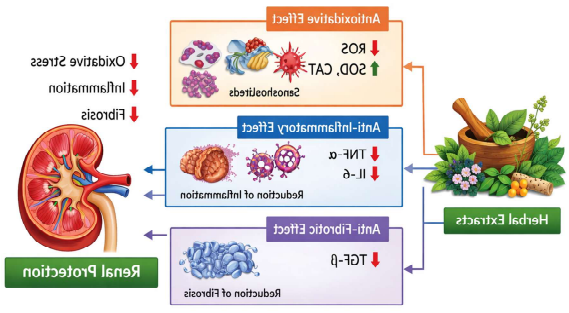

Fig 4: Role of Herbal extracts in renal protection

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