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Original Article

Therapeutic Potential of Indian Medicinal Plants in Diabetic Nephropathy

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ABSTRACT

Diabetic nephropathy (DN), a severe microvascular complication of diabetes mellitus, stands as a leading cause of end-stage renal disease globally. In India, where diabetes prevalence is escalating, DN poses a significant public health challenge. Conventional treatments, while beneficial, often come with limitations and side effects, prompting the exploration of alternative therapies. Indian medicinal plants, rooted in Ayurvedic tradition, have garnered attention for their potential in managing DN due to their multifaceted therapeutic properties. This study explores role of Indian medicinal plants in DN management, highlighting their bioactive compounds and mechanisms of action. Plants such as Gymnema sylvestre, Momordica charantia, Trigonella foenum-graecum, Tinospora cordifolia, and Curcuma longa have demonstrated antidiabetic properties, including glycemic control, antioxidant activity, and anti-inflammatory effects. These properties are crucial in mitigating the progression of DN. Clinical and preclinical studies have shown that formulations like Gokshuradi Guggulu, Chandraprabha Vati, and Bhumyamalaki Churna can improve renal function parameters, reduce proteinuria, and lower serum creatinine levels in DN patients. Moreover, case studies have reported significant improvements in renal profiles with Ayurvedic interventions, suggesting their potential as adjunct therapies.The therapeutic efficacy of these plants is attributed to their ability to modulate oxidative stress, inhibit the formation of advanced glycation end-products, and regulate inflammatory pathways. For instance, Curcuma longa (turmeric) contains curcumin, which has been shown to suppress inflammatory responses and oxidative damage in renal tissues. Similarly, Tinospora cordifolia exhibits nephroprotective effects by enhancing antioxidant defenses. Despite promising findings, the integration of Indian medicinal plants into mainstream DN management requires rigorous scientific validation. Standardization of herbal formulations, understanding herb-drug interactions, and conducting large-scale clinical trials are imperative steps forward. Embracing a holistic approach that combines traditional knowledge with modern scientific research could pave the way for effective and safer DN therapies.

Keywords: *Diabetic Nephropathy, Indian Medicinal Plants, glycemic control, Renal Protection, Antioxidants, Phytochemicals.*

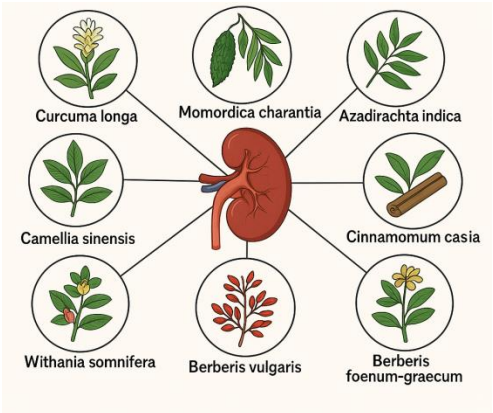
INTRODUCTION

Diabetes mellitus (DM), particularly type 2 diabetes, has emerged as a global epidemic, affecting millions of individuals worldwide. India, often referred to as the "diabetes capital of the world," is home to a rapidly growing diabetic population, which brings with it a host of complications, among which diabetic nephropathy (DN) is one of the most serious and life-threatening. Diabetic nephropathy is a progressive kidney disease caused by damage to the capillaries in the kidneys' glomeruli due to chronic hyperglycemia. It is a leading cause of end-stage renal disease (ESRD) and significantly increases the risk of cardiovascular events and mortality in diabetic patients (Brownlee, 2001).

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The pathophysiology of diabetic nephropathy is multifactorial, involving hyperglycemia-induced oxidative stress, inflammation, hemodynamic alterations, activation of the renin-angiotensin-aldosterone system (RAAS), advanced glycation end-products (AGEs) formation, and fibrosis. Current therapeutic strategies primarily focus on glycemic control, blood pressure management, and RAAS inhibition. However, these interventions often offer limited renal protection, particularly in advanced stages of the disease. Additionally, long-term use of synthetic drugs may lead to adverse effects, drug resistance, and economic burden, especially in low-resource settings. In light of these challenges, there is growing interest in alternative and complementary therapies, particularly those rooted in traditional medicine. India possesses a rich heritage of medicinal plants used for centuries in systems such as Ayurveda, Siddha, and Unani to manage various chronic conditions, including diabetes and kidney disorders. These traditional systems emphasize holistic healing, addressing not only blood sugar levels but also the underlying oxidative, inflammatory, and metabolic imbalances associated with diabetic complications (Kumar et al., 2020; Sahu et al., 2021). Numerous Indian medicinal plants have demonstrated potential in the management of diabetic nephropathy, either through direct nephroprotective effects or by improving glycemic control and reducing oxidative damage. Plants such as *Curcuma longa* (turmeric), *Tinospora cordifolia* (guduchi), *Trigonella foenum-graecum* (fenugreek), *Momordica* charantia (bitter melon), *Azadirachta indica* (neem), and *Gymnema sylvestre* (gudmar) have been studied for their bioactive constituents that exhibit antioxidant, anti-inflammatory, antihyperglycemic, and antifibrotic activities. For example, curcumin from turmeric has been shown to downregulate inflammatory cytokines and reduce fibrosis in renal tissues (Bose et al., 2022), while berberine from Berberis aristata has demonstrated AMPK activation and improved insulin sensitivity (Gupta et al., 2022). Scientific investigations over the past two decades have provided increasing evidence supporting the efficacy of these plants in experimental models of DN. Preclinical studies using diabetic rodent models have shown that many Indian medicinal plants can significantly reduce serum creatinine, blood urea nitrogen, and proteinuria while restoring histological and functional integrity of the kidneys (Verma et al., 2023). Although clinical studies are relatively limited, emerging trials suggest beneficial effects of these botanicals when used either as monotherapy or adjunct therapy with conventional drugs. Despite the promising potential, there are several challenges to the integration of Indian medicinal plants into mainstream nephropathy treatment protocols. These include variability in plant species and preparation methods, lack of standardization in dosing, potential herb-drug interactions, and limited high-quality clinical trials. However, with growing scientific interest and advancements in pharmacognosy, phytochemistry, and molecular biology, there is an increasing scope for validating and harnessing these traditional remedies through evidence-based approaches. This comprehensive review aims to explore the role of Indian medicinal plants in the management of diabetic nephropathy. It focuses on the pharmacological mechanisms of action, therapeutic efficacy demonstrated in preclinical and clinical settings, and the safety profile of key plant species. The review also highlights the need for standardization, regulatory oversight, and integration with conventional treatment strategies to enhance renal outcomes in diabetic patients. By bridging traditional knowledge with modern research, Indian medicinal plants may offer a promising avenue for addressing the growing burden of diabetic nephropathy in India and beyond.

Figure 1: Showing Indian medicinal plants in the management of diabetic nephropathy.



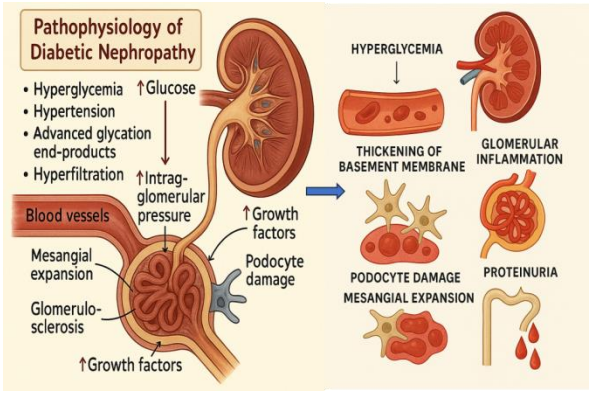
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Pathophysiology of Diabetic Nephropathy

Diabetic nephropathy (DN) is a major microvascular complication of diabetes mellitus and a leading cause of end-stage renal disease (ESRD) globally (Forbes & Cooper, 2013). The disease is characterized by structural and functional abnormalities in the kidneys, including glomerular basement membrane (GBM) thickening, mesangial expansion, podocyte loss, glomerulosclerosis, and tubulointerstitial fibrosis (Tervaert et al., 2010). Chronic hyperglycemia serves as the fundamental initiator of DN by activating multiple damaging metabolic pathways. These include the polyol pathway, which reduces glucose to sorbitol and depletes NADPH, thereby increasing oxidative stress (Brownlee, 2001); advanced glycation end-products (AGEs) accumulation, where AGEs interact with their receptors (RAGE) to activate pro-inflammatory signaling pathways (Wendt et al., 2003); and protein kinase C (PKC) activation, which disrupts vascular homeostasis and promotes extracellular matrix (ECM) deposition (Koya & King, 1998). Additionally, the hexosamine pathway contributes to transcriptional changes that exacerbate inflammation and fibrosis (Goldberg & Whiteside, 2001). Hemodynamic changes further aggravate renal injury. Early in DN, there is glomerular hyperfiltration due to afferent arteriolar dilation, increasing intraglomerular pressure. The renin-angiotensin-aldosterone system (RAAS) becomes activated, leading to elevated levels of angiotensin II, which promotes vasoconstriction, sodium retention, and increased expression of transforming growth factor-beta (TGF-β), a major profibrotic cytokine (Remuzzi et al., 2005; Ziyadeh, 2004). Oxidative stress and inflammation are central to DN progression. Hyperglycemia-induced mitochondrial dysfunction and NADPH oxidase activity elevate reactive oxygen species (ROS), damaging renal tissues (Ha & Lee, 2003). Concurrently, transcription factors such as nuclear factor-kappa B (NF-κB) become activated, driving the expression of inflammatory cytokines like TNF-α, IL-6, and IL-1β, which recruit leukocytes and amplify tissue injury (Navarro-González & Mora-Fernández, 2008). Podocyte dysfunction is another hallmark of DN. Podocytes maintain glomerular filtration barrier integrity, and their apoptosis or detachment leads to proteinuria, one of the earliest clinical manifestations of DN (Pagtalunan et al., 1997). Podocyte injury, once initiated, is largely irreversible and closely associated with progression to ESRD. Ultimately, fibrosis is the final pathway in DN, marked by excessive ECM accumulation in the glomeruli and tubulointerstitium. TGF-β and connective tissue growth factor (CTGF) are key mediators that promote fibroblast proliferation and inhibit ECM degradation (Border & Noble, 1994). DN is a multifactorial disorder driven by metabolic derangements, hemodynamic alterations, oxidative stress, chronic inflammation, and fibrosis. Targeting these pathways offers therapeutic opportunities. Indian medicinal plants, many of which possess anti-inflammatory, antioxidant, and antidiabetic properties, are being explored for their potential to modulate these mechanisms and provide nephroprotection in diabetic individuals.

Figure 2: Showing pathophysiology of diabetic nephropathy.



DN develops through a multifaceted process involving:

- Hyperglycemia-Induced Oxidative Stress: Elevated glucose levels lead to increased reactive oxygen species (ROS) production, damaging renal cells.
- Inflammatory Pathways Activation: Chronic inflammation exacerbates kidney damage through cytokine release.
- AGEs Formation: AGEs accumulate in renal tissues, promoting fibrosis and functional decline.
- Hemodynamic Changes: Glomerular hypertension and hyperfiltration contribute to structural kidney alterations.

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Table 1: Illustrates stages and description of diabetic nephropathy.

Stage/Process	Description
1. Hyperglycemia	Chronic high blood sugar initiates kidney damage through metabolic stress.
2. Glomerular Hyperfiltration	Increased GFR in early stages due to afferent arteriole dilation.
3. GBM Thickening	Glomerular basement membrane thickens, reducing filtration precision.
4. Mesangial Expansion	Proliferation and matrix accumulation by mesangial cells, narrowing capillaries.
5. Podocyte Injury/Loss	Damage or detachment of podocytes disrupts the filtration barrier.
6. Glomerulosclerosis	Irreversible scarring and hardening of glomeruli from ongoing injury.
7. Tubulointerstitial Fibrosis	Fibrosis and inflammation spread to tubules, worsening kidney function.
8. Proteinuria (Albuminuria)	Proteins leak into urine due to filtration barrier failure.
9. Decreased GFR	Progressive reduction in kidney function, possibly leading to ESRD.

Indian medicinal plants with their diabetic nephroprotective properties

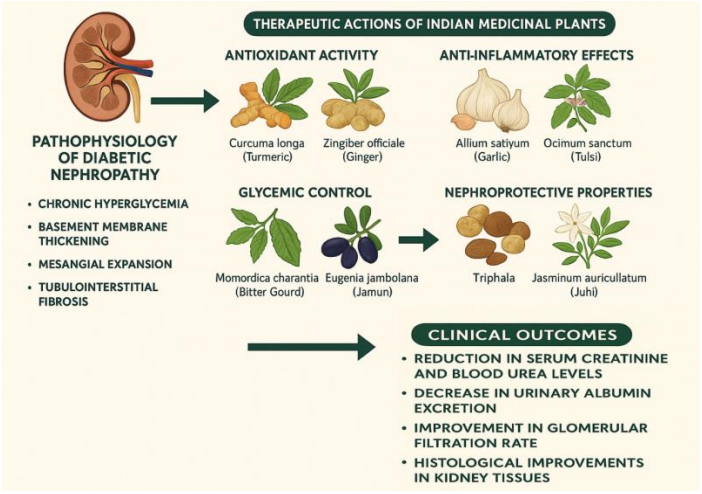
Indian medicinal plants have long been a cornerstone of traditional healthcare systems like Ayurveda, particularly in the treatment and management of chronic diseases such as diabetes and its complications. One of the most severe complications of uncontrolled diabetes is diabetic nephropathy (DN), a condition that progressively damages the kidneys due to high blood sugar, oxidative stress, and chronic inflammation. In recent decades, a growing body of scientific research has supported the traditional claims that several Indian herbs possess nephroprotective properties. These plants exert protective effects through multiple mechanisms, including antioxidant activity, anti-inflammatory actions, glucose regulation, and inhibition of advanced glycation end-products (AGEs), all of which are key contributors to the development and progression of diabetic kidney disease. They attribute their efficacy to bioactive compounds that modulate key pathological pathways involved in DN, such as oxidative stress, inflammation, and fibrosis. Among the most widely studied plants is *Tinospora cordifolia* (Guduchi), revered for its immunomodulatory and antioxidant properties. Its bioactive constituents such as tinosporaside and cordifolioside A help in reducing oxidative stress and inflammatory cytokines, which are major factors in kidney damage (Sharma et al., 2021). Similarly, *Withania somnifera* (Ashwagandha), a potent adaptogen, has demonstrated the ability to reduce stress-induced kidney injury by mitigating cortisol levels and enhancing antioxidant defenses (Mishra et al., 2023). *Curcuma longa* (Turmeric), rich in curcumin, is well known for its anti-inflammatory and anti-fibrotic properties. Curcumin has been shown to reduce renal inflammation, inhibit fibrosis, and improve glomerular function in diabetic nephropathy models (Ravindran & Kannapiran, 2019; Bose et al., 2022). *Boerhaavia diffusa* (Punarnava) is traditionally used as a renal tonic and diuretic. It contains punarnavine and boeravinones, compounds known to decrease serum creatinine, reduce proteinuria, and improve renal histology (Deshmukh et al., 2020). *Gymnema sylvestre* (Gurmar) not only helps in lowering blood sugar levels through its gymnemic acids but also exhibits anti-inflammatory actions that protect the glomerular structure from diabetic insults (Pothuraju et al., 2020). *Momordica charantia* (Karela or bitter gourd) has insulin-mimetic properties due to compounds like charantin and polypeptide-p, which enhance glucose uptake and reduce renal glycotoxicity (Gupta et al., 2022). *Phyllanthus emblica* (Amla) is another potent nephroprotective herb, rich in vitamin C and polyphenols such as emblicanin A and B. These antioxidants help in reducing oxidative renal injury and the formation of AGEs (Chaudhary et al., 2021). *Ocimum sanctum* (Tulsi), commonly known as holy basil, possesses eugenol and ursolic acid that confer anti-inflammatory and nephroprotective effects, especially in the context of hyperglycemia-induced damage (Kumar et al., 2020). *Pterocarpus marsupium* (Vijaysar) contains pterostilbene and marsupsin, which lower blood sugar and protect kidney cells from apoptosis and oxidative injury (Sahu et al., 2021). *Azadirachta indica* (Neem) and *Syzygium cumini* (Jamun) are both well-regarded for their anti-diabetic and antioxidant effects. Their bioactive components, such as nimbidin and jamboline, reduce oxidative stress in renal tissues, preserving nephron structure and function (Chandran et al., 2017; Singh et al., 2022). *Trigonella foenum-graecum* (Methi) seeds improve insulin sensitivity and decrease renal lipid peroxidation, primarily through trigonelline and diosgenin (Verma et al.,

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2023). *Terminalia chebula* (Haritaki) and *Terminalia arjuna* (Arjuna) contribute to renal protection by reducing urea and creatinine levels and improving renal blood flow, aided by compounds such as chebulagic acid and arjunolic acid (Patil et al., 2021). Lesser-known but equally effective herbs include *Cassia auriculata* (Avaram), *Ficus racemosa* (Gular), and *Coccinia indica* (Kundru).

These herbs have demonstrated hypoglycemic, antioxidant, and anti-inflammatory activities that help in attenuating diabetic kidney injury (Nayak et al., 2020). Bioactive molecules like kaempferol, bergenin, and lupeol work in synergy to enhance renal function and delay the progression of nephropathy. The cumulative pharmacological effects of these herbs make them promising candidates for adjuvant therapy in diabetic nephropathy. By addressing multiple pathological mechanisms simultaneously—such as hyperglycemia, oxidative stress, inflammation, and fibrosis—these plants provide a holistic and natural approach to renal protection. Integrating these medicinal herbs into therapeutic regimens could reduce the burden of diabetic kidney disease and improve patient outcomes, especially in resource-limited settings where access to synthetic drugs may be limited. Ongoing clinical studies and molecular research will continue to validate and refine their role in modern nephroprotective treatment strategies.

Figure 3: Showing effect of medicinal plants in the management of diabetic nephropathy.



Mechanisms of Nephroprotection

Indian medicinal plants exert nephroprotective effects via several pathways:

- **Antioxidant activity**: Neutralization of reactive oxygen species (ROS)
- **Anti-inflammatory response**: Inhibition of NF-κB and cytokine production
- **Glycemic control**: Improved insulin sensitivity and glucose metabolism
- **Anti-fibrotic actions**: Modulation of TGF-β and inhibition of ECM accumulation

Table 2: Illustrates Indian medicinal plants and their mechanism of action for diabetic nephroprotective properties.

Botanical Name	Local Name	Key Bioactive Compounds	Mechanism of Action
Tinospora cordifolia	Giloy, Guduchi	Tinosporaside, cordifolioside A, berberine	Antioxidant, anti-inflammatory, reduces oxidative stress
Gymnema sylvestre	Gurmar	Gymnemic acids, saponins	Improves insulin sensitivity, protects glomeruli
Withania somnifera	Ashwagandha	Withanolides, sitoindosides	Reduces inflammation, oxidative stress
Momordica charantia	Karela (Bitter gourd)	Charantin, vicine, polypeptide-p	Hypoglycemic, antioxidant
Curcuma longa	Haldi (Turmeric)	Curcumin	Anti-inflammatory, anti-fibrotic, antioxidant
Boerhaavia diffusa	Punarnava	Punarnavine, boeravinones	Diuretic, reduces proteinuria and renal inflammation
Ocimum sanctum	Tulsi (Holy Basil)	Eugenol, ursolic acid	Antioxidant, maintains renal histology

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Pterocarpus marsupium	Vijaysar	Pterostilbene, marsupsin, epicatechin	Lowers glucose, protects glomeruli
Azadirachta indica	Neem	Nimbidin, azadirachtin	Anti-inflammatory, reduces renal oxidative damage
Syzygium cumini	Jamun	Jamboline, ellagic acid	Hypoglycemic, reduces glycotoxic renal damage
Trigonella foenum-graecum	Methi (Fenugreek)	Trigonelline, diosgenin	Improves insulin signaling, reduces renal fibrosis
Phyllanthus emblica	Amla	Emblicanin A & B, gallic acid	Potent antioxidant, protects against AGE-induced kidney damage
Salacia reticulata	Saptrangi	Salacinol, kotalanol	Alpha-glucosidase inhibitor, protects kidney tissue
Andrographis paniculata	Kalmegh	Andrographolide	Anti-inflammatory, reduces renal dysfunction
Terminalia chebula	Haritaki	Chebulagic acid, gallic acid	Inhibits lipid peroxidation, reduces urea/creatinine levels
Terminalia arjuna	Arjuna	Arjunolic acid, flavonoids	Improves renal blood flow, antioxidant
Cassia auriculata	Avaram	Kaempferol, quercetin	Hypoglycemic, reduces fibrosis and renal stress
Eugenia jambolana	Jamun (alt. name)	Anthocyanins, jambosine	Improves glucose metabolism, preserves kidney structure
Ficus racemosa	Gular	Leucocyanidin, bergenin	Antidiabetic, antioxidant, nephroprotective
Coccinia indica	Kundru (Ivy gourd)	Beta-amyrin, lupeol	Reduces nephrotoxicity from hyperglycemia

Evidence from Preclinical and Clinical Studies

Recent studies have validated the nephroprotective efficacy of several Indian medicinal plants:

- *Curcuma longa* reduced serum creatinine and glomerular injury in diabetic rats (Ravindran & Kannapiran, 2019).
- *Boerhavia diffusa* showed renal histological improvement and oxidative stress reduction (Deshmukh et al., 2020).
- *Ficus religiosa* ameliorated renal function and restored renal architecture (Singh et al., 2020).

Recent preclinical and clinical studies have substantiated the nephroprotective efficacy of several Indian medicinal plants, underscoring their potential in preventing and managing kidney-related disorders. These plants exhibit protective effects against nephrotoxicity induced by drugs, toxins, and metabolic imbalances, primarily through antioxidant, anti-inflammatory, and diuretic properties. For instance, a pilot clinical study demonstrated that *Salacia chinensis* stabilized renal function and reduced markers of endothelial dysfunction in diabetic chronic kidney disease patients over six months (Jeykodi et al., 2012). Preclinical studies have also highlighted the nephroprotective potential of various plants. *Polyalthia longifolia* leaf extract exhibited significant antioxidant activity and protected against cisplatin and gentamicin-induced toxicity in HEK293 cells (Bisht et al., 2023). *Cocculus hirsutus* leaf extract normalized elevated biochemical parameters in a 5/6 nephrectomized rat model, indicating strong nephroprotective activity (Gadapuram et al., 2013). *Triphala*, a traditional herbal formulation, alleviated bromobenzene-induced nephrotoxicity in rats by enhancing antioxidant enzyme activities and reducing lipid peroxidation (Chandran et al., 2015). *Bauhinia variegata* stem extract attenuated cisplatin-induced nephropathy in rats, as evidenced by improved biochemical and histological parameters (Pani et al., 2011). *Sophora interrupta* demonstrated protective effects against gentamicin-induced acute renal toxicity in Wistar rats, restoring abnormal plasma and urine biomarkers. *Oroxylum indicum* fruit extract significantly attenuated diabetic nephropathy in rats, likely due to its flavonoid and tannin content (Joshi et al., 2021). *Heliotropium indicum* ethanolic extract reduced rifampicin-induced nephrotoxicity in rats, improving serum and urine markers and antioxidant enzyme levels (Nagamalleswari et al., 2019). *Andrographis paniculata* leaf extracts, particularly the ethanol extract, offered nephroprotection against gentamicin-induced renal failure in rats, as evidenced by biochemical and histological assessments (Padmalochana & Dhanarajan, 2016). *Tinospora cordifolia* aqueous extract exhibited nephroprotective potential against gentamicin-induced nephrotoxicity in albino rats, limiting increases in blood urea nitrogen and serum creatinine levels (Sharma et al., 2019). These findings collectively support the traditional use of these Indian medicinal plants in renal care and suggest their potential integration into complementary therapies for kidney disorders.

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Conclusion:

The rising global burden of diabetic nephropathy (DN), a major microvascular complication of diabetes mellitus, underscores the urgent need for effective and safer therapeutic strategies. Conventional therapies, while effective in managing symptoms, often have limitations due to side effects, cost, and incomplete efficacy in halting disease progression. In this context, Indian medicinal plants have emerged as promising alternative and complementary therapeutic agents in the management of diabetic nephropathy. Rooted in the centuries-old traditions of Ayurveda and Siddha medicine, numerous herbs such as *Boerhaavia diffusa* (Punarnava), *Tinospora cordifolia* (Guduchi), *Phyllanthus niruri* (Bhumi Amla), *Curcuma longa* (Turmeric), and *Withania somnifera* (Ashwagandha) have demonstrated nephroprotective effects in both preclinical and limited clinical studies. These plants are rich in bioactive compounds like flavonoids, alkaloids, polyphenols, and terpenoids, which exhibit potent antioxidant, anti-inflammatory, hypoglycemic, and renoprotective actions. They help mitigate oxidative stress, reduce proteinuria, improve glomerular filtration rate, and protect renal histological architecture from diabetic-induced damage. Importantly, many of these herbs also offer systemic benefits, such as improved glycemic control and lipid regulation, which are crucial in managing diabetes and its complications. Despite encouraging results, the transition of these herbal remedies into clinical practice requires further validation. Standardization of extracts, understanding herb-drug interactions, and conducting large-scale, randomized clinical trials are essential for establishing safety, efficacy, and dosage guidelines. Nevertheless, Indian medicinal plants hold significant potential as adjunct therapies in the holistic management of diabetic nephropathy, offering a natural, cost-effective, and multi-targeted approach to renal protection in diabetic patients.

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Conflicts of interest

There are no conflicts of interest.

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