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Histopathological Insights into Nephroprotective Effects of Traditional Herbal Remedies in Diabetic Nephropathy

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ABSTRACT

Diabetic nephropathy (DN), a microvascular complication of diabetes mellitus, is one of the most prevalent causes of end-stage renal disease globally. It is pathologically defined by glomerular basement membrane thickening, mesangial expansion, progressive glomerulosclerosis, and tubulointerstitial fibrosis. Despite significant advances in glycemic control and renin-angiotensin system (RAS) blockade, DN remains difficult to manage effectively, particularly in its later stages. Increasing attention has been given to traditional herbal remedies, which have demonstrated promising nephroprotective effects through the modulation of oxidative stress, chronic inflammation, fibrosis, and apoptosis. These botanical agents contain bioactive phytoconstituents such as flavonoids, saponins, alkaloids, and terpenoids, which act through diverse molecular pathways, including inhibition of TGF-β1 signaling, NF-κB activation, and oxidative damage pathways. This review synthesizes histopathological evidence from both experimental and limited clinical studies that highlight the capacity of traditional herbal medicines to preserve renal architecture and function. Herbal agents such as Astragalus membranaceus, Salvia miltiorrhiza, and Curcuma longa have shown beneficial effects in reducing mesangial proliferation, glomerular damage, and interstitial fibrosis. By evaluating the mechanisms and efficacy of these herbal therapies, this review aims to inform the development of integrative treatment strategies that complement conventional care in diabetic nephropathy.

Keywords: diabetic nephropathy, nephroprotection, histopathology, herbal remedies, oxidative stress, fibrosis, podocytes, traditional medicine

INTRODUCTION

Diabetic nephropathy (DN), also referred to as diabetic kidney disease, represents a serious and progressive microvascular complication of both type 1 and type 2 diabetes mellitus [1]. It is the leading cause of chronic kidney disease and end-stage renal failure globally, affecting up to 40% of diabetic patients [1]. DN is clinically characterized by persistent albuminuria, progressive decline in glomerular filtration rate (GFR), hypertension, and an increased risk of cardiovascular events [2]. Morphologically, DN is marked by structural abnormalities such as glomerular basement membrane (GBM) thickening, mesangial expansion, nodular glomerulosclerosis (Kimmelstiel-Wilson nodules), and tubulointerstitial fibrosis [3]. Despite the use of standard treatments including tight glycemic control, blood pressure regulation, and pharmacological inhibition of the renin-angiotensin-aldosterone system (RAAS), many patients continue to experience disease progression [4]. Consequently, there is a growing interest in exploring adjunctive therapies that can halt or reverse renal damage. Traditional herbal medicine, with centuries of empirical use, offers a rich repository of botanicals that possess anti-inflammatory, antioxidant, and anti-fibrotic properties [5]. Increasing experimental evidence supports the role of these herbs in attenuating renal dysfunction and restoring histological architecture. Histopathological evaluations serve as a cornerstone for assessing the severity of renal injury and the efficacy of therapeutic interventions. They provide crucial insights into cellular and extracellular matrix changes within renal compartments [6]. This review aims to consolidate histopathological findings from studies investigating traditional herbal remedies in DN, thereby illuminating their nephroprotective potential and therapeutic relevance.

Pathological Features of Diabetic Nephropathy

Diabetic nephropathy (DN) is a progressive microvascular complication of diabetes mellitus and stands as a primary contributor to end-stage renal disease (ESRD) globally [1]. The pathological features of DN are distinct and evolve over time, affecting various compartments of the kidney. One of the earliest morphological alterations is the thickening of the glomerular basement membrane (GBM), which compromises the selective permeability of the glomerular filtration barrier [7]. This structural abnormality contributes to persistent proteinuria, a key clinical indicator of DN. Concomitant with GBM thickening is mesangial expansion, primarily driven by the excessive accumulation of extracellular matrix (ECM) proteins, including fibronectin, laminin, and various types of collagen [8]. This expansion leads to mesangial cell hypertrophy and ultimately to nodular glomerulosclerosis, as seen in advanced stages of the disease (Kimmelstiel-Wilson nodules). Podocyte injury is a critical event in DN pathogenesis [3]. Podocyte loss, detachment, and effacement of foot processes disrupt the glomerular filtration barrier's integrity, exacerbating albuminuria and accelerating glomerular injury [9]. In later stages, tubulointerstitial damage becomes prominent, characterized by tubular atrophy, interstitial fibrosis, and infiltration of inflammatory cells [10]. These changes are often fueled by chronic hyperglycemia-induced oxidative stress, local inflammation, and ischemia [11]. Furthermore, arteriolar hyalinosis—marked by the deposition of eosinophilic hyaline material in afferent and efferent arteriolar walls—impairs renal perfusion and exacerbates ischemic injury [12]. This vascular pathology diminishes oxygen and nutrient delivery to renal tissues, further promoting fibrosis and functional decline [13]. Collectively, these pathological changes culminate in progressive nephron loss and renal failure [14].

Traditional Herbal Remedies with Nephroprotective Potential

1. Astragalus membranaceus

Astragalus contains astragaloside IV and flavonoids, known for anti-inflammatory and antifibrotic effects [15]. Histopathological studies show reduced mesangial matrix expansion and decreased interstitial fibrosis in diabetic models [15].

2. Curcuma longa (Turmeric)

Curcumin, the active compound in turmeric, restores normal tubular structure, reduces collagen deposition, and prevents glomerulosclerosis [16]. Its antioxidant properties counteract hyperglycemia-induced oxidative stress [17].

3. Salvia miltiorrhiza (Danshen)

Rich in tanshinones and salvianolic acids, Danshen has demonstrated attenuation of GBM thickening and vascular injury, improving overall glomerular function [18].

4. Panax ginseng

Ginsenosides in ginseng exert protective effects by reducing glomerular hypertrophy and preserving podocyte morphology, essential for maintaining the filtration barrier [19].

5. Gymnema sylvestre

Gymnemic acids help ameliorate tubular necrosis and preserve glomerular architecture. The herb also exhibits hypoglycemic and antioxidant properties [20].

6. Nigella sativa (Black seed)

Thymoquinone reduces renal oxidative stress, inflammatory cell infiltration, and tubular epithelial damage. It supports both glomerular and tubular health [21].

7. Phyllanthus niruri

Compounds such as lignans and flavonoids help reverse GBM thickening and reduce mesangial expansion, offering structural protection in DN [22].

Mechanistic Insights from Histopathological Evidence

Histopathological evaluations have provided significant insights into the mechanisms by which traditional herbal remedies exert nephroprotective effects in diabetic nephropathy. These mechanisms target multiple pathological pathways involved in renal injury, offering a holistic therapeutic approach. One major mechanism is the anti-inflammatory effect of phytochemicals. Chronic hyperglycemia activates pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and nuclear factor kappa B (NF-κB) [23]. Herbal agents such as curcumin, thymoquinone, and astragaloside IV have been shown to downregulate these inflammatory mediators, thereby reducing leukocyte infiltration and interstitial inflammation in renal tissues [24]. This contributes to the preservation of nephron architecture and reduced fibrotic progression. Another key mechanism is the antioxidant action of these compounds. Diabetic nephropathy is associated with excessive generation of reactive oxygen species (ROS), which damage cellular structures [25]. Phytochemicals enhance endogenous antioxidant defenses by upregulating enzymes such as superoxide dismutase (SOD) and

catalase, and activating the nuclear factor erythroid 2–related factor 2 (Nrf2) pathway [26]. This leads to reduced oxidative damage to glomeruli and tubules, as observed in histological sections showing less lipid peroxidation and mitochondrial preservation [27]. The anti-fibrotic response is another hallmark of effective nephroprotection. Transforming growth factor-beta (TGF-β) and its downstream Smad signaling are key drivers of extracellular matrix (ECM) accumulation and fibrosis [30]. Herbal agents such as silymarin and salvianolic acid inhibit TGF-β/Smad signaling, thereby limiting mesangial matrix expansion and interstitial collagen deposition [28,29]. Histopathological outcomes include reduced glomerulosclerosis and interstitial fibrosis [31] Lastly, podocyte preservation is critical for maintaining glomerular filtration function [32]. Herbal treatments help sustain the expression of structural proteins such as nephrin and podocin, essential for podocyte integrity [33]. Loss of these proteins is a defining feature of diabetic nephropathy [1]. Improved expression levels, confirmed via immunohistochemistry, correlate with reduced foot process effacement and improved filtration barrier function [1].

Comparative Analysis of Histopathological Outcomes

Comparative analysis of histopathological data from preclinical and limited clinical studies reveals varying degrees of efficacy among different herbal interventions [34]. While single-agent therapies show improvement in parameters such as glomerular structure, mesangial expansion, and tubular integrity, combinatorial formulations often provide more comprehensive protection [35]. Tables summarizing these outcomes indicate enhanced nephron preservation, normalized glomerular morphology, and reduced fibrosis when herbs are used in combination, supporting the rationale for polyherbal strategies in diabetic nephropathy management [1].

Safety, Standardization, and Clinical Translation

Despite the promising histopathological evidence supporting the use of traditional herbal remedies in diabetic nephropathy, several challenges remain before these therapies can be safely and effectively integrated into clinical practice. Toxicological considerations are critical, as the long-term safety profiles of many herbal compounds have not been adequately established [36]. While most studies suggest low toxicity at therapeutic doses, chronic toxicity studies are limited for several herbs, including Nigella sativa and Phyllanthus niruri [37]. Prolonged use, high doses, or herb-drug interactions could potentially lead to adverse effects, particularly in patients with multiple comorbidities or those on polypharmacy [38] Standardization challenges present another barrier to clinical translation. Herbal preparations often vary in composition due to differences in cultivation, harvesting, extraction methods, and formulation [39]. This variability leads to inconsistent bioavailability and therapeutic outcomes [40]. Standardization of active constituents, manufacturing processes, and dosing regimens is essential for ensuring reproducibility and regulatory approval. Clinical data gaps also limit the widespread adoption of herbal nephrotherapies [41]. Few randomized controlled trials (RCTs) have evaluated traditional remedies using histopathological endpoints, which are crucial for confirming tissue-level efficacy. Most available studies focus on biochemical markers like serum creatinine or urinary albumin, which may not fully capture structural renal improvements.

Future Directions

Future research should focus on integrating traditional remedies into conventional clinical protocols, especially for early-stage diabetic nephropathy. This requires collaborative efforts between nephrologists, herbal medicine specialists, and pharmacologists. Emerging technologies such as molecular imaging and digital pathology offer improved tools for non-invasive and quantitative assessment of renal changes in response to therapy. These tools could enhance the evaluation of herbal efficacy and safety. Additionally, integrating genomic and proteomic data with histological findings may uncover molecular signatures linked to herbal responses, paving the way for personalized phytotherapy approaches.

CONCLUSION

Histopathological studies strongly support the nephroprotective effects of various traditional herbal remedies in diabetic nephropathy. These herbs effectively modulate inflammation, oxidative stress, fibrosis, and structural damage. However, to move from bench to bedside, efforts must focus on safety validation, formulation standardization, and robust clinical trials with histopathological endpoints to ensure evidence-based integration into modern nephrology practice.

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