EURASIAN EXPERIMENT JOURNAL OF SCIENTIFIC AND APPLIED RESEARCH
(EEJSAR) ISSN: 2992-4146
©EEJSAR Publications Volume 7 Issue 3 2025

Herbal Antidiabetics and Organ Toxicity: A Review of Hepatic and Renal Histopathological Findings

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ABSTRACT

Herbal antidiabetic agents have attracted considerable global interest as alternative or complementary options for the management of diabetes mellitus, particularly in regions with limited access to conventional pharmaceuticals. Numerous plant-derived compounds, including alkaloids, flavonoids, terpenoids, and saponins, have demonstrated significant antihyperglycemic activity through mechanisms such as insulin sensitization, glucose uptake enhancement, and inhibition of carbohydrate-digesting enzymes. However, despite their therapeutic promise, concerns remain regarding the long-term safety of these agents, especially their potential hepatotoxic and nephrotoxic effects. This review critically examines histopathological evidence from preclinical animal models and available clinical studies to assess liver and kidney outcomes associated with commonly used herbal antidiabetic preparations. It identifies herbs and phytochemicals that not only provide glycemic control but also exhibit hepatoprotective and nephroprotective properties, such as curcumin, berberine, and silymarin. Mechanisms of toxicity—including oxidative stress, cytochrome P450 enzyme interference, and immune-mediated injury—as well as protective mechanisms like antioxidant enhancement and anti-inflammatory action are discussed. The review underscores the urgent need for comprehensive safety profiling, standardization of herbal formulations, and well-designed clinical trials with dual organ endpoints. Such efforts are critical to ensuring the safe integration of herbal antidiabetic therapies into mainstream diabetes care, particularly in resource-limited settings.

Keywords: herbal antidiabetics, liver toxicity, kidney toxicity, histopathology, phytochemicals, diabetes, organ safety, traditional medicine

INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder that continues to pose a significant global public health challenge, with rising incidence and prevalence in both developed and developing nations [1]. The disease is associated with serious long-term complications, including cardiovascular, renal, and hepatic damage, which contribute to substantial morbidity and mortality [2]. Despite advancements in pharmacotherapy, access to effective antidiabetic medications remains limited for many populations due to economic constraints, supply issues, and concerns about side effects from long-term drug use [3]. In this context, herbal remedies have gained renewed attention as accessible, culturally acceptable, and cost-effective alternatives or adjuncts to conventional treatments [4]. Rooted in various traditional medicine systems—including Ayurveda, Traditional Chinese Medicine, and folk remedies—these plant-based interventions are commonly perceived as safe due to their natural origin [5]. However, this perception often leads to unsupervised consumption, polyherbal self-medication, and lack of standardized dosing, which can pose significant health risks [6]. The liver and kidneys are highly susceptible to adverse effects from phytochemicals, as they play central roles in drug metabolism, biotransformation, detoxification, and excretion [7]. Consequently, hepatotoxicity and nephrotoxicity are critical concerns when evaluating the long-term safety of herbal antidiabetics [8]. Histopathological evaluation provides essential insights into microscopic tissue changes, including early signs of cellular injury, inflammation, fibrosis, and necrosis—well before clinical symptoms manifest [9]. This review synthesizes histopathological findings from both experimental and clinical studies to critically evaluate the safety and protective potential of commonly used herbal antidiabetic agents. It aims to bridge the gap

between traditional knowledge and modern toxicological assessment, providing evidence-based guidance for the safer use of herbal interventions in diabetes care.

Common Herbal Antidiabetics and Their Phytoconstituents

A wide range of medicinal plants have demonstrated antidiabetic effects through various mechanisms, including insulin mimetic action, pancreatic beta-cell regeneration, inhibition of intestinal glucose absorption, and modulation of hepatic gluconeogenesis. Momordica charantia (Bitter melon): Contains charantin and vicine, which exert hypoglycemic effects by enhancing insulin secretion and increasing glucose uptake in peripheral tissues [10]. Trigonella foenum-graecum (Fenugreek): Rich in 4-hydroxyisoleucine and diosgenin, it improves insulin sensitivity and delays gastric emptying [11]. Gymnema sylvestre: Known for gymnemic acids, which suppress sweet taste perception and regenerate pancreatic beta cells [12]. Azadirachta indica (Neem): Contains nimbin and azadirachtin, contributing to hypoglycemic and anti-inflammatory effects [13]. Tinospora cordifolia: Berberine and tinosporin are key bioactives with antidiabetic and antioxidant properties [14]. Allium sativum (Garlic): Allicin modulates insulin secretion and has lipid-lowering properties [15]. Ocimum sanctum (Holy basil): Contains eugenol and ursolic acid, both known for their anti-inflammatory and antihyperglycemic actions [16]. These herbs are widely used but require careful evaluation to distinguish beneficial effects from potential hepatorenal toxicity.

Histopathological Evidence of Organ Toxicity

Herbal antidiabetic agents, while offering potential therapeutic benefits, may also exert toxic effects on the liver and kidneys, particularly when consumed in high doses or over prolonged periods [17]. Histopathological investigations provide critical insights into the cellular and tissue-level changes associated with these exposures [9].

1. Hepatic Findings

Several studies have reported hepatic injury following administration of certain herbal antidiabetic agents. For instance, high-dose extracts of Azadirachta indica (neem) and Momordica charantia (bitter melon) have been associated with hepatic necrosis, vacuolar degeneration of hepatocytes, and bile duct hyperplasia [18]. These findings suggest that bioactive constituents, while pharmacologically potent, can become hepatotoxic at supra-therapeutic levels. Histological sections often reveal infiltration of inflammatory cells within the portal tracts and lobular regions, along with hepatocellular ballooning a hallmark of cellular stress [9]. These morphological changes are frequently accompanied by elevated serum transaminases (ALT and AST), alkaline phosphatase, and bilirubin, serving as biochemical markers of liver injury. Importantly, such changes may be reversible with dose reduction or discontinuation, but chronic exposure could predispose to fibrosis or impaired hepatic function [19].

2. Renal Findings

The kidney is equally vulnerable to phytochemical-induced toxicity. Histopathological evaluation has documented glomerular congestion, tubular epithelial cell degeneration, and interstitial edema following chronic administration of certain herbal preparations [20]. In some cases, the presence of proteinaceous casts within renal tubules and early signs of glomerulosclerosis have been observed, indicating progressive injury [21]. These changes correlate with functional impairments, such as elevated serum creatinine and urea, and reduced glomerular filtration rate [22]. Dose and duration are critical determinants; low to moderate doses may lead to reversible cellular stress, whereas prolonged or high-dose use can result in irreversible structural damage [23]. Studies emphasize the need for careful dosing, especially in populations with pre-existing renal compromise [24].

Herbal Agents with Hepatorenal Protective Effects

Conversely, several plant-derived compounds have demonstrated significant protective effects on liver and kidney tissues, making them valuable candidates for adjunct therapy in diabetes management. Curcuma longa (Curcumin): Exhibits strong antioxidant and anti-inflammatory properties [25]. It mitigates oxidative stress and inflammatory damage in hepatocytes and renal tubular cells, reversing histological abnormalities such as necrosis and cellular infiltration [26] Phyllanthus amarus: Known for its hepatoprotective activity, it stabilizes liver enzymes and maintains glomerular architecture [27]. Studies report preservation of normal hepatic cords and renal corpuscles following phytotherapeutic administration [28] Silybum marianum (Silymarin): Protects against toxin-induced oxidative injury in both the liver and kidneys by enhancing glutathione levels and reducing lipid peroxidation [29]. It promotes regeneration of hepatic and renal tissue [30] Berberis vulgaris (Berberine): Demonstrates antifibrotic and metabolic regulatory effects [31]. It normalizes liver and kidney histology and improves insulin sensitivity, making it beneficial in managing diabetes-related organ complications [32].

Mechanisms of Toxicity and Protection

The hepatotoxic and nephrotoxic effects observed with some herbal antidiabetic agents often stem from the generation of reactive oxygen species (ROS), leading to oxidative stress [33]. Excessive ROS disrupt cellular homeostasis by damaging lipids, proteins, and nucleic acids, ultimately impairing organ function [34]. The liver and kidneys are particularly susceptible due to their high metabolic activity and role in detoxification and excretion

[35]. Mitochondrial dysfunction is a central component of this toxicity [36]. Disruption of mitochondrial membranes leads to loss of membrane potential, decreased ATP production, and release of pro-apoptotic factors such as cytochrome c, triggering programmed cell death [37]. Furthermore, chronic or high-dose consumption of certain herbal products may lead to the accumulation of toxic secondary metabolites or plant-derived impurities [38]. These compounds can overload hepatic detoxification pathways or cause direct tubular damage in the kidneys [39]. Some phytochemicals may also interfere with the cytochrome P450 enzyme system, either inhibiting or inducing metabolic enzymes, which may alter the metabolism of both herbal and conventional drugs [40]. On the other hand, many herbal agents demonstrate protective effects against oxidative and inflammatory insults [41]. One key cytoprotective mechanism is the activation of the Nrf2 (nuclear factor erythroid 2–related factor 2) signaling pathway [41]. Nrf2 promotes the transcription of several antioxidant and detoxification enzymes, such as heme oxygenase-1 (HO-1), NAD(P)H quinone dehydrogenase 1 (NQO1), and glutathione S-transferase (GST), all of which enhance cellular resilience to oxidative stress [42]. Additionally, anti-inflammatory effects are mediated through the suppression of nuclear factor-kappa B (NF-κB) signaling and downregulation of pro-inflammatory cytokines including tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) [43]. Some phytochemicals also promote anti-apoptotic signaling pathways, supporting cellular repair and regeneration in hepatic and renal tissues [44].

Dose-Response and Synergistic Effects

The pharmacological and toxicological outcomes of herbal antidiabetic agents are strongly influenced by dose-response relationships [45]. At low to moderate doses, many phytochemicals exhibit therapeutic benefits, including improved glycemic control and antioxidant protection in liver and kidney tissues [46]. These doses may activate beneficial signaling pathways without overwhelming detoxification systems or causing cellular damage. However, at high doses or with prolonged exposure, the same compounds can exert toxic effects [47]. This is particularly concerning with unstandardized herbal products, where variability in phytochemical concentration may lead to inadvertent overdosing [48]. In polyherbal formulations, overlapping pharmacodynamics may produce synergistic toxicity, especially if multiple compounds act on the same metabolic or inflammatory pathways [49]. Additionally, herb-drug interactions are of increasing concern. Certain phytochemicals may modulate the activity of cytochrome P450 enzymes, altering the pharmacokinetics of concurrently administered antidiabetic or hepatotoxic drugs [50]. Such interactions may either potentiate toxicity or, in some cases, confer protective synergy [50]. Therefore, understanding and managing these interactions is critical for safe and effective integration of herbal agents into diabetes care.

Standardization and Safety Monitoring

Ensuring the safety and consistency of herbal antidiabetics requires rigorous standardization of plant extracts [51]. This includes accurate identification of botanical sources, standardized extraction procedures, and quantification of active constituents. Preclinical studies should include detailed toxicity screening, with a strong emphasis on histopathological endpoints for liver and kidney tissues. In clinical settings, pharmacovigilance systems must be strengthened to monitor adverse effects systematically. This includes regular biochemical assessments, imaging, and when necessary, histological evaluation to detect subclinical organ damage.

Future Perspectives

The evolving landscape of herbal antidiabetic research highlights the urgent need for more precise and proactive approaches to ensure safety and efficacy. A key future direction involves the development of organ-specific biomarkers capable of detecting early-stage hepatic and renal toxicity before overt clinical symptoms emerge. These biomarkers could significantly enhance monitoring during both preclinical studies and post-market use, facilitating early intervention and preventing irreversible damage. The integration of advanced omics technologies—including genomics, transcriptomics, proteomics, and metabolomics offers the potential to unravel complex interactions between phytochemicals and biological systems. These tools can help identify molecular signatures of toxicity or protection, as well as enable personalized phytotherapy based on individual genetic or metabolic profiles. In parallel, digital pathology and artificial intelligence can improve the precision and throughput of histological analysis, enabling more accurate detection of subtle organ-specific changes. Establishing robust regulatory frameworks is another critical priority. These should encompass stringent quality control of herbal products, standardized formulation protocols, batch-to-batch consistency, and mandatory toxicity evaluations. In addition, there is a pressing need for regulatory authorities to mandate comprehensive post-marketing surveillance programs that include real-world data collection, adverse event reporting, and public safety updates. These efforts, collectively, will ensure the responsible and safe advancement of herbal therapies.

CONCLUSION

Herbal antidiabetic agents present a promising complement to conventional diabetes management, particularly in low-resource settings. However, their long-term safety, especially regarding hepatic and renal health, requires rigorous scientific scrutiny. Histopathological findings provide crucial evidence linking phytochemical exposure to tissue-level effects, offering insights into both toxic and protective outcomes. The integration of traditional medicinal knowledge with modern biomedical research methods is essential to harness the full potential of these agents. A multidisciplinary approach—combining pharmacognosy, toxicology, pathology, clinical medicine, and regulatory science—will be pivotal in optimizing their therapeutic value while minimizing risks. Rational use, backed by standardization, safety monitoring, and evidence-based practice, is the way forward in incorporating herbal antidiabetics into mainstream healthcare.

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CITE AS: Omeye Francis I. (2025). Herbal Antidiabetics and Organ Toxicity: A Review of Hepatic and Renal Histopathological Findings. EURASIAN EXPERIMENT JOURNAL OF SCIENTIFIC AND APPLIED RESEARCH, 7(3):31-36