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# Toxicological Perspectives on Herbal and Nutraceutical Antioxidants in Diabetes Management: Benefits, Risks, and Hepatotoxicity Profiles

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**ABSTRACT**

Herbal and nutraceutical antioxidants are widely used as complementary therapies in type 2 diabetes mellitus (T2DM) to mitigate oxidative stress, improve glycaemic control, and prevent complications. Numerous plant- derived compounds-including polyphenols, flavonoids, carotenoids, and organosulfur molecules-have demonstrated antioxidant, anti- inflammatory, and insulin-sensitizing effects in preclinical and clinical studies. However, despite their perceived safety, emerging evidence highlights a "double- edged sword" nature: under certain conditions, these agents may exert pro- oxidant effects, interact adversely with other drugs, or induce liver injury. This review synthesizes the current mechanistic, toxicological, and clinical data on herbal and nutraceutical antioxidants in diabetes, focusing particularly on hepatotoxicity risks. We examine key antioxidants (resveratrol, curcumin, quercetin, α- lipoic acid, milk thistle, and anthraquinones such as chrysophanol), their beneficial metabolic actions, and the pathways by which they could damage the liver. We also discuss regulatory challenges, dose-dependent toxicity, and risk mitigation strategies. By offering a balanced and evidence-based assessment, this review underscores the importance of caution, quality control, and personalized use of antioxidant supplements in diabetic patients.

**Keywords**: herbal antioxidants, nutraceuticals, diabetes, hepatotoxicity, oxidative stress

## INTRODUCTION

Diabetes, particularly T2DM, is characterized by chronic hyperglycaemia, insulin resistance, and systemic low-grade inflammation[1]. Oxidative stress-excess reactive oxygen species (ROS) relative to antioxidant capacity-plays a central role in the pathogenesis of diabetic complications. Consequently, many patients turn to herbal and nutraceutical antioxidants, such as flavonoids and polyphenols, hoping to reduce oxidative damage and improve metabolic control[2]. Indeed, numerous plant-derived compounds have shown beneficial effects in preclinical and clinical models: they can scavenge ROS, enhance endogenous antioxidant defenses, modulate inflammation, and improve insulin sensitivity. However, despite their popularity, these natural products are not inherently benign[3]. Growing evidence points to potential toxicity, especially to the liver, and drug interactions that may compromise their safety in diabetic individuals. Hepatotoxicity from herbal medicines-also known as herb-induced liver injury (HILI)-is increasingly recognized, and antioxidant nutraceuticals are no exception[4]. Some compounds can paradoxically act as pro-oxidants under certain conditions (e.g., when they chelate metal ions). Furthermore, long-term use, high doses, poor quality control, and interactions with conventional antidiabetic drugs can exacerbate risk[5]. This review provides a nuanced examination of both the therapeutic promise and toxicological risks of herbal and nutraceutical antioxidants in diabetes management, with a special emphasis on hepatotoxicity[6]. We explore mechanisms of action, evidence from studies, and practical guidance for safe use.

### 2. Beneficial Effects of Herbal and Nutraceutical Antioxidants in Diabetes

#### 2.1 Mechanisms of Action

Herbal and nutraceutical antioxidants exert multifaceted effects on the metabolic pathways implicated in diabetes[7]. One of their primary actions is the direct scavenging of reactive oxygen species. By neutralizing free radicals, these compounds reduce oxidative damage to lipids, proteins, and nucleic acids, thereby protecting pancreatic beta cells, vascular endothelium, and other target organs from hyperglycaemia-induced injury. In

addition to direct scavenging, these antioxidants enhance endogenous defense mechanisms[8]. They can activate the Nrf2 signaling pathway, a master regulator of cellular antioxidant responses, resulting in increased transcription of detoxifying and cytoprotective enzymes such as heme oxygenase-1, catalase, and γ-glutamylcysteine ligase[9]. This upregulation strengthens the body's intrinsic capacity to manage oxidative stress and supports redox homeostasis. Another critical mechanism is the modulation of inflammation. Herbal antioxidants can downregulate pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6, while reducing levels of acute-phase proteins such as C-reactive protein. This anti-inflammatory effect is particularly relevant in diabetes, where chronic low-grade inflammation contributes to insulin resistance, endothelial dysfunction, and progressive beta-cell failure[10]. Beyond antioxidant and anti-inflammatory actions, certain plant-derived compounds influence metabolic regulation directly. For example, bioactives such as aspalathin from Rooibos tea can activate AMP-activated protein kinase (AMPK), improving lipid metabolism, enhancing insulin sensitivity, and promoting hepatic glucose regulation[11]. These multifaceted effects converge to stabilize glucose homeostasis, improve lipid profiles, and protect against diabetic complications.

### 2.2 Evidence from Preclinical and Clinical Studies

Preclinical studies in animal and in vitro models have consistently demonstrated the metabolic and antioxidant benefits of various plant-derived compounds[12]. Hypoglycemic plants including Trigonella foenum-graecum, Moringa oleifera, Centella asiatica, and Vitis vinifera improve oxidative stress biomarkers such as superoxide dismutase, glutathione, and catalase, while simultaneously reducing inflammatory mediators like TNF-α and IL-1β. Similarly, plants such as Curcuma longa, Azadirachta indica, Ginkgo biloba, and Psidium guajava have been shown to lower systemic inflammation, as reflected by reductions in C-reactive protein, and enhance antioxidant status in diabetic models[13]. Clinical evidence, although more variable, supports modest metabolic improvements in human populations. Meta-analyses indicate that antioxidant supplementation can reduce fasting plasma glucose, improve HbA1c, increase total antioxidant capacity, and lower markers of lipid peroxidation, such as malondialdehyde[14]. Specific nutraceuticals, including α-lipoic acid, have demonstrated both antioxidant and glucose-lowering properties, particularly in the management of diabetic neuropathy. Likewise, silymarin, derived from milk thistle, has shown hepatoprotective effects, while improving insulin sensitivity and reducing oxidative stress[15]. Collectively, these findings underscore the potential of herbal and nutraceutical antioxidants to complement conventional diabetes management, although careful attention to dose, quality, and safety remains essential.

## 3. Toxicological Risks and Hepatotoxicity Profiles

While herbal and nutraceutical antioxidants offer metabolic and antioxidant benefits in diabetes management, they are not without risks[16]. The perception that "natural" equates to "safe" can be misleading, particularly in patients with pre-existing metabolic or hepatic vulnerabilities. Toxicity may arise from several interrelated factors, including dose, duration of use, chemical composition, bioavailability, interactions with conventional medications, and individual patient susceptibility[17]. These factors collectively contribute to the potential for hepatotoxicity, which has emerged as a prominent concern in the clinical use of antioxidant supplements.

Dose and duration are critical determinants of safety[18]. Many antioxidant compounds exhibit biphasic dose-response characteristics, where low to moderate doses confer beneficial effects but high doses can paradoxically act as pro-oxidants. In the presence of transition metals such as iron or copper, excessive concentrations of flavonoids or polyphenols can undergo redox cycling, generating reactive oxygen species rather than neutralizing them[19]. This pro-oxidant activity can directly injure hepatocytes, especially in diabetic patients who often have subclinical or overt liver dysfunction. Similarly, chronic or long-term supplementation without monitoring can exacerbate cumulative oxidative or metabolic stress, increasing the likelihood of liver injury[20].

Quality control and standardization of herbal and nutraceutical products are additional sources of risk. Many commercially available supplements vary widely in the concentration of active compounds, purity, and the presence of contaminants or adulterants[21]. Mislabeling or contamination with hepatotoxic chemicals, pesticides, or heavy metals can potentiate liver injury. Furthermore, interactions with conventional antidiabetic medications or other drugs metabolized by hepatic cytochrome P450 enzymes may amplify hepatotoxic potential. For example, compounds such as resveratrol and curcumin can inhibit CYP3A4, leading to altered metabolism and accumulation of co-administered drugs, which may exacerbate hepatic stress[22]. Specific agents have been implicated in hepatotoxic events. High doses of curcumin, quercetin, and resveratrol have occasionally been associated with elevated liver enzymes or clinical liver injury, particularly in individuals with pre-existing hepatic impairment. Anthraquinone derivatives such as chrysophanol, found in certain herbal laxatives, can induce mitochondrial dysfunction, lipid peroxidation, and apoptotic death in hepatocytes[23]. Even traditionally hepatoprotective agents like silymarin can exert liver stress under supratherapeutic dosing or in combination with other bioactive compounds.

Herb-induced liver injury remains a clinically significant and underreported phenomenon. Clinical vigilance, including baseline liver function assessment and ongoing monitoring during supplementation, is essential[24]. Educating patients about the potential risks, adhering to recommended doses, and ensuring product quality are critical strategies to minimize hepatotoxicity. By recognizing that antioxidant supplements carry both therapeutic promise and inherent risk, clinicians can better balance efficacy with safety in diabetes management.

**4. Mechanistic Pathways of Hepatotoxicity**

Understanding the mechanisms by which herbal and nutraceutical antioxidants can induce liver injury is critical for safe diabetes management. Hepatotoxicity often arises from complex interactions among pro-oxidant activity, metabolic enzyme modulation, mitochondrial dysfunction, and immune-mediated stress[25]. These mechanisms may act individually or synergistically to compromise hepatocyte integrity. One major pathway is the paradoxical pro-oxidant effect of antioxidants at high doses or under specific cellular conditions[26]. While these compounds typically scavenge free radicals, excessive concentrations or the presence of transition metals such as iron and copper can promote redox cycling, generating reactive oxygen species instead of neutralizing them. The resulting oxidative stress can overwhelm hepatocellular defenses, damaging membranes, proteins, and nucleic acids, and ultimately leading to hepatocyte apoptosis or necrosis[27].

Herbal antioxidants may also interfere with hepatic metabolic enzymes, particularly cytochrome P450 isoforms[28]. Compounds such as resveratrol and curcumin can inhibit or modulate CYP3A4 and related enzymes, altering the metabolism of co-administered drugs or the supplement itself. Such interactions can result in the accumulation of hepatotoxic metabolites, increasing the risk of liver injury, especially in patients with pre-existing liver dysfunction or polypharmacy[29]. Mitochondrial dysfunction represents another central mechanism. Certain bioactive compounds, including anthraquinones and high-dose polyphenols, can disrupt mitochondrial membrane potential, impair electron transport, and induce lipid peroxidation. These effects trigger mitochondrial permeability transition, release of pro-apoptotic factors, and cell death, compromising liver function and regenerative capacity[30].

Finally, oxidative stress can elicit immune-mediated hepatotoxicity. Excessive ROS production may activate Kupffer cells and other resident immune cells, leading to the release of pro-inflammatory cytokines[31]. This inflammatory milieu exacerbates hepatocyte injury and can perpetuate chronic liver inflammation, particularly when supplementation is prolonged or combined with other hepatotoxic agents. Collectively, these pathways illustrate that even compounds with antioxidant and hepatoprotective properties can induce liver injury under specific conditions[32]. Recognizing the dose-dependent, metabolic, and immune-mediated mechanisms of hepatotoxicity is essential for guiding safe clinical use and monitoring of herbal and nutraceutical antioxidants in diabetes management.

**5. Clinical and Regulatory Considerations**

The safe integration of herbal and nutraceutical antioxidants into diabetes management requires careful clinical oversight and adherence to regulatory standards[33]. Clinicians should evaluate baseline liver function and assess patient-specific risk factors, including pre-existing hepatic impairment, polypharmacy, and metabolic comorbidities, before recommending supplementation. Monitoring liver enzymes periodically during long-term or high-dose use can help detect early hepatotoxicity and prevent serious adverse outcomes[34]. Patient education is equally essential; individuals should be informed that "natural" does not equate to "risk-free" and that adherence to recommended doses is critical. From a regulatory perspective, herbal and nutraceutical products often lack uniform quality control. Variations in active compound concentration, contamination, and adulteration can increase hepatotoxic risk[35]. Strengthening standards for product labeling, manufacturing practices, and third-party testing is essential. Additionally, establishing pharmacovigilance systems for reporting adverse events can improve the safety profile of these supplements[36]. Collectively, clinical vigilance, patient education, and regulatory oversight are vital to optimize therapeutic benefits while minimizing risks.

## CONCLUSION

Herbal and nutraceutical antioxidants hold considerable promise in the management of diabetes by attenuating oxidative stress, reducing inflammation, and improving glycaemic control. Compounds such as resveratrol, curcumin, quercetin, α-lipoic acid, and milk thistle have demonstrated beneficial preclinical and clinical effects. However, their use is not free from risk: at high doses or in susceptible individuals, these agents may act as pro-oxidants, impair drug metabolism, or directly injure the liver. Hepatotoxicity is a particularly serious concern, and clinicians, patients, and regulators must approach antioxidant supplementation with awareness and caution. Adequate quality control, patient monitoring, judicious dosing, and research into mechanism and safety are essential. By balancing the metabolic benefits with the toxicological risks, antioxidant nutraceuticals can be integrated more safely into diabetes care, maximizing their therapeutic potential while minimizing harm.

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