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# Targeting Oxidative Stress in Hepatorenal Injury: The Role of Antidiabetic Phytochemicals

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## ABSTRACT

Hepatorenal injury (HRI) is a significant and potentially life-threatening complication commonly associated with metabolic disorders, particularly diabetes mellitus. The pathophysiology of HRI is closely linked to oxidative stress, a condition in which an imbalance between reactive oxygen species (ROS) and the body's antioxidant defenses leads to cellular damage. ROS can overwhelm the cellular antioxidant systems, leading to inflammation, tissue fibrosis, and organ dysfunction, particularly in the liver and kidneys, which are highly susceptible to oxidative damage. These organs play a vital role in metabolism, detoxification, and waste elimination, making them particularly vulnerable in metabolic disorders. Recent research has highlighted the potential of antidiabetic phytochemicals in modulating oxidative stress and offering protective effects against hepatorenal injury. These natural compounds, often derived from medicinal plants, possess potent antioxidant, anti-inflammatory, and antidiabetic properties. Among the most studied phytochemicals are curcumin, berberine, and epigallocatechin gallate (EGCG), which have shown promising results in mitigating oxidative stress and preventing or treating hepatorenal damage. This review delves into the mechanisms of action of these compounds, examining their therapeutic potential, benefits, and challenges in clinical application. By understanding their role in combating oxidative stress, this review aims to provide insights into their future use in treating HRI, particularly in diabetic patients.

**Keywords:** Hepatorenal injury, Oxidative stress, Antidiabetic phytochemicals, Reactive oxygen species, Curcumin and berberine

## INTRODUCTION

Hepatorenal injury (HRI) is a significant cause of morbidity and mortality, often exacerbated by chronic metabolic diseases, especially diabetes mellitus [1]. In individuals with diabetes, the liver and kidneys are among the most affected organs due to their pivotal roles in metabolic processes such as glucose regulation, detoxification, and waste elimination [2]. HRI is characterized by the simultaneous damage to both the liver and kidney, which can result in severe complications, including liver cirrhosis, renal failure, and eventually systemic organ dysfunction [1]. A central mechanism driving the progression of HRI is oxidative stress, which occurs when there is an imbalance between the excessive production of reactive oxygen species (ROS) and the body's inadequate antioxidant defenses [3]. ROS are highly reactive molecules that cause cellular damage, inflammation, and fibrosis, particularly in the liver and kidneys, which are metabolically active and, thus, more vulnerable to oxidative damage [4]. The pathogenesis of diabetic complications, including HRI, is closely tied to this oxidative imbalance [5]. Despite significant advancements in pharmacological treatments for diabetes and its complications, managing conditions like HRI remains challenging. Current treatments primarily aim to control blood sugar levels, but they often fail to address the underlying oxidative stress that accelerates organ damage [1]. In this context, the therapeutic potential of natural compounds, particularly antidiabetic phytochemicals, has gained considerable attention. Phytochemicals are plant-derived bioactive compounds that possess a wide array of biological activities, including antioxidant, anti-inflammatory, and antidiabetic effects [6]. These compounds, such as curcumin, berberine, and epigallocatechin gallate (EGCG), have shown promise in modulating oxidative stress pathways, protecting against organ damage,

and improving overall metabolic health [7]. This review will explore the role of these phytochemicals in mitigating oxidative stress and preventing or treating hepatorenal injury, focusing on their molecular mechanisms, efficacy in preclinical models, and potential for clinical application in diabetic patients.

## Oxidative Stress in Hepatorenal Injury

### Mechanisms of Oxidative Stress in HRI



Oxidative stress occurs when the production of reactive oxygen species (ROS) exceeds the body's antioxidant capacity, resulting in cellular damage [8]. ROS include superoxide anions ($O_2^-$), hydrogen peroxide ($H_2O_2$), and hydroxyl radicals (OH•), which are generated as by-products of normal cellular metabolism, particularly within the mitochondria [9]. However, in pathological conditions such as diabetes mellitus, hyperglycemia amplifies ROS production, leading to an overproduction of these harmful molecules [5]. This imbalance can lead to extensive cellular damage, particularly in highly metabolically active tissues such as the liver and kidneys, both of which are crucial for maintaining homeostasis. In the liver, excess ROS cause hepatocyte injury by triggering inflammatory responses, inducing fibrosis, and impairing detoxification processes [10]. The damage to liver cells also compromises their ability to metabolize nutrients and detoxify harmful substances, exacerbating systemic dysfunction [11]. Similarly, in the kidneys, oxidative stress plays a significant role in glomerular injury, leading to glomerulosclerosis and tubulointerstitial fibrosis [12]. The accumulation of ROS contributes to renal dysfunction, which impairs the kidneys' ability to filter waste products from the bloodstream [13]. In both organs, mitochondrial dysfunction, apoptosis, and the activation of pro-inflammatory signaling pathways, such as nuclear factor-kappa B (NF-κB), are central to the progression of hepatorenal injury (HRI) [14]. These processes collectively enhance the severity of HRI and contribute to the deterioration of organ function.

### Role of Antioxidants in Mitigating HRI

Antioxidants, both endogenous and exogenous, are crucial in neutralizing ROS and restoring cellular homeostasis. Endogenous antioxidants, such as superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx), play essential roles in scavenging ROS and preventing oxidative damage [14]. However, in individuals with diabetes, the antioxidant defenses are often overwhelmed, leading to chronic oxidative stress and ongoing tissue damage [15]. As such, enhancing the body's antioxidant capacity, either through the modulation of endogenous pathways or the supplementation of exogenous antioxidants, represents a promising strategy for mitigating oxidative stress-induced complications like HRI. Phytochemicals, plant-derived bioactive compounds with antioxidant properties, have shown great potential in reducing oxidative stress and preventing organ damage [17]. These compounds, which include polyphenols, flavonoids, and alkaloids, can enhance the body's antioxidant defenses, directly neutralize ROS, and inhibit oxidative pathways [8]. In the context of HRI, dietary and therapeutic interventions with these phytochemicals offer a promising avenue for reducing oxidative damage, improving liver and kidney function, and ultimately preventing the progression of hepatorenal injury in individuals with metabolic diseases such as diabetes [1].

### Antidiabetic Phytochemicals and Their Mechanisms of Action

Numerous antidiabetic phytochemicals have been identified for their antioxidant, anti-inflammatory, and antidiabetic properties, making them ideal candidates for mitigating oxidative stress and preventing or treating hepatorenal injury. Below, we explore some of the most studied compounds and their mechanisms of action in combating oxidative damage. These include well-known bioactive compounds such as curcumin, berberine, and epigallocatechin gallate (EGCG), each with unique mechanisms to modulate oxidative stress and protect against hepatorenal damage. Their potential in clinical and preclinical studies offers valuable insights into alternative therapeutic strategies for managing HRI in diabetic patients.

#### 1. Curcumin

Curcumin, the active polyphenol in turmeric (Curcuma longa), is well known for its potent antioxidant and anti-inflammatory properties [18]. Curcumin has been shown to reduce ROS production and enhance antioxidant enzyme activity in both liver and kidney tissues [18,19]. In preclinical models of diabetes-induced HRI, curcumin supplementation significantly reduced hepatic and renal oxidative stress, protected against tissue damage, and improved organ function [20]. Curcumin achieves these effects through the modulation of several key molecular pathways, including the nuclear factor erythroid 2–related factor 2 (Nrf2) pathway, which regulates the expression of antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPx) [21].

### 2. Berberine

Berberine is an alkaloid found in several plants, including Berberis species, and has demonstrated antidiabetic, antioxidant, and anti-inflammatory effects [22]. Berberine exerts its antioxidant effects by enhancing the expression of antioxidant enzymes and suppressing ROS production [23]. Studies have shown that berberine can reduce oxidative stress in the liver and kidneys by activating the AMP-activated protein kinase (AMPK) pathway, which promotes cellular energy balance and mitochondrial function [24]. Additionally, berberine has been found to attenuate inflammatory cytokine production and protect against fibrosis in HRI [25].

### 3. Epigallocatechin Gallate (EGCG)

EGCG, a major polyphenol in green tea (Camellia sinensis), possesses strong antioxidant and anti-inflammatory properties. EGCG has been shown to reduce oxidative damage in both diabetic liver and kidney tissues by scavenging ROS and modulating the Nrf2/Keap1 signaling pathway [26]. In diabetic animal models, EGCG administration significantly reduced liver and kidney injury markers, improved antioxidant status, and protected against inflammation [27]. Furthermore, EGCG has been shown to regulate glucose metabolism, providing dual benefits in managing both diabetes and oxidative stress-induced organ damage [28].

### 4. Resveratrol

Resveratrol, a polyphenolic compound found in grapes, berries, and peanuts, has been extensively studied for its antioxidant, anti-inflammatory, and antidiabetic properties. Resveratrol enhances antioxidant defense mechanisms by activating Nrf2 and increasing the expression of antioxidant enzymes [29]. It also exerts anti-inflammatory effects by inhibiting the nuclear factor-kappa B (NF-κB) pathway, which is involved in the inflammatory response [30]. In animal models of diabetic nephropathy and hepatopathy, resveratrol supplementation has been shown to reduce oxidative stress, prevent tissue fibrosis, and improve organ function [31].

### 5. Quercetin

Quercetin is a flavonoid found in a variety of fruits, vegetables, and grains, known for its potent antioxidant and anti-inflammatory effects. Quercetin has been shown to reduce oxidative stress in the liver and kidneys by scavenging ROS and enhancing the activity of endogenous antioxidant enzymes [32]. Additionally, quercetin regulates several molecular pathways involved in inflammation and apoptosis, providing protection against tissue damage in diabetic models [33]. Its ability to modulate key cellular pathways, such as the Nrf2/ARE pathway, makes quercetin a promising therapeutic candidate for HRI [34].

## Therapeutic Potential and Challenges

### Efficacy in Preclinical and Clinical Studies

The majority of studies investigating the effects of antidiabetic phytochemicals on hepatorenal injury (HRI) have been conducted in animal models, where these compounds have consistently shown promising results in reducing oxidative stress, improving organ function, and mitigating the progression of tissue damage. For instance, curcumin, berberine, and epigallocatechin gallate (EGCG) have been demonstrated to significantly reduce oxidative damage, alleviate inflammation, and improve renal and hepatic function in diabetic animal models [19,24,27]. These findings suggest that these phytochemicals could potentially serve as effective adjunct therapies for preventing or treating HRI in diabetic patients [35]. However, translating these findings from preclinical models to human clinical trials remains a significant challenge. While some clinical studies have reported positive outcomes, such as improved antioxidant status and reduced markers of oxidative stress with the use of curcumin and EGCG, the evidence remains limited [36]. A number of clinical trials have suggested beneficial effects on managing diabetic complications, but larger and more rigorous trials are needed to confirm their efficacy, optimal dosages, and long-term safety in humans. Additionally, human studies often face challenges related to variability in response, small sample sizes, and differences in the underlying health conditions of participants, all of which complicate the interpretation of results [37].

### Challenges in Clinical Application

Despite their promising therapeutic potential, the clinical application of antidiabetic phytochemicals is hindered by several challenges. One of the most significant obstacles is their low bioavailability. Many of these phytochemicals, such as curcumin and EGCG, exhibit poor absorption and rapid metabolism in the body, which limits their effectiveness in clinical settings [38]. To overcome this, novel drug delivery systems, such as nanoparticles or liposomal formulations, are being explored to enhance their bioavailability [38]. Furthermore, the pharmacokinetics of these compounds are often poorly understood, and the optimal dosages for human use have not been established

[39]. There is also the potential for interactions with other medications commonly used in diabetes management, which could lead to adverse effects or reduced efficacy. Careful consideration of drug interactions, dosage optimization, and patient-specific factors is essential for the safe and effective use of these compounds in clinical practice [40]. Despite these challenges, ongoing research into the formulation of more bioavailable phytochemicals and their integration into therapeutic regimens holds great promise for improving the management of HRI in diabetic patients.



## CONCLUSION

Antidiabetic phytochemicals represent a promising class of natural compounds with the potential to mitigate oxidative stress and protect against hepatorenal injury. Curcumin, berberine, EGCG, resveratrol, and quercetin have shown significant promise in preclinical studies, demonstrating their ability to reduce oxidative damage, improve antioxidant defenses, and protect liver and kidney tissues from diabetes-induced injury. While further clinical trials are necessary to validate their therapeutic potential, these phytochemicals offer a natural, complementary approach to managing oxidative stress and preventing HRI in diabetic patients. Moving forward, the development of novel drug delivery systems and optimized formulations will be crucial in enhancing the bioavailability and efficacy of these compounds in clinical practice.

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