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# Sweeteners and Herbal Interactions in Diabetic Liver and Kidney Injury: Mechanistic and Histopathological Review

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## ABSTRACT

Diabetic liver and kidney injury (DLI) are prevalent complications of diabetes mellitus, contributing to significant morbidity and mortality. Oxidative stress, inflammation, and metabolic dysregulation are key mechanisms driving the progression of liver and kidney damage in diabetic patients. With the increasing prevalence of diabetes, the use of artificial and natural sweeteners has gained widespread attention as an alternative to sucrose. Concurrently, herbal therapies have been explored for their potential in mitigating the effects of diabetes and its associated complications. This review explores the mechanistic interactions between sweeteners and herbal compounds in the context of diabetic liver and kidney injury. Emphasis is placed on the biochemical pathways involved, the impact on oxidative stress and inflammation, and the histopathological changes observed in both liver and kidney tissues. A thorough examination of the current literature reveals the dual roles of sweeteners and herbs in modulating these pathophysiological processes, with some compounds showing promise in alleviating DLI through antioxidant, anti-inflammatory, and detoxifying effects. The review also highlights the challenges and future directions for integrating sweeteners and herbal treatments in diabetes management.

**Keywords:** Diabetic liver injury, Diabetic kidney injury, Sweeteners, Herbal interactions, Oxidative stress

## INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder that significantly affects multiple organs, with liver and kidney injuries being among the most prevalent and severe complications [1]. The liver and kidneys play pivotal roles in maintaining metabolic balance, detoxification, and waste elimination [2]. When these organs are impaired due to diabetes, it leads to a cascade of negative health effects, worsening the clinical burden of the disease. The progression of diabetic liver and kidney injury (DLI) is primarily driven by oxidative stress, inflammation, and fibrosis, which eventually lead to irreversible organ damage [3]. Oxidative stress results from the overproduction of reactive oxygen species (ROS) that overwhelm the body's natural antioxidant defense systems, thereby causing cellular damage in both liver and kidney tissues [4]. Inflammation, along with abnormal tissue fibrosis, further exacerbates organ dysfunction, leading to conditions like liver cirrhosis, diabetic nephropathy, and end-stage organ failure [5]. As part of ongoing efforts to manage diabetes and its complications, there has been a growing interest in non-nutritive sweeteners (NNS) and herbal compounds as complementary treatment options [6]. NNS, such as stevia, aspartame, and sucralose, are commonly used to regulate blood sugar levels while providing sweetness without adding extra calories [7]. While these compounds have become integral in managing blood glucose levels, their long-term impact on diabetic complications, particularly liver and kidney injury, remains controversial. Similarly, herbal compounds have gained attention for their potential therapeutic benefits, as they exhibit antioxidant, anti-inflammatory, and fibrotic properties that may help alleviate organ damage caused by diabetes [8]. However, the interactions between NNS and herbal treatments, particularly in the context of their effects on oxidative stress, inflammation, and tissue damage in the liver and kidneys, are not fully understood. This review seeks to synthesize current research on the synergistic effects of NNS and herbal compounds in alleviating DLI, focusing on their mechanistic pathways and histopathological outcomes. Understanding these interactions could pave the way for the development of more effective therapeutic strategies targeting the underlying processes of DLI.

## Mechanisms of Diabetic Liver and Kidney Injury

### Oxidative Stress in DLI

One of the most prominent mechanisms underlying liver and kidney injury in diabetes is oxidative stress. Hyperglycemia leads to the generation of excess reactive oxygen species (ROS), which damage cellular components, including lipids, proteins, and DNA [9]. In the liver, oxidative stress disrupts hepatocyte function, impairs glucose metabolism, and accelerates the progression of steatosis, fibrosis, and cirrhosis. In the kidneys, ROS contribute to endothelial cell dysfunction, glomerular damage, and tubulointerstitial fibrosis, ultimately leading to diabetic nephropathy [10]. Both organs exhibit significant mitochondrial dysfunction under oxidative stress, exacerbating tissue damage and inflammation [11].

### Inflammation and Fibrosis

Chronic inflammation is another key feature of diabetic complications. Inflammatory cytokines such as TNF-α, IL-1β, and IL-6 are elevated in both liver and kidney tissues in diabetic patients [12]. This inflammatory environment promotes the activation of fibrotic pathways, leading to extracellular matrix deposition and the progression of tissue scarring [13]. The fibrotic process is particularly problematic in the liver, where it can lead to cirrhosis, and in the kidneys, where it contributes to glomerulosclerosis and interstitial fibrosis [14].

### Sweeteners in Diabetic Liver and Kidney Injury

Non-nutritive sweeteners (NNS) such as aspartame, saccharin, stevia, and sucralose are commonly used as sugar substitutes in managing diabetes [7]. These sweeteners are known to have minimal impact on blood glucose levels, making them favorable alternatives for people with diabetes [15]. However, the long-term effects of these compounds on organ function, particularly in the liver and kidneys, are still under scrutiny. Some studies suggest that NNS may have both beneficial and detrimental effects on liver and kidney function [16].

### Beneficial Effects of NNS

Sweeteners like stevia have shown promise in alleviating oxidative stress in diabetic models [18]. Stevia, for example, has antioxidant properties that can reduce ROS production, helping to protect hepatocytes and renal cells from damage [17,18]]. Studies have also shown that stevia supplementation improves insulin sensitivity and reduces inflammation, which may indirectly benefit liver and kidney health [19]. Aspartame and sucralose, though commonly used, have shown mixed results, with some studies indicating potential renal toxicity, while others report no significant adverse effects [20,21,22].

### Detrimental Effects of NNS

Certain artificial sweeteners, particularly high doses of aspartame and sucralose, have been associated with increased oxidative stress and altered metabolic pathways in animal models [21,22]. There is evidence to suggest that excessive intake of NNS can induce liver dysfunction by promoting lipid peroxidation and inflammatory cytokine release [23]. Similarly, NNS may contribute to kidney damage by affecting renal filtration function and exacerbating oxidative stress [24].

### Herbal Interactions in Diabetic Liver and Kidney Injury

Herbal medicine has garnered significant attention for its potential therapeutic effects in managing diabetes and its complications, including liver and kidney injury [8]. Many herbal compounds possess a combination of antioxidant, anti-inflammatory, and hepatoprotective properties, making them valuable candidates for mitigating diabetic liver and kidney injury (DLI). These herbs not only help regulate blood sugar levels but also protect organ tissues from the harmful effects of oxidative stress, inflammation, and fibrosis, which are common in diabetic complications.

### Common Herbs with Protective Effects

**1. Curcumin (Turmeric**): Curcumin, the active ingredient in turmeric, is one of the most studied herbal compounds for its hepatoprotective and nephroprotective properties [25]. It has been shown to reduce oxidative stress, inflammation, and fibrosis in both liver and kidney tissues [25]. Curcumin's ability to activate the Nrf2/Keap1 signaling pathway plays a crucial role in enhancing the body's antioxidant defenses [26]. By modulating this pathway, curcumin helps protect hepatocytes and renal cells from oxidative damage and inflammatory responses, thus reducing the progression of steatosis and fibrosis in the liver and mitigating kidney damage [26]. Several studies have confirmed its potential to prevent hepatic and renal injury in diabetic models, making it a promising therapeutic candidate [27].

**2. Berberine (Berberis spp.):** Berberine, a bioactive alkaloid found in various plants, particularly from Berberis species, has demonstrated significant protective effects against diabetic liver and kidney injury [28]. Berberine works by reducing oxidative stress, inflammation, and fibrosis in both organs [28,29]. It modulates the AMP-activated protein kinase (AMPK) pathway, which is key to restoring metabolic balance [30]. AMPK activation not only enhances insulin sensitivity but also helps in regulating lipid metabolism, preventing the accumulation of fat in

liver cells (hepatic steatosis) [28]. Additionally, berberine's anti-inflammatory effects contribute to the reduction of glomerular damage and tubulointerstitial fibrosis in diabetic nephropathy, promoting kidney health [31].

**3. Ginseng (Panax ginseng):** Ginseng has been widely used in traditional medicine and is known for its potent antioxidant, anti-inflammatory, and antifibrotic effects [32]. In diabetic models, ginseng has shown the ability to prevent hepatic steatosis and fibrosis by regulating lipid metabolism and reducing the production of inflammatory cytokines [33]. Ginseng's adaptogenic properties help in reducing stress-related oxidative damage, providing protection against liver damage caused by elevated blood glucose levels [35]. Additionally, ginseng has demonstrated nephroprotective effects, improving renal function by modulating oxidative stress and inflammatory responses in the kidneys [34].



**4. Milk Thistle (Silybum marianum):** The flavonoid silymarin, derived from milk thistle, is renowned for its potent antioxidant and anti-inflammatory effects. Silymarin has been found to protect liver cells from oxidative damage and has shown promise in improving liver function in individuals with liver diseases, including those with diabetes-related hepatic dysfunction [36]. Moreover, milk thistle's ability to reduce nephropathy markers suggests that it may help improve kidney function in diabetic patients. Silymarin's anti-inflammatory action also contributes to reducing the fibrosis process, thereby protecting the kidneys from the progression of diabetic nephropathy [37].

## Synergistic Effects of Herbs and Sweeteners

There is growing interest in the potential synergistic effects of combining herbal compounds with non-nutritive sweeteners (NNS) to alleviate diabetic liver and kidney injury. The antioxidant properties of herbs such as curcumin, berberine, and ginseng can complement the actions of sweeteners like stevia, creating a more effective therapeutic approach. For instance, stevia has demonstrated its ability to reduce oxidative stress in diabetic models, which, when combined with the potent antioxidant effects of curcumin, may enhance liver and kidney protection [19]. The combination of curcumin with stevia has shown improved antioxidant effects, resulting in better organ function and reduced oxidative damage in both the liver and kidneys [38]. This suggests that the synergistic use of herbal compounds and sweeteners could offer a promising therapeutic strategy to manage DLI. Furthermore, other herbal compounds like berberine and ginseng, when combined with sweeteners, may work together to reduce inflammation, improve insulin sensitivity, and restore metabolic balance in the body [39]. The interaction between these compounds can help mitigate the harmful effects of high blood glucose levels, which contribute to the progression of liver and kidney injury in diabetes. Given the potential for these synergistic effects, further research into the combination of herbs and sweeteners could provide new therapeutic avenues for treating diabetic liver and kidney complications, offering patients a more holistic approach to managing their condition. In conclusion, while herbal compounds offer substantial protective benefits against diabetic liver and kidney injury, their interactions with sweeteners may provide an even more potent therapeutic effect. Combining these natural remedies holds the potential to improve organ function, reduce oxidative stress, and slow the progression of DLI, offering hope for better management of diabetes-related complications.

## Histopathological Changes in Diabetic Liver and Kidney Injury

Histopathological examination of liver and kidney tissues in diabetic animal models reveals distinctive and characteristic changes that reflect the progression of diabetic liver and kidney injury (DLI). In the liver, common histological findings include hepatocyte ballooning, a hallmark of cellular stress and damage, as well as the accumulation of fat in the liver cells, known as steatosis [40]. These conditions are often accompanied by the development of fibrosis, where excessive extracellular matrix components are deposited, and inflammatory cell infiltration, indicating an ongoing immune response to tissue damage [40]. Elevated serum liver enzyme levels, such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST), typically accompany these histological changes, serving as biomarkers of hepatocellular injury [41]. In the kidneys, diabetic nephropathy is characterized by glomerular hypertrophy, where glomeruli increase in size due to hyperfiltration, and mesangial expansion, where the mesangial matrix expands in response to increased pressure [42]. Tubulointerstitial fibrosis, which involves the thickening of kidney tissue around the renal tubules, and glomerulosclerosis, the scarring of the glomeruli, are also commonly observed. These histopathological changes are indicative of progressive kidney dysfunction and contribute to the loss of renal function in diabetes [43]. The combination of sweeteners and herbal treatments has shown promise in mitigating these histopathological changes. Herbal compounds, particularly those with antioxidant and anti-inflammatory properties, have been effective in reducing inflammatory cell infiltration, fibrosis, and oxidative damage in both liver and kidney tissues [44]. Additionally, these compounds have been found to promote cell regeneration, helping to repair damaged tissues and reverse the progression of liver and kidney injury.

## CONCLUSION

The interaction between sweeteners and herbal compounds offers a promising therapeutic approach for managing diabetic liver and kidney injury. While NNS can provide an alternative to sugar, their long-term effects on liver and kidney function require further investigation. Herbal compounds, such as curcumin, berberine, and ginseng, show significant potential in mitigating oxidative stress, inflammation, and fibrosis in diabetic complications. The combination of sweeteners with herbal therapies may enhance therapeutic outcomes by providing a multifaceted approach to reducing tissue damage and improving organ function. However, clinical trials are essential to validate the efficacy and safety of these interventions, and careful attention should be paid to potential interactions between sweeteners, herbs, and conventional medications used in diabetes management.



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