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Sweeteners and Liver Health: Evaluating Hepatotoxic Risks and Herbal Countermeasures

Kibibi Wairimu H.

School of Natural and Applied Sciences Kampala International University Uganda

ABSTRACT

With rising health consciousness and the global epidemic of obesity and diabetes, there has been a marked shift toward the consumption of low-calorie sweeteners (LCSs) as substitutes for refined sugars. While these sweeteners—both artificial (such as aspartame, sucralose, and saccharin) and natural (like stevia and monk fruit extracts)—are widely used and generally regarded as safe, growing evidence raises concerns about their long-term effects on liver health. This review critically examines the hepatotoxic potential of commonly consumed LCSs by exploring molecular mechanisms of liver injury, including oxidative stress, mitochondrial dysfunction, inflammation, and disruption of gut-liver axis signaling. Histopathological alterations such as steatosis, hepatocellular ballooning, and fibrosis are also discussed, alongside metabolic disturbances like dyslipidemia and insulin resistance. In parallel, the review evaluates emerging data on hepatoprotective interventions derived from medicinal plants and dietary phytochemicals—such as curcumin, silymarin, and resveratrol—that may counteract sweetener-induced hepatic damage. Traditional herbal formulations and integrative therapeutic strategies are also considered. By synthesizing current preclinical and clinical findings, this review highlights critical knowledge gaps and proposes future research directions to ensure safe dietary practices and inform the development of effective, evidence-based strategies for liver protection in the context of increasing sweetener use.

Keywords: sweeteners, hepatotoxicity, liver injury, herbal remedies, phytochemicals, oxidative stress, histopathology.

INTRODUCTION

The global burden of non-communicable diseases (NCDs) such as obesity, metabolic syndrome, and type 2 diabetes mellitus has prompted a significant shift in dietary patterns, particularly in the consumption of sugar substitutes [1]. In an effort to reduce caloric intake and glycemic load, low-calorie sweeteners (LCSs) and non-nutritive sweeteners (NNSs) have become widely integrated into food and beverage products, ranging from soft drinks and confectioneries to baked goods and pharmaceutical formulations [2]. These sweeteners, which are many times sweeter than sucrose yet contribute negligible calories, have been promoted as healthier alternatives to sugar, with potential benefits in weight management, glucose regulation, and dental health [3]. Initially regarded as safe and inert, many artificial and natural sweeteners received approval from global food regulatory authorities, including the U.S. Food and Drug Administration (FDA), the European Food Safety Authority (EFSA), and the Joint FAO/WHO Expert Committee on Food Additives (JECFA) [4]. However, the long-term metabolic effects of chronic sweetener intake are now under renewed scrutiny. Emerging experimental and epidemiological evidence suggests that some LCSs may exert unintended physiological effects, particularly on hepatic function. The liver, being the central hub of metabolic processing and detoxification, is particularly vulnerable to dietary and environmental toxins. Recent findings indicate that certain sweeteners may contribute to oxidative stress, hepatic inflammation, lipid accumulation, and dysbiosis, potentially increasing the risk for liver diseases such as non-alcoholic fatty liver disease (NAFLD), steatohepatitis, and fibrosis [5,6].

In light of these concerns, the search for protective strategies against sweetener-induced liver injury has gained momentum. Among the most promising avenues is the use of herbal medicine and phytochemicals—plant-derived compounds with bioactive properties. Traditional medical systems, such as Ayurveda, Traditional Chinese Medicine (TCM), and African ethnomedicine, have long relied on botanicals to treat liver disorders [7]. Modern

pharmacological research has begun to validate many of these traditional remedies, demonstrating antioxidant, anti-inflammatory, hepatoregenerative, and cytoprotective properties in various experimental models.

Phytochemicals such as curcumin (from Curcuma longa), silymarin (from milk thistle), resveratrol (from grapes), and glycyrrhizin (from licorice) have shown potential in ameliorating liver damage caused by oxidative and metabolic insults [8]. These compounds may exert protective effects through modulation of key molecular pathways, including the nuclear factor erythroid 2–related factor 2 (Nrf2) antioxidant pathway, nuclear factor-kappa B (NF-κB) inflammatory signaling, and AMP-activated protein kinase (AMPK)-mediated energy regulation [9]. Importantly, many of these natural agents are also capable of modulating gut microbiota, an increasingly recognized player in the pathogenesis of liver disease via the gut-liver axis [10]. This review aims to provide a comprehensive overview of the hepatotoxic potential of various classes of sweeteners, integrating mechanistic insights, histopathological evidence, and metabolic implications. It also explores the current landscape of herbal and phytotherapeutic interventions that may mitigate or reverse sweetener-induced hepatic damage. By bridging the fields of nutritional toxicology, hepatology, and herbal pharmacology, this review seeks to inform safe dietary practices and stimulate further research into integrative approaches for liver protection in the era of widespread sweetener use. As sweeteners continue to permeate global food systems, it is imperative to evaluate their safety profile not only in terms of glycemic impact but also their long-term effects on vital organs such as the liver. Understanding these effects and exploring complementary strategies for hepatic protection will be essential in guiding public health policies and clinical recommendations in the coming years.

Histopathological Evidence of Sweetener-Induced Liver Damage

Accumulating evidence from preclinical studies indicates that chronic exposure to various artificial and natural non-nutritive sweeteners can induce notable histopathological changes in liver tissue [11]. Animal models, particularly rodents exposed to sweeteners such as aspartame, sucralose, saccharin, and acesulfame-K, have demonstrated classical signs of hepatic injury. Among the most consistent findings are ballooning degeneration of hepatocytes, cytoplasmic vacuolation, and sinusoidal dilation [12]. These structural alterations reflect cellular stress, impaired metabolism, and altered microcirculation within the hepatic parenchyma.

In several studies, prolonged sweetener administration resulted in infiltration of inflammatory cells within the portal and lobular regions of the liver, indicating an immune-mediated component of hepatotoxicity [13,14]. This was often accompanied by an increase in fibrotic markers, suggesting a progression from steatosis and inflammation to early fibrosis in some experimental settings [15]. Cytoplasmic vacuolization, a marker of metabolic derangement and early-stage steatosis, has been frequently observed in response to artificial sweeteners [16]. Furthermore, some studies have reported hepatocellular necrosis and architectural disorganization in high-dose or long-term exposure models [17,18].

In contrast, human studies remain limited and somewhat inconclusive due to variability in exposure levels, dietary patterns, and co-existing metabolic conditions [19,20,21]. However, emerging epidemiological data suggest a possible link between high intake of low-calorie sweeteners and elevated liver enzymes such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST) [22]. Some observational studies have noted an association between frequent consumption of diet beverages and an increased risk of non-alcoholic fatty liver disease (NAFLD), particularly in individuals with obesity or insulin resistance [23]. While causality has not been established, these findings raise concerns about the long-term hepatic consequences of chronic sweetener use in humans.

Herbal and Phytochemical Countermeasures

The growing recognition of sweetener-associated liver injury has sparked interest in identifying safe and effective interventions. Herbal and phytochemical agents with hepatoprotective properties offer a promising avenue for mitigating these adverse effects.

Curcumin (Curcuma longa)

Curcumin, a polyphenolic compound found in turmeric, exhibits strong antioxidant and anti-inflammatory properties [24]. In animal models, curcumin has been shown to reverse hepatic damage induced by aspartame and other sweeteners by reducing oxidative stress, modulating inflammatory pathways, and restoring normal liver histology [25].

Silymarin (Silybum marianum)

Derived from milk thistle, silymarin is among the most extensively studied hepatoprotective agents. It stabilizes hepatic cell membranes, enhances hepatic protein synthesis, and acts as a free radical scavenger [26,27]. Silymarin has demonstrated protective effects in multiple models of chemically induced liver injury, including those involving sweetener exposure [28].

Green Tea Polyphenols (EGCG)

Epigallocatechin gallate (EGCG), the primary catechin in green tea, offers significant protection against oxidative liver injury [29]. It has also been shown to modulate lipid metabolism and improve gut microbial balance, both of which are implicated in sweetener-induced liver dysfunction [30].

Glycyrrhizin (Glycyrrhiza glabra)

Glycyrrhizin, found in licorice root, exerts hepatoprotective effects by reducing inflammation, inhibiting oxidative damage, and stabilizing cell membranes [31]. It has been used traditionally and in modern research settings to treat chronic liver disorders.

Berberine (Berberis spp.)

Berberine has gained attention for its ability to modulate lipid and glucose metabolism, regulate gut microbiota, and improve insulin sensitivity [32]. These mechanisms contribute to its protective role against NAFLD-like changes and make it a promising candidate for counteracting sweetener-induced hepatic alterations.

Integrative Approaches and Safety Considerations

As evidence grows regarding the potential hepatotoxic effects of chronic sweetener consumption, integrative approaches that combine dietary moderation with hepatoprotective herbal interventions are gaining attention. This dual strategy emphasizes reducing the intake of potentially harmful sweeteners while simultaneously supporting liver function through natural, evidence-based remedies [33]. Phytochemicals such as curcumin, silymarin, and berberine not only target oxidative stress and inflammation but also modulate lipid metabolism and gut-liver axis signaling, providing multifaceted protection [34]. However, while the use of herbal therapies offers promise, it must be approached with caution. Determining the optimal dosage for each phytochemical or herbal preparation is crucial, as under-dosing may render the treatment ineffective, while overdosing could lead to toxicity or adverse reactions [35]. Furthermore, the bioavailability of many herbal compounds, such as curcumin and resveratrol, is inherently low [36]. This has spurred interest in advanced formulations, including nano-delivery systems and bioenhancers like piperine, to improve absorption and therapeutic efficacy.

A key consideration in integrative therapy is the potential for herb-drug interactions. Many phytochemicals influence cytochrome P450 enzymes or drug transporters, which could alter the metabolism of concurrently administered medications. For example, silymarin and berberine are known to modulate liver enzymes and may interfere with the pharmacokinetics of drugs used in diabetes or cardiovascular conditions [37]. Therefore, careful assessment of a patient's medication profile and consultation with healthcare providers is essential before incorporating herbal remedies. Long-term safety is another area requiring close attention. Although most herbal compounds used for liver support are considered safe in the short term, their chronic effects, especially when used alongside synthetic drugs or in vulnerable populations (such as pregnant women, the elderly, or patients with liver disease), remain under-researched [35]. Regulatory oversight and rigorous clinical trials are needed to establish safety profiles and standardized dosing regimens for these compounds in the context of sweetener-induced liver injury.

Knowledge Gaps and Future Directions

Despite growing research, several knowledge gaps persist in understanding the full scope of sweetener-induced hepatotoxicity and the therapeutic potential of herbal countermeasures. Firstly, there is a lack of robust human clinical data directly linking specific sweeteners to liver damage [38]. Most evidence is derived from animal models, which, while informative, may not fully replicate human physiology or chronic exposure patterns [39]. Secondly, there is a need for standardized experimental models to evaluate liver injury induced by different classes of sweeteners. Variability in study design, sweetener dosage, and duration of exposure makes comparison across studies challenging [40]. Thirdly, research into synergistic effects of polyherbal formulations is still in its infancy. Traditional medicine often employs combinations of herbs for a more comprehensive therapeutic effect, but scientific validation of these combinations, including pharmacodynamics and safety profiles, is lacking [41] Lastly, there is significant potential in exploring the epigenetic and transcriptomic impacts of both sweeteners and phytochemicals on liver health. These molecular insights could uncover novel mechanisms and biomarkers for early detection and targeted therapy.

CONCLUSION

Low-calorie sweeteners, though beneficial in glycemic control and calorie reduction, may pose risks to liver health when consumed chronically. The evidence of oxidative stress, inflammation, and metabolic disruption calls for a reevaluation of their long-term safety. Herbal and phytochemical interventions offer promising protective strategies but must be grounded in scientific rigor and clinical evidence. Moving forward, an integrative and personalized approach—incorporating dietary

moderation, safe herbal use, and continued research—is essential to safeguard liver health in the era of widespread sweetener consumption.

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