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The Double-Edged Sword: Hepatorenal Toxicity of Synthetic Sweeteners and Protective Phytochemicals

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ABSTRACT

Synthetic sweeteners, including aspartame, sucralose, and saccharin, have become widely used as sugar substitutes due to their high sweetness potency and minimal caloric contribution. They are commonly recommended for individuals seeking to manage or prevent metabolic disorders such as obesity, type 2 diabetes, and metabolic syndrome. However, growing preclinical and limited clinical evidence suggests that chronic intake of these sweeteners may pose risks to vital organs, particularly the liver and kidneys. This review critically evaluates the current understanding of synthetic sweetener-induced hepatorenal toxicity, focusing on mechanistic insights derived from experimental studies. Key pathways implicated in organ damage include oxidative stress, mitochondrial dysfunction, inflammatory signaling, and disruptions in lipid and glucose metabolism. Histopathological findings from animal models reveal structural alterations such as hepatocellular degeneration, tubular necrosis, and inflammatory infiltrates. In parallel, the review explores the therapeutic potential of plant-derived phytochemicals—such as curcumin, silymarin, berberine, and green tea polyphenols—in attenuating sweetener-induced liver and kidney damage. These agents exhibit antioxidant, anti-inflammatory, and cytoprotective effects that may counteract the toxic impact of synthetic sweeteners. Finally, the review identifies critical research gaps, particularly in human clinical data, and underscores the need for integrative, evidence-based approaches to ensure the safe use of sweeteners and protect organ health.

Keywords: synthetic sweeteners, hepatotoxicity, nephrotoxicity, phytochemicals, oxidative stress, histopathology, herbal remedies, inflammation

INTRODUCTION

The dramatic global increase in metabolic disorders such as obesity, insulin resistance, and type 2 diabetes has driven significant dietary modifications, including a shift from refined sugars to synthetic sweeteners [1]. These non-nutritive compounds are widely incorporated into food, beverages, and pharmaceutical products due to their intense sweetness and negligible caloric contribution [2]. Synthetic sweeteners such as aspartame, sucralose, saccharin, and acesulfame potassium (acesulfame-K) have become central to dietary strategies aimed at glycemic control and weight management [4]. While initially promoted as safe sugar alternatives, emerging evidence raises concerns regarding their long-term effects on metabolic organs, particularly the liver and kidneys. The liver and kidneys serve as principal sites for metabolism, detoxification, and excretion of both endogenous and exogenous substances. As such, they are especially vulnerable to cumulative toxic insults. Increasingly, studies suggest that chronic exposure to synthetic sweeteners may disrupt hepatic and renal homeostasis through mechanisms involving oxidative stress, inflammation, mitochondrial dysfunction, and microbiota alterations [3]. Animal models have demonstrated histopathological changes in hepatic and renal tissues, while some human studies have reported altered liver enzyme levels and renal function markers in individuals with high sweetener intake [5].

Amid these concerns, there is growing interest in the role of plant-derived phytochemicals as protective agents. Compounds such as curcumin, silymarin, berberine, and epigallocatechin gallate (EGCG) exhibit antioxidant, anti-inflammatory, and cytoprotective properties [6,7,8]. Their potential to counteract synthetic sweetener-induced hepatorenal toxicity is an emerging area of scientific inquiry. These phytochemicals may modulate oxidative

pathways, regulate inflammatory mediators, and support mitochondrial integrity, thereby offering therapeutic promise [9] This review aims to provide a comprehensive overview of the metabolic fate of commonly used synthetic sweeteners, their mechanisms of toxicity in liver and kidney tissues, and the current evidence supporting the use of phytochemicals for prevention or mitigation of organ damage. Understanding these interactions is essential to guide public health recommendations and inform safer, integrative dietary practices.

Commonly Used Synthetic Sweeteners and Their Metabolic Fate

Aspartame

Aspartame is one of the most extensively used synthetic sweeteners. Upon ingestion, it is hydrolyzed in the gastrointestinal tract into its constituent amino acids—phenylalanine and aspartic acid—and methanol [10,11]. Although these metabolites are normally processed by the body, excessive intake may increase systemic oxidative stress and neurotoxicity, primarily due to methanol conversion to formaldehyde [12,13]. Aspartame has been implicated in hepatic oxidative damage and renal structural changes in several rodent studies [14].

Sucralose

Sucralose is a chlorinated disaccharide that is poorly absorbed in the gut. While most of it is excreted unchanged in the feces, a small fraction is absorbed and may accumulate in tissues, including the liver [15]. Sucralose has been shown to alter hepatic gene expression related to lipid metabolism and induce oxidative stress [16]. Additionally, its impact on gut microbiota composition may indirectly influence liver and kidney health through gut-liver and gut-kidney axis interactions [17].

Saccharin

Saccharin remains largely unmetabolized in the body and is excreted via the urine. Though once banned due to early concerns about carcinogenicity, it has since been re-approved by regulatory bodies [18]. Recent research has highlighted saccharin's potential to alter gut microbiota and promote low-grade inflammation, with implications for hepatic and renal function [19].

Acesulfame-K

Acesulfame potassium is rapidly absorbed and excreted, with minimal hepatic metabolism. Although considered stable, some studies have associated its chronic intake with alterations in renal oxidative markers and mild hepatic stress responses [20]. The compound's effects on microbiota and cellular signaling are still under investigation, but early data suggest a possible contribution to metabolic dysregulation [21].

Hepatorenal Toxicity: Mechanisms and Evidence

Synthetic sweeteners, although designed to be inert or minimally metabolized, have been increasingly associated with adverse effects on liver and kidney health [22]. Emerging mechanistic insights from preclinical studies reveal that several biological pathways are disrupted upon chronic exposure to these compounds [23].

Oxidative Stress

One of the most commonly reported mechanisms of sweetener-induced toxicity is oxidative stress [24]. Synthetic sweeteners such as aspartame and sucralose have been shown to increase the production of reactive oxygen species (ROS) in hepatic and renal tissues [25,26]. These ROS, if not adequately neutralized by antioxidant defenses, can cause damage to cellular lipids, proteins, and DNA [27]. The resulting lipid peroxidation leads to membrane instability and cellular dysfunction, contributing to hepatic steatosis and renal tubular injury [28]. Additionally, decreased activity of endogenous antioxidants like superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) has been observed following sweetener exposure [29].

Inflammatory Responses

Oxidative stress is closely linked to the activation of inflammatory signaling pathways [30]. Sweetener-induced tissue injury has been associated with upregulation of nuclear factor-kappa B (NF-κB), a key transcription factor involved in inflammation [31]. Activation of NF-κB leads to the increased expression of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), promoting hepatocellular and renal inflammation [32]. Sustained inflammatory responses can exacerbate tissue damage and contribute to the progression of fibrosis in both organs [33].

Mitochondrial Dysfunction

Mitochondria play a vital role in maintaining cellular energy homeostasis, especially in metabolically active organs like the liver and kidneys [34]. Chronic exposure to synthetic sweeteners has been shown to impair mitochondrial function, including a reduction in mitochondrial membrane potential, increased release of cytochrome c, and activation of caspase-dependent apoptotic pathways [35]. These changes compromise cellular respiration and energy production, leading to hepatocyte and renal tubular cell death.

Gut Microbiota Dysbiosis and the Gut-Liver-Kidney Axis

A growing body of research highlights the impact of synthetic sweeteners on gut microbiota composition. Alterations in microbial diversity and abundance can lead to increased intestinal permeability, commonly referred to as "leaky gut." This condition allows endotoxins such as lipopolysaccharides (LPS) to enter the bloodstream, promoting systemic inflammation [36]. Through the gut-liver and gut-kidney axes, this endotoxemia exacerbates hepatic inflammation and renal injury [37]. Dysbiosis has also been linked to changes in bile acid metabolism and uremic toxin production, further impairing organ function [38].

Histopathological Features of Toxicity

Histological examinations in animal models provide concrete evidence of organ damage associated with synthetic sweetener intake. In the liver, common findings include cytoplasmic vacuolation, which reflects metabolic disturbance; ballooning degeneration of hepatocytes, indicative of severe cellular injury; infiltration of inflammatory cells; and varying degrees of necrosis [39]. These alterations often resemble early stages of non-alcoholic steatohepatitis (NASH). In the kidneys, pathological changes include glomerular congestion, tubular cell degeneration, interstitial edema, and inflammatory infiltration [40]. In chronic settings, these may progress to interstitial fibrosis, a key marker of irreversible kidney damage [40].

Protective Phytochemicals Against Hepatorenal Toxicity

Phytochemicals, naturally occurring bioactive compounds found in medicinal plants, offer promising avenues for mitigating hepatorenal toxicity induced by synthetic sweeteners [41]. These compounds exert their protective effects through a range of mechanisms, including the scavenging of reactive oxygen species (ROS), inhibition of pro-inflammatory pathways, preservation of mitochondrial integrity, and modulation of gut microbiota [42]. Their multi-targeted actions make them valuable candidates for integrative therapeutic strategies aimed at preserving liver and kidney function.

Curcumin (Curcuma longa)

Curcumin, the principal curcuminoid of turmeric, exhibits potent antioxidant, anti-inflammatory, and mitochondrial-protective properties. It has been shown to significantly reduce oxidative stress by enhancing the activity of endogenous antioxidants such as superoxide dismutase and glutathione peroxidase [43]. In experimental models exposed to sucralose or aspartame, curcumin attenuated liver and kidney damage by lowering levels of inflammatory cytokines like TNF-alpha and IL-6, reducing lipid peroxidation, and preserving tissue architecture [44].

Silymarin (Silybum marianum)

Silymarin, extracted from milk thistle seeds, is a well-established hepatoprotective agent. It stabilizes hepatic cell membranes, stimulates protein synthesis, and enhances regeneration of damaged hepatocytes [45]. In toxicant-induced injury models, silymarin has been shown to improve liver histology and reduce elevated serum liver enzymes such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST), indicating functional recovery [46].

Resveratrol (Vitis vinifera)

Resveratrol, a polyphenolic compound found in grapes and red wine, offers protective effects through its antioxidant and anti-inflammatory activities. It supports mitochondrial function, inhibits NF-κB activation, and preserves renal and hepatic architecture [47]. In rodent studies, resveratrol has been found to reduce oxidative damage and inflammation in renal tubular and liver cells following sweetener exposure [48].

Quercetin

Quercetin is a flavonoid present in apples, onions, and berries, known for its ability to activate the Nrf2 signaling pathway. This activation enhances the transcription of genes involved in antioxidant defense and detoxification [49]. Quercetin also inhibits lipid peroxidation and suppresses the release of pro-inflammatory cytokines, offering dual protection to both liver and kidney tissues [50].

Berberine (Berberis spp.)

Berberine, an isoquinoline alkaloid, is recognized for its metabolic regulatory and anti-inflammatory effects. It alters gut microbiota composition, reduces systemic inflammation, and improves insulin sensitivity [51]. In experimental models of non-alcoholic fatty liver disease and renal fibrosis, berberine has shown efficacy in reducing inflammatory markers and restoring tissue integrity, supporting its role in preventing sweetener-induced organ toxicity [52].

Synergistic Herbal Formulations

Polyherbal formulations, which combine multiple plant-based compounds, offer enhanced protective effects through synergistic interactions. Such combinations have demonstrated the ability to reverse or attenuate histopathological changes in hepatic and renal tissues induced by synthetic sweeteners [53]. By targeting multiple pathways—oxidative stress, inflammation, and metabolic dysregulation—polyherbal therapies may provide broader and more sustained benefits than single compounds [54]. However, challenges remain regarding the standardization of

formulations, dose optimization, and mechanistic validation [55]. Without consistent phytochemical profiles and evidence-based dosing, their translation into clinical settings remains limited.

Safety and Toxicological Concerns of Phytochemicals

While phytochemicals are generally regarded as safe, their uncontrolled use may lead to adverse effects. At high doses or with prolonged use, certain compounds can exhibit hepatotoxicity, nephrotoxicity, or interfere with drug-metabolizing enzymes [56]. Herb-drug interactions are particularly concerning in patients on chronic medications for diabetes or cardiovascular disease [57]. Therefore, thorough toxicological assessments, including dose-response studies and safety profiling, are critical before recommending phytochemicals for widespread therapeutic use.

Knowledge Gaps and Research Directions

Significant gaps remain in understanding the hepatorenal risks of synthetic sweeteners and the protective potential of phytochemicals. Long-term human studies are scarce, and clinical trials on phytochemicals are limited. Advanced omics-based approaches, including metabolomics and transcriptomics, could help identify molecular signatures and therapeutic targets. Additionally, understanding the role of gut microbiota and organ cross-talk mechanisms is essential for developing integrated therapies.

CONCLUSION

While synthetic sweeteners are widely used for metabolic control, emerging evidence suggests potential risks to liver and kidney health with prolonged consumption. Mechanisms such as oxidative stress, inflammation, and gut microbiota disruption contribute to these adverse effects. Phytochemicals like curcumin, silymarin, and berberine show promise in mitigating such toxicity through antioxidant and anti-inflammatory pathways. However, clinical validation, safety profiling, and standardized dosing remain critical for their therapeutic use. A multidisciplinary research approach is essential to balance the benefits of sweeteners with potential harms and to integrate phytochemicals safely into preventive and therapeutic strategies.

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