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Phytochemicals as Dual Protectants Against Hepatotoxicity and Nephrotoxicity in Metabolic Syndrome

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ABSTRACT

Metabolic syndrome (MetS) is a multifactorial condition characterized by a constellation of interrelated metabolic abnormalities, including insulin resistance, central obesity, dyslipidemia, and hypertension. These components collectively contribute to a heightened risk of developing chronic liver and kidney diseases, making MetS a major global health concern. The concurrent manifestation of hepatotoxicity and nephrotoxicity in individuals with MetS significantly exacerbates disease burden and complicates clinical management. In recent years, growing attention has been directed toward the therapeutic potential of phytochemicals naturally occurring bioactive compounds found in plants. These compounds exhibit a wide spectrum of biological activities, notably antioxidant, anti-inflammatory, anti-fibrotic, and metabolic regulatory properties, which may confer simultaneous hepatoprotective and nephroprotective effects. This review comprehensively examines the current landscape of preclinical and clinical research exploring the dual organ-protective roles of phytochemicals in the context of MetS. Emphasis is placed on mechanistic pathways, including modulation of oxidative stress, inflammatory signaling, lipid metabolism, and mitochondrial function. Furthermore, histopathological and biomarker-based evidence supporting these effects is discussed. The review also highlights critical challenges limiting the translational potential of phytochemicals, such as poor bioavailability, variable safety profiles, and regulatory hurdles. Addressing these barriers is essential for optimizing their integration into evidence-based therapeutic strategies for MetS-associated liver and kidney complications.

Keywords: metabolic syndrome, hepatotoxicity, nephrotoxicity, phytochemicals, oxidative stress, curcumin, resveratrol, silymarin, quercetin, berberine

INTRODUCTION

Metabolic syndrome (MetS) represents a growing global health challenge, driven largely by sedentary lifestyles, increased consumption of energy-dense foods, and rising rates of obesity [1]. It encompasses a cluster of interrelated metabolic abnormalities, including central obesity, insulin resistance, hypertension, and dyslipidemia [2]. Collectively, these abnormalities predispose individuals to a heightened risk of developing a range of chronic conditions such as type 2 diabetes mellitus, cardiovascular disease, non-alcoholic fatty liver disease (NAFLD), and chronic kidney disease (CKD) [3]. Among the most affected organs in MetS are the liver and kidneys, given their central roles in systemic metabolic regulation, detoxification, and maintenance of homeostasis [4]. The liver functions as a metabolic hub, managing lipid and glucose metabolism, detoxifying xenobiotic s, and synthesizing essential proteins [5]. In parallel, the kidneys play a critical role in filtering blood, regulating electrolytes, maintaining acid-base balance, and eliminating metabolic waste [6]. In MetS, chronic exposure to elevated glucose levels, free fatty acids, and pro-inflammatory cytokines overwhelms the adaptive capacity of these organs, leading to progressive functional and structural damage [7]. Hepatotoxicity in this context often manifests as hepatic steatosis, inflammation, and fibrosis, while nephrotoxicity may present as glomerular hypertrophy, proteinuria, tubular atrophy, and interstitial fibrosis [8]. The co-existence of liver and kidney injury in MetS not only complicates disease management but also accelerates progression to end-stage organ failure [9].

In light of the limitations associated with conventional pharmacotherapy—including adverse effects, limited efficacy in multi-organ involvement, and lack of disease-modifying capabilities—there is increasing interest in complementary and integrative strategies for managing MetS and its complications [10]. Phytochemicals, a diverse group of bioactive compounds derived from plants, have emerged as promising agents in this context. These include flavonoids, alkaloids, phenolic acids, lignans, terpenoids, and saponins, many of which have been shown to possess potent antioxidant, anti-inflammatory, anti-fibrotic, and metabolic regulatory properties [11]. Preclinical and clinical studies have demonstrated the potential of various phytochemicals to ameliorate hepatic steatosis, improve lipid and glucose homeostasis, and attenuate renal damage by targeting multiple pathogenic pathways simultaneously [12]. Their ability to modulate oxidative stress, inhibit pro-inflammatory signaling cascades, enhance insulin sensitivity, and regulate lipid metabolism positions them as multifaceted therapeutic agents capable of addressing the complex pathophysiology of MetS [13]. Moreover, some phytochemicals have been shown to enhance mitochondrial function, restore redox balance, and prevent fibrosis in hepatic and renal tissues [14]. This review aims to synthesize current evidence on the dual hepatoprotective and nephroprotective effects of phytochemicals within the context of MetS. It explores the underlying mechanisms by which these compounds exert their protective effects, reviews histopathological and molecular findings from experimental models and clinical studies, and discusses the translational challenges associated with their therapeutic application. Special attention is given to issues such as bioavailability, safety, and integration into existing treatment paradigms, with the goal of informing future research and promoting evidence-based use of phytochemicals in the management of MetS-related organ damage.

Key Phytochemicals with Dual Hepatorenal Protective Effects

A growing body of evidence supports the therapeutic potential of phytochemicals in mitigating both hepatic and renal damage associated with metabolic syndrome (MetS). These bioactive compounds target multiple molecular pathways involved in oxidative stress, inflammation, fibrosis, and metabolic dysregulation, offering a holistic approach to organ protection.

1. Curcumin

Curcumin, a principal polyphenol in turmeric, is renowned for its potent anti-inflammatory and antioxidant properties. It has demonstrated efficacy in reducing hepatic steatosis by modulating lipid metabolism and suppressing inflammatory cytokines [15]. In renal tissue, curcumin mitigates fibrosis through downregulation of TGF-β and inhibition of the NF-κB pathway, thereby preventing excessive extracellular matrix deposition [16]. Additionally, curcumin enhances the activity of endogenous antioxidant enzymes such as superoxide dismutase (SOD) and catalase, protecting liver and kidney cells from oxidative insult [17].

2. Resveratrol

Resveratrol, a stilbene compound found in red grapes and berries, activates key metabolic regulators such as SIRT1 and AMPK [18]. Through these pathways, it improves insulin sensitivity and energy metabolism, thereby alleviating hepatic lipid accumulation and renal oxidative stress [19]. Resveratrol has been shown to enhance mitochondrial function, reduce lipid peroxidation, and attenuate inflammation in both liver and kidney tissues [20]. These effects contribute to its protective role against MetS-induced organ dysfunction.

3. Silymarin

Silymarin, a flavonolignan complex derived from milk thistle, has long been used for liver protection. It exerts antioxidant effects by scavenging free radicals and increasing glutathione levels [21]. In hepatic cells, silymarin stabilizes cell membranes, preventing toxin entry and lipid peroxidation. In the kidney, it protects against nephrotoxicity by enhancing membrane integrity and promoting cellular regeneration [22]. Silymarin also suppresses inflammatory markers and fibrogenic cytokines, facilitating tissue repair and functional recovery [23].

4. Quercetin

Quercetin, a dietary flavonoid, exhibits broad anti-inflammatory, anti-apoptotic, and antioxidant properties [24]. It inhibits the production of pro-inflammatory cytokines such as TNF-α and IL-6, thereby reducing hepatic inflammation and preventing glomerulosclerosis [25]. Quercetin has also been shown to attenuate lipid peroxidation in the liver and prevent renal tubular apoptosis, preserving organ architecture and function [26]. Its ability to modulate MAPK and PI3K/Akt signaling pathways further contributes to its dual protective actions [27].

5. Berberine

Berberine is an isoquinoline alkaloid known for its hypoglycemic and hypolipidemic effects [28]. It modulates the gut microbiota and activates AMPK signaling, thereby improving insulin resistance and reducing systemic inflammation [29]. In the liver, berberine inhibits lipogenesis and prevents steatosis [30]. In the kidney, it alleviates glomerular and tubular injury by reducing oxidative stress and pro-fibrotic signaling [31]. Its multitargeted actions make it a promising candidate for managing MetS-related hepatorenal complications. Together, these

phytochemicals offer a synergistic approach to mitigating liver and kidney damage in MetS by targeting overlapping molecular and cellular pathways implicated in disease progression.

Synergistic and Polyherbal Formulations

The therapeutic potential of phytochemicals is further enhanced when used in synergistic combinations. Individual phytochemicals often target distinct but interconnected pathways involved in oxidative stress, inflammation, fibrosis, and metabolic regulation. When combined, they may provide additive or even synergistic effects that enhance overall efficacy and reduce the required dosage of each component, thereby minimizing the risk of adverse effects [32]. Polyherbal formulations, which incorporate multiple plant-based bioactives, have a long history of use in traditional medicine systems such as Ayurveda, Traditional Chinese Medicine (TCM), and Unani [33]. These systems emphasize holistic and multi-targeted approaches, aligning well with the complex pathophysiology of metabolic syndrome and its impact on multiple organs. Recent research has investigated combinations such as curcumin with piperine (to enhance bioavailability), silymarin with resveratrol, and berberine with quercetin, showing improved outcomes in animal models of liver and kidney injury [34,35,36]. Polyherbal decoctions and standardized extracts have also demonstrated protective effects against hepatic steatosis and renal fibrosis, often outperforming single-compound therapies [37]. The integration of these formulations into therapeutic regimens, however, requires thorough pharmacodynamic and pharmacokinetic studies to ensure consistent efficacy and safety.

Challenges and Considerations

Despite promising preclinical data, several challenges hinder the translation of phytochemicals into effective clinical therapies for dual organ protection.

Bioavailability

Many phytochemicals exhibit poor oral bioavailability due to low solubility, instability in the gastrointestinal tract, rapid metabolism, and limited absorption. For instance, curcumin and quercetin are rapidly cleared from systemic circulation, reducing their therapeutic potential unless formulated with bioenhancers or novel delivery systems [38].

Safety Profiles

Although generally regarded as safe, high doses or chronic consumption of some phytochemicals may lead to toxicity. For example, excessive intake of berberine has been linked to gastrointestinal distress and potential hepatotoxicity [39]. Therefore, dose optimization and long-term safety assessments are crucial.

Standardization

One of the major barriers in phytochemical research is the lack of standardization across preparations. Variability in plant species, geographic origin, harvesting methods, and extraction techniques can lead to inconsistent concentrations of active ingredients [40]. This poses challenges for reproducibility and regulatory approval.

Clinical Validation

Human studies focusing on dual hepatorenal outcomes remain limited. Most clinical trials evaluate surrogate markers such as liver enzymes or renal filtration rate, rather than comprehensive histopathological or long-term functional endpoints [41]. Rigorous clinical trials are needed to validate efficacy and safety in diverse patient populations.

Future Directions

To overcome the current limitations in phytochemical-based therapies for metabolic syndrome, innovative research directions are being explored. A key focus is the development of advanced nanocarrier systems—such as liposomes, solid lipid nanoparticles, nanoemulsions, and polymer-based carriers—to improve the solubility, stability, and bioavailability of phytochemicals. These delivery systems can enhance gastrointestinal absorption, extend systemic circulation time, and facilitate targeted delivery to hepatic and renal tissues, thereby maximizing therapeutic efficacy while minimizing off-target effects. In parallel, the integration of omics technologies—including genomics, transcriptomics, proteomics, and metabolomics—is revolutionizing our understanding of how phytochemicals interact with biological systems. These tools enable the identification of molecular targets, signaling pathways, and responsive biomarkers that can guide personalized treatment strategies and monitor therapeutic outcomes in real-time. Another critical area is clinical validation. Future research must prioritize well-structured, multicenter randomized controlled trials (RCTs) that use standardized phytochemical formulations and dosing protocols. Trials should focus on comprehensive endpoints encompassing both liver and kidney function, using biochemical, imaging, and histopathological assessments. Furthermore, long-term safety data and studies involving diverse populations are essential to translate preclinical promise into clinical utility. These directions collectively hold the potential to establish phytochemicals as integral components of evidence-based strategies for managing metabolic syndrome and its organ-specific complications.

CONCLUSION

Phytochemicals offer a promising avenue for dual organ protection in metabolic syndrome, addressing both hepatotoxicity and nephrotoxicity through multi-targeted mechanisms. Their antioxidant, anti-inflammatory, and metabolic regulatory actions position them as potential complements or alternatives to conventional therapies. However, to fully realize their clinical utility, challenges related to bioavailability, safety, standardization, and clinical validation must be addressed. Future advancements in delivery technologies and translational research will be key to incorporating phytochemicals into evidence-based therapeutic protocols for metabolic syndrome and its complications.

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