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Hepatotoxicity of Herbal Supplements: Mechanistic Insights, Clinical Cases, and Regulatory Challenges

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ABSTRACT

Herbal supplements, widely used for their therapeutic properties, are often perceived as natural and safe. However, increasing reports of herb-induced liver injury (HILI) challenge this perception, drawing attention to the complex mechanisms and regulatory gaps surrounding their use. This review article explores the mechanistic underpinnings of herbal hepatotoxicity, including mitochondrial dysfunction, oxidative stress, immune-mediated injury, cytochrome P450 enzyme modulation, and idiosyncratic reactions. Prominent hepatotoxic herbs such as kava, green tea extract, black cohosh, and Polygonum multiflorum are discussed through documented clinical cases and epidemiological trends. The diagnostic challenges of HILI are highlighted, alongside the limitations of tools like the RUCAM scoring system. Furthermore, the article critically assesses global regulatory frameworks, emphasizing disparities in product oversight, quality control, and the implications of contamination and adulteration. Key public health recommendations include improving pharmacovigilance, mandating product standardization, and fostering international regulatory harmonization. The review underscores the need for interdisciplinary research and robust clinical protocols to ensure the safe integration of herbal products into mainstream healthcare.

Keywords: Herb-induced liver injury, Phytochemical toxicity, Cytochrome P450 modulation, Idiosyncratic hepatotoxicity, Herbal supplement regulation

INTRODUCTION

Herbal supplements are increasingly embraced worldwide as alternatives or complements to conventional medicine [1-4]. With roots in traditional medical systems such as Ayurveda, Traditional Chinese Medicine, and indigenous healing practices, these products have gained popularity for their purported benefits in managing chronic conditions, boosting immunity, improving vitality, and promoting general well-being [5-6]. The perception of being natural and therefore inherently safe has further fueled their widespread use. However, the growing body of scientific literature has highlighted a concerning paradox: the same herbal supplements believed to support health may, in some cases, pose significant health risks, particularly hepatotoxicity [7-10]. The liver plays a central role in the metabolism and detoxification of xenobiotics, including drugs, environmental toxins, and phytochemicals found in herbal preparations [11-14]. Consequently, it is a primary target organ for adverse reactions related to these compounds [15-18]. Hepatic injury from herbal supplements, also known as herb-induced liver injury (HILI), can range from asymptomatic elevation of liver enzymes to fulminant hepatic failure requiring transplantation [19-23]. Unlike conventional medications that undergo rigorous pre-market testing and post-market surveillance, many herbal supplements are subject to limited regulatory scrutiny, resulting in significant knowledge gaps concerning their safety profiles. Multiple factors contribute to the underestimation of herbal hepatotoxicity. These include the wide variability in product formulations, lack of standardization, unrecognized contaminants, and polyherbal combinations [24-28]. Additionally, herbal supplement users often do not disclose their usage to healthcare providers, further complicating diagnosis and treatment. Given these challenges, this review seeks to critically assess the mechanisms by which herbal supplements cause liver injury, highlight real-world clinical cases, explore diagnostic hurdles, and propose solutions for improved safety monitoring and regulatory oversight.

Mechanistic Insights into Herbal-Induced Hepatotoxicity

Herbal-induced hepatotoxicity results from a complex interplay of metabolic, immunological, and genetic mechanisms. Unlike conventional pharmaceuticals, herbal supplements consist of multiple phytochemicals, many of which possess potent biological activities that may adversely affect hepatic structure and function [29-33]. The risk of liver injury is influenced by the specific compounds in the herbal product, dosage, duration of use, underlying patient characteristics, and interactions with other drugs or xenobiotics [34-37]. Understanding the mechanisms underlying herbal hepatotoxicity is essential for developing safer formulations, identifying susceptible individuals, and improving diagnostic accuracy. Mitochondrial dysfunction is a central mechanism in the pathogenesis of herb-induced liver injury [38-43]. Mitochondria play a vital role in ATP production, redox balance, and regulation of apoptosis. Several herbal constituents disrupt mitochondrial electron transport, impair ATP synthesis, and cause mitochondrial membrane potential loss [44-49]. Green tea extract, which contains high concentrations of epigallocatechin gallate (EGCG), has been shown to depolarize mitochondrial membranes and induce hepatocyte apoptosis in vitro and in animal studies [11]. Mitochondrial damage can trigger the release of cytochrome c, leading to caspase activation and apoptotic cell death [50-52].

Oxidative stress is another critical pathway involved in herbal hepatotoxicity. Many phytochemicals undergo metabolic activation by hepatic enzymes, resulting in the formation of reactive oxygen species (ROS) and electrophilic intermediates [13]. When the generation of ROS exceeds the liver's antioxidant capacity, it leads to lipid peroxidation, protein carbonylation, and DNA fragmentation [14]. Kava (Piper methysticum) and chaparral (Larrea tridentata) are examples of herbs associated with significant oxidative liver injury [15]. This oxidative burden disrupts hepatocellular homeostasis, promotes inflammation, and sensitizes cells to additional insults, especially in individuals with compromised glutathione reserves [48-52].

Immune-mediated hepatotoxicity is characterized by hypersensitivity reactions to herbal compounds or their metabolites [17]. In such cases, small molecules act as haptens, binding covalently to hepatic proteins and forming neoantigens. These neoantigens are presented by antigen-presenting cells to T lymphocytes, initiating an immune cascade that results in hepatocyte destruction [18]. This process mimics autoimmune hepatitis, often presenting with positive autoantibodies and histological evidence of interface hepatitis. Herbs such as black cohosh (Actaea racemosa) and skullcap (Scutellaria lateriflora) have been associated with immune-mediated liver injury, especially in women and individuals with predisposing HLA haplotypes [19,20].

Cytochrome P450 (CYP450) modulation is another important contributor to herbal hepatotoxicity. CYP450 enzymes are responsible for the biotransformation of numerous drugs and xenobiotics [21]. Herbal supplements may induce or inhibit these enzymes, altering the metabolic clearance of co-administered drugs and leading to either increased toxicity or therapeutic failure. Polygonum multiflorum, widely used in traditional Chinese medicine, has been shown to alter CYP3A4 and CYP1A2 activity, increasing the risk of hepatotoxicity when taken with other hepatically cleared medications [22]. Moreover, induction of CYP enzymes can result in the formation of reactive metabolites that directly damage hepatocytes or initiate immune responses.

Idiosyncratic reactions to herbal supplements are unpredictable and occur independently of dose or duration of use [23]. These reactions may reflect individual genetic polymorphisms affecting drug metabolism, transport, or immune regulation. For instance, variations in genes encoding N-acetyltransferase, glutathione S-transferase, or HLA alleles may predispose certain individuals to hepatotoxic reactions to otherwise safe herbal doses [24]. Idiosyncratic hepatotoxicity underscores the need for personalized approaches in evaluating the safety of herbal products, including pharmacogenomic screening where feasible [23].

Additionally, contamination and adulteration of herbal products can introduce hepatotoxic compounds not inherently present in the plant. For example, herbal supplements may be contaminated with aflatoxins, heavy metals such as arsenic and lead, pesticides, or microbial toxins, all of which can cause liver damage [25]. Adulteration with synthetic drugs, such as corticosteroids or nonsteroidal anti-inflammatory agents, has also been documented in products marketed as herbal remedies, further complicating the identification of the true causative agent in cases of liver injury [26].

Clinical Cases and Epidemiological Trends

Case reports and retrospective studies have identified a variety of herbal products linked to liver injury. Kava (Piper methysticum), traditionally used for anxiety, has been implicated in cases of acute hepatitis, cholestatic injury, and fulminant liver failure, leading to its restriction or ban in several countries [27]. Green tea extract, popular in weight loss supplements, has caused hepatocellular injury in susceptible individuals, with several cases progressing to liver transplantation [28]. Polygonum multiflorum (He Shou Wu), a key ingredient in traditional Chinese medicine, is a well-documented cause of hepatotoxicity in Asia. Clinical presentations range from mild enzyme elevations to severe hepatic necrosis [30]. Likewise, black cohosh, marketed for menopausal symptoms, has been associated with

autoimmune-like hepatitis in several post-marketing surveillance reports [30]. Despite growing evidence, establishing causality in HILI remains difficult due to confounding factors such as polyherbal formulations, concurrent drug use, and product variability. The RUCAM (Roussel Uclaf Causality Assessment Method) scoring system is widely used to assess causality but is limited by its reliance on subjective clinical data [31].

Diagnostic and Regulatory Challenges

Diagnosing HILI is challenging because it often mimics other hepatic conditions. Symptoms are non-specific, laboratory findings are variable, and liver biopsy is rarely diagnostic [32]. Many patients do not voluntarily disclose herbal use, and physicians may not routinely inquire about it. Regulatory oversight of herbal supplements is inconsistent globally. In the United States, the Dietary Supplement Health and Education Act (DSHEA) allows supplements to be marketed without prior safety testing, relying on post-marketing surveillance [33]. In contrast, European and some Asian countries require pre-approval, though enforcement varies. Contaminants, misidentified botanicals, and lack of standardization further exacerbate risks [34].

Regulatory and Public Health Recommendations

Improving herbal supplement safety requires a multipronged approach:

* Strengthen pharmacovigilance systems to capture and evaluate adverse events
* Enforce manufacturing standards for consistency, quality, and purity
* Mandate accurate labeling and botanical verification
* Enhance consumer and clinician education regarding potential risks
* Support interdisciplinary research into hepatotoxic compounds and mechanisms
* Promote international collaboration on regulatory policies and enforcement

CONCLUSION

Herbal hepatotoxicity is an underrecognized but clinically significant issue. As herbal supplements become more popular, the potential for liver injury especially from contaminated, adulterated, or misused products demands attention from regulators, clinicians, and researchers alike. A better understanding of the mechanisms, improved diagnostic tools, and stronger regulatory oversight are essential for ensuring safe integration of herbal therapies into healthcare.

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