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Review Article

Natural Compounds in Hepatic Protection and Injury: A Dual-Spectrum Review of Medicinal Plants

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ABSTRACT

Hepatotoxicity remains a persistent global clinical challenge, driven by exposure to a broad spectrum of xenobiotics prescription drugs, over-the-counter medications, industrial chemicals, and increasingly, herbal supplements that disrupt the intricate balance of hepatic homeostasis. Paradoxically, a growing body of evidence demonstrates that many of these same medicinal plants exhibit dose-dependent hepatoprotective activities, highlighting the critical importance of delineating their dual-spectrum effects. In this review, we systematically classify a selection of widely used species into hepatotoxic and hepatoprotective cohorts, detailing their principal bioactive phytochemicals (e.g., pyrrolizidine alkaloids, flavonoids, triterpenoids), key molecular targets (including Nrf2/ARE, NF-κB, caspase cascades, and major CYP450 isoforms), and dose-response safety margins. We further summarize contemporary extraction and standardization methodologies such as supercritical fluid extraction, green solvent systems, and HPLC fingerprinting that ensure reproducibility and quality control across studies. Advanced *in vitro* and *in vivo* platforms, including three-dimensional hepatic spheroids and microfluidic liver-on-chip models, are reviewed for their enhanced physiological relevance and predictive capacity. Integration of preclinical data with findings from clinical trials investigating compounds like silymarin, glycyrrhizin, and EGCG is critically examined, with special attention to safety considerations such as herb drug interactions, cumulative toxicity thresholds, and idiosyncratic reactions. Finally, we propose future research trajectories leveraging network pharmacology, nanocarrier delivery systems, and international regulatory harmonization to accelerate the safe translation of phytochemical-based interventions for liver protection.

Keywords: Hepatotoxicity, Hepatoprotection, Phytochemicals, Nrf2, CYP450, Systems Pharmacology.

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INTRODUCTION

The liver is a central metabolic organ, performing over 500 physiological functions including detoxification of xenobiotics, protein synthesis, and regulation of lipid and carbohydrate metabolism.[1-3] Drug-Induced Liver Injury (DILI) accounts for approximately 10% of all adverse drug reactions and remains a leading cause of acute liver failure worldwide.[4,5] Concurrently, the use of herbal and dietary supplements has surged, contributing to a rise in Herb-Induced Liver Injury (HILI), which represents 10-15% of all DILI cases in Western countries.[6-8] Mechanistically, xenobiotic biotransformation involves Phase I enzymes (primarily cytochrome P450 isoforms) and Phase II conjugating enzymes (e.g., UDP-glucuronosyltransferases, sulfotransferases, glutathione-S-transferases), which together convert lipophilic compounds into excretable metabolites.[9-11] However, reactive intermediates can escape detoxification, resulting in oxidative stress, mitochondrial dysfunction, immune-mediated cytotoxicity, and cholestasis.[12-15] Phytochemicals often exhibit pleiotropic actions, modulating oxidative stress pathways (e.g., Nrf2/ARE), inflammatory cascades (e.g., NF-κB), and apoptotic regulators (e.g., caspases).[16-18] While compounds such as silymarin, glycyrrhizin, and Epigallocatechin-3-Gallate (EGCG) demonstrate robust hepatoprotective effects, other botanicals like *Chelidonium majus* and *Larrea tridentata* induce hepatotoxicity via formation of reactive metabolites or inhibition of bile acid transporters.[19-21] Understanding these dual spectrums is critical for safe clinical translation. Moreover, variability in plant chemistry due to geographic, genetic, and processing factors necessitates stringent standardization and quality control.[22-24] This review presents a comprehensive, mechanistic exploration of hepatotoxic versus hepatoprotective medicinal plants, integrating phytochemical profiles, molecular targets, advanced experimental models, clinical evidence, and safety considerations. We aim to guide future research and regulatory frameworks toward the development of effective, safe phytomedicines for liver disorders.

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Historical Perspective

Traditional healing systems such as Ayurveda and Traditional Chinese Medicine (TCM) have employed botanical remedies for over 3,000 years to treat liver ailments.[25,26] The Ebers Papyrus (1550 B.C.) lists >700 plant-based prescriptions for jaundice and hepatic disorders.[27] Dioscorides' *De Materia Medica* (1st century A.D.) catalogued 657 medicinal plants, many of which remain in use today.[28] The binomial nomenclature introduced by Linnaeus in *Species Plantarum* (1753) enabled systematic documentation of plant species and facilitated pharmacognostic research.[29] The 19th century saw isolation of alkaloids and glycosides (e.g., berberine, digitoxin), marking the advent of Phytochemistry.[30] Key milestones include identification of silymarin constituents in the 1960s and elucidation of flavonoid antioxidant mechanisms in the 1980s.[31,32] These historical foundations underpin current efforts to harness botanicals for hepatoprotection while mitigating HILI risks.

Liver Physiology and Mechanisms of Hepatotoxicity

Xenobiotic Metabolism

Xenobiotic metabolism in the liver proceeds through two sequential phases designed to render lipophilic compounds water-soluble for elimination. In Phase I reactions, Cytochrome P450 (CYP450) isoenzymes mainly CYP1A2, CYP2E1, and CYP3A4 introduce polar functional groups via oxidation, reduction, or hydrolysis, thereby increasing the reactivity of xenobiotics and preparing them for conjugation.[33] Subsequently, Phase II reactions incorporate conjugation with endogenous molecules such as glucuronic acid, sulfate, amino acids, or glutathione, which dramatically enhances water solubility and facilitates efficient biliary or renal excretion of the metabolites.[34] Together, these two phases safeguard against accumulation of lipophilic toxins, though incomplete reactions can yield reactive intermediates that contribute to liver injury.

Oxidative Stress and Mitochondrial Injury

Excessive generation of Reactive Oxygen Species (ROS) during xenobiotic metabolism overwhelms the intrinsic antioxidant defenses, leading to lipid peroxidation and loss of mitochondrial membrane potential. The compromised mitochondrial integrity results in the translocation of cytochrome c into the cytosol, which activates the intrinsic apoptotic cascade via caspase-9 and caspase-3, culminating in hepatocyte apoptosis and tissue damage.[35,36]

Immune-Mediated Cytotoxicity

Certain xenobiotics or their reactive metabolites form covalent adducts with cellular proteins, creating neoantigens that are recognized by resident liver macrophages (Kupffer cells). These macrophages present the antigenic peptides to CD^{8+} T lymphocytes, triggering targeted immune responses that lead to hepatocyte apoptosis and amplify overall liver injury.[37]

Cholestatic Injury

Cholestatic injury arises when key bile transporters primarily the Bile Salt Export Pump (BSEP) and Multidrug Resistance-Associated Proteins (MRPs) are inhibited or downregulated. Impairment of these transporters causes intrahepatic bile acid accumulation, which is cytotoxic to hepatocytes and leads to cholestatic hepatitis characterized by bile duct epithelial damage, bilirubin retention, and associated inflammatory responses.[38,39]

Steatosis and Fibrosis

Imbalances in lipid metabolism, marked by impaired mitochondrial βoxidation and increased de novo lipogenesis, result in excessive triglyceride accumulation within hepatocytes, defining the steatotic phenotype seen in Nonalcoholic Steatohepatitis (NASH).[40] Chronic steatosis provokes activation of hepatic stellate cells, which secrete extracellular matrix proteins leading to fibrogenesis. Persistent fibrotic remodeling disrupts normal liver architecture and can ultimately progress to cirrhosis if left unchecked.[41] Figure 1 provides a visual summary of how each of the reviewed plants engages these five major mechanisms.

Mechanisms of Hepatoprotection

As shown in Figure 2, antioxidant pathways are the most frequently targeted mechanism among the reviewed phytochemicals. Many botanicals achieve this through activation of the Nrf2/ARE signaling axis: for example, silymarin flavonolignans disrupt the Keap1-Nrf2 complex, enabling Nrf2 to translocate into the nucleus and drive transcription of antioxidant response elements such as Heme Oxygenase-1 (HO-1), NAD(P)H:Quinone Oxidoreductase-1 (NQO1), and the modulatory subunit of γ-Glutamylcysteine Ligase (GCLM).[42,43] In parallel, glycyrrhizin promotes glutathione homeostasis by upregulating γ-glutamylcysteine synthetase, thereby replenishing intracellular GSH pools and enhancing detoxification of electrophilic intermediates.[44]

Beyond mitigating oxidative stress, many phytochemicals exert potent anti-inflammatory effects. Epigallocatechin-3-Gallate (EGCG) from *Camellia sinensis* stabilizes IκBα, preventing nuclear translocation of the NF-κB p65 subunit and subsequent transcription of proinflammatory cytokines such as TNF-α, IL-1β, and IL-6.[45,46] Thymoquinone, the principal bioactive in Nigella sativa, attenuates MAPK phosphorylation in CCl_4-induced liver injury models, thereby reducing hepatic levels of TNF-α and IL-6 and limiting inflammatory cell infiltration.[47,48]

Mitochondrial protection represents another key hepatoprotective mechanism. Resveratrol, a stilbene from *Vitis vinifera*, preserves mitochondrial membrane potential by modulating the Bcl-2/Bax ratio and inhibiting opening of the mitochondrial permeability

transition pore, thus preventing cytochrome c release and downstream apoptotic signaling.[49] Enzyme modulation particularly of drug-metabolizing CYP450 isoforms is also critical. Andrographolide from Andrographis paniculata selectively inhibits CYP2E1, reducing the bioactivation of acetaminophen to its toxic N-Acetyl-P-Benzoquinone Imine (NAPQI) metabolite and consequently mitigating hepatocellular injury.[50] Finally, several phytochemicals display anti-fibrotic activity by targeting the TGF-β/Smad signaling cascade. Phyllanthin and related lignans downregulate TGF-β1 expression and inhibit phosphorylation of Smad2/3, which in turn suppresses collagen I and III synthesis by activated hepatic stellate cells, thereby impeding the progression of fibrosis.[51]

EXPERIMENTAL MODELS

In vivo Animal Models

Rodent models remain the cornerstone of preclinical hepatotoxicity research, with hepatocellular injury commonly induced by Carbon Tetrachloride (CCl_4), Thioacetamide, or Acetaminophen (APAP) in mice and rats. These agents reliably reproduce key features of liver damage oxidative stress, inflammation, and necrosis but interspecies differences in CYP450 isoenzyme expression and activity can complicate direct extrapolation of findings to humans.[52-54]

In vitro Systems

Primary hepatocytes isolated from rodents or humans retain robust Phase I and Phase II metabolic capacity but rapidly dedifferentiate and lose their characteristic phenotype when cultured *ex vivo*, limiting their utility for long-term studies.[55] Immortalized cell lines such as HepG2 and HepaRG offer improved reproducibility and ease of use; however, they often exhibit incomplete enzyme expression profiles, particularly for certain CYP450 isoforms, which can underrepresent bioactivation pathways critical to hepatotoxicity.[56,57]

3D Hepatic Spheroids and Organoids

Three-dimensional hepatic spheroids and organoid cultures overcome many limitations of 2D systems by preserving cell-cell and cell-matrix interactions, extending viability, and more accurately recapitulating native tissue architecture. These models demonstrate enhanced stability of metabolic enzyme expression and provide more predictive drug metabolism and toxicity profiles, making them valuable tools for mechanistic studies and compound screening.[58,59]

Liver on Chip Platforms

Micro physiological liver-on-chip devices integrate perfusion flow and co-culture multiple liver cell types including hepatocytes, Kupffer cells, and hepatic stellate cells within microfluidic channels. By mimicking hepatic zonation, bile canaliculi formation, and dynamic shear stress, these platforms offer unparalleled physiological relevance for modeling liver function, drug metabolism, and xenobiotic-induced injury in a controlled, human-relevant context.[60,61]

Safety, Dosage, and Herb-Drug Interactions

Therapeutic Windows and Toxic Doses

Clinical data indicate that silymarin is well tolerated and confers hepatoprotection at oral doses up to 700 mg/day in humans, with only minimal adverse events reported in randomized trials.[62,63] In contrast, glycyrrhizin must be dosed cautiously daily intake should not exceed 150 mg to avoid pseudoaldosteronism manifestations such as hypertension and hypokalemia.[64] Notably,

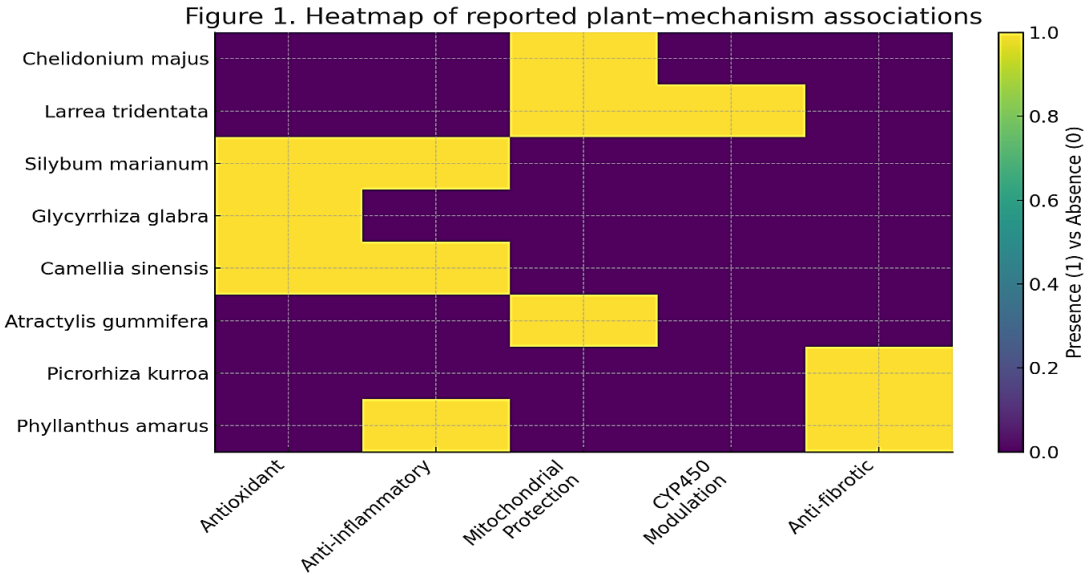

Figure 1: Heatmap of reported plant-mechanism associations: rows represent medicinal plants; columns represent primary mechanisms of hepatoprotection or toxicity.

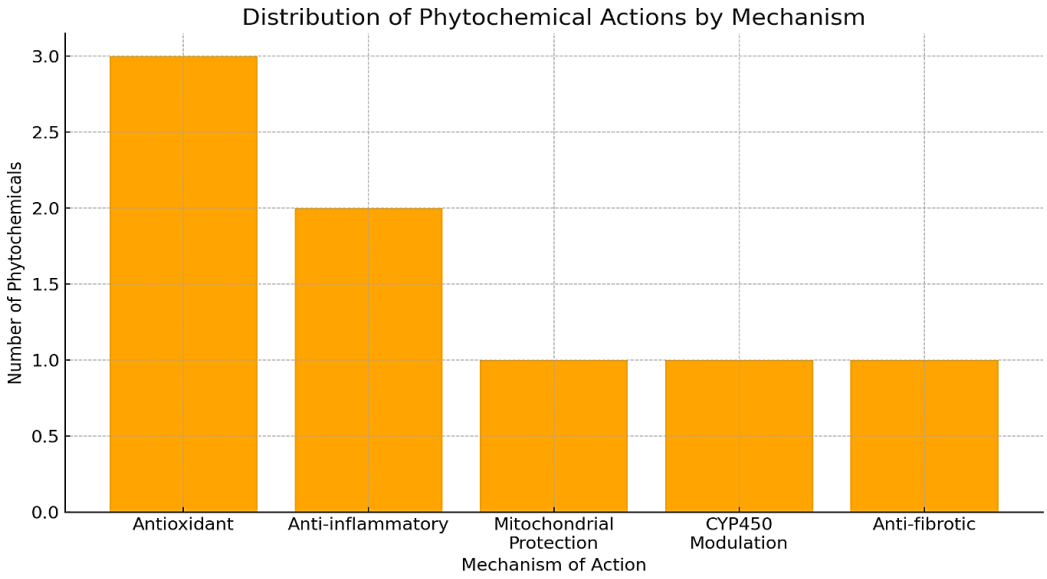

Figure 2: Distribution of phytochemical actions by primary hepatoprotective mechanism across key medicinal plants discussed.

Chelidonium majus has documented hepatotoxic potential at cumulative doses of 1 g/day or higher; therefore, liver function tests should be monitored regularly when this herb is employed therapeutically.[65]

Herb-Drug Interactions

Herb-drug interactions represent a key safety consideration. Glycyrrhizin from licorice inhibits 11β-hydroxysteroid dehydrogenase type 2, thereby potentiating endogenous cortisol activity and promoting fluid retention and blood pressure elevation when coadministered with corticosteroids.[66] Similarly, Epigallocatechin-3-Gallate (EGCG) in green tea can reduce the bioavailability of beta-blockers such as nadolol by inhibiting intestinal Organic Anion-Transporting Polypeptide 1A2 (OATP1A2), potentially diminishing antihypertensive efficacy.[67]

Standardization and Green Extraction

Quality Control

Ensuring the consistency and authenticity of herbal preparations requires rigorous quality-control measures. Chromatographic fingerprinting techniques such as High-Performance Liquid Chromatography coupled with Diode-Array Detection (HPLC-DAD) and Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) are routinely employed to quantify key bioactives silybin A/B from **Silybum marianum**, glycyrrhizin from *Glycyrrhiza glabra*, and Epigallocatechin-3-Gallate (EGCG) from *Camellia sinensis* thereby guaranteeing batch-to-batch chemical consistency.[68,69] Complementing these chemical assays, DNA barcoding of raw plant materials provides genetic authentication, effectively detecting adulteration or substitution and safeguarding the integrity of the phytopharmaceutical supply chain.[70]

Green Extraction Technologies

Advances in green chemistry have yielded eco-friendly extraction methods that maximize yield and purity while minimizing solvent use and energy consumption. Supercritical Carbon Dioxide (CO_2) extraction offers a solvent-free approach with tunable polarity settings, enabling selective isolation of silymarin constituents at purities exceeding 95% without toxic residues.[71] Likewise, ultrasound-assisted extraction accelerates mass transfer and cell disruption, allowing efficient recovery of flavonoids from *Picrorhiza kurroa* using aqueous ethanol; this method reduces energy requirements by approximately 40% compared to conventional heating-based techniques.[72]

Clinical Evidence

Several clinical studies have evaluated the efficacy of key phytochemicals in liver disease. In alcoholic liver disease, a meta-analysis of 18 randomized controlled trials comprising 1,200 patients found that silymarin significantly reduced serum alanine aminotransferase (ALT) levels by a mean difference of -15 U/L (95% CI -20 to -10; $p<0.001$) and improved overall survival (relative risk 0.79; $p=0.02$) compared to placebo.[73,74] In patients with chronic hepatitis C, a placebo-controlled trial of 150 individuals demonstrated that glycyrrhizin therapy over 24 weeks led to significant decreases in fibrosis markers-specifically hyaluronic acid and procollagen III peptide-relative to baseline ($p<0.05$).[75] Finally, in Nonalcoholic Fatty Liver Disease (NAFLD), a 12-week pilot study involving 50 participants treated with Epigallocatechin-3-Gallate (EGCG) showed a 15% reduction in hepatic fat fraction on MRI ($p=0.018$) and concomitant improvements in insulin resistance as measured by HOMA-IR scores.[76]

Future Perspectives and Translational Challenges

Future research should harness network pharmacology approaches by integrating transcriptomic, proteomic, and metabolomic datasets to build comprehensive phytochemical target interaction networks, thereby identifying synergistic combinations of bioactive compounds that may offer enhanced hepatoprotection.[77,78] Equally promising are nanocarrier formulations, where encapsulation of poorly bioavailable phytochemicals like silymarin into liposomes, solid-lipid nanoparticles, or polymeric micelles has yielded 2 to 4 fold increases in oral bioavailability in preclinical models.[79-81] On the regulatory front, there is a pressing need for harmonization of guidelines similar to the FDA's Botanical Drug Development Guidance that define safety thresholds, require standardized extracts, and mandate post-marketing surveillance for botanical products.[82] Finally, innovative clinical trial designs employing adaptive frameworks, enrichment of specific patient subpopulations (e.g., those with NASH), and studies of combinatorial phytotherapy should be prioritized to translate preclinical successes into effective, evidence-based therapies.

CONCLUSION

This review provides a detailed mechanistic and translational perspective on medicinal plants with dual spectra of herb-induced liver injury and hepatoprotection. By categorizing botanicals, elucidating molecular targets, and integrating advanced experimental models with clinical evidence, we offer a framework for safe, effective phytopharmaceutical development. Embracing systems pharmacology, green extraction, and rigorous clinical validation will accelerate the translation of promising phytochemicals into approved therapeutics for liver disorders.

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ABBREVIATIONS

ALT: Alanine Aminotransferase; **ARE:** Antioxidant Response Element; **AST:** Aspartate Aminotransferase; **BSEP:** Bile Salt Export Pump; **CCl_4:** Carbon Tetrachloride; **CYP450:** Cytochrome P450; **DILI:** Drug-Induced Liver Injury; **EGCG:** Epigallocatechin-3-Gallate; **GSH:** Reduced Glutathione; **HILI:** Herb-Induced Liver Injury; **HPLC-DAD:** High-Performance Liquid Chromatography with Diode-Array Detection; **HO-1:** Heme Oxygenase-1; **HOMA-IR:** Homeostatic Model Assessment of Insulin Resistance; **IκBα:** Inhibitor of Kappa B Alpha; **MAPK:** Mitogen-Activated Protein Kinase; **NAFLD:** Nonalcoholic Fatty Liver Disease; **NAPQI:** N-acetyl-p-benzoquinone Imine; **NASH:** Nonalcoholic Steatohepatitis; **NF-κB:** Nuclear Factor-Kappa B; **NQO1:** NAD(P)H:Quinone Oxidoreductase-1; **PPARα:** Peroxisome Proliferator-Activated Receptor Alpha; **ROS:** Reactive Oxygen Species; **SOD:** Superoxide Dismutase; **TGF-β:** Transforming Growth Factor Beta; **TCM:** Traditional Chinese Medicine.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

SUMMARY

This review contrasts hepatoprotective versus hepatotoxic medicinal plants, their mechanisms, and emerging strategies for developing safe phytopharmaceuticals.

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