Plant-Derived Hepatoprotective Agents A Comprehensive Review of Phytochemistry, Mechanisms, and Therapeutic Potential

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***Abstract*—The liver is the principal organ responsible for metabolic homeostasis, detoxification, and biosynthesis of essential molecules. Hepatic disorders - including drug-induced liver injury, viral hepatitis, alcoholic liver disease, and non-alcoholic fatty liver disease (NAFLD) - impose a severe global health burden. Despite the widespread prevalence of hepatic diseases, modern allopathic medicine offers limited comprehensive hepatoprotective options. Herbal medicine, with centuries of traditional use across diverse cultures, represents an invaluable reservoir of bioactive compounds with demonstrated hepatoprotective activity. This review comprehensively examines the role of the liver in human physiology, the pathophysiology of liver injury, the concept of hepatoprotection, and the mechanistic basis through which phytochemicals exert protective effects. Key phytoconstituents including silymarin, andrographolide, curcumin, glycyrrhizin, and phyllanthin are discussed in the context of their pharmacological action. A tabulated overview of twenty-one clinically relevant hepatoprotective plants - including Manilkara hexandra - is provided, detailing botanical nomenclature, plant family, part used, chemical constituents, experimental screening methods, and hepatoprotective mechanisms. This review aims to serve as a foundational reference for future drug discovery initiatives targeting liver disease.**

***Index Terms*—Hepatoprotection, phytochemicals, liver disease, silymarin, Manilkara hexandra, herbal medicine, oxidative stress, plant-derived agents, NAFLD.**

I. INTRODUCTION

1.1 The Liver: Anatomy, Physiology, and Functions

The liver is the largest parenchymal organ in the human body, weighing approximately 1.2-1.5 kg in the average adult, and is situated in the right upper quadrant of the abdominal cavity beneath the diaphragm. It is a complex; multifunctional organ whose roles span virtually every domain of human metabolism. Anatomically, the liver is divided into two principal lobes - right and left - further subdivided into eight functional segments according to the Couinaud classification. The hepatic lobule, the fundamental functional unit of the liver, consists of hexagonally arranged hepatocytes surrounding a central vein, with portal triads at the periphery containing branches of the portal vein, hepatic artery, and bile ductile.

Metabolically, the liver serves as the primary site of carbohydrate homeostasis through glycogenesis, glycogenolysis, and gluconeogenesis. It orchestrates lipid metabolism by synthesizing fatty acids, triglycerides, phospholipids, and cholesterol, and is responsible for the production of very-low-density lipoproteins (VLDL). Hepatocytes are the predominant site of amino acid catabolism and urea synthesis via the urea cycle. Furthermore, the liver synthesizes the majority of plasma proteins - including albumin, fibrinogen, clotting factors I, II, V, VII, IX, X, and complement proteins - rendering it indispensable for hemostasis and immune defense.

The detoxification function of the liver is its most clinically significant role. Xenobiotics - foreign chemical substances including drugs, alcohol, and environmental pollutants - undergo phase I and phase II biotransformation in the liver. Phase I reactions, primarily catalyzed by the cytochrome P450 (CYP) enzyme superfamily, introduce reactive functional groups into lipophilic molecules. Phase II conjugation reactions, including glucuronidation, sulfation, and glutathione conjugation, render metabolites sufficiently water-soluble for renal or biliary excretion. The liver produces approximately 600-1000 mL of bile daily, which facilitates digestion and

absorption of dietary fats and fat-soluble vitamins, and provides a route for elimination of bilirubin, cholesterol, and drug metabolites.

Additional hepatic functions include storage of glycogen, triglycerides, fat-soluble vitamins (A, D, E, K, B_{12}), and trace minerals such as iron and copper. Kupffer cells - the resident hepatic macrophages - constitute approximately 80-90% of the total body macrophage pool and play a central role in phagocytosis, pathogen clearance, and regulation of systemic inflammatory responses. The liver's remarkable capacity for regeneration following partial hepatectomy or injury underscores its unique biological plasticity and clinical resilience.

1.2 Liver Damage: A Serious Global Health Problem

Liver disease represents one of the most significant and rapidly growing global health challenges of the 21st century. Epidemiological data indicate that more than 800 million people worldwide are affected by chronic liver disorders, and over two million deaths annually are directly attributable to liver disease and its complications [1]. The spectrum of hepatic pathology is broad, encompassing acute and chronic conditions mediated by diverse etiological agents including viruses, alcohol, drugs, metabolic dysregulation, and autoimmune phenomena.

Viral hepatitis, caused principally by hepatitis B virus (HBV) and hepatitis C virus (HCV), affects an estimated 325 million people globally and remains the foremost infectious cause of liver-related mortality [2]. Non-alcoholic fatty liver disease (NAFLD) - encompassing a continuum from simple hepatic steatosis to non-alcoholic steatohepatitis (NASH), cirrhosis, and hepatocellular carcinoma (HCC) - has emerged as the most prevalent chronic liver condition in developed nations, with a global prevalence exceeding 25% [3]. Alcoholic liver disease (ALD) precipitates a spectrum of hepatic injury ranging from steatosis to alcoholic hepatitis and cirrhosis. Drug-induced liver injury (DILI), encompassing hepatotoxicity secondary to paracetamol, antitubercular drugs (isoniazid, rifampicin), and NSAIDs, constitutes the most common cause of acute liver failure in Western countries [4].

At the cellular level, hepatic injury is characterized by hepatocyte necrosis, apoptosis, oxidative stress, mitochondrial dysfunction, and fibrogenesis. Activation of Kupffer cells and hepatic stellate cells (HSCs) contributes to the perpetuation of hepatic inflammation and progressive deposition of extracellular matrix proteins, culminating in fibrosis and cirrhosis. Cirrhosis is associated with portal hypertension, ascites, hepatic encephalopathy, coagulopathy, and markedly elevated risk of HCC. The cumulative economic and societal burden of liver disease - encompassing hospitalization costs, liver transplantation, and loss of productivity - is enormous, underscoring the urgent need for safe and effective hepatoprotective interventions.

1.3 Herbal Medicines in Liver Protection

Traditional medicine systems across diverse cultures have long recognized the therapeutic potential of medicinal plants in managing hepatic disorders. Ayurveda prescribes formulations such as Liv.52 (containing Capparis spinosa and Cichorium intybus) for liver ailments. Traditional Chinese Medicine employs Glycyrrhiza uralensis, Schisandra chinensis, and Salvia miltiorrhiza for hepatic protection. The Unani and Greco-Arab medical traditions have extensively utilized Silybum marianum, Fumaria officinalis, and Cassia senna for liver disease management [5]. Among Indian traditional medicine, plants such as Manilkara hexandra, Picrorhiza kurroa, Boerhavia diffusa, and Tinospora cordifolia have been central to hepatoprotective formulations described in classical Ayurvedic texts.

Contemporary pharmacological research has validated the hepatoprotective activity of many traditionally used plant species through rigorous in vitro and in vivo experimental models, and through clinical trials. The global market for herbal hepatoprotective products exceeds several billion USD annually, reflecting both the unmet medical need and the growing integration of phytomedicine into mainstream healthcare [6]. The identification, isolation, and mechanistic characterization of bioactive phytoconstituents have provided molecular-level insights into hepatoprotective potential and have facilitated the development of standardized botanical preparations with defined pharmacological profiles.

II. HEPATOPROTECTION: DEFINITION, CONCEPT, AND PATHOPHYSIOLOGICAL BASIS

2.1 Definition and Concept of Hepatoprotection

Hepatoprotection, or hepatoprotective activity, refers to the capacity of a therapeutic agent - whether synthetic, biological, or natural - to prevent, attenuate, or reverse hepatocellular injury induced by chemical, biological, immunological, or metabolic stressors. The concept encompasses a broad range of protective strategies, including neutralization of reactive oxygen species (ROS), attenuation of inflammatory cascades, inhibition of hepatocyte apoptosis, prevention of fibrogenic activation of HSCs, and promotion of hepatocellular regeneration. A hepatoprotective agent does not merely mask elevated biochemical markers but should demonstrably preserve hepatocellular structural and functional integrity, promote resolution of inflammatory pathology, and retard or reverse fibrotic progression.

Hepatoprotective agents are evaluated based on their ability to normalize biochemical markers of hepatic injury - serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), and serum bilirubin - as well as functional parameters including serum albumin, prothrombin time, and histopathological architecture of the liver. These biomarkers serve as the primary endpoints in preclinical toxicological models and in clinical investigations of candidate hepatoprotective agents. The ratio of AST to ALT (De Ritis ratio) provides additional diagnostic specificity for the nature and severity of hepatic injury [7].

2.2 Mechanisms of Hepatoprotection

Hepatoprotective mechanisms operate across multiple intersecting biological pathways, and most effective agents exert their protective effects through pleiotropic actions rather than a single discrete mechanism. The following mechanistic categories represent the principal modes of hepatoprotective action established through current biomedical research:

Antioxidant and Free Radical Scavenging: Oxidative stress, resulting from an imbalance between the generation of ROS and cellular antioxidant defense capacity, is a central mediator of hepatocellular injury across diverse etiologies. ROS - including superoxide anion, hydrogen peroxide, and the hydroxyl radical - induce lipid peroxidation of hepatocyte membranes, oxidation of cellular proteins, and DNA strand breaks, culminating in mitochondrial dysfunction and cell death. Phytochemicals such as silymarin, curcumin, andrographolide, and quercetin directly scavenge ROS and enhance the activity of endogenous antioxidant enzymes including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), while upregulating glutathione (GSH) biosynthetic enzymes [8].

Nrf2/Keap1 Pathway Activation: The transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2) is the master regulator of the cellular antioxidant response. Under conditions of oxidative stress, Nrf2 dissociates from its cytoplasmic repressor Kelch-like ECH-associated protein 1 (Keap1) and translocates to the nucleus, where it activates transcription of cytoprotective genes encoding antioxidant enzymes including heme oxygenase-1 (HO-1), NAD(P)Quinone oxidoreductase-1 (NQO1), and glutamate-cysteine ligase (GCL). Curcumin, sulforaphane, andrographolide, withaferin A, and lupeol - the latter found in Manilkara hexandra - are documented Nrf2 activators, and this mechanism is increasingly recognized as a central determinant of hepatoprotection [9].

Anti-inflammatory Activity: Chronic hepatic inflammation, orchestrated by pro-inflammatory cytokines including TNF-α, IL-1β, IL-6, and the transcription factor NF-κB, drives the progression of hepatic injury, fibrosis, and carcinogenesis. Plant-derived agents inhibit inflammatory signalling through multiple mechanisms, including inhibition of NF-κB nuclear translocation, suppression of COX-2 and iNOS expression, and reduction of pro-inflammatory eicosanoid synthesis. Glycyrrhizin, curcumin, andrographolide, and wedelolactone are paradigmatic phytochemicals with potent NF-κB inhibitory activity [10].

Membrane Stabilization: Hepatocellular membrane integrity is essential for normal cellular function and prevention of enzyme leakage. Phytochemicals such as silymarin, triterpenoids (lupeol, β-amyrin from Manilkara hexandra), and flavonoids stabilize hepatocyte plasma membranes by binding membrane phospholipids, inhibiting lipid peroxidation, and competing with hepatotoxins for receptor-mediated cellular entry. This membrane-stabilizing effect directly correlates with reduced serum transaminase levels in experimental models of hepatotoxicity [11].

Inhibition of Hepatic Fibrosis: Hepatic fibrosis, resulting from pathological activation of HSCs and excessive accumulation of extracellular matrix

proteins (particularly type I collagen), is a critical step in the progression to cirrhosis. Phytochemicals inhibit fibrogenesis through suppression of TGF-β1 signalling, inhibition of HSC activation and proliferation, induction of HSC apoptosis, and promotion of ECM degradation through matrix metalloproteinases (MMPs). Curcumin, silymarin, and berberine have been extensively studied for antifibrotic properties in experimental models [12].

Stimulation of Hepatocellular Regeneration: Some phytochemicals enhance hepatocyte proliferative capacity following injury by upregulating growth factors including hepatocyte growth factor (HGF) and insulin-like growth factor-1 (IGF-1), activating STAT3 and MAPK/ERK signalling pathways, and promoting expression of anti-apoptotic proteins Bcl-2 and Bcl-xL. Silymarin, Picrorhiza kurroa, and Eclipta alba have been documented to stimulate hepatocyte regeneration in partial hepatectomy models [13].

Antiviral Mechanisms: Plant-derived agents including glycyrrhizin, phyllanthin, and polyphenols exert direct antiviral activity against HBV and HCV through inhibition of viral replication, interference with viral entry, and immunomodulatory effects that enhance antiviral immune responses. Glycyrrhizin interferes with HBsAg secretion and viral DNA polymerase activity, while Phyllanthus niruri extracts have demonstrated inhibition of HBsAg and HBeAg in clinical studies [14].

III. WHY PLANT-DERIVED AGENTS ARE USED FOR HEPATOPROTECTION

3.1 Limitations of Conventional Therapy

Despite significant advances in understanding liver disease pathophysiology, the therapeutic arsenal in conventional medicine for hepatoprotection remains limited. For viral hepatitis, nucleoside analogues (entecavir, tenofovir) and interferon-based regimens represent standard of care for HBV, while direct-acting antivirals (DAAs) have achieved HCV cure rates exceeding 95%. However, these agents are expensive, inaccessible in low-income settings, and associated with adverse effects including bone marrow suppression, psychiatric disturbances, and nephrotoxicity. For NAFLD/NASH, no pharmacological therapy has achieved regulatory approval, and management remains primarily lifestyle-based. For DILI, hepatotoxin withdrawal and supportive care remain the cornerstone of management, with N-acetylcysteine (NAC) as the sole established antidote for paracetamol overdose. This unmet therapeutic need underscores the imperative to develop novel hepatoprotective agents, and phytochemicals represent a biologically rich and clinically promising source [15].

3.2 Advantages of Phytotherapy in Hepatic Disease

Plant-derived agents offer several compelling advantages in the management of hepatic disorders. Their structural and chemical diversity - encompassing flavonoids, alkaloids, terpenoids, lignans, saponins, and polyphenols - provides a vast pharmacological repertoire with the potential to target multiple pathways simultaneously. This polypharmacological character may confer therapeutic advantages over single-target synthetic drugs, particularly in complex, multifactorial conditions such as NAFLD and cirrhosis.

The long history of traditional use of many hepatoprotective plants provides an empirical safety basis, and clinical experience accumulated over centuries in systems such as Ayurveda, TCM, and Unani medicine offers preliminary validation of their efficacy and tolerability. Plant-derived compounds are often bioavailable in their natural matrix, and synergistic interactions between multiple phytoconstituents within a crude extract may enhance efficacy compared to isolated single compounds. Affordability and accessibility of medicinal plants are of particular importance in resource-limited settings where liver disease burden is highest and access to conventional antiviral therapy is constrained [16].

Specific phytochemicals also demonstrate advantages in safety profiles compared to many synthetic drugs. For instance, silymarin exhibits an excellent tolerability record across decades of clinical use, with adverse effects being rare and generally mild. Similarly, Manilkara hexandra bark extracts, which contain triterpenoids and flavonoids, have demonstrated safety in experimental models alongside significant hepatoprotective activity. However, herbal medicines are not universally safe; certain plants including pyrrolizidine alkaloid-containing species have been associated with hepatotoxicity, and standardization of botanical preparations remains a critical challenge. The development of well-characterized phytomedicinal products with

rigorously established safety and efficacy profiles represents the critical path forward [17].

IV. OVERVIEW OF PLANT-DERIVED HEPATOPROTECTIVE AGENTS

4.1 Flavonoids and Polyphenols

Flavonoids constitute one of the most extensively characterized classes of phytochemicals with hepatoprotective activity. Silymarin, a standardized extract derived from the seeds of Silybum marianum (milk thistle), remains the most clinically validated herbal hepatoprotective agent. Its principal bioactive component, silybin (silibinin), exerts hepatoprotective effects through direct free radical scavenging, inhibition of lipid peroxidation, stabilization of hepatocyte membrane phospholipids, stimulation of ribosomal RNA synthesis, and inhibition of leukotriene synthesis. Clinical trials have demonstrated significant reductions in serum transaminase levels and improvements in histological parameters in patients with alcoholic liver disease, viral hepatitis, and toxic hepatopathy treated with standardized silymarin preparations [18].

Curcumin, the principal curcuminoid of Curcuma longa, is among the most extensively studied natural compounds in biomedical research. Its hepatoprotective activity encompasses antioxidant, anti-inflammatory, antifibrotic, and anticancer properties. Curcumin potently inhibits NF-κB activation, suppresses TGF-β1-induced HSC activation, and activates Nrf2-mediated antioxidant pathways. Despite remarkable in vitro and in vivo efficacy, clinical translation has been challenged by poor aqueous solubility, rapid metabolism, and low oral bioavailability. Novel delivery strategies including nanoparticulate formulations and phospholipid complexes have been developed to overcome these limitations [19].

Quercetin, kaempferol, and rutin - flavonols present in Moringa oleifera, Capparis spinosa, Berberis aristata, and Manilkara hexandra - have demonstrated significant hepatoprotective activity in CCl_4- and paracetamol-induced models, primarily through antioxidant mechanisms, inhibition of CYP2E1 activation, and anti-apoptotic effects. Wedelolactone from Eclipta alba exerts hepatoprotective effects by inhibiting the hepatic proteasome, reducing NF-κB activation, and stimulating protein synthesis in hepatocytes [20].

4.2 Alkaloids

Several hepatoprotective plants elaborate alkaloids as their principal bioactive constituents. Berberine, an isoquinoline alkaloid found in Berberis aristata and Tinospora cordifolia, has attracted considerable attention for its hepatoprotective, hypolipidemic, and insulin-sensitizing properties. Berberine activates AMP-activated protein kinase (AMPK) - a cellular energy sensor that inhibits lipogenic transcription factors (SREBP-1c, ChREBP) and reduces hepatic triglyceride accumulation - making it particularly relevant in the context of NAFLD and NASH [21]. Andrographolide from Andrographis paniculata inhibits NF-κB nuclear translocation, activates Nrf2/HO-1 signaling, and reduces the expression of pro-inflammatory cytokines. Alkaloids including tinosporin and cordifolide from Tinospora cordifolia exert immunomodulatory and hepatocyte regeneration-promoting activities [22].

4.3 Terpenoids and Saponins

Glycyrrhizin, the principal bioactive saponin of Glycyrrhiza glabra, is one of the most clinically established phytochemicals for hepatic disease management. Glycyrrhizin and its metabolite 18β-glycyrrhetinic acid exert hepatoprotective effects through inhibition of 11β-hydroxysteroid dehydrogenase, immunomodulation, reduction of TGF-β1 expression, and antiviral activity against HBV and HCV. Intravenous glycyrrhizin has been approved in Japan for treatment of chronic viral hepatitis, with demonstrated reduction in serum transaminases and retardation of fibrosis progression in long-term studies [23].

Triterpenoids are a major class of hepatoprotective terpenoids found in several important medicinal plants. Lupeol and β-amyrin, the principal triterpenoids of Manilkara hexandra, have demonstrated significant hepatoprotective activity in CCl_4-induced models. Lupeol exerts its protective effects through inhibition of lipid peroxidation, enhancement of hepatic GSH levels, normalization of serum liver function enzymes, and anti-inflammatory properties mediated through inhibition of NF-κB and MAPK signaling pathways. The bark of M. hexandra has been used traditionally in Indian ethnomedicine

(known as 'Khirni') for the management of hepatic disorders, and pharmacological studies have substantiated this traditional use through demonstration of significant reductions in ALT, AST, and ALP activities and preservation of hepatic histological architecture in experimental models [41,42].

Withanolides from Withania somnifera - particularly withaferin A and withanone - have been shown to protect against CCl_4- and ethanol-induced hepatic injury through antioxidant mechanisms, protection of mitochondrial membrane integrity, and anti-apoptotic effects mediated through Bcl-2 upregulation. Picroside I and picroside II (kutkoside), the principal iridoid glycosides of Picrorhiza kurroa, protect hepatocytes against multiple hepatotoxins through antioxidant mechanisms, immunomodulation, and bile secretion stimulation, with hepatoprotective potency comparable to silymarin in comparative experimental studies [24].

4.4 Lignans and Coumestans

Phyllanthin and hypophyllanthin, the principal lignans of Phyllanthus niruri, have been extensively studied for hepatoprotective and antiviral properties. These compounds inhibit HBsAg secretion and HBV DNA polymerase activity, and clinical studies have reported reductions in HBV antigenemia and improvement in liver function parameters in patients treated with Phyllanthus preparations. Phyllanthin also demonstrates potent antioxidant activity and inhibits paracetamol-induced hepatotoxicity through upregulation of GSH biosynthesis [25].

V. HEPATOPROTECTIVE PLANTS: SUMMARY TABLE

Table 1 provides a comprehensive summary of twenty-one clinically and pharmacologically relevant hepatoprotective plants. The table encompasses botanical nomenclature, plant family, plant part used, principal chemical constituents, experimental screening methods employed, key hepatoprotective mechanisms, and supporting literature references. Manilkara hexandra (Roxb.) Dubard - a member of the Sapotaceae family whose bark, leaves, and seeds have been used in Indian traditional medicine - is included based on documented triterpenoid content (lupeol, β-amyrin) and experimentally demonstrated hepatoprotective activity. This tabulation serves as a concise reference framework for researchers, clinicians, and pharmacognosists engaged in the study and development of phytomedicinal hepatoprotective agents.

Table 1: Hepatoprotective Plants - Botanical Profile, Phytochemistry, Screening Methods, and Mechanisms

Botanical Name	Family	Part used	Chemical Constituents	Screening Method	Key mechanism	Reference
Silybum marianum (L.) Gaertn.	Asteraceae	Seeds/Fruits	Silymarin (silybin, silydianin, silychristin), flavonoids	CCl_4-induced hepatotoxicity (rat); DPPH radical scavenging	Antioxidant, membrane stabilization, inhibition of lipid peroxidation, stimulation of protein synthesis	[26,27,28]
Phyllanthus niruri L.	Phyllanthaceae	Whole plant	Phyllanthin, hypophyllanthin, lignans, alkaloids, tannins	Paracetamol-induced hepatotoxicity; HBsAg inhibition assay	Antiviral (HBV), antioxidant, hepatocyte regeneration, downregulation of inflammatory cytokines	[29,30]

Curcuma longa L.	Zingiberaceae	Rhizome	Curcumin, demethoxycurcumin, bisdemethoxycurcumin, volatile oils	Thioacetamide/CCl_4-induced hepatotoxicity; NF-κB assay	Anti-inflammatory (NF-κB inhibition), antioxidant, anti-fibrotic, bile stimulation	[31,32]
Andrographis paniculata (Burm.f.) Nees	Acanthaceae	Leaves, whole plant	Andrographolide, neo andrographolide, diterpene lactones	Paracetamol- and CCl_4-induced hepatotoxicity	Antioxidant, anti-inflammatory, Nrf2/HO-1 pathway activation, hepatocyte protection	[33,34]
Glycyrrhiza glabra L.	Fabaceae	Root, rhizome	Glycyrrhizin, glycyrrhizic acid, flavonoids, saponins	CCl_4 and aflatoxin-induced hepatotoxicity; ALT/AST enzyme assay	Anti-inflammatory, antiviral, inhibition of CYP450 activation, lipid peroxidation suppression	[35,36,37]
Cichorium intybus L.	Asteraceae	Root, seeds, leaves	Chicoric acid, inulin, sesquiterpene lactones, coumarins	Paracetamol-induced hepatotoxicity; liver enzyme assays	Antioxidant, choleretic, anti-fibrotic, free radical scavenging	[38,39]
Terminalia chebula Retz.	Combretaceae	Fruits	Chebulic acid, chebulinic acid, tannins, gallic acid, ellagic acid	D-galactosamine-induced hepatotoxicity; DPPH assay	Antioxidant, free radical scavenging, hepatoprotective via enzyme normalization	[40,41]
Picrorhiza kurroa Royle ex Benth.	Plantaginaceae	Rhizome, roots	Picroside I & II (kutkoside), iridoid glycosides, apocynin	CCl_4- and paracetamol-induced liver injury; SGOT/SGPT measurement	Antioxidant, immunomodulatory, bile secretion stimulation, cell membrane stabilization	[42,43]
Boerhavia diffusa L.	Nyctaginaceae	Roots, whole plant	Punarnavine, boeravinone, flavonoids, alkaloids, steroids	CCl_4-induced hepatotoxicity; serum marker enzyme assays	Antioxidant, anti-inflammatory, diuretic activity enhancing liver function	[44,45]

Eclipta alba (L.) Hassk.	Asteraceae	Whole plant, leaves	Wedelolactone, ecliptine, alkaloids, coumestans, saponins	CCl_4 and ethanol-induced hepatotoxicity; histopathological studies	Antioxidant, anti-fibrotic, regeneration of hepatocytes, protein synthesis stimulation	[46,47]
Tinospora cordifolia (Willd.) Miers	Menispermaceae	Stem, roots	Berberine, tinosporin, cordifolide, giloin, alkaloids, glycosides	Paracetamol- and isoniazid-induced hepatotoxicity	Immunomodulatory, antioxidant, anti-inflammatory, regeneration of liver cells	[48/49]
Cassia fistula L.	Fabaceae	Pods, leaves, bark	Fistulic acid, sennosides, anthraquinones, tannins, gallic acid	Paracetamol-induced hepatotoxicity; ALT/AST assay	Antioxidant, hepatocyte protection, lipid peroxidation inhibition	[50,51]
Moringa oleifera Lam.	Moringaceae	Leaves, seeds, bark	Isothiocyanates, quercetin, kaempferol, moringin, glucosinolates	CCl_4-induced hepatotoxicity; oxidative stress markers	Antioxidant via Nrf2 activation, anti-inflammatory, prevention of oxidative damage	[52,53.54]
Capparis spinosa L.	Capparaceae	Roots, bark, fruits	Rutin, quercetin, alkaloids, glucosinolates, stachydrine	CCl_4- and thioacetamide-induced hepatotoxicity	Antioxidant, anti-fibrotic, inflammation suppression, liver enzyme normalization	[55.56]
Solanum nigrum L.	Solanaceae	Whole plant, berries	Solanine, solanidine, flavonoids, alkaloids, saponins	Paracetamol- and galactosamine-induced liver injury	Hepatocyte membrane stabilization, free radical scavenging, anti-inflammatory	[57,58]
Berberis aristata DC.	Berberidaceae	Root, stem bark	Berberine, berbamine, oxyacanthine, palmatine, tannins	CCl_4-induced hepatotoxicity; HPLC characterization	Antioxidant, anti-inflammatory, reduction of hepatic fat accumulation, bile stimulation	[59.60]
Withania somnifera (L.) Dunal	Solanaceae	Root, leaves	Withanolides, withanone,	CCl_4 and ethanol-induced hepatotoxicity	Adaptogenic, antioxidant, anti-	[61,62]

			withaferin A, alkaloids, saponins		inflammatory, mitochondrial function protection	
Azadirachta indica A. Juss.	Meliaceae	Leaves, seeds, bark	Nimbin, nimbidine, azadirachtin, quercetin, β-sitosterol	Paracetamol-induced hepatotoxicity; histopathological studies	Antioxidant, anti-inflammatory, enzyme normalization, hepatocyte membrane protection	[63,64]
Fumaria officinalis L.	Papaveraceae	Aerial parts	Fumaric acid, alkaloids (fumaritine, fumarophycine), flavonoids	CCl_4 and paracetamol-induced hepatotoxicity	Choleretic, antispasmodic, free radical scavenging, liver enzyme regulation	[65,66]
Aloe vera (L.) Burm.f.	Asphodelaceae	Leaf gel (pulp)	Aloin, barbaloin, anthraquinones, polysaccharides, acemannan	Isoniazid/rifampicin-induced hepatotoxicity	Antioxidant, cytoprotective, lipid peroxidation inhibition, liver enzyme restoration	[67,6869]

Abbreviations: CCl_4 = carbon tetrachloride; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ALP = alkaline phosphatase; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; DPPH = 2,2-diphenyl-1-picrylhydrazyl; HBsAg = hepatitis B surface antigen; NF-κB = nuclear factor-kappa B; Nrf2 = nuclear factor erythroid 2-related factor 2; HO-1 = heme oxygenase-1; HBV = hepatitis B virus; HPLC = high-performance liquid chromatography; CYP = cytochrome P450.

VI. CLINICAL EVIDENCE AND CHALLENGES IN TRANSLATIONAL HEPATOPROTECTION

While preclinical evidence for the hepatoprotective activity of numerous plant-derived agents is extensive and compelling, translation to the clinical domain presents significant challenges. Many clinical trials of herbal hepatoprotectives have been hampered by small sample sizes, lack of placebo control, absence of blinding, heterogeneous patient populations, variable endpoints, and inadequate follow-up duration, rendering their conclusions difficult to generalize.

Silymarin remains the phytomedicinal hepatoprotective agent with the most robust clinical evidence base. Randomized, placebo-controlled trials have demonstrated statistically significant reductions in serum transaminase levels and improvements in liver histology in patients with alcoholic liver disease, NAFLD, and viral hepatitis treated with standardized silymarin preparations [70]. Meta-analyses have confirmed its safety and tolerability profile, with adverse effects being rare and generally mild. However, the optimal dosage, treatment duration, and patient population for silymarin therapy require further delineation through large-scale, rigorous clinical trials.

Glycyrrhizin (SNMC) has demonstrated clinical benefit in Japanese trials involving patients with chronic HBV and HCV infection, including reduction of ALT levels, improvement of hepatic histology, and significant reduction in the incidence of hepatocellular carcinoma with long-term administration [71].

Phyllanthus species preparations have shown variable results in clinical trials for chronic HBV infection, with some studies reporting significant reductions in HBsAg levels and viral load, while others have failed to demonstrate a statistically significant effect, highlighting the importance of standardization and formulation in determining clinical outcomes.

For Manilkara hexandra, current evidence is primarily from traditional use documentation and preclinical experimental studies; rigorous clinical trials are warranted to establish its hepatoprotective efficacy and safety profile in human subjects. Key challenges in the clinical development of phytomedicinal hepatoprotectives include standardization and quality control of plant-derived materials, development of appropriate pharmacokinetic and bioavailability data for bioactive phytoconstituents, establishment of robust clinical trial designs with validated biomarker endpoints, and navigation of regulatory frameworks for botanical drug products. The FDA Botanical Guidance and EMA Guidelines on Herbal Medicinal Products provide regulatory pathways for clinical development of botanical drugs [72].

VII. SAFETY CONSIDERATIONS AND HERB-DRUG INTERACTIONS

Despite their widespread use and general perception as safe, herbal hepatoprotective agents are not without safety concerns. Paradoxically, a number of plant species traditionally used for liver disorders have been identified as causative agents of herb-induced liver injury (HILI), which shares clinical features with DILI but presents additional challenges in causality assessment and regulatory oversight [73]. Plants containing pyrrolizidine alkaloids (PAs) -including Symphytum officinale (comfrey), Tussilago farfara, and Senecio species - have been well-documented causes of hepatic sinusoidal obstruction syndrome (SOS) through formation of hepatotoxic pyrrole metabolites. Kava-kava (Piper methysticum) has been associated with severe hepatotoxicity, including fulminant hepatic failure requiring liver transplantation, leading to regulatory restrictions in several countries [74].

Herb-drug pharmacokinetic interactions are of particular clinical significance in patients with liver disease who frequently receive polypharmacy. St. John's Wort (Hypericum perforatum) is a potent inducer of CYP3A4, CYP2C9, and P-glycoprotein, significantly reducing plasma concentrations of immunosuppressants, antiretroviral agents, and warfarin. Patients with liver disease represent a particularly vulnerable population given altered hepatic drug-metabolizing enzyme activity [75]. The principles of responsible phytomedicine prescribing in hepatology include use of standardized preparations with defined phytoconstituent content, comprehensive medication reconciliation, adherence to established dosing guidelines, regular monitoring of hepatic biomarkers during prolonged herbal therapy, and prompt reporting of adverse events to relevant pharmacovigilance databases.

VIII. FUTURE PERSPECTIVES

The field of hepatoprotective phytomedicine is poised for significant advancement through the convergence of genomics, metabolomics, network pharmacology, and advanced drug delivery technologies. Network pharmacology approaches - integrating target identification, pathway enrichment analysis, and molecular docking - have facilitated the systematic elucidation of polypharmacological mechanisms of complex herbal preparations and have identified novel hepatoprotective targets for further validation [76]. These approaches are particularly valuable for multi-constituent extracts such as those derived from Manilkara hexandra, where multiple bioactive compounds act synergistically across several hepatoprotective pathways.

Nanotechnology-based drug delivery systems, including polymeric nanoparticles, liposomes, solid lipid nanoparticles, nanoemulsions, and cyclodextrin inclusion complexes, offer promising strategies to overcome the inherent limitations of phytoconstituents, particularly poor aqueous solubility (curcumin, quercetin, lupeol) and rapid first-pass metabolism (berberine, andrographolide). Nano formulation has been shown to markedly enhance oral bioavailability, tissue distribution, and therapeutic efficacy of encapsulated phytochemicals in experimental models of hepatic disease [77]. The application of gut microbiome research to hepatoprotection represents an emerging frontier, as gut dysbiosis and increased intestinal permeability contribute to endotoxin translocation and hepatic inflammatory activation, and several plant-derived

agents have been shown to modulate gut microbial composition and enhance intestinal barrier function.

IX. CONCLUSION

The liver occupies a central and indispensable position in human physiology, and hepatic disease represents a major unmet global health challenge with significant morbidity and mortality. The limitations of current pharmacological options for hepatoprotection, combined with the rich tradition of medicinal plant use in liver disease management, provide a strong rationale for the systematic investigation of plant-derived hepatoprotective agents. This review has synthesized current knowledge regarding hepatic physiology, the pathophysiological mechanisms of hepatic injury, the concept and mechanistic diversity of hepatoprotection, and the phytochemical basis of plant-derived hepatoprotective activity.

A diverse array of bioactive phytoconstituents - including silymarin, curcumin, andrographolide, glycyrrhizin, phyllanthin, berberine, wedelolactone, and the triterpenoids lupeol and β-amyrin from Manilkara hexandra - have demonstrated robust hepatoprotective activity in preclinical models, operating through complementary mechanisms including antioxidant defense, anti-inflammatory signaling, membrane stabilization, antiviral activity, inhibition of fibrogenesis, and promotion of hepatocellular regeneration. The tabulated overview presented in this review provides a comprehensive reference encompassing twenty-one of the most clinically and pharmacologically significant hepatoprotective plant species, including the Sapotaceae member Manilkara hexandra, with their phytochemical profiles, experimental screening methodologies, and mechanistic attributes.

Future progress necessitates the conduct of rigorously designed, adequately powered clinical trials with standardized botanical preparations, development of advanced formulation strategies to optimize phytoconstituent bioavailability, systematic pharmacovigilance to ensure safety, and integration of cutting-edge technologies including network pharmacology, nanotechnology, and multi-omics platforms. The convergence of traditional knowledge and modern biomedical science holds significant promise for the discovery and development of novel, safe, and effective plant-derived hepatoprotective agents for the management of the global burden of liver disease.

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