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Review Article

Herbal remedies for liver protection: Therapeutic potential and challenges

Pankaj Khuspe[1]*, Kishori Khuspe[2], Prashant Kumar Katiyar[3], Sujit Desai[4], Bhakti Sabale[5]

[1]Dept. of Pharmaceutics, Shriram Shikshan Sanstha's College of Pharmacy, Paniv, Maharashtra, India
[2]Devdikar Medical Center & Dialysis Unit, Akluj, Maharashtra, India
[3]Dept. of Pharmaceutical Chemistry, Kanpur Institute of Technology & Pharmacy, Kanpur, Uttar Pradesh, India
[4]ADT's School of Pharmacy & Research Centre, Baramati, Maharashtra, India
[5]Vidya Niketan College of Pharmacy, Lakhewadi, Maharashtra, India

Abstract

A significant worldwide health burden, liver illnesses are frequently brought on by long-term exposure to hepatotoxins, alcohol misuse, viral infections and metabolic problems. Alternative and complementary approaches are required because traditional medication for liver problems is often linked to side effects, high costs and poor efficacy. The hepatoprotective potential of herbal medications has drawn a lot of attention because of its bioactive ingredients, safety record and historical use. A broad range of medicinal plants used in traditional medicine for liver protection are methodically examined in this review. It emphasizes the hepatoprotective properties of phytochemicals like terpenoids, alkaloids, flavonoids and saponins. Critical analysis is done on the mechanisms of action, which include antioxidative activity, membrane stability, anti-inflammatory effects and improvement of liver regeneration. The pharmacological data, clinical significance and therapeutic efficacy of plants like *Phyllanthus niruri*, *Silybum marianum*, *andrographis paniculata*, *Boerhavia diffusa and Picrorhiza kurroa* have all been thoroughly evaluated. In addition, issues including pharmacokinetics, formulation development, standardization and regulatory constraints are discussed. Strong preclinical and clinical validation are necessary for the incorporation of herbal hepatoprotective medicines into contemporary treatment frameworks. In order to support evidence-based phytotherapy and promote more research on natural hepatoprotective substances, this review attempts to give a thorough grasp of herbal medications for liver protection.

Keywords: Hepatoprotective, Herbal medicine, Liver diseases, Phytochemicals, Traditional medicine.

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1. Introduction

1.1. Overview of liver diseases and global burden

The liver is a vital metabolic organ responsible for numerous essential physiological functions such as bile production, detoxification of xenobiotics, regulation of biochemical reactions, and synthesis of plasma proteins critical for homeostasis. Due to its central role in metabolism and detoxification, the liver is particularly vulnerable to various pathogenic insults. Globally, liver diseases have emerged as a major health challenge, significantly contributing to morbidity, mortality, and rising healthcare costs. According to the Global burden of disease (GBD) Study 2019, liver cirrhosis and associated conditions account for over 2 million deaths annually, with incidence rates increasing in both developed and developing countries. In the Indian context, liver disease is the tenth leading cause of death, and chronic liver disease (CLD), particularly cirrhosis, constitutes a significant proportion of deaths from non-communicable diseases. Additionally, non-alcoholic fatty liver disease (NAFLD) is estimated to affect 25–30% of the Indian population, mirroring the growing global epidemic of obesity and diabetes.[1]

1.2. Common liver diseases and their causes

Liver diseases encompass a wide spectrum of disorders, each with distinct etiologies and clinical progressions. Alcoholic liver disease (ALD) is a major consequence of chronic

*Corresponding author: Pankaj Khuspe
Email: khuspepankaj@gmail.com

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alcohol consumption and manifests as steatosis, steatohepatitis, fibrosis, and cirrhosis. Viral hepatitis, primarily caused by Hepatitis B virus (HBV) and Hepatitis C virus (HCV), affects approximately 296 million people worldwide and is a leading cause of hepatocellular carcinoma and chronic liver inflammation. Drug-induced liver injury (DILI) arises from the hepatotoxic effects of medications such as acetaminophen, methotrexate, isoniazid, and certain antibiotics. Metabolic conditions including obesity, insulin resistance, and dyslipidemia are central to the development of NAFLD, now the most prevalent liver disorder in urban populations. Autoimmune liver diseases such as autoimmune hepatitis, primary biliary cholangitis, and primary sclerosing cholangitis result from immune dysregulation and lead to chronic hepatic inflammation and fibrosis. A major challenge in the management of these diseases lies in their often asymptomatic progression, delaying diagnosis and intervention until advanced stages.[2,3]

1.3. Limitations and side effects of conventional hepatoprotective drugs

Conventional therapies for liver diseases primarily rely on synthetic drugs, including corticosteroids, immunosuppressants, antivirals, ursodeoxycholic acid, and antioxidants. While these agents can effectively manage symptoms and slow disease progression, they are associated with significant limitations. Prolonged use of these drugs may result in adverse effects such as nephrotoxicity, hematologic toxicity, gastrointestinal disturbances, and even hepatotoxicity. Interferon-based treatments for viral hepatitis, for example, are often linked to flu-like symptoms, anemia, and neuropsychiatric complications. These pharmacologic interventions are largely palliative aimed at symptom control rather than reversing liver damage or promoting hepatic regeneration. Other barriers include poor patient compliance due to side effects, high treatment costs, limited availability in low-resource settings, and the emergence of antiviral drug resistance. Polypharmacy in patients with comorbidities further increases the risk of drug-drug interactions and systemic toxicity.[4,5]

1.4. Importance of herbal alternatives

In response to the shortcomings of conventional therapies, there has been a renewed interest in herbal hepatoprotective agents due to their multi-targeted mechanisms, lower toxicity profiles, and cost-effectiveness. Rooted in traditional medicine systems such as Ayurveda, Siddha, and Traditional Chinese Medicine (TCM), these remedies have shown promise in both preclinical and clinical settings. Medicinal plants like *Phyllanthus niruri, Andrographis paniculata, Picrorhiza kurroa, Boerhavia diffusa,* and *Silybum marianum* (milk thistle) have demonstrated hepatoprotective properties through antioxidant defense, membrane stabilization, anti-inflammatory activity, and stimulation of liver regeneration. These effects are largely attributed to their bioactive constituents, including flavonoids, lignans, alkaloids, terpenoids, and phenolic compounds. Herbal formulations offer a promising complementary approach, particularly for chronic liver conditions that are unresponsive or unsuitable for conventional treatment. However, for their integration into mainstream medicine, rigorous pharmacological standardization, toxicological safety profiling, pharmacokinetic evaluation, and clinical validation are essential to ensure efficacy and safety.[6,7]

2. Phytochemistry of Hepatoprotective Herbs

A wide range of phytochemical elements give herbal medications used to treat and prevent liver problems their therapeutic potential. Through their interactions with several molecular and cellular targets involved in oxidative stress, inflammation, lipid metabolism and liver regeneration, these bioactive compounds demonstrate hepatoprotective properties. The main groups of phytochemicals that have shown notable liver-protective qualities are polyphenols, flavonoids, terpenoids, alkaloids, saponins and tannins.[8]

Among the most thoroughly studied antioxidants found in hepatoprotective plants are flavonoids. Strong free radical-scavenging properties are exhibited by compounds like quercetin and silymarin from Silybum marianum. These flavonoids reduce oxidative damage to hepatocytes by increasing the activity of endogenous antioxidant enzymes such as glutathione peroxidase (GPx), catalase (CAT) and superoxide dismutase (SOD). They enhance hepatic regeneration, stabilize hepatocyte membranes, stop lipid peroxidation and neutralize reactive oxygen species (ROS). **Table 1** lists the main phytochemical components of hepatoprotective plants along with their use.[9] Through immunomodulatory and anti-inflammatory processes, terpenoids such glycyrrhizin from *Glycyrrhiza glabra* and andrographolide from *Andrographis paniculata* demonstrate hepatoprotective effects. These substances suppress the nuclear factor-kappa B (NF-κB) signaling pathway, which lowers the expression of cytokines that promote inflammation, such as TNF-α, IL-1β and IL-6. Additionally, it has been demonstrated that glycyrrhizin modulates cytochrome P450 enzymes, promoting liver detoxification and avoiding drug-induced hepatotoxicity.[10]

Alkaloids that control hepatic metabolism, lower lipid buildup and strengthen antioxidant defense like punarnavine from *Boerhavia diffusa* help to promote hepatoprotection. These benefits, which together shield the liver from oxidative and inflammatory damage, are frequently linked to elevated production of antioxidant enzymes and prevention of lipid peroxidation. Other components, such as curcumin from *Curcuma longa* and picrosides from *Picrorhiza kurroa*, have strong antifibrotic effects by preventing the activation of hepatic stellate cells and downregulating fibrogenic cytokines like TGF-β. Curcumin alters transcription factors such as NRF2, which boosts the antioxidant response of cells and stops liver fibrosis from progressing.By lowering ROS production and preserving mitochondrial integrity,

polyphenolic chemicals and tannins, such *Terminalia chebula* improve hepatocellular defense. Also these substances aid in the regeneration and repair of damaged liver tissue.[11]

Table 1: Major phytochemical constituents in hepatoprotective herbs and their uses[9,10]

Phytochemical Constituent	Herbal Plant	Hepatoprotective Use
Silymarin	*Silybum marianum*	Antioxidant, liver cell regeneration
Phyllanthin	*Phyllanthus niruri*	Liver enzyme normalization, antiviral effect
Andrographolide	*Andrographis paniculata*	Anti-inflammatory, cytokine suppression
Punarnavine	*Boerhavia diffusa*	Antioxidant defense, detoxification
Kutkin (Picroside I & II)	*Picrorhiza kurroa*	Lipid peroxidation inhibition
Glycyrrhizin	*Glycyrrhiza glabra*	Membrane stabilization, anti-fibrotic activity
Curcumin	*Curcuma longa*	ROS scavenging, inhibition of fibrogenesis
Chebulagic acid	*Terminalia chebula*	Enhancement of antioxidant enzyme activity

Table 2: Key active constituents[10-12]

Herb	Active Compound	Structural Class
Silybum marianum	Silymarin / Silibinin	Flavonolignan
Andrographis paniculata	Andrographolide	Diterpenoid lactone
Phyllanthus niruri	Phyllanthin, Hypophyllanthin	Lignan
Boerhavia diffusa	Boeravinone B	Rotenoid (isoflavonoid)
Picrorhiza kurroa	Kutkin (Picroside I & II)	Iridoid glycosides

These phytoconstituents have a variety of multifaceted hepatoprotective mechanisms, including as antioxidant activity, anti-inflammatory actions, membrane stabilization, inhibition of fibrogenesis, enzyme modulation and liver cell regeneration stimulation. Herbal medications are a hopeful part of managing liver illness because of the synergistic effects of these phytochemicals, which not only shield the liver from harm but also aid in its functional recovery. The main Key Active Constituents are enlisted in **Table 2** and **Figure 1** gives structural representations of major hepatoprotective phytoconstituents from medicinal plants.[10-12]

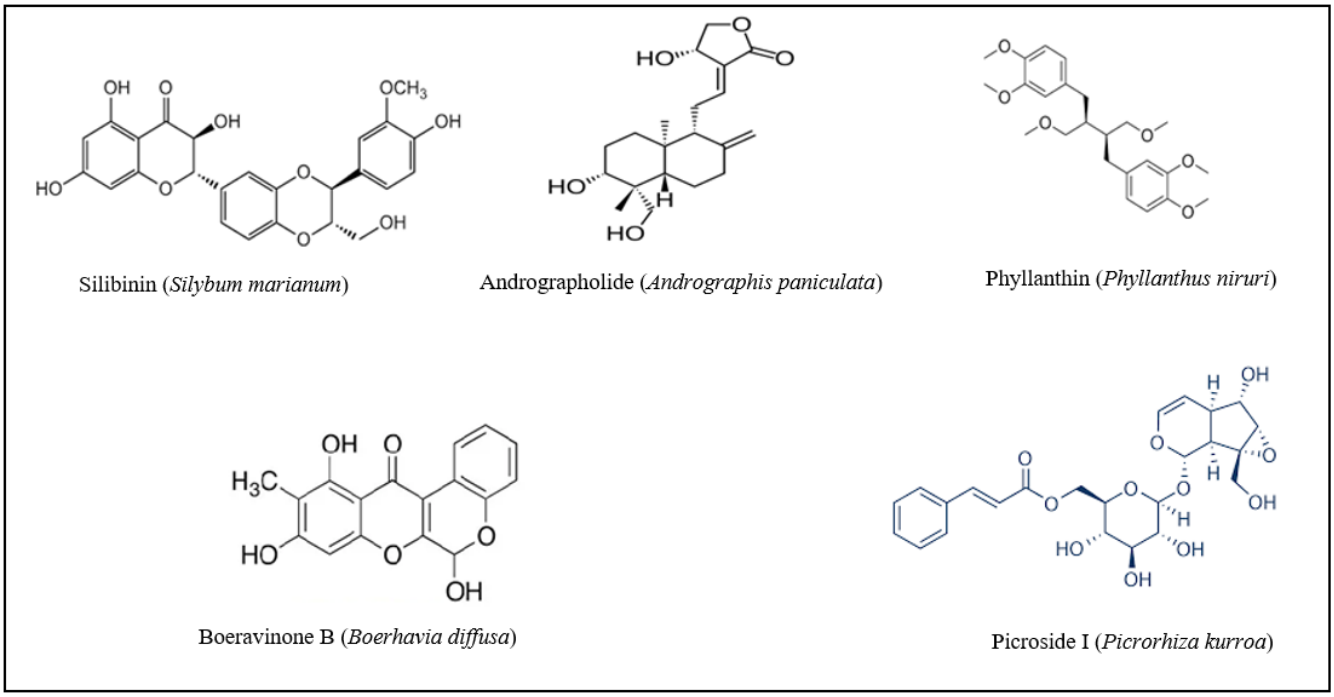

Figure 1: Structural representations of major hepatoprotective phytoconstituents from medicinal plants[10-12]

3. Key Medicinal Plants used for Liver Protection

The presence of bioactive phytochemicals that have anti-inflammatory, antioxidant, membrane-stabilizing and regenerative actions on hepatocytes is primarily responsible for the hepatoprotective effectiveness of herbal medications. Of the many medicinal plants that have been used historically to treat liver problems, the greatest research has been done on *Silybummarianum, Phyllanthusniruri, Andrographispaniculata, Boerhaviadiffusa, and Picrorhizakurroa*. Preclinical and clinical evidence support the use of these botanicals in a variety of ethnomedical systems.[13]

3.1. Silybum marianum (Milk Thistle)

One of the most studied hepatoprotective plants is milk thistle. Flavonolignans such silybin, silydianin and silychristin are part of silymarin, its active ingredient. By scavenging free radicals, inhibiting lipid peroxidation, modifying inflammatory cytokines and stimulating ribosomal RNA polymerase I, silymarin promotes hepatocyte regeneration and has hepatoprotective benefits.[14]

3.2. Phyllanthus niruri

Phyllanthus niruri also referred to as "Bhumi Amla," is a plant that contains flavonoids, tannins and lignans (phyllanthin and hypophyllanthin). Antiviral action (particularly against the hepatitis B virus), antioxidant defense and prevention of hepatic stellate cell activation are the main mechanisms by which it exerts its hepatoprotective effect. It is frequently used to treat hepatitis and jaundice in Ayurvedic medicine.[15]

3.3. Andrographis paniculata

Known as "Kalmegh," this plant contains a lot of andrographolide, a diterpenoid lactone that has strong anti-inflammatory and hepatoprotective effects. It protects hepatocytes from damage caused by toxins by suppressing pro-inflammatory mediators including TNF-α and IL-1β. Additionally, it strengthens natural antioxidant enzymes like catalase and SOD.[16]

3.4. Boerhavia diffusa

It is used in Ayurveda to treat hepatic failure and ascites and is called "Punarnava." Its diuretic and anti-inflammatory qualities are attributed to the presence of punarnavine, alkaloids and flavonoids. B. Diffusion helps the regulation of bile flow, lowers high liver enzymes and stabilizes hepatic membranes.[17]

3.5. Picrorhiza kurroa

Picroside I and II, found in *P. kurroa*, an endangered Himalayan herb, have potent immunomodulatory and hepatoprotective properties. In experimental studies, these iridoid glycosides prevent hepatotoxicity from paracetamol and CCl_4, reduce oxidative stress and suppress inflammatory mediators.[18]

3.6. Other up-and-coming prospects

A number of newly discovered medicinal plants have demonstrated encouraging hepatoprotective properties in preclinical and limited clinical research, in addition to the well-known hepatoprotective herbs. Because of their varied phytochemical profiles and modes of action, these botanicals are receiving more and more attention. Their scientific validity is still developing, despite the fact that some are traditionally recognized for liver-related diseases.[19]

3.6.1. Curcuma longa (Turmeric):

Curcumin, the main curcuminoid found in Curcuma longa, has strong anti-inflammatory, anti-fibrotic and antioxidant properties. It increases the activity of natural antioxidant enzymes including glutathione peroxidase and catalase while downregulating NF-κB, COX-2 and TNF-α. Curcumin has demonstrated promise in treating hepatic fibrosis, non-alcoholic fatty liver disease (NAFLD) and alcohol-induced liver damage.[20]

3.6.2. Glycyrrhiza glabra (Licorice)

The main triterpenoidsaponin in licorice, glycyrrhizin, has hepatoprotective properties via preventing oxidative stress, viral replication (especially HBV) and hepatocellular apoptosis. Additionally, it alters the immune system and has been a part of glycyrrhizin injections for the treatment of chronic hepatitis in Japan.[21]

3.6.3. Tinospora cordifolia (Guduchi)

This plant includes polysaccharides, diterpenoid lactones and alkaloids (magnoflorine, berberine) that have hepatoprotective, detoxifying and immunomodulatory properties. In animal models, it lessens liver damage brought on by paracetamol and CCl_4 and improves hepatic antioxidant defense.[22]

3.6.4. Terminalia chebula(Haritaki):

Packed with chebulinic and ellagic acids, T. Chebula exhibits hepatocellular membrane stability, anti-lipid peroxidation and free radical scavenging. In experimental studies, it has been shown to reduce hepatotoxicity brought on by toxins.[23]

3.6.5. Solanum nigrum (Black Nightshade):

It contains solasodine, flavonoids andglycoalkaloids and has been used traditionally to treat liver enlargement and jaundice. According to studies, there is a notable decrease in ALT and AST levels, improved liver histoarchitecture and defense against chemically induced liver damage.[24]

3.6.6. Eclipta alba (Bhringraj)

It contains ecliptine and wedelolactone, which have shown strong hepatoprotective benefits through anti-inflammatory

and antioxidant pathways. In Ayurveda, it is usually suggested for the health of the liver and hair. These up-and-coming prospects present encouraging paths for hepatoprotective treatments in the future. To convert traditional use into evidence-based modern medicine, however, thorough clinical studies, pharmacokinetic profiling and formulation standardization are essential.[25]

4. Preclinical and Clinical Evidence

Numerous preclinical and clinical studies have assessed the therapeutic potential of herbal medications for liver protection. Preclinical research, such as in vitro and in vivo models, offers mechanistic understanding and serves as the basis for the justification of further clinical trials. Clinical studies, meantime, confirm these herbal compositions' safety and effectiveness in treating liver diseases in human populations.[26]

4.1. In vitro and in vivo hepatoprotective studies

Clarifying the cellular and molecular mechanisms of action of herbal extracts requires in vitro research using primary liver cells and hepatocyte cell lines like HepG2. In these models, oxidative stress caused by hydrogen peroxide (H_2O_2), acetaminophen, carbon tetrachloride (CCl_4), or ethanol frequently results in liver damage. The ability of herbal extracts to lessen intracellular reactive oxygen species (ROS), decrease cytotoxicity and restore mitochondrial membrane integrity is evaluated. For example, by increasing glutathione peroxidase and catalase activity, *Silybum marianum* extract showed concentration-dependent cytoprotection in HepG2 cells against t-BHP-induced oxidative stress. In a similar manner, *Phyllanthus niruri* extract restored the mitochondrial membrane potential and prevented lipid peroxidation in hepatocytes exposed to ethanol. The pathophysiological circumstances of liver injury are simulated in in vivo animal models, especially in rodent systems. Hepatotoxins such as CCl_4, thioacetamide (TAA), or paracetamol are frequently used in these models to cause either acute or long-term liver injury. As demonstrated by normalized serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and better liver histology, *Picrorhiza kurroa* has reversed the hepatotoxicity caused by CCl_4 in Wistar rats. In models of TAA-induced hepatic damage, extract from *Andrographis paniculata* dramatically decreased pro-inflammatory cytokines (TNF-α, IL-6). Together, these investigations demonstrate that herbal extracts have hepatoprotective benefits through a variety of mechanisms, including anti-inflammatory action, hepatocyte membrane stabilization, liver regeneration stimulation and free radical scavenging.[27,28]

4.2 Clinical trials and outcomes

Validating the hepatoprotective efficacy of herbal medicines necessitates the transition from promising preclinical outcomes to well-structured human trials. Although limited, a growing body of randomized controlled trials (RCTs) has begun to evaluate the safety and efficacy of herbal agents in various liver disorders, including alcoholic liver disease, viral hepatitis, drug-induced liver injury (DILI), and non-alcoholic fatty liver disease (NAFLD). Among the most extensively studied herbal compounds is silymarin, derived from Silybum marianum. Multiple RCTs have demonstrated its ability to reduce serum liver enzymes such as ALT, AST, and gamma-glutamyl transpeptidase (GGT) in chronic liver disease patients. In a well-powered, double-blind, placebo-controlled trial involving 170 hepatitis C patients, oral silymarin therapy led to significant improvements in liver enzyme profiles and quality of life indices.[29] In another open-label clinical study, patients with chronic hepatitis B were administered Phyllanthus niruri extract. Results indicated antiviral and hepatoregenerative benefits, including a reduction in HBV DNA load and normalization of ALT levels.[27,28]

Andrographis paniculata, a bitter herb traditionally used for hepatic ailments, was tested in a 12-week randomized, placebo-controlled trial in NAFLD patients. The trial reported statistically significant improvements in hepatic enzyme levels and histological architecture, suggesting a possible role in halting disease progression. Similarly, small-scale, controlled cohort studies have suggested that Picrorhiza kurroa and Boerhavia diffusa, often used in polyherbal formulations, can improve hepatic biomarkers and reduce clinical symptoms in patients with hepatic dysfunction. Emerging evidence also points to Glycyrrhizin, derived from Glycyrrhiza glabra, as a potential hepatoprotective agent. A multicenter Japanese study demonstrated that long-term intravenous administration of glycyrrhizin significantly reduced ALT levels and delayed fibrosis progression in chronic hepatitis C patients. Curcumin, the active component of Curcuma longa, has also shown hepatoprotective effects in patients with NAFLD in multiple small trials, improving liver enzymes and reducing hepatic fat accumulation when compared to placebo. However, these encouraging results are constrained by several limitations. These include inconsistencies in herbal preparation standardization, variation in dosage forms, poor oral bioavailability, and lack of long-term safety evaluations. Moreover, the absence of harmonized pharmacokinetic and pharmacodynamic parameters hampers the extrapolation of findings across different populations.[29,30]

To strengthen the evidence base, there is an urgent need for multicenter, double-blind, placebo-controlled trials with large sample sizes, standardized herbal extracts, and long-term follow-ups. Additionally, integration of pharmacovigilance frameworks, bioavailability enhancement techniques (e.g., liposomal or nanoparticle carriers), and genomics-based stratification of patients may improve the efficacy and reliability of herbal interventions. While clinical studies have begun to substantiate the traditional claims surrounding hepatoprotective herbs, robust validation through rigorous and reproducible clinical trials is

imperative. The convergence of pharmacognosy, modern clinical pharmacology, and regulatory science will pave the way for evidence-based phytotherapeutics in mainstream hepatology.[31]

5. Formulation and Delivery Challenges

Even though herbal medications are becoming acknowledged as potent hepatoprotective agents, significant problems with formulation, quality control, pharmacokinetics and drug delivery technologies nevertheless make it difficult to incorporate them into contemporary therapeutic frameworks. In order for herbal hepato-protectives to be effective substitutes or supplements to synthetic medications, scientific focus needs to be placed on enhancing their safety, effectiveness and repeatability through creative pharmaceutical techniques.[32]

5.1. Standardization and quality control

One of the biggest obstacles in the creation of herbal medicines is standardization. The consistency and bioactivity of herbal products are greatly impacted by variations in phytochemical content brought on by geographic location, harvesting season, growing techniques and extraction processes. Herbal medications, in contrast to manufactured treatments, frequently contain intricate blends of several bioactive substances, which makes it challenging to establish exact pharmacopoeial requirements. For example, silybin is the primary active ingredient of silymarin, a mixture of flavonolignans found in *Silybum marianum*. For therapeutic consistency, silybin content must be consistent from batch to batch. For both quantitative and qualitative profiles, quality control procedures must use contemporary analytical methods as FTIR spectroscopy, LC-MS/MS, HPLC, HPTLC and NMR. To guarantee safety, it is also essential to assess pollutants including aflatoxins, pesticide residues, microbial load and heavy metals.[33]

5.2. Herbal drug interactions

Allopathic pharmaceuticals and herbal remedies are frequently taken together, particularly for long-term illnesses such liver disorders. Herb–drug interactions, on the other hand, might have antagonistic or synergistic effects, changing pharmacokinetics or pharmacodynamics, impacting therapeutic results, or causing toxicity. For example, cytochrome P450 enzymes (CYP3A4, CYP2C9) are inhibited by glycyrrhizin from *Glycyrrhiza glabra*, which may disrupt the metabolism of a number of traditional medications. Silymarin can affect the plasma levels of drugs taken together and prevent P-glycoprotein-mediated efflux. Additionally, herbal formulations may influence drug transporters and liver detoxification enzymes, or they may compete for plasma protein binding. To anticipate and track potential dangers related to co-administration, these interactions require thorough in vitro, in vivo and clinical research.[34,35]

5.3. Novel drug delivery systems (e.g., Nanoformulations)

Phytochemistry, pharmacology, nanotechnology and regulatory science must all be used in a multidisciplinary manner to formulate and administer herbal hepatoprotective medicines. While knowledge of herb-drug interactions is essential for patient safety, standardization guarantees consistent efficacy. Lastly, the bioavailability and therapeutic usefulness of these traditional herbal treatments could be completely transformed by the use of cutting-edge drug delivery methods. The limited oral bioavailability of herbal hepatoprotective medicines is one of the major obstacles to their therapeutic use. Poor water solubility, chemical instability in the gastrointestinal environment and substantial first-pass hepatic metabolism are the main causes of this. Several innovative drug delivery systems (NDDS) have been developed to improve the solubility, absorption and targeted hepatic distribution of bioactive herbal components in order to overcome these pharmacokinetic limitations. Nanoparticles have demonstrated tremendous potential among these; for example, encapsulating drugs like curcumin or silybin into lipid-based or polymeric nanoparticles greatly enhances liver-specific targeting and systemic availability the overview of novel drug delivery systems for herbal hepatoprotective agents are given in **Table 3**.[36,37]

In animal models, silymarin-loaded solid lipid nanoparticles (SLNs) have shown improved hepatoprotective effectiveness at lower therapeutic dosages. Phytosomes are molecular complexes of phospholipids and phytoconstituents that enhance membrane absorption and permeability. Interestingly, studies have shown that silybin-phosphatidylcholine phytosomes have significantly higher bioavailability than traditional silymarin formulations. As vesicular carriers, liposomes and niosomes also provide regulated release profiles, shield herbal active ingredients from enzymatic breakdown and provide targeted hepatic administration. Furthermore, hydrophobic herbal molecules are better soluble and absorbed by micelles and nanoemulsions, which act as effective colloidal carriers and increase the therapeutic efficiency of these compounds. The clinical translation of NDDS is still limited despite promising preclinical evaluation results because of issues with formulation stability, scalability, production costs and regulatory restrictions. Still, there is a lot of hope for closing the gap between bench research and clinical application in hepatoprotective medicine thanks to continuous developments in green nanotechnology, biocompatible excipients and precision liver-targeting techniques.[38]

Table 3: Overview of novel drug delivery systems (NDDS) for herbal hepatoprotective agents[31-37]

NDDS Type	Mechanism/Function	Herbal Examples	Advantages	Limitations
Nanoparticles	Encapsulation of actives in polymeric or lipid matrices	Curcumin, Silybin, Glycyrrhizin	Enhanced liver targeting, improved solubility, lower dose	Expensive, regulatory complexities
Phytosomes	Complexation of phytoconstituents with phospholipids	Silybin, Quercetin	Improved membrane permeability and oral absorption	Limited stability in high moisture environments
Liposomes	Phospholipid vesicles for encapsulating water-/lipid-soluble drugs	Silymarin, Berberine	Controlled release, protection from degradation	Physical instability, short shelf-life
Niosomes	Non-ionic surfactant-based vesicles	Andrographolide, Phyllanthin	Biocompatibility, stable than liposomes	Scale-up issues, entrapment efficiency varies
Micelles	Amphiphilic carriers that solubilize hydrophobic drugs	Curcumin, Oleanolic acid	High solubilizing capacity, enhanced GI absorption	Sensitive to dilution and pH changes
Nanoemulsions	Thermodynamically stable emulsions	Neem oil, Silibinin	High drug loading, rapid absorption	Limited long-term stability, high surfactant requirements

6. Safety, Toxicology and Regulatory Aspects

6.1. Adverse effects and contraindications

Because of their natural origin and historical application, herbal hepatoprotective medicines are frequently thought to be harmless. However, there is mounting evidence that their careless or uncontrolled usage may have negative consequences. Safety may be jeopardized by the intricacy of phytochemical ingredients as well as the potential for contamination, adulteration and formulation variations. Despite their potential for medicinal use, a number of herbal medications have demonstrated hepatotoxicity when taken incorrectly. For instance, although *Silybum marianum*, often known as silymarin, is usually well accepted, some people may get headaches, skin rashes, or gastrointestinal distress.[5] In a similar vein, consuming too much *Glycyrrhiza glabra* (licorice) has been associated with pseudoaldosteronism, a disorder marked by hypokalemia, hypertension and sodium retention, which makes it inappropriate for patients with renal or cardiovascular diseases. Furthermore, interactions between herbal medications and prescription medications can drastically change how drugs are metabolized, frequently by inhibiting the cytochrome P450 enzyme or by modulating P-glycoprotein. These interactions can sometimes result in toxicity and can either increase or decrease the therapeutic impact of medications taken together. Thus, thorough preclinical toxicological evaluations are necessary before human usage, including genotoxicity and mutagenicity assessments, as well as acute, subchronic and chronic toxicity studies. Moreover, post-marketing surveillance and pharmacovigilance are essential elements in tracking long-term safety in practical situations.[6,31]

6.2. Regulatory frameworks for herbal drugs

Herbal medications occupy a complicated and diverse regulatory environment across international countries. The Ayurvedic Pharmacopoeia of India and GMP certification procedures serve as quality standards for herbal formulations in India, which are governed by the Drugs and Cosmetics Act (1940) and administered by the Ministry of AYUSH. Scientific validation is required for proprietary Ayurvedic medications to guarantee that therapeutic claims are supported. In the United States, on the other hand, herbal products are classified as dietary supplements under the Dietary Supplement Health and Education Act (DSHEA, 1994), which holds manufacturers accountable for safety and honest labelling but does not require premarket approval. Under the direction of the Committee on Herbal Medicinal Products (HMPC), the European Medicines Agency (EMA) adopts a more methodical approach by classifying herbal medicines under traditional use registration, well-established usage, or full marketing authorization. China emphasizes the value of traditional prescriptions and regulatory control in its strict pharmacovigilance procedures for Traditional Chinese Medicine (TCM). In the meanwhile, the World Health Organization (WHO) has released international guidelines for member states to implement risk-based, scientifically proven regulatory frameworks for the integration of complementary and alternative medicine into their national healthcare systems. Inadequate clinical trial data, inconsistent worldwide regulation, inconsistent monographs and a lack of standardized quality standards continue to be major drawbacks in spite of these methods. Furthermore, customers are at serious risk for harm from problems including mislabeling, undetected synthetic adulterants and pesticide or heavy metal contamination. International collaboration,

uniform regulatory procedures, clinical validation funding and public education are all necessary to meet these obstacles. The safe integration of herbal hepatoprotective medicines into evidence-based clinical practice can only be achieved under a strict, open and standardized regulatory framework.[39]

7. Future Directions and Research Gaps

The need for new, safe and efficient treatment approaches is highlighted by the rising prevalence of liver illnesses worldwide, which include hepatitis, non-alcoholic fatty liver disease (NAFLD) and drug-induced liver injury. Because of their extensive pharmacological profiles and long history of use, herbal hepatoprotective medicines have become attractive options in the field of hepatology. To maximize their utilization and reach their full therapeutic potential, however, important research and clinical translation gaps need to be filled.[40]

7.1. Need for integrative medicine approach

The creation of an integrated medicine strategy, which combines the advantages of contemporary biomedical science with traditional herbal knowledge, is one of the most intriguing avenues for future research. At the moment, treatment paradigms are fragmented due to the contrast between indigenous herbal systems and standard Western medicine. Especially in chronic and complex liver disorders, bridging this gap with well-structured integrative protocols may improve treatment outcomes. For instance, standardized herbal extracts like silymarin or *Andrographis paniculata* may have additive or enhanced hepatoprotective benefits when used in conjunction with traditional hepatoprotective drugs like N-acetylcysteine or ursodeoxycholic acid. To avoid negative interactions and guarantee safety, such combinations necessitate thorough pharmacodynamic and pharmacokinetic research. Personalized liver care would also be made easier with an integrated approach, allowing patients to take advantage of both the long-term disease-modifying effects of botanicals and the quick action of allopathic medications.[41]

7.2. Recommendations for future studies

Future research should concentrate on a few crucial areas in order to solidify the scientific basis of herbal hepatoprotective drugs. First, to identify the precise cellular pathways that plant-derived chemicals affect, mechanistic studies employing molecular biology, metabolomics and transcriptomics are crucial. Although many herbal ingredients work through anti-inflammatory, anti-fibrotic and antioxidant processes, it is still unclear which specific hepatocytes, Kupffer cells and hepatic stellate cells they target. Second, to guarantee reproducibility and comparability across investigations, consistent preclinical models of liver injury should be used. To evaluate the entire therapeutic range of herbal medicines, animal models that mimic human-relevant liver diseases such alcoholic liver disease, viral hepatitis and nonalcoholic fatty liver disease are required. Thirdly, to confirm efficacy and safety, carefully planned, multicentric clinical trials with sufficient sample sizes, placebo controls and long-term follow-up are essential. Pharmacokinetic profiling, biomarker-based outcome evaluation and patient demographic and illness severity-based categorization ought to be incorporated into these trials. Crucially, clinical research must come after phytochemical fingerprinting, extraction process harmonization and dose standardization.[42]

Establishing safe therapeutic windows requires toxicological research, including examinations of reproductive, developmental and chronic toxicity. Institutionalizing herbal pharmacovigilance systems is necessary to gather actual data on adverse occurrences and interactions between drugs and herbs. Finally, to improve bioavailability, anticipate herb-drug interactions and speed up compound screening, new technologies like nanotechnology, bioinformatics and artificial intelligence should be used. Future precision hepatoprotective treatment may be made possible by the incorporation of herbal data into digital health frameworks. Although herbal medications have a wealth of hepatoprotective potential, strong scientific confirmation and an integrative therapy approach are necessary for clinical relevance. Future liver disease therapy paradigms will safely and effectively use herbal hepatoprotective drugs if traditional knowledge and modern pharmacological science are bridged. This will be backed by excellent research, standardized procedures and regulatory alignment.[43-45]

8. Discussion

The use of herbal drugs for liver protection has gained substantial scientific interest in recent decades due to the rising prevalence of hepatic disorders and the limitations associated with synthetic hepatoprotective agents. Liver diseases, both acute and chronic, are often the consequence of oxidative stress, inflammation, viral infections, or drug-induced toxicity. Herbal medicines, particularly those derived from *Silybum marianum*, *Phyllanthus niruri*, *Andrographis paniculata*, *Boerhavia diffusa*, and *Picrorhiza kurroa*, offer a multifaceted therapeutic approach that includes antioxidant, anti-inflammatory, antiviral, and regenerative activities. These effects are attributed to diverse phytochemicals such as flavonoids, alkaloids, lignans, and terpenoids, which modulate cellular signaling pathways, stabilize hepatocyte membranes, and enhance detoxification enzymes. Preclinical studies have provided substantial evidence for the efficacy of these herbal extracts in vitro and in vivo, demonstrating significant protection against hepatotoxins like carbon tetrachloride, paracetamol, and alcohol. Clinical investigations, although fewer, have shown promising outcomes in liver enzyme normalization, histological improvement, and viral load reduction in hepatitis. However, challenges persist, particularly

concerning standardization, quality control, and batch-to-batch reproducibility of herbal formulations. Variability in phyto-constituent content due to geographic and environmental factors makes quality assurance a critical issue. Moreover, herb–drug interactions, especially through modulation of cytochrome P450 enzymes, highlight the need for cautious use in polypharmacy settings.[6,46]

Another limitation lies in the poor oral bioavailability of many herbal constituents, which compromises their clinical efficacy. This has led to the exploration of novel drug delivery systems such as nanoparticles, phytosomes, liposomes, and nanoemulsions, which enhance absorption, stability, and liver-targeted delivery. Despite significant progress in preclinical nanotechnology applications, regulatory, cost, and scalability issues hinder their widespread clinical translation. Although generally perceived as safe, some herbal agents may exhibit adverse effects or contraindications, especially when used without guidance. The lack of harmonized global regulatory frameworks further complicates the approval and integration of these botanicals into mainstream medical practice. Looking forward, there is a pressing need for an integrative medicine approach that combines the benefits of traditional herbal knowledge with evidence-based clinical strategies. Future research should focus on mechanism-based studies, well-powered randomized controlled trials, advanced toxicological profiling, and harmonized regulatory policies. Overall, herbal hepatoprotective agents offer a promising yet underutilized avenue in liver disease management, contingent upon rigorous scientific validation and thoughtful integration into clinical practice.[47,48]

9. Conclusion

The liver is extremely vulnerable to harm from xenobiotics, infections and chronic metabolic diseases since it is essential for metabolic regulation, detoxification and homeostasis. Herbal medications have drawn a lot of interest as possible hepatoprotective medicines in recent decades because of their diverse mechanisms, which include modulation of hepatic enzymes, improvement of liver regeneration and antioxidative and anti-inflammatory effects. Important botanicals that have shown significant preclinical and clinical benefit in reducing liver injury across a variety of paradigms include *Silybum marianum*, *Phyllanthus niruri*, *andrographi spaniculata*, *Boerhavia diffusa* and *Picrorhiza kurroa*. The therapeutic potential and drawbacks of herbal hepatoprotectives are both highlighted in this review. Despite the fact that numerous substances derived from plants have demonstrated protective properties both in vitro and in vivo, issues with standardization, bioavailability and clinical validation still exist. To improve pharmacokinetic performance, new delivery methods such phytosomes and nanoformulations are being developed. However, thorough toxicological evaluations and standardized international norms are required to address concerns about safety, herb-drug interactions and regulatory discrepancies. In the context of liver health care, herbal hepatoprotective drugs are a useful supplement or substitute, especially in integrative medicine settings. Future research should focus on mechanistic studies, extensive clinical trials, toxicovigilance systems and policy reforms in order to fully realize their potential as a mainstream treatment. To move these natural therapies from tradition to evidence-based hepatology, a multidisciplinary strategy combining pharmacognosy, toxicology, clinical pharmacology and regulatory sciences would be essential.

10. Source of Funding

None.

11. Conflict of Interest

None.

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