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# Herbal Drugs Used in the Management of Hepatic Disorders: A Comprehensive Review

Neha Ramakant Tare[1]*, Nishita Rakesh Yadav[2], Dr. Swati Jogdhand[3], Dr. Swati Deshmukh[4]

[1,2,3,4,] *Department of Pharmacology, Siddhant College of Pharmacy, Maval, Pune- 412109*
**Corresponding Author*

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**ABSTRACT**: Hepatic disorders, including drug-induced liver injury (DILI), alcoholic liver disease (ALD), non-alcoholic fatty liver disease (NAFLD), viral hepatitis, and liver fibrosis/cirrhosis, remain major causes of morbidity and mortality worldwide. Although conventional therapeutic approaches have improved disease management, their long-term use is often limited by adverse effects, variable efficacy, and economic burden. Consequently, medicinal plants and their bioactive constituents have gained considerable attention as potential hepatoprotective agents owing to their diverse pharmacological activities and multi-target mechanisms of action.

This review provides a comprehensive overview of the pathophysiological processes underlying liver diseases and critically examines the therapeutic potential of herbal medicines in hepatic protection. Current evidence from experimental and clinical studies demonstrates that medicinal plants such as *Silybum marianum*, *Curcuma longa*, *Phyllanthus niruri*, *Glycyrrhiza glabra*, *Andrographis paniculata*, *Picrorhiza kurroa*, *Boerhavia diffusa*, *Eclipta alba*, *Aloe vera*, and *Tinospora cordifolia* exert significant hepatoprotective effects through multiple complementary pathways. These include enhancement of antioxidant defenses via Nrf2/HO-1 activation, suppression of inflammatory mediators through NF-κB and NLRP3 inflammasome inhibition, attenuation of fibrosis by modulation of TGF-β/Smad signaling, regulation of apoptosis through PI3K/Akt pathways, normalization of cytochrome P450 activity, and restoration of gut–liver axis homeostasis.

Particular attention is given to key phytoconstituents such as silybin, curcumin, glycyrrhizin, andrographolide, and wedelolactone, which exhibit pronounced multi-target efficacy and favorable pharmacological profiles. Emerging nano-herbal delivery systems, including phytosomes, liposomes, solid lipid nanoparticles, and polymeric nanoparticles, have further enhanced the therapeutic potential of these phytomolecules by improving solubility, bioavailability, stability, and liver-specific targeting. Despite encouraging preclinical and clinical findings, challenges related to standardization, quality assurance, herb–drug interactions, regulatory frameworks, and the scarcity of large-scale clinical trials continue to hinder widespread clinical adoption.

Advances in omics technologies, artificial intelligence-driven phytodrug discovery, and precision nanomedicine are expected to accelerate the development of evidence-based herbal therapeutics for liver disorders. Collectively, the available evidence supports the growing role of herbal medicines as promising and scientifically validated candidates for the prevention and management of hepatic diseases.

**KEYWORDS:** Hepatoprotective herbs; Liver diseases; Phytoconstituents; Herbal medicine; Oxidative stress; Nrf2; NF-κB; Nano-herbal delivery systems; Hepatic fibrosis; Precision hepatology

## I. INTRODUCTION:

The liver is one of the most vital organs of the human body, responsible for numerous physiological and biochemical functions including metabolism of carbohydrates, proteins, and lipids, detoxification of xenobiotics, synthesis of plasma proteins, bile secretion, storage of vitamins, and regulation of immune responses. Due to its central role in maintaining metabolic homeostasis, impairment of liver function can lead to severe systemic complications and increased mortality. Liver diseases therefore remain a major public health concern worldwide and continue to impose substantial clinical and economic burdens.

Globally, hepatic disorders account for nearly 2 million deaths each year and are recognized among the leading causes of morbidity and mortality. The spectrum of liver diseases includes viral

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hepatitis, alcoholic liver disease (ALD), non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), drug-induced liver injury (DILI), autoimmune hepatitis, hepatic fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). These disorders arise from diverse etiological factors such as viral infections, excessive alcohol consumption, metabolic abnormalities, environmental toxins, oxidative stress, prolonged drug therapy, and genetic predisposition.

Among chronic liver diseases, NAFLD has emerged as the most prevalent condition globally, affecting approximately 25–30% of the adult population. The rapid increase in obesity, sedentary lifestyle, insulin resistance, and type 2 diabetes mellitus has significantly contributed to its growing incidence. Furthermore, chronic infections caused by hepatitis B virus (HBV) and hepatitis C virus (HCV) continue to remain major contributors to cirrhosis and hepatocellular carcinoma, particularly in developing countries. Drug-induced liver injury is another clinically significant condition because of its unpredictable and idiosyncratic nature, making diagnosis and management difficult

The pathogenesis of hepatic disorders involves complex molecular mechanisms including oxidative stress, lipid peroxidation, inflammatory cytokine release, mitochondrial dysfunction, apoptosis, fibrosis, and immune dysregulation. Although several synthetic drugs are available for the management of liver diseases, their long-term use is often associated with limited therapeutic efficacy, adverse effects, drug resistance, and high treatment costs. Hence, there is increasing interest in the exploration of safer and more effective therapeutic alternatives.

Medicinal plants and herbal formulations have been used since ancient times in traditional systems of medicine such as Ayurveda, Traditional Chinese Medicine (TCM), Siddha, and Unani for the treatment of liver ailments. A large number of medicinal plants including Silybum marianum, Phyllanthus niruri, Curcuma longa, Glycyrrhiza glabra, Andrographis paniculata, and Picrorhiza kurroa have demonstrated significant hepatoprotective activities in experimental and clinical studies. These plants contain diverse phytoconstituents such as flavonoids, alkaloids, terpenoids, glycosides, tannins, and phenolic compounds that exhibit antioxidant, anti-inflammatory, antifibrotic, antiviral, and immunomodulatory properties.

Recent research has focused on understanding the molecular targets and signaling pathways involved in herbal hepatoprotection, including modulation of NF-κB, Nrf2, TGF-β, TNF-α, and apoptotic pathways. In addition, advances in nanotechnology-based herbal drug delivery systems have shown promising potential in improving the bioavailability, stability, and targeted delivery of phytoconstituents.

Despite promising therapeutic potential, herbal medicines still face several challenges such as lack of standardization, variability in phytochemical composition, insufficient clinical evidence, regulatory limitations, and possible herb–drug interactions. Therefore, systematic scientific evaluation and evidence-based validation of herbal hepatoprotective agents are essential.

The present review aims to comprehensively discuss the epidemiology and pathophysiology of major hepatic disorders, medicinal plants used in hepatoprotection, bioactive phytoconstituents and their mechanisms of action, molecular targets involved in hepatic protection, nano-herbal drug delivery approaches, and future prospects in the development of effective and safer therapies for liver diseases.

## II. Pathophysiology of Hepatic Disorders

### 2.1 Oxidative Stress and Redox Dysregulation

Oxidative stress represents the cornerstone mechanism in virtually all forms of hepatocellular injury, characterized by a pathological imbalance between pro-oxidant reactive oxygen species (ROS) generation and the endogenous antioxidant defense systems. [23]

ROS including superoxide anion ($O_2^{\bullet -}$), hydrogen peroxide ($H_2O_2$), and the highly reactive hydroxyl radical ($^{\bullet}OH$) are primarily generated within hepatocyte mitochondria via complex I and III of the electron transport chain, as well as by NADPH oxidase (NOX) isoforms expressed on Kupffer cells, hepatic stellate cells, and hepatocytes. [24]

Lipid peroxidation—the oxidative degradation of polyunsaturated fatty acids in cellular membranes—generates toxic aldehyde byproducts including malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE), which serve as reliable biomarkers of oxidative hepatic injury and are routinely assessed in experimental hepatotoxicity models. [25]

The Kelch-like ECH-associated protein 1/Nuclear factor erythroid 2-related factor 2 (Keap1/Nrf2) pathway constitutes the master regulator of cellular antioxidant response. Under basal conditions, Nrf2 is retained in the cytoplasm by Keap1 and targeted for proteasomal degradation.

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Upon oxidative activation, Nrf2 dissociates from Keap1, translocates to the nucleus, and transcriptionally activates antioxidant response element (ARE)-driven genes including heme oxygenase-1 (HO-1), NAD(P) H:quinone oxidoreductase-1 (NQO1), superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). [26,27]

Depletion of glutathione (GSH), the principal intracellular thiol antioxidant, is a critical event in hepatocellular injury, particularly in acetaminophen-induced DILI, where cytochrome P450 2E1 (CYP2E1)-mediated conversion of acetaminophen to the highly reactive intermediate N-acetyl-p-benzoquinone imine (NAPQI) rapidly depletes hepatic GSH reserves. [28]

### 2.2 Inflammatory Signaling: NF-κB, Cytokine Networks, and Kupffer Cell Activation

Hepatic inflammation is orchestrated through a complex intercellular cytokine network, with Kupffer cells—the resident macrophages of the liver—functioning as central inflammatory sentinels. [29]

Activation of toll-like receptor 4 (TLR4) by lipopolysaccharide (LPS) from gut-derived endotoxemia triggers canonical NF-κB signaling: IκB kinase (IKK) complex phosphorylates and targets IκBα for proteasomal degradation, liberating p65/p50 NF-κB heterodimers to translocate to the nucleus and drive transcription of pro-inflammatory mediators including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interleukin-1β (IL-1β), interleukin-8 (IL-8), cyclooxygenase-2 (COX-2), and inducible nitric oxide synthase (iNOS). [30,31]

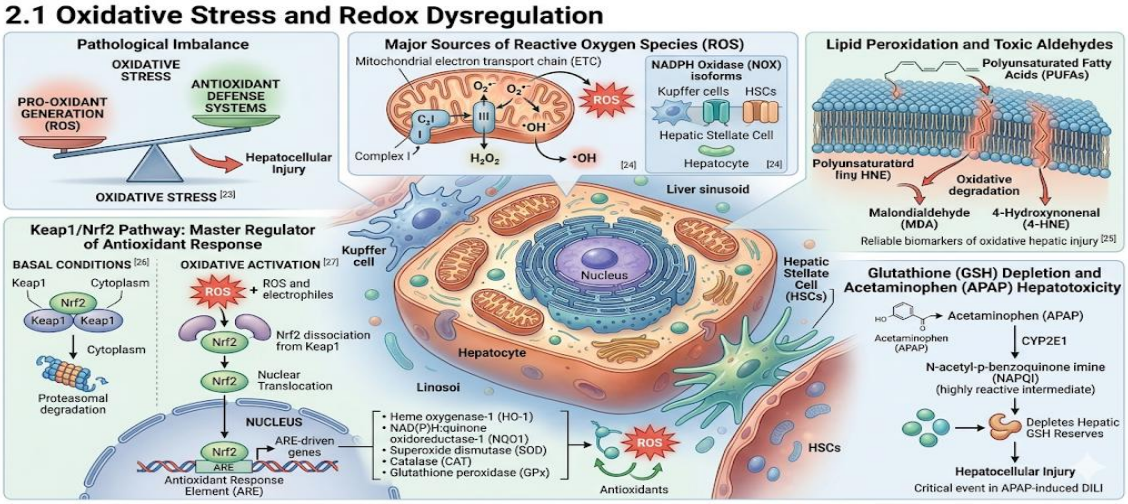


Fig No. 1

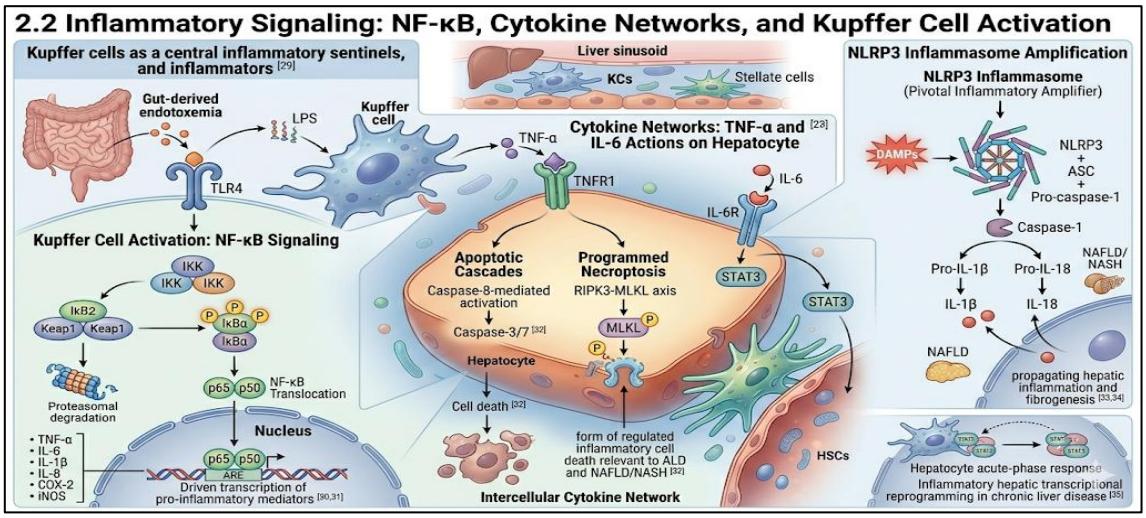


Fig No. 2

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TNF-α exerts pleiotropic hepatotoxic effects: through TNF receptor 1 (TNFR1) signaling, it activates caspase-8-mediated apoptotic cascades and, via RIPK3-MLKL axis, can induce programmed necroptosis—a form of regulated inflammatory cell death relevant to ALD and NAFLD/NASH pathophysiology. [32]

The NLRP3 (NOD-, LRR- and pyrin domain-containing protein 3) inflammasome has emerged as a pivotal inflammatory amplifier in hepatic disease, particularly in NAFLD/NASH. NLRP3 activation culminates in caspase-1 processing and secretion of mature IL-1β and IL-18, further propagating hepatic inflammation and fibrogenesis. [33,34]

The signal transducer and activator of transcription 3 (STAT3) pathway, activated downstream of IL-6, mediates hepatocyte acute-phase response and contributes to inflammatory hepatic transcriptional reprogramming in chronic liver disease.

### 2.3 Hepatic Fibrosis: TGF-β/Smad Pathway and Stellate Cell Biology

Hepatic fibrosis represents the pathological wound-healing response to sustained hepatocellular injury, characterized by progressive extracellular matrix (ECM) accumulation—predominantly type I and III collagens—mediated primarily by activated hepatic stellate cells (HSCs). [36]

Transforming growth factor-beta 1 (TGF-β1), the dominant pro-fibrogenic cytokine, is secreted by injured hepatocytes, activated Kupffer cells, portal fibroblasts, and HSCs themselves. TGF-β1 binds TGF-βR1/TGF-βR2 receptor complexes, activating canonical Smad2/Smad3 phosphorylation, Smad4 complex formation, and nuclear transcriptional induction of fibrogenic genes including α-smooth muscle actin (α-SMA), collagen type I alpha-1 (Col1A1), fibronectin, and tissue inhibitors of metalloproteinases (TIMPs). [37,38]

HSC activation also involves non-canonical TGF-β-independent pathways including PDGF/PI3K/Akt, Hedgehog, Wnt/β-catenin, and Yes-associated protein (YAP)/TAZ mechanosensing—each representing potential herbal therapeutic targets. [39]

Matrix metalloproteinases (MMPs) 2, 9, and 13, alongside their endogenous inhibitors TIMP-1 and TIMP-2, regulate ECM remodeling. The MMP/TIMP balance is disrupted toward net collagen deposition in progressive fibrosis, with TIMP-1 overexpression by activated HSCs being a critical event. [40]

### 2.4 Mitochondrial Dysfunction and Bioenergetic Failure

Hepatocellular mitochondria are primary targets and sensors of hepatotoxic stress. Mitochondrial dysfunction manifests as dissipation of the inner mitochondrial membrane potential (ΔΨm), impaired oxidative phosphorylation, adenosine triphosphate (ATP) depletion, mitochondrial permeability transition pore (mPTP) opening, and release of pro-apoptotic factors including cytochrome c, Smac/DIABLO, and apoptosis-inducing factor (AIF) into the cytoplasm. [41,42]

In NAFLD, mitochondrial β-oxidation of fatty acids generates excessive electron flux, promoting mitochondrial superoxide generation, which—in the context of impaired mitochondrial antioxidant defenses (particularly reduced mitochondrial SOD2/MnSOD and GSH)—leads to mitochondrial lipid peroxidation, protein nitration, and mtDNA damage. [43]

### 2.5 Apoptosis and Necrosis: Caspase Cascade and Bax/Bcl-2 Balance

Hepatocyte apoptosis in liver disease proceeds through extrinsic (death receptor-mediated, involving TRAIL-R/DR5 and FasL/Fas) and intrinsic (mitochondrial) pathways. The intrinsic pathway is regulated by the Bcl-2 family of proteins—where pro-apoptotic members Bax, Bak, Bad, Bid, and PUMA promote mPTP opening and cytochrome c release, while anti-apoptotic members Bcl-2 and Bcl-xL preserve mitochondrial integrity. [44]

The Bax/Bcl-2 ratio is a critical determinant of hepatocellular fate in oxidative and toxic liver injury, and numerous experimental studies employ immunohistochemical and Western blot quantification of this ratio as a primary pharmacodynamic endpoint. [45]

Caspase-3 and caspase-7 serve as executioner caspases in hepatocyte apoptosis, and their cleavage products (e.g., cleaved PARP) represent widely used apoptotic biomarkers in experimental hepatology. [46]

### 2.6 Drug-Induced Hepatotoxicity: CYP450-Mediated Mechanisms

CYP450 enzymes—particularly CYP2E1, CYP3A4, and CYP1A2—catalyze phase I biotransformation of diverse xenobiotics. While generally detoxifying, certain metabolic pathways generate reactive electrophilic intermediates that covalently adduct hepatic proteins, trigger oxidative stress, and initiate immune-mediated hepatocellular injury. [47]

The acetaminophen (APAP) hepatotoxicity model—the most extensively validated experimental DILI

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paradigm—involves CYP2E1/CYP3A4-mediated oxidation of APAP to NAPQI, which depletes GSH, forms protein adducts, induces JNK phosphorylation, and triggers mPTP opening, resulting in centrilobular necrosis. [48,49]

$CCl_4$-induced hepatotoxicity, another widely employed experimental model, proceeds via CYP2E1-mediated biotransformation of carbon tetrachloride to the trichloromethyl radical ($CCl_3$•), which initiates lipid peroxidation, mitochondrial dysfunction, and hepatocellular necrosis, rendering it a robust model for evaluating both hepatoprotective and anti-fibrotic activity. [50]

### 2.7 Gut–Liver Axis and Dysbiosis-Driven Hepatic Injury

The gut–liver axis—an anatomical and functional bidirectional communication network mediated through the portal venous system—has emerged as a mechanistically critical determinant of hepatic disease progression. [51]

Gut microbiota dysbiosis in the context of ALD, NAFLD, and cirrhosis is characterized by reduced Bacteroidetes:Firmicutes ratio, decreased abundance of commensal butyrate-producing bacteria (Faecalibacterium prausnitzii, Akkermansia muciniphila), overgrowth of Proteobacteria and endotoxin-producing gram-negative bacteria, and small intestinal bacterial overgrowth (SIBO). [52,53]

Increased intestinal permeability ('leaky gut') driven by tight junction protein (claudin-1, occludin, ZO-1) downregulation allows bacterial LPS translocation into the portal circulation, where it activates hepatic TLR4/NF-κB signaling in Kupffer cells—perpetuating inflammatory hepatic injury through the LPS–TLR4–NF-κB–TNF-α–IL-6 axis. [54]

### 2.8 Genetic and Epigenetic Regulation of Hepatic Disease

Epigenetic mechanisms—including DNA methylation, histone post-translational modifications (acetylation, methylation, phosphorylation), and non-coding RNA regulation—profoundly modulate hepatic gene expression programs in fibrosis, NASH, and HCC. [55]

MicroRNAs (miRNAs) serve as critical post-transcriptional regulators of hepatic disease pathobiology. miR-21, miR-155, miR-122, miR-221/222, and miR-146a have been identified as dysregulated in hepatic fibrosis, NAFLD, and viral hepatitis, modulating fibrogenic, inflammatory, and metabolic gene networks. [56,57]

Histone deacetylases (HDACs), particularly HDAC1, HDAC2, HDAC3 (class I), and SIRT1 (class III), regulate inflammatory and fibrogenic transcriptional programs, with SIRT1 deacetylation of p65 NF-κB and PGC-1α representing a critical nexus between metabolic regulation and hepatic inflammation. [58]

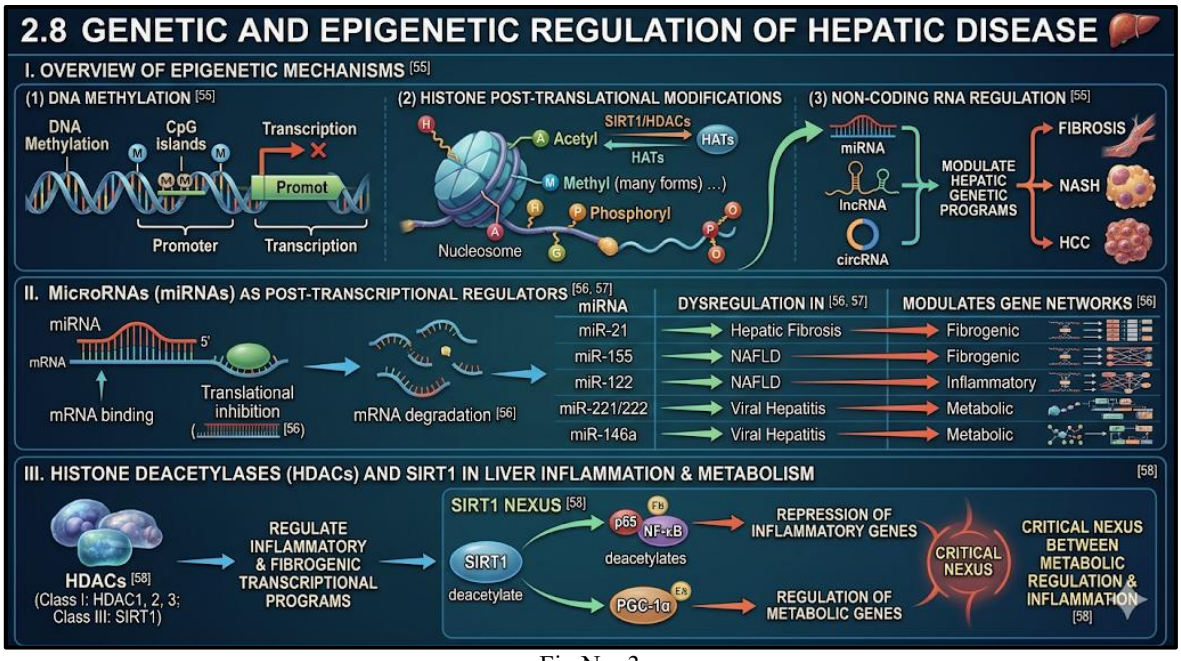


Fig No. 3

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## III. Herbal Drugs Used in the Management of Hepatic Disorders

Major medicinal plants with well-documented hepatoprotective activity are critically reviewed herein. For each plant, botanical characteristics, key phytoconstituents, molecular mechanisms, and comparative experimental and clinical evidence are discussed.

### *3.1 Silybum marianum (L.) Gaertn. — Milk Thistle*

**Botanical description:** Silybum marianum is an annual/biennial herb of the family Asteraceae (Compositae), native to the Mediterranean basin. The achene fruits contain the medicinally active standardized extract silymarin.

Silymarin is a complex of flavonolignans—comprising silybin A and B (the most pharmacologically active, ~50–70% of silymarin), silydianin, silychristin, isosilybin A and B, and the flavonoid taxifolin—extracted from the dried fruits of the plant. [59,60]

**Molecular mechanisms:** Silybin exerts hepatoprotective activity through multiple convergent molecular mechanisms: (i) potent antioxidant activity via direct ROS scavenging and induction of Nrf2/HO-1/NQO1 axis; (ii) inhibition of NF-κB p65 nuclear translocation and downstream pro-inflammatory cytokine transcription; (iii) inhibition of TGF-β1-stimulated HSC activation via Smad3 phosphorylation inhibition, reducing collagen synthesis and α-SMA expression; (iv) modulation of CYP2E1 activity, attenuating NAPQI generation in DILI; and (v) anti-apoptotic activity through upregulation of Bcl-2 and suppression of Bax, reducing caspase-3 activation. [61,62,63]

Experimental studies in $CCl_4$-, D-galactosamine (D-GalN)-, and APAP-induced hepatotoxicity models have consistently demonstrated silymarin's capacity to normalize serum ALT, AST, ALP, GGT, and bilirubin levels, restore hepatic GSH, reduce MDA, and attenuate histopathological hepatocellular damage. [64,65]

A double-blind, randomized clinical trial in patients with alcoholic liver disease demonstrated that silymarin (420 mg/day for 6 months) produced significant reductions in serum transaminases and improved clinical outcomes compared to placebo, though a Cochrane systematic review noted heterogeneity across trials. [66]

**Limitations:** Silybin's poor water solubility (logP ≈ 1.6) severely limits oral bioavailability (~23–47%). Phytosomal complexation with phosphatidylcholine (Siliphos®/IdB 1016) has been demonstrated to improve bioavailability 4.6-fold relative to conventional silymarin preparations. [67,68]

Fig No. 4

### *3.2 Curcuma longa L. — Turmeric*

**Botanical description:** *Curcuma longa* (family Zingiberaceae) is a perennial rhizomatous herb cultivated throughout tropical Asia. The rhizome yields the orange-yellow polyphenolic pigments curcuminoids.

Curcuminoids comprise curcumin (75–80%), demethoxycurcumin, and bisdemethoxycurcumin. Curcumin's bis-α,β-unsaturated β-diketone structure is pharmacophoric for its biological activity, enabling Michael acceptor reactions with nucleophilic residues in target proteins. [69]

**Molecular targets:** Curcumin modulates over 30 molecular targets relevant to hepatoprotection: (i) inhibition of IKKβ phosphorylation, preventing IκBα degradation and NF-κB nuclear translocation; (ii) Nrf2 activation via Keap1 Cys151/Cys273/Cys288 modification, inducing HO-1, NQO1, SOD, CAT, and GPx; (iii) TGF-β1/Smad3 anti-fibrotic pathway inhibition; (iv) AMPK activation with downstream mTORC1 inhibition, attenuating hepatic lipid accumulation in NAFLD; (v) NLRP3 inflammasome suppression; and (vi) FXR (farnesoid X receptor) agonism promoting bile acid homeostasis. [70,71,72,73]

In a meta-analysis of 13 RCTs (n = 837 patients), curcumin supplementation significantly reduced serum ALT, AST, GGT, fasting blood glucose, and HOMA-IR in patients with NAFLD, with a pooled effect size of SMD −0.72 (95% CI: −1.12 to −0.33, $p<0.001$) for ALT reduction. [74]

**Bioavailability challenge:** Curcumin's oral bioavailability is notoriously poor (<1%) due to low aqueous solubility, extensive first-pass metabolism (rapid glucuronidation and sulfation), and rapid intestinal elimination. Piperine co-administration (20 mg) enhances curcumin bioavailability by 2000%,

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while nanoformulations and phytosomes achieve sustained plasma exposure. [75,76]

Fig No. 5

### *3.3 Phyllanthus niruri L. — Stonebreaker / Bhumyamalaki*

*Phyllanthus niruri* (family Phyllanthaceae) is a pantropical annual herb traditionally used in Ayurveda as 'Bhumyamalaki' for liver disorders, jaundice, and viral hepatitis.

Key phytoconstituents include the lignan phyllanthin, hypophyllanthin, niranthin, phyltetralin, geraniin (an ellagitannin), corilagin, quercetin, rutin, amariin, and niruriside. Phyllanthin and hypophyllanthin are the principal hepatoprotective markers. [77]

Phyllanthin exhibits significant hepatoprotective activity in $CCl_4$ and thioacetamide (TAA)-induced hepatotoxicity models, with demonstrated reversal of elevated transaminases, amelioration of oxidative stress markers, and anti-apoptotic activity mediated through NF-κB inhibition and Bax/Bcl-2 ratio normalization. [78]

A systematic review and meta-analysis of clinical studies with Phyllanthus species in chronic HBV infection demonstrated significant HBsAg seroconversion rates and AST/ALT normalization in 6 RCTs, suggesting antiviral hepatoprotective efficacy potentially through HBsAg and HBV polymerase interference mechanisms. [79]

Fig No. 6

### *3.4 Glycyrrhiza glabra L. — Licorice*

*Glycyrrhiza glabra* (family Fabaceae) is a perennial herb yielding one of the most extensively investigated hepatoprotective phytomolecules—glycyrrhizin (glycyrrhizic acid) and its biologically active aglycone 18β-glycyrrhetinic acid (18β-GA).

Glycyrrhizin exhibits potent anti-inflammatory activity through inhibition of high mobility group box 1 (HMGB1) release, TLR4/NF-κB signaling suppression, and complement pathway modulation. Clinically, intravenous glycyrrhizin formulations (SNMC/Stronger Neo-Minophagen C) are approved in Japan for the treatment of chronic hepatitis B and C, demonstrating significant transaminase reduction and histological improvement. [80,81]

18β-GA inhibits 11β-hydroxysteroid dehydrogenase (11β-HSD), potentiating anti-inflammatory glucocorticoid activity. Additional mechanisms include Nrf2 activation, NF-κB inhibition, NLRP3 inflammasome suppression, and anti-fibrotic effects through TGF-β1 pathway modulation. [82]

Fig No. 7

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### *3.5 Andrographis paniculata (Burm.f.) Nees — Kalmegh / King of Bitters*

Andrographolide, the principal diterpenoid lactone of Andrographis paniculata (family Acanthaceae), is the pharmacologically active constituent responsible for its hepatoprotective, anti-inflammatory, anti-fibrotic, and antiviral activities. [83]

Andrographolide inhibits NF-κB activation by covalently modifying Cys62 of the p50 NF-κB subunit, preventing DNA binding. It additionally activates Nrf2/HO-1 signaling, suppresses NLRP3 inflammasome activation, inhibits JAK/STAT3 pathway, and exhibits TGF-β/Smad anti-fibrotic activity. Andrographolide's α-methylene-γ-butyrolactone moiety is the pharmacophoric Michael acceptor enabling covalent target engagement. [84,85]

In TAA-induced hepatic fibrosis in rats, andrographolide (100 mg/kg p.o. for 6 weeks) produced significant reductions in α-SMA expression, TGF-β1 levels, and hepatic collagen content (by hydroxyproline quantification), with concurrent normalization of biochemical markers and Sirius Red histological staining improvement. [86]

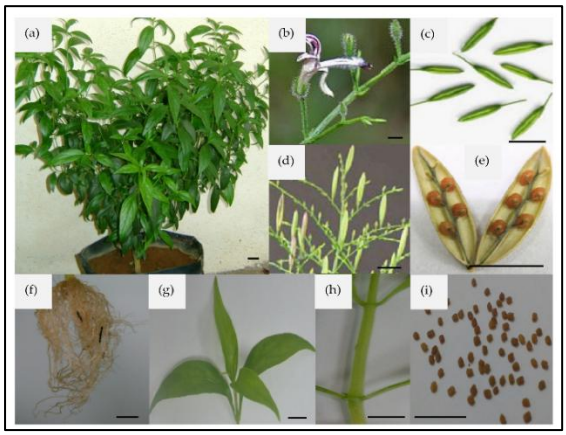


Fig No. 8

### *3.6 Picrorhiza kurroa Royle ex Benth. — Kutki*

Picrorhiza kurroa (family Plantaginaceae), endemic to the Himalayan highlands, contains the iridoid glycosides picrosides I–IV (particularly picroside I and II) and kutkin (a mixture of picroside I and kutkoside). These constitute the standardized pharmacopeial markers of hepatoprotective activity. [87]

Picroside II demonstrates mechanistic hepatoprotection through Nrf2/HO-1 antioxidant induction, NF-κB/iNOS/COX-2 inhibition, upregulation of Bcl-2, and inhibition of caspase-3/9 apoptotic cascade. Additionally, picroside II has been shown to inhibit lipopolysaccharide-stimulated Kupffer cell activation and TLR4 signaling in experimental cholestatic models. [88,89]

A clinical comparative study evaluating Picrorhiza kurroa extract (375 mg twice daily) against silymarin in viral hepatitis demonstrated comparable normalization rates of AST, ALT, and serum bilirubin over 30 days, suggesting therapeutic equivalence in acute hepatitis management. [90]

Fig No. 9

### *3.7 Boerhavia diffusa L. — Punarnava*

Boerhavia diffusa (family Nyctaginaceae) is an herbaceous perennial used in Ayurvedic hepatology. Major hepatoprotective phytoconstituents include boeravinones (rotenoids), punarnavoside (an alkaloid), liriodendrin, and hypoxanthine-9-L-arabinofuranoside. [91]

Punarnavine, the principal alkaloid, demonstrated hepatoprotective activity comparable to silymarin in $CCl_4$-induced hepatotoxicity, operating through free radical scavenging, GSH restoration, and suppression of TNF-α-mediated inflammatory signaling. Boeravinone B has been identified as a potent MDR1/P-glycoprotein modulator with potential DILI relevance. [92]

Fig No. 10

### *3.8 Eclipta alba (L.) Hassk. — Bhringraj*

Eclipta alba (synonym: Eclipta prostrata, family Asteraceae) contains wedelolactone (a coumestan),

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ecliptasaponin A, eclalbasaponin, luteolin, apigenin, β-sitosterol, oleanolic acid, and ursolic acid as major hepatoprotective phytoconstituents. [93]Wedelolactone exhibits hepatoprotective activity through multiple mechanisms: (i) inhibition of IKKβ phosphorylation and NF-κB nuclear translocation; (ii) caspase-11 inhibition, reducing LPS-induced inflammatory hepatocellular injury; (iii) Nrf2 activation and GSH restoration; and (iv) anti-fibrotic activity through downregulation of TGF-β1 and Smad3 in HSCs. Wedelolactone also demonstrates anti-HBV activity through inhibition of HBV surface antigen expression. [94,95]

Fig No. 11

### *3.9 Aloe vera (L.) Burm.f. — Ghritkumari*

Aloe vera (family Asphodelaceae) gel and latex contain acemannan (a β-1,4-acetylated polymannan), aloin A/B (anthraquinone glycosides), aloesin, aloe-emodin, and numerous polyphenolic compounds with demonstrated hepatoprotective potential. [96]

Acemannan exhibits immunomodulatory and anti-inflammatory properties through macrophage activation and NF-κB pathway modulation. Aloe-emodin demonstrates anti-fibrotic activity in activated HSCs through suppression of TGF-β1 signaling and induction of HSC apoptosis via mitochondrial pathway activation. However, aloin/anthraquinones at high doses exhibit hepatotoxic potential, necessitating standardized preparations with controlled anthraquinone content. [97,98]

Fig No. 12

### *3.10 Tinospora cordifolia (Willd.) Miers — Guduchi / Giloy*

Tinospora cordifolia (family Menispermaceae) is an Ayurvedic rasayana (adaptogen) with recognized hepatoprotective, immunomodulatory, and anti-inflammatory properties. Key phytoconstituents include berberine, tinosporide, tinosporaside, palmatine, magnoflorine, tinosporin, polysaccharides (arabinogalactan), and βdimer sitosterol. [99]

Berberine—the principal isoquinoline alkaloid—exerts hepatoprotective activity through AMPK activation (phosphorylation of Thr172-AMPKα), inhibiting hepatic lipogenesis (via SREBP-1c and FAS downregulation), reducing oxidative stress through Nrf2 activation, and suppressing NF-κB-mediated inflammatory signaling. AMPK activation by berberine also promotes hepatic autophagy, facilitating clearance of damaged mitochondria (mitophagy) in NAFLD. [100,101]

A placebo-controlled clinical trial demonstrated significant improvement in serum transaminases, hepatic steatosis grade (by ultrasound), and serum lipid profiles in NAFLD patients receiving Tinospora cordifolia standardized extract (300 mg thrice daily for 12 weeks) compared to placebo. [102]

Fig No. 13

## IV. Phytoconstituents Responsible for Hepatoprotective Activity

Hepatoprotective phytoconstituents span multiple chemical classes, with their hepatoprotective activity linked to distinct structural pharmacophores that determine target engagement, bioavailability, and mechanistic profile. [103]

### *4.1 Flavonoids and Flavonolignans*

Flavonoids are C6-C3-C6 benzo-γ-pyrone derivatives classified as flavones, flavonols, flavanones, isoflavones, anthocyanidins, and

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chalcones. Their hepatoprotective pharmacophore is principally constituted by the catechol B-ring (3',4'-dihydroxylation), C2=C3 double bond, and C3-hydroxyl, which confer metal chelation capacity, electron donation, and radical chain-breaking antioxidant activity. [104]

Quercetin, one of the most studied flavonols, demonstrates potent Nrf2/HO-1 activation, NF-κB inhibition, AMPK activation, and TGF-β1 anti-fibrotic activity. Quercetin's planarity facilitates intercalation with lipid bilayers, reducing membrane lipid peroxidation—a mechanism particularly relevant to alcohol-induced hepatic membrane disruption. [105]

### *4.2 Polyphenols and Tannins*

Polyphenols, including hydrolyzable tannins (ellagitannins, gallotannins) and condensed tannins (proanthocyanidins), exhibit hepatoprotective activity through multi-target antioxidant, anti-inflammatory, and gut microbiota prebiotic mechanisms. [106]

Ellagic acid—the hydrolysis product of ellagitannins—undergoes colonic biotransformation to urolithins (urolithin A, B, C) by gut microbiota, with urolithin A demonstrating potent Nrf2 activation, mitophagy induction, and NLRP3 inflammasome suppression, representing an emerging microbiome-mediated hepatoprotective mechanism. [107]

### *4.3 Alkaloids*

Berberine (isoquinoline alkaloid), andrographolide (diterpenoid alkaloid-like lactone), and vasicine (quinazoline alkaloid from Adhatoda vasica) represent structurally distinct alkaloids with relevant hepatoprotective mechanisms. Berberine's positive charge and planar ring system enable mitochondrial targeting, intercalation with mtDNA, and modulation of mitochondrial biogenesis through AMPK-PGC-1α signaling. [108]

### *4.4 Terpenoids*

Monoterpenes (limonene, thymol), sesquiterpenes (artemisinins), diterpenes (andrographolide, ginkgolides), triterpenes (ursolic acid, oleanolic acid, betulinic acid), and tetraterpenes (carotenoids, lycopene) constitute structurally diverse terpenoids with hepatoprotective potential. Oleanolic acid exhibits potent anti-fibrotic activity through inhibition of NF-κB, TGF-β1 signaling, HSC activation, and collagen synthesis, with barbaloin-mediated hepatoprotective effects documented in animal models. [109,110]

### *4.5 Lignans*

Lignans—biogenetically derived from phenylalanine via the monolignol pathway—represent a structurally important class of hepatoprotective phytoconstituents. Silybin (a flavonolignan), phyllanthin, schisandrin B (from Schisandra chinensis), and magnolol exhibit potent anti-fibrotic, antioxidant, and antiviral hepatoprotective activities. Schisandrin B's hepatoprotective mechanism includes mitochondrial protection, CYP450 modulation, and Nrf2/NQO1 induction, with demonstrated clinical activity in chronic hepatitis and DILI. [111]

## V. Molecular Mechanisms of Herbal Hepatoprotection

Herbal hepatoprotective agents exert their pharmacological effects through mechanistic diversity that parallels, and often surpasses, single-target synthetic drugs in breadth of coverage across the hepatic injury cascade. [112]

### *5.1 Nrf2/ARE Antioxidant Pathway Activation*

### *5.2 NF-κB Anti-inflammatory Pathway Inhibition*

NF-κB (particularly the p65/p50 heterodimer) inhibition by herbal phytoconstituents occurs through multiple convergent mechanisms: direct IKKβ inhibition (curcumin, andrographolide), prevention of IκBα phosphorylation/ubiquitination, stabilization of IκBα-p65 complex, inhibition of p65 nuclear translocation (silymarin, glycyrrhizin, berberine), and inhibition of p65 transactivation domain interactions with co-activators (CBP/p300). [115]

### *5.3 AMPK Pathway and Metabolic Hepatoprotection*

AMP-activated protein kinase (AMPK) activation by berberine, curcumin, and resveratrol produces multi-faceted hepatoprotection: (i) inhibition of mTORC1-SREBP-1c-FAS lipogenic axis, reducing hepatic steatosis; (ii) promotion of fatty acid β-oxidation via ACC phosphorylation and CPT1A upregulation; (iii) induction of hepatic autophagy through ULK1 phosphorylation; (iv) mitochondrial biogenesis through PGC-1α activation; and (v) NLRP3 inflammasome suppression. [116,117]

### *5.4 PI3K/Akt/mTOR Anti-apoptotic and Regenerative Signaling*

Several herbal phytoconstituents activate the PI3K/Akt survival pathway, promoting hepatocellular survival through phosphorylation of pro-apoptotic Bad, inhibition of cytochrome c-mediated caspase-9 activation, and activation of NF-

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κB-independent survival transcription. Concurrent mTORC1 activation promotes hepatocellular regenerative protein synthesis, while mTORC2-Akt positive feedback sustains the survival signaling loop. [118]

### *5.5 Anti-fibrotic Mechanisms: TGF-β/Smad and HSC Targeting*

Anti-fibrotic herbal mechanisms converge on: (i) TGF-β1 mRNA and protein expression suppression (curcumin, andrographolide, silybin); (ii) TGFβR1/TGFβR2 expression downregulation; (iii) Smad2/Smad3 phosphorylation inhibition; (iv) Smad7 (endogenous TGF-β signaling inhibitor) upregulation; (v) PDGF-BB-stimulated HSC proliferation inhibition; (vi) collagenase (MMP-1, MMP-13) induction with TIMP-1 suppression; and (vii) HSC apoptosis induction through TRAIL-DR5 sensitization. [119,120]

### *5.6 CYP450 Enzyme Modulation*

CYP450 modulation by herbal agents is mechanistically bidirectional. Silybin inhibits CYP2E1 and CYP3A4 in DILI contexts, reducing toxic reactive metabolite formation. Conversely, some herbal constituents induce CYP3A4 or CYP1A2 (e.g., St. John's Wort) or inhibit CYP2D6/CYP2C9, creating potential pharmacokinetic herb–drug interaction risks requiring clinical monitoring. [121]

## VI. Nanotechnology and Novel Herbal Drug Delivery Approaches

The poor aqueous solubility, low oral bioavailability, rapid first-pass metabolism, and inadequate hepatic targeting of most phytomolecules represent critical translational limitations that nanotechnology-based delivery systems are uniquely positioned to address. [122]

### *6.1 Phytosomes*

Phytosomes are binary complexes formed through stoichiometric interaction (typically 1:1 or 1:2) of polyphenolic phytomolecules with phosphatidylcholine. The polar head group of phosphatidylcholine forms hydrogen bonds with the phytomolecule, while the lipophilic acyl chains mediate membrane integration, substantially improving bioavailability. Silybin-phosphatidylcholine (Siliphos®) achieves a 4.6-fold greater AUC compared to unconjugated silymarin, with enhanced hepatocellular uptake. Curcumin-phosphatidylcholine complex (Meriva®) demonstrates approximately 29-fold improved relative bioavailability. [123,124]

### *6.2 Liposomal Herbal Formulations*

Liposomes—phospholipid bilayer vesicles encapsulating hydrophilic or lipophilic phytomolecules—offer liver-targeted delivery through passive accumulation via the enhanced permeability and retention (EPR) effect and active targeting via hepatic ASGPR (asialoglycoprotein receptor)-directed galactose or lactobionic acid surface functionalization. PEGylated silybin liposomes demonstrated significantly enhanced pharmacokinetic profile and superior hepatoprotection in APAP-induced hepatotoxicity compared to free silybin. [125]

### *6.3 Polymeric Nanoparticles*

PLGA (poly [lactic-co-glycolic acid]) and chitosan-based polymeric nanoparticles have been extensively investigated for hepatic delivery of curcumin, berberine, and andrographolide. PLGA-curcumin nanoparticles (NPs) exhibit sustained drug release over 96–120 hours, enhanced hepatic targeting, improved cellular uptake through endocytic pathways, and significantly amplified Nrf2 activation compared to free curcumin in $CCl_4$ hepatotoxicity models. [126,127]

### *6.4 Solid Lipid Nanoparticles (SLNs)*

SLNs—composed of solid lipid matrix (glyceryl monostearate, cetyl palmitate, or Compritol 888 ATO) with stabilizing surfactant shell—embed lipophilic phytomolecules within the lipid core, improving GI absorption and providing controlled release. SLN-andrographolide formulations demonstrated 3.2-fold higher Cmax, 4.8-fold greater $AUC_{0–24}$, and superior hepatic tissue concentration compared to andrographolide suspension in rats. [128]

### *6.5 Nano-Herbal Targeted Delivery Systems*

Active hepatic targeting strategies include: (i) galactose/lactobionic acid functionalization for ASGPR-mediated hepatocyte-specific uptake; (ii) anti-ASGPR antibody conjugation; (iii) lipid-polymer hybrid nanoparticles combining the stability of SLNs with PLGA's controlled release; (iv) self-emulsifying drug delivery systems (SEDDS) for improved GI solubilization; and (v) exosome-based delivery exploiting natural hepatocyte tropism. [129,130]

Current limitations of nano-herbal systems include: scalability and batch reproducibility challenges, lack of validated nano-specific toxicological assessment

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frameworks, regulatory uncertainty regarding nanoformulation approval pathways, and insufficient long-term in vivo safety data for novel excipient systems. [131]

## VII. Research Gaps and Challenges

Despite compelling preclinical evidence, the translation of herbal hepatoprotective agents into evidence-based clinical therapeutics is impeded by a constellation of methodological, regulatory, and pharmacological challenges that necessitate systematic scientific address. [132]

### *7.1 Standardization and Phytochemical Variability*

One of the most critical obstacles to herbal hepatoprotective drug development is the profound variability in phytochemical composition and potency arising from genetic (chemotype variation), agronomic (season, soil, altitude), post-harvest (storage, drying), and manufacturing (extraction solvent, temperature, particle size) factors. This variability renders batch-to-batch consistency a significant analytical and regulatory challenge, particularly for herbal preparations intended for clinical trials. [133]

### *7.2 Bioavailability and Pharmacokinetic Limitations*

Many pharmacologically active phytomolecules—including curcumin (F <1%), silybin (F ~23–47%), andrographolide (F ~30%), and berberine (F ~5%)—exhibit poor oral bioavailability due to physicochemical limitations (low aqueous solubility, high first-pass metabolism), limiting achievable hepatic tissue concentrations at standard dosing. Comprehensive human pharmacokinetic data, including tissue distribution to hepatic compartments, remain scarce for most phytomolecules. [134]

### *7.3 Clinical Evidence Quality and Trial Design Deficiencies*

A systematic Cochrane review of milk thistle for chronic liver diseases (2005, updated 2019) identified methodological limitations—including high risk of allocation concealment bias, heterogeneous patient populations, variable outcome measures, short follow-up durations, and absence of histological endpoints—as critical constraints on the interpretability and generalizability of clinical trial findings for herbal hepatoprotectants. [135]

### *7.4 Herb–Drug Pharmacokinetic Interactions*

Herb–drug pharmacokinetic interactions (HDI) via CYP450 enzyme inhibition/induction and P-glycoprotein modulation represent clinically significant safety concerns, particularly in hepatology patients receiving polypharmacy regimens including antiviral agents (entecavir, tenofovir), immunosuppressants (tacrolimus, cyclosporine), and anticoagulants (warfarin). Silymarin's inhibition of CYP3A4, CYP2C9, and UGT enzymes has been documented to affect indinavir, losartan, and warfarin pharmacokinetics. [136]

### *7.5 Toxicological Concerns and Hepatotoxic Potential*

A paradoxical but scientifically documented concern is the hepatotoxic potential of certain 'hepatoprotective' herbs at high doses or in specific patient populations. Pyrrolizidine alkaloid (PA)-containing plants (Symphytum spp., Heliotropium spp.), Kava (Piper methysticum), and high-dose Aloe vera anthraquinone preparations have been documented as causes of DILI in pharmacovigilance databases, reinforcing the critical importance of rigorous toxicological characterization and dose optimization. [137,138]

### *7.6 Regulatory and Translational Challenges*

The regulatory pathway for herbal hepatoprotective agents differs significantly across jurisdictions. While the United States FDA classifies most herbal preparations as dietary supplements (requiring GRAS/DSHEA compliance rather than IND/NDA efficacy evidence), the European Medicines Agency (EMA) Committee on Herbal Medicinal Products (HMPC) framework for Traditional Herbal Medicinal Products (THMP) and the Central Drugs Standard Control Organisation (CDSCO) regulatory framework in India each impose distinct evidence requirements that complicate global clinical development strategies. [139]

## VIII. Future Perspectives

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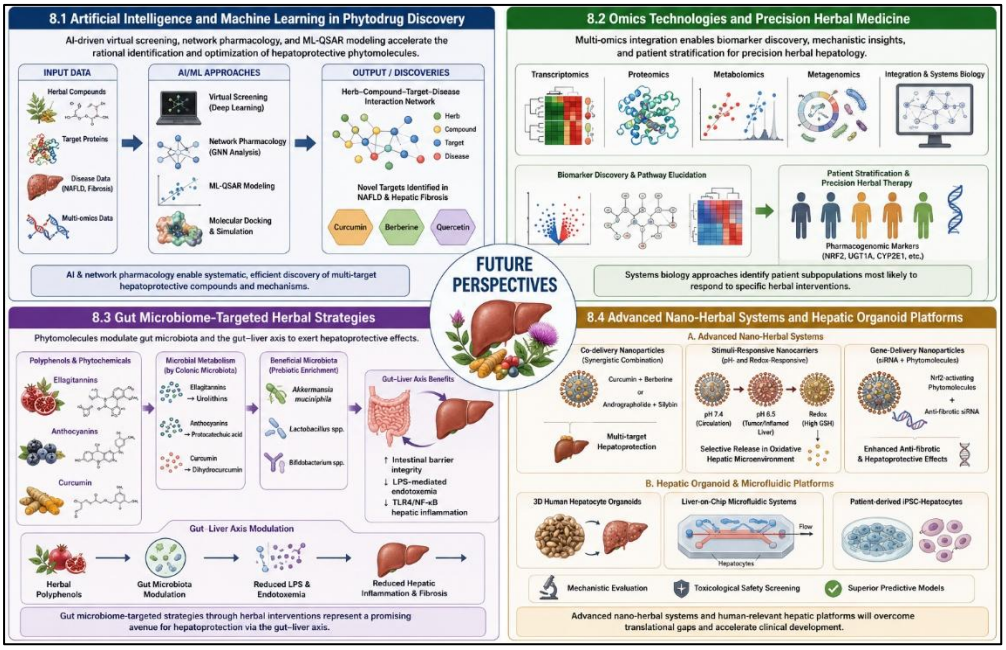


Fig No. 14

### *8.1 Artificial Intelligence and Machine Learning in Phytodrug Discovery*

AI-driven virtual screening, network pharmacology, and machine learning-based quantitative structure–activity relationship (ML-QSAR) modeling are rapidly transforming the rational identification and optimization of hepatoprotective phytomolecules. Network pharmacology—integrating herb–compound–target–disease interaction networks derived from multi-omics data with graph neural network (GNN) analysis—has successfully identified novel molecular targets of curcumin, berberine, and quercetin in NAFLD and hepatic fibrosis. [140,141]

### *8.2 Omics Technologies and Precision Herbal Medicine*

Transcriptomics, proteomics, metabolomics, and metagenomics (multi-omics integration) offer unprecedented capacity for biomarker discovery, mechanistic pathway elucidation, and patient stratification in herbal hepatology. Systems biology approaches enable identification of patient subpopulations most likely to respond to specific herbal interventions based on pharmacogenomic profiles (e.g., NRF2, UGT1A, CYP2E1 polymorphisms). [142]

### *8.3 Gut Microbiome-Targeted Herbal Strategies*

Emerging evidence demonstrates that hepatoprotective phytomolecules—particularly polyphenols metabolized by colonic microbiota (ellagitannins → urolithins; anthocyanins → protocatechuic acid; curcumin → dihydrocurcumin)—exert significant gut-liver axis modulatory activity through prebiotic enrichment of beneficial microbiota (Akkermansia muciniphila, Lactobacillus spp., Bifidobacterium spp.), restoration of intestinal barrier integrity, and attenuation of LPS-mediated endotoxemia driving TLR4/NF-κB hepatic inflammation. [143,144]

### *8.4 Advanced Nano-Herbal Systems and Hepatic Organoid Platforms*

Next-generation nano-herbal platforms including co-delivery nanoparticles (simultaneously delivering curcumin + berberine or andrographolide + silybin for synergistic multi-target hepatoprotection), stimuli-responsive (pH- and redox-responsive) nanocarriers releasing drugs selectively in the oxidative hepatic microenvironment, and gene-delivery nanoparticles co-administering Nrf2-activating phytomolecules with anti-fibrotic siRNA represent frontier strategies in pre-clinical development. [145]

Three-dimensional human hepatocyte organoids, liver-on-chip microfluidic systems, and patient-derived induced pluripotent stem cell (iPSC)-hepatocyte platforms are emerging as superior in vitro predictive models for mechanistic evaluation and toxicological safety screening of herbal hepatoprotective candidates, overcoming the translational limitations of conventional 2D hepatocyte culture models. [146]

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## IX. Conclusion

Hepatic disorders, with their multifactorial etiopathogenesis and convergent molecular mechanisms of oxidative stress, inflammation, fibrogenesis, mitochondrial dysfunction, and apoptosis, present a compelling therapeutic landscape for multi-target herbal interventions. The ten major medicinal plants reviewed—Silybum marianum, Curcuma longa, Phyllanthus niruri, Glycyrrhiza glabra, Andrographis paniculata, Picrorhiza kurroa, Boerhavia diffusa, Eclipta alba, Aloe vera, and Tinospora cordifolia—collectively embody a rich pharmacological armamentarium of phytoconstituents that engage hepatoprotective molecular networks through mechanistically distinct yet often synergistic pathways [147].

Silybin's combined Nrf2 activation, NF-κB suppression, and anti-fibrotic HSC targeting; curcumin's multi-target pleiotropic mechanism spanning NF-κB, Nrf2, AMPK, NLRP3, and FXR; and andrographolide's covalent NF-κB p50 modification represent pharmacologically sophisticated mechanisms comparable in mechanistic breadth to purpose-designed synthetic multi-target compounds [148].

Critically, the bioavailability limitations of most hepatoprotective phytomolecules—which have historically undermined clinical translation—are being systematically addressed by phytosome complexation, liposomal encapsulation, PLGA nanoparticle formulation, and active hepatocyte-targeted delivery approaches that amplify hepatic drug exposure and therapeutic efficacy [149].

Nevertheless, the field requires urgent investment in large-scale, multicenter, randomized, histologically-verified clinical trials with standardized herbal extracts, rigorous pharmacokinetic characterization, comprehensive herb–drug interaction evaluation, and long-term safety surveillance. The integration of AI-driven target identification, precision omics profiling, gut microbiome-targeted phytotherapy, and next-generation nano-herbal delivery will define the future trajectory of herbal hepatology toward individualized, evidence-based therapeutic practice [150].

In conclusion, herbal hepatoprotective medicine—grounded in ancient empirical knowledge and validated by modern molecular pharmacology—occupies an increasingly credible and scientifically rigorous position in the contemporary management of liver diseases, with significant potential for formal clinical integration when supported by appropriately powered, mechanistically informed, and standardization-compliant translational research programs.

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