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A Systematic Review on Potential Hepatoprotective and Antifibrogenic Activities of *Curcuma longa, Andrographis paniculata, Tinospora cordifolia and Glycine max*

[1]Dr. Sayyed Mateen, [2]Ms. Priya Haldar, [3]Ms. Sakshi Das, [4]Dr. Vinod Gupta, [5]Ms. Mayuri Prabhu.

[1,4]Associate Professor, Oriental College of Pharmacy, Sanpada West, Maharashtra- 400705

[2,3,5]M. Pharm Student, Oriental College of Pharmacy, Sanpada West, Maharashtra- 400705

[1,2,3,4,5]Department of Pharmacology

ABSTRACT

Hepatic fibrosis is a progressive pathological condition characterized by excessive accumulation of extracellular matrix proteins, primarily collagen, in response to chronic liver injury. If left untreated, fibrosis may progress to cirrhosis, liver failure, and hepatocellular carcinoma, representing a major global health concern. Therefore, effective treatment is critical to prevent irreversible damage and improve patient survival.[1]

Since time immemorial, medicinal plants have been employed for managing liver disorders due to their wide safety margin and multitargeted activity. Natural origin drugs such as Curcumin (*Curcuma longa*, Class: Liliopsida, Family: Zingiberaceae, Kingdom: Plantae), Giloy (*Tinospora cordifolia*, Class: Magnoliopsida, Family: Menispermaceae, Kingdom: Plantae), Kalmegh (*Andrographis paniculata*, Class: Magnoliopsida, Family: Acanthaceae, Kingdom: Plantae), and Soy (*Glycine max*, Class: Magnoliopsida, Family: Fabaceae, Kingdom: Plantae) are recognized for their hepatoprotective and antifibrogenic properties. Mechanistically, curcumin suppresses oxidative stress and hepatic stellate cell activation [2], Giloy enhances antioxidant enzyme activity and supports hepatocyte regeneration [3], Kalmegh's andrographolide reduces inflammatory and profibrotic mediators such as TGF-β1[4], and soy isoflavones improve lipid metabolism and modulate estrogen receptor pathways.[5]

Compared to synthetic agents, these phytoconstituents provide multitargeted hepatoprotection with fewer adverse effects, cost-effectiveness, and suitability for long-term use. Additionally, polyherbal combinations offer synergistic therapeutic benefits, making them promising candidates for the development of antifibrotic drugs. Thus, Curcumin, Giloy, Kalmegh, and Soy represent safe and effective natural strategies for hepatoprotection and antifibrogenic therapy.

KEY WORDS

Hepatoprotection, Antifibrogenic activity, Liver fibrosis, Polyherbal formulation, Herbal synergy, Herbal therapy.

INTRODUCTION

Curcuma longa (Turmeric), *Tinospora cordifolia* (Giloy), *Andrographis paniculata* (Kalmegh), and Glycine max (Soyabean) have recently gained substantial scientific attention due to their potential hepatoprotective and

antifibrogenic activities. Traditionally valued in various medicinal systems, these natural compounds are increasingly being explored for their therapeutic efficacy in managing liver disorders and hepatic fibrosis. Curcumin, the principal bioactive compound derived from turmeric, exhibits potent anti-inflammatory, antioxidant, and antifibrogenic properties. It mitigates liver fibrosis primarily by suppressing the activation of hepatic stellate cells central mediators of fibrogenesis through the downregulation of fibrosis-associated markers and the induction of apoptosis in these cells.[6]

The genus *Curcuma* has a rich legacy in traditional medicine and encompasses approximately 120 recognized species. Among them, *Curcuma longa* L. (turmeric) stands out as the most widely cultivated and therapeutically significant species, thriving in warm climates across diverse geographical regions. However, taxonomic classification within this genus remains complex due to its brief flowering period and challenges in herbarium preparation caused by the delicate nature of its tubers, rhizomes, and inflorescences. The rhizome most commonly utilized for medicinal purposes contains a rich composition of phytochemicals, including non-volatile curcuminoids (curcumin, demethoxycurcumin, and bisdemethoxycurcumin) and volatile oil constituents such as mono- and sesquiterpenoids.[7]

Species of *Curcuma* have been attributed with a broad spectrum of pharmacological properties, including antiproliferative, anti-inflammatory, anticancer, antidiabetic, hypocholesterolemic, antithrombotic, hepatoprotective, antidiarrheal, carminative, diuretic, antirheumatic, hypotensive, antimicrobial, antiviral, antioxidant, larvicidal, insecticidal, antivenom, and antityrosinase effects. Of the approximately 31 *Curcuma* species investigated so far, *C. longa* (turmeric) and *Curcuma zedoaria* (Christm.) Roscoe (zedoary) have emerged as the most extensively studied and pharmacologically relevant.[8]

For centuries, traditional healers across Asia have utilized the leaves and roots of *Andrographis paniculata* to manage a wide variety of ailments, including fever, diarrhea, and intestinal worm infestations. The plant is renowned for its use as a liver tonic, blood purifier, and antidote for venomous bites and stings from snakes, scorpions, and centipedes. It has also been traditionally applied to relieve burning sensations, promote wound healing, and treat skin diseases and leprosy. The powdered form of the plant is used to alleviate itching, while the juice and macerated leaves are commonly employed as home remedies for flatulence and diarrhea in children. In traditional medicine, these preparations are often formulated into tablets and recommended for infants suffering from colic and other gastrointestinal disturbances. [9][10]

Among tribal communities, *A. paniculata* has long been valued for its astringent, analgesic, tonic, and alexipharmic (antidotal) properties. Leaf decoctions or infusions are traditionally used to treat scabies, fever, anemia, and hepatic sluggishness, while tinctures of the root serve as tonics, stimulants, and mild aperients. Various parts of the plant, either used alone or combined with other indigenous herbs, are administered across Indian and Southeast Asian medicinal systems to alleviate neuralgia, support fever recovery, and enhance liver function. The herb also serves as a principal ingredient in traditional household formulations employed as febrifuges and bitter tonics.

Phytochemical analyses have revealed that the aerial parts and roots of *A. paniculata* contain a diverse array of bioactive compounds. Terpenoids constitute the major class of metabolites responsible for much of the plant's pharmacological activity, while other significant constituents include flavonoids, polyphenols, xanthones, and both macro- and trace elements.[9][10]

Tinospora cordifolia (commonly known as Giloy or Guduchi) has been a cornerstone of Ayurvedic medicine for centuries, prized as a rasayana for systemic rejuvenation, immune balancing and recovery from febrile and inflammatory conditions. Modern scientific interest has validated many of these traditional claims and, importantly for hepatology, a growing body of experimental work has demonstrated consistent hepatoprotective effects; reduced serum transaminases, lower lipid peroxidation, improved antioxidant enzyme activities, and better histological outcomes in chemical and toxicant-induced liver injury models – positioning Giloy as a promising natural adjunct for liver protection.[11][12][14]Its broad pharmacology (alkaloids, diterpenoid lactones, glycosides and polysaccharides) offers multimodal advantages: antioxidant and anti-inflammatory activity, immunomodulation, and stimulation of hepatic regenerative pathways, attributes that make it attractive as a pleiotropic hepatoprotective candidate in preclinical research and product development.[11][12][14]

Alongside these therapeutic signals, systematic surveillance during the COVID-19 era produced important safety-focused observations: large case series and multicenter studies reported instances where concentrated giloy preparations were temporally associated with acute, immune-mediated liver injury in a minority of users, a finding that highlights the need for standardized formulations and careful clinical evaluation rather than

undermining the herb's overall hepatoprotective promise.[13] This safety awareness has in fact sharpened research approaches encouraging rigorous phytochemical standardization, dose-finding, and mechanistic toxicology alongside efficacy studies which is essential if giloy's preclinical advantages are to be translated safely into clinical use.[13]

Soy and soy isoflavones (notably genistein and daidzein) complement this picture from a different historical angle: long-standing dietary use in East Asia provided a safe-use background that accelerated biomedical investigation of isoflavones for metabolic and hepatic disorders. Over the last decade (and particularly 2018–2025), mechanistic and preclinical studies have repeatedly shown that genistein exerts antioxidant, anti-inflammatory and antifibrogenic effects–it modulates NF-κB and other inflammatory pathways, attenuates hepatic stellate cell activation and reduces extracellular matrix accumulation in animal fibrosis models–giving soy isoflavones a clear advantage as lead compounds for antifibrotic strategies.[14][15][117] Translational momentum is visible in randomized clinical trials in NAFLD/NASH populations, where soy isoflavone supplementation has improved steatosis, liver enzymes and metabolic markers in short-term studies, even though longer trials are needed to confirm durable antifibrotic benefit.[16]

When combined, these botanicals offer a multifaceted therapeutic synergy–curcumin's redox regulation, andrographolide's hepatocellular recovery, Giloy's immunomodulation, and isoflavones' antifibrotic signaling together reinforce hepatocellular integrity, suppress oxidative and inflammatory cascades, and counteract extracellular matrix accumulation. Such a rationally assembled phyto-therapeutic formulation may thus provide broad-spectrum hepatoprotective and antifibrogenic efficacy, bridging traditional wisdom with mechanistic validation and offering an integrative approach for preventing the progression of liver injury toward fibrosis.

This review explores and consolidates the current understanding of the hepatoprotective and antifibrogenic potential of Curcumin, Giloy, Kalmegh, and Soy. This review aims to provide a comprehensive overview of their mechanisms and efficacy, thereby highlighting their potential roles in the management of liver diseases and fibrosis.

PATHOPHYSIOLOGY

Liver fibrosis is caused by chronic liver injury of two different etiologies: hepatotoxic and cholestatic injuries. Hepatotoxic injury is triggered by cellular injury from outside factors including: hepatitis B and C (HBV and HCV) viral infections, alcoholic (ASH) and non-alcoholic (NASH) steatohepatitis. Cholestatic injury, which is characterized by reduced or obstructed bile flow in the liver, is caused by primary (and secondary) disease including: primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC) and biliary atresia. Liver fibrosis results in accumulation of extracellular matrix (ECM) proteins, mostly collagens Type I and Type III, followed by formation of fibrous scar, which can ultimately compromise normal liver function. Regardless of the etiology, liver fibrosis is characterized by common molecular mechanisms such as hepatocyte death, chronic inflammation with cytokine release, activation of HSCs and disruption of the epithelial or endothelial barrier. Therefore, hepatic fibrogenesis is a complex process requiring cellular and extracellular signaling [18][19].

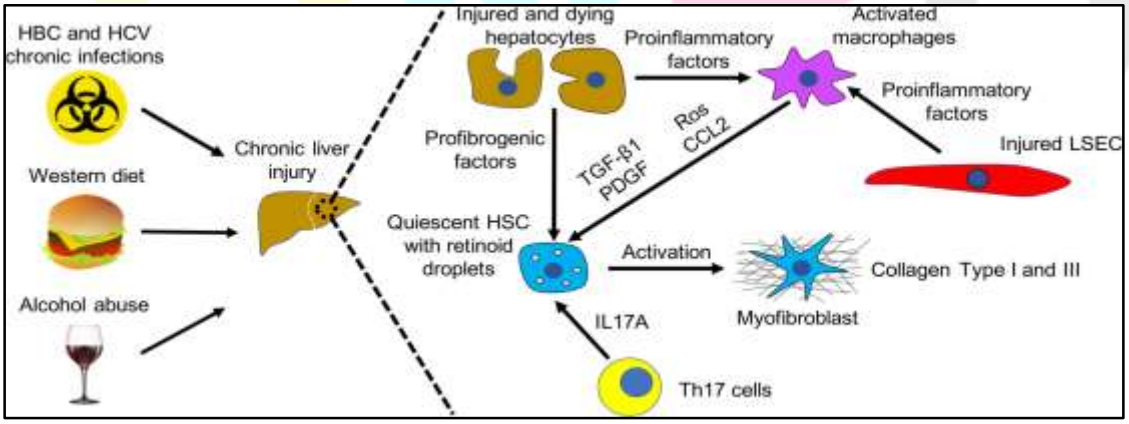

Fig. 1 Liver Fibrosis: Pathophysiology and Clinical Implications [23]

CELL TYPES IN LIVER FIBROSIS

Hepatic Stellate Cells

Hepatic stellate cells (HSCs) are the main cell type involved in liver fibrosis. In a healthy liver, HSCs remain quiescent and are located in the space of Disse, where they act as liver pericytes and store vitamin A within lipid droplets. Under conditions of continuous liver injury, HSCs reduce the expression of genes such as glial fibrillar acidic protein (GFAP) and peroxisome proliferator-activated receptor gamma (PPARγ), lose their lipid droplets, and become activated into myofibroblasts. These activated myofibroblasts express fibrogenic markers such as alpha-smooth muscle actin (α-SMA) and Collagen Type I, while proliferating and migrating to the site of liver injury to secrete extracellular matrix (ECM) components. Myofibroblasts also produce vascular endothelial growth factor (VEGF), which promotes further HSC proliferation. Liver fibrosis can be reversed when the underlying injury is removed, as myofibroblasts may undergo apoptosis or revert to an inactive state, leading to fibrosis regression. Several mechanisms are involved in HSC apoptosis; when fibrogenic signals decrease, HSCs increase the expression of death receptor-related genes like Fas and TNF receptor 1 (TNFR1), upregulate pro-apoptotic proteins such as p53, Bax, and caspase 9, and downregulate anti-apoptotic proteins like Bcl-2. Additionally, interferon-γ (IFNγ)-activated natural killer (NK) cells contribute to fibrosis resolution by eliminating activated HSCs. Beyond apoptosis and senescence, myofibroblasts can also revert to an inactivated phenotype during fibrosis regression, and these inactivated HSCs are more responsive to fibrogenic stimuli than their quiescent form [19][20].

Many studies have extensively explored the cellular origins of myofibroblasts. During liver fibrosis caused by carbon tetrachloride (CCl_4), hepatic stellate cells (HSCs) are recognized as the primary source of myofibroblasts. In contrast, during the early stages of cholestatic injury, myofibroblasts mainly arise from portal fibroblasts. These portal fibroblasts are located beneath the bile duct epithelium and, much like HSCs, become activated in response to biliary damage, expressing alpha-smooth muscle actin (α-SMA) and Collagen Type I. Additionally, bone marrow-derived cells such as fibrocytes and mesenchymal stem cells (MSCs) have been proposed as alternative sources of myofibroblasts. However, there is currently no evidence indicating that parenchymal cells like hepatocytes contribute to the myofibroblast population [19][20].

Hepatocytes

Following liver injury, hepatocytes produce fibrogenic factors like osteopontin, NOX4, TAZ, Indian Hedgehog, and Notch. They also release exosomes with miRNAs that activate hepatic stellate cells (HSCs). However, these factors alone cannot cause liver fibrosis without chronic inflammation [19].

Inflammatory cells and cytokines

While acute inflammation aids liver regeneration, chronic inflammation is harmful and crucial in liver fibrosis development. Inflammatory cells such as neutrophils, Kupffer cells, monocytes, and Th17 cells promote HSC activation by secreting cytokines and growth factors. Liver macrophages, especially Kupffer cells, are the primary source of TGF-β, a key factor in liver fibrogenesis. TGF-β activates HSCs into myofibroblasts, promoting collagen synthesis. Blocking TGF-β reduces liver fibrosis. Th17 cells secrete IL-17, another profibrogenic cytokine, and disrupting IL-17 signaling lessens liver fibrosis development [19][21][22].

Th17 cells secrete IL-22, which can either protect against or promote liver fibrosis depending on context. Macrophage-derived CCL2 recruits monocytes and activates hepatic stellate cells (HSCs), while platelet-derived growth factor (PDGF) acts as a strong mitogen driving HSC activation and fibrosis progression. Neutrophils and Kupffer cells generate reactive oxygen species (ROS) via NADPH oxidase (NOX1/NOX4), further promoting fibrosis; inhibiting these enzymes reduces liver injury and HSC activation. Conversely, macrophages also aid fibrosis resolution by inducing myofibroblast apoptosis, clearing debris, and releasing matrix metalloproteinases (MMP9, MMP12, MMP13), which degrade the extracellular matrix and suppress tissue inhibitor of metalloproteinases (TIMP1), thereby facilitating tissue repair [19][21][22].

Liver sinusoidal endothelial cells

In a healthy liver, liver sinusoidal endothelial cells (LSECs) regulate nutrient exchange, lymphocyte recruitment, and cytokine secretion. Their fenestrated structure and nitric oxide (NO) production help maintain hepatic stellate cells (HSCs) in a quiescent state. During chronic liver injury, however, LSECs lose fenestrations, reduce

endothelial NO synthase (eNOS) activity, and undergo capillarization, which eliminates their ability to suppress HSC activation. Damaged LSECs then release profibrogenic mediators such as TGF-β1, PDGF, TNFα, interleukins, and VEGF, promoting inflammation, angiogenesis, and HSC activation. Interestingly, VEGF has dual effects it contributes to fibrosis through angiogenesis but also supports fibrosis resolution by regulating vascular remodeling and macrophage activity. NO plays a crucial antifibrotic role by preventing HSC activation and inducing apoptosis of VEGF-stimulated HSCs via mitochondrial ROS generation. Overall, chronic hepatic injury leads hepatocytes and LSECs to release inflammatory and fibrogenic factors, causing sustained HSC activation, collagen deposition, and scar formation that compromise liver function[19][24][25].

Animal models of fibrotic liver diseases

Administration of carbon tetrachloride (CCl_4) in mice or rats is the most commonly used model of toxin-induced experimental liver fibrosis. In mice generally 0.5 to 2 mL/Kg body weight of CCl_4 is administered either intraperitoneally or by oral gavage two to three times per. CCl_4 treatment causes activation of HSCs followed by deposition of ECM and development of highly reproducible liver fibrosis after 4 to 6 weeks from the first CCl_4 injection. Cytochrome P450 2E1 (CYP2E1) in centrilobular hepatocytes metabolizes CCl_4 to generate toxic trichloromethyl (CCl_3) radicals, which promote liver necrosis. Interestingly, withdrawal of CCl_4 treatment results in full regression of liver fibrosis[19][26].

Thioacetamide (TAA) is another model of experimental liver fibrosis in rodents. TAA can be either administered either intraperitoneally (150–200 mg/Kg body weight) three times a week or orally by adding TAA (200 mg/L) to the drinking water. In rats TAA treatment causes fibrosis and cirrhosis between 12–16 weeks, in mice between 16–24 weeks. TAA affects both zone 1 and zone 3 hepatocytes causing portal-portal and portal-central fibrosis, which eventually recapitulates a state similar to human cirrhosis. Moreover, unlike CCl_4-induced fibrosis which regresses rapidly, fibrosis lasts for more than 2 months after cessation of TAA treatment. Similarly to CCl_4, TAA is also bioactivated by CYP2E1 in the liver, giving rise to *S S*-dioxide, which is most likely the agent causing hepatotoxicity[19][27].

Administration of dimethylnitrosamine (DMN) is less commonly used as fibrosis model. 10 mg/Kg body weight of DMN is administered intraperitoneally twice a week. DMN induces activation of HSCs and Kupffer cells with liver fibrosis development within 4 weeks. A disadvantage of using DMN is its carcinogenic properties, which may complicate interpretation of the results.

Paracetamol causes liver injury in a dose-dependent manner, with risks heightened by alcohol use, fasting, or infection. Normally, hepatocytes metabolize paracetamol through cytochrome P450 enzymes, mainly CYP2E1, producing harmless byproducts. In overdose, however, the reactive metabolite N-acetyl-p-benzoquinone imine (NAPQI) binds to mitochondrial proteins in the electron transport chain, leading to mitochondrial dysfunction. This dysfunction, rather than CYP-mediated ROS alone, is now recognized as the main source of oxidative stress. Excess activity of mitochondrial complex I increases free radical generation, while mitochondrial superoxide reacts with nitric oxide to form peroxynitrite an especially reactive molecule responsible for oxidative and nitrosative damage during paracetamol-induced hepatotoxicity[19][28].

Typical Dose for mice ranging from 250–500 mg/kg (oral or intraperitoneal, usually IP) given as a single dose after overnight fasting. For rats dose ranges from750–1000 mg/kg (oral or IP) single dose. Produces acute hepatocellular necrosis within 12–24 hours (ALT/AST elevation, histological necrosis). Paracetamol is excellent for modeling acute hepatotoxicity, but less reliable for producing fibrosis compared to CCl_4, TAA, or bile duct ligation models [19][28].

EXPLORATION OF HEPATOPROTECTIVE AND ANTI-FIBROGENIC POTENTIALS OF HERBAL DRUGS

1. *Curcuma longa*

Common Names:
English: Turmeric
Hindi: Haldi
Marathi: Halad

Active Constituent: Curcumin

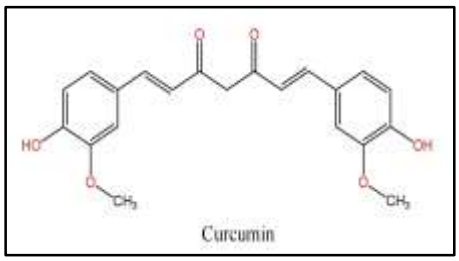

Fig. 2 Active Constituent of Curcuma longa

Mechanism of Action:

Liver injury is characterized by increased reactive oxygen species (ROS), NF-κB activation, and upregulation of TGF-β. Curcumin inhibits NF-κB, leading to a reduction in pro-inflammatory cytokines such as TNF-α and IL-1β. It also activates the Nrf2 pathway, enhancing the activity of antioxidant enzymes including SOD, CAT, and GSH. Furthermore, curcumin suppresses TGF-β/Smad signaling, which inhibits hepatic stellate cell activation (α-SMA expression) and reduces collagen deposition, ultimately contributing to fibrosis regression.

Uses:

Curcuma longa exhibits potent hepatoprotective effects by reducing oxidative stress and inflammation in the liver. It prevents hepatocellular injury induced by chemical toxins, alcohol, or metabolic disorders, and attenuates fibrosis by inhibiting hepatic stellate cell activation and collagen deposition. Curcumin's antioxidant and antifibrotic properties make it a strong candidate for preventing and managing liver fibrosis.[29][30][31]

2. *Andrographis paniculata*

Common Names:

English: Green Chiretta, King of Bitters.

Hindi: Kalmegh, Kiryat, Mahatit.

Marathi: Olen kirayat, Chimani.

Active Constituents: Andrographolide (diterpene lactone)

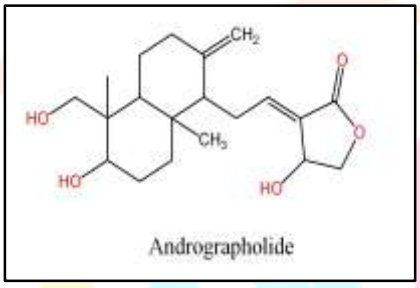

Fig. 3 Active Constituent of Andrographis paniculata

Mechanism of Action:

During liver injury, mitochondrial stress and inflammatory mediators are elevated. Andrographolide inhibits NF-κB, COX-2, and iNOS, resulting in decreased levels of pro-inflammatory cytokines such as TNF-α and IL-6. It enhances mitochondrial protection and increases detoxification enzyme activity. Additionally, andrographolide downregulates profibrotic genes, including TGF-β1 and COL1A1, which reduces hepatic stellate cell activation and extracellular matrix synthesis, thereby improving hepatic regeneration.

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downregulates profibrotic genes, including TGF-β1 and COL1A1, which reduces hepatic stellate cell activation and extracellular matrix synthesis, thereby improving hepatic regeneration.[32][33][34]

3. *Tinospora cordifolia*

Common Names:
English:Heart-leaved moonseed, Indian tinospora, Giloy
Hindi: Giloy, Guduchi, Gulancha
Marathi: Gulvel, Amrutvel, Amrita
Active Constituents: Tinosporaside (Diterpenoid lactones), Berberine, Magnoflorine (alkaloids), Polysaccharide

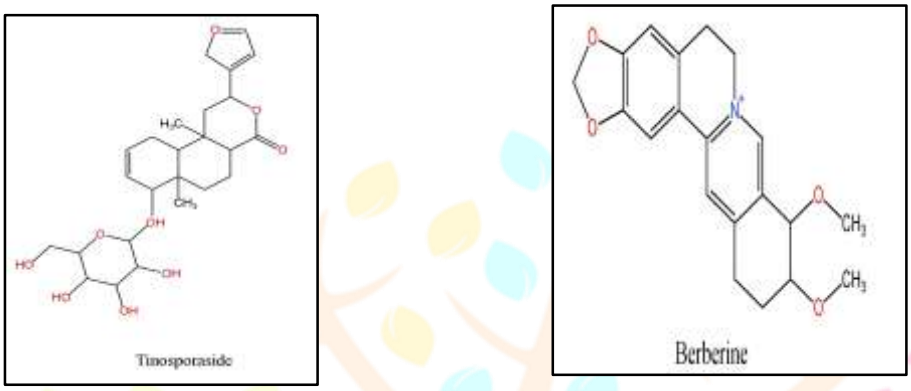

Fig. 4 Active Constituents of Tinospora cordifolia

Mechanism of Action:

In liver injury, oxidative stress and immune activation are prominent. *Tinospora cordifolia* scavenges ROS and increases the activity of antioxidant enzymes such as SOD, CAT, and GPx, reducing lipid peroxidation. It modulates the immune response by decreasing pro-inflammatory cytokines (TNF-α, IL-6) and increasing anti-inflammatory cytokines (IL-10). These effects improve mitochondrial and hepatic function, reduce hepatocellular damage, and enhance histological recovery. Preclinical studies also suggest possible downregulation of profibrotic signaling; however, some reports indicate idiosyncratic immune-mediated liver injury in humans, emphasizing the need for standardized formulations and careful monitoring.

Uses:

Tinospora cordifolia protects the liver by reducing oxidative stress, modulating immune responses, and improving mitochondrial and hepatic function. It has demonstrated efficacy in preventing hepatocellular damage in experimental models and shows potential antifibrotic activity through modulation of profibrotic signaling. Due to some reports of idiosyncratic liver injury in humans, clinical use requires standardized preparations and monitoring.[35][36][37]

4. *Glycine max*

Common Names:
English: Soybean or soya bean.
Hindi: Soyabean
Marathi: Soyabean
Active Constituents: Genistein, Daidzein (isoflavones)

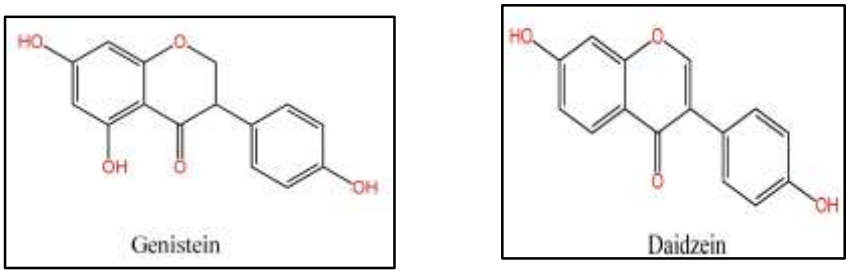

Fig. 5 Active Constituents of Glycine max

Mechanism of action:
In conditions such as NAFLD and toxin-induced liver injury, metabolic dysregulation and elevated TGF-β contribute to fibrosis. Genistein and other soy isoflavones downregulate TGF-β/Smad signaling and hepatic stellate cell activation, resulting in reduced α-SMA expression and collagen deposition. They also inhibit inflammatory pathways, including NF-κB, decreasing cytokine production. Additionally, soy isoflavones improve lipid metabolism and insulin sensitivity, which helps reduce steatosis and secondary fibrogenic stimuli, collectively exerting hepatoprotective and antifibrotic effects.

Uses:
Soy isoflavones exert hepatoprotective and antifibrotic effects by improving lipid metabolism, reducing inflammation, and inhibiting hepatic stellate cell activation. They are particularly useful in conditions such as NAFLD and metabolic liver disorders, where they decrease steatosis, improve insulin sensitivity, and reduce collagen deposition, thereby helping prevent progression to fibrosis.[38][39][40]

POLYHERBAL FORMULATIONS, SYNERGY AND CHALLENGES

Rationale:
Polyherbal formulations are conceptually attractive for complex, multifactorial diseases such as liver fibrosis because they combine complementary pharmacologic activities to target multiple pathogenic nodes simultaneously. Liver fibrogenesis involves hepatocellular injury, oxidative stress, inflammation, activation of hepatic stellate cells (HSCs) through TGF-β/Smad and related pathways, and metabolic drivers (insulin resistance, lipotoxicity). A rationally assembled combination that (a) reduces oxidative injury, (b) suppresses inflammation, (c) blocks HSC activation and ECM production, and (d) improves metabolic homeostasis therefore has a higher theoretical chance of interrupting progression to advanced fibrosis than a single-target agent. Network-pharmacology and experimental evidence increasingly support this multi-target approach for botanicals, provided pharmacokinetic compatibility, safety, and standardization are addressed up front.[50][51]

Mechanistic rationale: how multi-component combinations address fibrosis

- Multi-node coverage. Combining agents that (for example) inhibit NF-κB (reducing proinflammatory cytokines), activate Nrf2 (boosting antioxidant defenses), and inhibit TGF-β/Smad (preventing HSC trans-differentiation) attacks fibrosis at initiating, propagating, and effector levels of the disease cascade. This multi-node coverage reduces single-point failure risk and may permit lower individual component doses.[41][42][51]
- Complementary pharmacology. Some botanicals (e.g., curcumin) exert strong anti-TGF-β and antioxidant effects, while others (e.g., genistein) improve metabolic drivers (lipid handling, insulin sensitivity) that feed fibrogenesis. Andrographolide contributes anti-inflammatory and mitochondrial protective effects, while Tinospora provides immunomodulation and antioxidant support; together these complement and reinforce one another.[43][44][47][48]
- Systems/network validation. Modern network pharmacology and experimental validation studies show that multi-constituent extracts can act on overlapping gene/protein networks relevant to liver injury and fibrosis, justifying combination testing rather than single-compound testing alone.[49]

Evidence summary (Curcumin, Andrographolide, Tinospora, Soy)

- Curcumin (*Curcuma longa* - Turmeric)
  Curcumin has well-documented anti-oxidative, anti-inflammatory and antifibrotic activities. Mechanistically it inhibits NF-κB signaling and TGF-β/Smad pathways, and activates Nrf2-dependent antioxidant responses — effects repeatedly shown in animal models of CCl_4, TAA, and diet-induced liver injury and summarized in 2018–2024 reviews. These multi-target actions make curcumin a logical backbone for antifibrotic polyherbal design.[41][42]

- Andrographolide (*Andrographis paniculata* - Kalmegh)
  Preclinical studies (including an influential 2018 murine study) demonstrate that andrographolide attenuates liver inflammation and fibrosis by inhibiting TLR4/NF-κB and TGF-β1/Smad2 signaling, reducing cytokine

production, protecting mitochondria and decreasing HSC activation and collagen deposition. Subsequent reviews reinforce its promise as a hepatoprotective/antifibrotic phytochemical.[43][44]

- Tinosporaside (*Tinospora cordifolia* - Giloy)
  Tinospora extracts increase endogenous antioxidant enzymes (SOD, CAT, GPx), reduce lipid peroxidation and modulate immune responses (reducing TNF-α/IL-6 and elevating IL-10) in toxin models, producing hepatoprotective histological and biochemical improvements. However, several clinical case series since 2021 have raised safety signals for idiosyncratic, immune-mediated liver injury associated with some concentrated Giloy preparations — an essential translational caveat that mandates extract standardization and safety testing.[45][46][47]

- Genistein / Daidzein (*Glycine max* - Soyabean)
  Isoflavones exhibit antioxidant, anti-inflammatory and metabolic regulatory activity. Genistein downregulates TGF-β/Smad signaling and inhibits HSC activation in preclinical models and has shown beneficial effects on metabolic and inflammatory markers in small clinical studies of NAFLD/related disorders. Recent randomized trials and meta-analyses (2019–2024) report improvements in steatosis and transaminases, though robust long-term fibrosis endpoints require larger trials.[48]

Mechanisms of synergy - plausible molecular interactions

- Additive and complementary signaling suppression. Curcumin and genistein both reduce TGF-β-driven signaling through somewhat different molecular interactions. Together, they can achieve greater TGF-β suppression at lower doses. [41][42][48]
- Inflammation and metabolic correction. Andrographolide's anti-inflammatory and mitochondrial protective effects lower necroinflammation. Genistein improves insulin sensitivity. When combined, these reduce both the inflammatory and metabolic drivers of HSC activation. [43][48]
- Antioxidant stack. Tinospora's ability to scavenge free radicals and curcumin's Nrf2 activation support each other, restoring redox balance more effectively than either one alone. [41][47]
- Network synergy validated by in silico and omics. Studies in network pharmacology show overlapping target groups for multi-herb formulations. Experimental follow-up has demonstrated better functional outcomes for certain proven combinations. [49][51]

Safety signals, reports of herb-associated hepatotoxicity and toxicology requirements

- Although many of the botanicals have historical use, case reports and surveillance data indicate that herbal supplements can cause hepatotoxicity or idiosyncratic liver injury in susceptible individuals; furthermore, combining herbs will complicate causality assessment. For example, safety profiles for *T. cordifolia* are under scrutiny in pharmacovigilance databases and authoritative resources that discuss both purported hepatoprotection and reported adverse events have highlighted "idiosyncratic drug-induced liver injury" (DILI) linked to *T. cordifolia* or its multi-herbal formulations. These ADRs are thought to be immune-mediated or due to adulteration, misidentification (e.g., *T. crispa* instead of *T. cordifolia*), or overuse in individuals with pre-existing autoimmune or metabolic conditions [53][54][55][56]
- Regulatory toxicology testing must follow international guidance (e.g., OECD Test Guidelines 407/408/452 etc.) with acute, subacute and chronic toxicity, genotoxicity and, where relevant, reproductive and carcinogenicity testing to support clinical trials and labeling claims.

Translational gaps between animal models and humans

- Most hepatoprotective and antifibrogenic studies, including CCl_4-induced models, provide preclinical evidence, but human translation remains uncertain due to differences in metabolism, dose scaling, and disease etiology.[57]
- Moreover, rodent models simulate acute or subacute injury but not chronic fibrosis progression as observed in human liver disorders.[58] Bridging this gap requires clinically relevant models, long-term safety assessments, and biomarker-based translational endpoints.

FUTURE PROSPECTIVES

The integration of advanced omics technologies (metabolomics, proteomics, transcriptomics) with traditional phytochemistry offers a pathway to identify bioactive signatures responsible for hepatoprotection and fibrosis attenuation.[59] Future research should focus on:

- Formulation optimization through nanotechnology-based delivery systems.
- Mechanistic mapping of polyherbal synergy using AI-driven modeling and network pharmacology.
- Biomarker discovery for early detection of antifibrogenic activity.
- Clinical validation via well-designed randomized controlled trials assessing efficacy, safety, and pharmacokinetics.

Ultimately, the integration of ethnopharmacological wisdom with modern analytical and computational tools may pave the way for the rational design of evidence-based polyherbal hepato-therapeutics.[60]

CONCLUSION

The collective evidence from the literature highlights the significant hepatoprotective and antifibrogenic potential of Curcuma longa, Tinospora cordifolia, Glycine max, and Andrographis paniculata. These medicinal plants exert their protective effects mainly through antioxidant, anti-inflammatory, and antifibrotic mechanisms that alleviate hepatocellular injury and regulate key profibrogenic factors. Despite promising preclinical data, comparative and combinational studies exploring their synergistic effects remain limited. Therefore, further in-vivo investigations and mechanistic evaluations are needed to validate and optimize their therapeutic efficacy. The present review serves as a foundation for our ongoing experimental research designed to evaluate the hepatoprotective and preliminary antifibrogenic activities of these four herbal extracts in animal models.

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