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# Hepatoprotective Potential of Herbal Bioactive Components: Phytochemistry, Mechanism, and Therapeutic Insights

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**Keywords**

Hepatoprotection, Herbal medicine, Liver disease, Bioactive compounds, Natural antioxidants, etc

**Abstract**

Liver disease has emerged as a major global health challenge, accounting for millions of deaths annually and placing a substantial burden on healthcare systems worldwide. Its increasing prevalence is closely linked to excessive alcohol consumption, long-term drug exposure, industrial and environmental chemicals, viral infections, and metabolic disorders such as obesity and diabetes. Although synthetic hepatoprotective drugs are widely prescribed, their clinical application is often limited by adverse effects, high toxicity risk, variable therapeutic efficacy, and limited ability to promote liver regeneration. These shortcomings have intensified scientific interest in natural, plant-based hepatoprotective agents as safer and more effective alternatives. Herbal bioactive compounds—including flavonoids, alkaloids, phenolic acids, terpenoids, and saponins—exhibit a wide spectrum of pharmacological properties such as antioxidant, anti-inflammatory, anti-fibrotic, immunomodulatory, and cytoprotective activities. These compounds contribute to the restoration of liver architecture, enhancement of detoxification pathways, reduction of oxidative stress, and normalization of liver enzymes and biomarkers. Compared to many synthetic drugs, herbal agents often demonstrate improved safety profiles and better patient tolerance. However, despite promising preclinical and clinical findings, significant gaps remain in understanding their molecular mechanisms of action, bioavailability, pharmacokinetics, and long-term clinical efficacy. This review systematically evaluates evidence from both clinical trials and experimental studies on 13 major natural products, including Liv 52, probiotics, phospholipids, vitamin D, artichoke, berberine, and turmeric. It examines their botanical sources, active constituents, therapeutic applications, and underlying mechanisms of hepatoprotection in liver disorders such as non-alcoholic fatty liver disease (NAFLD), hepatitis, alcoholic liver disease, and drug-induced hepatotoxicity. Furthermore, this review critically assesses the quality of existing data and highlights the urgent need for standardized dosing, rigorous toxicity evaluation, and large-scale randomized clinical trials to fully harness the therapeutic potential of herbal medicines in liver disease management.

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## 1. Introduction

### 1.1. Global Burden of Liver Diseases

Liver disease is now an international epidemic rather than a silent issue. Alcohol, drugs, chemicals, infections, and even metabolic problems continue to be major pressures on health systems around the world, and complications associated with chronic liver impairment claim millions of lives each year [1]. Often referred to as the body's sanitation factory, the liver endures silent suffering until damage becomes irreversible. It's too late after that. Alcohol use alone is an important contributing factor. Drinking is the sole source of disorders including Alcohol Use Disorders (AUDs) and Alcoholic Liver Disease (ALD), which collectively contribute greatly to globally mortality and disability. Alcohol has really been linked to over half of all fatalities from chronic liver disease [2]. statistics don't just represent statistics; they also indicate young lives lost, families shattered, and communities burdened. Millions of people still die from hepatitis B and C. The hepatitis B virus (HBV) killed more over half a million people annually in 2019 and infected almost 296 million individuals. Over 58 million people were afflicted by the hepatitis C virus (HCV), which causes 300,000 fatalities annually [3]. These deaths—often young and frequently avoidable—are more than just statistics. The burden is greatest in areas like as Africa, the Western Pacific, and portions of Asia. The situation is exacerbated by poverty, low immunization rates, and

restricted access to care. But infections are not alone. Alcohol-related liver disease (ALD) remains a leading cause of cirrhosis and liver cancer [4]. In 2016, almost half of all global liver deaths—about 588,000—were linked directly to alcohol. Disability-adjusted life years (DALYs) lost to ALD cross into the tens of millions. Eastern Europe, West Africa, and Central Asia are among the worst hit. Yet, alcohol is everywhere. And its damage is often underestimated [5]. Then there is non-alcoholic fatty liver disease (NAFLD). Once overlooked, now an epidemic. Over 1.2 billion people worldwide are estimated to be living with NAFLD, driven by obesity, diabetes, and lifestyle changes. The Middle East, North Africa, China, and India show some of the highest numbers. Death rates from NAFLD are rising, silently but steadily. Unlike viral hepatitis, there is no vaccine. No quick cure. Chemicals and drugs add another layer. From industrial toxins to prescribed medications, hepatotoxicity is a hidden but significant contributor. Modern lifestyles and increasing drug exposure only magnify the risk. The truth is hard. Chronic liver disease is growing, not shrinking [6]. The drivers are multiple—alcohol, drugs, chemicals, infections, metabolism. Together, they form a storm. A preventable tragedy, unfolding globally. The burden is uneven but universal. Africa and Asia wrestle with HBV and HCV. The Middle East and North Africa with NAFLD. Eastern Europe and Central Asia with alcohol. High-income countries, on the other hand, now report increasing hepatocellular carcinoma, a reflection of shifting etiologies. What's striking is this: despite vaccines, despite antiviral drugs, despite knowledge—mortality still climbs. Disability-adjusted life years (DALYs) lost to liver disease are rising. Quality of life is eroded. The economic burden is staggering. And the pace of change is quick [7]. This is not just a disease problem. It is a societal one. Lifestyle, culture, poverty, health systems, they all shape the geography of liver disease. Different causes, same outcome. A global burden that is heavy. Growing. And mostly, preventable [8].

### 1.2. Limitations of Synthetic Drugs for Hepatoprotection

It is impossible to ignore the severe limits of synthetic medications created for hepatoprotection. Although they are a fundamental component of medical treatment and can appear to be essential, the truth is far less comforting. Drug-induced liver injury is not an uncommon occurrence; in fact, it is responsible for a startling 50% of all cases of acute liver failure, up to 10% of cases of acute hepatitis, and 5% of hospitalizations [9]. The fact that almost 75% of idiosyncratic drug reactions—those erratic and strange side effects—lead to liver transplantation or death is startling, and to be honest, unsettling. Vulnerable categories, such as older folks, those with pre-existing diseases, and those taking several medications, are particularly at danger from the growing list of synthetic drugs that have been stopped due to their hepatotoxicity [10]. Serious side effects only arise after the drugs are made available to the general public, as even thorough clinical trials and premarketing studies often stop near of capturing the full scope of the risks. Sometimes the liver's natural defenses, such as glutathione, are depleted by toxic metabolites, which can lead to catastrophic cellular damage [11]. At any moment, a medication meant for treatment can become the root cause of a fatal disease. Despite advances in technology, no artificial substance has yet to resolve the scarcity of transplantable organs or eradicate the unpredictable nature of liver damage. The medical community is increasingly looking for novel treatments and reexamining more conventional, older methods as a result of this crisis, but the problem is still unresolved, and every unpleasant case that is published puts more strain on patients and physicians. Long-term safety is called into question by the adverse effects of even well-known treatments, such as corticosteroids, interferons, or antiviral drugs, which include immunosuppression, depression, resistant virus strains, and organ damage [12]. Furthermore, traditional medications may provide nothing more than a slight respite and are not always curative; the efficacy of synthetic hepatoprotective medicines is extremely variable and frequently eclipsed by unfavorable results in real-world settings, particularly with chronic liver illnesses. The promise of novel medications usually falls short when confronted with human variability and intricate illness pathways, as there is mounting evidence that chemicals behave differently in laboratory models and human patients. Add to this the expense, the challenge of obtaining cutting-edge treatments, and the sobering fact that synthetic medications hardly ever result in the regeneration or reversal of liver tissue damage. There is still a chance of sudden organ failure [13]. The shortcomings of synthetic drugs for hepatoprotection have prompted active research into alternatives, especially plant-based compounds and nanomedicine—but even these approaches have their own obstacles to overcome in light of these issues and the continuous search for safe, effective, and reasonably priced solutions [14].

### 1.3. Importance of Natural and Herbal Compounds

So, here's the thing natural and herbal substances? Yeah, they're super crucial for keeping your liver in shape. Because, well, they've got these hepatoprotective properties. I mean, liver diseases are a huge problem, right? All over the world, people are struggling with issues caused by autoimmune troubles, metabolic syndromes, toxins from meds, drinking too much booze, and nasty viral infections [15]. And honestly, sometimes the usual treatments just don't cut it. They can be pretty harsh with side affects you don't want, or just don't work well enough, and man, some of them cost way too much! So, that's why people are really turning their eyes to natural bioactive stuff from plants. These look promising to fight off liver damage from toxins and all the messy complications that follow. Now, medicinal plants have this bunch of goodies in them antioxidants, anti-inflammatories, compounds that mop up harmful free radicals [16]. We're talking flavonoids, alkaloids, phenolic acids, terpenoids, saponins, the whole squad. They help protect liver

cells from stress, irritation, and scarring [17]. Plus, these substances help your liver cells heal and regenerate. They also bring down those pesky markers you often hear about AST, ALT, ALP the stuff doctors check to see if your liver is happy or not. These natural compounds? They're pretty attractive because they usually don't bring the harsh side effects like some drugs do, and hey, they tend to be affordable too. Lots of studies yeah, in test tubes, animals, even humans have proven their benefits. They've shown effects on a range of liver diseases like liver cancer, viral hepatitis, alcohol-related liver problems, and even fatty liver disease. But here's the catch — despite their long history and huge variety, science is still figuring out exactly how these compounds work at the molecular level [18]. And honestly, many of them don't get absorbed well or break down too quickly. So, there's ongoing research to make better versions that work more efficiently inside the body. All in all, natural and herbal substances seem to offer some serious hope. They mostly help by knocking down inflammation and oxidative damage, cleaning up toxins, and keeping liver function strong. So yeah, they're becoming a pretty important part of the global fight against liver diseases [19].

### 1.4. Aim of the Review

A Thorough Analysis of Clinical Trials on Natural Products as Hepatoprotective Agents (Plants 2024) This review primarily explores the results of clinical trials conducted on 13 chosen natural products, such as probiotics, phospholipids, vitamin D, algae (spirulina), plants and substances produced from them (e.g., artichoke, berberine, turmeric), and probiotics. Data on these products' effects on liver function will be gathered, and their use in NAFLD and other liver illnesses will be critically compared [20]. Based on clinical evidence, the review discusses which natural products would be most useful in supporting liver outcomes. The aim of this review is to systematically explore and document the potential of Bangladeshi ethnopharmacological plants in treating liver diseases, focusing on their sources, constituents, therapeutic uses, and mechanisms of action. It compiles in vivo, in vitro, and clinical studies on active compounds in plants traditionally used for liver disorders, highlighting a rich heritage of herbal medicines and their role in healthcare in Bangladesh. The preclinical and clinical data on Liv.52, a popular polyherbal formulation that has been used for more than 50 years in India and other nations, are the main subject of this review [21]. Examining its effectiveness and safety in treating chronic liver illnesses, such as alcoholic liver disease, hepatitis B, NAFLD, NASH, and drug-induced hepatotoxicity, is the goal. It assesses the mechanisms and therapeutic potential that enable the supportive treatment of chronic liver disease and help to alleviate its symptoms. This review analyzes the hepatoprotective potential of nine medicinally important herbs selected based on ethnomedicinal records in South Asia for treating various liver-related pathological conditions. It critically evaluates available toxicological and pharmacological data to guide future research and development of these natural products as potent hepatoprotective agents or dietary supplements [22]. The review aims to pave avenues for therapeutic formulation development by identifying promising plant species and their bioactive phytoconstituents. The objective of this review was to collect data on the hepatoprotective potential of Brazilian native plants studied in the last 15 years. It emphasizes the modes of extraction, activity indicators, and bioactive compound identification, focusing on animal models of hepatic lesions and in vivo confirmation of hepatoprotective effects. This study aims to highlight plants with potential for developing new hepatoprotective formulations and to support economic sustainability by utilizing plant parts with low commercial value (by-products, bio-residues). This study aimed to offer a novel perspective on a medicinal product originating from fresh young shoots of Rosmarinus officinalis L. by testing its hepatoprotective activity [23]. The objective was to evaluate the product's chemical composition (polyphenols and terpenoids) and to ascertain its hepatoprotective effect through an antioxidant mechanism in experimentally induced hepatotoxicity in rats. The study seeks to validate the plant as a potential source for hepatoprotective pharmaceutical formulations [24].

## 2. Overview of the Liver Injury and Hepatotoxicity

### 2.1. Causes

Liver damage is a multifaceted, smoldering process that may be sudden or insidious. It is not due to one cause. The liver is the busiest organ within the body, constantly filtering toxins, metabolizing drugs, and regulating metabolism. Yet the rhythm of the liver goes out of sync when the enormous amount of toxic chemicals it filters build up. It attempts to repair, but persistent or repetitive injury triggers scar tissue to replace regular tissue, leading to fibrosis and, in severe cases, liver failure [25]. The most common causes of liver damage seen daily and in the practice of medicine are as follows. Our livers filter a huge amount of stuff every day, such as medicines, vitamins, poisons, and even food additives. Nevertheless, it can take so much before collapsing. Some medications may be surprisingly uncomfortable despite their extensive use. Acetaminophen, a frequent painkiller used in many over-the-counter medicines, can overwhelm the detox system of the liver and lead to liver cell death, for instance, if taken in excess. Other medications, including some antibiotics, anticonvulsants, or "natural" herbal supplements, can also quietly damage the liver, particularly when taken on a regular basis or for a prolonged period [26]. The load is increased when environmental toxins such as the chemical toxins carbon tetrachloride are also involved. These substances increase oxidative stress by producing free radicals, which create internal damage to cells. The liver can recover and regenerate in new tissue in the early phases. But repair becomes scarring and the organ weaker and less flexible if the exposure continues. One of the world's most frequent

and avoidable causes of liver injury is still alcohol. chemicals such as acetaldehyde, which actually harm liver cells [27]. Fatty liver is the first phase, which is precipitated by inflammation and deposits of fat within the tissue of the liver over time. Individuals develop more advanced diseases such as cirrhosis, fibrosis, or alcoholic hepatitis from excessive consumption of alcohol, in which healthy cells are replaced with scar tissue. It is surprising to find that although nearly all heavy drinkers develop fatty liver, not everyone develops severe liver disease. This would suggest that the actual vulnerability or resilience of an individual's liver can be determined by his or her genetic makeup, diet, and other lifestyle factors [28]. Liver function is also seriously impaired by hepatitis viruses, especially types B and C. These viruses induce inflammation and cell death by infecting liver cells directly. The disease can quietly form scar tissue and lead to fibrosis or even liver cancer if it goes untreated for years. Viral hepatitis remains among the top causes of liver illness and mortality globally, even with enhanced vaccinations and antiviral drug cover. Viruses and alcohol are not the sole dangers to the liver caused by contemporary lifestyles. Non-alcoholic fatty liver condition (NAFLD), induced by ailments such as obesity, diabetes, and metabolic syndrome, is like the damage alcohol causes but does not involve alcohol consumption [29]. Inflammation starts when the liver gets too fat and causes non-alcoholic steatohepatitis (NASH). This condition brings together fibrosis, cellular damage, and fat deposits into one, vicious cycle. Genetic predispositions and insulin resistance exacerbate the problem, as does poor diet and a lack of exercise. These metabolic factors, unlike alcohol-related disorders, trace their origins to diet and lifestyle, indicating that our dietary and lifestyle choices might pose a higher danger to the liver today than the alcohol we drink [30].

### 2.2. Pathophysiology: Oxidative Stress, Inflammation, Fibrosis, Apoptosis

The primary mechanism behind hepatic injury often involves oxidative stress and inflammatory signaling. If hepatocytes are exposed to drugs or toxins, metabolic activation through enzymes like cytochrome P450 produces reactive intermediates that bind to cellular macromolecules. Free radicals and reactive oxygen species (ROS) in excessive amount initiate lipid peroxidation and mitochondrial dysfunction, leading to necrosis or apoptosis of liver cells. Also, chronic oxidative stress promotes fibrosis through the activation of hepatic stellate cells and the release of pro-fibrotic cytokines such as TGF-β and TNF-α. Drug-induced liver injury (DILI) remains a major cause of acute liver failure and drug withdrawal worldwide. It can be predictable (dose-dependent, like acetaminophen toxicity) or idiosyncratic (unexpected, such as with isoniazid or carbamazepine) [31]. The metabolites of these drugs often deplete glutathione (GSH), causing cellular damage when detoxification capacity is exhausted. Liver lesions manifest in various morphological forms including hepatocellular necrosis, cholestasis, The body metabolizes alcohol to create reactive fatty changes (steatosis), and vascular lesions. Acute injuries cause enzyme leakage of ALT, AST, and ALP into circulation, while chronic injury develops into fibrosis, cirrhosis, or hepatocellular carcinoma (HCC) if oxidative damage and inflammation persist. The natural progression usually follows stages initial oxidative injury, inflammatory cell infiltration, fibrotic remodeling, and ultimately necrotic replacement of parenchyma [32]. Persisting exposure to alcohol, viral hepatitis, or metabolic disorders accelerates this cycle, profoundly impacting global health: nearly two million deaths annually result from cirrhosis, hepatitis, or liver cancer complications. Despite advances in pharmacology, effective hepatoprotective agents are limited. Current drugs such as N-acetyl-L-cysteine (for acetaminophen overdose) restore GSH and quench free radicals but are only effective when given early. Transplantation remains the final option in end-stage liver failure. Natural compounds—rich in flavonoids, polyphenols, and terpenoids—show promising hepatoprotective potential through antioxidant and anti-inflammatory actions [33]. Flavonoids like quercetin, apigenin, and hesperetin modulate NF-κB, Nrf2, and MAPK signaling pathways, reducing oxidative load and inhibiting fibrotic progression. Herbal formulations from *Silybum marianum*, *Phyllanthus niruri*, and *Picrorhiza kurroa* are traditional yet biologically validated remedies enhancing liver regeneration and enzymatic balance. Synthetic molecules like bicyclol—derived from *Schisandra chinensis*—have also proven useful for viral and chemical hepatitis due to their antioxidant, immunomodulatory, and anti-fibrotic profiles [34]. Experimental data even suggest that hybrid molecules combining lipophilic antioxidants with herbal extracts (for instance, *Salsola Pall* formulations) produce synergistic restoration of liver enzyme activity and decrease lipid peroxidation markers. Nanomedicine and advanced drug delivery systems aim to improve the bioavailability of poorly soluble hepatoprotective compounds, yet challenges persist due to unpredictable cell uptake and Kupffer cell clearance within the hepatic microenvironment. Moreover, the balance between therapeutic efficacy and potential hepatotoxicity of herbal mixtures remains a critical research area, demanding standardized dosage and rigorous clinical evaluation [35]. In summary, liver injury arises from a convergence of toxic, metabolic, and inflammatory mechanisms. Its progression from oxidative insult to fibrosis and cancer represents a major biomedical concern. The exploration of natural antioxidants, synthetic analogs like bicyclol, and innovative delivery systems continues to expand the horizon for safe, effective hepatoprotective therapies capable of shielding this essential organ from chemical and biological harm [36].

### 2.3. Biomarkers of Liver Injury

The primary mechanism of liver injury is oxidative stress and inflammatory signaling. When hepatocytes are exposed to drugs or toxins, metabolic activation by enzymes like cytochrome P450 leads to reactive

intermediates that bind to cellular macromolecules and free radicals initiate lipid peroxidation and mitochondrial injury, leading to liver cell necrosis or apoptosis. Also, chronic oxidative stress promotes fibrosis via activation of hepatic stellate cells and secretion of pro fibrotic cytokines such as TGF β and TNF α. Drug induced liver injury (DILI) is a common cause of acute liver failure and drug withdrawal worldwide. It can be predictable (dose related, e.g., acetaminophen toxicity) or idiosyncratic (unpredictable, e.g., with isoniazid or carbamazepine). The metabolites of the drugs have a tendency to deplete glutathione (GSH) that cause cell injury after depletion of detoxification capacity [38]. Liver lesions present in various morphological forms including hepatocellular necrosis, cholestasis, fatty changes (steatosis), and vascular lesions. Cell injury from acute damage results in the leakage of enzymes like ALT, AST, and ALP into the circulation, while chronic damage turns into fibrosis, cirrhosis, or hepatocellular carcinoma (HCC) if there is persistent oxidative damage and inflammation. The natural history usually progresses through stages early oxidative injury, inflammatory cell infiltration, fibrotic reorganization, and ultimately necrotic parenchymal replacement [39]. Chronic exposure to alcohol, viral hepatitis, or metabolic illness accelerates the cycle and has profound implications for world health: nearly two million deaths annually are due to cirrhosis complications, hepatitis, or liver cancer. Despite how much pharmacology has advanced, there are few effective hepatoprotective medications. Current medications such as N acetyl L cysteine (for acetaminophen overdose) restore GSH and scavenge free radicals but are effective only if given early. Transplantation is a rescue measure in end stage liver failure. Natural products having high levels of flavonoids, polyphenols, and terpenoids show promising hepatoprotective activity via antioxidant and anti-inflammatory action [40]. Flavonoids quercetin, apigenin, and hesperetin modulate NF κB, Nrf2, and MAPK signaling pathways, reducing oxidative load and inhibiting fibrotic progression. Phyto preparations from Silybum marianum, Phyllanthus niruri, and covalently [37]. Excess reactive oxygen species (ROS) Picrorhiza kurroa are traditional but biologically established treatments enhancing liver regeneration and enzyme balance. Synthetic molecules like bicyclol-from Schisandra chinensis-are also been of use with viral and chemical hepatitis due to their anti-oxidant, immunomodulatory, and anti-fibrotic actions [41]. Experimental data even shows that hybrid molecules of lipophilic antioxidants with plant extracts (e.g., Salsola Pall preparations) produce synergistic recovery of activity of liver enzymes and decrease indicators of lipid peroxidation. Nanomedicine and more recently developed drug delivery systems aim to improve the bioavailability of insoluble hepatoprotectants, but problems persist due to unpredictable cell uptake and clearance by Kupffer cells in the hepatic microenvironment. Furthermore, the regulation of herbal formulations' therapeutic potency and possible hepatotoxicity remains a salient area of research necessitating standardized dosing and extensive clinical evaluation. To sum up, liver damage is caused by a convergence of toxic, metabolic, and inflammatory pathways. Its progression from oxidative insult to fibrosis and cancer is a continuing biomedical challenge. Continuing research in the area of natural antioxidants, synthetic mimics like bicyclol, and newer delivery systems keeps opening up a wider horizon for safer, more effective therapies for hepatotoxicity that can safeguard this all-important organ from chemical and biological injury [42].

## 3. Herbal Components with Hepatoprotective Potential

Table 1 summarizes major classes of herbal constituents with hepatoprotective potential and their underlying mechanisms. Flavonoids such as quercetin and silymarin act primarily as antioxidants and activate Nrf2 pathways. Alkaloids exhibit anti-inflammatory effects, while terpenoids and saponins regulate apoptosis and fibrosis. Polyphenols and other bioactives further support mitochondrial protection and oxidative stress reduction [43].

**Table 1:** Herbal Components with Hepatoprotective Potential

| S. No. | Class | Examples | Key Mechanisms | References |
|---|---|---|---|---|
| 1. | Flavonoids | Quercetin, Silymarin, Rutin | Antioxidant, free radical scavenging, Nrf2 activation | [44] |
| 2. | Alkaloids | Berberine, Piperine | Anti-inflammatory, modulation of signaling pathways | [45] |
| 3. | Terpenoids & Saponins | Glycyrrhizin, Ginsenosides | Anti-fibrotic, regulation of apoptosis | [46] |
| 4. | Polyphenols & Tannins | Curcumin, Resveratrol, Catechins | Antioxidant, mitochondrial protection | [47] |
| 5. | Other Bioactives | Phenolic acids, lignans, coumarins | Various: mitochondrial protection, anti-inflammatory, antioxidant effects | [48] |

## 4. Mechanisms of Hepatoprotection by Herbal Components

### 4. 1. Antioxidant Activity

Herbal constituents provide strong antioxidant activity that assists in safeguarding the liver by scavenging injurious reactive oxygen species (ROS) and increasing glutathione (GSH) levels, which are essential for preserving cellular redox balance. Most therapeutic plants like Phyllanthus emblica, Camellia sinensis (green tea), Mangifera indica, Punica granatum (pomegranate), and Acacia catechu have been investigated for their hepatoprotective potential mainly through antioxidant mechanisms. These plants contain bioactive compounds like polyphenols, flavonoids, tannins, and vitamins that strongly neutralize free radicals and reduce oxidative stress in liver cells [49]. In vitro studies using human hepatocarcinoma HepG2 cells showed that these herbal extracts significantly prevented tert-butyl hydroperoxide-induced cytotoxicity, increasing cell viability dose-dependently. Among them, Phyllanthus emblica demonstrated the strongest antioxidant and protective effect, with an IC50 comparable to silymarin, a well-known hepatoprotective agent. The antioxidant assays performed, such as ORAC, DPPH, ABTS, and cellular antioxidant activity assays, validated the potential of extracts to scavenge free radicals efficiently and prevent oxidative damage [50]. The enzymatic antioxidant system of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione reductase (GR) is important for detoxifying ROS in the liver. Herbal extracts enhance these activities of enzymes and replenish intracellular glutathione, which is usually lost in the course of oxidative stress. For example, it was found that pomegranate peel extract maintained GSH levels and antioxidant enzyme activities during liver damage. Mangifera indica bark extract also showed antioxidative activity by inhibiting lipid peroxidation and enhancing enzymatic antioxidants, mainly due to mangiferin, its active principle. Even Acacia catechu, while demonstrating lower protection than silymarin, had the most significant ORAC value, reflective of its excellent radical quenching activity, based mainly on its high tannin content. Its antioxidant activity prevents cellular macromolecule damage, sustains membrane integrity, and inhibits lipid peroxidation that initiates further oxidative damage and inflammation in hepatocytes. By limiting oxidative stress, these plant extracts not only shield liver cells from acute injury but also reduce exacerbation towards fibrosis and cirrhosis. Such scavenging of ROS and intracellular glutathione replenishment maintains hepatic detoxification mechanisms effectively and is responsible for their dominant position in herbal hepatoprotection with low side effects [51].

Figure 1 The figure depicts antioxidant mechanisms in liver cells, highlighting the role of *Phyllanthus emblica*, *Camellia sinensis*, and *Mangifera indica*. These plant extracts scavenge reactive oxygen species and enhance glutathione levels, thereby reducing oxidative stress, protecting mitochondria, and maintaining cellular integrity through improved endogenous antioxidant defense systems [52].

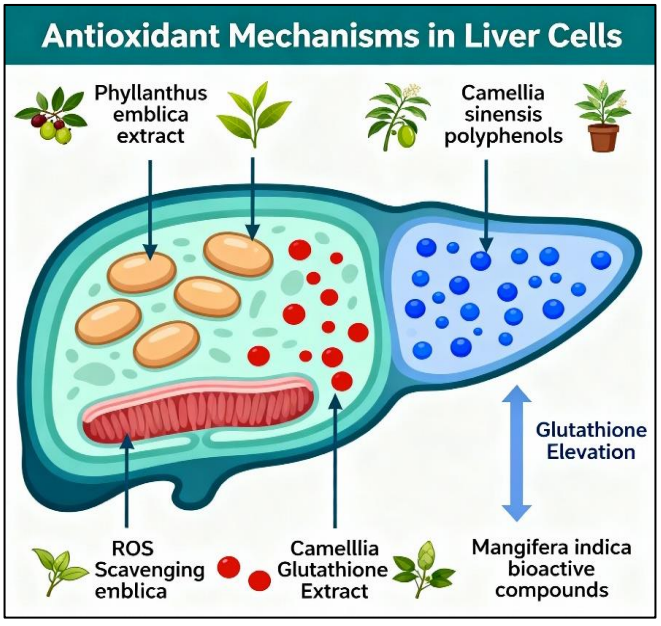


**Figure 1: Antioxidant mechanisms in liver cells mediated by plant-derived extracts.** The schematic illustrates the hepatoprotective effects of *Phyllanthus emblica* extract, *Camellia sinensis* polyphenols, and *Mangifera indica* bioactive compounds. These phytoconstituents enhance intracellular antioxidant defense by scavenging reactive oxygen species (ROS) and elevating glutathione levels, thereby reducing oxidative stress and protecting cellular organelles.

### 4. 2. Anti-inflammatory Effects

Herbal constituents have significant anti-inflammatory actions that are pivotal in safeguarding the liver from chronic injury. Among the key

molecular pathways mediating liver inflammation is pathway, which controls the expression of numerous inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6). These cytokines are involved in liver tissue damage by facilitating immune cell invasion and sustaining inflammation [53]. There are some phytochemicals from herbs that have been reported to suppress the activation of NF-κB, which is followed by diminished generation of pro-inflammatory cytokines and reduced liver inflammation. For instance, berbamine isolated from Berberis vulgaris and thymoquinone isolated from Nigella sativa seeds exhibited remarkable protective effects in mouse models of immune-mediated liver damage by inhibiting NF-κB nuclear translocation and reducing TNF-α and interferon-gamma (IFN-γ) levels. This NF-κB inhibition breaks the inflammatory cascade in acute hepatitis and presents promising therapeutic options for autoimmune and viral hepatitis [54]. Licorice (Glycyrrhiza glabra) and its bioactive compounds, glycyrrhizin and liquiritigenin, are also characterized by intense anti-inflammatory activity in inhibiting NF-κB and mitogen-activated protein kinase (MAPK) pathways. These compounds inhibit phosphorylation and degradation of the inhibitory protein IκBα, inhibiting NF-κB activation and downstream synthesis of inflammatory mediators like TNF-α, IL-6, inducible nitric oxide synthase (iNOS), and cyclooxygenase-2 (COX-2). Through suppression of these mediators, licorice extracts prevent hepatic inflammation and tissue damage, underpinning their widespread traditional application for liver disorders [55]. Syringic acid, a phytochemical in contemporary Chinese medicine, displays hepatoprotective anti-inflammatory properties through modulation of NF-κB and JAK-STAT signaling pathways. In chemical-induced liver inflammation models in rats, treatment with syringic acid markedly reduced levels of expression of NF-κB, IL-6, TNF-α, iNOS, and COX-2 in liver tissue, proving its efficacy in suppressing inflammatory reactions and oxidative stress, preventing subsequent liver injury. Similar anti-the nuclear factor kappa B (NF-κB) signaling inflammatory effects are shown by other significant herbal compounds such as curcumin, quercetin, and apigenin by controlling NF-κB and associated pathways. Curcumin inhibits p300 histone acetyltransferase, suppressing inflammation-related gene expression such as COX-2 and inhibiting cardiac and hepatic inflammation. Quercetin inhibits TLR4-induced NF-κB translocation, stabilizes the NF-κB/IκB complex, and inhibits production of pro-inflammatory cytokines. Apigenin modulates the polarization of macrophages, represses NF-κB activation, and decreases NO and pro-inflammatory cytokines and hence exerts its anti-inflammatory and hepatoprotective activity. Together, these plant constituents modulate key inflammatory signaling centers like NF-κB and MAPKs, suppress cytokine overexpression, and block enzymes like iNOS and COX-2 that perpetuate inflammation. By suppressing chronic liver inflammation, they safeguard hepatocytes from immune-mediated damage and facilitate tissue repair, making them promising therapeutic assets in the treatment of liver disorders catalyzed by chronic inflammation [56].

Figure 2 illustrates the role of key medicinal plants in modulating inflammatory signaling within hepatocytes. *Berberis vulgaris* is shown to inhibit NF-κB activation, thereby reducing downstream inflammatory responses. *Nigella sativa* contributes to the regulation of transcription factors and cytokine production, helping to control inflammation. *Glycyrrhiza glabra* acts by suppressing pro-inflammatory cytokines such as TNF-α and IL-6, thereby mitigating inflammatory damage at the cellular level. The diagram highlights how these phytoconstituents target multiple signaling pathways to collectively reduce inflammation, stabilize cellular membranes, and protect liver tissue from injury. This multi-targeted approach underscores the therapeutic potential of herbal compounds in managing liver inflammation and associated disorders [57].

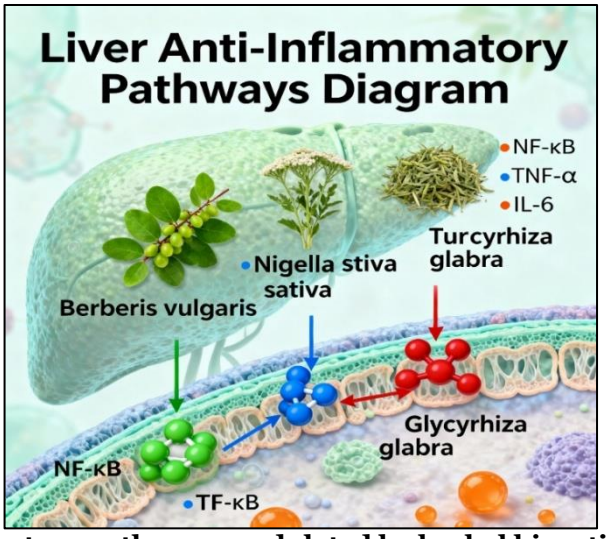


**Figure 2: Liver anti-inflammatory pathways modulated by herbal bioactives.** The diagram illustrates the effects of *Berberis vulgaris*, *Nigella sativa*, and *Glycyrrhiza glabra* on inflammatory signaling in liver cells. These phytoconstituents suppress key mediators such as NF-κB, TNF-α, and IL-6, thereby reducing inflammation and

protecting hepatocytes from inflammatory damage.

**4. 3. Anti-fibrotic Activity**

Liver fibrosis is a severe medical condition caused by the abnormal deposition of connective tissue in the liver, primarily as a consequence of chronic liver damage due to a variety of causes such as alcohol use, hepatitis infections, and metabolic diseases. At the forefront of this fibrogenic process are hepatic stellate cells (HSCs), which in normal liver are inactive cells that store vitamin A [58]. But under liver injury, these HSCs are activated and become proliferative myofibroblasts that synthesize and lay down profuse amounts of extracellular matrix (ECM) proteins like collagen types I and III, resulting in scar tissue formation and architectural distortion. This excess ECM deposition leads to fibrosis, which can become cirrhosis and even liver cancer if not treated. Herbal agents have displayed immense potential in combating liver fibrosis at multiple steps in this pathological process [59]. They suppress the activation and proliferation of HSCs, induce apoptosis or reversion to quiescence, and modulate the synthesis and degradation of ECM, efficiently suppressing collagen accumulation. Several natural compounds have been found from traditional Chinese medicines and herbal sources, such as alkaloids, flavones, terpenoids, saponins, phenylpropanoids, and polysaccharides that are responsible for these anti-fibrotic activities. One of the key molecular pathways for the activation of HSCs includes the TGF-β/Smad signaling pathway [60]. Herbal constituents including salvianolic acids, oxymatrine, curcumin, and tetrandrine have been found to inhibit this pathway, leading to downregulation of fibrogenic markers including α-smooth muscle actin (α-SMA) and collagen. For example, curcumin stops the production of TGF-β1 and downstream Smad2/3 phosphorylation, thus inhibiting the transformation of HSC and deposition of collagen. Oxymatrine regulates TGF-β, IL-6, and TNF-α signaling for the protection of the liver against fibrosis. These herbs also increase the expression of inhibitory molecules such as Smad7, which oppose fibrogenic signals [61]. Other relevant signaling pathways targeted by herbal constituents, in addition to TGF-β, are NF-κB, MAPK, and STAT3, and are implicated in inflammation and proliferation of HSCs. Several herbal extracts decrease the expression of pro-inflammatory cytokines TNF-α and IL-6, further inhibiting the activation of HSCs. In addition, herbal compounds usually activate antioxidant defense mechanisms and induce autophagy, mechanisms that contribute to restoring liver homeostasis as well as preventing fibrotic development [62]. Some of the herbal remedies, which are extensively employed in folk medicine, show multi-targeted activities characterized by inhibition of HSC activation, ECM suppression, as well as oxidative stress and inflammation reduction. Examples of such herbs include Fufang-Biejia-Ruangan pill, Yinchenhao decoction, and Xia-yu-xue decoction that have demonstrated effectiveness in research models by reducing α-SMA, collagen, and TGF-β1 levels and thus reversing fibrosis effects. In conclusion, herbal constituents reverse hepatic fibrosis through coordinated action of inhibiting stellate cells, regulating collagen and extracellular matrix synthesis, modulating pro-fibrotic and inflammatory pathways, and by strengthening antioxidant and autophagic mechanisms. These various actions form the basis of the hepatoprotective and anti-fibrotic properties of natural therapeutic products, providing hope for new treatments against a disease process where therapy at present has few effective options [63].

Figure 3 depicts the mechanisms by which phytoconstituents such as curcumin, salvianolic acids, oxymatrine, and tetrandrine exert anti-fibrotic effects in the liver. These compounds suppress hepatic stellate cell activation, a key event in fibrosis progression, and inhibit inflammatory signaling pathways. Additionally, they regulate collagen metabolism by reducing collagen synthesis, preventing cross-linking, and promoting its degradation. Collectively, these actions help in limiting extracellular matrix accumulation, preventing scar formation, and preserving normal liver architecture, highlighting the therapeutic potential of plant-derived compounds in managing liver fibrosis [64].

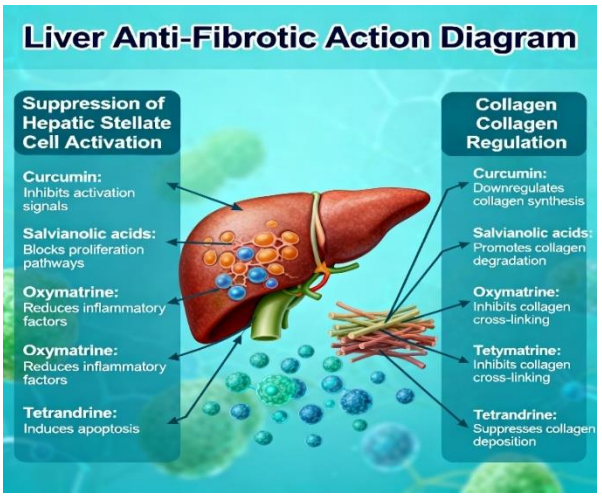

**Figure 3: Liver anti-fibrotic mechanisms mediated by phytoconstituents.** The diagram illustrates how bioactive compounds such as curcumin, salvianolic acids, oxymatrine, and tetrandrine inhibit hepatic stellate cell activation and regulate collagen metabolism. These agents reduce inflammation, suppress collagen synthesis and cross-linking, and promote collagen degradation, thereby preventing liver fibrosis progression.

### 4. 4. Effects Anti-apoptotic and Mitochondrial Protective

The conservation of liver cells against apoptosis and mitochondrial injury is an important element in herbal treatment. A majority of herbs possess bioactive molecules that are responsible for the prevention of programmed cell death, triggered during liver damage by toxins or oxidative stress [65]. Not only do these molecules suppress apoptotic pathways, but they also stabilize mitochondria—the energy-generating organelles within cells—so that they remain operational even under stressful conditions. One of the shared mechanisms is the modulation of mitochondrial membrane integrity. Herbs such as silymarin derived from milk thistle or curcumin derived from turmeric assist in maintaining the mitochondrial membrane potential and inhibiting the opening of the mitochondrial permeability transition pore (MPTP) [66]. When this pore is opened, it results in the loss of mitochondria to efficiently produce energy and initiates the release of pro-apoptotic factors such as cytochrome c, which in turn activate the caspases responsible for cell death. Herbal extracts also control the ratio of proteins that induce or suppress apoptosis. For instance, most herbal constituents enhance the levels of Bcl-2, an anti-apoptotic protein, and reduce amounts of Bax, a pro-apoptotic protein [67]. This change in balance supports the survival of the cell even in the presence of harmful substances attacking it. This is done partially by activating pathways such as PI3K/Akt, which enhance cell survival and mitochondrial integrity. Herbes such as examples are not only silymarin and curcumin but also some such as quercetin, which increases mitochondrial antioxidant defenses and prevents the triggering of caspases, the actual proteins that carry out cell death.

In addition, certain herbs stimulate the endogenous antioxidant defense mechanisms inside the mitochondria, such as superoxide dismutase (SOD) and glutathione peroxidase [68]. These enzymes deactivate the surplus ROS that is generated upon injury, and by doing so, safeguard the mitochondria and the entire cell directly from oxidative damage. Depletion of oxidative stress in the mitochondria also inhibits the release of inducers of apoptosis, giving rise to a positive cellular environment for hepatocyte recovery. By stabilizing mitochondrial function, lowering oxidative stress, and controlling apoptotic proteins, herbal constituents maintain the integrity of liver cells. This not only inhibits cell death but also enhances the regeneration of injured tissue, which is the basis for herbal medicine being a potential strategy in the management of liver disease. The combined action is preservation of liver function, inhibition of fibrosis, and enhancement of healing processes [69].

Figure 4 illustrates how phytoconstituents such as silymarin and quercetin contribute to hepatocyte survival by targeting mitochondrial and apoptotic pathways. These compounds help maintain mitochondrial membrane integrity, preventing the release of pro-apoptotic factors. They also modulate the balance between Bcl-2 (anti-apoptotic) and Bax (pro-apoptotic) proteins, favoring cell survival. Furthermore, inhibition of caspase activity reduces programmed cell death, thereby protecting liver cells from damage. Overall, the combined effects of mitochondrial stabilization, regulation of apoptotic signaling, and caspase inhibition highlight the therapeutic potential of these natural compounds in preventing liver injury and promoting cellular viability [70].

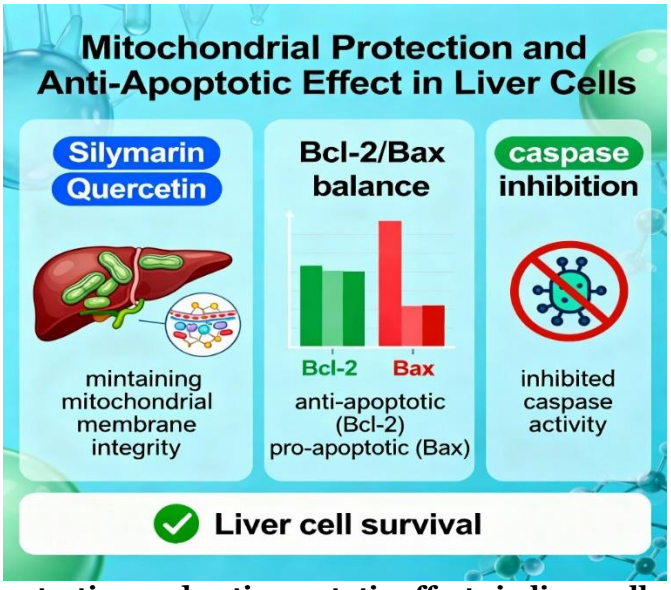


**Figure 4: Mitochondrial protection and anti-apoptotic effects in liver cells.** The figure illustrates the role of phytoconstituents such as silymarin and quercetin in preserving mitochondrial membrane integrity. These

compounds modulate the Bcl-2/Bax balance, enhancing anti-apoptotic signaling while suppressing pro-apoptotic pathways, and inhibit caspase activation, ultimately promoting hepatocyte survival.

**4. 5. Modulation of metabolic enzymes**

Herbal constituents confer significant protection to the liver by controlling metabolic enzymes, particularly the cytochrome P450 (CYP450) enzyme family. These enzymes are crucial for metabolizing drugs, toxins, and other foreign chemicals, but overactivation or imbalance can result in the generation of toxic reactive metabolites that induce liver damage [71]. Various herbal medicines control CYP450 enzymes by either inhibiting or inducing certain isoforms in order to regain metabolic balance within the liver. For instance, silymarin of Silybum marianum and glycyrrhizin of Glycyrrhiza glabra have been documented to guard liver cells against carbon tetrachloride (CCl4)-induced toxicity, a disease state in which CYP450 enzymes metabolically convert CCl4 into reactive free radicals that destroy cellular structures [72]. These plants suppress the activity of these oxidative enzymes and boost antioxidant defenses, decreasing lipid peroxidation and cell injury markers. By regulating CYP450, they inhibit the formation of toxic metabolites and salvage liver structure. Further, Malaysian medicinal herbs, flavonoids, alkaloids, and phenolics being rich, seem to harmonize the expression and activities of a number of CYP450 enzymes. This harmonizing activity enhances detoxification potential along with minimizing oxidative stress due to reactive metabolites. Andrographis paniculata, a plant among them, increases antioxidant enzyme activities and normalizes CYP450 metabolism, thereby blunting xenobiotic hepatotoxicity. Herbal modulation of CYP450 is a subtle process, as excessive inhibition may lead to drug interactions and inadequate modulation might be unable to safeguard the liver. The hepatoprotective herbs appear to modulate the enzymic activity in a way that harmful substances are metabolized safely without overproducing harmful intermediates. This polyfaceted modulation of CYP450, along with direct anti-inflammatory and antioxidant properties, is the basis for herbal liver protection, protecting the organ against chemical damage and facilitating recovery [73].

Figure 5 illustrates the regulatory effects of herbal bioactives such as silymarin, glycyrrhizin, and *Andrographis paniculata* on cytochrome P450 (CYP450) enzymes in hepatocytes. These compounds play a crucial role in maintaining metabolic homeostasis by modulating enzyme expression and activity. Silymarin is shown to inhibit the formation of toxic metabolites, thereby reducing hepatocellular damage. Glycyrrhizin contributes to the fine-tuning of enzymatic activity, ensuring balanced metabolic processes. Additionally, *Andrographis paniculata* is depicted as enhancing enzyme expression, supporting efficient detoxification pathways. The overall effect is the harmonization of CYP450-mediated metabolism, minimizing oxidative stress and preventing liver injury caused by xenobiotics and harmful intermediates [74].

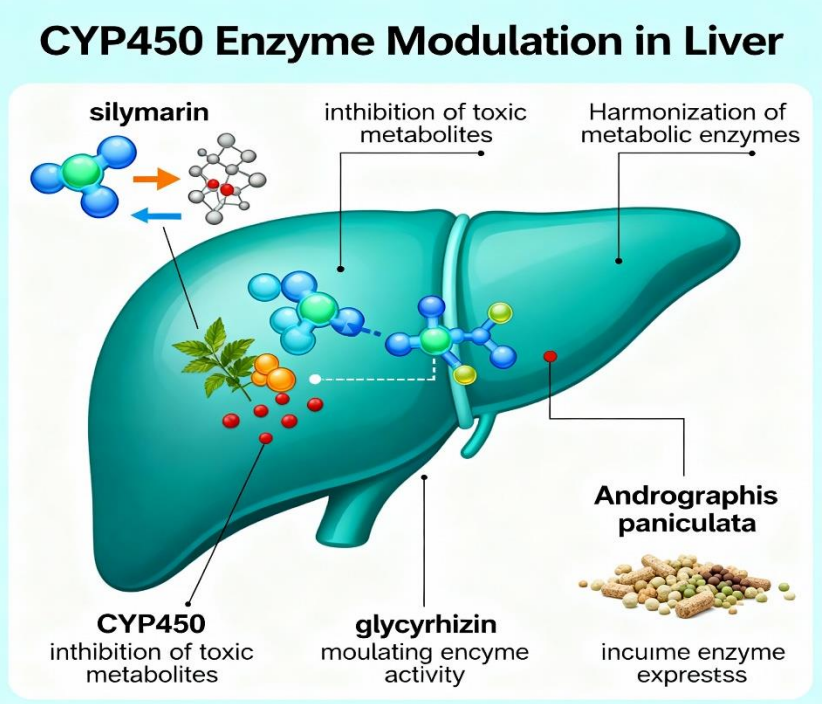


**Figure 5: Modulation of CYP450 enzymes by herbal bioactives in the liver.** The figure illustrates how phytoconstituents such as silymarin, glycyrrhizin, and *Andrographis paniculata* regulate cytochrome P450 enzyme activity. These compounds inhibit the formation of toxic metabolites, modulate enzymatic functions, and harmonize metabolic pathways, thereby enhancing detoxification and protecting hepatocytes from xenobiotic-induced damage.

**5. Experimental and Clinical Evidence**

**5.1. Preclinical: Hepatotoxicity Induced by $CCl_4$, Paracetamol, Alcohol, and Cyclophosphamide**

Hepatotoxicity models induced by chemicals such as carbon tetrachloride ($CCl_4$), paracetamol, alcohol, and cyclophosphamide have been extensively used in $CCl_4$ is a classic hepatotoxin that causes centrilobular necrosis via cytochrome P450-mediated formation of reactive free radicals, leading to lipid peroxidation, oxidative stress, inflammation, and subsequent liver regeneration. Its administration by intraperitoneal injection in rodents induces acute and chronic liver injury resembling human pathology. Paracetamol (acetaminophen) overdose induces hepatotoxicity primarily through metabolism to the toxic metabolite NAPQI, which depletes glutathione and causes oxidative stress and cellular necrosis. Mouse and rat models receiving high doses of paracetamol show elevated liver enzymes, mitochondrial dysfunction, and histopathological liver damage [76].

Alcohol-induced hepatotoxicity has been modeled by chronic and binge ethanol administration in rodents, often combined with other insults like $CCl_4$. This results in steatosis, inflammation, fibrosis, and preclinical animal studies. These models help elucidate mechanisms of liver injury and evaluate potential hepatoprotective agents [75]. transcriptomic patterns similar to human alcoholic hepatitis, including neutrophil infiltration and pericellular fibrosis. Cyclophosphamide, a chemotherapeutic agent, also causes dose-dependent hepatotoxicity in animal models characterized by hepatocyte necrosis, elevated liver enzymes, and histological tissue damage. Toxic metabolites such as acrolein contribute to oxidative stress and cellular injury [77].

Table 2 provides an overview of commonly used hepatotoxic agents in experimental animal models along with their mechanisms of liver injury. Carbon tetrachloride ($CCl_4$) induces oxidative stress through free radical formation, while paracetamol toxicity is mediated by NAPQI and glutathione depletion. Alcohol causes steatosis and inflammation, whereas cyclophosphamide leads to oxidative damage and hepatocyte necrosis [78].

**Table 2:** Summary of Hepatotoxicity Induced by Common Agents in Animal Models

| S. No. | Agent | Animal Model | Mechanism of Injury | Key Liver Damage Features | References |
|---|---|---|---|---|---|
| 1. | $CCl_4$ | Rats, mice (i.p. injection) | Metabolic activation to free radicals, lipid peroxidation, inflammation | Centrilobular necrosis, oxidative stress, fibrosis | [79] |
| 2. | Paracetamol | Mice, rats (i.p. or oral) | NAPQI metabolite formation, glutathione depletion, oxidative stress | Hepatocyte necrosis, elevated ALT/AST, mitochondrial dysfunction | [80] |
| 3. | Alcohol | Mice (oral, intragastric), often combined with $CCl_4$ | Chronic ethanol metabolism leads to steatosis, inflammation, fibrosis | Steatosis, neutrophil infiltration, pericellular fibrosis | [81] |
| 4. | Cyclophosphamide | Mice, rats (various doses) | Toxic metabolites cause oxidative injury, necrosis | Hepatocyte necrosis, raised liver enzymes, inflammation | [82] |

**5.2. Clinical Studies: Evidence of Silymarin, Curcumin, Licorice Extracts, and Other Natural Products in Human Trials**

Hepatoprotective effects of natural products such as silymarin, curcumin, and licorice extracts have been investigated extensively in human clinical trials targeting various liver diseases, including nonalcoholic fatty liver disease (NAFLD), liver cirrhosis, and alcoholic liver disease. These trials commonly measure improvements in liver function tests, particularly reductions in serum liver enzymes (ALT, AST, GGT), liver fat content, and fibrosis markers [83]. Silymarin (from milk thistle) is one of the most studied herbal agents, demonstrating significant improvement in liver enzymes and fibrosis scores in patients with chronic liver conditions. Daily doses ranging from 140 mg to 720 mg in randomized controlled trials resulted in reduced ALT and AST levels and enhanced liver function, with some studies indicating improved survival in alcoholic cirrhosis [84]. Curcumin, the active compound of turmeric, exhibits anti-inflammatory and antioxidant effects in NAFLD and liver cirrhosis patients. Clinical trials administering curcumin doses between 500 mg to 1500 mg daily observed reductions in liver enzymes, liver fat, and inflammatory markers, as well as improvements in ultrasonographic liver findings. Licorice (glycyrrhizin) extracts have shown hepatoprotective potential primarily through antioxidant and anti-inflammatory pathways. Human trials reveal decreased transaminase levels and improved liver histology following licorice supplementation, supporting its use as an adjunct in liver disease management. Other natural products such as berberine, green tea polyphenols, and probiotics have also shown promising clinical efficacy, reflected in improved biochemical liver profiles and histological outcomes. Nevertheless, the complexity of liver diseases and variability in study designs call for further large-scale randomized controlled trials to validate these findings [85].

Table 3 summarizes clinical trial evidence supporting

the efficacy of natural hepatoprotective agents in various liver disorders. Silymarin, curcumin, licorice extracts, and berberine have demonstrated steatosis, while probiotics improve liver function, significant improvements in liver enzymes, fibrosis, and metabolic parameters in conditions such as NAFLD and NASH. Green tea polyphenols reduce inflammation, and histopathological outcomes [86].

**Table 3:** Summary of Clinical Trial Evidence for Natural Hepatoprotective Agents.

| S. No. | Natural Product | Patient Population | Study Design | Dose Range | Key Clinical Outcomes | References |
|---|---|---|---|---|---|---|
| 1. | Silymarin | NAFLD, chronic hepatitis, alcoholic cirrhosis | Randomized controlled trials, double-blind | 140 - 720 mg/day | Decreased ALT/AST, improved liver fibrosis scores, enhanced survival in alcoholic cirrhosis | [87] |
| 2. | Curcumin | NAFLD, liver cirrhosis | Randomized controlled trials | 500 - 1500 mg/day | Reduced liver enzymes, decreased liver fat, improved ultrasonographic liver parameters | [88] |
| 3. | Licorice Extracts | NAFLD | Randomized controlled trials | Standardized extracts (~2 g/day) | Lowered ALT and AST, anti-inflammatory effects | [89] |
| 4. | Berberine | NAFLD, NASH | Randomized controlled trials | 500 - 1500 mg/day | Reduced ALT/AST, improved insulin sensitivity, decreased liver fat | [90] |
| 5. | Green Tea Polyphenols | NAFLD, NASH | Randomized controlled trials | 550 - 1080 mg/day of catechins | Significant decrease in liver enzymes, reduced steatosis on imaging | [91] |
| 6. | Probiotics | NAFLD, NASH, minimal hepatic encephalopathy | Randomized controlled trials | Multi-strain formulations | Improved liver enzymes, reduced inflammation, improved histopathology | [92] |

## 6. Comparative Analysis of Herbal Extracts vs. Synthetic Hepatoprotective Drugs

Herbal hepatoprotective agents such as silymarin, curcumin, and polyherbal formulations like Liv.52 have shown notable efficacy in clinical and experimental studies, often comparable to standard synthetic drugs such as ursodeoxycholic acid (UDCA), N-acetylcysteine (NAC), and steroids. Herbal extracts exert their effect by multi-target mechanisms including antioxidation, antifibrotic, anti-inflammatory, and membrane stabilization, while synthetic hepatoprotectives typically have more defined, single-target pathways (e.g., bile acid modulation by UDCA, glutathione replenishment by NAC) [93]. Several meta-analyses and head-to-head preclinical and clinical comparisons suggest that herbal extracts like silymarin can match or surpass synthetic agents in improving liver function parameters (ALT, AST, ALP), reducing oxidative stress, and alleviating symptoms, with superior safety and tolerability. For instance, studies show silymarin exerts efficacy similar to standard agents in NAFLD and hepatitis, but with less risk of side effects such as diarrhea or pruritus associated with UDCA, or bone marrow suppression linked with immunosuppressive steroids. Nonetheless, synthetic hepatoprotectives remain vital in acute liver failure or severe cases, where rapid, well-characterized pharmacologic action is necessary. Herbal therapies sometimes face challenges related to extract standardization, lower bioavailability, and variable regulatory oversight. Combination therapies using both classes are increasingly investigated for synergistic efficacy and side effect mitigation, especially in chronic liver diseases or where conventional therapies are limited [94].

Table 4 presents a comparative overview of herbal extracts and synthetic hepatoprotective agents based on their mechanisms, efficacy, and safety profiles. Herbal agents such as silymarin, curcumin, and polyherbal formulations (e.g., Liv.52) exhibit antioxidant, anti-inflammatory, and antifibrotic effects with generally better tolerability and fewer adverse effects. In many cases, they show comparable or supportive efficacy to conventional therapies, particularly in chronic liver conditions. In contrast, synthetic drugs like ursodeoxycholic acid, N-

acetylcysteine, steroids, and pentoxifylline are well-established in clinical practice, especially for specific indications such as primary biliary cholangitis, acute immunosuppression, and metabolic complications. Overall, the table highlights the potential of herbal agents as safer alternatives or adjuncts, while liver failure, or severe inflammation. However, their use is often associated with notable side effects, including gastrointestinal disturbances, synthetic drugs remain essential for targeted and acute interventions [95].

**Table 4:** Comparison of Herbal Extracts and Synthetic Hepatoprotective Drugs.

| S. No. | Agent/Class | Source/ Type | Mechanism | Efficacy | Adverse Effects | References |
|---|---|---|---|---|---|---|
| 1. | Silymarin (Milk Thistle) | Herbal | Antioxidant, anti-inflammatory, membrane stabilizer | Comparable or superior to UDCA and some conventional drugs for chronic liver disease in improving ALT, AST, histology | Mild GI symptoms, rare allergy | [96] |
| 2. | Curcumin | Herbal | Antioxidant, anti-inflammatory | Comparable to standard therapy in NAFLD; effective as add-on in clinical trials | Very well tolerated, low bioavailability | [97] |
| 3. | Liv.52 (Polyherbal) | Herbal (Ayurvedic) | Multi-target: antioxidant, anti-inflammatory, antifibrotic | Comparable or superior to conventional therapy for chronic/supportive care | Very rare mild symptoms reported | [98] |
| 4. | Ursodeoxycholic acid | Synthetic bile acid | Increases bile flow, cytoprotection | Standard of care in PBC/PSC; modest benefit in NAFLD | Diarrhea, pruritus, rarely paradoxical liver worsening | [99] |
| 5. | N-acetylcysteine (NAC) | Synthetic | Glutathione precursor, antioxidant | Highly effective in acute toxicity/ALF | Nausea, rare hypersensitivity | [100] |
| 6. | Steroids (e.g., prednisolone) | Synthetic | Immunosuppressive, anti-inflammatory | Lifesaving in select cases | Immunosuppression, bone loss, diabetes risk | [101] |
| 7. | Pentoxifylline | Synthetic | TNF-α inhibitor, anti-inflammatory | Add-on in steroid non-responders | GI upset, dizziness | [102] |

## 7. Safety, Toxicity, and Limitations

### 7.1. Possible Toxicity of Certain Herbal Compounds

Certain herbal compounds, notably pyrrolizidine alkaloids (PAs), pose significant toxicity risks despite the growing use of herbal products for hepatoprotection. PAs are naturally occurring secondary metabolites found in over 6000 plant species, predominantly in families such as Asteraceae, Boraginaceae, and Fabaceae. These compounds function as plant defense mechanisms but are hepatotoxic, genotoxic, and carcinogenic in humans and animals when ingested in sufficient amounts [103]. PAs are characterized by a pyrrolizidine ring structure with variations defining subclasses. Critically, unsaturated PAs (with a 1,2-double bond) are especially toxic. After absorption in the gastrointestinal tract, PAs are metabolized in the liver by cytochrome P450 enzymes to reactive pyrrole metabolites that form DNA and protein adducts, leading to cell death, liver necrosis, fibrosis, and veno-occlusive disease. These metabolites also cause genotoxicity and increase cancer risk. These alkaloids contaminate various food products including herbal teas, spices, honey, pollen, and dairy products, raising concerns about chronic dietary exposure. Even pyrrolizidine alkaloid N-oxides (PANOs), generally less toxic, can convert to harmful pyrroles in vivo. Contamination often arises from co-harvesting PA-containing weeds or cross-contamination during processing [104].

Toxic effects of PAs include acute symptoms like abdominal pain, nausea, vomiting, and diarrhea, as

well as chronic liver injury manifested as hepatic insufficiency, fibrosis, cirrhosis, and occasionally liver failure. The toxicity depends on dose, duration, species susceptibility, and individual metabolic capacity to detoxify Pas [105]. Regulatory agencies such as the European Commission and EFSA have set maximum limits for PA content in food and herbal products to minimize health risks. Analytical methods including high-performance liquid chromatography coupled with mass spectrometry (LC-MS) have been developed and refined for sensitive detection of PAs to ensure compliance with safety standards. Continued monitoring and control measures are essential given the toxicity of PAs and their presence in commonly consumed herbal products [106]

### 7.2 Dose Standardization Issues

Dose standardization remains a crucial challenge in the development and clinical application of herbal and nano-medicinal products. Variability in the composition of herbal extracts, differences in preparation methods, batch-to-batch inconsistencies, and the complex nature of multi-component formulations complicate the establishment of standardized dosing regimens [107]. Unlike synthetic drugs with well-defined active ingredients and clear dose-response relationships, herbal products often contain numerous bioactive compounds whose concentrations can vary significantly depending on the plant source, harvest time, extraction procedure, and formulation [108].

Pharmacokinetic and toxicokinetic factors play an important role in determining safe and effective dose ranges. Traditional toxicological dose-setting approaches, commonly relying on maximum tolerated dose (MTD), may not be suitable for natural products or nanomedicines due to their multi-component nature and complex interactions in the body. Modern approaches propose focusing on identifying the no-observed-adverse-effect level (NOAEL) and relevant kinetic maximum dose (KMD), which represent doses below which adverse effects are absent and biological systems can effectively metabolize and eliminate compounds [109]. In the case of nanomedicines and nanoparticulate drug delivery systems, maintaining dose consistency and quality control is also a significant challenge due to the physicochemical variability of nanoparticles, including particle size distribution, surface properties, and stability. These characteristics critically influence biodistribution, pharmacodynamics, and toxicity profiles. Thus, robust quality management systems and precise characterization methods are necessary to ensure reproducibility and to establish defined dose standards for clinical use [110].

Moreover, dose standardization difficulties are compounded by the lack of universally accepted analytical standards and protocols, particularly for complex herbal formulations and multifunctional nanoparticles. Regulatory frameworks are evolving to address these issues, emphasizing the need for standardization in extraction methods, dose quantification, bioavailability assessment, and comprehensive toxicity evaluations. Quality-by-Design (QbD) and Process Analytical Technology (PAT) frameworks have been proposed as strategic tools to enhance dose consistency and product safety throughout the development pipeline [111].

### 7.3. Lack of Large-Scale Clinical Trials

One of the most profound limitations hindering the clinical translation and robust validation of new liver therapeutics including nano biomaterials, cell-based therapies, and many targeted anticancer agents is the current scarcity of large-scale, multicenter clinical trials. Most clinical evidence to date is derived from small to moderate-size studies, often with limited geographic scope, short follow-up durations, and heterogeneous patient populations, which severely restricts the generalizability and statistical power of the resulting data [112]. Recent advances in drug development and molecular understanding of hepatocellular carcinoma (HCC) have yielded numerous breakthrough therapies and an unprecedented number of ongoing clinical trials for HCC, particularly for targeted therapies and immunotherapies. However, even in this dynamically evolving therapeutic area, large phase III trials frequently face challenges such as limited patient accrual, selective inclusion criteria, and underrepresentation of minorities or patients with comorbidities. Many promising interventions remain stuck in early development phases, without pivotal, adequately powered phase III studies to confirm efficacy and safety on a population scale [113].

The same limitation is seen in the development of advanced models for toxicity screening. While next-generation technologies like 3D liver models, organoids, and micro--physiological systems have shown promise in bridging the predictability gap between preclinical and clinical settings, their clinical validation is also hampered by the lack of coordinated, large-scale human studie. Many novel hepatoprotective interventions, including traditional medicines and cell therapies, are evaluated primarily in small case series or uncontrolled studies with inadequate statistical rigor [114].

Moreover, the heterogeneity of study design, limited patient numbers, and variation in endpoints and outcome measures further exacerbate the issue, making it difficult to compare findings across studies or perform powerful meta-analyses. As a result, regulatory approval and the integration of innovative therapies into clinical guidelines remain slow, despite the growing portfolio of molecular targets and treatment modalities. This lack of robust, large-scale clinical data restricts clinicians' confidence in adopting novel therapies and impedes their optimal use in broader patient populations [115].

## Conclusion

The accumulated evidence affirms that herbal bioactive components offer a promising pathway for

liver protection through a wide array of mechanisms, including antioxidant, anti-inflammatory, anti-fibrotic, and metabolic regulation. While the potential of plant-derived therapies is considerable profiling. To unlock the full clinical potential of herbal medicines for hepatic disorders, future research must emphasize well-designed large-scale trials, rigorous safety assessments, and optimized dosing strategies. Overall, medicinal plants and their active compounds stand out as vital candidates for innovative, safer hepatoprotective therapies that could complement or surpass conventional synthetic drugs in global liver disease management.

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**Author Contribution**

and supported by many experimental and clinical studies, challenges remain regarding standardization, quality assurance, and comprehensive toxicity

**GS:** Writing the original manuscript**; RC:** Proof reading**; MS:** Writing reviewing and editing; **SSK:** visualization and data curation.

**Conflict of Interest**
The authors declare no conflict of interest.

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**AI Declarations**
The authors declare that they used AI language tools (ChatGPT and Grammarly Premium) to enhance this manuscript's linguistic clarity and readability. They carefully reviewed and edited all generated text to ensure accuracy and alignment with the research's intended meaning.

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