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

[1]Gautam Saini*, [1]Reenu Chauhan, [1]Monika Singh, [1]S. Sadish Kumar

[1]Department of Pharmacy, I.T.S College of Pharmacy, I.T.S – The Education Group, Delhi–Meerut Road, Murad Nagar, Ghaziabad 201206, Uttar Pradesh, India.

Keywords

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Abstract

Liver disease is a major global health challenge associated with high morbidity and mortality, arising from factors such as alcohol abuse, chronic drug exposure, viral infections, environmental toxins, obesity, and diabetes. Although several synthetic hepatoprotective agents are available, their clinical utility is often limited by adverse effects, toxicity, inconsistent efficacy, and poor regenerative capacity. Consequently, there is growing interest in plant-derived therapeutics as safer and more effective alternatives. Herbal medicines contain diverse bioactive compounds, including flavonoids, alkaloids, phenolic acids, terpenoids, and saponins, which exhibit antioxidant, anti-inflammatory, antifibrotic, immunomodulatory, and cytoprotective activities. These phytochemicals protect hepatic tissue by reducing oxidative stress, modulating inflammatory pathways, enhancing detoxification mechanisms, and promoting liver regeneration. This systematic review summarizes current evidence from experimental studies and clinical trials on 13 widely investigated natural products, including Liv.52, probiotics, phospholipids, vitamin D, artichoke, berberine, and turmeric. Their botanical sources, active constituents, mechanisms of action, and therapeutic efficacy against non-alcoholic fatty liver disease, alcoholic liver disease, hepatitis, and drug-induced hepatotoxicity are comprehensively discussed. Additionally, this review critically evaluates the quality of existing evidence and highlights the need for standardized formulations, optimized dosing strategies, comprehensive toxicity assessments, pharmacokinetic investigations, and large-scale randomized clinical trials to facilitate the evidence-based integration of herbal medicines into liver disease management.

***Corresponding Author:**
Mr. Gautam Saini (sainigautam496@gmail.com)
ORCID: 0009-0009-5475-4805

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1. Introduction

1.1 Global Burden of Liver Diseases

The liver disease has ceased to be a secretive problem and has turned into an epidemic in the global context. Alcohol, drugs, chemicals, infections, and even metabolic issues remain to be significant strains on the health systems of any country of the globe, and complications related to the impaired liver in the long term take millions of lives annually. It is often called the sanitation factory of the body since the liver silently suffers until it is too late. After that, it is too late. The usage of alcohol alone is a significant factor. Alcohol consumption is the only cause of diseases such as the Alcohol Use Disorders (AUDs), alcoholic liver disease (ALD), which are leading causes of global mortality and disability. Alcohol has indeed been attributed to more than half of all deaths attributed to chronic liver disease. Statistics are not mere statistics; they are also a measure of young lives lost, broken families, and overloaded communities [1].

Hepatitis B and C continue to cause death to millions

of people. The hepatitis B virus (HBV) killed more over half a million people annually in 2019 and infected almost 296 million individuals. The hepatitis C virus (HCV) had been causing the disease to more than 58 million individuals and leads to the death of 300,000 every year. These are not mere statistics but deaths that are often young and most of the time avoidable. The pressure is highest in such regions as Africa, the Western Pacific and even some parts of Asia. Poverty, low immunization and poor access to care aggravate the situation. However, infections are not the only problem. The alcohol-related liver disease (ALD) is one of the major causes of cirrhosis and liver cancer. In 2016, nearly half of the total number of deaths related to liver in the whole world, which was approximately 588,000, was directly connected to alcohol. Disability-adjusted life years (DALYs) lost to ALD cross into the tens of millions. Some of the worst hit are Eastern Europe, West Africa and Central Asia. But there is alcohol everywhere. And its harm is too little reckoned [2].

Next is the non-alcoholic fatty liver disease (NAFLD). An epidemic after being neglected. It is estimated that more than 1.2 billion individuals globally are living with NAFLD due to obesity, diabetes and lifestyle modifications. Some of the highest figures are in the Middle East, North Africa, China, and India. The mortality rates of NAFLD are increasing at an insidious pace. In contrast to viral hepatitis, there is no vaccine. No quick cure. It is further complicated by chemicals and drugs. Hepatotoxicity is an insidious contributor to the industrial toxins and prescribed drugs. The risk is only increased by modern lifestyles and the growing exposure to drugs. The truth is hard. Chronic liver disease is not diminishing [3].

The causes are numerous - alcohol, drugs, chemicals, infections, metabolism. They combine to create a storm. A tragedy, which could have been avoided, is being played all over the world. The load is not even-distributed and is common. There is a fight against HBV and HCV in Africa and Asia. The Middle East and North Africa with NAFLD. Alcohol with Eastern Europe and Central Asia. Instead, high-income nations are also showing growing hepatocellular carcinoma, which is an indicator of changing etiologies [4].

What is notable here is that, even with vaccines, even with antiviral drugs, even with knowledge, mortality continues to increase. The lost disability-adjusted life years (DALYs) to liver disease are increasing. The quality of life is undermined. The financial cost is astonishing. And the pace of change is quick. It is not a mere disease issue. It is a socio-cultural one. The geography of liver disease is determined by lifestyle, culture, poverty, health systems, and so on. Various reasons, identical result. A heavy burden on the world. Growing. And mostly, preventable [5].

1.2 Limitations of Synthetic Drugs

One cannot disregard the harsh boundaries of synthetic drugs developed to protect the liver. Even though they are an essential part of medical therapy and may seem to be necessary, the reality is not as reassuring. Drug-induced liver injury is not an uncommon event; in fact, it causes an alarming 50 per cent of all acute liver failures, up to 10 per cent of all cases of acute hepatitis, and 5 per cent of all hospitalizations. The information that nearly three quarters of idiosyncratic drug reactions, which are the unpredictable and unusual side effects, result in liver transplantation or even death is shocking, and, to be quite frank, disturbing. The vulnerable groups (e.g., older adults, individuals with pre-existing conditions, patients who take many drugs) are especially at risk of the increasing number of synthetic drugs that have been discontinued because of its hepatotoxicity [6].

Only once the drugs are released to the general population do serious side effects become apparent, since even intensive clinical trials and premarketing studies usually terminate short of being able to fully capture the extent of the risks. In some cases, the liver natural defense mechanisms, including glutathione, are exhausted due to toxic metabolites, and that can cause disastrous cell damage. At any time, a treatment drug may turn out to be the seed of a fatal illness [7].

Even with the improvement in technology, there is still no synthetic material that can amend the shortage of organs that can be transplanted or eliminate the randomness 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 [8]. The side effects of even the most familiar treatments, including corticosteroids, interferons, or antiviral drugs, such as immunosuppression, depression, resistant virus strains, and organ damage, cast a long-term safety in a negative perspective. Moreover, conventional drugs can offer only a weak temporary relief and they are not always effective; the effects of synthetic hepatoprotective drugs are highly uneven and are often overshadowed by poor outcomes in the real life, especially in the chronic liver diseases [9].

The hope of new drugs often fails in the face of human inconsistency and complex disease mechanisms since there is growing evidence that drugs do not act the same in laboratory animals and human beings. To this add the cost, the difficulty of getting the state-of-the-art treatments, and the cold reality that artificial drugs rarely lead to the healing or recovery of liver tissue damage. It is not yet time to rule out the possibility of unexpected organ failure. These limitations in synthetic drugs as hepatoproteins have led to active efforts to find substitutes, in particular plant-derived compounds and nanomedicine but even these have their own challenges to face-due to these limitations and the ongoing quest to find safe, effective and affordable solutions [10].

1.3 Importance of Natural and Herbal Compounds

Here is the thing, then, natural and herbal substances? They are so good at working out your liver, yeah. Reasons being they have got these hepatoprotective properties. I say, the liver diseases are a very big thing, right? All the planet is grappling with problems of auto immune hassles, metabolic disorders, drug toxin, excess booze, and vile viral infections. And frankly, there are times when the conventional medications simply fail. They may be quite rough-side effects not to be desired, or not to work sufficiently, and man, some are too expensive! Hence, that is why people are actually looking to have their eyes on natural bioactive plant-based products. These are encouraging against liver damage by toxins and all the unsightly complications that ensue. Medicinal plants now contain this collection of goodies antioxidants, anti-inflammatories, substances that clean up dangerous free radicals. We are discussing flavonoids, alkaloids, phenolic acids, terpenoids, saponins, the entire team. They assist to prevent stress, irritation, and scarring of liver cells. Furthermore, these materials assist your liver cells to repair and renew themselves. They also lower those aggravating markers that you have so much talk about AST, ALT, ALP the stuff that doctors test to determine whether or not your liver is in a good mood or not [11].

These natural compounds? They are quite good looking since they do not necessarily cause the side effects like some drugs do and by the way, they are also cheap. There are loads of experiments, test tubes, animals, even humans, which have demonstrated their advantages. They have demonstrated their effects on various liver diseases such as liver cancer, viral hepatitis, alcohol related liver problems, and even fatty liver disease. The trick however is here, although they are old and have over 120 varieties, science is yet to discover the specifics of how such compounds actually act on the molecular level. And frankly, most of them do not get assimilated or dissipate too fast. Therefore, current studies are underway to develop improved ones that perform better in the body. Overall, some serious hope appears to be given by natural and herbal substances. They primarily assist by striking down inflammation and oxidative harm, eliminating toxins, and maintaining liver functioning robust. Thus, they are becoming a rather significant global player in the struggle against liver diseases, at least [12].

1.4 Aim of the Review

A Thorough Analysis of Clinical Trials on Natural Products as Hepatoprotective Agents (Plants 2024) The review mainly examines the outcome of clinical trials carried out on 13 selected natural products, including probiotics, phospholipids, vitamin D, algae (spirulina), plants and substances made out of it (e.g., artichoke, berberine, turmeric). The impacts of these products on liver functionality will be collected and the application of the products in NAFLD and other liver diseases will be critically compared. This review attempts to review and describe the potential of Bangladeshi ethnopharmacological plants in the treatment of liver diseases with references to their sources, constituents, applications in treatment, and their mechanisms of action. It summarizes *in vivo*, *in vitro* and clinical research on active compounds in plants used traditionally in liver disorders, demonstrating a rich herbal medicine legacy and its use in medicine in Bangladesh [13].

This review is primarily centered on the preclinical and clinical evidence of Liv.52, a renowned polyherbal preparation that has been in use in India and other countries over the last 5 decades. 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 evaluates the mechanisms and therapeutic promise that allow the supportive treatment of chronic liver disease and attempt to relieve its symptoms. The review examines the hepatoprotective potential of nine medicinally important hepatoprotective herbs identified according to the ethnomedical records in South Asia to treat different pathological conditions of the liver. It is highly critical in analyzing the availed toxicological and pharmacological information to inform upcoming research and development of these natural products as effective hepatoprotective agents or dietary supplements. The review will open the pathways of therapeutic formulation by establishing promising plant species and their bioactive phytoconstituents. This review aimed at gathering

information about the hepatoprotective properties of Brazilian native plants that have been examined within the past 15 years. It highlights the methods of extraction, activity parameters, and the identification of bioactive compounds, and concentrates on the animal models of hepatic lesions, and *in vivo* validation of hepatoprotective properties. The research is expected to identify plants that could be used to create new hepatoprotective preparations, as well as to contribute to economic sustainability, using plant parts that are of low commercial value [14].

This paper attempted to provide a new approach to a medicinal product that was based on fresh young shoots of *Rosmarinus officinalis* L. in order to evaluate its hepatoprotective effect. The aim was to test the chemical structure of the product (polyphenols and terpenoids) and to determine the hepatoprotective activity of the product using an antioxidant process in hepatotoxicity experimentally induced in rats. This research aims to legitimize the plant as a promising source of hepatoprotective pharmaceutical preparations [15].

2. Overview of Liver Injury and Hepatotoxicity

2.1 Causes

Damage to the liver is a complex, smoldering process which can be acute or chronic. It is not because of a single reason. The liver is the most active organ in the body, where toxins are filtered, the drugs are metabolised, and the metabolism is controlled. However the beat of the liver fails when the great number of poisonous chemicals it sifts accumulates. It tries to heal, however, with constant or recurring damage, scar tissue grows to resemble normal tissue causing fibrosis and in extreme cases, liver failure. The following are the most prevalent causes of liver damage that people encounter daily and in the sphere of medicine practice. Our livers are like filters that are able to filter a lot of stuff in a single day including medicines, vitamins, poisons and even food additives. Nevertheless, it can take so much before collapsing. There are drugs that are even quite uncomfortable despite their widespread use. Acetaminophen, a common analgesic found in numerous over-the-counter medications, may overwhelm the liver detoxification system and result in liver cells dying, e.g. in case it is taken in large quantities. Other drugs such as certain antibiotics, anticonvulsants or even natural herb supplements may silently harm the liver especially when used consistently or over a long period of time [16].

The load is increased when environmental toxins such as the chemical toxins carbon tetrachloride are also involved. These substances enhance oxidative stress because they generate free radicals which cause internal damage to the cells. In the early stages, the liver is able to regenerate through the creation of new tissues and recover. However, continued exposure leads to scarring and makes the organ weaker and less flexible. One of the world's most frequent and avoidable causes of liver injury is still alcohol. The alcohol is metabolised to form reactive chemicals like acetaldehyde which in fact damage the liver cells. The initial stage is fatty liver which is inflammatory and accumulates fat over time in the tissue of the liver. The excessive use of alcohol leads to more advanced diseases like the cirrhosis, fibrosis, or alcoholic hepatitis whereby the healthy cells are substituted with scar tissue. Surprisingly, fatty liver develops in almost all heavy drinkers but not all of them develop serious liver disease. This would imply that the true susceptibility or resistance of the liver of an individual can be established based on his or her genetic composition, diet and other aspects of lifestyle [17].

Liver function is also seriously impaired by hepatitis viruses, especially types B and C. The viruses lead to inflammation and death of liver cells by direct infection of liver cells. In case the disease is not treated in years, it may silently build scar tissue and cause fibrosis or even liver cancer. Regardless of improved vaccinations and antiviral drug coverage, viral hepatitis continues to be one of the leading causes of hepatology and death in the world. Viruses and alcohol are not the only threats of the liver presented by modern lifestyles. Non-alcoholic fatty liver disease (NAFLD), caused by diseases and conditions such as obesity, diabetes, and metabolic syndrome are similar to the damage caused by alcohol but do not involve alcohol use. Inflammation begins when the liver becomes excessively fat and leads to non-alcoholic steatohepatitis (NASH). This disorder unites fibrosis, cell damage and fat deposits into a single, vicious cycle. The problem is made worse by factors such as genetic predispositions and insulin resistance, poor diet and absence of exercise. These metabolic causes as opposed to alcohol-related disorders have roots in diet and lifestyle, which means that our dietary and lifestyle decisions may present a greater threat to the liver now than the alcoholic beverages that we consume today [18].

2.2 Pathophysiology

Oxidative stress and inflammatory signaling is the major process that causes hepatic injury. When hepatocytes are exposed to drugs or toxins the metabolic activation via enzyme such as cytochrome P450 forms reactive intermediates which bind to cellular macromolecules. Excessive amounts of free radicals and reactive oxygen species (ROS) cause

lipid peroxidation and mitochondrial dysfunction, which result in necrosis or apoptosis of liver cells. releasing pro fibrotic cytokines like TGF 00 and TNF 00. Drug induced liver injury (DILI) is a significant cause of acute liver failure and drug withdrawal in the world. It may be predictable, dose dependent (such as acetaminophen toxicity) or idiosyncratic (unexpected, such as with isoniazid or carbamazepine). These drugs are typically metabolized and lead to the depletion of glutathione (GSH), which results in cell damage in the event of breaking down capacity. Liver lesions present in different morphological appearances that comprise hepatocellular necrosis, cholestasis, fatty changes (steatosis) and vascular lesions [19].

Acute injuries lead to leakage of ALT, AST, and ALP into the bloodstream and chronic injury progresses to fibrosis, cirrhosis, or hepatocellular carcinoma (HCC) when oxidative damage and inflammation are persistent. The pathological sequence is typically sequential, beginning with oxidative damage, inflammatory cell infiltration, fibrotic remodelling, and eventually necrotic parenchymal replacement. Continued exposure to alcohol, viral hepatitis, or metabolic disorders increases this process, with a significant health burden worldwide: each year, it is almost two million deaths due to cirrhosis, hepatitis, or liver cancer complications [20].

Notwithstanding technology in the field of pharmacology, there are few effective hepatoprotective agents. The existing medications like N acetyl L cysteine (in acetaminophen overdose) reestablish GSH and suppress free radicals but can only work when administered at an early stage. End stage liver failure is a condition which has transplantation as its last resort. Existing natural compounds with abundant flavonoid, polyphenol, and terpenoid moieties have a potential hepatoprotective effect due to antioxidant and anti-inflammatory activity [21].

NF κB, Nrf2 and MAPK signaling pathways are regulated by flavonoids such as quercetin, apigenin, and hesperetin to decrease the oxidative burden and prevent fibrotic development. *Silybum marianum*, *Phyllanthus niruri* and *Picrorhiza kurroa* are traditional yet biologically validated herbal preparations that improve liver regeneration and enzymatic balance. Artificial molecules such as bicyclol- a derivative of *Schisandra chinensis* have also been found to be effective in viral and chemical hepatitis because of its antioxidant, immunomodulatory and anti-fibrotic effects [22].

There is even some experimental evidence to indicate Chronic oxidative stress is also known to trigger fibrosis by stimulating hepatic stellate cells and that hybrid molecules of lipophilic antioxidants and herbal extracts (e.g. *Salsola* Pall preparations) lead to synergistic recovery of hepatic enzyme activity and reduction of lipid peroxidation indicators. Nanomedicine and sophisticated drug delivery systems are expected to enhance the bioavailability of poorly soluble hepatoprotective compounds but this is still a challenge because cell uptake is unpredictable and Kupffer cell clearance in the hepatic microenvironment remains undetermined. Further, therapeutic activity versus possible hepatotoxicity of herbal preparations is a severe study area, and standardized dosage accompanied by stringent clinical scrutiny is crucially needed [23].

Altogether, liver damage occurs as a result of a combination of toxic, metabolic, and inflammatory processes. The fact that it develops into oxidative insult, then fibrosis and cancer is a significant biomedical issue. The discovery of naturally-occurring antioxidants, their synthetic equivalents such as bicyclol, and new delivery mechanisms continue to open new possibilities to safe, efficacious hepatoprotective therapy that can protect this vital organ against both chemical and biological damage [24].

2.3 Biomarkers

Oxidative stress and inflammatory signaling are the main causes of liver injury. When drugs or toxins enter the hepatocytes, enzymatic metabolic activation, such as cytochrome P450, results in the production of reactive intermediates binding to cellular macromolecules covalently. The surplus of reactive oxygen species (ROS) and free radicals trigger lipid peroxidation and mitochondrial damage that cause liver cell necrosis or apoptosis. Acute oxidative stress also contributes to fibrosis through activation of hepatic stellate cells and pro fibrotic cytokine release including TGF 02 and TNF 02. Drug induced liver injury (DILI) is a frequent cause of acute liver failure and drug withdrawal in the world. It is either predictable (dose related, e.g. acetaminophen toxicity) or idiosyncratic (unpredictable, e.g. with isoniazid or carbamazepine). The drugs metabolites have a disposition of depleting the glutathione (GSH) leading to cell injury following removal of the detoxification capacity. Liver lesions are in different morphological types such as hepatocellular necrosis, hepatocellular cholestasis, fatty (steatosis) and vascular lesions [25].

Acute damage causes cell injury resulting in the release of enzymes such as ALT, AST and ALP into the bloodstream, whereas chronic damage becomes

fibrosis, cirrhosis or hepatocellular carcinoma (HCC) in case of persistent oxidative damage and inflammation. The natural history typically follows stages, namely oxidative early damage, inflammatory cell invasion, fibrotic restructuring, and finally necrotic replacement of parenchyma. Repeated intoxication with alcohol, viral hepatitis, or metabolic disease speeds up the process and has significant consequences on the health of the world: almost 2 million deaths each year are caused by cirrhosis complications, hepatitis, or liver cancer [26].

Regardless of the level of development of pharmacology, there are limited effective hepatoprotective drugs. The existing drugs like N acetyl L cysteine (acetaminophen overdose) replace GSH and scavenge free radicals but only when administered promptly. In end stage liver failure, surgery is a salvage procedure. Natural products with high concentrations of flavonoids, polyphenols and terpenoids exhibit potential hepatoprotective effect through antioxidant and anti-inflammatory effect. NF κB, Nrf2, and MAPK signaling pathways are regulated by flavonoids, quercetin, apigenin, and hesperetin, decreasing the oxidative burden and halting fibrotic development. Traditional but biologically proven phyto preparations of *Silybum marianum*, *Phyllanthus niruri* and *Picrorhiza kurroa* are beneficial improving liver regeneration and enzyme balance. Artificial molecules such as bicyclol-of *Schisandra chinensis* - have also found application in viral and chemical hepatitis because of their anti-oxidant, immunomodulatory, and anti-fibrotic effects [27].

Experimental evidence goes so far as to demonstrate that lipophilic antioxidant hybrid molecules with plant extracts (e.g., *Salsola* Pall preparations) have synergistic restoration of activity of liver enzymes and reduce lipid peroxidation indicators. Nanomedicine and newer-established drug delivery systems are expected to enhance the bioavailability of insoluble hepatoprotectants, yet issues of unpredictable cellular uptake and clearance by Kupffer cells in the hepatic microenvironment still exist. More so, the therapeutic efficacy and potential hepatotoxicity of herbal preparations is a topical field of research that requires standard dosage and widespread clinical testing. A combination of toxic, metabolic, and inflammatory pathway leads to liver damage. The development of oxidative insult to fibrosis and cancer is an ongoing biomedical problem. Further studies in the field of natural antioxidants, synthetic analogs such as bicyclol and more recent delivery vehicles continue to expand an increasing horizon of safer and more effective therapies against hepatotoxicity capable of protecting this invaluable organ against chemical and biological damage [28].

3. Herbal Components with Hepatoprotective Potential

Table 1 summarizes the major classes of herbal bioactive compounds with reported hepatoprotective potential, together with representative examples and their principal mechanisms of action. These phytochemicals exert liver-protective effects through multiple pathways, including scavenging reactive oxygen species, activating endogenous antioxidant defense systems, suppressing inflammatory signaling, inhibiting hepatic fibrosis, regulating apoptosis, and preserving mitochondrial integrity. The synergistic actions of these natural compounds contribute to the prevention and attenuation of liver injury caused by oxidative stress, toxins, metabolic disorders, and chronic inflammation, highlighting their promise as complementary therapeutic agents for the management of various liver diseases [29].

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	[30]
2.	Alkaloids	Berberine, Piperine	Anti-inflammatory, modulation of signaling pathways	[31]
3.	Terpenoids & Saponins	Glycyrrhizin, Ginsenosides	Anti-fibrotic, regulation of apoptosis	[32]
4.	Polyphenols & Tannins	Curcumin, Resveratrol, Catechins	Antioxidant, mitochondrial protection	[33]
5.	Other Bioactives	Phenolic acids, lignans, coumarins	Various: mitochondrial protection, anti-inflammatory, antioxidant effects	[34]

4. Mechanisms of Hepatoprotection

4.1 Antioxidant Activity

The herbs have powerful antioxidant properties that help to protect the liver by mopping up harmful reactive oxygen products (ROS) and raising glutathione (GSH) concentrations, which play a vital role in maintaining cellular redox balance. Phytochemical activities are explored as hepatoprotective effects of most therapeutic plants such as *Phytanthus emblica*, *Camellia sinensis* (green tea), *Mangifera indica*, *Punica granatum* (pomegranate), and *Acacia catechu* predominantly via antioxidant effects. These plants have bioactive substances such as polyphenols, flavonoids, tannins and vitamins that are highly effective in countering free radicals and in alleviating oxidative stress in liver cells. *In vitro* experiments with human hepatocarcinoma HepG2 cells demonstrated that these herbal extracts had a stronger ability to inhibit cytotoxicity caused by tert-butyl hydroperoxide, dose-dependently increasing cell viability. The most potent antioxidant and protective activity was found in *Phyllanthus emblica*, not worse than silymarin, a famous hepatoprotective. The antioxidant tests conducted, including ORAC, DPPH, ABTS, and cellular antioxidant activity tests, confirmed the possibility of extracts to efficiently scavenge free radicals and prevent oxidative damage [35].

The enzymatic system of antioxidant superoxide dismutases (SOD), catalase (CAT), glutathione peroxidase (GPx) and glutathione reductase (GR) play a role in 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. To illustrate, pomegranate peel extract was found to sustain GSH levels and antioxidant enzyme activities in liver injury. *Mangifera indica* bark extract also demonstrated antioxidative property by preventing lipid peroxidation and increasing enzymatic antioxidants, primarily because of mangiferin, its active principle [36].

Although *Acacia catechu* showed the lowest protection as compared to silymarin, the highest ORAC value indicative of its good radical quenching activity was attributed to it, due to its high levels of tannin, primarily. Its antioxidant effect helps in inhibiting the damage of cellular macromolecules, membrane integrity, and lipid peroxidation, which triggers additional oxidative damage and inflammation in hepatocytes. These plant extracts prevent acute injury of liver cells by minimizing oxidative stress, and beneficially affect exacerbation to fibrosis and cirrhosis. This type of ROS and intracellular glutathione scavenging keeps hepatic detoxification systems up to date and is credited to their pre-eminent role in herbal hepatoprotection possessing minimal side effects [37].

Figure 1 illustrates the proposed hepatoprotective actions of selected herbal extracts, including *Phyllanthus emblica*, *Camellia sinensis*, and *Mangifera indica*. These phytochemicals enhance glutathione levels, scavenge reactive oxygen species (ROS), reduce oxidative stress, preserve cellular integrity, and improve antioxidant defense, thereby protecting hepatocytes against oxidative damage and liver injury [38].

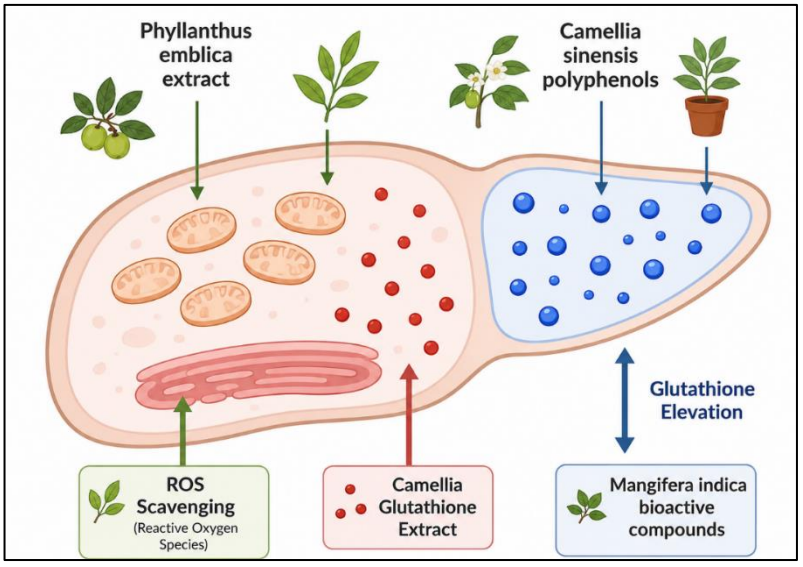

Figure 1: Proposed hepatoprotective mechanisms of selected herbal bioactive compounds.

4.2 Anti-inflammatory Effects

Herbal constituents possess high anti-inflammatory effects which play a key role in preventing chronic liver damage. Tumor necrosis factor-alpha (TNF-alpha), interleukin-1 beta (IL-1 beta), and interleukin-6 (IL-6) are some of the most important

inflammatory cytokines regulated by nuclear factor kappa B (NF-KB) signaling pathway, which is one of the most important molecular pathways of liver inflammation. These cytokines participate in the damage of liver tissue through the invasion of immune cells and the maintenance of inflammation [39].

Phytochemicals of herbs have been reported to inhibit the NF-kB activation leading to a decrease in the production of pro-inflammatory cytokines and the inflammation of the liver. As an example, berbamine (extracted out of *Berberis vulgaris*) and thymoquinone (extracted out of *Nigella sativa* seeds) showed outstanding protective activity in mouse models of immune-mediated liver damage by suppressing the nuclear translocation of NF-KB and TNF-A and interferon-gamma (IFN-G). This NF-kB inhibition interrupts the inflammatory cascade in acute hepatitis and offers promising treatment alternatives to autoimmune and viral hepatitis [40].

Intense anti-inflammatory effect in blocking NF-KB and mitogen-activated protein kinase (MAPK) pathways is also a characteristic in licorice (*Glycyrrhiza glabra*) and its bioactive compounds, glycyrrhizin and liquiritigenin. These substances prevent phosphorylation and degradation of the inhibitory protein I-kB-a, prevent NF-kB activation and down-stream production of inflammatory cytokines such as TNF-alpha, IL-6, inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2). By inhibiting these mediators, the licorice extracts inhibit hepatic inflammation and tissue injury, which is the basis of their common traditional use in liver conditions. Syringic acid is a phytochemical in modern Chinese medicine that exhibits anti-inflammatory effects and hepatoprotective effects by regulating NF-KB and JAK-STAT. Syringic acid treatment significantly lowered the expression of NF-KB, IL-6, TNF-alpha, iNOS, and COX-2 in liver tissue, and thus, demonstrated its ability to inhibit inflammatory responses and oxidative stress, which led to subsequent liver injury in chemical-induced liver inflammation models in rats [41].

Similar anti-inflammatory effects are shown by other significant herbal compounds such as curcumin, quercetin, and apigenin by controlling NF-κB and associated pathways. Curcumin inhibits the p300 histone acetyltransferase which suppresses inflammatory gene expression, including COX-2, and prevents cardiac and hepatic inflammation. Quercetin prevents the TLR4-mediated NF-KB translocation, stabilizes the NF-KB/IKB complex, and prevents pro-inflammatory cytokine production. Apigenin can alter the macrophage polarization, inhibit the activation of NF-kB, and reduce NO and pro-inflammatory cytokines and therefore perform its anti-inflammatory and hepatoprotective effects. Collectively, these plant constituents regulate major inflammatory signaling hubs such as NF-kB, MAPKs, inhibit cytokine expression, and inhibit inflammatory mediators such as iNOS and COX-2 that mediate inflammation. They reduce immune-mediated destruction of hepatocytes by inhibiting chronic liver inflammation, and promote tissue repair, making them useful therapeutic assets in the treatment of liver diseases triggered by chronic inflammation. Figure 2 illustrates the anti-inflammatory effects of selected medicinal plants, including *Berberis vulgaris*, *Nigella sativa*, and *Glycyrrhiza glabra*. Their bioactive constituents suppress key inflammatory mediators such as NF-κB, TNF-α, and IL-6, thereby reducing hepatic inflammation, preventing liver injury, and promoting hepatoprotection [42].

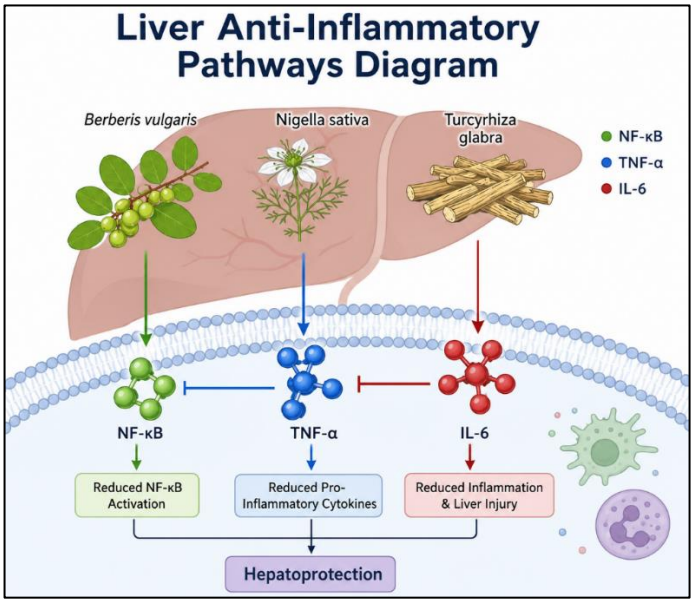

Figure 2: Anti-inflammatory mechanisms of selected herbal bioactive compounds in liver protection.

4.3 Anti-fibrotic Activity

Liver fibrosis is a serious medical disorder that occurs as a result of connective tissue deposition in the liver mainly because of chronic liver injury as a result of many causes which may include alcohol consumption, hepatitis infections and metabolic diseases. First in this fibrogenic reaction is the hepatic stellate cells (HSCs), which are in normal liver, dormant cells that accumulate vitamin A [43]. However, when the liver is injured, these HSCs are stimulated and transform into proliferative myofibroblasts that produce and depose profuse quantities of extra cellular matrix (ECM) proteins such as collagen types I and III, leading to scar tissue formation and architectural distortion. This over deposition of ECM results in fibrosis, which may turn out to be cirrhosis and liver cancer, should there be no treatment [44].

Herbal agents have already shown great promise with regard to fighting liver fibrosis at various stages in this pathological mechanism. They inhibit HSCs activation and proliferation, cause apoptosis or quiescence, and regulate ECM production and degradation, effectively preventing collagen deposition. The natural compounds that mediate these anti-fibrotic effects include alkaloids, flavones, terpenoids, saponins, phenylpropanoids, and polysaccharides which have been discovered as several natural compounds in traditional Chinese medicines and herbs [45].

The TGF-B/Smad signaling pathway is one of the most important molecular pathways of the HSCs activation. The herbal constituents such as salvianolic acids, oxymatrine, curcumin, and tetrandrine have been identified to block this pathway causing the down-regulation of the fibrogenic-markers such as α-smooth muscle actin (α-smooth muscle actin) and collagen. As an example, curcumin inhibits the synthesis of TGF-B1 and subsequent Smad2/3 phosphorylation thereby preventing the differentiation of HSC and collagen deposition. Oxymatrine regulates TGF-β, IL-6, and TNF-α signaling for the protection of the liver against fibrosis. These herbs also enhance the presence of inhibitory molecules like Smad 7 whose presence acts against the fibrogenic signals. Other signaling pathways of interest, besides TGF-β, that herbal constituents activate include NF-kB, MAPK and STAT3 and are involved in inflammatory and proliferative responses of HSCs. Some herbal extracts reduce the expression of pro-inflammatory cytokines TNF-alpha and IL-6, which also suppresses HSCs activation. 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 [46].

The HSC activation, ECM inhibition, and oxidative stress and inflammation reduction are multi-targeted activities demonstrated by some of the herbal remedies that are widely used in folk medicine. Some such herbs are Fufang-Biejia-Ruangan pill, Yinchenhao decoction, and Xia-yu-xue decoction, which have been shown to be effective in research models to reduce the effects of fibrosis by lowering α-SMA, collagen and TGF-B1 levels. Finally, herbal constituents reverse hepatic fibrosis through the concerted action of inhibiting stellate cells, balancing collagen and extra-cellular matrix synthesis, controlling pro-fibrotic and pro-inflammatory signalling, and enhancing antioxidant and autophagic function. It is these multiple actions that underlie the hepatoprotective and anti-fibrotic activities of natural therapeutic products that offer hope to a new therapy against an etiology where therapy currently has limited successful choices [47].

Figure 3 illustrates the anti-fibrotic effects of selected herbal bioactive compounds, including curcumin, salvianolic acids, oxymatrine, and tetrandrine, in the prevention and attenuation of liver fibrosis. These phytochemicals act through multiple complementary mechanisms to suppress hepatic stellate cell activation and proliferation, thereby limiting excessive extracellular matrix deposition. They also inhibit key inflammatory and profibrotic signaling pathways, reduce collagen synthesis and cross-linking, and enhance collagen degradation and matrix remodeling. Through these coordinated effects, the compounds help reduce fibrotic tissue accumulation, restore hepatic architecture, and mitigate progressive liver injury. Collectively, their multifaceted actions contribute to preserving normal hepatic structure and function while slowing fibrosis progression [48].

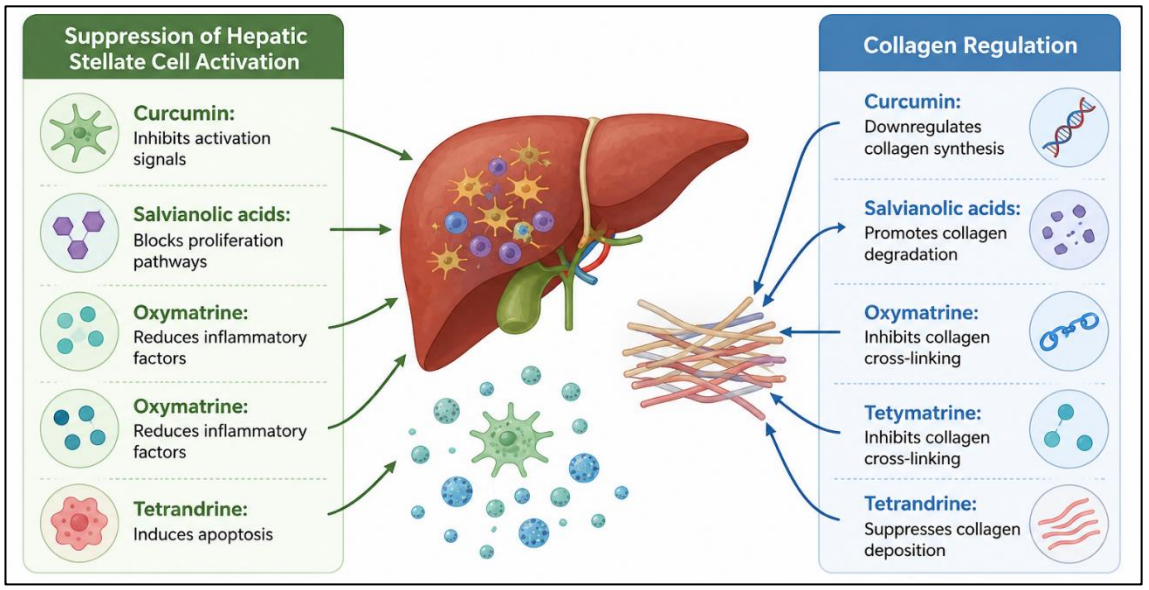

Figure 3: Anti-fibrotic mechanisms of selected herbal bioactive compounds in liver fibrosis.

4.4 Anti-apoptotic and Mitochondrial Protection

The conservation of liver cells against apoptosis and mitochondrial injury is an important element in herbal treatment. Most of the herbs contain bioactive molecules which cause the inhibition of programmed cell death, which occurs in liver damage by toxins or oxidative stress. These molecules do not only inhibit the apoptotic processes, but also stabilize mitochondria that act as energy-producing organelles in cells to ensure that they can continue functioning even under stress [49]. The modulation of mitochondrial membrane integrity is one of the common mechanisms. The herbs that help in sustaining the mitochondrial membrane potential and suppressing the opening of the mitochondrial permeability transition pore (MPTP) include herbs like silymarin made of the milk thistle or curcumin made of turmeric. The opening of this pore will lead to the loss of mitochondria to effectively generate energy and trigger the release of pro-apoptotic factors including cytochrome c that in turn activate the caspases that cause cell death [50].

The ratio of proteins that induce or suppress apoptosis is also regulated using herbal extracts. As an example, the majority of herbal constituents can increase the concentration of Bcl-2, the anti-apoptotic protein, and decrease the concentration of Bax, the pro-apoptotic protein. Such a shift in balance helps the cell to survive even when it is exposed to harmful substances that attack it. Part of it is achieved by the activation of pathways like PI3K/Akt which increase cell survival and mitochondrial integrity [51]. The examples of the herbs include not only silymarin and curcumin, but also such as quercetin, which enhances mitochondrial antioxidant defenses and inhibits the caspases, which are the real proteins, which cause cell death. Moreover, some herbs also activate the inherent antioxidant defense systems within the mitochondria including superoxide dismutase (SOD) and glutathione peroxidase. These enzymes inactivate the excess ROS that is produced during injury and in the process, protect the mitochondria and the whole cell itself, directly against oxidative damage [52].

Released inducers of apoptosis are also prevented in the mitochondria by depletion of oxidative stress resulting in a positive cellular environment in which hepatocyte recovery will occur. Herbal constituents preserve liver cell integrity by stabilizing the mitochondrial activity, reducing oxidative stress, and regulating apoptotic proteins. This does not only prevent cell death, but also promotes healing of injured tissue, and this is the reason why herbal medicine is one of the potential approaches in the treatment of liver disease. The overall effect is liver preservation, fibrosis inhibition, and healing. Figure 4 illustrates the hepatoprotective mechanisms of silymarin and quercetin through preservation of mitochondrial membrane integrity, regulation of the Bcl-2/Bax balance, and inhibition of caspase activation. These coordinated actions suppress apoptosis, maintain mitochondrial function, and enhance liver cell survival, thereby protecting hepatocytes from oxidative stress and injury [53].

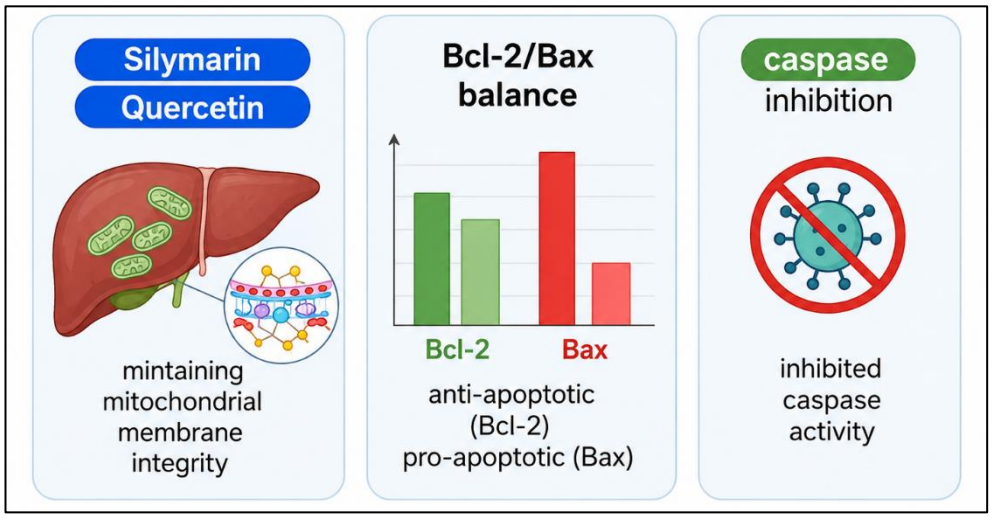

Figure 4: Mitochondrial protection and anti-apoptotic mechanisms of herbal bioactive compounds in liver cells.

4.5 Modulation of Metabolic Enzymes

The herbal constituents provide the liver with a great deal of protection by regulating the metabolism enzymes, specifically the cytochrome P450 (CYP450) enzyme family. These enzymes play a very important role in the metabolism of drugs, toxins, and other foreign chemicals, and excess or dysbalance may lead to the formation of toxic reactive metabolites that cause liver damage [54]. Different herbal medicine regulates the CYP450 enzymes by either inhibiting or inducing some of these isoforms to restore metabolic balance in the liver. An example of this is silymarin of *Silybum marianum* and glycyrrhizin of *Glycyrrhiza glabra* that have been reported to protect liver cells against CCl_4-induced hepatic toxicity, where the CYP450 enzymes metabolically transform CCl_4 to reactive free radicals that induce cellular destruction. These plants inhibit the activity of these oxidative enzymes and increase antioxidant defenses, reduce lipid peroxidation and cell injury indicators [55].

They interfere with the production of toxic metabolites and rescue liver structure by regulating CYP450. 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 action increases the detoxification capacity and reduces the oxidative stress because of reactive metabolites. One of these plants, *Andrographis paniculata*, enhances antioxidant enzyme activities and restores CYP450 metabolism, which consequently suppresses xenobiotic hepatotoxicity. Herbal regulation of CYP450 is a delicate mechanism because its over-inhibition can cause drug interactions whereas poor regulation may not protect the liver. The hepatoprotective herbs also seem to regulate the enzymic activity in such a manner that the toxic substances are metabolized safely, without excessive production of toxic intermediates. This multi-faceted CYP450 modulation, combined with the direct anti-inflammatory and antioxidant effects is the foundation of herbal liver protection, which prevents the organ against chemical damage and promotes healing [56].

Figure 5 illustrates the modulatory effects of bioactive compounds, including silymarin, glycyrrhizin, and *Andrographis paniculata*, on hepatic cytochrome P450 (CYP450) enzymes and related metabolic pathways. These phytochemicals can influence the activity and expression of specific CYP450 isoenzymes, thereby regulating the biotransformation of endogenous and exogenous substances. By modulating hepatic drug-metabolizing enzymes, they may limit excessive metabolic activation and reduce the formation of potentially toxic metabolites associated with chemical- and drug-induced liver injury. In addition, these compounds support endogenous antioxidant defenses, stabilize hepatocyte membranes, and help maintain cellular homeostasis and hepatic detoxification capacity. Their effects on CYP450-mediated metabolism may also contribute to improved clearance and reduced accumulation of harmful intermediates, although such interactions can vary depending on the compound, dose, and specific CYP isoenzyme involved. Overall, modulation of CYP450 activity, combined with antioxidant and hepatoprotective actions, may help preserve hepatocyte integrity, maintain normal hepatic metabolic function, and attenuate liver injury [57].

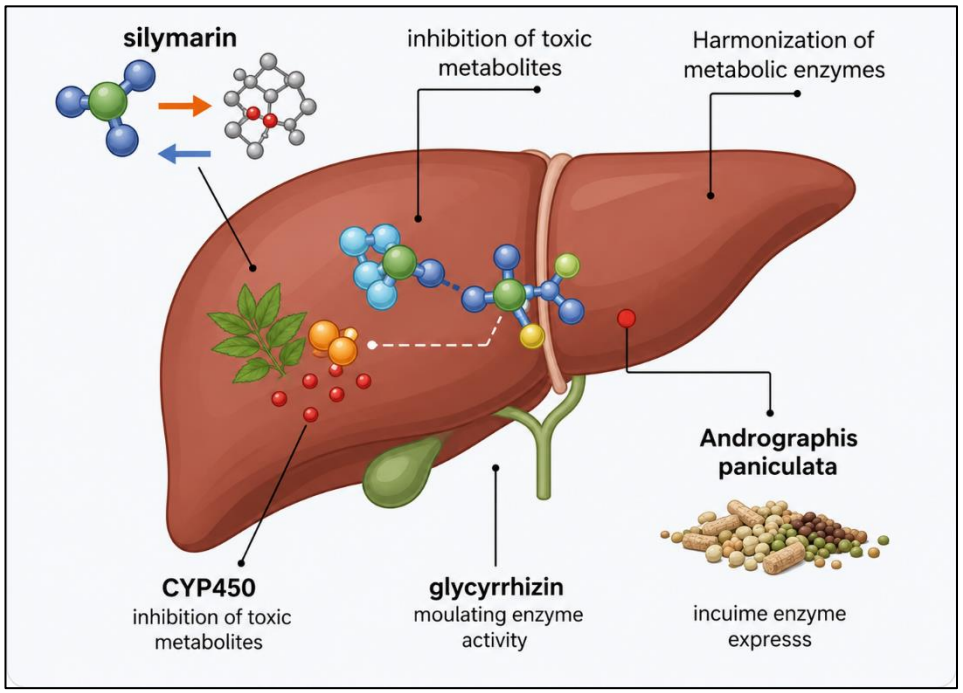

Figure 5: Modulation of CYP450 enzymes by hepatoprotective herbal bioactive compounds.

5. Experimental and Clinical Evidence

5.1 Preclinical Studies

Equally utilized in preclinical animal models is hepatotoxicity models induced by chemicals including carbon tetrachloride (CCl_4), paracetamol, alcohol and cyclophosphamide. The models are used to explain the liver injury mechanisms and to assess possible hepatoprotective agents [58]. CCl_4 is a prototypical CYP450-activated hepatotoxin, which induces centrilobular necrosis by creating reactive free radicals, which cause lipid peroxidation, oxidative stress, inflammation, and liver regeneration. When administered intraperitoneally in rodents, it causes acute and chronic liver damage similar to that in humans. Metabolism to the toxic metabolite NAPQI, which depletes glutathione and leads to oxidative stress and cellular necrosis, is the primary cause of hepatotoxicity in paracetamol (acetaminophen) overdose. High doses of paracetamol in mouse and rat models are associated with an increase in liver enzymes, mitochondrial dysfunction, and histopathological damage of the liver [59].

Chronic and binge ethanol induction of hepatotoxicity in rodents has been used as a model of alcohol-induced hepatotoxicity, frequently in combination with other offenses such as CCl_4. This causes steatosis, inflammation, fibrosis, and transcriptomic signatures of human alcoholic hepatitis such as neutrophil infiltration and pericellular fibrosis [60]. Another chemotherapeutic agent, cyclophosphamide also induces dose-dependent hepatotoxicity in animal models which manifested as hepatocyte necrosis, increased liver enzymes and histological tissue damage. Oxidative stress and cell injury are caused by the presence of toxic metabolites including acrolein [61].

Table 2 summarizes the most commonly used hepatotoxic agents employed in experimental animal models to investigate liver injury and evaluate the efficacy of hepatoprotective therapies. These models mimic different pathological mechanisms, including oxidative stress, lipid peroxidation, glutathione depletion, mitochondrial dysfunction, inflammation, and fibrosis. Carbon tetrachloride (CCl_4), paracetamol, alcohol, and cyclophosphamide are widely used because they reproducibly induce hepatic damage resembling human liver disorders. Such experimental models provide valuable insights into the pathogenesis of liver diseases and serve as reliable platforms for screening and validating the hepatoprotective potential of natural products and synthetic therapeutic agents [62].

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,	Centrilobular necrosis, oxidative stress, fibrosis	[63]

			inflammation		
2.	Paracetamol	Mice, rats (i.p. or oral)	NAPQI metabolite formation, glutathione depletion, oxidative stress	Hepatocyte necrosis, elevated ALT/AST, mitochondrial dysfunction	[64]
3.	Alcohol	Mice (oral, intragastric), often combined with CCl_4	Chronic ethanol metabolism leads to steatosis, inflammation, fibrosis	Steatosis, neutrophil infiltration, pericellular fibrosis	[65]
4.	Cyclophosphamide	Mice, rats (various doses)	Toxic metabolites cause oxidative injury, necrosis	Hepatocyte necrosis, raised liver enzymes, inflammation	[66]

5.2 Clinical Studie

The therapeutic use of silymarin, curcumin, and licorice extracts as natural products as hepatoprotective agents against liver diseases, including nonalcoholic fatty liver disease, liver cirrhosis and alcoholic liver disease has been the focus of numerous human clinical trials. Such tests are often used to assess changes in liver functional tests, especially a decrease in serum liver enzymes (ALT, AST, GGT), liver fat, and fibrosis indicators. Silymarin (milk thistle) is one of the most researched herbal agents, which has shown a significant effect on liver enzymes and scores of fibrosis in chronic liver disease patients. Randomized controlled trials of 140 mg to 720 mg of daily dose have shown decreased ALT and AST levels and increased liver functioning and some studies have shown improved survival in alcoholic cirrhosis [67].

The active ingredient of turmeric is curcumin, which has anti-inflammatory and antioxidant properties in NAFLD and liver cirrhosis patients. Doses of curcumin used in clinical trials ranging between 500 mg to 1500 mg per day showed a decrease in liver enzymes, liver fat, and inflammatory markers, and an improvement in ultrasonographic liver examination. Hepatoprotective potential via antioxidant and anti-inflammatory mechanisms has been demonstrated by licorice (glycyrrhizin) extracts. There is evidence of human trials showing a reduction in transaminase levels and liver improvement in liver histology after licorice supplementation and thus can be used as an adjunct to liver disease management. There are other natural products that have demonstrated promising clinical efficacy including the berberine, green tea polyphenol and probiotics which have demonstrated their efficacy reflected through the improvement of the biochemical liver profile and histological results. However, the multi-faceted nature of liver diseases and differences in study design designate the need to conduct additional large-scale randomized controlled studies to ascertain these results [68].

Table 3 summarizes the available clinical evidence supporting the therapeutic potential of selected natural hepatoprotective agents in patients with liver diseases. Randomized controlled trials have evaluated herbal products such as silymarin, curcumin, licorice extracts, berberine, green tea polyphenols, and probiotics in conditions including non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), chronic hepatitis, alcoholic cirrhosis, and minimal hepatic encephalopathy. These interventions have demonstrated beneficial effects, including reductions in serum liver enzymes, improvement in hepatic steatosis and fibrosis, enhanced insulin sensitivity, attenuation of inflammation, and improved liver function, highlighting their promise as complementary therapies in liver disease management [69].

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	[70]
2.	Curcumin	NAFLD, liver	Randomized	500 - 1500	Reduced liver	[71]

		cirrhosis	controlled trials	mg/day	enzymes, decreased liver fat, improved ultrasonographic liver parameters	
3.	Licorice Extracts	NAFLD	Randomized controlled trials	Standardized extracts (~2 g/day)	Lowered ALT and AST, anti-inflammatory effects	[30]
4.	Berberine	NAFLD, NASH	Randomized controlled trials	500 - 1500 mg/day	Reduced ALT/AST, improved insulin sensitivity, decreased liver fat	[72]
5.	Green Tea Polyphenols	NAFLD, NASH	Randomized controlled trials	550 - 1080 mg/day of catechins	Significant decrease in liver enzymes, reduced steatosis on imaging	[73]
6.	Probiotics	NAFLD, NASH, minimal hepatic encephalopathy	Randomized controlled trials	Multi-strain formulations	Improved liver enzymes, reduced inflammation, improved histopathology	[74]

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

Silymarin, curcumin and polyherbal preparations like Liv.52 have demonstrated significant efficacy in clinical and experimental trials and the efficacy of these herbal hepatoprotective agents is often equal to that of standard synthetic hepatoprotective drugs like ursodeoxycholic acid (UDCA), N-acetylcysteine (NAC) and steroids. The effect of herbal extracts is multifactorial (antioxidation, antifibrotic, anti-inflammatory and membrane stabilization) whereas synthetic hepatoprotectives are generally more specific (e.g., bile acid regulation by UDCA, glutathione replenishment by NAC) [75]. Various meta-analyses and head-to-head preclinical and clinical studies indicate that herbal extract such as silymarin has the potential to be equivalent or even superior to synthetic agents in terms of parameters of liver function (ALT, AST, ALP), oxidative stress, and symptoms, and with better safety and tolerability. As an example, silymarin is shown to be as effective as conventional agents in NAFLD and hepatitis, with minimal risk of diarrhea or pruritus caused by UDCA or bone marrow suppression by immunosuppressive steroids [76]

However, synthetic hepatoprotectives continue to play a crucial role in acute liver failure or other severe cases, in which an acute, well-characterized pharmacologic effect is required. The herbal therapies are occasionally a problem in terms of standardization of extracts, low bioavailability, and inconsistent regulatory control. Combination therapies between the two classes are also being explored to be used synergistically to reduce side effects and increase efficacy and particularly in chronic liver diseases or where alternative therapies are restricted [77].

Table 4 compares commonly investigated herbal extracts with conventional synthetic hepatoprotective drugs based on their source, mechanisms of action, therapeutic efficacy, and safety profiles. Herbal agents such as silymarin, curcumin, and Liv.52 exhibit multitarget pharmacological activities, including antioxidant, anti-inflammatory, membrane-stabilizing, and antifibrotic effects, with generally favorable safety profiles. In contrast, synthetic agents such as ursodeoxycholic acid, N-acetylcysteine, steroids, and pentoxifylline are well-established therapies for specific liver disorders but may be associated with adverse effects during prolonged use. This comparison highlights the potential of herbal medicines as complementary or alternative therapeutic options in liver disease management [78].

Table 4: Comparison of herbal extracts and synthetic hepatoprotective drugs.

S. No.	Agent/Class	Source/ Type	Mecha nism	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	[79]
2.	Curcumin	Herbal	Antioxidant, anti-inflammatory	Comparable to standard therapy in NAFLD; effective as add-on in clinical trials	Very well tolerated, low bioavailability	[80]
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	[81]
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	[82]
5.	N-acetylcysteine (NAC)	Synthetic	Glutathione precursor, antioxidant	Highly effective in acute toxicity/ALF	Nausea, rare hypersensitivity	[83]
6.	Steroids (e.g., prednisolone)	Synthetic	Immunosuppressive, anti-inflammatory	Lifesaving in select cases	Immunosuppression, bone loss, diabetes risk	[84]
7.	Pentoxifylline	Synthetic	TNF-α inhibitor, anti-inflammatory	Add-on in steroid non-responders	GI upset, dizziness	[85]

7. Limitations and Future Perspectives

7.1 Possible Toxicity of Certain Herbal Compounds

Some herbal extracts, especially the pyrrolizidine alkaloids (PAs) are highly toxic, in spite of the increase in the use of herbal products as hepatoprotectants. PAs are naturally occurring secondary metabolites occurring in more than 6000 plant species, including mostly in Asteraceae, Boraginaceae, and Fabaceae families. These substances act as plant defense systems but are hepatotoxic, genotoxic, and carcinogenic to the humans and animals when consumed in high dose.

The pyrrolizidine ring structure of PAs is characterized by variations to form subclasses. Most importantly, unsaturated PAs (having 1,2-double bond) are particularly toxic. Once absorbed in the gastrointestinal tract, PAs are processed in the liver by cytochrome P450 enzymes to reactive pyrrole metabolites that cause cell death, liver necrosis, fibrosis and veno-occlusive disease. These metabolites are also genotoxic and cancer-inducing. These alkaloids are poisonous to different food items such as herbal teas, spices, honey, pollen, and dairy items, and the chronic food ingestion is a matter of concern. Even less toxic pyrrolizidine alkaloid N-oxides (PANOs) can be converted to toxic pyrroles *in vivo*. The contamination is likely to be a result of co-harvesting of weeds with PA or rather cross-contamination during processing [86].

Adverse effects of PAs are both acute (pain, nausea, vomiting, and diarrhea) and chronic liver damage that is seen in the form of hepatic insufficiency, fibrosis, cirrhosis, and in rare cases, liver failure. Toxicity is dose-dependent, duration-dependent, species-specific, and person-dependent on their metabolic ability to eliminate PAs. To reduce the risks of health conditions, regulatory bodies like the European Commission and EFSA have established maximum levels of PA content in food and herbal products. Sensitive PAs detection methods such as

high-performance liquid chromatography combined with mass spectrometry (LC-MS) have been established and optimized to meet the safety standards. Monitoring and control measures should continue after the toxicity of PAs and their occurrence in widely used herbal products [91].

7.2 Dose Standardization Issues

The standardization of doses is an important issue in the creation and clinical use of herbal and nano-medicinal products. The composition of herbal extracts varies, there is variability in the way they are prepared, inconsistency between batches, and the multi-component nature of the formulations make it difficult to have standard dosing schedules. In contrast to synthetic drugs, whose active ingredients are well-characterized, and dose-response relationships are well understood, herbal products usually contain many bioactive compounds whose concentrations may differ significantly based on the plant source, harvest time, extraction procedure, and formulation [87].

The role of pharmacokinetic and toxicokinetic factors in safe and effective dose ranges is an important factor. The conventional dose-setting toxicological methods, which often use the maximum tolerated dose (MTD), might not be appropriate when dealing with natural products or nanomedicines because of their multi-component nature and multi-pathway interactions in the body. The more recent methods suggest concentrating on the no-observed-adverse-level (NOAEL) and actual kinetic maximum dose (KMD) reflecting doses at which adverse effects were not observed and at which biological systems could properly metabolize and excrete compounds [88].

The issue of dose consistency and quality control is also a major problem in the case of nanomedicines and nanoparticulate drug delivery systems because nanoparticles have physicochemical variability, which includes particle size distribution, surface properties, and stability. These properties play important roles in determining biodistribution, pharmacodynamics, and toxicity profiles. In this way, effective quality management practices and accurate characterization techniques are required to achieve reproducibility and also to put in place specific dose standards of clinical use [89]. Besides, challenges in dose standardization are further complicated by the absence of globally recommended analytical standards and procedures, especially in relation to complex herbal preparations and multifunctional nanoparticles. Regulation systems are changing to mitigate such concerns and standardization of extraction procedures, dose measurements, bioavailability analysis, and global toxicity tests are a requirement. Quality-by-Design (QbD), Process Analytical Technology (PAT) have been suggested as strategic approaches to improve dose consistency and product safety along the development pipeline [90]

7.3 Lack of Large-Scale Clinical Trials

The fact that large-scale, multicenter clinical trials are currently scarce is one of the most severe constraints to the clinical translation and strong validation of new liver therapeutics, such as nano biomaterials, cell-based therapies, and many targeted anticancer agents. The majority of clinical evidence currently available is based on small to medium scale studies, which are frequently limited in geographic coverage, follow-up time and possess a heterogeneous group of patients, which severely limits the extrapolation and statistical strength of the resulting information [91]. Recent progress in drug development and molecular insights into hepatocellular carcinoma (HCC) has provided many breakthrough therapies and a number of ongoing clinical trials into HCC, especially against targeted therapies and immunotherapies. Nevertheless, in this dynamically developing treatment field, in major phase III studies, lack of patient accrual, selective inclusion, and underrepresentation of minorities or comorbid patients are common. There are numerous potentially effective interventions at an early stage of development that do not have a phase III study that is pivotal, sufficiently powered, and can demonstrate efficacy and safety in a population-scale [92].

The same drawback is observed in the formation of advanced models of toxicity screening. Although the next-generation level of technologies such as 3D liver models, organoids, and micro-physiological systems promise to reduce the predictability gap between preclinical and clinical models, they are also impeded by the absence of large-scale studies of human models. Numerous new hepatoprotective therapies, such as traditional medications and cell therapies, are tested in small case-series or uncontrolled studies with insufficient statistical power [93].

Further, the heterogeneity of study design, small patient samples, and the variability of endpoints and outcome measures also complicate the situation and cannot be easily compared across studies or conduct powerful meta-analyses. Consequently, the development of new therapies and their integration into clinical practice is slow, although the number of molecular targets and treatment modalities continues to grow. Such a shortage of robust, large-scale clinical evidence limits the confidence of clinicians in implementing new therapies and their optimal application in more general patient groups [94].

Conclusion

The gathered data confirm that the herbal bioactive constituents can provide a bright prospect of liver protection in a broad spectrum of biologic activities, such as antioxidant, anti-inflammatory, anti-fibrotic, and metabolic control. Although the potential of plant-derived therapies has been enormous and backed by numerous experimental and clinical trials, there are still issues when it comes to standardization, quality assurance, and full toxicity profiling. In order to achieve maximum clinical potential of herbal medicines in hepatic diseases, future studies should focus on well-designed large-scale clinical trials, well-conducted safety trials, and optimized dosage regimens. In sum, medicinal plants and their active constituents emerge as crucial candidates of new hepatoprotective therapies, safer and more innovative, that can be used to complement or even replace the traditional synthetic drugs in the treatment of liver disease worldwide.

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Author Contributions

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Conflict of Interest

The authors declare no conflict of interest regarding the publication of this manuscript.

Ethics approval and consent to participate

Not applicable

AI Declaration

The authors declare that they did not use artificial intelligence (AI) tools to generate or draft the scientific content of this manuscript. ChatGPT and Grammarly AI were used solely to improve the language, grammar, readability, and clarity of the manuscript. All AI-assisted suggestions were carefully reviewed, verified, and edited by the authors, who take full responsibility for the accuracy, originality, and integrity of the final content.

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