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Emerging Natural Products for Liver Injury: From Traditional Medicine to Mechanism-Based Modern Pharmacotherapy

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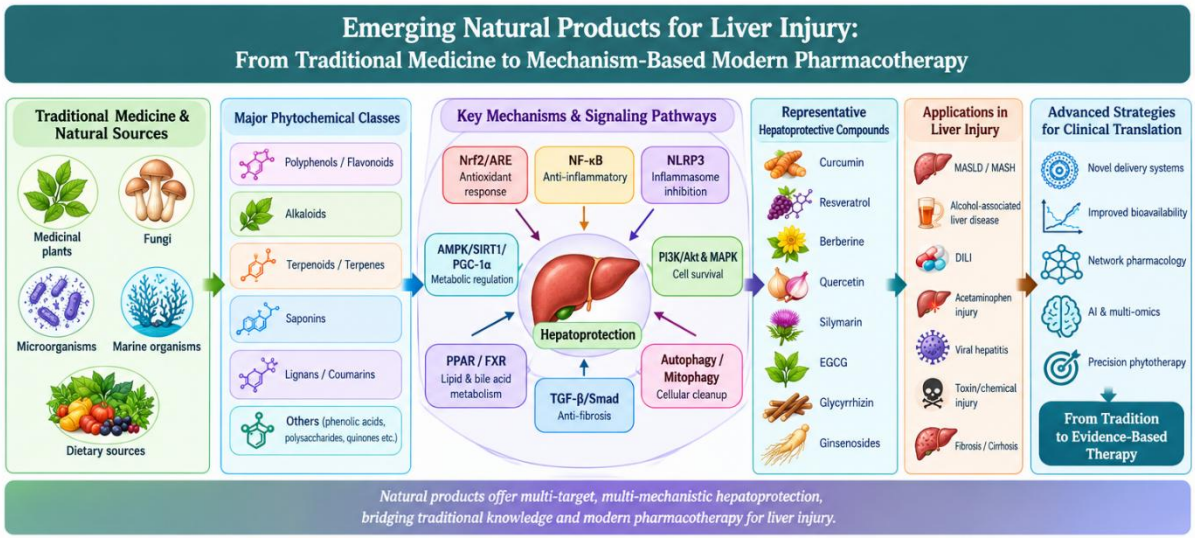
Abstract

Liver injury is a major health problem worldwide, associated with metabolic disorders, alcohol intake, exposure to drugs and chemicals, viral infections and immune-mediated diseases. Despite advances in the understanding of the pathophysiology of liver, effective treatments targeting multiple mechanisms of liver injury are still limited. Natural products isolated from medicinal plants, fungi, microorganisms, marine organisms, and dietary sources have gained considerable interest due to their diverse chemical structures and potential hepatoprotective activities. This review discusses the up-and-coming natural products for liver injury from the viewpoint of traditional medicinal knowledge and modern pharmacological investigation. It targets the major pathological mechanisms of hepatic injury including oxidative stress, mitochondrial dysfunction, inflammation, lipotoxicity, ER stress, impaired autophagy, regulated cell death, hepatic stellate cell activation, fibrosis and gut-liver axis dysfunction. The hepatoprotective potential of major phytochemical classes (polyphenols, flavonoids, alkaloids, terpenoids, saponins, lignans and other bioactive compounds) is discussed with special reference to molecular pathways including Nrf2/ARE, NF-κB, NLRP3 inflammasome, AMPK/SIRT1/PGC-1α, PI3K/Akt, PPAR, FXR, and TGF-β/Smad signaling. The representative compounds such as curcumin, resveratrol, berberine, quercetin, silymarin, epigallocatechin gallate, glycyrrhizin, ginsenosides and Schisandra lignans are reviewed in the light of preclinical and available clinical evidence. Moreover, the review discusses advanced pharmaceutical delivery systems, pharmacokinetic limitations, network pharmacology, artificial intelligence, multi-omics approaches and precision phytotherapy. Despite promising experimental findings, clinical translation is challenging due to poor bioavailability, inconsistent product standardization, lack of large-scale clinical trials and possible herb-drug interactions. Future research should emphasize standardized formulations, mechanism-based investigations, rigorous safety assessment, and well-designed clinical trials to establish natural products as reliable therapeutic candidates for liver injury.

Keywords: Hepatoprotection, natural products, oxidative stress, Nrf2, NF-κB, ferroptosis, fibrosis, MASLD, drug-induced liver injury, pharmacotherapy, and oxidative stress.



Graphical Abstract

Highlights

- Curcumin, resveratrol, berberine, and silymarin show promising hepatoprotective potential.
- Natural products target Nrf2/ARE, NF-κB, and NLRP3 signaling to regulate oxidative stress and inflammation.
- AMPK/SIRT1, PPAR/FXR, and TGF-β/Smad pathways link natural products to metabolic regulation and antifibrotic effects.
- Novel delivery systems aim to overcome poor bioavailability and enhance therapeutic efficacy.
- AI, multi-omics, and network pharmacology support mechanism-based discovery and clinical translation.

1. Introduction

The liver is a metabolically active organ, which maintains systemic homeostasis via nutrition metabolism, xenobiotic biotransformation, bile generation, protein synthesis, endocrine regulation, immunological surveillance and storage of vital nutrients. Hepatocytes are continuously exposed to endogenous metabolites and foreign substances and the liver is particularly susceptible to toxic, metabolic, inflammatory and oxidative insults [1]. If damage is severe or persistent, reversible hepatocellular stress may progress to steatosis, steatohepatitis, fibrosis, cirrhosis and eventually hepatocellular cancer. Liver injury is not a single pathological entity, but a complex biological response involving interactions between hepatocytes, Kupffer cells, hepatic stellate cells, sinusoidal endothelial cells, infiltrating immune cells, the extracellular matrix, and the gut microbiome [2]. Because oxidative stress, mitochondrial dysfunction, lipid accumulation, inflammatory signalling, endoplasmic reticulum stress, impaired autophagy and regulated cell death pathways often co-exist and reinforce each other. Thus, intervention targeting a single pathway may be insufficient to stop progression [3]. The increasing interest in natural products is related to the presence of many phytochemicals with antioxidant, anti-inflammatory, anti-lipotoxic, anti-fibrotic, immunomodulatory and metabolic properties.[5] The ability of natural products to act at multiple molecular targets may be particularly relevant to multifactorial liver diseases. This seeming advantage has to be balanced against important translational and pharmacokinetic limitations [5]. Available clinical evidence highlights both the potential and unpredictability of this field. A detailed review of clinical studies in 2024 concluded that various natural ingredients including artichoke, berberine, green tea, silymarin, spirulina, schisandra, probiotics and others may improve liver enzymes, but also underlined the need for more robust clinical evidence [6]. The review is organized in the uploaded review plan starting from mechanisms of liver injury and traditional medicine to phytochemical diversity, molecular mechanisms, disease-specific applications, advanced delivery, pharmacokinetics, pre-clinical and clinical evidence, precision medicine and artificial intelligence, safety, translational challenges and future perspectives [7].

1.1 Worldwide burden of liver injury and liver diseases

The global burden of liver disease has increased dramatically due to the metabolic syndrome, obesity, diabetes, alcohol exposure, viral infections, medication use and environmental toxicants. Metabolic dysfunction-associated steatotic liver disease (MASLD) has gained particular attention due to its association with obesity, insulin resistance, dyslipidemia, cardiovascular disease, and progression toward MASH and fibrosis [8]. Drug-induced liver injury (DILI) is another important clinical cause of acute and chronic hepatic dysfunction [9]. It may be due to intrinsic toxicity, a dose-dependent injury, or idiosyncratic immune/metabolic mechanisms. Acetaminophen is a classic example of intrinsic hepatotoxicity, whereas many other drugs cause idiosyncratic injury. The increasing incidence of liver diseases has resulted in the search for effective treatments that could simultaneously target several pathogenic processes [10]. Natural products are attractive in this regard since their chemical constituents can influence oxidative stress, inflammatory pathways, mitochondrial metabolism, lipid handling and fibrogenesis [11].

1.2 Major causes and clinical manifestations of liver injury

The most common causes of liver injury are metabolic dysfunction, alcohol, drugs, herbal preparations, industrial chemicals, pesticides, heavy metals, viral infections, autoimmune diseases, ischemia and inherited metabolic abnormalities [12]. Clinically, liver injury can present as asymptomatic elevation of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), fatigue, nausea, abdominal discomfort, jaundice, dark urine, pruritus, hepatomegaly, coagulopathy, encephalopathy, and in severe cases, acute liver failure [13]. Pathologically, hepatocellular, cholestatic, and mixed patterns of injury are possible. Chronic injury results in activation of wound-healing pathways and hepatic stellate cells with subsequent deposition of extracellular matrix and fibrosis [14].

1.3 Limitations of current pharmacological interventions

The limited availability of broadly acting hepatoprotective drugs has led to interest in natural products; however, "natural" does not necessarily imply safe or efficacious [15]. Herbal products can themselves cause liver injury; a systematic review of published herb-induced liver injury cases found that herbs accounted for about one-quarter of the analyzed DILI/HILI cases, highlighting the significance of pharmacovigilance [16]. Currently, treatment for metabolic liver disease is highly disease-specific; lifestyle modification, immunosuppression, removal of the offending drug, and supportive management [17].

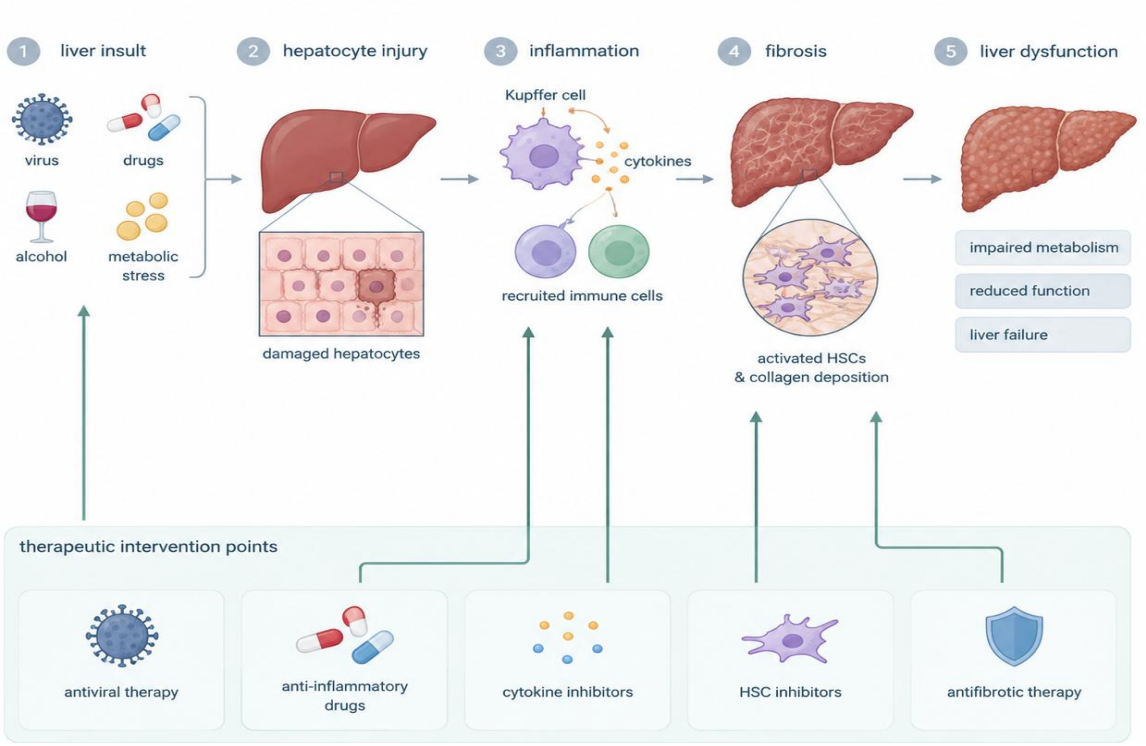


Figure 1. Pathophysiological cascade of liver injury and major therapeutic intervention points

1.4 Historical contribution of traditional medicine

Plants and plant medicines have been used in traditional medicinal systems for long to treat inflammatory diseases, digestive problems, jaundice and other symptoms that are now considered to be associated with liver malfunction [18]. There is ample medical knowledge in African ethnomedicine, Ayurveda, Traditional Chinese Medicine, and other indigenous systems. While traditional evidence alone cannot establish efficacy, it can be a starting point for drug discovery [19]. Modern research includes, among other things, identifying active ingredients, defining mechanisms, establishing dose-response relationships, and characterizing pharmacokinetics and assessing safety [20].

1.5 Emergence of natural products as modern therapeutic candidates

The modern paradigm of natural products has shifted from crude extracts to chemically defined compounds, standardized extracts, enhanced formulations and mechanism-based combinations [21]. Compounds like curcumin, resveratrol, berberine, silymarin, quercetin, EGCG, glycyrrhizin, baicalin and ginsenosides have become important candidates for study due to their effects on multiple pathways involved in liver injury. For example, natural products can up-regulate the expression of antioxidant-response genes and Nrf2/ARE signalling, a critical regulator of cellular antioxidant defence [22].

1.6 Rationale, scope, and objectives of the review

The review will provide a critical synthesis of formulation science, pre-clinical research, clinical data, phytochemical diversity, molecular pharmacology, traditional knowledge and emerging computational technologies [23]. This review is based on mechanism-based natural-product pharmacotherapy, not merely

listing hepatoprotective plants [24]. It also points out the barriers that have to be overcome to move natural products from experimental hepatoprotection to standardized modern medicines [25].

2. Pathophysiology of Liver Injury: From Cellular Stress to Fibrosis

2.1 Hepatocyte Injury and Mitochondrial Dysfunction

The main functional cells of the liver, hepatocytes, carry out various metabolic, synthesizing, detoxifying and energy-generating functions. The liver is exposed to a large amount of blood flow and continuous exposure to drugs, xenobiotics, alcohol, fatty acids and other potentially toxic substances, and thus, hepatocytes are particularly prone to cellular stress. Hepatocyte injury is one of the earliest and most important steps in the pathogenesis of liver disease. The first reversible cellular stress can progress to mitochondrial malfunction, oxidative stress, inflammation, controlled cell death and ultimately fibrosis, depending on the severity and duration of the harmful stimuli [26]. In the proposed review outline, the pathophysiological cascade that culminates in chronic liver injury and fibrosis begins with hepatocyte injury and mitochondrial dysfunction. Mitochondria are important for the maintenance of hepatocyte homeostasis due to their role in ATP production by oxidative phosphorylation and fatty acid oxidation, calcium homeostasis, generation of reactive oxygen species (ROS) and programd cell death. Under physiological conditions, mitochondrial ROS are kept under control by endogenous antioxidant systems within a certain range [27]. However, exposure to hepatotoxic drugs, excessive alcohol, free fatty acids, environmental pollutants or reactive metabolites may disrupt mitochondrial homeostasis. Excessive production of ROS and reactive nitrogen species can lead to damage of mitochondrial proteins, membrane lipids, mitochondrial DNA, and components of the electron-transport chain [28].

2.2 Oxidative and Nitrosative Stress

Oxidative and nitrosative stress are important in the pathogenesis and progression of liver injury. The liver is constantly exposed to endogenous and xenobiotic chemicals which are metabolized and can generate reactive oxygen species (ROS) and reactive nitrogen species (RNS). Under physiological conditions, the detoxification and antioxidant systems of cells maintain ROS and RNS at controlled levels. But the imbalance in Favor of oxidative and nitrosative stress is either the overproduction of these reactive species or the decrease of antioxidant defence. Such imbalance may damage cellular lipids, proteins, DNA, mitochondria and other intracellular components and may ultimately impair hepatocyte function [29]. Oxidative stress is closely associated with mitochondrial dysfunction, inflammation, endoplasmic reticulum stress, abnormal autophagy and programd cell death mechanisms in liver injury. The framework of the review proposes that oxidative and nitrosative stress are important early steps during the process of the development of fibrosis from the cellular damage. Reactive oxygen species include superoxide anion, hydrogen peroxide and hydroxyl radicals while nitric oxide and peroxynitrite are important reactive nitrogen species [30]. These compounds are produced by inflammatory reactions, cytochrome P450-mediated xenobiotic metabolism, normal mitochondrial respiration and other cellular functions . During liver injury, the high formation of ROS may overcome the antioxidant defense system including reduced glutathione (GSH), superoxide dismutase (SOD), catalase and glutathione peroxidase (GPx) . The loss of these protective mechanisms makes hepatocytes more vulnerable to oxidative damage. Specifically, an excess of ROS causes lipid peroxidation of cellular and mitochondrial membranes, generating the secondary reactive aldehydes 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA). These compounds can further amplify cellular dysfunction and modify proteins and nucleic acids [31].

2.3 Inflammation and Immune Dysregulation

Inflammation plays a major role in liver injury and is an important connection between early hepatocellular stress and fibrosis and chronic liver disease. Following drug, alcohol, metabolic disorders, infectious agents or other hepatotoxic stimuli, damaged hepatocytes release damage-associated molecular patterns (DAMPs) including mitochondrial components, ATP, DNA fragments and other intracellular chemicals. Hepatocytes, Kupffer cells, hepatic stellate cells and infiltrating immune cells express pattern-recognition receptors that recognize these signals and initiate an inflammatory response. Upon activation, these cells release pro-

inflammatory cytokines and chemokines, such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β) and interleukin-6 (IL-6), which might contribute to further hepatocyte injury. This early inflammatory response is useful because it assists in getting rid of damaged cells and stimulates the regeneration of tissue [32]. However, excessive or prolonged activation can be pathogenic and contribute to chronic liver injury. This review framework describes two important molecular pathways, NF-κB and NLRP3 inflammasome signaling, by which natural products may regulate hepatic inflammation. The nuclear factor-κB (NF-κB) pathway is important in hepatic inflammation. Activation of NF-κB induces the up-regulation of numerous inflammatory mediators and adhesion molecules, leading to enhanced recruitment and activation of immune cells. Activation of the NLRP3 inflammasome simultaneously induces maturation of IL-1β and IL-18 and can trigger pyroptotic cell death [33]. Oxidative stress, mitochondrial failure, NF-kB signalling and inflammasome activation interplay in a self-supporting inflammatory milieu. In chronic liver injury, this inflammatory milieu can activate hepatic stellate cells and promote extracellular matrix deposition. Therefore, natural products with antioxidant and anti-inflammatory effects are being explored for their ability to block the activation of NF-κB, inhibit NLRP3 inflammasome activation, regulate cytokine production, and restore the immunological homeostasis. However, for successful hepatoprotection, inflammation must be modulated not suppressed, as controlled inflammatory signalling is necessary for tissue repair and regeneration [34].

2.4 Lipotoxicity and Metabolic Dysfunction

Lipotoxicity, including metabolic dysfunction-associated steatohepatitis (MASH) and metabolic dysfunction-associated steatotic liver disease (MASLD), is a major cause of metabolic liver injury. Hepatocytes under physiological conditions control the uptake of fatty acids, de novo lipogenesis, mitochondrial β-oxidation, triglyceride synthesis and lipoprotein secretion to maintain lipid homeostasis [35]. This balance can be altered and the excess of lipid accumulation within the hepatocytes is promoted by metabolic disorders such as insulin resistance, obesity, high dietary lipid availability and defective lipid oxidation. Importantly, accumulation of toxic lipid species such as free fatty acids, diacylglycerols, ceramides and oxidized lipids can induce cellular stress and hepatocyte dysfunction beyond simple triglyceride accumulation. When the oxidative capacity of mitochondria is exceeded, an excess of intracellular fatty acids can increase mitochondrial β-oxidation and favor the generation of ROS. Moreover, lipopolytic metabolites may cause endoplasmic reticulum stress, activate inflammatory pathways, damage mitochondria and induce apoptosis or other forms of regulated cell death [36]. Insulin resistance promotes hepatic fat accumulation by increasing hepatic de novo lipogenesis and reducing proper metabolic control. Lipid overload, oxidative stress, inflammation and mitochondrial dysfunction combine to cause steatosis to progress to steatohepatitis and fibrosis. The review framework focuses on pathways, such as AMPK/SIRT1/PGC-1α and PPAR signalling, in which natural products are being explored for their potential to restore metabolic homeostasis [37].

2.5 Endoplasmic Reticulum Stress

The endoplasmic reticulum (ER) functions in protein folding, lipid synthesis, calcium storage, and intracellular protein homeostasis. Under conditions of extreme metabolic, oxidative, toxic or inflammatory stress in hepatocytes, the ER capacity for correct folding and processing of proteins can be exceeded, leading to failure to fold and/or process proteins properly. This condition is called endoplasmic reticulum stress. Cells react by activating the unfolded protein response (UPR), which was originally an adaptive pathway to restore ER homeostasis. However, excessive or prolonged ER stress can be maladaptive and result in hepatocyte loss, inflammation, and metabolic abnormalities [38]. The UPR is mainly mediated by three ER stress-sensing pathways, the protein kinase RNA-like ER kinase (PERK), the inositol-requiring enzyme-1 (IRE1) and the activating transcription factor-6 (ATF6) pathways. These processes first reduce the production of proteins, increase the ability of proteins to fold and promote the removal of damaged proteins. However, continued activation can result in pro-inflammatory and pro-apoptotic signalling [39]. ER stress is also closely associated with oxidative stress and mitochondrial dysfunction, as disruption of calcium homeostasis and protein metabolism can increase mitochondrial ROS production. Thus, ER stress can be bidirectionally related to oxidative damage, inflammation and fat accumulation [40].

2.6 Autophagy and mitophagy dysfunction

Autophagy is an intracellular quality-control system that degrades damaged proteins, organelles and other cellular components for recycling. The liver is a highly metabolic organ, constantly exposed to toxic and nutritional stresses, making autophagy especially important in hepatocytes. Autophagy contributes to cellular homeostasis and may protect hepatocytes against toxic and metabolic damage through removal of damaged cellular components. However, depending on the type, severity and duration of the hepatic insult, both increased activation and decreased autophagic flux may lead to disease [41].

2.7 Apoptosis, necroptosis, pyroptosis, and ferroptosis

Hepatocyte death is an important factor influencing the magnitude and development of liver injury. Apoptosis was previously considered to be the predominant type of hepatocyte death, but it is now clear that four different forms of regulated cell death, namely apoptosis, necroptosis, pyroptosis and ferroptosis, are involved in liver disease [42]. These pathways are associated with oxidative stress, inflammation, mitochondrial dysfunction, ER stress and metabolic disorders. These four pathways of cell death are incorporated into the uploaded review structure as an important part of the pathophysiology of liver injury [43].

2.8 Hepatic stellate-cell activation and fibrogenesis

The hepatic fibrogenesis depends mainly on hepatic stellate cells (HSCs), specialized perisinusoidal cells. In a normal liver, HSCs are mostly quiescent and store vitamin A and help to maintain the extracellular environment. Oxidative stress, inflammatory cytokines, signals from injured cells and ongoing hepatocyte injury can activate HSCs and modulate their phenotype to that of myofibroblasts. Activated HSCs produce abundant extracellular matrix proteins including fibrillar collagens, and gain enhanced proliferative and contractile properties [44].

2.9 Extracellular-matrix remodelling

Remodelling of extracellular matrix (ECM) is a key event in pathological fibrosis and repair of the normal liver. The hepatic extracellular matrix is composed of structural and signalling molecules such as collagens, laminins, fibronectin, proteoglycans and glycoproteins. In physiological conditions, ECM turnover is tightly regulated by a balance between matrix synthesis and degradation. Chronic liver damage results in continued activation of HSCs and other fibro genic cells that promote collagen and other extracellular matrix (ECM) production and deposition, while remodelling and degradation processes are no longer adequate to maintain normal tissue architecture [45].

2.10 Gut–liver axis dysfunction

The gut–liver axis refers to the portal circulation, which is the physical and functional connection between the gut and the liver. The gut supplies the liver with nutrients, microbial metabolites, signals related to bile acids and microbial products that are absorbed from the gastrointestinal tract. The intestinal epithelial barrier and healthy gut microbiota protect against the passage of potentially dangerous microbial compounds into the portal circulation. Conversely, liver injury, metabolic dysfunction, alcohol exposure, medications, and dietary modifications may lead to disruption of intestinal barrier integrity and changes in the composition and function of the gut microbiome [46].

Table 1. Major Types of Liver Injury, Pathological Mechanisms, and Therapeutic Targets [47-50].

Type of Liver Injury	Major Causes/Examples	Key Pathological Mechanisms	Major Therapeutic Targets
Drug-induced liver injury (DILI)	Paracetamol, antibiotics, NSAIDs, antitubercular drugs	Oxidative stress, reactive metabolites, mitochondrial dysfunction, inflammation, apoptosis	CYP450 modulation, Nrf2/ARE, antioxidants, mitochondrial protection, inflammatory pathways
Alcohol-associated liver injury	Chronic alcohol consumption	Acetaldehyde formation, oxidative stress, lipid accumulation, inflammation, gut–liver axis dysfunction	CYP2E1, Nrf2, NF-κB, lipid metabolism, intestinal barrier, inflammatory mediators
Metabolic dysfunction-associated liver disease (MASLD)	Obesity, insulin resistance, dyslipidemia	Lipotoxicity, insulin resistance, oxidative stress, mitochondrial dysfunction, inflammation	AMPK, PPARs, SREBP-1c, lipid metabolism, insulin signalling, Nrf2
Steatohepatitis (MASH)	Progressive metabolic liver disease	Hepatocellular injury, inflammation, oxidative stress, fibrosis	NF-κB, NLRP3 inflammasome, TGF-β, PPARs, Nrf2
Viral hepatitis	Hepatitis A, B, C, D and E viruses	Viral replication, immune-mediated hepatocyte injury, inflammation, oxidative stress	Viral polymerases/proteases, interferon pathways, inflammatory signalling, oxidative-stress pathways
Autoimmune hepatitis	Autoimmune-mediated hepatic injury	Loss of immune tolerance, T-cell activation, chronic inflammation	T-cell signalling, cytokines, NF-κB, immune-modulatory pathways
Cholestatic liver injury	Biliary obstruction, primary biliary cholangitis, primary sclerosing cholangitis	Impaired bile flow, bile-acid accumulation, oxidative stress, inflammation	Bile-acid transporters, FXR, TGR5, oxidative-stress and inflammatory pathways
Ischemia/reperfusion liver injury	Liver surgery, transplantation, shock	Hypoxia, ROS generation, mitochondrial dysfunction,	ROS, mitochondrial pathways, Nrf2, NF-κB, inflammatory cytokines

		inflammatory response	
Acute liver injury/failure	Drugs, toxins, viral infection, ischemia	Massive hepatocyte death, oxidative stress, inflammation, mitochondrial dysfunction	Antioxidant pathways, apoptosis/necrosis pathways, mitochondrial protection
Fibrotic liver injury	Chronic hepatitis, alcohol, metabolic disease, toxins	Hepatic stellate-cell activation, extracellular-matrix deposition, TGF-β signalling	TGF-β/Smad, hepatic stellate cells, collagen synthesis, inflammatory pathways
Toxicant-induced liver injury	Heavy metals, pesticides, environmental chemicals	ROS generation, lipid peroxidation, mitochondrial damage, inflammation	Nrf2, antioxidant enzymes, mitochondrial protection, detoxification pathways

3. Traditional Medicine as a Source of Hepatoprotective Natural Products

In the traditional medicine, the source of therapeutic agents for liver problems is one of the most extensive and oldest ones. Many civilizations have used medicinal plants, herbal preparations, decoctions, extracts and polyherbal formulations for centuries to treat hepatitis, jaundice, inflammation, digestive problems and other problems related to reduced liver function. The continuous use of these therapies has provided a wealth of ethnomedical knowledge that can form the basis for the recognition of natural hepatoprotective compounds. More recently, pharmacological research has tried harder to investigate these ancient treatments by means of experimental models, phytochemical characterization, molecular biology and analytical tools. The proposed review framework identifies Ayurveda, traditional Chinese medicine, African and other ethnomedical systems, traditional hepatoprotective herbs, ethnopharmacology-guided discovery and translational hurdles as the major aspects of this arena [51].

Table 2. Traditional Medicinal Plants and Natural Products with Reported Hepatoprotective Activity [52-54].

Medicinal Plant / Natural Product	**Major Phytoconstituents**	**Reported Hepatoprotective Actions**	**Major Mechanisms/Targets**
Silybum marianum (Milk thistle)	Silymarin, silibinin	Antioxidant, anti-inflammatory, anti-fibrotic	Nrf2, NF-κB, TGF-β
Curcuma longa (Turmeric)	Curcumin, curcuminoids	Antioxidant, anti-inflammatory, anti-steatotic	Nrf2, NF-κB, AMPK
Phyllanthus amarus	Phyllanthin, hypophyllanthin	Antioxidant, antiviral, hepatoprotective	Nrf2, oxidative-stress pathways
Andrographis paniculata	Andrographolide	Anti-inflammatory, antioxidant	NF-κB, Nrf2
Pterocarpus marsupium	Pterostilbene, flavonoids, phenolics	Antioxidant, anti-inflammatory, hepatoprotective	Nrf2, NF-κB

Glycyrrhiza glabra (Licorice)	Glycyrrhizin, flavonoids	Anti-inflammatory, antioxidant, anti-fibrotic	HMGB1, NF-κB, Nrf2
Camellia sinensis (Green tea)	EGCG, catechins	Antioxidant, anti-steatotic	Nrf2, AMPK, NF-κB
Zingiber officinale (Ginger)	Gingerols, shogaols	Antioxidant, anti-inflammatory	Nrf2, NF-κB
Allium sativum (Garlic)	Allicin, sulphur compounds	Antioxidant, anti-inflammatory	Nrf2, NF-κB
Resveratrol	Resveratrol	Antioxidant, anti-inflammatory, anti-fibrotic	SIRT1, AMPK, Nrf2

3.1 Ayurveda and Indian Traditional Medicine

One of the major traditional systems of medicine, Ayurveda utilizes medicinal plants for treatment and preservation of health. For the treatment of diseases related to impaired digestion, metabolism, bile function and systemic accumulation of toxic chemicals, plant-based formulations have been used since time immemorial in the Ayurvedic system. A range of medicinal herbs has been traditionally used for the treatment of diseases that generally correspond to jaundice and hepatic failure [55]. Plants like *Phyllanthus Amaru's, Andrographis paniculata, Picrorhiza kurroa, Tinospora cordifolia, Boerhavia diffusa, Eclipta alba and Terminalia chebula* have drawn much attention in present-day pharmacological research due to their traditional use and reported antioxidant, anti-inflammatory, hepatoprotective or metabolic effects. Importantly, traditional use alone does not prove therapeutic efficacy; it provides an ethnopharmacological rationale for investigation [56].

3.2 Traditional Chinese Medicine

Another major traditional medical system is Traditional Chinese Medicine (TCM), which has a large pharmacopeia of therapeutic herbs and multi-component herbal preparations. All kinds of illnesses related to liver malfunction, like indigestion, inflammation, jaundice etc., have been treated using traditional medicines. In TCM it is common to use combinations of medicinal plants to generate complementary or synergistic effects rather than a single active chemical. The scientific interest in this multi-component approach is growing, because liver injury is itself a process involving several interconnected pathways like oxidative stress, inflammation, metabolic dysfunction, mitochondrial damage, immunological dysregulation and fibrosis [57].

3.3 African and Other Ethnomedicinal Systems

African ethnomedicine is represented by a large number of traditional therapeutic methods and medicinal plants. In different parts of Africa, indigenous tribes have used locally available plants in the treatment of inflammatory disorders, infectious diseases, digestive problems and symptoms of liver disorders. Similar ethnomedical knowledge is found in other parts of the world such as Southeast Asia, Latin America, the Middle East and other indigenous medical systems. These traditions are a good source of information to identify plants that could have hepatoprotective properties [58].

3.4 Traditional Hepatoprotective Plants and Formulations

Many medicinal plants have been tested for the hepatoprotective properties which were used in the past to treat the liver-related conditions. They are frequently reported from *Phyllanthus spp., Picrorhiza kurroa, Andrographis paniculata, Eclipta spp., Tinospora cordifolia, Silybum marianum, Curcuma longa, Glycyrrhiza glabra* and few other medicinal species. Several mechanisms have been associated with their reported hepatoprotective effects, including reduction of oxidative stress, improvement of endogenous antioxidant

defences, inhibition of inflammatory signalling, preservation of mitochondrial function, modulation of lipid metabolism, and reduction of hepatocyte death [59].

3.5 Ethnopharmacology-Guided Natural-Product Discovery

Ethnopharmacology can systematically connect modern drug development with ancient medical knowledge. Knowledge of the traditional therapeutic uses of species can be used to prioritize species for pharmacological investigation rather than blindly screening large numbers of plants. A typical ethnopharmacological workflow starts with the documentation of traditional use. The subsequent steps include botanical identification, plant material collection and preparation, extraction, phytochemical profiling, biological testing, mechanism-based investigation, toxicity evaluation and finally pharmacokinetic and clinical trials. This approach, which brings together experimental research and historical knowledge, could enhance the discovery of natural products [60].

3.6 Challenges in Translating Traditional Knowledge into Modern Therapeutics

Although traditional medicine has a great potential source of hepatoprotective agents, translation into contemporary therapies still remains a challenge. The chemical complexity and diversity of herbal mixtures is one of the big problems. Plant species, cultivar, climate, soil conditions, harvest season, plant part, storage, extraction method and formulation process may affect the concentration of active ingredients. If standardization is not enough, two products sold under the same herbal name may have very different chemical and pharmacological profiles. This hinders the reproducibility of experimental results and the establishment of reliable clinical efficacy [61].

4. Chemical Diversity of Emerging Natural Products

4.1 Polyphenols and Flavonoids

The polyphenols are among the most studied groups of natural products because of their structural diversity and wide spectrum of biological activities. They are found in many fruits, vegetables, medicinal plants, spices and other botanical sources and have many phenolic hydroxyl groups. An important subclass of flavonoids are polyphenols with carbon skeleton of C6-C3-C6. Based on the structural features, flavonoids are classified into sub-classes including flavones, flavanols, flavanones, isoflavones, anthocyanins and their related sub-classes [62]. Their hepatoprotective potential has been attributed to antioxidant, anti-inflammatory, cytoprotective, metabolic and antifibrotic activities. Many flavonoids not only act as a direct radical scavenger, but also modulate endogenous cellular defense systems, especially the Nrf2/ARE pathway, and thus increase the expression of antioxidant and detoxifying enzymes [63].

4.2 Alkaloids

Alkaloids are a large and structurally diverse group of nitrogen-containing natural compounds, mostly of plant origin, but also produced by some bacteria and other animals. They consist of several sub-classes with very diverse chemical and biological properties. Alkaloids have been a major source of drug development in the past due to their strong interactions with specific molecular targets. Some alkaloids have been demonstrated to possess antioxidant, anti-inflammatory, antibacterial, metabolic and cytoprotective activities in experimental systems in the setting of liver injury [64].

4.3 Terpenoids and terpenes.

Terpenes and terpenoids are a large family of natural products that are biosynthetically built from isoprene-derived units. They are monoterpenes, sesquiterpenes, diterpenes, triterpenes, tetraterpenes, and related structures, depending on the number of carbon units. Terpenoids are in marine animals, bacteria and in a wide variety of therapeutic plants. Their structural diversity, which allows them to interact with a broad spectrum of biological pathways, make them attractive candidates for hepatoprotective research [65].

4.4 Saponins

Saponins are amphiphilic glycosides which consist of one or more sugar chains linked to a hydrophobic aglycone, the sapogenin. They are found in many medicinal plants and can be broadly classified as triterpenoid and steroidal saponins. Due to their amphiphilic character, they are able to interact with biological membranes and may affect immunological responses, cell signalling and absorption. Some saponin-containing and pure saponins have demonstrated hepatoprotective properties in experiments [66].

4.5 Phenolic acids.

Phenolic acids are relatively simple phenolic compounds found in fruits, vegetables, cereals, medicinal herbs and other natural sources. They are generally classified on the basis of their basic carbon structure into hydroxybenzoic acids and hydroxycinnamic acids. Examples are gallic acid, caffeic acid, ferulic acid, p-coumaric acid and its similar derivatives. The structures of these compounds can also allow for manipulation of cellular signalling pathways and phenolic hydroxyl groups provide chemical properties that allow for interaction with reactive species [67].

4.6 Lignans and coumarins

Lignans are substances derived from phenylpropanoids by oxidative coupling of phenylpropane units. And coumarins are a benzopyrone derivative with a fused aromatic lactone structure. These classes are found in many therapeutic plants and have drawn attention because of their metabolic, antibacterial, anti-inflammatory, and antioxidant properties. Some lignans have been shown to exert hepatoprotective effects by modulating oxidative stress and inflammatory response and coumarin derivatives may affect antioxidant defence, detoxification pathways and cellular signalling [68].

4.7 Polysaccharides

Natural polysaccharides are high-molecular-weight carbohydrates made up of monosaccharide units that are linked together by glycosidic bonds. They are found in medicinal plants, fungi, algae and micro-organisms and show great variations in molecular weight, monosaccharide composition, branching and three-dimensional structure. Unlike many small molecule natural products, the biological effects of polysaccharides are often mediated through immunomodulation, antioxidant mechanisms, regulation of the intestinal microbiota and enhancement of endogenous defence systems [69].

4.8 Quinones and related compounds

Quinones are aromatic compounds containing a conjugated cyclic dione system. They occur in a wide variety of plants, fungi and micro-organisms. Quinone-containing natural products possessing unique biological properties, and they can interact with cellular redox systems and may influence oxidative stress, mitochondrial function, inflammatory signalling and cell proliferation. Some quinones and related compounds have therefore been investigated for their hepatoprotective and more general pharmacological activities [70].

4.9 Marine-derived natural products

Marine organisms are an increasingly important source of chemically new natural products. The marine environment presents unique environmental conditions that may promote the evolution of unusual secondary metabolites. Marine-derived chemicals have come from algae, sponges, corals, mollusks, marine microbes and other creatures. Specialist metabolites such as unusual peptides, terpenoids, alkaloids, polyketides, sulfated polysaccharides and others may have chemical structures that vary greatly from those of terrestrial plant metabolites [71].

4.10 Microbial and fungal natural products

Fungi and microorganisms are very rich sources of natural compounds with great diversity of structural variations. Bacteria, actinomycetes, filamentous fungus and other microbes produce secondary metabolites such as polyketides, non-ribosomal peptides, alkaloids, terpenoids, macrolides and other chemically

complicated compounds. The significance of microbial natural products for drug discovery is exemplified by the many molecules that have already contributed to modern pharmacotherapy. It is of special interest that microbial metabolites can affect oxidative stress, inflammation, cell communication and the gut-liver axis, and therefore may be relevant for hepatoprotection [72].

5. Mechanism-Based Pharmacology of Natural Products in Liver Injury

5.1 Nrf2/ARE signalling and antioxidant defense

The nuclear factor erythroid 2-related factor 2 (Nrf2)/antioxidant response element (ARE) pathway is one of the major endogenous defense systems against oxidative and electrophilic stress. In basal conditions, Nrf2 is controlled and degraded by Kelch-like ECH-associated protein 1 (Keap1). In conditions of oxidative stress, changes in the Keap1-Nrf2 regulatory mechanism lead to the accumulation of Nrf2 and its translocation to the nucleus, where it binds to ARE sequences and induces the transcription of cytoprotective and antioxidant genes [73]. Polyphenols, flavonoids, phenolic acids and terpenoids, which are naturally occurring compounds, can improve this pathway and augment the cellular antioxidant capacity. Nrf2 activation can decrease ROS-mediated hepatocyte injury by inducing glutathione synthesis and antioxidant enzymes such as SOD, catalase, and glutathione-related enzymes. Thus, natural products are thought to protect the liver from oxidative stress, mitochondrial injury by Nrf2/ARE pathway [74].

5.2 NF-κB and inflammatory signalling

NF-κB is a key transcriptional regulator of liver inflammation. Prolonged oxidative stress, hepatocyte damage, endotoxins, and inflammatory mediators can activate NF-κB, leading to increased expression of TNF-α, IL-1β, IL-6, chemokines, and other inflammatory mediators. Thus, excessive activation of NF-κB may promote hepatic inflammation and contribute to the development of chronic liver disease and fibrosis after acute cellular injury. Natural compounds with anti-inflammatory properties may reduce NF-κB activation directly or indirectly by reducing oxidative stress and upstream inflammatory signals. Over-activation of NF-κB could lead to increased production of inflammatory cytokines and thus lead to hepatocyte injury. In the review framework, NF-κB is one of the major mechanisms by which natural products could regulate liver inflammation [75].

5.3 NLRP3 inflammasome and pyroptosis

The NLRP3 inflammasome is a crucial bridge between cellular stress and inflammatory cell death. Mitochondrial failure, ROS production, ATP imbalance, lipid stress, and other danger signals can activate NLRP3. This leads to activation of caspase-1 and maturation of inflammatory cytokines IL-1β and IL-18. Activation of the inflammasome can also lead to the process of pyroptosis, an inflammatory form of programd cell death associated with loss of integrity of cellular membranes. Thus, persistent NLRP3 activation could promote a cycle of hepatocyte damage and inflammation. Natural compounds can influence this pathway by decreasing ROS production, enhancing mitochondrial function, inhibiting upstream inflammation signalling, or directly targeting inflammasome components. Therefore, suppression of NLRP3 is an emerging approach for hepatoprotection mediated by natural products [76].

5.4 AMPK/SIRT1/PGC-1α signalling

The NLRP3 inflammasome is a crucial bridge between cellular stress and inflammatory cell death. Mitochondrial failure, ROS production, ATP imbalance, lipid stress, and other danger signals can activate NLRP3. This leads to activation of caspase-1 and maturation of inflammatory cytokines IL-1β and IL-18. Activation of the inflammasome can also lead to the process of pyroptosis, an inflammatory form of programd cell death associated with loss of integrity of cellular membranes. Thus, persistent NLRP3 activation could promote a cycle of hepatocyte damage and inflammation. Natural compounds may dampen this pathway through reduction of ROS production, improvement of mitochondrial function, inhibition of upstream inflammatory signaling or direct action on inflammasome components. NLRP3 inhibition is an emerging mechanism for natural-product-mediated hepatoprotection [77].

5.5 PI3K/Akt and MAPK pathways

The AMPK/SIRT1/PGC-1α axis is an important controller of cellular energy metabolism and mitochondrial function. AMPK is an intracellular energy sensor that responds to changes in the cellular energy status. Its activation suppresses energy-consuming anabolic processes and stimulates fatty acid oxidation. PGC-1α is a master regulator of oxidative metabolism and mitochondrial biogenesis and SIRT1 is a NAD+-dependent deacetylase that regulates metabolic and stress-response proteins. Dysregulation of this system may lead to oxidative stress, insulin resistance, fat accumulation and mitochondrial dysfunction. Natural products activate AMPK and/or SIRT1 and then affect PGC-1α activity, improving metabolic homeostasis and mitochondrial function. This pathway may be particularly relevant when considering a metabolic liver injury, where hepatic steatosis and the associated inflammation may be attenuated by restoration of energy balance and lipid oxidation [78].

5.6 PPAR-mediated metabolic regulation

Peroxisome proliferator-activated receptors (PPARs) are nuclear receptors that take part in energy control, inflammation, glucose homeostasis and lipid metabolism. While other PPAR isoforms are involved in glucose and lipid metabolism and inflammatory regulation, PPARα is specifically involved in fatty acid oxidation in the liver. Perturbation of PPAR signaling could lead to hepatic lipid accumulation and metabolic dysfunction. Natural products have the potential to modulate the activity of PPARs and enhance lipid handling, reduce metabolic stress and promote fatty acid oxidation. Regulation of PPAR pathways may be of particular importance in metabolic liver disorders characterized by excessive hepatic lipid accumulation. According to the review framework, AMPK/SIRT1/PGC-1α and PPAR signaling are the main metabolic pathways of hepatoprotective effects of natural products [79].

5.7 FXR and bile-acid homeostasis

The farnesoid X receptor (FXR), a member of the nuclear receptor family, plays a major role in the regulation of bile acid synthesis and transport, lipid and glucose metabolism. Bile acids are not only digesting molecules but also signalling chemicals that influence intestinal and hepatic function. Disruption of bile-acid homeostasis can lead to accumulation of potentially hazardous bile acids, in addition to contributing to hepatocellular stress and inflammation.[80] FXR activity regulates genes involved in bile-acid synthesis and transport and maintains hepatic bile-acid homeostasis. Natural products may modulate FXR signalling and related bile-acid pathways and therefore may provide a defense against bile-acid-induced damage to hepatocytes. Modulation of this pathway may have implications beyond bile-acid metabolism as FXR also interacts with metabolic and gut-liver signalling networks [81].

5.8 TGF-β/Smad signalling and hepatic fibrosis

Transforming growth factor-beta (TGF-beta) is a major profibrotic mediator of hepatic stellate-cell activation and extracellular matrix deposition. Chronic hepatocyte injury and inflammation can promote enhanced TGF-β signalling that in turn triggers Smad-dependent transcriptional processes and stimulates collagen and other extracellular matrix protein production. Prolonged activation of this system results in hepatic fibrosis and architectural distortion. Natural antifibrotic compounds can directly or indirectly inhibit the TGF-β/Smad signalling pathway by reducing inflammation and oxidative damage. Inhibition of HSC activation and excessive collagen deposition are thus important targets in the evaluation of natural products for antifibrotic activities. The review approach specifically identifies hepatic fibrosis and TGF-β/Smad signaling as important mechanism-based targets [82].

5.9 Autophagy and mitophagy

In particular, dysfunctional mitochondria are removed by mitophagy. Autophagy is an essential cellular quality control process responsible for the degradation of damaged proteins and organelles. Proper autophagic activity, especially during metabolic and toxic stress, is required for hepatocyte homeostasis. Defective autophagy can cause increased ROS production, inflammation, cell death and accumulation of damaged

mitochondria. However, excessive or dysregulated autophagy can be detrimental in some disease settings [83]. Natural compounds induce selective removal of damaged mitochondria and restore autophagic flux. Natural products can act on autophagy and mitophagy and in so doing can maintain cellular energy homeostasis, reduce oxidative stress and maintain mitochondrial integrity. This mechanism is important as mitochondrial failure has been strongly implicated in a number of different processes involved in liver disease [84].

5.10 Ferroptosis and iron homeostasis

Ferroptosis is a form of regulated cell death that is characterized by iron-dependent lipid peroxide accumulation and oxidative damage of cell membranes. Evidence is accumulating that ferroptosis is involved in multiple liver injuries including hepatic fibrosis, alcohol-associated liver injury, drug-induced liver injury, ischemia/reperfusion injury and metabolic dysfunction-associated steatotic liver disease (MASLD). Unlike apoptosis, ferroptosis is mainly associated with the loss of cellular membrane integrity induced by severe lipid peroxidation. Hepatocytes are especially vulnerable due to their high metabolic rate, their high content of polyunsaturated fatty acids and their aggressive iron metabolism. Thus, perturbation of iron homeostasis and antioxidant defense can lead to ferroptotic death of hepatocytes [85].

5.11 Mitochondrial quality control

Mitochondrial quality control (MQC) is a coordinated cellular defense mechanism to ensure energy production, redox balance, mitochondrial integrity and removal of damaged mitochondria. Disruption of mitochondrial quality control is a key contributor to liver injury, as hepatocytes are metabolically active and depend on mitochondrial oxidative phosphorylation. Failure of mitochondria leads to overproduction of reactive oxygen species (ROS), loss of ATP, impaired fatty acid oxidation, depolarization of the mitochondrial membrane, calcium dysregulation, and release of pro-death signals. These changes can then lead to oxidative stress, necroptosis, ferroptosis, apoptosis and inflammation. Therefore, mitochondrial quality control is increasingly recognized as an important aspect of hepatoprotection and a promising target for natural products pharmacology [86].

5.12 Epigenetic and non-coding RNA regulation

Epigenetic regulation and non-coding RNAs are the main regulators of gene expression in liver injury and regeneration. Epigenetic modifications are not permanent alterations in the DNA sequence but can modulate the activity of genes without changing the underlying nucleotide sequence. Environmental factors, diet, oxidative stress, inflammation, alcohol exposure, metabolic abnormalities, and xenobiotics can modulate epigenetic modifications. Major epigenetic mechanisms are DNA methylation, histone modification, chromatin remodelling and non-coding RNA regulation [87]. These mechanisms can modulate pathways that are involved in oxidative stress, inflammation, lipid metabolism, mitochondrial dysfunction, apoptosis, autophagy, ferroptosis, hepatic stellate cell activation, and fibrosis. Epigenetic regulation thus provides a key mechanistic link between environmental or metabolic stress and persistent alterations in liver cell function [88].

DNA methylation is one of the best characterized epigenetic mechanisms involving the addition of a methyl group to cytosine residues within CpG-rich regions. DNA methyltransferases (DNMTs) establish or maintain methylation patterns, whereas ten-eleven translocation (TET) enzymes are involved in active DNA demethylation processes. Altered DNA methylation patterns have been reported in metabolic liver disease, inflammation, fibrosis and hepatocarcinogenesis [89]. Changes in promoter methylation may impact the expression of genes involved in antioxidant defense, lipid metabolism, inflammatory signalling, and extracellular matrix regulation. Thus, natural products having the potential to modulate the activity of DNA methyltransferase or the expression of methylation associated genes may provide an epigenetic mechanism for hepatoprotection but the functional implications of individual methylation alterations need experimental validation [90].

Table 3. Major Phytochemicals, Molecular Targets, Signalling Pathways, and Mechanisms of Action [91-94].

Major phytochemical	Molecular targets	Signaling pathways	Experimental model	Dose*	Major outcome	Evidence type
Curcumin	Nrf2, NF-κB, AMPK	Nrf2/ARE, NF-κB, AMPK	Exposure of mice to NaAsO2(100 mg/L) in drinking wate	200 mg/kg	Antioxidant, anti-inflammatory, anti-steatotic effects	In vitro / animal / clinical
Silibinin	Nrf2, NF-κB, TGF-β	Nrf2/ARE, NF-κB, TGF-β/Smad	(APAP)-induced toxicity in primary rat hepatocytes;	10–20 mg/kg/day	Reduced oxidative stress, inflammation and fibrogenesis	In vitro / animal / clinical
Resveratrol	SIRT1, AMPK, Nrf2	SIRT1/AMPK, Nrf2/ARE	Primary rat hepatocytes treated with 500 μM t-BHP	50 and 75 μM	Antioxidant, metabolic and anti-inflammatory effects	In vitro / animal / clinical
Quercetin	Nrf2, NF-κB, NLRP3	Nrf2/ARE, NF-κB, NLRP3	Primary human hepatocytes treated with 100 mM ethanol	10–100 mg/kg	Reduced oxidative/inflammatory injury and apoptosis	In vitro / animal
Andrographolide	NF-κB, Nrf2	NF-κB, Nrf2/ARE	Acetaminophen-induced liver injury; intraperitoneal	200 mg/kg	Anti-inflammatory and antioxidant effects	In vitro / animal
Glycyrrhizin	HMGB1, NF-κB	HMGB1/NF-κB	MCD diet-induced liver injury in mice; intraperitoneal	50 mg/kg/day	Anti-inflammatory and hepatoprotective effects	In vitro / animal / clinical
EGCG	AMPK, Nrf2, NF-κB	AMPK, Nrf2/ARE, NF-κB	High-fat diet-induced fatty liver in C57BL/6J mice	25–50 mg/kg	Reduced oxidative stress, steatosis and inflammation	In vitro / animal / clinical
Pterostilbene	Nrf2, AMPK, SIRT1	Nrf2/ARE, AMPK/SIRT1	APAP-induced acute liver injury in rats.	50–100 mg/kg/day	Antioxidant and metabolic regulation	In vitro / animal

Berberine	AMPK, PPARs, NF-κB	AMPK, PPAR, NF-κB	APAP-induced hepatotoxicity in rats and mice; high-fat diet-induced fatty liver model in rodents.	4 mg/kg or 100–300 mg/kg/day	Improved lipid metabolism and reduced inflammation	In vitro / animal / clinical
Naringenin	Nrf2, AMPK, PPARα	Nrf2/ARE, AMPK, PPARα	CCl4-olive oil mixture (1 : 1) on days2 and 5 (i.p.	200–400 mg/kg	Reduced oxidative stress and steatosis; metabolic regulation	In vitro / animal

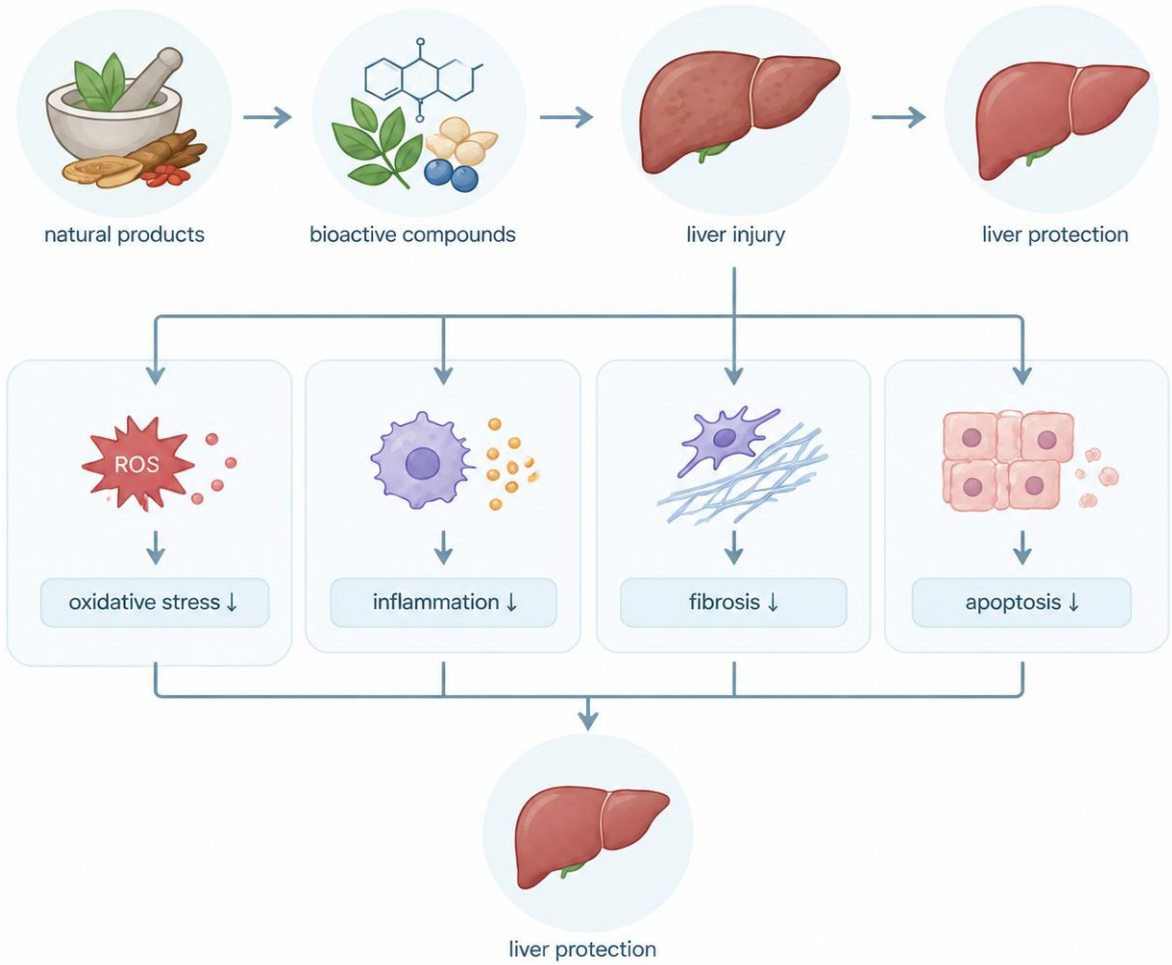


Figure 2. Multi-target mechanisms of natural products against liver injury

6. Natural Products in Different Forms of Liver Injury

6.1 Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)

Metabolic dysfunction-associated steatotic liver disease (MASLD), is characterized by excessive fat deposition in the liver in the setting of metabolic risk factors such as obesity, insulin resistance, dyslipidemia, and type 2 diabetes. The development of MASLD is associated with disruption of hepatic lipid homeostasis, increased supply of fatty acids to the liver, increased de novo lipogenesis, decreased fatty acid oxidation and altered lipid export. Simple steatosis may induce modest cellular damage in the beginning, but persistent

metabolic stress may increase the production of mitochondrial ROS, lipid peroxidation, endoplasmic reticulum stress and inflammatory signalling. Since several phytochemicals can simultaneously modulate lipid metabolism, oxidative stress, inflammation and mitochondrial function, natural products have received much attention [95].

6.2 Metabolic Dysfunction-Associated Steatohepatitis (MASH)

MASH is a more severe metabolic liver disease with hepatic steatosis, hepatocellular injury, inflammation and degrees of fibrosis. Lipotoxicity, oxidative stress, mitochondrial dysfunction, inflammatory activation, endoplasmic reticulum stress, and regulated cell death are all involved in the progression from simple steatosis to MASH. Toxic lipid species can activate Kupffer cells and other immunologic pathways to generate inflammatory mediators that further injure hepatocytes. Persistent damage then promotes extracellular matrix deposition and hepatic stellate-cell activation, connecting metabolic failure with fibrosis [96].

6.3 Alcohol-associated liver disease

Alcohol-associated liver disease encompasses the full spectrum of alcohol-associated liver injury including hepatic steatosis, alcohol-associated hepatitis, fibrosis, and cirrhosis. Besides the generation of acetaldehyde, ethanol metabolism causes intestinal barrier dysfunction, oxidative stress, mitochondrial dysfunction, altered lipid metabolism and inflammatory signalling. Additionally, chronic alcohol consumption can modify the gut microbiota and enhance intestinal permeability, facilitating the translocation of microbial products into the portal circulation. These changes can cause increased inflammation in the liver and the development of immune responses in the liver [97].

6.4 Drug-induced liver injury

Adverse drug reaction of clinical significance is drug induced liver damage (DILI). DILI can be caused by direct hepatotoxicity, reactive metabolites, mitochondrial dysfunction, immune mediated pathways or combinations of these processes. DILI may present with hepatocellular, cholestatic or mixed patterns of injury. These include oxidative stress, mitochondrial dysfunction, ER stress, inflammation, bile-acid disruption and regulated cell death. Moreover, there are differences in people's susceptibility, making it difficult to prevent or predict [98].

6.5 Acetaminophen-induced liver injury

Acetaminophen-induced liver damage is one of the most studied experimental models of acute hepatotoxicity. After therapeutic or excessive exposure, some acetaminophen is converted by cytochrome P450 enzymes to the reactive metabolite N-acetyl-p-benzoquinone imine (NAPQI). Under normal conditions, the primary mechanism for detoxifying NAPQI involves its conjugation with glutathione. Excessive exposure can lead to the depletion of hepatic glutathione, permitting NAPQI to bind to cellular proteins and increasing mitochondrial oxidative stress, culminating in hepatocyte damage and necrosis [99].

6.6 Viral hepatitis-associated liver injury

Viral hepatitis is associated with chronic situations of persistent infection, immune mediated injury of hepatocyte, inflammation, and progressive cirrhosis and fibrosis. In chronic viral hepatitis, most of the liver injury is due to host immune responses against infected hepatocytes, although viral replication may contribute to the course of the disease. Continuous inflammatory stimuli can lead to hepatic stellate cells activation and oxidative stress. As seen from chronic viral hepatitis, oxidative stress, fibrogenesis, inflammation and immunological modulation are all strongly related [100].

6.7 Chemical and Toxic Injuries to the Liver

Many hazardous substances can damage the liver, including industrial compounds, pesticides, heavy metals, mycotoxins and environmental pollutants. Hepatic metabolic enzymes bioactivate a variety of hepatotoxic substances, leading to the formation of reactive intermediates that cause oxidative stress and damage cellular

proteins, lipids, DNA and mitochondria. In addition, several toxins impair energy metabolism, membrane integrity, ER function and calcium homeostasis. The harm that results is dependent on the toxicant and exposure dose and may involve apoptosis, necrosis, ferroptosis, inflammation or fibrosis [101].

6.8 Liver injury caused by ischemia or reperfusion

Liver ischemia/reperfusion (I/R) injury occurs when blood flow to the liver is briefly interrupted and then restored. This is particularly relevant for hepatic surgery, trauma, liver transplantation and other clinical situations in which hepatic blood flow is transiently decreased. Ischemia-induced oxygen and nutrient deprivation impairs cellular metabolism and mitochondrial ATP synthesis. Reperfusion then leads to a rapid increase in production of ROS and immunological and inflammatory responses. Hepatocellular injury results from an interaction between mitochondrial dysfunction, endothelial injury, Kupffer-cell activation, neutrophil recruitment and oxidative stress [102].

6.9 Liver fibrosis and cirrhosis

Liver fibrosis is a wound healing response to chronic injury of the liver, characterized by excess deposition and remodelling of extracellular matrix. Chronic insults like alcohol exposure, medication toxicity, metabolic disorders, and chronic viral infection may continue to drive inflammatory and fibrogenic signalling. TGF-β/Smad signalling is important for the production of collagen and other extracellular matrix components. Activation of hepatic stellate cells is a major event. As fibrosis progresses, the architecture of the liver and vascular function becomes increasingly deranged and ultimately lead to cirrhosis and loss of functional hepatic reserve [103].

Table 4. Natural Products Investigated in MASLD/MASH, Alcohol-Associated Liver Disease, and Drug-Induced Liver Injury [104-107].

Natural Product	Major Phytoconstituent	Disease/ Model	Intervention	Dose	Experimental/Clinical	Major Outcome	Evidence Strength
Curcuma longa	Curcumin	MASLD/ MASH; DILI models	Curcumin or standardized formulation	Study-specific dose	Experimental; Clinical	↓ hepatic steatosis, oxidative stress, inflammation; improvement in liver enzymes reported	Moderate
Silybum marianum	Silymarin, silibinin	MASLD/ MASH; DILI	Silymarin/silibinin preparation	Study-specific dose	Experimental; Clinical	Antioxidant and hepatoprotective effects; ↓ inflammatory and fibrotic signaling	Moderate
Camellia sinensis	EGCG, catechins	MASLD/ MASH	EGCG/green-tea-derived preparation	Study-specific dose	Experimental; Clinical	↓ lipid accumulation and oxidative stress; metabolic effects	Moderate

Polygonum cuspidatum / *Vitis vinifera*	Resveratrol	MASLD/MASH; alcohol-associated liver disease	Resveratrol	Study-specific dose	Experimental; Clinical	↓ steatosis, inflammation and oxidative injury; metabolic regulation	Moderate
Glycyrrhiza glabra	Glycyrrhizin	DILI; alcohol-associated liver disease	Glycyrrhizin preparation	Study-specific dose	Experimental; Clinical	Anti-inflammatory and antioxidant effects; attenuation of hepatic injury	Low–Moderate
Andrographis paniculata	Andrographolide	DILI; MASLD/MASH models	Andrographolide/extract	Study-specific dose	Experimental	↓ inflammation and oxidative stress	Low–Moderate
Berberis spp.	Berberine	MASLD/MASH	Berberine	Study-specific dose	Experimental; Clinical	Improved lipid metabolism and insulin sensitivity; ↓ metabolic dysfunction	Moderate
Pterocarpus marsupium	Pterostilbene, flavonoids	DILI; experimental liver injury	Pterostilbene/extract	Study-specific dose	Experimental	Antioxidant and hepatoprotective effects; attenuation of oxidative injury	Low
Zingiber officinale	Gingerols, shogaols	MASLD/MASH; alcohol-associated liver disease	Ginger extract/phytoconstituents	Study-specific dose	Experimental	↓ oxidative stress and inflammation	Low–Moderate
Phyllanthus amarus	Phyllanthin, hypophyllanthin	DILI; viral-associated liver injury	*P. amarus* extract/phytoconstituents	Study-specific dose	Experimental; Clinical/observational where applicable	Antioxidant and hepatoprotective effects; modulation of inflammatory pathways	Low–Moderate

Table 5. Mechanism-Based Hepatoprotective Actions of Natural Products [108-111].

Mechanism	Natural Product	Target / Pathway	Experimental Model	Evidence
Inflammation suppression	Curcumin	NF-κB, NLRP3	Hepatocyte/macrophage models; experimental liver-injury models	Preclinical
Oxidative-stress reduction	Curcumin	Nrf2/ARE	Hepatocyte and animal liver-injury models	Preclinical
Antioxidant and anti-fibrotic activity	Silymarin/Silibinin	Nrf2, NF-κB, TGF-β/Smad	Hepatocyte and experimental fibrosis/liver-injury models	Preclinical; clinical evidence available
Metabolic regulation / autophagy	Resveratrol	SIRT1, AMPK, Nrf2	Hepatocyte and experimental MASLD/MASH models	Preclinical; clinical evidence available
Inflammation and oxidative-stress control	Quercetin	Nrf2, NLRP3, NF-κB	Hepatocyte and animal models of metabolic/toxic liver injury	Preclinical
Oxidative-stress and lipid-metabolism regulation	EGCG	Nrf2, NF-κB, AMPK	Hepatocyte and experimental MASLD/MASH models	Preclinical; clinical evidence available
Lipid metabolism and inflammation	Berberine	AMPK, NF-κB, NLRP3	Hepatocyte and animal models; human metabolic/liver studies	Preclinical; clinical evidence available
Anti-inflammatory / antioxidant activity	Andrographolide	NF-κB, Nrf2	Hepatocyte and experimental liver-injury models	Preclinical
HMGB1-mediated inflammation suppression	Glycyrrhizin	HMGB1, NF-κB	Experimental toxic/inflammatory liver-injury models	Preclinical; limited clinical evidence
Antioxidant and metabolic regulation	Pterostilbene	Nrf2, AMPK, SIRT1	Hepatocyte and experimental metabolic/toxic liver-injury models	Preclinical
Anti-ferroptotic / antioxidant activity	Sulforaphane	Nrf2, ferroptosis-related pathways	Hepatocyte and experimental oxidative/ferroptotic liver-injury models	Preclinical

Anti-inflammatory and anti-fibrotic activity	Baicalin	Nrf2, NF-κB, TGF-β/Smad	Hepatocyte and experimental fibrosis/inflammation models	Preclinical
Mitochondrial/metabolic protection and autophagy regulation	Ginsenoside Rg1	AMPK, Nrf2, autophagy pathways	Hepatocyte and experimental liver-injury models	Preclinical

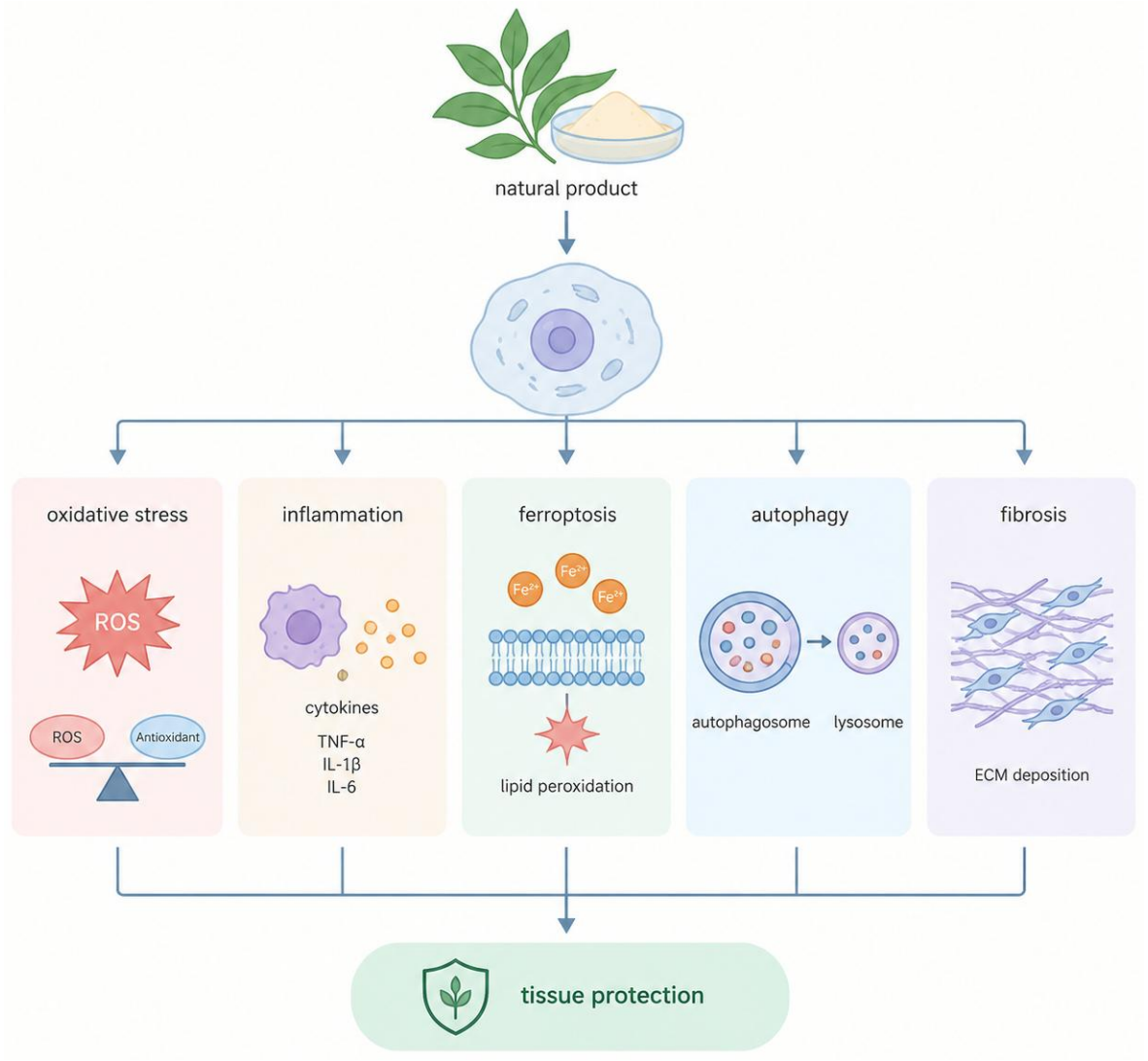


Figure 3. Natural-product regulation of oxidative stress, inflammation, ferroptosis, autophagy, and fibrosis

7. Multi-Target and Network Pharmacology of Natural Products

7.1 Single-target versus multi-target pharmacology

In the past, the traditional drug research has been concentrating on the search for a very selective chemical that interacts with a specific molecular target. This has led to many successful drugs, but complex diseases like chronic liver injury involve multiple pathogenic pathways, which are not always susceptible to control by a single target. One component can influence many proteins or signalling pathways. Natural products are often multi-component. For instance, a natural product may simultaneously target fibrosis via TGF-β/Smad signalling, lipid metabolism via AMPK or PPAR pathways, oxidative stress via Nrf2/ARE signalling, and inflammation via NF-κB. These concerted actions may contribute to an overall hepatoprotective effect [112].

7.2 Network pharmacology approaches

"Network pharmacology" is a systems-level approach to examine interactions among different substances, targets, pathways and disease processes. In natural product research, a typical workflow begins with the identification of chemical constituents, followed by the prediction or retrieval of potential protein targets. These targets can then be compared with targets of genes or proteins related to liver damage, and protein-protein interaction networks and pathway databases can be used to investigate the overlapping targets. Network analysis can then be used to find highly connected targets and biological pathways that may be important mechanisms of action [113].

7.3 Phytochemical–protein–pathway interactions

The pharmacological activity of a natural product can be illustrated by a hierarchical link consisting of phytochemical → protein target → signalling pathway → biological response. Specific phytochemicals can interact with enzymes, receptors, transcription factors, transporters, ion channels and other regulatory proteins. There are multiple pathways that involve these proteins and hence the downstream effects are interrelated. For example, a protein that regulates cellular redox status may affect cell survival, inflammation, oxidative stress and mitochondrial function at the same time [114].

7.4 Synergistic effects of phytochemical combinations

Since natural products are frequently mixtures of chemically related and unrelated ingredients, their biological effects may be due to additive, synergistic or antagonistic interactions. Synergy is the combined effect of two or more components being greater than the effect predicted from the individual effects. In hepatoprotective studies, different phytochemicals may affect complementing pathways. For instance, one molecule may improve the antioxidant defense, while the other one reduces inflammation or regulates lipid metabolism. Theoretically, this kind of complimentary pharmacology would lead to greater protection than either molecule on its own [115].

7.5 Systems biology and pathway enrichment

Systems biology integrates information across biological levels to understand complex processes of disease. In natural-product research, network analysis can be combined with transcriptomics, proteomics, metabolomics, lipidomics and other omics technologies to detect changes induced by treatment. Pathway-enrichment analysis can then be used to identify disproportionately represented biological pathways for the affected genes, proteins or metabolites [116].

7.6 Molecular Docking and Molecular Dynamics

Molecular docking is a computational method to assess possible binding modes and interaction energies and to predict how a small molecule may interact with the binding site of a protein. Docking can be employed in natural product research to rank phytochemicals for testing against possible proteins in experiments. Structural theories of pharmacological activity may be derived from possible interactions such as hydrogen bonding, hydrophobic interactions, electrostatic forces, and other molecule contacts [117].

7.7 Experimental validation

Computational predictions need to be mapped to biological evidence by experimental validation. Candidate targets identified by docking, molecular dynamics, network pharmacology or pathway analysis ought to be evaluated by appropriate experimental techniques. These include enzyme inhibition assays, receptor binding studies, gene expression analysis, Western blot, reporter assays, target knock down or knock out experiments, and pathway specific pharmaceutical inhibitors, depending on the hypothesis [118].

7.8 Limitations

Network pharmacology has a number of serious shortcomings, despite its advantages. First, the accuracy and completeness of public databases are important for target prediction; anticipated targets may contain false positives or omit physiologically significant targets. Second, many datasets are not sufficiently representative of differences in tissue distribution, illness status, dosage, metabolism or pharmacokinetics [119]. In theory, a phytochemical could interact with a protein in the liver, but it would never reach a high enough concentration in the liver. Third, some biological effects may be due to metabolites and not the original molecules because natural products are extensively absorbed, metabolized, conjugated, and transformed [120].

Table 6. Predicted Versus Experimentally Validated Molecular Targets of Hepatoprotective Natural Products [121-124].

Natural Product	Predicted Target(s)	Prediction Method / Basis	Experimentally Validated Target(s)	Validation Method	Disease / Experimental Context	Evidence Level	Interpretation
Curcumin	AKT1, STAT3, EGFR, TNF, CASP3 and multiple other network hubs	Network pharmacology, target databases, molecular docking, PPI analysis	Nrf2/ARE-related signaling, NF-κB signaling components and selected molecular targets demonstrated experimentally in liver-injury models	Western blotting, gene/protein expression, pathway inhibition/activation studies; selected biochemical/cellular studies	MASLD/MASH, APAP-, CCl_4-and inflammatory liver-injury models	Predicted + experimentally supported, target-specific	Do not treat the complete network-predicted target set as experimentally validated. Curcumin has extensive mechanistic evidence, but validation varies markedly among individual targets.
Resveratrol	SIRT1, AMPK, AKT1, TNF, IL6 and other metabolic/ inflammatory hubs	Network pharmacology, molecular docking, pathway enrichment	SIRT1/AMPK-associated signaling and downstream metabolic/inflammatory responses	Pharmacological assays, Western blotting, gene-expression analysis and pathway modulation studies	Experimental MASLD/MASH and metabolic liver injury	Predicted + experimentally supported	Network analysis identifies candidate hubs, whereas experimental studies support pathway modulation; direct binding of every predicted target should not be inferred.
Berberine	AKT1, IL6, TNF, IL1B,	Network pharm	AKT signaling and	Western blotting, RT-qPCR,	FFA-induced	Predicted + experi	Docking supports target hypotheses;

	TP53, BCL2 and other network targets	acology, PPI analysis and molecular docking	downstream lipid-metabolic/inflammatory responses experimentally demonstrated in hepatocyte models	lipid accumulation assays and pathway-response experiments	hepatocyte steatosis and experimental MASLD	mentally supported	experimental restoration of AKT phosphorylation and changes in inflammatory/lipogenic markers provide stronger functional evidence, but do not establish direct molecular binding for every predicted target.
Silymarin / Silibinin	Nrf2, NF-κB, TGF-β/Smad, STAT3 and multiple inflammatory/fibrotic targets	Network pharmacology and literature-based pathway mapping	Nrf2-associated antioxidant responses and NF-κB/TGF-β-associated signaling changes	Protein-expression analysis, pathway assays and experimental liver-injury/fibrosis studies	Oxidative, inflammatory and fibrotic liver-injury models	Predicted + experimentally supported	Strong pathway-level evidence exists, but individual protein targets should be classified separately according to the type of experimental validation available.
Quercetin	Nrf2, NLRP3, NF-κB, AKT1 and other inflammatory/oxidative-stress targets	Network pharmacology, molecular docking and enrichment analysis	Nrf2-, NF-κB- and inflammasome-associated signaling responses	Western blotting, cytokine analysis, ROS assays and pathway-modulation experiments	Oxidative/inflammatory and metabolic liver-injury models	Predicted + experimentally supported	Functional pathway modulation is better established than direct binding to each predicted target.
EGCG	AMPK, Nrf2, NF-κB, SREBP1c and other metabolic targets	Network pharmacology, docking and pathwa	AMPK/Nrf2-associated antioxidant and metabolic signaling; modulation	Protein/gene-expression studies and metabolic/lipid assays	Experimental MASLD/MASH and oxidative liver injury	Predicted + experimentally supported	Computational targets should remain labelled as predicted unless direct biochemical or genetic

		y analysis	of lipogenic pathways				validation is available.
Glycyrrhizin	HMGB1, NF-κB, TLR4 and inflammatory signaling nodes	Literature integration, network pharmacology and molecular docking	HMGB1-associated inflammatory signaling	HMGB1 measurement, inflammatory-marker analysis and mechanistic intervention studies	Inflammatory and toxic liver-injury models	Predicted + experimentally supported	HMGB1 represents a comparatively stronger mechanistic candidate; other network-associated proteins should not automatically be considered validated direct targets.
Andrographolide	NF-κB, Nrf2, MAPK and inflammatory signaling proteins	Network pharmacology, molecular docking and pathway enrichment	NF-κB/Nrf2-associated signaling changes demonstrated experimentally	Western blotting, reporter assays, cytokine analysis and animal studies	Experimental inflammatory/toxic liver injury	Predicted + experimentally supported	Evidence is stronger for functional pathway modulation than for direct target engagement across the complete predicted network.
Pterostilbene	Nrf2, AMPK, SIRT1, PPAR and metabolic signaling targets	Network pharmacology and docking	Nrf2/AMPK/SIRT1-associated metabolic and antioxidant responses	Gene/protein expression and metabolic assays	Experimental metabolic and oxidative liver injury	Predicted + experimentally supported	Mechanistic pathways are experimentally supported in selected models; individual predicted targets require target-specific validation.
Sulforaphane	Nrf2, KEAP1 and ferroptosis-related proteins	Target prediction, pathway analysis and molecular	Nrf2/ARE pathway activation and antioxidant-response genes	Reporter assays, nuclear translocation, gene/protein-	Oxidative and ferroptotic liver-injury models	Experimentally supported pathway; target-specifi	Nrf2 activation is substantially better supported than broad computationally predicted ferroptosis targets.

		docking		expression studies		c validation required	
Baicalin	Nrf2, NF-κB, TGF-β/Smad and inflammatory/fibrotic targets	Network pharmacology, docking and enrichment analysis	Nrf2-, NF-κB- and TGF-β/Smad-associated responses	Western blotting, cytokine assays and fibrosis-related molecular analyses	Experimental inflammatory and fibrotic liver injury	Predicted + experimentally supported	Experimental evidence generally supports pathway regulation rather than direct interaction with every predicted target.
Ginsenoside Rg1	AMPK, Nrf2, autophagy-related proteins and metabolic targets	Network pharmacology, docking and pathway analysis	AMPK/Nrf2/autophagy-associated signaling responses	Protein-expression analysis, autophagy markers and experimental liver-injury models	Oxidative/metabolic liver-injury models	Predicted + experimentally supported	Functional pathway evidence is available, but direct molecular target engagement should be demonstrated independently.
Naringenin	AMPK, PPARα, Nrf2, NF-κB and lipid-metabolism targets	Network pharmacology and molecular docking	Selected AMPK/PPAR/Nrf2-associated metabolic and antioxidant responses	Gene/protein expression and lipid-metabolism assays	Experimental metabolic liver injury	Predicted + experimentally supported	Candidate-target prediction should be distinguished from experimentally demonstrated pathway modulation.

8. Emerging Natural Products and Lead Phytochemicals

8.1 Curcumin and the curcuminoids

One of the most studied natural substances in hepatoprotective studies is curcumin, a major polyphenolic compound of Curcuma longa. Its biological activity has been associated with antioxidant, anti-inflammatory, metabolic and antifibrotic benefits. Curcumin can decrease NF-κB-dependent inflammatory signalling that is excessive and modulate antioxidant defense mediated by Nrf2/ARE. Effects on AMPK, PI3K/Akt, MAPK, NLRP3 inflammasome activation, autophagy, mitochondrial function and fibrogenic pathways have also been studied. These multi-target effects make curcumin particularly relevant to complex liver diseases such as fibrosis, toxic liver injury and steatotic liver disease associated with metabolic dysfunction [125].

8.2 Resveratrol

Resveratrol is a naturally occurring stilbene polyphenol mostly associated with grapes and related botanical sources. Its cytoprotective, metabolic, anti-inflammatory, and antioxidant properties have attracted attention. The effects of resveratrol on SIRT1, AMPK, Nrf2, NF-κB, mitochondrial function and autophagy have all been investigated. Through these routes, it may improve cellular energy metabolism, decrease oxidative stress and inhibit inflammatory reactions associated with hepatic damage [126].

8.3 Berberine 8.3.1 Description

Berberine, an isoquinoline alkaloid from many medicinal plants, has gained increasing interest for its effects on inflammation, cellular energy management, and glucose and fat metabolism. In liver disease research, the effects of berberine have been studied on hepatic steatosis and metabolic dysfunction. Its activities have been involved in AMPK activation, regulation of lipid metabolism, increased insulin sensitivity and suppression of inflammatory system. Berberine may also influence the hepatic metabolic balance by affecting the composition of the gut microbiota and the crosstalk between the gut and liver [127].

8.4 Quercetine

Quercetin is a flavonol found in fruits, vegetables, and medicinal plants. Its antioxidant, anti-inflammatory, metabolic and cytoprotective properties are well studied. Quercetin attenuates excessive inflammatory signalling through NF-κB and associated pathways and regulates Nrf2-mediated antioxidant defence. Its effects on lipid metabolism, autophagy, apoptosis, and mitochondrial function have been also studied. These features provide a molecular basis for the investigation of the role of quercetin in inflammatory, toxic and metabolic liver damage [128].

8.5 Silymarin and silibinin

Silibinin is the major active component of silymarin, a standardized flavonolignan extract from Silybum marianum. Silymarin is a well-known hepatoprotective candidate of main natural products with a long history of liver problems. Proposed mechanisms include antioxidant activity, membrane stability, modulation of the inflammatory response, regulation of cellular survival pathways and effects on hepatic fibrogenesis. The effects of silibinin on oxidative stress, mitochondrial function, inflammatory signaling and stellate-cell activation were also investigated [129].

8.6 Epigallocatechin gallate

Epigallocatechin gallate (EGCG) is one of the best characterized tea polyphenols and a major catechin in green tea. It has been studied in models of toxic and metabolic liver injury. It has anti-inflammatory and antioxidant properties. EGCG may influence lipid accumulation, AMPK-related metabolism, Nrf2/ARE antioxidant signalling, NF-κB inflammatory signalling, and mitochondrial function. Its effects on aberrant cellular proliferation and hepatic fibrosis are also discussed [130].

8.7 Glycyrrhizin and glycyrrhetinic acid

A significant metabolite is glycyrrhetinic acid, a major metabolite of glycyrrhizin, a triterpenoid saponin mainly obtained from Glycyrrhiza species. These substances have been studied for their anti-inflammatory, antioxidant, immunomodulatory and hepatoprotective properties. The biological activities may include regulation of cellular stress responses and inflammatory signalling. Glycyrrhizin has also attracted attention for its associations with endogenous danger-associated molecular pathways which might be involved in the regulation of hepatic inflammation [131].

8.8 Ginsenosides

Ginsenosides are a class of structurally diverse steroidal saponins mainly obtained from the Panax species. The sugar moieties and structures of aglycone of various ginsenosides may be quite different, which may lead to a difference in biological activity and absorption. All experimental work has focused on the antioxidant,

anti-inflammatory, metabolic, mitochondrial and cytoprotective actions of ginsenosides. Their potential effects include Nrf2, AMPK, NF-κB, PI3K/Akt, autophagy and mitochondrial pathways [132].

8.9 Baicalin and baicalein

Scutellaria baicalensis is linked to the flavonoid-type compounds baicalin and baicalein. Both have received attention for their cytoprotective, anti-inflammatory and antioxidant properties. Possible mechanisms of hepatoprotection include modulation of oxidative stress, inhibition of inflammatory signals, control of apoptosis and impacts on lipid metabolism. In addition, the signalling pathways Nrf2, NF-κB, MAPK and other pathways that respond to cellular stress have been investigated for their connection to baicalin and baicalein [133].

8.10 Schisandrin and lignans

Several lignans from Schisandra species, including schisandrin, have been reported to possess antioxidant and hepatoprotective effects. The effect of schisandra lignans on antioxidant defence, mitochondrial activity, inflammatory reactions, and hepatic drug-metabolizing systems was studied. They may protect hepatocytes against oxidative damage induced by chemicals and enhance the body's antioxidant capacity [134].

8.11 Other emerging phytochemicals

Besides the extensively investigated lead compounds mentioned above, a variety of other natural compounds are under investigation as potential hepatoprotective agents. These comprise anthocyanins, lignans, terpenoids, saponins, polysaccharides, quinones, alkaloids, and phenolic acids such as ferulic acid and caffeic acid. There is growing interest in compounds that can modulate specific processes such as ferroptosis, NLRP3 inflammasome activation, mitochondrial quality control, autophagy, bile-acid signaling, and the gut–liver axis. These compounds may provide new chemical scaffolds to target mechanisms inadequately addressed by current therapies [135].

9. Advanced Formulation and Drug-Delivery Strategies

9.1 Limitations of conventional formulations

The physicochemical and pharmacokinetic constraints of traditional natural product formulations are often problematic. Poor water solubility of many phytochemicals leads to poor gastrointestinal absorption after oral administration. Others may go bad during storaging or after being subjected to physiological conditions as they are chemically not stable. Intestinal and hepatic metabolism are extensive and further decrease the amount of active parent molecule reaching the systemic circulation. Finally, rapid clearance and nonspecific tissue dispersion may limit exposure at the site of hepatic damage. Such limitations may lead to a large gap between the achievable concentrations in vivo and the attractive in vitro activity [136].

9.2 Nanoparticles

Nanoparticle-based delivery systems can enclose or bind natural substances within nanoscale carriers, that may improve their solubility, stability, absorption and tissue distribution. Nanoparticles depending on their composition can offer controlled or sustained release and protect phytochemicals from premature degradation. In addition, their small size may influence biodistribution and cellular uptake. Nanoparticle systems have been investigated as a strategy to improve hepatic exposure to weakly bioavailable chemicals for hepatoprotective applications [137].

9.3 Liposomes and phytosomes

Liposomes are vesicular systems that can carry both hydrophilic and lipophilic substances. They are primarily formed by phospholipid bilayers. Encapsulation in liposome can improve the solubility, stability and cellular uptake of natural compounds by protecting them from degradation. Therefore, liposomal systems have been explored for the delivery of poorly water-soluble phytochemicals and enhancement of their pharmacological effects [138].

9.4 Nanoemulsions

Nanoemulsions are colloidal delivery systems consisting of tiny droplets of one phase dispersed in another, typically stabilized by surfactants or similar compounds. They may enhance gastrointestinal absorption and increase the apparent solubility and dispersion of water-insoluble phytochemicals. Their relatively larger interfacial area may facilitate interaction with biological membranes and formulation [139].

9.5 Solid lipid nanoparticles and nanostructured lipid carriers

Nanostructured lipid carriers (NLCs) are usually a combination of solid and liquid lipids that form a less ordered matrix, while solid lipid nanoparticles (SLNs) use a solid lipid matrix to entrap bioactive molecules. Both techniques are able to offer a controlled release and to enhance the stability and the solubility of the natural substances with poor water solubility. The less ordered lipid matrix of NLCs can incorporate a higher amount of incorporated drug which can provide a higher loading capacity than conventional solid lipid systems [140].

9.6 Polymeric nanoparticles

Polymeric nanoparticles are made from or adsorbed or chemically bound natural materials using biodegradable or biocompatible polymers. Depending on the polymer, these systems can provide controlled release, protection against degradation and modification of drug-distribution properties. The synthetic and natural polymers have been studied as carriers of bioactive chemicals [141].

9.7 Micelles and self-assembled systems

Amphiphilic molecules form micelles, structures that self-assemble with hydrophilic parts that interact with water and hydrophobic parts that may contain poorly water-soluble chemicals. This renders micelles attractive to enhance the apparent solubility and dispersibility of hydrophobic phytochemicals. Also, other amphiphilic substances such as surfactants, phospholipids, block copolymers can be used to create self-assembling systems [142].

9.8 Exosome-based delivery

Exosomes are small extracellular vesicles that naturally mediate the transfer of proteins, lipids, nucleic acids and other biological substances, and are involved in intercellular communication. Their natural biological origin and ability to interact with target cells have increased their interest as vehicles for drug delivery. Exosomes-based technologies can potentially be used for transporting weakly bioavailable natural substances or mixing phytochemicals with physiologically active vesicular components [143].

9.9 Liver-targeted delivery

The rationale of liver targeted delivery is to reduce non-specific exposure of other organs and to enhance the concentration of a therapeutic substance in the liver tissue. This strategy is particularly attractive for hepatoprotective natural products because the liver is a major organ involved in metabolism and clearance and the primary site of disease. Targeting can be achieved by the physicochemical properties of the carrier, passive accumulation or surface modification with ligands that can recognize specific receptors [144].

9.10 Stimuli-responsive formulations

Stimuli-responsive drug delivery devices are designed to release their therapeutic payload upon satisfying a set of biological or physicochemical conditions. Possible stimuli include changes in pH, redox state, enzyme activity, temperature, or other properties of the diseased microenvironment. These methods can increase the concentration of a natural product at the site of injury and offer a regulated release [145].

9.11 Strategies for improving oral bioavailability

Enhancement of oral bioavailability continues to be one of the most significant challenges to the pharmaceutical development of natural goods. Some of the techniques that can be used include particle-size reduction, amorphous solid dispersions, phospholipid complexes, lipid-based formulations, nanoemulsions, micelles, nanoparticles, cyclodextrin-based systems and chemical modification of lead compounds. Formulation strategies can be used to protect the drug from degradation, to improve intestinal permeability, to increase solubility or to reduce the effects of first-pass metabolism [146].

Table 7. Advanced Delivery Systems for Hepatoprotective Natural Products [147-150].

Delivery System	Examples	Major Advantages	Potential Application in Liver Injury
Liposomes	Curcumin, quercetin	Improved solubility, stability and bioavailability	Enhanced hepatic delivery and antioxidant activity
Phytosomes	Silybin, curcumin	Improved absorption and bioavailability	Better hepatoprotective efficacy
Polymeric nanoparticles	Resveratrol, curcumin	Controlled release and improved stability	Targeted delivery to injured hepatic tissue
Lipid nanoparticles	Curcumin, berberine	Enhanced oral absorption and protection from degradation	Improved systemic and hepatic exposure
Nanoemulsions	Curcumin, EGCG	Increased solubility and dissolution	Improved bioavailability of poorly soluble phytochemicals
Micelles	Curcumin, resveratrol	Enhanced aqueous solubility	Improved absorption and therapeutic activity
Solid lipid nanoparticles	Silymarin, curcumin	Sustained release and protection from degradation	Prolonged hepatoprotective effects
Nanostructured lipid carriers	Quercetin, curcumin	High loading capacity and controlled release	Enhanced hepatic delivery
Exosome-based systems	Plant-derived bioactive compounds	Biocompatibility and potential targeted delivery	Emerging approach for liver regeneration and protection
Hydrogels	Polyphenol-loaded formulations	Sustained and localized release	Potential application in tissue protection and regeneration

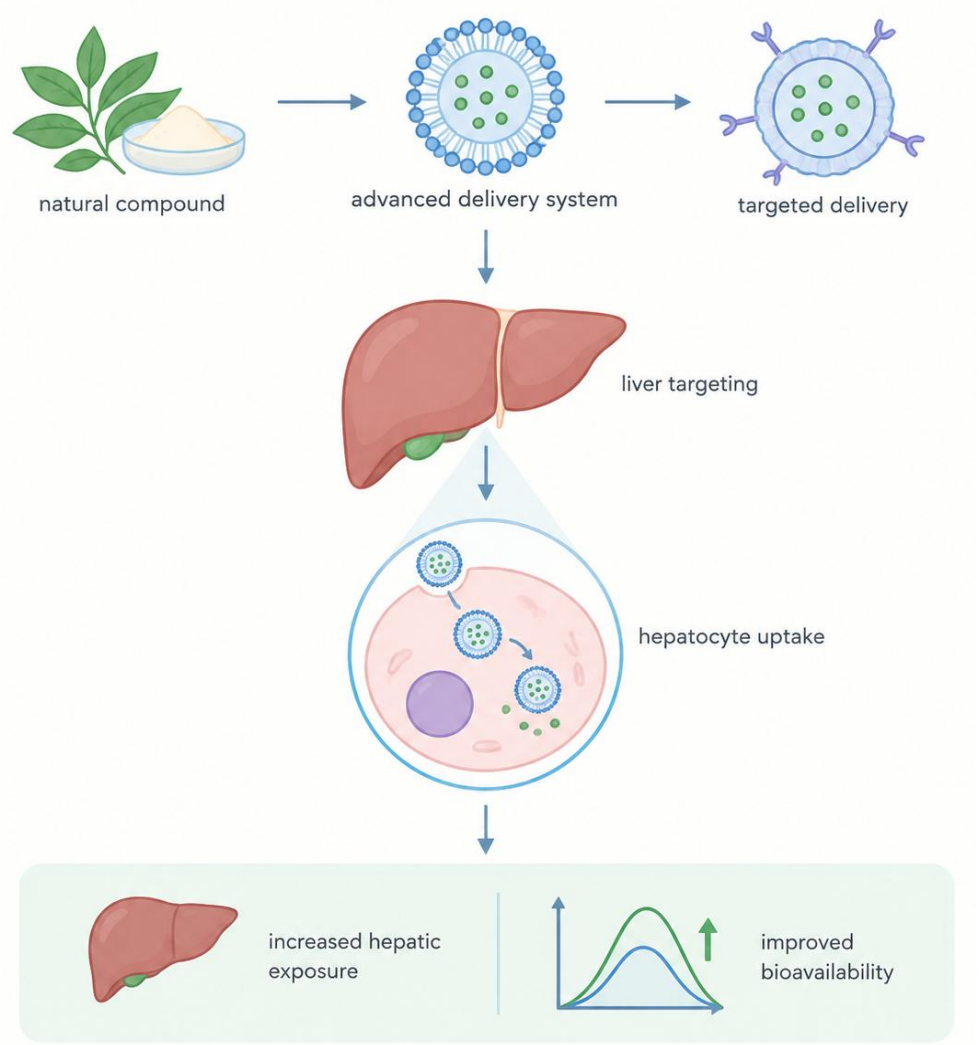


Figure 4. Advanced delivery systems for improving hepatic exposure and bioavailability

10. Pharmacokinetics, Bioavailability and Metabolism

10.1 Absorption and intestinal permeability

For a natural product to exert systemic pharmacological effects after oral administration, the product must dissolve in gastrointestinal fluids, be sufficiently stable, cross the intestinal epithelium, and reach the systemic circulation. Many phytochemicals have poor absorption in the intestine due to their large molecular size, strong hydrogen bonding, poor aqueous solubility or adverse lipophilicity. Absorption may also be affected by intestinal mucus, digesting enzymes, efflux transporters and epithelial-barrier properties. Some compounds, such as curcumin, quercetin, resveratrol, and EGCG, have strong in vitro activity, but this may not be easily translated into adequate systemic exposure [151].

10.2 First-pass metabolism

A major drawback of many natural compounds when taken orally is first-pass metabolism. Compounds absorbed from the gastrointestinal tract are transported to the liver by the portal circulation, where they may undergo extensive metabolic transformation before entering the systemic circulation. Intestinal metabolic enzymes and transporters may also contribute to presystemic clearance. Hence, only a small percentage of the injected dose may reach the systemic circulation as the unmodified parent molecule [152].

10.3 Plasma protein binding

Upon entering the systemic circulation, natural products may reversibly bind to plasma proteins, especially albumin and α1-acid glycoprotein. Protein binding influences the free fraction of a chemical available for tissue distribution or interaction with pharmacologic targets. Theoretically, displacement from binding sites

could alter the free concentration of either the natural product or concurrently administered drug, but highly protein bound substances may have altered distribution and elimination characteristics [153].

10.4 Hepatic uptake and tissue distribution

Hepatoprotective medicines are aimed mainly at the liver which is also a major site of drug metabolism and excretion. When natural products arrive in the liver via the portal circulation or systemic circulation, they can be taken up by hepatocytes, Kupffer cells, hepatic stellate cells, sinusoidal endothelial cells and other cell types in the liver. The degree of accumulation is determined by the physicochemical properties of the substance and its interaction with the cellular transport mechanisms. Hepatic uptake may be via passive diffusion or transporter proteins [154].

10.5 Phase I and Phase II Metabolism

Natural compounds are subject to extensive biotransformation in phase I and phase II metabolic processes. In general phase I reactions are catalyzed by cytochrome P450 enzymes and related systems. They usually are oxidation, reduction or hydrolysis. These reactions can increase the polarity or add functional groups that will allow for subsequent conjugation. In phase II metabolism, conjugation reactions take place, including glucuronidation, sulfation, methylation, acetylation, and glutathione conjugation. In general, these interactions improve water solubility and ease of removal [155].

10.6 Gut microbiota-mediated metabolism

Gut bacteria are essential to the metabolism and biological activity of many natural compounds. Gut microbes can reduce or modify aromatic structures, cleave glycosidic linkages and break intricate phytochemicals into smaller, potentially more absorbable molecules. Hence, the biological activity of some natural materials may be more dependent on their microbial metabolites than on the original substances [156].

10.7 Pharmacokinetic limitations

Several well-studied phytochemicals have major pharmacokinetic hurdles. For example, curcumin has fast elimination, high metabolism, low absorption and low water solubility. Resveratrol is characterized by low systemic exposure of the parent chemical and extensive conjugation. Quercetin and other such flavonoids are extensively metabolized in the intestine and liver to conjugated metabolites that enter circulation. Berberine has low systemic bioavailability, but marked pharmacological effects and EGCG is unstable and easily metabolized [157].

10.8 Pharmacokinetic–pharmacodynamic relationships

Pharmacokinetic-pharmacodynamic (PK-PD) interactions are defined as the relationship between drug exposure and the resulting biological or therapeutic effect. This relationship is important to establish for natural products as plasma concentrations of the parent compound may not accurately reflect the concentration of active metabolites or level of target engagement. PK–PD studies can relate the reductions in oxidative stress, inflammatory cytokines, serum transaminases, fat accumulation or fibrosis-associated markers to parameters like plasma exposure, hepatic tissue concentration, metabolite formation and molecular biomarkers [158].

Table 8. Pharmacokinetic Limitations and Bioavailability-Enhancement Strategies [159-162].

Pharmacokinetic Limitation	Examples	Effect on Therapy	Bioavailability-Enhancement Strategy
Poor aqueous solubility	Curcumin, quercetin	Low gastrointestinal absorption	Nanoemulsions, liposomes, phytosomes
Poor intestinal permeability	Polyphenols, flavonoids	Limited systemic exposure	Nanoparticles, lipid-based delivery
Rapid metabolism	Curcumin, resveratrol	Short half-life	Metabolism-resistant formulations, nanoparticles
Extensive first-pass metabolism	Flavonoids, polyphenols	Reduced bioavailability	Phytosomes, lipid formulations
Rapid elimination	Resveratrol, EGCG	Short duration of action	Sustained-release formulations
Chemical instability	Curcumin, anthocyanins	Degradation before absorption	Encapsulation, liposomes
P-gp/efflux transport	Several flavonoids	Reduced intestinal absorption	Nanocarriers, absorption enhancers
Low gastrointestinal stability	Polyphenols	Reduced active compound reaching circulation	Protective encapsulation
Poor tissue targeting	Many phytochemicals	Limited hepatic exposure	Liver-targeted nanoparticles
Variable absorption	Herbal extracts	Inconsistent therapeutic response	Standardized extracts and optimized formulations

11. Preclinical Evidence and Experimental Models

11.1 In vitro hepatocyte models

The in vitro hepatocyte models provide a very simple and controlled way for the preliminary evaluation of hepatoprotective natural compounds. Cultured liver cells can be exposed to specific hepatotoxic chemicals and then treated with a possible phytochemical or natural-product preparation. This allows us to analyze alterations in cell viability, intracellular ROS, mitochondrial membrane potential, lipid accumulation, inflammatory mediators and cell death pathways. Such models can be useful to screen a broad range of chemicals and to define preliminary concentration-response relationships prior to animal experiments [163].

11.2 Primary hepatocytes and hepatic cell lines

Primary hepatocytes isolated from human liver tissue or experimental animals are useful models as they retain many of the physiological functions of differentiated hepatocytes. They can provide insight into drug metabolism, oxidative stress, mitochondrial function and hepatocellular responses that immortalized cell lines may not fully capture. Human primary hepatocytes are especially useful to study species-specific metabolic responses and potential human relevance of natural chemicals [164].

11.3 3D liver models and organoids

Three-dimensional liver models and hepatic organoids have emerged as sophisticated experimental systems that can more accurately mimic aspects of liver architecture and cellular interactions than traditional two-dimensional cultures. Also, 3D models could be useful to preserve specific liver functions, which can be achieved by cell-cell and cell-matrix interactions. Liver organoids comprise hepatocyte-like cells and, depending on the model, other types of liver cells that support tissue architecture and responses to disease [165].

11.4 Animal models

Animal models still play an important role in preclinical hepatoprotective research, because they allow the evaluation of pharmacokinetics, systemic reactions, tissue distribution, biochemical alterations and histopathological results in the intact organism. Depending on the type of liver injury to be studied, a variety of experimental models can be selected including chemically induced hepatotoxicity, drug-induced injury, metabolic liver disease, alcohol-associated injury, fibrosis, ischemia/reperfusion injury and other pathological conditions [166].

11.5 Biomarkers of hepatoprotection

Biomarkers can be used to quantify hepatic damage, functional impairment, oxidative stress, inflammation and tissue healing. Examples include traditional biochemical markers like serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, which can rise following hepatocellular damage. Other markers such as alkaline phosphatase (ALP), γ-glutamyl transferase (GGT), bilirubin, albumin and total protein can provide further information about liver function and synthetic or cholestatic abnormalities [167].

11.6 Histopathological evaluation

Histopathological examination is an essential component of preclinical hepatoprotective studies and is direct morphological evidence of liver damage. Assessment of all these pathological changes such as hepatocyte degeneration, cellular edema, necrosis, infiltration of inflammatory cells, sinusoidal changes, steatosis, congestion can be done in the liver tissue. Specific staining techniques can also demonstrate details of fibrosis and collagen deposition [168].

11.7 Molecular and biochemical endpoints

Molecular and biochemical end points provide mechanistic support for the hepatoprotective action of a natural product. According to the study premise, these endpoints can include antioxidant enzymes, inflammatory cytokines, lipid-metabolism markers, mitochondrial proteins, apoptotic regulators, autophagy-related proteins, ferroptosis markers, and fibrosis-associated signaling molecules. Molecular approaches such as Western blotting, enzyme tests, immunohistochemistry and gene-expression analysis may be used to determine if expected pathways are indeed altered [169].

11.8 Limitations of conventional models

However, conventional experimental models, despite their importance, have some limitations. Two-dimensional cell cultures do not possess the complex architecture, vasculature, extracellular matrix, and multicellular interactions of the liver. In culture, primary hepatocytes can lose specialized functions and immortalized cell lines may not be representative of normal hepatic metabolism. Animal models are more biologically complex but may have substantial differences from humans in their immunological responses, microbiome, metabolism of drugs, disease progression and vulnerability to hepatotoxic agents [170].

12. Clinical Evidence and Translation to Modern Pharmacotherapy

12.1 Human clinical evidence

The most important level of evidence to establish whether a natural product may be considered as a therapeutically useful hepatoprotective intervention is human clinical evidence. Many plant-derived compounds and standardized preparations have been evaluated in clinical trials in patients with toxic liver injury, viral liver diseases, metabolic liver diseases and other hepatic diseases. Outcomes may include changes in liver enzymes, metabolic parameters, inflammatory biomarkers, imaging results and in some cases, histological features [171].

12.2 Randomized controlled trials

The most important level of evidence to establish whether a natural product may be considered as a therapeutically useful hepatoprotective intervention is human clinical evidence. Many plant-derived compounds and standardized preparations have been evaluated in clinical trials in patients with toxic liver injury, viral liver diseases, metabolic liver diseases and other hepatic diseases. Outcomes may include changes in liver enzymes, metabolic parameters, inflammatory biomarkers, imaging results and in some cases, histological features [172].

12.3 Clinical biomarkers and endpoints

Biomarkers are frequently used in the clinical setting to assess liver injury and response to treatment. Serum ALT and AST are frequently studied as they are easily obtainable markers of hepatic damage although ALP, GGT, bilirubin, albumin and other biochemical markers can provide additional information. Additional endpoints in metabolic liver disease include body weight, insulin sensitivity, lipid profiles, imaging-based measurements of hepatic fat as well as non-invasive markers of fibrosis [173].

12.4 Pharmacokinetic and pharmacodynamic evidence

Pharmacokinetic and pharmacodynamic studies are essential to establish if the exposure obtained in humans is adequate to produce the biological effects seen in experimental models. Important pharmacokinetic parameters are absorption, maximal plasma concentration, time to maximal concentration, exposure, half-life, metabolic conversion and tissue distribution. For natural products, the measurement of active metabolites may be particularly important, as the parent chemical may not be systemically available [174].

12.5 Safety and tolerability

Safety is a prerequisite for the clinical development of any natural product. It is a mistake to take a plant product for granted as harmless. Natural products may cause adverse effects when used in high doses, in continuous administration or as concentrated extracts. Some toxicities may involve the liver, kidney, cardiovascular system, gastrointestinal tract or other organs [175].

12.6 Herb–drug interactions

Another serious issue regarding the employment of natural products in conjunction with the conventional medicines is the possibility of herb-drug interactions. Phytochemicals can induce or inhibit cytochrome P450 enzymes and conjugating enzymes, drug transporters and other metabolic pathways. The interactions may increase or decrease the plasma concentrations of concomitant medications and thus alter their therapeutic effects or toxicity [176].

12.7 Standardization and quality control

Standardization is one of the most important prerequisites for the inclusion of natural ingredients in the pharmacotherapy of today. Unlike traditional synthetic medications, which consist of a single chemical element, botanical preparations can contain dozens or hundreds of chemical elements and their composition may differ depending on the type of plant, where it is grown, how long it is harvested, how it is stored, how it

is extracted and how it is manufactured. Lack of standardization can mean that two items sold under the same botanical name can have very different chemical and pharmacological properties [177].

12.8 Regulatory challenges

The regulatory category of the product can vary as per the classification of the product as a botanical drug, traditional medicine, dietary supplement, nutraceutical or pharmaceutical preparation. Regulatory requirements can vary in the amount of data required to demonstrate efficacy, safety, manufacturing quality and consistency. A key challenge is to achieve pharmaceutical grade control over a complex mixture while retaining physiologically relevant chemistry [178].

12.9 Reasons for the preclinical-to-clinical translation gap

The promising preclinical results and clinical development of natural products are often very different. One of the main reasons is the use of dosages or concentrations in experimental research that are difficult to achieve safely in humans. In vitro results may also be of further limited importance because of differences in absorption, metabolism, tissue distribution, and pharmacokinetics. In addition, the genetic diversity, metabolic characteristics, immune responses, microbiome composition, comorbidities and disease progression seen in human populations may not be recapitulated in animal models [179].

Table 9. Clinical Trials of Natural Products in Liver Diseases: Trial Design, Intervention Characteristics, Clinical Outcomes, Safety, and Translational Limitations [180-186]

Natural Product / Trial ID	Study Design	Sample Size	Population	Intervention / Formulation	Dose	Duration	Comparator	Primary Endpoint	Major Result	Adverse Events	Key Limitations
Vitamin E (RRR-α-tocopherol) – PIVENS; NCT00063635	Multicenter, randomized, double-blind, placebo-controlled, phase III	247	Adults with biopsy-confirmed NASH without diabetes or cirrhosis	Oral vitamin E capsule	**800 IU/day**	96 weeks	Placebo; pioglitazone arm	Histological improvement in NASH without worsening of fibrosis	Vitamin E significantly improved the predefined histological endpoint versus placebo and reduced ALT; however, not all histological components improved uniformly	Generally well tolerated; long-term safety remains an important consideration	Restricted to nondiabetic adults; long duration; historical NASH/NAFLD terminology; histological endpoint; long-term benefit/risk remains uncertain

Curcumin – Panahi et al.	Randomized, double-blind, placebo-controlled	102 randomized	Adults with ultrasonography-diagnosed NAFLD	Oral phytosomal curcumin	**1,000 mg/day (500 mg twice daily)**	8 weeks	Matched placebo	Metabolic and hepatic biochemical outcomes; hepatic steatosis assessed by ultrasonography	Reduced hepatic steatosis and improved several metabolic parameters, including total cholesterol, LDL-C, triglycerides, non-HDL-C and uric acid	Reported as well tolerated	Short duration; ultrasound rather than biopsy/MRI-PDFF; surrogate endpoints; insufficient evidence for fibrosis or long-term clinical outcomes; formulation-specific results may not generalize to other curcumin preparations
Turmeric/curcuminoid preparation – IRCT20150929244262N1	Randomized, double-blind, placebo-controlled	64	Adults with NAFLD	Oral turmeric preparation	**2 g/day**	8 weeks	Placebo	Liver enzymes and metabolic/oxidative-stress parameters	Significant reductions in AST, ALT and GGT, together with improvements in triglyce	No major safety signal reported	Small sample; short duration; turmeric preparation rather than chemically

									rides, LDL and MDA; no significant change in sonographic NAFLD grade		standardized curcumin; no histological endpoint; no evidence for fibrosis regression
Silymarin (Legalon®) – NCT00680407	Randomized, double-blind, placebo-controlled, multicenter phase II trial	78 randomized	Adults with suspected/biopsy-evaluated NASH without cirrhosis	Standardized oral silymarin (Legalon®)	**420 or 700 mg three times daily**	48–50 weeks	Placebo	Histological improvement defined by ≥2-point reduction in NAS without worsening of fibrosis	Primary endpoint was **not significantly different**: 19% (420 mg), 15% (700 mg) and 12% placebo achieved the endpoint in the overall randomized analysis	GI events were common; serious events occurred but were not considered related to study drug; overall tolerability was acceptable	Major histological-entry misclassification; small analyzable population; no significant primary endpoint; unusually high doses; limits confidence in efficacy interpretation
Silymarin – NCT02006498	Randomized, double-blind, placebo-contro	99	Adults with biopsy-confirmed NASH/NA	Oral silymarin	**700 mg three times daily**	48 weeks	Placebo	Improvement in NAS by ≥30% from baseline	Silymarin did **not demonstrate a significant**	Generally well tolerated	Surrogate histological endpoint; relatively

	lled trial		FLD with NAS ≥4						**improvement in the prespecified NAS endpoint**, although some fibrosis-related and biochemical measures showed potentially favorable signals		short duration for fibrosis; limited power for clinical outcomes; no demonstration of definitive disease-modifying benefit
Resveratrol – NCT02030977	Randomized, double-blind, placebo-controlled	50 randomized (25/25)	Adults with NAFLD	Oral resveratrol capsule	**500 mg/day**	12 weeks	Placebo plus lifestyle advice	ALT	Resveratrol significantly reduced ALT and was associated with reductions in inflammatory markers, NF-κB activity, cytokeratin-18 and hepatic steatosis grade	No adverse events reported in the study	Small sample; short treatment period; lifestyle intervention in both groups; biochemical/imaging outcomes rather than histological fibrosis or clinica

											l events
Resveratrol – NCT01464801	Randomized, quadruple-masked, placebo-controlled, parallel-group study	28 randomized	Adults with elevated transaminases and suspected NAFLD	Oral resveratrol tablets	**500 mg three times daily (1,500 mg/day)**	6 months	Placebo	Changes in hepatic steatosis/inflammation assessed by biochemical, MR and histological measures	Resveratrol reduced liver lipid content, but the difference from placebo was not statistically significant for the principal hepatic outcomes	GI symptoms and other minor events occurred; one serious adverse event involving febrile leukopenia/thrombocytopenia was reported in the resveratrol group	Very small sample; high dose; limited statistical power; histological/clinical efficacy not demonstrated; one serious adverse event warrants attention
Resveratrol – NCT01446276	Randomized, placebo-controlled, quadruple-masked parallel study	Small mechanistic clinical cohort	Obese men with NAFLD	Oral resveratrol capsules	**500 mg three times daily**	6 months	Placebo; non-NAFLD control group for selected comparisons	Hepatic VLDL-TG kinetics, liver fat and insulin sensitivity	No significant improvement in VLDL-TG kinetics or insulin sensitivity was demonstrated	No major safety signal highlighted	Mechanistic rather than therapeutic study; restricted male population; small sample; not powered for clinical liver outcomes
Berberine ursodeoxycholate	Phase II, randomized,	100	Overweight/obese	Oral berberine ursodeo	**500 or 1,000 mg**	18 weeks	Placebo	Change in liver fat content by	The **1,000 mg twice-**	No major treatment-related safety	Presumed rather than

(HTD1801) – NCT03656744	double-blind, placebo-controlled, proof-of-concept trial		adults with presumed NASH/fatty liver disease and type 2 diabetes	xycholate, an ionic salt of berberine and ursodeoxycholic acid	**twice daily**			MRI-PDFF	**daily** group achieved a significantly greater reduction in liver fat than placebo (absolute decrease −4.8% vs −2.0%; p=0.011), with additional improvements in glycemic control and liver enzymes	signal identified; overall treatment was tolerated	biopsy-confirmed NASH; short duration; MRI-PDFF rather than histological fibrosis endpoint; proprietary combination product cannot be equated with conventional berberine; industry-sponsored development context

Table 10. Clinical trials of natural products in liver diseases: compound, dose, formulation, duration, population, endpoints, biomarkers, adverse events, and trial ID [187-189].

Compound	Dose & Formulation	Duration	Population	Main Endpoints/Biomarkers	Adverse Events	Trial ID
Vitamin E (RRR-α-tocopherol)	800 IU/day, oral capsule	96 weeks	247 adults with NASH without diabetes	Histological improvement, ALT, AST, liver steatosis	Generally tolerated; long-term safety requires monitoring	PIVENS
Curcumin	1000 mg/day, phytosomal formulation	8 weeks	102 adults with NAFLD	ALT, AST, liver ultrasonography, BMI, waist circumference	Well tolerated	Not reported in source
Curcumin	500 mg/day formulation equivalent to 70 mg curcumin	8 weeks	Adults with NAFLD	Liver fat, ALT, AST, glucose, lipids	Not specifically reported	IRCT20141105117 63N18
Resveratrol	500 mg/day, oral capsule	12 weeks	50 patients with NAFLD	ALT, hepatic steatosis, metabolic parameters	No major safety signal reported	Not reported
Resveratrol	600 mg/day, trans-resveratrol capsules	12 weeks	60 patients with NAFLD	MDA, ox-LDL, TAC, SOD, GSH-Px, ALT, AST	Generally tolerated	Not reported
Resveratrol	1.5 g/day, oral	6 months	28 overweight patients with histological NAFLD	ALT, liver fat by MR spectroscopy, histology	One serious adverse event reported	Not reported

Table 11. Translational Status of Major Natural Products [190-193].

Natural Product	Traditional Use	Preclinical Evidence	Clinical Evidence	Development Stage
Silymarin/Silibinin	Liver disorders, dyspepsia	Strong hepatoprotective and anti-inflammatory evidence	Several human studies; results variable	Clinical research
Curcumin	Inflammation, digestive disorders	Strong antioxidant and anti-inflammatory evidence	Multiple NAFLD/MASLD studies	Clinical research
Resveratrol	Traditional dietary use	Antioxidant, metabolic and anti-inflammatory effects	Small clinical trials; inconsistent outcomes	Early clinical stage
Berberine	Gastrointestinal and metabolic disorders	Strong metabolic and hepatoprotective evidence	Clinical studies in metabolic liver disease	Clinical research
EGCG (Green tea)	Traditional tea medicine	Antioxidant and anti-steatotic effects	Human studies available; safety requires attention at high doses	Clinical research
Glycyrrhizin	Traditional treatment of liver and inflammatory disorders	Anti-inflammatory and hepatoprotective effects	Clinical use/evidence in selected liver conditions	Clinical/established use
Andrographolide	Traditional herbal medicine	Anti-inflammatory and antioxidant effects	Limited clinical liver-specific evidence	Preclinical–early clinical
Pterostilbene	Traditional plant-derived use	Antioxidant and metabolic effects	Limited human evidence	Preclinical/early clinical
Quercetin	Traditional dietary/medicinal use	Antioxidant and anti-inflammatory effects	Limited clinical evidence for liver disease	Preclinical/early clinical
Baicalin	Traditional Chinese medicine	Anti-inflammatory, antioxidant and anti-fibrotic effects	Limited clinical evidence	Preclinical stage

13. Precision and Personalized Phytotherapy

13.1 Patient-specific natural-product therapy

The aim of patient-specific natural product therapy is to select a phytochemical or botanical preparation according to the patient's risk factors, metabolic profile, treatment history, and characteristics of the illness. Since liver diseases are heterogeneous, patients with similar clinical diagnoses may have different underlying etiologies. For example, one patient may have significant inflammation or fibrosis while another may have major insulin resistance and hepatic steatosis. Thus, the response of one patient to a natural product mainly

stimulating the lipid metabolism and of another patient to a substance with more potent anti-inflammatory or antifibrotic properties may be different [194].

13.2 Pharmacogenomics

Pharmacogenomics is the study of how an individual's genetic inheritance affects their response to medications. Genetic variants affecting drug-metabolizing enzymes, transporters, receptors, antioxidant pathways and inflammatory signals may impact phytochemical absorption, metabolism, efficacy and toxicity. For example, genetic polymorphisms of enzymes involved in metabolism can alter the conversion of a natural product into its active or inactive metabolites, thus the systemic exposure can differ among individuals [195].

13.3 Pharmacometabolomic

Pharmacometabolomic refers to the study of metabolic alterations associated with drug exposure and pharmacological response. This is especially true for natural compounds, since many phytochemicals are extensively metabolized and may produce several active or inert metabolites. Thus, analysis of circulating or tissue metabolites, not solely the provided parent chemical, can provide information on actual biological exposure [196].

13.4 Gut microbiome-guided therapy

Gut microbiome is closely associated with pathophysiology and progression of liver diseases via gut-liver axis and has been identified as a major determinant of individual responses to natural products. The intestinal microbiota regulates digestion, microbial metabolite production, immune homeostasis, intestinal barrier integrity, bile acid metabolism and biotransformation of xenobiotics and phytochemicals. Gut dysbiosis, defined as alterations in microbial composition and activity, can increase intestinal permeability and facilitate translocation of bacterial products such as lipopolysaccharide (LPS) into the portal circulation. These microbial signals can activate hepatic immune pathways in addition to promoting inflammation, oxidative stress, metabolic dysfunction and fibrosis. Thus, interaction of microbiota and natural products can be one of the key foundations for the development of personalized hepatoprotective therapies [197].

13.5 Biomarker-guided treatment

Biomarker directed phytotherapy is treatment selection or monitoring based on measurable biological characteristics associated with response to treatment or disease etiology. Biomarkers include serum biochemical parameters, inflammatory mediators, oxidative stress, lipid profile, fibrosis-associated markers, metabolic signatures and molecular markers of some signaling pathways [198].

13.6 Disease-stage-specific phytotherapy

As the disease progresses, the molecular mechanisms of liver damage change from early metabolic inefficiency or steatosis to inflammation, fibrosis and finally cirrhosis. Therefore the best pharmaceutical target can be different according to the stage of the disease. Interventions on lipid metabolism, insulin sensitivity, redox balance and mitochondrial function may be particularly relevant at early stages of metabolic dysfunction. While approaches targeting hepatic stellate-cell activation, TGF-β/Smad signaling, ECM remodeling and fibrogenesis may be needed for established fibrosis, regulation of inflammatory and immunological pathways may be more important across progressive inflammatory disease [199].

13.7 Precision formulation

Precision formulation combines principles of personalized treatment and state-of-the-art drug delivery technologies to maximize the concentration of a natural product at the right biological site. Other sophisticated formulations such as nanoparticles, liposomes, phytosomes, lipid-based carriers, and polymeric systems can be engineered to improve bioavailability and hepatic transport. More complex systems may target specific hepatic cell types such as hepatocytes, Kupffer cells or hepatic stellate cells [200].

14. Emerging Technologies for Natural-Product Discovery

14.1 Artificial intelligence and machine learning

Because artificial intelligence and machine learning may find intricate links in big datasets that can be challenging to find using traditional methods, they are increasingly being used in natural product discovery. To predict whether a natural substance is likely to have a specific pharmacological action, machine-learning models can be trained utilizing chemical structures, biological activity data, gene-expression profiles, toxicity information, and pharmacokinetic features. Prioritizing phytochemicals with anticipated antioxidant, anti-inflammatory, antifibrotic, or metabolic properties prior to experimental confirmation may be aided by AI models in liver injury research. As a result, AI can assist concentrate experimental resources on the most promising candidates while reducing the number of chemicals that need preliminary laboratory screening [201].

14.2 multi-omics approaches

Multi-omics techniques combine data from several biological levels, such as transcriptomics, proteomics, metabolomics, lipidomics, and genomes. Instead of concentrating on a single molecular target, this integration offers a systems-level understanding of how a natural product affects liver biology. For instance, proteomics can identify changes in protein abundance, metabolomics can disclose changes in metabolic pathways, and transcriptome analysis can identify genes changed after treatment. Combining these datasets may reveal pathways that would go unnoticed in traditional single-endpoint studies and identify interconnected molecular networks responsible for hepatoprotective actions [202].

14.3 Metabolomics-guided discovery

Metabolomics offers an in-depth analysis of the small-molecule metabolites in biological systems, and can be used to study the composition of natural products and their effect on biological metabolism [203]. Metabolomic analysis of plant extracts can be used to distinguish active extracts from inert preparations and to identify chemical markers associated with biological activity. Metabolomics can also be used to identify metabolic disturbances associated with diseases in liver injury models and determine if a natural product treatment restores altered metabolic pathways [204].

14.4 Chemoinformatic

Chemoinformatics is the use of computational techniques to organize, analyze and predict compound properties from chemical structures and chemical databases. In natural-product research, chemoinformatics can be utilized to identify potential pharmacophores, predict physicochemical properties, assess structural similarities and rank compounds for biological assays. Structural databases can be integrated with information on known targets and pharmacological activities [205].

14.5 High-throughput screening

High-throughput screening (HTS) is an approach to rapidly test large numbers of chemicals or extracts against specific biological targets or cellular phenotypes. HTS can accelerate the discovery of extracts and specific compounds with desirable biological activity in natural products research. Automated assays can be used to measure cellular viability, oxidative stress, inflammatory signaling, lipid accumulation, mitochondrial function, and other disease-relevant features [206].

14.6 Digital pharmacology

Digital pharmacology combines databases, molecular simulations, systems pharmacology, computational modeling and quantitative biological data to understand how drugs work. Digital pharmacology can assist natural product research by linking phytochemicals to disease networks, signaling pathways, biological targets and potential adverse effects . Therefore, by developing theories on the effect of complex natural chemicals on various biological processes, it can help experimental pharmacology [207].

14.7 AI-assisted drug–target prediction

Machine learning and artificial intelligence algorithms can predict possible interactions of phytochemicals with proteins, receptors, enzymes, transporters or other biological targets. Such predictions can be obtained from molecular structures, known ligand-target relations, protein features, biological networks and experimental data sets . Candidate interactions can then be prioritized for molecular docking, molecular dynamics, biochemical assays or cellular studies [208].

14.8 AI-guided combination discovery

One of the most promising uses of AI in natural product development is to find potentially synergistic combinations of phytochemicals. Botanical extracts often contain multiple constituents that may act through different but related pathways. AI and network-based computational techniques are capable of analyzing chemical-protein-pathway interactions and they can also identify combinations that are predicted to have complementary or synergistic effects [209].

Table 12. AI, Multi-Omics, and Computational Approaches in Hepatoprotective Natural-Product Discovery [210-215].

Approach	Application	Major Advantage	Potential Outcome
Artificial Intelligence (AI)	Predicts active compounds and therapeutic targets	Rapid screening of large datasets	Identification of novel hepatoprotective candidates
Machine Learning (ML)	Predicts compound activity, toxicity and ADME properties	Reduces experimental workload	Improved candidate selection
Network Pharmacology	Maps compound–target–pathway interactions	Explains multi-target actions	Identification of key therapeutic pathways
Metabolomics	Profiles metabolic changes after treatment	Detects biomarkers and metabolic pathways	Mechanism and biomarker discovery
Transcriptomics	Analyzes gene-expression changes	Identifies regulated genes/pathways	Molecular mechanism identification
Proteomics	Evaluates protein-level changes	Identifies drug-responsive proteins	Target and pathway validation
Genomics	Studies genetic factors affecting response	Supports personalized approaches	Identification of susceptibility biomarkers
Multi-omics Integration	Combines genomics, transcriptomics, proteomics and metabolomics	Provides systems-level understanding	Comprehensive mechanism mapping
Molecular Docking	Predicts phytochemical–protein interactions	Estimates binding affinity	Identification of potential molecular targets
Molecular Dynamics (MD)	Evaluates stability of ligand–target complexes	Provides dynamic interaction information	Validation of promising drug–target interactions
Chemoinformatics	Analyzes chemical structures and biological activity	Facilitates virtual screening	Discovery and optimization of lead compounds
High-throughput Screening	Screens large natural-product libraries	Rapid identification of active candidates	Prioritization of compounds for experimental validation

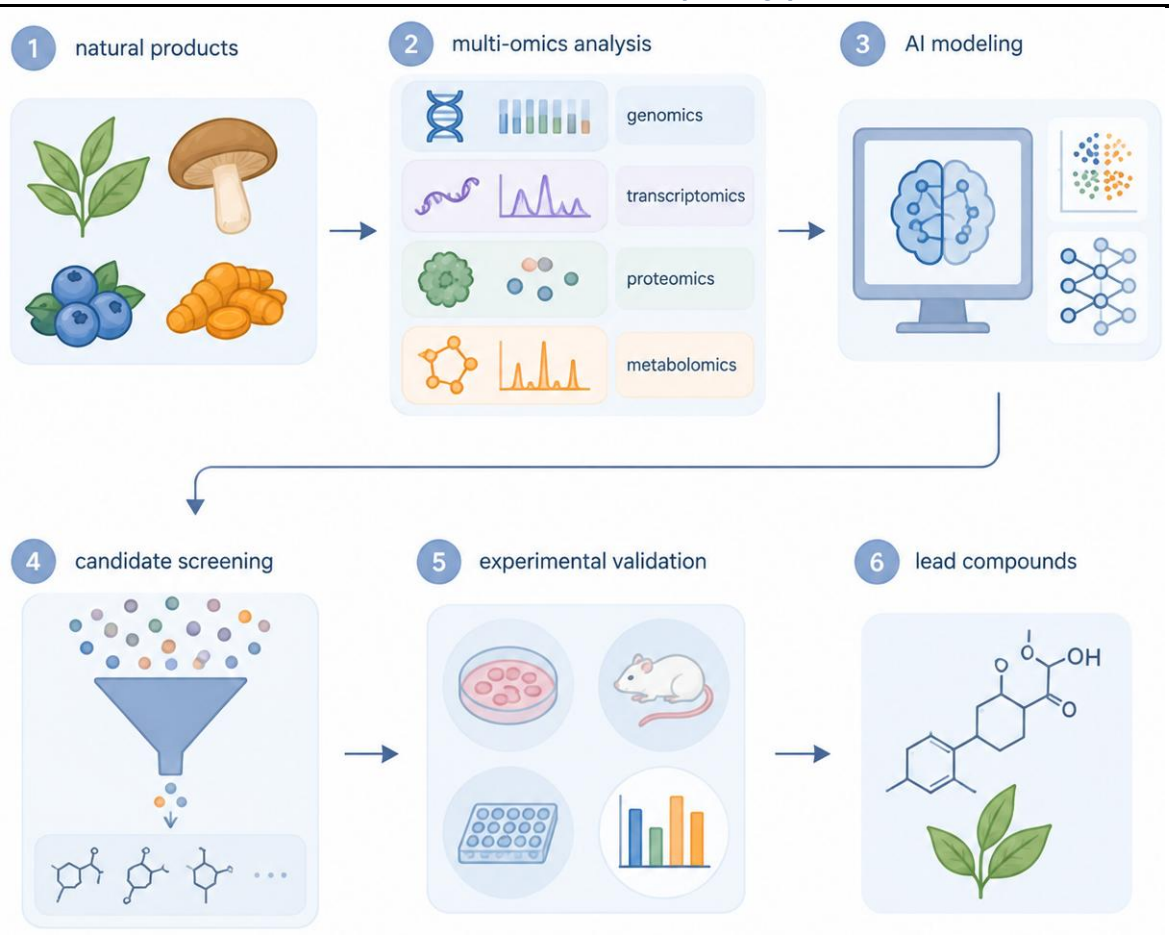


Figure 5. AI- and multi-omics-assisted natural-product discovery pipeline

15. Safety, Toxicology and Quality Control

15.1 Natural-product-associated hepatotoxicity

Many natural products have hepatoprotective, anti-inflammatory and antioxidant effects, but some medicinal plants and phytoconstituents may cause drug-induced liver injury (DILI) or herb-induced liver injury (HILI). Hepatotoxicity may arise from interaction with other substances, metabolic activation, high doses, inherent toxic components or idiosyncratic immunological responses [216]. Products containing impurities, too concentrated extracts, undisclosed substances or misidentified plant material may be more dangerous. Thus, the classical use of a preparation should not be regarded as adequate proof of its safety. Liver enzyme and histology assessment, and development of in vitro and in vivo models for monitoring adverse hepatic effects during clinical use, should be included in the toxicological assessment. “Major safety concerns with herbal medicines include plant toxicity, contamination, problems in manufacturing, lack of standardization and inadequate pharmacovigilance,” WHO says [217].

15.2 Dose-dependent toxicity

The amount and length of exposure greatly influence the positive and negative effects of natural materials. A phytochemical or plant extract that has beneficial antioxidant or anti-inflammatory effects at the right dose can have negative effects if it is taken in excess or over long periods of time. Therefore, dose-response correlations should be developed in preclinical research by means of well-designed acute, subacute and chronic toxicity investigations [218]. Where appropriate, parameters such as mortality, body weight, food and water consumption, hematological measures, serum biochemical parameters, organ weights, and histologic changes should be evaluated. The establishment of an appropriate therapeutic window is especially important for concentrated extracts because extraction can increase exposure to bioactive ingredients compared with standard preparations [219].

15.3 Long-term safety

The long-term safety of natural products is a major challenge, as many of these preparations are used repeatedly in the treatment of chronic diseases. The lack of toxicity in the short term does not often indicate long term safety, especially when substances are accumulating in the body, metabolically changing or having long term effects on hepatic and renal enzymes [220]. In chronic or repeated-dose studies, potential effects on major organs and on reproductive and developmental systems, when appropriate, as well as on biochemical and hematological parameters should be evaluated. Post-marketing pharmacovigilance is also important as relatively small clinical studies may miss rare or delayed adverse events. Pharmacovigilance is a key component of the surveillance of safety of herbal medicines, the WHO has clearly stated [221].

15.4 Herb–drug interactions

Another major safety issue is the herb-drug interactions (HDIs), particularly in patients who are taking multiple conventional medicines. Herbal constituents can change the absorption, metabolism, transport or elimination of drugs and therefore have the potential to increase toxicity or lower therapeutic efficacy. Cytochrome P450 enzymes, UDP-glucuronosyltransferases, drug transporters, and pharmacodynamic pathways can all be involved in interactions [122]. For example, WHO includes clinically relevant interactions between Hypericum perforatum (St. John's wort) and drugs including warfarin, ciclosporin, antiretrovirals, digoxin and some anticancer drugs. However, clinical relevance of many of the reported interactions remains unclear and needs to be confirmed in appropriate pharmacokinetic and clinical studies [123].

15.5 Contamination and adulteration

The quality and safety of natural products can be affected by the presence of microbial contamination, pesticides, heavy metals, mycotoxins, residual solvents, fumigants, environmental pollutants or radioactive materials. Adulteration can also take place by intentional or accidental substitution of the stated botanical species, addition of synthetic drugs or use of unsuitable plant parts. Such problems can greatly modify the pharmacological and toxicological profile of a preparation. The WHO lists a number of possible contaminants of herbal medicines, including micro-organisms, pesticides, toxic metals and other dangerous substances [124].

15.6 Batch-to-batch variability

A major challenge in developing botanical medicines is batch-to-batch variability because the concentration of active and potentially toxic constituents may vary between production batches. Variability may be due to differences in species or chemotype, geographical location, soil composition, climate, harvesting time, age of plant, storage conditions, extraction solvent, extraction temperature, extraction time and manufacturing processes [225]. Such variability may also result in differences in pharmacological activity, bioavailability and toxicity. Reproducibility of botanical preparations necessitates control of the entire production process comprising raw material authentication, processing, extraction, formulation, packaging and storage. Modern chromatographic and spectroscopic fingerprinting methods help ensure chemical consistency between batches [226].

15.7 Extract standardization

Standardization of extracts is important to ensure that natural product preparations are safe, effective and of reproducible quality. Some examples of standardization are authentication of the botanical material, identification of physicochemical properties, measurement of specific marker compounds, chromatographic fingerprinting and contamination control. Depending on the product type, different techniques such as HPLC, UHPLC, GC-MS, LC-MS, TLC/HPTLC, NMR and spectroscopic techniques can be applied [227]. Importantly, standardization should not be based on one marker chemical where many components have therapeutic effect. Integration of chemical fingerprints, quantitative measures, biological assays and exact manufacturing parameters can give a more meaningful picture of product consistency. WHO defines quality

control as the processes used to determine the identity and purity of pharmaceutical products, and it is also important to have the appropriate standards during the production and testing of the products [228].

15.8 Toxicological evaluation and regulatory requirements

Before natural products can be used as therapeutic agents, quality, safety, and efficacy must be validated by relevant scientific and regulatory data. Depending upon the intended use and regulatory process, toxicological assessment may include safety pharmacology, genotoxicity, reproductive and developmental toxicity, acute toxicity, repeated-dose toxicity and other studies [229]. Good manufacturing practices (GMP), validated analytical methods, appropriate specifications, documentation and batch testing are required to ensure consistency of product quality. WHO GMP guidelines require that pharmaceutical products be consistently produced and controlled to appropriate quality standards with specified, validated, documented and evaluated manufacturing and testing procedures [230].

16. Translational Challenges and Research Gaps

16.1 Reproducibility

Reproducibility is one of the biggest problems in natural product research. Experimental investigations are often inconsistent regarding plant authentication, plant part, extraction solvent, extraction conditions, dose selection, animal species, disease-induction technique, duration of treatment and result evaluations. Differences in cultivation and processing may result in chemically different extracts and thus in different biological effects, even if the same botanical species is investigated [231]. Poor documentation of extraction processes and phytochemical characterization further hamper replication by independent laboratories. Researchers should provide detailed information about botanical authentication, voucher specimens, extraction methods, chemical fingerprints, quantified marker compounds, experimental conditions and statistical methods for better reproducibility [232].

16.2 Poor standardization

Poor standardization of botanical extracts still remains one of the biggest obstacles to translational development. The complexity of the combinations of primary and secondary metabolites in natural products may vary in relation to several factors such as genotype, geographic origin, harvesting season, storage, processing and extraction technique. The same botanical name may, therefore, be used to refer to two preparations of very different pharmacological actions and molecular profiles [233].Standardization should include identification of a single active molecule, botanical authenticity, physicochemical characterization, chromatographic fingerprinting, quantitative determination of pertinent marker chemicals, and evaluation of contaminants [234].

16.3 Bioavailability

Poor oral bioavailability of many potential phytochemicals arises from low aqueous solubility, limited gastrointestinal absorption, chemical instability, extensive intestinal or hepatic metabolism, rapid elimination, or active efflux by transport proteins. Thus, doses which showed hepatoprotection benefit in cell or animals may not be achievable in humans with conventional oral administration [235]. Therefore, pharmacokinetic studies should be performed in parallel with efficacy studies to characterize absorption, distribution, metabolism and excretion, and to identify the active metabolites. Modern formulation techniques such as nanoparticles, liposomes, phytosomes, solid dispersions, nanoemulsions and other drug-delivery systems may improve solubility and systemic exposure [236].

16.4 Animal-to-human differences

Animal models are important for studying mechanisms and initial efficacy. However, the results of animal experiments are not always translatable to the human. The response to natural products can be affected by variability in hepatic metabolism, transporter expression, immunological responses, gut microbiota, pharmacokinetics, disease development and others [237]. Some features of liver disease in man can be

reproduced in experimental animals. For example, chemically induced acute liver injury may not adequately model the complex and chronic pathophysiology of metabolic dysfunction-associated steatotic liver disease, alcohol-associated liver disease, autoimmune liver disease or chronic drug-induced liver injury in humans [238].

16.5 Insufficient clinical evidence

Although a wealth of pre-clinical studies exist, clinical data are lacking for many naturally occurring hepatoprotective compounds. Many of the published trials are small, single center, short in duration, heterogeneous or poorly controlled making it difficult to show definitive therapeutic efficacy [239]. The differences in botanical preparations and doses make it more difficult to compare results from different clinical investigations. Future clinical trials should use chemically characterized and standardized preparations, well defined patient populations, appropriate comparator groups, clinically meaningful endpoints, validated biomarkers, adequate sample size and duration of follow-up . Pharmacokinetic and, where appropriate, pharmacodynamic measurements. The registry of clinical studies and reporting of positive and negative results would further strengthen the evidence base [240].

16.6 Formulation and manufacturing

Moreover, there are other translational challenges in the formulation and large-scale production of natural products. Plant-derived components may have different absorption properties, low solubility and instability to light, oxygen, temperature or pH. The phytochemical profile of the final preparation might not be similar when an extraction method is scaled up from laboratory to industrial manufacturing [241]. The procedures of production must be carefully optimized and validated for chemical and biological consistency. Critical factors such as quality of raw material, solvent of extraction, time and temperature of extraction, concentration, drying, selection of excipients, packing, storage conditions etc. need to be properly controlled. Stability studies should be used to establish a suitable shelf life and storage conditions [242].

16.7 Regulatory and intellectual-property barriers

Intellectual property and regulatory issues can heavily impact the development of natural products. Botanical preparations can be classified as traditional medicines, herbal medicinal goods, foods, nutritional supplements or pharmaceutical products, depending on their content, intended use and therapeutic claims. Consequently, quality, safety, efficacy, clinical evidence and manufacturing standards are changing. Intellectual property protection may also be difficult, as naturally occurring substances and traditional knowledge may have limited patentability in their unmodified forms [243].

16.8 Strategies to improve clinical translation

The clinical translation of natural products can be improved through proper plant authenticity, chemical standardization, repeatable extraction, and rigorous preclinical testing. The use of human-relevant models, such as primary human hepatocytes and liver organoids, can improve animal research. Pharmacokinetic, toxicological and formulation studies should be performed to ensure adequate exposure and safety [244]. Clinical trials well designed with standardized formulations are required to confirm efficacy and safety. Novel approaches like systems pharmacology, metabolomics, multi-omics and artificial intelligence can be instrumental for biomarker discovery, mechanism discovery and possible treatment discovery [245].

Table 13. Major Research Gaps and Proposed Strategies for Clinical Translation [246-251].

Major Research Gap	Key Problem	Proposed Strategy
Poor standardization	Variable phytochemical composition	Develop standardized extracts and chemical fingerprints
Limited reproducibility	Differences in experimental methods	Use validated and harmonized protocols
Poor bioavailability	Low absorption and rapid metabolism	Develop nanoformulations and advanced delivery systems
Insufficient pharmacokinetic data	Limited information on ADME	Conduct systematic PK/PD studies
Animal–human differences	Limited clinical predictability	Use human hepatocytes, organoids and organ-on-chip models
Limited clinical trials	Small and heterogeneous studies	Conduct large, randomized, controlled trials
Safety concerns	Toxicity and herb–drug interactions	Perform long-term toxicology and interaction studies
Batch variability	Inconsistent therapeutic activity	Implement GMP and stringent quality control
Unclear mechanisms	Multiple compounds and targets	Integrate network pharmacology and multi-omics
Regulatory barriers	Different requirements between countries	Establish clear quality, safety and efficacy standards
Limited precision medicine	Variable patient responses	Develop biomarker-guided and personalized therapies
Weak post-marketing evidence	Limited long-term safety information	Strengthen pharmacovigilance and real-world studies

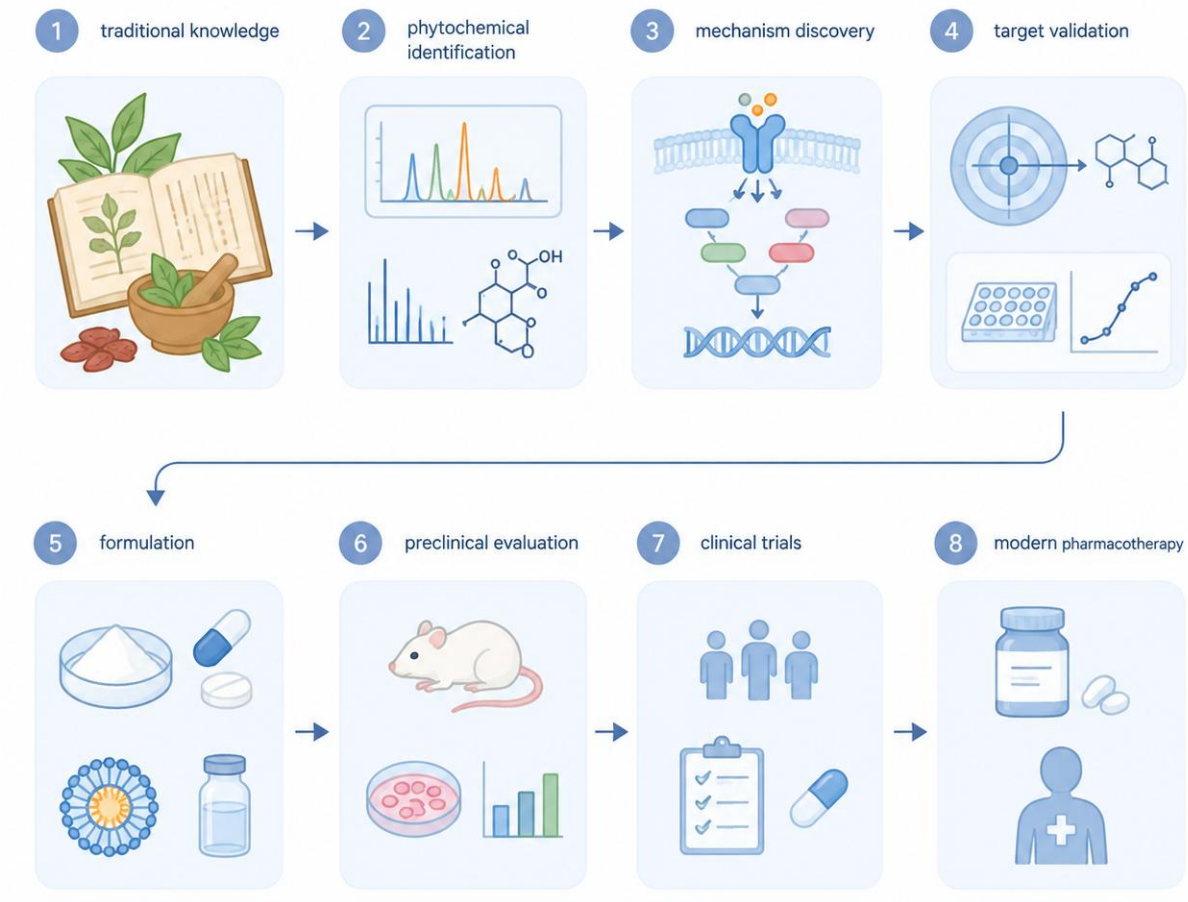


Figure 6. Translational roadmap: Traditional knowledge fi phytochemical identification fi mechanism discovery fi target validation fi formulation fi preclinical evaluation fi clinical trials fi modern pharmacotherapy

17. Future Perspectives

Mechanism-based and evidence-driven medication in the management of liver injury is replacing traditional hepatoprotective methods. Combination therapy with traditional medicines may have complementary therapeutic effects. Multi-target phytochemicals may simultaneously regulate oxidative stress, inflammation, apoptosis, fibrosis, and metabolic dysfunction [252]. The next generation nano-phytotherapeutics may enhance the solubility, bioavailability, stability and targeted distribution of poorly absorbed phytochemicals. Another new approach for the control of hepatic inflammation and metabolic disorders is the modification of the gut–liver axis and gut flora. Examples of new tools that accelerate the identification of natural products and enhance the prediction of toxicity and efficacy include advanced technologies such as artificial intelligence, metabolomics, liver organoids and organ-on-a-chip models [253]. Precision hepatotherapy may also allow for the selection of medications based on unique disease processes, biomarkers, genetics and microbiome profiles. The future clinical development of natural-product therapies for liver diseases should focus on standardized botanical preparations, well-characterized active constituents, pharmacokinetic and safety evaluation, reproducible manufacturing, adequately powered randomized clinical trials and long-term pharmacovigilance to establish safe, effective and clinically relevant natural-product therapies for liver diseases [254].

18. Conclusions

Natural products are a viable source of therapeutic agents for the prevention and treatment of liver injury, due to their ability to act on several pathogenic pathways and their various pharmacological effects. Preclinical studies have demonstrated that many plant-derived substances and extracts can inhibit oxidative stress, inflammation, mitochondrial dysfunction, apoptosis, lipid accumulation, fibrosis, and other pathways of liver damage. However, lack of standardization, variation in the botanical composition, bioavailability issues, inadequate pharmacokinetic information, potential herb-drug interactions, toxicity concerns, and inadequate clinical evidence continue to remain challenges in translating the findings into clinically validated therapies.

Thus, the future research must be focused on the authenticated and standardized natural products, mechanism-based evaluation, improved delivery systems for drugs, human-relevant models, gut-liver axis research, as well as cutting-edge technologies like metabolomics, multi-omics, artificial intelligence, organoids and organ-on-a-chip technologies. Well-designed randomized clinical trials and long-term safety monitoring are best to establish therapeutic efficacy and safety. To summarize, the combination of traditional knowledge and modern pharmacology, phytochemistry, toxicology, biotechnology, and precision medicine may be helpful in developing repeatable, safe, and scientifically proven natural-product treatments for liver damage.

LIST OF ABBREVIATIONS

Abbreviation	Full Form
AI	Artificial Intelligence
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATP	Adenosine Triphosphate
DILI	Drug-Induced Liver Injury
DNA	Deoxyribonucleic Acid
ECM	Extracellular Matrix
EGCG	Epigallocatechin-3-Gallate
ER	Endoplasmic Reticulum
FXR	Farnesoid X Receptor
GSH	Reduced Glutathione
HILI	Herb-Induced Liver Injury
HSCs	Hepatic Stellate Cells
IL-1β	Interleukin-1 Beta
IL-6	Interleukin-6
LPS	Lipopolysaccharide
MAPK	Mitogen-Activated Protein Kinase
MASLD	Metabolic Dysfunction-Associated Steatotic Liver Disease
MASH	Metabolic Dysfunction-Associated Steatohepatitis
MDA	Malondialdehyde
NAFLD	Non-Alcoholic Fatty Liver Disease
NASH	Non-Alcoholic Steatohepatitis
NF-κB	Nuclear Factor Kappa B
NLRP3	NOD-Like Receptor Family Pyrin Domain-Containing 3
Nrf2	Nuclear Factor Erythroid 2-Related Factor 2
PI3K	Phosphoinositide 3-Kinase
PPAR	Peroxisome Proliferator-Activated Receptor

ROS	Reactive Oxygen Species
SIRT1	Sirtuin 1
SOD	Superoxide Dismutase
TGF-β	Transforming Growth Factor Beta
TLR4	Toll-Like Receptor 4
TNF-α	Tumor Necrosis Factor Alpha
UPR	Unfolded Protein Response

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