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Review Article

Reactive oxygen species (ROS)-mediated oxidative stress in chronic liver diseases and its mitigation by medicinal plants

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Abstract: Reactive oxygen species (ROS) play a crucial role in cell survival regulation, and its low levels may act as indicators to encourage cellular proliferation. In contrast, elevated levels of ROS may lead to apoptosis. Stability between generating and eliminating ROS allows the retention of effective functioning of redox-sensitive signaling proteins under physiologic conditions. Cells typically maintain redox homeostasis to guarantee appropriate responses to internal and external stimuli. However, oxidative stress occurs when the oxidation product level exceeds the number of standard antioxidant systems. ROS can cause harm to all types of hepatic cells, including endothelial cells, hepatocytes, Kupffer cells, and stellate cells. High levels of ROS may lead to tissue edema, ischemia, fibrosis, cell death, or malignant transformation and may eventually lead to complete tissue damage. Antioxidants in our body exist in a homeostatic balance with other enzymes involved in the repair of cellular functions in addition to the non-enzymatic molecules such as urate, bilirubin, several vitamins, and reduced glutathione to maintain the levels of ROS in the interest of cellular homeostasis. This balance may, however, get disturbed in case of acute or chronic liver injury due to the accumulation of ROS. In the current manuscript, we aim to review the relevance of oxidative stress and its indicator of liver injury in chronic liver diseases such as alcoholic and non-alcoholic fatty liver diseases and hepatitis. Since reactive oxidation species may also lead to lipid peroxidation and promote ferroptosis, we have also evaluated their impact on epigenetic modifications, such as oxidative damage to histone proteins and DNA methylation, and the differential expression of genes related to cellular injury. We also want to highlight the potential of traditional herbal medicines as redox regulators for managing chronic liver diseases.

Keywords: Reactive oxygen species, oxidative stress, alcoholic liver disease, herbal medicine

Introduction

Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are molecules produced by hepatocytes, the liver's primary functional cells. They play crucial functions within the liver, contributing to critical physiological processes such as apoptosis, growth, oxidative respiration, regeneration, and safeguarding of the microsomes. ROS and RNS are involved in oxidative respiration, which is how cells generate energy from nutrient breakdown [1]. They are also crucial for cell signaling, enabling cell communication, and coordinating their activities. Additionally, these species participate in protein modification, influencing the function

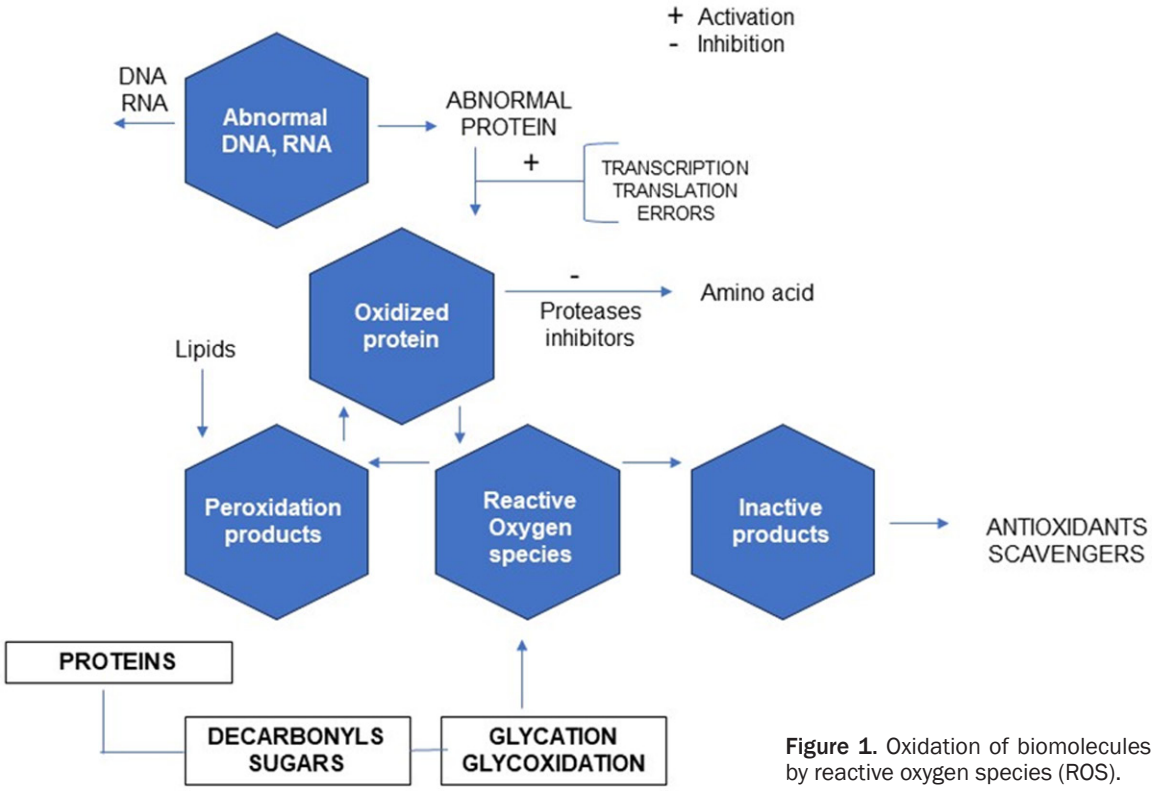

Figure 1. Oxidation of biomolecules by reactive oxygen species (ROS).

and activity of proteins within cells. In normal situations, the production of the ROS and RNS in the liver is highly regulated and contributes to the normal development and functioning of hepatocytes. They are necessary for growth, regeneration, apoptosis, and microsomal protection. However, a disparity between the intracellular antioxidant defense system and the generation of ROS/RNS can lead to oxidative stress. This imbalance can arise from excessive ROS/RNS production or a reduction in the cellular antioxidant capability [2, 3].

Oxidative stress can have harmful effects on liver cells. It may lead to programmed cell death, localized cell death, fibrosis (excessive scar tissue formation), or oncogenic effects (cancer development) [4]. The liver is especially prone to oxidative stress because of its elevated metabolic rate and exposure to toxins and xenobiotic substances [5, 6]. Prolonged hepatic disorders, such as viral hepatitis, alcoholic liver disease, and non-alcoholic fatty liver disease, are frequently linked to heightened oxidative stress [7-9]. Gaining insight into the function of RNS and ROS in liver physiology and the consequences of oxidative stress is crucial for developing strategies to maintain liver health and manage liver diseases, which includes interventions aimed at reducing oxidative stress, promoting antioxidant defense mechanisms, and addressing underlying causes such as toxin exposure or metabolic abnormalities (**Figure 1**).

Since ancient times, herbs have been used to heal various illnesses. Traditional Indian medicine heavily relies on plant-based remedies, including Ayurveda, Siddha, and Unani. Ayurvedic medicines, in particular, have gained significance and popularity due to their efficacy, safety, and affordability the replacement of they are sought after to and being practiced in both developed and developing nations.

Ayurvedic plants with natural therapeutic value are abundant worldwide, and several formulations are marketed for liver protection. (**Table 1**) lists some of these plants [10-13]. This manuscript explores the potential of herbal treatments for managing and treating chronic liver disease. It focuses on plants that promote reactive oxygen species (ROS) and evaluates their market potential and absence of side effects. The review summarizes the role of ROS in the pathophysiology of the liver using hepa-

Table 1. Investigation of the hepatoprotective potential of the marketed drug's composition

S. No.	Plants present in formulations	Branded Ayurvedic formulation	Company
1	*Terminalia arjuna, Tamarix gallica, Solanum nigrum, Cichorium intybus, Cassia occidentalis, Capparis spinosa, Achillea millefolium.*	LIV 52®	Himalaya Drug, Bangalore
2	*Apium graveolens, Asteracantha longifolia, Cassia angustifolia, Trachyspermum ammi, Trigonella foenum-graecum, Andrographis Paniculate.*	LIVERGEN®	Standard Pharma. Serampore, West Bengal
3	*Trigonella foenum-graecum, Terminalia chebula, Terminalia arjuna, Andrographis paniculata, Tephrosia purpurea, Apium graveolens, Solanum nigrum, Berberis lyceum, Cichium intybus, Plumbago zeylanica, Cyperus rotundus, Carum copticum, Ipomaea turpethum, Ecplita alba, Picrrorhiza kurroa, Hygrophila spinosa, Oldenlandia corymbosa.*	LIVOKIN®	Herbo-med, Kolkata
4	*Phyllanthus niruri, Arogyavardhini rasa.*	OCTOGEN®	Plethico pharma. Ltd., Indore
5	*Justicia procumbens Eclipta alba, Phyllanthus niruri, Andrographis Paniculata.*	STIMULIV®	Franco- Indian Pharma. Pvt. Ltd., Mumbai
6	*Terminalia chebula, Tephrosia purpurea, Solanum nigrum, Phyllanthus niruri, Picrorhiza kurroa, Andrographis paniculata, Ecplita alba, Piper longum.*	TEFROLIV®	TTK Pharma Pvt. Ltd., Chennai
7	*Picrorhiza kurroa, Andrographis paniculate, Phyllanthus amarus, Boerhaavia diffusa, Azadirachta indica, Triphala (Terminalia chebula, Terminalia bellirica, Emblica officinalis), Eclipta alba, Zingiberis officinalis, Piper longum.*	HEPATOCARD®	Surajmani Enterprises, Daman
8	*Phyllanthus urinaria, Embelia ribes, Taraxacum officinale, Nyctanthes arbortristis, Terminalia arjuna, Tecoma undulata.*	KAMALAHAR®	Khatore Ayurvedic Pharma., Barbil Orissa
9	*Berberis aristata, Eclipta alba, Cichorium intybus, Tinospora cordifolia, Trigonella foenumgraecum, Boerhaavia diffusa, Paunella domestica, Heliotropum strigosum.*	LIV-77®	Globe Pharmaceuticals, Jalandhar
10	*Andrographis paniculata, Eclipta alba, Ficus religiosa, Tephrosia purpurea, Citrulus colocynthis, Terminalia chebula, Piper chaba, Zingiber officinale, Baliospermum montana, Cassia sophera, Plumbago zeylanica, Boerhaavia diffusa, Lawsonia inermis, Trachyspermum ammi, Salvadora persica, Acorus calamus, Operculina turpethum, Embelia ribes, Jateorhiza palmata, Tinospora cordifolia, Aphanamixis olystachya, Ocimum sanctum.*	LIVIN®	Arya Aushadhi Pharm., Indore
11	*Andrographis paniculata, Senna angustifolia, Trigonella foenumgraecum, Glycyrrhiza glabra, Odenlandia corymbosa, Trachysparmum ammi, Asteracantha longifolia.*	LIVATONA®	Scientific Research Industries, Lucknow
12	*Solanum xanthocarpum, Oldenlandia corymbosa, Boerhaavia diffusa, Eclipta alba, Hygrophila spinosa, Aphanamixis polystachya, Tinospora cordifolia, Carum copticum, Embelia ribes, Cassia angustifolia, Holarrhaena antidysentrica, Andrographis paniculata, Piper nigrum, Aloe indica.*	LIVODIN®	Madona Pharm. Res., Calcutta
13	*Aconitum heterophyllum, Piper longum, Tamarix gallias, Embelia ribes, Achillea millifolium, Swertia chirata, Cassia occidentalis, Solanum nigrum.*	LIVER®	Bhatiya Aushadh Normanshala, Gujarat
14	*Triphala (Terminalia chebula, Terminalia bellarica, Emblica officinalis), Tinospora cordifolia, Phyllanthus niruri.*	LIVOZON®	Hind Chemicals, Kanpur
15	*Cassia angustifolia, Melia azedarach, Oldenlandia corymbosa, Picrorhiza kurroa, Rubia cordifolia, Andrographis Paniculata.*	LIVER RIN®	Herbs ERA Pharm., West Bengal
16	*Trachyspermum ammi, Trigonella foenum-graecum, Asteracantha longifolia, Apium graveolens, Oldenlandia corymbose, Andrographis Paniculata.*	LIVOPEP®	Anakam Lab., Calcutta
17	*Kutki, Guggulu, Triphala, Shilajeet, Chitrak, Neem Juice.*	LIVER DETOX®	Gynoveda, Mumbai
18	*Makoy, Apamar, Jhau, Dugdh Feni, Kaal megh, Rohitak, Sarpunkha, Kashni, Vidanga, Harshringar, Daru Haridra.*	LIVER RE-LIVE® Juice	Krishna's Herbal and Ayurveda, Rajasthan
19	*Jasada Bhasma, Punarnavadi, Mandur Bhasma, Gokshuradi Churna, Tankana Bhasma, Kalmegh Bringaraj, Surakshara Kaseesa.*	LIVERCURE®	Jammi Pharmaceuticals, Chennai
20	*Daruhaldi (Berberis aristata), Kutki (Picrorhiza kurroa), Punernva (Boerhaavia diffusa), Bhringraj (Eclipta alba), Kasni (Chichorium intybus), Bhumyamalki (Phyllanthus niruri), Sarpankha (Tephrosia purpurea).*	LIVOCAP®	Ikvans Pharma

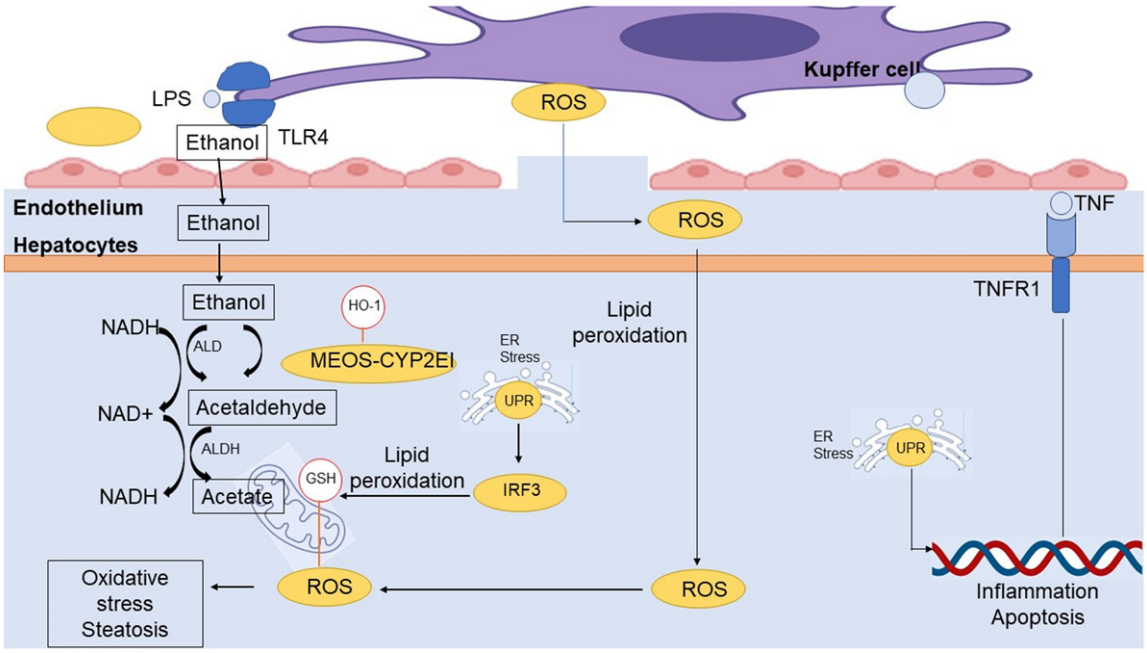

Figure 2. Ethanol metabolism and hepatocyte damage. Abbreviations: ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase; CYP2E1, cytochrome P450 2E1; ER, endoplasmic reticulum; GSH, reduced glutathione; HO-1, heme oxygenase 1; IRF3, interferon regulatory factor 3; LPS, lipopolysaccharide; MEOS, microsomal ethanol oxidation system; NAD, nicotinamide adenine dinucleotide; ROS, reactive oxygen species; TNFR1, tumor necrosis factor receptor 1; TLR-4, Toll-like Receptor 4; UPR, unfolded protein response.

tocytes and examines existing herbal extracts and Ayurvedic interventions for their ability to prevent ROS. Additionally, clinical studies provide insights into the tools, standards, and responsibilities for managing chronic liver disease. The aim is to showcase the potential of herbs in treating liver disease evaluating their safety and efficacy.

Traditional medicine offers a promising avenue for managing liver disease by harnessing the power of herbs. This review aims to shed light on the effectiveness of herbal interventions and their role in reducing ROS-mediated liver damage. It also highlights the importance of clinical studies in establishing credibility and understanding the practical aspects of using herbal treatments in liver disease. Overall, this review emphasizes the use of herbal remedies for managing and treating chronic liver disease, considering their natural therapeutic properties, safety profiles, and cost-effectiveness.

Cell injury and metabolism of ethanol in alcoholic liver disease (ALD)

Fatty liver disease rarely causes noticeable symptoms, but it is a crucial warning sign of harmful alcohol consumption levels [14, 15]. Due to its small molecular size, ethanol readily permeates through cell membranes. Various factors, such as gender, age, identity, and body weight, can influence the absorption and metabolism of ethanol. Organs like the lungs, kidneys, and sweat glands rapidly eliminate more than 10% of ethanol in its original form [16, 17]. The primary metabolic process for ethanol within living cells is its oxidation into acetaldehyde, as depicted in (**Figure 2**). MEOS stands for Alcohol dehydrogenase, and the system is responsible for microsomal ethanol oxidation, which plays a significant role in converting ethanol to acetaldehyde, generating ROS. ROS induces endoplasmic reticulum (ER) stress, oxidative stress, and steatosis. Moreover, the stimulation of NADPH oxidase in Kupffer cells produces ROS [18]. These modifications in hepatic cell metabolism contribute to inflammation and apoptosis.

Apart from oxidation, ethanol can be metabolized through catalase and the system for microsomal ethanol oxidation. However, catalase is present in small quantities in the liver. At the same time, the system for microsomal ethanol oxidation depends on specific cyto-

chromes P450, notably CYP2E1. Irrespective of the particular routes engaged, the predominant conversion of acetaldehyde occurs through aldehyde dehydrogenase, present in both the cytoplasm and mitochondria, leading to the formation of acetate. The NAD+/NADH ratio facilitates this process and results in an increased concentration of NADH in the liver. Since hepatocytes contain aldehyde dehydrogenase and alcohol dehydrogenase CYP2E1, they are particularly susceptible to ethanol's direct cellular toxicity [19-21].

Ethanol metabolism is exacerbated by the release of proinflammatory cytokines, hypoxia, and bacterial translocation, resulting in the accumulation of ROS, such as superoxide anion (O_2^-) and hydrogen peroxide (H_2O_2) [22, 23]. These released radicals readily interact with iron or ethanol atoms, giving rise to metabolically active byproducts such as hydroxyethyl radical (CH_3CHOH), hydroxyl radical (OH-), or ferrous oxide (FeO). These reactive metabolites contribute to the peroxidation of cell membrane lipids. Kupffer cells (via NADPH oxidase), mitochondria (through the respiratory chain), and the endoplasmic reticulum (via CYP2E1) serve as the primary contributors of ROS. Additionally, iron plays a role in oxidative stress during alcohol-induced liver damage and promotes fibrosis by catalyzing ROS production [24, 25]. In summary, chronic alcohol consumption leads to fatty liver disease, with ethanol metabolism resulting in the generation of ROS and subsequent cell damage. This process involves the oxidation of ethanol into acetaldehyde, activating various enzymes and systems, and accumulating ROS, resulting in inflammation, oxidative stress, and hepatic injury. Understanding the intricate mechanisms of ethanol metabolism and its consequences is crucial for explaining the progression and development of alcohol-related liver diseases.

Redox in pathological hepatocytes

Redox plays a significant role in cell function and dysfunction in pathological hepatocytes. Elevated generation RNS and ROS and impaired oxidation protective mechanisms disrupt the delicate balance of redox homeostasis [25, 26]. Pathologic conditions, such as liver diseases, result in elevated ROS generation primarily from dysfunctional enzymes like NADPH oxidase and CYP2E1 and mitochondria. The resulting oxidative imbalance causes DNA damage, lipid peroxidation, and protein oxidation, contributing to inflammation, fibrosis, and hepatocellular injury. An imbalanced redox state activates signaling pathways that perpetuate inflammation and cell death [27].

Alongside ROS, RNS, including peroxynitrite (ONOO-) and oxidative stress, causes lipid peroxidation, protein oxidation, and DNA damage, influencing redox signaling. Excessive NO production leads to the formation of peroxynitrite, which contributes to cellular damage. The disrupted redox balance in pathological hepatocytes is associated with hepatic problems such as liver fibrosis, alcoholic liver disease, nonalcoholic fatty liver disease, and viral hepatitis [28]. Restoring redox homeostasis in pathological hepatocytes is a therapeutic approach for mitigating oxidative stress. Antioxidant therapies aim to scavenge ROS and reduce oxidative damage. Preclinical and clinical studies have explored the use of artificial and natural antioxidants to restore redox balance and alleviate liver disease progression [29]. In summary, redox imbalance in pathological hepatocytes increases ROS and RNS production, impairing antioxidant defense mechanisms. This disruption leads to oxidative stress, inflammation, and liver injury. Therapeutic strategies targeting redox homeostasis offer the potential for managing liver diseases by reducing oxidative stress and restoring cellular function.

Transplantation-associated ischemia/reperfusion injury

This injury can occur in two primary circumstances: following surgical intervention or transplant, or resulting from hepatic anorexia, ischemia, or conditions of systemic hypoxia/low flow linked to infection or trauma. Preexisting liver conditions and the duration of the insult influence the severity of the injury. Warm ischemia/reperfusion is characterized by an exacerbated redox imbalance and mitochondrial dysfunction, leading to liver cirrhosis and damage to multiple organs.

Transplantation-related injury occurs when cold ischemia impairs cellular respiration, reduces ATP levels, and promotes elevated glucose metabolism. Fundamental conditions such as cirrhosis and steatosis make the hepatic more vulnerable to impaired function.

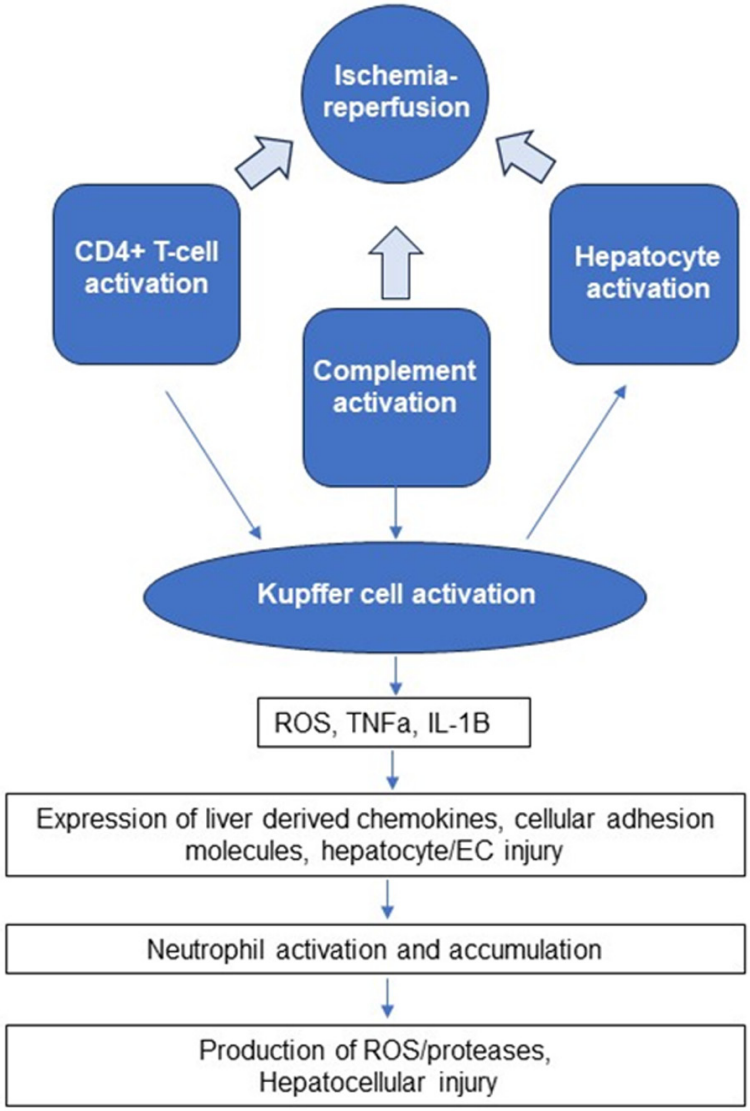

Figure 3. Immune responses in ischemia-reperfusion injury.

In contrast, preparations such as embolization or preoperative chemotherapy can increase hepatic susceptibility to hypoxic stress [30]. Ischemia-reperfusion injury frequently leads to primary graft dysfunction, resulting in heightened mortality and morbidity rates during liver transplantation. **Figure 3** shows that a high generation of reactive oxygen species ROS and RNS, as well as the depletion of antioxidants in conjunction with apoptosis and cell death, can, at least in part, be attributable to ischemia and reperfusion injury. ROS and RNS species are produced when there is hypoxia, leading to more significant cell injury. As a subsequent response to hypoxia, the mitochondria first undergo a reduction due to changes in the respiratory chain. As a result, there is a decrease in adenosine triphosphate (ATP), which disrupts membrane ions and leads to sodium inflow as the ATP-dependent sodium/potassium ATPase is inhibited. The cell may enlarge and break due to the ensuing sodium inflow [31]. Calcium that builds up inside cells activates a phospholipase that breaks down phospholipids and damages membranes. Cells enlarge, lysosomes are damaged, walls rupture, producing cell spillage, and mitochondria become more porous [32, 33]. Reactive oxygen species, TNFα, and IL-1β are produced due to the first complement and T-cell activation during ischemic/reperfusion injury. Chemokines, neutrophil activation, elevated ROS, and hepatocellular damage happen in the late phase.

Sepsis-induced liver injury

Fever, tachycardia, tachypnea, and increased leucocytes are the hallmarks of sepsis, a clinical illness brought on by a systemic inflammatory response following a bloodstream infection. It is recognized that pathogens, such as bacteria, viruses, and parasites, can cause ROS/RNS, along with NO (nitric oxide). Depending on the pathogen's pathogenicity and the host's immune response, sepsis entails a widespread inflammatory response that impacts many body functions. The main topic of conversation is the influence of NO on hepatocytes during sepsis. Numerous liver functions make NO defensive against these pathogenic intruders. NO can enter these organisms during sepsis and harm their lipids, proteins, enzymes, and DNA. By reducing lipid peroxidation and collagen deposition, NO reduces the oxidative imbalance caused by exogenous compounds such as carbon tetrachloride (CCL4) and hypochlorite (ClO-) [34]. L-arginine therapy was observed to

Table 2. Overview of antioxidant medications for hepatic ischemia-reperfusion injury with beneficial results

Antioxidant	Category	Species	Injury type
α-Tocopherol	Vitamin-based diet	Rat	Warm Ischemia (WI)
α-Tocopherol	Vitamin-based diet	Rat	Warm Ischemia/Cold Ischemia (WI/CI)
α-Tocopherol/Ascorbate	Vitamin-based diet	Clinical	Warm Ischemia (WI)
Ascorbate	Vitamin-based diet	Rat	Warm Ischemia (WI)
Coenzyme Q/pentoxyfylline	In vivo low molecular mass agent	Rat	Warm Ischemia (WI)
Idebenone	Coenzyme Q derivative	Pig	Cold Ischemia (CI)
Lipoic acid	In vivo low molecular agent	Rat	Cold Ischemia (CI)
Desferrioxamine	Iron chelator	Dog	Cold Ischemia/Warm Ischemia (CI/WI)
Trimetazidine	Metal chelator	Rat	Warm Ischemia (WI)
Quercetin	Plant phenol	Rat	Warm Ischemia (WI)
Cyanidin	Plant phenol	Rat	Warm Ischemia (WI)
Extracts of green tea	Plant extracts (catechins)	Rat	Warm Ischemia (WI)
Extract of Magnifera indica	Plant extract	Rat	Warm Ischemia (WI)
Alpha-glutathione S-transferase	Low: molecular weight molecule in vivo study	Rat	Warm Ischemia (WI)
Alpha-glutathione S-transferase	Low: molecular weight molecules in vivo study	Rat	Cold Ischemia/Warm Ischemia (CI/WI)
N-acetylcysteine	Thiol compounds	Rabbit	Warm Ischemia (WI)
N-acetylcysteine/melatonin	Thiol compound	Rat	Warm Ischemia (WI)
N-acetylcysteine	Thiol compound	Clinical	Cold Ischemia/Warm Ischemia (CI/WI)
Derivatives of SOD	Intracellular catalyst	Rat	Warm Ischemia (WI)
Derivatives of CAT	Intracellular catalyst	Rat	Warm Ischemia (WI)
Allopurinol	Inhibitor of xanthine oxidase	Rat	Warm Ischemia (WI)
Aminoguanidine	iNOS inhibitor	Pig	Cold Ischemia/Warm Ischemia (CI/WI)

reduce the production of collagen, the extent of enzymes in the liver, and the loss of glycogen but had no impact on lipid peroxidation. When combined with L-NMMA, IFN-γ can enhance the clearance inside the cell of plasmodial parasites within hepatocytes infected with malaria [35].

Iron overload in hepatic disorders

Hemochromatosis, inherited severe alpha and beta thalassemia, myelodysplastic syndrome (MDS), sideroblastic anemias, and chronic liver disorders are among the conditions that can lead to excessive iron deposition in the liver. The buildup of ferric ions disrupts oxidation-reduction. Balance within the liver's cells leads to oxidation imbalance. Elevated iron levels facilitate heightened lipid peroxidation and oxidative damage to subcellular organelles, notably impacting mitochondria's structural and functional integrity. The combination of transition metal iron and oxygen in the Haber-Weiss reaction can generate ROS (**Table 2**). The catalytic properties of iron can intensify the cytotoxic effects caused by other substances that generate ROS, including alcohol, viruses, or toxins.

Iron overload further contributes to liver fibrogenesis, cirrhosis, and hepatocyte damage, evidenced by increased levels of procollagen α1, TGF-β1, and lipid peroxidation. The reactive oxygen species generated by utilizing the Haber-Weiss process target lipids that possess carbon-carbon double bonds, resulting in the production of lipid hydroperoxides and free radicals such as alkoxyl (RO-) and peroxyl (ROO-) free radicals. In cases of iron overload, non-alcoholic liver disease levels are relatively high, while toxic hydroxy alkenes levels are often low. Patients with iron overload also exhibit elevated levels of ethanol DNA adducts, indicating lipid peroxidation. Although the function of nitric oxide (NO) in hemochromatosis is not well understood, an increase in the manifestation of inducible nitric oxide synthase (iNOS) in the liver suggests an additional source of reactive nitrogen species (RNS). Hemochromatosis patients with excessive iron absorption from food exhibit high levels of HNE-protein and MDA-protein, indicating increased lipid peroxidation. Experimental animal models of iron accumulation also demonstrate collagen type 1 deposition, resembling the pathophysiology of hereditary hemochromatosis in humans [36]. **Table 2** provides an overview of various

antioxidant medications and their effectiveness in treating liver reperfusion injury. The antioxidants listed in the table include α-Tocopherol, ascorbate, Coenzyme Q/pentoxyfylline, Idebenone, Lipoic acid, Desferrioxamine, Trimetazidine, Quercetin, Cyanidin, Green tea extracts, *Magnifera indicia*, GSH, N-acetylcysteine, SOD derivatives, CAT derivatives, Allopurinol, and Aminoguanidine. These antioxidants belong to different categories: vitamin diet, in vivo low molecular weight (LMM) agents, coenzyme Q derivatives, iron chelators, metal chelators, plant phenols, plant extracts, and intracellular enzymes. They have been studied in various species, including rats, pigs, dogs, and rabbits, and clinical trials.

The types of liver injury targeted by these antioxidants include warm ischemia (WI), cold ischemia (CI), and a combination of both (CI/WI). The beneficial results of these antioxidant interventions vary depending on the specific antioxidant and the type of injury being treated. Regarding the scope of future herbal or Ayurvedic interventions, it is worth noting that some antioxidants in the table are derived from natural sources such as plants and plant extracts, such as Quercetin, Cyanidin, and green tea extracts, which suggests the potential for exploring herbal or Ayurvedic interventions for liver reperfusion injury. Further research and studies on herbal or Ayurvedic antioxidants could help identify new interventions with benefits in treating liver reperfusion injury. Traditional medicinal systems like Ayurveda offer a rich repository of herbal remedies and antioxidant-rich plant extracts that could be investigated for their efficacy in combating oxidative stress and promoting liver health.

However, it is essential to conduct rigorous scientific studies and clinical trials to evaluate these herbal interventions' safety, efficacy, and optimal dosage. Collaboration between traditional medicine experts and modern medical researchers can help bridge the gap and explore the potential of herbal or Ayurvedic interventions in managing liver reperfusion injury.

Alcohol-induced liver disease

Studies have explored the administration of single antioxidants and combined antioxidant treatments to address alcohol-induced liver damage. The choice of antioxidants is often based on previous research indicating an insufficient antioxidant level in individuals with this condition.

One study by Wenzel et al. demonstrated that D-alpha-tocopherol, Selenium, and zinc provided adequate treatment for individuals with acute alcohol-induced hepatitis. The mortality rate significantly decreased from 40% to 6.5% in patients who received supplemental antioxidant therapy compared to control subjects [36]. However, other trials investigating the combination of antioxidants as therapeutic interventions for alcohol-induced liver damage did not yield similarly promising results. In the management of acute ethanol-induced hepatitis, the use of a blend of free radical scavengers instead of corticosteroids reduced sepsis and death within a shorter period (1 month) but did not have long-term benefits (1 year) compared to corticosteroid-treated patients [37]. It was not until Stewart et al. conducted a study examining the outcomes of exclusive antioxidant treatment or in combination with corticosteroids in acute alcohol-induced hepatitis that a proper control group with corticosteroids and antioxidants was established [38]. The free radical scavenger treatment combined Selenium, zinc, copper, magnesium, folic acid, coenzyme Q, N-acetylcysteine, vitamins A-E, biotin, and manganese. However, none of these interventions, whether administered individually or combined with corticosteroids, demonstrated improvement in the 6-month survival rate. Vitamin E administration for alcoholic liver damage has shown mixed results.

In a study, vitamin E treatment improved compensation in stationary pattern alcoholic cirrhotic patients, with reduced hyaluronic acid levels in mild to moderate alcoholic hepatitis. However, no additional improvements were observed in liver function tests [39]. A meta-analysis by Miller et al. reported increased all-cause mortality in patients with various medical conditions following high-dose vitamin E treatment. However, the clinical significance of this finding remains unclear due to significant patient variability [40]. Adenosylmethionine (SAMe), a methylating agent, has shown promise as a treatment for alcohol-induced liver damage. It acts as a precursor to glutathione, regulates cytokine metabolism, and possesses antioxidant properties. SAMe treatment im-

proved mortality rates and reduced the need for transplantation in alcohol-induced liver damage [41]. The collective evidence suggests that SAMe or a combination of antioxidant treatments may be more effective than vitamin E treatment for alcoholic hepatitis. However, due to the diversity of the research findings, definitive conclusions cannot be drawn. Further studies are needed to explore antioxidants' effectiveness and optimal combinations in treating alcohol-induced hepatic damage.

Viral hepatitis

Although using antioxidants to reduce infectious diseases has yielded mixed results in animals and humans, there is significant involvement of (RNS/ROS) in the initiation and progression of hepatitis C and its malignant transformation [42-44]. Limited data from von Herbay et al. suggested that vitamin E improved aminotransferase levels in patients with a specific condition. Look et al. found that patients treated with a combination of IFN-α and vitamin E showed better overall improvement and lower viral load than those treated with IFN-α alone. While these studies have limitations, they raise interesting research questions [45].

The most comprehensive human studies on the impact of antioxidants in the context of hepatitis C virus (HCV) infection have been undertaken. In a particular study, individuals with chronic HCV infection received a blend of oral antioxidants, including silymarin, lipoic acid, Schisandra, glycyrrhizin, L-glutathione, ascorbic acid, and alpha-tocopherol. As a result of this treatment, there were notable enhancements in viral load (25%), liver enzymes (44%), histologic changes (36%), and life expectancy [46] in another phase 2 trial, which was double-blinded, randomized, and placebo-controlled, the effectiveness of intravenous and orally administered antioxidants as compared to patients with chronic hepatitis C. Patients receiving a combination of oral and IV antioxidant therapy showed improvements in liver function, histopathology, and virological parameters. In contrast, those receiving only oral medication did not significantly improve [47]. These observations indicate a potential benefit of antioxidant treatment, although the administration methods in these studies differed. Additional investigation is required to ascertain the optimal types, dosages, and delivery methods of antioxidant drugs.

In summary, while antioxidants have shown possible benefits in improving liver function and lowering the viral load in persons with prolonged hepatitis C, the results of studies have been varied. Subsequent investigations should prioritize the refinement of antioxidant utilization, encompassing the identification of optimal combinations, dosages, and administration routes. This approach aims to maximize the therapeutic efficacy of antioxidants within the framework of infectious hepatic problems.

Non-alcoholic fatty liver disease (NAFLD)

NAFLD is a prevalent liver condition marked by fat buildup in the liver cells, leading to inflammation and liver damage. Redox imbalance, which involves an altered balance between ROS and antioxidants, plays a crucial pathogenic function and progression of NAFLD [48]. Elevated oxidative imbalance and impaired antioxidant protective systems contribute to liver cell injury, inflammation, and fibrosis in NAFLD. In NAFLD, excess liver fat accumulation increases lipid peroxidation, generating ROS and triggering oxidative stress. ROS can cause harm to cellular structure, including DNA, lipids, and protein, and promote inflammation and fibrosis. Moreover, ROS-induced mitochondrial dysfunction further exacerbates oxidative imbalance and contributes to the progression of NAFLD [49].

Protective antioxidant systems are essential in maintaining redox homeostasis and shielding liver cells from oxidative harm [50]. However, in NAFLD, these antioxidant systems are often compromised. Decreased levels of endogenous antioxidants, such as glutathione, and impaired antioxidant enzyme activities, including catalase and superoxide dismutase, disrupt the clearance and production of ROS. Given the involvement of redox imbalance in NAFLD, there is growing interest in the use of herbal drugs and herbal treatments to modulate oxidative stress and improve liver health. Herbal medicines derived from various plant sources possess diverse bioactive substances with antioxidant and anti-inflammatory properties. These compounds can scavenge ROS, enhance antioxidant defense mechanisms, and attenu-

ate hepatic oxidative stress [51]. Several herbal drugs and treatments have shown promise in preclinical and clinical studies for NAFLD management. For example, curcumin, derived from turmeric, demonstrates strong antioxidant properties and anti-inflammatory effects and has demonstrated efficacy in improving liver steatosis, inflammation, and fibrosis in NAFLD models. Other herbs, such as silymarin (derived from milk thistle), resveratrol (found in grapes and berries), and green tea extract, have also shown beneficial effects on oxidative stress and liver health in NAFLD [52].

Furthermore, traditional herbal formulations, such as Ayurvedic medicines, often combine herbs targeting pathways involved in NAFLD pathogenesis, including oxidative stress. These formulations may include herbs like Andrographis paniculata, Picrorhiza kurroa, and Phyllanthus niruri, which possess antioxidant and hepatoprotective properties [53-55]. While the potential of herbal drugs and treatments for NAFLD is promising, further research is needed to validate their efficacy, determine optimal dosages and treatment duration, and understand their mechanisms of action. Standardized formulations, rigorous clinical trials, and mechanistic approaches are necessary to investigate the purpose and function of herbal interventions in managing NAFLD and to integrate them into evidence-based treatment approaches.

In this view, redox and oxidative imbalance play a significant role in the progression and development of NAFLD. Herbal drugs and herbal treatments are potentially adjunctive therapeutic options for NAFLD, targeting oxidative stress and improving liver health. However, further research is required to establish their effectiveness and safety profiles, paving the way for developing herbal interventions to manage NAFLD.

Liver cirrhosis

Several factors contribute to ROS production in liver cirrhosis. Chronic liver injury, such as that caused by viral hepatitis, alcohol abuse, or NAFLD, triggers inflammation and immune responses, resulting in the secretion of inflammatory mediators and immune cell stimulation. These activated cells, such as Kupffer cells and neutrophils, generate large amounts of ROS in the inflammatory process [56].

The sustained presence of ROS in liver cirrhosis leads to oxidative stress, which causes damage to various cell components, including proteins, DNA, and protein. Lipid peroxidation, initiated by ROS, generates toxic byproducts that further exacerbate liver injury and inflammation [57]. Moreover, oxidative stress disrupts cellular signaling pathways, impairs mitochondrial function, and promotes fibrogenesis, contributing to the advancement of hepatic fibrosis and cirrhosis.

In addition to direct damage, ROS stimulates hepatic stellate cells (HSCs), the key players in hepatic fibrosis. ROS stimulates HSCs to activate and transform into myofibroblasts, responsible for excessive extracellular matrix production and scar tissue formation [58], perpetuating the fibrotic process and leading to the architectural distortion and functional impairment characteristic of liver cirrhosis. Antioxidant defense mechanisms, including enzymatic antioxidants (such as superoxide dismutase, catalase, and glutathione peroxidase) and non-enzymatic antioxidants (such as glutathione and vitamins C and E), are essential for counteracting ROS and maintaining redox homeostasis. However, in liver cirrhosis, antioxidant defenses are often compromised due to reduced antioxidant enzyme activity, depletion of antioxidant reserves, and increased consumption of antioxidants in response to oxidative stress. Overall, the disruption between the production of ROS and protective mechanisms in liver cirrhosis leads to sustained oxidative stress, which contributes to liver injury, inflammation, fibrosis, and the progression of cirrhosis [59]. Understanding the role of ROS and oxidative stress in liver cirrhosis provides valuable insight for developing therapeutic strategies to target oxidative stress and mitigate disease progression.

Ayurvedic concept

Ayurveda, as described in classic texts like Caraka Samhita, Susruta Samhita, Astanga Hrudaya, and others, addresses liver conditions like cirrhosis, cholelithiasis, and various specific disorders including Kumbha Kamala, Yakritpliha Dara, Yakrit Kshaya, Jalodara, Kamala, Yakritdalhadara, and Halimaka Pandu.

Treating hepatobiliary diseases in Ayurveda often involves managing abdominal disorders known as Udara roga. Panchakarma, a comprehensive detoxification procedure, is recommended for treating Shakha srita kamala, and the specific purification technique called virechan (medicated purgation) is considered optimal. Additionally, Ayurvedic formulations such as kokilashyadi kasaya, kumaya sava, PatolaKaturohinyadi kashayam, rohitakarista, yakrit plihadara churna, yakritdari lauha, punnanvadi kasaya, yakrit plihadari lauha, Arogya vardhini vati, rohitaka lauha, lokanath rasa, and yakritdari lauha are used for liver diseases [60]. The usage of traditional healers and herbal remedies in the treatment of liver illness is prevalent in our nation. According to a study conducted by Seef et al. (2001), it was discovered that 41% of individuals with hepatic illness reported a history of herbal remedy usage [61]. Medicinal plants with properties like Kapha nasak (reducing Kapha), agnivardhaka (carminative), vata samaka (balancing Vata), rechana (purgative), mutrala (diuretic), ama, and meda are preferred for treating hepatic biliary problems. Some examples of such plants include Phyllanthus niruri (Phyllanthin), Picrorhiza kurroa (Picroliv), Andrographis paniculata (Andrographiloid), Eclipta alba (Wed elolactone), and Glycyrrhiza glabra (Glycyrrhizin). Curcuminoids from Curcuma longa (turmeric) have shown hepatoprotective effects in animal models by activating antioxidant enzymes [62]. The hepatoprotective mechanism involves the regulation of nuclear factor-κB activation, prevention of hepatocyte apoptosis, heme oxygenase-1 activity stimulation, inhibition of NO production, and are involved in the stimulation of heme oxygenase-1 activity [63]. Ayurvedic therapies like Rohitaka grita, Amalaki grita, Panchakola grita, and Panchagabya grita are recommended for managing and treating hepatic disorders. Virechana (medicated purgation) is the preferred treatment for liver disorders, particularly Jalodara [64]. Clinical studies have also shown the effectiveness of Vardhama pippali yoga in hepatic cirrhosis (Patel et al., 2015) (**Table 3**).

Mechanisms of action of herbal remedies in ameliorating the redox imbalance in chronic liver diseases

Herbal medicines and formulations are often categorized based on the plants used or the compounds extracted from those plants. However, when it comes to treating prolonged hepatic disorders, it is essential to identify specific plants or potential compounds that target receptors or mechanisms related to the disease, significant in ethanol-induced hepatic disorders, which can be treated using herbal remedies. The positive effects of medicinal herbs in chronic liver disease may be attributed to several mechanisms. These encompass various beneficial effects, such as anti-inflammation, facilitation of mitochondrial fatty acid β-oxidation, antioxidation, and suppression of de novo lipid synthesis within the liver. These mechanisms help combat oxidative stress, reduce inflammation, regulate lipid metabolism, and reduce the decomposition of fatty acids in the liver. **Figure 4** illustrates the interplay between these mechanisms and how medicinal herbs can positively impact chronic liver disease. By targeting these specific mechanisms, herbal remedies may benefit individuals with chronic liver disease. It is worth noting that further research and scientific investigation are necessary to identify the specific plants and compounds that exhibit the desired effects on the target receptors involved in ethanol-induced liver disease pathogenesis.

Amelioration of oxidative stress by herbal remedies

Now widely acknowledged is the role that ethanol-mediated chronic damage plays in developing chronic liver disease [65]. Alcohol consumption acutely and chronically raises ROS generation, such as superoxide, hydroxyl radicals, and hydrogen peroxide. It lowers cellular antioxidant capacity, which leads to free radical damage in many organs, particularly the liver [66]. Because alcohol can interact with many of these biological components to inactivate enzymes or denatured proteins, damage DNA, and increase lipid peroxidation of cellular membranes, alcohol-induced Production of ROS is harmful to hepatocytes and creates a vicious cycle where oxidative stress tries to interfere with biological processes, and ROS production increases [66]. Antioxidative stress is crucial in how herbal remedies guard against alcohol-induced liver damage. It has been demonstrated that 30 of the 34 retrieved herbal remedies or components have solid antioxidant action through various routes.

Table 3. Evidence for preclinical hepatoprotective effect of medicinal plants

S. No	Botanicals	Compounds/Extracts	Effective Dose	Animal study	Functions/Mechanisms
1	Antrodia camphorate, Also known as *Antrodia cinnamomea Chang & Chou* (Polyporaceae)	Ethanolic extract	95.6 and 47.8 mg/kg	Acute ethanol-Sprague-Dawley rats	Antioxidation: kMDA; mGSH; mGPX; mSOD
2	*Agrimonia eupatoria L. (Rosaceae)*	Hydro extract	30 mg/kg	Chronic ethanol-fed Sprague-Dawley rats	Antioxidation: kMDA; mGSH Antiinflammation: kTNF-a; kIL-6; kTLR4; kNF-kB; kMyD88; kCOX-2
3	Barley, also known as *Hordeum vulgare L. (Poaceae)*	Preparation through fermentation	Not given	Chronic ethanol-fed Wistar rats	Antioxidation: mGPX; mSOD; mCAT; kMDA
	Oryza sativa L. Japonica (Poaceae)	Extract rich in anthocyanins	500 mg/kg Caffeine (at doses of 5, 10, and 25 mg/kg)	Chronic ethanol-fed Kunming mice	Antioxidation: kROS; kMDA; mSOD; mGPX Antiinflammation: kTNF-a; kIL-1b; kIL-6; kMCP-1 FA synthesis: kSREBP-1c; kFAS; kACC; kSCD-1
4	Cajanus cajan Linn also known as *Cajanus cajan (L.) Millsp. (Leguminosae)*	Extract of leaf	50 mg/kg	Chronic ethanol-fed Sprague-Dawley rats	Antioxidation: mGSH; mSOD; mCAT; mGST
5	*K. Koch (Juglandaceae) and Carya illinoensis (Wangenh.)*	The Pecan nutshell can be used to obtain an aqueous extract	3327 mg/kg	Chronic ethanol-fed Wistar rats	Antioxidation: mGSH; mCAT; mSOD
6	Cinnamon, also known as *Cinnamomum verum J. Presl (Lauraceae)*	Alcoholic bark extract	Not given	C57BL/6 mice subjected to acute alcohol exposure	Antiinflammation: kMyD88
7	*Cusson (Apiaceae) Cnidium monnieri (L.)*	Osthole	20 and 40 mg/kg	Kunming mice subjected to chronic alcohol exposure	Antioxidation: kMDA; mGSH Antiinflammation: kTNF-a
8	*Curcuma longa L. (Zingiberaceae)*	Curcumin	200 and 600 mg/kg	Kunming mice subjected to chronic alcohol exposure	Antioxidation: kMDA Antiinflammation: kNF-kB
9	*Theobroma cacao L. (Malvaceae)*	Flavonoid extract	400 mg/kg	Chronic ethanol-fed Sprague-Dawley rats	Antioxidation: kMDA Antiinflammation: kNF-kB
10	*Corn, also known as Zea mays L. (Poaceae)*	Corn oligopeptides	900 mg/ kg	Chronic ethanol-fed Wistar rats	Antioxidation: mSOD; kMDA
11	*Ecklonia cava Kjellman (Phaeophyceae)*	Dieckol-rich phlorotannins	25 mg/kg	Chronic ethanol-fed Wistar rats	Antioxidation: mSOD; kMDA
12	*Gentiana manshurica Kitag. (Gentianaceae)*	Methanolic extract	200 mg/kg	BALB/c mice subjected to chronic alcohol exposure	Antioxidation: kMDA; mGSH; mGPX; mSOD; mCAT; kCYP2E1 FA synthesis: kSREBP-1c
13	*Ginkgo biloba L. (Ginkgoaceae)*	Extract of Ginkgo biloba	200 mg/kg	C57BL/6 mice subjected to acute alcohol exposure	Antioxidation: kMDA; mGSH Antiinflammaction: kTNF-a
14	*Green Tea also known as Camellia sinensis (L.) Kuntze (Theaceae)*	Catechin	50 mg/kg	Chronic alcohol-fed S.D. rats	Antioxidation: kMDA; mGSH; mSOD; mCAT Antiinflammation: kNFkB; kTNF-a
15	*Hovenia dulcis Thunb. (Rhamnaceae)*	Semen Hoveniae extract	300 and 600 mg/kg	Chronic alcohol-fed Kunming mice	Antioxidation: kMDA; mGSH; mGST; mSOD
16	*Ligularia fischeri (Ledeb.) Turcz. (Compositae)*	Hydro-extract	200 mg/kg	Chronic ethanol-fed Sprague-Dawley rats	Antioxidation: kMDA; mGSH Antiinflammation: kTNF-a
17	*E.H. Wilson (Magnoliaceae) Magnolia officinalis Rehder*	Ethanolic bark extract.	45 mg/kg	Chronic ethanol-fed Sprague-Dawley rats	Antioxidation: kMDA; mGSH Antiinflammation: kTNF-a
18	*Platycodon grandiflorus (Jacq.) A.DC (Campanulaceae)*	Platycodi radix	Not provided	Chronic ethanol-fed Wistar rats	Antioxidation: mSOD; kMDA
19	*Pueraria lobate (Willd.) Ohwi (Leguminosae)*	Ethanol (70%)	3 g/kg	Chronic ethanol-fed Wistar rats	Antioxidation: mSOD; kMDA
20	*Scutellaria baicalensis Georgi (Lamiaceae)*	Baicalin	200 mg/kg	Chronic ethanol-fed Sprague-Dawley rats	Antiinflammation: kTLR4; kMyD88; kNF-kB; kTNF-a; kIL-6; kCOX-2
21	*Trigonella foenum-graecum (Leguminosae)*	Fenugreek seed polyphenol	200 mg/kg	Chronic ethanol-fed Wistar rats	Antioxidation: mSOD; mCAT; mGPX; mGSH; mVit-E; mVit-C
22	*Ziziphus mauritiana var. abyssinica*	Hydro-extract of leaf	200 and 400 mg/kg	Chronic ethanol-fed Wistar rats	Antioxidation: mGSH

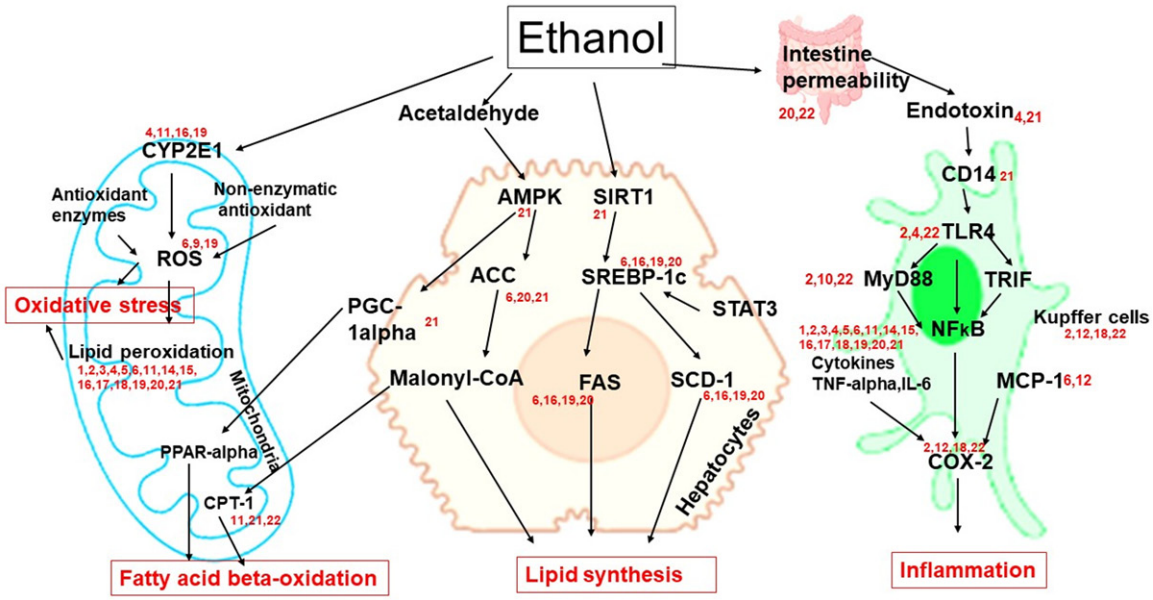

Figure 4. Possible therapeutic targets for various phytoconstituents in alcoholic liver disease. Abbreviations: PPARA, peroxisome proliferator-activated receptor alpha; CPT-1, carnitine palmitoyl transferase I; AMPK, AMP-activated protein kinase; CYP2E1, cytochrome P450 2E1; ER, endoplasmic reticulum; SIRT1, Sirtuin 1; ACC, acetyl-CoA; SREBP-1, sterol regulatory element-binding protein 1; PGC-1, Peroxisome proliferator-activated receptor gamma coactivator 1-alpha; STAT3, Signal transducer and activator of transcription 3; MyD88, Myeloid differentiation primary response 88; TRIF, TIR domain-containing adaptor protein; NFkB, Nuclear factor-κB; MCP-1, Monocyte chemoattractant protein-1; COX-2, cyclo-oxygenase; LPS, lipopolysaccharide; ROS, reactive oxygen species; TNFR1, tumor necrosis factor receptor 1; TLR-4, Toll-like Receptor-4.

Hence, augmenting the levels of these antioxidants can aid in the elimination of ROS and alleviate oxidative stress caused by alcohol consumption. Previous studies have shown that crude extracts or isolated compounds derived from plants such as Cassia auriculata [67] and Pueraria lobata (Willd.) Ohwi (Leguminosae) [68], Hovenia dulcis Thunb. (Rhamnaceae) [69], Antrodia cinnamomea, Green Tea, Ligularia fischeri (Ledeb.) Turcz. (Compositae) (referred to as Ligularia fischeri var. spiciformis Nakai), Ginkgo biloba L. (Ginkgoaceae) (referred to as Ginkgo biloba) (Yao et al., 2007), Trigonella foenum-graecum L. (Leguminosae) (referred to as Trigonella foenum graecum) [70], Cajanus cajan (L.) Millsp. (Leguminosae) (referred to as Cajanus cajan Linn.) [71], and Gentiana manshurica can increase the levels of hydrolytic antioxidants like GSH and enhance the activity of endogenous enzymatic antioxidants such as CAT, GPX, or SOD. Additionally, Hovenia dulcis semen hoveniae extract and Oryza sativa anthocyanin-rich extract have been shown to increase GST activity. Alcohol use depletes endogenous vitamins E and C, the non-enzymatic antioxidants, although fenugreek seed polyphenol and Cassia auriculata leaf water extract can replace them [72, 73].

Anti-inflammatory properties of herbal formulations

Fat buildup makes the liver vulnerable to additional harm, causing infection in the form of inflammation. The development of alcoholic hepatic steatosis into steatohepatitis, defined by an inflammatory infiltrate and hepatocellular destruction, is one example of how inflammation is critical to the pathophysiology and development of ALD [74]. As a result, decreasing inflammation during alcohol consumption may prevent or delay the development of ALD. It has been demonstrated that components from natural remedies, such as betaine and EGCG [73], can lower circulating lipopolysaccharide amounts raised by consuming alcohol. Pueraria lobata's ethanol extract effectively suppresses ALD by reducing the increase in gut microbiome penetration caused by alcohol; this protective role on intestinal barrier stability is linked to the restoration of zonula occludens-1 (ZO-1), a protein that forms an intestine make a critical

barrier [75]. Baicalin, derived from Scutellaria baicalensis Georgi (Lamiaceae), cinnamon bark ethanol extract (Yuan et al., 2006), and aqueous extract of Agrimonia eupatoria L. (Rosaceae) (Yoon et al., 2012), have been documented by Kim and Lee (2012) for their ability to decrease the expression of TLR4 and MyD88, consequently reducing the nuclear translocation of NF-κB. Additionally, curcumin from Curcuma longa and catechin from green tea have shown inhibitory effects on NF-κB activation in the liver [74-76]. Meanwhile, the precise processes driving these impacts still need to be clarified.

Herbal extracts as inhibitors of lipid synthesis

The liver's most prevalent and first reaction to ethanol in alcohol consumption is hepatic steatosis, defined by TG buildup in the hepatocytes. It may represent the beginning of more severe kinds of liver failure. According to solid evidence, alcohol use can slow the development of ALD by lowering the amount of fat that builds up in the liver [77, 78]. Increased lipogenesis, which results in increased de novo fats and TG production in hepatic cells, is one of the most significant pathogenic mechanisms underpinning hepatic TG deposition in ALD. It is now well acknowledged that the transcription factor sterol-regulating element-binding protein-1c (SREBP-1c) controls the expression of more than 30 lipogenic genes, serving as a critical regulation for lipid homeostasis. Scientific investigations have revealed that alcohol consumption-induced increased maturation of SREBP-1c in the liver can be impeded by administering herbal extracts. For instance, ethanol extract from Magnolia Officinalis [79], methanol extract from Gentiana manshurica, and Green Tea extract [80] have demonstrated inhibitory effects. Additionally, certain individual compounds like resveratrol [81], honokiol [82], and caffeine [83] have also been shown to exhibit inhibitory properties on SREBP-1c maturation in the liver.

Herbal extracts as promoters of fatty acid β-oxidation

With the help of the mitochondrial β-oxidation pathway, fatty acids are transported from the cytoplasmic into the mitochondria by the carnitine palmitoyltransferase-1 (CPT-1). Malonyl-CoA production is reduced, and its breakdown rate is accelerated when AMPK-induced inhibition of ACC occurs. Consequently, the decrease in malonyl-CoA levels can alleviate the inhibition of mitochondrial CPT-1, leading to enhanced transportation of fatty acids into the mitochondria and ultimately promoting their oxidation. Alcohol consumption impairs mitochondrial fatty acid oxidation and suppresses CPT-1 gene expression, possibly leading to fatty acid overloading and ensuing hepatic fat formation [84]. Among the person herbal medicinal products included resveratrol, ostiole from Cnidium monnieri [85], and EGCG from green tea [86], which have been shown to increase the expression of CPT1 in mRNA or protein levels, leading to an exponential increase in protein.

Current targeted approaches to manage CLD

Patients with severe liver cirrhosis and moderate to severe cirrhosis are significantly affected by infection regarding their prognosis. At admission, 25% of patients with severe alcoholic hepatitis have a disease, and another 25% will acquire an infection within two months of starting corticosteroids [1]. Supplement deficits, reduced macrophage phagocytic activity, neutrophil dysfunction, increased disease migration, and impaired immune response are the leading causes of this increased vulnerability to infections [87]. Given this increased vulnerability to pathogens, it is intriguing to consider the therapeutic use of antibiotics in ALD. Research on easily-absorbed antibiotics (such as quinolones and amoxicillin-clavulanate) and nonabsorbable antibiotics is now being conducted in this area, as reported in **Table 1**. TLR4 antagonists are promising contenders for evaluation in alcoholic cirrhosis and hepatitis, given TLR4's detrimental impact on acute infections and its involvement in the pathogenesis of ALD [88]. Currently, these compounds are being assessed for various purposes, including treating severe illnesses. Recent findings from translational research and animal models suggest that it is crucial to investigate the primary pathways implicated in hepatotoxicity when developing new medications. Effective treatments for patient populations with liver cirrhosis often involve targeting inflammatory responses through substances such as TLR4 receptor antagonists or anakinra (such as IL-1 receptor

antagonists), as well as addressing bacterial translocation, hepatic regeneration, and apoptosis (e.g., Emricasan). The critical research advancements in innovative targeted therapeutics for ALD are outlined in (**Table 4**).

An outlook on using herbal remedies for chronic liver disease

In recent years, there has been a growing focus on developing herbal medications as a novel therapy for chronic liver disease. These medications have shown promise in diagnosing, managing, and treating liver impairment caused by alcohol consumption. The functions and effects of natural medications and organic plant compounds have been summarized and studied in this field. **Figure 2** demonstrates how medicinal herbs and their bioactive components work through various mechanisms to alleviate the symptoms of chronic liver disease. These mechanisms include anti-inflammation, antioxidation, inhibition of lipogenesis, and increased fatty acid β-oxidation, indicating that medicinal herbs are highly encouraging options for managing chronic liver disorders. However, some areas require further improvement in the existing experimental trials exploring the effects of natural medications on chronic liver disease:

i. Molecular Mechanisms: The molecular processes underlying herbal remedies' preventive and curative effects for chronic liver disease have yet to be fully elucidated. Despite the potential and multi-targeted action of various extracts and molecules derived from herbal remedies, it is important to continue researching the deeper, more organized systems that underlie the therapeutic effects of these medications.

ii. Identification of Active Chemicals: Further investigation is needed to determine the critical chemical components and their contributions to the preventive role of medicinal herbs against chronic liver disease. The examination of more single components is necessary to gain a comprehensive understanding of their effects.

iii. Standardization and Chemical Profiling: The chemical nature of herbal ingredients may vary depending on the herb's origin and processing. It is essential to employ standardized plant supplements of consistently high quality and profile their chemical structure using modern analytical techniques to ensure the accuracy and reproducibility of experimental results.

iv. Clinical Validation: The results of experimental studies must be validated in human subjects through additional randomized placebo-controlled clinical trials. This step is crucial for confirming the therapeutic profile of medicinal herbs in managing and treating CLD.

Medicinal herbs, whether used as single components, extracts, or preparations, hold great potential for developing safe and effective medicinal drugs for chronic liver disease. However, further research, standardization, and clinical validation are necessary to harness their full therapeutic benefits. Advancements in analytical chemistry and molecular biology techniques have expanded our understanding of the biological targets for liver diseases and the use of multicomponent treatment strategies. By utilizing the pharmacological mechanisms of herbal medications in a well-defined biological network, the curative effects of herbal treatments can be enhanced. This approach makes herbal treatments potent, safe, and promising options for managing and treating hepatobiliary system diseases. Utilizing polyherbal compositions with liver-protective and immune-modulating properties shows great potential in developing phototherapies for liver and biliary diseases. This approach harnesses the power and synergistic effects of herbal remedies to create effective treatments for these conditions.

Conclusion

This review highlights the potential of herbal remedies in managing the progression of chronic liver disease. Over the past several years, herbal medications have gained considerable attention as an alternative to treating the complexity of CLD. We have conducted a comprehensive analysis has summarized the mechanisms underlying the efficacy of various herbal remedies and their phytoconstituents derived from medicinal plants in treating and preventing prolonged hepatic problems.

The findings of this review suggest that herbal extract offer promising remedies for the prevention and treatment of chronic liver disease.

Table 4. Clinical evaluation of different interventions in chronic liver diseases

NCT Number	Title	Status	Conditions	Interventions
NCT03938662	S-adenosylmethionine Plus Choline in Treatment of Patients With Alcoholic Liver Disease	Unknown status	Alcoholic Liver Diseases	Dietary Supplement: formulation containing S-Adenosyl methionine and choline Dietary Supplement: Placebo
NCT03267069	Evaluating Alcohol Use in Alcoholic Liver Disease	Recruiting	Alcoholic Liver Disease	Other: survey
NCT03295812	Stratification of Chronic Alcoholic Liver Diseases (SCALEStudy)	Unknown status	Alcoholic Liver Disease	Other: standard therapy
NCT03113929	Quantitative MRI for Non-invasive Assessment of Severity of Alcoholic Liver Disease (ALD)	Active, not recruiting	Alcoholic Liver Disease	Radiation: MRI
NCT02140294	Long-Term Effect of Aggressive Nutritional Management on Survival in Patients With Alcoholic Liver Disease	Completed	Alcoholic Liver Disease	Dietary Supplement: Polymeric nutritional supplements Dietary Supplement: Standard Nutritional Treatment
NCT01501162	Effect of Probiotics on Gut-Liver Axis of Alcoholic Liver Disease	Completed	Alcoholic Liver Disease	Drug: hepatitis, alcohol, probiotics Drugs: alcohol, hepatitis, Placebo
NCT00708617	fibro scan Validation and Interest of Fibrotest-FIBROSCAN Association for Fibrosis Diagnosis in Alcoholic Liver Disease	Completed	Alcoholic Liver Disease	
NCT01701687	Biomarkers for the Prognosis of Decompensated Alcoholic Liver Disease	Completed	Alcoholic Liver Diseases Decompensated Cirrhosis	
NCT04858412	Study of HMB-enriched Amino Acid Supplementation in Patients With Alcoholic Liver Disease and COVID-19	Recruiting	Alcoholic Liver Disease COVID-19 Pneumonia	Dietary Supplement: #-hydroxy #-methyl butyrate (HMB) enriched amino acid Dietary Supplement: Balanced amino acid
NCT01711125	Baclofen in the Treatment of Alcohol Dependence With or Without Alcoholic Liver Disease	Completed	Alcoholic Liver Disease Alcohol Dependence	Drug: Baclofen 30 mg/day Drug: Baclofen 75 mg/day Drug: Placebo
	Herbal Supplements for Improvement of Liver Function in Participants With Alcoholic Liver Disease	Not yet recruiting	Alcoholic Liver Disease	Drug: Livitol-70
NCT03503708	Influence of Adiponutrin on Chronic Liver Disease	Completed	Alcoholic Liver Disease	
NCT01122797	Study of Alcohol-related Liver Disease in Europe	Recruiting	Alcoholic Liver Disease	
NCT04400604	Cognitive Function of Alcoholic Compensated Liver Cirrhosis	Completed	Alcoholic Liver Disease	Other: Cognitive function test
NCT04557774	Study of T Cell Phenotype Activation Pathway in Human Alcoholic Liver Disease	Completed	No Results Available	Alcoholic Liver Disease Chronic Hepatitis C Virus
NCT00610597	Role of CCL2 in Alcoholic Liver Diseases	Completed	No Results Available	Alcoholic Liver Disease
NCT01128010	Study of Genetic Determinants in Alcoholic Hepatitis and Establishment of a Multicenter Prospective Cohort of Patients With Alcoholic Liver Disease	Recruiting	No Results Available	Alcoholic Liver Disease Severe Alcoholic Hepatitis Alcoholic Cirrhosis
NCT02200029	Study With Heptral in Subjects With Liver Disease Due to Alcohol Consumption	Completed	No Results Available	Intrahepatic Cholestasis Associated With Alcoholic Liver Disease
NCT03863730	Profermin®: Prevention of Progression in Alcoholic Liver Disease by Modulating Dysbiotic Microbiota	Active, not recruiting	No Results Available	Alcoholic Liver Disease, Liver Cirrhosis, Alcoholic Probiotics Liver Fibrosis
NCT00990639	Effect of Candesartan on Alcoholic Liver Fibrosis	Completed	No Results Available	Alcoholic Liver Disease
NCT05428072	Text Messaging to Reduce Alcohol Relapse in the Liver Transplant Patients	Completed	No Results Available	Alcoholic Liver Disease
NCT05428072	Alcohol, Gut Leakiness, & Liver Disease	Completed	No Results Available	Alcoholic Liver Disease
NCT04736966	Guselkumab (Anti- IL 23 Monoclonal Antibody) for Alcohol Associated Liver Disease	Recruiting	No Results Available	Alcoholic Liver Disease
NCT04320199	Effect of Fermented Protaetia Brevitarsis Seulensis Powder on Alcohol-induced Liver Disease	Completed	No Results Available	Alcoholic Liver Disease

NCT05007470	Alcoholic Liver Disease and the Gut Microbiome	Recruiting	No Results Available	Alcohol Use Disorder Alcoholic Liver Disease Microbiome
NCT02335632	Effect of Probiotics on Gut-Liver Axis of Alcoholic Hepatitis	Unknown status	No Results Available	Alcoholic Liver Disease
NCT03209791	Ethanol Induces Skeletal Muscle Autophagy	Recruiting	No Results Available	Alcoholic Liver Disease
NCT02381769	The immunological effects and metabolic tolerance of lipid infusion in patients with cirrhosis	Completed	No Results Available	Alcoholic Liver Disease
NCT00573313	Effects of SAMe in Patients With Alcoholic Liver Disease	Completed	Has Results	Liver Disease, Alcoholic
NCT03224949	Comparison of ALD, NASH, and Healthy Control Patients	Recruiting	No Results Available	ALD - Alcoholic Liver Disease
NCT03388320	Using Addiction Comprehensive Health Enhancement Support System (ACHESS) in an Alcoholic Liver Disease Population	Unknown status	No Results Available	Liver Diseases, Alcoholic
NCT02319252	Gastric-Versus Jejunal Feeding Tubes in Liver Diseases Alcoholic	Completed	No Results Available	Malnutrition Liver Diseases, Alcoholic
NCT03533660	Alcohol Biosensor Monitoring for Alcoholic Liver Disease	Completed	Has Results	Alcohol Use, Unspecified
NCT03773887	Comparison of Inflammatory Profiles and Regenerative Potential in Alcoholic Liver Disease	Recruiting	No Results Available	Liver Diseases Acute Chronic Hepatic Failure
NCT03474328	AlcoChange: An Open-Label Pilot Study of Smartphone Monitoring for Alcoholic Liver Disease	Unknown status	No Results Available	Alcohol-Related Disorders
NCT00851981	Randomized, Controlled Trial of S-adenosylmethionin e in alcoholic Liver Disease	Completed	No Results Available	Alcoholic Hepatitis
NCT01504295	A Novel Pharmacotherapy for Alcoholism and Alcohol Liver Disease	Completed	No Results Available	Alcoholism, Alcoholic Liver Disease
	sgp130 in Chronic Human Liver Disease	Completed	No Results Available	Alcoholic Liver Disease Chronic Hepatitis C Virus Infection
NCT00770198	Value on Survival of Liver Volume After an Acute Decompensation of an Alcoholic Cirrhosis	Terminated	No Results Available	Alcoholic Cirrhosis Alcoholic Liver Disease
NCT03508388	Early Detection of Alcoholic Liver Disease	Not yet recruiting	No Results Available	Alcoholic Liver Disease Alcoholic Fibrosis of the Liver Alcoholic Cirrhosis Excessive Drinking Alcohol Abuse Alcohol Use Disorder Alcohol Dependence Alcohol-Related Disorders
NCT02796469	Meta-Analysis of Drug Therapy in Patients With Severe Alcoholic Hepatitis	Completed	No Results Available	Alcoholic Hepatitis Alcoholic Liver Disease
NCT02281929	Efficacy of Antibiotic Therapy in Severe Alcoholic Hepatitis Treated With Prednisolone	Completed	No Results Available	Alcoholic Hepatitis Alcoholic Liver Disease
	Double-blind Randomized Controlled Trial in Severe Alcoholic Hepatitis	Completed	No Results Available	Alcoholic Hepatitis Alcoholic Liver Disease
NCT01214226	Transient Elastography in the Determination of Advanced Fibrosis in Alcoholic Liver Disease.	Completed	No Results Available	Alcoholism Liver Disease Liver Fibrosis
NCT02331745	RCT Study on Granulocyte Colony-stimulating Factor (G-CSF) Treatment of Hepatic Failure	Unknown status	No Results Available	Liver Failure Hepatitis B Alcoholic Liver Disease
NCT05018481	HA35 Moderate Alcoholic Hepatitis (AH) Study	Recruiting	No Results Available	Alcoholic Hepatitis
NCT02737345	Correlation of Hepatitis C, Alcoholic Liver Disease and Renal Failure With Hyperfibrinolysis in Liver Failure	Completed	No Results Available	Cirrhosis
NCT03915002	Integrated Approaches for Identifying Molecular Targets of liver Disease	Recruiting	No Results Available	Alcoholic Liver Disease Non-Alcoholic Fatty Liver Disease Steatohepatitis, Non-alcoholic Steatohepatitis
NCT04666402	Integrated Diagnostics for Early Diagnosis of Liver Disease	Recruiting	No Results Available	Non-Alcoholic Fatty Liver Disease Non-alcoholic Steatohepatitis, Alcoholic Liver Disease Liver Fibrosis
NCT04234139	Cohort/Ethics Study of Patients With Severe Alcoholic Hepatitis Undergoing Early Liver Transplantation	Enrolling by invitation	No Results Available	Liver Diseases, Alcoholic Alcohol-Related Disorders Transplant; Failure, Liver Transplant; Complication, Rejection Liver Diseases, Hepatitis, Alcoholic Alcohol-Induced Disorders

*All trials are listed at www.clinicaltrials.gov.

These remedies exert their beneficial effects through multiple mechanisms, including antioxidation, anti-inflammation, inhibition of lipid synthesis, and promotion of fatty acid β-oxidation. By targeting these crucial pathways, herbal remedies demonstrate their ability to alleviate the key hallmarks of the disease. However, further research and clinical studies are warranted to elucidate the specific therapeutic benefits, optimal dosage, and side effects of individual herbal remedies in the context of chronic liver disease.

Standardizing herbal formulations, identifying active compounds, and evaluating their safety profiles will contribute to their wider acceptance and integration into conventional treatment strategies. In this review, the accumulated evidence strongly supports the inclusion of herbal remedies as an adjunctive therapy or potential alternative to conventional approaches in managing chronic liver disease. Their natural origin, diverse mechanisms of action, and possible synergistic effects make them an intriguing area for future exploration. Continued scientific investigation in this field holds promise for advancing our understanding and improving patient outcomes in managing chronic liver diseases.

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Disclosure of conflict of interest

None.

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