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NARRATIVE
REVIEW

The Hepatoprotective Potential of Alpha-Lipoic Acid: Mechanisms and Translational Evidence

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Abstract

Background: Liver diseases remain a major global health challenge with limited effective therapies. Alpha-lipoic acid (ALA), a mitochondrial cofactor, has gained attention for its antioxidant and anti-inflammatory properties.
Objective: To review the hepatoprotective potential of ALA based on preclinical and clinical evidence.
Material and Methods: Studies were identified from PubMed, Scopus, Web of Science, and Google Scholar (2000–2025). Eligible preclinical and clinical studies reporting ALA dose and liver-related outcomes were included. Data were synthesized narratively.
Results: Preclinical studies consistently show that ALA attenuates liver injury by improving liver enzymes, oxidative stress markers, inflammatory cytokines, and histopathological changes, typically at doses of 50–200 mg/kg in rodents. Clinical studies, mainly in MASLD and drug-induced liver injury, used doses of 300–1,200 mg/day and reported improvements in transaminases and insulin sensitivity. However, clinical evidence remains limited by small sample sizes and short durations.
Conclusion: ALA demonstrates consistent hepatoprotective effects in preclinical models, while clinical evidence remains preliminary. Further well-designed clinical trials are required to confirm its therapeutic role.

1. Introduction

The liver is central to maintaining physiological balance, supporting nutrient storage, metabolic regulation, biosynthesis, detoxification, and elimination of waste [1]. As the primary site of xenobiotic biotransformation, it contains numerous phase I (oxidation, reduction, and hydrolysis) and phase II (glucuronidation, sulfation, and glutathione conjugation) enzymes [2]. Although these processes are essential, they generate reactive intermediates, such as N-acetyl-p-benzoquinone imine (NAPQI) from acetaminophen (N-acetyl-p-aminophenol or APAP) or acyl-glucuronides from diclofenac, which deplete glutathione, impair mitochondria, and trigger immune-mediated liver injury [3,4].

Liver diseases represent a major global health burden, causing ~2 million deaths annually and 4% of global mortality [5]. Acute liver damage often arises from viral infections, whereas drug-induced liver injury (DILI) is increasingly reported [6]. Chronic liver diseases are linked to alcohol use, hepatitis B and C, and the rising prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD; previously known as non-alcoholic fatty liver disease [NAFLD]). Progression frequently results in fibrosis, cirrhosis, or hepatocellular carcinoma (HCC), contributing substantially to morbidity and mortality [7].

Oxidative stress, driven by excess reactive oxygen species (ROS), is a central mechanism underlying liver injury. ROS accumulation disrupts redox balance, damages

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mitochondria and macromolecules, and promotes inflammation via Kupffer cell–derived cytokines and hepatic stellate cell activation [8,9].

Although antioxidants such as silymarin, curcumin, and glycyrrhizin have shown hepatoprotective effects, clinical outcomes remain inconsistent [10,11]. Alpha-lipoic acid (ALA), also known as the 'universal antioxidant', combines antioxidant and anti-inflammatory properties with mitochondrial support and redox recycling. These unique features position ALA as a promising hepatoprotective agent [12]. The aim of this review is to critically assess mechanistic pathways, preclinical evidence, and clinical studies supporting the hepatoprotective potential of ALA while underscoring current limitations and outlining future directions for its therapeutic application.

2. Methodology

Research on ALA and liver protection was identified through PubMed, Scopus, Web of Science, with additional studies retrieved from Google Scholar and reference lists. The search covered publications from 2000 to 2025, restricted to English, using keywords such as "alpha-lipoic acid," "ALA," "liver," "hepatoprotection," "oxidative stress," and "clinical trial." Eligible studies included preclinical (*in vivo* and *in vitro*) and clinical (trials and observational) investigations reporting ALA dose, route, and at least one liver-related outcome. Reviews, abstracts without primary data, and studies unrelated to liver injury or lacking dose/outcome data were excluded. From each eligible study, data were extracted on study type, model or disease context, dose and route, and key effects. Owing to heterogeneity in designs and outcomes, findings are synthesized as a narrative summary rather than a meta-analysis.

3. Alpha-Lipoic Acid

3.1. Background

Alpha-lipoic acid, also called thioctic or dithioctanoic acid, was first extracted from liver tissue by Reed *et al.* in 1951 [13]. Endogenously synthesized in mitochondria, it functions as a cofactor for enzyme complexes essential to cellular energy metabolism. ALA occurs naturally in foods of plant and animal origin, being most abundant in metabolically active organs (liver, heart, and kidneys) [14] and in plant sources, such as spinach, broccoli, tomatoes, peas, Brussels sprouts, and rice [15]. However, dietary levels are insufficient to achieve therapeutic efficacy [16].

3.2. Chemistry

Alpha-lipoic acid is a disulfide derivative of octanoic acid, chemically identified as 5-(1,2-dithiolan-3-yl)pentanoic acid. Its disulfide bond undergoes reversible reduction to dihydrolipoic acid (DHLA) via nicotinamide adenine dinucleotide phosphate (NADPH)-dependent enzymes, such as lipoamide dehydrogenase and glutathione reductase, forming a redox pair ($E^{\circ\prime}$ = -0.32 V) that underlines its antioxidant activity and mitochondrial cofactor role [15]. Its amphipathic disposition permits activity in both aqueous and lipid environments, including the central nervous system (CNS), as it crosses the blood–brain barrier [16,17]. ALA is chiral, existing as two enantiomers, R-ALA and S-ALA (Figure 1). R-isomer (R-ALA) is synthesized naturally and active physiologically, with higher affinity for mitochondrial enzymes [18].

3.3. Pharmacokinetics

After oral administration, plasma levels peak within 30–60 min. Absorption is greater on empty stomach, and distribution occurs mainly to metabolically active tissues (liver, heart, and skeletal muscles). R-ALA shows greater tissue uptake than S-ALA, explaining its higher bioactivity [20]. In the liver, ALA is metabolized mainly via β-oxidation and conjugation, and metabolites are excreted in urine [21].

3.4. Bioavailability and safety

Alpha-lipoic acid is generally safe at therapeutic doses, with mild gastrointestinal adverse effects reported occasionally. In diabetic patients, high doses may enhance

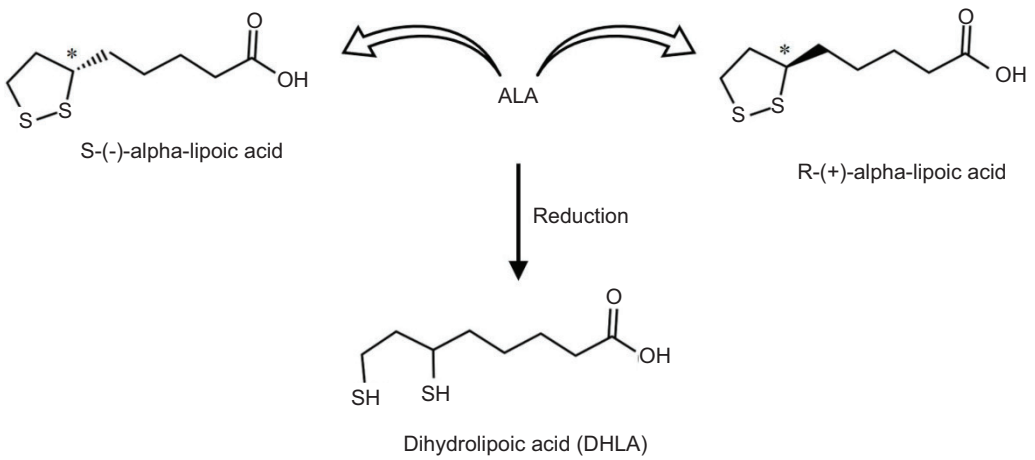

Figure (1): Chemical structures of alpha-lipoic acid (ALA) enantiomers (R-ALA and S-ALA) and its reduced form, dihydrolipoic acid (DHLA) [19].

insulin sensitivity and risk hypoglycemia when combined with antidiabetic drugs [22]. Although R-ALA is more bioavailable and effective biologically, most supplements contain a racemic mixture. Strategies to improve bioavailability include stabilized R-ALA formulations and co-administration with absorption enhancers [23].

4. Mechanisms of Hepatoprotection

Alpha-lipoic acid exerts its hepatoprotective effects through a range of interconnected mechanisms, forming the basis for its potential therapeutic role in liver diseases.

4.1. Antioxidant Functions

Alpha-lipoic acid exerts potent antioxidant effects through its redox coupled with DHLA, functioning in both aqueous and lipid environments. Both act as direct scavengers of reactive species, with DHLA showing stronger activity. Both inhibit protein carbonyl formation induced by hypochlorite and effectively neutralize hydroxyl radicals and hypochlorous acid, although they display limited reactivity toward hydrogen peroxide [20,24]. Owing to its low molecular weight and amphipathic disposition, DHLA efficiently scavenges peroxyl radicals even in the absence of other antioxidants, such as glutathione (GSH) or α-tocopherol, thereby suppressing lipid peroxidation and preserving membrane integrity [12]. It also scavenges ascorbyl radicals generated during ascorbate oxidation. Interestingly, singlet oxygen interacts specifically with ALA, forming thiosulfinates and thiosulfonates through its disulfide moiety, whereas DHLA lacks this reactivity [25].

In addition to radical scavenging, ALA and DHLA chelate redox active metals, thereby limiting free radical generation without disrupting essential trace elements. DHLA forms stable complexes with cobalt, nickel, cadmium, copper, zinc, lead, mercury, and ferric iron, while ALA chelates manganese, copper, zinc, and lead, generating lipophilic Cu^{2+} complexes that inhibit lipid peroxidation [26,27].

Alpha-lipoic acid and DHLA also regenerate other antioxidants. DHLA recycles vitamins C and E, strengthening the cellular antioxidant network [20]. Furthermore, ALA enhances intracellular GSH levels by promoting cystine uptake through the cystine/glutamate antiporter system Xc^- and by activating nuclear factor erythroid 2-related factor 2 (Nrf2), which upregulates γ-glutamylcysteine ligase and other GSH biosynthetic enzymes [15]. These actions amplify endogenous antioxidant defenses and reinforce resistance to oxidative stress [28].

4.2. Anti-Inflammatory Effects

Alpha-lipoic acid also exerts significant anti-inflammatory activity. It reduces hepatic inflammation by lowering tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) through Nrf2 activation and inhibition of nuclear factor-κB (NF-κB) signaling, with effects sustained during continued administration [25,29]. NF-κB, a master regulator of inflammatory gene expression, is suppressed by ALA via stabilization of its inhibitor κB (IκB). By preventing IκB degradation, ALA blocks NF-κB nuclear translocation and thereby limits the transcription of pro-inflammatory genes, ultimately reducing cytokine production and tissue injury [25]. Additionally, ALA inhibits the NLRP3 inflammasome, which regulates the maturation of interleukin-1β (IL-1β), further contributing to its anti-inflammatory action [30]. These combined effects highlight ALA's dual antioxidant and anti-inflammatory mechanisms as summarized in Figure 2.

4.3. Mitochondrial Protection and Metabolic Regulation

Mitochondrial dysfunction is a hallmark of liver injury, and ALA contributes to hepatoprotection by preserving mitochondrial membrane potential (Δψm), regulating fusion–fission dynamics, and enhancing generation of adenosine triphosphate (ATP) via tricarboxylic acid (TCA) cycle enzymes [32,33]. In addition, ALA acts as a metabolic

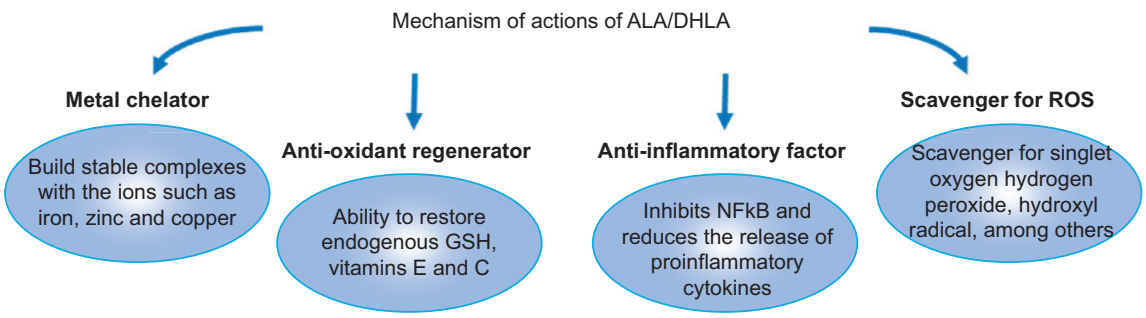

Figure (2): Summary of main hepatoprotective mechanisms of alpha-lipoic acid (ALA) and its reduced form, dihydrolipoic acid (DHLA). Antioxidant actions include radical scavenging, metal chelation, and regeneration of endogenous antioxidants (e.g., GSH and vitamins C and E), while anti-inflammatory effects involve inhibition of NF-κB signaling and suppression of cytokines and inflammasome activity [31]. Adapted from [31]. Published by MDPI under the terms of the Creative Commons Attribution (CC BY) license.

regulator through activation of adenosine monophosphate (AMP)-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), promoting mitochondrial biogenesis, increasing lipid oxidation, and reducing lipogenesis, thereby improving hepatic metabolic balance [12,34]. These key mechanisms are summarized in Figure 3.

5. Preclinical Studies

Preclinical investigations, in both *in vivo* and *in vitro* models, consistently demonstrated the hepatoprotective effects of ALA across drug- and chemical-induced injuries, stressor-related damage, and experimental liver diseases, as outlined in the following segments. An overview of these models is presented in Figure 4.

5.1. Liver Injury Models

In experimental models of liver damage induced by drugs, toxins, or chemicals, ALA reduces liver injury and improves the overall hepatic function.

5.1.1. Drug-Induced Liver Injury

Alpha-lipoic acid demonstrates protective effects in several drug-induced liver injury models, particularly with hepatotoxic agents, such as APAP, chemotherapeutics, immunosuppressants, and antiepileptics. Acetaminophen, although widely used as an analgesic and antipyretic, causes severe liver injury in overdose through oxidative stress and glutathione depletion [35]. The reactive metabolite NAPQI, formed via cytochrome P450, depletes glutathione and binds to mitochondrial proteins, triggering oxidative stress, necrosis, and inflammation [36].

Alpha-lipoic acid has shown significant protective effects against APAP-induced liver injury (AILI) in rats. Across various dosing protocols—such as 750 mg/kg (single dose) or 1 g/kg/day for 4 weeks—APAP consistently elevated serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), total bilirubin, and oxidative stress markers such as malondialdehyde (MDA) and nitric oxide (NO) while reducing superoxide dismutase (SOD), catalase (CAT), and GSH levels [37–39]. Oral ALA (50–200 mg/kg) reversed these changes, particularly before and after APAP exposure, and improved liver histology by reducing hepatocellular degeneration and inflammation.

In comparative studies, ALA was particularly effective in restoring antioxidant balance, while silymarin exerted more pronounced effects on normalizing liver enzymes. Furthermore, when ALA was combined with other antioxidants, such as ascorbic acid or thymoquinone, the regimen enhanced anti-inflammatory activity and preserved liver structure [37,38]. ALA also downregulated cyclooxygenase-2 (COX-2) and vascular endothelial growth factor receptor 1 (VEGFR1), indicating modulation of IL-6-related signaling. *In vitro* MTT (3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide) assays showed only modest hepatocyte proliferation, suggesting a primarily cytoprotective role [38].

Cisplatin is a widely used chemotherapeutic agent but its clinical utility is often limited by organ toxicity, including hepatotoxicity [40]. In rats models, a single intraperitoneal (i.p.) dose (7.5 mg/kg) elevated serum ALT and AST, reduced albumin levels, increased hepatic MDA, and

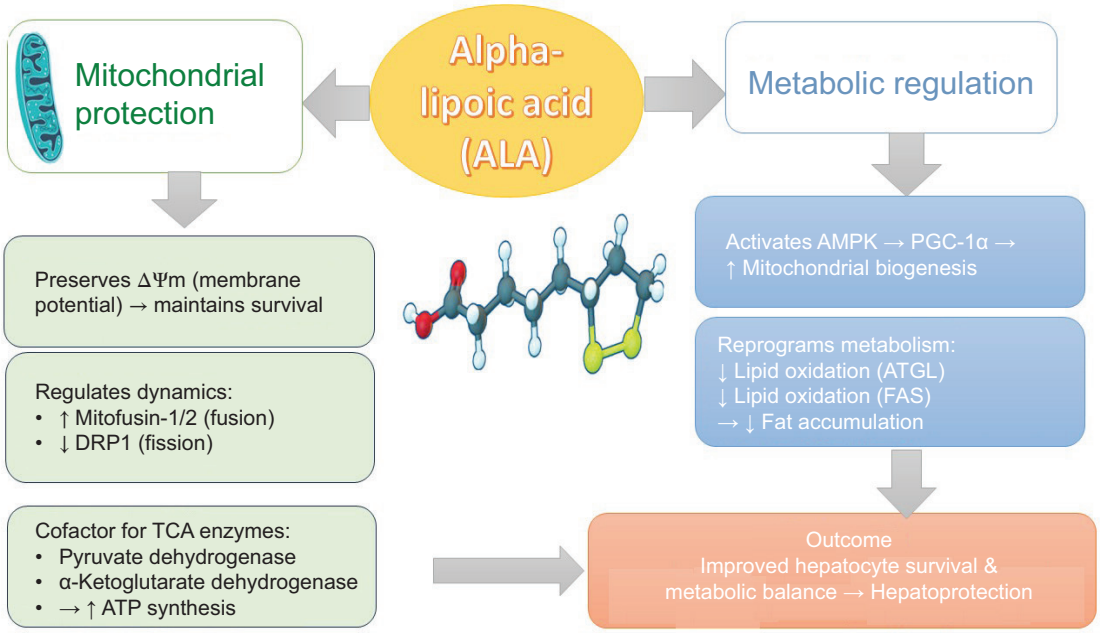

Figure (3): Alpha-lipoic acid (ALA) in mitochondrial protection and metabolic regulation.Notes: Δψm: mitochondrial membrane potential; DRP1: dynamin-related protein 1; TCA: tricarboxylic acid cycle; AMPK: AMP-activated protein kinase; PGC-1α: peroxisome proliferator-activated receptor gamma coactivator 1-alpha; ATGL: adipose triglyceride lipase; FAS: fatty acid synthase.

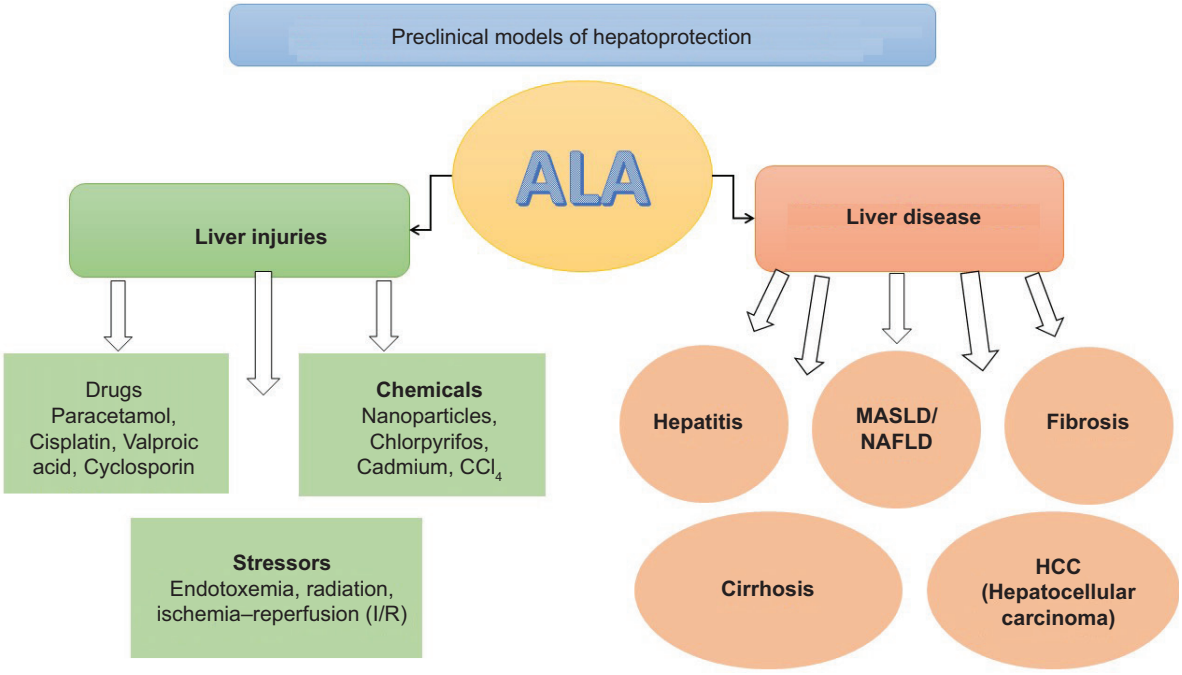

Figure (4): Preclinical models in which alpha-lipoic acid (ALA) has shown hepatoprotective effects, grouped into liver injuries (drugs, chemicals, and stressors) and liver diseases (hepatitis, metabolic dysfunction-associated steatotic liver disease [MASLD; previously known as NAFLD], fibrosis, cirrhosis, and hepatocellular carcinoma).

suppressed catalase and GSH activity. Histological evaluation revealed focal necrosis, hydropic degeneration, and caspase-3 upregulation, indicating apoptosis. Daily intake of oral ALA (100 mg/kg) reversed these effects, restoring enzyme levels, antioxidant status, and reducing apoptosis. While flaxseed oil (FXO) also conferred hepatoprotection, ALA provided stronger antioxidant and anti-apoptotic benefits. Their combination yielded synergistic improvements, nearly restoring liver function and histological integrity [41].

Valproic acid, commonly used in epilepsy and bipolar disorder, is associated with hepatotoxicity via mitochondrial dysfunction and lipid peroxidation [42]. Up to 44% of patients on chronic therapy may show elevated liver enzymes and oxidative stress [43]. In rats, valproic acid (500 mg/kg, i.p.) increased ALT, AST, and MDA while reducing GSH and SOD activity. ALA (100 mg/kg, orally) reversed these changes, improving liver function and redox balance. Molecular analysis showed valproic acid downregulated sirtuin-1 (Sirt1) and Nrf2, elevated TNF-α levels. ALA restored Sirt1 and Nrf2 expression and suppressed TNF-α, confirming its modulatory effects on redox-sensitive and inflammatory signaling, consistent with findings in APAP and cisplatin models [44].

Cyclosporine A, a cornerstone immunosuppressant in transplantation and autoimmune therapy, is limited by dose-dependent liver toxicity [45]. In male Wistar rats, oral cyclosporine A (25 mg/kg for 3 weeks) induced marked hepatotoxicity, with elevated liver enzymes (ALT, AST, ALP, and GGT), fibrosis, and inflammatory histological changes. Co-treatment with ALA (100 mg/kg, orally, administered 1 h prior to intake of cyclosporine A) improved liver function and reduced tissue damage. ALA enhanced antioxidant defenses—elevating GSH, SOD, catalase, and total antioxidant capacity (TAC)—while lowering MDA and NO levels. It also upregulated Nrf2 and its downstream target heme oxygenase-1 (HO-1). Inflammatory markers, including TNF-α, NF-κB, CD68, COX-2, and inducible nitric oxide synthase (iNOS), were downregulated, and Caspase-3 activity was reduced, highlighting ALA's antioxidant, anti-inflammatory, and anti-apoptotic effects in cyclosporine-induced liver injury [46]. Evidence from other drug-induced liver injury models involving ALA is compiled in Table 1.

The liver is vulnerable to pollutants such as heavy metals and pesticides [56]. Preclinical studies showed that ALA reduces related liver damage and preserves its functioning.

Gold nanoparticles (AuNPs), widely used in medical and industrial products, cause hepatotoxicity with repeated exposure because of oxidative stress [57]. Their toxicity is influenced by size, surface charge, and coating; smaller particles and positively charged AuNPs are generally more harmful, while surface modifications, such as PEGylation, reduce hepatic accumulation and oxidative damage [58]. In a 7-day rat model, AuNP exposure elevated serum ALT, AST, and gamma-glutamyl transferase (GGT), and reduced nuclear expression of Nrf2. Pro-apoptotic markers Bax and caspase-3 were upregulated, while Bcl2 and HO-1 were downregulated. ALA (200 mg/kg, i.p.) restored Nrf2, decreased the Bax–Bcl2 ratio, and improved liver histology, leaving only mild vacuolization. These findings highlight ALA's ability to activate Nrf2-related antioxidant defenses and stabilize mitochondrial functioning [59].

Chlorpyrifos (CPF), an organophosphate pesticide, is bioactivated in the liver to CPF-oxon, which inhibits acetylcholinesterase and triggers oxidative and inflammatory

Table (1): Effects of alpha-lipoic acid (ALA) in drug-induced liver injury.

Model	ALA treatment	Key effects	Ref.
Cyclophosphamide (CP)	25 mg/kg/day orally for 4 weeks with CP (5 mg/kg, orally, 3x/week).	Significant reduction in ALT, AST, and MDA levels; increased SOD activity; improved liver histopathology and ultrastructure (less vacuolation, degeneration, and necrosis); better than royal jelly in efficacy.	[47]
Adriamycin	75 mg/kg/day i.p. 24 h before single i.p. dose of 15 mg/kg adriamycin.	ALA pretreatment reduced liver enzyme levels (ALT and AST), restored antioxidant levels (GSH, CAT, and SOD), and decreased lipid peroxidation (MDA); it also protected against oxidative stress caused by adriamycin.	[48]
5-Fluorouracil (5-FU)	400 mg/kg/day orally post i.p. 5-FU 50 mg/kg.	ALA post-treatment reversed 5-FU-induced elevations in NF-κB, TNF-α, AST, ALT, ALP, triglycerides, cholesterol, and LDL; restored albumin and total protein levels; and reduced necrosis, improving liver architecture.	[49]
Methotrexate (MTX)	60 mg/kg i.p. for 5 days before MTX (20 mg/kg i.p. on day 6).[1]	ALA pretreatment reduced MTX-induced liver enzyme levels (ALT, AST, and ALP), lipid peroxidation, and restored GSH and TAC. It activated the Nrf2/HO-1 antioxidant pathway, inhibited inflammation (decreased TNF-α, iNOS, and COX-2), and reduced apoptosis marker (caspase-3). Additionally, ALA pretreatment reduced fibrosis markers (α-SMA and hydroxyproline).	[50]
Gliclazide	60 mg/kg orally in diabetic rats treated with gliclazide (15 mg/kg).	ALA co-administration prevented gliclazide-induced liver damage; decreased ALT, AST, ALP, inflammation (iNOS), and apoptosis (caspase-3); improved antioxidant defense; liver histology close to healthy control.	[51]
Lopinavir/ritonavir (LPV/r)	10 mg/kg/day orally for 60 days with LPV/r (22.9/5.71–91.2/22.9 mg/kg/day).	ALA pretreatment mitigated LPV/r-induced hepatotoxicity, decreasing ALT, AST, ALP, and MDA levels while increasing liver antioxidant enzymes (SOD, CAT and GSH). The results improved further when combined with melatonin.	[52]
Amiodarone (AMD)	100 mg/kg orally daily for 14 days before + 7 days after 4-week AMD (40 mg/kg orally).	ALA treatment decreased AMD-induced ALT, AST, glucose, and TGF-β1; increased TAC and GSH; reduced the expression of fibrotic marker α-SMA; and improved liver histology, reducing hepatic inflammation and fibrosis.	[53]
Isoniazid/rifampicin (INH–RIF)	ALA co-administered with INH–RIF (50 mg/kg each for 14 days).	ALA co-treatment with INH–RIF reduced elevated liver enzymes and lipid profile disturbances; restored GSH, SOD, CAT, and MPO activity; reduced lipid peroxidation and nitrite levels; preserved liver histology.	[54]
Chloroquine (CQ)	10, 30, and 100 mg/kg/day orally: 7 days before + 3 days after CQ (970 mg/kg orally, single dose).	ALA reduced CQ-induced elevations in liver enzymes, bilirubin, lipids, TBARS, and hydroperoxides; restored GSH, vitamins C and E; most affective dose: 100 mg/kg; provided superior protection than silymarin.	[55]

Notes: The original article reported ALA dose as "60 mmol/kg." This corresponds to ~12 g/kg, which is pharmacologically implausible. Based on standard experimental range, the value was corrected to 60 mg/kg for accuracy.
MPO: myeloperoxidase; GSH: glutathione; SOD: sodium dodecyl sulfate; CAT: catalase; α-SMA: alpha-smooth muscle actin.5.1.2. Chemical Pollutant-Induced Liver Injuries.

injury [60]. In rats exposed to CPF (18 mg/kg/day, subcutaneously [s/c] for 14 days), liver enzymes and bilirubin increased, while glutathione peroxidase (GPx), SOD, and catalase activities declined. Bax and caspase-3 expression also ascended. ALA (10 mg/kg/day, i.p.) restored antioxidant enzyme levels, reduced lipid peroxidation, and suppressed apoptotic signaling. Histology confirmed improved hepatic architecture with reduced necrosis and inflammation [61].

Cadmium, typically administered as soluble salts such as cadmium chloride, is a persistent environmental toxin, accumulates in the liver, and disrupts redox homeostasis [62]. In HepG2 (HB-8065) cells exposed to cadmium (25 μM), total and phosphorylated Nrf2 levels declined along with its downstream antioxidant genes. Pre-treatment with ALA (50 μM) restored Nrf2 activity, increased intracellular GSH and GSH–glutathione disulfide (GSSG) ratio, and rescued cell viability. These effects were

abolished by the Nrf2 inhibitor brusatol, confirming that ALA's protection depends on Nrf2 activation [63].

Carbon tetrachloride (CCl_4), a classical hepatotoxin, induces oxidative injury and fibrosis [64]. In a co-culture model of CCl_4-induced injury (6 mM, 6 h), adipose-derived stem cells (ADSCs) pretreated with ALA (2 μM) enhanced hepatocyte viability, reduced ALT, ALP, and bilirubin, and increased synthesis of albumin. Analysis of gene expression showed upregulation of Bcl-2-like protein 1 (Bcl2l1), albumin, hepatocyte nuclear factor 4-alpha (HNF-4α), and cytokeratin-8 (CK-8), while Bax, cytochrome P450 2E1 (Cyp2e1), and alpha-fetoprotein (AFP) were downregulated. Inflammatory cytokines (TNF-α and IL-6) decreased, while HO-1 and NADPH quinone dehydrogenase 1 (NQO1) were upregulated, suggesting that ALA enhances the paracrine antioxidant and anti-inflammatory properties of stem cells [65]. ALA's protective effects against additional chemical pollutants are summarized in Table 2.

5.1.3. Stressor-Induced Liver Injuries

Beyond pharmaceuticals and environmental toxins, non-chemical stressors, such as ionizing radiation, ischemia-reperfusion (IR), and endotoxemia, also induce significant liver injury, primarily through oxidative stress and inflammation.

Radiation-induced liver injury is a known complication of abdominal radiotherapy, where ionizing radiation generates excess ROS, leading to lipid peroxidation and antioxidant depletion [74]. In an experimental model, rats exposed to whole-body gamma irradiation (30 Gy) exhibited pronounced hepatic oxidative stress. However, pretreatment with oral ALA at 50 mg/kg/day for 3 consecutive days led to a marked reduction in MDA levels and restoration of SOD activity ($P < 0.001$). Histological evaluation supported these biochemical findings, showing reduced hepatic necrosis and preserved tissue structure in ALA-treated animals [75].

Similarly, ischemia-reperfusion injury represents a major clinical condition, particularly in liver transplantation, hepatic surgery, and trauma. The initial ischemic phase leads to energy depletion and cellular stress, while the subsequent reperfusion paradoxically intensifies the injury by generating ROS and triggering a robust inflammatory response [76]. In a rats model of partial hepatic IR, i.p. administration of ALA, reported by the authors as 25 mg/mL and equivalent to approximately 250 mg/kg when given at 1 mL/100 g body weight, 15 min prior to reperfusion, significantly lowered serum ALT levels, maintained hepatic GSH content, and restored antioxidant enzyme activity. On a molecular level, ALA suppressed the expression of NF-κB p65 and downregulated the messenger RNA (mRNA) expression of pro-inflammatory mediators, such as macrophage inflammatory protein-2 (MIP-2) and inducible nitric oxide synthase (iNOS). These results collectively suggest that ALA offers dual protection by attenuating oxidative stress and dampening the inflammatory cascade associated with reperfusion injury [77].

Endotoxemia, another potent inducer of liver injury, is commonly modeled using lipopolysaccharide (LPS), a component of Gram-negative bacterial cell walls. LPS activates Kupffer cells, leading to a burst of pro-inflammatory cytokines and ROS that contribute to hepatic dysfunction [78]. In a rats model, oral pretreatment with ALA (60 mg/kg/day for 4 weeks) or vitamin E (40 mg/kg twice weekly) was followed by administration of LPS (1 mg/kg, i.p.). LPS alone caused significant elevations in serum liver enzymes (ALT, AST, and ALP) and MDA, beside reduced hepatic levels of GSH and catalase. While both antioxidants ameliorated these effects, ALA was notably more effective in restoring antioxidant defenses and reducing oxidative stress. Furthermore, ALA showed enhanced immunomodulatory effects, evidenced by a more significant reduction in pro-inflammatory cytokines TNF-α and IL-6, along with a simultaneous increase in anti-inflammatory cytokine IL-10. These findings suggest that ALA not only corrects redox imbalance but also actively regulates immune responses during LPS-induced systemic inflammation [79]. The effects of ALA across all previously described liver injury models are summarized in Table 3.

5.2. Liver Disease Models

Alpha-lipoic acid has shown protective effects in experimental models of hepatitis, MASLD, fibrosis, cirrhosis, and HCC.

5.2.1. Hepatitis

Hepatitis is an inflammation of the liver, most often because of viral infections. However, it is also caused by alcohol, drugs, toxins, or autoimmune diseases [80]. Although acute hepatitis typically resolves on its own, chronic inflammation may lead to liver fibrosis, cirrhosis, HCC, and portal hypertension [81]. In chronic hepatitis, Kupffer cells release pro-inflammatory cytokines and ROS, activating the NF-κB pathway, which perpetuates liver injury [82].

The hepatoprotective effects of ALA are demonstrated in both chemically and immune-mediated models of hepatitis. In a chronic hepatitis model induced by thioacetamide (TAA), rats were administered TAA at 200 mg/kg (i.p.) thrice per week for 4 weeks, resulting in significant hepatic fibrosis and inflammation [83]. Oral treatment with ALA at 200 mg/kg for 7 weeks markedly improved liver function, as evidenced by reduced serum ALT, AST, and total bilirubin. Levels of serum albumin increased as well, reflecting restored liver synthetic function. Oxidative stress ameliorated, with elevated hepatic GSH and reduced MDA levels. Inflammatory mediators, such as TNF-α and IL-6, were significantly downregulated, and activation of NF-κB was inhibited. ALA also reduced hepatic infiltration of $CD68^+$ macrophages. Histological analysis confirmed a marked reduction in both inflammation and fibrosis. The protective effects of ALA were found to be comparable to those of curcumin, which showed stronger suppression of pro-inflammatory cytokines, while ALA more effectively restored redox balance. Both were superior to silybin phytosome (ultrathistle), which exhibited weaker antioxidant and histological improvements [83].

Table (2): Effects of alpha-lipoic acid (ALA) in chemical pollutant-induced liver injury.

Model	ALA treatment	Key effects	Ref.
Imidacloprid	60 mg/kg orally for 30 days.	ALA pretreatment resulted in improved redox balance (decreased MDA, and increased SOD and CAT), improved liver function (decreased ALT and AST), reduced DNA damage (comet assay), and improved liver histology.	[66]
Malathion	20 mg/kg orally before 100 mg/kg malathion for 30 days.	ALA pretreatment resulted in enhanced liver and kidney function (decreased ALT, AST, ALP, ACP, urea, and creatinine), restored protein levels (increased albumin and total protein), and preserved tissue structure.	[67]
Acrylamide	35 mg/kg i.p. before 50 mg/kg acrylamide for 4 weeks.	ALA co-treatment resulted in partial antioxidant restoration (increased GSH, GPx, and CAT), reduced oxidative DNA damage and ascorbic acid depletion, with unchanged SOD.	[68]
Copper nanoparticles (CNPs)	100 mg/kg orally with 40 mg/kg CNPs, 5 days/ week for 2 months.	ALA pretreatment resulted in improved oxidative/nitrosative status (decreased MDA and NO; increased GSH, SOD, and CAT), downregulated apoptotic genes (C-myc and C-jun), and histological recovery.	[69]
Silver nanoparticles (AgNPs)	100 mg/kg orally with 50 mg/kg i.p. AgNPs for 30 days.	ALA pretreatment resulted in lower oxidative damage (decreased MDA), restored antioxidant gene expression (PGC-1α and Nrf2), improved calcium regulation, decreased ALT, AST, and ALP, and improved liver structure.	[70]
Cigarette smoke	100 mg/kg orally for 8 weeks.	ALA pretreatment resulted in reduced oxidative and inflammatory damage (decreased MDA, AST, bilirubin, and TNF-α), enhanced antioxidant enzymes (CAT and SOD), and improved histology.	[71]
Aflatoxin B1 (AFB1)	300 mg/kg in feed for 3 weeks with 74 μg/kg AFB1.	ALA pretreatment resulted in reduced oxidative damage (decreased MDA; increased GSH and GPx), improved liver enzymes (decreased ALT, AST, and ALP), increased albumin and total protein, and preserved liver structure.	[72]
Bromobenzene (BB)	150 mg/kg orally for 1 week before 10 mmol/ kg BB	ALA pretreatment resulted in normalized redox state (increased GSH, and decreased MDA and NO), reduced ALT, preserved hepatocyte structure, and reduced necrosis.	[73]

Table 3. Core actions of alpha-lipoic acid (ALA) in liver injury models.

Mechanistic target	Effect
Nrf2, HO-1	Upregulation of antioxidant gene expression.
SOD, CAT, GSH, and GPx	Enhancement of antioxidant enzymes.
TNF-α, IL-6, NF-κB, and iNOS	Suppression of inflammatory mediators.
MDA and NO	Reduction in lipid peroxidation/ oxidative stress.
Caspase-3 and Bax	Inhibition of apoptosis.
α-SMA and TGF-β1	Attenuation of fibrosis markers.

In an acute hepatitis model triggered by concanavalin A (Con A, a carbohydrate-binding protein), an immune stimulant that induces T-cell-mediated liver injury, ALA was administered with 100 mg/kg (i.p.) for 4 consecutive days prior to a single intravenous dose of Con A (15 mg/ kg) [84]. ALA pretreatment significantly lowered serum ALT and AST levels, preserved hepatic histoarchitecture, and reduced levels of pro-inflammatory cytokines, including TNF-α, IL-6, and interferon-gamma (IFN-γ). At the same time, it increased the anti-inflammatory cytokine IL-10. Oxidative stress was also mitigated, as shown by decreased MDA and myeloperoxidase (MPO) levels, along with enhanced antioxidant defenses, including increased SOD activity and a higher GSH–GSSG ratio. At the molecular signaling level, ALA suppressed the activation of NF-κB and multiple mitogen-activated protein kinase (MAPK) pathways, such as c-Jun N-terminal kinase (JNK), p38 MAPK, and extracellular signal-regulated kinase (ERK). These findings demonstrate ALA's ability to alleviate hepatic inflammation, oxidative stress, and fibrosis in both toxic and immune-mediated hepatitis models.

5.2.2. Metabolic Dysfunction-Associated Steatotic Liver Disease

Metabolic dysfunction-associated steatotic liver disease is the most common chronic liver condition affecting approximately 25% of people globally [85]. It is characterized by excessive fat buildup in the liver without significant alcohol consumption, and it is closely linked to obesity, insulin resistance, type 2 diabetes, and abnormal lipid levels [86]. The disease process includes a higher influx of free fatty acids into the liver, increased *de novo* lipogenesis, and reduced mitochondrial beta-oxidation [87]. Adipokine imbalances, such as reduced adiponectin and elevated leptin levels, contribute to hepatic insulin resistance, inflammation, and fibrogenesis [88]. Injured hepatocytes release arachidonic acid and other lipotoxic mediators, which activate Kupffer cells and hepatic stellate cells (HSCs) via NF-κB and JNK signaling, promoting the

progression of steatosis to steatohepatitis, fibrosis, and ultimately cirrhosis [89,90].

The hepatoprotective properties of ALA are demonstrated in both *in vivo* and *in vitro* models of metabolic liver injury, particularly in high-fat diet (HFD)-induced steatosis and lipotoxicity. In rats subjected to HFD, oral ALA treatment at a dose of 500 mg/kg for 8 weeks significantly reduced hepatic lipid accumulation and redirected lipid metabolism in favor of anti-inflammatory omega-3 fatty acid synthesis. Concurrently, it suppressed the generation of pro-inflammatory eicosanoids derived from arachidonic acid (AA). These beneficial effects were associated with attenuated hepatic inflammation, primarily through downregulation of NF-κB signaling and upregulation of Nrf2 activation. Furthermore, administration of ALA led to marked reduced levels of inflammatory mediators, such as IL-6, IFN-γ, macrophage inflammatory protein-1 alpha (MIP-1α), and vascular endothelial growth factor (VEGF) [91]. In a related model using diabetic Goto-Kakizaki (GK) rats—an established non-obese model of type 2 diabetes—fed with HFD, ALA administered with 50 mg/kg (i.p.) thrice per week for 3 months improved glycemic control, lipid profile, and liver enzyme levels. ALA also enhanced hepatic antioxidant defenses by increasing GSH, activating Nrf2, and suppressing TNF-α [92].

In vitro studies further corroborate these findings. In HepG2 liver cells, lipotoxicity induced by palmitic acid (250 μM) and oleic acid (500 μM) was markedly attenuated by ALA, where low concentrations (1–5 μM) reduced both oxidative stress and endoplasmic reticulum (ER) stress. It stabilized mitochondrial membrane potential and promoted mitochondrial biogenesis through upregulation of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) and Sirt1. Mitochondrial dynamics were also improved, with increased expression of fusion proteins (MFN1 and MFN2) and reduced expression of fission protein FIS1. ALA enhanced cellular energy metabolism, reflected by elevated ATP, NAD^+, and NADPH levels. In addition, ALA lowered the expression of inflammatory markers, such as IL-8, IL-1β, and TNF-α, and reduced lipid peroxidation, as indicated by decreased MDA levels. It also reversed oxidative stress by restoring glutathione levels and modulating antioxidant gene expression (e.g., HO-1), decreased cellular senescence markers (β-galactosidase), and regulated stress adaptation pathways, including autophagy and the unfolded protein response. Together, these effects support ALA's role in maintaining hepatocyte stability and counteracting metabolic injury [93,94].

5.2.3. Fibrosis

Liver fibrosis is a progressive, yet potentially reversible, condition caused by ongoing liver damage from infections, toxins, or metabolic issues. It involves the buildup of extracellular matrix (ECM) proteins—mainly collagen type I and alpha-smooth muscle actin (α-SMA), which disrupt the normal structure and functioning of liver tissues. If not treated, fibrosis can advance to cirrhosis and HCC [95,96]. The activation of HSCs is central to fibrogenesis. Upon liver injury, quiescent HSCs transform into myofibroblast-like cells that secrete ECM proteins and pro-fibrogenic cytokines. This activation is fueled by autophagy, which provides metabolic substrates through the degradation of lipid droplets [97]. Oxidative stress, particularly from NADPH oxidase (NOX)-generated ROS, further amplifies activation of HSC and collagen synthesis [98].

The anti-fibrotic potential of ALA is demonstrated across multiple experimental models of liver fibrosis, involving chemically, immunologically, and parasitically induced injury. In a rats model of advanced liver fibrosis induced by TAA, daily oral administration of ALA (30 mg/kg for 8 weeks) significantly reduced hepatic collagen deposition. This effect is supported by decreased hepatic hydroxyproline levels and lower expression of tissue inhibitor of metalloproteinase-1 (TIMP-1), both markers of fibrotic burden. Histological analysis confirms reduced fibrotic septa, indicating structural improvement of liver tissues. At the molecular level, ALA downregulates key fibrogenic mediators, including transforming growth factor-beta 1 (TGF-β1) and platelet-derived growth factor-BB (PDGF-BB), which are essential for activation of HSC and production of ECM. Expression of α-SMA, a hallmark of activated HSCs, is also reduced. Moreover, ALA promotes apoptosis of activated HSCs via caspase-3 activation and impairs their survival by inhibiting autophagy through reduced levels of microtubule-associated protein 1A/1B-light chain 3-II (LC3-II), thereby limiting metabolic support for fibrogenesis [99].

In an immune-mediated model of liver fibrosis induced by Con A, administration of ALA (50 mg/kg, i.p.) results in decreased hepatic hydroxyproline content and downregulation of α-SMA and TGF-β1. ALA also suppresses the expression of NADPH oxidase isoforms NOX-1 and NOX-4, suggesting attenuation of ROS-driven fibrogenic signaling. Although the NOX inhibitor apocynin showed slightly greater efficacy in certain parameters, ALA alone produced a substantial anti-fibrotic effect, supporting its use as a single-agent therapy in immune-related liver fibrosis [100].

In a parasitic model of liver fibrosis, mice chronically infected with Schistosoma japonicum received ALA (50 mg/kg/day, i.p.) for 8 weeks. Treatment resulted in reduced granuloma size and decreased expression of collagen type I and α-SMA, indicating suppressed fibrotic activity. These effects were accompanied by the restoration of mitochondrial membrane integrity and improved functioning of mitochondrial respiratory chain complexes. Additionally, ALA enhanced the phosphorylation of dynamin-related protein 1 (drp1), suggesting that modulation of mitochondrial fission may contribute to the resolution of fibrosis [101].

5.2.4. Cirrhosis

Liver cirrhosis is a chronic disease marked by progressive hepatocyte damage and fibrotic remodeling, resulting in abnormal liver architecture [102]. Major causes include alcohol abuse, viral infection, and exposure to hepatotoxic drugs or chemicals [103]. It contributes to a significant global health burden, with around one million deaths annually, accounting for 2% of global mortality [5].

In a rat model of cirrhosis induced by 8 weeks of CCl_4 exposure, daily co-administration of ALA (50–100 mg/kg) significantly improved liver architecture. These improvements are evident both histologically and biochemically, with notable reduction in serum ALT and AST levels. ALA also reduces hepatic hydroxyproline content and the expression of collagen type I alpha 1 (COL1A1), both key markers of collagen deposition and severity of fibrosis. On molecular level, ALA suppresses α-SMA expression and inhibits the TGF-β–SMAD family member 3 (Smad3) signaling pathway, which plays a central role in hepatic stellate cell activation and fibrogenesis. In addition to its anti-fibrotic effects, ALA helps to restore autophagic balance. This is evidenced by decreased expression of autophagy markers Beclin-1 and LC3-II, along with increased levels of p62, suggesting improved autophagic flux and reduced cellular stress. Furthermore, ALA activates the AKT–mTOR pathway, which supports hepatocyte survival and promotes regeneration of the liver, indicating that ALA exerts broader cytoprotective effects beyond suppression of fibrosis [104]. The anti-fibrotic and autophagy-modulating properties of ALA in cirrhosis models confirm its ability to disrupt fibrosis and slow the progression of cirrhosis, similar to earlier fibrosis studies.

5.2.5. Hepatocellular Carcinoma

Hepatocellular carcinoma is a major contributor to global cancer mortality and often develops because of chronic liver diseases [105]. Its development involves the transformation of inflamed liver tissues into dysplastic nodules and aggressive tumors with high metastatic potential. The disease often progresses silently, and by the time it is diagnosed, curative options, such as surgery or liver transplantation, are often limited [106,107].

Alpha-lipoic acid has demonstrated promising antitumor activity in HCC by inducing oxidative stress and activating unfolded protein response. In both rat (FaO) and human (HepG2, C3A, and Hep3B) liver cancer cell lines, ALA increased ROS production and upregulated ER stress markers, leading to apoptosis and G0/G1 cell cycle arrest [108,109]. These effects were further confirmed by Annexin V/propidium iodide (PI) staining and increased caspase activity. In addition to promoting cell death, ALA inhibited tumor cell migration and invasion, two key features of cancer progression, particularly in p53-wild-type cell lines (HepG2 and C3A). In these models, ALA reversed epithelial–mesenchymal transition (EMT) by increasing E-cadherin and reducing SNAIL (Snail1) expression, a key EMT-inducing transcription factor that suppresses epithelial characteristics and promotes tumor cell motility. In contrast, its effects were attenuated in p53-deficient Hep3B cells, suggesting a partial dependence on functional p53 for ALA's anti-metastatic action [109].

These mechanistic findings align with clinical data from the Cancer Genome Atlas (TCGA), which shows that HCC patients with high matrix metalloproteinase-9 (MMP9) expression and mutant p53 have significantly worse survival, compared to those with low MMP9 and wild-type p53. Together, these results suggest that ALA may be particularly effective in treating p53-intact HCC by enhancing apoptosis and suppressing metastasis [110]. Together, these findings suggest that ALA's anti-metastatic and pro-apoptotic effects may offer particular benefit in patients with p53-intact HCC.

Table 4 summarizes ALA's effects in liver disease models. The consistency across diverse experiments supports its advancement to the clinical evaluation of human liver disease treatment.

6. Clinical Trials

Building on the reliable hepatoprotective effects observed in preclinical studies, clinical trials examined ALA's therapeutic potential in patients with liver conditions.

In the context of drug-induced liver injury, a double-blind, placebo-controlled trial assessed the effectiveness of a combination therapy comprising ALA (250 mg), acetyl-L-carnitine (ALCAR, 250 mg), and coenzyme Q10 (CoQ10, 200 mg) in preventing hepatotoxicity linked to anti-tuberculosis (anti-TB) medications. The intervention significantly lowered serum ALT and AST levels compared to placebo ($P = 0.003$), and the occurrence of drug-induced liver injury was notably lower in the treatment group (6.8%) than in the placebo group (25.6%) ($P = 0.017$). These findings suggest that ALA, particularly when combined with mitochondrial cofactors, may offer effective prophylactic support during high-risk treatments, such as anti-TB therapy [111].

Alpha-lipoic acid's function in managing chronic hepatitis C virus (HCV) infection is investigated as well. In a case report involving three patients with advanced liver dysfunction, treatment with a combination of ALA (600 mg/day), silymarin (900 mg/day), and selenomethionine (400 μg/day) led to significant clinical improvements, with all patients avoiding liver transplantation. While the individual contribution of ALA cannot be segregated from the combined regimen, the findings highlight the potential cost-effectiveness of antioxidant-based therapy in advanced cases [112]. An open-label 20-week trial further evaluated antioxidant supplementation in 50 chronic HCV patients, using a regimen of seven oral and four intravenous antioxidants. A favorable clinical response was observed in 48% of participants: 44% achieved ALT normalization, and 36.1% demonstrated histological improvement. Additionally, over half of the patients reported improved quality of life, with no major adverse events noted [113]. In a randomized controlled trial involving 100 interferon-nonresponsive HCV patients, antioxidant therapy led to significantly greater ALT reduction in 52% of patients versus 20% in the placebo group ($P = 0.05$). A decrease of ≥1 log in HCV RNA was achieved by 28% of the treated patients, compared to 12% in the control group [114]. While some studies also reported modest reduction in viral load, these findings have been inconsistent, and the main reproducible benefit of ALA-containing antioxidant regimens appears as improved liver enzyme levels and liver function rather than antiviral effects.

Table (4): Mechanistic summary of alpha-lipoic acid (ALA) in preclinical liver disease models.

Liver disease model	Pathological features	ALA mechanisms of action	Key outcomes	Ref.
Hepatitis (TAA and Con A)	Inflammation, cytokine release, oxidative stress	↓ TNF-α, IL-6, IFN-γ; ↑ IL-10; inhibits NF-κB and MAPKs; ↑ GSH and SOD; ↓ MDA and MPO	Reduced liver enzymes; preserved histology; attenuated inflammation and oxidative damage	[83,84]
MASLD (HFD, diabetic models)	Lipotoxicity, steatosis, and insulin resistance	↓ NF-κB, IL-6, TNF-α; ↑ Nrf2, GSH, antioxidant enzymes; improved mitochondrial dynamics; ↓ ER stress	Improved lipid profile, glycemia, and liver function; restored redox balance	[91,92]
Fibrosis (TAA, Con A, schistosomiasis)	ECM accumulation, HSC activation, and ROS production	↓ TGF-β1, α-SMA, PDGF-BB, and NOX-1/4; ↑ caspase-3; ↓ LC3-II; ↑ Drp1	Suppressed HSC activity; reduced fibrosis markers and collagen content	[99–101]
Cirrhosis (CCl_4)	Fibrotic remodeling, hepatocyte damage, autophagy dysregulation	↓ TGF-β/Smad3, α-SMA, Beclin-1, LC3-II; ↑ p62; ↑ AKT/mTOR activation	Improved liver architecture; normalized enzyme levels; and slowed fibrosis progression	[104]
Hepatocellular carcinoma	Tumor proliferation, invasion, EMT, UPR dysfunction	↑ ROS, CHOP, GRP78, PERK, IRE1, and caspases; ↓ SNAIL; ↑ E-cadherin; p53-dependent effects	Induced apoptosis and UPR; inhibited migration and EMT; selective cytotoxicity in p53-WT cells	[108,109]

Table (5): Summary of randomized controlled trials evaluating ALA supplementation in patients with MASLD.

Sample size (N per group)	Intervention (dose and regimen)	Duration	Key outcomes	Ref.
25 ALA vs. 25 placebo (with vitamin E in both groups)	ALA 1,200 mg/day + vitamin E 400 mg vs. placebo + vitamin E	12 weeks	Insulin levels declined significantly ($P = 0.019$), accompanied by reduction in HOMA-IR ($P = 0.024$) and fetuin-A concentrations ($P = 0.042$). Histological evaluation showed steatosis diminishing in 87.5% of patients, compared with 59.1% in the placebo group, yielding a number-needed-to-treat of 4 for achieving at least a one-grade improvement.	[115]
ALA 300 mg (n = 40), vitamin E 700 IU (n = 40), combo (n = 40), placebo (n = 35)	ALA 300 mg/day ± vitamin E 700 IU	6 months	TNF-α levels were reduced by 82.6% with a combination therapy, compared to 12.5% with placebo. ALT decreased by 44.8%, and HbA1c declined by 17.7% in the combination group. HOMA-IR improved markedly (76.1% vs. 7.1% with placebo). Adiponectin concentrations more than doubled, showing an increase of 111%.	[116]
25 ALA vs. 25 placebo (both with vitamin E)	ALA 1,200 mg/day + vitamin E 400 mg vs. placebo + vitamin E	12 weeks	ALT, AST, and ALP levels decreased significantly in the ALA group ($P < 0.05$); MDA levels declined ($P = 0.016$), and TAS increased ($P = 0.031$). No significant between-group differences were observed for liver enzymes, although oxidative stress markers showed significant improvement with ALA.	[117]
23 ALA vs. 22 placebo (both with vitamin E)	ALA 1,200 mg/day + vitamin E 400 mg vs. placebo + vitamin E	12 weeks	ALT levels declined ($P = 0.031$), AST decreased ($P = 0.020$), IL-6 was reduced ($P = 0.013$), and ferritin levels descended ($P = 0.018$), while adiponectin levels ascended ($P = 0.022$). Steatosis lessened in 91.3% cases of the ALA group, compared to 54.5% cases in the placebo group, although the between-group difference was not statistically significant.	[118]
25 ALA vs. 25 placebo	ALA 1,200 mg/day vs. placebo	12 weeks	Insulin levels declined (P = 0.024), Quicki scores improved ($P = 0.007$), leptin concentrations were lowered ($P = 0.042$), resistin levels diminished ($P = 0.009$), adiponectin concentrations developed ($P = 0.022$), and the adiponectin–leptin ratio enhanced ($P = 0.027$); ALT and AST showed within-group reduction (not between groups); steatosis lessened in both groups but without significant between-group differences.	[119]

Several randomized trials (n = 40–155) have investigated ALA in MASLD (NAFLD) patients. Supplementation with 1,200 mg/day of ALA, often combined with vitamin E, for 12 weeks–6 months led to improvement in insulin resistance (homeostasis model assessment of insulin resistance [HOMA-IR]), liver enzymes (ALT and AST), oxidative stress markers, and adipokine profiles. Some studies also reported histological improvement in steatosis, although effects on fibrosis were limited. Key findings, including sample size and effect estimates, are summarized in Table 5.

7. Limitations and Future Perspectives

While current evidence supports the hepatoprotective effects of ALA, several limitations must be acknowledged. Most clinical studies feature small sample size and brief durations, which limit how broadly their findings can be applied. Additionally, many trials use ALA in combination with other antioxidants, complicating the interpretation of its independent effects. In preclinical studies, although ALA has shown consistent antioxidant, anti-inflammatory, and anti-fibrotic properties, variability in animal models, doses, and treatment timelines may influence translational outcomes.

Future research should aim to confirm ALA's efficacy through large-scale, well-controlled clinical trials focused on monotherapy or clearly defined combinations. Standardizing experimental protocols and outcome measures will improve consistency across studies. Moreover, exploring ALA's effects in advanced stages of liver disease, such as cirrhosis or HCC, remains an important area for future investigation. Long-term safety and disease-modifying effects also warrant further evaluation.

8. Conclusions

Alpha-lipoic acid demonstrates consistent hepatoprotective effects in diverse preclinical models, largely through antioxidant defense, modulation of inflammatory pathways, and mitochondrial protection. Early clinical studies, including those in MASLD, hepatitis C, and drug-induced liver injury, provide encouraging signals but remain limited in number, size, and methodological rigor. At present, the evidence base is insufficient to support routine clinical use, and further well-designed, large-scale clinical trials are required to confirm its therapeutic value. Given its favorable safety profile and reproducible biological actions, ALA represents a promising candidate for adjunctive therapy in liver injury of various etiologies. Importantly, most clinical investigations have employed racemic (RS)-ALA formulations (300–1,200 mg/day) containing an equal mix of enantiomers R-ALA and S-ALA; future studies should also assess the relative efficacy of enantiomer R-ALA, compared with RS-ALA.

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