Liu *et al. Nutrition & Metabolism* (2025) 22:56
https://doi.org/10.1186/s12986-025-00954-9

Nutrition & Metabolism

REVIEW

Open Access

Lipoic acid in metabolic dysfunction-associated steatotic liver disease: a review

Fangli Liu[1†], Jingjing Lv[1†], Yuanyuan Chen[2,3], Linfeng Wang[2,3], Zhuoxin Liu[4] and Xingke Li[2,3*]

Abstract

The incidence and prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD), a chronic liver disease characterized by hepatic steatosis without substantial alcohol consumption, are rapidly increasing worldwide. Liver cirrhosis and cancer are relatively common in MASLD patients. Therefore, it is essential to take proactive measures in preventing its onset or initiating prompt treatment. However, there is a lack of approved medications for effectively treating this ailment. Lipoic acid (LA), a compound with antioxidant, insulin-sensitization, anti-inflammatory, and prooxidant activities, has been proven to inhibit lipid deposition. Many studies have shown that supplementation of LA can alleviate MASLD. Therefore, the latest evidence on the relationship between LA and MASLD is presented in this review. The effect of LA on the accumulation of fat in the liver is emphasized following different diet models (normal, high fat, high fructose, choline deficiency) and other models (gene mutation, diabetes), with the main mechanisms from mitochondrial function to inflammation and oxidative stress being summarized. LA possesses excellent preventive effects on MASLD, which can provide new opportunities for clinical research.

Keywords Lipoic acid, Metabolic dysfunction-associated steatotic liver disease, Hepatic fat accumulation, Mechanisms, Prevention

Introduction

According to recent studies, it has been disclosed that the global prevalence of fatty liver disease among adults stands at 24% [1]. Fatty liver disease arises from an excessive build-up of fat within the liver, potentially leading to functional impairments and disruptions in its regular operations. Consequently, this condition may gravely jeopardize the health of vital organs such as the heart, kidneys, brain, and gallbladder. In addition, Fatty liver significantly elevates the risk of progressing from simple fibrosis to cirrhosis, and ultimately, liver cancer. [2, 3]. The incidence of liver fibrosis is up to 25%, and about ~ 8% of patients can progress to cirrhosis. Fatty liver disease is divided into two main categories depending on the history of alcohol consumption, namely, alcoholic fatty liver disease (AFLD) and metabolic dysfunction-associated steatotic liver disease (MASLD). Although AFLD is usually considered a benign and static lesion, it can develop irreversible liver damage in a short period of time, MASLD is caused by high-fat diet (HFD), high-fructose diet, methionine- and choline-deficient diet (MCD), gene mutations, and heavy-metal poisoning. The pathogenesis of MASLD is complex and includes

†Fangli Liu and Jingjing Lv contributed equally to this work.

*Correspondence:
Xingke Li
tianxing1230@henu.edu.cn
[1] School of Nursing and Health, Henan University, Kaifeng 475004, China
[2] College of Life Sciences Institute of Biological Engineering, Henan University, Kaifeng 475004, China
[3] Engineering Research Center for Applied Microbiology of Henan Province, Kaifeng 475004, China
[4] School of Medical Sciences, Xinjiang Medical University, Urumqi 830000, China

© The Author(s) 2025. **Open Access** This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by-nc-nd/4.0/.

mitochondrial dysfunction, inflammation, and oxidative stress (Fig. 1) [4–8].

The prevalence of MASLD has been escalating rapidly, demonstrating a consistent upward trend year on year, notably among younger individuals [9, 10]. It is estimated that about 30% of the global population is affected by nonalcoholic fatty liver disease. In China, about 400 million people are affected by 2024, and the prevalence of MASLD is as high as 29.2%, making it the largest liver disease. Non-alcoholic fatty liver disease is a progressive disease, without effective intervention, can gradually deteriorate into non-alcoholic steatohepatitis, fatty liver fibrosis, liver cirrhosis and even liver cancer, and may become the main cause of end-stage liver disease in the future [11].

Therefore, it is very important to prevent fatty liver actively to prevent the progression of chronic liver disease and improve the prognosis. And there have been a growing number of research papers published on the prevention and mitigation of MASLD [12]. It is crucial to promptly explore innovative approaches to tackle MASLD. Extensive experiments have provided substantial evidence for the effectiveness of various natural substances, such as Polygonum multiflorum, Artemisia annua leaves, berberine (BBR) [13], and curcumin, in alleviating MASLD. It is worth emphasizing that lipoic acid (LA), a naturally occurring disulfide compound in the human body, may be a safer choice. Abundant research has confirmed that LA effectively inhibits lipid accumulation in both living organisms and laboratory experiments [14–17]. Aside from this, LA is extensively used to induce remission of diverse conditions, including Alzheimer's disease, Down syndrome, diabetes [18–20], and even MASLD. Based on the above research evidence, the study hypothesis is that supplemeting LA appropriately to combat MASLD may be effective. In addition, LA has a number of advantages (widely available in foods, easy to supplement and relatively safe) that help to justify the hypothesis mentioned above. In this paper, the latest evidence on the relationship between LA and MASLD is reviewed to provide valuable insights for future explorations into mechanisms and to aid clinical investigations.

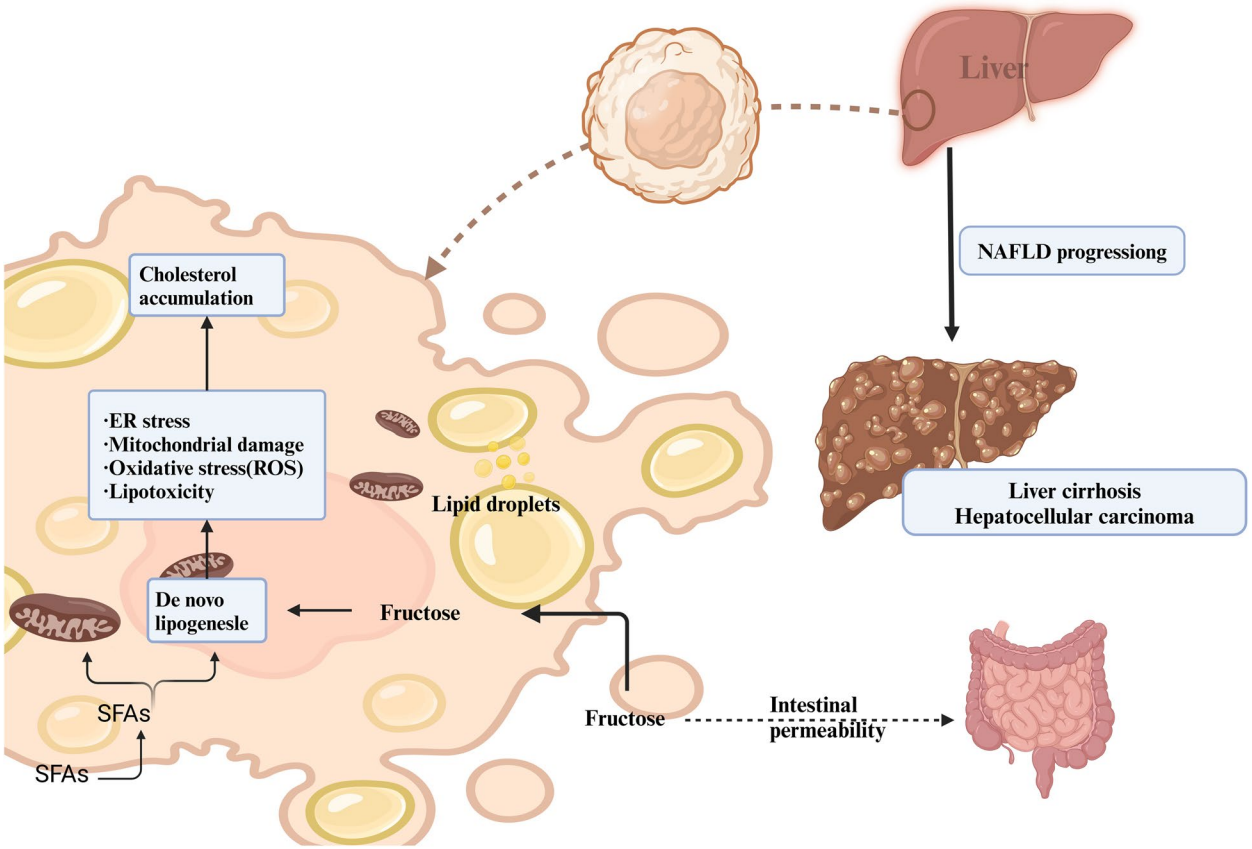

Fig. 1 The pathogenesis of MASLD

Lipoic acid

Source and synthesis

LA, which was first isolated from bovine liver in 1951 [21], was previously regarded as a vitamin. However, it was later determined that LA is biosynthesized by animals. LA can be obtained from plants such as spinach and potatoes, but also from animal viscera (Fig. 2) [22, 23]. Although humans can only synthesize a small amount of LA from fatty acids and cysteine, LA can be easily absorbed from exogenous dietary sources [24] to ensure some functions of human growth physiology.

LA—i.e., 1, 2-dimercaptiol-3-valeric acid—consists of a single chiral center and an asymmetrical carbon, which leads to the presence of two optical isomers. As a molecule that occurs naturally, LA can be synthesized internally in the mitochondria in small quantities from octanoic acid through the action of LA synthase (LASY) [25]. The impaired production of LA leads to a disruption in the overall antioxidant defense system, thereby promoting inflammation and dysfunction of the mitochondria [22, 23]. In vivo, LA exists as free and protein-bound (predominant form) and is formed by the substitution of sulfur groups for hydrogen at positions 6 and 8 of octane groups [26]. Only R-LA is endogenously synthesized, so this isomer is essential for biological systems [27].

In vivo, LA can be reduced to dihydro LA (DH-LA) by dihydrolipoamide dehydrogenase [28]. Dithiol rings are present in both the oxidized state (LA) and the reduced state (DH-LA), endowing both forms with powerful natural antioxidant properties. LA, which are both hydrophilic and hydrophobic [29], readily traverse biological membranes, thereby effectively penetrating all cellular compartments. Notably, LA, while remaining relatively stable in its solid state, undergoes polymerization when subjected to temperatures exceeding its melting point (47.5 °C) or when dissolved in a neutral solution under the presence of light [30].

Biological function

Oxidation mechanism of lipoic acid

LA is a natural cofactor with antioxidant capacity, and scavenges reactive oxygen species (ROS) and chelates metal ions [31]. In mitochondria, LA is a vital cofactor for several enzymes (the oxoglutarate dehydrogenase complex [OGDC], pyruvate dehydrogenase complex [PDHC], branched-chain α-ketoacid dehydrogenase complex [BCKDC]) that contribute to aerobic metabolism and nucleic acid synthesis [32, 33]. LA maintains the cellular antioxidant state indirectly through activating the NRF2 pathway, and the NRF2 pathway governs the expression of antioxidant genes (such as γ-glutamylcysteine synthetase (γ-GCL), NAD(P)H quinone oxidoreductase 1 (NQO-1), and superoxide

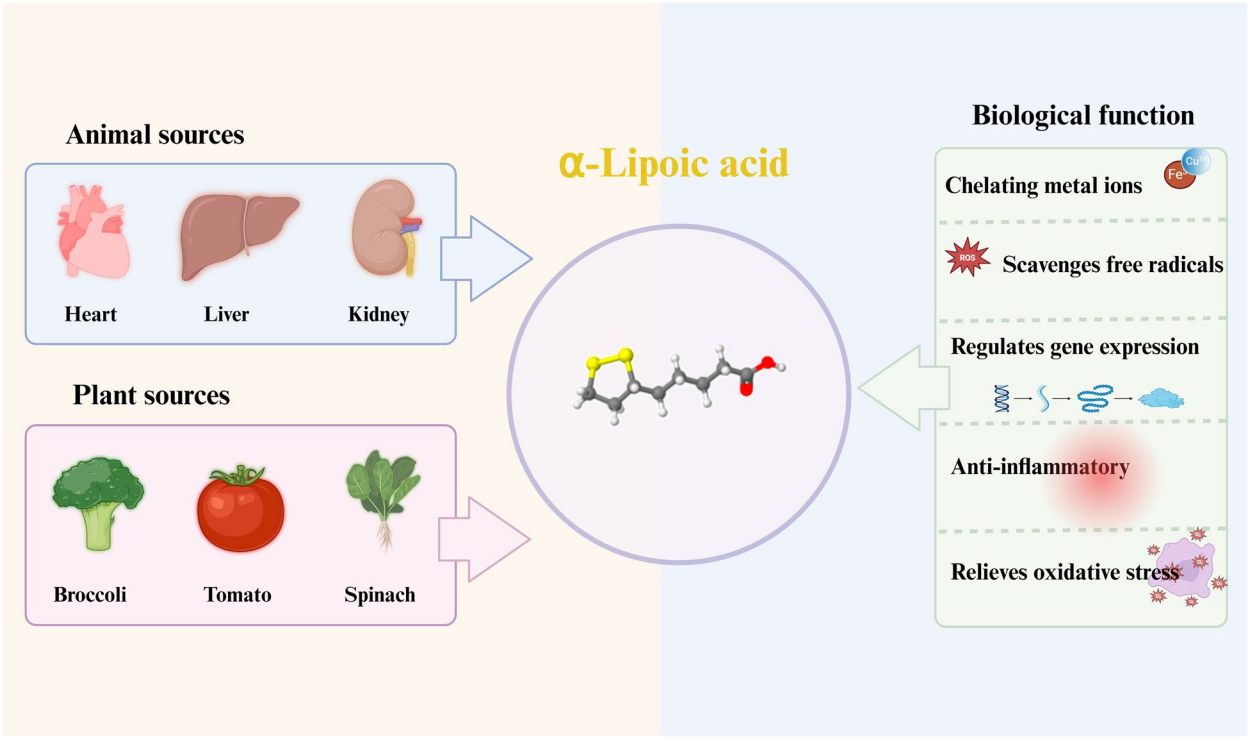

Fig. 2 Source and biological function of lipoic acid

dismutase (SOD)) for enhancing the cell's antioxidant capacity and anti-inflammatory response [34, 35].

Additionally, free LA can provide the following biological effects. LA (DH-LA) can directly scavenge ROS and reactive nitrogen species (RNS), thereby reducing oxidative damage [36]. It is worth noting that LA has both antioxidant and prooxidant capacities, where the exact effect depends mainly on the cellular redox status and physiological status [37]. Excessive use of antioxidants is harmful to the organism in both physiological and pathological states and may produce prooxidant effects. Specifically, it has been shown that 100 mg LA/kg body weight/day for 2 weeks i.p. [38], which is equivalent to 5–10 LA g/day in humans, increases oxidative damage in aged rats. Therefore, the prooxidant effect of LA cannot be ignored in the subsequent studies.

Regulation of other signalling pathways

LA can inhibit the production of proinflammatory nuclear factor-kappa B (NF-κB) [39] and stimulate the translocation of glucose transporter 4 (GLUT4), thereby improving insulin sensitivity [40, 41]. Cell proliferation and apoptosis can also be controlled by LA via activating extracellular regulated protein kinase 1/2 (ERK 1/2) [42], protein kinase C δ (PKCδ) [43], and mitogen-activated protein kinase (MAPK) [44]. LA can activate AMP-activated protein kinase (AMPK) [45] to promote the production of new mitochondria. These biological functions give LA therapeutic potential in body organs [45–50].

Absorption and metabolism

Pharmacokinetic studies have shown that LA (50–600 mg p.o.) is completely absorbed within 30–60 min (half-life: 30 min), which leads to the attainment of the highest concentration of LA in the bloodstream [51]. The human body absorbs around 20–40% of an oral dosage of LA [52]. Food intake reduces the bioavailability of LA. Compared with fasting, the peak and total plasma concentrations of LA decrease by about 30 and 20%, respectively, when LA is ingested during a meal. Therefore, humans need to consume LA 30 min before or 2 h after eating [24]. Furthermore, research has demonstrated that the acidic pH of the stomach is conducive to the absorption of ALA via the stomach. Consequently, ALA supplements are advisable to be consumed on an empty stomach to capitalize on the acidic stomach pH. Additionally, taking it on an empty stomach can also mitigate the competition with other nutrients for absorption [53]. Severe kidney impairment and food intake can influence the pharmacokinetic parameters of ALA [54, 55]. In addition, Due to its rapid metabolism, LA in tissues exists in limited quantities [56]. The bioavailability of LA is approximately 30% (20–38%), primarily due to the first-pass effect in the liver [18].

Adverse reactions and pharmaceutical safety

One study showed that 2400 mg LA/day, p.o., for 2 weeks did not result in any adverse effects compared with placebo [57]. Similarly, 600 mg LA/day, i.v., for 3 weeks showed no adverse effects [58], and 1800 mg LA/day, p.o., for 6 months was also safe [59]. While LA is safe in these doses (2400 mg/day, p.o., for 2 weeks. 1800 mg/day, p.o., for 6 months. 600 mg/day, i.v., for 3 weeks), it is important to note that certain populations, such as pregnant women [60], aged individuals [61], and children [62], may experience a higher likelihood of side effects.

The most common adverse effect of LA is anaphylaxis (e.g., hives [63] and delayed hypersensitivity [64]). It has also been shown that 100 mg LA/kg body weight/day, i.p., for 2 weeks [38], which is equivalent to 5–10 g LA/day in humans—increases oxidative damage in elderly rats. Considering the efficacy and safety of LA in disease treatment and health maintenance, it is important to pay special attention to the possible adverse reactions during its application.

The clinical application of alpha-lipoic acid in metabolic dysfunction-associated steatotic liver disease

Metabolic Dysfunction-associated Steatotic Liver Disease is a chronic liver disease characterized by excessive fat accumulation in the liver, insulin resistance, oxidative stress and inflammatory responses, which can progress to non-alcoholic steatohepatitis, fibrosis, cirrhosis and even hepatocellular carcinoma.

Six articles were found regarding ALA use in patients with a diagnosis of MASLD. Some of these studies evaluated the benefits of ALA in the management of MASLD symptoms and of metabolic side effects related to the disease(Table 1).

Lipoic acid and hepatic fat

The mechanism of LA on NAFLD under different causes, The specific mechanism is given in Fig. 3.

Effects of lipoic acid on hepatic fat accumulation in rats fed normal diets

Anomalous metabolism and fat accumulation have been indicated by the noticeable rise in quantity and size of hepatic dense bodies that house lipofuscin deposits, consisting of a considerable amount of fat, in aged rats fed a regular diet [72]. Reduced mitochondrial number and their increased deformation may damage the normal oxidative decomposition of fat, thereby increasing hepatic fat content. Characteristic features of metabolic dysfunction (insulin resistance, diabetes mellitus type 2 [T2DM],

Table 1 ALA in the Treatment of Metabolic Dysfunction-Related Fatty Liver Disease

Authors	Disease	Outcome	Total number of subjects	Number of subjects receiving ALA	Mean period and dosage of treatment	Results
Helda [65]	MASLD	The effects of α-lipoic acid on metabolic parameters and liver function in patients with MASLD	92	21	1200 mg/day (8 weeks)	Improved metabolic parameters and hepatic steatosis
Alessandro [66]	PCOS	Evaluating the effects of α-lipoic acid on hormonal and metabolic parameters in a cohort of overweight/obese polycystic ovary syndrome (PCOS) patients	32	32	400 mg/day (12 weeks)	ALA administration significantly improved insulin sensitivity in all subjects and reduced ALT and AST plasma levels. The HIE index showed a greater reduction. ALA administration enhanced peripheral insulin sensitivity and hepatic insulin clearance, an effect that may lower the risk of MASLD and diabetes in PCOS patients
Sonya [67]	MASLD	The effect of ALA supplementation on liver enzymes and inflammatory markers in obese MASLD patients	45	23	1200 mg/day (12 weeks)	Improved serum adiponectin and IL-6 levels in obese NAFLD patients without altering serum liver enzymes or hepatic steatosis
Alireza [68]	MASLD	Effects of α-LA Supplementation on Adipokines and Hepatic Steatosis in Obese MASLD Patients	50	25	1200 mg/day (12 weeks)	Supplementation with α-LA for 12 weeks improved insulin resistance, serum insulin, adiponectin, and leptin levels, without altering anthropometric measurements, serum liver enzymes, resistin, or irisin
Mehrangiz [69]	MASLD	Evaluating the effects of alpha-lipoic acid supplementation on fetuin-A, sirtuin1 (SIRT-1), cytokeratin 18 (CK-18), hepatic steatosis, inflammation, and serum levels in MASLD patients	46	24	1200 mg/day (12 weeks)	supplementation with 1200 mg/day of ALA for 12 weeks significantly improved hepatic steatosis, insulin resistance, and serum levels of fetuin-A in patients with NAFLD
Sonya [70]	MASLD	Determine the effects of ALA supplementation on liver enzymes, insulin sensitivity, glucose markers, and lipid profiles in MASLD patients	45	23	1200 mg/day (12 weeks)	MASLD patients may benefit from ALA supplementation, at least partially through enhanced insulin sensitivity and improved blood lipid levels
Farshad [71]	MASLD	Evaluating the effects of α-lipoic acid supplementation on anthropometric indices, dietary intake, and oxidative stress-related parameters in obese MASLD	50	25	1200 mg/day (12 weeks)	Improved oxidative stress markers in patients with MASLD, which can be regarded as an adjunctive therapy to prevent the progression of MASLD

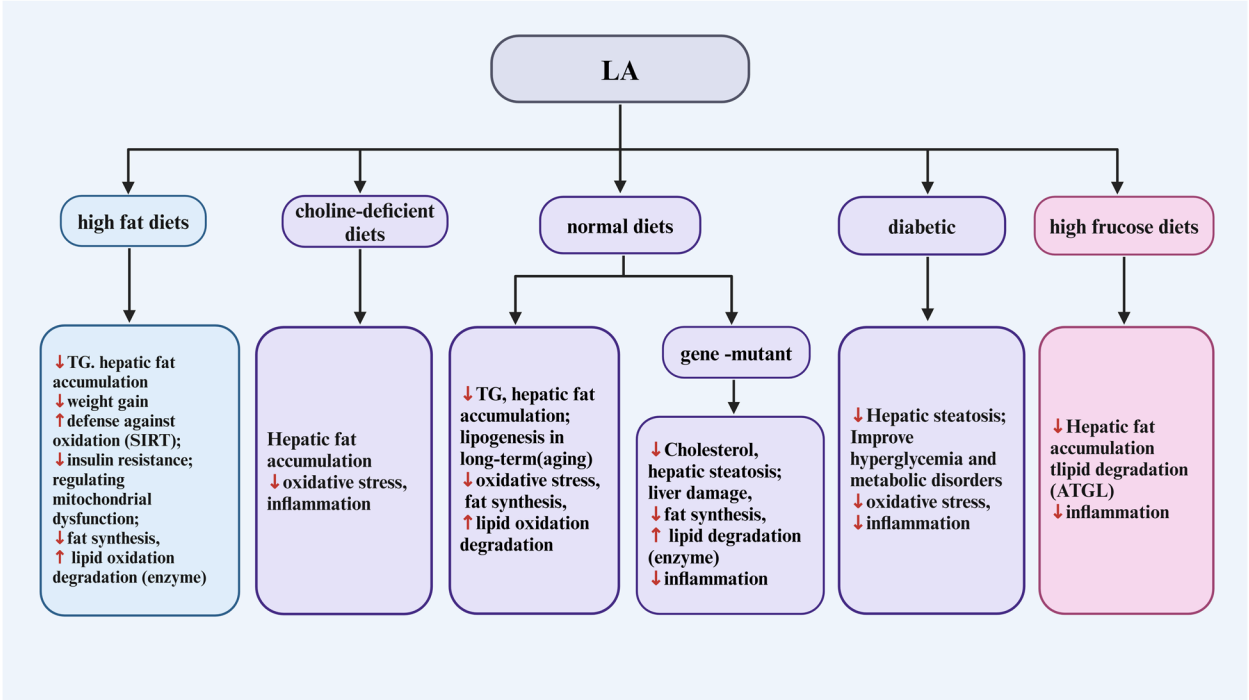

Fig. 3 Mechanisms of LA on MASLD caused by different causes

and hyperlipidemia) appearing in young subjects are also tightly associated with fatty liver, besides fatness [73]. Therefore, ascertaining and reducing fat accumulation in healthy subjects as early as possible may be a very important way to prevent the occurrence of fatty liver. Several studies on the influence of LA on hepatic lipid accumulation have been conducted in young, adult, and aged animals fed normal diets with 4–10% fat content. Many studies have shown that LA treatment ameliorates plasma triglycerides (TG), oxidative stress, and hepatic fat accumulation (Table 2) in young and aged animals fed normal diets. The mechanism of LA-induced decrease in hepatic fatty contents may be related to inhibited fat synthesis or increased lipid oxidative degradation in the livers by reducing oxidative stress or regulating some signaling molecules increased expression of miR-3548.

There have been inconsistent results in these studies about the effects of LA on fat metabolism in the liver in different ages and dietary fat contents. First, LA treatment (0.2 and 0.25% in diet) decreases hepatic fat synthesis in rats fed a diet with 4.6–12.5% fat and increases lipid oxidative degradation in the liver. Second, LA (1–5 g/kg) in diet inhibits hepatic fat synthesis in rats fed a 10% fat diet, and as the dosage increases, the effect also improves. Therefore, a higher dose of LA may be needed to achieve better effects (either by inhibiting fat synthesis or increasing fat oxidation) in attenuating fatty liver in animals fed a high-fat diet. Notably, LA supplementation can also alter circadian rhythms. Lower doses of LA are even adverse for hepatic fat metabolism in normal diet with 4% fat content. For example, in mice fed a 4% fat diet, short-term (4 weeks) or long-term (74 weeks) treatment with LA (20 mg/kg body weight) produced no improvement in systemic hypertriglyceridemia (HTG) and hepatic fat contents, and even significantly increased cholesterol content in rat livers despite enhanced mRNA expression of lipid oxidation–related genes (fibroblast growth factor-21 [Fgf21], peroxisome proliferators–activated receptor alpha[pparα], acyl coenzyme A oxidase [acox1], carnitine palmitoyl transferase 1a and 2 [cpt1a and cpt2], recombinant retinoid X receptor a [rxra]), and ATP-binding cassette transporter A1 [abca1]). The long-term (74 weeks) treatment also induced lipogenesis (increased expression of fatty acid synthase [FAS]), in contrast to decreased FAS expression in rat livers after the short-term treatment. However, the difference between the short-term and long-term treatments may rather be caused by the aging of the tested mice than by the long-term treatment. Increased fat synthesis based on enhanced glycolytic activity (pklr1, sterol regulatory element-binding protein-1 [SREBP1c], fas, and liver X receptor a [lxra]) in aged mice partly accounted for hepatic steatosis (increased leukocytic infiltration) and necrosis (increased plasma aspartate aminotransferase [AST] activity), compared with reduced srebp1c and fas mRNA levels in young mice. The lower doses of LA

Table 2 Effects of lipoic acid on hepatic fat accumulation in rats fed normal diets

In vivo studies				
Species	**Fat in diets**	**Treatments**	**Hepatic effects and mechanisms**	**Refs**
C57BL6/J	4.2%	α-LA (20 mg/kg BW) for 4 WKS or 74 WKS (p.o.)	↑rxra and lxra mRNA expression ↑β-oxidation(fgf21↑, pparα↑, and its target genes↑:acox1, cpt1a, and cpt2). ↑Glycolytic activity. ↓lipogenesis in short-term(fas↓, SREBP1c mRNA↓), but↑lipogenesis in long-term	[74]
SD	12.5%	α-LA (0.2%) for 5 WKS (p.o.)	↓TGs ↓Fat synthesis (↓fatty acid-binding protein 1 (FABP1) and ↓FASN (miR-3548↑)); ↑fat degradation (↑hormone-sensitive lipase (p-HSL))	[75]
6-week-old Wistar	4.6%	α-LA (0.25%) for 8 WKS (p.o.)	↓Energy efficiency, ↓TGs ↓Fat synthesis (modulating mitochondrial function: electron transport chain (ETC) complexes↓, oxidative phosphorylation (OP)↓, ATP↓). ↑fat degradation (↑β-oxiation genes: Cpt1a, Acadl and sirtuin(Sirt3)). deacetylating Forkhead box protein O 3a (FOXO3 A)	[76]
SD	10%	LA (1, 2.5, 5 g/kg) for 21 ds(p.o.)	↓TGs, ↓concentration of cholesterol ↓Fat synthesis and some mRNA levels(FAS↓,glucose 6-phosphate dehydrogenase (G6PD)↓,malic enzyme(ME) ↓,PK↓,spot 14↓, ADPN↓,stearoyl-CoA desaturase 1(SCD1)↓,△5 and △6 desaturases)	[77]
Young (3 ms) and old (24 ms) male Fischer 344	4%	LA (0.2%) for 2 WKS (p.o.)	Altering circadian rhythm ↓Transcripts of lipid synthesis genes (Acacβ↓, Fasn↓)	[78]
Wistar	5%	LA (100 mg/kg*BW/d) for 7 and 14 ds(i.p.)	Inhibiting lipid peroxidation	[79]
SD	10%	α-LA (2.5 g/kg); fish oil (0, 20, 100 g/kg) for 21 ds*(p.o.)*	↓Lipogenesis ↓lipogenic enzymes and mRNA levels, ↓fish oil-mediated oxidative stress	[80]
SD	10%	sesamin 0, 2 g/kg and α-LA 0, 2.5 g/kg in diet for 22 ds(p.o.)	↓TG, ↓lipogenic enzymes and mRNA levels, attenuating sesamin-mediated oxidative stress (fatty acid oxidation enzymes activity↓, carnitine concentration↓)	[81]

may be the key factor that led to these results. In contrast, another study has shown that higher doses of LA (100 mg/kg body weight) for different durations (7 and 14 days) can produce better effects in improving the fat contents in the liver, and even the effects of aging, which depresses the effect of LA on improving fatty liver, can be easily abolished by adding LA.

In addition, the content of polyunsaturated fatty acids (PUFAs) in the diet is another key factor affecting hepatic fat metabolism. Although PUFAs play important physiological roles in promoting growth and development, high PUFA intake can cause fat accumulation, fatty acid oxidation, lipid peroxidation, and even severe injury in the liver [82]. An increased proportion of PUFAs in normal diet also induces oxidative stress (increased malondialdehyde [MDA]), reduces cellular defense against oxidative stress (metallothionein) in the liver, and promotes oxidative degradation of DNA (elevated 8-hydroxy-2'-deoxyguanosine levels serum) in a content-dependent manner despite increased fat oxidation and decreased fat synthesis [80]. Therefore, the content of PUFAs in normal diet influences the effect of LA on attenuating fatty accumulation in the liver. A previous study has shown that despite reducing lipid oxidation, LA supplementation decreases hepatic fat content and the activity and mRNA expression levels of lipogenic enzymes (acetyl-CoA carboxylase α [ACCα], FAS, ATP-citrate lyase [ACLY], and PK) in the livers of rats fed a diet with 10% fat content, in which fish oil was replaced by vegetable oil to different proportions (20% and 100%), and another study (sesamin and LA) found the same. Meanwhile, LA treatment significantly inhibited oxidative stress (increased activity of γ-glutamyl cysteine synthase [γ-GCS] and glutathione [GSH] levels. decreased MDA) and oxidative degradation of DNA in the liver. In contrast to n-6 PUFAs, n-3 PUFAs in normal diet earlier induce lipid peroxidation when reducing hepatic lipid accumulation. Two studies (about fish oil and sesamin) have shown that LA treatment can significantly inhibit oxidative stress in the livers of rats and fish fed diets with n-3 PUFAs content, although hepatic lipid contents are not affected. Moreover, LA treatment prevents the inhibition of connective tissue hyperplasia in

mouse liver injuries caused by the normal diet administration with high n-3 PUFAs content for 8 weeks. Therefore, LA can be used to ameliorate lipid accumulation in the liver even in normal diet with high PUFA contents (especially n-3 PUFAs).

Lipoic acid attenuates hepatic fat accumulation in gene-mutant obesity rats fed normal diets

Recently, some studies have shown that gene mutation is another factor that induces obesity and fatty liver. For example, mutations in the thyroid hormone receptor beta (THRb) gene [83], the rs17618244 G > A β-Klotho (KLB) variant [84], germline hedgehog pathway [85], and polymerase I and transcript release factor [86], can also induce the occurrence of fatty liver. Hence, investigation of the possible effects of LA on the development of fatty liver due to genetic mutations would expand the range of LA utilization to such cases. So far, two types of gene-mutation animal models, including OLETF rats (the deficiency of cholecystokinin receptor 1) and Zucker rats (GmiCrl-fa/fa), have been used as models of fatty liver to verify the protective effects of LA. A latest study has shown that the overexpression of the LA synthase gene (Lias) significantly attenuated oxidative stress (Tfam) and histological steatosis in the livers of db/dbC57BL/6 mice fed a normal diet [87]. Lipid metabolism was improved, including decreased SREBP1 and FAS and increased PRKaa2 and Cpt1a mRNA levels.

The improved liver mitochondrial ultrastructure and function (increased levels of PGC-1α protein and Ucp2 mRNA) and inflammatory response (lower levels of IL-1β and TNFα) also contribute to the reduction of MASLD progression by LA. This suggests that exogenous LA supplementation may attenuate hepatic steatosis in gene-mutation animals.

Several studies (Table 3) have shown that LA significantly reduces body fat mass, hepatic clearance of TG-rich lipoproteins, and lipid droplets through upregulating the expression levels of hepatic lipolytic enzymes (ATGL, acyl-CoA thioesterase [Acot1], Acot2, Acsf2, and Crat) and downregulating the expression levels of liver lipogenic enzymes (patatin-like phospholipase domain protein [Pnpla3], Pnpla5, Elovl6, Acly, sn-glycerol-3-phosphate acyltransferase 1 [Gpat], Aacs, FASN, ACC, and SCD-1). The involved signaling pathways include increased pAMPK, SIRT1, fibroblast growth factor-21, and decreased ChREBP. LA can also decrease hepatic damage in the process of steatosis by inhibiting inflammation (by reducing the expression of high-mobility group protein box-1 [HMGB-1], Toll-like receptor-4 [TLR-4], vascular cell adhesion molecule-1 [VCAM-1], and COX-2). Except for the beneficial effects in the model animals fed normal diets, LA treatment with the

Table 3 Lipoic acid attenuates hepatic fat accumulation in gene-mutant obesity rats fed normal diets

In vitro studies				
Cell lines	Gene mutations	Treatments	Hepatic effects and mechanisms	Refs
Zucker/McA-RH7777 (hepatic tumor cell)	GmiCrl-fa/fa in normal diet	LA 200 g/kg*bw* day for 2 WKS *(p.o.)*	↓Secretion of VLDL and improving HTG. ↑CREBH, Insig-1 and Insig-2a, SREBP-1c precursor to nuclear SREBP-1c, ↓liver lipogenic gene (FASN, ACC and SCD-1); ↓(VLDL)-associated apolipoproteins, apoB100 and apoE	[89]
Species	Gene mutations	Treatments	Hepatic effects and mechanisms	Refs
OLETF	Lacking cholecystokinin receptor 1	LA (200 mg/kg*day) for 16 WKS *(p.o.)*	↓Steatosis (↓ SREBP-1c, ↓ACC, ↑ GLUT-4); ↓oxidative stress (antioxidant enzymes: ↑heme oxygenase-1 (HO-1), ↑Cu/Zn-SOD); ↓immune (↓TLR-4, ↓HMGB1); ↓inflammation(↓VCAM-1, ↓COX-2)	[90]
Obese Zucker	GmiCrl-fa/fa in normal diet	LA (200 g/kg*bw*day) for 5 WKS *(p.o.)*	↓TGs ↓liver lipogenic gene mRNA levels (GPAT1)↓,DGAT2↓), ↓TG secretion, ↑clearance of TG-containing lipoproteins	[91]
Zucker	GmiCrl-fa/fa in normal diet	LA (200 g/kg*bw*day) for 2 WKS *(p.o.)*	↓Lipogenic genes (Pnpla3, Pnpla5, Elovl6, Acly, Gpam, and Aacs); ↑FA metabolism (Acot1, Acot2, Acsf2, and Crat)	[92]
Zucker	GmiCrl-fa/fa in normal diet	LA (200 g/kg*bw* day) for 2 WKS *(p.o.)*	Correcting HTG ↑ Fgf21; ↓lipogenic gene: Acly, Acaca, Fasn, Gpam, Pnpla3; ↓ ACC1/2, FASN and 5′-AMPKα;stimulating PPARα target genes Cpt1b and Acot1	[93]

same dose significantly attenuated hepatic TG accumulation (via increasing ACC and decreasing FAS) in gene-mutant obesity animals fed an HFD (40% energy from fat) and high-cholesterol diet [88]. However, LA increased hepatic cholesterol and reduced LDL receptor protein conversion regulatory factors compared with the model group despite reduced mRNA expression of hepatic cholesterol synthesis enzyme (HMG-CoAr) and blood levels of cholesterol and LDL. This is because LA treatment cannot effectively inhibit cholesterol absorption (lower cholesterol content in the feces) in the intestines compared with higher cholesterol content in the feces after other functional components (e.g., phytosterols treatment). Although LA can reduce hepatic fatty accumulation and SAT/PUFA ratios to a great extent, the effects of LA on reducing liver steatosis in gene-mutant obesity may be influenced by the high levels of cholesterol or TG present in the diet. Therefore, it should be noticed in future clinical studies.

Effect of lipoic acid on liver fat accumulation in rats with abnormal diet

The effects of LA on hepatic fat accumulations in rats fed HFD

HFD is an important factor that causes fatty liver. HFD can metabolic dysfunction-associated steatotic liver disease (MASLD) by increasing the uptake of free fatty acids by hepatocytes, disrupting the balance between de novo synthesis and oxidative degradation of fatty acids, leading to excessive deposition of triglycerides (TG) in hepatocytes. Although weight loss can improve fatty liver, weight loss is prone to rebound, and some people with normal weight but high liver fat cannot improve fatty liver through weight loss. In such cases, LA can reduce liver fat without losing weight.

The effect of LA on hepatic lipid accumulation in animals fed an HFD has been investigated. Most studies (Table 4) have shown that LA treatment can improve plasma TG, liver fat accumulation, and weight gain in animals fed an HFD, ultimately producing liver-protective effects. The mechanisms by which LA reduces liver fat content in HFD animals may be related to suppressing oxidative stress and lipid peroxidation, improving mitochondrial dysfunction, inhibiting insulin resistance, and regulating some related factors or genes (such as ROS-scavenging enzyme genes) to inhibit excessive fat synthesis in the liver.

In rats with HFD, liver fat accumulation can be prevented by the regulation of mitochondrial dysfunction through the mechanisms adopted by LA. In an animal study, male Wistar rats were subjected to HFD and administered 0.25 g LA/100 g body weight. This dosage showed the potential to trigger an elevation in the number of mitochondria and upregulation in the expression of the Ucp2 gene, which has a crucial role in regulating the mitochondrial processes associated with energy balance to prevent excessive weight gain. Another study in rats on the same HFD plus 0.25 g LA/100 g body weight demonstrated that SIRT1 and SIRT3 enhanced LA's antioxidant defense by deacetylating Foxo3a and PGC1β, thereby reducing oxidative damage of mitochondrial DNA, restoring oxidative balance, and resisting oxidative stress.

Numerous studies have provided evidence that LA can reverse the advancement and course of MASLD in individuals with insulin resistance to HFD. LA (100 or 200 mg/kg) can act by preventing the activation of the SIRT1/liver kinase B1 (LKB1) AMPK pathway and the translocation of SREBP1 into the nucleus and FOXO1) into the cytoplasm. LA additionally enhances nuclear NF-E2-related factor 2 (Nrf2) and downstream targets by activating the SIRT1 pathway. LA increases adipose triacylglycerol lipase (ATGL) and decreases FAS, thereby reducing TG levels. This phenomenon has a hepatoprotective effect. LA can also decrease metabolic disorders and insulin resistance, maintain blood glucose homeostasis, and avert MASLD in HFD C57BL/6 J rats. The prevalence of fatty liver disease is high among individuals who are obese and have insulin resistance. The expression of SREBP-1c, a critical factor in liver steatosis, is influenced by several factors such as insulin, AMPK, LXRs, and specific protein 1 (SP1). ALA supplementation suppresses SP1 and LXR in C57BL/6 mice that are fed an HFD or given LXR agonists. ALA can also increase the phosphorylation of AMPK and SREBP-1 C in the liver. LA can regulate the specific genes (β-oxidation and ROS-scavenging enzymes), thereby leading to a reduction in liver fat accumulation among HFD rats.

In young rats, a diet rich in n-6 PUFAs can induce fatty liver, inflammation, and even liver fibrosis, and LA can influence these effects. In rats fed 10% oxidized rapeseed oil, supplementation with α-LA inhibits the increase of antioxidant enzyme activity and lipid peroxidation caused by oxidized oil. In hepatocytes, MASLD is associated with palmitic acid (PA). The supplementation of LA can effectively decrease caspase 3 activation triggered by PA while simultaneously curbing lipid accumulation. This is achieved by mitigating PA uptake, promoting fatty acid oxidation, and encouraging lipid phagocytosis, all of which work in synergy to impede fat apoptosis. In addition, it has been noted that α-LA heightens the proliferation capability of hepatocytes following PA stimulation (Table 3).

Notably, as shown in a study of Zucker rats, not only does LA hinder hepatic fat accumulation, but it also increases fatty acid consumption in muscles. In summary, LA protects from hepatic fat deposition and damage

Table 4 The effects of LA on hepatic fat accumulations in rats fed HFD

In vivo studies				
Species	**Fat in diets**	**Treatments**	**Hepatic effects and mechanisms**	**Refs**
SD	HFD	α-LA (20,40 mg/kg*d) for 12 WKS *(i.g.)*	Improving MASLD. ↓oxidative stress and lipid peroxidation	[94]
SD	HFD	LA (0.25%,0.5%) *(p.o.)*	↓TGs; improving liver lipids	[95]
Albino	HFD	LA (50 μg/kg*bw/d) for 10 WKS *(i.g.)* (LA alone or combined with Co-Q)	↑Fat oxidation(↑activity of lipoprotein lipase(LPL))	[96]
Wistar	HFD	LA (0.25%) for 8 WKS *(p.o.)*	↓Fatty liver Regulating lipogenesis and mitochondrial β-oxidation genes (mitochondrial copy number and in Ucp2 gene expression ↑) and improving insulin sensitivity; Modulating mitochondrial function (ETC↓, ATP↓)	[97]
Wistar	HFD	LA (0.25%) for 8 WKS *(p.o.)*	Preventing TG and oxidative damage. Antioxidant: ↓H2O2; ↑mitochondrial antioxidant defenses(mtDNA oxidative damage↓, mitochondrial copy number↑); ↑superoxide dismutase (SOD2) and GPx activities, ↑GSH: oxidized glutathione (GSSG) ratio, ↑UCP2 mRNA levels; ↓The acetylation levels of Foxo3a and PGC1β through the stimulation of SIRT3 and SIRT1	[98]
C57BL/6 J	HFD	LA (100, 200 mg/kg) in for 24 WKS *(p.o.)*	↓TGs. ↑Lipid metabolism(↑SIRT1, ↑ AMPK, ATGL↑); ↓ Fas abundance; ↑Oxidation resistance Nrf2↑(via the SIRT1 pathway)	[99]
C57BL/6 J	HFD	LA (100, 200 mg/kg/d) for 24 WKS *(p.o.)*	Alleviating HFD-induced MASLD. ↑lipid metabolism(PKB/Akt and GSK3β phosphorylation↑, and nuclear carbohydrate response element binding protein (ChREBP)↑)	[100]
SD; C57BL/6	HFD	LA (0.5%) for 3 ds(p.o.); LA (100 mg/kg) in saline*(i.p.)*; LA (0.5%) for 7 ds*(p.o.)*	↓Steatosis and SREBP-1c expression (AMPK phosphorylation↑); ↓ DNA binding activity and transcriptional activity of both Sp1 and LXR	[101]
C57BL/6	HFD	LA (0.1%) for 6 WKS *(p.o.)*	↓Lipid peroxidation ↑β-oxidation and free radical scavenger enzymes genes, ↓cholesterol synthesis genes	[102]
Wistar albino	n-6 PUFA rich diet	After 4 WKS diet, LA (35 mg/kg) *(i.p.)*	Preventing degenerative effects of PUFA (fatty liver, inflammation, and apoptosis) ↑GSH,↓TUNEL and caspase-3 positive cells	[103]
Wistar	HFD (PA)	LA (0.25%) for 56 ds *(p.o.)*	↓PA-mediated lipid accumulation and preventing adipocyte apoptosis Resisting oxidative stress (early nuclear translocation of Nrf2, PA uptake↓, FA oxidation↑, lipophagy↑, hepatocytes proliferation↑, mitochondrial apoptosis↓)	[104]
Wistar	HFD	LA (10 mg/kg b.m.) for12 WKS *(p.o.)*	Counteracting the increased activity of antioxidant enzymes and lipid peroxidation caused by oxidized rapeseed oil. ↓SOD, ↓glutathione peroxidase (GSH-Px), ↓glutathione reductase (GR), ↓G6PD; counteracting the production of oxygen radicals and MDA	[105]
Zucker	HFD	LA (0.25%) for 30 ds *(p.o.)*	↓Fat accumulation. ↓Lipogenic response(hepatic Acac and Fas↓); ↑hepatic fat oxidation (CPT1 A↑); ↑VLDL export(hepatic diacylglycerol acyltransferase (DGAT)↑ and microsomal triglyceride transfer protein(MTP)↑)	[106]

caused by HFD in MASLD through various ways, and can also prevent obesity and hypercholesterolemia.

Effects of lipoic acid on hepatic fat accumulation in rats fed high fructose diets

High-carbohydrate diets are effectively converted to specific FAS in the liver via upregulation and activation of lipogenic enzymes, most notably FAS and ACC, corresponding to higher plasma TG and total FA concentrations but lower hepatic TG and total FAs [107]. Fructose-rich diet is more closely associated with higher plasma and liver TG levels than glucose-rich diet [108]. As fructose is abundant in fruits, vegetables, prepared foods, and drinks, it often triggers fatty liver. The mechanism mainly relies on stimulating lipid synthesis and accumulation, rather than on direct conversion of fructose to fatty acids [109]. Situations with an excess uptake of lipids by the liver require an adaptive increase in mitochondrial oxidative capacity. Under these conditions, mitochondrial dysfunction will compromise metabolic performance in association with increased reactive oxygen species (ROS) generation.

Therefore, high fructose intake is an important factor for fatty liver.

Several studies have shown that LA pretreatment can attenuate fatty deposition in animal livers with high-fructose diets to varying degrees (Table 5). LA pretreatment (35 mg/kg for 20 days, or 4 g/kg body weight for 30 days) before the occurrence of fatty liver can impede lipid accumulation in the liver both in higher (60% in diet) and in lower (10% in drinking water) fructose intake. However, LA treatment after the development of fructose-induced fatty liver can only restore normal hepatic lipid contents in rats fed a lower-fructose diet. Therefore, earlier pretreatment is important for attenuating fatty liver to impede the effects of high fructose intake. Notably, in an experiment with a high-fructose (60%, 8 weeks) diet, although the use of LA did not reduce TG levels, LA reversed mild portal endotoxemia–induced inflammation. In a previous study, researchers established a HepG2 cells model containing glucose (30 mM) and palmitic acid (0.1 mM). The findings demonstrated that treatment with α-LA stimulated the expression of ATGL via the AMPK/FOXO1 signaling pathway, resulting in a decrease in liver fat accumulation.

Therefore, LA can reduce liver fat accumulation caused by high-fructose diet and it is more effective when given before the development of fatty liver.

Effects of lipoic acid on hepatic fat accumulation in rats fed methionine-and choline-deficient diet

It has been shown that the diet of MCD can lead to the accumulation of intrahepatic fat, the mechanism is mainly due to the lack of choline in the diet caused by the body lecithin synthesis. Methionine is Essential amino acid for the synthesis of carrier proteins, and a lack of methionine leads to a reduction in Low-density lipoprotein synthesis and therefore the inability to transport TG out of the liver, leading to the accumulation of fatty liver [115] and steatohepatitis with similar histopathological features to human NASH [116–118]. Without being limited to normal diet, hypercaloric contents (high fat and high fructose) in an MCD diet more easily cause metabolic changes characteristic of obesity, which may promote the occurrence of hepatic steatosis.

Several studies have shown that LA supplementation significantly decreases hepatic lipid accumulation and function in a normal MCD diet and a hypercaloric MCD diet (Table 6). LA can decrease liver injuries in MCD rats through decreasing oxidative stress (by increasing SOD, GSH, glutathione peroxidase [GPx], and paraoxonase-1, and decreasing TBARS and 4-HNE) and inflammatory reactions. The effect of LA on attenuating fatty liver occurs earlier in animals fed a normal MCD diet than in those fed a hypercaloric MCD diet.

As shown in a study with MCD plus LA (61 mg/kg body weight/day), ALA inhibits obesity but increases oxidative stress and liver lipid accumulation in Wistar rats. In precancer models induced by MCD, LA aggravates liver damage and promotes the formation of precancer lesions. Therefore, LA may be used as a liver-protective substance in hepatic fatty accumulation caused by MCD, but it needs to be used with caution.

Effects of lipoic acid on hepatic fat accumulation in diabetic rats

MASLD occurs in 70%–90% of cases with T2DM or IR [126]. ALA can improve metabolic disorders, hyperglycemia, and liver inflammation [127, 128]. Previous studies have shown that HFD-fed animals with T2DM show significant liver steatosis and decreased liver extract fraction. In contrast, α-LA improved hyperinsulinemia and the higher levels of free fatty acids of the T2DM rats [129], increases antioxidant defense through Nrf2, and reduces inflammation in T2DM (decreases TNF-α and Inhibit the expression of NLRP3 and downstream inflammatory factors IL-18 and IL-1β) to prevent liver steatosis and relieve HFD-induced liver lipid accumulation in T2DM rats (Table 7). NAM and streptozotocin (STZ)-induced T2DM also leads to hepatic damage, including disrupted antioxidant status, aberrant intrahepatic lipid accumulation, and inflammation. In a previous study, oral administration of LA has been shown to simultaneously activate SIRT1 and AMPK to decrease lipids, and another study has shown that LA can target the liver sulfane sulfur/hydrogen sulfide signaling pathway to prevent liver damage caused by diabetes.

Effects of lipoic acid on patients with alcoholic fatty liver disease and nonalcoholic fatty liver disease in clinical trials

First, as a common liver manifestation, AFLD can further develop into alcoholic hepatitis and cirrhosis. In addition to making the diagnosis according to the clinical symptoms (fever, jaundice, hepatomegaly, and other complications, such as hepatic encephalopathy, variceal bleeding, and ascites accumulation) for patients with acute alcoholic hepatitis, AFLD is usually discovered in health examinations for chronic alcoholic hepatitis. At present, controlling alcohol consumption is the best measure to impede the development of AFLD. As absolute abstinence is difficult to achieve, applying hepatoprotective agents is necessary. According to a prior clinical investigation [134] 300 mg LA/day for 6 months given to individuals with precirrhotic alcohol-induced liver damage does not markedly influence the subsequent progression of alcohol-related liver disease. Still, treatment with LA improves aspartate transaminase, serum gamma glutamyl transpeptidase, and histological scores of the liver

Table 5 Effects of lipoic acid on hepatic fat accumulation in rats fed high fructose diets

In vitro studies

Cell lines	Models	Treatment	Hepatic effects and mechanisms	Refs
HepG2 cells	glucose (30 mM), palmitate	LA (0.25–1.0 mM)	↓Lipid accumulation ↑AMPK phosphorylation, and inducing ATGL expression; (dephosphorylating FOXO1 and reversing the nuclear exclusion of FOXO1)	[110]

Species	Models	Treatment	Hepatic effects and mechanisms	Refs
Wistar	60% fructose for 20 ds	LA (35 mg/kg*bw) for 20 ds(i.p.)	↓ Lipid; ↓ cholesterol, TGs, FFA, phospholipid, ↑Lipid decomposition,↓synthesis (↑LPL, lecithin cholesterol acyl transferase(LCAT), ↓HMG-CoA(hydroxy methyl glutaryl–coenzyme A) reductase)	[111]
Wistar	10% fructose in drinking water for 30 ds	LA (0.4% wt/wt) from day 14 of gestation to day 20 in offspring lactations*(p.o.)*	↓ TGs Restoring Fasn, Srebf1, Ppard, and Pparg, and the antioxidant capacity	[112]
Wistar	7.2% fructose in drinking water for 10 ws	LA (100 mg/kg*day) for 6 WKS *(p.o.)*	↓oxidative stress and apoptosis	[113]
SD	fructose (60%) for 8 WKS	α-LA (60 mg/kg*day) for 4 WKS *(p.o.)*	↓Inflammation	[114]

Table 6 Effects of lipoic acid on hepatic fat accumulation in rats fed methionine-and choline-deficient diet

In vitro studies				
Cell lines	Models	Treatment	Hepatic effects and mechanisms	Refs
HepG 2 cells	MCD	incubating (FFA, carnitine and carnitine complexes)	Preventing lipotoxicity. ↑Mitochondrial β-oxidation, ↓oxidative stress	[119]
Species	Models	Treatment	Hepatic effects and mechanisms	Refs
C57BL/6	MCD	LA (100 mg/kg *day) for 2 WKS (i.p.)	Ameliorating lipid peroxidation and nitrosative stress (↑SOD, ↑GSH); ↑palmitic, stearic, arachidonic, and DHA	[120]
C57BL/6	MCD	LA (0.5% wt/wt) for 4 WKS (p.o.)	↓lipid accumulation, inflammation, TBARS, 4-HNE, and plasma ALT and AST (↓CYP2E, ↓ER stress, ↓MAPK, ↓NF-κB)	[121]
Wistar	high-calorie choline-deficient diet (HCCDD)	LA (75 mg/kg bw) for 8 WKS (p.o.)	↓Leptin, ↑ghrelin	[122]
Wistar	HCCDD	LA (61 mg/kg* day bw) for 8 WKS	↓TG ↑The activity of GSH-Px, paraoxonase-1(PON1), antioxidant; ↓liver transaminase activity	[123]
Wistar	HCCDD	LA (75 mg/kg*day bw), for 8 WKS (p.o.)	↓Apoptosis, anti-inflammatory (↓IL-17 A(interleukin), ↓IL-1α, ↑IL-10)	[124]
Fischer	pre-neoplastic lesions generated by a model of HCCDD	LA (0.2%) for 6/10 WKS (p.o.)	↑Fat accumulation, lipid peroxidation, hepatocyte death, expressions of tumor necrosis factor-α(TFN-α), cytochrome 2E1, COX-2; ↑c-Jun N-terminal kinase (JNK), signal transducer and activator transcription 3(Stat3), and hepatocyte proliferation	[125]

Table 7 Effects of lipoic acid on hepatic fat accumulation in diabetic rats

In vivo studies				
Species	**Models**	**Treatments**	**Hepatic effects and mechanisms**	**Refs**
Goto-Kakizaki	T2DM with HFD	3 ds/week LA (50 mg/kg, BW) in soybean oil for 3 months*(i.p.)*	Ameliorating cholesterol, TG, steatosis. ↓TNF-α, ↓oxidative stress(nuclear Nrf2 activity↑)	[130]
Wistar	HFD/STZ-induced T2DM	LA (50, 100, 200 mg/kg BW) for 13 WKS *(p.o.)*	↓TGs. ↓NLRP3 inflammasome activation (↓NLRP3, ↓caspase-1, ↓IL-1β); ↓synthesis (SREBP-1c); ↑oxidation (CPT)	[131]
STZ/NA- induced diabetes mouse fed HFD	HFD	LA (200 mg/kg) *(p.o.)*	↓fat. ↑SIRT1(NAD +/NADH ratio↑); ↑AMPK and ACC(palmitate β-oxidation↑). ↑ATGL and ↓FAS protein	[132]
SD	standard chow NAM + STZ-induced T2DM	LA (60 mg/kg/day) for 6 WKS *(p.o.)*	↓lipid accumulation ↑hepatic sulfane sulfur/hydrogen sulfide pathway (↑CGL (cystathionine γ-lyase), ↑3MST (3-mecaptopyruvate sulfotransferase))	[133]

to a certain degree. The result may be due to long-term alcohol consumption (over 15 years in these subjects). The accumulating precirrhotic liver lesions (fatty infiltration, alcoholic hepatitis, and fibrosis) may be responsible for the weak effects of 6-month LA administration. However, Kravchuk et al. found that LA supplementation (600 mg/day) in combined therapy with herbal medicine for 28 days greatly decreased the severity of fatty hepatocytic dystrophy and fibrotic development in patients with alcoholic hepatitis. There are direct preventive effects of LA in the early stage of AFLD development. Therefore, the clinical effects of LA should be examined in the early stage of AFLD, or a higher dose of LA should be considered.

According to one study, the supplementation of LA (600 mg/d, IV (1–7 days). p. o. (8–28 days)) in the combined therapy for AH decreased the severity of fatty hepatocytic dystrophy, hepatic inflammatory, and necrotic changes. Moreover, no fibrotic changes were observed in the liver [135]. Nevertheless, despite the administration of a higher dose of LA for a prolonged period (1200 mg/day for 12 weeks), the intensity of liver steatosis in obese patients with MASLD was not significantly enhanced. Only the serum indexes, including

levels of insulin, insulin resistance, adiponectin, leptin, and IL-6, showed improvement [67, 68].

LA combination therapy has great clinical significance for liver disease. A previous study has shown that the combination of LA (400 mg/day) with UDCA (300 mg/day) for 12 months was safe. It decreased AST, ALT, and GGT, and increased MASLD fibrosis and AST/ALT ratio. This effect was particularly prominent in individuals following low-caloric diets [136]. Based on triple antioxidant therapy, the formula (silymarin plus organic selenium and LA) improved chronic liver disease [137].

Several clinical products and new diets containing LA are currently available. For example, a previous study was conducted to enhance dietary therapy for individuals diagnosed with NASH by optimizing therapeutic nutrition through the use of SP (SP-1, SP-2) formulations and technology. These SP formulations, characterized by a specific chemical composition, were intended to improve the dietary interventions for NASH patients [138]. The food for special dietary use is safe for patients with NASH, and it can reduce fat, and even achieve weight loss and other health effects [139].

Mechanism of lipoic acid in the treatment of metabolic dysfunction-associated steatotic liver disease

In preclinical studies, LA has been shown to improve nonalcoholic fatty liver disease by modulating a variety of molecular pathways. The specific mechanism of lipoic acid treatment for non-alcoholic fatty liver disease are presented in (Fig. 4).

Effects of LA on initial fatty degeneration

LA regulates hepatic lipid metabolism by activating the AMPK pathway. Specifically, activated AMPK suppresses ACC activity to curb fatty acid synthesis [140]. In addition, LA up-regulates CPT-1 expression, promoting fatty acid β-oxidation and reducing hepatic lipid accumulation to alleviate steatosis. Moreover, LA may enhance fatty acid oxidation by modulating the PPARα pathway, as activated PPARα induces the expression of genes related to fatty acid oxidation [74].

Insulin resistance is a key driver of steatosis. LA can enhance insulin sensitivity by improving the insulin signaling pathway. It may achieve this by reducing oxidative stress and inflammation, thereby optimizing intracellular insulin signaling and down-regulating genes involved in

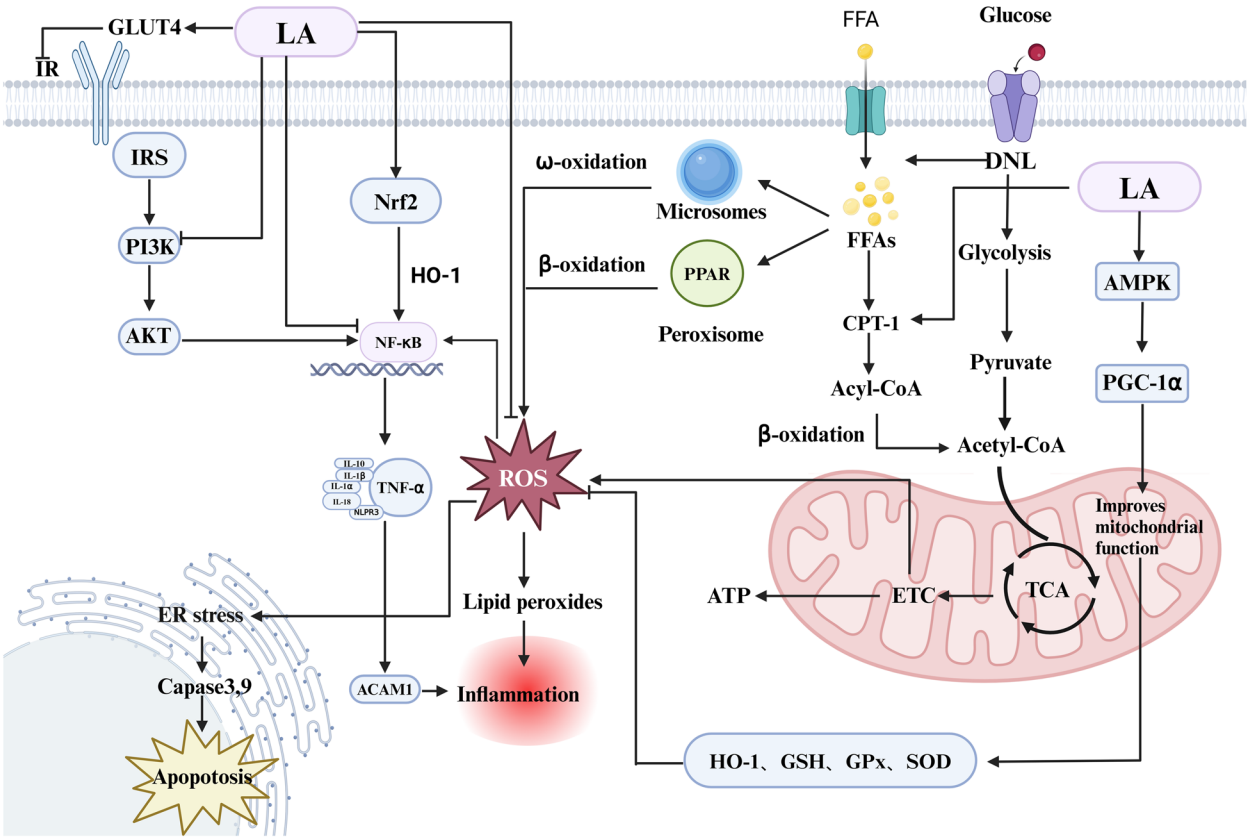

Fig. 4 Mechanism of action of LA in MASLD

hepatic lipid synthesis [141], such as FASN. Additionally, LA may increase the efficiency of insulin signaling by regulating the expression and phosphorylation of IRS, subsequently decreasing hepatic lipid synthesis and storage.

In terms of carbohydrate metabolism, LA participates in glycolysis and the citric acid cycle, enhancing energy metabolism while reducing gluconeogenesis and lipid synthesis in the liver [142]. For example, it can regulate pyruvate dehydrogenase (PDH) activity, promoting the conversion of pyruvate into the citric acid cycle and increasing energy production. Regarding fatty acid metabolism, besides promoting β-oxidation, lipoic acid can inhibit fatty acid synthesis by regulating key enzymes like FASN, lowering hepatic fatty acid levels and reducing lipid accumulation.

Effects of LA on MASH (inflammation and oxidative stress)

LA directly scavenges free radicals like O_2^- and ·OH, mitigating ROS/RNS-induced oxidative stress. It also enhances the body's antioxidation defense by boosting the activity of antioxidant enzymes SOD, GSH-Px, and CAT, reducing levels of lipid peroxidation products MDA and 4-HNE to protect hepatocytes and alleviate inflammation [143]. Moreover, it activates the Nrf2 pathway, inducing the expression of antioxidant and detoxification enzymes to reinforce cellular antioxidant capacity. In addition, both ASLD and MASLD are characterized by altered gut permeability that permits bacterial translocation. In this context, classical results have shown that LA is endowed with antioxidant properties that are protective in the spleen against the deleterious actions of Gram-negative bacterial endotoxin [144]. Other important data showed that LA eliminated the adverse effects of dimethyl nitrosamine on the spleen of mice by antioxidant [145]. These findings are consistent with the primary role of the spleen in the development and progression of MASLD [146].

LA exerts anti—inflammatory effects through multiple pathways. It inhibits NF-κB pathway activation, reducing the production of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α [130, 131]. By inhibiting IKK activity, it prevents IκB degradation, NF-κB nuclear translocation, and pro-inflammatory gene expression. Additionally, it modulates inflammasome activation, such as suppressing NLRP3 inflammasome assembly, to reduce inflammatory cytokine release and alleviate hepatic inflammation. It also regulates MAPK pathways like p38 MAPK and JNK to inhibit inflammation-related signaling.

Furthermore, LA modulates immune cell function. It suppresses macrophage activation and infiltration, reducing inflammatory mediator release and improving the liver's immune microenvironment. By enhancing Tregs and inhibiting Th17 cell differentiation, it balances the immune response and mitigates hepatic inflammatory damage [147].

Effects of LA on fibrosis

HSC activation is pivotal in hepatic fibrosis development. LA can inhibit this process via multiple mechanisms. It suppresses the TGF-β/Smad pathway, reducing the expression of ECM-related genes like collagen I and III [148]. By inhibiting TβRI expression and phosphorylation, it blocks signal transmission, thus preventing HSC activation. LA also modulates the Wnt/β-catenin pathway, inhibiting β-catenin nuclear translocation and its binding to downstream targets, which in turn inhibits HSC proliferation. Moreover, it promotes HSC apoptosis, reducing their number and ECM synthesis, thereby alleviating fibrosis.

The antioxidant and anti-inflammatory properties of thiamine help reduce fibrosis. By reducing ROS and pro-inflammatory cytokines, it inhibits oxidative stress and inflammation, indirectly preventing HSC activation. For example, it suppresses NF-κB pathway activation, decreasing the production of TNF-α and IL-1β, and in turn reducing HSC activation and ECM synthesis.

LA can restore the balance of ECM degradation and synthesis. It increases MMPs (e.g., MMP-2, MMP-9) activity and inhibits TIMPs (e.g., TIMP-1, TIMP-2) expression [149], promoting ECM degradation and reducing its accumulation. Furthermore, it modulates the ILK pathway to influence ECM assembly and cell–matrix interactions, further regulating ECM metabolism.

Effects of LA on cirrhosis and HCC

Currently, limited studies have examined the direct impact of LA on liver cirrhosis and HCC. However, based on its early-stage MASLD mechanisms, it may hold preventive and therapeutic potential for these conditions.

LA may slow cirrhosis progression by reducing hepatic inflammation, oxidative stress, and fibrosis. In early cirrhosis, it could improve liver structure and function, lowering cirrhosis risk. While its role in established cirrhosis is limited, it might serve as an adjuvant therapy to enhance patient outcomes.

LA may reduce HCC risk through its antioxidant and anti-inflammatory effects. It can also inhibit hepatocyte proliferation and transformation by modulating signaling pathways and gene expression. For instance, it suppresses abnormal Wnt/β-catenin activation, reducing β-catenin binding to oncogenes like c-Myc and cyclin D1, and inhibiting tumor development [150]. Additionally, it enhances p53 tumor-suppressive functions and promotes hepatocyte apoptosis. However, conclusive clinical evidence is still needed to confirm its efficacy against HCC.

Strengths and limitations

In this article, we comprehensively summarized the effect of LA on lipid accumulation triggered by diverse factors and highlighted the potential of LA to prevent MASLD. However, it is important to acknowledge the limitations of this review. There is a possibility of overlooked contributors (such as viral hepatitis) to fat accumulation, and the available data from clinical studies regarding the influence of LA on MASLD may be inadequate. The combination of LA with other compounds may have more therapeutic potential than monotherapy. In this regard, the relationship between LA dose and its potential side effects, as well as the impact of different routes of administration on LA bioavailability, may be a future research topic.

Conclusions

In this study, LA was found to have an alleviating effect on MASLD and could be used for the prevention thereof. Notably, MASLD pathogenesis was conducted and the effects and mechanisms of LA on excessive liver fat accumulation were determined based on the causes.

As such, the MASLD models reviewed in this paper could provide investigation and experimental bases for the subsequent clinical prevention of MASLD by LA. However, other models (such as viral hepatitis) not summarized in this paper should be treated with caution.

Abbreviations

MASLD	Dysfunction-associated Steatotic Liver Disease
LA	Lipoic acid
AFLD	Alcoholic fatty liver disease
HFD	High-fat diet
MCD	Methionine- and choline-deficient diet
BBR	Berberine
LASY	LA synthase
DH-LA	Dihydro LA
OGDC	Oxoglutarate dehydrogenase complex
PDHC	Pyruvate dehydrogenase complex
BCKDC	Branched-chain α-ketoacid dehydrogenase complex
γ-GCL	γ-Glutamylcysteine synthetase
NQO-1	NAD[P]H quinone oxidoreductase 1
SOD	Superoxide dismutase
RNS	Reactive nitrogen species
NF-κB	Nuclear factor-kappa B
ERK 1/2	Extracellular regulated protein kinase 1/2
PKCδ	Protein kinase C δ
MAPK	Mitogen-activated protein kinase
AMPK	AMP-activated protein kinase
T2DM	Diabetes mellitus type 2
TG	Triglycerides
HTG	Hypertriglyceridemia
Fgf21	Fibroblast growth factor-21
Pparα	Peroxisome proliferators–activated receptor alpha
acox1	Acyl coenzyme A oxidase
cpt1a and cpt2	Carnitine palmitoyl transferase 1a and 2
rxra	Recombinant retinoid X receptor a
abca1	ATP-binding cassette transporter A1
FAS	Fatty acid synthase
SREBP1c	Pklr1, sterol regulatory element-binding protein-1
Lxra	Liver X receptor a
AST	Aspartate aminotransferase
PUFAs	Polyunsaturated fatty acids
MDA	Malondialdehyde
ACCα	Acetyl-CoA carboxylase α
ACLY	ATP-citrate lyase
γ-GCS	γ-Glutamyl cysteine synthase
GSH	Glutathione
THRb	Thyroid hormone receptor beta
HMGB-1	High-mobility group protein box-1
TLR-4	Toll-like receptor-4
VCAM-1	Vascular cell adhesion molecule-1
HMG-CoAr	Hepatic cholesterol synthesis enzyme
Nrf2	NF-E2-related factor 2
ATGL	Adipose triacylglycerol lipase
SP1	Specific protein 1
PA	Palmitic acid
ROS	Reactive oxygen species
GPx	Glutathione peroxidase
STZ	Streptozotocin
SOD	Superoxide dismutase
GPx	Glutathione peroxidase
TNF-α	Tumor necrosis factor alpha
IL-6	Interleukin-6
CPT-1	Carnitine palmitoyltransferase I
PPARα	Peroxisome proliferator-activated receptor α
FASN	Fatty acid synthase
IRS	Insulin receptor substrates

Acknowledgements

Not applicable.

Authors' contributions

Fangli Liu: Writing – original draft, Writing – review & editing. Jingjing Lv:original draft, writing – review and editing, creation of figures/tables Yuanyuan Chen: Conceptualization, review & editing. Zhuoxin Liu: review & editing. Linfeng Wang: Writing – review & editing. Xingke Li: Conceptualization, Writing – review & editing.

Funding

This work was supported by Youth Crossing Fund General Project (S23060Y). Youth Crossing Fund General Project,(S23060Y).

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 15 April 2025 Accepted: 27 May 2025
Published online: 07 June 2025

References

1. Z. Younossi, Anstee, QM, Marietti, M., et al. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol 2018;15 (1):11–20. https://doi.org/10.1038/nrgastro.2017.109
2. J. Alharthi; Eslam, M., Biomarkers of Metabolic (Dysfunction)-associated Fatty Liver Disease: An Update. Journal of Clinical and Translational Hepatology 2021;10 (1):134–139.https://doi.org/10.14218/jcth.2021.00248

3. I. Bazwinsky-Wutschke; Zipprich, A.; sciences, F. D. J. I. j. o. m., Endocannabinoid System in Hepatic Glucose Metabolism, Fatty Liver Disease, and Cirrhosis. 2019, 20 (10).https://doi.org/10.3390/ijms20102516
4. S. H. Caldwell; Swerdlow, R. H.; Khan, E. M., et al., Mitochondrial abnormalities in non-alcoholic steatohepatitis. J Hepatol 1999, 31 (3), 430–434.https://doi.org/10.1016/s0168-8278(99)80033-6
5. H. Cortez-Pinto; Chatham, J.; Chacko, V. P., et al., Alterations in liver ATP homeostasis in human nonalcoholic steatohepatitis: a pilot study. Jama 1999, 282 (17), 1659–1664.https://doi.org/10.1001/jama.282.17.1659
6. G. Serviddio; Bellanti, F.; Tamborra, R., et al., Alterations of hepatic ATP homeostasis and respiratory chain during development of non-alcoholic steatohepatitis in a rodent model. Eur J Clin Invest 2008, 38 (4), 245–252.https://doi.org/10.1111/j.1365-2362.2008.01936.x
7. K. Hensley; Kotake, Y.; Sang, H., et al., Dietary choline restriction causes complex I dysfunction and increased H(2)O(2) generation in liver mitochondria. Carcinogenesis 2000, 21 (5), 983–989.https://doi.org/10.1093/carcin/21.5.983
8. G. Serviddio; Bellanti, F.; Tamborra, R., et al., Uncoupling protein-2 (UCP2) induces mitochondrial proton leak and increases susceptibility of non-alcoholic steatohepatitis (NASH) liver to ischaemia-reperfusion injury. Gut 2008, 57 (7), 957–965.https://doi.org/10.1136/gut.2007.147496
9. C. Ding; Fu, X.; Zhou, Y., et al., Disease burden of liver cancer in China from 1997 to 2016: an observational study based on the Global Burden of Diseases. BMJ Open 2019, 9 (4), e025613.https://doi.org/10.1136/bmjopen-2018-025613
10. Z. M. Younossi; Marchesini, G.; Pinto-Cortez, H., et al., Epidemiology of Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis: Implications for Liver Transplantation. Transplantation 2019, 103 (1), 22–27.https://doi.org/10.1097/tp.0000000000002484
11. N. Stefan; Cusi, K., A global view of the interplay between non-alcoholic fatty liver disease and diabetes. The lancet Diabetes & endocrinology 2022, 10 (4), 284–296.
12. Z. Younossi; Tacke, F.; Arrese, M., et al., Global Perspectives on Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis. Hepatology 2019, 69 (6), 2672–2682.https://doi.org/10.1002/hep.30251
13. J. Xie; Li, L.; Zhao, L., Mechanism of Natural Drugs on Nonalcoholic Fatty Liver Disease. Mini Rev Med Chem 2021, 21 (19), 3030–3036.https://doi.org/10.2174/1389557521666210405160658
14. K.-G. Park; Min, A.-K.; Koh, E. H., et al., Alpha-lipoic acid decreases hepatic lipogenesis through adenosine monophosphate-activated protein kinase (AMPK)-dependent and AMPK-independent pathways. 2008, 48 (5), 1477–1486.https://doi.org/10.1002/hep.22496
15. M. P. Valdecantos; Pérez-Matute, P.; González-Muniesa, P., et al., Lipoic acid administration prevents nonalcoholic steatosis linked to long-term high-fat feeding by modulating mitochondrial function. 2012, 23 (12), 1676–1684.https://doi.org/10.1016/j.jnutbio.2011.11.011
16. Y. Yang; Li, W.; Liu, Y., et al., Alpha-lipoic acid improves high-fat diet-induced hepatic steatosis by modulating the transcription factors SREBP-1, FoxO1 and Nrf2 via the SIRT1/LKB1/AMPK pathway. 2014, 25 (11), 1207–1217.https://doi.org/10.1016/j.jnutbio.2014.06.001
17. M. Fernández-Galilea; Pérez-Matute, P.; Prieto-Hontoria, P. L., et al., α-lipoic acid reduces fatty acid esterification and lipogenesis in adipocytes from overweight/obese subjects. 2014, 22 (10), 2210–2215.https://doi.org/10.1002/oby.20846
18. G. P. Biewenga; Haenen, G. R.; pharmacology, A. B. J. G., The pharmacology of the antioxidant lipoic acid. 1997, 29 (3), 315–331.https://doi.org/10.1016/s0306-3623(96)00474-0
19. M. B. Gomes; Diabetology, C. A. N. J.; syndrome, m., Alpha-lipoic acid as a pleiotropic compound with potential therapeutic use in diabetes and other chronic diseases. 2014, 6 (1), 80.https://doi.org/10.1186/1758-5996-6-80
20. Y.-H. Zhang; Wang, D.-W.; Xu, S.-F., et al., α-Lipoic acid improves abnormal behavior by mitigation of oxidative stress, inflammation, ferroptosis, and tauopathy in P301S Tau transgenic mice. 2018, 14, 535–548.https://doi.org/10.1016/j.redox.2017.11.001
21. L. J. Reed; De, B. B.; Gunsalus, I. C., et al., Crystalline alpha-lipoic acid; a catalytic agent associated with pyruvate dehydrogenase. Science 1951, 114 (2952), 93–94.https://doi.org/10.1126/science.114.2952.93
22. S. Matsugo; Yan, L. J.; Konishi, T., et al., The lipoic acid analogue 1,2-dielenolane-3-pentanoic acid protects human low density lipoprotein against oxidative modification mediated by copper ion. 1997, 240 (3), 819–824.https://doi.org/10.1006/bbrc.1997.7711
23. H. Moini; Packer, L.; Toxicology, N.-E. L. S. J., et al., Antioxidant and prooxidant activities of alpha-lipoic acid and dihydrolipoic acid. 2002, 182 (1), 84–90.https://doi.org/10.1006/taap.2002.9437
24. C. H. Gleiter; Schug, B. S.; Hermann, R., et al., Influence of food intake on the bioavailability of thioctic acid enantiomers. Eur J Clin Pharmacol 1996, 50 (6), 513–514.https://doi.org/10.1007/s002280050151
25. N. Okudan; Nurullahoğlu Atalik, K. E.; Gökbel, H., et al., Alpha lipoic acid treatment improved endothelium-dependent relaxation in diabetic rat aorta. Yakugaku Zasshi 2011, 131 (5), 739–744.https://doi.org/10.1248/yakushi.131.739
26. J. A. Mayr; Feichtinger, R. G.; Tort, F., et al., Lipoic acid biosynthesis defects. J Inherit Metab Dis 2014, 37 (4), 553–563.https://doi.org/10.1007/s10545-014-9705-8
27. S. Park; Karunakaran, U.; Jeoung, N. H., et al., Physiological effect and therapeutic application of alpha lipoic acid. Curr Med Chem 2014, 21 (32), 3636–3645.https://doi.org/10.2174/0929867321666140706141806
28. L. Packer; Witt, E. H.; Tritschler, H. J., alpha-Lipoic acid as a biological antioxidant. Free Radic Biol Med 1995, 19 (2), 227–250.https://doi.org/10.1016/0891-5849(95)00017-r
29. L. Packer, alpha-Lipoic acid: a metabolic antioxidant which regulates NF-kappa B signal transduction and protects against oxidative injury. Drug Metab Rev 1998, 30 (2), 245–275.https://doi.org/10.3109/03602539808996311
30. A. Gorąca; Huk-Kolega, H.; Piechota, A., et al., Lipoic acid - biological activity and therapeutic potential. Pharmacol Rep 2011, 63 (4), 849–858.https://doi.org/10.1016/s1734-1140(11)70600-4
31. F. A. Moura; Andrade, K. Q. d.; Santos, J. C. F. d., et al., Lipoic Acid: its antioxidant and anti-inflammatory role and clinical applications. 2015, 15 (5), 458–483.https://doi.org/10.2174/1568026615666150114161358
32. L. J. R. J. P. s. a. p. o. t. P. Society, From lipoic acid to multi-enzyme complexes. 1998, 7 (1), 220–224.https://doi.org/10.1002/pro.5560070125
33. A. Solmonson; chemistry, R. J. D. J. T. J. o. b., Lipoic acid metabolism and mitochondrial redox regulation. 2018, 293 (20), 7522–7530.https://doi.org/10.1074/jbc.TM117.000259
34. B. Skibska; Kochan, E.; Stanczak, A., et al., Antioxidant and Anti-inflammatory Effects of α-Lipoic Acid on Lipopolysaccharide-induced Oxidative Stress in Rat Kidney. Arch Immunol Ther Exp (Warsz) 2023, 71 (1), 16.https://doi.org/10.1007/s00005-023-00682-z
35. A. K. Tripathi; Ray, A. K.; Mishra, S. K., et al., Molecular and Therapeutic Insights of Alpha-Lipoic Acid as a Potential Molecule for Disease Prevention. Rev Bras Farmacogn 2023, 33 (2), 272–287.https://doi.org/10.1007/s43450-023-00370-1
36. A. R. Smith; Shenvi, S. V.; Widlansky, M., et al., Lipoic acid as a potential therapy for chronic diseases associated with oxidative stress. 2004, 11 (9), 1135–1146.https://doi.org/10.2174/0929867043365387
37. G. A. J. Y. m. journal, Antioxidant effects of sulfur-containing amino acids. 2004, 45 (5), 776–788.https://doi.org/10.3349/ymj.2004.45.5.776
38. U. Cakatay; Biogerontology, R. K. J., Plasma protein oxidation in aging rats after alpha-lipoic acid administration. 2005, 6 (2), 87–93.https://doi.org/10.1007/s10522-005-3462-x
39. M. A. Hofmann; Schiekofer, S.; Kanitz, M., et al., Insufficient glycemic control increases nuclear factor-kappa B binding activity in peripheral blood mononuclear cells isolated from patients with type 1 diabetes. 1998, 21 (8), 1310–1316.https://doi.org/10.2337/diacare.21.8.1310
40. D. K. J. Antioxidants; signaling, r., Utilization of the insulin-signaling network in the metabolic actions of alpha-lipoic acid-reduction or oxidation? 2005, 7 (7–8), 1032–1039.https://doi.org/10.1089/ars.2005.7.1032
41. D. E. Estrada; Ewart, H. S.; Tsakiridis, T., et al., Stimulation of glucose uptake by the natural coenzyme alpha-lipoic acid/thioctic acid: participation of elements of the insulin signaling pathway. 1996, 45 (12), 1798–1804.https://doi.org/10.2337/diab.45.12.1798
42. S. S. Shi; Day, R. M.; Halpner, A. D., et al., Homocysteine and alpha-lipoic acid regulate p44/42 MAP kinase phosphorylation in NIH/3T3 cells. 1999, 1 (1), 123–128.https://doi.org/10.1089/ars.1999.1.1-123
43. C. K. Sen; Sashwati, R.; death, L. P. J. C., et al., Fas mediated apoptosis of human Jurkat T-cells: intracellular events and potentiation by redox-active alpha-lipoic acid. 1999, 6 (5), 481–491.https://doi.org/10.1038/sj.cdd.4400514

44. D. Konrad; Somwar, R.; Sweeney, G., et al., The antihyperglycemic drug alpha-lipoic acid stimulates glucose uptake via both GLUT4 translocation and GLUT4 activation: potential role of p38 mitogen-activated protein kinase in GLUT4 activation. 2001, 50 (6), 1464–1471.https://doi.org/10.2337/diabetes.50.6.1464
45. Y. Wang; Li, X.; Guo, Y., et al., alpha-Lipoic acid increases energy expenditure by enhancing adenosine monophosphate-activated protein kinase-peroxisome proliferator-activated receptor-gamma coactivator-1alpha signaling in the skeletal muscle of aged mice. 2010, 59 (7), 967–976.https://doi.org/10.1016/j.metabol.2009.10.018
46. L. Packer; Tritschler, H. J.; biology, K. W. J. F. r., et al., Neuroprotection by the metabolic antioxidant alpha-lipoic acid. 1997, 22 (1–2), 359–378.https://doi.org/10.1016/s0891-5849(96)00269-9
47. B. Skibska; medicine, A. G. J. O.; longevity, c., The protective effect of lipoic acid on selected cardiovascular diseases caused by age-related oxidative stress. 2015, 2015, 313021.https://doi.org/10.1155/2015/313021
48. S. Topsakal; Ozmen, O.; Cankara, F. N., et al., Alpha lipoic acid attenuates high-fructose-induced pancreatic toxicity. 2016, 16 (3), 347–352.https://doi.org/10.1016/j.pan.2016.03.001
49. I. Damnjanovic; Kocic, G.; Najman, S., et al., Chemopreventive potential of alpha lipoic acid in the treatment of colon and cervix cancer cell lines. 2014, 115 (10), 611–616.https://doi.org/10.4149/bll_2014_118
50. M. A. Oktan; Heybeli, C.; Ural, C., et al., Alpha-lipoic acid alleviates colistin nephrotoxicity in rats. 2021, 40 (5), 761–771.https://doi.org/10.1177/0960327120966043
51. K. Breithaupt-Grögler; Niebch, G.; Schneider, E., et al., Dose-proportionality of oral thioctic acid--coincidence of assessments via pooled plasma and individual data. 1999, 8 (1), 57–65.https://doi.org/10.1016/s0928-0987(98)00061-x
52. J. Teichert; Kern, J.; Tritschler, H. J., et al., Investigations on the pharmacokinetics of alpha-lipoic acid in healthy volunteers. 1998, 36 (12), 625–628.
53. M. Brufani, Figliola, R. (R)-α-lipoic acid oral liquid formulation: pharmacokinetic parameters and therapeutic efficacy. Acta Biomed 2014;85(2):108–115.
54. H. Róbert; Niebch, G.; Harald, O. B., et al., Enantioselective pharmacokinetics and bioavailability of different racemic α-lipoic acid formulations in healthy volunteers. European Journal of Pharmaceutical Sciences 1996.https://doi.org/10.1016/0928-0987(95)00045-3
55. T. Jens; Tina, T.; Achenbach, H., et al., Pharmacokinetics of Alpha-Lipoic Acid in Subjects With Severe Kidney Damage and End-Stage Renal Disease. The Journal of Clinical Pharmacology 2005.https://doi.org/10.1177/0091270004270792
56. F. I. Milagro; Mansego, M. L.; Miguel, C. D., et al., Dietary factors, epigenetic modifications and obesity outcomes: progresses and perspectives. 2013, 34 (4), 782–812.https://doi.org/10.1016/j.mam.2012.06.010
57. V. Yadav; Marracci, G.; Lovera, J., et al., Lipoic acid in multiple sclerosis: a pilot study. 2005, 11 (2), 159–165.https://doi.org/10.1191/1352458505ms1143oa
58. V. Borcea; Nourooz-Zadeh, J.; Wolff, S. P., et al., alpha-Lipoic acid decreases oxidative stress even in diabetic patients with poor glycemic control and albuminuria. 1999, 26 (11–12), 1495–1500.https://doi.org/10.1016/s0891-5849(99)00011-8
59. D. Ziegler; Hanefeld, M.; Ruhnau, K. J., et al., Treatment of symptomatic diabetic polyneuropathy with the antioxidant alpha-lipoic acid: a 7-month multicenter randomized controlled trial (ALADIN III Study). ALADIN III Study Group. Alpha-Lipoic Acid in Diabetic Neuropathy. 1999, 22 (8), 1296–1301.https://doi.org/10.2337/diacare.22.8.1296
60. E. Parente; Colannino, G.; Picconi, O., et al., Safety of oral alpha-lipoic acid treatment in pregnant women: a retrospective observational study. 2017, 21 (18), 4219–4227.
61. U. Cakatay; Kayali, R.; Sivas, A., et al., Prooxidant activities of alpha-lipoic acid on oxidative protein damage in the aging rat heart muscle. 2005, 40 (3), 231–240.https://doi.org/10.1016/j.archger.2004.09.001
62. B. Hadzik; Grass, H.; Mayatepek, E., et al., Fatal non-accidental alpha-lipoic acid intoxication in an adolescent girl. 2014, 226 (5), 292–294.https://doi.org/10.1055/s-0034-1372622
63. J. P. Velasco-Amador; Prados-Carmona, Á.; dermatitis, F. J. N.-T. J. C., Contact urticaria syndrome caused by alpha-lipoic acid in a master formula for vulvar lichen sclerosus. 2023.https://doi.org/10.1111/cod.14353
64. A. Rizzi; Nucera, E.; Buonomo, A., et al., Delayed hypersensitivity to α-lipoic acid: look at dietary supplements. 2015, 73 (1), 62–63.https://doi.org/10.1111/cod.12393
65. H. Tutunchi; Arefhosseini, S.; Ebrahimi-Mameghani, M., Clinical effectiveness of α-lipoic acid, myo-inositol and propolis supplementation on metabolic profiles and liver function in obese patients with NAFLD: A randomized controlled clinical trial. Clinical Nutrition ESPEN 2023, 54, 412–420.https://doi.org/10.1016/j.clnesp.2023.02.016
66. A. D. Genazzani; Battipaglia, C.; Rusce, L., et al., Alpha lipoic acid administration improved both peripheral sensitivity to insulin and liver clearance of insulin reducing potential risk of diabetes and nonalcoholic fatty liver disease in overweight/obese PCOS patients. Gynecol Endocrinol 2024, 40 (1), 2341701.https://doi.org/10.1080/09513590.2024.2341701
67. S. Hosseinpour-Arjmand; Amirkhizi, F.; Ebrahimi-Mameghani, M., The effect of alpha-lipoic acid on inflammatory markers and body composition in obese patients with non-alcoholic fatty liver disease: A randomized, double-blind, placebo-controlled trial. J Clin Pharm Ther 2019, 44 (2), 258–267.https://doi.org/10.1111/jcpt.12784
68. A. Rahmanabadi; Mahboob, S.; Amirkhizi, F., et al., Oral α-lipoic acid supplementation in patients with non-alcoholic fatty liver disease: effects on adipokines and liver histology features. Food Funct 2019, 10 (8), 4941–4952.https://doi.org/10.1039/c9fo00449a
69. M. Ebrahimi-Mameghani; Asghari, S.; Naeini, F., et al., Assessing the clinical and biochemical efficacy of alpha-lipoic acid in patients with non-alcoholic fatty liver disease: A randomized placebo-controlled clinical trial. Journal of Functional Foods 2024, 114, 106050.https://doi.org/10.1016/j.jff.2024.106050
70. S. Hosseinpour-Arjmand; Hamedi-Shahraki, S.; Ebrahimi-Mameghani, M., et al., The Effect of Alpha-Lipoic Acid on Liver Function and Metabolic Markers in Obese Patients with Non-Alcoholic Fatty Liver Disease: A Double - Blind Randomized Controlled Trial. Iranian Red Crescent Medical Journal (IRCMJ) 2024, 20 (3), 1–11.https://doi.org/10.5812/ircmj.65925.
71. F. Amirkhizi; Hamedi-Shahraki, S.; Hosseinpour-Arjmand, S., et al., Effects of Alpha-Lipoic Acid Supplementation on Oxidative Stress Status in Patients with Non-Alcoholic Fatty Liver Disease: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial. Iranian Red Crescent Medical Journal (IRCMJ) 2024, 20 (9), 1–11.https://doi.org/10.5812/ircmj.67615.
72. Y. I. Mahmoud; Biotechnic, H. G. H. J.; Commission, h. o. p. o. t. B. S., Ginger and alpha lipoic acid ameliorate age-related ultrastructural changes in rat liver. 2016, 91 (2), 86–95.https://doi.org/10.3109/10520295.2015.1076578
73. J. B. Schwimmer; Pardee, P. E.; Lavine, J. E., et al., Cardiovascular risk factors and the metabolic syndrome in pediatric nonalcoholic fatty liver disease. 2008, 118 (3), 277–283.https://doi.org/10.1161/circulationaha.107.739920
74. A. Kuhla; Derbenev, M.; Shih, H. Y., et al., Prophylactic and abundant intake of α-lipoic acid causes hepatic steatosis and should be reconsidered in usage as an anti-aging drug. 2016, 42 (2), 179–189.https://doi.org/10.1002/biof.1262
75. S. Guo; Yan, K.; Fang, X., et al., α-Lipoic Acid Alleviates Hepatic Lipid Deposition by Inhibiting FASN Expression via miR-3548 in Rats. 2021, 13 (7).https://doi.org/10.3390/nu13072331
76. M. P. Valdecantos; Pérez-Matute, P.; Prieto-Hontoria, P., et al., Impact of dietary lipoic acid supplementation on liver mitochondrial bioenergetics and oxidative status on normally fed Wistar rats. 2019, 70 (7), 834–844.https://doi.org/10.1080/09637486.2019.1572716
77. D. T. T. Huong; nutrition, T. I. J. T. B. j. o., Dietary lipoic acid-dependent changes in the activity and mRNA levels of hepatic lipogenic enzymes in rats. 2008, 100 (1), 79–87.https://doi.org/10.1017/s0007114507876227
78. L. A. Finlay; Michels, A. J.; Butler, J. A., et al., R-α-lipoic acid does not reverse hepatic inflammation of aging, but lowers lipid anabolism, while accentuating circadian rhythm transcript profiles. 2012, 302 (5), R587–597.https://doi.org/10.1152/ajpregu.00393.2011
79. P. Arivazhagan; Panneerselvam, S. R.; Chinnakkanu Panneerselvam %J The journals of gerontology. Series A, B. s., et al., Effect of DL-alpha-lipoic acid on the status of lipid peroxidation and lipids in aged rats. 2003, 58 (9), B788–791.https://doi.org/10.1093/gerona/58.9.b788

80. T. I. J. E. j. o. nutrition, Physiological activities of the combination of fish oil and alpha-lipoic acid affecting hepatic lipogenesis and parameters related to oxidative stress in rats. 2018, 57 (4), 1545–1561.https://doi.org/10.1007/s00394-017-1440-0
81. T. Ide; Azechi, A.; Kitade, S., et al., Combined effect of sesamin and α-lipoic acid on hepatic fatty acid metabolism in rats. 2013, 52 (3), 1015–1027.https://doi.org/10.1007/s00394-012-0408-3
82. R. Rukkumani; Aruna, K.; Varma, P. S., et al., Comparative effects of curcumin and an analog of curcumin on alcohol and PUFA induced oxidative stress. 2004, 7 (2), 274–283.
83. C. Chaves; Bruinstroop, E.; Refetoff, S., et al., Increased Hepatic Fat Content in Patients with Resistance to Thyroid Hormone Beta. Thyroid 2021, 31 (7), 1127–1134.https://doi.org/10.1089/thy.2020.0651
84. N. Panera; Meroni, M.; Longo, M., et al., The KLB rs17618244 gene variant is associated with fibrosing MAFLD by promoting hepatic stellate cell activation. EBioMedicine 2021, 65, 103249.https://doi.org/10.1016/j.ebiom.2021.103249
85. M. J. Guillen-Sacoto; Martinez, A. F.; Abe, Y., et al., Human germline hedgehog pathway mutations predispose to fatty liver. J Hepatol 2017, 67 (4), 809–817.https://doi.org/10.1016/j.jhep.2017.06.008
86. Q. Li; Bai, L.; Shi, G., et al., Ptrf transgenic mice exhibit obesity and fatty liver. Clin Exp Pharmacol Physiol 2018, 45 (7), 704–710.https://doi.org/10.1111/1440-1681.12920
87. G. Xu; Yan, T.; Peng, Q., et al., Overexpression of the Lias gene attenuates hepatic steatosis in Leprdb/db mice. J Endocrinol 2021, 248 (2), 119–131.https://doi.org/10.1530/joe-19-0606
88. T. C. Rideout; Carrier, B.; Wen, S., et al., Complementary Cholesterol-Lowering Response of a Phytosterol/α-Lipoic Acid Combination in Obese Zucker Rats. J Diet Suppl 2016, 13 (3), 283–299.https://doi.org/10.3109/19390211.2015.1008616
89. X. Tong; Christian, P.; Zhao, M., et al., Activation of hepatic CREBH and Insig signaling in the anti-hypertriglyceridemic mechanism of R-α-lipoic acid. J Nutr Biochem 2015, 26 (9), 921–928.https://doi.org/10.1016/j.jnutbio.2015.03.011
90. T. S. Jung; Kim, S. K.; Shin, H. J., et al., α-lipoic acid prevents non-alcoholic fatty liver disease in OLETF rats. Liver Int 2012, 32 (10), 1565–1573.https://doi.org/10.1111/j.1478-3231.2012.02857.x
91. J. A. Butler; Hagen, T. M.; Moreau, R., Lipoic acid improves hypertriglyceridemia by stimulating triacylglycerol clearance and downregulating liver triacylglycerol secretion. Arch Biochem Biophys 2009, 485 (1), 63–71.https://doi.org/10.1016/j.abb.2009.01.024
92. A. Pashaj; Yi, X.; Xia, M., et al., Characterization of genome-wide transcriptional changes in liver and adipose tissues of ZDF (fa/fa) rats fed R-α-lipoic acid by next-generation sequencing. Physiol Genomics 2013, 45 (23), 1136–1143.https://doi.org/10.1152/physiolgenomics.00138.2013
93. X. Yi; Pashaj, A.; Xia, M., et al., Reversal of obesity-induced hypertriglyceridemia by (R)-α-lipoic acid in ZDF (fa/fa) rats. Biochem Biophys Res Commun 2013, 439 (3), 390–395.https://doi.org/10.1016/j.bbrc.2013.08.063
94. B. Wang; Yang, R. N.; Zhu, Y. R., et al., Involvement of xanthine oxidase and paraoxonase 1 in the process of oxidative stress in nonalcoholic fatty liver disease. Mol Med Rep 2017, 15 (1), 387–395.https://doi.org/10.3892/mmr.2016.6025
95. E. Y. Seo; Ha, A. W.; Kim, W. K., α-Lipoic acid reduced weight gain and improved the lipid profile in rats fed with high fat diet. Nutr Res Pract 2012, 6 (3), 195–200.https://doi.org/10.4162/nrp.2012.6.3.195
96. M. A. Al-Ghamdi; Choudhry, H.; Al-Doghather, H. A., et al., POTENTIAL ADMINISTRATION OF LIPOIC ACID AND COENZYME Q AGAINST ADIPOGENSIS: TARGET FOR WEIGHT REDUCTION. Afr J Tradit Complement Altern Med 2017, 14 (1), 272–277.https://doi.org/10.21010/ajtcam.v14i1.29
97. M. P. Valdecantos; Pérez-Matute, P.; González-Muniesa, P., et al., Lipoic acid administration prevents nonalcoholic steatosis linked to long-term high-fat feeding by modulating mitochondrial function. J Nutr Biochem 2012, 23 (12), 1676–1684.https://doi.org/10.1016/j.jnutbio.2011.11.011
98. M. P. Valdecantos; Pérez-Matute, P.; González-Muniesa, P., et al., Lipoic acid improves mitochondrial function in nonalcoholic steatosis through the stimulation of sirtuin 1 and sirtuin 3. Obesity (Silver Spring) 2012, 20 (10), 1974–1983.https://doi.org/10.1038/oby.2012.32
99. Y. Yang; Li, W.; Liu, Y., et al., Alpha-lipoic acid improves high-fat diet-induced hepatic steatosis by modulating the transcription factors SREBP-1, FoxO1 and Nrf2 via the SIRT1/LKB1/AMPK pathway. J Nutr Biochem 2014, 25 (11), 1207–1217.https://doi.org/10.1016/j.jnutbio.2014.06.001
100. Y. Yang; Li, W.; Liu, Y., et al., Alpha-lipoic acid attenuates insulin resistance and improves glucose metabolism in high fat diet-fed mice. Acta Pharmacol Sin 2014, 35 (10), 1285–1292.https://doi.org/10.1038/aps.2014.64
101. K. G. Park; Min, A. K.; Koh, E. H., et al., Alpha-lipoic acid decreases hepatic lipogenesis through adenosine monophosphate-activated protein kinase (AMPK)-dependent and AMPK-independent pathways. Hepatology 2008, 48 (5), 1477–1486.https://doi.org/10.1002/hep.22496
102. R. L. Yang; Li, W.; Shi, Y. H., et al., Lipoic acid prevents high-fat diet-induced dyslipidemia and oxidative stress: a microarray analysis. Nutrition 2008, 24 (6), 582–588.https://doi.org/10.1016/j.nut.2008.02.002
103. F. Kaya-Dagistanli; Tanriverdi, G.; Altinok, A., et al., The effects of alpha lipoic acid on liver cells damages and apoptosis induced by polyunsaturated fatty acids. Food Chem Toxicol 2013, 53, 84–93.https://doi.org/10.1016/j.fct.2012.11.026
104. M. Pilar Valdecantos; Prieto-Hontoria, P. L.; Pardo, V., et al., Essential role of Nrf2 in the protective effect of lipoic acid against lipoapoptosis in hepatocytes. Free Radic Biol Med 2015, 84, 263–278.https://doi.org/10.1016/j.freeradbiomed.2015.03.019
105. J. Zalejska-Fiolka; Wielkoszyński, T.; Kasperczyk, S., et al., Effects of oxidized cooking oil and α-lipoic acid on liver antioxidants: enzyme activities and lipid peroxidation in rats fed a high fat diet. Biol Trace Elem Res 2010, 138 (1–3), 272–281.https://doi.org/10.1007/s12011-010-8628-y
106. B. Carrier; Wen, S.; Zigouras, S., et al., Alpha-lipoic acid reduces LDL-particle number and PCSK9 concentrations in high-fat fed obese Zucker rats. PLoS One 2014, 9 (3), e90863.https://doi.org/10.1371/journal.pone.0090863
107. S. N. Dankel; Bjørndal, B.; Lindquist, C., et al., Hepatic Energy Metabolism Underlying Differential Lipidomic Responses to High-Carbohydrate and High-Fat Diets in Male Wistar Rats. J Nutr 2021, 151 (9), 2610–2621.https://doi.org/10.1093/jn/nxab178
108. Y. Maruhama; Macdonald, I., Incorporation of orally administered glucose-U-14C and fructose-U-14C into the triglyceride of liver, plasma, and adipose tissue of rats. Metabolism 1973, 22 (9), 1205–1215.https://doi.org/10.1016/0026-0495(73)90208-4
109. E. J. Parks; Skokan, L. E.; Timlin, M. T., et al., Dietary sugars stimulate fatty acid synthesis in adults. J Nutr 2008, 138 (6), 1039–1046.https://doi.org/10.1093/jn/138.6.1039
110. Y. T. Kuo; Lin, T. H.; Chen, W. L., et al., Alpha-lipoic acid induces adipose triglyceride lipase expression and decreases intracellular lipid accumulation in HepG2 cells. Eur J Pharmacol 2012, 692 (1–3), 10–18.https://doi.org/10.1016/j.ejphar.2012.07.028
111. V. Thirunavukkarasu; Anitha Nandhini, A. T.; Anuradha, C. V., Effect of alpha-lipoic acid on lipid profile in rats fed a high-fructose diet. Exp Diabesity Res 2004, 5 (3), 195–200.https://doi.org/10.1080/15438600490486778
112. M. B. Rabaglino; Moreira-Espinoza, M. J.; Lagares, C., et al., Maternal intake of alpha-lipoic acid prevents development of symptoms associated with a fructose-rich diet in the male offspring in Wistar rats. J Dev Orig Health Dis 2021, 12 (5), 758–767.https://doi.org/10.1017/s2040174420001178
113. S. Topsakal; Ozmen, O.; Ozgocmen, M., Effects of alpha-lipoic acid on high fructose induced hepatic pathology. Biotech Histochem 2019, 94 (4), 271–276.https://doi.org/10.1080/10520295.2018.1552019
114. Y. F. Tian; He, C. T.; Chen, Y. T., et al., Lipoic acid suppresses portal endotoxemia-induced steatohepatitis and pancreatic inflammation in rats. World J Gastroenterol 2013, 19 (18), 2761–2771.https://doi.org/10.3748/wjg.v19.i18.2761
115. Q. M. Anstee; Goldin, R. D., Mouse models in non-alcoholic fatty liver disease and steatohepatitis research. Int J Exp Pathol 2006, 87 (1), 1–16.https://doi.org/10.1111/j.0959-9673.2006.00465.x
116. R. Veteläinen; van Vliet, A.; van Gulik, T. M., Essential pathogenic and metabolic differences in steatosis induced by choline or methione-choline deficient diets in a rat model. J Gastroenterol Hepatol 2007, 22 (9), 1526–1533.https://doi.org/10.1111/j.1440-1746.2006.04701.x
117. J. George; Pera, N.; Phung, N., et al., Lipid peroxidation, stellate cell activation and hepatic fibrogenesis in a rat model of chronic

steatohepatitis. J Hepatol 2003, 39 (5), 756–764.https://doi.org/10.1016/s0168-8278(03)00376-3
118. I. A. Leclercq; Farrell, G. C.; Field, J., et al., CYP2E1 and CYP4A as microsomal catalysts of lipid peroxides in murine nonalcoholic steatohepatitis. J Clin Invest 2000, 105 (8), 1067–1075.https://doi.org/10.1172/jci8814
119. D. W. Jun; Cho, W. K.; Jun, J. H., et al., Prevention of free fatty acid-induced hepatic lipotoxicity by carnitine via reversal of mitochondrial dysfunction. Liver Int 2011, 31 (9), 1315–1324.https://doi.org/10.1111/j.1478-3231.2011.02602.x
120. M. N. Stanković; Mladenović, D.; Ninković, M., et al., The effects of α-lipoic acid on liver oxidative stress and free fatty acid composition in methionine-choline deficient diet-induced NAFLD. J Med Food 2014, 17 (2), 254–261.https://doi.org/10.1089/jmf.2013.0111
121. A. K. Min; Kim, M. K.; Kim, H. S., et al., Alpha-lipoic acid attenuates methionine choline deficient diet-induced steatohepatitis in C57BL/6 mice. Life Sci 2012, 90 (5–6), 200–205.https://doi.org/10.1016/j.lfs.2011.11.012
122. N. A. Riger; Trushina, E. N.; Mustafina, O. K., et al., [Pathogenetic mechanisms for the development of hematological disorders in induced fatty liver disease in Wistar rats and assessment of the regulatory effects of carnosine and α-lipoic acid]. Vopr Pitan 2021, 90 (3), 6–19.https://doi.org/10.33029/0042-8833-2021-90-3-6-19
123. L. V. Kravchenko; Aksenov, I. V.; Nikitin, N. S., et al., Lipoic Acid Exacerbates Oxidative Stress and Lipid Accumulation in the Liver of Wistar Rats Fed a Hypercaloric Choline-Deficient Diet. Nutrients 2021, 13 (6).https://doi.org/10.3390/nu13061999
124. E. N. Trushina; Riger, N. A.; Mustafina, O. K., et al., [Effect of carnosine and α-lipoic acid on hepatocyte apoptosis and the cytokine profile in induced fatty liver disease in Wistar rats]. Vopr Pitan 2020, 89 (5), 6–16.https://doi.org/10.24411/0042-8833-2020-10061
125. A. Perra; Pibiri, M.; Sulas, P., et al., Alpha-lipoic acid promotes the growth of rat hepatic pre-neoplastic lesions in the choline-deficient model. Carcinogenesis 2008, 29 (1), 161–168.https://doi.org/10.1093/carcin/bgm205
126. A. Kotronen; Yki-Järvinen, H., Fatty liver: a novel component of the metabolic syndrome. Arterioscler Thromb Vasc Biol 2008, 28 (1), 27–38.https://doi.org/10.1161/atvbaha.107.147538
127. M. A. K. Abdelhalim; Moussa, S. A. A.; Qaid, H. A., et al., Potential effects of different natural antioxidants on inflammatory damage and oxidative-mediated hepatotoxicity induced by gold nanoparticles. Int J Nanomedicine 2018, 13, 7931–7938.https://doi.org/10.2147/ijn.S171931
128. M. C. Castro; Villagarcía, H. G.; Massa, M. L., et al., Alpha-lipoic acid and its protective role in fructose induced endocrine-metabolic disturbances. Food Funct 2019, 10 (1), 16–25.https://doi.org/10.1039/c8fo01856a
129. C. Y. Ko; Xu, J. H.; Lo, Y. M., et al., Alleviative Effect of Alpha-Lipoic Acid on Cognitive Impairment in High-Fat Diet and Streptozotocin-Induced Type 2 Diabetic Rats. Front Aging Neurosci 2021, 13, 774477.https://doi.org/10.3389/fnagi.2021.774477
130. C. M. Sena; Cipriano, M. A.; Botelho, M. F., et al., Lipoic Acid Prevents High-Fat Diet-Induced Hepatic Steatosis in Goto Kakizaki Rats by Reducing Oxidative Stress Through Nrf2 Activation. Int J Mol Sci 2018, 19 (9).https://doi.org/10.3390/ijms19092706
131. C. Y. Ko; Lo, Y. M.; Xu, J. H., et al., Alpha-lipoic acid alleviates NAFLD and triglyceride accumulation in liver via modulating hepatic NLRP3 inflammasome activation pathway in type 2 diabetic rats. Food Sci Nutr 2021, 9 (5), 2733–2742.https://doi.org/10.1002/fsn3.2235
132. W. L. Chen; Kang, C. H.; Wang, S. G., et al., α-Lipoic acid regulates lipid metabolism through induction of sirtuin 1 (SIRT1) and activation of AMP-activated protein kinase. Diabetologia 2012, 55 (6), 1824–1835.https://doi.org/10.1007/s00125-012-2530-4
133. G. J. Dugbartey; Alornyo, K. K.; Adams, I., et al., Targeting hepatic sulfane sulfur/hydrogen sulfide signaling pathway with α-lipoic acid to prevent diabetes-induced liver injury via upregulating hepatic CSE/3-MST expression. Diabetol Metab Syndr 2022, 14 (1), 148.https://doi.org/10.1186/s13098-022-00921-x
134. A. W. Marshall; Graul, R. S.; Morgan, M. Y., et al., Treatment of alcohol-related liver disease with thioctic acid: a six month randomised double-blind trial. Gut 1982, 23 (12), 1088–1093.https://doi.org/10.1136/gut.23.12.1088
135. A. Kravchuk Iu; Mekhtiev, S. N.; Uspenskiĭ Iu, P., et al., [Device laboratory and postmortem parallels in alcoholic hepatitis during combined therapy using thioctic (alpha-lipoic) acid]. Klin Med (Mosk) 2004, 82 (6), 55–57.
136. V. Gianturco; Troisi, G.; Bellomo, A., et al., Impact of combined therapy with alpha-lipoic and ursodeoxycolic acid on nonalcoholic fatty liver disease: double-blind, randomized clinical trial of efficacy and safety. Hepatol Int 2013, 7 (2), 570–576.https://doi.org/10.1007/s12072-012-9387-y
137. E. Dumitru; Condur, L.; Alexandrescu, L., et al., Triple Antioxidant Therapy, an Alternative for Patients with Chronic Liver Disease - A Prospective Multicenter Interventional Study. Maedica (Bucur) 2020, 15 (4), 433–439.https://doi.org/10.26574/maedica.2020.15.4.433
138. V. M. Vorobyeva; Vorobyeva, I. S.; Morozov, S. V., et al., [Specialized products for dietary correction of the diet of patients with non-alcoholic steatohepatitis]. Vopr Pitan 2021, 90 (2), 100–109.https://doi.org/10.33029/0042-8833-2021-90-2-100-109
139. A. N. Sasunova; Morozov, S. V.; Sobolev, R. V., et al., [Efficacy of newly developed food for special dietary use in the diet of patients with non-alcoholic steatohepatitis]. Vopr Pitan 2022, 91 (2), 31–42.https://doi.org/10.33029/0042-8833-2022-91-2-31-42
140. C. Tian; Huang, R.; Xiang, M., SIRT1: Harnessing multiple pathways to hinder NAFLD. Pharmacological Research 2024, 203, 107155.https://doi.org/10.1016/j.phrs.2024.107155
141. L. Longhitano; Distefano, A.; Musso, N., et al., (+)-Lipoic acid reduces mitochondrial unfolded protein response and attenuates oxidative stress and aging in an in vitro model of non-alcoholic fatty liver disease. J Transl Med 2024, 22 (1), 82.https://doi.org/10.1186/s12967-024-04880-x
142. A. Solmonson; DeBerardinis, R. J., Lipoic acid metabolism and mitochondrial redox regulation. J Biol Chem 2018, 293 (20), 7522–7530.https://doi.org/10.1074/jbc.TM117.000259
143. A. Uskoković; Dinić, S.; Jovanović, J. A., et al., Liver Diseases: Epigenetic Mechanisms, Oxidative Stress and Use of Alpha-Lipoic Acid. In Handbook of Nutrition, Diet, and Epigenetics, Patel, V.; Preedy, V., Eds. Springer International Publishing: Cham, 2017; pp 1–21.
144. A. Gorąca; Huk-Kolega, H.; Kleniewska, P., et al., Effects of lipoic acid on spleen oxidative stress after LPS administration. Pharmacol Rep 2013, 65 (1), 179–186.https://doi.org/10.1016/s1734-1140(13)70976-9
145. N. S. El-Shenawy; Hamza, R. Z.; Khaled, H. E., Protective effect of α–lipoic acid against spleen toxicity of dimethylnitrosamine in male mice: Antioxidant and ultrastructure approaches. Biomedicine & Pharmacotherapy 2017, 96, 459–465.https://doi.org/10.1016/j.biopha.2017.10.010
146. G. Tarantino; Citro, V.; Balsano, C., Liver-spleen axis in nonalcoholic fatty liver disease. Expert Rev Gastroenterol Hepatol 2021, 15 (7), 759–769.https://doi.org/10.1080/17474124.2021.1914587
147. B. He; Wu, L.; Xie, W., et al., The imbalance of Th17/Treg cells is involved in the progression of nonalcoholic fatty liver disease in mice. BMC Immunol 2017, 18 (1), 33.https://doi.org/10.1186/s12865-017-0215-y
148. C. Y. Zhang; Yuan, W. G.; He, P., et al., Liver fibrosis and hepatic stellate cells: Etiology, pathological hallmarks and therapeutic targets. World J Gastroenterol 2016, 22 (48), 10512–10522.https://doi.org/10.3748/wjg.v22.i48.10512
149. Z. Cavdar; Ozbal, S.; Celik, A., et al., The effects of alpha-lipoic acid on MMP-2 and MMP-9 activities in a rat renal ischemia and re-perfusion model. Biotech Histochem 2014, 89 (4), 304–314.https://doi.org/10.3109/10520295.2013.847498
150. X. Pei; Hu, F.; Hu, Z., et al., Neuroprotective Effect of α-Lipoic Acid against Aβ(25–35)-Induced Damage in BV2 Cells. Molecules 2023, 28 (3).https://doi.org/10.3390/molecules28031168

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.