The Potential of Alpha-Lipoic Acid Supplementation for Non-Alcoholic Fatty Liver Disease: A Systematic Review

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ABSTRACT

***Background**: Insulin resistance, genetic susceptibility, oxidative stress, and inflammation lead to the development of non-alcoholic fatty liver disease (NAFLD). Alpha lipoic acid (ALA) has demonstrated benefits in enhancing insulin sensitivity and reducing inflammatory reactions in both human and animal studies. This study aims to determine the effectiveness of ALA against NAFLD.*

***Methods**: Detailed searches were conducted across several databases, including PubMed, CENTRAL, Europe PMC (medRxiv and bioRxiv), EBSCOhost (Medline), and ProQuest, using keywords such as lipoic acid, metabolic-associated fatty liver disease, steatohepatitis, and non-alcoholic fatty liver disease. Risk of bias was assessed using the Cochrane risk-of-bias tool for randomized trials.*

***Results**: Four studies were included in which the ALA effect was compared with placebo or no intervention. A significant reduction in BMI ($p<0.001$), lipid profiles ($p<0.05$), glycemic markers ($p<0.05$), liver enzymes ($p<0.05$), oxidative stress ($p<0.05$), and fibrosis score ($p<0.05$) was seen in NAFLD patients with ALA supplementation.*

***Conclusion**: This study shows that ALA may help manage NAFLD. However, further research is required to establish robust evidence.*

***Keywords:** Alpha Lipoic Acid, Non-Alcoholic Fatty Liver Disease, Systematic Review*

ABSTRAK

***Latar Belakang**: Resistensi insulin, kerentanan genetik, stres oksidatif, dan peradangan menyebabkan perkembangan penyakit hati berlemak non-alkohol (NAFLD) melalui steatosis dan peradangan di hati. Asam alfa lipoat (ALA), antioksidan yang telah menunjukkan manfaat dalam meningkatkan sensitivitas insulin dan mengurangi reaksi peradangan pada penelitian manusia dan hewan. Penelitian ini bertujuan untuk menentukan efektivitas ALA terhadap NAFLD.*

***Metode**: Pencarian detail dilakukan di beberapa basis data, termasuk PubMed, CENTRAL, Europe PMC (medRxiv dan bioRxiv), EBSCOHost (Medline), dan ProQuest menggunakan kata kunci seperti asam lipoat, penyakit hati berlemak terkait metabolik, steatohepatitis, dan penyakit hati berlemak non-alkohol. Risiko bias dilakukan dengan menggunakan alat risiko bias Cochrane untuk uji coba acak.*

***Hasil**: Empat penelitian disertakan di mana efek ALA dibandingkan dengan plasebo atau tanpa intervensi. Penurunan signifikan pada BMI ($p<0,001$), profil lipid ($p<0,05$), penanda glikemik ($p<0,05$), enzim hati ($p<0,05$), stres oksidatif ($p<0,05$), dan skor fibrosis ($p<0,05$) terlihat pada pasien NAFLD dengan suplementasi ALA.*

***Kesimpulan**: Studi ini mengungkapkan bahwa asam alfa lipoat merupakan suplemen yang dapat berkontribusi dalam mengelola NAFLD. Namun, penelitian lebih lanjut diperlukan untuk mendapatkan bukti yang kuat.*

***Keywords:** Alpha Lipoic Acid, Non-Alcoholic Fatty Liver Disease, Systematic Review*

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD), the most common cause of chronic liver disease, is induced by metabolic stress correlated with genetic susceptibility and insulin resistance.[1] Its clinical spectrum ranges from steatosis to non-alcoholic steatohepatitis, leading to hepatic cirrhosis and hepatic cancers.[2] Corresponding with the increased global incidence of obesity, NAFLD has emerged as the most prevalent chronic liver disorder, affecting 25-30% of the adult population. The prevalence of NAFLD is estimated to grow by 21% in 2030.[3,4] Recent developments in the field have resulted in a change in terminology, with the condition now designated as Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD) or Metabolic-Associated Steatotic Liver Disease (MASLD), indicating an expanded comprehension of its metabolic origins and systemic consequences. Nonetheless, the term NAFLD remains prevalent in clinical and scientific settings owing to its recognized status and its capacity to include a broad spectrum of non-alcoholic liver disorders while including significant clinical differences.[5] The transition from NAFLD to MAFLD or MASLD aligns with a growing focus on the metabolic dysfunctions that contribute to liver disease, such as insulin resistance, obesity, and metabolic syndrome. Several studies continue to use the term NAFLD, which remains deeply ingrained in clinical practice and research, particularly in the context of liver pathology and therapeutic interventions, despite evolving terminology. The retention of the NAFLD terminology also ensures continuity in the existing body of literature and its alignment with longstanding diagnostic criteria and treatment guidelines. Additionally, while the new terms emphasize the metabolic basis of liver disease, NAFLD remains the preferred term in many clinical settings due to its simplicity and historical context.[6,7]

The pathogenesis of non-alcoholic fatty liver disease (NAFLD) remains complex and not yet fully understood. Its progression is characterized by excessive lipid accumulation in hepatocytes, primarily in the form of triglycerides, exceeding 5% of liver weight.[8] Increased fatty acid oxidation within the liver promotes oxidative stress, leading to the production of reactive oxygen species (ROS), which contribute to hepatocellular damage and reduced cell viability.[9] Studies, including both experimental models and randomized clinical trials, have demonstrated that antioxidant therapies, such as α-lipoic acid (ALA), can mitigate these effects by improving liver function and pathology.[10–12] The α-lipoic acid is a multi-potent antioxidant that interferes with free radical release and lipid oxidation, promotes insulin sensitivity, regulates other antioxidants, and suppresses cytokine-induced inflammation.[8] A meta-analysis shows that ALA supplementation is an effective intervention to control lipid peroxidation and has been proven as a robust dietary antioxidant.[13] However, the efficacy of ALA in NAFLD is still unclear. This systematic review aims to evaluate the effects of ALA supplementation, compared with placebo or any supplementation, on liver function and metabolic parameters in patients with NAFLD.

METHODS

This systematic review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.[14] The protocol was prospectively registered with the International Prospective Register of Systematic Reviews (registration number CRD42023453955) in August 2023.[15] A.P., N.T., and H.T. conducted the literature search across multiple databases—PubMed, EuroPMC, ProQuest, EBSCO, and CENTRAL (Cochrane Central Register of Controlled Trials)—without restrictions on the publication date. The search strategy **(Table 2)** employed a combination of keywords, including "lipoic acid," "metabolic-associated fatty liver disease," "steatohepatitis," and "NAFLD." Studies were retrieved regardless of language; however, only articles available in full text, randomized controlled trials (RCTs), and studies designed in a randomized controlled trial (RCT) design and written in English were assessed for eligibility. Titles and abstracts were screened independently by three reviewers, and any discrepancies were resolved by consensus with two additional authors. Studies meeting the inclusion criteria were RCTs evaluating lipoic acid in patients diagnosed with NAFLD or NASH by ultrasonography (USG). The quality of included studies was assessed independently by the three reviewers using Version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2), with disagreements discussed and resolved collectively.[16] Primary outcomes included changes from baseline in metabolic parameters (lipid profile, HbA1c, and glycemic levels) and hepatic function markers (AST, ALT, alkaline phosphatase, and GGT). Secondary outcomes included anthropometric measures (body mass and BMI), oxidative stress markers, inflammatory markers, iron indices, hematological parameters, steatosis and fibrosis grading, and histopathological

findings from liver biopsies. Of the included studies, seven reported outcomes as mean ± standard deviation, while one study reported percentage changes.

RESULTS

From a total of 3.034 articles, 809 duplicates, and 2.211 ineligible records were removed. Fourteen studies were assessed for eligibility, of which 10 were removed due to overlapping populations or failure to meet the inclusion criteria. Four studies (seven reports) encompassing a total of 497 NAFLD patients were included **(Figure 1).** A meta-analysis was not performed because the heterogeneity among the included studies was significant, and the reported parameters and outcomes varied substantially across trials.

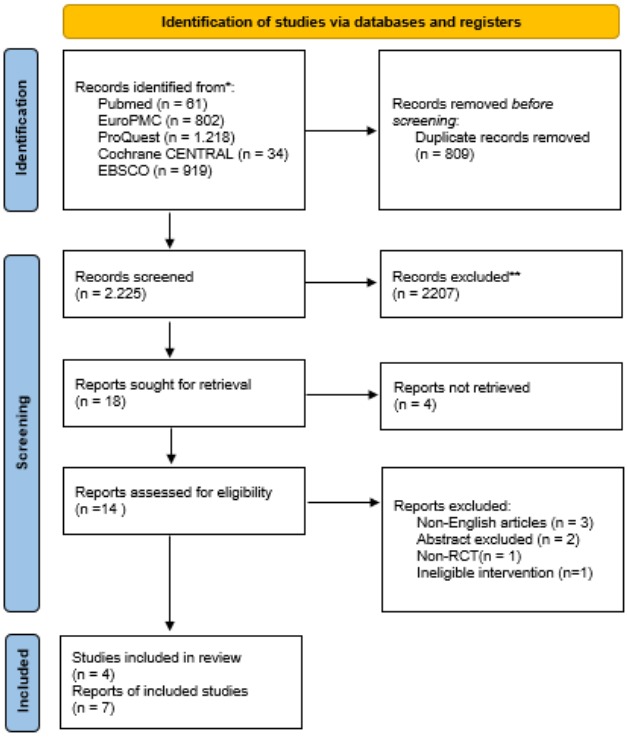

Figure 1. Study Selection

As seen in **Table 1**, eight randomized controlled trials conducted in Iran, the USA, and Italy evaluated the effects of α-lipoic acid (ALA), alone or combined with vitamin E or UDCA, in patients with NAFLD or NASH. Doses ranged from 300 to 1200 mg/day, with follow-up durations between 8 weeks and 12 months. Most studies reported improvements in BMI, liver enzymes (ALT, AST, GGT), lipid profile, glycemic parameters (HbA1c, insulin), and liver steatosis. Some also observed increased adiponectin levels, reduced inflammatory and oxidative stress markers, and histological improvements.

Several studies found improvement in BMI after ALA supplementation. Tutunchi et al found a significant reduction in BMI before and after treatment with 1200 mg of ALA supplementation ($p<0.001$).[17] In addition, Rahmanabadi et al had a similar outcome with 1200 mg of ALA daily ($p<0.0001$).[18]

Lipid levels were reduced in some studies. Basu et al. found a 34.4% reduction in triglyceride levels after 6 months of ALA supplementation at 300 mg.[8] In line with this, Amirkhizi et al concluded that total cholesterol levels ($p=0.011$), LDL-C ($p=0.021$), HDL-C ($p=0.120$), and LDL/HDL ratio ($p=0.038$) were improved after 12 weeks of supplementation with 1200 mg ALA and 400 mg vitamin E.[19] Tutunchi et al also found a similar outcome with LDL-C reduction after treatment ($p = 0.008$).[17] Leptin was also reduced by 44.8%; on the other hand, adiponectin levels increased by 122.2%.[8] Rahmanabadi et al also found changes in adiponectin ($p=0.022$), leptin ($p=0.042$), resistin ng/mL ($p=0.009$), and adiponectin/leptin ratio ($p=0.027$).[11]

The glycemic marker in patients with NAFLD improved with the use of alpha-lipoic acid. The reductions in fasting blood sugar, serum insulin, and QUICKI score were greater after the intervention. Rahmanabadi et al. found that administering 1200 mg of alpha-lipoic acid (600 mg 2 times per day) can reduce fasting blood sugar levels compared with placebo ($p=0.003$). Serum insulin was also found to decrease ($p=0.010$).[11] In the study of Basu et al, HbA1c levels reduced by 13.9% after the administration of 300 mg of alpha lipoic acid per day, accompanied by vitamin E 700 IU.[8] This shows that administration of alpha lipoic acid was effective in improving the glycemic profile of NAFLD.

Liver enzymes were reduced in several studies. Basu et al found significant changes with a 20.8% reduction in ALT after treatment.[8] In addition, Amirkhizi et al and Gianturco et al found similar results with a reduction in AST ($p=0.015$ and $p = 0.002$) and ALT ($p=0.032$ and $p = 0.003$) after supplementation of 1200 mg ALA/400 mg vitamin E and 400 mg ALA/300 mg UDCA, respectively.[19,20] Furthermore, GGT ($p=0.005$) and platelet ($p=0.04$) levels were also improved with significant changes.[20]

Oxidative stress markers, such as malondialdehyde (MDA), decreased significantly after daily supplementation with 1200 mg ALA for 12 weeks ($p=0.016$). Conversely, a significant increase in serum total antioxidant status (TAS) was observed ($p=0.031$). However, it did not affect glutathione peroxidase (GSH-Px) and copper-zinc superoxide dismutase (Cu/Zn-SOD) antioxidant enzyme activities compared to the baseline values.[21]

In addition, the fibrosis score decreased in NAFLD, approaching the cutoff for the indeterminate score (0.675) at the 12-month evaluation. This suggests that the liver shows structural improvement ($p = 0.02$).[20] This is in line with the study of Basu et al, which found that there was a decrease of 5.9% in fibrosis score from baseline (0.17 vs 0.16). Furthermore, the inflammatory marker represented by IL-6 was reduced after treatment with 1200 mg ALA and 400 mg vitamin E (15.1 ± 4.7 vs 12.5 ± 4.4; $p = 0.013$).[8]

The risk of bias assessment, evaluated using the Cochrane RoB 2 tool, showed that most included studies had a low risk across all key domains, including random sequence generation, blinding, outcome assessment, and reporting. However, the study by Basu et al. (2014) raised some concerns regarding allocation concealment and blinding of participants and personnel, suggesting potential selection and performance bias **(Figure 2).**

Table 1. Study Characteristics

No	Authors	Year	Location	N	Patients Characteristics	Intervention	Comparison	Follow-up duration	Primary outcome
1	Helda Tuntunchi et al.	2023	Iran	92	Age range = 18-50 years old, BMI = ≥ 30 kg/m2	ALA 1200 mg/day	Placebo	8 weeks	↓ BMI, ↓ LDL-C, ↓ ALT, ↓ liver steatosis
2	Basu P, et al	2014	USA	155	Age = 24-46 years old, BMI = 28-33 kg/m2	ALA 300mg/day and Vitamin E 700mg/day	Placebo	6 months	↓ TNF-alpha levels, ↓ triglyceride, ↓ RBP-4, ↓ leptin, ↓ HbA1c, and ↓ ALT levels, ↑ steatosis score, ↑ adiponectin
3	Vincenzo Gianturco et al.	2012	Italy	200	Age range = 57-69 years old, BMI = 30 kg/m2	ALA 400 mg/day and UDCA 300 mg/day	Placebo	12 months	↓ AST, ↓ ALT, ↓ GGT, ↓ NAFLD score
4	Rahmanabadi A et al.	2019	Iran	50	Age = 20-50 years old, BMI = 30-40 kg/m2	ALA 1200 mg/day and Vitamin E 400 mg/day	Placebo (starch) and vitamin E 400 mg	12 weeks	↑ adiponectin levels, ↓ insulin levels
5	Amirkhizi F et al.	2018	Iran	50	Age = 20-50 years old, BMI = 30-40 kg/m2	ALA 1200 mg/day and 400 mg vitamin E/day	Placebo and vitamin E 400 mg	12 weeks	↓ MDA level, ↑ TAS level
6	Hosseinpour - Arjmand S et al.	2018	Iran	45	Age = 20-50 years old, BMI = 30-40 kg/m2	ALA 1200 mg/day and 400 mg vitamin E/day	Placebo and vitamin E 400 mg	12 weeks	↑ serum adiponectin
7	Hosseinpour - Arjmand S et al.	2018	Iran	45	Age = 20-50 years old, BMI = 30-40 kg/m2	ALA 1200mg/day and Vitamin E 400 mg/day	Placebo (starch) and vitamin E 400 mg	12 weeks	↓ insulin serum, ↓ IL-6, ↑ adiponectin, ↑ QUICKI score

Table 2. Search Strategy

Pubmed	("thioctic acid"[MeSH Terms] OR "Alpha Lipoic" OR "Lipoic acid" OR "α-lipoic" OR "alpha-lipoic" OR "Alpha lipoic acid" OR "α-lipoic acid") AND ("non alcoholic fatty liver disease"[MeSH Terms] OR "fatty liver"[MeSH Terms] OR "Metabolic-associated Fatty Liver Disease" OR "metabolic dysfunction-associated steatotic liver disease" OR "Fatty Liver" OR "Steatohepatitis" OR "non-alcoholic steatohepatitis" OR "nonalcoholic steatohepatitis" OR "non alcoholic fatty liver disease" OR "MAFLD" OR "NASH" OR "NAFLD")
EuroPMC	("thioctic acid" OR "Alpha Lipoic" OR "Lipoic acid" OR "α-lipoic" OR "alpha-lipoic" OR "Alpha lipoic acid" OR "α-lipoic acid") AND ("non alcoholic fatty liver disease" OR "fatty liver" OR "Metabolic-associated Fatty Liver Disease" OR "metabolic dysfunction-associated steatotic liver disease" OR "Fatty Liver" OR "Steatohepatitis" OR "non-alcoholic steatohepatitis" OR "nonalcoholic steatohepatitis" OR "non alcoholic fatty liver disease" OR "MAFLD" OR "NASH" OR "NAFLD")
ProQuest	((MESH(lipoic acid)) OR "Alpha Lipoic Acid" OR "Lipoic Acid" OR "α-lipoic acid" OR "thiotic acid") AND ((MESH(fatty liver disease)) OR "steatohepatitis" OR "nonalcoholic steatohepatitis" OR "nonalcoholic fatty liver disease" OR "metabolic associated fatty liver disease" OR "NASH" OR "NAFLD")
EBSCOHost	(("non-alcoholic fatty liver disease") OR ("steatohepatitis" OR "nonalcoholic steatohepatitis" OR "nonalcoholic fatty liver disease" OR "metabolic associated fatty liver disease" OR "NASH" OR "NAFLD")) AND (("Alpha Lipoic Acid" OR "Lipoic Acid" OR "α-lipoic acid" OR "thiotic acid"))
Cochrane Central	#1 MeSH descriptor: [Thioctic Acid] explode all trees #2 MeSH descriptor: [Non-alcoholic Fatty Liver Disease] explode all trees #3 MeSH descriptor: [Fatty Liver] explode all trees #4 {OR #2-#3} AND #1 #5 {OR #2-#3} OR "non alcoholic fatty liver disease" OR "nonalcoholic fatty liver disease" OR "fatty liver disease" OR "metabolic-associated fatty liver disease" OR mafld OR nash OR nafld OR masld OR "metabolic dysfunction-associated steatotic liver disease" OR "non-alcoholic steatohepatitis" OR "nonalcoholic steatohepatitis" OR "non alcoholic fatty liver disease" #6 #1 OR "alpha lipoic acid" OR "alpha-lipoic acid" OR "α-lipoic acid" OR "α lipoic acid" OR "lipoic acid" OR "alpha lipoic" OR "alpha-lipoic" OR "α lipoic" OR "α-lipoic" #7 #5 AND #6

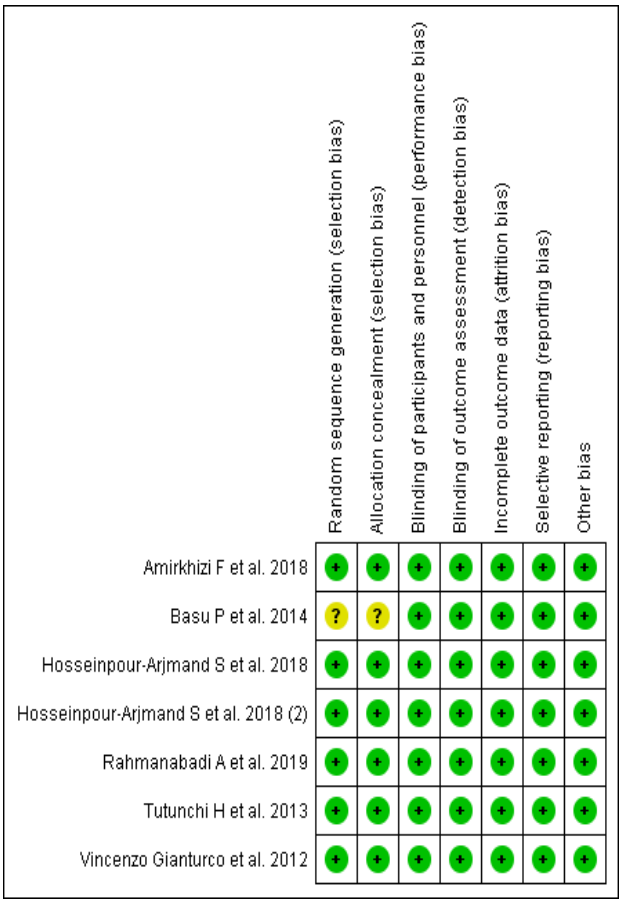

Figure 2. Risk of Bias

DISCUSSION

Supplementation with ALA showed promising results in patients with NAFLD. There was an improvement in BMI, lipid levels, glycemic markers, liver enzymes, oxidative stress parameters, and fibrosis after supplementation of ALA. ALA has been found to exert antioxidant and anti-inflammatory effects against chronic liver disorders.[22]

The reduction in BMI is consistent with Kucukgoncu et al. In this study, weight loss was significantly lower with placebo.[23] The mechanism relating ALA to weight loss can be speculated by its effect on suppressing hypothalamic AMP-activated protein kinase activity (AMPK), leading to reduced food intake and increased energy usage.[24]

A meta-analysis by Akbari et al found a significant reduction in glucose, serum insulin, and HbA1c in patients with metabolic disease. This is consistent with our findings in NAFLD patients.[25] Several mechanisms of ALA in improving glycemic markers have been described. ALA can preserve beta cell function, leading to better glycemic control.[26] Additionally, ALA decreases insulin resistance through AMPK in beta cells and skeletal muscle cells.[27]

The decrease in lipid levels observed is supported by previous in vitro and in vivo studies. The mechanism of ALA's action in reducing lipid levels was elucidated in an in vitro study by Kuo et al.[28] This study found that ALA induces adipose triglyceride lipase (ATGL) expression and reduces intracellular lipid accumulation by activating the FOXO1/ATGL pathway in HepG2 cells. An in vivo study by Ko et al found that ALA has the potential to suppress the nucleotide-binding domain and leucine-rich-containing family pyrin domain-containing 3 (NLRP3) inflammasome, leading to a reduction in lipid accumulation in the livers of rats with a high-fat diet and streptozotocin-induced type 2 diabetes mellitus.[10] On the other hand, Kravchenko et al found that ALA increases hepatic lipid accumulation in rats fed a hypercaloric choline-deficient diet. Therefore, studies on the effects of lipoic acid on lipid profiles are still needed to provide evidence. Unfortunately, no other research examines the direct impact of lipoic acid on changes in iron profile and adiponectin. [29]

The results of studies on the role of ALA in reducing oxidative stress have been previously conducted using cell lines and rats. Reis et al found that ALA could reduce inflammation resulting from tobacco-induced NAFLD.[30] ALA's reduced inflammatory effects may occur due to decreased stress on the endoplasmic reticulum and inflammation within HepG2 cells.[31] Stanković et al found that dietary supplementation with ALA in rats with methionine-choline deficiency could reduce the severity of hepatic steatosis and decrease levels of liver malondialdehyde, nitrate, and nitrite.[32] Conversely, ALA increases various antioxidant molecules, including superoxide dismutase (SOD) and the proportion of saturated acid, docosahexaenoic acid (DHA), and arachidonic acid. Studies have found that ALA can inhibit progression from steatosis to steatohepatitis by suppressing inflammation and the rate of hepatocyte apoptosis in rats fed a high-calorie, choline-deficient diet. In addition to the liver, the anti-inflammatory effects of ALA have been tested in animals under toxic conditions that can accelerate liver cell apoptosis (Saad, Mozaffarian) and oxidative processes in organs outside the liver.[33]

Previous studies on the impact of ALA on liver enzymes, primarily conducted in animal models, have consistently demonstrated that ALA has advantageous effects on serum aminotransferases.[34–37] As an antioxidant, ALA can decrease oxidative stress, hence enhancing the levels of HDL-cholesterol. Additionally, ALA decreased endoplasmic reticulum stress and the activity of MAP kinase. In a study conducted by Min et al, it was shown that ALA (0.5% mixed in food) in the diet of mice fed on a methionine-choline-deficient diet resulted in improved levels of serum aminotransferases compared to animals on a diet without ALA.[37]

Daily ALA supplementation significantly minimized chronic liver damage, leading to a decrease in fibrosis score, demonstrated by an improvement of serum ALT and AST levels to standard values. Meanwhile, ALA successfully preserved the liver's intact structure, indicating its ability to protect liver cell membranes. During chronic liver damage, hepatic cells release ROS, which enhances the oxidative stress in hepatocytes. This, in turn, induces apoptosis in hepatocytes and activates hepatic stellate cells (HSCs).[38]

A systematic review has not been conducted investigating ALA's role and benefits in NASH and NAFLD. A systematic search utilizing various databases was employed in this study. The strength of our review lies in the comprehensive assessment of bias and the quality of each trial discussed. The authors acknowledge several limitations encountered in the implementation of this study. Language limitations posed a significant challenge, leading the authors to include only studies published in English. Furthermore, the authors found a scarcity of trials investigating ALA's role, highlighting the need for additional studies to conclusively establish ALA's significance in NAFLD.

CONCLUSION

This study indicates that alpha-lipoic acid may offer potential benefits in NAFLD by influencing glycemic markers and oxidative stress, with possible modest improvements in liver injury and fibrosis. Nevertheless, the current evidence is constrained by the limited number of available and heterogeneous trials, which primarily assess indirect outcomes. As a result, the overall certainty of these findings remains low. Alpha-lipoic acid warrants further exploration, but stronger, more rigorously designed human studies are required to determine its actual effectiveness in NAFLD.

Conflict of interest

No conflict of interest.

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Author Contribution

Conceptualization: A.P., N.T., H.T.; acquisition of data: A.P., N.T., H.T.; analysis and/or interpretation of data: A.P., N.T., H.T.; drafting the manuscript: A.P., N.T., H.T.; revising the manuscript critically for important intellectual content: A.P., N.T., H.T., R.T., L.L.; approval of the version of the manuscript to be published: A.P., N.T., H.T., R.T., L.L.

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