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LIPID-LOWERING EFFECT OF ALPHA-LIPOIC ACID: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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Abstract

Alpha-lipoic acid (ALA) has various effects on health, one of which is its impact on lipid levels in the blood. Preclinical studies have demonstrated this effect. Nonetheless, the outcomes of clinical evaluations have been contradictory. Systematic reviews on this subject have also yielded conflicting findings. This study conducted a systematic review and meta-analysis of randomized controlled trials to evaluate the effects of ALA on changes in various blood lipid levels. We discovered that ALA significantly reduced triglyceride (TG) levels (-6.299 $mgdL^{-1}$ 95% CI -10.104 to -2.494); however, the studies contributing to this significant finding were found to confer a high risk of bias. In contrast, no significant effects were observed on the levels of total cholesterol (TC; 0.304 $mgdL^{-1}$ 95% CI -3.436 to 4.044), High-density Lipoprotein (HDL; -1.460 $mgdL^{-1}$ 95% CI -5.445 to 2.525), or Low-density Lipoprotein (LDL; 0.226 $mgdL^{-1}$ 95% CI -0.711 to 1.163). Although the dose of ALA and the duration of administration did not show statistically significant effects, it was observed that ALA doses not exceeding 1,200 mg per day and administration for approximately 16 weeks were more effective in reducing TG levels. We discovered that our study also contained research with small sample sizes and high degree of heterogeneity between studies. These findings highlight the potential lipid-modifying consequence of ALA, especially triglyceride-lowering effect, emphasizing the prominence of appropriate dosing along with duration of treatment.

Keywords: Alpha-lipoic acid, triglycerides, cholesterol, cardiovascular diseases, systematic review, meta-analysis

Introduction

The prevalence of dyslipidemia, characterized by abnormal lipid levels, is a well-known significant risk determinant for cardiovascular diseases (Libby et al., 2009). From recent studies, there were significant link between elevated triglycerides (TG) and increased risk of cardiovascular disease, in which the pathophysiology seemed to be complicated with available treatment options (Miller et al., 2011). From contemporary years, there has been exponential attention in dietary supplements which aid in lipid

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management. Niacin and fish oil also plays role in lowering the lipid level in the blood, although some concerns arise with these agents, for instance, fish oil also elevate low-density lipoprotein (LDL) cholesterol while niacin can cause gastrointestinal upset, flushing, and hyperglycemia (Pashaj et al., 2015). There is now a growing body of research studying dietary supplements with potential lipid-lowering effects. Alpha-lipoic acid (ALA), also known as thioctic acid, is a substance that contained eight carbon with a disulfide bond, found in both plants and animals. However, in humans, this compound is produced in a miniscule amounts, making dietary intake essential, with sources including meat, vegetables, and fruits . ALA is discovered in mitochondria and is necessary for the functioning of enzymes involved in the citric acid cycle, which is crucial in cellular activity. In mitochondria, ALA binds to the E2 subunit and acts as an organic molecule essential for the functioning of pyruvate dehydrogenase and also α-ketoacid dehydrogenase complexes. It is also participated in metabolism of lipid and glucose, functions as an antioxidant, reduces inflammation in the body, chelates heavy metals, prevents LDL oxidation by free radicals in the bloodstream, and inhibits the enzyme HMG-CoA reductase (Ghibu et al., 2009; Gorąca et al., 2011; Salehi et al., 2019).

There are pre-clinical researches that probed the potential lipid-modifying effect of ALA (Asztalos et al., 2007; Butler et al., 2009; Carrier et al., 2014; M. Y. Kim et al., 2011; Lee et al., 2008; Seo et al., 2012). Recently, several studies have investigated the lipid-decreasing properties of ALA in human. While few studies have found that ALA can reduce lipid levels, others have not shown significant effects. This signify the inconsistencies from prior works. The presence of additional randomized controlled trials (RCTs) may provide clearer evidence of ALA's potential to lower lipid levels. This study hopes to clarify disparities in prior work on the effects of ALA on lipid profiles by applying strict inclusion criteria, with an emphasis on studies using oral administration.

Therefore, the purpose of this study is to conduct a systematic and up-to-date review of the literature to assess the lipid-lowering effects of ALA and determine how dosage and duration affect these effects.

2. Materials and Methods

Literature Search

A inclusive literature inspection was demonstrated across various sources to identify randomized controlled trials that scrutinized the effects of ALA on lipid profiles. The sources include Pubmed, Scopus, Cochrane Library, Ovid, ScienceDirect, and GoogleScholar. Inclusion criteria was randomized controlled trials in human with the age of 18 or more, analysis in blood lipid response including total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL), and/or low-density lipoprotein (LDL) as primary or secondary endpoints, dose of ALA, publication in English, treatment period of at

least 1 month, and oral ALA administration. Exclusion criteria include usage of other lipid-lowering drugs or antioxidant known to interfere the ALA effect, multiple intervention (e.g., another supplement) in the treatment arm, which does not exist in control arm, type of research as case report, abstract or review, using the intravenous ALA, and measuring the cholesterol and triglyceride in subcutaneous adipocyte.

Data Extraction

The author extracted data from the following aspects of the studies: the primary researcher, study title, country of study, publication year, study population and location, sample size of the group receiving ALA and the placebo or control division, age of participants, types of blood lipids measured, dose of ALA used in each study, duration of the study, method of administration of ALA, and study outcomes, which were evaluated based on levels of TC, TG, HDL, and LDL obtained from blood.

Quality Assessment

The quality of the chosen studies was estimated via the quality assessment tool according to the Cochrane Handbook for Systematic Reviews of Interventions (version 6.4) published in 2023 (Higgins et al., 2023). The assessment utilized the Cochrane risk-of-bias tool for randomized trials (RoB 2), which is separated into five main topics to determine the risk of bias (Jonathan A C Sterne et al., 2019). Each domain was assessed using a set of signalling questions, with possible responses being "yes," "probably yes," "probably no," "no," or "no information.". The responses to these signalling questions were aggregated by the analysis software, which then determined the overall risk of bias in each topic. The possible outcomes were low risk of bias, some concerns, or high risk of bias. Out of the 20 studies, 7 were recognized as low risk, 6 as containing some concerns, and 8 as high risk. The most frequent issues were related to the randomization procedure and noncompliance from the purposed interventions, particularly in older studies, as seen in Figure 1

Statistical Analysis

The pooled effect of continuous data was analysed using the weight mean difference (MD) to compare outcomes and presented with Forest plot, with statistical significance indicated by the 95% confidence interval (CI). The random-effects model, specifically with the aid of the DerSimonian and Laird method, was implemented for the calculations due to the expected heterogeneity among the included studies, which could result from differences in study design, populations, ALA dosages, and outcome measurements. Statistical heterogeneity was appraised by means of Cochrane Q and I^2 statistic. Subgroup analysis was conducted for exploration of potential sources in heterogeneity, provided there were sufficient studies available. Sensitivity analysis was done to focus on specific groups of interest based on the selected studies. We investigated the relationship between dose of ALA or duration of

ALA administration with lipid change by polynomial regression. Publication bias was evaluated using a Funnel plot, together with statistical tests conducted using Begg's test and Egger's test. The obtained results were summarized following the guideline from Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020. Data entry and analysis were performed using RStudio program. Significance in statistical parameters was obtained with the significant level of $p<0.05$ while other cut off, mainly $p<0.1$, was implemented for Begg's test and Egger's test.

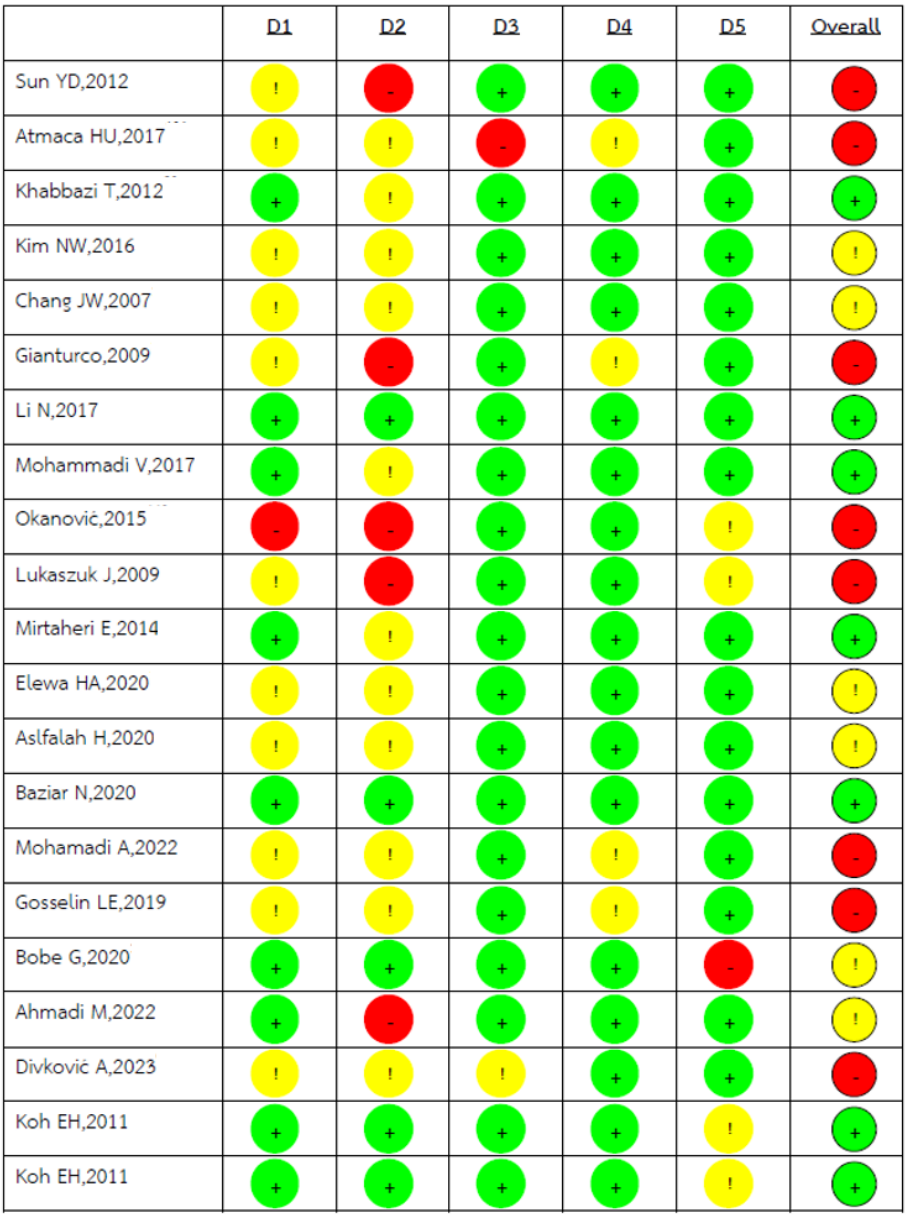

Figure 1: Risk of Bias 2 (RoB2) was used as assessment tool for the risk of bias. Each component of assessment includes D1 to D5 as bias originating from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. The summarized results are interpreted as low risk of bias

(green), some concerns (yellow), or high risk of bias (red). From the figure, there were 7 studies, 6 studies, and 8 studies with low risk, some concerns, and high risk of bias respectively.

3. Results and Discussion

A complete list of 14,823 articles were recruited across multiple sources, including 5,124 studies from PubMed, 638 from the Cochrane Library, 3,660 from Google Scholar, 2,196 from Scopus, 189 from Ovid, and 3,016 from ScienceDirect. These studies were collected up until February 23, 2024. After removing 2,506 duplicate articles, 12,317 articles remained for screening based on their titles and abstracts. In this stage, 12,099 articles were excluded as they were not relevant to the study's focus, leaving 218 articles for full-text screening according to inclusion criteria. There are 20 relevant studies included in our study, as depicted in Figure 2.

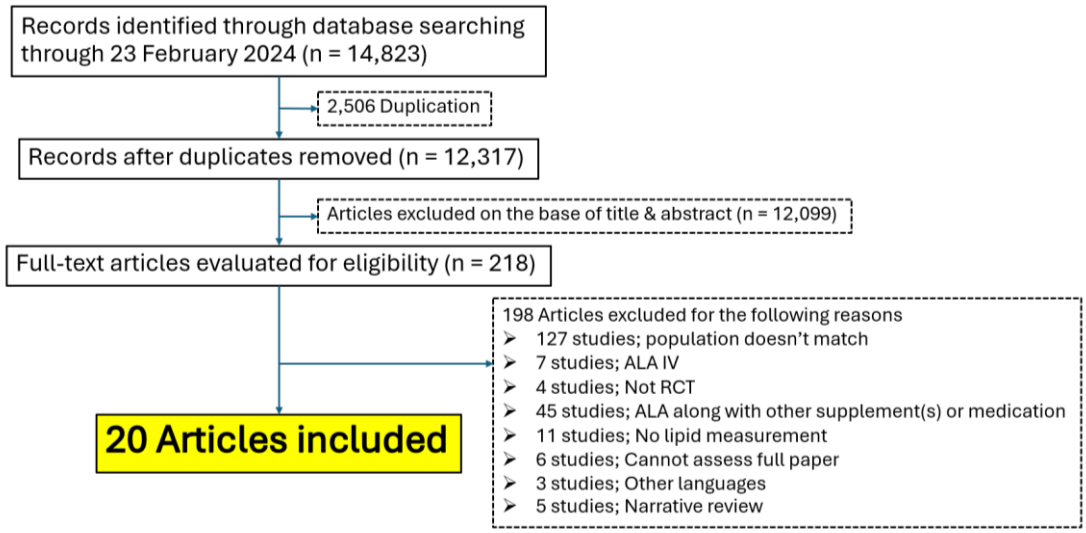

Figure 2: Steps and number of literatures from each screening process

We included 20 randomized, double-blinded, placebo-controlled studies conducted between 2006 and 2023, primarily in Iran, with others from South Korea, the United States, and various other countries. This studies involved diverse participant groups, along with individuals with type 2 diabetes, obesity, and various other health conditions. The administered doses of ALA scoped from 100 mg to 1,800 mg per day, with most studies using 600 mg per day, over durations ranging from 1 month to 24 weeks. The methods of ALA administration varied, with some studies specifying intake before meals and others during or after meals. Notably, the literature by Koh et al., which explored the effects of ALA in overweight participants, administered two different doses of ALA—1,200 mg and 1,800 mg per day. Therefore, this study was split into two separate analyses, as seen in Table 1. Additionally, the study by Atmaca et al. (Usta Atmaca & Akbas, 2017) was kept out from our analysis on an account of the

deprived of information about the blood lipid levels in the control group, therefore determination of lipid difference cannot be done.

Fraction of the studies comprised in our review reported comparisons of various blood lipid levels before and after taking ALA or between lipid levels after taking ALA versus after taking a placebo. However, these comparisons may not be entirely accurate and could lead to misunderstandings. To determine whether alpha-lipoic acid effectively reduces lipid levels compared to a placebo, it is necessary to compare the differences in lipid levels before and after ALA administration with the differences in lipid levels before and after placebo administration. This approach ensures that any reduction in lipid levels is genuinely due to ALA and not the placebo effect or other factors. Reanalysis of these studies using the correct comparison method might yield results that are not statistically significant or that differ from the original findings. Among the researches incorporated in this study, only three researches conducted the correct type of comparison: Bobe et al, Khabbazi et al, and Koh et al (Bobe et al., 2020; Khabbazi et al., 2012; Koh et al., 2011). This difference in analysis methods contributed to the distinct findings of this article compared to other reviews on similar topic. Moreover, from the literature consolidated in this article, we noticed that most of the studies had lipid changes reported as secondary outcomes. This diminishes the reliability of the findings regarding the consequence of ALA on different lipid types. The primary outcomes of each literature were used to determine the sample size, and the reporting of secondary outcomes was not systematically planned in all studies. As a result, the reliability of these secondary outcomes is more uncertain, which may be one reason why the conclusions drawn from this review differ from those of previous studies.

A meta-analysis of 19 studies involving 1,379 participants found that ALA significantly reduced TG levels with a mean difference of -6.299 mg/dL (95% CI: -10.104 to -2.494). However, the heterogeneity among studies was very high ($I^2 = 90\%$, $p < 0.01$). Subgroup analyses was done and depicted no significant differences based on study quality, dosage, study duration, participant condition, or timing of administration, with the significant value of TG in the subgroup of duration of more than 8 weeks (not shown here). Sensitivity analysis performed by removing certain studies, particularly Okanovic et al. (Okanović et al., 2015), affected the overall results, suggesting these studies had a significant influence, as in Supplemental figure 1. Despite this, the overall findings remained robust, though the high I^2 indicates substantial variability between studies as in Figure 2B.

Table 1: Patient characteristics and brief result of each studies

Study	Country	Patient Group	Sample Size (ALA/Control)	Age of Participants (Mean (SD) or Median (IQR))	Parameter(s)	ALA Dose (mg)	Duration of Study	ALA Administration Method	Study Findings on ALA Effects
Sun et al., 2012	China	Age-related macular degeneration (AMD)	32/30	65.78(7.93)/64.47(8.13)	TC, TG, HDL, LDL	600	3 months	Not reported	Insignificant effect in TC, TG, HDL, and LDL after ALA compared to before ALA
Usta Atmaca & Akbas, 2017	Turkey	Type 2 diabetes mellitus	23/21	56.1(6.6)/36.3(7.5)	TC, TG, HDL, LDL	600	6 weeks	30 minutes before meal	Insignificant effect in TC, TG, HDL, and LDL after ALA compared to before ALA
Khabbazi et al., 2012	Iran	End stage renal disease with regular hemodialysis	31/32	53.83(13.29)/54.30(14.56)	TC, TG, HDL, LDL	600	8 weeks	After breakfast	No significant effect in TC, TG, HDL, and LDL after ALA compared to after placebo
Kim et al., 2016	South Korea	Schizophrenia	10/12	40.5(6.65)/40.08(9.14)	TC, TG	1200	12 weeks	30 minutes before meal	No significant effect in TC and TG after ALA compared to after placebo
Chang et al., 2007	South Korea	End stage renal disease with regular hemodialysis	25/25	63(6)/66(7)	TC	600	12 weeks	Not reported	No significant effect in TC after ALA compared to before ALA

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Gianturco et al., 2009	Italy	Type 2 diabetes mellitus	7/7	61(7)/58(16)	TC, TG, HDL, LDL	400	4 weeks	Not reported	Significant effect in HDL but no significant effect in TC and TG after ALA compared to after placebo
Li et al., 2017	China	Obese and overweight patients	103/103	44(39-47)/43(38-47)	TC, TG, HDL	1200	8 weeks	30 minutes before meal	No significant effect in TC, TG, and HDL after ALA compared to before ALA
Mohammadi et al., 2017	Iran	Stroke	33/34	62.33(6.19)/64.23(8.01)	TC, TG, HDL, LDL	600	12 weeks	1 hour before or 2 hours after lunch	Significant reduction in TC, TG, and LDL and significant elevation in HDL after ALA compared to after placebo
Okanović et al., 2015	Bosnia	Type 2 diabetes mellitus, overweight, with peripheral neuropathy	30/30	64.4(1.87)/61.0(1.7)	TG	600	20 weeks	Not reported	Significant reduction in TG after ALA compared to after placebo
Lukaszuk et al., 2009	USA	Type 2 diabetes mellitus	13/7	53.14(5.9)/56(6.7)	TC, TG, HDL, LDL	600	13 weeks	30 minutes before meals	Insignificant effect in TC, TG, HDL, and LDL after ALA compared to after placebo
Mirtaheri et al., 2014	Iran	Female patients with rheumatoid	33/32	36.09(8.77)/38.28(8.63)	TC, TG, HDL, LDL	1200	8 weeks	30 minutes before meals	Insignificant effect in TC, TG, HDL, and LDL after ALA

	arthritis in remission						compared to before ALA
Elewa, 2020	Egypt	End stage renal disease with regular hemodialysis	35/35	49.17(11.16)/46.94(8.67)	TC, TG, HDL, LDL	600 13 weeks	Not reported	No significant effect in TC, TG, HDL, and LDL after ALA compared to control group
Aslfalah et al., 2020	Iran	Conceivable female potential for gestational diabetes mellitus	30/30	30.96(5.09)/31.10(5.03)	TC, TG, HDL, LDL	100 8 weeks	Not reported	No significant effect in TG after ALA compared to after placebo
Baziar et al., 2020	Iran	Type 2 diabetes mellitus	35/35	52.66(4.81)/53.34(4.45)	TC, TG, HDL, LDL	120 8 weeks 0	30 minutes before meals	Significant reduction in TG but insignificant changes in TC, HDL, and LDL before and after ALA and placebo administration
Mohamadi et al., 2022	Iran	Intensive care unit patients	40/40	46.9(17.5)/53.0(19.4)	TC, TG, HDL, LDL	600 8 weeks	1 hour before lunch or 2 hours after lunch	Significant reduction in LDL after ALA compared to before ALA
Gosselin et al., 2019	USA	Prediabetes with sedentary life	12/12	47.1(2.9) all patients	TC, TG, HDL, LDL	600 1 month	Taken with meals	Insignificant effect in TC, TG, HDL, and LDL after ALA administration
Bobe et al., 2020	USA	Overweight participants	31/33	38(10)/40(8)	TC, TG, HDL, LDL	600 24 weeks	30 min before meals	Insignificant effect in TC, TG, HDL, and LDL

						with lots of fluid	after ALA administration
Ahmadi et al., 2022	Iran	Patients with metabolic syndrome	23/19	40.39(8.90)/43.68(3.52)	TC, TG, HDL, LDL	600 12 weeks	Not reported	Significant decrement in TG and TC; insignificant effect in HDL and LDL after ALA compared to placebo group
Divković et al., 2023	Bosnia	Patients with low-grade squamous intraepithelial lesions	41/48	43(34-47)/37(28-46)	TC, TG, HDL, LDL	600 3 months	Not reported	Significant LDL increment after ALA compared to placebo group
Koh et al., 2011	South Korea	Obesity patient	73/74	41.6(1.1)/40.7(1.1)	TC, TG, HDL	1200 20 weeks	30 minutes before meals	No significant effect on TC, TG, and HDL
			82/73	41.4(1.0)/40.7(1.1)	TC, TG, HDL	1800 20 weeks	30 minutes before meals	No significant effect on TC, TG, and HDL

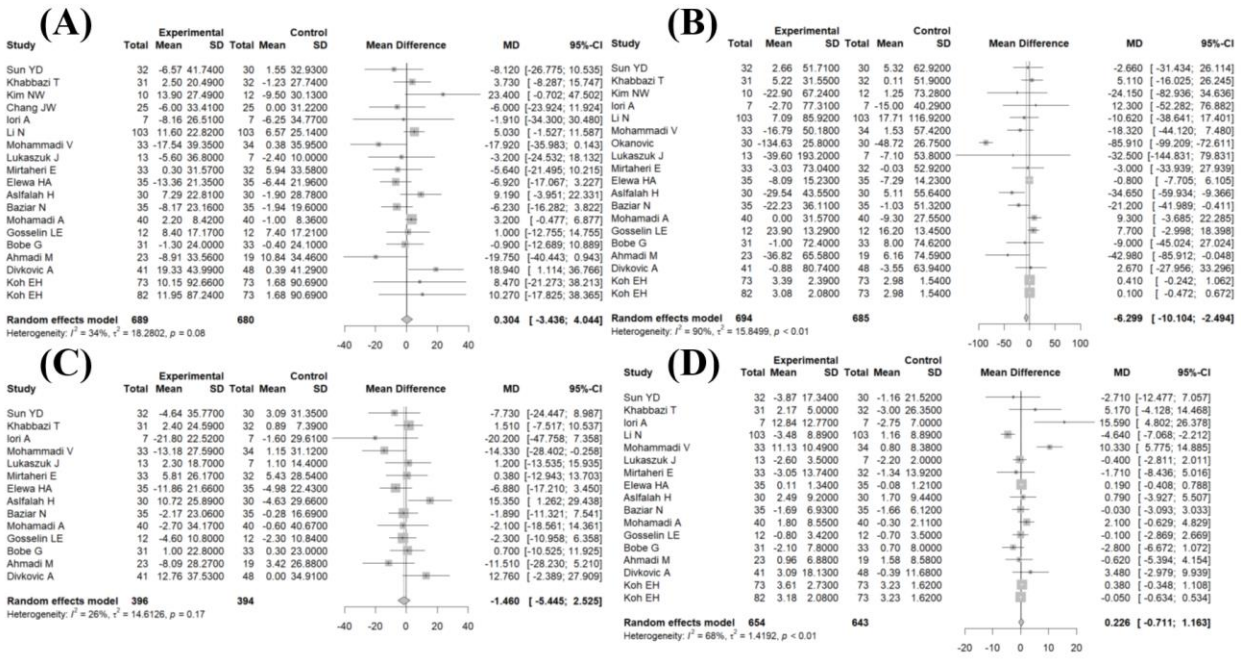

Figure 2: Forest plot regarding pooled effect (mean difference) of ALA to TC (A), TG (B), HDL (C), and LDL (D). There was a significant result of ALA to lower the TG levels in figure B, while TC, HDL, and LDL did not show statistically significant difference of ALA effect.

The represented results of this study indicated that ALA significantly reduces TG levels, aligning with the analysis conducted by Mousavi et al. (Mousavi et al., 2019) However, Mousavi's study did not specify whether the studies they included involved only oral administration or other methods, such as intravenous route. When reviewing the studies included by Mousavi et al. and examining the forest plot for changes in TG levels, three studies likely contributed to statistically significant results: Zhang et al., Salwa et al., and Okanovic et al. (El-Nabarawy et al., 2011; Okanović et al., 2015; Zhang et al., 2011) Among these, Zhang's study administered ALA intravenously for two weeks, which does not align with our inclusion criteria. Salwa's study was not a randomized controlled trial and lacked baseline lipid data before ALA administration. The Okanovic study, which was included in this meta-analysis, was assessed as having a high risk of bias, particularly owing to subjects in randomization, deviation from intended intervention, and selective reporting.

On the contrary, the article published by Haghighatdoost et al. (Haghighatdoost & Hariri, 2019) did not find a statistically significant change in TG levels but did find significant reductions in TG in both diabetic and non-diabetic patients when compared to placebo in a subgroup analysis. The differences in results between this study and Haghighatdoost's study may be attributed to disagreement regarding inclusion criteria, including conglomeration of studies with both oral and intravenous administration of ALA. Furthermore, when examining the forest plot, three studies likely influenced the overall effect size: Zhang et al., Gianturco et al., and Mohammadi et al. (Gianturco et al., 2009; Mohammadi et al.,

2017; Zhang et al., 2011) Gianturco's study involved a very small sample size of only seven participants per group, and when analyzed with the correct method, the results were not statistically significant. Mohammadi's study involved elderly stroke patients, who are typically on statins for secondary prevention, which, may not indicated in study, might interfere with the influence of ALA on lipid levels.

The mechanism by which ALA reduces TG remains unclear. Studies on animals, for instance, demonstrated by Butler et al. (Butler et al., 2009), have shown that ALA reduced appetite in mice, leading to decreased TG levels. Another study by Fernandez et al. (Fernández-Galilea et al., 2014) in overweight women suggested that the reduction in TG could be due to the inhibition of lipid synthesis, as indicated by the decrease in the DGAT1 enzyme involved in this process. Additionally, ALA was found to enhance the AMPK signaling pathway, which regulates energy balance by reducing lipid synthesis.

Analysis with the polynomial regression was conducted to examine the association between the dose of ALA and the duration of intake on changes in various blood lipid levels. The p-values of the F-statistics, which assess whether the regression models adequately explain the relationship between the independent variables (dose of ALA or duration of administration) and the dependent variables (blood lipid levels), did not significantly explain the association between the ALA dose and changes in blood lipid levels, as seen in Figure 2 and Figure 3. However, the graphs show that the reduction in TG does not vary much with doses of ALA up to 1,200 mg per day. Interestingly, the reduction of TG tends to be less pronounced at 1,800 mg per day compared to doses of 1,200 mg or less. In analyzing the relationship between the duration of ALA intake and changes in blood lipid levels, the result suggests that the regression models did not significantly explain the connection between the duration of ALA intake and variability in blood lipid levels. Nevertheless, the graphs indicated that the reduction in TG was most pronounced when ALA was taken for approximately 16 weeks, with less reduction observed for durations shorter or longer than 16 weeks.

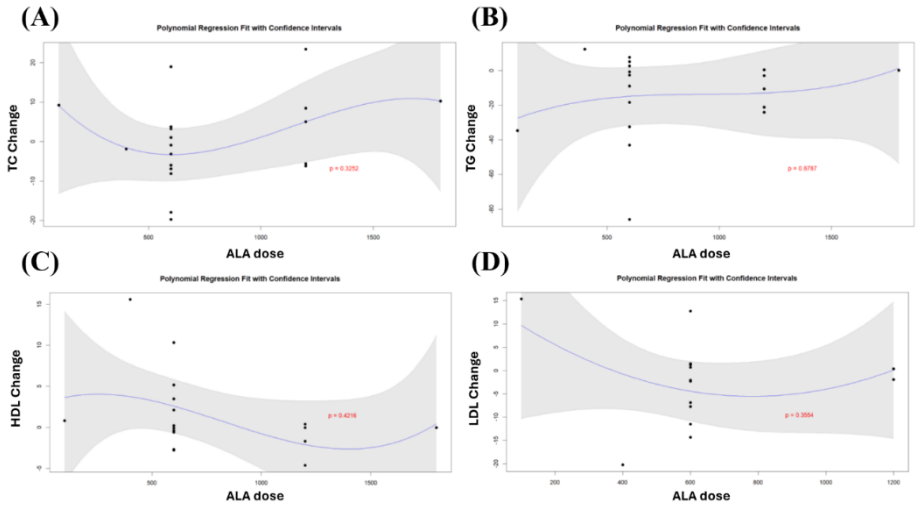

Figure 2: Display the analysis results using polynomial regression of the daily dose of ALA in milligrams on the horizontal axis against the change in TC (A), TG (B), HDL (C), and LDL change (D) in milligrams per deciliter on the vertical axis. The p-value indicated in each graph represents obtained from polynomial regression analysis.

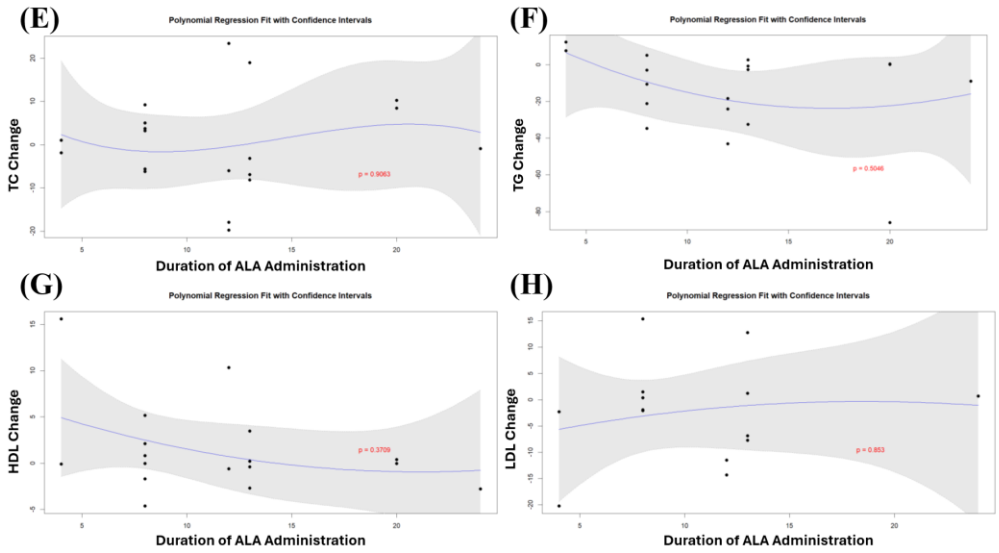

Figure 3: Display the analysis results using polynomial regression of the duration of ALA administration in weeks on the horizontal axis against the change in TC (A), TG (B), HDL (C), and LDL change (D) in milligrams per deciliter on the vertical axis. The p-value indicated in each graph represents obtained from polynomial regression analysis.

Meta-regression analysis in Mousavi's study found no linear relationship between the dose or duration of ALA administration and changes in lipid levels (Mousavi et al., 2019). Therefore, we considered using polynomial regression to better capture nonlinear relationships. Although the results were not statistically significant, they suggested that the optimal duration for TG reduction is around 16 weeks, consistent with the subgroup analysis that indicated a significant reduction in TG with a study duration of more than 8 weeks. This implies that extending ALA administration beyond 16 weeks may not provide additional benefits, but aforementioned result requires further investigation. Regarding the dose of ALA, polynomial regression analysis and the accompanying graphs indicated that doses of up to 1,200 mg per day showed minimal variation in TG reduction, suggesting that higher doses might not yield additional TG-lowering benefits. Several studies that administered ALA at doses greater than 600 mg reported a high dropout rate among participants, which may be due to the side effect of ALA in higher dosage. This could lead to missing data and affect the results. Studies conducted with higher dose of ALA included in the studies also yielded a non-significant reduction in lipid profile, including TG, which complied with our study. In spite of the conflicting findings, this study may point to a possible advantage for patients with mild dyslipidemia or those at risk of cardiovascular disease as a cost-effective alternative to standard lipid-lowering medicines. The outcomes are demonstrating once more time the fact that ALA can be used in the form of a supplement for lipid-lowering therapy and in conjunction with prescribed medications. While the lipid profile is being improved, ALA can be an

additive to a therapy which is a very important one for people who are not able to achieve lipid control through the standard therapies they are using. The redox-modulatory features of this molecule assist in preventing oxidative stress and consequently in the improvement of vascular endothelial function. This wide-spectrum natural substance with antioxidants, provides patients an innovative option to treat these illnesses.

Our meta-analysis found that ALA did not significantly influence TC, HDL, and LDL levels (MD 0.304 (95% CI: -3.436 to 4.044), 0.226 (95% CI: -0.711 to 1.163), and -1.460 (95% CI: -5.445 to 2.525) respectively), illustrated by Figure 2A, 2C, and 2D. Subgroup analyses revealed no significant differences based on each characteristic (not shown here).

The changes in total cholesterol and LDL were not statistically significant, which contrasts with the findings of the others (Haghighatdoost & Hariri, 2019; Mousavi et al., 2019). One reason for this discrepancy could be the differences in inclusion and exclusion criteria, for example, the recruitment of literatures with both oral and intravenous ALA administration, which have different pharmacokinetics and pharmacodynamics. Additionally, differences in data analysis methods, as previously discussed, may have contributed to varying results. Pre-clinical studies, such as the one by Ghelani et al. (Ghelani et al., 2017), found that ALA increased HDL levels in mice, possibly due to its anti-inflammatory effects, which reduce endothelial lipase and increase apolipoprotein A-I, a component of HDL. However, most human studies, including this one, have not demonstrated a statistically significant increase in HDL levels, despite some studies showing a trend toward increased HDL.

There was high order of heterogeneity observed among the researches, as predicted by the I^2 statistic for statistical heterogeneity, and methodological heterogeneity resulted from differences in study populations and methods. The heterogeneity reported in this meta-analysis may raise from a result of different study designs, demographic variables, changes in ALA supplementation dosage and duration, and inconsistency in outcome measuring methodologies which may affect on the data generalizability. Most studies focused on patients with conditions associated with dyslipidemia, but few specifically conducted the direct potentials of ALA on lipid levels in individuals underlying hyperlipidemia without other complications. Further research is demanded in the aforementioned subject to clarify the effects of ALA on lipid levels.

For publication bias, it can be observed that the graphs are generally symmetrical. Furthermore, Begg's and Egger's tests also yielded non-significant results. Overall, the graphs and statistical tests did not indicate any clear evidence of publication bias (Supplemental figure 2).

There are some limitations. First, this study only investigated the oral administration of ALA, excluding other routes such as intravenous administration, which could potentially alter the results due to different

pharmacokinetic and pharmacodynamic effects. However, the authors considered the clinical application, where oral administration might be more practical. If more studies involving intravenous ALA that meet the study criteria become available, they could be included in future analyses. Second, this study did not include research that was reported in non-English languages, limiting access to studies from some countries, such as China. Third, the studies included did not specifically scrutinize the outcomes of ALA on lipid metabolism or in populations contained elevated blood lipid levels without other confounding factors such as lipid-lowering medications. Future studies should exclude participants with potential confounding factors to better isolate the efficiency of ALA. Regarded the suggestion for the future studies, authors suggested investigating the long-standing effects (e.g., more than 24 weeks) of ALA on different types of lipids in blood in various populations to observe potential long-term variability in each demographic group.

4. Conclusion

In conclusion, ALA has demonstrated a significant TG-lowering effect, with appropriate dosage of not more than 1,200 mg per day for 16 weeks duration, making it a potential dietary supplement for individuals at risk of cardiovascular diseases. With regard of our limitation, such as exclusion of non-English studies and high heterogeneity between included studies, further studies are required to seek the effect of ALA without other confounding medication and its long-standing capability for profitable dosing regimens.

Declaration of Interest Statement.

The authors state that they pertain no conflict of interests.

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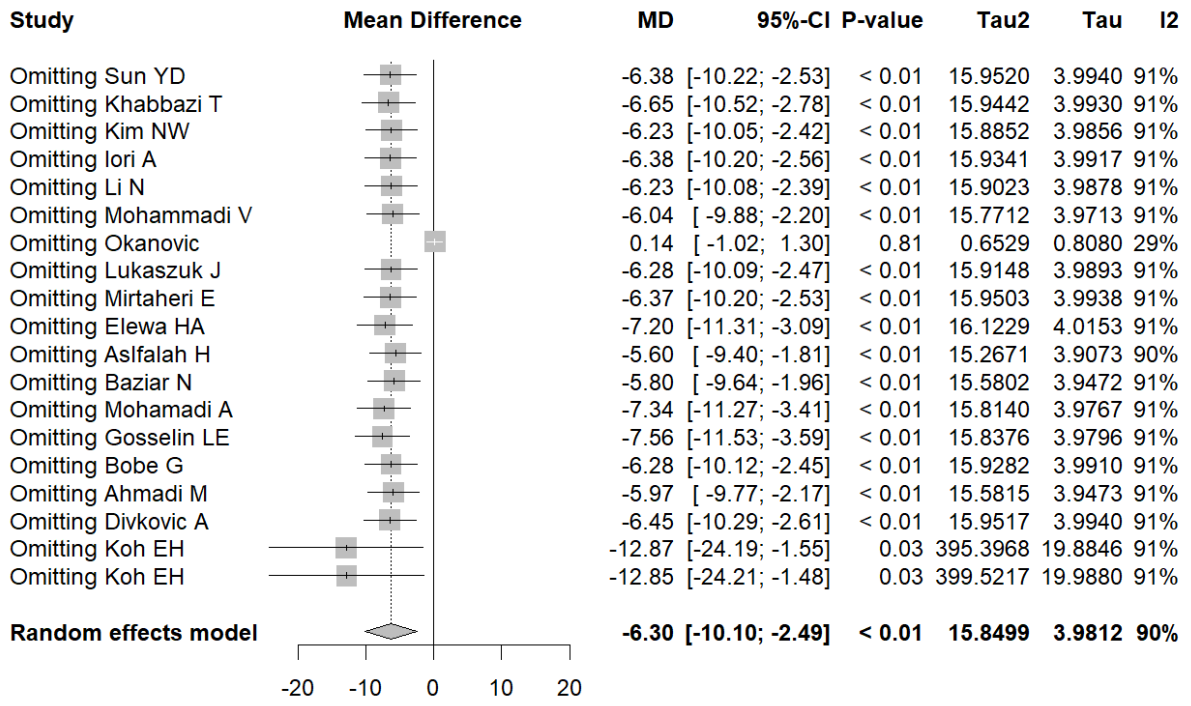
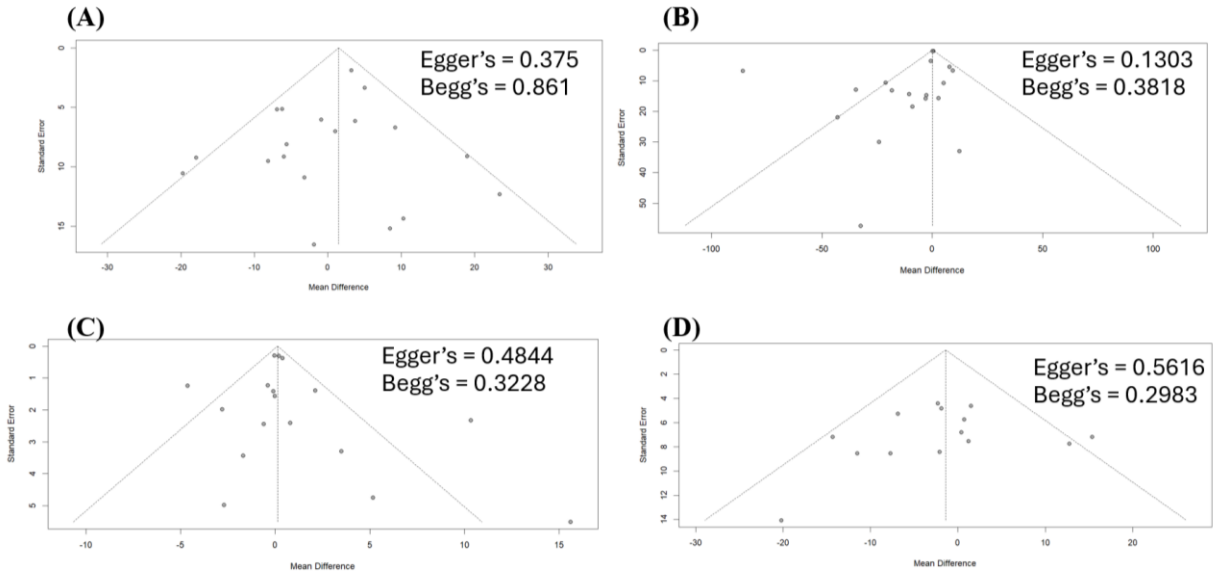
Appendix

Include other supplementary details here



Supplemental Figure 1: Sensitivity analysis of the studies on TG levels by excluding each study one by one and reanalyzing the outcomes. When the research conducted by Okanovic et al. was excluded, the mean difference became 0.14 mg/dL, with a p-value of 0.81, pointing out no statistical significance. This proposed that excluding this study may alter the overall outcome.



Supplemental Figure 2: Funnel plot along with publication bias assessed by Egger's and Begg's test of the effect of ALA to TC (A), TG (B), HDL (C), and LDL (D). The plot suggested that there was no significant publication bias from these statistical tests.

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