

Blood pressure lowering effects of alpha-lipoic acid supplementation: a meta-analysis of randomized controlled trials

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Abstract

Background: The aim of the present meta-analysis was to detect the effect of α -lipoic acid (ALA) supplementation on systolic and diastolic blood pressure (BP).

Material and methods: The related records were selected from several electronic databases from the earliest date 1980 until October 2019. The heterogeneities were assessed by I² test (I² < 50%) and χ^2 test on Cochrane's Q statistic. Standardized mean difference (SMD) and their 95% confidence intervals (CIs) were considered for net change in systolic blood pressure (SBP) and diastolic blood pressure (DBP). Subgroup analyses were also conducted by baseline BP, health status, doses of supplementation, study duration and supplement utilization.

Results: As a result, a total of 10 studies with 612 subjects were included in the final analysis. Alpha-lipoic acid supplementation significantly reduced SBP (SMD = -0.50, 95% CI: -0.84, -0.16, p = 0.004) and DBP (SMD = -0.40, 95% CI: -0.71, -0.09, p = 0.01), compared to the controls, with the reduction of 6.1 mm Hg and 3.6 mm Hg of the mean SBP and DBP, respectively. Heterogeneities were explored in both SBP and DBP. Moreover, a statistically significant reduction in BP was detected in elevated BP and hypertensive patients as compared with the normotensive subjects.

Conclusion: ALA supplementation could be considered as a BP-lowering agent, especially in subjects with higher blood pressure.

Key words: α -lipoic acid; blood pressure; systematic review; meta-analysis; RCT

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Introduction

Alpha lipoic acid (ALA), as a naturally occurring dithiol compound and a organosulfur compound is essential as a cofactor for mitochondrial α -ketoacid dehydrogenases [1].

It is synthesized by the liver [2] and is present in animal and vegetable sources [3]. The antioxidant

effect of ALA has been demonstrated by the ability of ALA to clear reactive oxygen species (ROS) and activating the endogenous antioxidant system [4, 5]. Additionally, it has been shown that ALA could improve endothelium function and play a role in nitric oxide synthesis [6, 7]. According to the latter role, different studies were conducted in vivo, which emphasizes the effect of ALA supplementation on blood

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pressure (BP) [4, 8, 9]. It is well established that hypertension condition (BP) can result in several cardiovascular disorders while decreasing blood pressure reduces cardiovascular risk, myocardial infarction, heart failure, and stroke [10, 11]. The administration of different doses of ALA has been examined in several studies. Ergür et al. conducted a study in which ALA was administered orally in rats at a dosage of 100 mg/kg, and reported a significant reduction of secondary hypertension [8]. However, the findings of human trials are controversial [12–14]. In a recent study by Mohammadi et al., the daily supplementation of ALA with a dose of 600 mg on subjects with cardiovascular risk factors and chronic spinal cord injury revealed the systolic and diastolic blood pressure lowering effects [12]. However, other trials did not observe any significant blood pressure-lowering effect of ALA supplementation, after four months of oral supplementation with 800 mg ALA [15] and after twenty months of oral supplementation with 1800 mg ALA [16]. Although there is a systematic review showed that supplementation with ALA did not appear to be efficient on BP [4], we conducted the present meta-analysis to better clarify the potential effect of ALA supplementation on BP.

Material and methods

We carried out the present meta-analysis and designed the strategies according to the PRISMA guidelines [17].

Literature search strategy

Several electronic databases including Pubmed™, Scopus™, EMBASE™, and Google Scholar™ were searched from inception until October 2019. In addition to electronic searching, we tried to hand-search the reference list and citations of papers to detect more potential eligible studies. Search terms used were as follow: (ALA OR “ α -lipoic acid” OR “lipoic acid” OR “alpha lipoic acid”) AND (“Hemodynamic parameters” OR “Blood pressure” OR “Systolic blood pressure” OR “Diastolic blood pressure” OR “BP” OR “SBP” OR “DBP”).

Selection criteria

To be included for meta-analysis, the studies had to meet the following inclusion criteria: 1) being a trial in human species with either cross-over or parallel design, 2) providing the possible effects of ALA supplementation on either systolic or diastolic blood pressure, 3) reporting sufficient data on SBP/DBP including baseline/end of supplementation or mean

changes and related standard deviations in both intervention and placebo groups, 4) the study had to use a control or placebo group for the treatment group and, 6) subjects had to take ALA supplements for at least 2 weeks. Studies were excluded according to the following criteria: 1) lack of a control group, 2) lack of adequate data regarding SBP or DBP in each group, or lack of required data for computing the indices

Data abstraction

The data from all included articles were extracted independently by two authors. Any possible disagreement was solved by a third author through consensus and discussion. The following data was obtained from the each of eligible studies: author identification, publication year, study design and location, duration of supplementation and follow-up, the dose of ALA supplementation, the sample size in both intervention and control groups, demographic indices (age, gender), clinical condition, baseline SBP, and DBP values, and observed significant outcomes.

Validity assessment

We estimated the quality of studies according to the Jadad scale with the following criteria: (1) randomization (one score for mentioning random allocation and one more score for explaining the method of randomization appropriately), (2) blinding (One score for stating that the trial was blinded and one more score for describing the method of blinding properly, and (3) reporting of dropouts, in addition to reasons for withdrawals (one score for reporting of dropouts and the withdrawal reasons). The total score varies between 0 to 5, in which the trials with the score of ≥ 3 are considered as high-quality trials.

Data synthesis

We analyzed the data using two software including RM Software (Review Manager 5.3) and Biostat Comprehensive Meta-Analysis. We defined the treatment effects by standardized mean difference (SMD) and 95% confidence intervals (CIs) of outcomes. Moreover, we assessed the possible heterogeneity by χ^2 test on Cochrane's Q statistic and I2 test, by which $p < 0.05$ or $I2 > 50\%$ was considered as heterogeneous. We used the random-effects model to calculate the pooled effect size. Moreover, we conducted subgroup and sensitivity analyses in accordance with the Cochrane guidelines for exploring any possible sources of heterogeneity between included studies [18]. We performed the sensitivity analysis by removing a single included trial and re-calculating the effect

size to detect any potential effect on the final overall effect size [19].

To find any potential publication biases, Begg's rank correlation test, funnel plots, and Egger's regression test were used. A p value < 0.05 was considered as statistically significant.

Results

Selection of trials

Figure 1 shows the process of trial selection. In general, a number of 218 articles were primarily detected, in which 194 articles were excluded due to duplication ($n = 101$) or were irrelevant to the current meta-analysis including non-original research (letters, case reports, and series, reviews, experimental or animal studies) ($n = 93$). More studies were excluded because of the following reasons: inappropriate reporting data on SBP or DBP, supplementation of ALA in less than two weeks, improper study design such as non-randomized trial, and lack of control group. Finally, ten studies were included in the meta-analysis [12–16, 20–24].

Characteristics of included trials/quality assessment

The descriptions of all included studies of the current meta-analysis are shown in Table 1. The year of publication of included studies varied between 1997 and 2019, of which five studies were conducted in Iran [12–14, 21, 24], two in the USA

[20, 22], and the remaining included studies were carried out in the Republic of Korea [16], Italy [23] and Germany [15].

Totally, ten clinical trials with 612 subjects (Intervention, $n = 311$, and control, $n = 301$), were included in the present synthesis. The number of participants in included trials ranged from 7 to 82 subjects. Supplementation duration was between 8 weeks to 20 weeks, and the dose of supplementation varied from 300 to 1800 mg/d. Of the ten included trials, five recruited Type 2 Diabetic patients [13–16, 20], one trial was performed in chronic spinal cord injury patients [12], one trial included subjects with stroke [24], two studies elected participants with obesity [16, 23], the patients with metabolic syndrome and coronary artery disease were used in one study [22] and one more trial was conducted in patients with rheumatoid arthritis [21]. The mean age of subjects varied between 11.5 to 62.3 years. Among included trials, in accordance with the updated guidelines of the American College of Cardiology/American Heart Association (ACC/AHA); two have been categorized as elevated blood pressure subjects [20, 21], one study as normotensive subjects [23], and seven remaining studies as hypertensive patients which ranged from 117 to 144 and 69.4 to 87.85 for systolic and diastolic blood pressure, respectively [12–16, 22, 24]. The quality of studies was assessed using the Jadad score scale. According to Jadad scale method, all included studies were categorized as high-quality studies (Tab. 2). Six out of 10 included trials described the blinding method

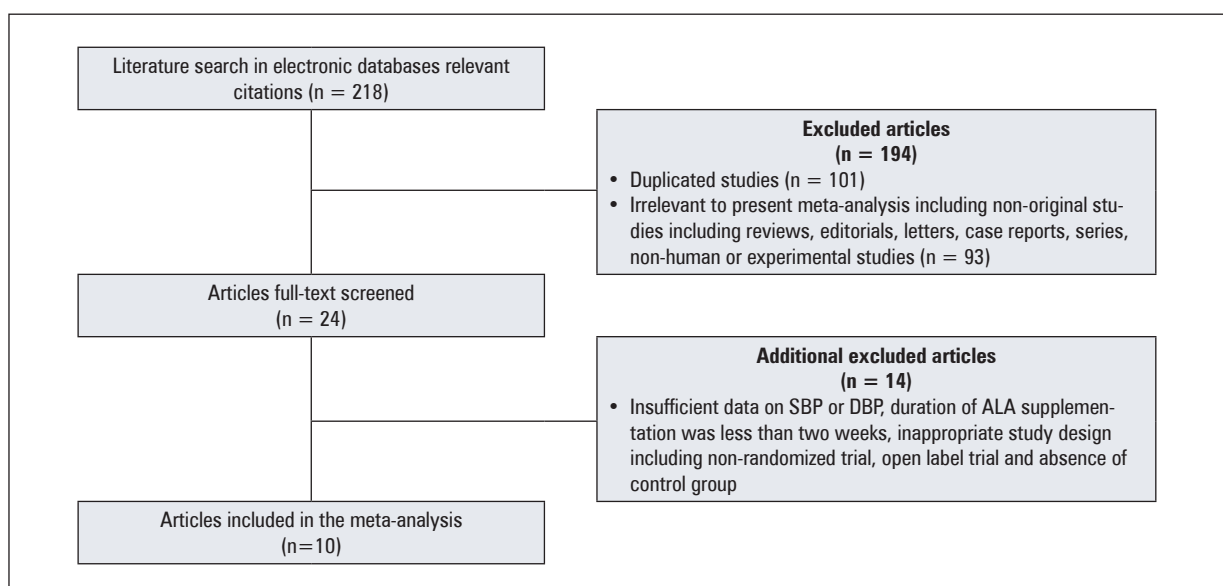


Figure 1. The flow diagram of literature search and study selection of the meta-analysis. SBP — systolic blood pressure; DBP — diastolic blood pressure; ALA — α -lipoic acid

Table 1. Characteristics of included research

Author	Year	Design of studies	Country	No. of subjects in case group	No. of controls	Gender	Age of intervention (mean) \pm SD	Follow-up duration (weeks)	Clinical condition	Dosage [mg/d]	Significant outcome	Baseline BP (SBP/DBP)
Koh	2011	Randomized, double-blind, placebo-controlled	Republic of Korea	82	73	M F	41.4	20	Obese, HT, DM, or hypercholesterolemia	1800	Treatment with ALA was not associated with significant reductions in BP	132.97 82.4
Lukaszuk	2009	Double-blind study pre-/post-test control group	USA	13	7	M F	56	13	T2DM	600	There were minor, not significant, downward trends in the ALA group (as opposed to upward trends in the placebo group) in DBP	127.6 78.3
Mazloom	2009	Randomized, double-blind, placebo-controlled trial	Iran	29	28	M F	49	8	T2DM	300	A significant decrease in both SBP and DBP at the end of study in the ALAd	133.4 80.1
McMackin	2007	Double-blind, placebo-controlled, crossover	USA	15	21	M F	62	8	Coronary artery disease, metabolic syndrome	400 mg of ALA and 1000 mg of acetyl-L-carnitine	Active treatment tended to decrease SBP for the whole group	131 71
Mohammadi	2015	Randomized, double-blind, placebo-controlled clinical	Iran	28	30	M	39	12	Chronic spinal cord injury	600	There was significant reduction in BP	126.43 87.85
Mohammadi	2018	Randomized, double-blind, placebo-controlled clinical	Iran	33	34	M F	62.33	12	Stroke	600	After the intervention period, SBP, DBP reduced in ALA group compared with placebo group, significantly	133.18 84.24
Noori	2013	Randomized, double-blind, placebo-controlled trial	Iran	17	17	M F	60.0	12	Diabetic nephropathy	800 mg ALA and 80 mg pyridoxine	SBP decreased significantly in the supplement group compared to the placebo group	142 77
Pourghasem	2015	Randomized, double-blinded, placebo-controlled clinical trial	Iran	33	32	F	36.09	8	Rheumatoid arthritis	1200	SBP and DBP in ALA group was significantly decreased in comparison with placebo group ($p < 0.05$). But, CRP and IL-6 serum levels did not indicate any significant within- and between group changes	121.59 77.04
Tromba	2019	Double-blind, placebo-controlled randomized trial	Italy	32	32	M F	11.5	12	Overweight/obese children	800	There were no significant differences within each group for BP	117 69.4
Ziegler	1997	Randomized, double-blind placebo controlled multicenter trial	Germany	29	27	M F	57.9	4 months (16 wks)	NIDDM patients with cardiac autonomic neuropathy	800	Mean BP did not differ between the groups at baseline and during the study	144 81.4

HT — hypertension; DM — diabetes mellitus; T2DM — type 2 diabetes mellitus; NIDDM — non-insulin-dependent diabetes; ALA — alpha-lipoic acid; BP — blood pressure; DBP — diastolic blood pressure; SBP — systolic blood pressure; CRP — C-reactive protein; IL-6 — interleukin 6

Table 2. Quality of the 10 studies as assessed by the Jadad score

Study [year]	Blinding	Randomization	Withdrawals and dropouts descriptions	Score
Koh [2011]	2	2	1	5
Lukaszuk [2009]	2	1	1	4
Mazloom [2009]	1	2	1	4
McMackin [2007]	2	2	1	5
Mohammadi [2015]	1	2	1	4
Mohammadi [2018]	2	2	1	5
Noori [2013]	1	2	0	3
Pourghasem [2015]	2	2	1	5
Tromba [2019]	2	2	1	5
Ziegler [1997]	1	2	1	4

appropriately [16, 20–24] and most of the included studies (9 of 10) provided a sufficient and acceptable description of the method of randomization [12–16, 21–24]. All studies except one study [13] stated the dropouts descriptions and the associated reasons.

Blood pressure-lowering effects of ALA supplementation

The synthesis was carried out based on the data of 612 participants from 10 clinical trials reporting blood pressure values (intervention, $n = 311$, and placebo, $n = 301$). As it has been shown in Figure 2, ALA supplementation statistically significantly reduced both SBP (SMD = -0.50 , 95% CI: -0.84 , -0.16 , $p = 0.004$) with the reduction of 6.1 mm Hg in the SBP mean and DBP (SMD = -0.40 , 95% CI: -0.70 , -0.09 , $p = 0.01$) with the reduction of and 3.6 mm Hg in the DBP mean. Additionally, a significant heterogeneity was observed between the included studies regarding both SBP and DBP (SBP: $p < 0.001$, $I^2 = 74\%$ and DBP: $p < 0.001$, $I^2 = 69\%$). According to the Cochrane guidelines, we conducted a stratified analysis to detect possible sources of heterogeneity.

Stratified analysis

Stratified analyses according to baseline blood pressure, follow-up duration, the dosage of supplementation, clinical conditions, and supplement utilization were conducted to explore the effect of ALA supplementation on blood pressure (Tab. 3). In accordance with the updated guidelines of the American College of Cardiology/American Heart Association (ACC/AHA), three subsets were investigated as normotensive, elevated BP, and hypertensive patients. Considering the baseline blood pressure, subgroups of elevated BP and hypertensive patients showed

statistically significant reduction in blood pressure as compared with normotensive patients [elevated BP: SMD of DBP, -0.6 (95% CI: -1.04 , -0.16 , $p = 0.008$), hypertensive subjects: SMD of SBP, -0.64 (95% CI: -1.03 , -0.25 , $p = 0.001$), SMD of DBP, -0.44 (95% CI: -0.83 , -0.05 , $p = 0.03$)].

The supplementation duration was separated into ≤ 12 weeks and > 12 weeks. With respect to clinical condition of subjects, two specific groups were divided to non-diabetic/diabetic subjects. As far as the dose of supplementation was considered, higher-dose (> 600 mg/day) and lower-dose (≤ 600 mg/day) were separated as two distinct subsets. As presented in Table 3, There was a considerable reduction in subgroups of studies categorized in respect to duration of supplementation of ≤ 12 weeks [SMD of SBP, -0.67 (95% CI: -1.10 , -0.23 , $p = 0.003$), SMD of DBP, -0.52 (95% CI: -0.92 , -0.13 , $p = 0.01$)], ALA dose of ≤ 600 mg/day weeks [SMD of SBP, -0.80 (95% CI: -1.22 , -0.37 , $p < 0.001$), SMD of DBP, -0.71 (95% CI: -1.14 , -0.29 , $p < 0.001$)], and non-diabetic subjects [SMD of SBP, -0.62 (95% CI: -1.22 , -0.02 , $p = 0.04$), SMD of DBP, -0.63 (95% CI: -1.15 , -0.11 , $p = 0.02$)]. Subgroup analysis according to different utilization (single/multi-component) of supplements revealed both systolic and diastolic-lowering effect of single component supplementation [SMD of SBP, -0.48 (95% CI: -0.87 , -0.08 , $p = 0.02$), SMD of DBP, -0.46 (95% CI: -0.82 , -0.10 , $p = 0.01$)].

Sensitivity analysis

We performed a sensitivity analysis to investigate the effect of each trial on the estimated overall pooled effect size. Removal of each study and re-calculating the effect size did not show any significant alteration in the overall effects of ALA supplementation on SBP

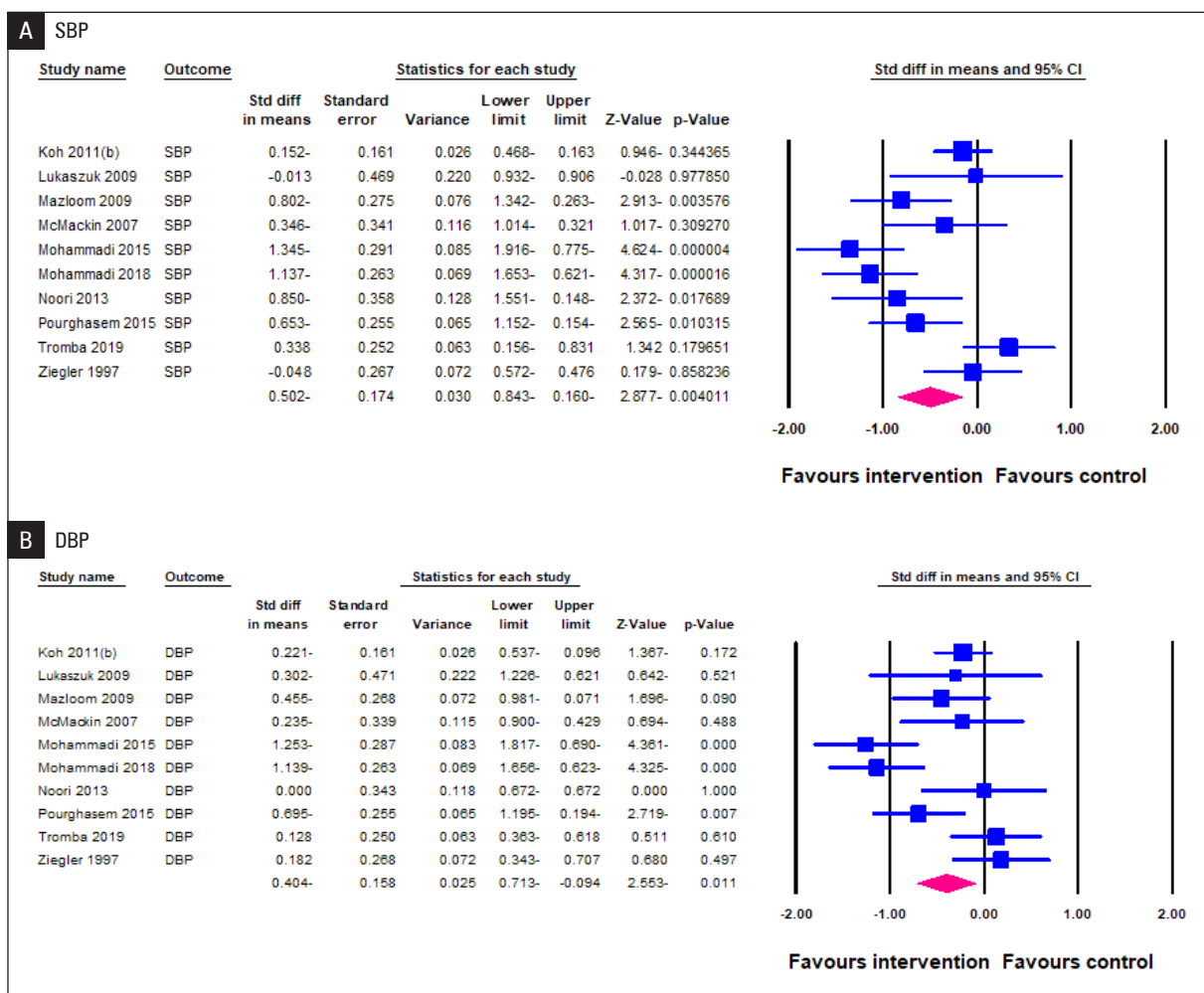


Figure 2. Forest plot of comparison of blood pressure between ALA supplementation and control groups. **A.** Systolic blood pressure (SPB); **B.** Diastolic blood pressure (DBP). Random effects model was used to pool the standard mean differences of indicators. CI — confidence interval; I — squared inconsistency

with the range of -0.40 (95% CI = $-0.72, -0.08$) to -0.60 (95% CI = $-0.92, -0.27$) and DBP with the range of -0.31 (95% CI = $-0.59, 0.02$) to -0.47 , 95% CI = $-0.79, -0.15$) (Fig. 3).

Publication bias

We investigated the publication bias of the present meta-analysis by the funnel plot analysis. As it has been shown in Figure 4, the symmetrical pattern of funnel plots regarding to both SBP and DBP hypnotized that there are no specific potential biases in the included trials. Moreover, Egger's linear regression for both SBP (intercept: -1.98 ; standard error: 2.41 ; 95% CI: $-7.54, 3.58$; $t = 0.82$, $df = 8$; two-tailed $p = 0.43$) and DBP (intercept: -0.71 ; standard error: 2.31 ; 95% CI: $-6.05, 4.62$; $t = 0.30$, $df = 8$; two-tailed $p = 0.76$) confirm the finding. Additionally, Begg's rank correlation test did not explore potential publication bias (SBP: Kendall's Tau with

continuity correction: -0.22 ; $z = 0.89$; two-tailed $p = 0.37$); DBP: Kendall's Tau with continuity correction: -0.08 ; $z = 0.35$; two-tailed $p = 0.72$).

Discussion

This is the comprehensive systematic review and meta-analysis which summarizes the data from 10 trials involving a total of 612 subjects.

The results of the present meta-analysis reveal that ALA supplementation causes a significant reduction in DBP in elevated BP subjects and a reduction in SBP and marginally DBP in hypertensive subjects. The definition and explanation of hypertension have been changed in the past years. One of the most recent definitions belongs to the American College of Cardiology and American Heart Association (ACC/AHA). This is an updated version of the guidelines

Table 3. Subgroup analysis

			WMD (95% CI)	Test for overall effect	Test for heterogeneity	I ² (%)
Baseline BP	Normal	SBP	0.33 [-0.16, 0.83]	p = 0.19	Not applicable	Not applicable
		DBP	0.13 [-0.36, 0.62]	p = 0.61	Not applicable	Not applicable
	Elevated	SBP	-0.45 [-1.02, 0.12]	p = 0.12	p = 0.24	29
		DBP	-0.60 [-1.04, -0.16]	p = 0.008	p = 0.46	0
	Hypertension	SBP	-0.64 [-1.03, -0.25]	p = 0.001	p < 0.001	74
		DBP	-0.44 [-0.83, -0.05]	p = 0.03	p < 0.001	74
Follow-up duration [weeks]	≤ 12	SBP	-0.67 [-1.10, -0.23]	p = 0.003	p < 0.001	76
		DBP	-0.52 [-0.92, -0.13]	p = 0.010	p = 0.001	72
	> 12	SBP	-0.11 [-0.37, 0.14]	p = 0.39	p = 0.92	0
		DBP	-0.13 [-0.39, 0.13]	p = 0.34	p = 0.42	0
Dosage [mg/d]	≤ 600	SBP	-0.80 [-1.22, -0.37]	p < 0.001	p = 0.06	57
		DBP	-0.71 [-1.14, -0.29]	p < 0.001	p = 0.05	58
	> 600	SBP	-0.23 [-0.59, 0.13]	p = 0.21	p = 0.03	64
		DBP	-0.14 [-0.43, 0.16]	p = 0.36	p = 0.11	47
Clinical condition	Diabetic patients	SBP	-0.35 [-0.69, -0.01]	p = 0.04	p = 0.11	46
		DBP	-0.17 [-0.39, 0.05]	p = 0.13	p = 0.53	0
	Non-diabetic subjects	SBP	-0.62 [-1.22, -0.02]	p = 0.04	p < 0.0001	84
		DBP	-0.63 [-1.15, -0.11]	p = 0.02	p = 0.001	78
Supplement	Single supplement	SBP	-0.48 [-0.87, -0.08]	p = 0.02	p < 0.001	79
		DBP	-0.46 [-0.82, -0.10]	p = 0.01	p < 0.001	75
	Multi supplement	SBP	-0.57 [-1.06, -0.09]	p = 0.02	p = 0.32	0
		DBP	-0.12 [-0.59, 0.36]	p = 0.63	p = 0.63	0

BP — blood pressure; SBP — systolic blood pressure; DBP — diastolic blood pressure; SMD — standard mean difference; CI — confidence interval; I² — percentage score for heterogeneity

related to the prevention, evaluation, detection, and management of hypertension in adults. This is distinguished by removing the category of prehypertension and separating it into two distinct levels: elevated blood pressure/stage 1 hypertension [25].

The association of hypertension and elevated blood pressure with morbidity and mortality of cardiovascular disorders has been well established [11, 26]. Abundant Epidemiologic data support that the risk of cardiovascular disorders disease increases with elevating blood pressure values. It has been reported that the blood pressure starting at ≥ 115/75 mm Hg results in such a manner [11, 27, 28]. There are evidence that both oxidative stress and a diminished capacity for scavenging free radicals play major roles in the development of hypertension and cardiovascular disorders. Moreover, SBP and DBP have been reported to positively relate to oxidative stress markers and negatively relate to plasma antioxidant capacity and free radicals could participate in the development of hypertension complications [29, 30].

Disruption of endothelial function leads to a diminished production or availability of NO and sub-

sequent impaired NO bioactivity. This results in an imbalance between the endothelium- vasoconstrictors, and vasodilators derived from endothelium [30]. Multiple cardiovascular risk factors are related to the possible changes in endothelial function including sedentary and inappropriate lifestyle, hypercholesterolemia, aging, arterial hypertension, and a family history of atherosclerotic disorders [31]. Thus, most updated guidelines suggest improvements in lifestyle including limiting daily dietary sodium, exercise, and reasonable weight-loss in high-risk patients.

According to the previous evidence, ALA is considered as an efficient antioxidant with both lipid and aqueous solubility [4]. Furthermore, ALA supplementation may exert anti-inflammatory and hypoglycemic characteristics of the subjects with various conditions [32]. Beyond the main function of ALA as an antioxidant [33, 34], ALA can also increase NO synthesis which results in an improvement in endothelial function [35]. Moreover, many enzymatic and metabolic reactions are dependent on ALA as a potential co-enzyme, and enhancing agent in the

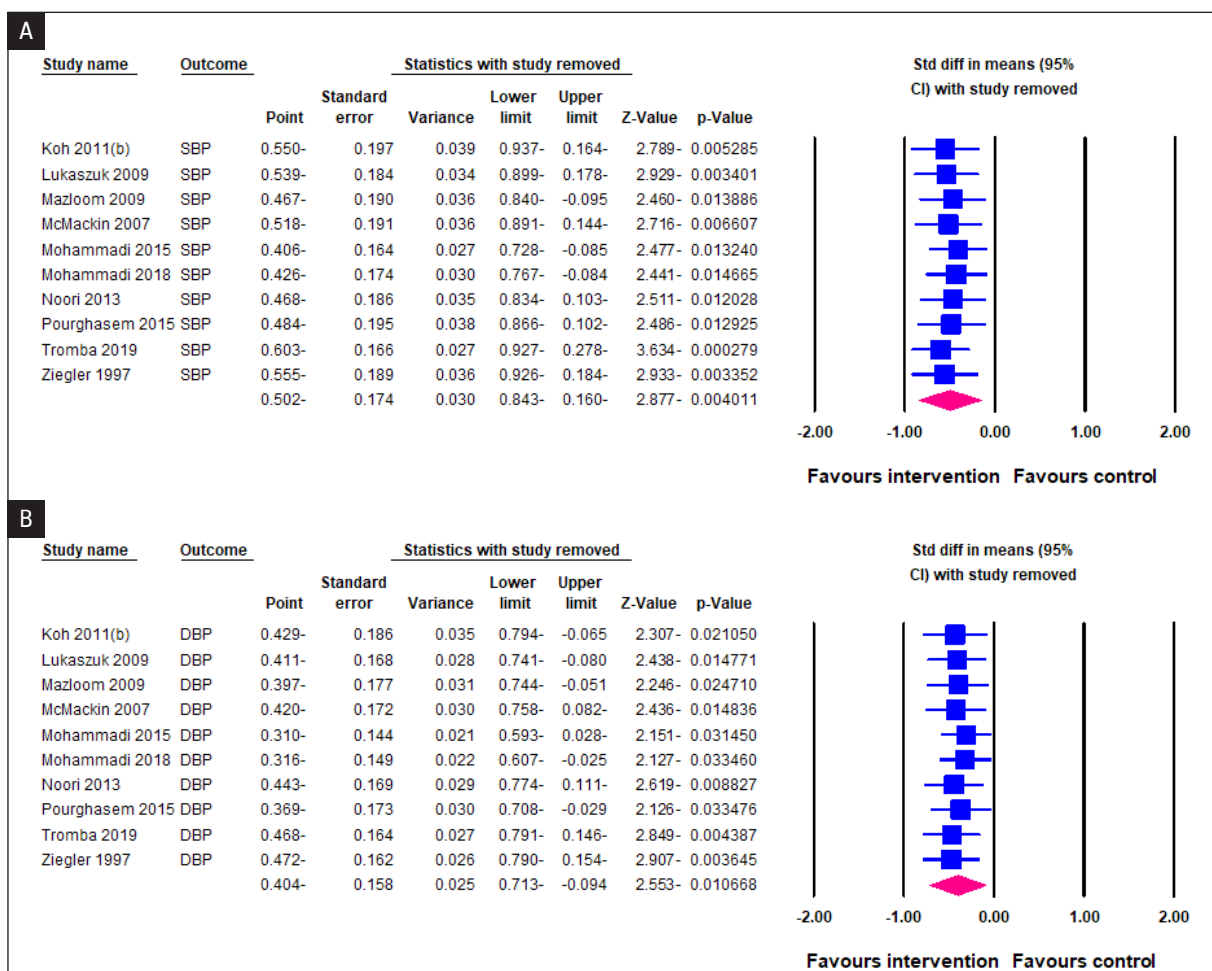


Figure 3. Sensitivity analysis for the effect of α -lipoic acid (ALA) supplementation on systolic blood pressure (SBP) (A) and diastolic blood pressure (DBP) (B)

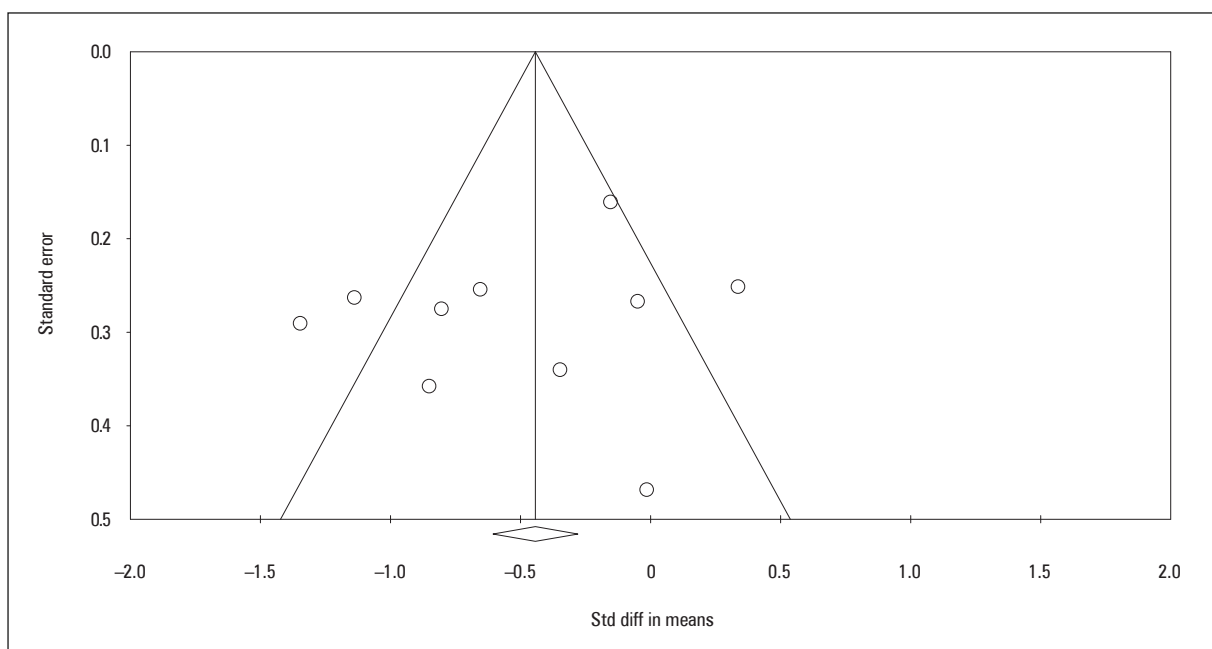


Figure 4. Funnel plot detailing publication bias of included studies. SMD — standard mean difference; SE — standard error

regeneration of endogenous antioxidants including vitamin C, vitamin E, and glutathione [36]. As stated before, ALA supplementation may play a role in anti-inflammatory mechanisms. Interestingly, these mechanisms are considered as the potential predictors of cardiovascular disorders and type II diabetes development [37–39]. In general, our meta-analysis reveals the reductions in DBP and SBP after ALA supplementation in elevated BP and hypertensive subjects, respectively; however, the blood lowering effect of ALA supplementation was not observed in normotensive subjects. Therefore, this could be assumed that ALA supplementation may have the beneficial effects on lowering blood pressure when the hypertension is manifested as both subclinical and clinical condition. ALA may exert its antihypertensive and hypoglycemic effects and the subsequent anti-cardiovascular effects by an attenuation of the oxidative stress which is reflected by the decrement in the basal O₂- synthesis in vessels and by the retention of the glutathione-peroxidase activity of the plasma [9].

Despite some strengths of the present meta-analysis, multiple limitations should be noted. First, most of the included trials enrolled limited participants, which result in misleading in final estimates of treatment effects, as trials with small sample sizes might be methodologically less considerable and are prone to report the values somewhat larger than their actual effect sizes. Moreover, the heterogeneity between included studies was considerable even after performing subgroup analyses which may potentially reduce the influence of the final results.

Nonetheless, the present analysis had some strength: the first point is that we systematically and comprehensively searched through several databases. Defined inclusion criteria/clear approach in gathering data and in-depth quality assessment of studies are considered as other points. Finally, lacking the potential biases should be considered as another strength point.

Conclusion

The current meta-analysis observed a beneficial effect of ALA supplementation in lowering BP in subjects with elevated blood pressure. The beneficial effect of this compound in alleviating blood pressure is maybe by its anti-oxidative and vascular endothelial properties. However, future precision randomized trials should establish whether different doses of ALA or longer-term supplementation of ALA could

provide a hypotensive role and reduce cardiovascular risk.

Conflict of interest

No conflict of interest was declared regarding the present manuscript.

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