Review

An updated systematic review and dose-response meta-analysis of the randomized controlled trials on the effects of alpha-lipoic acid supplementation on inflammatory biomarkers

Editor's Choice

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Abstract: Data about the effects of alpha-lipoic acid (ALA) supplementation on inflammatory markers are inconsistent. This systematic review and dose-response meta-analysis of randomized controlled trials was performed to summarize the effects of ALA supplementation on inflammatory markers such as C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) in adults. A comprehensive literature search was conducted in the electronic databases of PubMed, Web of Science, ProQuest, Embase, and SCOPUS from inception to February 2020. Among all of the eligible studies, 20 articles were selected. The weighted mean differences (WMD) and 95% confidence intervals (CI) were calculated to evaluate the pooled effect size. Between-study heterogeneity was evaluated using Cochran's Q test and I^2. Subgroup analysis was done to evaluate the potential sources of heterogeneity. The dose-response relationship was evaluated using fractional polynomial modeling. Twenty eligible studies with a total sample size of 947 participants were included in the current meta-analysis. The findings of the meta-analysis showed that ALA supplementation significantly reduced CRP (WMD: −0.69 mg/L, 95% CI: −1.13, −0.26, P=0.002), IL-6 (WMD: −1.83 pg/ml, 95% CI: −2.90, −0.76, P=0.001), and TNF-α concentrations (WMD: −0.45 pg/ml, 95% CI: −0.85, −0.04, P=0.032). No evidence of departure from linearity was observed between dose and duration of the ALA supplementation on serum CRP, IL-6 and TNF-α concentration. In subgroup analysis, ALA dosage, baseline concentrations of the parameter, sample size, and gender were considered as possible sources of heterogeneity. In summary, ALA supplementation improves inflammatory markers without any evidence of non-linear association to dose or duration of the trial.

Keywords: Alpha-lipoic acid, Inflammatory markers, Interleukin-6, Tumor necrosis factor-alpha, C-reactive protein, Dose-response, Meta-analysis

Abbreviations

ALA	Alpha-lipoic acid
CRP	C-reactive protein
IL-6	Interleukin-6
TNF-α	Tumor necrosis factor alpha
COX-2	Cyclooxygenase-2
ROS	Reactive oxygen species
T_2DM	Type 2 diabetes
RCT	Randomized controlled trial
WMD	Weighted mean difference
SD	Standard deviation
MESH	Medical subject headings
CI	Confidence intervals

Introduction

Inflammation is a physiological response of the immune system which is essential to health promotion [1, 2]. Innate immunity response as the first line of the human body defense system protects it against pathogenic factors, toxic compounds, infectious agents, damaged cells, harmful stimuli or metabolic dysfunctions, and consequent

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inflammation [1–3]. But the persistence of exposure to these agents and inflammatory conditions activates cytokines and chemokines. The Inflammation induced by these factors, triggers the activation of a cascade of inflammatory signaling pathways such as nuclear factor kappa-B (NF-κB), mitogen-activated protein kinase (MAPK), and Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathways [1, 2]. Inflammation has been recognized to have a critical role in the pathogenesis and initiation of several chronic health conditions including obesity, cardiovascular diseases, gastrointestinal and pulmonary problems, diabetes, arthritis, and cancer [1–4]. Moreover, interleukin (IL)-6, tumor necrosis factor (TNF)-α, and C-reactive protein (CRP) which are produced by lymphocytes, macrophages, and liver cells are considered as determinants of inflammatory status. Following the high prevalence of chronic diseases, developing new approaches to minimize the burden of inflammation is needed [2, 3]. In this regard, dietary compounds are good candidates to achieve the target. Numerous supplements including vitamins A, C, E, omega 3 and 6, coenzyme Q10 and alpha-lipoic acid (ALA) have been assumed to have antioxidant and anti-inflammatory properties [5]. ALA has been developed as one of the therapeutic supplements for reducing inflammation [6]. ALA or thioctic acid (TA), chemically named 1,2-dithiolane-3-pentanoic acid (C8 H14O2S2), is an amphipathic compound with potent antioxidant and anti-inflammatory properties [5, 7]. Disulfide and dithiol; dihydrolipoic acid (DHLA) is the oxidized and reduced form of ALA with potential antioxidant properties [7]. It is synthesized in human tissues such as the liver and is catabolized through mitochondrial β-oxidation [7]. ALA enhances antioxidant defense through scavenging of reactive oxygen species (ROS), hydroxyl radicals, hypochlorous acid, and chelating metallic ions (e.g. iron and copper) to attenuate their adverse effects [7–11]. Moreover, activation of the NF-κB induced by oxidative stress and inflammatory pathways can be inhibited by ALA via activating MAPK/ERK pathway as an inflammatory modulator [8, 10, 12]. In addition, ALA exerts an important structural role as a cofactor to several mitochondrial bioenergetic enzymes such as pyruvate dehydrogenase, a-keto-glutarate dehydrogenase, and branched-chain alpha-keto acid dehydrogenase [10, 13–15].

Numerous studies investigated the effects of ALA supplementation on inflammatory parameters and have shown conflicting results. Several studies have demonstrated the beneficial effects of ALA supplementation against inflammation [13, 16]. Marfella et al. [17] reported anti-inflammatory properties for ALA in the cardiomyopathy process; while other studies did not confirm these beneficial effects [8, 14, 18, 19]. Due to the controversial findings of the published studies conducted in this field, the real effect of ALA supplementation on inflammatory markers has not been clearly understood yet. There was a published meta-analysis including 31 trials that reported the effects of ALA supplementation on inflammatory markers [20], however, the meta-analysis did not evaluate the dose-response relation between dosage and duration of ALA supplementation on inflammatory parameters; moreover, some of the studies that were included in that meta-analysis evaluated the effect of ALA in combination with several other supplements rather than evaluating its isolated action. Therefore, a comprehensive meta-analysis considering a dose-response model evaluating the effects of ALA supplementation on inflammation is needed. In the present systematic review and meta-analysis including the studies until February 2020, we summarized the results of studies investigating the impact of ALA supplementation on inflammatory markers in a systematic review and meta-analysis of randomized controlled trials (RCTs).

Method

Search strategy

The current meta-analysis was performed under the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (Table E1, Electronic Supplementary Material 1) [21]. We searched SCOPUS, PubMed, Embase, Web of Science, and ProQuest for randomized controlled human trials examining the effect of ALA supplementation on inflammatory biomarkers from database inception to February 2020 without any language limitation. The key search strategy is available in Table E2, ESM 1. We used the combination of following MeSH (Medical Subject Headings) terms for the result as the search strategy: "alpha lipoic acid" OR "alpha-lipoic acid" OR "α-lipoic acid" OR "α lipoic acid" OR "thioctic acid" AND "inflammation" OR "inflammat*" OR "Tumor Necrosis Factor alpha" OR "TNF alpha" OR "Tumor Necrosis Factor-alpha" OR "Tumor Necrosis Factor" OR "TNF-alpha" OR "C reactive protein" OR "C-Reactive Protein" OR "CRP" OR "interleukin*" OR "IL-6" OR "IL6" OR "interleukin 6" OR "Interleukin-6". Also, handsearching from reference lists of all related articles, previous reviews, and meta-analyses were reviewed to find additional relevant manuscripts. The study was carried out using the PICO (Population, Intervention, Comparator, and Outcome) design. The abbreviation PICO stands for Population (general adult populations), Intervention (supplementation with ALA), Comparison (with control

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or placebo groups), and outcomes (changes in CRP, IL-6, and TNF-α levels). The protocol of the current meta-analysis has been registered in the International prospective register of systematic reviews (PROSPERO) and its registration number is CRD42020180226. Moreover, the ethics committee of Tabriz University of Medical Sciences has approved the study's protocol (Registration number: IR.TBZMED.VCR.REC.1399.287).

Eligibility criteria and study selection

Published articles were included according to the following criteria: (1) original articles (2) placebo-controlled randomized trial (either crossover or parallel design) in human adults (18 years or older) (3) reported the effect of ALA supplementation on inflammatory markers such as CRP, IL-6, and TNF-α. If several studies with the same data set were recognized, only the most complete ones were considered in this meta-analysis. We excluded: (1) observational studies (2) experimental and in vitro studies (3) reviews (4) grey literature (comments, book chapters, letters, conference papers, and seminars) (5) studies performed on pregnant women and children (6) studies that have measured inflammatory mediators in tissue. Also, we excluded studies that had assessed ALA effects in combination with other supplements. The search results were uploaded into EndNote software (version X8, for Windows, Thomson Reuters, Philadelphia, PA, USA) to merge retrieved citations, remove duplications, and to facilitate the review process. Two independent reviewers (MV and MM) evaluated all articles retrieved for eligibility for inclusion in the meta-analysis in two steps, first based on title and abstract and second based on full text. Full texts of related manuscripts meeting the eligibility criteria were retrieved and assessed. Studies not meeting the eligibility criteria were excluded. Any disagreement between reviewers was resolved by consulting a third reviewer (MAF).

Data extraction

Two independent researchers (MV and MAF) screened the full text of selected eligible articles and extracted the following characteristics: (1) surname of the first author (2) type of study population (3) sex and age of participants (4) geographical area (5) year of publication (6) study design (7) sample size (8) number of study participants placebo and treatment group medication dosage (9) duration of the treatment (10) type of ALA supplement (11) ALA dosage (12) baseline BMI of participants and outcomes (mean and standard deviation of CRP, TNF-α and IL-6 before and after intervention).

Quality assessment

Two researchers (MV and MAF) independently evaluated the risk of bias in each study. The Cochrane risk-of-bias tool [22] was used to assess the methodological quality of the included studies. This scale contains of 7 criteria as follows: random sequence generation, allocation sequence concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. According to the Cochrane guideline, studies were stratified as "Low," "High," or "Unclear" risk of bias. The detailed explanations of the quality assessments are presented in Table E3 in ESM 1.

Statistical methods

We examined the effects of ALA supplementation on inflammatory biomarkers (CRP (mg/l), TNF-α (pg/ml), and IL-6 (pg/ml) using weighted mean difference (WMD) with the 95% confidence interval (CI). The mean difference and standard deviation (SD) of change in inflammatory biomarkers between the intervention (ALA supplementation) and control or placebo groups were used to calculate the overall effect size in the meta-analysis. When SD of the mean difference was not available from the studies, we calculated it using the following formula: SD change= square root [(SD baseline 2+SD final 2)−(2×0.8×SD baseline×SD final)] [23], SD=IQR/1.35 (symmetrical data distribution) and SD=SEM×sqrt (n), where n is the number of participants, IQR is the interquartile range and SEM is the standard error of the mean. The DerSimonian and Laird random-effects model was used to estimate the pooled WMD. The non-linear potential effects of ALA duration and dosage of intervention on CRP, TNF-α, and IL-6 were examined using fractional polynomial modeling [24]. We examined within-and-between-study heterogeneity using Cochran's Q test and the I^2 statistic. I^2<25% represents no heterogeneity; I^2=25–50% represents moderate heterogeneity; and I^2>50% represents heterogeneity at high level. The heterogeneity was considered statistically significant if P<0.1 and/or I^2>50% [25]. Sensitivity analysis was carried out to examine the effect of individual study on the overall analysis. A subgroup analysis was then performed (according to the duration of intervention, ALA dosage of supplementation, baseline values of the parameter, health status, sample size, region, gender, and study's quality to explore potential sources of heterogeneity among studies. Sensitivity analysis was accomplished to examine the effect of each study on the overall result. The assessment of publication bias was carried out by visually inspecting funnel plots and Egger's and Begg's tests [26].

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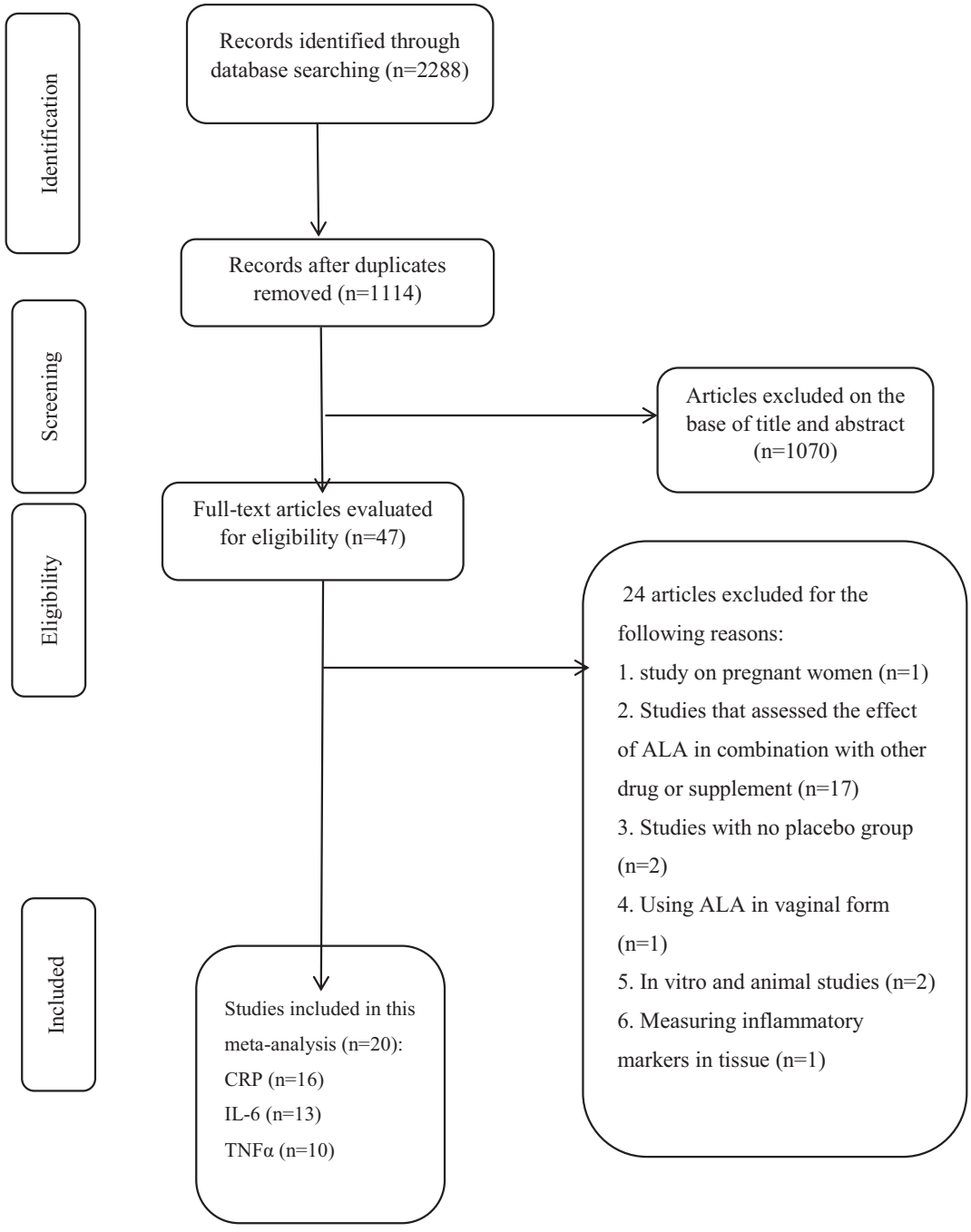

Figure 1. Flow diagram of study screening and selection process.

Results

Search results

As shown in Figure 1, originally, the systematic search recognized 2,288 studies, of which 1,174 were duplicates and 1,070 were unrelated and were excluded at the primary screening of the title and abstract. 47 full-text articles were evaluated to examine their eligibility for inclusion in the present study, and 24 of these articles were excluded for the following reasons: (1) studies that had no placebo or control group (n=2), (2) in vitro and animal studies (n=2), (3) articles that examined the effect of ALA in combination with other supplement or drugs (n=17) and (4) articles done on pregnant women (n=1). Additionally, as Nasole et al. [27] assessed inflammatory markers in tissues, and Costantino

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et al. [28] used ALA vaginally, their trials were not included in our study. As a result, 20 studies [5, 6, 8–19, 29–37] were selected for the present systematic review and meta-analysis. Of those, 16 trials reported the effect of ALA on CRP [5, 6, 8, 10–13, 15, 17, 19, 30–35, 37], 13 articles on IL-6 [5, 6, 8, 10–12, 14–16, 29, 30, 36], 10 articles [5, 6, 10, 12, 14, 16–18, 29, 30] on TNF-α and 3 articles on IL-10 [5, 6, 9].

Study characteristics

Characteristics of the 20 eligible articles are summarized in detail in Table 1. This meta-analysis included 947 participants and the total sample size of each study ranged from 14 to 80. The mean age of the subjects ranged between 18 and 80 years. Sixteen studies included both genders [5, 8, 12, 14, 16–19, 29–32, 34–37], and four studies [6, 10, 11, 15] included only female or male subjects. ALA supplementation dosage ranged from 300 to 1200 mg/day and the length of the interventions was between 1 [37] and 48 [6, 17, 30] weeks. Thirteen studies [6, 10–12, 15, 18, 19, 29–31, 34–36] employed a randomized, double-blind, controlled design; they were published between 2005 and 2019. Most studies were conducted in Iran and Italy [6, 8, 10, 11, 17–19, 29, 31, 32, 36]. The remaining studies were performed in China [16, 33, 37], Korea [12, 35], New Zealand [30], Virginia [34], Spain [15], and Mexico [5]. Included studies had recruited patients with type 2 diabetes [5, 32], type 1 diabetes [31], impaired fasting glucose [16], chronic spinal cord injury [11], rheumatoid arthritis [10, 12], peripheral arterial disease [34], metabolic syndrome [30], atrial fibrillation [6], obese and overweight people [15], acute coronary syndrome [37], Takotsubo Cardiomyopathy (TCM) [17], relapsing-remitting multiple sclerosis [29], patients undergoing hyperbaric oxygen therapy [36], and hemodialysis [8, 14, 18, 19, 35]. Out of these studies, 5 recognized significant effects of ALA supplementation on CRP as compared with the placebo group [5, 6, 15, 17, 37], whereas changes in CRP were not statistically significant in other studies. As for IL-6, 4 studies [5, 15, 16, 36] had reported a significant reduction in the ALA group compared with the placebo group, while changes in IL-6 were not statistically significant in other studies. Furthermore, a significant decrease in TNF-α was also observed in only 4 studies [5, 6, 16, 17].

The results of the meta-analysis of the effects of ALA supplementation on CRP

Sixteen eligible studies [5, 6, 8, 10–12, 15, 17, 19, 30–32, 34, 35, 37] including a total of 754 participants examined the effect of ALA supplementation on CRP. Manning et al. [30] assessed the effects of ALA over two time periods (24 and 48 weeks). Therefore, we considered the result of 024 weeks as one study and 0–48 weeks as another study. Combined results from the random-effects model presented a significant reduction in CRP following ALA supplementation (Weighed Mean Difference (WMD): −0.69 mg/L, 95% CI: −1.13, −0.26, P=0.002) with significant heterogeneity among the studies (I^2=83.2%, P=0.000) (Figure 2). The subgrouping revealed that ALA dosage, baseline CRP concentrations, sample size and gender are possible sources of heterogeneity (Table E4 in ESM 1).

The results of the meta-analysis of the effects of ALA supplementation on IL-6

Thirteen studies [5, 6, 8, 10–12, 14–16, 29, 30, 36] with 13 treatment arms including a total of 585 participants reported IL-6 as an outcome measure. In the pooled effect analysis, supplementation significantly reduced serum IL-6 concentrations (WMD: −1.83 pg/ml, 95% CI: −2.90, −0.76, P=0.001) with significant heterogeneity among the studies (I^2=98.7%, p=0.000) (Figure 3). In subgrouping, study duration and gender were considered as heterogeneity sources (Table E5 in ESM 1).

The results of the meta-analysis of the effects of ALA supplementation on TNF-α

The effect of the ALA supplementation on TNF-α was investigated in 10 clinical trials [5, 6, 10, 12, 16–18, 29, 30] with 10 treatment arms (483 participants) and found a significant effect on TNF-α reduction (WMD: −0.45 pg/ml, 95% CI: −0.85, −0.04, P=0.032) with significant between-study heterogeneity (I^2=94.9%, p=0.000) (Figure 4). Also, the results of subgrouping revealed that baseline TNF-α concentration were, to some extent, the possible source of heterogeneity (Table E6 in ESM 1).

The results of dose-response meta-analysis for the association between the dose and duration of ALA supplementation against inflammatory parameters

The dose-response association between duration and dosage of ALA on study parameters are presented in Figures 5A–5F. Based on the dose-response assessment, ALA supplementation did not change serum CRP concentrations significantly based on the dosage of ALA administration ($P_{non\text{-}linearity}$=0.816) or duration ($P_{non\text{-}linearity}$= 0.291) in non-linear method (Figures 5A and 5B).

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Table 1. General characteristics of included studies included in the systematic review and meta-analysis

Journal/first author	Years/ Country	Subjects	Sample size (intervention/ control)	Age range (years)	Duration (weeks)	Intervention		Baseline BMI (kg/m^2) IN/Con	Time of consumption	Design	Male %	Main results
						ALA dose mg/day	Placebo					
Oxidative med. cell. longev/Mendoza-Núñez V [5]	2019/Mexico	T_2DM	50/35	64±1	4	Racemic ALA 600	Microcrystalline cellulose (295 mg) plus magnesium stearate (5 mg)	IN: 28 69±0 64 Cont: 28 96±1 03	Unclear	Quasi-experimental study	27.40	A significant negative correlation with TNF-α (r=−0 250, p<0 05), IL-6 (r=−0 249, p<0 05), and IL-1β (r=−0 329, p<0 01).
Am J Cardiol/Sardu C [6]	2017/Italy	Patients with AF	33/40	18–75	48	600	Unclear	IN: 29.6±4.8 Cont: 28.9±2.5	Unclear	Randomized, prospective, double-blind, controlled placebo trial	52.05	↓ Sig. in CRP. TNF α in ALA treatment group
The Journal of Nutrition/Huerta A [15]	2016/Spain	Healthy overweight or obese women	19/21	20–50	10	300	Sunflower oil	–	Unclear	Double-blind, randomized placebo-controlled trial	0	↓Sig. CRP in ALA treatment group compared to other groups. ↓Sig. IL-6 in ALA treatment group compared to baseline.
J. Cardiol./ Marfella R [17]	2015/Italy	TCM	22/21	IN: 63.7±6.5 CON: 63.9±5.2	48	600	Unclear	–	Unclear	Double-blind, placebo	0	↓ Sig. in CRP, TNF-α after ALA supplementation.
Spinal Cord/ Mohammadi V [11]	2015/Iran	SCI	28/30	30–50	12	600	Wheat flour	IN: 27.77±4.33 Cont: 28.02±5.09	Before breakfast	Randomized, double-blind, placebo-controlled clinical trial	100	NS reduction in IL-6, hs-CRP after intervention
JACN/Mirtaheri E [10]	2015/Iran	Rheumatoid arthritis	33/32	20–50	8	1200	Maltodextrin	IN: 29.00± 6.4 Cont: 29.02±4.71	Every 12 hours, 30 minutes prior to breakfast and dinner	Randomized, double-blind, placebo-controlled clinical trial	0	NS in IL-6, hs-CRP differences between the 2 groups. NS in IL-6, hs-CRP differences in both treatment and intervention groups
Int Urol Nephrol/ Safa J [18]	2014/Iran	HD	30/31	IN: 59.3±10.47 CON: 55.20±13.43	8	600	Unclear	–	Unclear	Double-blinded randomized clinical trial	68.85	NS reduction in IL-8, TNF-α after intervention. NS differences in IL-8, TNF-α between 2 groups
Neuroimmunomodulation/ Khalili M [29]	2014/Iran	MS	24/22	18–50	12	1200	Unclear	IN: 23.9±2.3 Cont: 24.1±2.9	Unclear	Double-blind, placebo-controlled, randomized clinical trial	26.66	NS differences in TNF-α, IL-6 between 2 groups.
Nutr Metab Cardiovasc Dis/Manning P [30]	2013/ New Zealand	MetS	34/40	27–80	48	600	Unclear	IN: 31.7 ±6.2 Cont: 31.3 ±5.3	30 min prior to food	Randomized, double-blind, placebo-controlled trial	39.18	NS changes in CRP, IL-6, TNF-α in ALA treatment group
Int J Nephrol Renovasc Dis/El-Nakib G [14]	2013/Egypt	CRF undergoing HD	22/22	IN: 49.1±16.2 CON: 46.2±14.4	12	600	Control group without placebo	–	Unclear	Randomized, placebo-controlled trial	54.54	NS changes in MDA, IL-6, TNF-α after ALA treatment
Iran J Kidney Dis/Ahmadi A [8]	2013/Iran	HD	20/24	20–60	8	600	Unclear	IN: 23.4±5.2 Cont: 25.5±12.1	Randomized placebo-controlled trial	Randomized placebo-controlled trial	52.27	NS reduction in hs-CRP in intervention group.

(Continued on next page)

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Table 1. (Continued)

Journal/first author	Years/ Country	Subjects	Sample size (intervention/ control)	Age range (years)	Duration (weeks)	Intervention: ALA dose mg/day	Intervention: Placebo	Baseline BMI (kg/m^2) IN/Con	Time of consumption	Design	Male %	Main results
Tohoku J. Exp. Med./Li R [37]	2013/China	ACS	33/30	49–72	1	600 (IV)	Saline (IV)	–	Unclear	Randomized	85.71	↓ Sig. hs-CRP in ALA treatment group (P<0.05)
Diabetes Care/Mollo R [31]	2012/Italy	Type 1 diabetic patients	26/25	–	5	600	Unclear	–	Unclear	Randomized, double-blind, placebo-controlled	–	NS changes in CRP between 2 groups
J Ren Nutr/Khabbazi T [19]	2012/Iran	HD	24/28	22–79	8	600	Starch	IN: 25.46 6 4.18 Cont: 26.16 6 4.75	After breakfast meal	Double-blinded, randomized, placebo-controlled clinical trial	65.38	NS reduction in hs-CRP, MDA in ALA treatment group
Obesity/Zhang Y [16]	2011/China	Obese patients with IGT	13/9	IN: 52.5±8.2 CON: 52.6±6.2	2	600 mg ALA in normal saline 250 ml	Saline	IN: 30.2±1.4 Cont: 30.4±2.1	Unclear	Randomized, double-blind	45.45	↓ Sig. in MDA, TNF-α, IL-6 in ALA treatment group. Sig. changes in MDA, TNF-α, IL-6 between 2 group
Arch Gerontol Geriatr/ Gianturco V [32]	2009/Italy	T_2DM	7/7	>50	4	400	Unclear	–	Unclear	Randomized, palcebo-controlled study	57.14	NS differences in CRP between experiment and placebo group.
JACN/Bae S [12]	2009/Korea	Rheumatic Diseases	5/9	52.1±10.3	4	300	Cornstarch	22.3±3.1	With each meal	Randomized, placebo-controlled, double-blind, three-treatment, cross-over trial	5	NS changes in IL-6, IL-1, TNF-α, CRP between 2 groups
J Altern Complement Med/Vincent H [34]	2007/Virginia	PAD	16/12	>50	12	600	Microcrystalline cellulos	IN: 28.7±5.6 Cont: 30.7±5.5	Unclear	Randomized, double-blind, controlled study	53	NS differences in hs-CRP in ALA treatment group. NS changes in hs-CRP between 2 groups
Am J Nephrol/Chang J [35]	2007/Korea	HD	25/25	IN: 63±86 CON: 66±87	12	600	Control group without placebo	IN: 21.8±1.91 Cont: 20.6±1.78	Unclear	Randomized, double-blind, controlled study	54	NS reduction in hs-CRP in treatment group
Biochem Biophys Res Commun/Alleva [36]	2005/Italy	Patients undergoing hyperbaric oxygen therapy	10/10	75±12	5.7	600	Unclear	–	Unclear	Double-blind randomized	40	↓Significant IL-6 in treatment group.

Abbreviations: NS, Not Significant; IN, intervention group; CON, control group; TNF-α, Tumor Necrosis Factor-alpha; IL-6, Interleukin-6; hs-CRP; high sensitive C-Reactive Protein, hs-CRP; high sensitive-C Reactive Protein, MDA, Malondialdehyde; HD, hemodialysis; PAD, peripheral artery disease; IGT, impaired glucose tolerance; T_2DM, type 2 diabetes mellitus; ACS, acute coronary syndrome; CRF, chronic renal failure; CSI, chronic spinal cord injury; MetS, Metabolic syndrome; MS, multiple sclerosis; TCM, takotsubo cardiomyopathy; AF, arterial fibrillation. Data are presented as mean.

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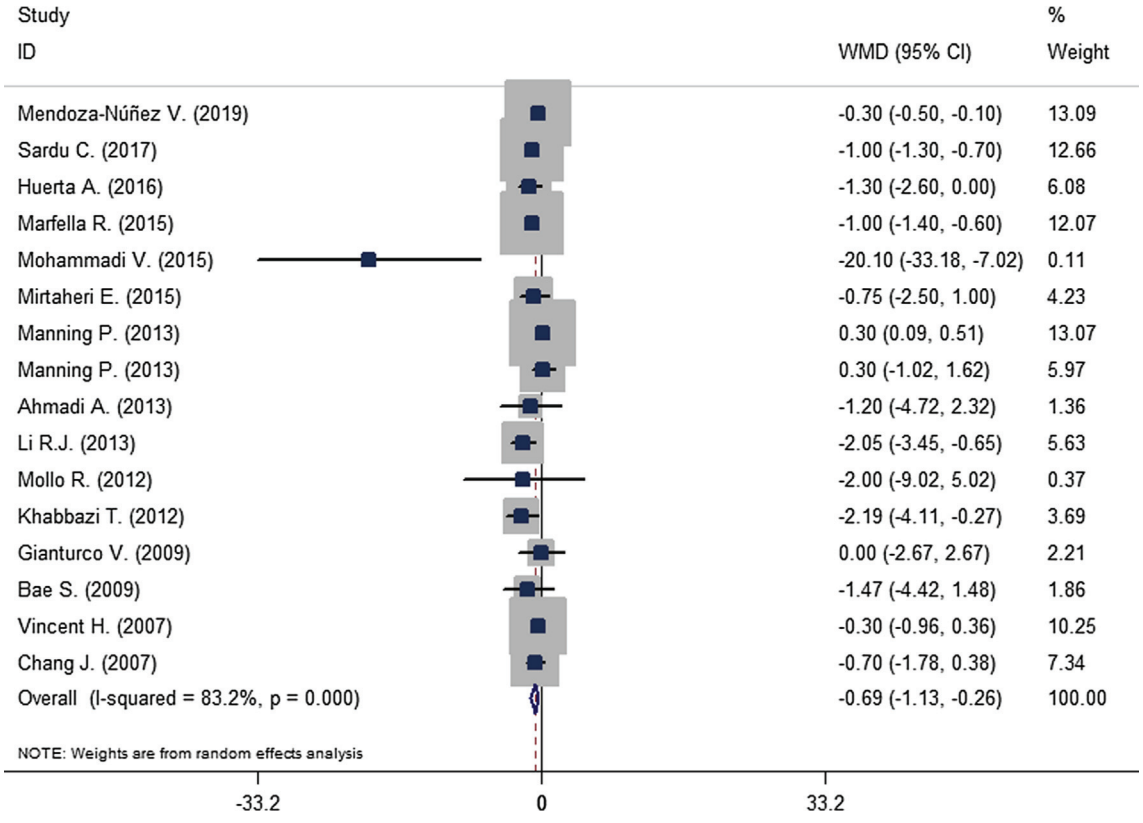

Figure 2. The forest plot showing the weighted mean difference (WMD) of the effect of ALA on CRP concentrations.

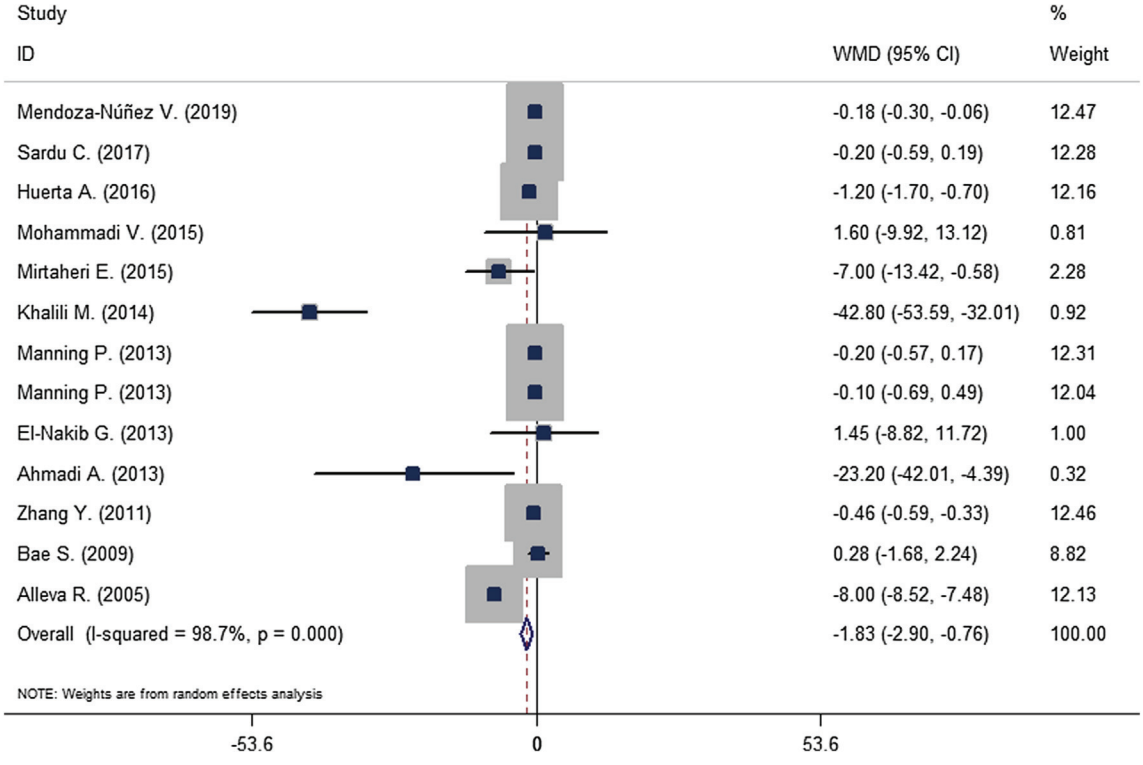

Figure 3. The forest plot showing the weighted mean difference (WMD) of the effect of ALA on IL-6 concentrations.

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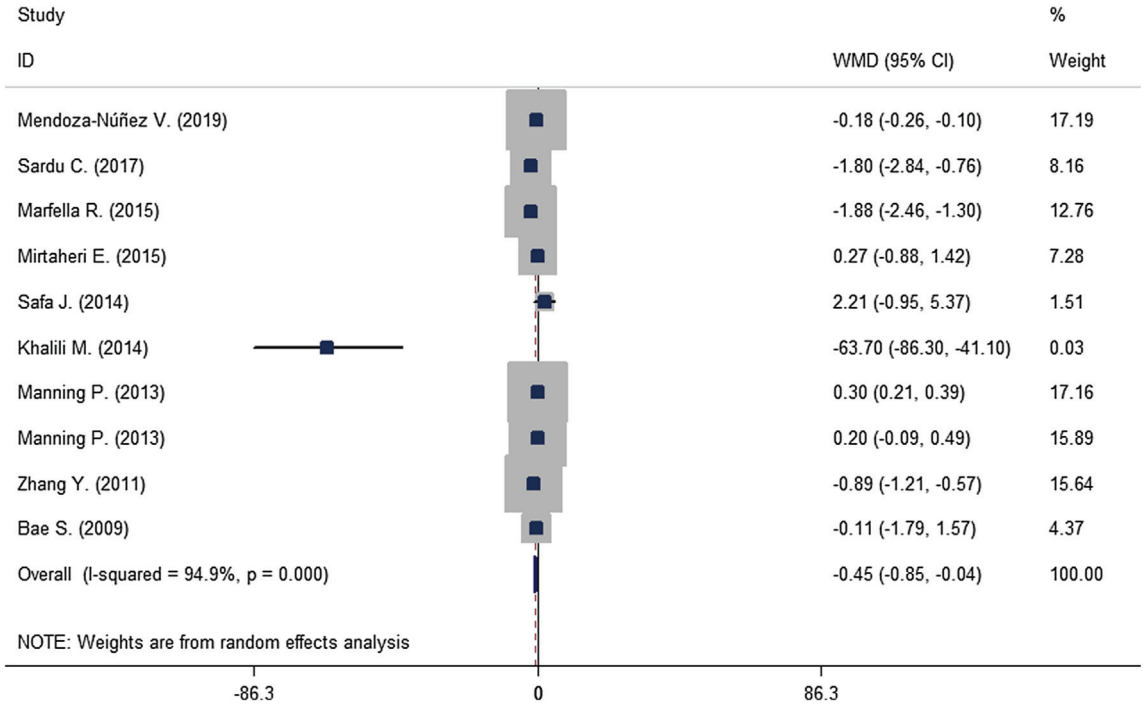

Figure 4. The forest plot showing the weighted mean difference (WMD) of the effect of ALA on TNF-α concentrations.

Similarly, non-linear dose-response analysis did not display a significant effect of ALA dosage ($P_{non\text{-}linearity}$=0.506) and duration of ALA administration ($P_{non\text{-}linearity}$=0.266) on IL-6 (Figures 5C and 5D). Similarly, for the dose-response association between ALA supplementation and TNF-α (Figures 5E and 5F), ALA dosage ($P_{non\text{-}linearity}$=0.638) and duration of supplementation did not show any evidence of departure from linearity ($P_{non\text{-}linearity}$=0.455).

Sensitivity analysis

To explore the effect of every single trial on the pooled effect size, we removed each study from the analysis, one by one. We did not find any significant effect regarding any individual study on the overall effect size of study outcomes.

Publication bias

There was no evidence of publication bias for trials examining the effect of ALA supplementation on CRP (Begg's test, P=0.787; Egger's test, P=0.077), IL-6 (Begg's test, P=0.088; Egger's test, P=0.217) or TNF-α (Begg's test, P=0.929; Egger's test, P=0.207). Also, no evidence of publication bias was evident from visual inspection of funnel plots was also used to identify publication bias (Figure E1A–C, ESM 1).

Discussion

In the current systematic review and dose-response meta-analysis, we summarized the available data from twenty trials that examined the effect of ALA supplementation on several key inflammatory mediators such as CRP, IL-6, and TNF-α. As far as we know, no dose-response meta-analysis on this issue is available. In this article, the findings revealed that supplementation with ALA significantly reduced CRP, IL-6, and TNF-α concentration in a meta-analysis of more than 16 trials. However, in our dose-response analysis, we found that the dosage and duration of ALA supplementation were non-significantly associated with the reduction of CRP, IL-6, and TNF-α concentration. As showed in our subgroup analysis, subgrouping according to duration, ALA dosage, sample size, and gender reduced the heterogeneity, and these parameters were mainly responsible for the high heterogeneity values.

Our study confirms the results of Rahimlou et al. [20], Akbari et al. [38], and Haghighatdoost et al. [39] meta-analyses that evaluated the effects of ALA supplementation on serum TNF-α, IL-6, and CRP concentrations. However, their study [39] also included articles that evaluated the effects of ALA in combination with other drugs or supplements. Therefore, the results of their study do not show the net effects of ALA on inflammatory markers. Besides, unlike the previous meta-analysis [38], we did not restrict our study population to patients with specific conditions

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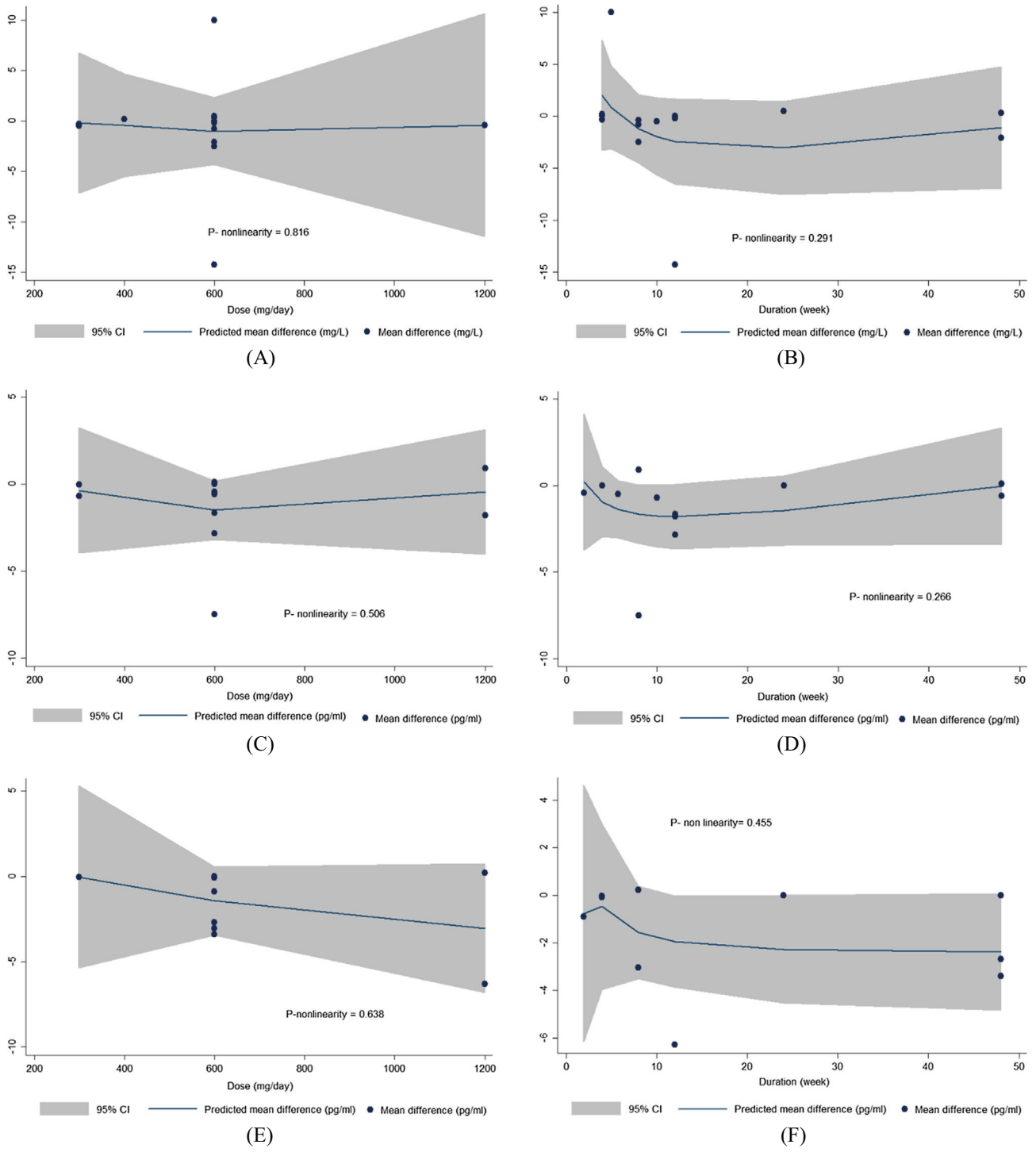

Figure 5. Dose-response model for CRP dose (A), CRP duration (B), IL-6 dose (C), IL-6 duration (D), TNF-α dose (E) and TNF-α duration (F) association with ALA supplementation.

like metabolic syndrome. Additionally, the number of included studies in our study was more than the other meta-analysis [38, 39]. The age range was more than 18 years old, and studies among children, adolescents, pregnant women, and gestational diabetes mellitus were not included in the present meta-analysis.

Inflammation is a clinical condition underlying several serious diseases [40, 41]. Adipocytokines such as TNF-α and IL-6 are produced in adipose tissue and modulate inflammatory responses [42], and CRP is a circulating mediator of low-grade inflammation [43]. It is well established that increased levels of CRP, TNF-α, IL-6, and other

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inflammatory mediators are associated with several diseases such as type 2 diabetes [40] and cardiovascular disease (CVD) [41]. The use of drugs for improving inflammation may cause avoidable side effects while nutraceuticals such as dietary supplements (including ALA) have been confirmed to be a potential therapeutic tool with minimum or no side effects in improving inflammation [8, 19, 44]. Therefore, our results may be important for the clinical conditions and clinicians who work on inflammatory diseases. In the current meta-analysis, ALA administration significantly reduced serum concentrations of CRP, IL-6, and TNF-α. Our results supported the beneficial effect of ALA supplementation on lowering inflammatory mediators. It is well established that excessive production of reactive oxygen species (ROS) could cause an antioxidant-oxidant imbalance, playing an important role in regulating inflammation [45]. ROS can increase the expression of pro-inflammatory markers and then up-regulate the nuclear factor kappa B (NF-κB) pathway. NF-κB is a transcription factor expressed in a wide range of cell types involved in various functions, including immune and inflammatory responses and cell survival [46]. ALA is known as a potent ROS scavenger and immunomodulatory factor and recent studies have shown its potential anti-inflammatory role [8, 47]. ALA supplementation has been revealed to be beneficial in several oxidative-stress-related diseases including diabetes [48], cataract [49], and ischemia-reperfusion injury [50]. Several mechanisms explain the beneficial effect of ALA supplementation on some inflammatory mediators. The probable mechanisms for the anti-inflammatory effect of ALA are the improvement of gene expression with an anti-oxidative effect such as Nuclear erythroid 2-related factor (Nrf2) [51], and the suppression of NF-κB activity [52, 53] due to its inhibitory influence on the degradation of the factor inhibitor protein κB (IKK) via the mitogen-activated protein kinases (MAPK) pathway; these properties of ALA lead to inhibition of production of pro-inflammatory markers [54, 55]. NF-κB is an important regulatory factor in cytokine production, and it has been suggested that it regulates transcription of the inducible nitric oxide synthase (iNOS) gene [56, 57]. Yamada et al. [58] have shown that ALA reduces the expression of the iNOS gene and decreases pro-inflammatory markers. Additionally, it has been established that ALA supplementation can increase intracellular glutathione synthesis via increasing cellular uptake of cysteine, which is a strong cellular antioxidant and decreases the level of inflammatory biomarkers as one of the key regulatory components for thiol redox signal [59, 60]. Glutathione is involved in the recycling of antioxidant vitamins including vitamins C and E, which contribute to controlling the activity of superoxide dismutase enzyme (SOD). Also, ALA supplementation increases cellular antioxidant defense and phases 3 enzymes including catalase, glutathione-S-transferase, and glutathione reductase [61]. Cyclooxygenase-2 (COX-2) is a pro-inflammatory and inducible enzyme that mediates the production of prostaglandins [62], and several studies have shown that COX-2 inhibitors can relieve inflammatory reaction. It has been revealed that ALA intake might have a potential effect on inhibiting the production of prostaglandins and the expression of adhesion molecules by inhibition of COX-2 activity [63]. Furthermore, ALA prompts the production of the immune-modulator cAMP in human inflammatory cells via stimulating prostaglandin E2 (PGE2), through its receptors EP2 and EP4 [64]. ALA also helps to chelate ionic metals and neutralize their oxidizing effects, which gives it considerable antioxidant activity [65].

The results of the studies on the effect of ALA on serum IL-6, CRP, and TNF-α levels are conflicting. In line with our results, ALA supplementation for 48 weeks significantly reduced serum levels of IL-6, CRP, IL-8, and TNF-α in patients with paroxysmal atrial fibrillation [6]. In a study by Ahmadi et al. [8], supplementation with 600 mg of ALA for 8 weeks significantly decreased IL-6 compared to placebo. Huerta et al. [15] reported that ALA supplementation (300 mg/day for 10 weeks) significantly reduced CRP concentrations and leukocyte count in healthy overweight Caucasian women. Carbonelli et al. [66] have shown that treatment with 800 mg/day ALA for 16 weeks reduced the TNF-α and CRP levels in obese subjects, whereas no such effects (in TNF-α, CRP, and IL-6) were reported in other trials [14, 29–31]. In contrast to our results, Chang et al. [35] reported no significant change in hs-CRP levels after supplementation with ALA (600 mg/day for 8 weeks) in patients undergoing hemodialysis (HD). In addition, Manning et al. [18] did not observe statistically significant changes in CRP, IL-6, and TNF-α levels in individuals with metabolic syndrome, who consumed 600 mg/day of ALA for 48 weeks in comparison with the placebo group. Overall, these inconsistent results may partly be due to different sample sizes, study duration, study design, and different dosages of ALA used along with clinical features of study subjects. Results of dose-response analyses showed that the dose and duration of ALA supplementation were non-significantly associated with the reduction of CRP, IL-6, and TNF-α. It appears that the effect of ALA is different in various diseases and every population needs special doses.

Strengths and limitations

The current study is the most comprehensive dose-response meta-analysis to date, which has assessed the effect of ALA administration on some inflammatory mediators in the adult population. However, this study also

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had some limitations. First, it was not possible to examine the effects of ALA on other inflammatory mediators (IL-8, IL-10. . .) due to an inadequate number of studies. Second, the included eligible studies were on participants with different health statuses and several age groups, which may have affected our findings. Additionally, the eligible studies were heterogeneous due to sex of subjects, sample size, dose, and duration of intervention, and some included trials had a small number of study participants, which may have impacted the outcome.

Conclusion

The present dose-response meta-analysis pooled results from 20 studies, including 947 participants. In summary, our findings support the use of ALA supplementation for the improvement of inflammatory markers such as TNF-α, IL-6, and CRP. Further, more clinical trials using different doses of ALA are needed to shed light on this issue.

Electronic Supplementary Material

The electronic supplementary material is available with the online version of the article at https://doi.org/10.1024/0300-9831/a000702

ESM 1. Including information about PRISMA checklist, subgroup analysis and Begg's Funnel plots.

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History
Received July 29, 2020
Accepted February 26, 2021
Published online April 8, 2021

Acknowledgement
The research protocol was approved & supported by Student Research Committee, Tabriz University of Medical Sciences (grant number: 65137).

Conflict of interest
The authors declare that there are no conflicts of interest.

Ethical approval and consent to participate
The protocol of the current meta-analysis has been registered in the International prospective register of systematic reviews (PROSPERO) and its registration number is CRD42020180226. Moreover, the ethics committee of Tabriz University of Medical Sciences has approved the study's protocol (Registration number: IR.TBZMED.VCR.REC.1399.287).

Funding
The current work has been supported by a grant from Tabriz University of Medical Sciences (Identifier: IR.TBZMED.REC.1399.287).

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