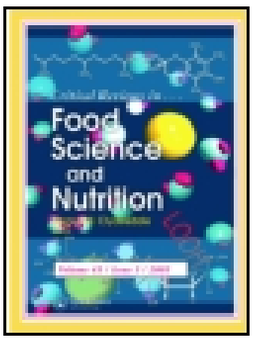

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Lipid-lowering activity of artichoke extracts: A systematic review and meta-analysis

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ABSTRACT

Artichoke is a component of the Mediterranean diet. Therefore, the aim of this meta-analysis was to determine if artichoke extract supplementation affected human lipid parameters. The search included PubMed-Medline, Scopus, Web of Science and Google Scholar databases up to March 28, 2017, to identify RCTs investigating the impact of artichoke extracts on plasma lipid levels. Quantitative data synthesis was performed using a random-effects model, with weighed mean difference (WMD) and 95% confidence interval (CI) as summary statistics. Meta-analysis of data from 9 trials including 702 subjects suggested a significant decrease in plasma concentrations of total cholesterol (WMD: −17.6 mg/dL, 95%CI: −22.0, −13.3, $p < 0.001$), Low Density Lipoprotein-Cholesterol (LDL-C; WMD: −14.9 mg/dL, 95%CI: −20.4, −9.5, $p = 0.011$) and triglycerides (WMD: −9.2 mg/dL, 95%CI: −16.2, −2.1, $p = 0.011$). No significant alteration in plasma High Density Lipoprotein-Cholesterol (HDL-C) concentrations was observed (WMD: 1.0 mg/dL, 95%CI: −1.1, 3.1, $p = 0.333$). A significant association between the LDL-lowering effect of artichoke and baseline LDL-C concentrations (slope: −0.170; 95%CI: −0.288, 0.051; $p = 0.005$) was observed. Thus, supplementation with artichoke extract was associated with a significant reduction in both total and LDL-C, and triglycerides, suggesting that supplementation may be synergistic with lipid-lowering therapy in patients with hyperlipidemia.

KEYWORDS

Artichoke leaf extract; hypercholesterolemia; meta-analysis; randomized clinical trial; triglycerides

Introduction

Hypercholesterolemia is an independent risk factor for cardiovascular disease (Catapano et al. 2016) and a recognized target of pharmacological therapeutic agents in both primary and secondary prevention. However, there is increasing interest for the use of natural lipid-lowering compounds that may delay or circumvent drug therapy (Cicero and Colletti, 2016; Pirro et al. 2017; Mannarino et al. 2014), though much of the clinical evidence of efficacy is based on a number of small short-term trials. (Sahebkar et al. 2016)

The Mediterranean diet is particularly rich in vegetable active compounds contributing to its positive effect on human health (Di Daniele et al. 2017), of which artichoke is one of the traditional components in some long-lived countries. (Rondanelli et al. 2016)

Pre-clinical and clinical investigations have suggested that the artichoke leaf extract (ALE) has potential lipid-lowering and hepatoprotective effects. The beneficial effects of artichoke may be mainly attributed to its antioxidant components: the main substances are mono- and dicaffeoylquinic acid (cynarin and chlorogenic acid), caffeic acid (1%) and volatile sesquiterpene and flavonoids (1%) that include the glycosides luteolin-7-beta-rutinoside (scolymoside), luteolin-7-beta-D-glucoside and luteolin-4-beta-D-glucoside (Ben Salem et al. 2015).

Several mechanisms of action for the lipid lowering effect of artichoke have been proposed. Luteolin interacts with Hydroxy-Methyl-Glutaryl-Coenzyme A (HMG-CoA) reductase, as well as with liver sterol regulatory element-binding proteins (SREBPs) and acetyl-CoA C-acetyltransferase (ACAT) (Gebhardt, 2002; Safaa et al., 2013). In addition, ALE might reduce hypercholesterolemia by increasing the fecal excretion of bile acids (Qiang et al., 2012).

The Cochrane Collaboration performed a meta-analysis of three randomized clinical trials involving 262 participants that investigated the effect of ALE on LDL-cholesterol and concluded that the trials, although of adequate methodological quality, had some shortcomings particularly regarding the standardization of quality and dosage of artichoke extracts used (Wider et al., 2013).

Therefore, this meta-analysis was undertaken with the updated literature available to determine the LDL-lowering effect of ALE in humans.

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Artichoke supplementation for dyslipidemia

Methods

Search strategy

This study was designed according to the guidelines of the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement (Moher et al., 2009). In order to find randomized placebo-controlled trials investigating the effects of artichoke-containing products on plasma lipids, PubMed-Medline, Scopus, ISI Web of Knowledge databases were searched using the following search terms in titles and abstracts: (artichoke OR Cynara OR "*Cynara cardunculus*" OR "*Cynara scolymus*") AND (placebo). Retrieved articles were further searched using key words such as "cholesterol", "low-density lipoprotein", LDL, LDL-C, LDL-cholesterol, "high-density lipoprotein", HDL- HDL-C, HDL-cholesterol, triglyceride, hyperlipidemia, hyperlipidemic, dyslipidemia, dyslipidemic, lipid and lipoprotein. The wild-card term "*" was used to increase the sensitivity of the search strategy. The literature was searched from inception to March 28, 2017.

Study selection

Original studies were included if they met the following inclusion criteria: (i) being a randomized controlled trial with either parallel or cross-over design, (ii) investigating the impact of artichoke products versus placebo on plasma/serum concentrations of lipids, and, (iii) presentation of sufficient information on lipids concentrations at baseline and at the end of follow-up in each group or providing the net change values. Exclusion criteria were: (i) non-randomized trials, (ii) lack of a placebo control group in the study design, (iii) observational studies with case-control, cross-sectional or cohort design, and (iv) lack of sufficient information on baseline or follow-up (or net change) lipid concentrations.

Data extraction

Eligible studies were reviewed and the following data were abstracted: (1) first author's name, (2) year of publication, (3) country where the study was performed, (4) study design, (5) number of participants in the artichoke and placebo groups, (6) type of artichoke product used in the study, (7) dose of artichoke, (8) treatment duration, (9) age, gender and body mass index (BMI) of study participants, and (10) baseline and follow-up plasma concentrations of lipids (Table 1).

Quality assessment

Risk of bias in the studies considered in this meta-analysis was evaluated according to the Cochrane instructions (Higgins and Green, 2009). Selection bias, performance bias, attrition bias, detection bias, reporting bias and other sources of bias were judged to be high, low or unclear in each of the included studies (Table 2).

Quantitative data synthesis

Meta-analysis was conducted using Comprehensive Meta-Analysis (CMA) V2 software (Biostat, NJ) (Borenstein et al., 2005). Effect size was calculated as: (measure at the end of follow-up in the treatment group − measure at baseline in the treatment group) − (measure at the end of follow-up in the control group − measure at baseline in the control group). A random-effects model (using DerSimonian-Laird method) and the generic inverse variance weighting method were used to compensate for the heterogeneity of studies in terms of study design, treatment duration, and the characteristics of populations being studied (Sutton et al., 2000). All values were collated as mg/dL, using a conversion factor of 0.0259 (for cholesterol) and 0.0113 (for triglycerides) to change from mmol/L to mg/dL. Standard deviations (SDs) of the mean difference were calculated using the following formula: SD = square root $[(SD_{pre\text{-}treatment})^2 + (SD_{post\text{-}treatment})^2 - (2R \times SD_{pre\text{-}treatment} \times SD_{post\text{-}treatment})]$, assuming a correlation coefficient (R) = 0.5. If the outcome measures were reported in median and range (or 95% confidence interval [CI]), mean and SD values were estimated using the method described by Hozo et al. (2005). Where standard error of the mean (SEM) was only reported, SD was estimated using the following formula: SD = SEM × sqrt (n), where n is the number of subjects. Effect sizes were expressed as weighted mean difference (WMD) and 95% CI. In order to evaluate the influence of each study on the overall effect size, a sensitivity analysis was conducted using the leave-one-out method (i.e. removing one study each time and repeating the analysis) (Banach et al. 2015a; Banach et al. 2015b).

Meta-regression

As potential confounders of treatment response, dose and duration of treatment with ALE were entered into a meta-regression model to explore their association with the estimated effect size in each lipid species.

Publication bias

Evaluation of funnel plot, Begg's rank correlation and Egger's weighted regression tests were employed to assess the presence of publication bias in the meta-analysis. When there was an evidence of funnel plot asymmetry, potentially missing studies were imputed using the "trim and fill" method. In case of significant result, the number of potentially missing studies required to make the p-value non-significant was estimated using the "fail-safe N" method as another marker of publication bias (Duval and Tweedie, 2000).

Results

Effect of artichoke supplementation on plasma lipid concentrations

Overall, 66 articles were found following multi-database search. After screening of titles and abstracts, 18 articles were assessed in full text. Of these 9 articles were excluded because they did not measure plasma lipid concentrations, leaving 9 eligible articles for meta-analysis (Figure 1). (Bundy et al., 2008; Englisch et al., 2000; Fallah Huseini et al., 2012; Rangboo et al., 2016: Roghani-Dehkordi and Kamkhah., 2009; Rondanelli

Table 1. Demographic characteristics of the included studies.

Author	Study design	Target Population	Treatment duration	n	Study groups	Age, years	Female (n, %)	Total Cholesterol (mg/dL)	LDL-C (mg/dL)	HDL-C (mg/dL)	TG (mg/dL)
Bundy et al. (2008)	Randomized, double-blind, placebo-controlled	Mild to moderate hypercholesterolemia	3 months	38	ALE 1280 mg/day	~55	24 (63)	271 ± 24	199 ± 19	52 ± 11	121 ± 23
				35	Placebo	~55	24 (68)	267 ± 21	191 ± 20	51 ± 10	127 ± 23
Englisch et al. (2000)	Randomized, double-blind, placebo-controlled	Moderate to severe hypercholesterolemia	6 weeks	71	ALE 1800 mg/day	NA	47 (66)	296 ± 22	213 ± 37	45 ± 29	202 ± 89
				72	Placebo	NA	49 (68)	298 ± 17	221 ± 38	45 ± 30	202 ± 90
Fallah Huseini et al. (2012)	Randomized, double-blind, placebo-controlled	Mild to moderate hypercholesterolemia in type 2 diabetes	8 weeks	36	ALE 1200 mg/day	51.5 ± 9.3	43 (55.1)	223 ± 20	126 ± 11	45 ± 12	229 ± 66
				36	Placebo	50.6 ± 11.8	33 (54.0)	233 ± 14	134 ± 18	46 ± 11	195 ± 84
Rangboo et al. (2016)	Randomized, double-blind, placebo-controlled	Non hypercholesterolemic or mild hypercholesterolemic NASH patients	8 weeks	30	ALE 2700 mg/day	47.3 ± 8.1	9 (30.0)	206 ± 31	122 ± 30	46 ± 10	193 ± 86
				30	Placebo	49.8 ± 12.8	9(30.0)	213 ± 48	116 ± 29	45 ± 7	180 ± 46
Roghani-Dehkordi & Kamkhah (2009)	Randomized, double-blind, placebo-controlled	Non hypercholesterolemic or mild hypercholesterolemic hypertensive patients	12 weeks	39	CAJ 50	44.1 ± 1.4	NA	178 ± 10	123 ± 6	50 ± 3	120 ± 10
				35	CAJ 100	43.8 ± 1.4	NA	179 ± 8	117 ± 6	49 ± 4	120 ± 10
				33	Placebo	43.7 ± 1.3	NA	184 ± 9	120 ± 6	52 ± 3	120 ± 10
Rondanelli et al. (2011)	Randomized, double-blind, placebo-controlled	Non hypercholesterolemic or mild hypercholesterolemic overweight patients	8 weeks	20	ALE 600 mg/day	50.3 ± 8.0	12 (60)	228 ± 45	147 ± 45	54 ± 10	148 ± 131
				19	Placebo	49.2 ± 8.0	12 (63)	226 ± 30	144 ± 33	54 ± 12	116 ± 119
Rondanelli et al. (2013)	Randomized, double-blind, placebo-controlled	Mild hypercholesterolemic patients	8 weeks	46	ALE 500 mg/day	54.2 ± 6.6	26 (56)	252 ± 27	147 ± 27	81 ± 19	115 ± 53
				46	Control	53.8 ± 9.0	25 (54)	253 ± 15	155 ± 16	74 ± 23	116 ± 50
Rondanelli et al. (2014)	Randomized, double-blind, placebo-controlled	Non hypercholesterolemic or mild hypercholesterolemic IFG patients	8 weeks	26	ALE 600 mg/day	54.7 ± 11.6	15 (58)	228 ± 39	155 ± 35	54 ± 15	124 ± 53
				29	Control	53.6 ± 8.2	15 (52)	232 ± 31	151 ± 17	58 ± 27	122 ± 31
Skarpanska-Stejnborn et al. (2008)	Randomized, placebo-controlled	Non hypercholesterolemic young men	5 weeks	12	ALE 1200 mg/day	20.8 ± 0.9	0 (0)	174 ± 17	97 ± 15	58 ± 6	74 ± 15
				10	Placebo	19.1 ± 0.2	0 (0)	177 ± 14	101 ± 17	57 ± 5	66 ± 15

ALE = Artichoke leaf extract, CAJ = Concentrated artichoke juice, IFG = Impaired fasting glucose, NASH = Non-alcoholic steatohepatitis

Table 2. Quality of bias assessment of the included studies according to the Cochrane guidelines.

Study	Sequence generation	Allocation concealment	Selective outcome reporting	Other sources of bias	Blinding of participants, personnel and outcome assessors	Incomplete outcome data
Bundy et al. (2008)	L	L	L	U	L	L
English et al. (2000)	L	L	L	U	L	L
Fallah Huseini et al. (2012)	U	U	L	U	L	L
Rangboo et al. (2016)	U	L	L	U	L	L
Roghani-Dehkordi & Kamkhah (2009)	U	U	L	U	U	L
Rondanelli et al. (2011)	U	U	L	U	L	L
Rondanelli et al. (2013)	U	L	L	U	L	L
Rondanelli et al. (2014)	U	U	L	U	L	L
Skarpanska-Stejnborn et al. (2008)	U	U	L	U	U	L

U = Unclear risk of bias, L = Low risk of bias.

et al., 2011; Rondanelli et al. 2013; Rondanelli et al. 2014; Skarpanska-Stejnborn et al., 2008)

Meta-analysis of data from 9 trials including 702 subjects suggested a significant decrease in plasma concentrations of total cholesterol (WMD: −17.6 mg/dL, 95% CI: −22.0, −13.3, $p < 0.001$), LDL-C (WMD: −14.9 mg/dL, 95% CI: −20.4, −9.5, $p < 0.011$) and triglycerides (WMD: −9.2 mg/dL, 95% CI: −16.2, −2.1, $p = 0.011$) (Figure 2). The reductions in plasma total cholesterol and LDL-C but not triglycerides levels were robust in the leave-one-out sensitivity analysis (Figure 3). No significant alteration in plasma HDL-C concentrations was observed following artichoke supplementation (WMD: 1.0 mg/dL, 95% CI: −1.1, 3.1, $p = 0.333$) (Figure 2).

Meta-regression

Random-effects meta-regression was performed to assess the impact of potential confounders on the observed LDL-C-lowering activity of artichoke. The results did not suggest any significant association between the changes in plasma concentrations of LDL-C with either dose (slope: −0.004; 95% CI: −0.012, 0.003; $p = 0.239$) or duration (slope: 1.72; 95% CI: −0.387, 3.827; $p = 0.110$) of artichoke supplementation. However, a significant inverse association was observed between the LDL-C-lowering effect of artichoke and baseline LDL-C concentrations (slope: −0.170; 95% CI: −0.288, 0.051; $p = 0.005$) (Figure 4).

Publication bias

Although the results of Egger's linear regression test (intercept = 0.83, standard error = 1.42; 95% CI = −2.44, 4.10, $t = 0.59$, df = 8, two-tailed $p = 0.574$) and Begg's rank correlation test (Kendall's Tau with continuity correction = 0.36, $z = 1.43$, two-tailed p-value = 0.152) did not suggest the presence of publication bias in the meta-analysis of artichoke's effects on plasma

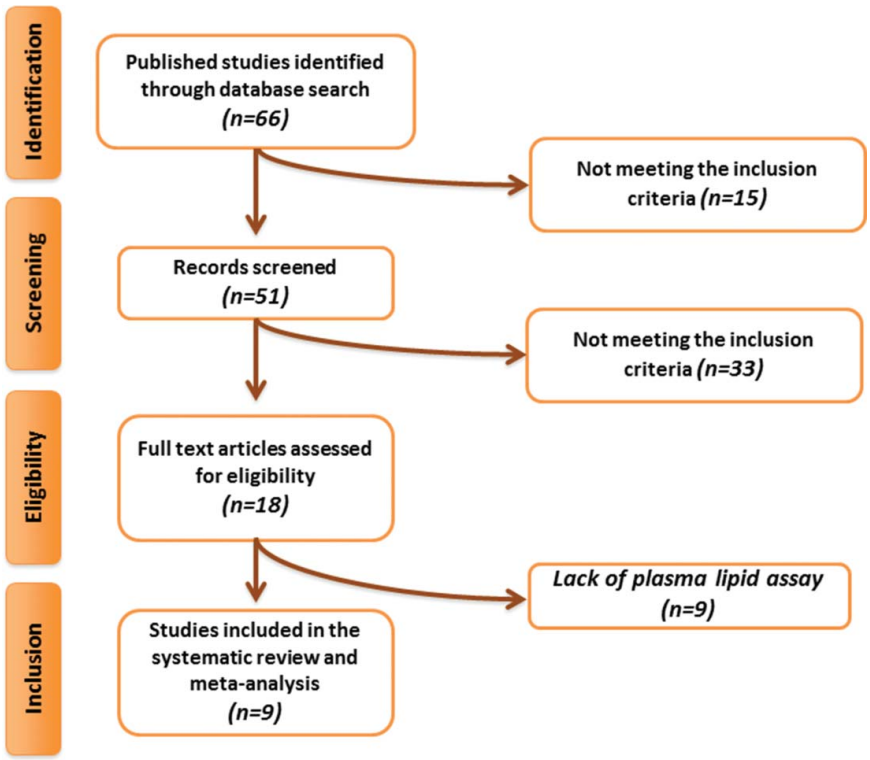

Figure 1. Flow chart of the number of studies identified and included into the meta-analysis.

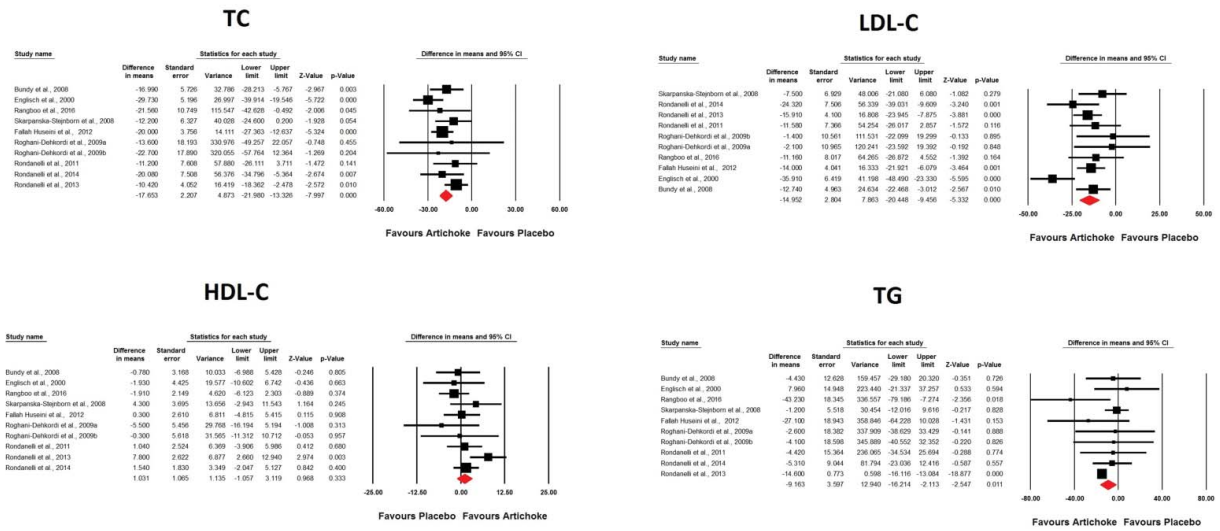

Figure 2. Forest plot displaying weighted mean difference and 95% confidence intervals for the impact of artichoke supplementation on plasma lipids concentrations. TC: total cholesterol, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, TG: triglycerides.

LDL-C levels, the funnel plot of standard error by effect size (WMD) was slightly asymmetric. Using "trim and fill" method, two potentially missing studies were imputed yielding an adjusted effect size (WMD) of −16.51 mg/dL (95% CI: −21.94, −11.08) (Figure 5). The "fail-safe N" test showed that 130 missing studies would be needed to bring the effect size down to a non-significant ($p > 0.05$) value.

Discussion

In our meta-analysis of 9 RCTs we observed that artichoke extract supplementation was associated with a significant reduction in both total and LDL-C, without an effect on either triglycerides or HDL-C levels. The cholesterol-lowering effect appeared to be unrelated to dose and duration of treatment, but the efficacy seemed to be directly related to the baseline LDL-C level.

Our results of a significant effect of ALE in reducing total and LDL-C levels are in accord with the meta-analysis performed by the Cochrane collaboration (Wider et al., 2013), in which ALE-induced LDL-C reduction ranged from 6.1% to 9.9%; however, our meta-analysis was more comprehensive, including 9 RCTs compared with the 2 suitable trials for data pooling in the Cochrane analysis.

This meta-analysis showed that 5 RCTs were showed a significant LDL-C-lowering effect of ALE (Bundy et al., 2008; Englisch et al., 2000; Fallah Huseini et al. 2012; Rondanelli et al., 2013; Rondanelli et al., 2014). In 4 out of these 5 studies baseline LDL-C levels were elevated, ranging from 147 to 213 mg/dL among patients randomized to receive ALE supplementation (Bundy et al., 2008; Englisch et al., 2000; Rondanelli et al., 2013; Rondanelli et al., 2014). Among these 5 RCTs, only the study by Fallah Huseini et al. (Fallah Huseini et al. 2012) randomized patients with lower mean baseline LDL-C levels

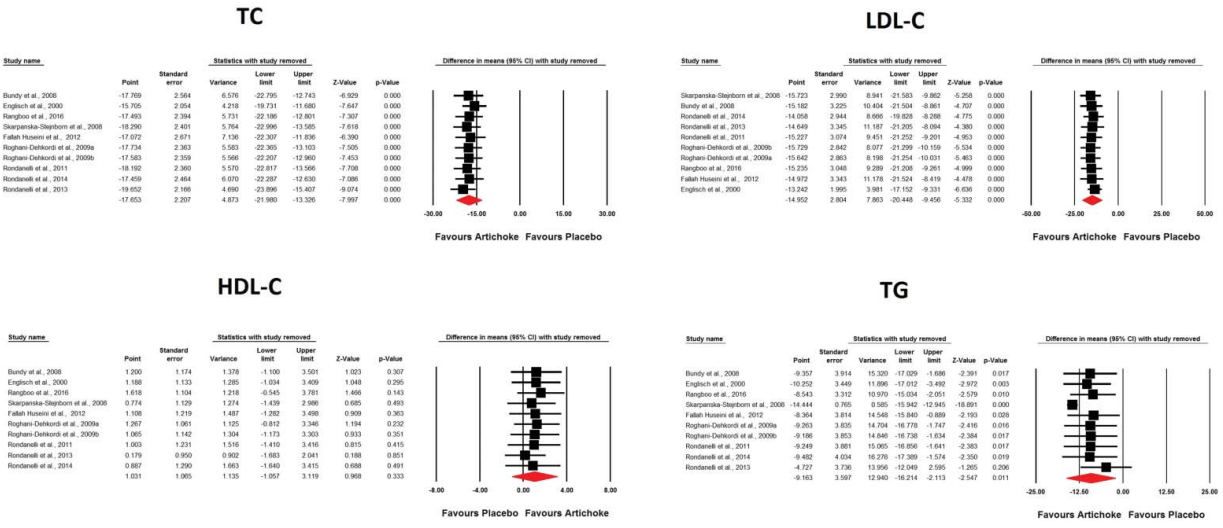

Figure 3. Leave-one-out sensitivity analyses for the impact of artichoke supplementation on plasma lipids concentrations. TC: total cholesterol, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, TG: triglycerides.

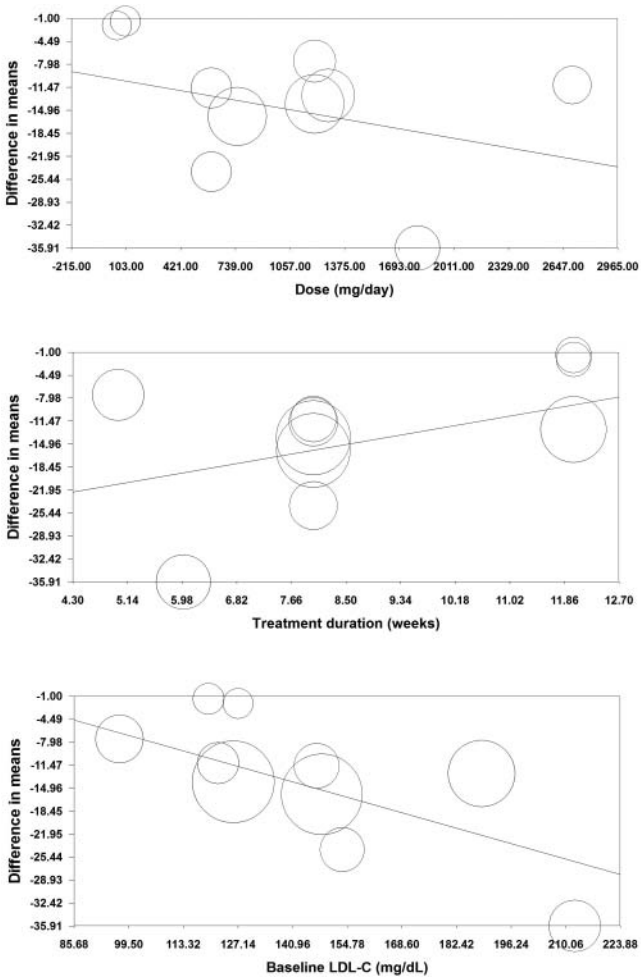

Figure 4. Meta-regression bubble plots of the association between mean changes in plasma low-density lipoprotein cholesterol (LDL-C) concentrations with dose, duration of supplementation and baseline LDL-C concentrations. The size of each circle is inversely proportional to the variance of change.

(126 mg/dL) to ALE supplementation; however, in this RCT patients with type 2 diabetes mellitus were included, which are characterized by increased cholesterol synthesis (Ooi et al., 2009; Simonen et al., 2002) and possibly by a greater LDL-C response to HMG-CoA reductase inhibition by ALE, leading to a significant LDL-C-lowering effect (Fallah Huseini et al. 2012). Conversely, 4 (Rangboo et al., 2016; Roghani-Dehkordi and Kamkhah, 2009, Rondanelli et al., 2011) out of 9 studies did not show a LDL-C-lowering effect of artichoke extract (Roghani-Dehkordi and Kamkhah, 2009; Rondanelli et al., 2011). A common characteristic of 3 studies (Rangboo et al., 2016; Roghani-Dehkordi and Kamkhah, 2009; Rondanelli et al., 2011) where LDL-C reduction did not occur was the relatively low baseline LDL-C level of the included participants, ranging from 97 to 123 mg/dL. Other confounders included a combination of *Phaseolus vulgaris* and *Cynara scolymus* (Roghani-Dehkordi and Kamkhah, 2009) instead of a single artichoke-derived nutraceutical that was compared with placebo. In the study by Skarpanska-Stejnborn et al. (2008), 12 young non-hypercholesterolemic men received the ALE supplementation, whereas in the study by Roghani-Dehkordi and Kamkhah (2009) 100–200 mg/day of a concentrated artichoke juice was used instead of an ALE supplementation of 500–2700 mg/day used in the other studies (Bundy et al., 2008; Englisch et al., 2000; Fallah Huseini et al., 2012; Rangboo et al., 2016; Rondanelli et al., 2011; Rondanelli et al., 2014; Skarpanska-Stejnborn et al., 2008). Hence, low baseline LDL-C levels, low-dose artichoke preparations, possible interference with other nutraceuticals and population size might have influenced the potential LDL-C-lowering effect of ALE in the 4 trials showing no significant LDL-C effects of artichoke supplementation (Rangboo et al., 2016; Roghani-Dehkordi and Kamkhah, 2009; Rondanelli et al., 2011; Skarpanska-Stejnborn et al., 2008).

Baseline LDL-C appeared to be an important feature predicting ALE lipid lowering, particularly seen in the study of moderate-to-severe hypercholesterolemic patients with a mean baseline LDL-C level of 213 mg/dL (Englisch et al., 2000) where an impressive 35.9 mg/dL reduction of plasma LDL-C level was observed (Englisch et al., 2000), greater compared with the overall LDL-C reduction observed in this meta-analysis (14.9 mg/dL) and the 7.5 mg/dL LDL-C reduction observed in the study with normocholesterolemic patients with a baseline LDL-C level of 97 mg/dL who received ALE (Skarpanska-Stejnborn et al., 2008).

Neither dose nor duration of ALE supplementation affected the LDL-C-lowering effect of this nutraceutical. Indeed, the lowest LDL-C-lowering efficacy was reported in the study using the lowest artichoke dose (Roghani-Dehkordi and Kamkhah,

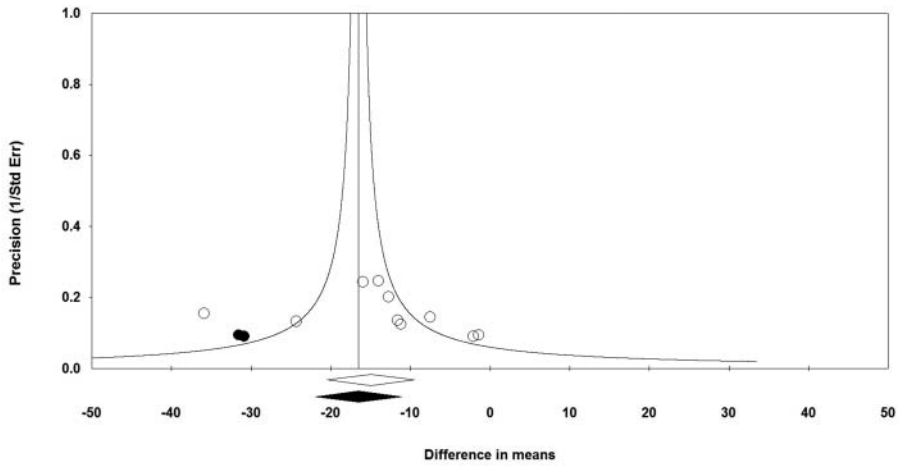

Figure 5. Funnel plot detailing publication bias in the studies reporting the impact of artichoke supplementation on plasma LDL-C concentrations.

2009) suggesting that it may be preparation depended. However, these data support the potential clinical use of ALE supplementation for a mild but significant cholesterol reduction. Whether this mild cholesterol-lowering would translate into a positive effect on clinical outcomes remains to be proven, though this is supported by an anti-atherosclerotic effect of ALE in rats (Samochowiec, 1962), and a serum reduction in vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) in humans, while brachial flow-mediated vasodilation increased (Lupattelli et al., 2004).

ALE treatment had no effect on triglyceride and HDL-C levels, though in all but 3 RCTs (Englisch et al., 2000; Fallah Huseini et al., 2012; Rangboo et al., 2016) patients had normal plasma triglyceride levels and baseline HDL-C were above 40 mg/dL in all 9 RCTs. Therefore, it is not possible to comment whether ALE would have had an additional effect in hypertriglyceridemia or low HDL-C levels.

Other studies identified, but not included, in this meta-analysis were those where artichoke extract was in combination with other nutraceuticals and while they had a positive effect (Ogier et al., 2013; Cicero et al. 2017) it was difficult to determine the individual lipid-lowering contribution of artichoke.

Reported adverse events suggest that artichoke extract is well tolerated with mild and transient side effects (Cicero et al., 2012), though with such few trials long-term safety and risk of pharmacological interactions are unclear.

Our meta-analysis has some limitations. Firstly, we had to exclude a large number of small positive studies because their design or information was poorly documented. Studies of artichoke in combination with several other lipid-lowering nutraceuticals were excluded (Barrat et al., 2013; Cicero et al., 2017). The extracts tested in the selected studies were of different dosages with different standardization and concentration. However, the observed effect was overall homogeneous, and supported a mild but significant lipid-lowering effect of artichoke extract in humans. In addition, the results showed that the significance of estimated pooled effect size was not biased by any single study.

In conclusion, this meta-analysis of available RCTs suggests a significant benefit of artichoke extract supplementation in decreasing plasma LDL-C concentrations in mild to moderate hypercholesterolemic subjects, though the duration of that effect could not be determined.

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Disclosure statement

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