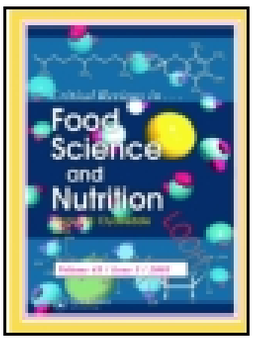

Critical Reviews in Food Science and Nutrition

ISSN: 1040-8398 (Print) 1549-7852 (Online) Journal homepage: http://www.tandfonline.com/loi/bfsn20

Lipid-modifying activity of curcuminoids: A systematic review and meta-analysis of randomized controlled trials

Luis E. Simental-Mendía, Matteo Pirro, Antonio M. Gotto Jr., Maciej Banach, Stephen L. Atkin, Muhammed Majeed & Amirhossein Sahebkar

To cite this article: Luis E. Simental-Mendía, Matteo Pirro, Antonio M. Gotto Jr., Maciej Banach, Stephen L. Atkin, Muhammed Majeed & Amirhossein Sahebkar (2017): Lipid-modifying activity of curcuminoids: A systematic review and meta-analysis of randomized controlled trials, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2017.1396201

To link to this article: https://doi.org/10.1080/10408398.2017.1396201

Published online: 29 Nov 2017.

CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
https://doi.org/10.1080/10408398.2017.1396201

Lipid-modifying activity of curcuminoids: A systematic review and meta-analysis of randomized controlled trials

Luis E. Simental-Mendía[a], Matteo Pirro [b], Antonio M. Gotto Jr.[c], Maciej Banach[d,e], Stephen L. Atkin[f], Muhammed Majeed[g], and Amirhossein Sahebkar [h]

[a]Biomedical Research Unit, Mexican Social Security Institute, Durango, Mexico; [b]Unit of Internal Medicine, Angiology and Arteriosclerosis Diseases, Department of Medicine, University of Perugia, Perugia, Italy; [c]Weill Cornell Medical College, New York, NY, United States; [d]Department of Hypertension, WAM University Hospital in Lodz, Medical University of Lodz, Zeromskiego 113, Lodz, Poland; [e]Polish Mother's Memorial Hospital Research Institute (PMMHRI), Lodz, Poland; [f]Weill Cornell Medicine Qatar, Doha, Qatar; [g]Sabinsa Corporation, East Windsor, NJ, United States; [h]Biotechnology Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

ABSTRACT

Objective: The aim of this systematic review and meta-analysis was to determine and clarify the impact of curcuminoids on serum lipid levels. **Methods**: Randomized controlled trials (RCTs) investigating the effects of curcuminoids on plasma lipids were searched in PubMed-Medline, Scopus, Web of Science databases (from inception to April 3rd, 2017). A random-effects model and generic inverse variance method were used for quantitative data synthesis. Sensitivity analysis was conducted using the leave-one-out method. A weighted random-effects meta-regression was performed to evaluate the impact of potential confounders on lipid concentrations. **Results**: A meta-analysis of 20 RCTs with 1427 participants suggested a significant decrease in plasma concentrations of triglycerides (WMD: −21.36 mg/dL, 95% CI: −32.18, −10.53, $p < 0.001$), and an elevation in plasma HDL-C levels (WMD: 1.42 mg/dL, 95% CI: 0.03, 2.81, $p = 0.046$), while plasma levels of LDL-C (WMD: −5.82 mg/dL, 95% CI: −15.80, 4.16, $p = 0.253$) and total cholesterol (WMD: −9.57 mg/dL, 95% CI: −20.89, 1.75, $p = 0.098$) were not altered. The effects of curcuminoids on lipids were not found to be dependent on the duration of supplementation. **Conclusion**: This meta-analysis has shown that curcuminoid therapy significantly reduces plasma triglycerides and increases HDL-C levels.

KEYWORDS
Curcumin; Turmeric; Dyslipidemia; Cardiovascular disease; Cholesterol; Triglycerides

Introduction

Dyslipidemia is an important risk factor for cardiovascular diseases (CVD) that includes an elevated low-density lipoprotein cholesterol (LDL-C), decreased high-density lipoprotein cholesterol (HDL-C) and high triglyceride levels (Arca M 2007). Elevated levels of LDL-C are causally related with the development of atherosclerotic cardiovascular disease (Stone NJ 2014) leading to increased morbidity and mortality worldwide (Yusuf S 2001). Statin therapy are the pharmacological agents employed for both primary and secondary prevention of CVD through lowering plasma LDL-C levels (Baigent C 2005, Stone NJ 2014, Taylor F 2013, Vrecer M 2003, Ž. 2013); however, statin-treated patients, even those achieving therapeutic LDL-C targets, still have residual CV risk. Increased plasma triglycerides and reduced HDL-C may contribute to this residual CV risk in statin-treated individuals, and those lipid indices are not effectively modulated by statins (Sampson et al. 2012, Sirimarco et al. 2014). Therefore, additional treatments to address this residual CV risk from increased plasma triglycerides and reduced HDL-C would be of benefit.

In recent years a number of nutraceuticals have been proposed as possible adjuvants to improve the lipid profile (Johnston et al. 2017, Pirro et al. 2016, Pirro et al. 2017). Among them, curcuminoids, lipophilic phytochemicals found in turmeric (*Curcuma longa* Linn), are of particular interest (Martin RC 2012). Curcumin is a polyphenolic agent that makes up about 75–85% of the curcuminoids and it is widely consumed in Asian countries for its medicinal effects (Anand P 2007, Shishodia S 2005). Curcumin has had a number of biological activities reported that are relevant for CV prevention (e.g., antioxidant, anti-inflammatory, antithrombotic), in addition to antitumor, hepatoprotective, antiarthritis and antidepressant properties (A. 2013, A. 2014, Anand P 2007, Ganjali et al. 2014, Panahi Y 2016a, Panahi Y 2015a, Panahi Y 2015b, Panahi Y 2014a, Panahi Y 2016b, Panahi Y 2012, Panahi Y 2014b, Sahebkar A 2013, Shishodia S 2005). A number of studies have suggested that curcumin has a beneficial effect on lipid profiles in both experimental animal models (Manjunatha H 2007, Shin SK 2011, Soudamini KK 1992) and clinical trials (Baum L 2007, Panahi Y 2014a, Ramirez Boscá A 2000, Soudamini KK 1992); nonetheless, results from the human studies are inconsistent. The aim of this systematic review and meta-analysis was to determine and clarify the impact of curcumin on serum lipid levels.

CONTACT Amirhossein Sahebkar, PharmD, PhD sahebkara@mums.ac.ir, amir_saheb2000@yahoo.com Department of Medical Biotechnology, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran, P.O. Box: 91779-48564, Iran.

Color versions of one or more figures in this article can be found online at www.tandfonline.com/bfsn.

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 controlled trials (RCTs) investigating the effects of curcuminoids on plasma lipids, PubMed-Medline, Scopus and Web of Science databases were searched using the following search terms in titles and abstracts: (curcuminoid OR curcuminoids OR curcumin OR *Curcuma*) AND (cholesterol OR "low-density lipoprotein" OR LDL OR LDL-C OR LDL-cholesterol OR "high-density lipoprotein" OR HDL-cholesterol OR HDL-C OR triglyceride OR hyperlipidemia OR hyperlipidemic OR dyslipidemia OR dyslipidemic OR lipid OR lipoprotein. The wild-card term "*" was used to increase the sensitivity of the search strategy. The literature was searched from inception to April 03, 2017.

Study selection

Original studies were included if they met the following inclusion criteria: (i) being an RCT with either parallel or cross-over design, (ii) investigating the impact of curcuminoids on plasma/serum concentrations of lipids, and, (iii) presentation of sufficient information on lipid concentrations at baseline and at the end of follow-up in each group, or providing the net change values. Exclusion criteria were: (i) uncontrolled trials, (ii) 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 curcuminoids and control groups, 6) control assignment, 7) dose of curcuminoids, 8) treatment duration, 9) age, gender and body mass index (BMI) of study participants, and, 10) baseline and follow-up plasma concentrations of lipids.

Quality assessment

Risk of bias in the studies considered in this meta-analysis was evaluated according to the Cochrane instructions (Higgins JPT 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.

Quantitative data synthesis

Meta-analysis was conducted using Comprehensive Meta-Analysis (CMA) V2 software (Biostat, NJ). Effect size was calculated as: (measure at the end of follow-up in the curcuminoids group – measure at baseline in the curcuminoids 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 (Hozo SP 2005). 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 Wanet al (Wan X 2014). 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. When the data were not tabulated, but presented only as graphs, the software GetData Graph Digitizer 2.24 (http://getdata-graph-digitizer.com/) was applied to digitize and extract the data. In order to avoid the double-counting problem in trials comparing multiple treatment arms versus a single control group, the number of subjects in the control group was divided by the number of treatment arms. Heterogeneity was quantitatively assessed using I^2 index. 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).

Meta-regression

As potential confounders of treatment response, duration of treatment with curcuminoids and baseline lipid levels were entered into a random-effects meta-regression model to explore their association with the estimated effect size on each lipid species.

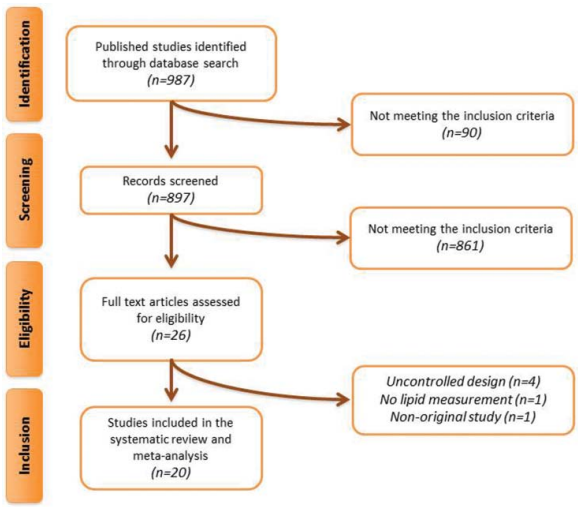

Figure 1. Flow chart of the number of studies identified and included into the meta-analysis.

Table 1. Demographic characteristics of the included studies.

Author	Study design	Target Population	Treatment duration	n	Study groups	Age, years	Female (n, %)	BMI, (kg/m^2)	Total cholesterol (mg/dl)	LDL cholesterol (mg/dl)	HDL cholesterol (mg/dl)	Triglycerides (mg/dl)
Alwi et al. (2008)	Randomized, double-blind, placebo-controlled	Acute coronary syndrome	2 months	15	Curcumin 45 mg/day	58.6 ± 13.7	5 (33.3)	25.0 ± 3.1	202.6 ± 59.6	139.0 ± 55.0	42.1 ± 10.4	151.5 ± 91.3
				14	Curcumin 90 mg/day	54.2 ± 9.4	3 (21.4)	25.1 ± 2.8	211.7 ± 55.1	149.5 ± 40.8	40.5 ± 9.1	145.6 ± 47.9
				15	Curcumin 180 mg/day	54.4 ± 8.7	3 (20.0)	25.0 ± 3.6	190.8 ± 36.1	133.8 ± 33.4	41.1 ± 8.8	119.4 ± 34.0
				26	Placebo	54.3 ± 8.5	3 (13.0)	25.8 ± 3.8	207.2 ± 58.2	148.7 ± 49.3	38.0 ± 8.8	146.1 ± 63.1
Baum et al. (2007)	Randomized, double-blind, placebo-controlled	Elderly subjects	6 months	31	Overall	74.3 ± 8.8	9 (29.0)	ND	212.7 ± 42.5	123.7 ± 38.7	61.9 ± 15.5	141.7 ± 70.9
				7	Curcumin 1 g/day	ND	ND	ND	200.7 ± 18.6	112.5 ± 20.9	66.1 ± 8.9	109.8 ± 33.7
				11	Curcumin 4 g/day	ND	ND	ND	228.2 ± 36.0	138.1 ± 37.5	60.3 ± 19.7	150.6 ± 69.1
				8	Placebo	ND	ND	ND	226.6 ± 53.0	131.9 ± 44.1	65.0 ± 17.4	149.7 ± 70.9
Chuengsamarn et al. (2014)	Randomized, double-blind, placebo-controlled	Type 2 diabetes	6 months	107	Curcumin 1.5 g/day	59.1 ± 10.3	57 (53.3)	27.0 ± 5.3	199.4 ± 45.1	117.8 ± 36.1	49.7 ± 10.3	158.2 ± 101.3
				106	Placebo	59.5 ± 10.2	59 (55.7)	26.8 ± 4.3	195.8 ± 44.1	113.4 ± 32.9	49.2 ± 13.0	166.9 ± 101.4
Cox et al. (2015)	Randomized, double-blind, placebo-controlled	Healthy older population	1 month	30	Curcumin 80 mg/day	67.5 ± 4.4	18 (60)	25.5 ± 3.4	ND	ND	ND	ND
				30	Placebo	69.4 ± 6.5	20 (66.6)	27.2 ± 4.8	ND	ND	ND	ND
DiSilvestro et al. (2012)	Randomized, Placebo-controlled, clinical trial	Healthy middle aged people	1 month	19	Curcumin 80 mg/day	47 ± 5	17 (89.4)	ND	ND	ND	ND	ND
				19	Placebo	48 ± 6	17 (89.4)	ND	ND	ND	ND	ND
Funamoto et al. (2016)	Randomized, double-blind, placebo-controlled	Chronic obstructive pulmonary disease	6 months	22	Curcumin 180 mg/day	69.6 ± 6.6	3 (13.6)	22.1 ± 2.6	ND	106.8 ± 27.6	62.1 ± 17.2	146.3 ± 70.2
				17	Placebo	69.9 ± 6.3	2 (11.7)	24.4 ± 4.3	ND	104.5 ± 21.6	60.1 ± 9.6	160.1 ± 86.8
Kocher et al. (2016)	Randomized, double-blind, placebo-controlled, cross-over	Hyperlipidemia	6 weeks	42	Overall	ND	25 (59.5)	ND	ND	ND	ND	ND
				42	Curcuminoids 294 mg/day	ND	25 (59.5)	ND	234.5 ± 45.1	162.0 ± 37.8	55.5 ± 13.0	120.6 ± 56.5
				42	Placebo	ND	25 (59.5)	ND	232.5 ± 51.9	157.8 ± 39.5	55.0 ± 13.3	115.2 ± 47.5
Mirzabeigi et al. (2015)	Randomized, double-blind, placebo-controlled	Coronary artery disease	2 months	17	Curcumin 2 g/day	61.5 ± 8.7	7 (41.1)	27.9 ± 3.6	172.5 ± 45.7	118.0 ± 44.0	39.0 ± 10.8	145.9 ± 52.7
				16	Placebo	64.3 ± 8.4	2 (12.5)	28.5 ± 3.6	165.2 ± 24.3	95.2 ± 20.7	43.1 ± 10.8	108.5 ± 42.2
Mohammadi et al. (2013)	Randomized, double-blind, placebo-controlled, cross-over	Hyperlipidemia	1 month	15	Curcuminoids 1 g/day	39.0 ± 9.0	ND	33.4 ± 3.7	195.6 ± 30.4	119.7 ± 23.6	46.3 ± 9.8	105.7 ± 30.2
				15	Placebo	37.9 ± 12.7	ND	31.8 ± 3.4	190.7 ± 27.7	120.3 ± 27.9	46.6 ± 7.8	126.2 ± 57.1
Na et al. (2013)	Randomized, double-blind, placebo-controlled	Type 2 diabetes	3 months	50	Curcuminoids 300 mg/day	55.4 ± 6.4	26 (52)	27.1 ± 2.2	236.3 ± 47.3	166.3 ± 46.4	53.0 ± 10.1	197.5 ± 46.9
				50	Placebo	54.7 ± 8.3	25 (50)	27.4 ± 3.0	235.1 ± 48.0	167.1 ± 44.5	51.4 ± 10.8	194.0 ± 92.1
Panahi et al. (2014)	Randomized, double-blind, placebo-controlled	Metabolic syndrome	2 months	50	Curcuminoids 1 g/day	44.8 ± 8.6	23 (46)	25.4 ± 2.4	220.2*	190.4*	31.5*	199.6*
				50	Placebo	43.4 ± 9.7	27 (54)	22.8 ± 5.3	184.0*	157.1*	35.4*	185.6*
Panahi et al. (2016)	Randomized, placebo-controlled	NAFLD	2 months	44	Curcumin 1 g/day	44.9 ± 12.5	20 (45.5)	28.9 ± 3.4	199.5 ± 40.8	130.6 ± 33.4	46.8 ± 9.8	151.4 ± 75.6
				43	Placebo	47.2 ± 10.2	16 (37.2)	29.0 ± 3.4	184.0 ± 46.8	108.9 ± 46.2	47.4 ± 10.6	150.0 ± 68.4
Panahi et al. (2017)	Randomized, double-blind, placebo-controlled	Type 2 diabetes	3 months	50	Curcuminoids 1 g/day	43 ± 8	25 (50)	26.5 ± 2.3	217.3 ± 41.6	169.1 ± 30.7	40.8 ± 5.4	229.7 ± 81.8
				50	Placebo	41 ± 7	24 (48)	27.3 ± 1.5	231.0 ± 70.9	199.0 ± 54.4	39.4 ± 6.0	207.6 ± 54.6
Pashine et al. (2012)	Randomized, double-blind, placebo-controlled	Hyperlipidemia	3 months	53	Turmeric 1.4 g/day	ND	28 (58.3)	ND	231.9 ± 52.2	140.0 ± 50.4	48.4 ± 16.1	217.1 ± 113.8
				52	Placebo	ND	20 (51.3)	ND	209.1 ± 52.0	120.4 ± 55.7	51.8 ± 10.0	184.5 ± 60.0
Pungcharoenkul et al. (2011)	Randomized, single-blind, controlled	Healthy subjects	7 days	24	Overall	29.3 ± 5.4	8 (33.3)	29.3 ± 5.4				
				10	Curcumin 500 mg/day	ND	ND	ND	205 ± 22.1	ND	ND	110 ± 66.4
				9	Curcumin 6 g/day	ND	ND	ND	203 ± 36	ND	ND	93 ± 39
				5	Vitamin E 200 IU/day	ND	ND	ND	196 ± 31.3	ND	ND	78 ± 44.7
Rahimi et al. (2016)	Randomized, double-blind, placebo-controlled	Type 2 diabetes	3 months	35	Curcumin 80 mg/day	56.3 ± 11.1	18 (51.5)	ND	163.4 ± 33.9	96.5 ± 33.9	54.3 ± 14.0	109 (94.7)**
				35	Placebo	60.9 ± 10.7	21 (60)	ND	162.4 ± 38.5	99.7 ± 30.3	60.3 ± 15.9	142 (97.5)**
Rahmani et al. (2016)	Randomized, double-blind, placebo-controlled	NAFLD	2 months	40	Curcumin 500 mg/day	46.3 ± 11.5	21 (52.5)	30.8 ± 4.4	198.5 ± 41.7	107.0 ± 31.3	44.2 ± 11.8	199.6 ± 91.4
				40	Placebo	48.9 ± 9.7	21 (52.5)	31.3 ± 5.6	187.7 ± 32.9	115.5 ± 22.3	42.6 ± 6.6	160.2 ± 61.9
Sukandar et al. (2013)	Randomized, double-blind, controlled	Hyperlipidemia	3 months	19	Turmeric 1.2 g/day+	55.3 ± 8.7	ND	25.1 ± 3.0	251.2 ± 33.1	163.4 ± 40.5	49.7 ± 10.8	190.3 ± 125.9
				20	Garlic 1.2 g/day Simvastatin 10 mg/day	55.9 ± 7.1	ND	26.7 ± 5.3	246.3 ± 31.7	162.9 ± 27.7	47.7 ± 12.9	187.9 ± 108.6
Usharani et al. (2008)	Randomized, placebo-controlled	Type 2 diabetes	2 months	23	Curcumin 600 mg/day	55.5 ± 10.7	11 (47.8)	24.6 ± 2.4	195.0 ± 41.1	120.3 ± 42.1	38.7 ± 7.6	176.3 ± 27.6
				21	Placebo	49.7 ± 8.1	10 (47.6)	23.9 ± 2.3	196.9 ± 35.7	125.2 ± 34.9	36.3 ± 7.6	170.1 ± 47.5
Yang et al. (2014)	Randomized, double-blind, placebo-controlled	Metabolic syndrome	3 months	33	Curcumin 1890 mg/day	59.0 ± 10.1	21 (63.6)	30.6 ± 4.1	195.6 ± 41.8	120.2 ± 36.2	40.7 ± 8.5	177.1 ± 83.6
				32	Placebo	59.6 ± 14.0	15 (46.8)	28.7 ± 4.8	178.6 ± 33.3	107.3 ± 24.0	41.8 ± 11.8	153.4 ± 80.4

Values are expressed as mean ± SD
* Mean only
**Median (IQR)
Abbreviations: ND, no data; BMI, body mass index; NAFLD, non-alcoholic fatty liver disease; IQR, interquartile range.

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 (Duval S 2000). 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.

Results

Flow and characteristics of included studies

Overall, 26 studies were found following multi-database search. After screening of titles and abstracts, 26 articles were assessed in full text. Of these, 6 articles were excluded because of uncontrolled design, not reporting original data and not measuring plasma lipid concentrations, leaving 20 eligible articles (comprising 25 treatment arms) (Alwi I 2008, Baum L 2007, Chuengsamarn S 2014, Cox KH 2015, DiSilvestro RA 2012, Funamoto M 2016, Kocher A 2016, Mirzabeigi P 2015, Mohammadi A 2013, Na LX 2013, Panahi Y 2014a, Panahi Y 2017, Panahi Y 2016b, Pashine L 2012, Pungcharoenkul K 2011, Rahimi HR 2016, Rahmani S 2016, Sukandar EY 2013, Usharani P 2008, Yang YS 2014) for meta-analysis (Figure 1). Overall, 1427 subjects (737 in the curcuminoids and 690 in the control group) were included in the selected studies. Characteristics of the included clinical trials are shown in Table 1.

Risk of bias assessment

Several of the assessed studies did not provide sufficient information about random sequence generation and one study had high risk of bias for this criterion (DiSilvestro RA 2012). Additionally, the majority of included trials exhibited lack of information regarding allocation concealment and only one study showed high risk of bias (DiSilvestro RA 2012). With respect to the blinding of participants, personnel, and outcome assessment, some studies were characterized by insufficient information, and three trials had high risk of bias for this parameter (DiSilvestro RA 2012, Panahi Y 2016b, Usharani P 2008). Almost all of the evaluated studies exhibited low risk of bias for incomplete outcome data, only one trial showed lack of information (Cox KH 2015). Finally, all included studies had low risk of bias according to selective outcome reporting. Details of the quality of bias assessment are shown in Table 2.

Effect of curcuminoids supplementation on plasma lipid concentrations

The meta-analysis showed a significant decrease in plasma concentrations of triglycerides (WMD: −21.36 mg/dL, 95% CI: −32.18, −10.53, $p < 0.001$; $I^2 = 65.55\%$), and an elevation in plasma HDL-C levels (WMD: 1.42 mg/dL, 95% CI: 0.03, 2.81, $p = 0.046$; $I^2 = 37.24\%$), whilst plasma levels of LDL-C (WMD: −5.82 mg/dL, 95% CI: −15.80, 4.16, $p = 0.253$; $I^2 = 85.64\%$) and total cholesterol (WMD: −9.57 mg/dL, 95% CI: −20.89, 1.75, $p = 0.098$; $I^2 = 84.25\%$) were unaltered (Figure 2). The impact of curcuminoids on plasma levels of triglycerides was robust in the leave-one-out sensitivity analysis while the estimated effect sizes for total cholesterol, LDL-C and HDL-C were sensitive for some studies (Figure 3).

In subgroup analyses, no significant difference was observed between the subsets of RCTs administering curcuminoids for < 12 and ≥ 12 weeks on plasma levels of total cholesterol, LDL-C, HDL-C and triglycerides (Table 3).

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

Study	Sequence generation	Allocation concealment	Blinding of participants, personnel and outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Alwi et al. (2008)	L	U	U	L	L	U
Baum et al. (2007)	U	U	L	L	L	U
Chuengsamarn et al. (2014)	L	L	U	L	L	L
Cox et al. (2015)	U	U	U	H	L	U
DiSilvestro et al. (2012)	H	H	H	L	L	U
Funamoto et al. (2016)	U	U	U	L	L	U
Kocher et al. (2016)	U	U	U	L	L	U
Mirzabeigi et al. (2015)	U	U	U	L	L	U
Mohammadi et al. (2013)	U	U	U	L	L	U
Na et al. (2013)	L	U	L	L	L	L
Panahi et al. (2014)	U	U	U	L	L	U
Panahi et al. (2016)	U	U	H	L	L	U
Panahi et al. (2017)	U	L	U	L	L	U
Pashine et al. (2012)	L	U	U	L	L	U
Pungcharoenkul et al. (2011)	U	U	U	L	L	U
Rahimi et al. (2016)	L	L	U	L	L	U
Rahmani et al. (2016)	U	U	L	L	L	U
Sukandar et al. (2013)	U	U	L	L	L	U
Usharani et al. (2008)	U	U	H	L	L	U
Yang et al. (2014)	L	L	L	L	L	L

L, low risk of bias; H, high risk of bias; U, unclear risk of bias.

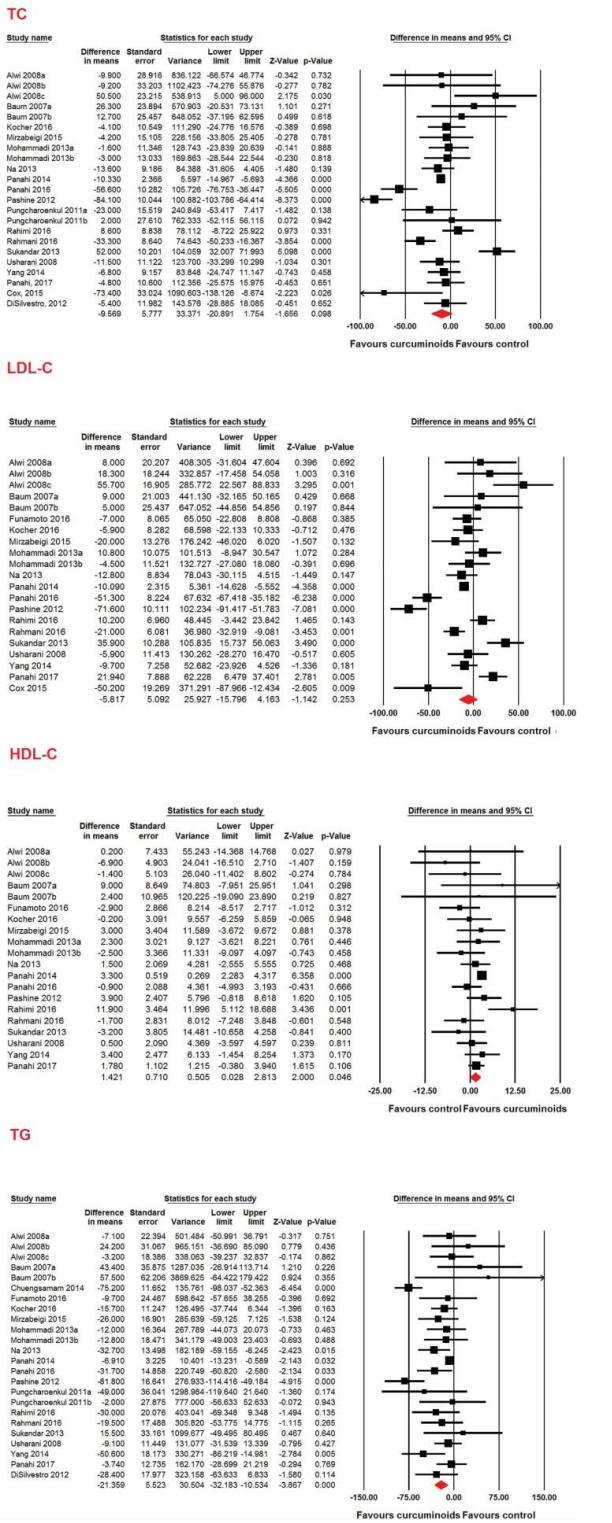

Figure 2. Forest plot displaying weighted mean difference and 95% confidence intervals for the impact of curcuminoids supplementation on plasma lipids concentrations. TC: total cholesterol, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, TG: triglycerides.

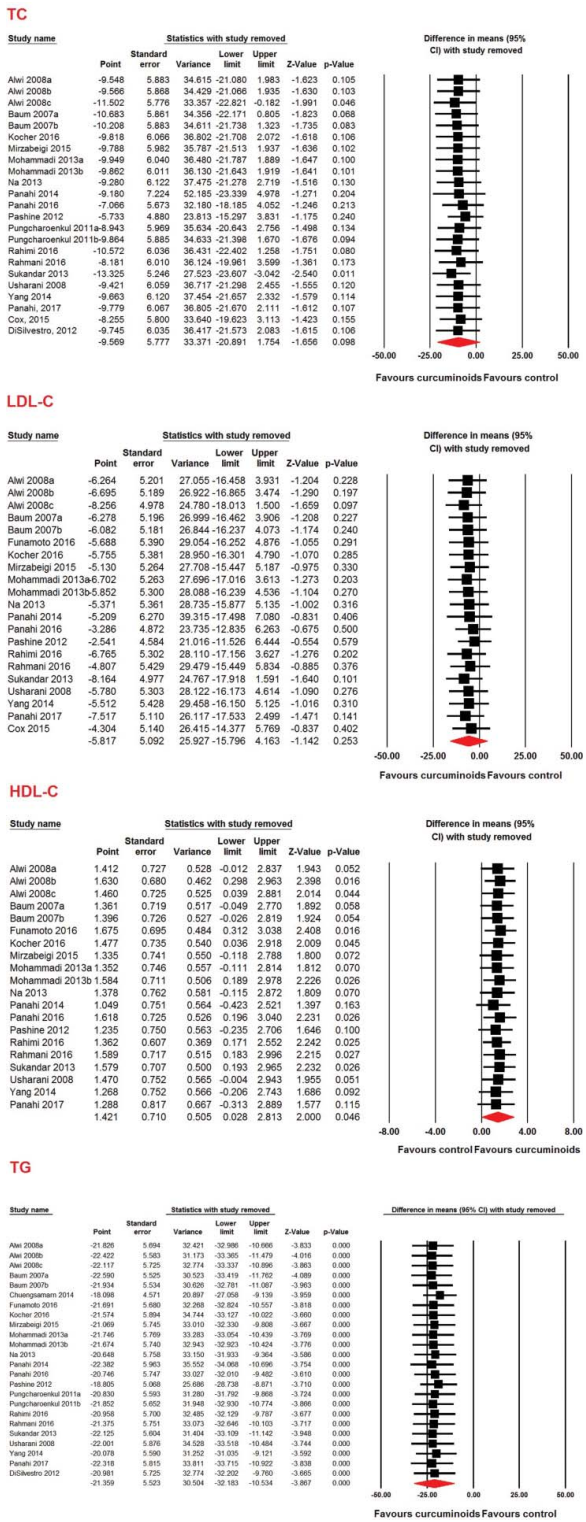

Figure 3. Leave-one-out sensitivity analyses for the impact of curcuminoids supplementation on plasma lipids concentrations. TC: total cholesterol, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, TG: triglycerides.

Meta-regression

Random-effects meta-regression was performed to assess the impact of potential confounders on the effects of curcuminoids on plasma lipid levels. The results did not suggest any significant association between the changes in plasma concentrations of total cholesterol, triglycerides, and LDL-C with either supplementation duration or baseline levels of the respective lipid parameter ($p > 0.05$) (Figures 4 and 5). However, a significant inverse association was observed between the HDL-C-increasing effect of curcuminoids and duration of supplementation (slope: −0.11; 95% CI: −0.21, −0.02; $p = 0.018$) (Figure 4) while there was no association with baseline HDL-C levels ($p > 0.05$) (Figure 5).

Table 3. Effects of curcuminoids on plasma lipids in trials lasting < 12 and ≥ 12 weeks.

Lipid parameter	< 12 weeks	≥ 12 weeks	*p*-value
Total cholesterol	−14.59 (−25.81, −3.37)	−2.80 (−28.44, 22.84)	0.409
LDL-cholesterol	−8.55 (−20.23, 3.13)	−2.71 (−22.24, 16.81)	0.615
HDL-cholesterol	0.68 (−1.22, 2.57)	2.39 (−0.09, 4.86)	0.282
Triglycerides	−9.70 (−14.92, −4.74)	−28.52 (−52.92, −4.13)	0.139

Values are weighted mean difference (95% confidence interval). LDL-C: low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol.

Publication bias

Visual inspection of Begg's funnel plots revealed potential publication bias in the meta-analyses of curcuminoids' effects on plasma lipid levels. Using "trim and fill" method, 7, 6, 4 and 5 potentially missing studies were identified for the meta-analyses of total cholesterol, LDL-C, HDL-C and triglycerides, respectively (Figure 6). Imputation for these missing studies led to an adjusted effect size that was statistically significant for all lipid factors (Table 4). The results of Egger's linear regression test, Begg's rank correlation test and "fail-safe N" test are summarized in Table 4.

Safety

Curcuminoids were reported to be generally safe and well tolerated in the selected studies for this meta-analysis. Few adverse events were reported in the curcuminoids group and included hot flashes, headache, skin rash, constipation, nausea, diarrhea, flatulence, abdominal pain, vomiting, feeling cold and bruising (Baum L 2007, Chuengsamarn S 2014, Mirzabeigi P 2015, Mohammadi A 2013, Panahi Y 2014a, Pungcharoenkul K 2011, Rahmani S 2016, Sukandar EY 2013, Usharani P 2008, Yang YS 2014) all of which were of mild intensity and short duration. Only one study reported insufficient information regarding adverse effects (Na LX 2013) though other trials did not provide any safety information (Alwi I 2008, DiSilvestro RA 2012, Funamoto M 2016, Pashine L 2012, Rahimi HR 2016).

Discussion

In this meta-analysis of RCTs, we found a significant decrease in triglycerides levels and an elevation in HDL-C concentrations following curcuminoids supplementation. This is in contrast to our previous meta-analysis of RCTs investigating the effects of curcumin on blood lipid levels where there appeared that curcumin did not affect serum total cholesterol, LDL-C, triglycerides and HDL-C levels (Sahebkar 2014); however, this previous meta-analysis was relatively small and underpowered compared to this study (1427 subjects from 20 RCTs) as it included only 5 studies comprising 10 treatment arms with only 133 subjects in the curcumin treatment arm and 90 in the control arm (Sahebkar 2014). The hypotriglyceridemic action of curcuminoids may be linked to their ability to increase lipoprotein lipase activity, resulting in increased hydrolysis of circulating triglyceride-rich lipoproteins and reduction of plasma triglycerides concentrations (Na LX 2013). In addition, a number of other modulatory mechanistic effects on

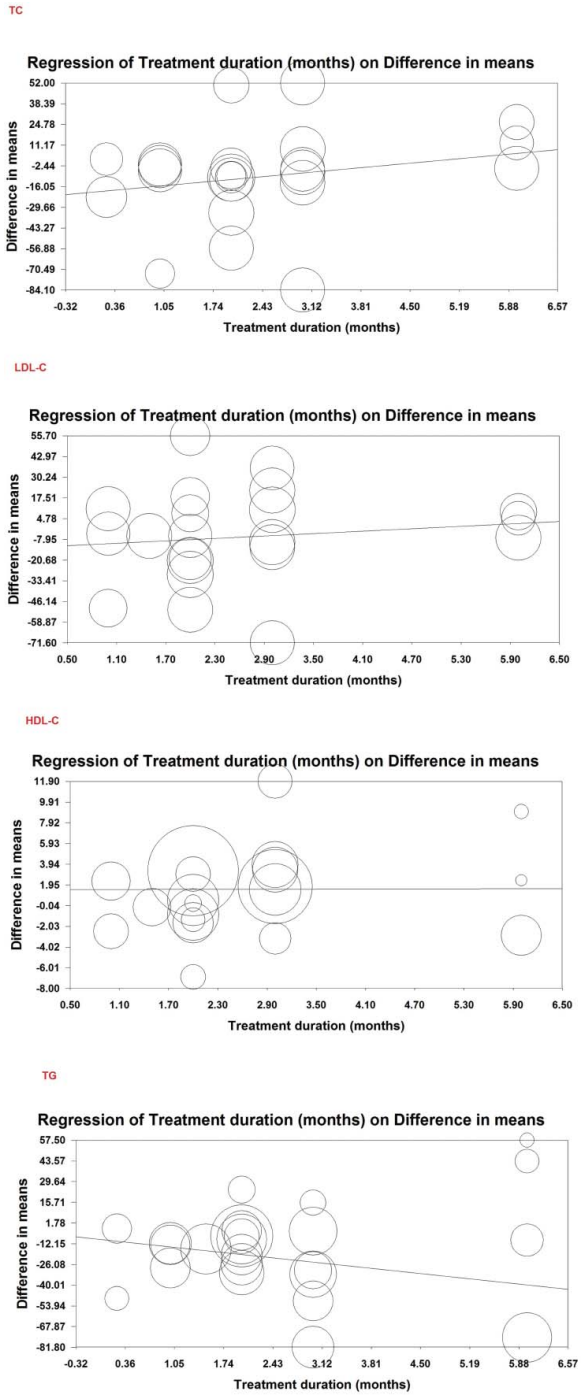

Figure 4. Meta-regression bubble plots of the association between mean changes in plasma lipids concentrations and duration of supplementation with curcuminoids. The size of each circle is inversely proportional to the variance of change.

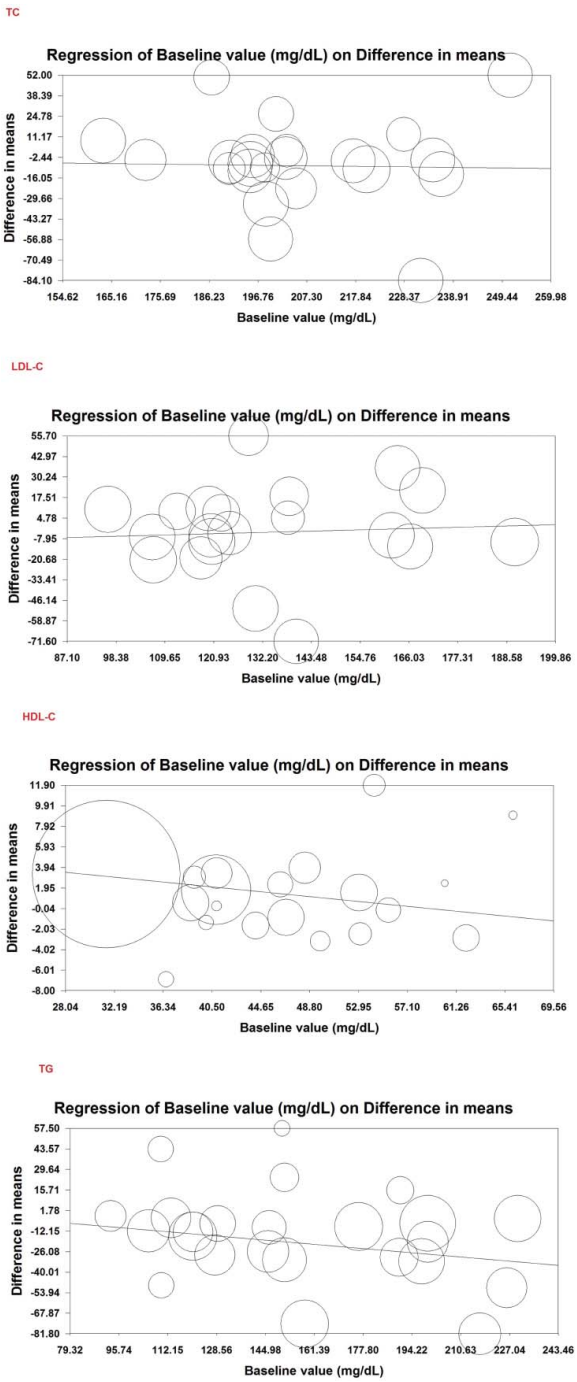

Figure 5. Meta-regression bubble plots of the association between mean changes in plasma lipids concentrations and baseline concentrations of lipids. The size of each circle is inversely proportional to the variance of change.

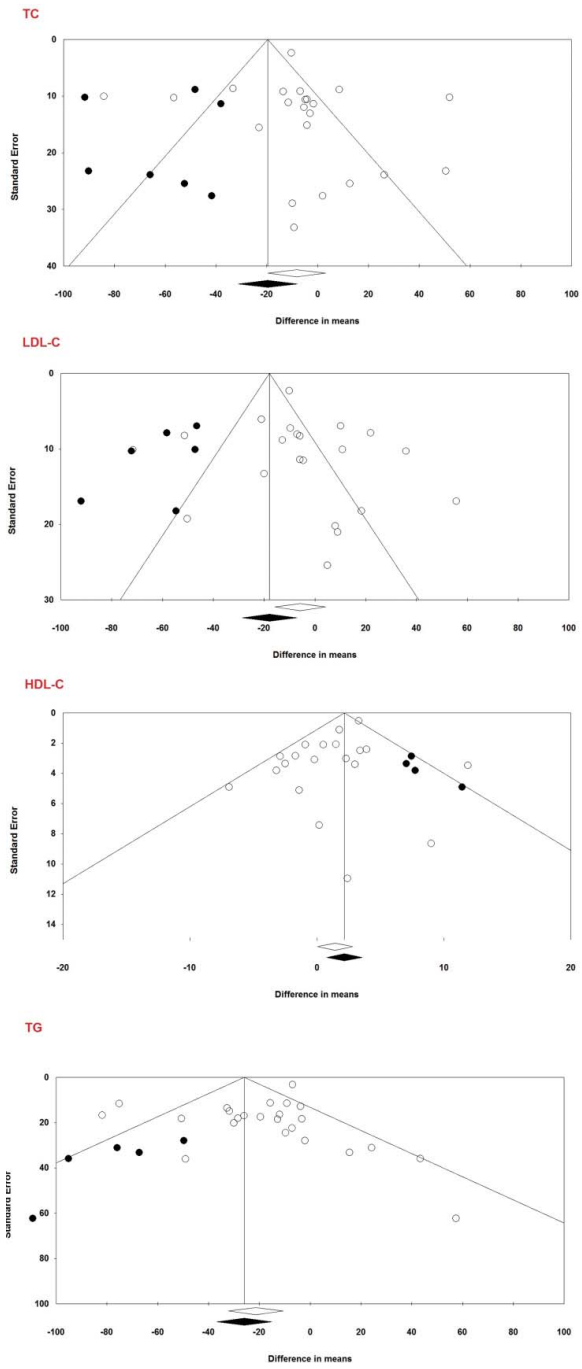

Figure 6. Funnel plot detailing publication bias in the studies reporting the impact of curcuminoids supplementation on plasma lipids concentrations.

lipogenesis, including induction of PPARα, have been described for curcuminoids (Sahebkar 2014, Um et al. 2013).

In accord with our findings, previous clinical trials have reported an increase in serum HDL-C concentrations after curcuminoids supplementation (Ramirez Boscá A 2000, Soudamini KK 1992, Yang YS 2014). Lowering of plasma triglycerides has been shown to reduce HDL clearance by lipases (Gomaraschi et al. 2015, Lamarche et al. 1999), and therefore the curcuminoid-induced reduction of plasma triglycerides is likely to have driven a concurrent increase in plasma HDL-C levels. In addition, curcuminoids have been shown in experimental studies to enhance several indices of HDL functionality that may reflect a better indicator for HDL status compared with the level of HDL-C (Ganjali et al. 2017), these include overexpression of ABCG1 leading to an increase in HDL-dependent cholesterol efflux and an elevation of HDL-C levels (Peschel D 2007), suggesting a potential cardioprotective property for this natural product. However, the curcumin effect increasing HDL-C levels was modest, and influenced by some studies in the leave-one-out sensitivity analysis.

The combined effect of curcuminoids to reduce plasma triglyceride and to raise HDL-C levels may be of clinical relevance. Evidence from epidemiological, genome-wide

Table 4. Assessment of publication bias in the meta-analysis of curcuminoids' effects on plasma lipids.

	No. missing studies	Imputed effect size	Begg's rank correlation test (*p*-value)	Egger's linear regression test (*p*-value)	fail-safe N[a]
TC	7	−19.64 (−31.32, −7.95)	0.499	0.717	77
LDL-C	6	−17.85 (−28.60, −7.10)	0.415	0.560	49
HDL-C	4	2.17 (0.77, 3.57)	1.000	0.066	24
TG	5	−25.92 (−36.73, −15.10)	0.107	0.273	202

TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TG: triglycerides.
[a] Number of potentially missing studies required to bring the *p*-value to a non-significant level.

association and Mendelian randomization studies suggested that triglycerides and triglyceride-rich lipoproteins are causally associated with the risk of atherosclerotic CVD. In addition there is consistent evidence suggesting that atherogenic dyslipidemia, characterized by elevated triglycerides and low levels of HDL-C, is common in patients with CVD and contributes to CV residual risk (Chapman et al. 2010, Fruchart et al. 2008). Hence, the presence of high triglyceride levels, possibly when accompanied by low HDL-C levels, might represent an important therapeutic target particularly in statin-treated patients with a high residual CV risk (Budoff 2016, Maki and Dicklin 2017). However, whether the modest increase in plasma HDL-C shown here has clinical relevance is unclear, particularly taking into account the recent evidence suggesting that isolated HDL-C reduction is currently not a valid target for drug therapy (Marz et al. 2017), although clarification is likely when Anacetrapib (REVEAL) trial reports on the benefit from raising HDL-C (Landray et al. 2017) .

Several *in vitro* and *in vivo* studies have proposed multiple molecular mechanisms for the lipid-modifying properties of curcuminoids such as free radical scavenging, modification of transduction signals (Akt, AMPK), and modulation of the activity of specific transcription factors (FOXO1/3a, NRF2, SREBP1/2, CREB, CREBH, PPARγ, and LXRα) that regulate the expression of genes linked to free radical scavenging (catalase, MnSOD, and heme oxygenase-1) and lipid homeostasis (aP2/FABP4, CD36, HMG-CoA reductase and carnitine palmitoyl transferase-I) (Zingg JM 2013). Whilst several studies included in the meta-analysis showed significant LDL-C reduction following curcuminoids supplementation, the estimated pooled effect size in the present meta-analysis did not suggest a significant alteration of plasma LDL-C levels. Whether the type of curcuminoids administered, the doses used and the short duration of supplementation reflected this lack of efficacy on LDL-C-lowering needs further clarification.

Limitations of the current meta-analysis include the short treatment period (<2 months) for some studies (Cox KH 2015, DiSilvestro RA 2012, Mohammadi A 2013, Pungcharoenkul K 2011) that was of insufficient duration to affect the lipid parameters. Several included studies used unformulated curcuminoids that may have low systemic bioavailability and therefore their lipid effects may have been limited. In addition, the trials differed with respect to the target population and characteristics; hence, despite a random-effects model of analysis that was applied to reduce the inter-study heterogeneity, heterogeneity could still have an impact.

In conclusion, the results of this meta-analysis suggested a significant reduction in plasma concentrations of triglycerides and an increase in HDL-C levels following curcuminoids supplementation, though the clinical relevance of these observations needs clarification through targeted clinical trials with standardized curcuminoid preparations.

Conflict of interests

Dr. Gotto is a consultant for Merck, Kowa, Amgen and a board member of Esperion, Aegerion and Arisaph. Dr. Banach has served on speaker's bureau and as an advisory board member for Amgen, Sanofi-Aventis and Lilly. Dr. Majeed is the Founder & Chairman of Sabinsa Corporation and Sami Labs Limited.

Author contributions

LES and AS contributed to literature search, article screening, data acquisition and abstraction. AS contributed to statistical analysis. LES, AS and MM contributed to interpretation of the results and drafting of the manuscript. MB, MP, AMG and SLA contributed to critical revision of the manuscript. All authors approved the final version of the manuscript for submission.

ORCID

Matteo Pirro http://orcid.org/0000-0002-5527-4821
Amirhossein Sahebkar http://orcid.org/0000-0002-8656-1444

References

A., S. 2013. Why it is necessary to translate curcumin into clinical practice for the prevention and treatment of metabolic syndrome? *Biofactors* 39:197–208. doi:10.1002/biof.1062.

A., S. 2014. Are curcuminoids effective C-reactive protein-lowering agents in clinical practice? Evidence from a meta-analysis. *Phytother Res* 28:633–642. doi:10.1002/ptr.5045.

Alwi I, S. T., S. Suyono, B. Sutrisna, F. D. Suyatna, S. B. Kresno, and S. Ernie. 2008. The effect of curcumin on lipid level in patients with acute coronary syndrome. *Acta Med Indones* 40:201–210.

Anand P, K. A., R. A. Newman, and B. B. Aggarwal. 2007. Bioavailability of curcumin: problems and promises. *Mol Pharm* 4:807–818. doi:10.1021/mp700113r.

Arca M, M. A., S. Valiante, F. Campagna, G. Pigna, V. Paoletti, R. Antonini, F. Barillà, G. Tanzilli, A. Vestri, and C. Gaudio. 2007. Usefulness of atherogenic dyslipidemia for predicting cardiovascular risk in patients with angiographically defined coronary artery disease. *Am J Cardiol* 100:1511–1516. doi:10.1016/j.amjcard.2007.06.049.

Baigent C, K. A., P. M. Kearney, L. Blackwell, G. Buck, C. Pollicino, A. Kirby, T. Sourjina, R. Peto, R. Collins, and R. Simes; Cholesterol Treatment Trialists' (CTT) Collaborators. 2005. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 366:1267–1278.

Baum L, C. S., V. C. Mok, L. C. Lam, V. P. Leung, E. Hui, C. C. Ng, M. Chow, P. C. Ho, S. Lam, J. Woo, H. F. Chiu, W. Goggins, B. Zee, A. Wong, H. Mok, W. K. Cheng, C. Fong, J. S. Lee, M. H. Chan, S. S. Szeto, V. W. Lui, J. Tsoh, T. C. Kwok, I. H. Chan, and C. W. Lam. 2007.

Curcumin effects on blood lipid profile in a 6-month human study. *Pharmacol Res* 56:509–514. doi:10.1016/j.phrs.2007.09.013.

Budoff, M. 2016. Triglycerides and Triglyceride-Rich Lipoproteins in the Causal Pathway of Cardiovascular Disease. *The American journal of cardiology* Jul 01;118:138–145. doi:10.1016/j.amjcard.2016.04.004.

Chapman, M. J., J. S. Redfern, M. E. McGovern, and P. Giral. 2010. Niacin and fibrates in atherogenic dyslipidemia: pharmacotherapy to reduce cardiovascular risk. *Pharmacology & therapeutics* Jun;126:314–345. doi:10.1016/j.pharmthera.2010.01.008.

Chuengsamarn S, R. S., B. Phonrat, R. Tungtrongchitr, and S. Jirawatnotai. 2014. Reduction of atherogenic risk in patients with type 2 diabetes by curcuminoid extract: a randomized controlled trial. *J Nutr Biochem* 25:144–150. doi:10.1016/j.jnutbio.2013.09.013.

Cox KH, P. A., and A. B. Scholey. 2015. Investigation of the effects of solid lipid curcumin on cognition and mood in a healthy older population. *J Psychopharmacol* 29:642–651. doi:10.1177/0269881114552744.

DiSilvestro RA, J. E., S. Zhao, and J. Bomser. 2012. Diverse effects of a low dose supplement of lipidated curcumin in healthy middle aged people. *Nutr J* 11:79. doi:10.1186/1475-2891-11-79.

Duval S, T. R. 2000. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* 56:455–463. doi:10.1111/j.0006-341X.2000.00455.x.

Fruchart, J. C., F. Sacks, M. P. Hermans, G. Assmann, W. V. Brown, R. Ceska, M. J. Chapman, P. M. Dodson, P. Fioretto, and H. N. Ginsberg, et al. 2008. The Residual Risk Reduction Initiative: a call to action to reduce residual vascular risk in patients with dyslipidemia. *The American journal of cardiology* Nov 17;102:1K–34K. doi:10.1016/j.amjcard.2008.10.002.

Funamoto M, S. Y., Y. Katanasaka, Y. Miyazaki, A. Imaizumi, H. Kakeya, H. Yamakage, N. Satoh-Asahara, M. Komiyama, H. Wada, K. Hasegawa, and T. Morimoto. 2016. Highly absorptive curcumin reduces serum atherosclerotic low-density lipoprotein levels in patients with mild COPD. *Int J Chron Obstruct Pulmon Dis* 11:2029–2034. doi:10.2147/COPD.S104490.

Ganjali, S., C. N. Blesso, M. Banach, M. Pirro, M. Majeed, and A. Sahebkar. 2017. Effects of curcumin on HDL functionality. *Pharmacological research* Feb 10;119:208–218. doi:10.1016/j.phrs.2017.02.008.

Ganjali, S., A. Sahebkar, E. Mahdipour, K. Jamialahmadi, S. Torabi, S. Akhlaghi, G. Ferns, S. M. Parizadeh, and M. Ghayour-Mobarhan. 2014. Investigation of the effects of curcumin on serum cytokines in obese individuals: a randomized controlled trial. *TheScientificWorldJournal* 2014:898361. doi:10.1155/2014/898361.

Gomaraschi, M., M. P. Adorni, M. Banach, F. Bernini, G. Franceschini, and L. Calabresi. 2015. Effects of established hypolipidemic drugs on HDL concentration, subclass distribution, and function. *Handbook of experimental pharmacology* 224:593–615. doi:10.1007/978-3-319-09665-0_19.

Higgins JPT, G. S., eds. 2009. *Cochrane Handbook for Systematic Reviews of Interventions* London.

Hozo SP, D. B., and I. Hozo. 2005. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol* 5:13.

Johnston, T. P., T. A. Korolenko, M. Pirro, and A. Sahebkar. 2017. Preventing cardiovascular heart disease: Promising nutraceutical and non-nutraceutical treatments for cholesterol management. *Pharmacological research* Jun;120:219–225.

Kocher A, B. L., C. Schiborr, and J. Frank 2016. Highly bioavailable micellar curcuminoids accumulate in blood, are safe and do not reduce blood lipids and inflammation markers in moderately hyperlipidemic individuals. *Mol Nutr Food Res* 60:1555–1563.

Lamarche, B., S. Rashid, and G. F. Lewis. 1999. HDL metabolism in hypertriglyceridemic states: an overview. *Clinica chimica acta; international journal of clinical chemistry* Aug;286:145–161.

Landray, M. J., Reveal Collaborative G, L. Bowman FCESJCHKWW-SEV-MSWCPCEBRC. 2017. Randomized Evaluation of the Effects of Anacetrapib through Lipid-modification (REVEAL)-A large-scale, randomized, placebo-controlled trial of the clinical effects of anacetrapib among people with established vascular disease: Trial design, recruitment, and baseline characteristics. *American heart journal* May;187:182–190.

Maki, K. C., and M. R. Dicklin. 2017. Do triglyceride-lowering drugs decrease risk of cardiovascular disease? *Current opinion in lipidology* 28 (4):374–379.

Manjunatha H, S. K. 2007. Hypolipidemic and antioxidant effects of dietary curcumin and capsaicin in induced hypercholesterolemic rats. *Lipids* 42:1133–1142.

Martin RC, A. H., D. Malik, and Y. Li. 2012. Effect on pro-inflammatory and antioxidant genes and bioavailable distribution of whole turmeric vs curcumin: Similar root but different effects. *Food Chem Toxicol* 50:227–231.

Marz, W., M. E. Kleber, H. Scharnagl, T. Speer, S. Zewinger, A. Ritsch, K. G. Parhofer, A. von Eckardstein, U. Landmesser, and U. Laufs. 2017. HDL cholesterol: reappraisal of its clinical relevance. *Clinical research in cardiology: official journal of the German Cardiac Society* Mar 24. doi:10.1007/s00392-017-1106-1. [Epub ahead of print]

Mirzabeigi P, M. A., M. Salarifar, K. Gholami, M. Mojtahedzadeh, and M. R. Javadi. 2015. The Effect of Curcumin on some of Traditional and Non-traditional Cardiovascular Risk Factors: A Pilot Randomized, Double-blind, Placebo-controlled Trial. *Iran J Pharm Res* 14:479–486.

Mohammadi A, S. A., M. Iranshahi, M. Amini, R. Khojasteh, M. Ghayour-Mobarhan, and G. A. Ferns. 2013. Effects of supplementation with curcuminoids on dyslipidemia in obese patients: a randomized crossover trial. *Phytother Res* 27:374–379. doi:10.1002/ptr.4715.

Moher, D., A. Liberati, J. Tetzlaff, D. G. Altman, and P. Group. 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Bmj* Jul 21;339:b2535. doi:10.1136/bmj.b2535.

Na LX, L. Y., H. Z. Pan, X. L. Zhou, D. J. Sun, M. Meng, X. X. Li, and C. H. Sun. 2013. Curcuminoids exert glucose-lowering effect in type 2 diabetes by decreasing serum free fatty acids: a double-blind, placebo-controlled trial. *Mol Nutr Food Res* 57:1569–1577. doi:10.1002/mnfr.201200131.

Panahi Y, A. G., S. Parvin, and A. Sahebkar. 2016a. Mitigation of Systemic Oxidative Stress by Curcuminoids in Osteoarthritis: Results of a Randomized Controlled Trial. *J Diet Suppl* 13:209–220. doi:10.3109/19390211.2015.1008611.

Panahi Y, B. R., G. R. Karami, and A. Sahebkar. 2015a. Investigation of the efficacy of adjunctive therapy with bioavailability-boosted curcuminoids in major depressive disorder. *Phytother Res* 29:17–21. doi:10.1002/ptr.5211.

Panahi Y, G. M., S. Bashiri, A. Hajihashemi, and A. Sahebkar. 2015b. Short-term Curcuminoid Supplementation for Chronic Pulmonary Complications due to Sulfur Mustard Intoxication: Positive Results of a Randomized Double-blind Placebo-controlled Trial. *Drug Res (Stuttg)* 65:567–573.

Panahi Y, K. N., M. S. Hosseini, M. Abbasinazari, and A. Sahebkar. 2014a. Lipid-modifying effects of adjunctive therapy with curcuminoids-piperine combination in patients with metabolic syndrome: results of a randomized controlled trial. *Complement Ther Med* 22:851–857. doi:10.1016/j.ctim.2014.07.006.

Panahi Y, K. N., E. Sahebi, S. Namazi, Z. Reiner, M. Majeed, and A. Sahbekar. 2017. Curcuminoids modify lipid profile in type 2 diabetes mellitus: A randomized controlled trial. *Complement Ther Med* 33:1–5. doi:10.1016/j.ctim.2017.05.006.

Panahi Y, K. P., R. Mohtashami, R. Jafari, L. E. Simental-Mendía, and A. Sahebkar. 2016b. Curcumin Lowers Serum Lipids and Uric Acid in Subjects With Nonalcoholic Fatty Liver Disease: A Randomized Controlled Trial. *J Cardiovasc Pharmacol* 68:223–229. doi:10.1097/FJC.0000000000000406.

Panahi Y, S. A., M. Amiri, S. M. Davoudi, F. Beiraghdar, S. L. Hoseininejad, and M. Kolivand. 2012. Improvement of sulphur mustard-induced chronic pruritus, quality of life and antioxidant status by curcumin: results of a randomised, double-blind, placebo-controlled trial. *Br J Nutr* 108:1272–1279. doi:10.1017/S0007114511006544.

Panahi Y, S. A., F. Beiraghdar, and A. Sahebkar. 2014b. Adjuvant therapy with bioavailability-boosted curcuminoids suppresses systemic inflammation and improves quality of life in patients with solid tumors: a randomized double-blind placebo-controlled trial. *Phytother Res* 28:1461–1467. doi:10.1002/ptr.5149.

Pashine L, S. J., A. K. Vaish, S. K. Ojha, and A. Mehdi. 2012. Effect of turmeric (curcuma longa) on overweight hyperlipidemic subjects: double blind study. *Indian J Community Health* 24:113–117.

Peschel D, K. R., N. Nass. 2007. Curcumin induces changes in expression of genes involved in cholesterol homeostasis. *J Nutr Biochem* 18:113–119. doi:10.1016/j.jnutbio.2006.03.007.

Pirro, M., M. R. Mannarino, V. Bianconi, L. E. Simental-Mendia, F. Bagaglia, E. Mannarino, and A. Sahebkar. 2016. The effects of a nutraceutical combination on plasma lipids and glucose: A systematic review and meta-analysis of randomized controlled trials. *Pharmacological research* Aug;110:76–88. doi:10.1016/j.phrs.2016.04.021.

Pirro, M., C. Vetrani, C. Bianchi, M. R. Mannarino, F. Bernini, and A. A. Rivellese. 2017. Joint position statement on "Nutraceuticals for the treatment of hypercholesterolemia" of the Italian Society of Diabetology (SID) and of the Italian Society for the Study of Arteriosclerosis (SISA). *Nutrition, metabolism, and cardiovascular diseases: NMCD* Jan;27:2–17. doi:10.1016/j.numecd.2016.11.122.

Pungcharoenkul K, T. P. 2011. Effect of different curcuminoid supplement dosages on total in vivo antioxidant capacity and cholesterol levels of healthy human subjects. *Phytother Res* 25:1721–1726. doi:10.1002/ptr.3608.

Rahimi HR, M. A., M. Dastani, M. R. Jaafari, K. Abnous, M. Ghayour Mobarhan, and R. Kazemi Oskuee. 2016. The effect of nano-curcumin on HbA1c, fasting blood glucose, and lipid profile in diabetic subjects: a randomized clinical trial. *Avicenna J Phytomed* 6:567–577.

Rahmani S, A. S., G. Askari, M. Keshvari, M. Hatamipour, A. Feizi, and A. Sahebkar. 2016. Treatment of Non-alcoholic Fatty Liver Disease with Curcumin: A Randomized Placebo-controlled Trial. *Phytother Res* 30:1540–1548. doi:10.1002/ptr.5659.

Ramirez Boscá A, S. A., M. A. Carrión-Gutiérrez, D. Pamies Mira, J. Pardo Zapata, J. Diaz-Alperi, A. Bernd, A. E. Quintanilla, and J. Miquel 2000. An hydroalcoholic extract of Curcuma longa lowers the abnormally high values of human-plasma fibrinogen. *Mech Ageing Dev*. 114:207–210. doi:10.1016/S0047-6374(00)00089-0.

Sahebkar, A. 2014. Curcuminoids for the management of hypertriglyceridaemia. *Nature reviews Cardiology* Feb;11:123. doi:10.1038/nrcardio.2013.140-c1.

Sahebkar A, M. A., A. Atabati, S. Rahiman, S. Tavallaie, M. Iranshahi, S. Akhlaghi, G. A. Ferns, and M. Ghayour-Mobarhan 2013. Curcuminoids modulate pro-oxidant-antioxidant balance but not the immune response to heat shock protein 27 and oxidized LDL in obese individuals. *Phytother Res* 27:1883–1888. doi:10.1002/ptr.4952.

Sampson, U. K., S. Fazio, and M. F. Linton. 2012. Residual cardiovascular risk despite optimal LDL cholesterol reduction with statins: the evidence, etiology, and therapeutic challenges. *Current atherosclerosis reports* Feb;14:1–10. doi:10.1007/s11883-011-0219-7.

Shin SK, H. T., R. A. McGregor, and M. S. Choi. 2011. Long-term curcumin administration protects against atherosclerosis via hepatic regulation of lipoprotein cholesterol metabolism. *Mol Nutr Food Res* 55:1829–1840. doi:10.1002/mnfr.201100440.

Shishodia S, S. G., B. B. Aggarwal. 2005. Curcumin: getting back to the roots. *Ann N Y Acad Sci* 1056:206–217. doi:10.1196/annals.1352.010.

Sirimarco, G., J. Labreuche, E. Bruckert, L. B. Goldstein, K. M. Fox, P. M. Rothwell, and P. Amarenco, Perform, Investigators S, Committees. 2014. Atherogenic dyslipidemia and residual cardiovascular risk in statin-treated patients. *Stroke* May;45:1429–1436. doi:10.1161/STROKEAHA.113.004229.

Soudamini KK, U. M., K. B. Soni, and R. Kuttan. 1992. Inhibition of lipid peroxidation and cholesterol levels in mice by curcumin. *Indian J Physiol Pharmacol* 36:239–243.

Stone NJ, R. J., A. H. Lichtenstein, C. N. Bairey Merz, C. B. Blum, R. H. Eckel, A. C. Goldberg, D. Gordon, D. Levy, D. M. Lloyd-Jones, P. McBride, J. S. Schwartz, S. T. Shero, S. C. Smith, Jr, K. Watson, P. W. Wilson, K. M. Eddleman, N. M. Jarrett, K. LaBresh, L. Nevo, J. Wnek, J. L. Anderson, J. L. Halperin, N. M. Albert, B. Bozkurt, R. G. Brindis, L. H. Curtis, D. DeMets, J. S. Hochman, R. J. Kovacs, E. M. Ohman, S. J. Pressler, F. W. Sellke, W. K. Shen, S. C. Smith, Jr, and G. F. Tomaselli; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2014. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 129:S1–45. doi:10.1161/01.cir.0000437738.63853.7a.

Sukandar EY, S. P., J. I. Sigit, N. P. E. Leliqia, and F. Lestari. 2013. Safety of Garlic (Allium Sativum) and Turmeric (Curcuma domestica) Extract in Comparison with Simvastatin on Improving Lipid Profile in Dyslipidemia Patients. *Journal of Medical Sciences* 13:10–18. doi:10.3923/jms.2013.10.18.

Taylor F, H. M., A. F. Macedo, T. H. Moore, M. Burke, G. Davey Smith, K. Ward, and S. Ebrahim. 2013. Statins for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev.1*:CD004816.

Um, M. Y., K. H. Hwang, J. Ahn, and T. Y. Ha. 2013. Curcumin attenuates diet-induced hepatic steatosis by activating AMP-activated protein kinase. *Basic & clinical pharmacology & toxicology* Sep;113:152–157. doi:10.1111/bcpt.12076.

Usharani P, M. A., M. U. Naidu, Y. S. Raju, and N. Chandra. 2008. Effect of NCB-02, atorvastatin and placebo on endothelial function, oxidative stress and inflammatory markers in patients with type 2 diabetes mellitus: a randomized, parallel-group, placebo-controlled, 8-week study. *Drugs R D* 9:243–250. doi:10.2165/00126839-200809040-00004.

Vrecer M, T. S., J. Drinovec, and A. Mrhar. 2003. Use of statins in primary and secondary prevention of coronary heart disease and ischemic stroke. *Meta-analysis of randomized trials. Int J Clin Pharmacol Ther* 41:567–577. doi:10.5414/CPP41567.

Wan X, W. W., J. Liu, and T. Tong. 2014. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol* 14:135. doi:10.1186/1471-2288-14-135.

Yang YS, S. Y., H. W. Yang, Y. H. Lee, J. I. Chou, and K. C. Ueng. 2014. Lipid-lowering effects of curcumin in patients with metabolic syndrome: a randomized, double-blind, placebo-controlled trial. *Phytother Res* 28:1770–1777. doi:10.1002/ptr.5197.

Yusuf S, R. S., S. Ounpuu, and S. Anand. 2001. Global burden of cardiovascular diseases: part I: general considerations, the epidemiologic transition, risk factors, and impact of urbanization. *Circulation* 104:2746–2753. doi:10.1161/hc4601.099487.

Ž., R. 2013. Statins in the primary prevention of cardiovascular disease. *Nat Rev Cardiol* 10:453–464. doi:10.1038/nrcardio.2013.80.

Zingg JM, H. S., and M. Meydani. 2013. Molecular mechanisms of hypolipidemic effects of curcumin. *Biofactors* 39:101–121. doi:10.1002/biof.1072.