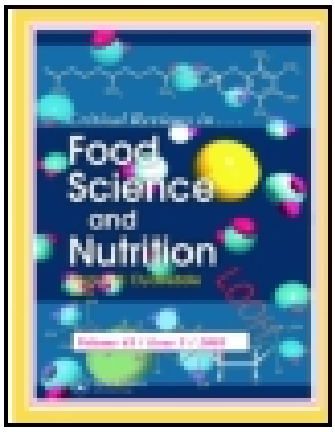

Critical Reviews in Food Science and Nutrition
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/bfsn20

Effects of Quercetin Supplementation on Lipid Profile: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Amirhossein Sahebkar Pharm.D, Ph.D[ab]
[a] Biotechnology Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
[b] Cardiovascular Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
Accepted author version posted online: 21 Apr 2015.

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Amirhossein Sahebkar, Pharm.D, Ph.D

[a]*Biotechnology Research Center, Mashhad University of Medical Sciences, Mashhad, Iran.*

[b]*Cardiovascular Research Center, Mashhad University of Medical Sciences, Mashhad, Iran.*

***Correspondence:**

- Amirhossein Sahebkar, Biotechnology Research Center, Mashhad University of Medical Sciences, Mashhad 91775-1365, Iran. Tel: +98 511 8823255-66; Fax: +98 511 8823251; E-mail: amir_saheb2000@yahoo.com

Running Title: Effect of quercetin on blood lipids

Declaration of Interest: The author has no competing interests to declare.

Abstract word count: 350

Manuscript text word count: 3815

Number of Tables: 4

Number of Figures: 5

Number of references: 77

Abbreviations

ACVD	Atherosclerotic cardiovascular disease
BMI	Body mass index
CI	Confidence interval
CMA	Comprehensive meta-analysis
HDL-C	High-density lipoprotein cholesterol
HOMA-IR	Homeostasis model assessment-estimated insulin resistance
LDL-C	Low-density lipoprotein cholesterol
SD	Standard deviation
SEM	Standard error of the mean
WMD	Weighed mean difference

Abstract

Background: In spite of promising experimental findings, randomized controlled trials (RCTs) have yielded mixed results on the impact of quercetin supplementation on plasma lipid levels.

Aim: The present study aimed to quantify the effects of quercetin on plasma lipids using a meta-analysis of RCTs.

Methods: A systematic literature search of Medline was conducted for RCTs that investigated the efficacy of quercetin supplementation on plasma lipids comprising total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides. Weighted mean differences (WMDs) and 95% confidence intervals (CIs) were calculated for net changes in lipid concentrations using a random-effects model. Meta-regression analysis was conducted to assess the effect of quercetin dose and duration of supplementation as moderators on the calculated effect measures.

Results: Five RCTs totaling 442 subjects (221 in the quercetin and 221 in the control group) fulfilled the eligibility criteria and selected for analyses. Combined estimate of effect size for the impact of quercetin on plasma LDL-C (WMD: 1.43 mg/dL, 95% CI: -0.92-3.78, $p = 0.23$), HDL-C (WMD: 0.26 mg/dL, 95% CI: -0.74-1.25, $p = 0.61$) and triglycerides (WMD: -9.42 mg/dL, 95% CI: -27.80-8.96, $p = 0.32$) was not statistically significant. However, a borderline significant but clinically non-relevant increase in total cholesterol was observed (WMD: 3.13 mg/dL, 95% CI: -0.01-6.27, $p = 0.05$). When the analysis was confined to the subgroups of studies with quercetin doses $\geq$ 500 mg/day and follow-up of $\geq$ 4 weeks, a significant increase in total cholesterol (WMD: 3.57 mg/dL, 95% CI: 0.21-6.92, $p = 0.04$) and a decline in triglycerides (WMD: -24.54 mg/dL, 95% CI: -33.09 to -15.99, $p < 0.00001$) was observed, but LDL-C and

HDL-C concentrations remained unchanged ($p > 0.05$). Changes in plasma triglycerides, but not other indices of lipid profile, were significantly associated with quercetin dose (slope: -0.057; 95% CI: -0.103 to -0.010; $p = 0.02$) and duration of supplementation (slope: -5.314; 95% CI: -9.482 to -1.147; $p = 0.01$).

Conclusion: Available evidence from RCTs does not suggest any clinically relevant effect of quercetin supplementation on plasma lipids, apart from a significant reduction of triglycerides at doses above 50 mg/day.

Keywords: Flavonoid; Polyphenol; Systematic review; Dyslipidemia; Cardiovascular disease.

Introduction

Accumulating evidence over the past decades has shown that circulating lipid concentrations is a major determinant of the risk of atherosclerotic cardiovascular disease (ACVD) [1-3]. Dyslipidemia is a leading, yet modifiable, risk factor for ACVD that is characterized by increased plasma levels of low-density lipoprotein cholesterol (LDL-C) and/or triglycerides, and/or diminished levels of high-density lipoprotein cholesterol (HDL-C). Although several classes of lipid-modifying agents are available, the efficacy of such agents to achieve optimal lipid targets is limited [4]. Besides, there are safety concerns associated with the use of statins and fibrates, as the most widely used hypolipidemic drugs, due to the incidence of adverse effects such as myopathy and hepatotoxicity [5, 6]. Given these drawbacks, there has been a surge of interest to find new agents with lipid-modifying properties to be used as adjuncts to low-dose statins in patients who cannot tolerate higher doses [7-11]. Natural products with lipid-modifying properties often possess several pleiotropic properties important for the proper functioning of CV system and have greater safety compared to the chemically synthesized agents [12-16].

Flavonoids are a superfamily of phytochemicals with over 6000 identified compounds that are regarded as the most potent naturally occurring antioxidants [17]. Flavonoids are produced ubiquitously in plants as secondary metabolites and are structurally classified into flavones, flavonols, flavanones, flavanols (catechins), isoflavones and anthocyanidins [18, 19]. Based on the epidemiological findings, dietary intake of flavonoids is inversely associated with the risk of CVD [20-23]. One of the major dietary flavonoids is quercetin (2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-chromen-4-one) [24]. Quercetin belongs to the flavonol subclass of flavonoids

and is abundantly found in fruits, vegetables, wine and tea [25]. Extensive *in vitro* and experimental research during the past three decades has identified quercetin as one of the most promising antioxidant and anti-inflammatory natural products [26]. Quercetin possesses direct free radical scavenging properties, inhibits lipid peroxidation and down-regulates the activity and/or expression of several critical enzymes involved in the production of oxidant species e.g. inducible nitric oxide synthase and xanthine oxidase [26-29]. Furthermore, quercetin can attenuate the expression of pro-inflammatory cytokines, inhibit NF-κB, cyclooxygenase and lipoxygenase [26, 29, 30]. Owing to these antioxidant and anti-inflammatory properties, quercetin can serve as a versatile molecule in promoting cardiovascular health. A plethora of cardioprotective properties have been reported for quercetin which include anti-atherosclerotic [31, 32], endothelial function-improving [33, 34], vasodialtory [35], anti-thrombotic [36] and hypotensive properties [37]. In addition, animal studies have shown that quercetin supplementation can modulate circulating levels of lipoproteins [38-40]. Nonetheless, clinical trials investigating the anti-dyslipidemic properties of quercetin have shown mixed results [41-48]. Since most of the performed trials suffer from small population size, the present study aimed to provide a conclusive effect size for quercetin on plasma lipid concentrations by meta-analysis of available evidence.

Methods

Search Strategy

This study was designed according to the guidelines of the 2009 preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement [49]. Medline

(http://www.ncbi.nlm.nih.gov/pubmed) was searched using the combination of following search terms in titles and abstracts: (hyperlipidemia OR hyperlipidaemia OR hyperlipidemic OR hyperlipidaemic OR hypolipidemic OR hypolipidaemic OR dyslipidemia OR dyslipidaemia OR dyslipidemic OR dyslipidaemic OR hypercholesterolemia OR hypercholesterolaemia OR hypercholesterolemic OR hypercholesterolaemic OR hypocholesterolemic OR hypocholesterolaemic OR "low-density lipoprotein" OR "high-density lipoprotein" OR cholesterol OR triglycerides OR hypertriglyceridemia OR hypertriglyceridaemia OR hypotriglyceridemic OR hypotriglyceridaemic) AND (quercetin). The search was limited to studies in humans. The literature was searched from inception to July 10, 2013. Selected articles were hand searched to identify further relevant studies.

Study Selection

Original studies were included if they met the following inclusion criteria: i) be a randomized clinical case-control or case-cross-over trial, ii) investigated the impact of quercetin on any of the lipid profile parameters including total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides, iii) having an appropriate controlled design, and iv) presentation of sufficient information on plasma/serum lipid levels at baseline and at the end of study in both quercetin and control groups. Exclusion criteria were i) non-clinical studies, ii) lack of control group, iii) presenting no evidence of randomization, iv) using quercetin-containing extracts or mixture of quercetin with other bioflavonoids/agents without appropriate masking, and v) lack of sufficient information on lipid levels. Exclusion of

an article for the latter reason was done if no feedback was received after contacting the author(s).

Data extraction

Eligible studies were reviewed and the following data were abstracted: 1) first author's name; 2) year of publication; 3) study location; 4) number of participants in the case and control groups; 5) age, gender and body mass index (BMI) of study participants; 6) circulating concentrations of total cholesterol, LDL-C, HDL-C, triglycerides, high-sensitivity C-reactive protein (hs-CRP) and glucose; and 7) systolic and diastolic blood pressures.

Quality assessment

Eligible studies were systematically assessed for potential risk of bias using instructions described in the Cochrane Handbook for Systematic Reviews of Interventions [50]. The items used for the assessment of each study were adequacy of sequence generation, allocation concealment, blinding, addressing drop-outs (incomplete outcome data), selective outcome reporting, and other potential sources of bias. According to the recommendations of the Cochrane Handbook, a judgment of “Yes” was indicative of low risk of bias, whilst “No” indicated high risk of bias. Labeling as ’Unclear’ indicated unclear or unknown risk of bias.

Quantitative Data Synthesis

Meta-analysis was conducted using the Cochrane Program Review Manager version 5.1 (Cochrane Collaboration, Oxford, UK). Blood lipid and glucose levels were collated in mg/dL. A

multiplication by 38.6, 88.5 or 18.0 was used to convert cholesterol (total cholesterol, HDL-C or LDL-C), triglyceride and glucose levels expressed in mmol/L into mg/dL, respectively. Standard deviations (SDs) of the mean difference were calculated using the following formula: SD = square root [$(SDpre\text{-}treatment)^2$ + $(SDpost\text{-}treatment)^2$ – (2R × SDpre-treatment × SDpost-treatment)], assuming a correlation coefficient (R) = 0.5. In case of reporting SEM, SD was estimated using the following formula: SD = SEM × sqrt (*n*), where *n* is the number of subjects. Net changes in measurements (change scores) were calculated for parallel and cross-over trials, as follows: (measure at end of follow-up in the treatment group − measure at baseline in the treatment group) − (measure at end of follow-up in the control group − measure at baseline in the control group). A random-effects model and the generic inverse variance method were used to compensate for the heterogeneity of studies in terms of design (parallel or cross-over), quercetin dose, duration of quercetin supplementation and demographic characteristics of included populations (underlying disease, age, gender and etc). Effect size was expressed as weighed mean difference (WMD) and 95% confidence interval (CI). In order to evaluate the influence of each study on the overall effect size, sensitivity analysis was conducted using the one-study remove (leave-one-out) approach [51]. Heterogeneity analysis was performed using the Cochran Q test and I2 index [51].

Meta-regression

Random-effects meta-regression was performed using unrestricted maximum likelihood method to evaluate the association between calculated net changes in plasma lipids (total cholesterol,

HDL-C, LDL-C and triglycerides) and putative moderators i.e. quercetin dose and duration of supplementation.

Publication bias

Potential publication bias was explored using visual inspection of Begg's funnel plot asymmetry, and Begg's rank correlation and Egger's weighted regression tests. Duval & Tweedie "trim and fill" method was used to adjust the analysis for the effects of publication bias [52]. Comprehensive Meta-Analysis (CMA) V2 software (Biostat, NJ) [53] was used for performing meta-regression and publication bias analyses.

Results

Flow of included studies

Overall 161 articles were screened for eligibility including 150 articles from the initial literature search in Medline and an additional 11 articles from hand searching in retrieved articles and other databases. Out of these 161 articles, 18 were selected for full-text assessment. After careful assessment, 5 articles met the inclusion criteria and selected for meta-analysis [41, 44, 46-48] Reasons for rejecting the other 13 articles were: not having a randomized controlled design [54-56], not measuring any of the lipid profile parameters (total cholesterol, LDL-C, HDL-C or triglycerides) [57, 58], using quercetin in the form of extract or in combination with other agents that are not allocated to the control group [42, 45, 59-61], reporting duplicate data on the impact of quercetin on plasma lipids [62], and insufficient data on the baseline and post-trial plasma lipid concentrations [43,63]. A summary of study selection process is illustrated in **Figure 2**.

Characteristics of included studies

A total of 442 subjects were included in the 5 eligible studies, comprising 221 subjects in each of the quercetin and control groups (subjects in the cross-over trial were counted in both groups). The largest study had a population size of 93 subjects [44] whilst the smallest study recruited 10 subjects [48]. Included studies were published during the period of 2007-2013, and were conducted in USA [47], Germany [44,46], Iran [41] and UK [48]. All studies had a cross-over design whilst the study apart from that of Zahedi et al [41]. which was conducted as a parallel-group trial. Two studies were conducted among male subjects [46, 48] and one trial among females [41]. Quercetin dosing ranged between 30 mg/day [48] and 730 mg/day [47]. Duration of supplementation varied from 2 [48] to 10 weeks [41], Inclusion criteria defined by the studies were central obesity plus hypertriglyceridemia and/or elevated hsCRP [44], type 2 diabetes [41], and prehypertension or hypertension [47]. Two trials were conducted among healthy subjects [46, 48]. Plasma quercetin was determined in three studies using high performance liquid chromatography coupled with a fluorescence [44], visible [47] or mass-spectrometry [46] detector. In three of the selected studies, included subjects had baseline plasma levels of LDL-C and triglycerides above the normal range [44, 46, 48]. Baseline total cholesterol was elevated in three studies [44, 46, 48] as well as the hypertensive (but not prehypertensive) subgroup of one study [47]. All selected studies had baseline HDL-C levels within the normal range. Demographic and baseline biochemical parameters of included studies are illustrated in **Table 1**.

Quality assessment

Most of the selected studies did not provide sufficient data regarding the methods applied for random sequence generation and allocation concealment. However, other potential sources of bias were sufficiently addressed by most of the included trials. All selected studies were double-blind. Reasons for dropouts were defined by all studies and mainly included non-medical reasons or gastrointestinal side effects. Financial support other than supplying quercetin was not reported by any of the selected trials. Details on the risk of bias among included trials are summarized in **Table 2.**

Quantitative data synthesis

A complete lipid profile analysis comprising total cholesterol, LDL-C, HDL-C and triglycerides was performed in all trials selected for this meta-analysis. Combined estimate of effect size for the impact of quercetin on plasma LDL-C (WMD: 1.43 mg/dL, 95% CI: -0.92-3.78, $p = 0.23$), HDL-C (WMD: 0.26 mg/dL, 95% CI: -0.74-1.25, $p = 0.61$) and triglycerides (WMD: -9.42 mg/dL, 95% CI: -27.80-8.96, $p = 0.32$) was not statistically significant. However, a borderline significant increase in total cholesterol was observed (WMD: 3.13 mg/dL, 95% CI: -0.01-6.27, $p = 0.05$). Forest plots summarizing the meta-analysis of trials on each lipid parameter are illustrated in **Figure 3**.

Estimated effect sizes for the impact of quercetin on plasma LDL-C and HDL-C were robust in sensitivity analyses. However, quercetin's effect on plasma triglycerides was sensitive to the study by Egert et al. [44]. Removing the mentioned study from the analysis resulted in a significant effect ($p < 0.00001$). As for total cholesterol, the results were sensitive to the studies by Edwards et al. [34] ($p = 0.04$), Egert et al. [44] ($p = 0.04$) and Zahedi et al. [41] ($p = 0.73$).

The results of sensitivity analysis for total cholesterol, LDL-C, HDL-C and triglycerides are summarized in **Table 3**.

In subgroup analysis, a significant increase in plasma total cholesterol (WMD: 3.57 mg/dL, 95% CI: 0.21-6.92, $p = 0.04$), and a significant decrease in plasma triglyceride concentrations (WMD: -24.54 mg/dL, 95% CI: -33.09 to -15.99, $p < 0.00001$) was observed in the subset of studies with quercetin doses ≥ 500 mg/day and follow-up duration of ≥ 4 weeks, but there was no alteration in plasma LDL-C and HDL-C levels ($p > 0.05$) (**Table 4**).

Meta-regression

Meta-regression analysis was conducted to evaluate the association between changes in plasma lipid concentrations and quercetin dose and duration of supplementation. Random effects meta regression did not indicate any association between plasma changes in total cholesterol, LDL-C and HDL-C with either quercetin dose [total cholesterol → slope: 0.003; 95% CI: -0.021-0.027; $p = 0.81$; LDL-C → slope: -0.003; 95% CI: -0.023-0.018; $p = 0.80$; HDL-C → slope: 0.003; 95% CI: -0.006-0.013; $p = 0.46$] or duration of supplementation [total cholesterol → slope: 1.269; 95% CI: -0.567-3.106; $p = 0.18$; LDL-C → slope: 0.617; 95% CI: -1.01-2.25; $p = 0.46$; HDL-C → slope: 0.553; 95% CI: -0.167-1.273; $p = 0.13$]. In contrast, plasma changes in triglycerides concentrations were significantly associated with both quercetin dose (slope: -0.057; 95% CI: -0.103- -0.010; $p = 0.02$) and duration of supplementation (slope: -5.314; 95% CI: -9.482- -1.147; $p = 0.01$). Meta-regression plots are illustrated in **Figures 3** and **4**.

Publication bias

Visual inspection of funnel plot asymmetry suggested potential publication bias for the effects of quercetin on plasma total cholesterol, LDL-C and HDL-C (**Figure 5**). However, Begg's rank correlation test suggested no evidence of bias and Egger's linear regression tests indicated publication bias only for total cholesterol [(intercept = -0.74, SE = 0.25, 95% CI = -1.45 to -0.04, *t*-value = 2.92, df = 4.00, two-tailed p = 0.04). Imputation for publication bias using Duval & Tweedie "trim and fill" method led to the calculation of a relatively similar effect size: WMD → 3.89, 95% CI: 0.97-6.81.

Discussion

The present study aimed to summarize the findings of randomized controlled trials on the efficacy of quercetin supplementation on circulating levels of lipids. Meta-analysis indicated a trend towards a slight and clinically non-relevant increase in total cholesterol, and a significant reduction of plasma triglycerides (at doses ≥ 500 mg/day) following quercetin supplementation whilst no significant effect was observed on other lipid indices i.e. LDL-C and HDL-C. This finding is somewhat unexpected and contradicts previous findings in experimental studies [38, 39, 64, 65] The lipid-lowering mechanisms of quercetin in experimental studies have been attributed to increasing of the fecal cholesterol and bile acid excretion [39], and inhibition of denovo triglyceride synthesis leading to reduced VLDL-triglycerides concentrations [64]. The disparity between the experimental and clinical findings may be due to the different lipid metabolism in man. For instance, efficient inhibition of hepatic cholesterol biosynthesis has been observed with 3,4-dihydroxytoluene - a quercetin metabolite – in primary rat hepatocytes but not human HepG2 cells [65]. Since quercetin – like other flavonoids – undergoes rapid and extensive

intestinal metabolism [66-68], its metabolites like 3,4-dihydroxytoluene are considered to account for a considerable fraction of observed biological activities. Another possible explanation for the inconsistencies is the higher dose of quercetin generally used in animal studies [69-71]. Furthermore, lipid-lowering properties of quercetin have been investigated in experimental models under high-fat diet in which lipid homeostasis is impaired, and thus these models are more prone to respond to lipid-lowering therapy [69-71]. However, not all of the studies selected for this review were conducted among dyslipidemic subjects. Finally, the impact of quercetin on plasma lipid levels in the selected trials might have been influenced by genotypic differences. The impact of genotype on the lipid-modulating effects of quercetin has been previously reported for the E3 and E4 variants of the *APOE* gene [56], though this effect is still controversial [46]. Unlike genotype, diet does not appear to introduce any inter-study heterogeneity as 4 of the included trials monitored dietary pattern of participants and did not find significant difference between quercetin and control groups in terms of dietary intake of nutrients [41, 44, 47, 48].

Large scale epidemiological studies have reported a significant inverse association between dietary intake of quercetin and mortality from ischemic heart disease [72]. However, observational studies are always confounded by imprecisions due to the lack of sufficient control over dietary, sociodemographic and all other factors that might potentially affect circulating levels of lipids. Hence, any definitive judgment on the lipid-modulating effects of dietary supplements needs to be verified by randomized controlled trials. In this study, the only lipid parameter that was found to be favourably altered by quercetin supplementation was plasma triglyceride level. This hypotriglyceridemic effect was observed with high (≥ 500 mg/day) but

not lower doses of quercetin. Reduction of plasma triglycerides by quercetin is an important effect owing to the emerging role of triglyceride-rich lipoproteins, particularly remnant lipoprotein particles, in the pathophysiology of atherothrombosis [73]. Although quercetin was found to lack any beneficial and clinically relevant effect on other lipid indices in this meta-analysis, it has other biological effects that can explain the previously observed cardioprotective properties [74-76]. Among these effects is the inhibition of LDL oxidation which is one of the initial triggering steps in the pathogenesis of atherosclerosis. It is possible that quercetin decreases LDL susceptibility to oxidative modification without necessarily changing its cholesterol content. Interestingly, this effect of quercetin has been shown in randomized controlled trials [44, 48].

Based on the meta-regression results, changes in plasma lipid concentrations are independent of quercetin dose and duration of supplementation, apart from triglycerides levels which are associated with both mentioned covariates. Hence, it might be speculated that consumption of higher doses of quercetin over a prolonged period would result in significant changes in plasma triglycerides levels. That the greatest effect size calculated in the present study pertains to the effect of quercetin on triglycerides concentrations (-9.42 mg/dL and -22.57 mg/dL after exclusion of the study by Egert et al. [44]) supports this hypothesis. Moreover, mechanistic studies have indicated inhibition of microsomal triglyceride transfer protein and diacylglycerol acyltransferase by quercetin, leading to the inhibition of VLDL and chylomicron secretion from liver and intestine, respectively [64, 67].

Several limitations to this meta-analysis need to be acknowledged: The most important one lies in the fact that the total number of included studies were few and the population size of

individual studies was generally small. Therefore, although this meta-analysis provides a considerably greater population compared to the individual studies, it might have been still underpowered to detect significant effects of quercetin on lipid profile. Second, the present review included only published studies. Hence, potential publication bias cannot be definitely excluded particularly for the effect of quercetin on total cholesterol. Although the presence of publications bias was ruled out by Begg's and Egger's tests for LDL-C, HDL-C and triglycerides, the reliability of such tests decreases when the number of studies is few and the size of individual studies is small. Furthermore, trials selected for this study recruited subjects with different backgrounds in terms of cardiovascular risk e.g. healthy, type 2 diabetes, obesity and hypertension, thereby making the total population heterogeneous. Finally, doses of quercetin that were used in the included studies were different (30-730 mg/day), and duration of supplementation was generally short (2-10 weeks). Future trials are recommended to be conducted in patients with dyslipidemia and high cardiovascular risk who might be more prone to respond to the putative cardioprotective effects of quercetin.

Conclusions

To sum up, the present systematic review was the first to provide a thorough synthesis of results from randomized controlled trials on the lipid-modulating effects of quercetin. The results indicated a hypotriglyceridemic effect of quercetin at doses above 400 mg/day, but neutral effects on plasma LDL-C, HDL-C, and a small increase in total cholesterol levels which is not of clinical relevance. Since the impact of quercetin on triglycerides concentrations were dose- and

duration-dependent, future large-scale trials are warranted to assess the hypotriglyceridemic effects of quercetin supplements at higher doses and over prolonged follow-up periods.

Conflict of Interest

The author has no competing interests to declare.

Statement of authorship

AS conceived the study and performed the literature search, statistical analysis manuscript drafting and submission.

Funding

The author has received no funds for this study.

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Tables

Table 1. Demographic characteristics of the included studies.

Study		Zahedi et al.	Egert et al.	Pfeuffer	Edwards (preHTN)*	Edwards (HTN)*	Chopra et al.
# Ref		[41]	[44]	[46]	[47]	[47]	[48]
Year		2013	2009	2013	2007	2007	2000
Location		Iran	Germany	Germany	USA	USA	UK
Design		Randomized double-blind placebo-controlled parallel trial	Randomized double-blind placebo-controlled cross-over trial	Randomized double-blind placebo-controlled cross-over trial	Randomized double-blind placebo-controlled cross-over trial	Randomized double-blind placebo-controlled cross-over trial	Randomized double-blind placebo-controlled cross-over trial
Duration of trial		10 weeks	6 weeks	8 weeks	4 weeks	4 weeks	2 weeks
Inclusion criteria		Type 2 diabetic women	central obesity plus serum triacylglycerides > 1.7 mmol/L (1500 mg/L) and/or hs-CRP > 2.0 mg/L.	Healthy subjects	Subjects with prehypertension	Subjects with stage I hypertension	Healthy subjects
Quercetin intervention		500 mg/day	150 mg/day	150 mg/day	730 mg/day	730 mg/day	30 mg/day
Participants	**Case**	34	93	49	19	22	10
	Control	28					
Age (yrs)	**Case**	45.8±4.9	45.1 ± 10.53	59.4 ± 6.3	47.8 ± 15.26	49.2 ± 13.60	ns
	Control	47.4±4.1					
Female (%)	**Case**	100	54.84%	0	31.58	40.91	0
	Control	100					

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Smoker (%)	**Case**	NS	0	NS	0	0	0
	Control	NS			0	0	
BMI (kg/m^2)	**Case**	NS	30.6 ± 3.23	26.3 ± 2.1	29.6 ± 5.7	29.3 ± 6.1	NS
	Control	NS			29.8 ± 5.7	29.5 ± 6.6	
Glucose (mg/dL)	**Case**	NS	95.5 ± 9.9	100.9 ± 10.1	107.9 ± 19.6	108.1 ± 16.9	NS
	Control	NS			102.3 ± 14.1	114.8 ± 23.7	
LDL-C (mg/dL)	**Case**	106.1 ± 5.5	130.52 ± 35.5	135.52 ± 32.4	115.83 ± 33.7	124.71 ± 43.5	141.31 ± 40.1
	Control	103.6 ± 4.5			116.99 ± 28.6	115.06 ± 38.0	
HDL-C (mg/dL)	**Case**	45.2 ± 1.7	55.21 ± 17.4	53.28 ± 13.5	47.88 ± 21.9	47.5 ± 16.3	52.51 ± 12.4
	Control	46.8 ± 2.4			47.88 ± 20.2	49.0 ± 14.5	
Total cholesterol (mg/dL)	**Case**	189.2 ± 7.5	224.32 ± 40.1	209.65 ± 37.9	198.07 ± 38.7	206.2 ± 39.8	214.67 ± 37.8
	Control	177.6 ± 6.4			197.68 ± 40.4	205.4 ± 38.0	
Triglycerides (mg/dL)	**Case**	198.4 ± 20.5	197.35 ± 104.4	106.19 ± 43.3	205.31 ± 92.6	205.31 ± 161.8	105.31 ± 61.1
	Control	151.0 ± 9.4			161.06 ± 92.6	209.73 ± 141.2	
	Control	NS					
Diabetes (%)	**Case**	100	NS	0	0	0	NS
	Control	100					
SBP (mmHg)	**Case**	117 ± 2	130.3 ± 16·4	138.4 ± 16.1	132 ± 4.4	145 ± 9.4	NS
	Control	110 ± 2			135 ± 13.1	141 ± 9.4	
DBP (mmHg)	**Case**	79 ± 1	81.6 ± 9.3	84.4 ± 9.1	85 ± 4.4	97 ± 4.7	NS
	Control	73 ± 1			84 ± 4.4	94 ± 9.4	
hs-CRP (mg/L)	**Case**	3 ± 0.4	4.1 ± 5.2	4.28 ± 1.12	NS	NS	NS
	Control	2.7 ± 0.3			NS	NS	

Values are expressed as mean ± SD or median (interquartile range). NS: not stated; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; SBP: systolic blood pressure; DBP: diastolic blood pressure; hs-CRP: high-sensitivity C-reactive protein; BMI: body mass index; HTN: hypertension. *Information of this study was presented for prehypertensive (preHTN) and hypertensive (HTN) subgroups, separately.

Table 2. Quality assessment of studies selected for analysis.

Study	# Ref	Random sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective reporting	Free of other bias
Egert et al.	[44]	L	U	L	L	L	L
Chopra et al.	[48]	U	H	L	L	L	L
Pfeuffer et al.	[46]	U	L	L	L	L	L
Zahedi et al.	[41]	L	L	L	U	L	L
Edwards et al.	[47]	U	U	L	L	L	U

Criteria defined for quality assessment are based on the Cochrane guidelines. H: high risk of bias; L: low risk of bias; U: unclear or unrevealed risk of bias.

Table 3. Leave-one-out sensitivity and heterogeneity analyses for the impact of quercetin supplementation on plasma lipids.

			Quantitative data synthesis				Heterogeneity analysis			
	Quercetin group (*n*)	**Control group (*n*)**	**Overall effect size**	**95% CI**	***Z*-value**	***p*-value**	**Tau^2**	***Q***	***df* (*Q*)**	**I^2**
Total cholesterol										
Overall effect	221	221	3.13	-0.01-6.27	1.96	0.05	0.00	2.24	5	0
Leave-one-out sensitivity analysis										
Chopra et al.	211	211	3.14	-0.01-6.29	1.95	0.05	0.00	2.24	4	0
Edwards et al. (preHTN)	202	202	3.33	0.17-6.50	2.06	0.04	0.00	1.28	4	0
Edwards et al. (HTN)	199	199	3.29	0.12-6.46	2.03	0.04	0.00	1.75	4	0
Egert et al.	128	128	3.48	0.22-6.75	2.09	0.04	0.00	1.66	4	0
Pfeuffer et al.	172	172	3.18	-0.02-6.39	1.95	0.05	0.00	2.22	4	0
Zahedi et al.	193	193	-1.40	-9.24-6.43	0.35	0.73	0.00	0.71	4	0
Low-density lipoprotein cholesterol										
Overall effect	221	221	1.43	-0.92-3.78	1.19	0.23	0.00	1.53	5	0
Leave-one-out sensitivity analysis										
Chopra et al.	211	211	1.40	-0.96-3.75	1.16	0.25	0.00	1.36	4	0
Edwards et al. (preHTN)	202	202	1.51	-0.86-3.88	1.25	0.21	0.00	1.25	4	0
Edwards et al. (HTN)	199	199	1.54	-0.82-3.90	1.28	0.20	0.00	0.70	4	0
Egert et al.	128	128	1.55	-0.86-3.97	1.26	0.21	0.00	1.34	4	0

Pfeuffer et al.	172	172	1.40	-0.99-3.79	1.15	0.25	0.00	1.51	4	0
Zahedi et al.	193	193	-0.60	-7.47-6.27	0.17	0.86	0.00	1.15	4	0
High-density lipoprotein cholesterol										
Overall effect	221	221	0.26	-0.74-1.25	0.51	0.61	0	3.97	5.00	0%
Leave-one-out sensitivity analysis										
Chopra et al.	211	211	0.32	-0.68-1.31	0.62	0.53	0.00	2.33	4	0
Edwards et al. (preHTN)	202	202	0.27	-0.72-1.27	0.53	0.59	0.00	3.81	4	0
Edwards et al. (HTN)	199	199	0.27	-0.73-1.26	0.52	0.60	0.00	3.93	4	0
Egert et al.	128	128	0.38	-0.63-1.40	0.74	0.46	0.00	2.50	4	0
Pfeuffer et al.	172	172	0.17	-0.84-1.19	0.34	0.74	0.00	3.27	4	0
Zahedi et al.	193	193	-1.01	-4.12-2.10	0.64	0.52	0.00	3.26	4	0
Triglycerides										
Overall effect	221	221	-9.42	-27.80-8.96	1.00	0.32	239.35	11.71	5	57%
Leave-one-out sensitivity analysis										
Chopra et al.	211	211	-9.82	-29.99-10.35	0.95	0.34	278.85	11.32	4	65%
Edwards et al. (preHTN)	202	202	-6.64	-27.21-13.93	0.63	0.53	290.26	11.53	4	65%
Edwards et al. (HTN)	199	199	-10.89	-29.80-8.02	1.13	0.26	244.60	10.65	4	62%
Egert et al.	128	128	-22.57	-30.40 to -14.74	5.65	< 0.00001	0.00	2.82	4	0%
Pfeuffer et al.	172	172	-6.08	-33.17-	0.44	0.66	510.52	11.39	4	65%

				21.01						
Zahedi et al.	193	193	-1.62	-21.58-18.35	0.16	0.87	135.91	5.44	4	26%

*Information of this study was presented for prehypertensive (preHTN) and hypertensive (HTN) subgroups, separately.

Table 4. Subgroup analyses for the impact of quercetin supplementation on plasma lipids.

			Quantitative data synthesis				Heterogeneity analysis			
	Quercetin group (*n*)	**Control group (*n*)**	**Overall effect size**	**95% CI**	***Z*-value**	***p*-value**	**Tau^2**	***Q***	***df* (*Q*)**	**I^2**
Total cholesterol										
Dose ≥ 500 mg/day[a]	69	69	3.57	0.21-6.92	2.08	0.04	0	1.62	2	0%
Dose < 500 mg/day	152	152	0.12	-8.72-8.97	0.03	0.98	0	0.12	2	0%
LDL-C										
Dose ≥ 500 mg/day[a]	69	69	1.49	-0.98-3.95	1.18	0.24	0	1.16	2	0%
Dose < 500 mg/day	152	152	0.88	-6.86-8.62	0.22	0.82	0	0.34	2	0%
HDL-C										
Dose ≥ 500 mg/day[a]	69	69	0.37	-0.67-1.41	0.70	0.49	0	0.22	2	0%
Dose < 500 mg/day	152	152	-1.20	-5.76-3.36	0.52	0.61	6.16	3.21	2	38%

Triglycerides										
Dose ≥ 500 mg/day[a]	69	69	-24.54	-33.09 to -15.99	5.63	< 0.00001	0	1.38	2	0%
Dose < 500 mg/day	152	152	1.41	-23.83-26.66	0.11	0.91	238.84	3.92	2	49%

[a]Mean duration of follow-up ≥ 4 weeks.

Figure Legends

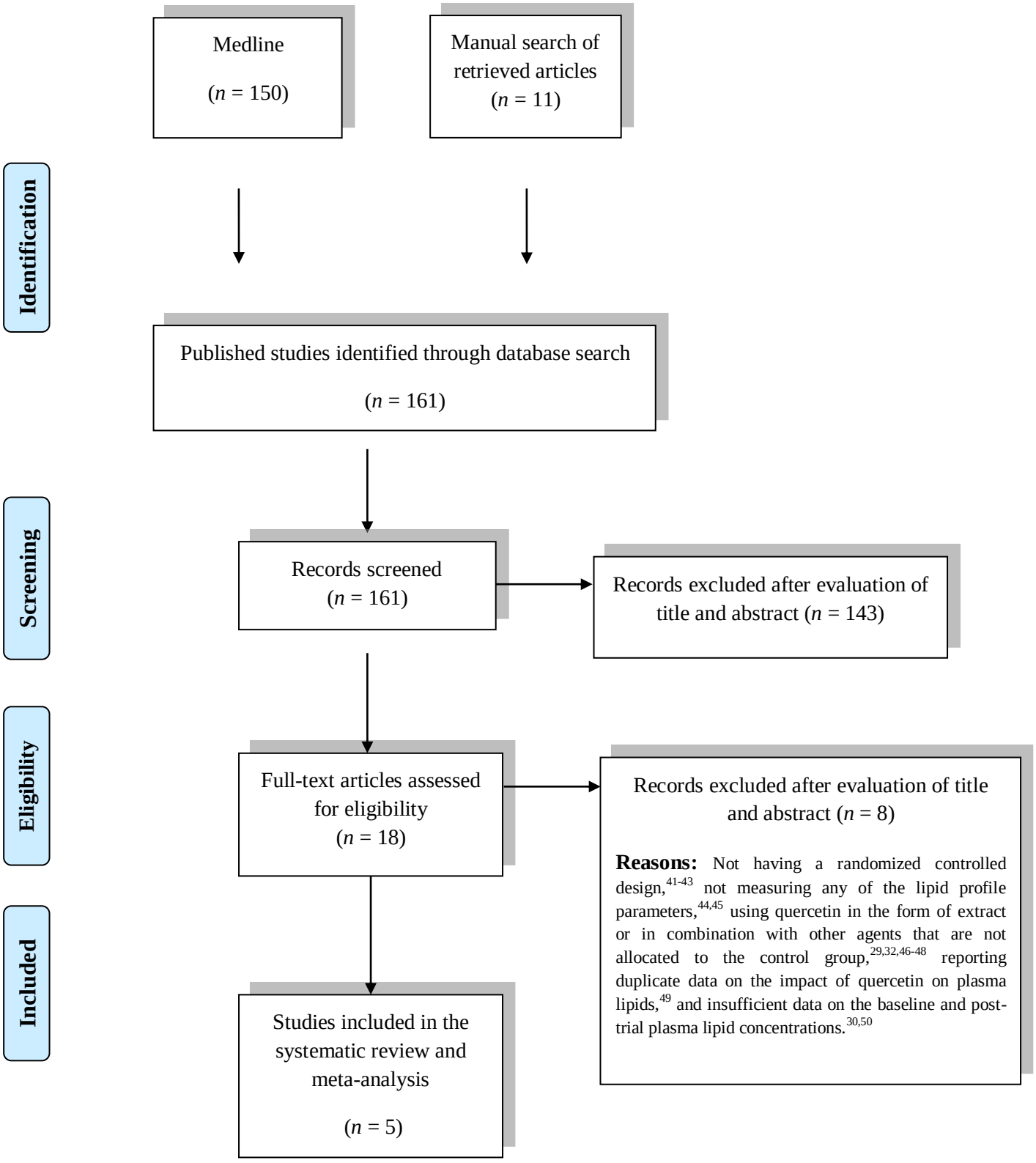

Figure 1. Flow diagram of the study selection procedure showing the number of eligible randomized controlled trials for the meta-analysis of the impact of quercetin supplementation on plasma lipids.

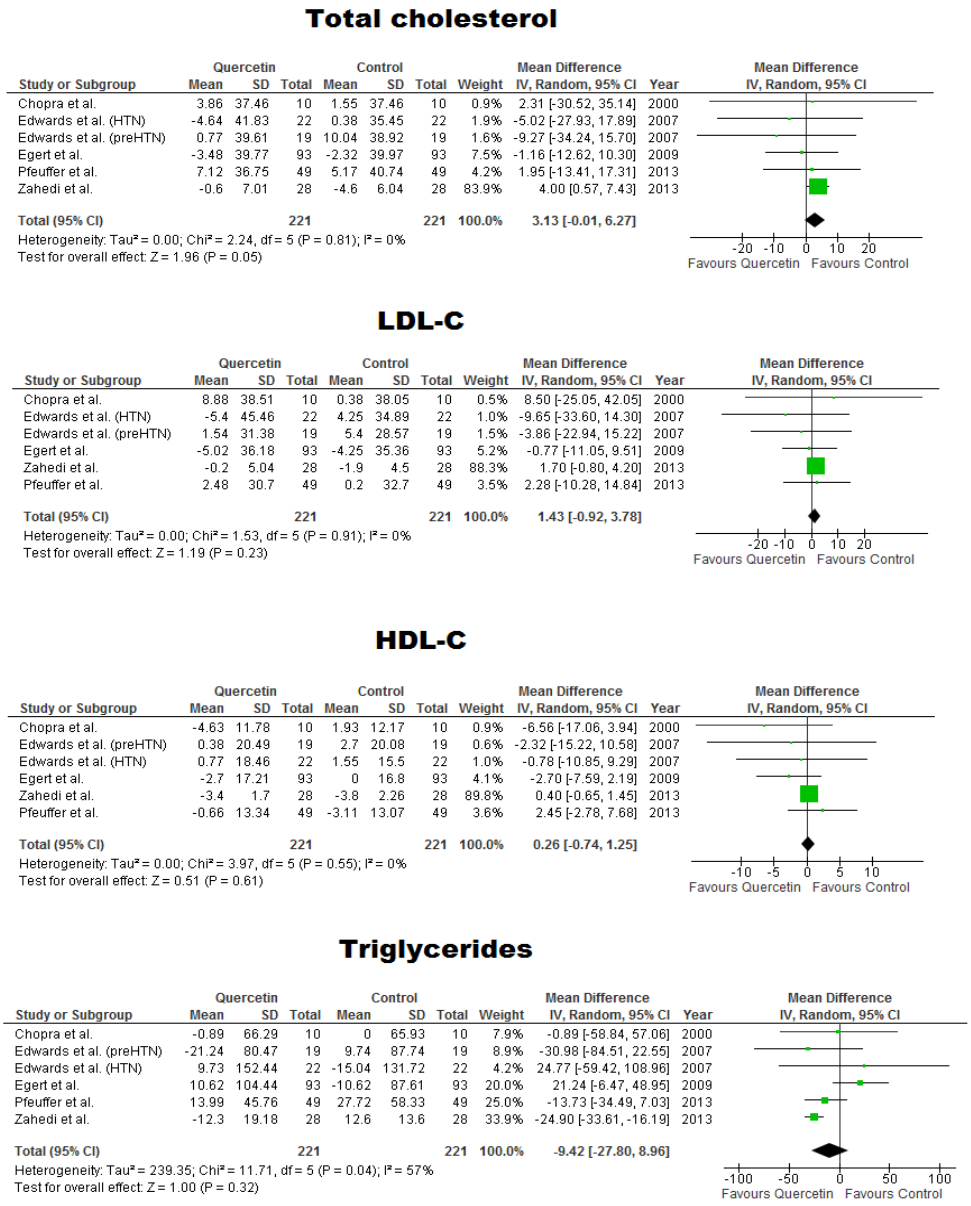

Figure 2. Forest plot detailing weighted mean difference and 95% confidence intervals for the impact of quercetin supplementation on plasma lipids.

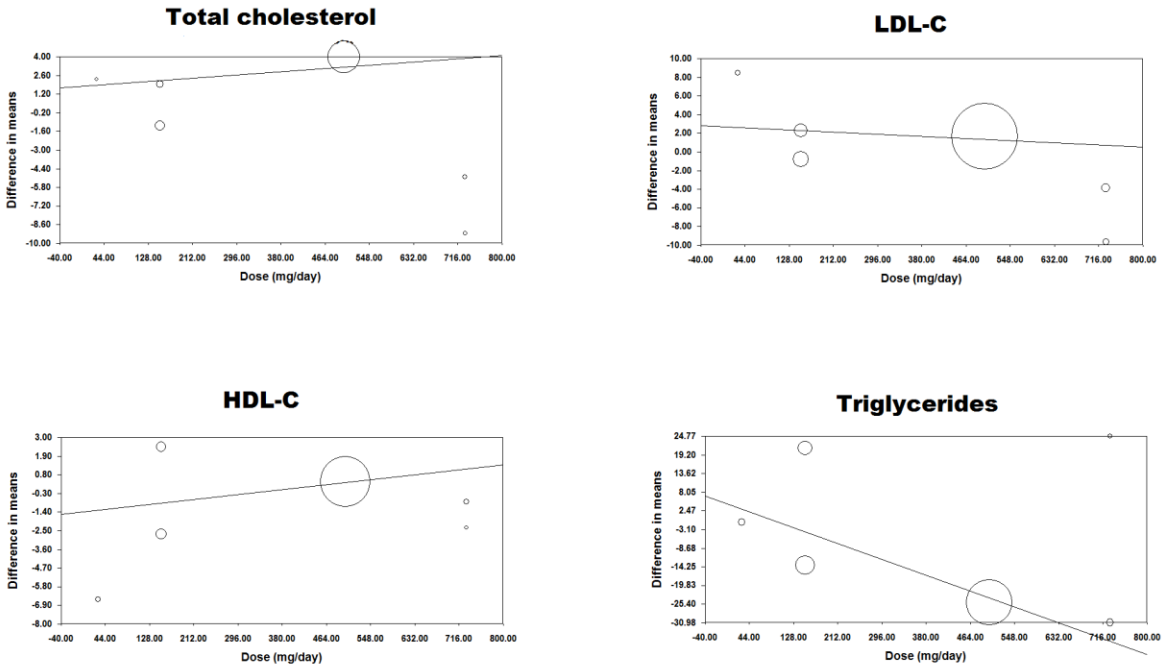

Figure 3. Moderator effect of quercetin dose on the net change in plasma lipid concentrations (meta-regression analysis). The size of each circle is inversely proportional to the variance of change. LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol.

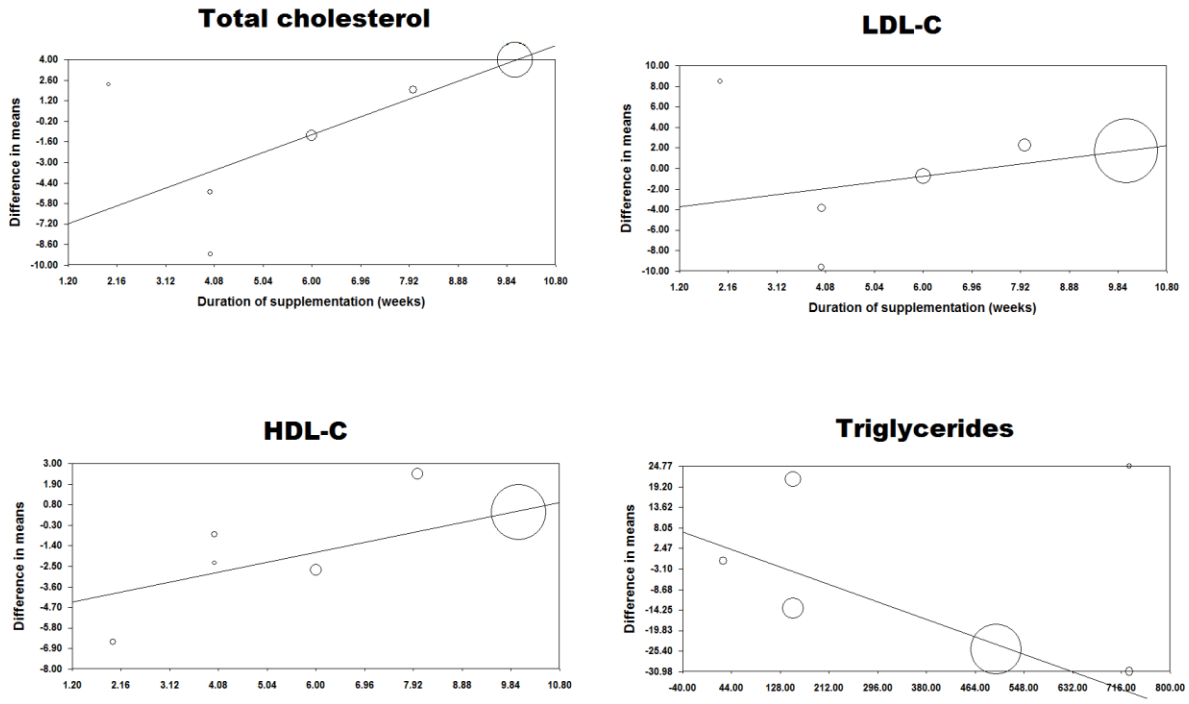

Figure 4. Moderator effect of quercetin duration of supplementation on the net change in plasma lipid concentrations (meta-regression analysis). The size of each circle is inversely proportional to the variance of change. LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol.

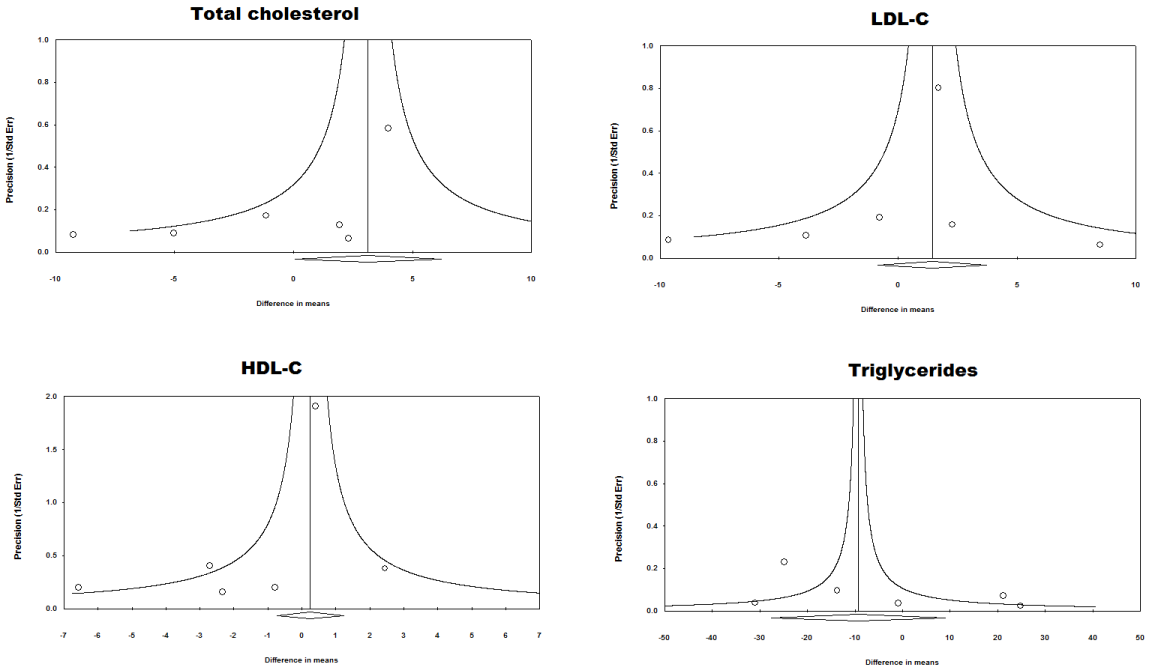

Figure 5. Funnel plots detailing publication bias in the studies selected for analysis. LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol.

