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European Journal of Clinical Nutrition (2017), 1–7
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REVIEW

Effects of supplementation with quercetin on plasma C-reactive protein concentrations: a systematic review and meta-analysis of randomized controlled trials

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Promising experimental studies suggest that quercetin has potential anti-inflammatory effects. However, the results of current clinical trials on quercetin's effects on the C-reactive protein (CRP), a sensitive inflammatory biomarker, are ambiguous. We conducted a meta-analysis of available randomized controlled trials (RCTs) to resolve this inconsistency and quantify the net effect of quercetin on circulating CRP concentrations. A systematic search was performed in several databases including SCOPUS, PubMed–Medline and Google Scholar until 16 June 2016. We used a random-effects model in combination with weight mean difference (WMD) and 95% confidence intervals (CI) for data analysis. Standard methods were used for the assessment of heterogeneity, meta-regression, sensitivity analysis and publication bias. The meta-analysis of seven RCTs (10 treatment arms) showed a significant reduction of circulating CRP levels (WMD: − 0.33 mg/l; 95% CI: − 0.50 to − 0.15; $P < 0.001$) following quercetin supplementation. In the subgroup analysis, a significant reducing effect was observed in trials with ⩾500 mg/day dosage (WMD: − 0.34 mg/l; 95% CI: − 0.52, − 0.16; $P \leqslant 0.001$) and in those with CRP < 3 mg/l (WMD: − 0.34 mg/l; 95% CI: − 0.51, − 0.18; $P \leqslant 0.001$). In meta-regression, there was no association between changes in CRP concentrations, dose of supplementation and CRP baseline values. Our findings showed a significant effect of quercetin supplementation on the C-reactive protein—especially at doses above 500 mg/day and in patients with CRP < 3 mg/l.

European Journal of Clinical Nutrition advance online publication, 24 May 2017; doi:10.1038/ejcn.2017.55

INTRODUCTION

With more than 6000 identified compounds, flavonoids are structurally categorized into a variety of sub-classes, including flavones, flavanones, flavanols, isoflavones and anthocyanidins.[1] Quercetin is found ubiquitously in plants[2] as well as in some fruits and vegetables, including apples, onions, berries, red grapes, broccoli and citrus fruits. Besides, capers, cocoa powder, red wine, bark roots, flowers, green tea and black tea are rich sources of quercetin.[3] Quercetin has a broad range of biological effects in vascular health[4,5] and can serve as a potent anti-inflammatory and antiatherosclerotic agent, with several promising properties,[6] including reduction of the pro-inflammatory cytokines expression,[7] improved vascular endothelial function[8] and antithrombotic properties.[9] The combination of these putatively beneficial properties with other beneficial effects, such as antidiabetic,[10] antiobesity,[11] anticarcinogenic,[12] antiproliferative and antioxidative effects,[13] makes this multipotent bioflavonoid the most promising 'nutraceutical' for cardiovascular disease prevention.

Furthermore, the circulating C-reactive protein (CRP) is recognized as a strong predictor of cardiovascular disease[14,15] that plays an important role in atherosclerotic progression.[16] The potential role of quercetin in reducing inflammation in animals[17,18] and humans[19] encouraged us to test whether quercetin supplementation reduces cardiovascular disease incidence and protects atherosclerotic progression by decreasing the CRP level. Several clinical trials have assessed quercetin supplementation on the circulating CRP level in different populations.[20–23] However, the survey of available randomized controlled trials (RCTs) shows inconsistencies in the findings. Some trials have shown positive CRP-reducing effects of quercetin,[19,24] while others have not seen any change in this inflammatory marker[20–22] following quercetin supplementation. Considering the inconsistencies among the studies and to address this gap in knowledge, we performed this meta-analysis to sum up the data from various RCTs to discover the effects of quercetin on CRP concentrations.

METHODS

Search strategy

PRISMA statement guidelines were followed as a framework for reporting meta-analyses of RCTs.[25] A systematic literature search was conducted in medical databases including PubMed–Medline, SCOPUS and Google Scholar up to November 2016 using the following subject headings (MeSH) and non-MeSH keywords: (('Quercetin'[Mesh]) AND (((((C-Reactive Protein'[Mesh]) OR 'Inflammation'[Mesh]) OR 'inflammatory markers'[Title/Abstract]) OR CRP*[Title/Abstract]) OR 'hs-CRP'[Title/Abstract])) AND (((((((Randomized Controlled Trial' [Publication Type]) OR 'Clinical Trial' [Publication Type]) OR randomized [Title/Abstract]) OR clinical [Title/Abstract]) OR trial [Title/Abstract]) OR placebo [Title/Abstract]) OR randomly [Title/Abstract]). The search was

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Received 4 November 2016; revised 12 March 2017; accepted 15 March 2017

confined to RCTs exploring the influence of quercetin supplementation on CRP concentrations using the English language, and only studies among human participants were included. The reference list of related articles, reviews and meta-analyses were hand-searched for additional relevant studies.

Study selection

Two independent investigators (SSH and DF) screened titles and abstracts for relevant studies, and discrepancies were resolved using a third investigator (MMS). Publishes studies were included if they met the following criteria: (i) being an RCT with either parallel or crossover designs in adults (age $\geqslant 18$ years old), (ii) having an intervention duration of least 4 weeks; (iii) having an appropriate controlled design—that is, if quercetin was administered as an adjunct to another drug/supplement, the control group containing that drug/supplement; and[4] presenting sufficient information on CRP concentrations and their corresponding standard deviation (s.d.) at baseline and at the end of follow-up in quercetin and the control group. The exclusion criteria were: (i) non-RCTs, (ii) the study lacked a suitable control group in the study design, (iii) duplicate publication from the same study and (iv) the study lacked adequate information on baseline or follow-up CRP concentrations.

Data extraction

We used the inclusion–exclusion screening form to select eligible articles. After selecting the eligible articles, the data of RCTs were reviewed independently by two authors and the following data were abstracted using a standardized electronic form: first author's name, publication year, study location, study design, duration of the intervention, number of participants in the quercetin and control groups, inclusion criteria, form and administered dose of quercetin, content of placebo, and the age, gender and body mass index of the study participants. We also extract the mean concentration and s.d. of the circulating CRP at study baseline, post-intervention and/or the change between baseline and post-intervention. We converted the CRP into the same unit (mg/l) for all studies. Each arm in double arm (2×2) crossover trials was considered as a single study.

Quality assessment

The quality of eligible studies was evaluated using the quantitative 5-point Jadad scale.[26] Articles were assigned 0 or 1 point for each of the following five criteria: (1) randomization, (2) suitable method of randomization, (3) double blinding, (4) suitable method of double blinding and (5) explanation and reason of withdrawals and dropouts.[26] Articles with scores with $\geqslant 3$ and $\leqslant 2$ were considered high and low quality, respectively.[27]

Quantitative data synthesis and statistical analysis

The primary end point was change in circulating CRP concentrations due to quercetin supplementation. Effect sizes for the meta-analysis were defined as weighted mean difference (WMD; value at end trial minus the value at baseline) and 95% confidence interval (CI).[28] In the event of no reported s.d. of the mean difference, it was calculated as follows: s.d. = square root [(s.d. pre-intervention)^2+(s.d. post- intervention)^2 − ($2R \times$ s.d. pre-intervention $\times$ s.d. post-intervention)]. A correlation coefficient of 0.5 was assumed as this R-value is a conservative estimate between 0 and 1. When s.e. was reported in place of s.d., we converted it to s.d. for analyses: s.d. $= \text{s.e.} \times \sqrt{n}$, where n is the number of participants in each group. Statistical heterogeneity between studies was evaluated using Cochran's Q-test (significance set at $P < 0.1$) and I^2 ($\geqslant 50\%$ assumed to indicate substantial heterogeneity among

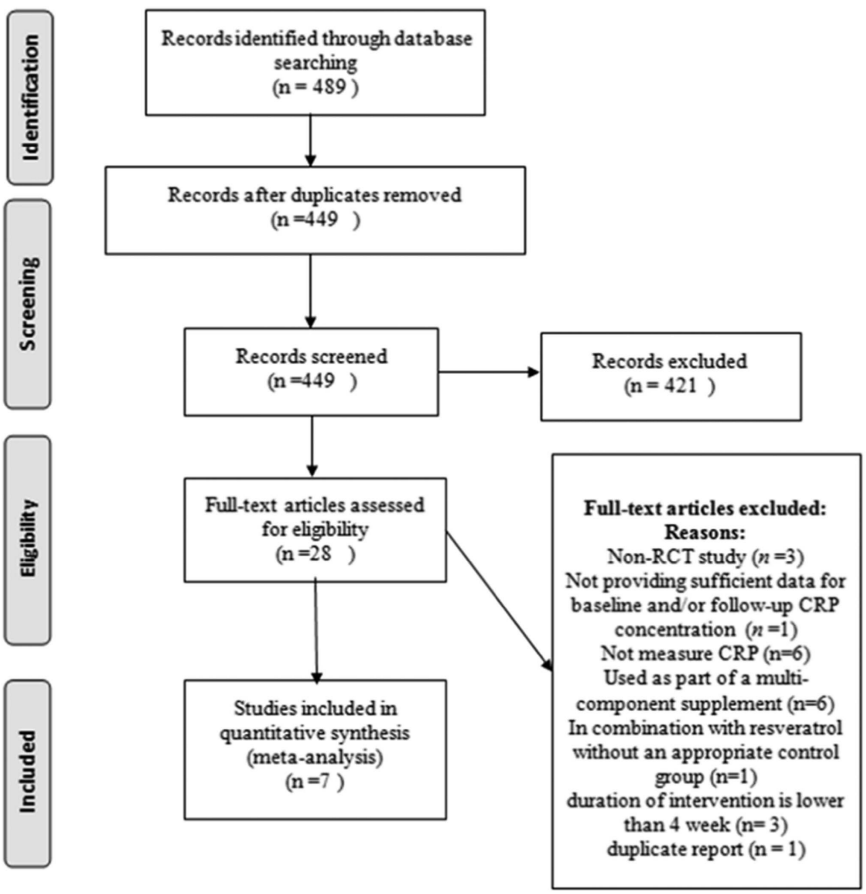

Figure 1. Flowchart of the number of studies identified and included in the meta-analysis.

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Table 1. Demographic characteristics and baseline parameters of the included studies

	Location	*Population*	*Sample size (n)*	*Age (years)*	*Women (%)*	*Design*	*Duration (weeks)*	*Quercetin dose (mg/day)*	*Baseline CRP (mg/l)*		*Jadad score*
									Case	*Control*	
Askari[9]	Iran	Non-professional athletes	60	20.9	0	Parallel	8	500	1.37 ± 0.06	1.28 ± 0.15	3
Brull[29]	Germany	Overweight and obese patients	68	47.4	50	Crossover	6	162	2.2 ± 1.99	2.4 ± 2.33	5
Egert[21]	Germany	Overweight and obese patients	93	45.1	55	Crossover	6	150	5.07 ± 9.42	3.96 ± 3.84	4
Egert[20]	Germany	Overweight and obese patients	93	45	55	Crossover	6	150	5.0 ± 6.2[a] 2.4 ± 1.8[b]	4.29 ± 4.13[a] 2.18 ± 0.42[b]	4
Javadi[22]	Iran	Rheumatoid arthritis	40	46.55	100	Parallel	8	500	2.89 ± 2.95	3.28 ± 3.32	4
Pfeuffere[30]	Germany	subjects with *APOE* genotype	49	54.9	NR	Crossover	8	150	4.40 ± 0.38[a] 4.21 ± 0.1[b]	4.40 ± 0.38[a] 4.21 ± 0.1[b]	3
Zahedi[23,34]	Iran	Type 2 diabetes	62	46.4	100	Parallel	10	500	5.7 ± 0.8	2.7 ± 0.3	5

[a,b]These studies have two treatment arms.

studies). In the presence of heterogeneity, pooled effect size was calculated using a random-effects model; otherwise, we applied a fixed-effects model. Predefined subgroup analyses and meta-regression analyses were conducted to explore the possible source of heterogeneity among the trials. We assessed the dose of quercetin, trial duration, baseline CRP level, type of trial, mean age of subjects and location of the study for the subgroup analysis, and were considered as predefined sources of heterogeneity. Sensitivity analysis was used to explore the extent to which inferences might depend on a particular study using the leave-one-out method (that is, removing a single trial at a time and repeating the analyses). Meta-regression was performed using the unrestricted maximum likelihood method to evaluate the association between the overall estimate of effect size and quercetin dose, duration of supplementation, and baseline CRP concentrations. Publication bias was assessed by funnel plot, Begg's rank correlation and Egger's weighted regression tests. In the event of publication bias, the Duval and Tweedie 'trim-and-fill' and 'fail-safe N' methods were utilized. All statistical analyses were performed using Comprehensive Meta-Analysis software (Biostat, Englewood, NJ, USA) with a level of significance of $P < 0.05$.

RESULTS

Flow and characteristics of included studies

Briefly, our search retrieved 489 articles. After removing the duplicates, 449 articles remained and were included for title and abstract screening. Of the 449 articles, 420 were excluded because they were not RCTs in humans or the articles were not related to our present meta-analysis in accordance with the inclusion criteria. Therefore, 28 potentially relevant articles were selected for a careful full-text evaluation. After the precise evaluation, seven eligible randomized controlled studies met our objectives and were selected for meta-analysis.[19–23,29] The remaining 21 articles were excluded for several reasons: not being a randomized placebo-controlled studies ($n = 3$), lack of CRP measurements ($n = 6$), inadequate information about baseline or the follow-up CRP level ($n = 1$), quercetin used as part of a multicomponent supplement ($n = 6$), use of quercetin in combination with resveratrol without a suitable control group ($n = 1$), duration of intervention lower than 4 weeks ($n = 3$) and duplicate report ($n = 1$). The study selection process is shown in Figure 1.

Study characteristics

The characteristics of the study, which met all the inclusion criteria of the meta-analysis, are presented in Table 1. Data were pooled from seven eligible studies comprising 10 treatment arms that included 549 subjects, with 298 subjects in the quercetin arm and 291 in the control arm. The studies were published between 2009 and 2016; they were conducted in Iran (three studies)[19,22,23] and Germany (four studies).[20,21,29,30] One study[29] investigated 162 mg/day, three studies[20,21,30] investigated 150 mg/day and three studies[19,22,23] investigated 500 mg/day of quercetin. Two trials were conducted exclusively on women,[22,23] while other trials were conducted on both sexes.[19–21,29,30] The largest trial had a sample size of 93 subjects and the smallest recruited 40 subjects. The range of supplementation periods was from 6 weeks up to 10 weeks. The selected studies enrolled subjects with systematic and regular exercise,[19] overweight or obese with metabolic syndrome traits,[21] overweight to obese with pre-hypertension and stage 1 hypertension,[29] women with rheumatoid arthritis,[22] women with type 2 diabetes,[23] men with different apolipoprotein E isoforms[30] and overweight patients by apolipoprotein E genotype.[20] The mean age of these subjects ranged from 21 to 59.5 years and the mean body mass index ranged from 21.4 to 31.1 kg/m^2. The average baseline CRP concentration ranged from 1.37 to 5.07 mg/l. One trial[19] had four arms comparing quercetin, placebo, vitamin C and quercetin+ vitamin C.

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Table 2. Pooled estimates of effects on CRP within various subgroups

Group	*No. of comparisons*	*Net change (95% CI)*	P	P-*heterogeneity*	I^2*(%)*
Total	10	−0.33 (−0.50, −0.15)	< 0.001	0.018	54.86
Baseline CRP (mg/l)	—	—	—	—	—
⩾3	4	0.30 (−0.83, 1.43)	0.602	0.322	14.10
< 3	6	−0.34 (−0.51 to −0.18)	< 0.001	0.010	66.73
Quercetin dose (g)				—	—
⩾500	4	−0.34 (−0.52 to −0.16)	< 0.001	0.003	78.78
< 500	6	−0.16 (−0.93, 0.60)	0.667	0.098	13.45
Intervention duration (weeks)					
⩾8	6	−0.30, (−0.50, −0.11	0. 002	0.002	72.91
< 8	4	−0.68 (−1.46, 0.097)	0. 086	0.969	0.00
Type of RCTs					
Parallel design	4	−0.34 (−0.52, −0.16)	< 0.001	0.329	13.45
Crossover design	6	−0.16 (−0.27, 0.64)	0.667	0.003	78.78
Mean age (years)					
> 45	5	−0.17 (−0.61, 0.26)	0.424	0.292	19.32
⩽45	5	−0.37 (−0.60, −0.14)	0.001	0.005	73.22

Assessment of quality of studies

The quality of these seven studies ranged from 2 to 5 (maximum score), and all the studies had a higher quality as assessed by the Jadad scale (Table 2). All the studies were randomized, double-blind and placebo-controlled; four had a crossover design and three had a parallel design. Only one study did not explain the randomization procedure,[30] while four of them did not clearly mention the blinding procedure of the study.[19–22] All the studies reported the details of withdrawals.

Effect of quercetin on circulating CRP concentrations

Forest plots summarizing the meta-analysis of trials on CRP concentrations are illustrated in Figure 2. The meta-analysis of data from nine treatment arms showed significant alterations in circulating CRP concentrations (WMD: −0.33 mg/l; 95% CI: −0.50 to −0.15; $P < 0.001$) following supplementation with quercetin (Figure 2, upper plot). This effect size was robust in the leave-one-out sensitivity analysis—that is, the removal of each trial did not have a significant effect on meta-analysis results (Figure 2, lower plot). The result was obtained using a random-effects model as we observed a significant study heterogeneity in the effects of quercetin on circulating CRP concentrations (*Q*-statistic $P = 0.018$, $I^2 = 54.86\%$).

Subgroup analysis

Considering that the initial concentrations of the CRP, intervention dose, study duration, RCT type (parallel or crossover design), age and study location may influence the net changes of the CRP, we conducted subgroup analysis based on these variables to clarify the heterogeneity. The results are shown in Table 2. When the studies were categorized in accordance with the dose of supplementation, there was a significant CRP-reducing effect in trials with ⩾500 mg/day (WMD: −0.34 mg/l; 95% CI: −0.52, −0.16; $P \leqslant 0.001$), but not with < 500 mg/day dosage (WMD: −0.16 mg/l; 95% CI: −0.93, 0.60; $P = 0.667$; Table 2). We also categorized studies according to the baseline of CRP concentrations, and a significant reduction was observed with CRP < 3 mg/l (WMD: −0.34 mg/l; 95% CI: −0.51, −0.18; $P \leqslant 0.001$), but not with CRP > 3 mg/l (WMD: 0.30 mg/l; 95% CI: −1.83, 1.43; $P = 0.602$; Table 2). Among other prespecified characteristics assessed as potential sources of heterogeneity, the effect of quercetin on the CRP appeared to be potentially stronger in trials with a parallel design. We also found a significant reduction of the CRP in people belonging to the age group of lower than 45 years and in those trials performed in Iran (Table 2).

Meta-regression

Meta-regression analysis was conducted to evaluate the association between changes in plasma CRP concentrations and potential moderator variables. The results suggested that the pooled estimate is independent of quercetin dose (slope: −0.00045; 95% CI: − 0.002, 0.001; $P = 0.658$), CRP baseline levels (slope: 0.077; −0.13 to 0.29; $P = 0.475$) and duration of supplementation (slope: −0.041; 95% CI: −0.11, 0.19; $P = 0.598$; Figure 3).

Publication bias

Visual inspection of funnel plot did not suggest a significant potential publication bias in the meta-analysis of quercetin supplementation on circulating CRP concentrations (Figure 4). This observation was confirmed by the Egger's linear regression (intercept = −0.39; s.e. = 0.51; 95% CI: −1.59, 0.79; $t = 0.76$; df = 8; two-tailed $P = 0.466$) and Begg's rank correlation (Kendall's Tau with continuity correction = −0.00; $z = 0.00$; two-tailed *P*-value = 1.00) tests. Duval and Tweedie 'trim-and-fill' correction result in the imputation of one potentially missing studies and an adjusted effect size of −0.24 (95% CI: −0.25 to −0.23). The result of 'fail-safe N' test showed that 690 studies would be required to bring the effect size to a nonsignificant ($P > 0.05$) value.

DISCUSSION

To the best of our knowledge, the current systematic review and meta-analysis are the first studies to evaluate the effect of quercetin supplementation on circulating CRP concentrations from available RCTs. The meta-analysis of data from seven RCTs indicate a significant effect of quercetin supplementation on plasma CRP concentrations. However, a significant reduction of the circulating CRP was observed only at doses higher than 500 mg/day and in trials with baseline CRP less than 3 mg/l.

The anti-inflammatory influences of quercetin have been obviously stated in *in vitro* studies.[31] The overall effect of quercetin on circulating CRP concentrations in this meta-analysis is confirmed by previous experimental[32,33] and clinical trial

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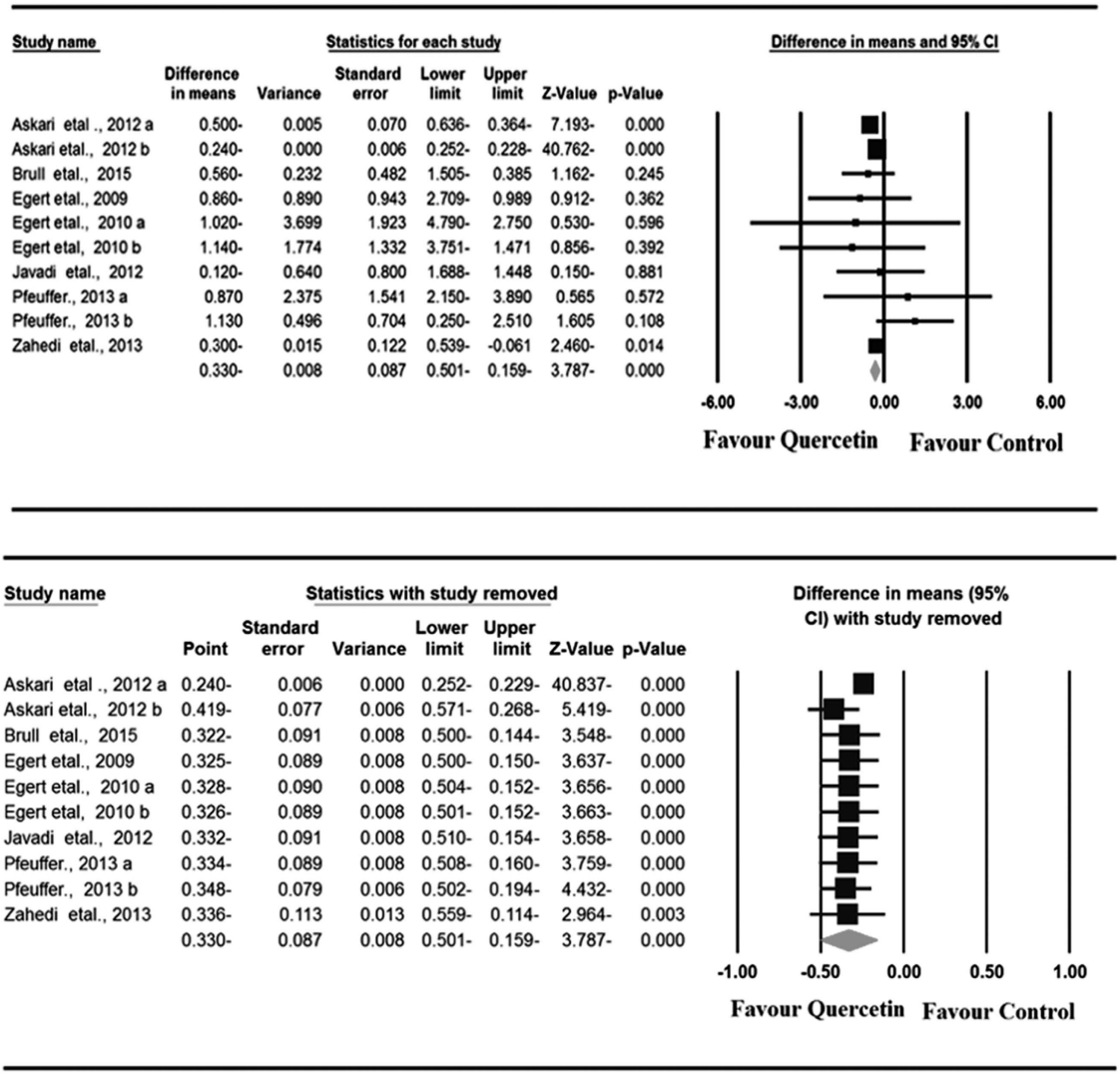

Figure 2. Forest plot displaying mean difference (WMD) and 95% confidence intervals for the impact of quercetin on plasma CRP concentrations. Lower plot shows leave-one-out sensitivity analysis. Analysis was performed using a random-effect model with inverse variance weighting.

findings.[19,34] However, these anti-inflammatory effects are different in humans and animals,[21,35,36] which may be the result of diverse levels of inflammatory status or physiological dissimilarities between animals and humans. Moreover, the considerable heterogeneity between the studies complicates the explanation of our results. This evident heterogeneity among the studies suggests that quercetin supplementation may have a stronger influence on the CRP in some populations and weaker effects in others. The subjects of these trials included overweight/obese adults, women with rheumatoid arthritis, women with type 2 diabetes, healthy adults and specially patients with the apolipoprotein E4 genotype.

There have been inconsistent findings on the effect of quercetin supplementation on the circulating CRP: some studies reported slight or no reduction,[21,22,29] while some trials reported significant effects[19] as our finding. The mechanisms by which quercetin exerts its effect on the inflammatory marker CRP are not clear. However, according to previous studies, several mechanisms exist for the anti-inflammatory and potential CRP-lowering role of quercetin. Inhibition of nuclear factor-kB signaling pathways, inhibition of leukotriene B4 formation in leukocytes[37] and suppression of tumor necrosis factor-α and nitric oxide production[38] are some of the hypotheses that have been tested in experimental and clinical trials.

In our subgroup analysis, this significant reduction effect of quercetin was observed only in trials with doses $\geqslant$500 mg/day dosage, but not in lower doses. This finding appears to be similar to animal studies that report the dose-dependency effects of quercetin on inflammation.[36] Since in the experimental studies higher doses of quercetin are needed for anti-inflammatory effects,[36] it seems that lower doses are not sufficient to affect the anti-inflammatory status.[21]

Contrary to our expectations, subgroup analyses showed that the supplementation of quercetin significantly decreases the circulating CRP levels in the subset of trials with CRP levels lower than 3 mg/l, while it has no effect when CRP levels are equal or more than 3 mg/l. Caution should be used for several reasons in interpreting the results of the sub-analysis based on the baseline CRP. The observed heterogeneity can mainly be described by the changes in baseline CRP levels. Moreover, we found that the mean baseline CRP levels were higher in those trials that used a low-dose quercetin compared with those using a higher dose.

Quercetin supplementation may be helpful for reducing the risk of cardiovascular disease via CRP reduction,[5] so rich sources of

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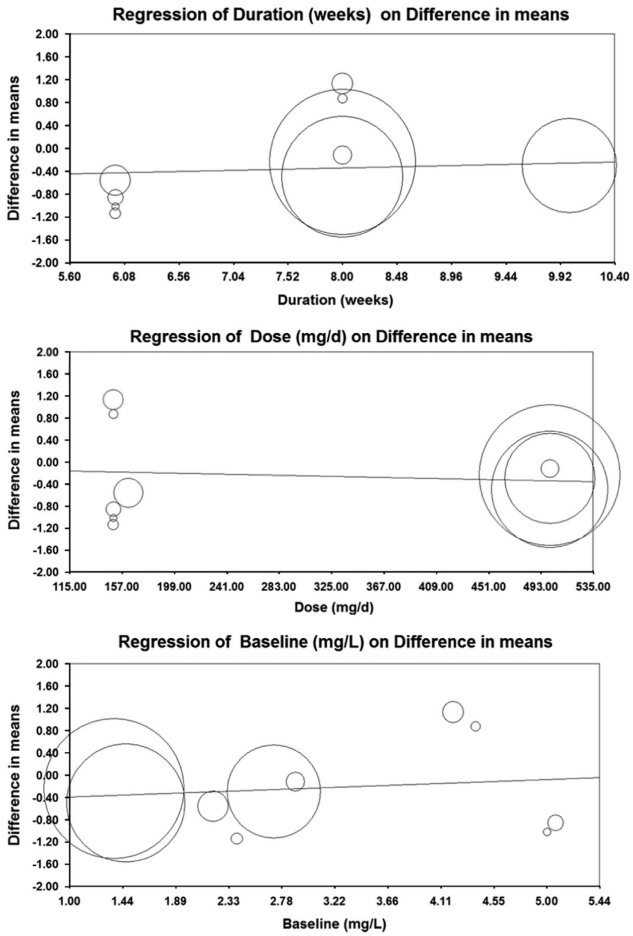

Figure 3. Meta-regression plots of the association between mean changes in plasma CRP concentrations values after quercetin supplementation with quercetin dose, CRP baseline and duration of supplementation. The size of each circle is inversely proportional to the variance of change.

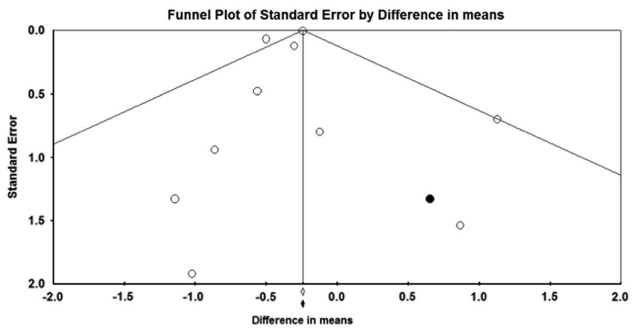

Figure 4. Funnel plot detailing publication bias in the studies reporting the impact of quercetin on plasma CRP concentrations.

quercetin such as broccoli, apples, citrus fruits, onions, berries, grapes, cherries and tea (*Camellia sinensis*) could be incorporated in our diet. In particular, other than minor side-effects, such as nausea and headache, that are only observed in long-term supplementation with doses at 1000 mg/day, it appears that quercetin is safe and the available evidence supports its addition to food[39] with no risk of carcinogenicity, as shown by numerous long-term experimental animal studies.[40–42]

There were several strong points in our analysis. All trials were double-blind and thus strengthened the inference of a cause-and-effect relationship. Moreover, the qualified RCTs had a high quality, as assessed by the Jadad scale. The present study has several limitations that should be considered. First, we could not perform further analyses on the relationship between plasma levels of quercetin and CRP reduction due to the limited related data. The included RCTs had a modest sample size (only two had more than 70 patients), which resulted in inadequate statistical power to identify a meaningful effect in individual trials and in the present meta-analysis. In addition, the qualified trials were heterogeneous regarding the sample size, dose administration, duration of treatment and CRP baseline. Potential differences in CRP baseline between treatment and control groups may have a confounding effect on CRP changes during intervention.

CONCLUSION

In conclusion, sufficient evidence was found regarding the significant effect of quercetin on circulating CRP levels in our meta-analysis. This is more evident in doses higher than 500 mg/day. Additional high-quality well-designed studies should be performed to approve our findings.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

MMS and ZM conceived the study. MMS carried out the literature search and wrote the manuscript. SSH and DF carried out data extraction and independent reviewing. MMS and ZM assessed the quality of included studies. MMS and MGH performed data analysis and interpretation. ZM revised the manuscript. The manuscript has been read and approved by all authors.

REFERENCES

1 Knekt P, Jarvinen R, Reunanen A, Maatela J. Flavonoid intake and coronary mortality in Finland: a cohort study. *BMJ* 1996; **312**: 478–481.
2 Ferreyra MLF, Rius SP, Casati P. Flavonoids: biosynthesis, biological functions, and biotechnological applications. *Front Plant Sci* 2012; **3**: 222.
3 Erlund I. Review of the flavonoids quercetin, hesperetin, and naringenin. Dietary sources, bioactivities, bioavailability, and epidemiology. *Nutr Res* 2004; **24**: 851–874.
4 D'Andrea G. Quercetin: a flavonol with multifaceted therapeutic applications? *Fitoterapia* 2015; **106**: 256–271.
5 Guillermo Gormaz J, Quintremil S, Rodrigo R. Cardiovascular disease: a target for the pharmacological effects of quercetin. *Curr Top Med Chem* 2015; **15**: 1735–1742.
6 Kleemann R, Verschuren L, Morrison M, Zadelaar S, van Erk MJ, Wielinga PY *et al.* Anti-inflammatory, anti-proliferative and anti-atherosclerotic effects of quercetin in human in vitro and in vivo models. *Atherosclerosis* 2011; **218**: 44–52.
7 Lakhanpal P, Rai DK. Quercetin: a versatile flavonoid. *Internet J Med Update* 2007; **2**: 22–37.
8 Sanchez M, Lodi F, Vera R, Villar IC, Cogolludo A, Jimenez R *et al.* Quercetin and isorhamnetin prevent endothelial dysfunction, superoxide production, and overexpression of p47phox induced by angiotensin II in rat aorta. *J Nutr* 2007; **137**: 910–915.
9 Hubbard G, Stevens J, Cicmil M, Sage T, Jordan P, Williams C *et al.* Quercetin inhibits collagen-stimulated platelet activation through inhibition of multiple components of the glycoprotein VI signaling pathway. *J Thromb Haemost* 2003; **1**: 1079–1088.
10 Alam MM, Meerza D, Naseem I. Protective effect of quercetin on hyperglycemia, oxidative stress and DNA damage in alloxan induced type 2 diabetic mice. *Life Sci* 2014; **109**: 8–14.
11 Nabavi SF, Russo GL, Daglia M, Nabavi SM. Role of quercetin as an alternative for obesity treatment: you are what you eat!. *Food Chem* 2015; **179**: 305–310.
12 Men K, Duan X, Wei X, Ling Gou M, Juan Huang M, Juan Chen L *et al.* Nanoparticle-delivered quercetin for cancer therapy. *Anti-Cancer Agents Med Chem* 2014; **14**: 826–832.
13 Bischoff SC. Quercetin: potentials in the prevention and therapy of disease. *Curr Opin Clin Nutr Metab Care* 2008; **11**: 733–740.

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14 Collaboration ERF. C-reactive protein, fibrinogen, and cardiovascular disease prediction. *N Engl J Med* 2012; **2012**: 1310–1320.
15 Venugopal SK, Devaraj S, Jialal I. Effect of C-reactive protein on vascular cells: evidence for a proinflammatory, proatherogenic role. *Curr Opin Nephrol Hypertens* 2005; **14**: 33–37.
16 Pasceri V, Willerson JT, Yeh ET. Direct proinflammatory effect of C-reactive protein on human endothelial cells. *Circulation* 2000; **102**: 2165–2168.
17 Das N, Sikder K, Bhattacharjee S, Majumdar SB, Ghosh S, Majumdar S *et al.* Quercetin alleviates inflammation after short-term treatment in high-fat-fed mice. *Food Funct* 2013; **4**: 889–898.
18 González-Segovia R, Quintanar JL, Salinas E, Ceballos-Salazar R, Aviles-Jiménez F, Torres-López J. Effect of the flavonoid quercetin on inflammation and lipid peroxidation induced by Helicobacter pylori in gastric mucosa of guinea pig. *J Gastroenterol* 2008; **43**: 441–447.
19 Askari G, Ghiasvand R, Feizi A, Ghanadian SM, Karimian J. The effect of quercetin supplementation on selected markers of inflammation and oxidative stress. *J Res Med Sci* 2012; **17**: 637–641.
20 Egert S, Boesch-Saadatmandi C, Wolffram S, Rimbach G, Müller MJ. Serum lipid and blood pressure responses to quercetin vary in overweight patients by apolipoprotein E genotype. *J Nutr* 2010; **140**: 278–284.
21 Egert S, Bosy-Westphal A, Seiberl J, Kürbitz C, Settler U, Plachta-Danielzik S *et al.* Quercetin reduces systolic blood pressure and plasma oxidised low-density lipoprotein concentrations in overweight subjects with a high-cardiovascular disease risk phenotype: a double-blinded, placebo-controlled cross-over study. *Br J Nutr* 2009; **102**: 1065–1074.
22 Javadi F, Eghtesadi S, Ahmadzadeh A, Aryaeian N, Zabihiyeganeh M, Foroushani AR *et al.* The effect of quercetin on plasma oxidative status, C-reactive protein and blood pressure in women with rheumatoid arthritis. *Int J Prev Med* 2014; **5**: 293–301.
23 Zahedi M, Ghiasvand R, Feizi A, Asgari G, Darvish L. Does quercetin improve cardiovascular risk factors and inflammatory biomarkers in women with type 2 diabetes: a double-blind randomized controlled clinical trial. *Int J Prev Med* 2013; **4**: 777–785.
24 Dower JI, Geleijnse JM, Gijsbers L, Schalkwijk C, Kromhout D, Hollman PC. Supplementation of the pure flavonoids epicatechin and quercetin affects some biomarkers of endothelial dysfunction and inflammation in (pre) hypertensive adults: a randomized double-blind, placebo-controlled, crossover trial. *J Nutr* 2015; **145**: 1459–1463.
25 Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M *et al.* Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015; **4**: 1.
26 Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJM, Gavaghan DJ *et al.* Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Controlled Clin Trials* 1996; **17**: 1–12.
27 Moher D, Cook D, Jadad A, Tugwell P, Moher M, Jones A *et al.* Assessing the quality of reports of randomised trials: implications for the conduct of meta-analyses. *Health Technol Assess* 1999; **3**: 1–98. i.
28 Borenstein M, Hedges L, Higgins J, Rothstein H. *Comprehensive Meta-Analysis Version 2*. Biostat: Englewood, NJ, 2005, pp 104.
29 Brüll V, Burak C, Stoffel-Wagner B, Wolffram S, Nickenig G, Müller C *et al.* Effects of a quercetin-rich onion skin extract on 24 h ambulatory blood pressure and endothelial function in overweight-to-obese patients with (pre-)hypertension: a randomised double-blinded placebo-controlled cross-over trial. *Br J Nutr* 2015; **114**: 1263–1277.
30 Pfeuffer M, Auinger A, Bley U, Kraus-Stojanowic I, Laue C, Winkler P *et al.* Effect of quercetin on traits of the metabolic syndrome, endothelial function and inflammation in men with different APOE isoforms. *Nutr Metab Cardiovasc Dis* 2013; **23**: 403–409.
31 Erdman JW, Balentine D, Arab L, Beecher G, Dwyer JT, Folts J *et al.* Flavonoids and heart health: proceedings of the ILSI North America flavonoids workshop, May 31–June 1, 2005, Washington, DC. *J Nutr* 2007; **137**: 718S–737S.
32 Bhaskar S, Kumar KS, Krishnan K, Antony H. Quercetin alleviates hypercholesterolemic diet induced inflammation during progression and regression of atherosclerosis in rabbits. *Nutrition* 2013; **29**: 219–229.
33 García-Mediavilla V, Crespo I, Collado PS, Esteller A, Sánchez-Campos S, Tuñón MJ *et al.* The anti-inflammatory flavones quercetin and kaempferol cause inhibition of inducible nitric oxide synthase, cyclooxygenase-2 and reactive C-protein, and down-regulation of the nuclear factor kappaB pathway in Chang Liver cells. *Eur J Pharmacol* 2007; **557**: 221–229.
34 Zahedi M, Ghiasvand R, Feizi A, Asgari G, Darvishi L. Does quercetin improve cardiovascular risk factors and inflammatory biomarkers in women with type 2 diabetes: a double-blind randomized controlled clinical trial. *Int J Prev Med* 2013; **4**: 777–785.
35 Boots AW, Wilms LC, Swennen EL, Kleinjans JC, Bast A, Haenen GR. In vitro and ex vivo anti-inflammatory activity of quercetin in healthy volunteers. *Nutrition* 2008; **24**: 703–710.
36 Rivera L, Morón R, Sánchez M, Zarzuelo A, Galisteo M. Quercetin ameliorates metabolic syndrome and improves the inflammatory status in obese Zucker rats. *Obesity* 2008; **16**: 2081–2087.
37 Loke WM, Proudfoot JM, Stewart S, McKinley AJ, Needs PW, Kroon PA *et al.* Metabolic transformation has a profound effect on anti-inflammatory activity of flavonoids such as quercetin: lack of association between antioxidant and lipoxygenase inhibitory activity. *Biochem Pharmacol* 2008; **75**: 1045–1053.
38 Kumazawa Y, Kawaguchi K, Takimoto H. Immunomodulating effects of flavonoids on acute and chronic inflammatory responses caused by tumor necrosis factor alpha. *Curr Pharm Des* 2006; **12**: 4271–4279.
39 Harwood M, Danielewska-Nikiel B, Borzelleca J, Flamm G, Williams G, Lines T. A critical review of the data related to the safety of quercetin and lack of evidence of in vivo toxicity, including lack of genotoxic/carcinogenic properties. *Food Chem Toxicol* 2007; **45**: 2179–2205.
40 Ambrose AM, Robbins DJ, Deeds F. Comparative toxicities of quercetin and quercitrin. *J Am Pharmaceut Assoc* 1952; **41**: 119–122.
41 Saito D, Shirai A, Matsushima T, Sugimura T, Hirono I. Test of carcinogenicity of quercetin, a widely distributed mutagen in food. *Teratog Carcinog Mutagen* 1980; **1**: 213–221.
42 Hirono I, Ueno I, Hosaka S, Takanashi H, Matsushima T, Sugimura T *et al.* Carcinogenicity examination of quercetin and rutin in ACI rats. *Cancer Lett* 1981; **13**: 15–21.

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