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ORIGINAL RESEARCH

Effects of Quercetin on Blood Pressure: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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***Background*—**Quercetin, the most abundant dietary flavonol, has antioxidant effects in cardiovascular disease, but the evidence regarding its effects on blood pressure (BP) has not been conclusive. We assessed the impact of quercetin on BP through a systematic review and meta-analysis of available randomized controlled trials.

***Methods and Results*—**We searched PUBMED, Cochrane Library, Scopus, and EMBASE up to January 31, 2015 to identify placebo-controlled randomized controlled trials investigating the effect of quercetin on BP. Meta-analysis was performed using either a fixed-effects or random-effect model according to I^2 statistic. Effect size was expressed as weighted mean difference (WMD) and 95% CI. Overall, the impact of quercetin on BP was reported in 7 trials comprising 9 treatment arms (587 patients). The results of the meta-analysis showed significant reductions both in systolic BP (WMD: −3.04 mm Hg, 95% CI: −5.75, −0.33, P=0.028) and diastolic BP (WMD: −2.63 mm Hg, 95% CI: −3.26, −2.01, P<0.001) following supplementation with quercetin. When the studies were categorized according to the quercetin dose, there was a significant systolic BP and diastolic BP-reducing effect in randomized controlled trials with doses ≥500 mg/day (WMD: −4.45 mm Hg, 95% CI: −7.70, −1.21, P=0.007 and −2.98 mm Hg, 95% CI: −3.64, −2.31, P<0.001, respectively), and lack of a significant effect for doses <500 mg/day (WMD: −1.59 mm Hg, 95% CI: −4.44, 1.25, P=0.273 and −0.24 mm Hg, 95% CI: −2.00, 1.52, P=0.788, respectively), but indirect comparison tests failed to significant differences between doses.

***Conclusions*—**The results of the meta-analysis showed a statistically significant effect of quercetin supplementation in the reduction of BP, possibly limited to, or greater with dosages of >500 mg/day. Further studies are necessary to investigate the clinical relevance of these results and the possibility of quercetin application as an add-on to antihypertensive therapy. **(*J Am Heart Assoc*. 2016;5:e002713 doi: 10.1161/JAHA.115.002713)**

Key Words: blood pressure • flavonoids • high blood pressure • hypertension • lipids • meta-analysis • nutrition • quercetin

Nutraceuticals and flavonoid-containing dietary supplements are becoming increasingly popular in the treatment and prevention of cardiovascular disease.[1–4] Flavonols, flavanols, and anthocyanidins are the main members of the group of natural phenolic compounds called flavonoids.[5] The intervention-based human studies performed as early as 1993 have shown a positive correlation between the dietary intake of flavonoids and reduced incidence and mortality from cardiovascular disease.[6] The Zutphen Elderly Study has shown that flavonoids, including quercetin, reduced the risk

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of coronary death by 68% in men who consumed >29 mg flavonols/day compared with men who consumed <10 mg flavonols/day.[6] Quercetin (3, 3′, 4′, 5, 7-pentahydroxyflavone) has been singled out among flavonoids because of its ubiquitous presence and abundance in fruits and vegetables, as such or bound to sugar moieties in various glycosides.[7] Quercetin can be found in apples, capers, cocoa powder, berries, red grapes, red wine, citrus fruits, broccoli, onions, bark roots, flowers, green tea, and black tea.[8] This particular flavonol is the subject of about one third of the 35 000 studies on flavonoids.[9] Prominent effects include antioxidant, anticarcinogenic,[10,11] antithrombotic,[12] anti-allergic,[13] antidiabetic,[14] antiobesity,[15] immune and inflammation-modulating activities,[16] or different cell signaling effects.[17] Anti-atherosclerotic, antiproliferative, and anti-inflammatory effects of quercetin have been documented in many human in vitro and in vivo models.[18] Its positive effect on hypertension was documented for the first time on spontaneously hypertensive rats, in an experimental model that mimics human hypertension.[19] Since then, many experimental and human studies showed that quercetin exerts vasodilator, antiplatelet, and antiproliferative effects, decreasing oxidative status, blood pressure (BP), and end-organ damage.[20–24] The BP-lowering effect of quercetin is more evident in subjects with certain comorbidities such as metabolic syndrome or in smokers.[25] Different studies tried to establish a connection between the antihypertensive effect of quercetin and certain phenotypes such as the apolipoproteins (apo) E3 and E4, but so far results are conflicting.[26]

However, evidence of the effects of quercetin on BP has not been conclusive. Therefore, we systematically reviewed all available randomized controlled trials (RCTs) investigating the impact of quercetin on BP.

Subjects and Methods

Design

This study was designed according to the guidelines of the 2009 preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement[1]) SCOPUS (http://www.scopus.com), Medline (http://www.ncbi.nlm.nih.gov/pubmed), Cochrane Library (www.cochranelibrary.com), and EMBASE (http://www.embase.com) databases were searched using the following search terms in titles and abstracts (also in combination with MESH terms): (quercetin) AND (blood pressure). The wild-card term "*" was used to increase the sensitivity of the search strategy. No language restriction was used in the literature search. The search was limited to studies in humans. The literature was searched from inception to January 31, 2015.

Because of the study design (meta-analysis of RCTs), no Institutional Review Board approval, as well as no patients' informed consents were obtained.

Study Selection

Original studies were included if they met the following inclusion criteria: (1) randomized clinical trial in either parallel or crossover design versus placebo control, (2) investigated the impact of quercetin on BP, (3) presentation of sufficient information on baseline and at the end of study in both quercetin and control groups, and (4) administering quercetin for a period of at least 2 weeks. Exclusion criteria were the following: (1) nonclinical studies, (2) uncontrolled trials, (3) lack of sufficient information on baseline or follow-up BP, and (4) administration of an active comparator in the control group.

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 quercetin and control groups; (5) dose and duration of supplementation with quercetin; (6) age, sex, and body mass index of study participants; (7) circulating concentrations of total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, and glucose; (8) prevalence of smoking, type 2 diabetes, dyslipidemia, hypertension, and coronary heart disease; and (9) systolic blood pressure (SBP) and diastolic blood pressure (DBP).

Access to Study

All authors had access to the study data and reviewed and approved the final manuscript.

Quality Assessment

A systematic assessment of bias in the included studies was carried out using the Cochrane criteria.[27] The items used for the assessment of each study were as follows: adequacy of sequence generation, allocation concealment, blinding, addressing of dropouts (incomplete outcome data), selective outcome reporting, and other potential sources of bias. According to the recommendations of the Cochrane Handbook, a judgment of "yes" indicated low risk of bias, while "no" indicated high risk of bias. Labeling an item as "unclear" indicated an unclear or unknown risk of bias.

Statistical Analysis

Meta-analysis was conducted using the Comprehensive Meta-Analysis (CMA) V2 software (Biostat, NJ).[28] SBP and DBP were

collated in mm Hg. SDs of the mean difference were calculated using the following formula: SD=square root [$(SD_{pretreatment})^2+(SD_{posttreatment})^2 - (2R\times SD_{pretreatment}\times SD_{posttreatment})$], assuming a correlation coefficient (R)=0.5. In case of reporting SEM, SD was estimated using the following formula: SD=SEM×square root (n), where n is the number of subjects.

Net changes in measurements (change scores) were calculated for parallel and crossover 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). Meta-analysis was performed using either a fixed-effects or random-effect model according to I^2 statistic. I^2 values <50% and ≥50% suggested the use of fixed-effects and random-effects model, respectively. The generic inverse variance method was used to weight each individual study included in the meta-analysis. Interstudy heterogeneity was assessed using Cochrane Q statistic and quantified by I^2 statistic. Effect size was expressed as weighted mean difference (WMD) and 95% CI. In order to evaluate the influence of each study on the overall effect size, sensitivity analysis was conducted using the 1-study remove (leave-1-out) approach.

In the absence of trials making head-to-head comparison, the effects of different doses and supplementation durations of quercetin were compared using adjusted indirect comparison according to the method proposed by Song et al[29] and Bucher et al.[30] In this method, treatment effects estimated for each dose or administration duration in the random-effects model could be compared indirectly through common controls.

Meta-Regression

Meta-regression was performed in order to evaluate the association between calculated WMD in SBP and DBP values with dose and duration of quercetin supplementation in the included studies. Meta-regression was performed under a fixed-effects or random-effects (using unrestricted maximum likelihood method) model according to the results of heterogeneity analysis and I^2 values. A covariance matrix was built to assess the covariance between regression coefficients of different confounders.

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 and Tweedie "trim and fill" and "fail-safe N" methods were used to adjust the analysis for the effects of publication bias.[31]

Results

Search Results

The preliminary screening ruled out articles whose titles and/or abstracts were obviously unimportant. After evaluation, 7 articles with 9 quercetin treatment arms met the inclusion criteria and were chosen for the final meta-analysis. For crossover studies with a 2×2 crossover design, each of the study arms (placebo-quercetin or quercetin-placebo) was treated as a separate study. A listing of the study selection procedure is displayed in Figure 1.

Trial Characteristics

In total, 587 participants were randomized, of whom 299 were allocated to quercetin supplementation and 288 to the control group in the 7 selected studies with 9 treatment arms.[32–38] The number of participants in these trials ranged from 13 to 93. Included studies were published between 1998 and 2014, and were conducted in the United States, Iran, Canada, Germany, and Korea. Ranges of doses from 100 to 1000 mg/day of quercetin were administered in the included trials. Duration of supplementation with quercetin ranged between 4 and 10 weeks. Five trials were designed as parallel-group studies and 2 trials as 2×2 crossover design. Among all studies included in this meta-analysis, only 1 study included men and women with prehypertension and stage 1 hypertension.[35] All other studies included patients without hypertension. Demographic and baseline parameters of the included studies are shown in Table 1. Oral quercetin administration was safe and well tolerated in all of the RCTs included in this review, with no report of serious adverse events.

Risk of Bias Assessment

The assessment of risk of bias in the included studies using Cochrane criteria is shown in Table 2.

Effect of Quercetin on SBP

Meta-analysis of data from 9 treatment arms showed significant reductions in SBP (WMD: −3.04 mm Hg, 95% CI: −5.75, −0.33, *P*=0.028) following supplementation with quercetin (Figure 2 upper part). Removal of the study by Zahedi et al[33] from the meta-analysis yielded a nonsignificant effect size equivalent to −1.78 mm Hg; 95% CI: −4.07, 0.52, *P*=0.129. When the RCTs were stratified according to the duration of supplementation, there was no significant effect in the subsets of studies lasting <8 weeks (WMD: −2.18 mm Hg, 95% CI: −5.00, 0.64, *P*=0.130), while a marginally significant reducing effect was observed in trials

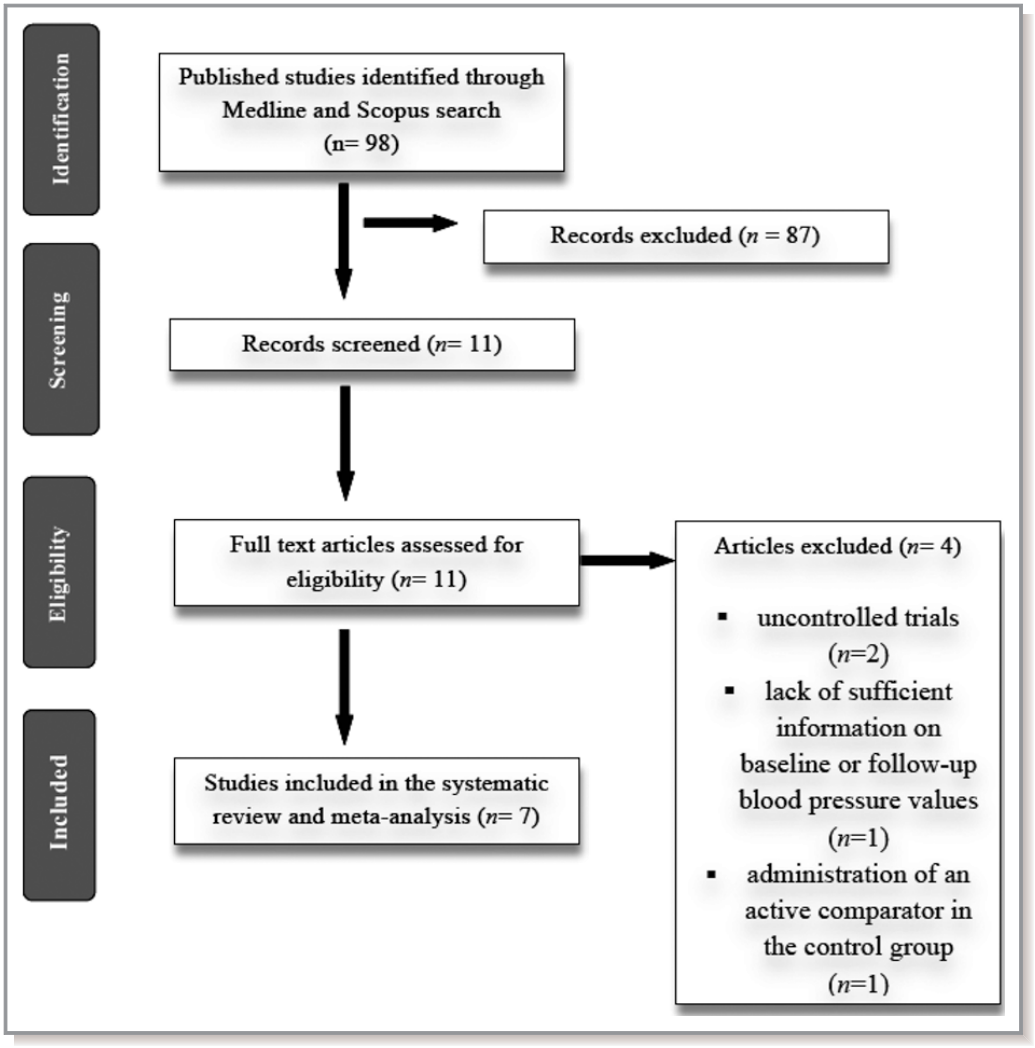

Figure 1. Flow chart of number of studies identified and included in the review.

with ≥8 weeks of follow-up (WMD: −3.57 mm Hg, 95% CI: −7.51, 0.37, *P*=0.076). Likewise, a significant effect of quercetin was observed in the subset of trials administering doses ≥500 mg/day (WMD: −4.45 mm Hg, 95% CI: −7.70, −1.21, *P*=0.007) but not in the subset with <500 mg/day doses (WMD: −1.59 mm Hg, 95% CI: −4.44, 1.25, *P*=0.273) (Figure 3). When dose classification was set at ≤500 and >500 mg/day, no significant change was observed in either of the subgroups (*P*>0.05 for both). Adjusted indirect comparison did not suggest any significant difference between either of the dose (ΔWMD: −5.01 mm Hg, 95% CI: −9.19, −0.83, Δ*z*-score: −2.35, *P*>0.05) and supplementation duration (ΔWMD: −4.35 mm Hg, 95% CI: −8.46, −0.24, Δ*z*-score: −2.08, *P*>0.05) subgroup pairs.

Effect of Quercetin on DBP

Combined analysis of 9 RCT arms revealed a significant reduction of DBP (WMD: −2.63 mm Hg, 95% CI: −3.26, −2.01, *P*<0.001) following supplementation with quercetin (Figure 2 lower part). Removal of the study by Zahedi et al[33] yielded an effect size equivalent to −0.98 mm Hg (95% CI: −2.44, 0.49, *P*=0.191). In subgroup analysis, a marginally significant effect was found in the subset of trials with <8 weeks of follow-up (WMD: −1.85 mm Hg, 95% CI: −3.72, 0.02, *P*=0.053) but not in the subset lasting ≥8 weeks (WMD: −0.88 mm Hg, 95% CI: −3.23, 1.47, *P*=0.464) (Figure 3). When the studies were categorized according to administered quercetin dose, there was a greater DBP-reducing effect in trials with ≥500 mg/day (WMD: −2.98 mm Hg, 95% CI: −3.64, −2.31, *P*<0.001) versus those with <500 mg/day dosage (WMD: −0.24 mm Hg, 95% CI: −2.00, 1.52, *P*=0.788) (Figure 4). This result was also consistent when the dose classification was set at ≤500 and >500 mg/day (*P*>0.05 and <0.05, respectively). However, adjusted indirect comparison did not suggest any significant difference between either of the dose (ΔWMD: −2.74 mm Hg, 95% CI: −4.34, −1.14, Δ*z*-score: −3.36, *P*>0.05) and supplementation duration (ΔWMD:

Table 1. Demographic Characteristics of the Included Studies

Study	Javadi et al[32]	Zahedi et al[33]	Conquer et al[34]	Edwards et al[35]	Egert et al[36]	Lee et al[37]	Pfeuffer et al[38]
Year	2014	2013	1998	2007	2009	2011	2013
Location	Iran	Iran	Canada	USA	Germany	Korea	Germany
Design	Randomized, double-blind placebo-controlled clinical trial	Randomized, double-blind placebo-controlled clinical trial	Randomized, double-blind placebo-controlled clinical trial	Randomized, double-blind, placebo-controlled, crossover trial	Randomized, double-blind, placebo-controlled crossover trial	Randomized, double-blinded, placebo-controlled clinical trial	Randomized, double-blind, placebo-controlled crossover trial
Duration of study	8 weeks	10 weeks	4 weeks	4 weeks	6 weeks of treatment separated by a 5-week washout period	10 weeks	8 weeks of treatment separated by a 3-week washout period
Inclusion criteria	Women age 19 to 70 y old, unchanged type and dose of medications from previous month and no pregnancy or lactation	Women with a history of T2DM for at least 3 y, age between 35 to 55 y, not smoking and addiction, lack of insulin, lack of severe heart diseases, stroke, severe liver and renal diseases, gastrointestinal disorders, thyroid dysfunction, rheumatoid arthritis, and infectious diseases	Healthy men and women with cholesterol levels of 4.0 to 7.2 mmol/L	Men and women with prehypertension and stage 1 HTN	Patients with the following traits of the metabolic syndrome: central obesity (waist circumference ≥94 cm for men and ≥80 cm for women); serum concentration of TAG ≥1500 mg/L and/or serum concentration of hs-CRP ≥2.0 mg/L	Healthy male smokers in the age range of 30 to 60 y	Healthy male patients with apolipoprotein E genotype
Route of administration	Oral	Oral	Oral	Oral	Oral	Oral	Oral
Quercetin dose	500 mg/day	500 mg/day	1000 mg/day	730 mg/day	150 mg/day	100 mg/day	150 mg/day
Primary end point(s)	Changes in oxidant status, BP and C-reactive protein	Changes in lipids, BP and inflammatory factors	Changes in plasma quercetin levels, cardiovascular and thrombotic factors	Changes in BP	Changes in BP	Changes in cardiometabolic risk	Changes in endothelial function
Participants							
Case	20	34	13	19*	93	49	49
				22†			
Control	20	28	14	19‡	93	43	49
				22§			

Continued

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Table 1. Continued

Study	Javadi et al[32]	Zahedi et al[33]	Conquer et al[34]	Edwards et al[35]	Egert et al[36]	Lee et al[37]	Pfeuffer et al[38]
Age, y							
Case	46.5±9.9	46.4 (±4.5)	42.0±2.7	47.8±3.5*	45.1 (10.53)	46.1±7.1 (32–62)	59.4±0.9
				49.2±2.9†			
Control	48.0±8.4		41.5±2.9	47.8±3.5‡	45.1 (10.53)	42.4±8.2 (23–55)	59.4±0.9
				49.2±2.9§			
Male (%)							
Case	0	0	NS	68.4*	45.2	100	100
				59.1†			
Control	0	0	NS	68.4‡	45.12	100	100
				59.1§			
BMI, kg/m^2							
Case	27.99±4.4	NS	26.2±1.1	29.6±1.3*	30.6 (3.23)	24.7±3.0	26.3±0.3
				29.3±1.3†			
Control	30.70±4.6	NS	26.0±1.3	29.8±1.3‡	30.6 (3.23)	24.9±2.8	26.3±0.3
				29.5±1.4§			
TC, mg/dL							
Case	NS	189.2±7.5	196.83±10.05	198.37±8.89*	221.19 (39.83)	193.5±32.1	209.98±5.41
				206.49±8.51†			
Control	NS	177.6±6.4	197.22±9.67	197.99±9.28‡	219.64 (40.60)	194.3±36.4	209.98±5.41
				205.72±8.12§			
LDL-C, mg/dL							
Case	NS	106.1±5.5	109.82±8.89	116.01±7.73*	138.82 (37.51)	113.2±20.3	135.73±4.64
				124.90±9.28†			
Control	NS	103.6±4.5	111.37±6.57	117.17±6.57‡	137.27 (36.35)	115.6±24.7	135.73±4.64
				115.24±8.12§			
HDL-C, mg/dL							
Case	NS	45.2±1.7	58.00±4.25	47.95±5.03*	52.20 (17.79)	44.3±6.9	53.36±1.93
				47.56±3.48†			
Control	NS	46.8±2.4	60.71±4.64	47.95±4.64‡	50.27 (16.63)	45.0±5.3	53.36±1.93
				49.11±3.09§			

Continued

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Table 1. Continued

Study	Javadi et al[32]	Zahedi et al[33]	Conquer et al[34]	Edwards et al[35]	Egert et al[36]	Lee et al[37]	Pfeuffer et al[38]
TG, mg/dL							
Case	NS	198.4±20.5	112.49±19.48	177.15±21.26* 205.49±34.54†	161.20 (86.80)	163.5±87.7	106.29±6.20
Control	NS	151±9.4	124.89±20.37	161.20±21.26‡ 209.92±30.11§	172.72 (87.69)	185.0±91.6	106.29±6.20
Glucose, mg/dL							
Case	NS	NS	NS	107.82±4.5* 108.00±3.6†	98.82 (12.24)	108.3±18.1	100.8±1.44
Control	NS	NS	NS	102.24±3.24‡ 114.66±5.04§	97.92 (12.6)	109.9±28.5	100.8±1.44
Smoking %							
Case	0	0	NS	0* 0†	0	100	NS
Control	0	0	NS	0‡ 0§	0	100	NS
T2DM %							
Case	NS	100	NS	0* 0†	0	0	0
Control	NS	100	NS	0‡ 0§	0	0	0
Dyslipidemia %							
Case	NS	NS	NS	0* 0†	NS	NS	0
Control	NS	NS	NS	0‡ 0§	NS	NS	0
HTN %							
Case	0	NS	NS	0* 53.65†	0	0	0
Control	0	NS	NS	0‡ 53.65§	0	0	0

Continued

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Table 1. Continued

Study	Javadi et al[32]	Zahedi et al[33]	Conquer et al[34]	Edwards et al[35]	Egert et al[36]	Lee et al[37]	Pfeuffer et al[38]
CHD %							
Case	NS	NS	NS	NS*	0	0	NS
				NS†			
Control	NS	NS	NS	NS‡	0	0	NS
				NS§			
SBP, mm Hg							
Case	113.75±18.47	117.0±2.0	121.6±4.2	132±1*	130.3 (16.4)	132.9±14.9	132.9±2.2
				145±2†			
Control	121.13±15.99	110±2.0	120.4±3.5	135±3‡	130.3 (16.4)	135.5±11.3	132.9±2.2
				141±2§			
DBP, mm Hg							
Case	78.13±9.96	79±10	79.3±2.8	85±1*	81.6 (9.3)	88.7±9.9	80.8±1.3
				97±1†			
Control	86.75±9.50	73±10	75.5±2.4	84±1‡	81.6 (9.3)	86.9±10.4	80.8±1.3
				94±2§			

Values are expressed as mean±SD or median (25–75 percentiles). BMI indicates body mass index; BP, blood pressure; CHD, coronary heart disease; DBP, diastolic blood pressure; DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; HTN, hypertension; LDL-C, low-density lipoprotein cholesterol; NS, not stated; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TAG, triacylglycerol; TG, triglycerides.

*730 mg quercetin/day—prehypertension patients.

†730 mg quercetin/day—stage 1 HTN patients.

‡Placebo—prehypertension patients.

§Placebo—stage 1 HTN patients.

Table 2. Risk of Bias Assessment in the Studies Included in This Meta-Analysis

Study	Reference	Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Outcome Reporting	Other Potential Threats to Validity
Javadi et al	32	L	U	L	L	L	L	L
Zahedi et al	33	L	L	L	L	L	L	L
Conquer et al	34	U	U	L	L	L	L	L
Edwards et al	35	U	U	L	L	U	L	L
Egert et al	36	L	U	L	L	L	L	L
Lee et al	37	U	U	L	L	L	L	L
Pfeuffer et al	38	U	U	L	L	L	L	L

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

−0.88 mm Hg, 95% CI: −2.68, 0.92, Δ*z*-score: −0.96, *P*>0.05) subgroup pairs.

Meta-Regression Analysis

Potential associations between the antihypertensive effects of quercetin with dose and duration of supplementation were evaluated using meta-regression analysis. SBP-lowering effect of quercetin was associated with duration of supplementation (slope: −0.92; 95% CI: −1.52, −0.32; *P*=0.003) but not the administered dose (slope: −0.003; 95% CI: −0.01, 0.07; *P*=0.548). With respect to DBP, there was a dose–response association (slope: −0.07; 95% CI: −0.01, −0.002; *P*=0.005) but the observed effect size was independent of

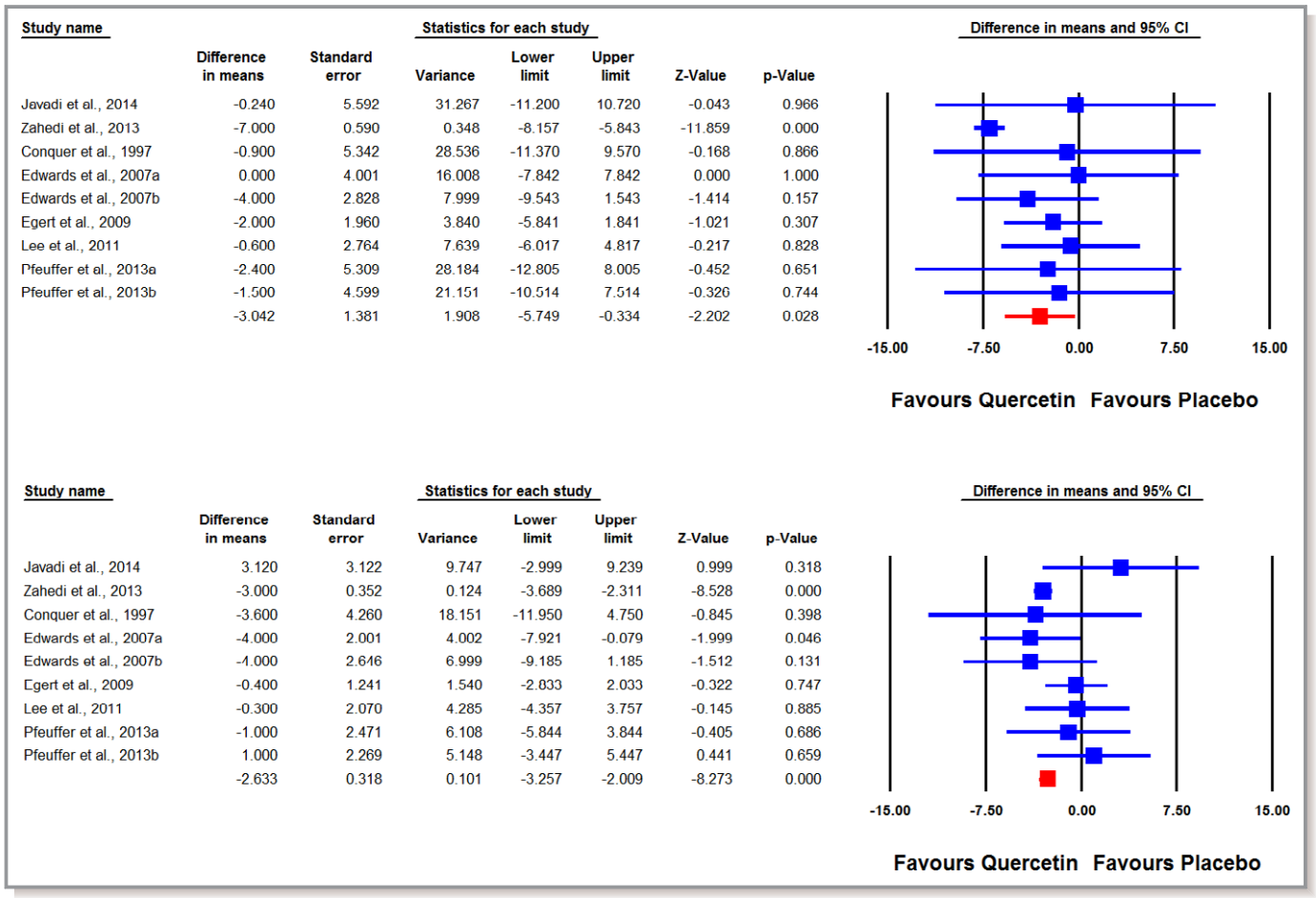

Figure 2. Forest plot displaying weighted mean difference and 95% CIs for the impact of quercetin on systolic (upper plot) and diastolic (lower plot) blood pressures.

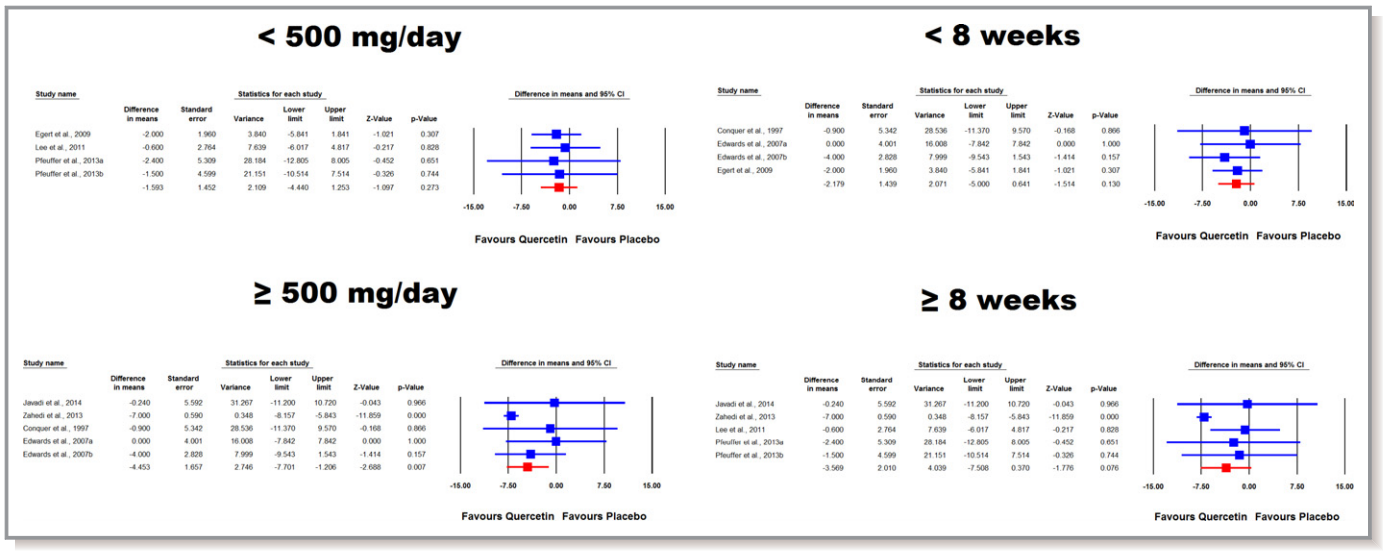

Figure 3. Forest plot displaying weighted mean difference and 95% CIs for the impact of quercetin on systolic blood pressure in different subgroups of trials stratified according to the administered quercetin dose and duration of supplementation.

supplementation duration (slope: −0.22; 95% CI: −0.62, 0.18; P=0.276) (Figure 5). Using a covariance matrix analysis of regression coefficients, the covariance of treatment dose and duration was 0 for SBP analysis and −0.0001 for DBP analysis.

Publication Bias

Visual inspection of the funnel plot of SE versus effect size (mean difference) suggested a potential publication bias for the impact of quercetin on both SBP and DBP. Using trim-and-fill correction, 4 and 3 potentially missing studies were imputed for the analysis of SBP and DBP, respectively. The imputed effect sizes of quercetin on SBP and DBP were −4.51 mm Hg (95% CI: −6.55, −2.47; P<0.05) and −2.83 mm Hg (95% CI: −3.44, −2.22; P<0.05), respectively (Figure 6).

In addition to visual inspection of funnel plots, presence of publication bias was explored using Begg's rank correlation test, Egger's linear regression test, and "fail-safe N" test. The results of these tests are summarized in Table 3.

Discussion

To our knowledge, the present meta-analysis is the first to assess the effects of quercetin supplementation on BP based

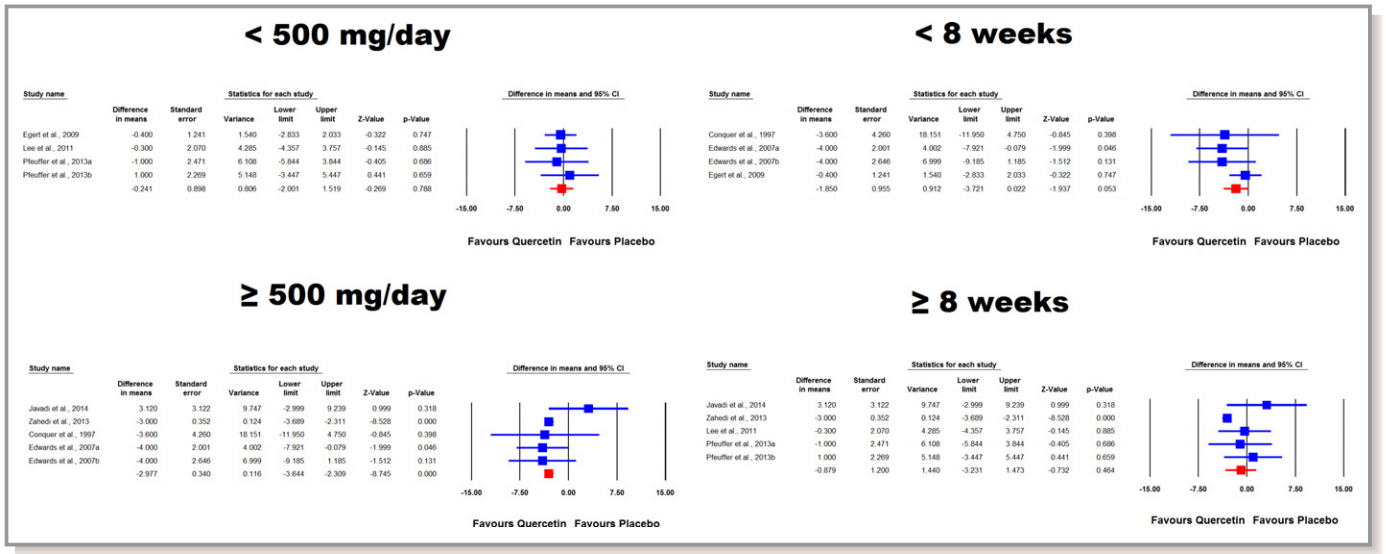

Figure 4. Forest plot displaying weighted mean difference and 95% CIs for the impact of quercetin on diastolic blood pressure in different subgroups of trials stratified according to the administered quercetin dose and duration of supplementation.

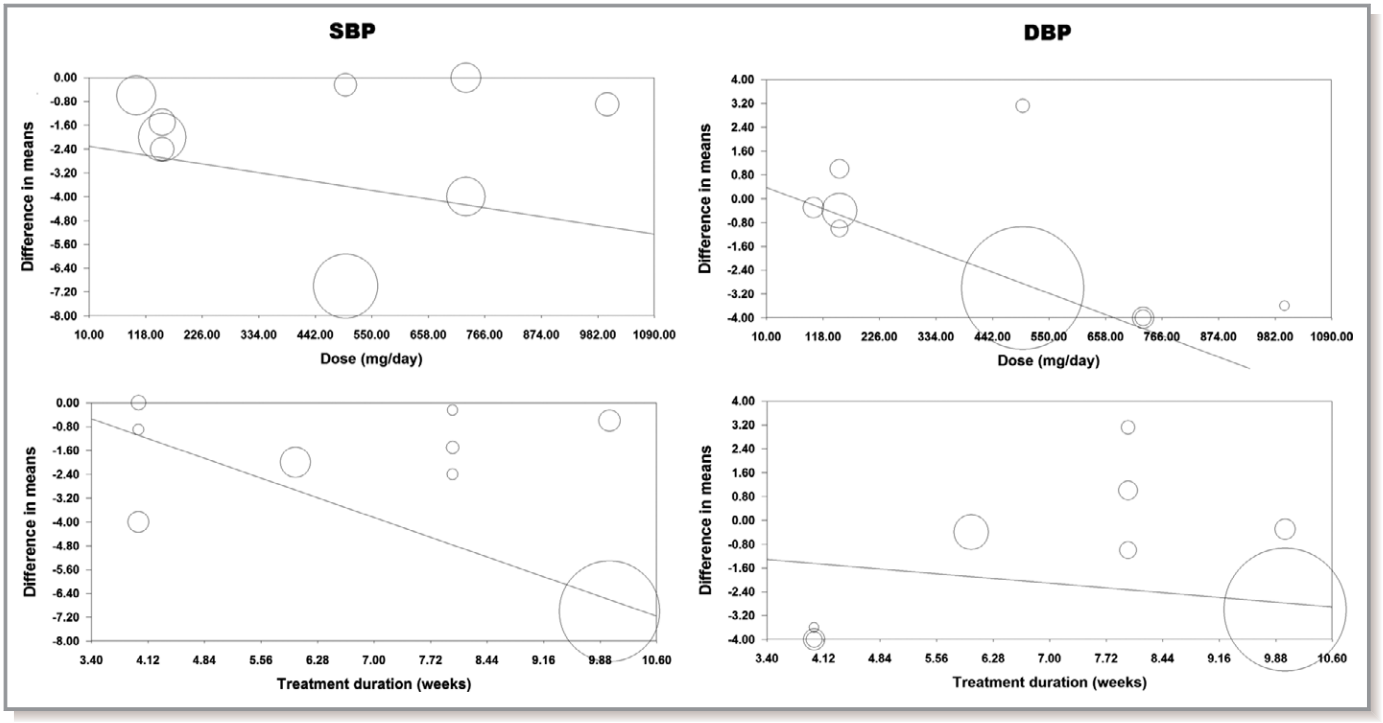

Figure 5. Meta-regression bubble plots of the association between mean changes in systolic and diastolic blood pressure values after quercetin supplementation with quercetin dose and duration of supplementation. The size of each circle is inversely proportional to the variance of change.

on the results from RCTs. Meta-analysis of data from 9 treatment arms showed significant reductions in SBP and DBP following supplementation with quercetin. The estimated effect sizes for the impact of quercetin on BP were sensitive only to the study of Zahedi et al.[33] The distinctive feature of this study in comparison to other studies included in the meta-analysis is recruitment of diabetic subjects. Hence, the greater effect size observed by Zahedi et al[33] might be attributed to the higher activity of quercetin in diabetic subjects attributable to the reported hypoglycemic and insulin-sensitizing activities of this phytochemical in diabetes, which can eventually lead to attenuation of diabetes-induced vasoconstriction.[7,39] In addition, the heightened state of oxidative stress in diabetes might justify a more sizable effect of quercetin as an efficient antioxidant,[25] providing another potential mechanism for the antihypertensive effect of quercetin.

The calculated BP-lowering effect of quercetin is substantial (−3.04, −2.63 mm Hg SBP/DBP), particularly considering that the cohorts of the studies included were largely made up of normotensive individuals. When the RCTs were stratified according to the duration of supplementation, there was no significant effect in the subsets of studies lasting <8 weeks, while a marginally significant reducing effect was observed in trials with ≥8 weeks of follow-up. Likewise, a significant effect of quercetin was observed in the subset of trials administering doses ≥500 mg/day, but not in the subset with <500 mg/day doses. The results indicated a significant antihypertensive effect of quercetin supplementation on both SBP and DBP. In interpreting the results of the subanalyses based on length of administration and dose, caution should be used because of loss of statistical power attributable to RCT stratification, and because indirect comparison tests failed to confirm statistically significant differences. Clearly, studies directly comparing different doses or treatment duration are necessary.

The mechanisms accountable for these effects of quercetin are not completely understood, with multiple modulation in cell signaling and gene expression being the most probable. Some attempts to clarify the mechanism of action of quercetin in hypertension were performed.[40,41] Hypotheses tested in different experimental and clinical trials included the following: lowering of oxidative stress,[19] interference with the renin–angiotensin system,[42] improvement of endothelial function,[43] downregulation of endothelin-1 expression,[44] downregulation of nicotinamide adenine dinucleotide phosphate-oxidase,[45] increasing of endothelial nitric oxide synthase activity,[45] downregulation of angiotensin II 1a receptor expression in the kidney, or improving the balance between circulating endothelin-1 and NO.[22] Also, the exact contribution of quercetin metabolites to the overall antihypertensive effect must be clarified: about 90% of dietary quercetin is not absorbed and undergoes extensive metabolization by colic

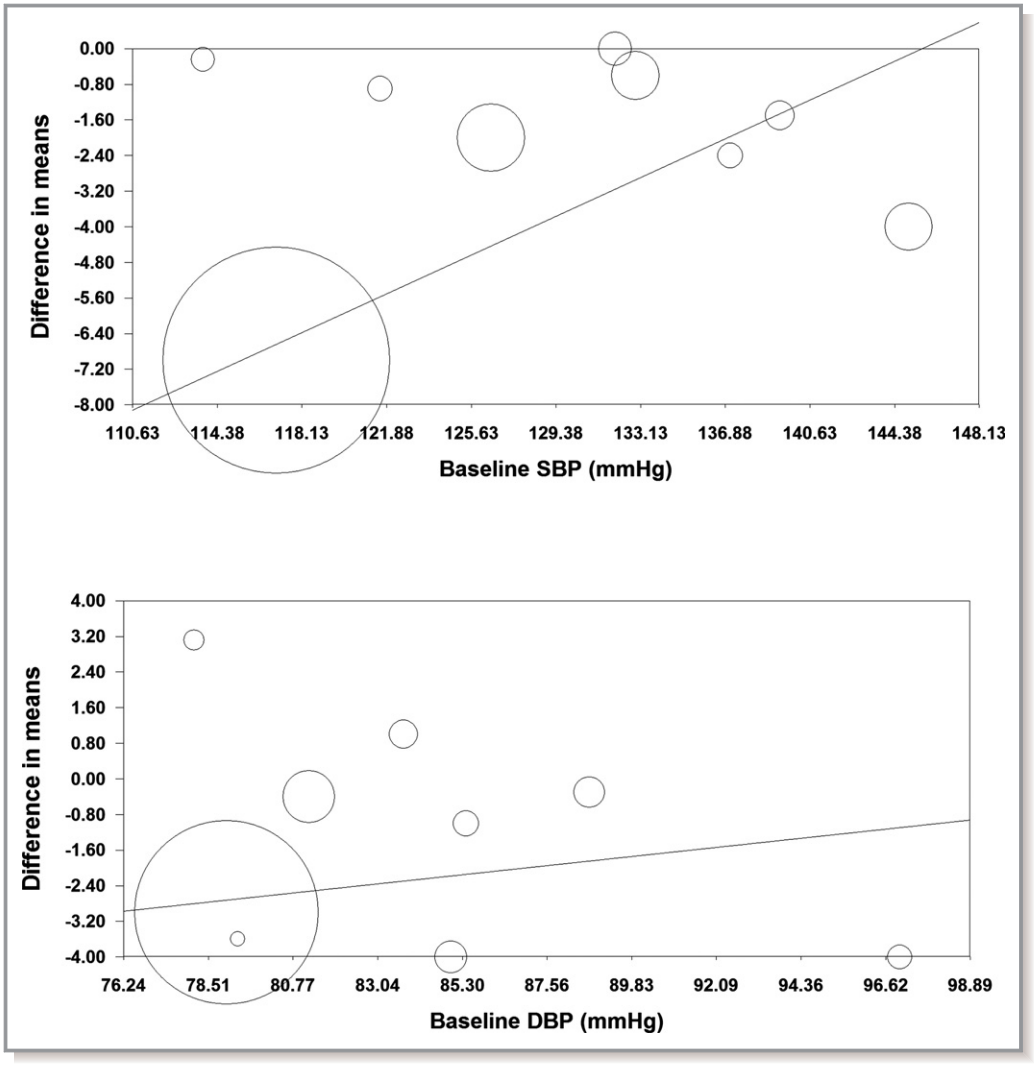

Figure 6. Funnel plot displaying publication bias in the studies reporting the impact of quercetin on systolic (upper plot) and diastolic (lower plot) blood pressure. The size of each circle is inversely proportional to the variance of change.

microbiota, resulting in phenolic acids, compounds that have not been investigated yet in the context of hypertension.[46] Furthermore, the antihypertensive effects of quercetin and captopril were similar in an experimental study on Dahl salt-sensitive rats.[22]

A challenge to the explanation of quercetin bioactivity was represented, until recently, by the contradiction between its extremely low plasma concentration after oral administration and the demonstrable systemic effects.[47] The resolution of this inconsistency, termed the "flavonoid paradox" came with the full comprehension of the conjugation–deconjugation steps of these compounds in humans.[9] It has been proven that after oral absorption, quercetin is rapidly converted to circulating conjugates through glucuronidation, sulfatation, or

Table 3. Assessment of Publication Bias in the Impact of Quercetin on Blood Pressure

	Begg's Rank Correlation Test			Egger's Linear Regression Test					Fail-Safe N Test
	Kendall's Tau*	*z*-Value	*P* Value	Intercept	95% CI	*t*	*df*	*P* Value	n†
SBP, mm Hg	−0.08	0.31	0.754	1.69	0.91, 2.47	5.12	7	0.001	54
DBP, mm Hg	0.08	0.31	0.754	0.94	−0.24, 2.13	1.88	7	0.102	31

DBP indicates diastolic blood pressure; SBP, systolic blood pressure.
*With continuity correction.
†Number of theoretically missing studies.

methylation, as a measure of classical xenobiotic detoxification.[46] This accounts for the very low aglycone concentrations in human plasma (in the nanomolar range).[48] At a vascular level, quercetin glucuronides, but not sulfoconjugates, are freed of their sugar moiety by a deconjugation process performed by β-glucuronidases, and the free aglycone is delivered to tissues.[9] Given the importance of quercetin glucuronide deconjugation, β-glucuronidase activity is crucial for the therapeutic effectiveness of this flavonol.[9] Furthermore, correlations between β-glucuronidase activity and apo E phenotype[49] may explain the efficacy of quercetin in patients with apo E3 phenotype as opposed to those expressing apo E4 phenotype.[50] On the other hand, an increased activity of β-glucuronidase under inflammatory conditions has also been pointed out, raising the hypothesis that quercetin may be more effective under inflammatory conditions—a valuable aspect since hypertension may be associated with comorbidities having an inflammatory component.[51]

Our findings that higher doses (>500 mg) of quercetin yield greater effect size on BP are to a certain extent opposite to those obtained in the Cancer Prevention Study II Nutrition Cohort that reported that even relatively small quantities of flavonoid-rich foods may be beneficial in reducing the risk of cardiovascular disease.[52] This could be explained by the fact that the amounts used in most dietary intervention studies are higher than those used in the general public. Indeed, a recent trial showed that the habitual intake of flavonoids in Europe is much below the amounts found to have a significant health effect.[53]

Quercetin has a generally recognized as safe status according to the U.S. Food and Drug Administration; only some minor side-effects such as headache, nausea, and tingling of the extremities were observed in long-term quercetin supplementation at 1000 mg/day.[54] In 2011, the European Food Safety Authority released a variety of health claims underlying the protective effects of quercetin against oxidative damage.[55] Considering the seasonality of food extracts of flavonoids, the Recommended Dietary Allowance of total flavonoids might be between 250 and 400 mg/day.[56]

This meta-analysis has several limitations. Most importantly, eligible RCTs involved in this meta-analysis had small populations and short durations of follow-up. The number of included studies also was not large enough to allow robust subgroup analyses. Moreover, there is considerable heterogeneity in the groups studied: females with rheumatoid arthritis, females with diabetes, healthy people, overweight high-risk subjects, and male smokers. Finally, most of the individuals included were normotensive or prehypertensive. It will be necessary to evaluate the effects of quercetin supplementation on long-term control of hypertension and its complications.

In conclusion, the results of this meta-analysis showed a significant effect of quercetin supplementation in the reduction of BP, which suggest that this nutraceutical might be considered as an add-on to antihypertensive therapy. Further well-designed trials are necessary to elucidate the clinical value of quercetin supplementation in hypertension therapy, to adjust the dosage, and to explore possible drug interactions between quercetin and antihypertensive drugs, as this flavonol is metabolized by the cytochrome P450 system.[57,58] Additional long-term studies on quercetin safety at pharmacological doses are warranted as well, since quercetin supplementation as an antihypertensive implies a 10- to 60-fold increase in its average dietary intake. Exploration of possibly greater benefits of quercetin supplementation in RCTs among hypertensive and/or diabetic populations merits further investigations.

Appendix

The Lipid and Blood Pressure Meta-analysis Collaboration (LBPMC) Group members are the following: Maciej Banach, MD, PhD, FAHA, Maria-Corina Serban, MD, PhD, Amirhossein Sahebkar, PharmD, Alberto Zanchetti, MD, PhD, Dimitri P. Mikhailidis, MD, PhD, George Howard, DrPH, Diana Antal, PharmD, Florina Andrica, PhDs, Ali Ahmed, MD, MPH, Wilbert S. Aronow, MD, Paul Muntner, PhD, Gregory Y.H. Lip, MD, Ian Graham, MD, PhD, Nathan Wong, MD, PhD, and Jacek Rysz, MD, PhD.

Disclosures

None. This meta-analysis was written independently; no company or institution supported it financially. Some of the authors have given talks, attended conferences, and participated in trials and advisory boards sponsored by various pharmaceutical companies. No professional writer was involved in the preparation of this meta-analysis.

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