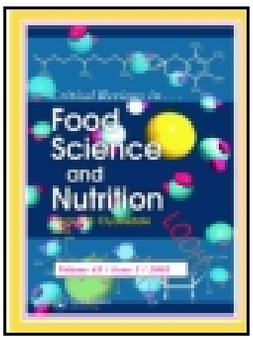

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REVIEW

The effects of catechin on endothelial function: A systematic review and meta-analysis of randomized controlled trials

Rana Shafabakhsh[a], Alireza Milajerdi[b], Željko Reiner[c], Fariba Kolahdooz[d], Elaheh Amirani[a], Hamed Mirzaei[a], Maryam Barekat[e], and Zatollah Asemi[a]

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ABSTRACT

The findings of trials investigating the effect of catechin on endothelial function are controversial. This meta-analysis of randomized controlled trials (RCTs) was performed to summarize the existing evidence and determine the effects of catechin supplementation on endothelial function. Two authors independently searched electronic databases including MEDLINE, EMBASE, Cochrane Library, and Web of Science from inception until March 2019, in order to find relevant RCTs. The quality of selected RCTs was evaluated using the Cochrane Collaboration risk of bias tool. Cochrane's Q test and *I*-square (I^2) statistic were used to determine the heterogeneity of included trials. Data were pooled using a random-effects model and weighted mean difference (WMD) was considered as the overall effect size. A total of 16 studies with 22 effect sizes were included in this meta-analysis. A significant increase in flow mediated dilation (FMD) in 10 studies was found after catechin supplementation including 13 effect sizes (WMD: 1.53; 95% CI: 0.93, 2.14). The pooled analysis of 7 effect sizes from 4 studies showed a significant reduction in pulse wave velocity (PWV) after catechin supplementation (WMD: −0.32; 95% CI: −0.44, −0.20) and combining 5 effect sizes from 3 studies in augmentation index (AI) (WMD: −3.57; 95% CI: −6.40, −0.74). Catechin supplementation significantly increased FMD, and significantly reduced PWV and AI, but did not affect other markers of endothelial function.

KEYWORDS

Catechin; endothelial function; ICAM-1; endothelin; meta-analysis

Introduction

The endothelium which lines the surface of the blood vessels, has pivotal role in maintenance of vascular integrity and regulates thrombosis, vascular tone, vascular wall function, inflammation, and angiogenesis by releasing of different signaling molecules (Godo and Shimokawa, 2017; Lara et al., 2016). Disbalance of factors which are derived from endothelium, results in endothelium dysfunction (Vanhoutte et al., 2009). Endothelium dysfunction causes pathogenesis and progression of atherosclerosis, cardiovascular disease (CVD), inflammatory diseases such as vasculitides, and hypertension (Konukoglu and Uzun, 2017). Assessment of endothelial function can predict future cardiovascular events and provides an appropriate marker of CVD. In addition, endothelial function could be an appropriate therapeutic target in for prevention of these diseases (Davignon and Ganz, 2004; Landmesser et al., 2004).

It has been indicated that drugs with endothelium-protective characteristics might be beneficial in treatment of these diseases (Konukoglu and Uzun, 2017). Catechins are polyphenolic compounds which are present in food and plants, particularly in tea and cocoa (Matsui, 2015; Xiang et al., 2016). Catechins is a common name for four substances including epicatechin (EC), epicatechin gallat, epigallocatechin, and epigallocatechin galate (Chen et al., 2005). They are secondary metabolites belonging to the group of flavanols which is a part of the family of flavonoids. A large amount of evidence exists about the relationship between consumption of catechin-rich foods and prevention of several human diseases, including CVD (Chen et al., 2016; Mangels and Mohler, 2017). Several studies also investigated the effects of catechin on endothelial function (Neale et al., 2017; Saarenhovi et al., 2017). However, their results are controversial. In a small study, after 2 weeks of taking cocoa flavanol by healthy young (<35 years) and elderly (50–80 years) man, flow mediated dilation (FMD) significantly improved in young and elderly men, pulse wave velocity (PWV) decreased, and total peripheral resistance was lowered, while arteriolar and microvascular vasodilator capacity and diastolic blood pressure decreased (Heiss et al., 2015). Lekakis et al. (2005) demonstrated that polyphenolic compounds from red grapes

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significantly improved endothelial function in patients with coronary heart disease (CHD). However, intake of pure EC (2×50 mg EC) in healthy subjects did not significantly improve FMD (Saarenhovi et al., 2017).

There are many randomized controlled trials (RCTs) which analyzed the effect of catechin on endothelial function. Differences in several aspects of these RCTs including study design, dosage of catechins used, characteristics of participants, and duration of intervention obviously caused inconsistent results. So far, no meta-analysis was performed and no earlier study has systematically reviewed findings from RCTs on the effects of catechin supplementation and endothelial function. Therefore, this study was performed to systematically summarize the present evidence of RCTs on the effects of catechin on endothelial function and to make a meta-analysis of RCTs.

Methods

Search and studies selection strategies

In this meta-analysis we used following databases: Pubmed, Web of Science, Scopus, and Google Scholar. The databases were searched from inception up to March 2019. A search strategy was developed using the following MeSH and text keywords; intervention ("catechin" AND "intake" OR "supplementation" OR "drink" OR "beverage"), and biomarkers ("FMD" OR "PWV" OR "augmentation index (AI)" OR "endothelin-1 (ET-1)" OR "intercellular adhesion molecule-1 (ICAM-1)" OR "vascular adhesion molecule-1 (VCAM-1)" OR "nitric oxide (NO)."

Inclusion and exclusion criteria

All RCTs with either parallel or cross-over design that analyzed the effects of catechin administration on endothelial function and with standard deviation (SD) and related 95% confidence interval (CI) for the both intervention and control/placebo groups. Other studies such as case reports, animal experiments, in vitro studies, observational studies, trials without a control group, and studies that did not achieve the least quality score were excluded from this meta-analysis.

Data extraction and quality assessment

Two independent authors (RS and EA) screened the articles for the eligibility. In the first step the title and abstract of studies were reviewed. Then, the full-text of relevant studies was analyzed and assessed to ascertain the suitability of a study for inclusion into the meta-analysis. Any disagreement was discussed and resolved by the third author (ZA).

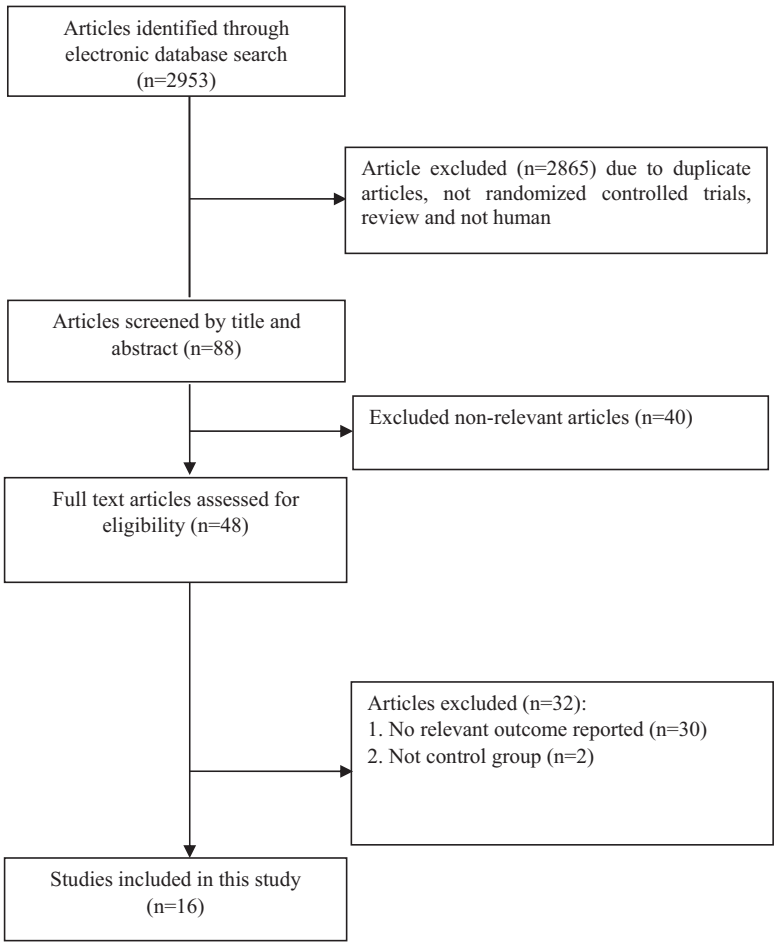


Figure 1. Literature search and review flowchart for selection of studies.

Table 1. Characteristics of included studies

Authors (ref)	Publication year	Sample size (control/ intervention)	Country/population	Intervention (name and daily dose)	Duration	Age (y) (control, intervention)	Presented data
Basu et al. (a) (2011)	2011	5/11	USA/obese subjects with metabolic syndrome	Green tea (4 cups/day, each cup contains 232 mg catechin)	8 weeks	44.6 ± 8.4, 42.8 ± 8.6	ICAM-1, VCAM-1
Basu et al. (b) (2011)	2011	6/7	USA/obese subjects with metabolic syndrome	Green tea extract (2 capsules/day, each capsule contains 435 mg catechin)	8 weeks	44.6 ± 8.4, 39.5 ± 9.9	ICAM-1, VCAM-1
Hill et al. (2007)	2007	19/19	Australia/overweight or obese postmenopausal women	2 Teavigo capsules/day (total EGCG intake 300 mg/day) + moderate intensity exercise	12 weeks	45–70	FMD
Rodriguez-Mateos et al. (a) (2018)	2018	8/15	Germany/healthy	DP1–10 capsules (containing 130 mg epicatechin)	1 month	23 ± 2, 23 ± 2	FMD, PWV
Rodriguez-Mateos et al. (b) (2018)	2018	7/15	Germany/healthy	DP2–10 capsules (containing 20 mg epicatechin)	1 month	23 ± 2, 25 ± 2	FMD, PWV
Widlansky et al. (2007)	2007	42/42	USA/patients with CAD	Epigallocatechin gallate (300 mg/day)	2 weeks	58 ± 10, 59 ± 8	FMD, ICAM
Hollands et al. (a) (2018)	2018	21/42	UK/adults with moderately elevated blood pressure	Apple extract (delivering 70 mg catechin + PCs)	4 weeks	63 ± 7	ET-1, PVW, AIX, NO
Hollands et al. (b) (2018)	2018	21/42	UK/adults with moderately elevated blood pressure	Apple extract (delivering 140 mg catechin + procyanidins)	4 weeks	63 ± 7	ET-1, PVW, AIX, NO
Oyama et al. (a) (2010)	2010	10/10	Japan/smokers	Green tea beverages (containing 80 mg catechin)	14 days	34.8 ± 2.3, 36.6 ± 2.4	NO
Oyama et al. (b) (2010)	2010	10/10	Japan/smokers	Green tea beverages (containing 580 mg catechin)	14 days	34.8 ± 2.3, 35.2 ± 1.8	NO
Hsu et al. (2007)	2007	30/14	Taiwan/hemodialysis patients	Catechins (455 mg/day)	3 months	58.1 ± 15.0, 60.1 ± 14.8	ICAM-1
Farouque et al. (2006)	2006	19/19	Australia/subjects with CAD	Flavanol-rich chocolate bar and cocoa beverage (containing 444 mg of flavanols daily; ≈107 mg of epicatechin monomer/day)	6 weeks	61 ± 35.7, 61 ± 40.2	FMD, ICAM-1, VCAM-1
Sansone et al. (2015b)	2015	50/50	Germany/healthy	Cocoa flavanol drink (containing 146 mg catechin)	1 month	44 ± 9, 45 ± 8	FMD, PWV, AIX
Heiss et al. (a) (2015)	2015	11/11	Germany/young healthy	Cocoa flavanol drink (containing 146 mg catechin)	2 weeks	26 ± 1	FMD, PWV, AIX
Heiss et al. (b) (2015)	2015	10/10	Germany/elderly healthy	Cocoa flavanol drink (containing 146 mg catechin)	2 weeks	60 ± 2	FMD, PWV, AIX
Jeong et al. (2016)	2016	25/26	Korea/patients with metabolic syndrome	Black raspberry capsule (containing 167.2 catechin + vitamin C + thiamin + riboflavin + niacin + folate + vitamin A + b-carotene + IU vitamin A + vitamin E + c-tocopherol + cyaniding + pelargonidin + quercetin + myricetin + proanthocyanidins/day)	12 weeks	60.7 ± 10.4, 56.4 ± 9.2	ICAM-1, VCAM-1
Flammer et al. (2012)	2012	10/10	Switzerland/patients with heart failure	Flavanol-rich chocolate (FRC) (containing 46.8 mg catechin) twice per day	4 weeks	58.1 ± 11.9, 60.3 ± 10.1	FMD
Njike et al. (a) (2011)	2011	18/32	USA/overweight adults	Sugar-free cocoa beverage (containing 69 mg total catechin + procyanidins)	6 weeks	51.9 ± 10.8, 52.5 ± 10.4	ET-1, FMD
Njike et al. (b) (2011)	2011	18/33	USA/overweight adults	Sugar-free cocoa beverage (containing 69 mg total catechin + procyanidins)	6 weeks	51.9 ± 10.8, 52.2 ± 11.0	ET-1, FMD
Engler et al. (2004)	2004	10/11	USA/healthy adult subjects	High-flavonoid dark chocolate (containing 46 mg epicatechin + procyanidin)	2 weeks	32.5 ± 9.17, 31.8 ± 10.59	FMD
Mellen et al. (2010)	2010	50/50	USA/subjects with or at risk for cardiovascular disease	Muscadine grape seed supplement containing 7.5 mg total catechin + resveratrol + proanthocyanidin	4 weeks	52.1 ± 8.1	FMD
Muniyappa et al. (2008)	2008	20/20	USA/essential hypertension	150 ml flavanol-rich cocoa drink twice a day (containing 900 mg flavanols/day, 236 mg catechin/day)	2 weeks	51 ± 6.7	ICAM-1, VCAM-1

FMD: flow mediated dilation; PWV: pulse wave velocity; AIX: augmentation index; ET-1: endothelin-1; sICAM-1: soluble intercellular adhesion molecule-1; sVCAM-1: soluble vascular adhesion molecule-1; NO: nitric oxide; CAD: coronary artery disease; COMT: catechol-*O*-methyltransferase; EGCG: epigallocatechin galate

Table 2. The effects of catechin supplementation on markers of endothelial function in participants of included studies

				Heterogeneity	
Variables	Number of effect sizes	Weighted mean difference	CI 95%	I^2 (%)	*P*-value heterogeneity
FMD	13	1.53	0.93, 2.14	96.4	<0.001
VCAM-1	5	22.27	−2.52, 47.07	44.9	0.12
Endothelin	4	0.16	−0.14, 0.47	95.1	<0.001
PWV	7	−0.32	−0.44, −0.20	39.2	0.13
ICAM-1	7	11.69	−5.03, 28.42	70.6	0.002
AIX	5	−3.57	−6.40, −0.74	88.4	<0.001
NO	4	5.10	−6.76, 16.95	63.8	0.04

FMD: flow Mediated dilation; VCAM: vascular cell adhesion protein; PWV: pulse wave velocity; ICAM: intercellular adhesion molecule; AIX: augmentation index; NO: nitric oxide.

Table 3. Subgroup analyses for the effects of catechin supplementation on markers of endothelial function in participants of included studies

Variables		Subgroups	Number of effect sizes	Pooled WMD	95% CI	I^2 (%)	P-value (Between group)
FMD	Participants' age	<45 years	4	1.74	1.52, 1.96	91.4	0.017
		≥45 years	9	1.44	1.34, 1.54	97.3	
	Study sample size	$n < 50$	9	1.74	1.56, 1.91	85.6	0.001
		$n \geq 50$	4	1.40	1.30, 1.51	98.9	
	Study design	Parallel	11	1.57	1.48, 1.67	96.0	<0.001
		Cross-over	2	−0.48	−0.92, −0.04	30.0	
	Participants' health condition	Healthy	10	1.47	1.38, 1.56	97.1	0.001
		Heart diseases	3	2.67	1.96, 3.38	78.2	
VCAM-1	Study duration	<8 weeks	2	5.99	−26.56, 38.53	0.0	0.13
		≥8 weeks	3	44.84	6.54, 83.13	58.8	
PWV	Participants' age	<45 years	3	−0.34	−0.52, −0.17	65.6	0.668
		≥45 years	4	−0.29	−0.46, −0.13	22.4	
ICAM-1	Study duration	<8 weeks	3	12.19	0.65, 23.74	47.4	0.38
		≥8 weeks	4	4.96	−6.40, 16.32	81.1	
	Study design	Parallel	5	4.00	−5.34, 13.33	74.9	0.05
		Cross-over	2	22.25	5.99, 38.52	0.0	

FMD: flow mediated dilation; VCAM: vascular cell adhesion protein; PWV: pulse wave velocity; ICAM: intercellular adhesion molecule.

Following data were then extracted and included into an Excel database: first authors' name, year of publication, study location, study design, sample size, dosage, duration of study, type of disease, the mean and SD for FMD, VCAM, endothelin, PWV, ICAM, AI, and NO in each intervention group. The quality of studies included was assessed by the same independent authors using the Cochrane Collaboration risk of bias tool based on the following criteria: "randomization generation, allocation concealment, blinding of participants and outcome assessors, incomplete outcome data, and selective outcome reporting, and other sources of bias."

Data synthesis and statistical analysis

We fitted random effects models and used forest plots to display the weighted mean differences (WMDs) with 95% CI for FMD, VCAM, endothelin, PWV, ICAM, AI, and NO which were calculated from mean changes of these variables by comparing catechin supplementation to placebo. Baseline and final values or mean changes with SD of the investigated biomarkers for both intervention and placebo groups were extracted from included studies.

Heterogeneity and publication bias

Between-study heterogeneity of included studies was evaluated using Cochrane's Q test (with significant *P*-value < 0.1) and *I*-square test. I^2 greater than 50% was considered as significant heterogeneity. Visual inspection of the funnel plot as well as Egger's regression test was used to explore the publication bias. Both STATA 11.0 (Stata Corp., College Station, TX, USA) and Review Manager 5.3 (Cochrane Collaboration, Oxford, UK) were used for data analysis.

Results

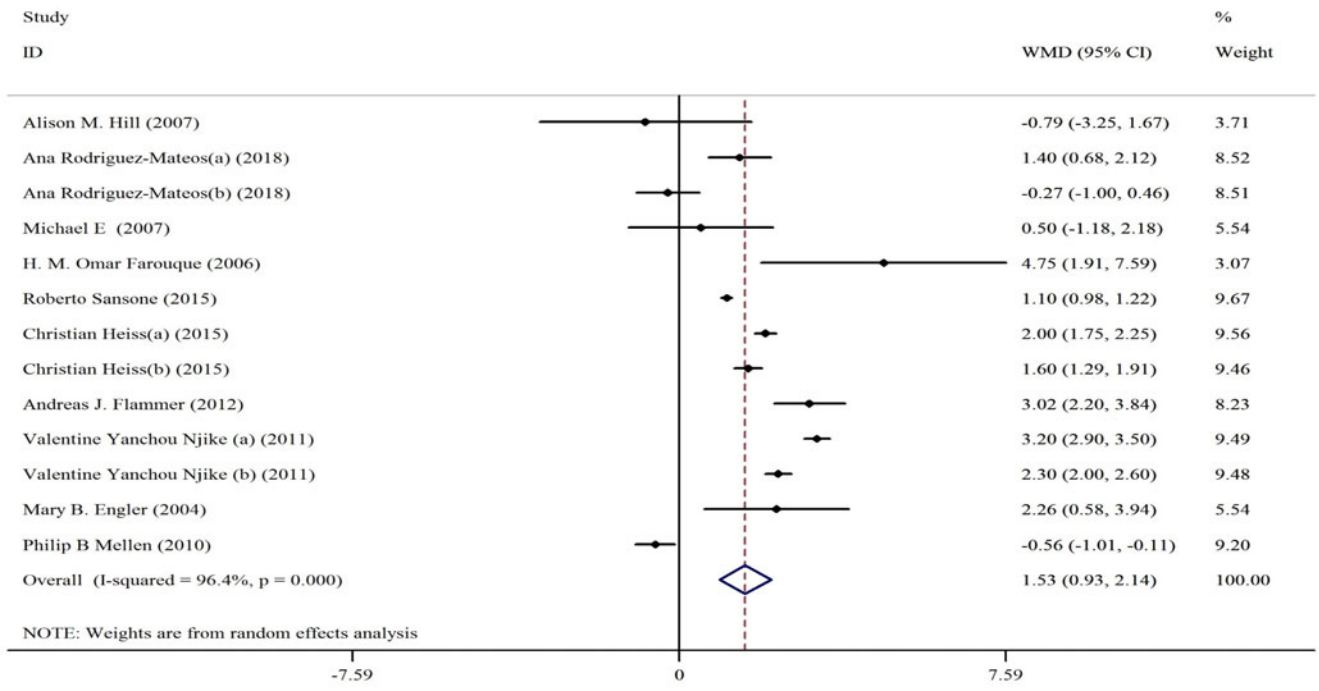
Systematic review

Around 16 studies with 22 effect sizes were included in our meta-analysis. Flow-diagram of studies selected is provided in Figure 1. These studies were published between 2004 and 2018. Characteristics of included studies are summarized in Table 1. Healthy subjects, patients with heart diseases and those with renal diseases were recruited for these studies. Green tea, catechin itself, catechin-containing cocoa, and other catechin-containing foods were used in these studies. ICAM-1, VCAM-1, endothelin, FMD, AI, PWV, and NO were measured as biomarkers in these studies.

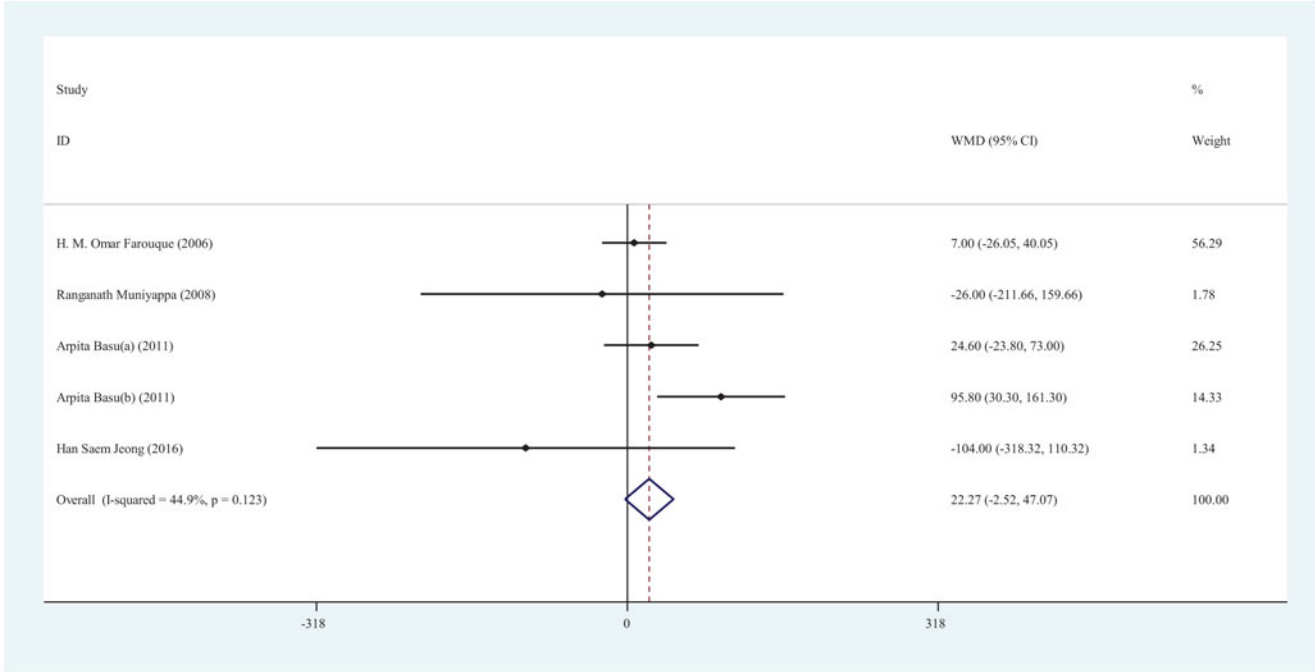
Meta-analysis

Effects of catechin on FMD

Combining 13 effect sizes from 10 studies, we found a significant increase in FMD following catechin supplementation (WMD: 1.53; 95% CI: 0.93, 2.14) (Table 2 and Figure 2a). Nevertheless, we found a significant reduction in FMD



A: FMD



B: VCAM

Figure 2. Meta-analysis glycemic control weighted mean difference estimates for (a) FMD, (b) VCAM, (c) endothelin, (d) PWV, (e) ICAM, (f) AI, and (g) NO in the catechin supplements and placebo groups (CI = 95%).

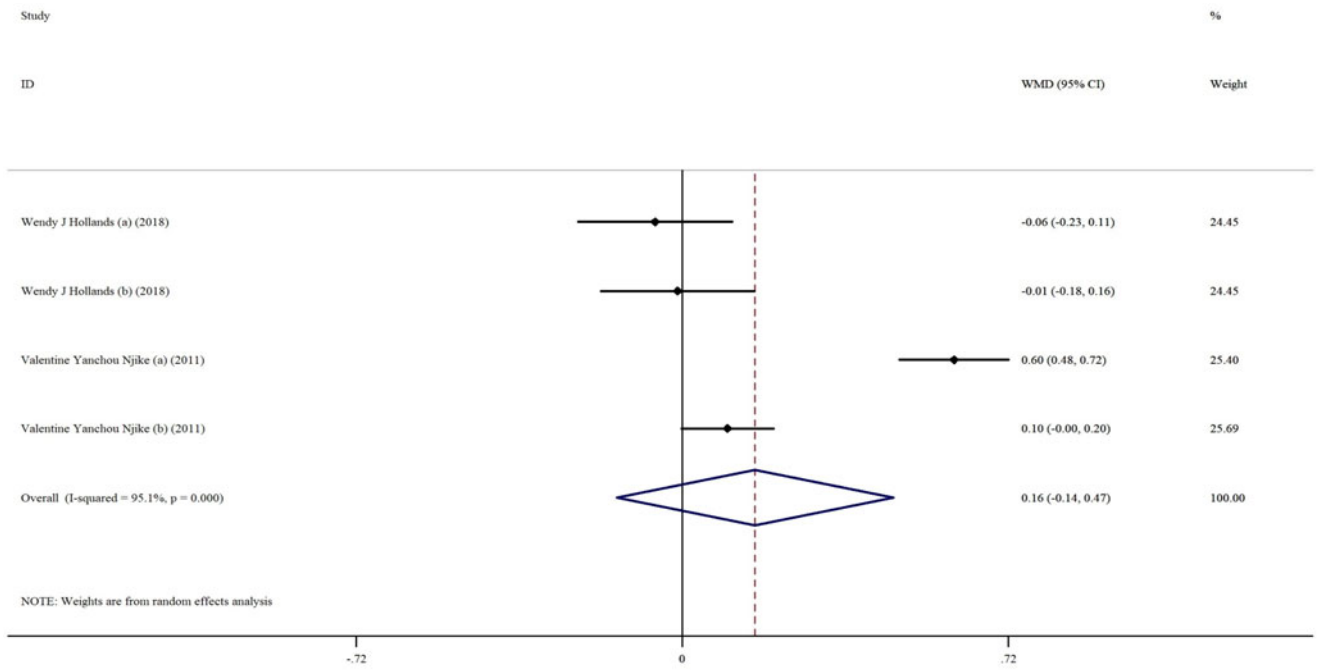
after catechin supplementation in cross-over RCTs (WMD: −0.48; 95% CI: −0.92, −0.04) (Table 3).

Effects of catechin on VCAM-1

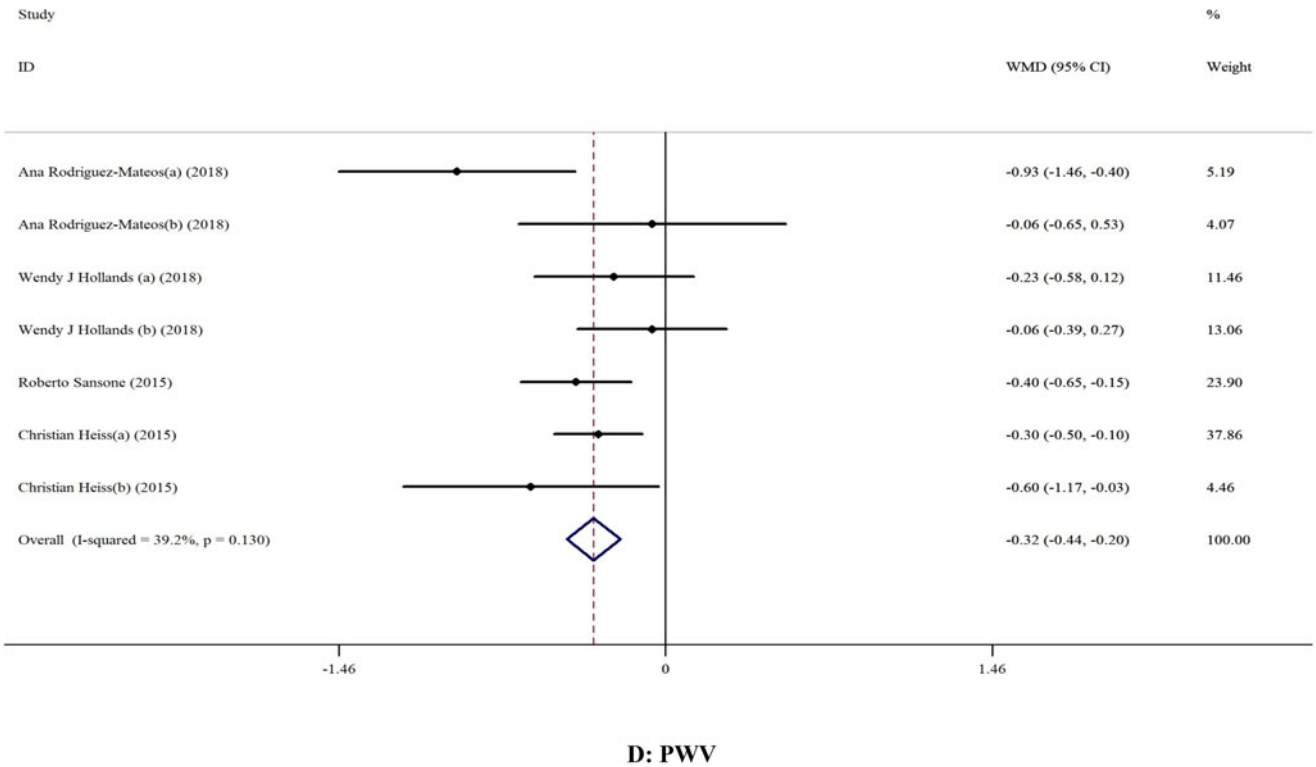
Pooling data from 4 studies with 5 effect sizes did not show any significant effects of catechin on VCAM-1 levels (WMD: 22.27; 95% CI: −2.52, 47.07) (Table 2 and Figure 2b). However, subgroup analysis showed a significant increase in this marker in studies with a duration of ≥8 weeks (WMD: 44.84; 95% CI: 6.54, 83.13) (Table 3).

Effects of catechin on endothelin

Catechin caused no significant effect on endothelin levels. We found this in 2 studies including 4 effect sizes (WMD: 0.16; 95% CI: −0.14, 0.47) (Table 2 and Figure 2c). (Table 3).



C: Endothelin



D: PWV

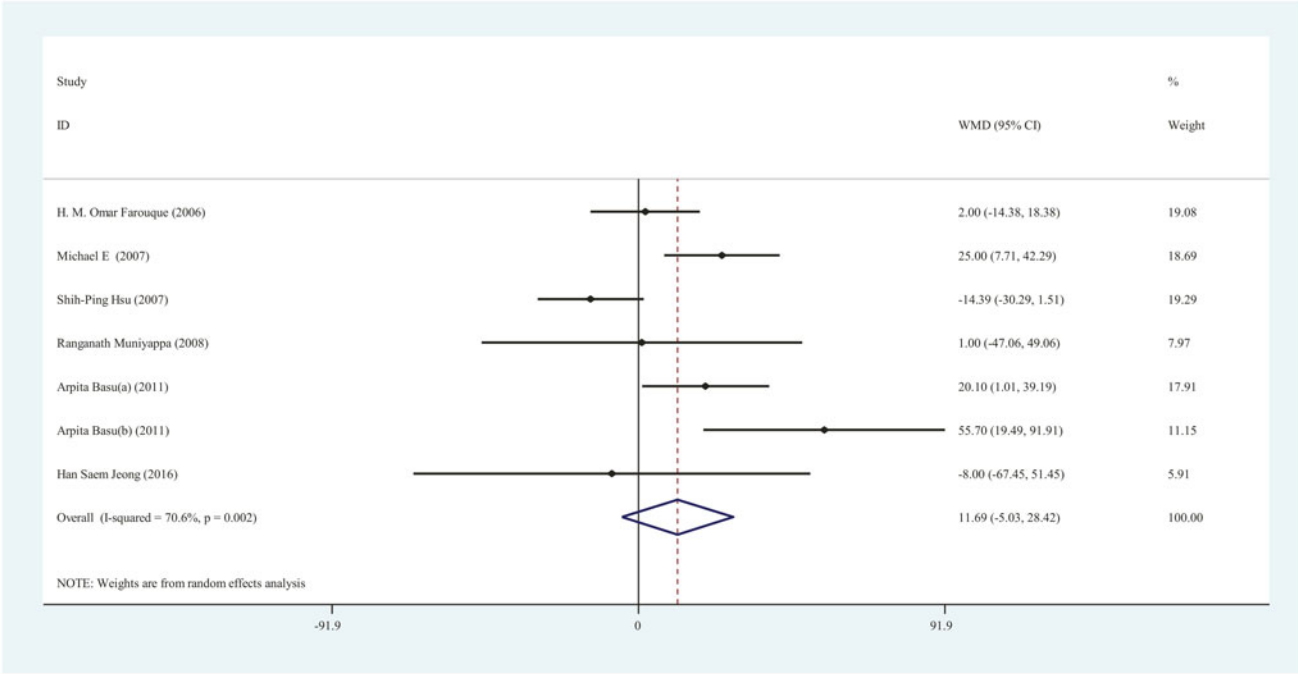
Figure 2. Continued.

Effects of catechin on PWV

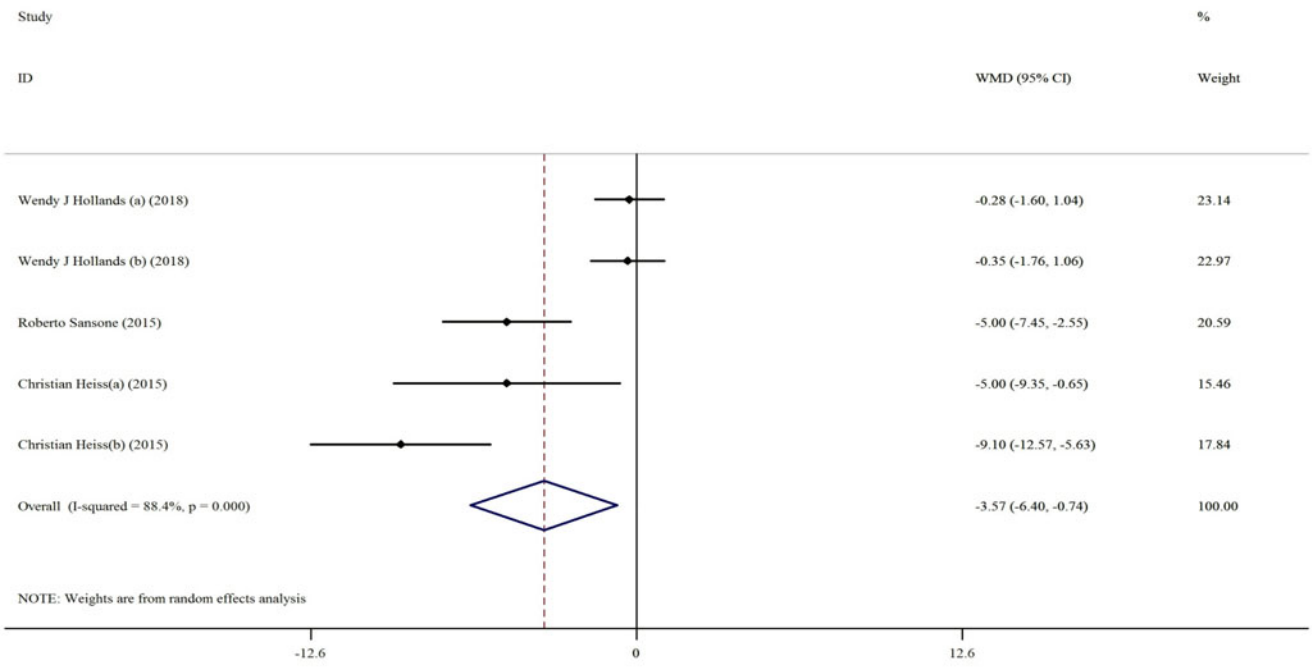
The pooled analysis of 7 effect sizes from 4 studies showed a significant reduction in PWV after catechin supplementation (WMD: −0.32; 95% CI: −0.44, −0.20) (Table 2 and Figure 2d). It was also significant in subgroup analysis of age (Table 3).

Effects of catechin on ICAM-1

When we combined data from 6 studies with 7 effect sizes, no significant effect on ICAM-1 was seen after catechin supplementation (WMD: 11.69; 95% CI: −5.03, 28.42) (Table 2 and Figure 2e). This finding did not change after subgroup analysis in



E: ICAM



F: AI

Figure 2. Continued.

studies with ≥8 weeks' duration (WMD: 4.96; 95% CI: −6.40, 16.32) and parallel RCTs (WMD: 4.00; 95% CI: −5.34, 13.33) (Table 3).

Effects of catechin on other markers

Combining 5 effect sizes from 3 studies, a significant reduction in AI was found as a result of catechin supplementation (WMD: −3.57; 95% CI: −6.40, −0.74) (Table 2 and Figure 2f). However, catechin had no significant effect on NO concentrations. This was found in 2 studies with 4 effect sizes (WMD: 5.10; 95% CI: −6.76, 16.95) (Table 2 and Figure 2g).

Discussion

This is the first meta-analysis to evaluate the effect of catechin on endothelial function. We analyzed 16 studies with

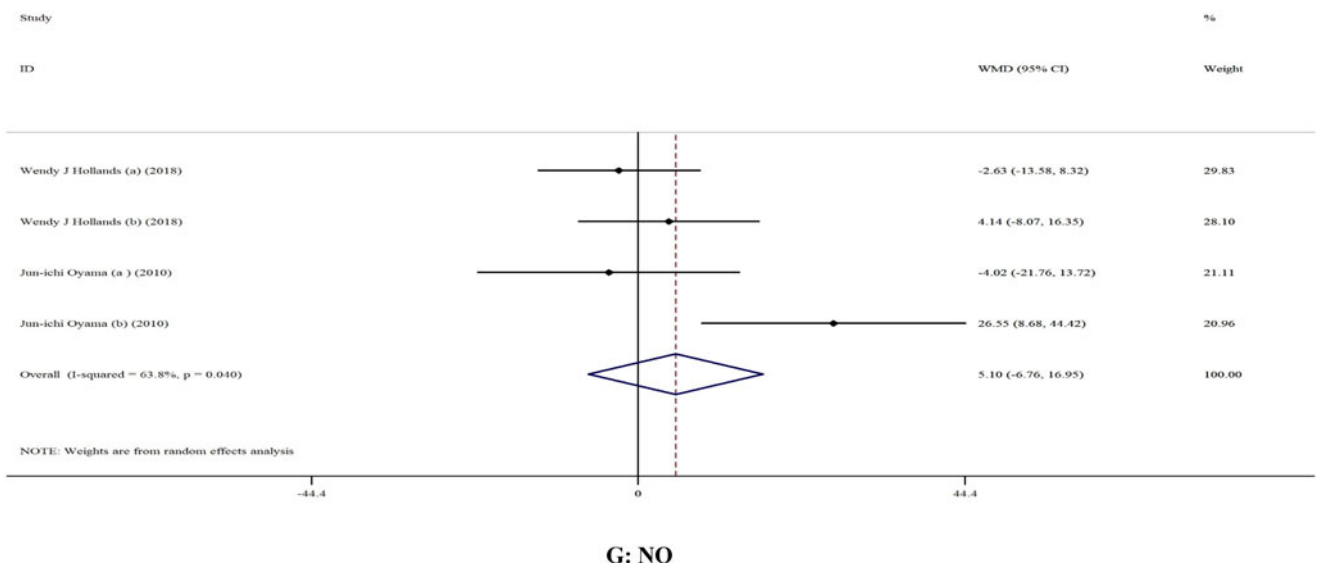


Figure 2. Continued.

22 effect sizes. In this meta-analysis, we found that catechin supplementation significantly increased FMD, and significantly reduced PWV and AI, but did not affect other markers of endothelial function.

Arterial endothelial dysfunction has been associated with cardiovascular morbidity and all-cause mortality (Yaron et al., 2016). A recent meta-analysis documented that 1% decrease in FMD and one SD decrease in FMD are correlated with 8% and 22% elevations in the risk of future cardiovascular events, respectively (Inaba et al., 2010). Risk factors that have been associated with impaired endothelial function, especially impaired FMD responses include increasing age, hypertension, cigarette smoking, dyslipidemia, passive smoking, and obesity (Benjamin et al., 2004; Kuvin et al., 2005). However, dietary factors that have been reported to improve FMD responses include, for example, higher intake of vitamin C (Thosar et al., 2015), vitamin D3 (Harris et al., 2011), and flavonoids (Heiss et al., 2007). Many flavonoids are potent antioxidants in vitro. Higher intake of flavonoid-rich foods has been correlated with reduced cardiovascular morbidity and mortality in humans (Buijsse et al., 2006; Mink et al., 2007). In a study by Lekakis et al.(2005), polyphenolic compounds from red grapes significantly improved endothelial function in patients with CHD. In addition, findings of this meta-analysis are consistent with several prior studies indicating an improved endothelial function following consumption of a flavonoid-containing beverage in patients with coronary artery disease (Duffy et al., 2001) and healthy subjects (Agewall et al., 2000). Heiss et al.(2003) also demonstrated a doubling of brachial artery FMD 2 h after consumption of flavanol-rich cocoa with a catechin plus 282 mg procyanidins. In another study, cocoa flavanol intake in healthy women and men significantly decreased PWV towards values that are usually seen in people several years younger (Sansone et al., 2015). The parallel changes in PWV and AI suggest that these substances may have positive effects on cardiac function. Also, following 2 weeks of taking cocoa flavanol by healthy men, significantly increased FMD in both young and elderly, reduced PWV and total peripheral resistance, and increased arteriolar and microvascular vasodilator capacity and diastolic blood pressure (Heiss et al., 2015). However, as already mentioned, intake of pure EC (2×50 mg EC) in healthy subjects did not significantly improve FMD (Saarenhovi et al., 2017). Furthermore, no significant improvement in endothelial function, that is (FMD) after intake of the dietary supplement EC could be seen (Saarenhovi et al., 2017). These differences in findings might be partially due to the fact that the effect of catechin supplementation on markers of endothelial function might be influenced by some factors, such as catechin dosage used, duration of intervention, and characteristics of participants. Cocoa flavanol-related vascular effects have been associated with a significant increase in nitric oxide synthase activity (Del Rio et al., 2013). In addition, cocoa flavanol intake improves tissue perfusion, at least partially, by enhancing dilatory capacity of arterioles and increasing red blood cells deformability. An explanation of the effects of catechin on endothelial function can be offered by the data indicating that catechin as well as several other natural phenolic compounds, for example, berberine, thymoquinone, celastrol, apocynin, resveratrol, curcumin, hesperidine and G-hesperidine, and quercetin which are all NOX inhibitors have some potential inhibitory effect on NADPH oxidase activity and direct scavenging of free radicals (Yousefian et al., 2019).

There are several strengths for this study. Higher numbers of studies included in the present meta-analysis have added to the value of this meta-analysis. In addition, all included studies were placebo-controlled randomized trials with acceptable methodological quality and the least probable chance of bias. This meta-analysis has a few limitations. There were a modest number of participants to be included in the meta-analysis. Various doses of catechin were administered for intervention in the included studies. Due to the heterogeneity between studies, as a result of variations in frequency or duration of catechin intake, and dosage of

catechin used, the results of this meta-analysis should be interpreted with caution.

It can be concluded that catechin supplementation significantly increased FMD, and significantly reduced PWV and AI, but did not affect other markers of endothelial function.

Availability of data and material

The primary data for this study is available from the authors on direct request.

Disclosure statement

The authors declare no conflict of interest.

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