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Meta-analysis

Tea consumption and its effects on primary and secondary prevention of coronary artery disease: Qualitative synthesis of evidence from randomized controlled trials

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SUMMARY

Background and aims: There is a general interest in understanding how the consumption of tea impacts cardiovascular function in individuals at risk of developing cardiovascular disease (CVD). The current review focuses on evidence from randomized controlled trials (RCTs) reporting on associations between tea consumption and endothelial function, in the primary and secondary prevention of coronary artery disease (CAD).

Methods: PubMed, EMBASE, and Google Scholar databases/search engines were used to identify eligible studies. Included studies had to report on the impact of tea supplementation of endothelial function or CAD related markers. In addition to flow-mediated dilation (FMD), makers of oxidative stress and inflammation such as oxidized low-density lipoprotein and C-reactive protein were considered as determinants of endothelial function. A total of 34 RCTs met the inclusion criteria, and these reported on the impact of tea consumption on endothelial function in individuals at risk of CVD or patients with CAD.

Results: The current qualitative synthesis of literature demonstrates that beyond enhancing nitric oxide bioavailability and lowering blood pressure, regular consumption of tea and its active ingredients such as epigallocatechin gallate may be beneficial in reducing markers of oxidative stress and inflammation. Moreover, the reduction of oxidized low-density lipoprotein and C-reactive protein levels, could be a sign of improved endothelial function in individuals at increased risk of developing CVD.

Conclusions: The cumulative evidence also suggests that the development of epigallocatechin gallate as a nutraceutical or enriching foods with this bioactive compound could be a feasible strategy to improve endothelial function and lower CVD-risk. However, well-designed RCTs are still necessary to confirm long-term benefits of tea consumption on vascular health.

1. Introduction

Tea is a widely consumed aromatic beverage that is generating a lot of interest due to its anticipated health benefits. Although the consumption of tea dates back for centuries [1], its novel biological

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properties have been continually reported in recent studies [2]. Tea can be produced from *Camellia sinensis*, an evergreen shrub that is indigenous to East Asia (Fig. 1). Several reviews have been published which report on the impact of tea consumption on cardiovascular-related complications. For example, earlier evidence from a meta-analysis by Peters and colleagues [3] showed that three cups of tea per day may reduce the incidence of myocardial infarction., and this was dependent on the geographic region analyzed. A comprehensive follow-up review by McKay and Blumberg [4] summarized evidence on the beneficial effects of tea and its flavonoids against various chronic diseases, with an emphasis on its impact on diverse cardiovascular diseases (CVDs). The authors further reported that the consumption of tea may reduce the risk of CVD and some forms of cancer, through the modulation of diverse physiological responses. Since then, others [4–8] have also assessed the bioavailability profile, blood pressure and low-density lipoprotein (LDL) lowering properties, as well as ameliorative effects against metabolic syndrome-linked complications such as inflammation and oxidative stress. Tea and some of its polyphenolic compounds improve intracellular antioxidants and attenuate undesired inflammatory response by modulating molecular pathways such as nuclear factor erythroid 2-related factor 2 and nuclear factor kappa-light-chain-enhancer of activated B cells [6]. From reviewed literature, it has also become clear that maintaining endothelial health is one of the essential mechanisms by which tea exerts its beneficial effects on the cardiovascular system [9,10].

The endothelium forms a significant part of the vasculature and regulates homeostasis [11]. Beyond regulating blood fluidity and vascular tone, the endothelium plays a vital role in platelet homeostasis, including inflammation and angiogenesis [11,12]. These actions are modulated through the release of various vasoactive endothelial cell-derived factors, such as angiotensin II, reactive oxygen species (ROS), arachidonic acid metabolites and nitric oxide (NO) [13]. Notably, an imbalance in the synthesis or release of these endothelial factors may promote endothelial dysfunction, which precedes cardiovascular disease. For example, some studies have explored the NO-dependent regulation of vascular tone in response to various stimuli, in efforts of to determining their impact on endothelial function [14]. Likewise, various non-invasive methods, like flow-mediated dilation (FMD) have been used to assess vascular function in different clinical populations [15]. The current evidence in published literature suggests that FMD is decreased in patients with CAD and that this reduction is correlates to the severity of the disease [12]. Therefore, endothelial dysfunction represents one of the earliest events linked with the development of CVDs, including CAD.

Although randomized controlled trials (RCTs) have reported on the impact of tea on endothelial function in people with or without CAD, the available evidence has not been critically evaluated to inform on the beneficial effects of tea consumption in improving cardiovascular health. Thus, by focusing on RCTs published in the last 20 years, the current review aims to assess whether the consumption of tea provides any benefit in the primary prevention of CAD in the general population or in patients at risk of developing CVD.

2. Methodology

The Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines were followed in this systematic review and meta-analysis (Supplementary file 1). Importantly, we searched the International Prospective Register Of Systematic Reviews (PROSPERO) to ensure that there is no registered systematic

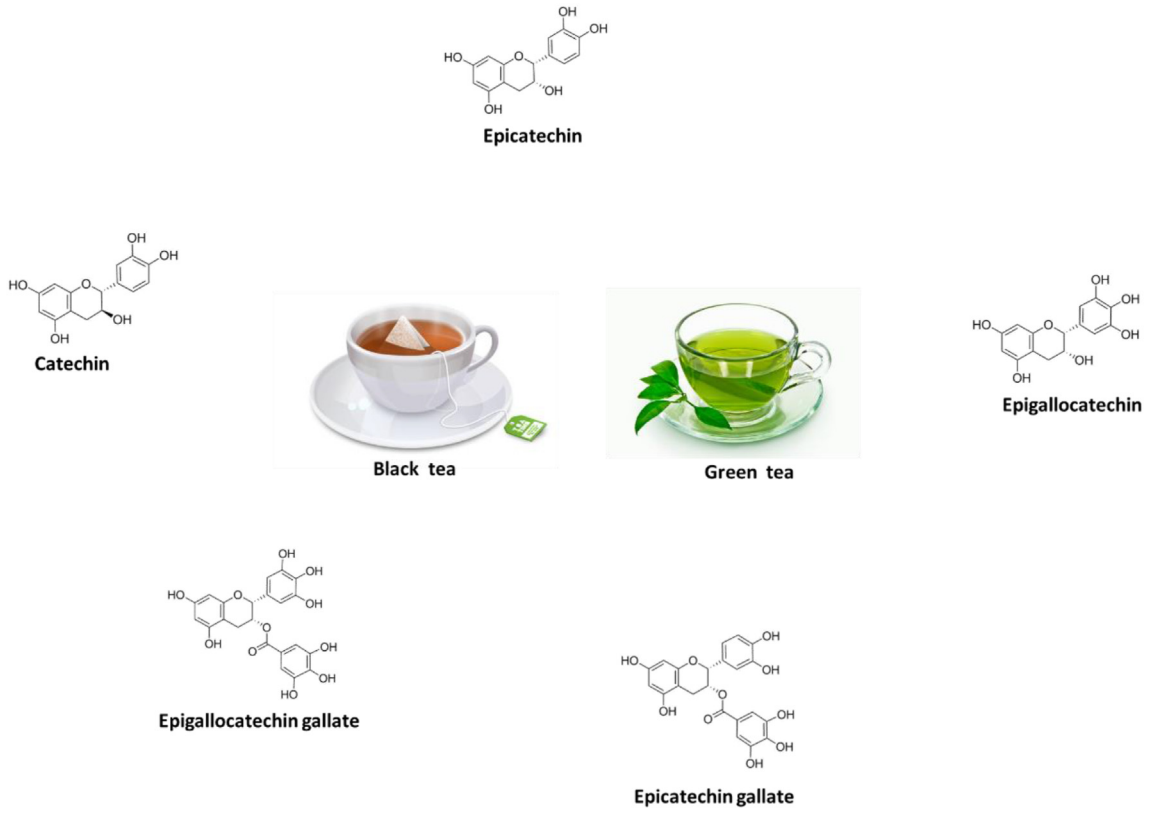

Fig. 1. Chemical structures of major flavonoids in tea, usually associated with its bioactivity, include catechin (PubChem CID: 9064), epicatechin (PubChem CID: 72276), epigallocatechin (PubChem CID: 72277), epicatechin gallate (PubChem CID: 107905), and epigallocatechin gallate (PubChem CID: 65064).

review that is investigating a similar topic. Subsequently, the systematic search for eligible RCTs was conducted by two independent investigators (PVD and TMN), with the help of an experienced librarian, making use of electronic databases such as MEDLINE, Cochrane Library, and EMBASE from inception up to 30 May 2020. Inconsistencies, during the selection of studies were resolved by consulting with a third reviewer (BBN). The primary search included all studies reporting on the impact of tea consumption/intake on endothelial function, in those with or without CAD. Medical Subject-Heading (MeSH) and text words "tea", "endothelial function", "coronary artery disease", and their matching synonyms "herbal medicine", "vascular dysfunction", "atherosclerosis" were applied for an optimal search strategy. There were no language limitations applied to the search strategy, whereas EndNote version 10 (Clarivate Analytics, Philadelphia, USA) was used to manage the reference list and remove duplicates.

The current systematic review was performed to address the following questions;

Question 1: Does the consumption of tea lower CVD-risk by improving endothelial function in patients with CAD?

Question 2: Does tea consumption improve endothelial function in patients at increased risk of CVD?

2.1. Eligibility criteria

We included studies that met the following criteria;

2.2. Participants

Patients with CAD or individuals at increased risk of developing CVDs.

2.3. Intervention

The intervention involved the consumption of tea.

2.4. Comparator

The comparator group comprised of a placebo group or individuals who did not consume tea.

2.5. Outcome

The primary outcome of this systematic review was to determine the impact of tea consumption on endothelial function in patients with CAD. The secondary outcome was to assess the effects of tea consumption on endothelial function in individuals at risk of developing CVDs.

3. The quality of included RCT studies

The overall quality of studies was independently evaluated by two investigators (KM and VM) using the modified Downs and Black checklist [16]. The four main domains assessed using the checklist include reporting, external and internal validity as well as confounding bias. We found that the quality of the included 34 studies ranged from poor to good with a median and a range of 16 (11–21), respectively. Three studies [17–19] were rated as poor with a score range of 11–12, sixteen RCTs [20–35] were rated as fair with a range of 13–18, the other outstanding studies presented with good quality evidence, with a score range of 19–21. Accordingly, all included studies were rated good on reporting bias with a score of 8 out of 10 possible scores, rated poor on external validity with a score of 0.8 out of 3 possible scores, rated fair in internal validity with a 3 out of 7 possible scores, and lastly rated good with a score of 4 out of possible 6 scores for selection bias domain.

4. Assessment of evidence on tea consumption and its effect on endothelial function

The systematic search of literature through major electronic databases identified 41 eligible RCTs. Overall, 34 studies met the inclusion criteria, published in peer-reviewed journals between 1997 and 2019 (Fig. 2). Included RCTs were predominantly from Europe, the United States, and Japan; with fewer studies from Australia, Brazil, Iran, Korea, Mauritius, and United Kingdom. Studies reporting on cancer or not on tea consumption were excluded. All included studies were RCTs reporting on tea consumption and its effect on endothelial function-related outcomes. In addition to FMD, makers of oxidative stress and inflammation such as oxidized low-density lipoprotein and C-reactive protein were considered as determinants of endothelial function. In the following subsections, included RCTs are discussed based on the impact of tea consumption on endothelial function in individuals at risk of CVD or who already have CAD. Those at CVD-risk were individuals who are smokers or having a cluster of metabolic complications such as dyslipidemia, type 2 diabetes or hypertension.

4.1. Tea consumption and endothelial function in individuals at risk of cardiovascular disease

Oxidized-LDL is progressively studied for its role in the development of CVD-related complications. Several studies have linked peculiarly elevated oxidized-LDL levels with the initiation of atherogenesis [36,37]. As such, there has been a general need to understand how dietary compounds or high phenolic content-rich foods modulate LDL-levels to improve endothelial function and lower CVD-risk [38,39]. Interestingly, the initial evidence on the beneficial effects of tea consumption at 750 ml/d (5 cups/d) for 4 weeks was related to its capability to lower oxidized-LDL levels in normolipidemic healthy volunteers, not taking any other antioxidant supplements [40]. Others [26,41] showed that green tea consumption in the form of capsules or an equivalent of 6 cups for 3–4 weeks could indeed lower oxidized-LDL and total cholesterol: HDL ratio in individuals at risk of CVD.

Evidence summarized in Table 1 gives an overview of different formulations of tea that have been assessed for their impact on endothelial function in relation to those with increased CVD-risk. For example, Grassi et al. [42], demonstrated that the consumption of black tea twice a day could dose-dependently increased FMD, while reducing systolic and diastolic blood pressure as well as arterial stiffness index. Schreuder et al. [30], also showed that 3 cups of black tea could improve FMD without impacting endothelial ischaemia–reperfusion. In fact, while some studies supported the beneficial effects of tea ingestion in improving endothelial function [35], it was evident that these effects could be influenced factors such as addition of milk [43] or short intervention period [33]. Dietary supplements containing tea extracts, or ingestion of mg epigallocatechin gallate as a pure compound [21,44,45], had a limited effect in improving endothelial function as measured suing FMD. However, other findings either using powdered black tea solids for 3 months [46] or green tea-rich starch confections [19] and ice cream for 2–3 h, reported improved outcomes that were related to weight gain, increased FMD, and enhanced antioxidant capacity. Thus, from these findings, it is apparent that the early intake of tea can be helpful in improving endothelial function in those susceptible to CVD-related complications. However, additional studies are required to confirm dose selection and intervention period.

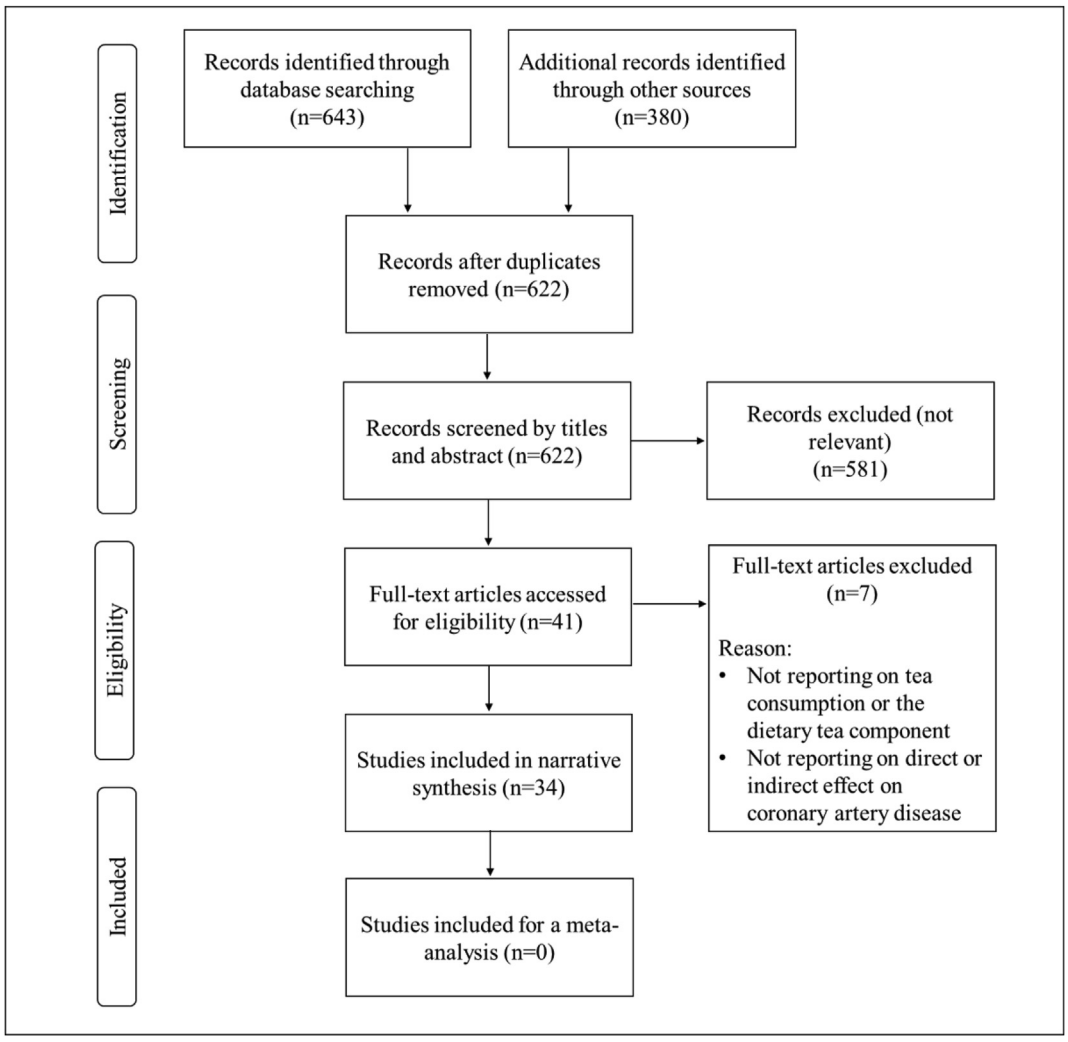

Fig. 2. An overflow diagram for included studies.

4.2. Tea consumption and endothelial function in smoking subjects

Available clinical evidence continues to link cigarette smoking with increased CVD-risk [47,48]. In particular, uncontrolled free radical components of cigarette smoke and aggravated inflammation are known to be responsible for inducing endothelial damage, consistent with enhanced CVD-risk [47,49]. Table 2 gives an overview of evidence reporting on the impact of tea ingestion on endothelial function in smoking individuals. Nagaya et al. [17], demonstrated that 400 ml green tea ingestion for 2 h could improve endothelium-dependent vasodilatation. In this study, subjects were studied on two separate days, at least one week apart, at 8:30 in the morning after they had fasted for at least 12 h. Others [18,28] confirmed these findings showing that green tea consumption (8 g/day) for 2 weeks could enhance FMD in smoking subjects. Oyama et al. [29], observed a significant increase in plasma NO, together with the reduction of oxidative stress and inflammation makers such as malondialdehyde and 4-hydroxynonenal, CRP, monocyte chemotactic protein-1, and soluble CD40 ligand levels were detected after chronic consumption of high-dose green tea catechins for 2 weeks. In contrast, de Maat and colleagues [20] did not observe any positive effects with consumption of black or green tea for 4 weeks in terms of ameliorating inflammation, or improving hemostasis and endothelial markers. Overall, evidence summarized in Table 2 suggests that tea consumption could have a beneficial effect in improving endothelial function by ameliorating oxidative stress and inflammation in smoking individuals.

4.3. Tea consumption and endothelial function in patients with coronary artery disease

Impaired endothelial function remains a major predictor of CAD [11,50]. Thus, there is an increased need to uncover novel therapeutics to improve endothelial function to prolong the lives of CAD patients. Table 3 gives an overview of evidence reporting on the impact of tea ingestion on endothelial function-related outcomes in patients with CAD. In 2001, Duffy et al. [51], showed that in addition to plasma flavonoids levels, consumption of either 450 and 900 ml black tea for 2 h or 4 weeks improved endothelium-dependent FMD of the brachial artery. Tea consumption did not affect endothelium-independent nitroglycerin-induced dilation in individuals with CAD. The same group demonstrated that although can increase plasma catechin levels, the consumption of tea at similar doses did not affect ex vivo platelet aggregation, antioxidant capacity, and inflammation markers in these patients [22,25]. Hodgson et al. [52], showed that tea consumption after a meal was beneficial in enhancing endothelium-dependent dilatation in

Table 1
An overview of randomized clinical trials reporting on the impact of tea on endothelial function-related outcomes in healthy subjects.

Study	Country	Sample size, Average age	Tea dosage and duration	Main findings
Ishikawa et al., 1997 [40]	Japan	Sample size = 22 Average Age = 22	5 cups of black tea (750 ml/d) for 4 weeks	Prolonged lag time before low-density lipoprotein (LDL) oxidation
Inami et al., 2007 [26]	Japan	Sample size = 40 Average Age = 32	Catechin (500 mg: equivalent to 6 or 7 cups of green tea) for 4 weeks	Reduced oxidized LDL, while plasma LDL-C, triglyceride, and high density (HDL)-C concentrations did not change
Frank et al., 2009 [41]	Germany	Sample size = 33 Average Age = 40	6 green tea extract capsules (2 before each principal meal) for 3 weeks	Reduced the ratio of total: HDL cholesterol but did not affect endothelial-dependent and -independent vascular reactivity
Grassi et al., 2009 [42]	Italy	Sample size = 19 Average Age = 33	Black tea (0, 100, 200, 400 and 800 mg tea flavonoids/day) twice a day for 1 week	Dose-dependently increased flow-mediated dilation (FMD) and reduced office systolic and diastolic blood pressure (BP)
Bøhn et al., 2014 [46]	Norway	Sample size = 77 Average Age = 56	3 cups per day of either powdered black tea solids for 3 and 6 months	Significantly reduce weight gain and waist circumference for only 3 months, and did not affect fasting glucose, insulin or endothelial function
Schreuder et al., 2014 [30]	The Netherlands	Sample size = 20 Average Age = 55	3 cups of black tea per day for 7 days	Tea ingestion improved FMD
Soare et al., 2014 [44]	United States	Sample size = 54 Average Age = 45	10 dietary supplements each day for 6 months	Did not affect arterial stiffness, body fat, BP, plasma lipids, glucose, insulin, and markers of inflammation and oxidative stress
Dower et al., 2015 [21]	The Netherlands	Sample size = 37 Average Age = 66	(−)-epicatechin (100 mg/d), quercetin-3-glucoside (160 mg/d) for 4 weeks	Did not significantly affect endothelial dysfunction but affect levels for inflammatory markers such as sE-selectin and interleukin (IL)-1β
Sapper et al., 2016 [19]	United States	Sample size = 15 Average Age = 25	Starch confections (50 g carbohydrate) formulated with or without catechin-rich green tea extract (1 g) at 30 min intervals for 3 h	FMD was significantly decreased only at 60 min regardless of confections containing tea
Lorenz et al., 2017 [45]	Germany	Sample size = 50 Average Age = 34	200 mg epigallocatechin gallate (EGCG) was applied in three different formulas (as green tea beverage, green tea extract, and isolated EGCG)	FMD significantly improved after consumption of green tea containing, 200 mg EGCG. However, green tea extract and EGCG had no significant effect on FMD
Sanguigni et al., 2017 [34]	Italy	Sample size = 14 Average Age = 38	100 g of either antioxidant ice cream containing dark cocoa powder and hazelnut and green tea extracts for 2 h	Serum polyphenols, nitric oxide (NO), ferric-reducing ability of plasma, FMD, and reactive hyperemia index increased significantly, oxidative stress decreased; H_2O_2, and the double product was improved only after antioxidant ice cream ingestion
Ahmad et al., 2018 [43]	Australia	Sample size = 17 Average Age = 22	Received hot water, (ii) black tea and (iii) black tea with milk for 4 weeks	Black tea increased FMD, however addition of milk decreased this effect
Greyling et al., 2018 [33]	The Netherlands	Sample size = 20 Average Age = 62	Black tea containing ~400 mg flavonoids (equivalent to 2–3 cups of tea), for 2 h	Did not affect endothelium-dependent vasodilation of forearm resistance arteries
Woodward et al., 2018 [35]	United Kingdom	Sample size = 20 Average Age = 59	A single dose of 200 ml black tea	Acute tea ingestion enhanced cutaneous vascular responses to gradual local heating to 42 °C in healthy, middle-aged participants, possibly through a mechanism related to activation of endothelium-derived chemical mediators, such as NO

Table 2
An overview of randomized clinical trials reporting on the impact of tea on endothelial function-related outcomes in smoking subjects.

Study	Country	Sample size, Average age	Tea dosage and duration	Main findings
de Maat et al., 2000 [20]	The Netherlands	Sample size = 64 Average Age = 34	Black tea, green tea, green tea polyphenol isolate and mineral water (13–16 per group) for 4 weeks	Different dosages of tea polyphenols had no effect on inflammation, haemostasis and endothelial markers
Nagaya et al., 2004 [17]	Japan	Sample size = 20 Average Age = 33	400 ml green tea or hot water, we measured the response of forearm blood flow (FBF) for 2 h	Improved endothelium-dependent vasodilatation. In contrast, green tea had no effect on the increase in FBF after sublingual administration of glyceryl trinitrate, an index of endothelium-independent vasodilatation
Kim et al., 2006 [18]	Korea	Sample size = 20 Average Age = 28	Green tea consumption (8 g/day) for 2 weeks	Improved FMD after 2 weeks
Alexopoulos et al., 2008 [28]	Greece	Sample size = 14 Average Age = 30	Three separate occasions on which they took: (a) 6 g of green tea, (b) 125 mg of caffeine (the amount contained in 6 g of tea), or (c) hot water	Increased FMD
Oyama et al., 2010 [29]	Japan	Sample size = 30 Average Age = 35	3 groups and given green tea beverages containing 0 mg (control group), 80 mg (medium-dose group) or 580 mg (high-dose group) of green tea catechins daily for 2 weeks	The FBF response to acetylcholine significantly increased at 2 h and 1 and 2 weeks after green tea catechins intake in the high-dose grou

Table 3
An overview of randomized clinical trials reporting on the impact of tea on endothelial function-related outcomes in patients with coronary artery disease.

Study	Country	Sample size, Average age	Tea dosage and duration	Main findings
Duffy et al., 2001 [51]	United States	Sample size = 49 Average Age = 55	450 and 900 ml black tea or water daily for 2 h or 4 weeks	Both short- and long-term tea consumption improved endothelium-dependent flow-mediated dilation (FMD) of the brachial artery.
Duffy et al., 2001 [22]	United States	Sample size = 50 Average Age = 55	450 ml of black tea consumed initially, followed by 900 ml of tea or water daily for 4 weeks	Plasma flavonoids increased with acute and chronic tea consumption, indicating adequate absorption of tea flavonoids
Shimada et al., 2004 [34]	Japan	Sample size = 22 Average Age = 64	Consumed oolong tea (1000 ml) for one month in our ran	There was a significant difference in plasma adiponectin levels before and after oolong tea, and in plasma level low-density lipoprotein (LDL) particle size
Hodgson et al., 2005 [52]	Australia	Sample size = 20 Average Age = 62	Three cups of black tea (consumed at time = 0, 1.5 and 3 h) with and without a high-fat (50 g) meal: a total of 4 random treatments	Systolic blood pressure was significantly increased by tea
Widlansky et al., 2005 [25]	United States	Sample size = 66 Average Age = 54	Collected samples at baseline, 2 h after 450 ml of black tea (acute), after 4 weeks of 900 ml of black tea per day (chronic)	Tea consumption did not improve plasma antioxidant capacity and did not reduce urinary 8-hydroxy-2′-deoxyguanosine, or urinary 8-isoprostane levels
Widlansky et al., 2007 [27]	United States	Sample size = 42 Average Age = 59	Epigallocatechin gallate, two hours after an initial dose of (300 mg), and after two weeks of treatment with a dose of (150 mg twice daily)	Brachial artery flow-mediated dilation improved two hours after the first dose of 300 mg of the compound, but was similar to baseline after two weeks of treatment with the final measurements made approximately 14 h after the last dose
Bahorun et al., 2010 [53]	Mauritius	Sample size = 263 Average Age = 26-60	9 g of black tea (equivalent to three cups of tea) daily for 12 weeks without additives followed by a 3-week wash-out	Reduced the levels of C-reactive protein
Koutelidakis et al., 2014 [54]	Greece	Sample size = 43 Average Age = 63	Breakfast consisting of bread, butter and 330 ml tea (4.5 g green tea/330 ml, providing approximately 400 mg catechins) before withdrawal of blood after 1.5, 3 and 5 h	Did not affect tested biomarkers such as pancreatic lipase, CRP, total cholesterol, HDL-C, LDL-C and glucose levels

individuals with CAD, although these effects were not significant with the use of tea alone. Bahorun et al. [53], demonstrated that administration of 9 g of black tea, an equivalent to three cups of tea, daily for 12 weeks could significantly reduce CRP levels in individuals susceptible to CVD-risk. Other findings showed that tea or its active ingredients such as epigallocatechin gallate could improve brachial artery FMD, plasma antioxidant capacity and adiponectin levels, while reducing LDL-particle size [24,27,54]. These studies assessed the consumption of oolong tea (1000 ml) for 1 month, breakfast consisting of bread, butter and 330 ml tea (4.5 g green tea/330 ml, providing approximately 400 mg catechins), or epigallocatechin gallate for 2 h after an initial dose of 300 mg, and after two weeks of treatment with a dose of (150 mg twice daily). Overall, some beneficial could be observed with tea consumption in improving endothelial function in patients with CAD.

4.4. Tea consumption and endothelial function in individuals with metabolic syndrome

The metabolic syndrome presents with a cluster of disorders that are associated to impaired endothelial function, development of atherosclerosis, and accelerated CVD-risk. For instance, such conditions are consistent with elevated serum lipid profiles, impaired blood glucose control, and abnormal blood pressure regulation [55–57]. Table 4 provides an overview of studies reporting on the impact of tea consumption on endothelial function in conditions of metabolic syndrome. Hodgson et al. [23], showed that 5 cups of black tea per day for 4 weeks could enhance endothelium-dependent dilatation in adults with mild elevations in serum cholesterol or triglyceride levels. In overweight men with mildly elevated plasma CRP concentrations, Bakker et al., 2010 [58] demonstrated that 2 hard capsules and 2 soft capsules containing resveratrol, green tea extract (40% epigallocatechin gallate; daily dose equivalent to 300 ml green tea) daily at breakfast with 200 ml of plain yogurt and at dinner for 5 weeks, could elevate plasma adiponectin levels. In contrast Balsan et al., 2019 [59] showed that 1000 ml green tea (a sachet of 1 g of tea for each 200 ml of hot water, five times a day, totaling a volume of 1000 ml) consumption for 8-weeks did not significantly affect paraoxonase-1 and leptin levels. In patients with type 2 diabetes, Azimi et al. [31], demonstrated that although 3 g ginger with three glasses of black tea for 8 weeks could reduce blood pressure and soluble intercellular adhesion molecule-1 concentrations, this treatment did not significantly influence endothelial function. Alternatively, in hypertensive patients, administration of the combination of extracts from grape seed and skin (330 mg), green tea (100 mg), resveratrol (60 mg) and a blend of quercetin, ginkgo biloba and bilberry (60 mg) for 2 weeks could reduce diastolic pressure although not impacting serum angiotensin-converting enzyme activity [32]. Others showed that consumption of tea or 3 capsules containing either 500 mg of green tea extract (an equivalent of 2 cups of tea), from early as 8 days to 4 weeks, could improve vascular function and significantly reduce systolic blood pressure, in part by preventing endothelial dysfunction in hypertensive patients [60,61]. However, although preliminary findings suggest that tea consumption improves blood pressure in hypertensive patients, the molecular mechanisms involving the modulation of oxidative stress and inflammation, remain unknown.

5. Discussion

Overwhelming evidence summarized in this review supports the beneficial effects of tea in improving endothelial function in individuals with or without CAD. In addition to lowering the levels

Table 4
An overview of randomized clinical trials reporting on the impact of tea on endothelial function-related outcomes in patients with metabolic syndrome.

Study	Country	Sample size, Average age	Complication/condition	Tea dosage and duration	Main findings
Hodgson et al., 2002 [23]	Australia	Sample size = 21 Average Age = 59	Subjects with mild elevations in serum cholesterol or triglyceride concentrations	5 cups per day of black tea for 4 weeks	Increased endothelium-dependent dilatation
Bakker et al., 2010 [58]	The Netherlands	Sample size = 36 Average Age = 46	Overweight men with mildly elevated plasma C-reactive protein concentrations	2 hard capsules and 2 soft capsules daily at breakfast with 200 ml plain yogurt and at the evening meal for 5 weeks	Increased plasma adiponectin concentrations and did not affect C-reactive protein
Azimi et al., 2016 [31]	Iran	Sample size = 204 Average Age = 54	Patients with type 2 diabetes mellitus	3 g cinnamon, 3 g cardamom, 1 g saffron or 3 g ginger with three glasses of black tea for 8 weeks	Could affect BP and soluble intercellular adhesion molecule-1 concentrations
Biesinger et al., 2016 [32]	United States	Sample size = 18 Average Age = 44	Subjects with hypertension	Combination of extracts from grape seed and skin (330 mg), green tea (100 mg), resveratrol (60 mg) and a blend of quercetin, ginkgo biloba and bilberry (60 mg) for 2 weeks	Reduced diastolic pressure, but did not affect systolic pressure
Grassi et al., 2016 [61]	Italy	Sample size = 19 Average Age = 51	Subjects with hypertension	Black tea (150 mg polyphenols) twice a day for eight days	Increased the number of circulating angiogenic cells and preventing endothelial dysfunction
Nogueira et al., 2017 [60]	Brazil	Sample size = 20 Average Age = 41	Subjects with hypertension	3 capsules containing either 500 mg of green tea extract for 4 weeks	Decreased in systolic blood pressure at 24 h, and night-time
Balsan et al., 2019 [59]	Brazil	Sample size = 142 Average Age = 50	Subjects affected by overweight or obesity	1000 ml green tea daily, during 8-weeks	Induced no significant difference in the levels of paraoxonase-1 and leptin

of oxidized-LDL, consumption of black tea twice to three times a day is associated with a dose-dependent increase in FMD, consistent to the reduction of systolic and diastolic blood pressure in individuals at risk of CVD (Table 1). In smoking individuals, green tea improved endothelium-dependent vasodilatation, within 2 h or daily for 2 weeks post consumption [18,28]. In patients with CAD, variable findings have been reported (Table 3). For instance, limited advantages of black tea consumption in improving endothelial function have been reported [51], however when consumed with breakfast or once a day for a period of 12 weeks, increased brachial artery FMD, plasma antioxidants and adiponectin levels, while reducing LDL and CRP levels [24,27,53,54]. From our analysis, only a few studies assessed the impact of tea consumption on endothelial function in patients with metabolic syndrome (Table 4). However, preliminary findings suggest that both black and green tea consumption, or its enriched extracts improve endothelial function in patients with hypertension, type 2 diabetes or inflammatory conditions (Table 4).

Indeed, the overall the findings from the included RCTs suggest tea consumption reduces the risk of CVD-related complications such as reducing blood pressure and enhancing endothelium-dependent FMD. These results are in line with previous meta-analysis, showing that moderate (2–3 cups) tea consumption significantly enhances endothelial-dependent vasodilation in individuals at risk of developing CVD [62]. Similarly, a recent meta-analysis showed that the daily intake of tea as part of a healthy habitual dietary pattern may be related to reduced CVD-risk and all-cause mortality among adults [63]. Although these quantitative studies [62,63] provide strong evidence to the beneficial effects of tea consumption in reducing CVD-risk, the implicated mechanisms remain relatively unknown. The current analysis of literature demonstrates that beyond enhancing NO bioavailability, tea and its active ingredients exert their beneficial effects by reducing markers of oxidative stress and inflammation markers including oxidized-LDL and CRP levels, thereby improving endothelial function (Fig. 3). Notably, elevated oxidized-LDL levels, which is a prominent feature of dyslipidemia, are known to promote a pro-inflammatory state through the formation of macrophage-derived foam cells [64,65]. This process can affect differentiation and proliferation of vascular smooth muscle cells while exacerbating atherosclerosis. Various in vitro and animal studies support this notion, together with enhanced oxidized-LDL levels and platelet-monocyte adhesion were shown to be consistent with atherosclerotic buildup and endothelial dysfunction [64,66,67].

Although such positive benefits were observed with regular tea consumption, most of these data could not be confirmed quantitatively or by performing a meta-analysis. Most included RCTs reported on diverse outcomes that could not be pooled to address the current question, or lacked well-defined controls, making it impossible to be used for the statistical analysis. Nonetheless,

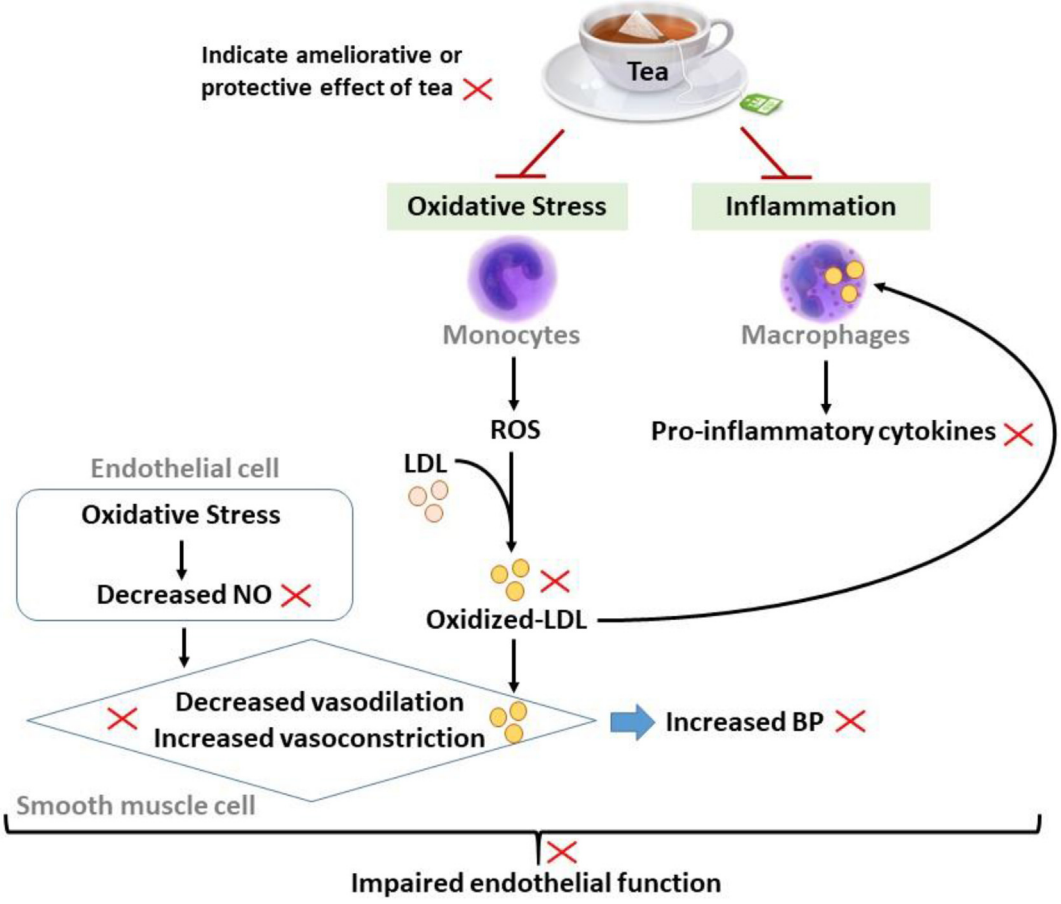

Fig. 3. The current analysis of literature demonstrates that beyond enhancing nitric oxide bioavailability and lowering blood pressure (BP), tea and its active ingredients exert their beneficial effects by reducing markers of oxidative stress and inflammation markers including oxidized-LDL (low-density lipoprotein) and C-reactive protein levels, thereby improving endothelial function.

although not targeting CAD directly, recent meta-analysis by other groups have indicated that regular consumption of green tea is linked with significantly decreased fasting glucose levels in those with diabetes [68], reduced body weight of obese subjects [69], and lowered lowers LDL and total cholesterol under different metabolic conditions [70].

6. Conclusions and future perspective

The current study shows the strong association between tea consumption and improved endothelial function in patients with CAD. Moreover, improvement in endothelial function, mostly through enhanced FMD, was consistent with the reduction in makers of oxidative stress and inflammation such as a oxidized-LDL and CRP in individuals at risk of CVD. However, although quality of evidence of included trials remains fairly good, there is considerable inconsistency in published data. For example, while regular consumption of both green and black tea is deemed beneficial, studies reporting on the molecular mechanisms involved in the long-term effects on vascular function are still needed. A clear understanding as to how tea consumption impacts those on currently used cardioprotective agents is also still unknown. Importantly, while partial evidence indicates that tea consumption can lower basic markers of oxidative stress and inflammation, this is not consistent based on type of preparation or cups consumed, across reported findings, and has to be confirmed in well-designed RCTs.

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Author contribution

PVD, BBN and LT-concept and original draft; PVD, BBN, SEM-M and TMN - literature search and data extraction; VM and KM – assessed quality of evidence; PVD, BBN, SEM-M, TMN, FM, IC, KZ, FN, VM, KM, JS, JL and TL-writing and final approval of the manuscript.

Data availability

Data related to search strategy, study selection, and extraction items will be made available upon request after the manuscript is published.

Ethics approval

This is a review of already published studies and thus it does not require ethical approval.

Consent for publication

Not applicable. No individual person's data has been included in this manuscript.

Declaration of competing interest

The authors declare no conflict of interest.

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Abbreviations

CAD	coronary artery disease
CRP	C reactive protein
CVDs	cardiovascular diseases
eNOS	nitric oxide synthase
FMD	flow-mediated dilation
LDL	low-density lipoprotein
NO	nitric oxide
RCTs	randomized controlled trials
ROS	reactive oxygen species

Appendix A. Supplementary data

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