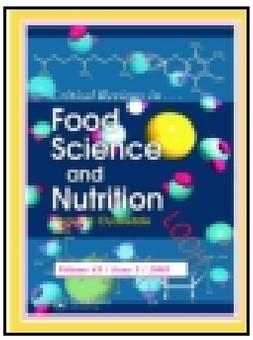

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Critical Reviews in Food Science and Nutrition

ISSN: 1040-8398 (Print) 1549-7852 (Online) Journal homepage: http://www.tandfonline.com/loi/bfsn20

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To cite this article: Roodabeh Bahramsoltani, Farnaz Ebrahimi, Mohammad Hosein Farzaei, Armaghan Baratpourmoghaddam, Pardis Ahmadi Borkani, Pourouchista Rostamiasrabadi, Amir Hosein Rasouli Amirabadi & Roja Rahimi (2017): Dietary polyphenols for atherosclerosis: A comprehensive review and future perspectives, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2017.1360244

To link to this article: http://dx.doi.org/10.1080/10408398.2017.1360244

Accepted author version posted online: 16 Aug 2017.

Dietary polyphenols for atherosclerosis: A comprehensive review and future perspectives

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Abstract

Atherosclerosis is one of the most prevalent reasons for premature death in adults. Despite the several conventional drugs in the market; many patients are not completely treated. Here we comprehensively review current clinical evidence regarding the efficacy of dietary polyphenols in atherosclerosis and related complications. PubMed, Cochrane library and Scopus were searched from inception until August 2016 to obtain clinical trials in which polyphenols were evaluated in cardiovascular parameters related to atherosclerosis. From total of 13031 results, 49 clinical trials were finally included. Tyrosol derivatives from virgin olive oil, catechins and theaflavins from green and black tea, cocoa polyphenols, and red grape resveratrol, as well as anthocyanins were the most studied polyphenolic compounds which could regulate lipid profile, inflammation and oxidative stress, blood pressure, endothelial function, and cell adhesion

molecules. The most important limitations of the included trials were small sample size, short follow up, and unqualified methodology. Future well-designed clinical trials are necessary to provide better level of evidence for clinical decision making.

Keywords

Dietary Supplements, atherosclerosis, phytochemical, lipid profile, blood pressure, adhesion molecule

Abbreviations

LDL-C: low density lipoprotein; TC: total cholesterol; HDL-C: high density lipoprotein-cholesterol; TAG: triacylglycerol; BP: blood pressure; ACE-activity: angiotensin-converting enzyme activity; ET-1: endothelin-1; FMD: flow-mediated dilation; HR: heart rate; STC: Serum thromboxane concentration; SBP: systolic blood pressure; DBP: diastolic blood pressure; SOD: super oxide dismutase; PNO: plasma nitric oxide; ACE I: angiotensin I-converting enzyme; LPL: lipoprotein lipase; malondialdehyde: MDA;8-EP F2: 8-epi-prostaglandin F2;LP(a): lipoprotein(a); FBS: fasting blood sugar; HbA1c: hemoglobin A1c; hsCRP: highly sensitive C-reactive protein; CT: catalase; TNF; tumor necrosis factor; ICAM: intercellular adhesion molecule; VCAM: vascular cell adhesion protein; IL: interleukin; IFN: interferon; FPI: fasting plasma insulin; ACS: acute coronary syndrome; PON-1: paraoxonase; MCP-1: Monocyte chemoattractant protein-1; IL8RA: interleukin 8 receptor α; ADRB2: adrenergic beta-2 receptor; OLR1: oxidized LDL-C (lectin-like) receptor 1; OLAB: oxidized LDL-C autoantibodies; apo: apolipoprotein; CCR2: Chemokine receptor 2; PWV: pulse wave velocity; Ox-LDL-C: oxidized LDL-C; CAT: catalase; BMI: body mass index; PBMC: peripheral blood mononuclear cells; GSH: reduced glutathione; NF-κB: nuclear factor κB; MAP kinase: mitogen-activated protein kinase; RANTES: Regulated on Activation Normal T cell Expressed and Secreted; PF4: platelet factor 4; PI3K: phosphatidylinositol-3-kinase; vit C: vitamin C; eEC-SOD: extracellular superoxide dismutase; 20-HETE: hydroxyeicosatetraenoic acid; EGCG: Epigallocatechin gallate; CF: cocoa flavonols; TF: theaflavin, TAC: total antioxidant capacity; LPO: lipid peroxidation; OGTT: oral glucose tolerance test; 8-iso-PGF2: 8-iso prostaglandin F2; BW: body weight, WC: waist circumference; HC: hip circumference; HTN: hypertension; MAP: mean arterial pressure; NO: nitric oxide; MPO: myeloperoxidase; ASA: Aspirin; DM: diabetes mellitus; CCA-IMT: carotid artery; PP: pulse pressure; AI: atherogenic index; SLeX: Sialil-Lewis X; LFA-1: lymphocyte function-associated antigen-1

Introduction

Atherosclerosis is referred to as a multifactorial disease with an inflammatory pathogenesis which is considered as one of the most prevalent cardiovascular disorders all over the world. The

disease is associated with ischemic heart disease as well as peripheral arterial disorders (Barquera *et al*., 2015). Abnormally increased level of blood low-density lipoprotein cholesterol (LDL-C) caused endothelial dysfunction and stimulates an inflammatory response via attraction of monocytes to the site of inflammation. The result is aggregation of lipids and foam cells under which tissue necrosis as well as arterial wall thickening and stiffness can be observed (Barquera *et al*., 2015).

Hypertension, diabetes mellitus and smoking are major risk factors for atherosclerosis. Statistics represented a decreasing trend in the global prevalence of the atherosclerosis and related complications, yet the disease is considered as one of the top reasons for premature death in adults (Herrington *et al*., 2016). Current treatment in atherosclerosis consist of antihyperlipidemics to manage dyslipidemia as the prime suspect in the pathogenesis of the disease (Stone *et al*., 2014), along with antiplatelet agents; nevertheless, only 30--40% of cardiovascular events are preventable with this therapeutic regimen (Maranhao and Leite, 2015). Thus, investigations are still ongoing to find better choices for the prevention and treatment of atherosclerosis.

Natural products have long been used as complementary and alternative medicine (CAM) by different nations all over the world (Farzaei *et al*., 2015b; Farzaei *et al*., 2016b). Most of the currently marketed chemical drugs originate from natural sources, especially medicinal plants. The famous and widely used antiplatelet agent, aspirin or acetyl salicylic acid (ASA), was designed through chemical modification of “salicin”, the glycosylated form of salicylic acid which was purified from the bark of *Salix* species (Jack, 1997). Thus, medicinal plants have always been the corner stone of the discovery of new pharmacologically active ingredients. Despite the global investigations regarding the phytochemical and pharmacological analysis of medicinal plants, several plant species as well as their phytocomponents are not yet fully assessed.

Amongst several categories of phytochemical, polyphenolic compounds seem to be the most attractive ones, especially for medicinal purposes (Manach *et al*., 2004). Polyphenols are a variety of secondary plant metabolites with several hydroxyl functional groups in their chemical

structure. Polyphenols are classified into several subcategories. Flavonoids are a subgroup of polyphenols which are widely distributed in fruits and vegetables of human diet. These compounds are usually found as yellow, orange or red pigments in the peel or flesh of the edible fruits as well as several vegetables. Anthocyanins are also categorized as a small group under the division of flavonoids and has a significant role in human health (Sodagari *et al*., 2015; Tsao, 2010). Tannins form another subgroup of polyphenols and are mostly well known for their astringent effects. Oak fruit and gall, pomegranate peel, and myrobalan fruit are the most famous natural sources of tannins (Ardekani *et al*., 2011). Anthraquinons are tricyclic polyphenols which can be found in plants like *Rheum* spp. (rhubarb), *Cassia* spp. (senna) and *Rhamnus purshiana* (cascara sagrada) and are widely used due to their laxative effects (Cirillo and Capasso, 2015). Lignans are another group of polyphenols which are also classified as phytoesterogens. Flaxseed and sesame lignans are widely studies for their beneficial effects on human health (Adlercreutz, 2007). Stilbenes, are a relatively small subclass of polyphenols. The most famous stilbene is resveratrol from the red grape which is well-studied in animal and human models of several disorders (Reinisalo *et al*., 2015).

Although each polyphenol has demonstrated a series of specific pharmacological and biological activities, some mutual features among polyphenolic compounds caused these structures to be notably interesting for the medicinal purposes (Chen *et al*., 2016; Chen *et al*., 2017; Xiao *et al*., 2016; Xiao *et al*., 2017). Several polyphenols have represented significant antioxidant activities through *in vitro* and *in vivo* studies (Hatia *et al*., 2014; Davatgaran-Taghipour *et al*., 2017). Flavonoids are widely studied for their anti-inflammatory properties (Farzaei *et al*., 2015a; Farzaei *et al*., 2016b; Fraga *et al*., 2010). Numerous numbers of polyphenolic structures have been evaluated for their antineoplastic activity and a considerable amount of which have exhibited specific toxicity toward the cancerous cells (Farzaei *et al*., 2016a). Natural polyphenols could also act as chemoprotective agents in several tissues like liver, kidney and brain as well as cardiovascular system (Fraga *et al*., 2010).

Literature review showed that polyphenols have demonstrated beneficial effects in animal models of several cardiovascular disorders like hypertension, atherosclerosis, endothelial

dysfunction, dyslipidemia and diabetes-related cardiovascular complications (Gormaz *et al*., 2016; Khurana *et al*., 2013; Tangney and Rasmussen, 2013). Additionally, there are several clinical investigations on the efficacy of purified polyphenols and polyphenol-enriched plant extracts in patients with different types of cardiovascular complications. The aim of this paper is to provide an overview of the current state of the art on the clinical application of polyphenols in atherosclerosis and related complications.

Search strategy

Electronic databases including Medline, Scopus, and Cochrane library were searched with the following search formula: ("plant" OR "herb" OR "phytochemical" OR "polyphenol" OR "flavonoid")[all fields] AND ("atherosclerosis" OR "dyslipidemia" OR "hypercholesterolemia" OR "hypertension")[title/abstract/keyword]. In addition, specific names of most popular clinically used polyphenols including curcumin, resveratrol, catechin were individually searched in order not to miss any clinical study on well-known polyphenols. Articles were searched form the date of inception to August 2016. Only articles with English full-texts were included in this review. Inclusion criteria were clinical trials in patients with atherosclerosis, dyslipidemia, type II diabetes, metabolic syndrome, cardiovascular complications or healthy subjects in which the effect of the treatment on a cardiovascular parameter was measured. Exclusion criteria were animal or cellular studies, human studies other than clinical trials (e.g. case reports and cohort studies) and studies evaluating total extracts without assessing polyphenol-enriched fractions or purified polyphenols. Primary search results were screened through reading titles and abstracts by two independent investigators to find relevant studies. The selected articles were then checked by their full-text and final included articles were chosen to be summarized in a tabular form. Full-text articles were carefully screened to obtain type of the assessed polyphenol, study design, sample size (the final number of patients), administered dose, duration of study and outcomes. To have a better comparison between the methodology of the trials, Jadad score was calculated for each included study (Jadad *et al*., 1996). Figure 1 shows a flow diagram of study selection process.

Outcomes

Anthocyanins

Anthocyanins are a group of phenolic glycosides which produce a wide variety of colors in response to different PH values. These compounds are mostly found as purple, violet or blue pigments in several plants, especially edible berries like blueberry, cranberry, bilberry, chokeberry and elderberry (Sodagari *et al*., 2015).

Kuntze *et al*. reported antioxidant effects of an anthocyanin rich beverage, prepared from red grape and bilberry, in the forms of juice and smoothie with anthocyanin content of 983.7 mg/l and 840.9 mg/l, respectively. Two-week administration of both preparations in healthy female volunteers showed significantly higher antioxidant activity in comparison to the control juice in which the anthocyanins were reduced to 8.9 mg/l. Malondialdehyde (MDA), as an indicator of lipid peroxidation, was reduced in plasma and urine samples of subjects received anthocyanin rich beverages which was in line with the elevation of endogenous antioxidant enzymes, superoxide dismutase (SOD) and catalase (CAT) (Kuntz *et al*., 2014). In another trial with a mixture of anthocyanin rich fruits, blood level of reduced glutathione (GSH) was increased and DNA oxidative damage was significantly inhibited; however, no effect on lipid peroxidation, urine isoprostanes & DNA-binding activity of nuclear factor κB (NF-κB) was detected (Weisel *et al*., 2006). Anthocyanins with a dose of 320 mg/day were administered to hypercholesterolemic patients in a randomized, double-blind, placebo-controlled trial for a period of 24 weeks. It was demonstrated that the supplement could reduce plasma level of the cell adhesion molecule P-selectin, as well as β-thromboglobulin (β-TG: an inflammatory mediator released from activated platelets). Regulated on activation normal T cell expressed and secreted (RANTES), an indicator of inflammatory condition of arteries (Veillard *et al*., 2004), was also reduced by the supplement. In addition, in isolated platelets of patients received anthocyanins, the levels of pro-inflammatory and pro-thrombotic factors were significantly decreased (Song *et al*., 2014); thus, anthocyanin supplementation could reduce inflammation and thrombotic status within the blood vessels.

Cocoa polyphenols

Theobroma cacao L. from the family Malvaceae is a tropical tree native to Brazil. The plant fruit contain large seeds which are used for the production of one of the most popular snacks all over the world, chocolate. Various processes have different effects on the nutraceutical content of the finally produced chocolate (Wollgast and Anklam, 2000). Unprocessed cocoa seeds contain a large quantity of polyphenolic compounds which may be reduced during the processing procedure. In recent years, scientists have understood that phenolic compounds of unprocessed cocoa have several beneficial health promoting effects; thus, instead of removing polyphenols, new types of chocolates with higher amounts of phenolic compounds and lower sugar content were introduced, known as dark chocolate (Farhat *et al*., 2014).

In a randomized, double-blind study in postmenopausal women with hypercholesterolemia, hot cocoa beverages with low and high flavonoid contents were administered for 6 weeks. Flavonoid-enriched hot chocolate beverage could successfully reduce soluble vascular cell adhesion molecule-1 (sVCAM-1) and improve HDL-C in comparison to low-flavonoid cocoa beverage; however, no effect on other parameters of lipid profile was observed. Additionally, high-flavonoid cocoa beverage improved hyperemia as well as endothelial function which was reflected by increase in flow-mediated dilation (FMD) (Wang-Polagruto *et al*., 2006). To investigate the effect of cocoa flavanols on acute hyperglycemic situation, twelve healthy individuals received dark or white chocolate in a randomized crossover design and cardiovascular parameters were measured before and after oral glucose tolerance test (OGTT). Serum levels of endothelin-1, biomarker of blood vessels stiffness, was significantly increased after intake of dark chocolate with high flavanol content. Improvement of FMD and wave reflection, as well as decrease in the serum 8-iso-prostaglandin F2α (8-iso-PGF2α: a product of lipid peroxidation) also reflect the positive role of cocoa polyphenols in decreasing arterial stiffness in acute hyperglycemia (Grassi *et al*., 2012). Another study assessed the effect of dark chocolate in type 2 diabetic patients with hypertension. Eight-week consumption of polyphenol-enriched chocolate (with 450 mg/ day of flavonoids) could significantly reduce both systolic and diastolic blood pressure (SBP and DBP) in comparison to white chocolate. Dark chocolate could

also regulate the level of apolipoproteins (apo B and apo A1) and decreased fasting blood glucose (FBS) as well as C-reactive protein (CRP) (Rostami *et al*., 2015). In postmenopausal diabetic women receiving statin therapy, the effect of long-term intake of polyphenol-enriched chocolate on the progress of atherosclerosis was assessed. In comparison with those received placebo, polyphenol-enriched chocolate could reduce the variability of pulse pressure; however, no other significant effect was observed on BP, intima-media thickness of the common carotid artery (an indicator of atherosclerosis progression) or biochemical markers of cardiovascular damage (Curtis *et al*., 2013). Another randomized, double-blind, placebo-controlled crossover study in type 2 diabetic patients under treatment with oral antihyperglycemic agents demonstrated the effect of polyphenol-enriched chocolate to reduce ratio of TC/HDL-C compared with the baseline values. No other significant change was detected in the glycemic parameters or lipid profile (Mellor *et al*., 2010).

Curcuminoids

Curcuminoids are diarylheptanoid yellow pigments isolated from *Curcuma longa* L. (turmeric); however, it is found in other species of the genus *Curcuma* as well as some other plants of the family Zingiberaceae (Shishodia *et al*., 2005). Although curcumin is the most studied curcuminoid in the literature, it should be mentioned that in most of the studies, the administered formulations contain a mixture of curcuminoids, i.e. a high percentage of curcumin along with small amounts of demethoxycurcumin and bisdemethoxycurcumin (Farzaei *et al*., 2016a; Péret-Almeida *et al*., 2005). Curcumin is widely evaluated for its beneficial effects in human health including antioxidant, anticancer (Farzaei *et al*., 2016a), hepatoprotective (Vera-Ramirez *et al*., 2013), anti-inflammatory and cardioprotective (Srivastava and Mehta, 2009) activities. Due to the high safety profile, purified curcumin has been introduced to clinic and is globally available as various supplements.

One of the problems regarding the drug delivery of curcumin is the poor oral bioavailability; thus, investigators have tried several novel formulations to improve the pharmacokinetics of the drug amongst which the most important ones are curcumin nanoformulation and lipid based preparations. DiSilvestro *et al*. evaluated the effect of a lipidated curcumin product in healthy

volunteers. Compared to placebo, curcumin could significantly improve plasma catalase (CAT) and NO, as well as myeloperoxidase (MPO); though, there were no elevation in ceruloplasmin or in CRP which can suggest the effect of curcumin to reduce white cells inflammation. Curcumin could also successfully decrease salivary amylase activity which proposes a modifying effect for curcumin in adrenergic nervous system (DiSilvestro *et al*., 2012). Another method to improve the absorption of curcumin is to add some substances to the formulation which are known as bioavailability enhancers. Piperine, an alkaloid from the plant *Piper nigrum* L. (black pepper), is one of the popular bioavailability enhancers in curcumin oral dosage forms. It is worthy to mention that in spite of the wide demonstrated biological activities of piperine, the amount of the substance used as bioavailability enhancer does not produce any additional pharmacological activity. Panahi *et al*. administered a curcumin-piperine formulation in patients with metabolic syndrome for a period of eight weeks. The results showed the beneficial effects of curcumin on modifying all lipid parameters, including TC, LDL-C, non-HDL-C, HDL-C, TAG and lipoprotein a (LP(a)); though, the difference in small dense LDL-C (sdLDL-C) failed to reach a statistically significant level (Panahi *et al*., 2014). Similar to the study of Panahi *et al*., Moohebati *et al*. evaluated the same formulation of curcumin in obese dyslipidemic patients, which could not show a significant effect on sdLDL-C after one-month curcumin intervention either; however, no measurement of other lipid profile parameter was reported (Moohebati *et al*., 2014). Curcuminoids/piperine preparation was also assessed as antihyperlipidemic in obese patients. In this study, the only reduced parameter was TAG and neither lipid profile parameters, nor anthropometric parameters were significantly affected by the supplement (Mohammadi *et al*., 2013). A randomized, double-blind, placebo controlled trial assessed the effect of low (45 mg/day), moderate (90 mg/day), or high (180 mg/day) dose of curcumin in patients with acute coronary syndrome. Results of the two-month intervention demonstrated a trend toward the reduction of TC and LDL-C, as well as elevation of HDL-C in patients received the low dose of curcumin; however, high dose of curcumin increased the level of TC and LDL-C. In addition, curcumin with all doses increased the level of TAG. None of the obtained values were statistically significant from placebo group (Alwi *et al*., 2008). Since the study included patients with a complicated disease condition and concomitant therapy with other cardiovascular drugs,

the heterogeneous outcomes may be the result of the effect of curcumin on pharmacokinetics/ pharmacodynamics of the other administered drugs (Bahramsoltani *et al*., 2017). A study on type 2 diabetic patients demonstrated the positive effect of six-month supplementation with a high dose (1.5 g as six capsules per day) of curcumin in biological indicator of arterial stiffness, PWV. Curcumin also modified lipid profile via decrease in TAG and leptin as well as elevation of adiponectin level which was in coordination with reduction of insulin resistance. Furthermore, the treatment exhibited numerical, but not statistical significant decrease in the levels of TC, LDL-C, waist circumference (WC), and increase in the level of HDL-C (Chuengsamarn *et al*., 2014).

Green and black tea polyphenols: catechins and theaflavin derivatives

Tea, with the scientific name of *Camellia sinensis* (L.) Kuntze (Synonym: *Thea sinensis* L.), is one of the mostly consumed beverages all over the world, especially in European and Asian countries. Different nations have various types of processing (mainly different degrees of fermentation) which results in several diverse types of tea (Pan *et al*., 2016). Green tea, the unprocessed form of the tea, has been widely studied for its antioxidant, anticancer and anti-inflammatory effects. The most important polyphenolic compounds of green tea include the flavonoid catechin and its derivatives like epicatechin gallate (ECG), epigallocatechin (EGC) and epigallocatechin gallate (EGCG). On the contrary, black tea has the highest degree of fermentation and contains another class of flavonoids, called theaflavins (Leung *et al*., 2001; Pan *et al*., 2016).

In a study by Inami *et al*., supplementation with a commercial green tea preparation providing 500 mg catechin per day could decrease LDL-C oxidation; though, no significant change in other lipid parameters were observed (Inami *et al*., 2007). Another study also confirmed the positive effect of a single-dose of catechin (1 g) to reduce LDL-C oxidation and elevation of serum antioxidant capacity (Suzuki-Sugihara *et al*., 2016). In another study with medium (80 mg/day) and high (580 mg/day) dose of green tea catechins, a significant improvement in endothelial-dependent vasodilation was demonstrated; whereas the endothelial-independent vasodilation was not influenced. In addition to reduction of monocyte chemoattractant protein-1 (MCP-1) and

CD40, which are markers of monocytes and platelets activation, high-dose catechin administration also increased the level of NO and reduced plasma asymmetric dimethylarginine (ADMA) (Oyama *et al*., 2010). In a randomized, double-blind, placebo-controlled trial in hypercholesterolemic subjects, a preparation containing a mixture of catechins (150 mg, from green tea) and theaflavins (75 mg, from black tea) was compared along with a theaflavin preparation, as well as placebo capsules. None of the preparations could improve lipid profile parameters after 4, 8 or 11 weeks of treatment (Trautwein *et al*., 2010). Catechin supplementation in a group of elderlies (mean age of 69 years old) could improve anthropometric parameters including WC and hip circumference (HC), as well as lipid profile in comparison to baseline levels (Miyazaki *et al*., 2013). In addition, the effect of epicatechin on endothelial dysfunction biomarkers was evaluated in hypertensive subjects. The 100 mg daily dose of epicatechin could reduce the level of soluble endothelial selectin (E-selectin), which participates in leukocytes adhesion to endothelium, after one-month supplementation; however, no effect on other biomarkers of inflammation including other soluble adhesion molecules and different cytokines were observed (Dower *et al*., 2015). Juar tea, another type of tea which is prepared using *C. sinensis* grown in Africa, has also been assessed for the beneficial effects of its polyphenols in patients with metabolic syndrome. In comparison to barley tea which contains trace amounts of polyphenols, Juar tea could increase the level of endothelium-bound extracellular superoxide dismutase which is an important vascular antioxidant enzyme. It should be mentioned that none of the consumed teas showed considerable effect on lipid profile parameters (Uto-Kondo *et al*., 2013).

In an open-label, randomized, controlled trial in patients with mild to moderate hypertension, a polyphenol-enriched regimen was administered for a period of 6 months. The regimen contained three sources of natural polyphenols including dried apple slices, dark chocolate and green tea, which provided a total daily amount of 450.8 ±13.9 mg of epicatechin. The four groups of the trial received captopril alone, captopril + polyphenol-enriched diet, telmisartan alone, or telmisartan along with polyphenol-enriched diet. Results of the study showed synergistic effect of dietary flavonoid in combination with the antihypertensive drugs in regard to the reduction of SBP/DBP, TAG level, and leptin in comparison to antihypertensive therapy alone. All treatments

had the same reductive effect on the level of CRP. None of the lipid parameters except than TAG showed between-group significant difference (Jesus Romero-Prado *et al*., 2015).

Olive oil polyphenols

Olive tree, with the scientific name of *Olea europaea* L. is an evergreen tree native to Asian, European and African countries (Medail *et al*., 2001). Although the olive leaves are used in traditional and folk medicine of different countries for several indications, the most important olive product which attracted global attention to the health benefits of the plant is the fruit oil. Olive oil is a popular part of the traditional foods in Mediterranean culinary. Nutritional studies demonstrated the protective impact of Mediterranean diet in comparison to Western diet against a wide range of oxidative stress-related disorders, including cardiovascular diseases, which, in a great deal, is ought to the high intake of olive oil in Asian countries. In recent years, several studies assessed the impact of virgin olive oil in primary prevention of several disorders. Virgin olive oil is an unfiltered type of the oil in which the antioxidant polyphenolic components, mainly tyrosol and its derivatives, are not removed; thus, has a significantly higher antioxidant activity in comparison to purified olive oils (Covas *et al*., 2015).

A randomized, crossover, controlled trial in a group of non-smoking healthy volunteers evaluated the effect of dietary intake of low and high-polyphenol olive oils with a daily intake of 25 ml for a period of three weeks. The results demonstrated significant effect of high-polyphenol olive oil on TC and LDL-C, as well as oxidized LDL-C; however, no effect on HDL-C and TAG was observed (Castaner *et al*., 2012). High-polyphenol olive oil also decreased body mass index (BMI) and showed an effect toward the reduction of DBP ($P = 0.043$). CD40 is a leukocyte surface antigen which plays a key role to form a type of stable atherosclerotic plaque (Lievens *et al*., 2009); thus, increased level of CD40 is suggested to be a risk factor for atherosclerotic plaque formation. Monocyte chemoattractant protein-1 (MCP-1), being produced following the activation of CD40, is another molecule attracting monocytes to the site of atherosclerotic lesion. High-polyphenol olive oil could significantly reduce the level of both soluble CD40 ligand and MCP-1 compared with the other treatment groups. It should be mentioned that interferon γ (IFNγ) and ICAM-1, which are other agents involved in the white cells adhesion, were also

measured; however, no significant difference was detected between the two treatment groups (Castaner *et al*., 2012). Another study with the same intervention showed better effect of high-polyphenol olive oil in decreasing oxidized LDL-C autoantibodies (Castaner *et al*., 2011). A single-dose administration of olive oil with three different content of polyphenols in healthy subjects showed a dose dependent trend toward the reduction of LDL-C oxidation. In addition, serum level of olive phenolic compounds was increased after ingestion which demonstrated the ability of olive oil to increase the antioxidant capacity of plasma (Covas *et al*., 2006). In another single-dose study comparing high-polyphenol (400 ppm) and low-polyphenol (80 ppm) olive oil in hypercholesterolemic patients, high-polyphenol olive oil showed less elevation of lipid peroxides and 8-iso-PGF2α which are formed as a result of fatty acid oxidation (Davi *et al*., 1997). Ischemic reactive hyperemia, an indicator of endothelial function, was also assessed using Laser Doppler perfusion monitoring which showed significantly better improvement in patients received high-polyphenol olive oil (Ruano *et al*., 2005). In another randomized, double-blind, trial in patients with early atherosclerosis, participants took olive oil with 340 mg/kg of polyphenols or EGCG-enriched olive oil, containing total of 600 mg/g of polyphenols, for a period of 4 months. Interestingly, natural olive oil represented better efficacy in reduction of intercellular adhesion molecule-1 (ICAM-1). Furthermore, both groups showed better endothelial function in comparison to the beginning of the trial; however, this difference was not significant between the two groups (Widmer *et al*., 2013). Another trial in healthy subjects showed the positive effects of olive oil with a high polyphenolic content (366 mg/kg) on the level of apo B 100, as well as small LDL-C particles in comparison to a low-dose (2.7 mg/kg) of olive polyphenols (Hernáez *et al*., 2015).

Citrus flavonoids

Citrus fruits are defined as different species of the genus *Citrus* from the family Rutaceae which comprise a group of worldwide popular fruits such as orange, lemon, citron, lime and tangerine. Both peels and flesh are globally used for culinary and medicinal applications. The fruit peel is mostly used to obtain different citrus essential oils; whereas the fruit itself is rich in flavonoids

and phenolic acids. Narigenin, hesperidin, kaempferol, apigenin and luteolin are among the most important flavonoids detected in citrus fruits (Tripoli *et al*., 2007).

Demonty *et al*. assessed a four-week supplementation with hesperidin (800 mg/day) or naringin (500 mg/day) in hypercholesterolemic patients. Biochemical parameters of lipid profile revealed that naringin did not make any significant change in the TC, LDL-C, HDL-C, or TAG compared to placebo, nor did hesperidin; thus, this trial could not support the antihyperlipidemic effect of the two flavonoids in these patients (Demonty *et al*., 2010). On the other hand, another clinical trial with naringin showed significant improvement in lipid parameters in comparison to baseline values. In this trial, the two treatment groups, including healthy individuals and hypercholesterolemic patients, received 400 mg/day of naringin supplement for 8 weeks. The results represented significant reduction in TC and LDL-C in hypercholesterolemic patients without any significant change in healthy control subjects (Jung *et al*., 2003).

Pycnogenol

Pycnogenol is a commercial extract of French pine bark, with the scientific name of *Pinus pinaster* Aiton, which is shown to have positive effects on cardiovascular system, possibly due to the antioxidant and anti-inflammatory properties of its polyphenolic compounds. The preparation mostly contains flavonoids like taxifolin and catechin, as well as condensed polymeric molecules (Hosseini *et al*., 2001).

Hosseini *et al*. assessed the effect of Pycnogenol in mildly hypertensive subjects. The daily dose of 200 mg of Pycnogenol demonstrated reduction in both SBP and DBP which was statistically significant in comparison to placebo (Hosseini *et al*., 2001). Another study in patients with coronary artery disease supported the beneficial effects of 2-months supplementation with Pycnogenol on FMD as the indicator of endothelial function. Furthermore, Pycnogenol could improve antioxidant status which was defined as the decreased level of plasma 15-F2t-isoprostane (a marker of oxidative stress in cardiovascular diseases) (Enseleit *et al*., 2012). Flavonoids from the bark of another species of pine, *P. radiata*, were also evaluated in chronic smokers. The commercial preparation of the flavonoids (480 mg), Enzogenol, in combination

with vitamin C (60 mg) was compared with vitamin C alone for a period of 12 weeks. The results represented a significant improvement in endothelial function in comparison with baseline values based on the measurement of FMD; however, this effect was not significantly different between the two treatment groups. In addition, a significantly lower protein oxidation was observed in subjects treated with Enzogenol + vitamin C versus vitamin C monotherapy (Young *et al.*, 2006).

Quercetin

Quercetin is one of the most popular flavonoids in human diet. Quercetin and its derivatives like rutin and quercitrin are widely distributed in human dietary fruits and vegetables like apple, onion, cherry and grape (D'Andrea, 2015; Nabavi *et al.*, 2015). Several therapeutic activities have been attributed to this phytochemical including anticancer, antioxidant, and anti-inflammatory, as well as its positive effects in obesity and diabetes (D'Andrea, 2015).

In a randomized, double-blind, placebo-controlled, crossover trial, a single-dose of purified quercetin aglycone was administered to 5 normotensive subjects and twelve stage I hypertensive patients. While no effect was observed in normotensive volunteers, quercetin could reduce the mean blood pressure in hypertensive subjects. It should be mentioned that in contrast with the authors' primary hypothesis, this effect was not correlated with a significant change in heart rate and FMD, nor was it related to the endothelin-1, nitrite or angiotensin converting enzyme (ACE) activity (Larson *et al.*, 2012). Boesch-Saadatmandi *et al*. evaluated the effect of three dose levels of quercetin (50, 100 and 150 mg/day) on the activity of paraoxonase-1 (PON-1), an enzyme involved in the protection of HDL-C and LDL-C oxidation and atherosclerosis prevention. Despite the induction of PON-1 by quercetin in the animal model, no such effect was detected in healthy human subjects (Boesch-Saadatmandi *et al.*, 2010). Additionally, quercetin could decrease endothelial adhesion molecule, E-selectin, and pro-inflammatory cytokine, IL-1β (Dower *et al.*, 2015).

Resveratrol

Resveratrol is a stilbene, a subgroup of polyphenolic compounds, which is mostly isolated from grape seed and skin; however, it can be detected in other sources like peanut, as well (Nabavi *et al*., 2014). Resveratrol has always been discussed as a potent antioxidant with several therapeutic and biological properties like anticancer, hepatoprotective, cardioprotective and antiatherosclerotic effects (Farzaei *et al*., 2016a; Bishayee *et al*., 2010; Fan *et al*., 2008).

A single-dose of resveratrol could improve FMD in obese patient with untreated borderline HTN (Wong *et al*., 2011). Four-week supplementation with resveratrol in healthy individuals significantly decreased the expression of cell adhesion molecules including ICAM and VCAM as well as the level of pro-inflammatory cytokine, IL-8. Fasting insulin level was also reduced in resveratrol treated subjects; however, no significant change in other inflammatory markers like TNF-α, IL-1β and IL-6 was observed (Agarwal *et al*., 2013). Tomé-Carneiro *et al*. also reported the positive effects of resveratrol in reducing pro-inflammatory and soluble cell adhesion molecules (Tome-Carneiro *et al*., 2012). On the contrary, another study on the effect of concomitant resveratrol supplementation and exercise showed that resveratrol has a negative impact on the cardiovascular parameters improved by exercise. In this randomized, double-blind, placebo-controlled clinical trial in aged men, both treatment and placebo groups had the same exercise pattern during a two-month period. In patients received placebo, exercise reduced mean arterial pressure (MAP) and vasodilator prostacyclins, improved lipid parameters, and increased muscle thromboxane synthase compared to baseline values; whereas in those received resveratrol, none of these positive improvements in cardiovascular parameters were observed which suggest a negative role for resveratrol in aged patients with cardiovascular disease (Gliemann *et al*., 2013). Despite the small sample size (27 patients) in this study, it seems that the administration of antioxidant phytochemicals, specifically resveratrol, should be reconsidered in patients with cardiovascular complications. Additionally, long-term studies with larger sample sizes maybe helpful to make a definite conclusion.

Wine and beer polyphenols

There have been always controversial data regarding the beneficial effects of beer and wine on human health. Some studies associate the positive effects of beer and wine to their polyphenolic compounds rather than the alcohol, whereas others believe that alcohol can also be involved in the cardioprotective properties of these beverages. Red wine and beer polyphenols mainly consist of anthocyanins, flavonoids and cinnamic acid derivatives. In addition, red wine which is usually produced from red grape fermentation also contains the stilbene resveratrol (Arranz *et al*., 2012)

Chiva-Blanch *et al*. (2015) compared cardiovascular effects of three types of beverages include beer (containing both polyphenols and alcohol), non-alcoholic beer (containing only polyphenols) and gin (alcoholic drink without polyphenols). Non-alcoholic beer reduced SBP and biomarkers of inflammation including different types of ILs as well as cell adhesion molecules like lymphocyte function-associated antigen-1 (LFA-1), E-selectin and its ligand Sialil-Lewis X (SLe^X). Both alcoholic beverages increased HDL-C and apolipoprotein levels; however, only beer was able to reduce lymphocyte and monocyte expression of LFA-1 and SLe^X. Authors have concluded that the polyphenolic fraction of beer shows cardioprotective effects through decrease in inflammation and cell adhesion; while the alcohol content modifies the lipid profile parameters (Chiva-Blanch *et al*., 2015).

A human study compared antihypertensive effect of two red wines with low (280 mg) and high (560 mg) polyphenolic content. After four-week consumption of the beverages, no significant improvement in blood pressure of the patients and related parameters were observed (Botden *et al*., 2012).

Polyphenols with fewer clinical evidence

In addition to the above mentioned polyphenols, there are some other polyphenol-enriched preparations which are less studied.

Sesamin is an active component of the plant *Sesamum indicum* L. (Sesame) with lignan structure. 20-hydroxyeicosatetraenoic acid (20-HETE) is a main metabolite of cytochrome P450 during the

oxygenation of arachidonic acid which can act as a vasoconstrictor and is proposed to be involved in the pathogenesis of hypertension. In a crossover trial in overweight men and postmenopausal women, daily consumption of dietary sesame (standardized based on sesamin content) for five weeks showed significant reduction in the plasma and urinary 20-HETE excretion; however, no considerable change in the blood pressure and urinary electrolytes was detected (Wu *et al.*, 2009).

Another plant which has been assessed for antihypertensive effect of its polyphenolic compounds is *Hibiscus sabdariffa* L., commonly known as "sour tea". There are several studies on the antihypertensive properties, but only one study evaluated the therapeutic activity of a polyphenol-enriched preparation (Joven *et al.*, 2014). In an uncontrolled trial in patients with metabolic syndrome, four-week supplementation with sour tea polyphenols could reduce blood pressure. Both SBP and DBP were decreased in comparison to the baseline values. The preparation also represented antioxidant activity through reduction of 8-iso-PGF2α, a byproduct of fatty acid oxidation (Ren *et al*., 2013), and improvement in paraoxonase activity, an enzyme which protects body lipids against peroxidation (Litvinov *et al*., 2012). Despite a mild angiotensin I-converting enzyme inhibitory activity in cellular evaluations, no such effect was observed in patients (Joven *et al*., 2014).

Polyphenols of Japanese plum, with the scientific name of *Prunus mume* Siebold & Zucc., was assessed as an antihypertensive supplement in patients with mild HTN; though, there was no significant improvement in SBP or DBP after 12 weeks of consumption (Takemura *et al*., 2014).

Fiit-ns which is a mixture of polyphenols from grapefruit, green tea, grape, black carrot and guarana was administered to obese patients for a period of 12 weeks. The preparation could successfully improve anthropometric parameters, lipid profile, and biomarkers of inflammation as well as oxidative damage (Cases *et al*., 2015). It should be mentioned that the sample size of this study was only 17 patients which is relatively low and larger sample sizes are needed for more conclusive result.

Ecklonia cava Kjellman is a kind of brown algae that contains a subgroup of polyphenols called phlorotannins which are polymers of phloroglucinol (Queguineur *et al*., 2012). Twelve-weeks supplementation with *Ecklonia cava* phlorotannins in overweight subjects could decrease TC and LDL-C and elevate HDL-C in comparison to placebo. In patients treated with high dose (144 mg/ day) of the supplement, there was also a significant reduction in plasma glucose as well as SBP; whereas no such effect was observed with low dose (72 mg/ day). In addition, anthropometric parameters were also modified with both low and high dose of the supplement (Shin *et al*., 2012).

Daidzein, one of the major soybean isoflavones, was evaluated as an antihypertensive agent in mildly hypertensive postmenopausal women in comparison to whole soybean supplement as well as placebo. Despite a long follow up period of 6 months in 253 patients, neither the whole soybean nor the purified daizein showed significant effect on the blood pressure of patients (Liu *et al*., 2015).

Apple polyphenols, from the species *Malus domestica* Borkh., were consumed by hypercholesterolemic subjects as a dietary intervention in the form of lyophilized apples, equal to daily amount of 135 g fresh apple with high (1.43 g) or low (0.21 g) polyphenol content. FMD as indicator of endothelial function, lipid profile parameters, homocysteine as an important contributor in cardiovascular disorders, and antioxidant capacity were measured after a four-week period; however, none of the mentioned parameters were significantly changed in comparison to baseline levels (Auclair *et al*., 2010).

Chlorgenic acid, a phenolic acid from green coffee beans, was assessed in mildly hypertensive subjects for a period of two weeks. The supplement could successfully reduce both SBP and DBP in a significant manner; while no change in heart rate and BMI was observed (Watanabe *et al*., 2006).

Discussion

Atherosclerosis is a multifactorial inflammatory disease which is considered as one of the top reasons of mortality worldwide. Despite significant developments in the discovery of

antiatherosclerotic drugs, a considerable number of patients is not satisfyingly treated with the current therapeutic approaches. In addition, several side effects are reported for current available pharmacotherapies. As an example, a recently published meta-analysis showed that long-term statin therapy is associated with the risk of new onset diabetes (Casula *et al*., 2017). Thus, investigations are conducted for the discovery of further treatment options.

Since ancient times, medicinal plants and their isolated phytochemicals could demonstrate several health promoting effects. Numerous number of papers have assessed the effects of herbal medicines in cardiovascular diseases (Chalvon-Demersay *et al*., 2017; Miller *et al*., 2004).

Here, we reviewed clinical trials assessed the effectiveness of polyphenolic compounds from different plant sources in atherosclerosis and related complications. Virgin olive oil, dark chocolate, green and black tea, different berries, turmeric, pine bark, citrus fruits, and grape are the most well-known sources of polyphenols assessed in the included studies (Table 1). Figure 2 shows the structure of well-known polyphenols (https://pubchem.ncbi.nlm.nih.gov/). Phenolic compounds could act through different mechanisms of action to improve the cardiovascular status of patients. Modifying lipid profile parameters i.e. improving HDL-C, and reducing LDL-C, TC and TAG, is one of the common mechanisms of polyphenols in the prevention and treatment of atherosclerosis. Another mechanism is the modulation of inflammatory processes via controlling the levels of pro-inflammatory cytokines such as different ILs and TNF-α. As it has been discussed in several studies (Hansson and Libby, 2006; Ribatti *et al*., 2008), inflammation can be considered as a double-edged sword, meaning it can have beneficial effects, or destructive activity during the progression of a disease. Primary inflammation attracts the immune system elements to the site of lesion which helps to repair the damage; whereas long-term presence of inflammatory cells can cause tissue dysfunction which needs external interventions to be controlled. Polyphenolic compounds can act as this external modifier through modification of inflammation process which has been indicted by decreased levels of TNF-α, IFNγ and different types of interleukins (Table 1). In addition, antioxidant properties of polyphenols help to reduce LDL-C oxidizability. It is suggested that oxidized LDL-C can stimulate toll-like receptor 4 (TLR-4) and induce further inflammation (Xu *et al*., 2001).

Decreased urinary excretion of isoprostans is another indicator of reduced oxidative stress by phenolic compounds. Polyphenols also demonstrated a regulatory activity on the lipid parameters, causing increase in HDL-C and decrease in LDL-C and TC. Polyphenols were able to reduce TAG levels, as well. Although the link between TAG levels and atherosclerosis is not as clear as in case of cholesterol, there are reports discussing the pro-atherogenic role of triacylglycerol-rich lipoproteins (Cullen, 2003).

One of the other mechanisms by which polyphenols can prevent the development of atherosclerosis is reducing adhesion molecules like sICAM, sVCAM, E-selectin and P-selectin (platelet selectin) (Table 1). These adhesion molecules induce the attachment of blood leukocytes to the endothelium of blood vessels and promote the process of atherosclerosis (Chi and Melendez, 2007; Poredos and Jezovnik, 2015); thus, reducing the level of these molecules can protect against the disease progression.

Hypertension as a key contributor of atherosclerosis can stimulate the production of both inflammation and oxidative stress (van Rooy and Pretorius, 2014). In addition to anti-inflammatory and antioxidant properties, polyphenols could directly affect the blood pressure and reduce SBP and/or DBP; thus, can manage the negative vascular effects of high blood pressure through multiple mechanisms (Table 1).

Studies revealed that obesity is closely linked with the development of atherosclerosis (McGill *et al*., 2002). Included trials assessed the effect of phenolic compounds on anthropometric parameters including BMI, WC, HC and BW which were successfully effective in several cases. Adiponectin as a regulator of the metabolism of lipids and glucose (van Rooy and Pretorius, 2014), which is suppressed in obese patients, is also recovered by polyphenols to a normal level (Table 1).

All of the above mentioned mechanisms show that polyphenolic compounds could act via diverse pathways in the prevention and treatment of atherosclerosis; however, some limitations regarding the current available data make clinical decision making absolutely difficult.

One of the important limitations in the currently published clinical trials is the small sample size. The largest sample size amongst included articles were 253 patients (Liu *et al*., 2015) (with respect to the number of patients successfully finished the trial) and only six studies had a sample size equal or larger than 100 patients (Table 1). As a result, one of the reasons for the controversial data obtained from different studies with the same plant source of polyphenols may be the small sample size.

Another important limitation is the methodology of the trials, compared using Jadad score in which randomization, blindness, and withdrawal reasons are considered (Jadad *et al*., 1996). As it is represented in table 1, only three studies had Jadad score of 5 and only seven studies had Jadad score of 4 which demonstrates the need for further well-designed clinical trials.

Short follow up period is also a limitation in currently performed trials. Only 4 trials had a study duration longer than 6 months which remains the long-term effect of the supplements to be unknown.

Assessing the structure-activity relationship (SAR) of polyphenols by researchers of medicinal chemistry is also of great importance. As an example, studies revealed that the presence of both *p*-hydroxy phenolic functional group and *ortho* electron-releasing structures on benzene ring, as well as the methylene structure are important for antioxidant activity of curcumin analogues. On the other hand, analogues with electron withdrawing groups on the aromatic ring seem to have higher anti-inflammatory activity in regard to the inhibition of TNF-α (Arshad *et al*., 2017). Antioxidant activity of flavonoids like catechin depends on the number and position of hydroxyl groups on B-ring (Babu and Liu, 2008). Also in resveratrol analogues, presence of *ortho* and *para* hydroxyl substituents significantly increases the antioxidant activity (Ovesná and Horváthová-Kozics, 2005). Discussing SAR of polyphenols in detail can help to develop new semisynthetic structures with improved safety and efficacy

Conclusion remarks

Taking together, polyphenol compounds in the form of pharmaceutical or dietary supplements showed beneficial effects on cardiovascular parameters of atherosclerosis and related

complications via different mechanisms. Despite the above mentioned limitations, current evidence supports the positive effects of some polyphenols toward the prevention and treatment of atherosclerosis. These include virgin olive oil polyphenols, green tea polyphenols, anthocyanins, and cocoa polyphenols. Since these natural sources of polyphenols are a usual part of human diet and contain generally safe ingredients, addition of these polyphenol-enriched foods can be recommendable in cardiovascular patients; however, future clinical trials are recommended for better confirmation of the currently available data. Other mentioned polyphenols need to be further investigated in future well-designed clinical trials to obtain higher level of evidence since the available studies have several limitations. It should be kept in mind that due to sensitive condition of patients with cardiovascular diseases, addition of any natural supplement should be under observation of physicians and patients should be advised not to add any dietary supplement without consultation with their doctor.

Conflict of interest

The authors confirm that this article content has no conflicts of interest.

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Table 1. Clinical studies on the efficacy of polyphenols in atherosclerosis and related complications

Polyphenol name	Natural source	Study design	Intervention/ dosing (per day)	Duration	Jadad score	Concomitant therapy	Outcomes	References
Anthocyanins	Purified anthocyanins	Randomized, double-blind, placebo-controlled clinical trial in 146 hypercholesterolemic patients	320 mg of anthocyanins OR placebo	24 w	3	-	↓P-selectin, PF-4, β-TG, RANTES, & TGF-β1 ↓*In vitro* platelet α-granule secretion, dense granule secretion, lysosome secretion, thrombin-stimulated platelet MAP kinase phosphorylation & PI3K/Akt signaling	(Song *et al*., 2014)
Anthocyanins	Red grape, blackberry, sour cherry, black currant & chokeberry	Randomized, controlled clinical trial in 27 healthy non-smoking men	700 ml of juice containing 1659 mg/l of polyphenols OR control juice (297.4 mg/l polyphenols)	4 w	1	-	↓Oxidative DNA damage, ↑GSH No significant change in MDA, urine isoprostanes & DNA-binding activity of NF-κB in PBMCs	(Weisel *et al*., 2006)
Anthocyanins	Red grapes & bilberry (*Vaccinium myrtillus*)	Randomized, double-blind, placebo-controlled, crossover clinical trial in 30 healthy female	330 ml of 983.7 OR 840.9 OR 8.9 (as placebo) mg/l of anthocyanin	2 w	2	-	↑SOD & CAT activities ↑Trolox equivalent antioxidant capacity ↓plasma &	(Kuntz *et al*., 2014)

							urinary MDA	
Apple polyphenols	*Malus domestica*	Randomized, double-blind, crossover clinical trial in 30 hypercholesterolemic patients	1.43 g OR 0.21 g polyphenols	4 week	3	-	No significant difference in FMD, lipid profile, homocysteine & antioxidant capacity	(Auclair *et al*., 2010)
Beer polyphenols	Beer	Randomized, open, crossover, controlled clinical trial in 33 male moderate alcohol consumers	Beer (30 g alcohol+1209 mg polyphenol), non-alcoholic beer (1243 mg polyphenol) OR gin (30 g alcohol)	4 w	3	-	Beer: ↑HDL-C, apo A1, apo A2 & adiponectin ↓lymphocyte expression of LFA-1, lymphocyte & monocyte expression of SLe^X & CCR2, fibrinogen & IL-5 Non-alcoholic beer: ↓SBP, apo A1, apo A2, homocysteine ↑receptor antagonist of IL-1, folic acid concentration	(Chiva-Blanch *et al*., 2015)

							↓lymphocyte expression of LFA-1, lymphocyte & monocyte expression of SLe^X, monocyte expression of CCR2, & TNF-β & E-Selectin, IL-6r, IL-15, RANTES and TNF-β Gin: ↑HDL-C, apo A1, apo A2 & adiponectin ↓fibrinogen & IL-5 ↑receptor antagonist of IL-1, No significant change in DBP, FBS, BW, BMI & waist/hip ratio	
Catechin	Green tea	Randomized, controlled clinical trial in 40 healthy subjects	500 mg catechin	4 w	2	-	↓Ox-LDL-C No significant change in LDL-C, HDL-C & TAG	(Inami *et al*., 2007)
Catechin	Green	Randomized,	0, 80 OR	2 w	1	-	↑Forearm	(Oyama *et*

	tea	controlled clinical trial in 30 healthy male smokers	580 mg catechin				blood flow response to acetylcholine ↑NO ↓asymmetrical dimethylarginine, MDA, 4-hydroxynonenal, CRP, MCP-1, soluble CD40 ligand	*al*., 2010)
Catechin	Green tea	Randomized, double-blind, placebo-controlled, crossover clinical trial in 19 healthy men	1 g catechins OR placebo	Single dose	3	-	↓LDL-C oxidizability, ↑TAC	(Suzuki-Sugihara *et al*., 2016)
Catechin	Green tea	Randomized, double-blind, placebo-controlled clinical trial in 48 older adults	630.9 mg catechins OR placebo	14 w	4	-	↓WC, HC, TC, LDL-C & LDL-C/HDL-C ratio in comparison to baseline levels but not vs. placebo	(Miyazaki *et al*., 2013)
Catechin & TF	Green & black tea	Randomized, double-blind, placebo-controlled, parallel design clinical trial in 99 hypercholesterolemic subject	77.5 mg TFs OR 75 mg TFs + 150 mg catechin + 195 mg other tea polyphenols OR placebo	11 w	4	-	No significant change in TC & LDL-C	(Trautwein *et al*., 2010)
Chlorogenic acid	Green coffee	Randomized, placebo-controlled clinical trial in 28 mildly	140 mg of chlorogenic acid OR placebo	2 w	3	-	↓SBP & DBP, No significant change in	(Watanabe *et al*., 2006)

		hypertensive patients					HR, BMI	
Cocoa polyphenol	Cocoa	Randomized, double-blind, placebo-controlled, crossover clinical trial in 12 DM patients	16.6 mg OR >2 mg of epicatechin	8 w	3	Metformin, statins, antihypertensive agents	↓TC/HDL-C ratio	(Mellor *et al*., 2010)
Cocoa polyphenols	Cocoa	Randomized, double-blind, parallel-design, placebo-controlled clinical trial in 93 postmenopausal women with DM	90 mg epicatechin (850 mg total flavan-3-ols & 100 mg iso-flavones) OR placebo	1 y	4	Oral antihyperglycemics, antihypertensives, antihyperlipidemics, insulin	No significant change in CCA-IMT, augmentation index, ET-1, NO, ACE, & BP Improved PP variability	(Curtis *et al*., 2013)
Cocoa polyphenols	Cocoa	Randomized, controlled, crossover clinical trial in 12 healthy subjects	447 mg epicatechin, 59 mg catechin, & 14 mg quercetin	3 d	2	-	↑Wave reflections, FMD, BP, ET-1 & ↓8-iso-PGF2 elevation after OGTT, No change in glucose & insulin responses	(Grassi *et al*., 2012)
Cocoa polyphenols	Cocoa	Randomized, placebo-controlled clinical trial in 60 DM patients	450 mg flavonoids OR placebo	8 w	3	-	↑apo A1, ↓apo B, FBS, HbA1C, CRP, SBP & DBP	(Rostami *et al*., 2015)

Cocoa polyphenols	Cocoa	Randomized, double-blind, controlled clinical trial in 17 hypercholesterolemic postmenopausal women	High CF: 12.4 mg total CFs/g (446 mg of total flavanols) OR low CF: 1.2 mg total CFs/g (43 mg of total flavanols)	6 w	3	-	↑HDL-C in high CF & ↓HDL-C in low CF group, ↓sVCAM-1in the high CF group & ↑sVCAM-1 in the low CF group, ↑FMD in the high CF group, & ↓ in the low CF group ↑hyperemic blood flow in both groups, No significant changes in HR, TC LDL-C, TC:HDL-C ratio & TAG	(Wang-Polagruto *et al*., 2006)
Curcumin	Turmeric	Randomized double-blind, placebo-controlled clinical trial in 70 ACS patients	45, 90, OR 180 mg curcumin OR placebo	8 w	3	Antiplateletes, oral antidiabetics, Antihypertensives, antihyperlipidemics	↓TC & LDL-C with low dose & opposite effect with high dose, ↑HDL-C & TAG with high dose All changes were numerically but not statistically significant	(Alwi *et al*., 2008)

Curcumin	Turmeric	Randomized, double-blind, placebo-controlled clinical trial with parallel design in 213 patients with DM	1.5 g curcumin OR placebo	6 months	4	-	↓PWV, ↑adiponectin ↓leptin, HOMA-IR, TAG, uric acid, visceral & total body fat	(Chuengsamarn *et al*., 2014)
Curcumin	Turmeric	Placebo-controlled clinical trial in 38 healthy subjects	80 mg curcumin	4 w	0	-	↓TAG, salivary amylase, ↑salivary radical scavenging capacities, ↑CAT activity, NO, MPO ↓plasma β amyloid protein concentrations, sICAM & ALT activity No significant change in CRP, ceruloplasmin, SOD & Gpx	(DiSilvestro *et al*., 2012)
Curcuminoids	Turmeric	Randomized, double-blind,	1 g curcuminoi	4 w	4	-	No significant	(Moohebati *et al*.,

		placebo-controlled, crossover clinical trial in 21 obese dyslipidemic subjects	ds OR placebo				change in serum small dense LDL-C	2014)
Curcuminoids	Turmeric	Randomized, double-blind, placebo-controlled, parallel-group clinical trial in 100 patients with metabolic syndrome	1 g curcuminoids OR placebo	8 w	4	Antihyperglycemics, Antihyperlipidemics, antihypertensives	↓LDL-C, non-HDL-C, TC, TAG & LP(a)	(Panahi *et al*., 2014)
Curcuminoids	Turmeric	Randomized, double-blind, placebo-controlled, crossover clinical trial in 30 obese subjects	1 g curcuminoids OR placebo	4 w	4	-	↓TAG, No significant change in other lipid parameters, anthropometric parameters & CRP	(Mohammadi *et al*., 2013)
Daidzein	Soybeans	Randomized, double-blind, placebo-controlled clinical trial in 253 postmenopausal pre-hypertensive women	Soy flour, low-fat milk powder+63 mg daidzein OR low-fat milk powder (control)	6 month	5	-	No significant change in BP & vascular function	(Liu *et al*., 2015)
Ecklonia cava polyphenols (phlorotannins)	*Ecklonia cava*	Randomized, double-blind, clinical trial in 97 overweigh subjects	144 mg OR 72 mg of polyphenols OR placebo	12 w	4	-	↓AI, SBP, TC, LDL-C, FBS, BW, BMI, body fat ratio & WC, ↑HDL-C, No significant change in TAG	(Shin *et al*., 2012)

Enzogenol	*Pinus radiata*	Randomized, double-blind clinical trial in 44 chronic smokers	480 mg Enzogenol + 60 mg vit C OR 60 mg vit C alone	12 w	3	-	↑FMD compared with baseline but no difference between two groups, ↓fibrinogen & protein oxidative damage compared with vit C alone	(Young *et al*., 2006)
Epicatechin	Green tea, red apple & cacao beans	Open-labeled, randomized, controlled clinical trial in 79 HTN patients	450.8 ±13.9 mg of epicatechin individually or in combination with antihypertensive therapy (captopril/ telmizartan)	6 months	1	Captopril or telmisartan	↓SBP/DBP, leptin, & TAG	(Jesus Romero-Prado *et al*., 2015)
Epicatechin & Quercetin	Cocoa, Tea	Randomized, double-blind, placebo-controlled, three-armed, crossover clinical trial in 35 HTN patients	100 mg epicatechin, 160 mg quercetin-3-glucoside, or placebo	4 w	2	-	Epicatechin: ↓E-selectin Quercetin: ↓E-selectin & IL-1β No significant change in other biomarkers inflammation and endothelial function	(Dower *et al*., 2015)

Fiit-ns (multicomponent polyphenol preparation)	Grapefruit, green tea, grape, black carrot and guarana	Randomized, double-blind, parallel-design clinical trial in 17 obese subjects	900 mg of total polyphenol	12 w	2	-	↓BW, BMI, WC, HC & abdominal fat, ↓TC, LDL-C, TG, MDA, CRP & fibrinogen ↑SOD	(Cases *et al*., 2015)
Japanese plum polyphenols	*Prunus mume*	Randomized, double-blind, placebo-controlled, pilot trial in 15 healthy subject	800 mg of polyphenols OR placebo	12 w	3	-	No significant change in BP	(Takemura *et al*., 2014)
Juar tea polyphenols	*Camellia sinensis*	Randomized, open-labeled, crossover clinical trial in 20 men with metabolic syndrome	Juar tea (2 g) OR barley tea (8.5 g)	4 w	1	-	↑eEC-SOD levels, No significant change in LDL-C oxidizability	(Uto-Kondo *et al*., 2013)
Naringin	Citrus fruits	Clinical trial in 30 hypercholesterolemic subjects vs. 30 healthy control group	All subjects received 400 mg of naringin	8 w	0	-	↓LDL-C & TC ↓apo B1 but not apo A1	(Jung *et al*., 2003)
Naringin & hesperidin	Citrus fruits	Randomized, double-blind, placebo-controlled, parallel design clinical trial in 194 hypercholesterolemic patients	800 mg of hesperidin OR 500 mg/d of naringin, OR placebo	4 w	3	ASA	No significant change in TAG, HDL-C, TC & LDL-C	(Demonty *et al*., 2010)

Olive oil polyphenols	Olive oil	Randomized, crossover clinical trial in 186 healthy men	25 ml low (2.7 mg/kg), medium (164 mg/kg), & high (366 mg/kg) polyphenol olive oil	3-week	1	-	↑OLAB	(Castaner *et al.*, 2011)
Olive oil polyphenols	Olive oil	Randomized, double-blind, crossover clinical trial in 12 healthy subjects	0.097 mg, 5.92 mg, OR 13.2 mg of polyphenols	Single-dose administration	3	-	↑Total phenolic compounds in LDL-C ↑tyrosol, hydroxytyrosol & 3-O-methyl-hydroxytyrosol	(Covas *et al.*, 2006)
Olive oil polyphenols	Olive oil	Randomized, controlled, crossover clinical trial in 25 healthy men	2.7 mg/kg OR 366 mg/kg olive oil polyphenols/day	3 w	1	-	↓apo B100 & small LDL-C particles with high dose intervention ↑apo B100 & small LDL-C particles with low dose intervention ↑LDL-C oxidation lag time & LPL gene expression after the high dose intervention	(Hernáez *et al.*, 2015)
Olive oil polyphenol	Olive oil	Randomized, Sequential,	400 ppm OR 80	Single dose	1	-	↑NO, ↓LPO & 8-	(Ruano *et al.*, 2005)

s		crossover trial in 21 hypercholesterolemic subjects	ppm of olive polyphenols				epi prostaglandin-F2α elevation ↑ischemic reactive hyperemia	
Olive oil polyphenols	Olive oil	Randomized, double-blind clinical trial in 82 patients with early atherosclerosis	340 mg/kg of olive polyphenols OR 600 mg/kg EGCG-enriched olive polyphenols	4 months	2	-	↓ICAM-1, WBC, lymphocytes, monocytes in normal olive oil group but not in EGCG-enriched group No significant change in lipid profile	(Widmer *et al.*, 2013)
Olive oil polyphenols	Olive oil	Randomized, crossover, controlled clinical trial in 18 nonsmoking healthy men	25 ml low-polyphenol (2.7 mg/kg) or high-polyphenol (366 mg/kg) olive oil	3 w	2	-	↓Systemic LDL-C oxidation & MCP-1 ↓expression of proatherogenic genes in peripheral blood mononuclear cells ↓CD40, ADRB2 & IL8RA gene expression ↓ICAM-1 & OLR1 gene expression ↑tyrosol & hydroxytyro	(Castaner *et al.*, 2012)

							sol in urine	
Polyphenols	*Hibiscus sabdariffa*	Uncontrolled clinical trial in 31 patients with metabolic syndrome	125 mg/kg polyphenols	4 w	0	-	↓SBP & DBP ↓8-isoprostane-F2α ↑Diuresis & PON activity	(Joven *et al*., 2014)
Pycnogenol	*Pinus pinaster*	Randomized, double-blind, placebo-controlled, crossover clinical trial in 23 patients with coronary artery disease	200 mg	8 w	5	Anihypertensives, antihyperlipidemics, antiplatelets	↑FMD ↑Antioxidant status ↓15-F2t-Isoprostane No significant change in biomarkers of inflammation, platelet adhesion & BP	(Enseleit *et al*., 2012)
Pycnogenol	*Pinus pinaster*	Randomized, double-blind, placebo-controlled, crossover clinical trial in 11 HTN patients	200 mg OR placebo	8 w	2	-	↓SBP & DBP ↓TXB2	(Hosseini *et al*., 2001)
Quercetin	Apples, onions, berries,	Randomized, double-blind, placebo-	1095 mg quercetin OR	Single-dose administr	2	-	↓Mean BP No significant	(Larson *et al*., 2012)

	and red grape	controlled, crossover clinical trial in 5 normotensive men & 12 stage I HTN patients	placebo	ation			change in plasma ACE activity, HR, ET-1, nitrites & brachial artery FMD	
Quercetin	Apples, onions, berries, and red grape	Randomized, double-blind, parallel design, controlled clinical trial in 35 healthy subjects	50, 100 OR 150 mg quercetin	2 w	2	-	No significant change in plasma PON1 activity	(Boesch-Saadatmandi *et al.*, 2010)
Red wine polyphenols	Grape	Randomized, double-blind, placebo-controlled, three-period, crossover clinical trial in 58 HTN patients	280 mg OR 560 mg red wine polyphenols OR placebo	4 w	4	-	No significant effect on BP, aortic augmentation index or pulse wave reflection index	(Botden *et al.*, 2012)
Resveratrol	Grape	Randomized, double-blind, placebo-controlled clinical trial in 41 healthy subjects	400 mg trans-resveratrol + 400 mg grape skin extract+ 100 mg quercetin OR placebo	4 w	3	-	↓VCAM, ICAM & IL-8 mRNA expression ↓IFN-γ & FPI, No significant change in FBS, leptin, IL-1β, IL-6, & TNF-α	(Agarwal *et al.*, 2013)
Resveratrol	Grape	Randomized, double-blind, crossover	30, 90 OR 270 mg of resveratrol	Single dose	5	-	↑FMD	(Wong *et al.*, 2011)

		clinical trial in 19 overweight/ obese subjects with untreated borderline hypertension	OR placebo					
Resveratrol	ND	Randomized, double-blind, placebo-controlled clinical trial in 27 healthy aged men	Exercise training + placebo or exercise training + 250 mg resveratrol	8 w	2	Antihyperlipidemics	Negative effects: ↑Maximal oxygen uptake after exercise in placebo group but not in resveratrol group Improvement in lipid profile in placebo but not in resveratrol group ↓MAP in placebo group but not in resveratrol group ↓vasodilator prostacyclins ↑muscle thromboxane synthase No significant change in VCAM-1 &	(Gliemann *et al.*, 2013)

							Sirtuin 1	
Resveratrol	Grape	Randomized, triple-blinded, placebo-controlled clinical trial in 75 subjects with high CVD risk	8 mg resveratrol OR resveratrol-free grape extract OR placebo	12 months	4	Antihypertensives, antihyperlipidemics	↓CRP, TNF-α, PAI-1, sICAM-1 & IL-6/IL-10 ratio ↑IL-10 & adiponectin	(Tome-Carneiro *et al.*, 2012)
Sesamin	Sesame	Randomized, placebo-controlled, crossover clinical trial in 33 overweight men & postmenopausal women	26.2 g of sesame seeds (151 mg sesamin /100 g of seeds) OR placebo	5 w	2	-	↓Plasma & urinary 20-HETE, No significant change in BP, urinary sodium & potassium	(Wu *et al*., 2009)

LDL-C: low density lipoprotein; TC: total cholesterol; HDL-C: high density lipoprotein-cholesterol; TAG: triacylglycerol; BP: blood pressure; ACE-activity: angiotensin-converting enzyme activity; ET-1: endothelin-1; FMD: flow-mediated dilation; HR: heart rate; STC: Serum thromboxane concentration; SBP: systolic blood pressure; DBP: diastolic blood pressure; SOD: super oxide dismutase; PNO: plasma nitric oxide; ACE I: angiotensin I-converting enzyme; LPL: lipoprotein lipase; malondialdehyde: MDA;8-EP F2: 8-epi-prostaglandin F2;LP(a): lipoprotein(a); FBS: fasting blood sugar; HbA1c: hemoglobin A1c; hsCRP: highly sensitive C- reactive protein; CT: catalase; TNF; tumor necrosis factor; ICAM: intercellular adhesion molecule; VCAM: vascular cell adhesion protein; IL: interleukin; IFN: interferon; FPI: fasting plasma insulin; ACS: acute coronary syndrome; PON-1: paraoxonase; MCP-1: Monocyte chemoattractant protein-1; IL8RA: interleukin 8 receptor α; ADRB2: adrenergic beta-2 receptor; OLR1: oxidized LDL-C (lectin-like) receptor 1; OLAB: oxidized LDL-C autoantibodies; apo: apolipoprotein; CCR2: Chemokine receptor 2; PWV: pulse wave velocity; Ox-LDL-C: oxidized LDL-C; CAT: catalase; BMI: body mass index; PBMC: peripheral blood mononuclear cells; GSH: reduced glutathione; NF-κB: nuclear factor κB; MAP kinase: mitogen-activated protein kinase; RANTES: Regulated on Activation Normal T cell Expressed and Secreted; PF4: platelet factor 4; PI3K: phosphatidylinositol-3-kinase; vit C: vitamin C; eEC-SOD: extracellular superoxide dismutase; 20-HETE: hydroxyeicosatetraenoic acid; EGCG: Epigallocatechin gallate; CF: cocoa flavonols; TF: theaflavin, TAC: total antioxidant capacity; LPO: lipid peroxidation; OGTT: oral glucose tolerance test; 8-iso-PGF2: 8-iso prostaglandin F2; BW: body weight, WC: waist circumference; HC: hip circumference; HTN: hypertension; MAP: mean arterial pressure; NO: nitric oxide; MPO: myeloperoxidase;

ASA: Aspirin; DM: diabetes mellitus; CCA-IMT: carotid artery; PP: pulse pressure; AI: atherogenic index; PON: paraoxonase; SLe^X: Sialil-Lewis X; LFA-1: lymphocyte function-associated antigen-1

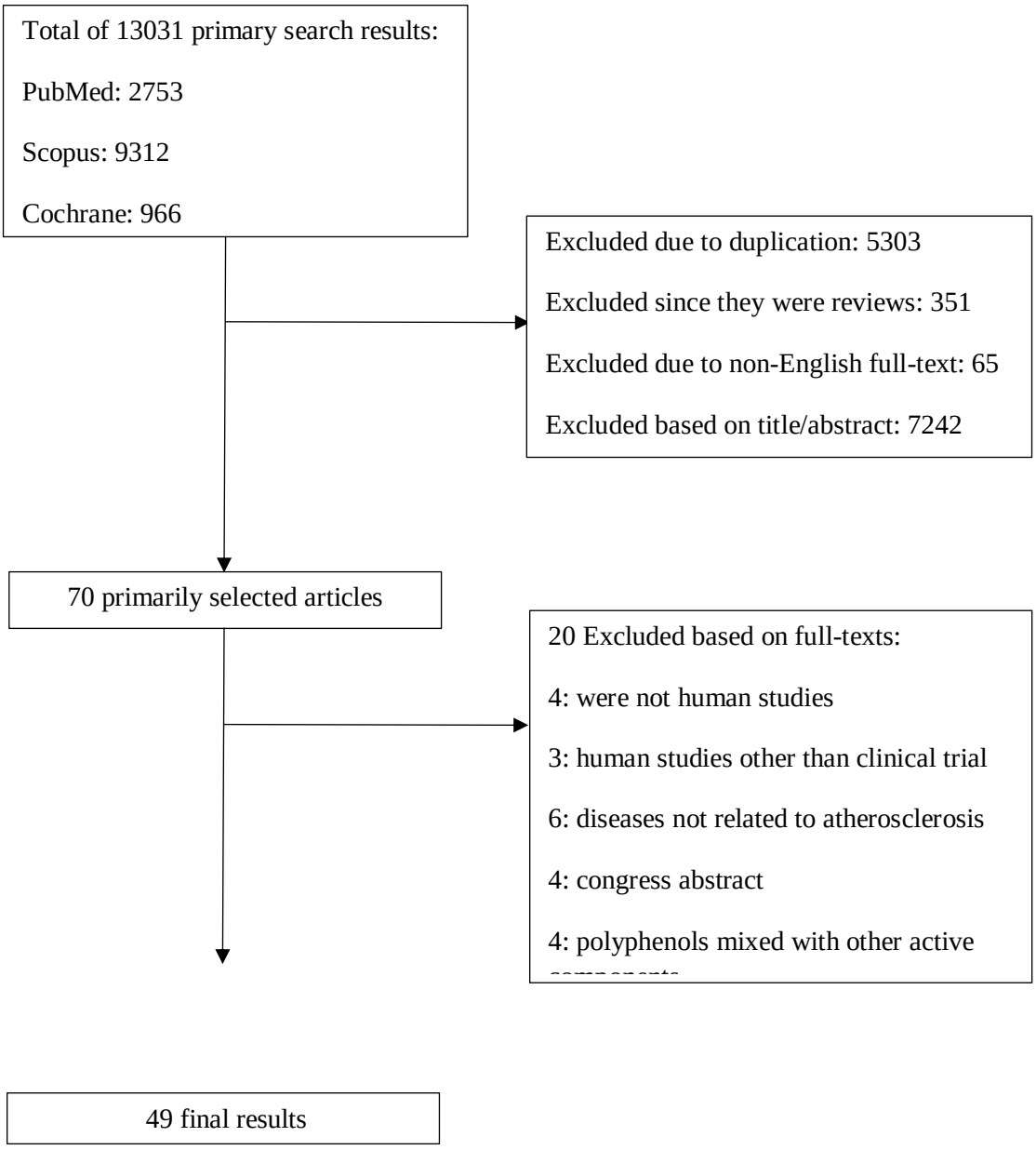

Figure 1. Flow diagram of study selection design

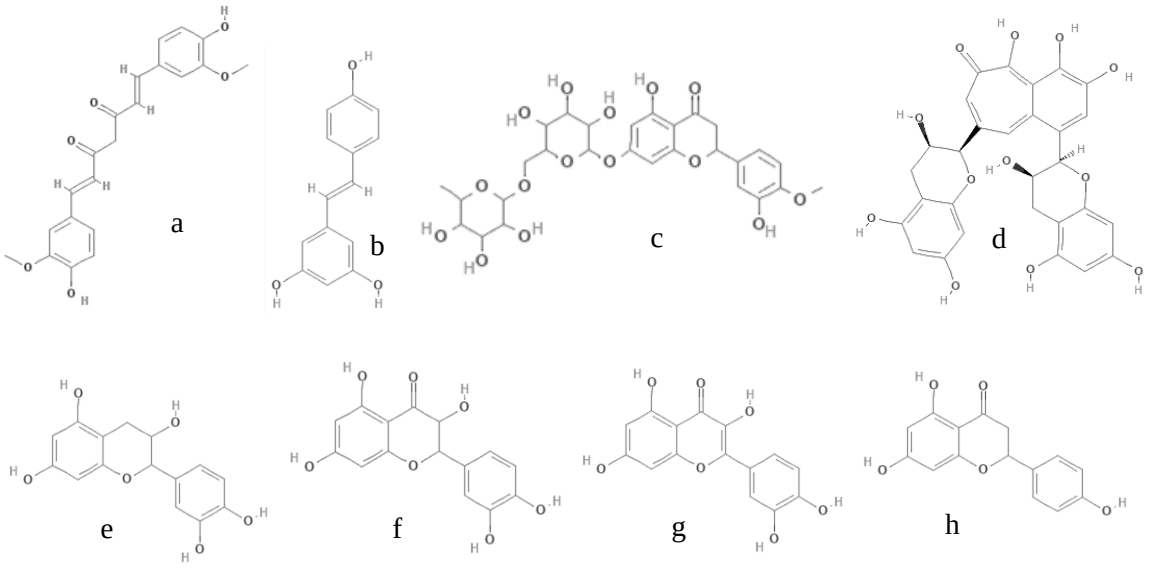

Figure 2- Structure of the main polyphenolic compounds assessed in atherosclerosis. a: curcumin, b: resveratrol, c: hesperidin, d: theaflavins, e: catechin, f: taxifolin, g: quercetin, h: naringenin