A comprehensive Review on Cardio Protective Potential of Polyphenols

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Abstract

The polyphenols are organic compounds containing at least one aromatic ring and a hydroxyl group are the secondary metabolites of plants increasing scientific interest because of their possible beneficial effects on human health. Diets rich in plant polyphenols play a vital role in health through the regulation of metabolism, weight, chronic disease, and cell proliferation. Epidemiologic, animal and human studies show that various polyphenols have antioxidant and anti-inflammatory properties that could have reduced risk of different chronic disease like cardiovascular diseases. It is a global term used for the group of diseases affecting the heart and/or blood vessels and includes coronary artery disease, cerebrovascular disease, peripheral artery disease, congenital heart disease, hypertension, heart failure and stroke. Polyphenols is reported to prevent platelet aggregation and relax the arterial blood vessels, disrupting the oxidation of low density lipoprotein (LDL) cholesterol, hyperlipidemia, inflammation and atherosclerosis by altering lipid profiles, inhibition of macrophage foam cell formation, its antioxidative effect, and anti-inflammatory action may be associated with reduced incidence of cardiovascular disorders by acting at the molecular level, improve endothelial function and inhibit platelet aggregation. This review summarizes the main cardioprotective effect of polyphenols as an abundance of health benefits associated with the cardiovasular diseases, atherosclerosis and hypertension.

Key words: Poly phenols, cardiovascular disease, atherosclerosis, hypertension

Introduction

Diets rich in plant polyphenols play a vital role in health through the regulation of metabolism, weight, chronic disease, and cell proliferation. Polyphenols, organic compounds containing at least one aromatic ring and a hydroxyl group [Durazzo et al., 2019].Polyphenols may contribute to the bitterness, astringency, color, flavor, odor and oxidative stability in food as they are abundant in plants, including fruits, nuts, vegetables, and cereals, as well as derived beverages such as tea, coffee, and wine [D. M. Archivio et al., 2007]. The polyphenols and other food phenolics are the secondary metabolites of plants increasing scientific interest because of their possible beneficial effects on human health. In excess of 8,000 polyphenols have thus far been identified which are classified into phenolic acids, stilbenes, phenolic alcohols, lignans, and flavonoids [Dai and Mumper, 2010].Among them, flavonoids are the most widely distributed and can be divided into six major subclasses: flavonols, flavanols, flavanones, flavones, isoflavones, and anthocyanins [Valdes et al., 2015]. Epidemiologic, animal and human studies show that various polyphenols have antioxidant and anti-inflammatory properties that could have reduced risk of different chronic diseases, including cancer, obesity, metabolic and neurodegenerative disorders and CVDs [Lecour and Lamont, 2011;Singh et al., 2011].

Cardiovascular diseases are responsible for one-third of deaths in individuals over age 35 and the first cause of death worldwide [Ho et al., 2013].The prevalence of heart diseases increases with age for both men and women [Sanchis-Gomar F et al., 2016].Cardiovascular disease (CVD) is a global term used for the group of diseases affecting the heart and/or blood vessels and includes coronary artery disease, cerebrovascular disease, peripheral artery disease, congenital heart disease, hypertension, heart failure and stroke [Nicholson et al., 2008]. Dyslipedemia a metabolic disorder, which is identified by high total cholesterol, low density lipoprotein (LDL) cholesterol, triglyceride contents and a low in high-density lipoprotein (HDL) cholesterol levels in the blood. Increased level of Low-density lipoproteins, triglycerides and cholesterol cause fat deposition and plaque formation in arteries which lead towards ischemic heart disease [Kim SJ et al., 2018].Coronary artery disease and ischaemic stroke, as well as peripheral artery disease, are underpinned by a common pathological process atherosclerosis [Le Brocq et al., 2008]. Atherosclerosis is a multifactorial, progressive disorder of medium-sized and large conduit arteries, which is fuelled by deposition of modified lipids and oxidation of excessive cholesterol in the vessel wall [Megson et al., 2016].

Evidence suggests that polyphenols consumption of fruit and vegetables that are rich in polyphenolic compounds is known to be associated with health benefits related to cardiovascular function [TresserraRimbau et al., 2014] by improve endothelial function [Vita, 2005], inhibit abnormal platelet aggregation [Tangney and Rasmussen, 2013], reduce inflammation and improve plasma lipid profiles [Arranz et al., 2012], thereby offering protection to cardiovascular health at a number of levels.In addition, polyphenols inhibit pro-inflammatory transcription factors by interacting with proteins involved in gene expression and cell signaling, leading to protective effects against many inflammation-mediated chronic diseases [EFSA Panel, 2015].For example, grapes seeds as well as in the skin are comprised of a wide variety of polyphenols including resveratrol (stilbene),flavonoids and its derivatives, flavons, flavonols, and anthocyanins has focused on the reduction of LDL oxidation in vivo and in vitro. Another example, resveratrol found in red wine, is reported to prevent platelet aggregation and relax the arterial blood vessels, disrupting the oxidation of low density lipoprotein (LDL) cholesterol [Zhang et al., 2016; Berman et al., 2017;Guo et al., 2013].However, in the face of numerous studies conducted in kin to cardiovascular diseases by way of polyphenols, the mechanisms through which these compounds wield cardioprotective activities are not yet fully implicit and as a result, the link between cardiovascular diseases and polyphenols is not firmly upheld. Current review disscus about the influence of polyphenols in cardiovascular diseases as a cardioprotective agent.

Polyphenols Overview

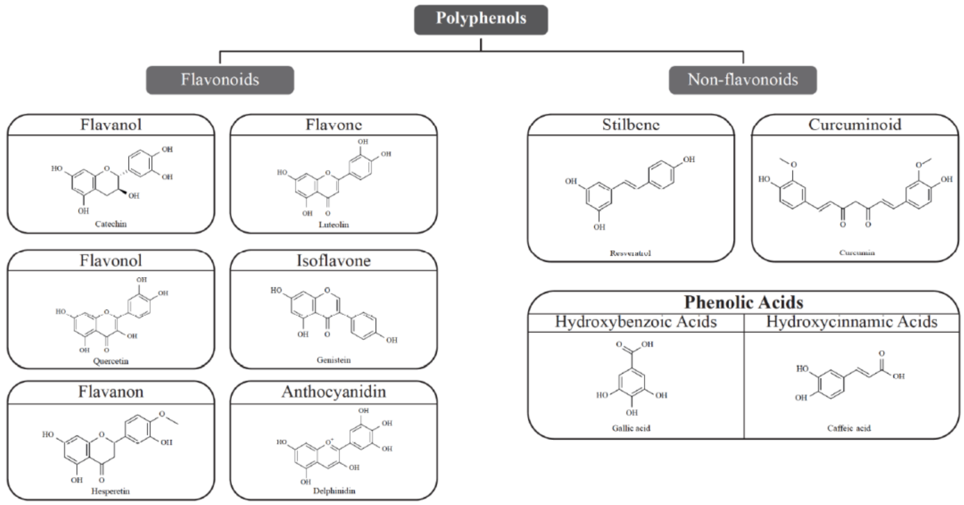

Fig. (1).Adapted: Ana C. Silveira et al., [2019].

Polyphenols are a large group of naturally occurring plant products widely found in fruits, nuts,cereals, beverages, legumes, spices and many others[Han et al., 2007;Davis et al., 2000] as secondary metabolites that protect plants from ultraviolet radiation, oxidative stress and some herbivores, but also to attract insects pollinators [Lakey-Beitia et al., 2015].In food, they may contribute to the bitterness, astringency, color, flavor, odor and oxidative stability[Zamora-Ros et al., 2016]. They have a wide variety of diverse structures, which belong to two main classes: non-flavonoids (particularly phenolic acids, stilbenes and lignans) and flavonoids, which are characterized by the basic C6-C3-C6 skeleton. The two aromatic rings within the flavonoid structure are linked by a heterocyclic ring, which differs in the degree of oxidation and leads to the following sub-classifications: flavones, flavonols, isoflavones, flavanones, anthocyanins and flavanols, usually called catechins. Some of the widespread representatives of natural phenolic compounds are kaempherol (flavonol), quercetin (flavonol), luteolin (flavone) and resveratrol (stilbenoid)(Figure:1).Based on their phenolic rings and the structural elements binding the rings, dietary polyphenols are categorised into glycones(the sugar-phenolic group) and aglycones (the non-sugar group) [D'Archivio et al., 2010]. Apart from flavanols, which are usually found as aglycones, most dietary polyphenols are glycones with the hydroxyl group conjugated by one or more sugar residues. A characteristic property of phenolic compounds, particularly of those whose hydroxyl groups occur in the orthoorpara-position, is their role in redox reactions, where they act as reducing agents and hydrogen donors [Lakey-Beitia et al., 2015] therefore,interfere with the oxidation of biomoleculesby promptly donating protons to radicals or by reacting with radicals to form compounds that prevent them to react with other molecules [Ajila et al., 2011].

Dietary Polyphenols and its Consumption

Table: 1 Adapted [Dasha Mihaylova et al., 2018

Food Group	Some Major Sources of Polyphenols
Fruit	oranges, apples, grapes, peaches, grapefruit juice, cherries, blueberries, pomegranate juice, raspberries, cranberries, black elderberries, blackcurrants, plums, blackberries, strawberries, apricots
Vegetables	spinach, onions, shallots, potatoes, black and green olives, globe artichoke heads, broccoli, asparagus, carrots
Whole grains	whole grain wheat, rye, and oat flours
Nuts, seeds, and legumes	roasted soybeans, black beans, white beans, chestnuts, hazelnuts, pecans, almonds, walnuts, flaxseed
Beverages	coffee, tea, red wine
Fats	dark chocolate, virgin olive oil, sesame seed oil
Spices and seasonings	cocoa powder, capers, saffron, dried oregano, dried rosemary, soy sauce, cloves, dried peppermint, star anise, celery seed, dried sage, dried spearmint, dried thyme, dried basil, curry powder, dried ginger, cumin, cinnamon

Polyphenols are important for pigmentation, reproduction, growth, and protection against pathogens can be found in every plant species. Fruit and beverages such as tea and red wine constitute the main sources of polyphenols. Certain polyphenols such as quercetin are found in all plant products (fruit, vegetables, cereals, leguminous plants, fruit juices, tea, wine, infusions, etc), whereas others are specific to particular foods (flavanones in citrus fruit, isoflavones in soya, phloridzin in apples). In most cases, foods contain complex mixtures of polyphenols, which are often poorly characterized. Apples, for example, contain flavanol monomers (epicatechin mainly) or oligomers (procyanidin B2 mainly), chlorogenic acid and small quantities of other hydroxycinnamic acids, 2 glycosides of phloretin, several quercetin glycosides, and anthocyanins such as cyanidin 3-galactoside in the skin of certain red varieties. Apples are one of the rare types of food for which fairly precise data on polyphenol composition are available. Differences in polyphenol composition between varieties of apples have notably been studied. The polyphenol profiles of all varieties of apples are practically identical, but concentrations may range from 0.1 to 5 g total polyphenols/kg fresh wt and may be as high as 10 g/kg in certain varieties of cider apples (Guyot et al., 1998; Sanoner et al., 1999). For many plant products, the polyphenol composition is much less known, knowledge is often limited to one or a few varieties, and data sometimes do not concern the edible parts. Some foods, particularly some exotic types of fruit and some cereals, have not been analyzed yet. Furthermore, numerous factors other than variety may affect the polyphenol content of plants; these factors include ripeness at the time of harvest, environmental factors, processing, and storage.

Because of the abundance of polyphenols in nature, it is not surprising that they can be found in fruits, vegetables, coffee, tea, chocolate, and soy. Once ingested, polyphenols have several possible fates, including absorption in the small intestine or colon, and/or excretion in the feces or urine. The site and rate of absorption depend on the chemical structure, degree of glycosylation/acylation, conjugation of other phenolics, molecular size, degree of polymerization, and solubility. In the small intestine, polyphenols can enter the mucosa through passive diffusion. In some instances, hydrophobic moieties must be cleaved for absorption to take place. In the colon, polyphenols are initially digested into smaller phenolic structures by gut microflora. After this initial digestion is complete, the polyphenols and their metabolites may be absorbed. Once absorption has taken place, polyphenols and their metabolites are transported to the liver. Further digestion may occur there, and then polyphenol metabolites may be transported to extrahepatic tissues or to the kidneys where they are excreted in the urine. For the majority of polyphenols, the maximum concentration in the plasma is apparent 1–2 h after ingestion. Polyphenols may also be incorporated into bile, returned to the small intestine, and eventually be excreted in the feces[Scalbert and Williamson , 2002;Bravo, 1998].

Effect of Polyphenols in Plasma Lipid Profiles

There is emerging evidence to suggest that dietary supplementation with food products rich in polyphenols might improve cardiometabolic risk factors such as hypertension and the lipid profile [Taheri Rouhi SZ et al., 2017;Wang et al., 2018]. For example, quercetin is not only beneficial in diabetic or inflammatory conditions; it also induces reduction of fatty acid and triacylglycerol synthesis and inhibits LDL oxidation in hepatocytes of healthy rats, thereby promoting cardiovascular protective functions [Patel et al., 2018].Additionally, catechin supplementation has been shown to significantly increase flow-mediated dilation and significantly reduce pulse wave velocity, diastolic blood pressure, and augmentation index, which are parameters for cardiovascular health in humans. This has been shown in several studies performed in both young and elderly healthy individuals as well as in individuals with cardiovascular disease risk through the administration of pure catechin supplements in quantities between 20 and 300 mg/day and extracts from foods rich in catechins, such as apples, grapes, and cacao in quantities estimated between 7.5 and 146 mg/day in a time period ranging between 2 and 12 weeks [Shafabakhsh et al., 2019].Consequently, the anthocyanin- and ellagitannin-active constituents of pomegranate juice (POMj) can protect LDL against cell-mediated oxidation via the scavenging of reactive oxygen and nitrogen species or through their accumulation in arterial macrophages [Aviram et al., 2004].

Effect of Polyphenols in EndotheLial Function

Endothelial cells line play a crucial role in maintaining cardiovascular homeostasis, attenuating vascular inflammation and controlling blood flow and vascular tone in circulatory system [P. Rajendran et al., 2013; S. Tribolo et al., 2016].Endothelial dysfunction tends to be the initial indicator in proinflammatory state leads to macrovascular complications like such as coronary artery disease, peripheral arterial disease, stroke, atherosclerosis and other cardiovascular diseases and microvascular complications, such as nephropathy, neuropathy, and retinopathy[K. Stromsnes et al., 2020]. Numerous strategies have been developed to protect endothelial cells, of which the role of polyphenolic compounds in modulating the differentially regulated pathways has been proven to be beneficial [N. Suganya et al., 2016]. Daily intake of polyphenol, catechin-comprised red wine extract and resveratrol has shown to have a beneficial effect on aortic expression of endothelial dysfunction biomarkers include VCAM-1, ICAM-1, E-selectin, and LOX-1 as well as proin flammatory cytokines such as TNF-α and IL-6 in hyperhomocysteinemic mice [C. Noll et al., 2013]. Catechin also improves redox imbalance and mitochondrial dysfunction, a prominent feature of cardiovascular disease, by stimulating phosphorylation of AMPK and ACC, inhibiting the key enzymes of de novo lipogenesis, and blocking the TNF-α induced insulin signaling pathway [Mi et al., 2018; Bartelt and Heeren, 2014].Studies in vitro further confirm the beneficial effects of resveratrol on endothelial metabolism and inflammation. In a study with TNF-α-activated endothelial cells, the polyphenol intervention of 5-20 μM significantly reduced the levels of VEGF, ROS, and proinflammatory mediator such as IL-8 and ICAM-1 [I. M. Toaldo et al., 2016].

Effect of Polyphenols in Inflammation and Cell Signalling

Atherosclerosis is a Chronic inflammatory disease plays a crucial role in development and progression of cardiovascular disease(CVD). Polyphenols are likely to promote their anti-inflammatory properties by modulating transcriptional networks and/or signalling cascades that modulate gene expression, leading to inhibition of inflammatory mediators. They exert anti-inflammatory activities by altering the recruitment of inflammatory cells by decreasing production of pro-inflammatory molecules such as TNF-α, IL-6 and C-reactive protein, and inhibiting the production of adhesionmolecules [VCAM-1 and intercellular adhesion molecule 1 (ICAM-1)] by the endothelium, thereby suppressing cellular migration of monocytes into the subendothelial space (Tangney and Rasmussen, 2013).Gallic acid, a trihydroxy benzoic acid has been significant reduction in secretion of the adhesion molecules [ICAM-1 and VCAM-1] and of the chemokine CCL2, when endothelial cells were pretreated with gallic acid (10–100 µM), but concentrations likely to be attainable in vivo (1 µM) were less effective in this regard (Hidalgo et al., 2012).Similarly, other polyphenols like anthocyanins, delphinidin- and cyanidin-3-O-glucosides (0.1–50 µg·mL1; 200 nM–100 µM) also inhibit LPS-induced VCAM-1 expression in porcine iliac artery endothelial cells (Zhu et al., 2013). Moreover, delphinidinaglycone (50–200 µM) decreased ox-LDL induced expression of adhesion molecules (ICAM-1 and P-selectin) in a human endothelial hybrid cell line, as well as decreasing adhesion of monocytes to endothelial cells by reducing intracellular ROS, p38MAPK expression, inhibitor of κ-B α (IκB-α) degradation and NF-κB transcription activity (Chen et al., 2011). Moreover, quercetin (125 µM) partly suppressed leptin-induced TNF-α secretion and significantly inhibited leptin-induced NF-κB expression in HUVECs (Indra et al., 2013), epicatechin (1–100 µg·mL1; approximately 3–340 µM), suppressed production of the proinflammatory cytokines, IL-6 and IL-8, with a simultaneous increase in expression of the anti-inflammatory cytokine IL-10 in whole blood cultures (Al-Hanbali et al., 2009) and apigenin (30 µM) and kaempferol (30 µM), but not resveratrol (50 µM), suppressed expression of LPS-induced IL-1. All of these polyphenols, and resveratrol in particular, effectively decreased LPS-induced expression of TNF-α in J774 macrophages (Kowalski et al., 2005).

eNOS plays major role NO production in endothelial cells in the presence of its substrate L-arginine and cofactors such as NADPH, FAD, FMN and BH4 [Alderton et al., 2001].Under normal condition, eNOS is regulated at multiple sites by phosphorylation of serine (Ser), threonine (Thr) and tyrosine (Tyr) residues by Akt kinase, cyclic AMP (cAMP)-dependent PKA and AMPK in endothelial cells(Mount et al., 2007;Barbosa et al., 2013). Inturn, response to fluid shear stress and numerous agonists via cellular events such as increased intracellular calcium, interaction with substrate and cofactors, protein phosphorylation and cellular factors such as VEGF, IGF and so on. Dysregulation of these processes attenuates eNOS expression and reduces NO· levels, a characteristic of numerous pathophysiological disorders. Polyphenolslikeresveratrol, quercetin, epigallocatechin gallate (EGCG), hesperetin, α-linolenic acid, ferulic acid and catechin hydrate are considered to be the effective antioxidants. Research on polyphenols has been reported to restore the IRS-1/Akt/eNOSsignalling pathway in endothelial cells under palmitate-induced insulin resistance [Liu et al., 2015]. Further, it is effective in restoring the vascular functions mediated through eNOS in diabetic rats also [Arrick et al., 2011]. Recently,a study reported the vasoprotective role of quercetin has been evidenced by phosphorylating eNOS at Ser1179 through cAMP/PKA signalling and enhancing the production of NO· in aortic tissues of diabetic rats[Li et al., 2012].

Overview of Polyphenols as Cardioprotective Activity

Polyphenols are a large group of bioactive plant compounds for which beneficial effects in the prevention and treatment of cardiovasular diseases (CVDs)[Corrêa, et al., 2019]. Many polyphenols amend hyperlipidemia, inflammation and atherosclerosis via amelioration of lipid profiles, inhibition of macrophage foamcell formation, its antioxidative effect, and anti-inflammatory action. For example hesperidin ameliorated high fat diet (HFD)-induced hyperlipidemia and suppressed HFD-induced hepatic steatosis, atherosclerotic plaque area, and macrophage foam cell formation[Sun et al., 2017] and oil palm phenolics (OPP) recovered from the aqueous waste of oil palm millingprocess contains numerous water-soluble phenolic compounds has been shown cardioprotective effects via several mechanisms such as cholesterol biosynthesis pathway, antioxidant and anti-inflammatory properties[Nurul 'Izzah Ibrahim et al., 2020].Date palm (Phoenix dactylifera L.) fruit is promising and significant source of high nutritional value of polyphenols compounds such as anthocyanins, isoquercetrin, quercetin, quercetrin, procyanidins, apigenin, luteolin, and rutin, respectively shown significant reduction in low density lipoproteins, very low density lipoproteins cholesterol and enhancement in high density lipoprotein They also increase the antioxidant enzymes such as paraoxonase 1 arylesterase, glutathione peroxidase and superoxide dismutase in serum that block free radicals production[Sidra Khalid et al., 2020].Recently, marine crude-drugs are emerging as potential treatments inmanynoncommunicable conditions, including those involving the cardiovascular system. Among the active compounds responsible for these activities, seaweed polyphenols seem to play a key role[Manuel Gómez-Guzmán et al., 2018].The supplementation of humans with polyphenol-rich extracts from algae has been shown to exert some positive effects on fasting blood glucose, total cholesterol and LDL-cholesterol[Murray et al., 2017].

Conclusion

Cardiovascular diseases (CVDs) constitute the leading cause of disease with a high mortality rate, accounting for one third of global deaths.Studies suggest that diets rich in polyphenols amend hyperlipidemia, inflammation and atherosclerosis via amelioration of lipid profiles, inhibition of macrophage foamcell formation, its antioxidative effect, and anti-inflammatory action may be associated with reduced incidence of cardiovascular disorders by acting at the molecular level, improve endothelial function and inhibit platelet aggregation. In view of their potential protective properties, particularly on endothelial function and platelets aggregation,polyphenol supplement for cardiovascular diseases are not being tested clinically and require more preliminary studies to allow this possibility.

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