Polyphenol Effects on Cardiovascular Disease

Subjects: Cardiac & Cardiovascular Systems

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Several studies have demonstrated that polyphenol-enriched diets may have beneficial effects against the development of cardiovascular disease. This activity is exerted by multiple mechanisms, mainly described in in vitro studies. However, long-term studies on humans provided controversial results, making the prediction of polyphenol impact on health uncertain. This entry provides an overview and critical analysis of the literature related to the effects of the principal dietary polyphenols on cardiovascular disorders. We critically considered randomized controlled clinical trials involving subjects taking polyphenol-based supplements for at least two weeks. Although pharmacological doses of polyphenols are likely to beneficially affect several CVD hallmarks, such as hypertension, dyslipidemia, endothelial dysfunction and inflammation, further studies aiming to fully characterize polyphenols pharmacokinetics and safety are necessary to unravel their potential preventive role in real life.

Keywords: polyphenols ; prevention ; cardiovascular disease ; dietary supplements

1. Impact of Polyphenols on Cardiovascular Disease in Humans

Globally, Cardiovascular Disease (CVD) is the major cause of morbidity and mortality, accounting for 32% of all causes and for 44% of all non-communicable disease deaths. Of these, 85% are due to ischemic heart disease and stroke [1]. In the last 18 years, the risk of dying from cardiovascular disease or other non-communicable diseases showed a slight, but constant decrease. This trend could be caused by the implementation of several preventive measures, including actions to reduce key risk factors such as unhealthy diet and alcohol consumption, physical inactivity, tobacco use, and constant exposure to air pollution [2]. The pharmacological treatment of CVD has also greatly improved life expectancy and quality, in either primary or secondary prevention, but side-effects and limited adherence to treatments have often dampened drug effectiveness. In addition to pharmacological therapy, dietary supplements, functional foods and nutraceutical products are being increasingly used for cardiovascular health, despite the lack of high-quality human trials evaluating the efficacy of such additional interventions [3][4]. Based on the recent recommendations for high-quality research [5] and with the aim to provide a critical review of the recent evidence on the impact of polyphenol in the cardiovascular field, we herein focused on intervention studies, conducted in primary prevention, and in which polyphenols were taken as nutraceuticals or other titrated formulations. Two excellent reviews extensively treated the impact of common polyphenol-based nutraceuticals and dietary products on cardiovascular health [6][7]; readers are invited to refer to them for a comprehensive reading. In the present work, only trials evaluating the effects of the administration of polyphenol-enriched extracts or isolated compounds were considered, while those contemplating polyphenol-rich food consumption, such as tea, coffee, chocolate or fruit, in any formulations (e.g., whole fresh or dried product, beverages, etc.), or multiple compound-enriched preparations, were excluded. Particular attention was paid to relatively long (more than two weeks) studies and those with well-defined cardiovascular endpoints. The following narrative part discusses multiple endpoints from recent (last five years) trials.

Amongst all the investigated CVD hallmarks, hypertension, dyslipidemia, endothelial dysfunction and systemic inflammation were the most reported in selected literature. Specific markers have been used for evaluating cardiovascular health. Increased total or low density lipoprotein cholesterol (LDL-C), or diminished high density lipoprotein cholesterol (HDL-C) levels, are consolidated markers of increased cardiovascular risk and directly contribute to the atherosclerotic plaque physiopathology [8]. In addition, other proteins like apolipoprotein A–I or paraoxonase-1, which are constitutive components of HDL particles, mainly displaying atheroprotective effects, have been inversely correlated with cardiovascular risk. Specific markers of endothelial activation and dysfunction, causal drivers of vascular damage, may be measured both in plasma and through minimally invasive ultrasound techniques. For example, endothelin-1, soluble endothelial-derived adhesion molecules (sICAM-1, sVCAM-1), asymmetric dimethylarginine, exerting pro-inflammatory actions on vascular endothelium, as well as high-sensitive C-reactive protein (hs-CRP), tumor necrosis factor alpha (TNF-α) and interleukin-1 beta, systemic inflammation markers, are commonly used [9][10]. Moreover, the brachial artery flow mediated dilation (FMD) has found wide application. It is defined as the percent change in brachial artery diameter,

following to reactive hyperaemia, typically induced by a five-minutes circulatory arrest through a supra-systolic cuff occlusion, causing NO release and vasodilation [11].

High heterogeneity in experimental design, study population, compounds and endpoints evaluated, as well as the paucity of data about the biological activity of the different metabolites hampered the possibility of clear comparisons or univocal conclusions.

A small randomized, double-blind placebo-controlled clinical trial evaluated the effects of 200 mg/day of red grape seed extract-derived oligomeric proanthocyanidin complexes for eight weeks, on 70 mild to moderate hyperlipidemic subjects. Argani H. and colleagues [12] observed a significant reduction of plasma total cholesterol (−14.8 mg/dL ± 19.7 vs. baseline, p = 0.001), triglycerides (−19.4 mg/dL ± 42.4 vs. baseline, p = 0.001) and LDL-C (−13.1 mg/dL ± 20.6 vs. baseline, p = 0.002). In the same study, anti-atherogenic components of plasma, such as apolipoprotein A–I (9.3 mg/dL ± 11.7 vs. baseline, p = 0.001), paraoxonase-1 (4.5 IU/L ± 7.7 vs. baseline, p = 0.03) and HDL-C (2.1 mg/dL ± 3.7 vs. baseline, not significant) increased as a consequence of treatment.

In another study, 70 subjects were randomized to receive 162 mg/day of quercetin from onion peel extract or placebo in a double-blinded, placebo-controlled cross-over trial with six-week treatment periods separated by a six-week washout period [13]. This study is of particular interest because subjects were also controlled for plasma concentrations of quercetin, its monomethylated derivatives tamarixetin (4′-*O*-methyl quercetin), isorhamnetin (3′-*O*-methyl quercetin) and the dehydroxylated quercetin metabolite kaempferol. In the subgroup of the hypertensive subjects, quercetin significantly decreased systolic blood pressure (SBP) by −3.6 mmHg (p = 0.022) when compared with placebo (mean treatment difference, −3.9 mmHg; p = 0.049). Notwithstanding, vasoactive biomarkers including endothelin-1, sICAM-1, sVCAM-1, asymmetric dimethylarginine, angiotensin-converting enzyme activity, vascular/endothelial function (evaluated by peripheral arterial tonometry, a technology to assess the reactive hyperaemia index), parameters of oxidation, were not affected by quercetin in the total group and in the subgroup of hypertensives. In the same cohort [14], authors did not find any significant changes in serum concentrations of leptin and adiponectin, homeostasis model assessment-adiponectin (HOMA-AD), glucose, insulin, homeostasis model assessment of insulin resistance (HOMA-IR), blood biomarkers of liver and renal function, hematology, serum electrolytes, hs-CRP and plasma TNF-α. On the contrary, a randomized double-blind, placebo-controlled study involving 72 healthy, overweight, and obese participants, randomly assigned to receive 100 mg/day of quercetin for 12 weeks did not find any significant difference in blood pressure between treatment and placebo arm, nor versus baseline [15]. However, treatment was effective in ameliorating endothelial function evaluated by percent FMD (from 12.5 ± 5.2% to 15.2 ± 6.1%; p = 0.002), and circulating endothelial progenitor cells counts by flow cytometry (44.2 ± 25.6% vs. 52.3 ± 18.6%; p = 0.005), compared with the baseline values.

A randomized, double-blind, placebo-controlled crossover trial evaluated the effects of pure (−)-epicatechin (100 mg/day) and quercetin-3-glucoside (160 mg/day) on biomarkers of endothelial dysfunction and inflammation [16] or vascular function and cardiometabolic health [17], in a cohort of 37 apparently healthy pre-hypertensive (SBP = 125=−160 mmHg) men and women aged 40–80 years. The first analysis showed reduced plasma levels of markers of vascular inflammation, such as soluble endothelial-selectin or interleukin-1 beta. However, the differences were not significant in most cases.

In the second analysis, epicatechin supplementation improved fasting plasma insulin and HOMA-IR, without affecting blood pressure, arterial stiffness, nitric oxide (NO), endothelin-1, or blood lipid profile. Quercetin-3-glucoside supplementation had no effect on FMD, insulin resistance, or other CVD risk factors. Although the compliance and polyphenol absorption were monitored after four weeks of treatment by measuring plasma and urine epicatechin and quercetin concentrations, no further analysis of metabolites was carried out. However, studying pure flavonoids instead of the original complex matrixes may raise some important issues. In fact, if on the one hand, this approach reduces the burden of potential confounding factors, on the other, it may exclude potential favorable interactions with other flavonoids and compounds naturally present in original sources, like cocoa or tea.

2. Mechanisms of Cardioprotection

The role of oxidative stress as a promoter of endothelial dysfunction, that in turn is a driver of early atherosclerosis and consequent cardiovascular related disorders, is no longer in doubt and provides a support for the anti-inflammatory and anti-oxidant strategy in the field of cardioprotection [18]. The widely described antioxidant properties of polyphenols relies on the presence of hydroxyl groups that can be readily oxidized to produce the corresponding O-quinones [19]. This conversion results in an effective scavenger activity towards reactive oxygen species, which occurs through the entrapment of free radicals into stabilized chemical complexes, thus preventing further reactions [20]. This so-called

“biochemical scavenger theory” is currently the most validated one to explain the beneficial effects towards a broad range of non-communicable diseases, including CVD. However, it has to be noted that, although the antioxidant capacity of polyphenols has been largely tested, the results of in vitro tests not always translate in an increased antioxidant status in humans. This lack of consistency may be due to high variability of the single in vitro assays, as well as to individual-related factors [21].

Beyond the inhibition of oxidative stress, polyphenols also display indirect antioxidant effects, occurring through the activation of the transcription nuclear factor erythroid 2-related factor 2 (Nrf2). This event induces endogenous antioxidant systems and is likely to be responsible also for polyphenol-mediated maintenance of the correct redox balance of cells, achieved through the equilibrium of phase I and II enzyme activity [22]. The anti-inflammatory properties of polyphenols are strictly connected with the modulation of oxidative stress and of the balance of redox cellular homeostasis [23]. Multiple mechanisms, most of which are mediated by the inhibition of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB), account for polyphenol’s anti-inflammatory activity. These compounds are able to decrease the cellular production of pro-inflammatory mediators [24][25][26] and to inhibit the expression of adhesion molecules [27], thus impairing the chemotaxis of monocytes within the inflamed tissues. Additional mechanisms accounting for the cardioprotective action of polyphenols target lipid metabolism, whose impairment represents a causative factor of atherosclerosis development [28]. An exhaustive appraisal of polyphenol-enriched food capacity to beneficially modulate lipid and lipoprotein metabolism has been recently reviewed by our group [29]. The widely reported decrease of total and LDL-C following the intake of polyphenols is possibly related to mechanisms occurring at hepatic and intestinal level. In the former, the reduction of cholesterol synthesis, the increase of LDL receptor expression and activity [30] and the increase of the cholesterol transporters ATP-Binding Cassette G5/ATP-Binding Cassette G8 expression [31] have been described in in vivo models. In the latter, polyphenol (i.e., epigallocatechin gallate) capacity to displace cholesterol from intestinal micelles have been associated with increased cholesterol fecal elimination in vivo [32]. The effect on triglyceride plasma level is possibly related to the reduction of apolipoprotein B48 and apolipoprotein B100 production in the liver and intestine, as demonstrated in obese subjects [33], or to the interference with lipoprotein lipase expression, as evidenced in pigs [34]. The mechanisms accounting for the increase of HDL-C are limited to in vitro evidence. Among them, the increase in apolipoprotein A–I synthesis has been reported in cultured hepatic or intestinal cells exposed to cocoa polyphenols [35].

Polyphenols could also be able to positively affect endothelial function, whose impairment is an established key factor for the development of atherosclerosis. This activity has been demonstrated as an amelioration of FMD in humans, although the effective dose was significantly higher than the typical dietary intake [36]. The mechanism accounting for improved FMD probably relies on the increase of NO synthase activity, as suggested by in vitro [37] and human studies [38]. This NO-mediated vasodilation, together with the influence on the renin-angiotensin system [39], is responsible for the reduction of blood pressure, an additional cardioprotective activity of polyphenols. Interestingly, this effect is also evident upon consumption of low, habitual amount of polyphenol-rich food [40].

Finally, polyphenols cardiovascular benefit may be ascribed to the peculiar pharmacokinetic properties mentioned above. While these compounds mainly reach the distal tract of gastrointestinal system unchanged, once modified by the gut microbiota, they may exert a prebiotic-like activity [41], causing the selective growth of beneficial bacteria [42][43][44], together with the inhibition of harmful strains [43][44][45]. This effect has been demonstrated in intervention studies, as well as in ex vivo models of fecal fermentation, possibly accounting for the amelioration of markers of CVD.

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