Phytomedicine 23 (2016) 1145–1174

Contents lists available at ScienceDirect

Phytomedicine

journal homepage: www.elsevier.com/locate/phymed

Polyphenol-based nutraceuticals for the prevention and treatment of cardiovascular disease: Review of human evidence

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ARTICLE INFO

Article history:
Received 31 August 2015
Revised 28 October 2015
Accepted 30 October 2015

Keywords:
Cardiovascular disease
Nutraceuticals
Functional foods
Polyphenols
Randomized controlled trials

ABSTRACT

Background: In addition to prescription drugs, nutraceuticals/functional foods/medical foods are being increasingly added as adjunct treatment of cardiovascular disease (CVD), even though most of them have been exclusively studied in vitro.
Hypothesis/Purpose: We review the available evidence (focusing on when the amount of polyphenols' intake was measured) coming from randomized controlled trials (RCTs) of (poly)phenol-based supplements.
Conclusion: We conclude that (poly)phenol-based nutraceuticals and functional foods might be indeed used as adjunct therapy of CVD, but additional long-term RCTs with adequate numerosity and with clinically relevant end points are needed to provide unequivocal evidence of their clinical usefulness.

Introduction

Cardiovascular disease (CVD) is the major cause of mortality and morbidity in the Western world (Micha et al. 2012). Preventive, i.e. public health measures are being implemented worldwide and include campaigns aimed at smoking cessation, reduction of salt consumption, increased physical activity, and, in general, education to proper lifestyle (Micha et al. 2012). Pharmacological treatment of CVD has also improved greatly over the past decades and several effective drugs, e.g. statins, beta-blockers, ACE inhibitors/AIIRAs, anti-platelets are now available. However, side effects and limited adherence to treatment often limit pharmacological effectiveness.

In addition to prescription drugs, nutraceuticals/functional foods/medical foods are being increasingly added as adjunct treatment of CVD or to prevent it in high-risk (real or perceived) subjects, even though there are no published high-quality human trials comparing drug vs. drug + nutraceuticals (Dutta et al. 2014; Mahabir 2014). Notable examples include phytosterols, soluble fiber, or soy protein to lower blood cholesterol concentrations and fish oil for hypertriglyceridemia, for which clinical evidence is solid enough to recommend their use. Because of the strong epidemiological correlation between plant-based diets and lower CVD incidence (Visioli et al. 2005a), much research is being devoted to clarify the biological activities of phytochemicals, namely of (poly)phenols. Indeed, (poly)phenols are endowed with very interesting healthful properties, most of which – alas – have only been demonstrated in vitro (Visioli and Davalos 2011). Yet, the nutraceutical industry is rapidly cashing in on basic research and many (poly)phenol-based products are now available on the market to target CVD. Of note, several (poly)phenol-based products are currently being labeled as antioxidants (in a quixotic search for the most potent one), even though - due to bioavailability and kinetic constraints issues - modern research is disproving direct antioxidant activities (Chiva-Blanch and Visioli 2012; Visioli 2015).

In recent years, many human dietary interventions aimed at investigating the potential cardiovascular health effects of (poly)phenol-derived preparations on cardiovascular risk markers have been carried out to back their often unrealistic health claims. Herein, we will

Abbreviations: AIx, carotid augmentation index; ATCNs, anthocyanins; BP, blood pressure; CAD, coronary arterial disease; CAS, carotid artery stenosis; CF, cocoa flavanols; CGA, chlorogenic acids; C-IMT, carotid artery intima-media thickness; CHD, coronary heart disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; EDV, end-diastolic velocity; EGCG, epigallocatechin gallate; FMD, endothelium-dependent flow-mediated vasodilation; GAE, gallic acid equivalents; GCE, green coffee bean extract; GE, grape extract; GSE, grape seed extract; GTE, green tea extract; HDLc, high-density lipoprotein cholesterol; HHQ, hydroxyhydroquinone; HOMA, Homeostasis Model Assessment; HPOO, high phenolic olive oils; HT, hydroxytyrosol; LDLc, low-density lipoprotein cholesterol; MDA, malondialdehyde; NMP, N-methylpyridinium; OLE, olive leaf extract; oxLDL, oxidized low-density lipoprotein; PJ, pomegranate juice; PPE, pomegranate polyphenol extract; PSV, peak systolic velocity; PWV, carotid-femoral pulse velocity; RCTs, randomized controlled trials; RHR, reactive hyperemia ratio; SBP, systolic blood pressure; T2DM, type II diabetes; TP, total polyphenols; TXB_2, thromboxane B_2; VOO, virgin olive oil.

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http://dx.doi.org/10.1016/j.phymed.2015.10.018
0944-7113/

almost exclusively focus on reviewing the available evidence (largely when the amount of polyphenols' intake was measured) coming from randomized controlled trials (RCTs) where the effects of preparations derived from several routinely consumed foodstuffs on CVD risk markers were investigated. Specifically, this review focuses on the outcomes of established CVD hallmarks (hypertension, endothelial dysfunction, arterial stiffness, dyslipidemia, inflammation, oxidative status and altered glycemia) and also on altered microbiota (which is associated with CVD), following the consumption of grape-, pomegranate-, apple-, olive-, tea-, tea, coffee-, berries-, and soy-derived (poly)phenol-enriched preparations.

Hypertension

High blood pressure (BP) and hypertension are one of the leading causes of cardiovascular morbidity and mortality throughout the world and BP-lowering strategies do reduce the risk of cardiovascular complications such as coronary heart disease (CHD), stroke and congestive heart failure, among others (Mancia et al. 2014).

Grape-based polyphenol-enriched preparations

The effects described for grape-derived products on BP are far from being established, as a growing number of studies still investigate this issue and evidence keeps building up. Several RCTs have been carried out with subjects in diverse health statuses (healthy, hypercholesterolemic, pre- and hypertensive, at high CVD risk, coronary arterial disease (CAD) patients, type 2 diabetic (T2DM), suffering from metabolic syndrome, etc.). Also, intervention periods have ranged from acute (hours) to chronic (up to 1 y) and with daily amounts of total polyphenols (TP) supplementation oscillating considerably (tens of mg up to more than 1 g). In addition, diverse matrixes were used, such as grape extract (GE), grape seed extract (GSE), wine grape mix extract, grape juice and red wine (either conventional or dealcoholized). After the interventions, some studies found a significant reduction effect on systolic BP (SBP) alone (Barona et al. 2012), or in both SBP and diastolic BP (DBP) (Chiva-Blanch et al. 2012; Draijer et al. 2015; Sivaprakasapillai et al. 2009; Terauchi et al. 2014). On the other hand, no effects were seen in a number of randomized placebo-controlled trials over the last few years, with no significant differences from the placebo group being found at the end of the intervention periods (Botden et al. 2012; Chaves et al. 2009; Hodgson et al. 2014; Krikorian et al. 2012; Mellen et al. 2010; Sano et al. 2007; Tome-Carneiro et al. 2013; van Mierlo et al. 2010). In a very recent placebo-uncontrolled trial, Diaz-Rubio et al. 2015 found no within-group differences before and after intervention with a mixed pomegranate and grape juice (19.2 mg TP/day) for 8 weeks. A meta-analysis, including 9 RCTs (comprising 390 participants in total), concluded that GSE significantly lowered SBP and heart rate, but had no significant effect on DBP (Feringa et al. 2011). Nevertheless, many other RCTs have been published since then and the need for actualized meta-analyses is evident. In the particular case of resveratrol, supplementation with this polyphenol does not produce a significant effect on SBP and DBP according to a very recent meta-analysis, which included data from 10 RCTs (Sahebkar et al. 2015). In this respect, it should be underscored that the activities of resveratrol in humans are questionable and never been really proven, mostly because this molecule is not bioavailable (Tang et al. 2014; Visioli 2014).

Pomegranate-based antioxidants polyphenol-enriched preparations

In randomized placebo-controlled trials with healthy subjects, pomegranate juice (PJ) consumption, as compared to the control groups, resulted in a significant decrease in SBP and DBP (~1044 mg TP (GAE)/day for 6 weeks) (Lynn et al. 2012) and acutely ameliorated a postprandial increase in SBP (652–948 mg TP (GAE)) (Mathew et al. 2012). In a recent RCT with hypertensive patients, Shema-Didi et al. 2014 found a significant decrease in SBP and DBP in the PJ group, although post-interventional values were not different from the placebo group. In agreement, placebo-uncontrolled trials with carotid artery stenosis (CAS) patients (Aviram et al. 2004) and hypertensive patients (Aviram and Dornfeld 2001) also found significant within-group decreases in SBP; however, results from two recent trials carried out in hemodialysis patients reported a lack of effect on BP. In one of them, volunteers received PJ (650 GAE/day), pomegranate extract (650 GAE/day), or placebo for 4 weeks (Rivara et al. 2015) and in the other, although there was a reduction in SBP and DBP in a purified pomegranate polyphenol extract (PPE) consuming group (~980 mg TP/day for 6 months), differences were no longer significant after controlling for baseline BP (Wu et al. 2015).

Apple-based polyphenol-enriched preparations

A randomized crossover trial with hypercholesterolemic volunteers showed that a 4-week consumption of polyphenol-poor (210 mg TP/day) or polyphenol-rich (1430 mg TP/day) apples did not modify BP (Auclair et al. 2010). In agreement, no effect was found on BP in healthy subjects who consumed a daily dose of whole apples (239 mg TP), apple pomace (75 mg TP), clear apple juice (145 mg TP), and cloudy apple juice (108 mg TP) for 4 weeks (Ravn-Haren et al. 2013). Conversely, a decrease in SBP was seen in a placebo-controlled trial evaluating the acute effects of flavonoid-rich apples (184 mg quercetin + 180 mg (−)-epicatechin) in healthy subjects (Bondonno et al. 2012). According to the authors, since an improvement in endothelial function with dietary flavonoids may result from acute rather than chronic exposure this could help to explain the discrepancy. Also, there was a higher quercetin and (−)-epicatechin (coming from apple skin) intake in the Bondonno et al. study, which may be more bioactive than higher molecular weight flavonoids, such as the procyanidins. Furthermore, in another randomized placebo-controlled trial, there was no improvement on BP in pre-hypertensive volunteers after pure (-)-epicatechin (100 mg/day) consumption for 4 weeks (Dower et al. 2015b).

Cocoa-based polyphenol-enriched preparations

Several studies reported improvements in BP after the consumption cocoa-derived polyphenol-enriched products, mainly dark chocolate. Two RCTs with hypertensive subjects, performed by Grassi et al. (2008,2005), showed that a 2-week consumption of flavanol-rich dark chocolate (500–1080 mg TP/day) resulted in a significant reduction in SBP and DBP compared to flavanol-free white chocolate. Similar results were obtained acutely in overweight healthy adults (Faridi et al. 2008). Concurringly, a meta-analysis comprising 20 RCT with a minimum duration of 2 weeks indicated that flavan-3-ol rich cocoa products had a significant effect in lowering both SBP and DBP (Ried et al. 2012). In addition, very recent clinical studies have reinforced the notion that cocoa flavanols (CF) exert a beneficial effect on BP. For example, in T2DM and hypertension medicated individuals, high polyphenol chocolate consumption for 8 weeks resulted in significant decreases in SBP and DBP compared to white chocolate (Rostami et al. 2015). Moreover, healthy young and elderly individuals, who consumed either a CF-containing drink (900 mg CF/day) for 2 weeks, presented a reduction in SBP (elderly) and in DBP (both) when compared to a nutrient-matched, CF-free control drink (Heiss et al. 2015). In a similar context, elderly individuals without known CVD presented significant reductions in SBP and DBP after an 8-week consumption of high-(993 mg CF/day) and intermediate-flavanol drinks (520 mg CF/day) when compared with a low-flavanol drink (48 mg CF/day) (Mastroiacovo et al. 2015). Nevertheless, a lack of effect on BP has been observed in some cases. For example, a 4-week intervention trial with high-risk CHD volunteers receiving a cocoa