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Review

Polyphenol protection and treatment of hypertension

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ABSTRACT

Introduction: High blood pressure is the major risk factor for cardiovascular diseases and the rising prevalence of human hypertension precedes the trend toward a global epidemic of unhealthy ageing. A focus on lifestyle and dietary interventions minimizes dependency on pharmacological antihypertensive therapies.

Review: Observational studies indicate that the intake of dietary flavonoids is associated with a decreased risk of cardiovascular disease (CVD). The evidence suggests that the dietary intakes of polyphenol-rich foods, herbs and beverages including flavonols, anthocyanidins, proanthocyanidins, flavones, flavanones, isoflavones and flavan-3-ols, improves vascular health, thereby significantly reducing the risk of hypertension and CVD. Consumption is associated with an improvement in endothelial function via vascular eNOS and Akt activation. Increased NO bioavailability improves vasodilation and blood circulation, effects protein kinases, ion channels and phosphodiesterases, counteracting vascular inflammation and LDL oxidative stress. Importantly, some polyphenols also inhibit the activity of matrix metalloproteinases, inhibit angiotensin converting enzyme activity and thereby improving SBP and DSB. We review the improvement of polyphenol intake on blood pressure and endothelial function for the treatment of hypertension, including not only observational but also RCTs and pre-clinical studies.

Conclusion: The antihypertensive phytotherapy of polyphenol-rich foods for protection and improving endothelial function with vascular relaxation occurs via the NO-cGMP pathway and ACE inhibition. OPCs stimulate endothelium-dependent vasodilation, suppress vasoconstrictor ET-1 synthesis, activate a laminar shear stress response in endothelial cells and also inhibit the activity of metalloproteinases including ACE lowering blood pressure.

Introduction

In 2012 and 2013 in the United States, antihypertensives (2013 Trends and Statistics 2015) were the most dispensed prescriptions (698 million). The number of treated patients (Aitken et al. 2014) (tp in millions) in 2013 across multiple therapies slightly increased: hypertension (45.7), cholesterol (24.4), antidepressants (22.3), anti-ulcerants (15.3), narcotics (14.9), and antidiabetes (14.0). The magnitude of these numbers of patients mirrors the Western lifestyle of consumer diets (Hügel 2015) stress, and poor work-life balance contributing to the reliance on pharmacological therapies for hypertension, lipid regulators, antidiabetes, antidepressants, and mood regulators to offset unhealthy habits. This dependence is typical of modern global trends.

Cardiovascular disease (CVD) is the most serious public health challenge throughout the world. The World Health Organization (WHO) estimates that the cost of not engaging and investing in CVD prevention and therapy could amount to as much as $47 trillion worldwide in the next 25 years (Ganna and Ingelsson 2015) and the impact will be more severe in developing countries, as 80% of cardiovascular deaths occur in low and middle income countries. Elevated blood pressure plays a significant role in cardiovascular disease. Preventative strategies and resourceful management of hypertension that can be used by everyone are urgently needed. It is also a heritable trait, experienced by many and is the biggest contributor to the global burden of disease and mortality. This health problem is predicted to increase over the next decade.

Abbreviations: CVD, cardiovascular disease; ENOS, endothelial nitric oxide synthase; Akt, protein kinase B; NO, nitric oxide; LDL, low density lipoprotein; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; tp, total population; mm Hg, millimeter mercury; CAD, coronary artery disease; CHD, coronary heart disease; FFAs, free fatty acids; HDL, high density lipoproteins; FMD, flow mediated dilation; ET-1, endothelin-1; OPCs, oligomeric procyanidins; NO-cGMP, nitric oxide-cyclic guanosine monophosphate; RNS, reactive nitrogen species; RAAS, renin-angiotensin–aldosterone system; ACE, angiotensin converting enzyme; ARBs, angiotensin receptor blockers.

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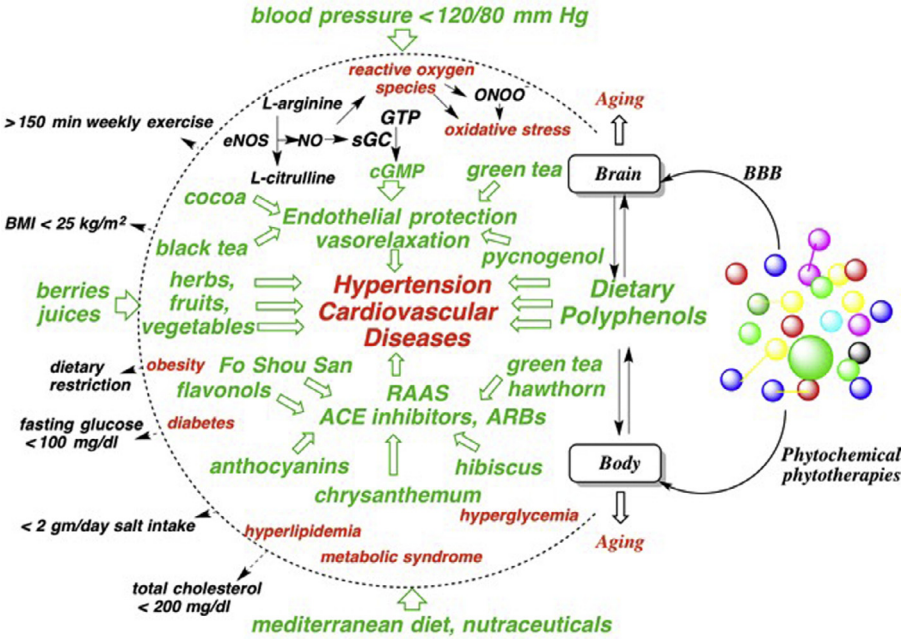
The rise in demand for preventative strategies and resourceful hypertension management that are within the reach of everyone are urgently needed. The causes of hypertension are poorly understood, aging is a risk factor as most of the hypertensive population is 60 years or older, and it is a major risk factor of myocardial infarction, heart failure, kidney disease and stroke. Hypertension research suggests multiple links with lifestyle and personal management of hypertension including stopping smoking, having an active lifestyle and managing diabetes, obesity, electrolyte imbalance, stress, and alcohol consumption is highly probable. Lifestyle changes in particular can lower blood pressure and reduce the risk of heart disease. Among the comprehensive lifestyle modifications, dietary adjustment is one of the most effective measures for modulating hypertension (Wengreen et al. 2013). Even a small lowering of blood pressure is considered to have a significant impact on the severity of hypertension and would reduce the risk of heart disease mortality (Prospective Studies Collaboration 2002). In this review we examine the literature concerning the effectiveness and extent the regular consumption of polyphenol-rich foods, herbs and beverages including flavonols, anthocyanidins, proanthocyanidins, flavones, flavanones, isoflavones and flavanols, as a preventative strategy to improve endothelial function, reduce blood pressure, consequently sustaining cardiovascular health in low-risk subjects and in significantly lowering and managing hypertension, CHD and CVD in medium and high-risk subjects (Scheme 1).

Endothelial dysfunction and hypertension

Flavonoids: composition and mode of action

Polyphenols are plant secondary metabolites that are present in many fruits and vegetables of which flavonoids are the major class of natural products. Flavonoids are polycyclic compounds having a C6ring–C3–C6ring structure substituted with varying numbers of hydroxyl groups, with the major subgroups of dietary value: anthocyanins, isoflavones, flavones, flavonols, flavanones, flavan-3-ols, and the related oligomeric and polymeric proanthocyanidins [also known as condensed tannins] illustrated in Fig. 1 (Crozier et al. 2006a; Rodriguez-Mateos et al. 2014). The oxidative coupling of (−)-epicatechin and/or (+)-catechin occurring between the C-4 of the heterocycle and the C-6 or C-8 positions of the adjacent unit creates type B (or type C) proanthocyanidins that can occur as polymers of up to 50 units in length. Those consisting exclusively of (−)-epicatechin units are called procyanidins (refer to procyanidin C1, Fig. 1). Generally food proanthocyanidins are hetero-oligomers with monomeric units that vary in the number and pattern of hydroxylation. Dark chocolate is a rich source of proanthocyanidins derived from the roasted seeds of cocoa (*Theobroma cacao)* that are also found in red wine and berries. Green tea contains substantial amounts of flavan-3-ols, mainly (−)-epigallocatechin, (+)-gallocatechin, (−)-epicatechin-3-O-gallate and (−)-epigallocatechin-3-O-gallate. However the monomer levels decline during fermentation of the tea leaves so that the major components in black tea are theaflavin-3-O-gallate, theaflavin-3′-O-gallate and theaflavin-3,3′-O-digallate and more substantial quantities of the high molecular weight thearubigins. Black teas contain more than 500 thearubigin components in molecular weights ranging 1–2 kdaltons (Balentine et al. 1997; Kuhnert et al. 2010a; Kuhnert et al. 2010b).

Dietary flavonoids exhibit characteristics of both antioxidant and as signaling molecules. The antioxidant activity of flavonoids is attributed to the scavenging of oxygen-derived radicals (Lin et al. 2002; Miyake et al. 2006). By their ability to: donate hydrogen, metal ion binding, and resonance stabilization of phenoxyl radicals, flavonoids can exhibit antioxidant activity (Rice-Evans et al. 1996; Bors et al. 2001). Flavonoids function as reducing agents, metal chelators, reactive oxygen species (ROS) scavengers, chain-breaking antioxidants, quenchers of singlet oxygen formation, and protectors of ascorbic acid. As signaling molecules, flavonoids interact with key cellular receptors or proteins (kinases and enzymes) that are involved in signaling cascades to catalyze or regulate signaling or regulatory pathways, resulting in physiological responses or gene expression (Williams et al. 2004).



Scheme 1. Antihypertensive phytotherapy: A snapshot of the risk reduction promoted by various types of dietary polyphenols against hypertension and major health risk factors contributing to CVD. The red colors are health risks and problems to be minimized; peripheral inward green arrows, and black outward arrows represent contributions to wellbeing, dietary metrics for minimizing cardiovascular diseases. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)