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Review

Dietary polyphenols regulate endothelial function and prevent cardiovascular disease

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ABSTRACT

Vascular endothelial cell (EC) dysfunction strongly induces development of cardiovascular and cerebrovascular diseases. Epidemiologic studies demonstrated a preventative effect of dietary polyphenols toward cardiovascular disease. In studies using cultured vascular ECs, polyphenols were recognized to regulate nitric oxide and endothelin-1 (ET-1) production. Furthermore, epigallocatechin-3-gallate inhibited the expression of adhesion molecules by a signaling pathway that is similar to that of high-density lipoprotein and involves induction of Ca^{2+}/calmodulin-dependent kinase II, liver kinase B, and phosphatidylinositol 3-kinase expression. The effects of polyphenols on ECs include antioxidant activity and enhancement of the expression of several protective proteins, including endothelial nitric oxide synthase and paraoxonase 1. However, the observed effects of dietary polyphenols in vitro do not always translate to an in vivo setting. As such, there are many questions concerning their physiological mode of action. In this review, we discuss research on the effect of dietary polyphenols on cardiovascular disease and their protective effect on EC dysfunction.

Introduction

Polyphenols are found in a variety of foods, including fruits, vegetables, soybeans, tea, wine, and cocoa. These foods are thought to have a preventative effect on the development of cardiovascular disease (CVD) [1], which is supported by the so-called "French paradox," wherein, despite their consumption of large amounts of milk fat that is associated with higher rates of CVD-related death, the French CVD mortality rate is lower, presumably due to their higher rates of wine intake compared with other European countries. Taking the French paradox into consideration, polyphenol and epidemiologic studies exploring disease development carried out in several countries found that CVD mortality rates were inversely related to dietary polyphenol intake [1–4]. Although the French paradox generally is considered related to the consumption of red wine, a recent study indicated that the French paradox also applies to Mediterranean regions [5]. Furthermore, red wine consumption alone cannot explain the French paradox, so other components of the typical French diet could be responsible for the decreased CVD mortality seen in these regions [6,7].

In epidemiologic studies, polyphenols inhibited vascular system cell injury, including defects in vascular endothelial cell (EC) functions, indicating that polyphenols may have a preventative effect on CVD [8]. Polyphenol molecules and components typically carry several hydroxyl groups and more than 4000 to 7000 varieties are present in plants. Polyphenols can be categorized into flavonoids and non-flavonoids (Fig. 1) [9]. The flavonoid group has a phenyl chroman frame (C 6-C 3-C6), and based on differences in side-chain structures can be classified into flavones (e.g., apigenin, luteolin), isoflavones (e.g., genistein, daidzein), flavanones (e.g., hesperidin, naringenin), flavonols (e.g., quercetin, myricetin, catechin, and epigallocatechin), and anthocyanins (e.g., delphinidin, malvidin) (Fig. 2) [9]. Typical non-flavonoids include tannins, chlorogenic acid, gallic acid, caffeic acid, curcumin, and resveratrol.

In in vitro studies, protective actions of polyphenols toward ECs and vascular smooth muscle cells (SMCs) have been demonstrated. These reports indicated that polyphenols help maintain normal EC functions, and contribute to a critical inhibition of CVD. Polyphenols have an antioxidant effect in vascular

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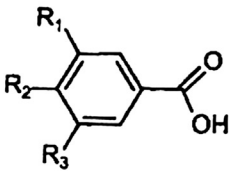
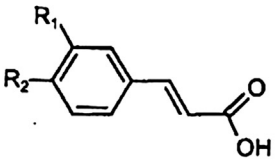


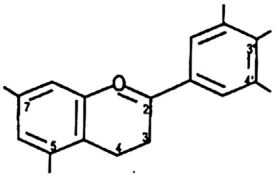
R1	R2	R3	
OH	OH	H	Protocatechuic acid
OH	OH	OH	Gallic acid

Hydroxybenzonic acids



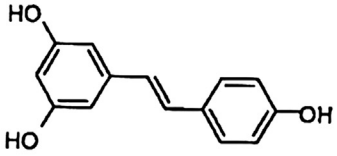
R1	R2	R3	
OH	H	H	Coumanic acid
OH	OH	H	Caffeic acid
OCH_3	H	OH	Ferulic acid

Hydroxycinnamic acids



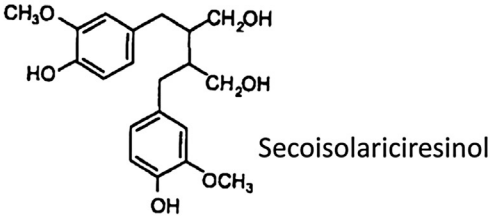
(Subgroup is indicated in Figure 2)

Flavonids



Resveratrol

Stilbenes



Secoisolariciresinol

Lignans

Fig. 1. Chemical structures of the polyphenols.

ECs, and induce nitric oxide (NO) production by promoting EC nitric oxide synthase (eNOS) expression, generating vascular relaxing factors such as prostacyclin (PGI_2) and inhibiting synthesis of the vasoconstrictor endothelin-1 (ET-1) [10,11]. Red wine polyphenols increase NO production by enhancing calcium release [12], which is important for NO-producing signaling pathways. Furthermore, the flavonol quercetin attenuated ET-1 release while simultaneously enhancing tissue plasminogen activator (tPA) and PGI_2 levels in vascular ECs [13]. However, the physiological action of dietary polyphenols is quite complex and many questions concerning their precise mechanism of action remain.

There is a wide variety of polyphenols present in foods, and their absorption and metabolism vary according to the polyphenolic type. Furthermore, the pharmacokinetics of different polyphenols differ and provide additional complicating factors to understanding polyphenol activity. This review considers the results of studies that explored the effects of polyphenols present in fruits and vegetables as well as their effects on vascular EC function.

Epidemiologic studies

In light of the French paradox, epidemiologic studies to determine the relationship between myocardial or cerebral infarction and polyphenol uptake from fruits, vegetables, and wine were performed. These studies found that consumption of larger amounts of fruits and vegetables was inversely related to development of ischemic heart disease [14–16].

In a cohort study conducted in Japan, soy isoflavones were reported to reduce the critical risk for myocardial infarction (MI) [17]. In this study, the consumption of dietary polyphenols by ~40 500 Japanese postmenopausal women (ages 40–59 y) from 1990 to 1992 (with a follow-up survey in 2002) was monitored and the incidence of cerebral infarctions and MIs relative to polyphenol intake was examined. This study showed that an increase in soybean isoflavone intake reduced the critical risk of cerebral infarctions and MIs. An Ohsaki National Health Insurance cohort study examining the relationship between green tea consumption and CVD mortality for ~40 530 Japanese individuals, ages 40 to 79 y (without anamnesis, e.g., stroke, ischemic heart disease, and cancer) during 1995 to 2005 found an inverse relationship between the amount of green tea consumed and the incidence of stroke [18]. Furthermore, another study [19] examined the beneficial effects of green tea in ~1400 Japanese men living in the same area and found that serum triacylglycerol and total cholesterol were reduced and high-density lipoprotein (HDL) levels increased with increasing amounts of green tea intake. One study evaluated 340 individuals to determine whether risk for MI could be reduced by tea consumption compared with caffeinated and decaffeinated coffee. Individuals who drank more than one cup of tea per day had a 44% reduction in CVD compared with those who drank nothing, although no significant relationship between CVD and coffee intake was observed [20].