Pharmacology & Therapeutics 162 (2016) 23–34

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

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

Associate Editor: Y. Zhang

Polyphenols: Potential source of drugs for the treatment of ischaemic heart disease

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ARTICLE INFO

Available online 23 April 2016

Keywords:
Ischaemic heart diseases
Polyphenols
Flavonoids

ABSTRACT

Polyphenols, which are naturally present in plants, have been studied for their chemical and pharmacological properties. Polyphenols have been found to exhibit various bioactivities such as antioxidant, free radical scavenging and anti-inflammatory effects, in addition to regulating the intracellular free calcium levels. These bioactivities are related to the underlying mechanisms of ischaemic heart diseases. Pharmacological studies have proven polyphenols to be effective in treating cardiovascular diseases in various ways, particularly ischaemic heart diseases. Based on their mode of action, we propose that some polyphenols can be developed as drugs to treat ischaemic heart diseases. For this purpose, a strategy to evaluate the therapeutic value of drugs for ischaemic heart diseases is needed. Despite several advances in percutaneous coronary intervention (PCI), the incidence of myocardial infarction and deaths due to cardiovascular diseases has not decreased markedly in China. Due to their pleiotropic properties and structural diversity, polyphenols have been of great interest in pharmacology. In the present review, we summarize the pharmacological effects and mechanisms of polyphenols reported after 2000, and we analyse the benefits or druggability of these compounds for ischaemic heart diseases.

Contents

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ADMA, asymmetric dimethylarginine; ADP, adenosine diphosphate; ADR, adenosine receptor; AMPK, adenosine monophosphate-activated protein kinase; CAD, coronary artery disease; cGMP, cyclic guanosine monophosphate; COPD, chronic obstructive pulmonary disease; COX, cyclooxygenase; EC, endothelial cell; EGCG, epigallocatechin gallate; ER, oestrogen receptor; FAO, fatty acid oxidation; GPx1, glutathione peroxidase 1; HUVECs, human umbilical vein endothelial cells; IHD, ischaemic heart disease; LPO, lipid peroxidation; NADPH, nicotinamide adenine dinucleotide phosphate; NF-κB, nuclear factor kappa B; NO, nitric oxide; PDEs, phosphodiesterases; OPR, opioid receptor; PA, protocatechuic acid; PCI, percutaneous coronary intervention; PGI2, prostacyclin I2; PI3K, phosphoinositide 3-kinase; PKA, protein kinase A; SalA, salvianolic acid A; SalB, salvianolic acid B; SIRT1, deacetylase sirtuin 1; SOD, superoxide dismutase; SP-1, specificity protein-1; TXA2, thromboxane A2.

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http://dx.doi.org/10.1016/j.pharmthera.2016.04.008
0163-7258/

1. Introduction

Ischaemic heart disease (IHD) is considered the leading cause of death and disability worldwide. It is characterized by insufficient blood supply to the heart due to the pathological narrowing of coronary vessels, typical of atherosclerosis. The clinical characteristics of IHD include temporary pain (angina), irregular heartbeat (arrhythmia), permanent heart muscle damage (myocardial infarction) and loss of muscle activity (heart failure).

IHD is managed with medication and surgery. The following drugs are used to manage IHD: 1) nitroglycerine, which decreases oxygen demand and increases oxygen supply by causing the coronary artery to dilate; 2) statins, which reduce cholesterol level, improve vascular endothelial function, dilate blood vessels and inhibit inflammatory reaction; 3) angiotensin-converting enzyme (ACE) inhibitors, which reduce angiotensin II production by inhibiting ACE, increase myocardial blood flow, reduce myocardial oxygen consumption, inhibit inflammatory responses and may lower the risk of recurrent myocardial infarction; 4) calcium channel blockers, which exert cardioprotective effects by lowering the intracellular calcium level, relaxing vascular smooth muscle and dilating the blood vessels; 5) β-receptor antagonists, which reduce myocardial oxygen consumption by suppressing the effects of adrenaline; 6) anti-platelet agents, such as aspirin and clopidogrel, to inhibit platelet aggregation and lower the risk of atheromatous plaque formation; and 7) cell- and protein-based therapies, which help restore organ function and myocardial regeneration.

At present, percutaneous coronary intervention (PCI) with drug-eluting stents (DESs) is used to reduce cardiovascular events in patients with coronary artery disease (CAD) and IHD. Although it significantly reduced restenosis rates, the use of DES increased the risk of both late stent thrombosis and atherosclerosis, and in turn late stent failure. Many patients, especially the elderly, are deemed unsuitable for revascularization due to co-morbid diseases, unsuited anatomy or the risks inherent to the procedure (Bonetti et al., 2003). Moreover, despite several advances in PCI, the incidence of myocardial infarction and deaths due to cardiovascular disease has not decreased visibly in China (Sui et al., 2015). Therefore, pharmacological interventions for IHD have been of great interest recently.

Polyphenols constitute a large group of natural products widely distributed across the plant kingdom. Based on the number of phenol rings and the binding structural properties, polyphenols are divided into several subclasses such as phenolic acids, flavonoids, stilbenes, lignans and tannins. In the past decades, several different polyphenols have been isolated and identified from plants, in addition to their pharmacological activities (Goszcz et al., 2015). The evidence points to the multiple pharmacological effects of polyphenols against cardiovascular diseases, particularly IHD. For IHD, the underlying mechanisms of action of polyphenols have been elucidated. These include reducing myocardial oxygen consumption and/or increasing oxygen supply, enhancing myocardium metabolism after ischaemia/reperfusion (I/R), inhibiting platelet aggregation and thrombosis, regulating lipid metabolism and inflammation to inhibit the formation of atheromatous plaques, promoting angiogenesis or endothelial cell (EC) repair, protecting the remaining myocardial cells and restoring myocardial contraction (Harasym & Oledzki, 2014; Raj et al., 2015).

For this review, we systematically searched the EMBASE, PubMed and Cochrane Library databases, and the references of relevant papers. Combined with the results obtained in our laboratory, we presented an overview of the advances in elucidating the effects of polyphenols (including their derivatives and analogues) against IHD. In the following sections, we classify their pharmacological activity and functional mechanisms, particularly those with therapeutic potential for IHD.

2. Polyphenols

2.1. Flavonoids

Flavonoids are an important class of polyphenols abundantly found in vegetables, fruits and different plants; they are usually yellow in colour. Approximately 2% of the total carbon in a plant is ultimately converted to flavonoids or similar compounds. Chrysin (Fig. 1A) was the first flavonoid to be isolated (1814). To date, >4000 flavonoids have been isolated and identified (Iwashina, 2000). Flavonoids such as quercetin (Fig. 1B), rutin (Fig. 1C) and hesperidin (Fig. 1D), isolated from fruits, are most commonly studied for their cardiovascular effects. Furthermore, anthocyanins are common dietary flavonoids that help prevent cardiovascular disease. Although many flavonoids have been isolated, several more flavonoids are yet to be discovered.

The basic skeleton of flavonoids is composed of C_6–C_3–C_6, generally containing two aromatic rings, a central three-carbon chain and a 4-carbonyl group. Flavonoids are widely used as antioxidants as they possess several phenolic hydroxyl groups that donate active hydrogen atoms and stop/delay the automatic oxidation of lipids. Many flavonoids have been found to exhibit various pharmacological actions except antioxidation. For example, pinocembrin (Fig. 1E), isolated from honey and propolis, is an anti-inflammatory and antimicrobial agent that acts on diastolic arteries (Estevinho et al. 2008; Li et al., 2013; Rasul et al., 2013). Baicalein (Fig. 1F), isolated from the roots of the labiate *Scutellaria baicalensis*, can scavenge oxygen-derived free radicals and protect the heart, cerebral vessels and neurons (Xin, et al., 2014). It is worth noting that Veregen contains a mixture of known active compounds, including catechins (Fig. 1K). On 31 October 2006, the Food and Drug Administration (FDA) approved the use of Veregen for treating perianal and genital condyloma (Hara, 2011).

2.2. Phenolic acids

Phenolic acids constitute another important class of polyphenols found in plants with well-established bioactivities. Both in vivo and in vitro, most of the phenolic acids showed antioxidative, anti-inflammatory and free radical scavenging activities, and could protect cells against injuries induced by various harmful factors.

Phenolic acids with varying chemical structures show different bioactivities. For example, phenolic acids isolated from a variety of legumes showed significant differences in phytochemical content and functional activities (Yao et al. 2011). Protocatechuic acid (PA) is a naturally occurring phenolic acid found abundantly in >500 plants. It is structurally similar to other well-known antioxidants such as gallic acid, caffeic acid and vanillic acid. It exhibits different pharmacological effects such as its antioxidant activities, anti-inflammatory properties and interaction with several enzymes (Kakkar & Bais, 2014). Ferulic acid is a simple phenolic acid found in cereals. Spontaneously hypertensive rats (SHRs) treated with ferulic acid (50 $mg \cdot kg^{-1} \cdot d^{-1}$) showed reduced systolic blood pressure, left ventricular diastolic stiffness, attenuated inflammatory cell infiltration, etc. (Alam et al., 2013). In rats fed an atherogenic diet, veratric acid was found to significantly attenuate systolic and diastolic blood pressure and lipid peroxidation products after oral administration (40 mg/kg) for 30 days. In particular, it showed protective effects against atherogenic diet-induced hyperlipidaemia (Raja et al., 2012). Salvianolic acids have been isolated from *Salvia miltiorrhiza* for use against cardiovascular

Fig. 1. The chemical structures, molecular formulas and molecular weights of selected flavonoids. These flavonoids were selected because they were most commonly studied with significant cardiovascular effects. **A**: chrysin; **B**: quercetin; **C**: rutin; **D**: hesperidin; **E**: pinocembrin; **F**: baicalein; **G**: 3′-O-methyl-quercetin; **H**: quercetin-3-O-glucuronide; **I**: genistein; **J**: daidzein; and **K**: catechin.