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Botanical Flavonoids on Coronary Heart Disease

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Abstract

Ischemic heart disease (IHD) is one of the leading causes of death in Western countries. Prevention rather than treatment of heart disease can significantly improve patients' quality of life and reduce health care costs. Flavonoids are widely distributed in vegetables, fruits and herbal medicines. Regularly consuming botanicals, especially those containing flavonoids has been associated with a reduction in cardiovascular disease; thus, it is important to investigate how flavonoids improve cardiac resistance to heart disease and their related mechanisms of action. It has been shown that cardiomyocyte injury and death can result from ischemia-reperfusion, which is pathognomonic of ischemic heart disease. Massive reactive oxygen species (ROS) release at the onset of reperfusion produces cell injury and death. "Programming" the heart to either generate less ROS or to increase strategic ROS removal could reduce reperfusion response. Additionally, profuse nitric oxide (NO) release at reperfusion could be protective in "preconditioning" models. Botanical flavonoids induce preconditioning of the heart, thereby protecting against ischemia-reperfusion injury. In this article, we will discuss two herbs containing potent flavonoids, *Scutellaria baicalensis* and grape seed proanthocyanidin, which can potentially offer cardiac protection against ischemic heart disease.

Keywords

Cardiovascular Disease; Ischemic Heart Disease; Ischemia-Reperfusion Injury; Reactive Oxygen Species; Nitric Oxide; Flavonoids; *Scutellaria baicalensis*; Grape Seed Proanthocyanidin

Introduction

Cardiac injury following ischemia-reperfusion (I-R), clinically known as ischemic heart disease (IHD) or coronary artery disease, is one of the leading causes of death in the United States. The high mortality results from the massive myocardial injury that occurs when the ischemic heart is re-oxygenated, called reperfusion. Thus, preventing the reperfusion oxidant injury has been identified as the fundamental strategy for reducing the morbidity of acute cardiac injury (Ostadal, 2009).

A significant reduction in coronary artery disease incidence has been linked the consumption of herbal flavonoids (Keli *et al.*, 1996; Arts *et al.*, 2001; Mann *et al.*, 2007), suggesting that the flavonoids may enhance tolerance to cardiac I-R injury. Flavonoids, which possess significant antioxident potential, are widely distributed in edible vegetables, fruits and many herbal medicines (Chao *et al.*, 2009; Huang *et al.*, 2009; Yook *et al.*, 2010). Flavonoids' protective effects against ischemic heart disease is based on several clinical studies that positively correlate flavonoid intake to a reduced incidence of the disease.

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Consuming flavonoids like catechin, which is present in plant seeds and teas, resulted in a 20% reduction in the incidence of the disease (Arts *et al.*, 2001). A meta-analysis of prospective cohort studies concluded that high flavonoid intake from fruits, vegetables, tea, and red wine is associated with a reduced risk of ischemic heart disease (Huxley and Neil, 2003; Li *et al.*, 2010). In a study of approximately 5,000 subjects, the intake of dietary flavonoids and tea was inversely associated with myocardial infarction (Geleijnse *et al.*, 2002). It seems likely that flavonoid-containing botanicals have remarkable potential in protecting cardiac injury.

Scutellaria baicalensis extract (SbE) and grape seed proanthocyanidin extract (GSPE) contain flavonoid components which have been extensively tested for their antioxidant activity (Heim *et al.*, 2002; Tong *et al.*, 2009; Chan *et al.*, 2010). In this article, after an introduction of the related background information, the role of SbE and GSPE in improving cardiac reserve against reperfusion injury will be reviewed.

Pathophysiology of Ischemia-Reperfusion Injury

By definition, reperfusion is the reestablisment of normoxic conditions after a period of hypoxia or ischemia. The hallmark of reperfusion is a significant burst of reactive oxygen species (ROS) which results in oxidant injury to myocardial tissue. Thus, interventions that reduce the injury could positively impact recovery and survival. The simplistic approach of administering antioxidants to reduce ROS-induced injury, however, has not always yielded beneficial results (Violi *et al.*, 2004). The protective potential of an antioxidant depends on the scavenging of specific ROS species and its access to strategic intracellular sites (Becker, 2004; Yu *et al.*, 2009). Alternatively, “programming” the heart to either generate less ROS or to increase strategic ROS removal by endogenous mechanisms could reduce reperfusion response.

During I/R, toxic ROS are released from within the cardiomyocytes and other locations (Zweier *et al.*, 1987). While the non-cardiomyocyte sources, such as neutrophils, are equally important in producing oxidant injury, ROS generated within the cardiomyocytes probably inflict rapid and severe cell damage as evidenced in a cardiomyocyte model of simulated I/R and mitochondrial inhibition (Vanden Hoek *et al.*, 2000; Yin *et al.*, 2010). Conditions associated with oxygen deprivation such as ischemia and hypoxia predominantly result in mitochondrial ROS generation (Duranteau *et al.*, 1998). With I/R, both mitochondrial and cytosolic sources release toxic ROS (Mohazzab *et al.*, 1997).

Nitric oxide (NO) is an important trigger as well as mediator of delayed preconditioning. NO is released during ischemia and at the beginning of reperfusion by activation of the NOS enzyme, particularly cNOS. The effect of NO release on the outcome of I-R injury appears to depend on various factors such as species and study design, and ranges from beneficial to harmful (Schulz *et al.*, 2004). Although increasing NO concentrations has demonstrated benefit, a simultaneous presence of excess ROS could result in the formation of peroxynitrite, a highly injurious reactive species. Thus, for NO to be beneficial, ROS levels during reperfusion need to be attenuated (Xie *et al.*, 1998).

The protective effect of “preconditioning” the heart against I-R injury has been demonstrated in cardiomyocyte and animal models, and pharmacological agents can perform this preconditioning. The preconditioning effect can be seen in two windows: the early window is within minutes to 4 hours after the induction phase is initiated by receptor-ligand interaction while the delayed window is observed from 12 hours to 72 hours and requires *de novo* protein synthesis (Baxter and Ferdinandy, 2001). The delayed pharmacological preconditioning is a more promising phenomenon with considerable therapeutic potential. Clinical applicability of the preconditioning mechanism is profound given the significant

statistics of mortality, morbidity and the associated health care expenses of IHD. Since ischemic preconditioning has demonstrated significant delayed preconditioning, studying the related cellular and molecular pathways evoked in these models would allow the definition of the characteristics of the protected prototype. Pharmacological agents, including herbal antioxidants, that activate similar mechanisms could be a more clinically practical method to inducing preconditioning. *Scutellaria baicalensis* extract (SbE) and grape seed proanthocyanidin extract (GSPE) contain flavonoid components which have been extensively tested for antioxidant activity (Heim *et al.*, 2002; Shao *et al.*, 2003a; Mehendale *et al.*, 2007). The flavonoids from SbE and GSPE possess stimulating mechanisms that are protective against I-R injury during IHD.

Scutellaria baicalensis Extract (SbE)

Scutellaria baicalensis Georgi (Labiatae) is widely used in the traditional medical systems of China and Japan for inflammatory diseases, hyperlipemia and arteriosclerosis (Gasiorowski *et al.*, 2011). The major constituents of SbE are flavonoids like baicalin, baicalein, wogonoside and wogonin (Fig. 1A).

Flavonoids in SbE are effective scavengers of hydroxyl and peroxyl radicals and superoxide anions (Jovanovic *et al.*, 1998). An example of the antioxidant reaction of these components is the scavenging of hydrated electrons (e_{aq}^- radicals) by baicalin. E_{aq}^- radicals are formed when biological molecules are exposed to ultraviolet light and ionizing radiation such as ion beams or gamma-rays. Thus the e_{aq}^- scavenging abilities of flavonoids should be considered in the diet (Cai *et al.*, 1999).

Using *in vitro* and *in vivo* models, the antioxidant effects have been demonstrated in both the extract and its active flavonoids (Yune *et al.*, 2009). Hamada *et al.* investigated *in vitro* radical scavenging activities of baicalein and quantified superoxide and hydroxyl radicals by electron spin resonance spectrometry (Hamada *et al.*, 1993). They reported that in a hypoxanthine-xanthine system, baicalein strongly reduced superoxide radicals. Electron paramagnetic resonance data showed that baicalin and baicalein scavenged hydroxyl radicals, DPPH radicals and alkyl radicals dose-dependently; wogonin and wogonoside had no effect on these radicals. This result suggests the need to study the actions of individual constituents of an extract to define the most effective constituent. When rats were pretreated with either oral or intraperitoneal SbE or its constituents, lipid peroxidation, a marker of oxidant injury, was attenuated, suggesting antioxidant protection (Gao *et al.*, 1995).

It is believed that the antioxidant action of SbE is mediated by direct ROS scavenging, to which baicalein and wogonin contribute significantly (Bochorakova *et al.*, 2003). Direct intracellular antioxidant activity has been shown from experiments in our group. SbE and baicalein attenuated oxidation of intracellular fluorescent probes in chick cardiomyocytes exposed to I/R (Shao *et al.*, 2002). A rapid antioxidant protection by baicalein in the cardiomyocyte model was observed. As this system is devoid of other sources of ROS such as neutrophils or endothelial cells, the reduction of fluorescence clearly indicates rapid intracellular scavenging by baicalein. The flavonoid structure and a low-molecular weight endow such molecules with intracellular antioxidant properties.

When rats were pretreated with either oral or intraperitoneal SbE or its constituents, lipid peroxidation was attenuated, suggesting antioxidant protection (Kimura, 1982; Gao *et al.*, 1995). SbE also prevented apoptosis by increasing the anti-apoptotic protein activity, demonstrating indirect antioxidant effects (Choi *et al.*, 2002). It has been reported that SbE flavonoids also inhibit NO production (Kim *et al.*, 2001).

Grape Seed Proanthocyanidin Extract (GSPE)

Grapevines are classified into the genus *Vitis*. A single *Vitis* species, *V. vinifera*, originated in Europe and has been thoroughly studied. Approximately 34 species have been characterized in North America and Central America, whereas more than 30 species are native to China (Vivier and Pretorius, 2002). GSPE possesses a broad spectrum of therapeutic properties (Ray *et al.*, 2001) and is a popular herbal supplement with patients suffering from cardiovascular disease. Interest in grape seed as a possible cardioprotective agent peaked following demonstration of the "French paradox," a positive correlation between the high intake of saturated fat and increased wine consumption, but a reduced risk of IHD (Renaud and de Lorgeril, 1992). Moderate consumption of wine, particularly red wine, has been associated with a reduced mortality from IHD (Rimm *et al.*, 1991; Das, 1999).

GSPE is a potent ROS scavenger (Bagchi *et al.*, 1997; Sato *et al.*, 1999). In GSPE, the main polyphenolic oligomeric and polymeric proanthocyanidins are catechin, epicatechin, epicatechin gallate and procyanidin B2 (Fig. 1B) (Gonzalez-Paramas *et al.*, 2004). Among these proanthocyanidins, procyanidin B2 has been shown to be the most effective compound in trapping oxygen free radicals (Da Silva *et al.*, 1991). Proanthocyanidins and catechins are also found in wine (Das, 1999).

The capacity of the constituents of GSPE to act as antioxidants depends upon their molecular structure. The position of hydroxyl groups and other features are important for their free radical scavenging activities. Phenolic antioxidants (PPH) inhibit lipid peroxidation by a rapid donation of a hydrogen atom to the peroxyl radical ($ROO^{\cdot}$) resulting in formation of alkyl (aryl) hydroperoxide (ROOH), as illustrated in the following reaction: $ROO^{\cdot} + PPH \rightarrow ROOH + PP^{\cdot}$. The polyphenol phenoxyl radical ($PP^{\cdot}$) produced can be stabilized by further donation of a hydrogen atom and formation of quinines (Stohs, 1995); or by reacting with another radical, including another phenoxyl radical, to generate new components (Hosny and Rosazza, 2002), thereby interrupting the initiation of a new chain reaction.

We reported direct, acute antioxidant effects in cardiomyocytes exposed to H_2O_2 and I/R (Shao *et al.*, 2009). The studies suggested rapid bioavailability of GSPE inside the cardiomyocytes. Long-term consumption of GSPE has demonstrated cardiovascular benefits in animal models (Sato et al., 1999). Indirect antioxidant effects such as NADPH oxidase inhibition and reduced ROS-mediated apoptosis have been shown (Fitzpatrick *et al.*, 2002). Other observed cardiovascular benefits from GSPE include reduced thrombosis and improved blood flow (Stein *et al.*, 1999; Wollny *et al.*, 1999). These effects are probably caused by the stimulated NO-release by various GSPE fractions in endothelium (Fitzpatrick et al., 2002). In chick cardiomyocytes, NO release is stimulated by low concentrations of GSPE and may trigger preconditioning (our unplished data).

Comparing and Contrasting SbE and GSPE

The constituent flavonoids of these two extracts differ structurally at very specific sites (Fig. 1 A and B). Flavonoids in GSPE possess the 3′-4′ catechol structure in the B-ring, and an OH group in position 3 which makes the GSPE flavonoids extremely potent antioxidants (C-ring). While these features are absent in the SbE flavonoids, the presence of a 4-oxo and 2-3 double bond (C-ring) imparts them with antioxidant activity, in addition to a pro-oxidant activity (Heim et al., 2002).

The flavonoids are potent ROS scavengers but paradoxically are capable of producing ROS depending upon experimental conditions (Chang *et al.*, 2009; Wang *et al.*, 2009; Lu *et al.*,

2010). Flavonoids in SbE, particularly baicalein, may stimulate ROS production from the mitochondria (Hodnick *et al.*, 1994). In the presence of excess ROS, baicalein acts as a scavenger and forms stable semiquinone radicals. The stability of the radical prevents pro-oxidant toxicity except in conditions of high flavonoid concentrations for extended intervals (Heim et al., 2002). GSPE is also known to be a pro-oxidant at concentrations that are significantly higher than the commonly used dose (Shao *et al.*, 2003b). The ROS-scavenging by flavonoids may affect ROS-dependent signaling and the biological effects will represent the sum total of these disparate properties.

With respect to NO, flavonoids in SbE such as wogonin and baicalein, suppress its release by inhibiting NOS/guanylate cyclase (Kim et al., 2001). In normal tissue GSPE stimulates NO release via a purinergic pathway (Fitzpatrick et al., 2002; Mendes *et al.*, 2003). GSPE has shown a reduced NO release, although only in models of inflammation, which could be an indirect effect of suppression of iNOS upregulating cytokines (Roychowdhury *et al.*, 2001). Our unplished data suggest that cardiomyocytes show a non-toxic ROS response to SbE treatment but NO release with GSPE treatment during the induction phase. It is appears that the two extracts may induce two distinct preconditioning mechanisms (Fig. 2).

The flavonoid constituents are absorbed rapidly and are bioavailable after oral consumption (Yamashita *et al.*, 2002; Lai *et al.*, 2003). In a cardiomyocyte model, rapid intracellular access of both baicalein and GSPE have been demonstrated as well (Shao *et al*., 2002). In cultured cells, the low molecular weight compounds of GSPE enter via paracellular pathways, with the more lipophilic compounds diffusing across membranes (Konishi *et al.*, 2003). Thus, effects of the flavonoids in a cellular model should reflect those in intact animals.

Summary

Based on the compelling epidemiological data linking flavonoid use to reduced myocardial injury, the ongoing flavonoid studies should significantly advance our understanding of the cellular mechanisms involved in the protective actions of the heart. Evidence suggests that the use of herbal flavonoids has cardioprotective effects while the use of antioxidant vitamins does not reduce the incidence of IHD (Gavagan, 2002; Vivekananthan *et al.*, 2003). Herbal flavonoids, such as those found in SbE and GSPE, may play a vital role in modulating cardiomyocyte response against reperfusion injury in a novel paradigm. Herbal extracts, by virtue of being composed of a mixture of active compounds, could act through more than one mechanism, and hence could potentially exert multiple beneficial effects. Exploration of pathophysiological mechanisms of SbE and GSPE in modulating cardiovascular function will promote safe and effective use of botanical flavonoids in the treatment and prevention of coronary heart disease.

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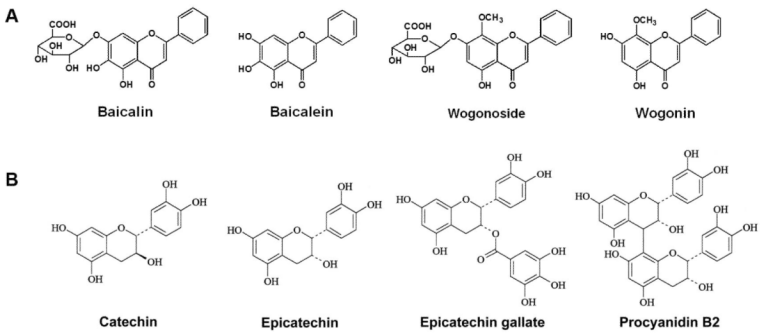

Figure 1.
Flavonoids in *Scutellaria baicalensis* extract *(*SbE) (A) and grape seed proanthocyanidin extract (GSPE) (B).

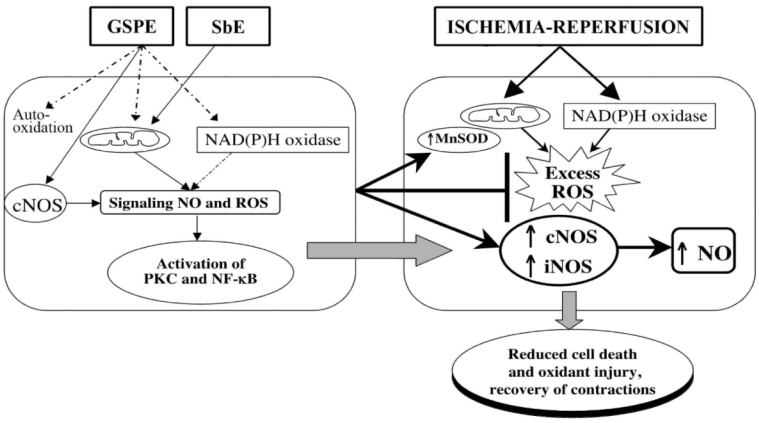

Fig. 2.

Potential mechanisms of *Scutellaria baicalensis* extract *(*SbE) and grape seed proanthocyanidin extract (GSPE) in delayed preconditioning in cardiomyocytes. NO-nitric oxide; ROS-reactive oxygen species; PKC-protein kinase C; MnSOD-manganese superoxide dismutase; cNOS-constitutive nitric oxide synthase; iNOS-inducible NOS.