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Commonly Used Antioxidant Botanicals: Active Constituents and their Potential Role in Cardiovascular Illness

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Abstract

Cardiovascular disease continues to be the leading cause of death in the US. Recent studies found that reactive oxygen species (ROS) have been incriminated in the pathogenesis of both acute and chronic heart disease. Many botanicals possess antioxidant properties, and these herbal antioxidants may protect against cardiovascular diseases by contributing to the total antioxidant defense system of the human body. In this article, we reviewed the antioxidant components and properties of four putative antioxidant botanicals (i.e., grape seeds, green tea, *Scutellaria baicalensis*, and American ginseng), and their potential role in treating cardiovascular illness. The antioxidant activities of the herbal active constituents, and the relationship between their chemical structures and biological functions were also discussed. Further investigations are needed on the mechanisms of action of these botanicals as they affect salient cellular and molecular pathways involved in major diseases. Data obtained from future studies will have the potential for translation into practical benefits for human health.

Keywords

Cardiovascular Disease; Reactive Oxygen Species; Grape Seeds; *Vitis vinifera*; Green Tea; *Camellia sinensis*; *Scutellaria baicalensis*; American Ginseng; *Panax quinquefolius*

Introduction

Botanical ingredients in dietary supplements, including traditional herbal medicines and foods, contain bioactive constituents with potential health benefits. Many herbal medicines possess antioxidant properties, which play an important role in therapeutics (Cadenas and Packer, 2002; Chang *et al.*, 2005) Recent studies found that reactive oxygen species (ROS) have been incriminated in the pathogenesis of both acute and chronic heart disease.

Antioxidants are compounds that protect cells against the damaging effects of ROS, such as superoxide, hydrogen peroxide, singlet oxygen, peroxyl radicals, hydroxyl radicals and peroxynitrite (Stohs, 1995). Some ROS, such as superoxide and hydrogen peroxide, are normally produced in cells as by-products of biochemical reactions or as signaling molecules (Cadenas and Packer, 2002; Stohs, 1995). When ROS-generating reactions are activated excessively, pathological quantities of ROS are released to create an imbalance between antioxidants and ROS. Oxidative stress has been linked to cardiovascular disease, diabetes, pulmonary disease, cancer, and other degenerative diseases (Stohs, 1995). Herbal antioxidants may protect against these diseases by contributing to the total antioxidant defense system of

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the human body (Liu *et al.*, 2006; Ichikawa *et al.*, 2006). The efficacy of herbal antioxidants has been suggested in several studies. For example, epidemiological studies have shown that intake of flavonoids, a group of herbal antioxidants, is inversely related to mortality from coronary heart disease and to the incidence of heart attacks (Chang *et al.*, 2006).

Currently, a considerable amount of research focuses on the ROS-mediated pathophysiology of different diseases. These illness cause significant patient morbidity and escalate healthcare costs (Cadenas and Packer, 2002). Several medications for the treatment of these diseases are believed to act through an antioxidant mechanism. Thus, one can envision the scope and impact of the use of antioxidant herbs. They could mediate health benefits by partially eliminating pathological amounts of ROS (Lee *et al.*, 2006). If their value in promoting antioxidant tissue defense is established using contemporary methods, antioxidant herbs may also have a potential role in preventing and treating diseases (Chung *et al.*, 2006; Yang *et al.*, 2006b).

Antioxidant botanicals may reduce ROS activity either directly or indirectly. The active constituents found in several antioxidant herbs are known to react directly with ROS by scavenging and reducing ROS activity (Choi *et al.*, 2002; Hamada *et al.*, 1993; Stangl *et al.*, 2006). This article reviews four commonly used antioxidant herbs (grape seeds, green tea, *Scutellaria baicalensis* and American ginseng) with diverse antioxidant active components such as flavonoids and ginsenosides. In addition to scavenging, the active constituents found in several antioxidant herbs can affect cellular functions, including gene expression and enzymes that promote ROS dynamics (Dalton *et al.*, 1999; Park *et al.*, 2006). The ability of antioxidant herbs to affect various pathological processes mediated by ROS depends on their ability to access the sites or sub-cellular compartments (i.e., mitochondria, cytosolic organelles, nucleus) of biochemical activity. The issues of access of antioxidant herbs in various cellular regions, which is a function of their chemical characteristics, and the relationship between chemical structures of the constituents and biological functions, will also be discussed.

Grape Seeds (*Vitis vinifera*)

There are many species of grapevines, but most wine grapes are from *Vitis vinifera* L. (Vitaceae). Grape seed proanthocyanidins extract (GSPE) which possesses a broad spectrum of pharmacological, medicinal and therapeutic properties (Ray *et al.*, 2001; Wang *et al.*, 2005; Chang *et al.*, 2006), is a popular herbal supplement with patients suffering from cardiovascular disease in the US. Grape seed proanthocyanidins are polyphenolic bioflavonoids, present in lignified portions of grape clusters, especially in the seeds. Tannins are natural polyphenol. On the basis of structural characteristics, tannins are divided into four major groups: gallotannins, ellagitannins, complex tannins, and condensed tannins. Polyphenols from grape seeds, which are oligomeric and polymeric proanthocyanidins that belong to condensed tannins, are the main antioxidant components in grape seed extracts.

Polyphenolic compounds are ubiquitous in nature. They are categorized according to chemical structure as flavonoids (such as flavanols, flavonols, flavones, flavanones, isoflavones, and anthocyanidins). More than 4,000 flavonoids have been identified, many of which are found in fruits, vegetables, tea, coffee, beer, wine, and fruit drinks. Over the past several years, increasing evidence has strongly suggested that moderate consumption of wine or alcohol has been associated with a reduced incidence of mortality and morbidity from coronary heart disease (Rimm *et al.*, 1991).

The capacity of flavonoids to act as antioxidants depends upon their molecular structure. The position of hydroxyl groups and other features in the chemical structure of flavonoids are important for their antioxidant and free radical scavenging activities. In GSPE, the main polyphenol components are (+)-catechin (C), (-)-epicatechin (EC), (-)-epicatechin gallate (ECG) and proanthocyanidin dimer B2 (EC-EC) (Fig. 1). Polyphenols are powerful

antioxidants. Phenolic antioxidants (PPH) inhibit lipid peroxidation by a rapid donation of hydrogen atom to the peroxyl radical (ROO) resulting in formation of alkyl (aryl) hydroperoxide (ROOH), as illustrated in the following reaction: ROO + PPH → ROOH + PP. The polyphenol phenoxyl radical (PP) produced can be stabilized by further donation of a hydrogen atom and formation of quinones (Fig. 2, Cadenas and Packer, 2002), or by reacting with another radical, including another phenoxyl radical, to generate new components (Fig. 3,Hosny and Rosazza, 2002), thereby interrupting the initiation of a new chain reaction.

The antioxidant components in GSPE are catechins, similar to those in green tea extract (see below). However, their structure differs from the polyphenols of green tea. In GSPE, polyphenols are composed of C, EC and gallic acid (GA) unit; the composition units of polyphenols in green tea extract are mostly (-)-epigallocatechin (EGC) and GA.

The antioxidant properties of GSPE were previously summarized (Bagchi *et al.*, 2000). The GSPE attenuated H_2O_2-induced oxidant stress in cardiomyocytes. Antioxidant action is associated with an increase in cardiomyocyte survival and contractile function. The extract had cardioprotective effects against reperfusion-induced injury by reducing or removing, directly or indirectly, free radicals in the myocardium of an isolated rat heart that was reperfused after ischemia.

Postprandial hyperlipemia is a well-defined risk factor for atherosclerosis (Yang *et al.*, 2006a). The supplementation of a meal with GSPE minimizes the postprandial oxidative stress by decreasing the oxidants and increasing the antioxidant levels in plasma. As a consequence, it enhances the resistance to oxidative modification of LDL in human subjects. GSPE is superior to conventional antioxidants such as vitamin E and vitamin C. In one study, TPA-induced lipid peroxidation in mice brain and liver was significantly attenuated with GSPE pretreatment compared to that with conventional antioxidants (Bagchi *et al.*, 1998).

Direct scavenging activity of GSPE appears to be an important component of its antioxidant protection. GSPE successfully scavenged superoxide, hydroxyl and peroxyl radicals. When compared its scavenging ability for superoxides and hydroxyl radicals, GSPE scavenged more superoxides than hydroxyl radicals (Yamaguchi *et al.*, 1999). When GSPE was combined with vitamin E, all radicals, such as superoxides, hydroxyl, and methyl were scavenged (Yamaguchi *et al.*, 1999). This result suggests herbs with varied scavenging potentials can be combined to increase the radical scavenging activities.

Other mechanisms of antioxidant effects may be involved, such as nitric oxide-releasing action, which could help to attenuate oxidant formation. GSPE reduced the apoptotic effect of chemotherapeutic agents, thus reducing their toxicity (Joshi *et al.*, 1999). Since apoptotic genes are regulated via ROS signaling, these results may suggest modulation of ROS signaling.

Green Tea (*Camellia sinensis*)

Tea is a popular and socially acceptable drink consumed every day by hundreds of millions of people across all continents. Tea from the *Camellia sinensis* L. of the Theaceae family is one of the most ancient and the second most widely consumed beverage in the world. Tea can be classified into three types: green, oolong, and black. Green tea is non-fermented and derived directly from drying and steaming fresh tea leaves.

Based on chemical studies, green tea contains polyphenolic compounds. Catechins are the most predominant group of substances in green tea accounting for 16–30% of the dry weight. The major catechins are (-)-epigallocatechin-3-gallate (EGCG), (-)-epigallocatechin (EGC), (-)-epicatechin-3-gallate (ECG), and (-)-epicatechin (EC) (Fig. 4). EGCG is the most predominant

catechin in tea. On the basis of recent studies, it is believed that EGCG is responsible for much of the biological activity mediated by green tea.

Polyphenols in green tea are composed of EGC, EC and gallic acid (GA) such as EGCG (EGC + GA) and ECG (EC + GA). These combinated units, EGC, EC and GA, are structures of phenols, and this series of structures is easily oxidized. Compounds that are easier to oxidize are often better antioxidants, as is true of green tea. The catechol group reacts readily with oxidants in the form of free radical reactive oxygen species to form a stable radical, the semiquinone radical. The compounds with catechol or 1,4-dihydroquinone functionality are especially easy to oxidize because the resulting phenoxyl radical can be stabilized on another oxygen molecule (see Fig. 2). An EGC and GA unit can also react readily with free radicals to form stable radicals (Fig. 5).

In green tea extracts, oligomeric and polymeric proanthocyanidins are the main polyphenols, similar to the components from grape seeds. For green tea and grape seeds extracts, proanthocyanidins are composed from basic units such as EGC, EC, catechin (C) and GA. The differences between components from green tea and grape seeds are the composed units. For green tea, EGCG (EGC + GA) and EGC are main components. For grape seeds, the main components are catechin and epicatechin. The major units in oligomeric proanthocyanidins are also C and EC. On the other hand, in American ginseng (see below), because of the antioxidant activities of triterpene saponin, it has been suggested that the effect of scavenging free radicals by ginsenosides comes from the protection mechanism for the antioxidant-related protein or enzymes (Kitts *et al.*, 2000). In *Scutellaria baicalensis* (see below), flavones are the antioxidant components.

In Oriental cultures, it has been widely believed for a long time that tea has medicinal efficacy for prevention and treatment of many diseases. Modern scientific studies of biological and pharmacological properties, however, were started only recently (Yanagimoto *et al.*, 2003; An *et al.*, 2005; Luo *et al.*, 2006). Green tea and its major constituents have multifaceted functions. In the past decade, much attention has been focused on the antioxidant, cardiovascular disease, fatty-acid synthase, lipid oxidation in LDL, antimutagenic, anticancer and antiviral activities of green tea (Yanagimoto *et al.*, 2003; Cabrera *et al.*, 2006). Most of these activities have been attributed to its antioxidant and free radical scavenging properties, particularly to the high content of polyphenolic compound and microelements. Green tea polyphenol is known to be an excellent antioxidant that directly scavenges free radicals and inhibits lipid peroxide formation.

Green tea extract has been shown to protect against cardiovascular and renal diseases in several *in vitro* and *in vivo* models (Stangl *et al.*, 2006). Green tea catechins delay the oxidation reactions by inhibiting the formation of free radicals or interrupting the propagation of the free radical chain reaction caused by the toxic compounds. This protection attenuates the progress of atherosclerosis and thrombosis. The catechin derivatives in green tea have been demonstrated to be protective agents in cardiovascular disease (Ding *et al.*, 1992). Epidemiological studies show that individuals consuming four or more cups of green tea per day lower their risk of atherosclerosis and coronary heart disease. Increased consumption of green tea is associated with decreased total cholesterol and triglyceride levels in the blood and is, therefore, inversely related to the risk of coronary heart disease. One study concluded that green tea has more health benefits than an equal volume of black tea in terms of antioxidant capacity (Lee *et al.*, 2002).

Tea polyphenols act as antioxidants *in vitro* by scavenging reactive oxygen and nitrogen species and chelating redox-active transition metal ions. They may also function indirectly as antioxidants through different pathways: 1) inhibition of redox-sensitive transcription factors,

nuclear factor-kB and activator protein-1; 2) inhibition of “pro-oxidant” enzymes, such as inducible nitric oxide synthase, lipoxygenases, cyclooxygenases and xanthine oxidase; and 3) induction of phase II and antioxidant enzymes, such as glutathione S-transferases and superoxide dismutases (Frei and Higdon, 2003). McConnell *et al.* used three model systems to measure oxidation/nitration damage caused by peroxynitrite (McConnell *et al.*, 2003). A combination of green tea extract and fruits produced more complete antioxidant protection. Oxidative and nitrosative damage to biological systems from peroxynitrite or its carbon dioxide derivative has not been recognized as a key system to be controlled in chronic diseases (McConnell *et al.*, 2003). However, the active constituents of green tea and the mechanisms responsible for the antioxidant effects on cardiovascular systems are not fully understood.

Scutellaria Baicalensis

While other three dietary supplements are commonly used herbal antioxidants in the US, *Scutellaria baicalensis* Georgi (Labiatae) is a widely used herb in the traditional medical systems of China and Japan. Based on many reports of the beneficial effects of the herb, *Scutellaria baicalensis* has been used as an ingredient in botanical formulations in China and Japan in recent years with positive results. The dried root of *Scutellaria baicalensis* has been used for inflammatory diseases, allergies, hyperlipemia, arteriosclerosis and cancer (Huang, 1999; Shieh *et al.*, 2006). The major constituents of *S. baicalensis* are a group of polyhydroxy phenols that include baicalin, baicalein and wogonin (Fig. 6). These flavonoids are considered to be associated with antioxidant actions of *S. baicalensis* extract (SbE).

The constituents of *S. baicalensis* are flavones, a group of antioxidants. Flavones are effective scavengers of hydroxyl and peroxyl radicals and superoxide anion (Cadenas and Packer, 2002). An example of the antioxidant reaction of these components is scavenging hydrated electrons (e_{aq}^- radicals) of baicalin. E_{aq}^- radicals are formed when biologic molecules are exposed to ultraviolet light and ionizing radiation such as ion beams or gamma-rays via ionization. Thus, the e_{aq}^- scavenging abilities of flavonoid and phenolic acids should be considered in the diets of patients who are receiving radiotherapy. E_{aq}^- first attacks the keto group of flavonoids and phenolic acids and forms a ketyl radical ion. The ketyl radical ion is unstable and quickly protonizes into the same transient as that of H-adduct, which may exist in several resonance states. The mechanism of baicalin reacting with e_{aq}^- is illustrated in Fig. 7 (Cai *et al.*, 1999).

Components from *S. baicalensis* are flavones, which belong to flavonoids. Flavanols, another group of flavonoids, are the main constituents in green tea and grape seeds extracts. Components of American ginseng are ginsenosides, which are triterpene saponins, whose structures are completely different from flavonoids.

The antioxidant effects of SbE have been demonstrated in *in vitro* and *in vivo* experiments using both the extract and its active flavonoids (Gao *et al.*, 1995). Antioxidant protection is possible by direct scavenging of radicals by SbE or its constituents. 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). Compared to conventional antioxidants such as vitamin E, baicalein was more significantly effective as a free radical

scavenger in improving the survival of cultured fibroblasts. Baicalein processes potent antioxidant effects (Fig. 8), and wogonin may reduce antioxidant potential (Morimoto *et al.*, 1998). It seems that not all constituents reflect the properties shown by the whole extract.

It appears difficult to find an efficacious antioxidant that displays the physical characteristic of expeditious access to ROS-forming sites in the intracellular and interstitial compartments while remaining in the system for a reasonable duration. Using a Langendorff model, Omar and McCord (1991) showed that achieving adequate interstitial concentration after exogenous administration was the key to antioxidant protection during reperfusion. They also demonstrated that the charge and the size of the antioxidant molecule significantly affected the rate of equilibrium with the interstitium. Kilgore *et al.* demonstrated that a low molecular weight superoxide dismutase-mimetic compound provided antioxidant protection when administered during reperfusion (Kilgore *et al.*, 1994).

When copious quantities of ROS are released during oxidant stress, the innate intracellular oxidant defenses are overwhelmed. The antioxidant herbal extracts can provide cell protection (Shen *et al.*, 2005; Yu *et al.*, 2006). 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 ischemia/repufursion. We observed a rapid antioxidant protection by baicalein in our cardiomyocyte model. 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. We believe that the flavonoid structure and a low-molecular weight endow such molecules with intracellular antioxidant properties. Thus, these compounds are excellent candidates for cardiac antioxidants (Shao *et al.*, 2002).

Direct radical scavenging does not appear to be the sole mechanism of action. SbE and its constituents may exert antioxidant effects via indirect mechanisms. Shieh *et al.* (2000) showed that although wogonin does not possess direct radical scavenging activities, it can significantly inhibit enzyme xanthine oxidase activity. Xanthine oxidase may not be present in appreciable quantity in the cardiomyocyte, suggesting that these flavonoids are not solely oxidant scavengers, but may possess an additional dimension of antioxidant activity. This notion is supported by another study which demonstrated that mitochondrial oxidases, such as succinooxidase and NADH oxidase, could be inhibited by flavonoids like baicalein (Hodnick *et al.*, 1994). The SbE could also alter signaling levels of ROS to modulate gene expression, which is mediated through redox-mediated transcription factor activation (Dalton *et al.*, 1999).

Besides cardiovascular diseases, oxidative stress can be linked to the pathological process of neurodegenerative illness. Flavones from SbE attenuated oxidant stress and protected neuronal cells from lethal oxidant damage (Choi *et al.*, 2002) and may be used to cure head-injury related to free-radical assault. SbE also prevented apoptosis by increasing the Bcl-2/Bax ratio and phosphorylating Bcl-2 (Choi *et al.*, 2002). It was suggested that baicalein could be a key template for the development of therapeutic agents to selectively modulate inflammatory responses and cellular apoptosis in CNS. In addition, nausea and vomiting are significant side-effects associated with the use of chemotherapy in cancer patients. Treatment of nausea and vomiting caused by cisplatin, a potent emetogenic agent, requires a combination of different anti-emetic drugs. Cisplatin generates free radicals and releases reactive oxygen species. Recently, we observed that SbE pretreatment decreased cisplatin-induced nausea in a rat model, suggesting that SbE plays a therapeutic role in chemotherapy-induced emesis (Aung *et al.*, 2003).

Mediators like NO and PKC could affect the antioxidant effects of SbE. Baicalin and baicalein enhanced PE induced contractions of vascular rings suggesting an inhibition of endothelial NO production. SbE also inhibited microglial NO production. Wogonin inhibited nitric oxide production was accompanied by suppression of iNOS protein induction. This study demonstrated that three active flavonoids in the herbal extract SbE, i.e., wogonin, baicalin and baicalein, caused inhibition of nitric oxide synthesis with some differential activities. There is evidence suggesting that baicalein inhibits the activity of measured PKC using PKC related expression of endothelial adhesion molecules (Kimura *et al.*, 2001). Several studies have reiterated that individual active components within SbE may have different actions, and the overall action of the herb represents the interactions of the various biologically active constituents.

American Ginseng (*Panax quinquefolius*)

Ginseng root has been used for centuries in Oriental medicine as a panacea that promotes longevity (Xie *et al.*, 2004). Several studies demonstrate beneficial effects of Asian ginseng (Xie *et al.*, 2005; Liou *et al.*, 2005; Yoo *et al.*, 2006). However, relatively few studies focus on American ginseng (*Panax quinquefolius* L., Araliaceae), which is a popular herbal supplement in patients suffering from cardiovascular disease in the US (Xie *et al.*, 2005; Wang *et al.*, 2006a), while cardiovascular disease is also the most common complication of diabetes.

It is believed that the main bioactive constituents of American ginseng extract are dammarane saponins, commonly referred to as ginsenosides (Fig. 9), which are present in the root, leaf and berry of the plant (Wang *et al.*, 2006a;Wang *et al.*, 2006b). More than 30 ginsenosides such as Rb_1, Rb_2, Rc, Rd, Re, and Rg_1 have been identified in American ginseng. The chemical structures of ginsenosides are different from polyphenols that can be found in grape seed, green tea, and *Scutellaria baicalensis*. Whether ginsenosides share some of the similar antioxidant pathways of other antioxidants is to be the focus in the current and future studies.

Diabetes mellitus is also a major health problem, affecting approximately 5% of the population in the US and 3% of the population worldwide. Hyperglycemia and various life-threatening complications (e.g., cardiovascular disease) resulting from long-term hyperglycemia are the most common features (Hayasaka *et al.*, 2006). Effective control of blood glucose level is a key in preventing or reversing diabetic complications and improving quality of life. Antioxidants are also important in treating diabetes. Low levels of plasma antioxidants are a risk factor for the development of the disease, and circulating levels of radical scavengers impair function throughout the progression of diabetes. An anti-diabetic effect in addition to the antioxidant activity of American ginseng berry extract was observed. Using the C57BL/6J *ob/ob* mouse, a profoundly obese and hyperglycemic model that phenotypically resembles human type 2 diabetes, we demonstrated that in addition to berry extract, the root and leaf of American ginseng can reduce high blood glucose levels (Xie *et al.*, 2004).

Several beneficial effects on the cardiovascular system, such as anti-ischemic, anti-arrhythmic and anti-hypertensive effects, have been attributed to the use of American ginseng, thus explaining its popularity as an alternative in cardiovascular therapeutics. These pharmacologic effects are, to a significant extent, considered to be linked to the antioxidant properties of the herb. In an early pilot clinical trial, ginsenosides prevented acute oxidant injury following reperfusion (Zhan *et al.*, 1994). In a subsequent *in vitro* study (Kitts *et al.*, 2000; Xie *et al.*, 2006), American ginseng extract showed antioxidant activity in both lipid-soluble and water-soluble medium by chelating metal ions and directly scavenging 1,1-diphenyl-2-picrylhydrazyl (DPPH) and hydroxyl radicals. Since there is no typical antioxidant structure in ginsenosides, it has been suggested that ginsenosides scavenge free radicals with a protection mechanism for the antioxidant-related protein or enzymes (Kitts *et al.*, 2000). In another study, ginsenosides

extracted from American ginseng inhibited activation of protein tyrosine kinase induced by ischemia reperfusion, another antioxidant mechanism (Dou *et al.*, 2001). Interestingly, American ginseng root extract (AGE) failed to demonstrate this activity, which was only found with individual ginsenosides, implying that the constituents of AGE interact for antagonizing effects. It is equally probable that synergistic effects of individual ginsenosides can be demonstrated. Using a chick cardiomyocyte model, we recently studied the antioxidant effect of American ginseng berry extract (AGBE) and ginsenoside Re. Both AGBE and ginsenoside Re attenuated oxidant stress and protected cells from lethal oxidant damage (Xie *et al.*, 2006).

The antioxidant effect of AGE was demonstrated with low concentrations of ginsenosides (in μg/ml), which significantly decreased low-density lipoprotein (LDL) oxidation and reduced $CuSO_4$-induced oxidative changes in the presence of vitamin C (Li *et al.*, 2000). At high concentrations (in mg/ml), ginsenosides reduced LDL oxidation directly (Li *et al.*, 1999). The authors of the study suggested that along with an antioxidant that acts in an aqueous medium such as vitamin C, synergistic antioxidant effects were observed with ginsenosides.

Ginseng also activates nitric oxide release. Nitric oxide attenuates the activity of pro-oxidant enzymes such as reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (Fujii *et al.*, 1997), which could be another mechanism of antioxidant protection conferred by American ginseng.

Summary

In this article, we discussed the four putative antioxidant botanicals which have significant pharmacological activities in the body, especially in the cardiovascular system. The relationship between herbal constituent activities and chemical structures were also presented. Further investigations are needed on the mechanisms of action of these herbs as they affect salient cellular and molecular pathways involved in the major diseases. Data obtained from future studies will have the potential for translation into practical benefits for human health.

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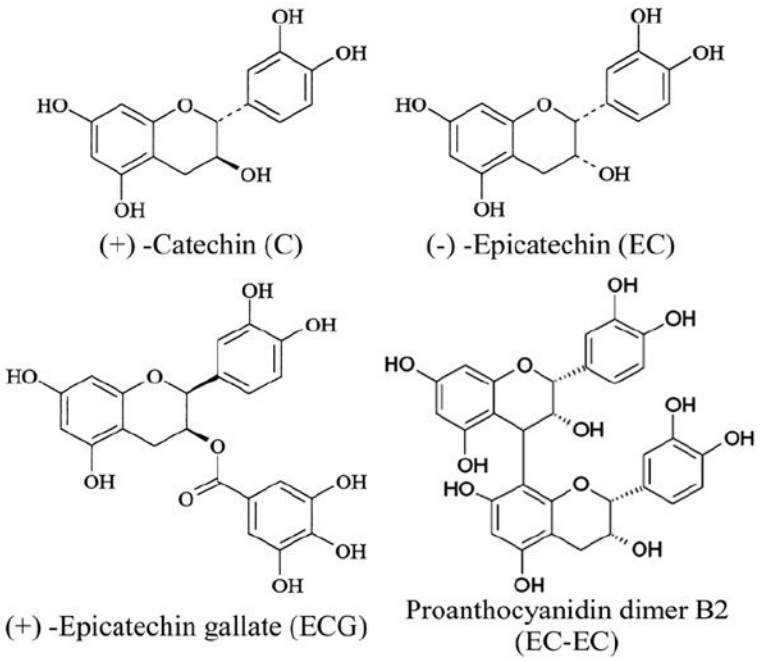


Figure 1.
Four antioxidant components in grape seeds.

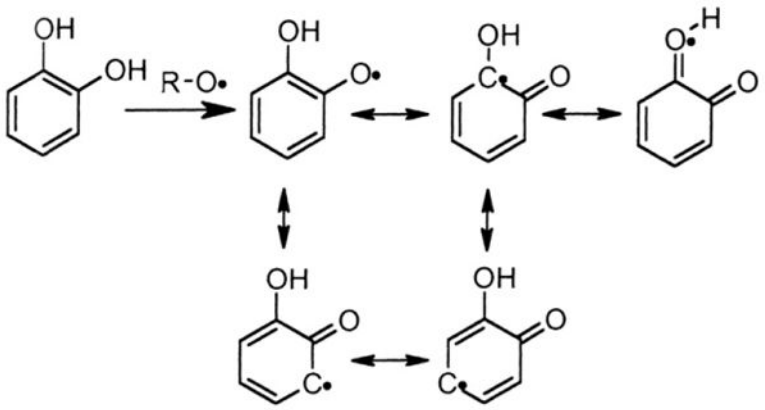


Figure 2.
Resonance stabilization of semiquinone radical.

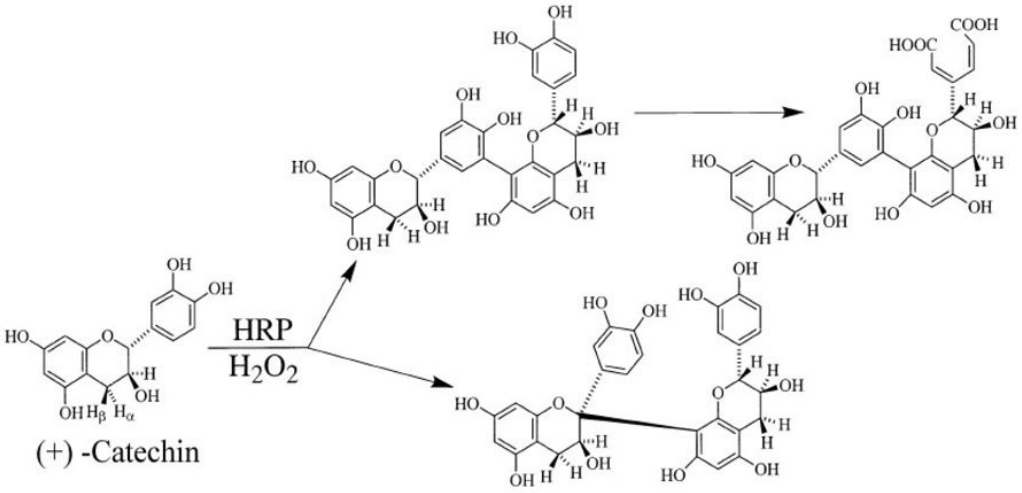


Figure 3.
Products obtained by H_2O_2-dependent horseradish peroxidase (HRP) oxidation of catechin.

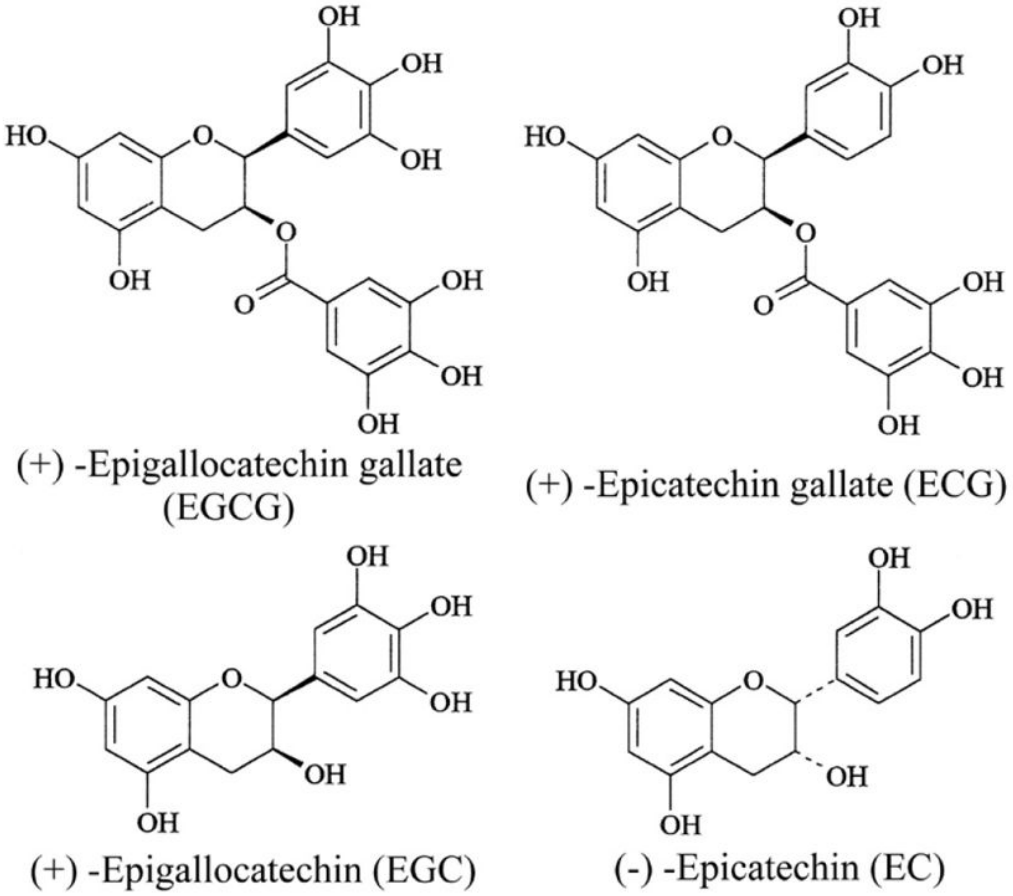


Figure 4.
Four antioxidant components in green tea.

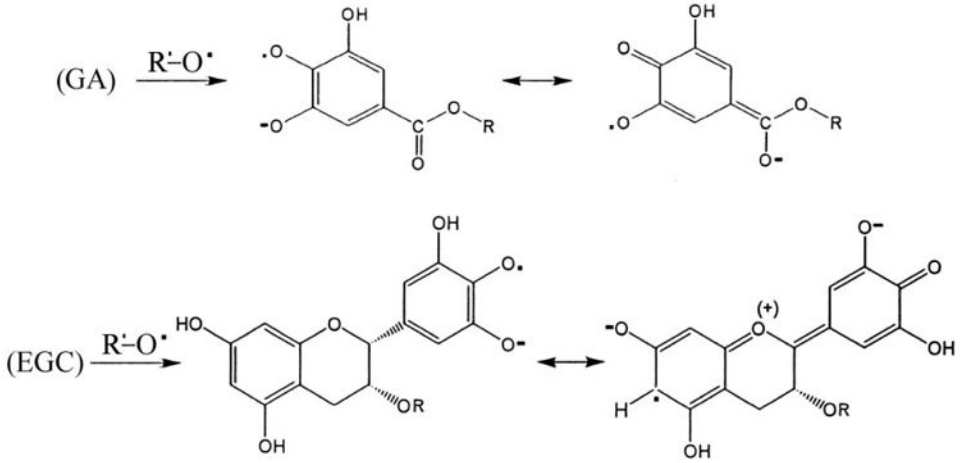


Figure 5.
Antioxidant reaction of gallic acid (GA) and epigallocatechin (EGC).

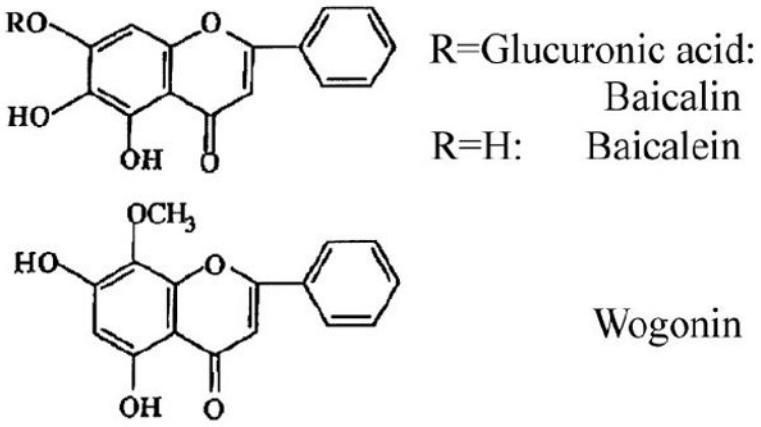


Figure 6.
Three flavonoids from *S. baicalensis*.

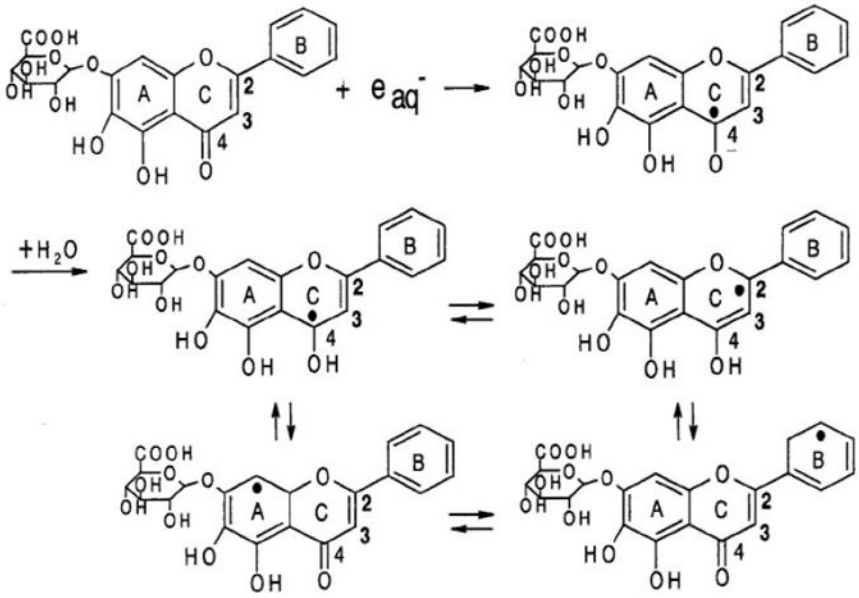


Figure 7.
Reaction mechanism of baicalin with e_{aq}^{-}.

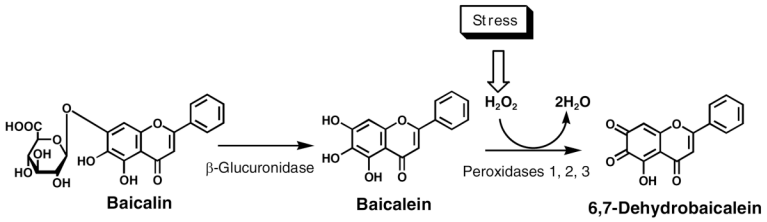
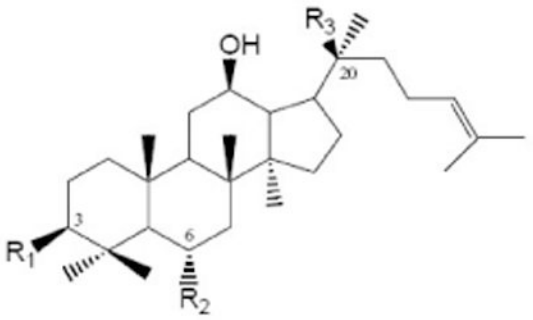


Figure 8.
Metabolic pathway of baicalin against oxidative burst.



Compound	R1	R2	R3
Rb_1	-O-Glc-Glc	-H	-O-Glc-Glc
Rb_2	-O-Glc-Glc	-H	-O-Glc-Ara(pyr)
Rc	-O-Glc-Glc	-H	-O-Glc-Ara(fur)
Rd	-O-Glc-Glc	-H	-O-Glc
Re	-OH	-O-Glc-Rha	-O-Glc
Rg_1	-OH	-O-Glc	-O-Glc

Glc : glucose Ara : arabinose Rha : rhamnose

Figure 9.
Six ginsenosides in American ginseng.