Edible berries: Bioactive components and their effect on human health

Shivraj Hariram Nile M.Sc., Ph.D.*, Se Won Park M.Sc., Ph.D.*

Department of Molecular Biotechnology, College of Life and Environmental Sciences, Konkuk University, Seoul, South Korea

**A R T I C L E    I N F O**

Received 14 March 2013
Accepted 11 April 2013

Keywords:
Phytochemicals
Human health
Blueberries
Blackberries
Raspberries
Strawberries

**A B S T R A C T**

The importance of food consumption in relation to human health has increased consumer attention in nutraceutical components and foods, especially fruits and vegetables. Berries are a rich source of a wide variety of non-nutritive, nutritive, and bioactive compounds such as flavonoids, phenolics, anthocyanins, phenolic acids, stilbenes, and tannins, as well as nutritive compounds such as sugars, essential oils, carotenoids, vitamins, and minerals. Bioactive compounds from berries have potent antioxidant, anticancer, antimutagenic, antimicrobial, anti-inflammatory, and antineurodegenerative properties, both in vitro and in vivo. The following is a comprehensive and critical review on nutritional and non-nutritional bioactive compounds of berries including their absorption, metabolism, and biological activity in relation to their potential effect on human health.

© 2014 Elsevier Inc. All rights reserved.

**Introduction**

Increased consumption of fruits and vegetables is recommended in dietary guidelines worldwide and the intake of fruits like berries which are rich in nutrients and phytochemicals can prevent various diseases and disorders. Most berries are delicious and powerful disease-fighting foods and make up the largest proportion of fruit that is consumed in the human diet [1]. Berry fruits are popularly consumed not only in fresh and frozen forms but also as processed and derived products, including dried and canned fruits, yogurts, beverages, jams, and jellies [2]. Among the colorful fruits, berries such as blackberry (Rubus species), black raspberry (Rubus occidentalis), blueberry (Vaccinium corymbosum), cranberry (Vaccinium macrocarpon), red raspberry (Rubus idaeus), and strawberry (Fragaria ananassa) are popularly used in the human diet either fresh or in processed forms. Additionally, there has been a growing trend in the use of berry extracts as ingredients in functional foods and dietary supplements, which may be combined with other colorful fruits, vegetables, and herbal extracts. Extracts of fruits from various blackberry, raspberry, and gooseberry cultivars act effectively as free radical inhibitors [3]. Berries provide significant health benefits because of their high levels of polyphenols, antioxidants, vitamins, minerals, and fibers [4]. Polyphenols comprise a wide variety of compounds, divided into several classes like hydroxybenzoic acids, hydroxycinnamic acids, anthocyanins, proanthocyanidins, flavonols, flavones, flavanols, flavonanes, isoflavones, stilbenes, and lignans that occur in berry fruits. It has already been demonstrated that a wide diversity of phytochemical levels and antioxidant capacities exist within and across genera of small fruits [5,6]. Furthermore, accumulating evidence suggests that genotype has a profound influence on concentrations of bioactive compounds in berries [7]. Berry extracts are widely consumed in botanical dietary supplement forms for their potential human health benefits. Many laboratory and animal studies have shown that berries have anticancer, antioxidant, and antiproliferative properties [2,8]. Berry bioactive components impart anticancer effects through various complementary and overlapping mechanisms of action, including the induction of metabolizing enzymes, modulation of gene expression and their effects on cell proliferation, apoptosis, and subcellular signaling pathways [9]. Some berries, such as strawberries and black raspberries, have been identified as sources of phenolic compounds like gallic and ellagic acid, which have potential cancer chemopreventive activity [10]. These different bioactive phenolic compounds, including flavonoids, tannins, and phenolic acids, have received considerable interest in bearing possible relations to human health. This review focuses specifically on recent data, related to in vitro and in vivo studies that have been conducted with berries, emphasizing the role of phytochemicals. It is noteworthy that recent and significant advances have been made in understanding the...
bioavailability and metabolism of phenolic acids and flavonoids present in berries, which are discussed herein. Studies on the absorption, metabolism, tissue distribution, in vitro and in vivo biological effects, and mechanisms of action of berry phenolic acids and flavonoids are necessary to evaluate their effect on human health and diseases. In fact, the chemistry and biology of phenolic acids and flavonoids are important in the context of their biological effects exerted in the human body.

### General chemical composition

Berries contain high levels of a diverse range of phytochemicals, most of which are phenolic molecules. These phytochemicals include a variety of beneficial compounds, such as essential minerals, vitamins, fatty acids, and dietary fibers. Berries are an important source of provitamin A, minerals, vitamin C, and B-complex vitamins. Berry fruits contain about 15% soluble solids (mainly sugars) and their high level of fructose makes them valuable for individuals with diabetes. The high dietary fiber content is important because fruit pectin acts as an intestinal regulator [11]. Some of the known chemopreventive agents present in berries include vitamins A, C, and E, and folic acid; calcium and selenium; carotene and lutein; phytosterols such as sitosterol and stigmasterol; triterpene esters; and phenolic molecules such as anthocyanins, flavonols, flavanols, proanthocyanidins, ellagitannins, and phenolic acids (Fig. 1). The chemistry of berry phenolics directly influences their bioavailability, metabolism, and biological effects in vivo [12]. The structural diversity of berry phenolics is observed in several ways including the following:

1. Their degree of oxidation and the substitution patterns of hydroxylation,
2. Their abilities to exist as stereoisomers,
3. Glycosylation by sugar moieties and other substituents, and
4. Conjugation to form polymeric molecules such as tannins and other derived molecules [2,9].

The berry phenolis serve many diverse biological functions including roles in plant growth, development, and defense. They provide pigmentation, antimicrobial and antifungal functions, insect-feeding deterrence, ultraviolet radiation protection, chelation of toxic heavy metals, and antioxidant quenching of free radicals generated during photosynthesis [13,14].

### Bioactive compounds

#### Vitamins

Berries contain a large amount of vitamins A, C, and E, and the B-complex vitamins. These vitamins help to boost the immune system and reduce inflammation. They also are considered anti-oxidants, which help to fight the effects of oxidative stress leading to chronic diseases such as heart disease, diabetes, and certain cancers. Vitamins are highly concentrated in honeyberry and blackcurrants varieties, which are greater than the concentrations in strawberries, raspberries, gooseberries [15,16]. Berries are very important sources of ascorbic acid, which is a water-soluble compound that fulfills several roles in living systems. It is widely distributed in fresh fruits and vegetables. The content of vitamin C in berry fruits is determined by numerous factors, including species, variety, cultivation, climate, weather conditions, ripeness, region, storage time, and conditions. Vitamin C is reported in high amounts in blackcurrant and strawberries, which are the richest source among all the berry fruit species reported [17].

#### Minerals

Berries are rich in both macro- and micronutrients, among which honeyberry is a rich source of these minerals. The major mineral elements found in berries are phosphorus, potassium, calcium, magnesium, iron, manganese, copper, sodium, and aluminum. Berries accumulate much iron, calcium, phosphorus, and sodium minerals from environment and retain leadership among all other fruiting plants [18]. Mineral nutrients are scientifically recognized as essential or potentially essential constituents for human health as they play an important role in development of bones and teeth and provide strength to muscles in humans. These major and trace mineral elements are involved in various important physiological and biochemical processes in humans by affecting water and electrolyte balance, metabolic catalysis, oxygen binding, and hormone functions and are important factors for bone and membrane formation. Table 1 presents the selective mineral content of berries [19].

#### Anthocyanins

Anthocyanins are a subgroup of flavonoids that are commonly found in nature. They are widely distributed in fruits and vegetables, such as blueberries, blackberries, raspberries, strawberries, blackcurrants, elderberries, grapes, cranberries, red cabbage, red radishes, and spinach. Anthocyanins are colored pigments that act as powerful antioxidants; they are especially abundant in berries with red, blue, or purple pigments. These colors have been associated with a lower risk for certain cancers, urinary tract health, improved memory, and normal aging. Along with fresh berries, a variety of berry products such as juice, wine, jam, and food colorants (extracted from grape skin, blackcurrants, and other plant materials) contribute significantly to the intake of anthocyanins [20]. There is considerable current interest in the possible health effects of anthocyanins in humans owing to their potential antioxidant effects and their reported positive effects on blood vessels. More intensive use of berry anthocyanins as food colorants as well as antioxidants is an interesting prospect for the food scientist. Anthocyanins are important in the food industry, being regarded as potential replacements for synthetic food colorants, and in human nutrition as agents that protect against some diseases [21]. Anthocyanins from berries have extensively been examined for their effects on mouse model of endotoxin-induced uveitis (EIU) that shows retinal inflammation, as well as uveitis, by injecting lipopolysaccharide. Anthocyanin-rich berry extract prevented the impairment of photoreceptor cell function, as measured by electroretinogram. At the cellular level, he found that the EIU-associated rhodopsin decreased and the shortening of outer segments in photoreceptor cells was suppressed in the berry extract-treated animals. Moreover, the extract prevented both STAT3 activation, which induces inflammation-related rhodopsin decrease, and the increase in interleukin-6 expression, which activates STAT3. In addition to its anti-inflammatory effect, the anthocyanin-rich berry extract ameliorated the intracellular elevation of reactive oxygen species (ROS) and activated nuclear factor-kB, a redox-sensitive transcription factor. These findings strongly suggest that anthocyanins are absorbed and display several physiological activities and health benefits. Oral administration of berry anthocyanins may be a safe and promising supplement for patients with open angle
glaucoma in addition to antiglaucoma medication, whereas anthocyanin-rich berry extract has a protective effect on visual function during inflammation [5–10,12].

**Catechins**

A catechin is a polyphenolic antioxidant found in berries as a major phytochemical. The most prominent dietary catechins are catechin, gallocatechin, epicatechin, epigallocatechin, epicatechin 3-gallate, and epigallocatechin 3-gallate. The term catechin also is commonly used to refer to the related family of flavonoids and the subgroup flavan-3-ols (or simply flavanols). Catechins are differentiated from the ketone-containing flavonoids such as quercetin and rutin (flavonols), which support the antioxidant defense system. Catechins found in caneberries are very similar to those found in green tea, which may contribute to cancer prevention. Catechins are more abundant in the external tissues of fruits than in the internal tissues. Additionally, catechins are more abundant in the skin than in the remainder of the fruit [22,23].

**Ellagic acid**

The presence of bioactive compounds such as flavonoids and ellagic acid derivatives makes the consumption of strawberries and other berries (raspberries, blackberries, and cranberries) suitable for potential health benefits. Ellagic acid comprises 51% of the total phenolic compounds, and it can exist as the free form, as glucosides, or linked as ellagitannins esterified with glucose. Ellagic acid is of particular interest from a dietary viewpoint as it has been reported to have antiviral, antioxidant activity, and to provide protection against cancers of the colon, lung, and esophagus [24]. Ellagic acid is a phenolic compound that is known as a potent anticarcinogen, antiviral, and antibacterial bioactive compound. Ellagic acid has been detected in many studies with fruits, nuts, and berries in which the total ellagic acid concentration was measured by analyzing the ellagic acid concentration of extracts after acid hydrolysis. In raspberries, free ellagic acid comprises only a minor part of the total ellagic acid pool and ellagitannins are the primary source of ellagic acid released by acid hydrolysis. However, many other ellagic acid-containing compounds also are present in raspberries [25,26]. There is a particular interest in ellagic acid because of evidence of its potential chemopreventive, anti-inflammatory, antioxidant, and antibacterial effects [27,28].

**Gallic acid**

Gallic acid is a potent antioxidant found in berries, black tea, and red wine. It inhibits cell proliferation and cell death in
prostate cancer cells. Gallic acid itself has a major antioxidant activity (Trolox equivalent antioxidant capacity) that is three times that of vitamin C or E, indicating that its three hydroxyl groups can function independently as electron acceptors. Its derivatives, therefore, also are powerful antioxidants with free hydroxyl groups available for radical scavenging [29]. Gallic acid has cytotoxic activity in vitro against various cancer cell lines, but at levels that are unlikely to correspond to plasma concentrations that might be achieved by dietary means. Animal studies have demonstrated its hepatoprotective effect against carbon tetrachloride toxicity but at gallic acid levels that could not be expected in normal human diets. Even heavy and regular consumers of foods rich in hydroxyl benzoic acids (tea, red wine, herbs, spices, berries) consume very small amounts of these substances and it would be hard to increase the dietary burden of hydroxybenzoic acids because of their strong taste and limited acceptability to most palates [30].

Quercetin

Quercetin is one of the most abundant flavonoids in fruits and vegetables. Raspberries contain quercetin gluconide,
which has a rich history in folk medicine as a cold and flu remedy or as a diuretic and antiinflammatory. Quercetin is a potent antioxidant that has additional important biologic, pharmacologic, and medicinal properties, which inhibits human platelet aggregation in vitro. It exhibits potential anticancer properties, the first one by inducing cell differentiation, the second one, as its glycoside, by inhibiting protein tyrosine kinase [10,31].

**Tannins**

Tannins are an important component of berry fruits. In berry fruits, the largest quantity of condensed tannins with a high degree of polymerization is found in the chokeberry. Small quantities of tannins are found in the honeyberry and the blackberry [32,33]. They comprise both condensed non-hydrolysable tannins, known as proanthocyanidins, and esters of gallic acid and ellagic acid defined as hydrolysable tannins. Tannins play an essential role in shaping the sensory properties of fruit and fruit products. They are responsible for the tart taste and for changes in the color of fruit and fruit juice [34,35]. The tart taste results from the interactions among tannins, the proteins of mucous membranes, and gustatory receptors. As enzyme inhibitors, tannins decrease the nutritive value of some plant products. In fruits rich in anthocyanins, tannins stabilize anthocyanins by binding to them to form copolymers. Most fruits contain condensed tannins. Hydrolysable tannins (derivatives of gallic and ellagic acids) are less frequently encountered and have been found in strawberries, raspberries, and blackberries [36,37].

**Aroma and volatile compounds**

The aroma of the blackberry is one of the major characteristics affecting quality in either fresh or processed fruits. Certainly, the balance of acid and sugar is directly related to the delicate flavors in fruits. The volatile compounds responsible for fruit flavor are biosynthesized through metabolic pathways during ripening, harvest, postharvest, and storage; they also depend on many factors related to the species and the type of technological treatment [38]. Although blackberry has been widely planted, the study of blackberry flavor is still very limited. The major volatile includes 2-heptanol, p-cymen-8-ol, 2-heptanone, 1-hexanol, a-terpineol, pulegone, 1-octanol, isoborneol, myrtenol, 4-terpineol, carvone, elemicin, and nonanal. Furfural and its derivatives were also found to be abundant in some blackberries [39]. Ethyl 2-methylbutanoate, ethyl 2-methylbutanoate, 2,5-dimethyl-4-hydroxy-3-(2H)-furanone, 2-ethyl-4-hydroxy-5-methyl-3-(2H)-furanone, 4-hydroxy-5-methyl-3-(2H)-furanone, 4,5-dimethyl-3-hydroxy-2-(5H)-furanone, and 5-ethyl-3-hydroxy-4-methyl-2-(5H)-furanone, dimethyl trisulfide, linalool, and methional are the major aroma compounds in blackberries [40,41]. The comparative account on total phenolics, flavonoids, and anthocyanins content of berries (mg/g fresh weight) is given in Table 2.

**Health benefits**

From research labs worldwide there is growing evidence that berries are an important part of a healthy diet. Various phytochemicals from berries are thought to be antioxidants, which help to protect the body against various diseases and disorders and the damaging effects of free radicals, which results in chronic diseases that are associated with aging. Berries are the source of many naturally occurring antioxidants, such as various flavonoids, phenolic acids, and vitamins C and E. The high tannin content and the resultant antiseptic properties of berries make them good for tightening tissues as well as treating minor bleeding. Because berries are rich in antioxidants, they help the body to fight free radicals and thus to avoid various types of cancer. The anthocyanins (pigments that account for their attractive colors) are among the most studied berry phenolics [8,10]. Anthocyanins have a wide range of bioactivities including antioxidant, anticancer, and anti-inflammatory properties. However, advances in tannin/polyphenol research have increased our knowledge of the roles that these large molecules play in human health [42,43]. In fact, among commonly consumed berries, blueberries and cranberries contain predominantly proanthocyanidins, whereas blackberries, black raspberries, red raspberries, and strawberries contain predominantly ellagitannins. Therefore, the class (and specific chemical structures) of tannins present in a particular berry type may contribute significantly to the unique biological properties. For example, the bacterial anti-adhesive properties observed for the cranberry appears to be unique among berry fruits. This property is due to its oligomeric proanthocyanidins, which possess an A-type structural linkage. Similarly, the distinct biological effects observed for blueberries (a proanthocyanidin-rich fruit) and strawberries (an ellagitannin-rich fruit) on neuronal function and behavior in aging animals may be due to the effects of the individual classes of tannins in different regions of the brain [44,45]. Berry phenolics are best known for their ability to act as antioxidants, but the biological activities exerted by berry phytochemicals in vivo extend beyond antioxidation. In fact, a large and growing body of evidence shows that berry phytochemicals regulate the activities of metabolizing enzymes; modulate nuclear receptors, gene expression, and subcellular signaling pathways; and repair DNA oxidative damage, and more. However, berry phenolics are extensively metabolized and also further converted by the colonic microflora into related molecules. These compounds may persist in vivo, accumulate in target tissues, and contribute significantly to the biological effects that have been observed for berry fruits [46,47]. Raspberries, like blueberries, cranberries, and strawberries contain a good deal of vitamin C, which is helpful for development of strong connective tissues and provides protection to the immune system from attacks of various pathogenic microorganisms. Raspberry juice is not enough to cure all disorders and diseases but the bioactive compounds present in the berries play an important role in preventing many diseases. These substances include phenolic acids, flavonoids, vitamins, minerals, and nutrients. The phytochemicals from berries such as raspberries, cranberries, strawberries, and blueberries contain bioactive compounds that could prevent infections of microorganisms in the liver, bladder, or kidney; inflammation; or cancer. Bioactive compounds from berries could also possibly block the entry of microorganism by preventing them from adhering to the human cells that line the walls of the liver, kidneys or urinary tract [48]. Raspberry and its isolated compounds like lutein, vecetin, quercetin, and rutin play an important role for development of normal vision in human beings. The pigments from raspberries, cranberries, strawberries, and blueberries are responsible for the prevention of the development of many types of disorders and diseases in humans and may be responsible for their blue and red hue. The berries' fruits and leaves can be used to relieve sore mouths, sore throats (soothing), nausea, aphtha, stomatitis, diabetes, diarrhea, cancer, inflammation, and dysentery [49,50] (Fig. 2 and Table 3).
Nutrition and aging

Berries, along with other colorful fruits and vegetables, test high in their ability to subdue free radicals. These free radicals, which can damage cell membranes and DNA through a process known as oxidative stress, are blamed for many of the dysfunctions and diseases associated with aging. Although blueberries themselves are not a cure all, they contain a number of substances that have health benefits. These substances include, but are not limited to, fructose, fiber, vitamins, and antioxidants. Antioxidants thus far seem to have the most conclusive role in the prevention or delay of cancer, heart disease, and diseases of the aging process. However, only a limited number of studies, especially long-term studies of humans, are available. Blueberries are a source of vitamins, minerals, dietary fiber, phenolics, and flavonoids. They are very low in fat and sodium. Research findings by nutritionists from laboratories worldwide agree that there are health benefits to be derived by eating raspberries [51,52].

Antioxidant properties

Phytochemicals such as flavonoids and other phenolics may have antioxidant activity that helps protect cells against the oxidative damage caused by free radicals. Recently, there has been increasing attention given to the health benefits of consuming berries such as blueberries [18]. Antioxidants are thought to help protect the body against the damaging effects of free radicals and the chronic diseases associated with the aging process. Fresh fruits, including blueberries, and vegetables contain many of these naturally occurring antioxidants such as anthocyanins, vitamins C and E, which exhibit antioxidant activity and inhibit low-density lipoprotein (LDL) oxidation [53]. One study reported that blueberries possess considerably high antioxidant activity that is attributed in part to their anthocyanin content [54]. Other studies have assessed the antioxidant activity of berries, including black and red raspberries, by measuring the superoxide scavenging activity [55]. Extracts of berries of several cultivars of blackberries, black and red currants, blueberries, and black and red raspberries showed a remarkably high scavenging activity toward chemically generated superoxide radicals [56]. Blackcurrants were highly active toward xanthine oxidase, possibly due to their high anthocyanin and polyphenol content. By using an artificial peroxyl radical model system, the extract of fresh strawberries had a greater total antioxidant capacity than extracts of plum, orange, red grape, kiwi fruit, pink grapefruit, white grape, banana, apple, tomato, pear, and honeydew melon. Strawberry, thorn-less blackberry, and red and black raspberry have high oxygen radical absorbance activity against peroxyl radicals. Antioxidant activities can vary among berry cultivars [57].

Anticancer properties

Numerous in vitro studies have demonstrated activity of various berry extracts against different aspects of the tumorigenic process and proved that the diets high in fruits and vegetables protect against cancer. Epidemiologic studies suggest that consumption of a phytochemical-rich diet, which includes fruits and vegetables, contributes toward reducing the risk for certain types of human cancers [51]. Berry bioactive phenolics impart anticancer effects through various complementary and overlapping mechanisms of action including the induction of metabolizing enzymes; modulation of gene expression; and their effects on cell proliferation, apoptosis, and subcellular signaling pathways. A large number of laboratory and animal studies have shown that berries have anticancer properties [58]. The anthocyanins present in blackberries and raspberries are important for the beneficial health effects associated with their antioxidant, anti-inflammatory, and chemopreventative

### Table 2

<table>
<thead>
<tr>
<th>Berries</th>
<th>Flavonoids</th>
<th>Phenolics</th>
<th>Anthocyanins</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blueberry</td>
<td>276</td>
<td>486</td>
<td>82–326</td>
<td>[57,90]</td>
</tr>
<tr>
<td>Blackberry</td>
<td>157</td>
<td>315</td>
<td>67–140</td>
<td>[91,92]</td>
</tr>
<tr>
<td>Cranberry</td>
<td>44</td>
<td>525</td>
<td>300</td>
<td>[45,93]</td>
</tr>
<tr>
<td>Bilberry</td>
<td>6.0</td>
<td>121</td>
<td>99</td>
<td>[74,94]</td>
</tr>
<tr>
<td>Raspberry</td>
<td>42</td>
<td>104</td>
<td>45–791</td>
<td>[95,96]</td>
</tr>
<tr>
<td>Elderberry</td>
<td>46</td>
<td>29–60</td>
<td>44</td>
<td>[97,98]</td>
</tr>
<tr>
<td>Blackcurrant</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
properties; the biological activity of black raspberry against esophageal, colon, and oral cancers has been demonstrated. It has long been established that cyanidin-3-glucoside and cyanidin-3-rutinoside are the respective major and minor anthocyanins in blackberries [2,59]. In addition to anthocyanins, these fruits are also a rich natural source of other chemopreventative phytochemicals such as flavonols, phenolic acids, ellagic acid, vitamins C and E, folic acid, and β-sitosterol. It is not uncommon for fruits or any other plant material of related species to demonstrate varying degrees of biological activities ranging from some species being totally inactive to others exhibiting exceptional activity [60].

Antimutagenic properties

Several chemical species from berry extracts have been isolated and found to possess antimutagenic activity, which block cancer cell metabolism or kill cancer cells in culture, inactivate free radicals and active oxygen species, exhibit antiestrogenic activity, and inhibit mutagenesis. The most intensively studied antimutagenic agents are the ellagitannins, especially ellagic acid [61,62]. The anticarcinogenic and anti-inflammatory effects of fruits and berries have been well documented. Several plant extracts inhibit the replication of cancer cells in culture, and many plant compounds are highly effective in pure form, the most thoroughly studied of these being from black raspberries and resveratrol [63,64]. The researchers reported that the extracts from raspberries, strawberries, and blueberries to inactivate mutagenesis by benzo[a] pyrene and cause suppression by blackberries for mutagenesis by 2-amino anthracene and found the magnitude of the effect to vary with the variety of berries grown in the same orchard under identical conditions [65,66]. The inactivation of metabolically activated carcinogens is caused by components of the berry extracts that inhibit the cytochrome P450 system responsible for converting carcinogenic compounds into forms capable of covalent binding with DNA. Less understood is the ability of blackberry extracts to inhibit ultraviolet-induced mutagenesis [67]. In addition to their effects on mutagenesis, raspberries, blackberries, and muscadine grapes almost completely inhibit the activity of the matrix metalloproteinases 2 and 9 involved in the invasion and metastasis of cancer cells. Although antioxidants can clearly protect cells from mutagenesis at the initiation stage of carcinogenesis, their role in the destruction of transformed cells is less clear [68]. Boivin and others (2007) measured the antioxidant activity and anti-proliferative activities of berries and found red raspberries to be

![Berry phenolics and flavonoids and their biological activities.](image-url)
among the most effective in blocking proliferation of different types of cancer cells. However, they found no correlation between antioxidant activity and the ability to inhibit cancer cell replication [60]. Likewise, Liu and others (2002) found no correlation between antioxidant activity and antiproliferative activity when comparing four different varieties of raspberries. In addition to its antioxidant effect, each extract also contains numerous compounds that can affect cell survival and replication by interacting with different replicative and metabolic pathways [69].

Table 3
Comparative account on bioactive components and biological properties of berries

<table>
<thead>
<tr>
<th>Berries</th>
<th>Phytochemicals</th>
<th>Biological Properties</th>
<th>References</th>
</tr>
</thead>
</table>
| Blueberry | - High in antioxidants, vitamin C, B complex, E, and A  
- High in selenium, zinc, iron, and manganese. Contains β-carotene, lutein, and zeaxanthin | Anticancer, anti-inflammatory, anti-diabetic. Prevents weight loss, macular degeneration. Helps prevent Alzheimer’s disease; reverses signs of aging; protects and enhances circulation; reduces cholesterol. | [90,100] |
| Blackberry | - High in antioxidants, polyphenols, manganese, folate, fibers, cyaniding-3-O-glucoside, and vitamin C.  
- Contains salicylate and high tannin. | Fights free radical damage; antiseptic, antibacterial/viral, anticancer; reduces cholesterol; delays process of aging; is an analgesic and pain reliever; provides strength to blood vessels. | [101,102] |
| Cranberry | - High in vitamins C, A, calcium, iron, folate, magnesium, and manganese.  
- Contains higher percentage of phenolics than other berries studied. | Antibacterial, antiseptic, and diuretic; aids digestion; removes fats from lymphatic system; and promotes cardiovascular health. | [103,104] |
| Bilberry | - High in anthocyanins, flavonols.  
- High in vitamins C, E, and manganese.  
- Contains carotenoid, lutein, and zeaxanthin. | Good for eyes, mouth, and gum health. Provides strength; powerful anti-inflammatory; protects blood vessels and strengthens arteries; and improves circulation. | [17,45] |
| Raspberry | - Rich in vitamins C, B, ω-3, fibers, gallic acid, ellagic acid, and acts as a strong antioxidant.  
- Contains folate, iron, potassium, copper, and lutein. | Anticancer; prevents free radical damage; antimicrobial; and increases metabolic rate, which burns fats. Great for eye health and strength. | [17,45] |
| Elderberry | - Rich in vitamins C, A, and B.  
- Contains high amounts of flavonoids and carotenoids.  
- High in calcium and iron. | Protects DNA damage from free radicals; aids in arthritic conditions; improves respiration and asthma; boosts immune system; and stimulates digestive system. | [105,106] |
| Blackcurrant | - High in anthocyanins, calcium, zinc, magnesium, potassium, vitamins A, B2, and gibberellic acids. | Anti-inflammatory, cleans and reduces blood cholesterol; stimulates digestion, the liver, pancreas, spleen, and kidneys. | [75,107] |

Antimicrobial properties

Certain berries rich in tannins have been found to increase bacterial infections. Two different types of polymeric tannins in these berries protect against pathogenic bacteria. Presence of the A-type linkage of cranberry (Vaccinium macrocarpon) proanthocyanidins may enhance both in vitro and urinary bacterial anti-adhesion activities [70]. Additionally, other tannin-containing berries may contribute to this effect, as berry juices of a mixture of cranberries (Vaccinium oxycoccus) and lingonberries as well as
cloudberry juice protect against urinary tract infection [71,72]. Among the berries, cranberries, cloudberries, red raspberries, strawberries, and bilberries possess clear antimicrobial effects against human pathogens. Berry ellagitannins are strong antimicrobial agents acting as possible anti-adherence compounds in preventing the colonization and infection of many pathogens [34,35]. The phenolic extract of cloudberry, which is comprised primarily of ellagitannins, has the strongest antimicrobial effect, followed by red raspberry and strawberry. Salmonella spp., Staphylococcus spp., Helicobacter spp., and Bacillus spp. are the bacteria that are most sensitive to berry phenolics. Additionally, the growth of Escherichia spp., Clostridium spp., and Campylobacter spp., but not the growth of Lactobacillus spp. and Listeria spp., is inhibited by berry phenolics [41,73]. Red raspberry phenolics and its ellagitannin fraction also have powerful antimicrobial properties against the growth of human colonial pathogens, Klebsiella oxytoca and Proteus mirabilis [74]. Several mechanisms of action in the inhibition of bacteria are involved, such as destabilization of cytoplasmic membrane, permeabilization of plasma membrane, inhibition of extracellular microbial enzymes, direct actions on microbial metabolism, and deprivation of the substrates required for microbial growth [34,35]. The berry extracts inhibited the growth primarily of gram-negative bacteria but had no effect on gram-positive bacteria. However, there is very little information about the antimicrobial capacity of phenolics present in berries, except in cranberry. Extracts of the aerial parts of bearberry and lingonberry were active against the gram-negative bacteria E. coli and P. vulgaris. The activity is known to be due to the phenolic glycosides arbutin and methylarbutin. Cloudberry, raspberry, and strawberry extracts were the strongest inhibitors of gram-negative bacteria, especially Typhimurium [73,75]. Ellagic acid inhibits a range of pathogenic organisms including Vibrio cholerae, Shigella dysenteriae, and Campylobacter spp. It can be hypothesized that ellagitannins could be one of the components in cloudberries, raspberries, and strawberries causing the inhibition against Salmonella. The antimicrobial effects of berry extracts against gram-negative bacteria decreased in the following order: cloudberry > raspberry > strawberry > lingonberry > blueberry > cranberry > sea buckthorn berry > blackcurrant [41,76].

Anti-inflammatory properties

There are many health benefits of consuming berries, such as blueberries that contain anthocyanins, the flavonoid pigment responsible for their red to bluish hue. Anthocyanins exhibit antioxidant activity and inhibit oxidation of LDL. They also have vasoprotective and anti-inflammatory activity. Anthocyanin-rich extracts from European berries such as the bilberry (Vaccinium myrtillus) have been sold commercially to treat microcirculation disease and to maintain normal vascular permeability [77]. Extensive pharmacologic and clinical studies have demonstrated that flavonoids are the active substances that are largely responsible for the action of the drug. The main pharmacologic activities of berries are primarily cardiovascular ones, including cardiotoxic, antiarrhythmic, hypotensive, and hypolipidemic effects [78]. Raspberry phytochemicals beneficially modulate enzyme activity, cellular pathways, and gene expression. In addition to reducing oxidized-LDL formation via their antioxidant activity, raspberry phytochemicals have demonstrated anti-atherosclerotic and anti-inflammatory activities, which may provide protection against cardiovascular diseases [79]. Many studies have demonstrated the ability of raspberry phytochemicals to reduce cancer cell growth in vitro. Anthocyanins have the ability to down-regulate cyclooxygenase-2 expression and enzyme activity, a mechanism for its antiproliferative actions on many different human cancer cell lines [31,80]. In contrast, ellagic acid’s mechanism for its antiproliferative actions across many different human cancer cell lines is via induction of apoptosis. Despite the antiproliferative activities of both anthocyanin and ellagic acid, it is the ellagitannin fractions that mostly account for this biological effect by red raspberry extracts. In vitro studies also have found phytochemicals from black raspberry extracts to be effective in reducing vascular endothelial growth factor expression, a promoter of angiogenesis, which is a critical step for tumor metastasis [81,82].

Neuroprotective properties

Foods and food ingredients, in particular components chemically classified as antioxidants, have been reported to exert a beneficial effect in neurodegeneration. In the developed world, life expectancy is increasing, with a concomitant increased incidence of many age-related diseases, such as cancer, cardiovascular troubles, and neurodegeneration [83,84]. Substantial evidence supports the hypothesis that oxidative stress plays a major role in the pathogenesis of neurodegenerative disease. Oxidative stress is generally caused by the excessive accumulation of ROS in cells and has been implicated in the development of many neurodegenerative diseases, including Parkinson’s disease, Huntington’s disease, amyotrophic lateral sclerosis, and Alzheimer’s disease [85,86]. Behavioral studies in rodents have revealed an attenuation of brain aging when strawberries, blueberries, or blackberries are ingested. Evidence is increasing that these phytochemicals, and by association the foods, have beneficial effects on human health and reduce the risk of cardiovascular disease and type 2 diabetes [87,88].

Conclusion

This review demonstrates that a number of in vitro and in vivo studies, using cell cultures of animal and human cells, have suggested that bioactive compounds of berries positively show an effect on human health. The presented characteristics of various berry fruits point to vast differences in the type of their bioactive compounds; such differences are observed with regard to both the content and the qualitative composition of those compounds. The most significant health benefits are ascribed to phenolic compounds and vitamin C, which result mostly from antioxidant, anticancer, antimutagenic, antimicrobial, anti-inflammatory, and neuroprotective properties. The use of all these biological activities presented in this review related to berry bioactive phenolics and flavonoids might promote the development of alternative berry compounds for the prevention and control of various diseases and disorders. This issue will be critical for future research priorities that may offer numerous opportunities for berries to be used in the food industry and medicine and will provide a wide range of health benefits. Further research is needed on this subject regarding the issues related to plant breeding and genetic approaches at the interface with the synthesis of compounds for nutrition and health purposes should receive more emphasis and attention.

Acknowledgments

This work was supported by a grant from Bio-Green 21 Program (No. PJ009074), Rural Development Administration, Republic of Korea.
References


