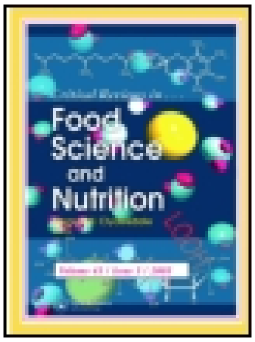

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# Antioxidant and anticancer properties of berries

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# Antioxidant and anticancer properties of berries

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## Abstract

The enduring relationship between dietary patterns and human health has led us to investigate the bioactive components present in fruits and vegetables for a very long time. Berries, notably the popular ones such as strawberry, raspberry, blueberry, blackberry and the Indian gooseberry, are among the best known dietary sources due to the presence of a wide range of bioactive nutritive components. Bioactive components in berries include phenolic compounds, flavonoids and tannins apart from vitamins, minerals, sugars and fibers. Individually or synergistically these have been shown to provide protection against several disorders. Mounting evidence suggests that consumption of berries confer antioxidant and anticancer protection to humans and animals. Free radical scavenging, protection from DNA damage, induction of apoptosis, and inhibition of growth and proliferation of cancer cells are just to name a few. This review comprehensively



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summarizes the key phytochemicals present in berries and their biological action in preventing oxidative stress and carcinogenesis.

**Keywords**

strawberry, raspberry, blackberry, blueberry, Indian gooseberry, anticancer

 

## Introduction

The earliest evidence of cancer was found in ancient Egyptian mummies and manuscripts dating back to 3000 B.C. The word ‘cancer’ was coined by the Greek physician Hippocrates (460-370 BC) to describe carcinoma tumors. The uncontrolled growth, proliferation and spread of abnormal cells in the human body results in the formation of cancer (Feitelson et al., 2015; Otto & Sicinski, 2017). It is now the second leading cause of mortality with 14.2 million new cases and 8.2 million deaths. It was estimated that by the end of 2030, the global burden is expected to rise to 21.7 million new cases with deaths of 13 million (American Cancer Society, 2015). Since cancer prevalence is increasing at an alarming rate in both developed and developing countries, it has become a major health concern worldwide. Altered genes, use of tobacco, unhealthy diet, lack of physical activity, and exposure to harmful radiations are some of the leading causes of cancer. The close association between cancer prevention and healthy diet has been attributed to the presence of chemopreventive and antioxidant properties of fruits and vegetables (Béliveau & Gingras, 2007). Fruits, especially berries, are excellent sources of natural antioxidants and represent an important component of healthy diet. Consumption of fruits in sufficient amount reduces the risk of major chronic diseases like cancer, type 2 diabetes mellitus, obesity and cardiovascular disorders (Skrovankova et al., 2015). World Health Organization (WHO) guidelines recommend a minimum intake of 400 gm of fruits and vegetables every day to provide protection from several serious diseases and also to alleviate micronutrient deficiencies (World Health Organization, 2003). Numerous studies have shown that bioactive components in berries possess anticancer, antidiabetic, antiinflammatory, antimicrobial and antioxidant properties (Puupponen-Pimiä et al., 2001; Nohynek et al., 2006; Seeram et al., 2006; Heinonen


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M. 2007; Bowen-Forbes et al., 2010; Joseph et al., 2014; Sheik Abdulazeez 2014; Huang et al., 2014; Khalifa et al., 2015; Skrovankova et al., 2015). These beneficial properties of berries are directly associated with the high amount of diverse groups of phytochemicals present in these fruits. Berries are normally consumed fresh or in frozen/processed form (Nile & Park, 2014). Apart from vitamins, minerals, sugars and fibers, they are rich in bioactive compounds including phenolics, flavanoids, and tannins. These phytochemicals have been reported to possess anticancer and antioxidant activities (Castro & Teodoro, 2015). The antioxidant mechanism involves the scavenging of reactive oxygen species (ROS) that can cause oxidative damage to cellular macromolecules including DNA, RNA, proteins and lipids. Thus accumulation of oxidative DNA damage promotes the formation of tumor and a growing body of evidence supports the fact that oxidative stress is one of the major reason for enhancing carcinogenesis (Sosa et al., 2013). Studies indicate that antioxidant effect of berries are directly associated with its anticancer potential (Juranic & Zizak, 2005). Some of the most commonly cultivated and consumed berries include strawberry (*Fragaria* × *ananassa*), raspberry (*Rubus idaeus*), blueberry (Cyanococcus), blackberry (Rubus) and Indian gooseberry (*Emblica officinalis*). These berries are highly recommended because the effects of their antioxidant compounds on human health have been explored by various *in vitro* and *in vivo* studies (Skrovankova et al., 2015; Juranic & Zizak, 2005). *In vitro* and *in vivo* studies of berries as antioxidant and anticancer agents have furthered our understanding of the underlying mechanism and its effect on human health and diseases. Therefore, the current review comprehensively summarizes what is currently known about the phytochemical composition and the antioxidant and chemopreventive potential of these berries.

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## Berries

### *Strawberry*

Strawberry (wild: *Fragaria virginiana*, cultivated: *Fragaria × ananassa*) is an important fruit belonging to the Rosaceae family and is widely consumed due to their high nutrient and fiber content (Seeram, 2007). They are a rich source of essential micronutrients such as minerals, vitamin C, folates and various antioxidant components, which makes them important for human nutrition. Strawberry is one of the richest sources of vitamin C and folates among fruits and the former constitutes up to 80mg/100g and the latter is in the range of 20 to 25mg/100gm fresh fruit weight (Giampieri et al., 2012; Sapei & Hwa, 2014). It is also a good source of minerals such as manganese, potassium, iodine, magnesium, iron, phosphorous and copper (Giampieri et al., 2012). Beside this, it contains a remarkable combination of polyphenolic phytochemicals such as flavonoids, phenolic acids, stilbenes, lignans and tannins (Giampieri et al., 2012; Giampieri et al., 2014). These bioactive constituents of strawberries act as natural antioxidants by neutralizing or scavenging free oxygen radicals, decreasing ROS concentration and preventing DNA damage (Giampieri et al., 2014).

### *Raspberry*

Raspberry (Rubus sp.) belongs to the Rosaceae family and are edible fruits with attractive color and a unique flavor. The two main types of raspberries are red raspberry (*Rubus idaeus*) and black raspberry (*Rubus occidentalis*). Different cultivars and varieties of raspberries are grown worldwide, primarily in Europe, North America and the North and West of Asia (Strik, 2007). They contain a rich blend of phytochemicals particularly, ellagitannins and anthocyanins and also contain a variety of beneficial compounds including essential minerals, vitamins, dietary fiber, potassium and fatty acids (Rao & Snyder, 2010; Probst, 2015). They are an excellent source of vitamin C which is available at a concentration of around 32mg/100g of the fresh fruit weight (de Ancos et al., 2000). Red raspberries are economically important and widely consumed than black raspberries, which are less commonly grown.

*Blackberry*

Blackberry (*Rubus fruticosus L.)* belongs to the family of Rosaceae and are also a rich source of minerals, essential vitamins, such as vitamin A and B, calcium and polyphenolic compounds such as anthocyanins and ellagic acid. These have been grown in Europe for thousands of years and are cultivated from mid-south United States to northern Canada. The medicinal property of blackberries has been known amongst Europeans since the 16$^{th}$ century. Blackberry juice was used to treat infections of the mouth and the eye (Kaume et al., 2012). Blackberries contain minerals, vitamins and carbohydrates other than polyphenolic compounds. The primary sugars in blackberries are glucose and fructose and are present in ratio ranged from 0.81 to 1.17 g/100g fresh fruit (Fan-Chiang & Wrolstad, 2010). They are high in antioxidant radical scavengers and have been known to play a role in reducing cancer risk, cardiovascular and other related diseases.

*Blueberry*

Blueberry (*Vaccinium ssp*.) belongs to the Ericaceae family and are native to North America. It is now grown commercially in the Americas, Australia and Europe (Mainland, 2012). Blueberries consist of a large array of bioactive compounds that include polyphenols, phenolic acids, and stilbene derivatives (Jones, 2016). Beside these compounds, blueberries are a good


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source of dietary fiber that constitute 3%-3.5% of fruit weight and a moderate source of vitamin C, which constitute 10mg/100g of fresh fruit weight (Michalska & Łysiak, 2015). Antioxidant compounds in blueberry can been known to reduce the risk of coronary, cardiovascular and neurodegenerative diseases (Michalska & Łysiak, 2015).

*Indian gooseberry*

Indian gooseberry (*Phyllanthus emblica* L.) also known as *Emblica officinalis* or Amla belongs to the family Euphorbiaceae and is widely cultivated in the tropical and subtropical areas of China, India and south-east Asia (Sahni, 1998; Singh et al., 2012). It possesses several pharmacological properties including antioxidant and chemoprotective activities (Mayachiew & Devahastin, 2008). Amla has been used in several preparations in Ayurveda, the traditional Indian form of herbal treatment, for treating various illness including cancer. It is highly nutritious and is an excellent dietary source of vitamin C with an average content of 600 mg/100 gm in the fruit pulp (Jain & Khurdiya, 2004 Guo & Wang, 2016). It contains minerals like phosphorous, iron and calcium and various bioactive compounds such as flavonoids, tannins and alkaloids (Barthakur et al., 1991).

**Nutrient composition of berries**

In addition to the valuable phenolic compounds, berries contain natural compounds including carbohydrates, essential vitamins, dietary fibers and minerals (Table 1). Berries are rich in sugars with fructose being the main sugar form but are low in calories and lipids. They, especially raspberry, blackberry and Indian gooseberry are good source of dietary fibers. The amount of vitamin C, potassium and folates in these berries exhibit substantial health benefits. The range of vitamin C was reported to be between 9.7 to 600 mg/100g among these berries - blueberry had the lowest while Indian gooseberry had the highest. Strawberries are excellent source of vitamin C and is a good source of folate (vitamin B9) and potassium. Among the five berries, raspberries are rich in dietary fibers and also a good source of minerals such as potassium, phosphorous, magnesium, manganese and vitamins such as vitamin C and K. Blackberries contain higher amount of beta-carotene and is equivalent to raspberry and blueberry in vitamin K content. Blueberries are high in sugars and vitamin K. Indian gooseberry has been shown to possess the highest vitamin C content among these fruits; around ten times than strawberries (Jain & Khurdiya, 2004; Tarwadi & Agte, 2007).

**Phytochemicals**

Phytochemicals or secondary metabolites are group of compounds synthesized by plants in response to specific environmental stimuli, pathogen attacks, or nutrient deprivation (Kennedy & Wightman, 2011). Berries are excellent sources of these bioactive components that are believed to hold a broad spectrum of biomedical functions including antioxidant and anticancer properties.

Phytochemicals in strawberry include an extensive class of phenolic compounds including flavonoids, mainly anthocyanins, followed by hydrolyzable tannins and phenolic acids such as hydroxybenzoic acids and hydroxycinnamic acids (Seeram et al., 2006; Giampieri et al., 2012). Anthocyanins are quantitatively the most important polyphenolic compound in strawberries. The quantitative determination of anthocyanin content in strawberries was conducted by several studies and it ranges from 150mg/kg to 600 mg/kg of fresh fruit weight. (Clifford & Scalbert, 2000, da Silva et al., 2007; Jakobek et al, 2007; Horbowicz et al., 2008). These compounds are responsible for the red color of strawberries and have been identified as glycosides of pelargonidin and cyanidin. More than 25 distinct anthocyanins have been identified in different strawberry varieties and selections using HPLC coupled to diode array and MS detection. Pelargonidin-3-glucoside is the major anthocyanin in strawberries that constitutes about 77-90%, followed by pelargonidin-3-rutinoside which constitutes 6-11% (da Silva et al., 2007). Similarly, in another study, pelargonidin 3-glucoside (347.8 mg/100gm) was found to be the principal anthocyanin in strawberry followed by pelargonidin-3-rutinoside (52.4 mg/100g) (Marhuenda et al, 2016). However, the presence of cyanidine-3-glucoside seems constant in strawberry varieties independent of genetic and environmental factors. Glucose and rutinose are the common substituting sugars in anthocyanins although arabinose and rhamnose conjugates were also identified in some strawberry cultivars (da Silva et al., 2007). Acylated anthocyanins with different aliphatic acids such as acetic, malic, malonic and succinic acids were also reported (Giusti et al., 1999). Hydrolysable tannins are another group of phenolic compounds in strawberries along with raspberries and blackberries. Ellagitannins are the major group of compounds among hydrolyzable tannins and they consist of glucose esterified with hexahydroxydiphenic acid and gallic acid (Maatta-Riihinen et al., 2004; Aaby et al., 2005; Seeram et al., 2006; Hukkanen et al., 2007; Buendía, et al., 2010). The total ellagitannin content in strawberries has been reported as 75.4mg/100g of fresh weight in one study (Koponen et al., 2007) while another summary put this between 25 to 59mg/100g (Giampieri, et al., 2012). Galloyl-bis-HHDP-glucose moieties and ellagic acid glycosides are the major ellagitannin constituents present in strawberries (Seeram et al., 2006). Koponen et al reported that the total


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ellagic acid content in strawberry varies with cultivars and seasons and it typically ranges from 68.3 to 85.3 mg/100g (Koponen et al., 2007). The main flavonols identified in strawberries are glucosides and glucoronides of quercetin and kaempferol. Other phenolic compounds present in strawberries include hydroxybenzoic and caffeic derivates, esters of hydroxycinnamic acids, especially of p-coumaric acid ellagic acid and ellagic acid glycosides (Aaby et al., 2005; Buendía et al., 2010). Besides these compounds strawberries are rich in volatile compounds that are responsible for its flavor and aroma. It was estimated by gas chromatography and mass spectrometry that the majority of volatile compounds were esters (49.4%), aldehydes and alcohols (27.6%) followed by furans, terpenes and ketones (23.0%) (Schwieterman et al., 2014).

In red raspberries, anthocyanins and hydrolyzable tannins, particularly, cyanidine glycosides and ellagitannins are the most abundant phenolic compounds. Mullen et al. reported eleven anthocyanins in red raspberries in which cyanidin-3-sophoroside and cyanidin-3-($2^G$-glucosylrutinoside) and cyanidin-3-glucoside were the most abundant (Mullen et al., 2002). The total anthocyanin content, however, appears to vary depending on the study. The average anthocyanin content in red raspberries reported in one study was 92.1 mg/100g of fresh fruit of which 98% were cyanidins and 2% were pelargonidins (Bowen-Forbes et al., 2010). Another study by Jakobek et al used pH-differential and Folin-Ciocalteau method to examine the total anthocyanin content in red raspberry. The study reported that the total anthocyanin content in red raspberry fruit extract was only 24.3 mg/100g (Jakobek et al, 2007). Several studies have also attempted to quantify the ellagitannin compounds in raspberries. The most common ellagitannins present in red raspberries are lambertianin C and sanguiin H-6 and the actual content varies according to the cultivar and ranges 360-750mg/kg for sanguiin H-6 and 280-630 mg/kg for

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lambertianin C (Gasperotti et al., 2010; Klewicka et al., 2016). The average content of ellagitannin reported in red raspberries is 297.3 mg/100 g of fresh fruit. Flavonoids and flavonols identified in red raspberries include quercetin 3-glucoside, quercetin 3-rutinoside, quercetin 3-glucuronide and kaempferol glucuronide conjugates (Mullen et al., 2002; Sariburun et al., 2010). The abundant flavan-3-ols present in red raspberry are (-)-epicatechin and (+)-catechin with lesser amounts of gallocatechins (Sariburun et al., 2010). Five anthocyanins have been identified and characterized in black raspberry - cyanidin 3-glucoside, cyanidin 3-rutinoside, cyanidin 3-sambubioside, cyanidin 3-xylosylrutinoside and pelargonidin 3-rutinoside (Nybom, 1968; Torre & Barritt, 1977; Tian et al., 2006; Tulio et al., 2008). Cyanidin-3-rutinoside and cyanidin-3-xylosylrutinoside are the predominant ones with the former constituting 20-40% and the latter 49-58% of the total anthocyanins in black raspberries (Tulio et al., 2008). It was observed that among raspberry cultivars, black raspberries (upto 400mg/100g) have a higher anthocyanin content than red, orange and yellow raspberries (Bowen-Forbes et al., 2010). Red and black raspberries have been shown to have a high amount of hydrolyzed ellagic acid than other fruits and nuts (Wu et al., 2006). Apart from these nutraceutical compounds, volatile compounds in raspberries also play a major role in their flavor and aroma. Concentrations of these compounds are influenced by various factors including climatic changes, cultivar variation, and ripeness of the fruit. The main volatile compounds in this berry include monoterpenes, acids, alcohols, esters, aldehydes, ketones, hydrocarbons, C-13 norisopernoids, lactones, sesquiterpenes, furans, sulphur and phenols (Aprea et al., 2015).

Blackberries are an important source of antioxidants due to the high content of phenolic compounds such as anthocyanins, ellagitannins, flavonols and flavanols (Cho et al., 2004;

Zadernowski et al., 2005; Wu et al., 2006). The total blackberry phenolics range from 114 to 1056 mg/100 g of fresh fruit (Kaume et al., 2012). Flavonoids, mainly anthocyanins, and hydrolyzable tannins, mainly ellagitannins, are the major phenolic compounds present in blackberry. Anthocyanins of blackberry are responsible for the color and are present mainly as cyanidin derivatives with sugar moeities glucose, rutinose, xylose or arabinose attached to the C3 carbon. The major anthocyanins identified in blackberry include cyanidin 3-glucoside, cyanidin 3-galactoside, cyanidin 3-xyloside, cyanidin 3-dioxalyl-glucoside, cyanidin 3-rutinoside, cyanidin 3-sophoroside, cyanidin 3-glucosylrutinoside, cyanidin 3-arabinoside, malvidin 3-arabinoside, pelargonidin 3-glucoside, cyanidin 3-(3-malonyl)glucoside, and cyanidin 3-(6-malonyl) glucoside. Total anthocyanin content in six blackberry genotypes range from 114.39 to 241.54 mg/100 mg of the fruit (Cho et al., 2004). This content range agrees with another study by Sellappan and colleagues which reported an average total anthocyanin content of 116.59 mg/100 g of fresh fruit (Sellappan et al., 2002). Another study by Oszmiański et al detected thirty four different phenolic compounds from twenty three different wild blackberry fruit samples which includes 8 anthocyanins, 15 flavonols, 3 hydroxycinnamic acids, 6 ellagic acid derivatives and 2 flavones (Oszmiański et al, 2015). Ellagitannins are the major hydrolyzable tannins in blackberry with sanguiin H-6 and lambertianin C being the predominant ones representing 67% of total ellagitannins (Hager et al., 2008; Gasperotti et al., 2010). Gasperotti et al reported the identification of 11 ellagitannins from the flesh, seed and torus of Apache cultivar of blackberry through high-performance liquid chromatography analysis. Blackberries contain an average 108 mg/100 mg of ellagitannins and 20 mg/100 mg of ellagic acid conjugates (Gasperotti et al., 2010). Free ellagic acid represents 37% of total ellagic acid conjugates in blackberry and are present at a concentration slightly higher than its conjugates (Gasperotti et al., 2010). Hydroxybenzoic acids and hydroxycinnamic acids are the major group of phenolic acids present in blackberry (Schuster & Herrmann, 1985). It contains a significant amount of flavonols as well present mostly in the glycosylated form. Cho et al reported that the level of flavonol in six blackberry genotypes range from 10.20 mg/100 mg to 16.02 mg/100 mg of fresh fruit. Quercetin 3-glucoside and quercetin 3-galactoside were the predominant flavonol in the varieties studied (Cho et al., 2004). Apart from these compounds, the flavor and aroma of these berries were determined by the presence of volatile compounds like 2-heptanol, p-cymen-8-ol, 2-heptanone, 1-hexanol, α-terpineol, pulegone, 1-octanol, isoborneol, myrtenol, 4-terpineol, carvone, elemicine, and nonanal (El Hadi et al., 2013; Jacques et al., 2014).

Blueberries are a rich source of natural phenolic compounds with an average of 300mg/100g of fresh fruit. The total phenolic compounds present in blueberries vary depending on the cultivar, environmental conditions and maturity (Sellappan et al., 2002). Phenolic acids, flavonoids, polyphenols, anthocyanins, procyanidins, chlorogenic acid, ascorbic acid, quercetin, kaempferol, catechin, epicatechin, p-coumaric acid, gallic acid, caffeic acid, ferulic acids and hydroxycinnamic acid are the major bioactive components that are present in this fruit. These compounds contribute to the major health promoting function of these fruits (Huang et al., 2012; Nicoletti et al., 2015). Anthocyanin content in blueberry was shown to be around 212 mg/100 g of fresh fruit and occurs mainly in glycosylated forms with sugar moieties such as glucose, galactose and arabinose attached to C3 carbon. Cho et al. reported the total anthocyanin content of five blueberry genotypes range from 143.52--822.73 mg/100 mg (Cho et al., 2004). The anthocyanin level in blueberry depends on size, ripening stage, environmental and storage conditions and are mainly found in the skin of the fruit. The common anthocyanins present in blueberry are delphinidin, malvidin, petunidin, and cyanidin that constitute 56.6%, 30.6%, 7.9%, 4.2% and 0.6% respectively (Kalt et al., 1999; Szajdek & Borowska, 2008; Yuan, 2011). The amount of anthocyanin in blueberries is considered as a marker for assessing the quality of the fruit (Routray & Orsat, 2011). The high amount of anthocyanin is an indicator of the antioxidant capability of these fruits. Using two-dimensional gas chromatography and time-of-flight mass spectrometry (HS-SPME/GC*GC-TOFMS), the highest concentration of volatile compounds present in blueberries were identified to be alcohol (51.8%) followed by ester (32.8%) and carboxylic acid (6.9%) (Dymerski et al., 2015).

Apart from being a rich natural source of vitamin C, amla contains a variety of polyphenolic compounds including tannins, flavonoids, phenolic acids and flavone glycosides. Chromatographic analysis of the juice of the *E. officinalis* fruit was used to quantify the vitamin C and other phytoconstituents including phenolic acids, chlorogenic acid and flavonoids such as myricetin, quercetin and kaempferol (Bansal et al., 2014). Amla is rich in tannins, which constitute 4% of the fresh fruit and 35% of the dried fruit powder (Jacob, et al., 1988; Wu & Zhou, 1996; Yang & Liu, 2014). These tannins include ellagitannins and gallotannins which on hydrolysis produces ellagic acid, gallic acid and glucose. The fruit, leaves and bark of amla are rich in tannins. Tannins present in the fruit include ellagic acid, glucogallin (1-O-galloyl-beta-D-glucose), pedunculagin and punigluconin (Ghosal et al., 1996; Bhattacharya et al., 1999; Puppala et al., 2012). Zhang and colleagues reported the isolation of six new ellagitannins - phyllanemblinins A, B, C, D, E and F - from the fruit juice, leaves and bark extracts. Phyllanemblinin A together with other hydrolyzable tannins 1(β)-O-galloylglucose, 1(β),6-di-O-galloylglucose, 1(β),2,3,6-tetra-O-galloylglucose, chebulanin, chebulagic acid, corilagin, elaeocarpusin, mallonin, punicafolin, putranjivain A and tercatain were isolated from 60% aqueous extract of the fruit juice. Phyllanemblinin B, C, D, E and F along with (β)-O-galloylglucose, 1(β), 4-di-O-galloylglucose, 3,6-di-O-galloylglucose, carpinusnin, corilagin, chebulanin, chebulagic acid, chebulic acid, (-)-epiafzelechin, (-)-epicatechin, epicatechin-(4βf8)-epigallocatechin, (-)-epigallocatechin, flavogallonic acid bislactone, furosin, gallic acid 3-O-β- D -glucoside, (+)-gallocatechin, gallic acid 3-O-(6′-O-galloyl)-β- D -glucoside, geraniin, mallonin, neochebulagic acid, putranjivains A and B, prodelphinidins B-1 and B-2 and prodelphinidin B-2 3′-O-gallate were isolated and identified from the fresh leaves and branches of *P. emblica* (Zhang et al., 2001). Phyllemblin is another major active ingredient present in amla with significant pharmacological properties. Bioactive flavonoids reported in amla include quercetin, kaempferol-3-O-alpha-L (6" methyl) rhamnopyranoside, kaempferol-3-O-alpha-L (5"ethyl) rhamnopyranoside (Habib ur et al., 2007). Gas chromatography studies suggest that esters are the main oxygenated volatile compounds present in *P. emblica* forming 33.26% followed by hydrocarbons (30.29%), aldehydes (20.99%), alcohols (6.28%) and ketones (5.31%) (El Amir et al., 2014).

In short, extensive studies on phytochemical composition of these berries have shown that flavonoids, mainly anthocyanins and ellagitannins are the predominant phytochemical class found in these berries. Pelargonidin-3-glucoside is the major anthocyanin seen in strawberries while cyanidines are common in red raspberries. Sanguiin H-6 and lambertianin C are the major tannins found in raspberries and blackberries. Delphinidin and malvidin are the primary anthocyanins in blueberries while *P. emblica* is rich in tannins. A summary of phytochemicals identified in berries are presented in Table 2.

**Antioxidant properties of berries**

Antioxidant property of fruits and vegetables are associated with the presence of efficient oxygen radical scavengers such as vitamin C, carotenoids and phenolic compounds. Oxygen radical absorbance capacity *(*ORAC*)* value of several fruits and vegetables have been calculated (Haytowitz & Bhagwat, 2010). Among fruits, berries rank in the top with high antioxidant capacity. A systematic screening study of the total antioxidants in a variety of dietary plants including fruits, vegetables, cereals and pulses also placed berries in the top ranked group with high antioxidant content (Halvorsen et al, 2002). The antioxidant level of berries are 4 times higher than other fruits and 10 times higher than vegetables (Giampieri et al, 2012). Within the fruit group strawberries are one of the most important sources of antioxidants and are considered as a functional fruit due to the presence of a diverse range of bioactive components and high levels of vitamin C, vitamin E, folates, phenolic compounds and fiber. They are rich in phytochemicals, specifically polyphenolic compounds consisting of aromatic rings with one or more hydroxyl groups (Dai & Mumper, 2010). The free hydroxyls of these phenols can scavenge free radicals by donating its hydrogen and making the molecule stable (Flora, 2009). The polyphenolic content of strawberries, specifically, anthocyanins, have been positively correlated with the high antioxidant activity (da Silva et al, 2007). Wang et al., studied the total antioxidant capacity (TAC) of different fruits and concluded that the antioxidant capacity of strawberry is higher (2 to 11 fold) than apples, peaches, pears, grapes, tomatoes, oranges and kiwifruit (Wang

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et al., 1996). Extracts from ripe fruit contains higher antioxidant activity when compared to unripe fruits due to the presence of a larger number of phenolic compounds in ripe fruit (Amini et al., 2013). Studies have demonstrated that the antioxidant ability of this fruit is closely associated with its efficient phenolic compounds and vitamin C (Wang et al., 1997; Kalt et al., 1999; Wang & Millner, 2009). Tulipani and co-workers assessed individual contribution of the main antioxidant compounds in strawberry cultivars and found that vitamin C is the most important antioxidant component, followed by anthocyanins and then hydroxycinnamic acids, mainly p-coumaric acid derivatives and flavanols. Anthocyanins contributed approximately 25% to nearly 40% of the total antioxidant capacity and pelargonidin derivatives were the most represented anthocyanins making the main contribution to the total antioxidant capacity (Tulipani et al., 2008). The primary antioxidant enzymes that are found in strawberries are superoxide dismutase, ascorbate peroxidase, monodehydroascorbate reductase, dehydroascorbate reductase, guaiacol peroxidase, glutathione peroxidase and glutathione reductase (Wang et al., 2007). Experimental studies have demonstrated that acute strawberry consumption increased plasma antioxidant capacity and reduced oxidative damage of plasma proteins (Romandini et al., 2013). A daily intake of 250 g of frozen strawberries notably increased antioxidant activity in the serum which in turn improved body's defense mechanism (Henning et al., 2010). Consumption of strawberries increased plasma antioxidant capacity and vitamin C concentrations and it also enhanced erythrocytes resistance to hemolysis (Tulipani et al., 2011; Prymont-Przyminska et al., 2014). The antioxidant role of strawberry protects the skin from oxidative stress and damage (Giampieri et al., 2014). Furthermore, strawberry extracts have been shown to prevent ethanol induced gastric damage in an experimental *in vivo* model. Thus, diet rich in strawberry might exert a positive action on gastric diseases induced by oxidative damage (Alvarez-Suarez et al., 2011).

The beneficial effects of raspberries could also be directly associated with their unique phytochemical composition. They have high radical scavenging activity due to the abundance of antioxidant components (Mullen et al., 2002). Interestingly, Beekwilder and colleagues suggest that raspberries have a highest antioxidant capacity than strawberries, kiwi, broccoli, leek, apple and tomato (Beekwilder et al., 2005). These berries are good functional food products which provide numerous health benefits as part of a healthy diet. Studies on lyophilized aqueous extracts of domesticated and wild types of raspberry found that p-coumaric acid was the main phenolic acid responsible for the radical scavenging activity of raspberries (Dvaranauskait et al., 2006). Anthocyanins, ellagitannins and polyphenols also exhibited antioxidant and tumor proliferation inhibitory activities (Bowen-Forbes et al., 2010). It was estimated that nearly 75% of antioxidant capacity in raspberry fruits could be attributed to anthocyanins and ellagitannins (Beekwilder, Hall, & de Vos, 2005). Specifically, cyanidin 3-rutinoside and cyanidin 3-xylosylrutinoside in black raspberry were found to be the primary phenolic antioxidants based on the potency and concentration. These compounds, in conjunction with other naturally occurring bioactive constituents in black raspberry, have shown potential biological activity in clinical trials for the treatment of various types of cancer (Tulio et al., 2008).

Blackberries are also a valuable source of bioactive compounds that are directly related to promoting health. This can be attributed to the presence of phenolic acids, flavonoids, anthocyanins, vitamins and minerals (Zia-Ul-Haq et al., 2014) The rich antioxidant content of these berries reduces oxidative stress and maintains a healthy balance between free radicals and antioxidant systems (Kaume et al., 2012). Studies on the scavenging capacity of different berries have shown that blackberries and strawberries have the highest antioxidant capacity on superoxide radical ($O_2^{-}$), hydrogen peroxide ($H_2O_2$), hydroxyl radical ($^{\cdot}OH$) and singlet oxygen ($O_2^{-}$) (Wang & Jiao, 2000; Wang & Lin, 2000). Blackberries possess high antioxidant capacity with high ORAC that could be attributed to the anthocyanins and phenolics present in the berry (Wada & Ou, 2002). Wang & Lin, on the basis of the wet weight of ripe fruits, showed that black raspberries and blackberries had higher antioxidant activities than red raspberries. They also found that blackberries and strawberries had the highest ORAC values during the green stage than the ripe stage (Wang & Lin, 2000). Blackberries and black raspberries contain high amounts of cyanidin glycosides which are strong antioxidants whereas strawberries are rich in vitamin C and pelargonidin-3-glucoside which are weaker antioxidants (Gil et al., 1997). This radical scavenging activity of blackberries is directly related to its anthocyanin content. It was estimated that a single strength blackberry juice contains 46mg/100g of anthocyanin (Monteiro et al., 2011). The most prominent anthocyanin found in blackberry is cyanidin 3-glucoside in a non-acylated form (Koca & Karadeniz, 2009; Kaume et al., 2012; Kostecka-Gugała et al., 2015). This compound is present in blackberry juice and blackberry extract and plays a protective role against peroxynitrite-induced DNA strand breakage in cultured human vascular endothelial cells. This suggests that blackberry juice containing cyanidin-3-*O*-glucoside is a scavenger of peroxynitrite and protects the cells from oxidative stress (Serraino et al., 2003). Cyanidin 3-glucoside rich blackberry extract suppressed topoisomerase poisons I and II in colon carcinoma cells, HT29 cells and leads to the protection of DNA (Esselen et al., 2011). Blackberry has also shown strong chemopreventive and antioxidant activity by inhibiting growth proliferation and migration of human lung carcinoma cell line (A549). *In vitro* analysis showed a reduction in size of A549 tumor xenograft growth and inhibition of metastasis in nude mice (Ding et al., 2006).

Blueberries have a pharmacological effect on oxidative stress due to the presence of high amounts of polyphenols, procyanidins and anthocyanins. In their prominent oxidative role, they serve as radical scavengers and could be useful in preventing several disorders including cancer (Routray & Orsat, 2011). Much of the protective nature of blueberries is directly correlated with its phenolic profile. Antioxidant capability of blueberries are higher in initial maturation stage and early ripening stage than in ripe berries. This is due to the presence of higher concentrations of hydroxycinnamic acid and flavonols in immature berries (Castrejón et al., 2008). Similarly, it has been shown that freezing blueberries significantly improved the antioxidant ability during the third month of storage, followed by decrease at the end of the sixth month (Reque et al., 2014). In addition to this, high oxygen treatment of freshly harvested berries also improved their antioxidant capacity (Zheng et al., 2003). *In vitro* studies have shown that anthocyanins and hydroxycinnamic acids from blueberries were effective in reducing $H_2O_2$ induced reactive oxygen species production in red blood cells (Youdim et al., 2000). Polyphenols from blueberries were reported to reduce increased oxidative stress in endothelial cells at both the membrane and cytosolic level (Youdim et al., 2002). Wilms and colleagues studied the effect of blueberry juice on *ex vivo* induced lymphocytic DNA damage in humans for 4 weeks. After the intervention period, there was a notable increase in plasma concentrations of quercetin and vitamin C, as well as trolox equivalent antioxidant capacity (TEAC) and a 20% reduction in oxidative damage (Wilms et al., 2007). The anthocyanin rich juice of blueberries exhibited strong radical scavenging activity and anti-proliferative activity against murine melanoma (B16F10), ovarian cancer (A2780) and cervical cancer (HeLa) cell lines (Bunea et al., 2013; Diaconeasa et al., 2015). These observations suggest that phytochemicals in blueberries are effective in preventing carcinogenesis through their ability to reduce oxidative DNA damage.

Indian gooseberry holds an important position in the field of traditional medicine due to its nutritional and therapeutic properties (Bhagat, 2014). The phenolic compounds and tannins found in these berries can effectively scavenge free radicals in a concentration dependent manner and thus protects the body from oxidative stress (Mayachiew & Devahastin, 2008; Poltanov et al., 2009). The total antioxidant capacity of five *P. emblica* cultivars were measured by the ORAC assay and the value ranges from 8708.1±784.7 μmol of TE/100 g to 14387.0±707.2 μmol of TE/100 g. In addition, the study also showed a significantly positive relationship between total phenolics and ORAC values (Li et al., 2015). Interestingly, all the five cultivars of *P. emblica* showed much higher level of cellular antioxidant activity than previously reported vegetables and fruits (Wolfe et al., 2008; Song et al., 2010). Dried amla showed the highest antioxidant activity (261.5 mmol/100 g) among 119 different berries and berry products (Carlsen et al., 2010). Antioxidant activity of phenolic compounds of *E. officinalis* was attributed mainly to the phenolic content in which gallic acid and tannic acid were identified as the major antioxidant components in the phenolic fractions of this fruit (Kumar et al., 2006).

In short, several studies on the antioxidant properties of these berries have concluded that raspberries have more antioxidant potential than strawberries. Moreover, extracts from ripe strawberries possess higher antioxidant activity than unripe ones due to the presence of larger amounts of phenolic compounds in the ripe fruit. Surprisingly, antioxidant capability of

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blueberries is higher in the initial maturation stage than in ripe berries. The antioxidant property of blackberry is exemplified by its high ORAC rate. The ORAC value for the berries are presented in Table 3.

**Anticancer properties of berries**

The antioxidant property of strawberries provide insight into their potential anticancer properties. Several studies have established the anti-carcinogenic activity of strawberries in various human cancer cell lines and animal models. Methanolic extract of strawberry was shown to induce intrinsic pathway of apoptosis through a p53 independent mechanism in breast cancer cells. In addition to this, strawberry extracts significantly reduced tumor volume and extended the lifespan of the mice model (Somasagara et al., 2012). In a similar vein, phytochemicals in strawberry inhibited azoxymethane/dextran sodium sulfate-induced colon carcinogenesis in a murine model (Shi et al., 2015). Furthermore, an *in vitro* study by Zhang and colleagues demonstrated the anti-proliferative effect of strawberry crude extracts with ellagic acid on human colon (HT-29 and HCT-116), oral (KB and CAL-27) and prostate (LNCaP and DU145) cell lines in a dose dependent manner (Zhang et al., 2008). In another study they calculated the inhibitory concentration ($IC_{50}$) of strawberry extracts on the proliferation of human tumor cell lines. The $IC_{50}$ values of strawberry extracts on tumor cell lines such as colon HT-29 and HCT116, prostate LNCap, breast MCF-15 and oral KB, CAL27 was calculated to be 114.20, 62, 178, 180, 81.51 and 102 respectively. An evaluation of the pro-apoptotic effects of different berry extracts on HT-29 colon cancer cell line that expresses COX-2 showed that strawberry extracts induced apoptosis 2.8 fold over untreated controls (Seeram et al., 2006). Fruit extracts of different genotypes of strawberry showed significant antiproliferative activities on the growth of human lung epithelial cancer A549 cells *in vitro* (Wang, et al., 2007). The proliferation of HepG2 human liver cancer cells was significantly inhibited in a dose-dependent manner by eight strawberry cultivar extracts. In a comparative study, strawberry showed highly potent anti-proliferative effects on HepG2 cell proliferation among 11 common fruits (Sun et al., 2002; Meyers et al., 2003). Data suggests that constituents of strawberry may target multiple signaling pathways thereby exhibiting cancer inhibitory effects. Strawberry fractions were shown to inhibit nuclear factor of activated T cell (NFAT) activation, which is an important transcription factor involved in cell's response to environmental carcinogens, such as nickel subsulfide, vanadium, asbestos as well as BaPDE-induced Cl 41 cell transformation (Li et al., 2008). Antioxidant and anti-proliferative properties of both organically and conventionally cultivated strawberries have also been studied. Organically grown strawberries have shown higher inhibitory property than conventionally grown varieties. Ellagic acid, anthocyanins and total phenolics were found to be higher in organically grown strawberries. Strawberry extract was shown to reduce the proliferation of colon cancer cells HT29 and breast cancer cells MCF-7 (Olsson et al., 2006). Freeze-dried strawberries, when provided at concentrations of 5% and 10% in the diet of mice inhibited N-nitrosomethylbenzylamine (NMBA)-esophageal tumorigenesis in a dose-dependent manner (Stoner et al., 1999). In a randomized phase II trial, the dietary intake of freeze-dried strawberry by individuals with esophageal dysplastic lesions resulted in a regression of precancerous growth in the esophagus. Strawberry significantly inhibited the expression of iNOS COX-2, pNFκB-p65 and pS6 proteins in human esophageal mucosa and in addition Ki-67 labeling index of cell proliferation was found to be reduced in the biopsy of human esophage

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tissue (Chen et al., 2012). Interestingly, consumption of whole strawberries after a nitrate and an amine-rich diet, significantly reduced the excretion of carcinogen N-nitrosodimethylamine (NDMA) in urine by 70% and could thus reduce cancer risk (Chung et al., 2002).

Several studies have demonstrated the ability of phytochemicals in raspberry to inhibit carcinogenesis. It was reported that anthocyanins found in raspberries were effective in downregulating cyclooxygenase expression and activity and produces antiproliferative action on several human cancer cell lines including MCF-7 (breast), SF-268 (central nervous system, CNS), HCT-116 (colon), and NCI-H460 (lung) (Seeram et al., 2003; Seeram et al., 2006). One of the predominant phytocompounds found in raspberries is ellagic acid which is a dimeric derivative of gallic acid. It was estimated that the concentration of ellagic acid in 100 g of raspberry extract is around 40 mg (Komorsky-Lovrić & Novak, 2011). Studies have evaluaated the antiproliferative mechanism of ellagic acid on different human cancer cell lines (Edderkaoui, 2008; Vanella et al., 2013). It would appear that ellagic acid inhibits the proliferation of pancreatic cancer cell lines by inducing apoptosis by caspase 3 activation and cytochrome C release. It also downregulated NF-κB activity in pancreatic cancer cells (Edderkaoui, 2008). Besides inhibiting pancreatic cancer, raspberry extracts was also shown to prevent the growth of human oral (KB, CAL-27), breast (MCF-7), colon (HT-29, HCT116), and prostate (LNCaP) tumor cell lines in a concentration dependent manner (Seeram et al., 2006). Anthocyanins derived from black raspberries demethylated tumor suppressor genes - CDKN2A, SFRP2, SFRP5 and WIFI - by inhibiting the activity of DNA methyl transferase 1 (DNMT1) and DNMT3B in human colon cancer cells (Wang et al., 2013). Coates and colleagues have demonstrated the ability of raspberry phytochemicals to interact with colon cells. The *in vitro* digestion of raspberry extract produced colon-available raspberry extract which showed significant protective effects against DNA damage. It also reduced proliferation of colon cancer cell line HT29 in G1 phase of the cell cycle. This extract also significantly reduced the spread of cancer to other tissues. Data suggests that at high concentrations it reduced *in vitro* cell invasiveness by up to 95% (Coates et al., 2007). Furthermore, the unfractionated aqueous extract of raspberry was shown to inhibit mutagenesis by both direct-acting and metabolically activated carcinogens (Wedge et al., 2001). Dietary administration of lyophilized black raspberries inhibited events associated with initiation and post-initiation phases of NMBA-induced esophageal tumorigenesis in F344 rats. The inhibitory action produced significant reduction in tumor multiplicity, cellular proliferation and reduction in the formation of preneoplastic lesions (Kresty et al., 2001). Similarly, in another study, 12 week feeding of freeze-dried black raspberries inhibited intestinal tumor incidence and multiplicity in Apc1638+/− and Muc2−/− mouse models of colorectal cancers. The tumor development inhibition was associated with suppression of β-catenin signaling and chronic inflammation pathways and reduction in intestinal cell proliferation (Bi et al., 2010). Black raspberry extracts showed anti-cancer effects on benzoapyrene diol-epoxide (BaPDE) induced signaling pathways in mouse epidermal JB6 Cl 41 cells. Black raspberry fractions specifically inhibited the activation of activator protein-1 (AP-1) and nuclear factor κB (NF-κB) and nuclear factor of activated T cells (NFAT) by BaPDE as well as their upstream PI-3K/Akt-p70$^{S6K}$ and mitogen-activated protein kinase pathways (Li et al., 2008).

In addition to its antioxidant potential, Seeram and colleagues evaluated the ability of blackberry extracts to inhibit the growth and proliferation of human oral (KB, CAL-27), breast (MCF-7),

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colon (HT-29, HCT116), and prostate (LNCaP) tumor cell lines. They concluded that the berry extract inhibited cell proliferation in a dose dependent manner and exhibited significant proapoptotic activity in HT-29 colon cancer cell lines (Seeram et al., 2006). Anthocyanins in blackberries are thought to alter the cell signaling pathways that are responsible for activating activated protein 1 (AP-1) and nuclear factor kB (NF kB) thereby regulating cellular proliferation (Duthie, 2007). Quercetin, a flavonol extracted from blackberry, showed preferential cytotoxic effect on actively proliferating human carcinoma cell lines, HT29 and Caco-2 cells (Agullo et al., 1994). Extracts from eight varieties of blackberry - Navajo, Kiowa, Hull, Triple Crown, Chester, Arapaho, Chickasaw and Chotaw - grown under the same conditions, suppressed 2-amino anthracene (2AA) induced mutagenesis. Among the varieties, Arapaho, Chickasaw and Navajo caused more than 95% reduction in the number of mutations by 2AA (Tate et al., 2003). Blackberries treated with methyl jasmonate significantly enhanced the total anthocyanin and phenolic content in the fruit and enhanced inhibition of human lung, A549 cells and HL-60 leukemia cell proliferation and it also induced apoptosis of Hl-60 cells (Wang et al., 2008).

Blueberries are promising chemopreventive agents against breast, esophageal and colon cancers. Adams and colleagues investigated the chemopreventive role of blueberry extract against triple negative breast cancer cell lines *in vitro* and *in vivo.* They concluded that phytochemicals in blueberry inhibits the growth and proliferation of cancer cell lines by modulating the PI3K/AKT/NFκB pathway (Adams et al., 2010). In another study, they demonstrated that oral intake of whole blueberry powder was effective in reducing MDA-MB-231--derived triple negative breast tumor growth and metastasis in mice (Adams et al., 2011). These findings suggest that blueberry ingestion could perturb tumor growth and metastasis by regulating key signaling pathways. ACI rats that are susceptible to estrogen induced mammary tumors were treated with powdered raspberries and blueberries. Blueberry treated group produced a 40% reduction in tumor volume (Aiyer H et al., 2008). Thus, consumption of blueberry rich diet could be an effective strategy against estrogen mediated breast cancer (Jeyabalan et al., 2013). The inhibition of cancer cell proliferation was correlated with phenolic constituents, flavonoids and antioxidant capacity (Olsson et al., 2004). Studies have suggested that blueberry extracts rich in anthocyanins act as potent antioxidants in Caco-2 cells. Similarly, in another study, anthocyanins such as delphinidin and malvidin from blueberry extract blocked the proliferation of DLD-1 and COLO205 human colorectal carcinoma through the induction of apoptosis (Bornsek et al., 2012; Zu et al., 2010). Furthermore, anthocyanin extract from blueberry significantly reduced breast cancer cell proliferation at a dose of 250 μg/mL after 24 hours of cell incubation (Faria et al., 2010). Wang and colleagues found that rats that consumed diets containing residue fractions of berries (blueberry, raspberries and strawberries) were effective in reducing NMBA-induced esophageal tumorigenesis irrespective of their ellagitannin content (Wang et al., 2010). These findings suggest that chemopreventive and anti proliferative action of blueberries is not limited to a single phytochemical content but rather a cocktail of phytochemicals acting synergistically. Furthermore, it was observed that fruit and fruit juice of blueberries possess chemopreventive action by reducing the formation of azoxymethane (AOM)-induced aberrant crypt foci (ACF) in Fisher male rats (Boateng et al., 2007). It was also reported that pterostilbene, an active constituent of blueberries, was effective in inducing apoptosis and cell cycle arrest in human gastric carcinoma cells. Induction of apoptosis was achieved by activating caspase -2, -3, -8 and -

9 enzymes along with the Bcl family of proteins. It also blocked cell cycle progression at G1 phase in a concentration dependent manner (Pan et al., 2007). Thus these studies demonstrate the antioxidant and anticancer potential of blueberries (Johnson & Arjmandi, 2013).

A dietary supplementation with the fruit extract of *E. officinalis* was shown to significantly reduce the cytotoxic effects of carcinogen 3,4-benzo(a)pyrene in mice (Nandi et al., 1997). Additionally, ethanolic extract of the fruit of *E. officinalis* has been reported to provide protection against the toxicity induced by the carcinogen 7,12-dimethyabenz(a)anthrecene (DMBA) by significantly increasing the liver antioxidants in mice (Banu, 2004). Gooseberry extract was found to inhibit DMBA-induced skin carcinogenesis in mice. Tumor incidence, yield and cumulative number of pappillomas were higher in control than in gooseberry extract treated groups (Sancheti et al., 2005). An *in vitro* antiproliferative comparative study of gooseberry extracts along with nine other plants reported that pyrogallol from *E. officinalis* was the active component responsible for inhibiting cell proliferation of human erythromyeloid K562, B-lymphoid Raji, T-lymphoid Jurkat, and erythroleukemic HEL cell lines (Khan et al., 2002). The efficacy of polyphenol fraction of gooseberries was evaluated on the induction of apoptosis in mouse and human carcinoma cell lines and also N-nitrosodiethylamine (NDEA) induced liver tumors in rats. Results showed that gooseberry extracts induced apoptosis and significantly reduced the development of liver tumor. Interestingly, it was reported that the levels of serum alkaline phosphatase (ALP), glutamate pyruvate transaminase (GPT), bilirubin, liver glutathione S-transferase (GST) and glutathione (GSH) were notably reduced by gooseberry extract treatment (Rajeshkumar et al., 2003). Ngamkitidechakul and coworkers found that the aqueous extract of this fruit notably reduced the proliferation of six human cancer cell lines (A549 (lung), HepG2 (liver), HeLa (cervical), MDA-MB-231 (breast), SK-OV3 (ovarian) and SW620 (colorectal). *E. officinalis* extract induced DNA fragmentation, increased activity of caspase-3/7 and -8 and up-regulated Fas expression in HeLa cells indicating a death receptor-mediated mechanism of apoptosis. Treatment of amla extract on mouse skin treated with DMBA/TPA resulted in over 50% reduction in tumor number and volume (Ngamkitidechakul et al., 2010). Rajeshkumar et al investigated the efficacy of *E. officinalis* polyphenol fraction (EOP) on inducing apoptosis in mouse and human carcinoma cells, Dalton's Lymphoma Ascites (DLA) and CeHa cell line. Their study also indicated that EOP treatment could decrease tumor development in liver tumor induced by N-nitrosodiethylamine (NDEA) (Rajeshkumar et al., 2003). The polyphenolic extract of *E. officinalis* was further shown to induce cell cycle arrest at G2/M and inhibition of cell proliferation in cervical cancer cells. The extract of *E. officinalis* triggered apoptosis induced the activation of apoptotic marker proteins Fas, FasL and the cleavage of caspase-8 (Zhu et al., 2013).

An analyses of the antiproliferative activity of nineteen different constituents including sesquiterpenoids, phenolic compounds and tannins from root, fruit juice and leaves from *E. officinalis* against human gastric adenocarcinoma (MK-1), cervical carcinoma (HeLa) and murine melanoma (B16F10) cells indicated that the glycosides of norsesquiterpenoid, phenolic compounds and tannins showed inhibitory activity against the three tumor cell lines. However, the aglycone and monoglucoside of norsesquiterpenoid showed no cytotoxicity in these tumor cells (Zhang et al., 2004). An *in vitro* and *in vivo* examination of the treatment of the extract of *E. officinalis* in ovarian cancer cell lines demonstrated that it inhibited tumor growth by activating autophagy and inhibiting angiogenesis. The treatment showed an inhibition of the production of angiogenesis associated proteins, hypoxia-inducible factor 1α (HIF-1α) in human ovarian cancer cells, OVCAR3 *in vitro* and induced the expression of authophagic proteins in mouse xenograft tumors (De et al., 2013).

Berries are known to be a good source of polyphenols and the major phenolic compounds are anthocyanins, ellagitannins and phenolic acids. Among the five berry fruits described in this review, strawberry, raspberry, blackberry and blueberry are excellent sources of anthocyanins while amla is rich in tannins. Strawberry, raspberry, blackberry and amla are known to contain predominantly hydrolysable tannins such as ellagitannins and gallotannins whereas blueberry is known to contain condensed tannins such as proanthocyanins. The polyphenolic content positively correlates with their antioxidant property. Black raspberries and blackberries contain high amount of cyanidin glycosides, which are strong antioxidants, while strawberries are rich in pelargonidin 3-glucoside as well as vitamin C. The ORAC values of cyanidin glycosides is 2.24 and pelargonidin 3-glucoside is 1.54 (Wang et al., 1997). Therefore, blackberries and black raspberries have higher mean values of total antioxidant capacity than strawberries. Vitamin C is the most important component contributing to the antioxidant property of strawberry, followed by anthocyanins and then hydroxycinnamic acids. The antioxidant capacity in raspberry could be attributed to anthocyanins and ellagitannins. Specifically, cyanidin 3-rutinoside and cyanidin 3-xylosylrutinoside were found to be the primary phenolic antioxidants based on potency and concentration. Studies have demonstrated that cyandin-3-glucoside is the predominant anthocyanin in blackberry that can scavenge free radicals (Koca & Karadeniz, 2009; Kaume et al., 2012). Antioxidant capability of blueberries are higher in initial maturation stage and early ripening stage than in ripe berries due to the presence of a higher concentration of hydroxycinnamic acid and flavonols in immature berries. Antioxidant activity of *E. officinalis* has been attributed to the phenolic compounds in which gallic acid and tannic acid were identified as the major antioxidant components. The antioxidant activity of these berries are related to their anticancer potential and several studies have demonstrated the anti-carcinogenic activity of these berries on various human cancer cell lines and animal models. In short, a large body of work now indicates that these berries possess anti proliferative activity against breast, lung, prostate, colon, pancreatic cancer cell lines. The synergistic activity of several phytochemicals acting on multiple target seems to bring about this effect.

**Conclusions**

Numerous *in vitro* and *in vivo* studies now indicate that berries have positive impact on human health by acting as strong anticancer and antioxidant agents. They are an ideal dietary source of bioactive components and could play a role in reducing the cancer risk. The unique phytochemical constituents in the berry extracts act individually or synergistically to provide protection against several health disorders including cancer and cardiovascular disorders. The major bioactive components of berries include polyphenols, anthocyanins and ellagitannins. Anthocyanins and hydrolysable tannins are the major polyphenolic compounds in strawberry, raspberry, blackberry and blueberry whereas Indian gooseberries are rich in tannins. As evident from this review much has been done, but much more needs to be done to precisely identify the molecular mechanisms associated with the vast majority of beneficial phytochemicals that make up these nutritious fruits.


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**Table 1: Nutritive composition of fresh fruit berries per 100 g**

| Group | Nutrient | Strawberry [1] | Raspberry[1] | Blackberry [1] | Blueberry[1] | Indian Gooseberry |
|---|---|---|---|---|---|---|
| | | Fragaria X ananassa | Rubus spp. | Rubus spp. | Vaccinium spp | |
| Proximates | Water (g) | 90.95 | 85.75 | 88.2 | 84.21 | 81.8 [2] |
| | Energy (kcal) | 32 | 52 | 43 | 57 | 58 [2] |
| | Protein (g) | 0.67 | 1.2 | 1.39 | 0.74 | 0.5 [2] |
| | Lipid (g) | 0.3 | 0.65 | 0.49 | 0.33 | 0.1 [2] |
| | Carbohydrate (g) | 7.68 | 11.94 | 9.61 | 14.49 | 13.7 [2] |
| | Dietary fiber (g) | 2 | 6.5 | 5.3 | 2.4 | 3.4 [2] |
| | Sugars (g) | 4.89 | 4.42 | 4.88 | 9.96 | - |
| | Sucrose | 0.47 | 0.2 | 0.07 | 0.11 | - |
| | Glucose | 1.99 | 1.86 | 2.31 | 4.88 | - |
| | Fructose | 2.44 | 2.35 | 2.4 | 4.97 | - |
| Minerals | Calcium (mg) | 16 | 25 | 29 | 6 | 50 [2] |

 

| | | | | | | |
|---|---|---|---|---|---|---|
| | Copper (mg) | 0.05 | 0.09 | 0.17 | 0.06 | 0.22 [3] |
| | Iron (mg) | 0.41 | 0.69 | 0.62 | 0.28 | 1.2 [2] |
| | Magnesium (mg) | 13 | 22 | 20 | 6 | - |
| | Manganese (mg) | 0.39 | 0.67 | 0.65 | 0.34 | - |
| | Phosphorous (mg) | 24 | 29 | 22 | 12 | 20 [2] |
| | Potassium(mg) | 153 | 151 | 162 | 77 | - |
| | Selenium(µg) | 0.4 | 0.2 | 0.4 | 0.1 | - |
| | Sodium(mg) | 1 | 1 | 1 | 1 | - |
| | Zinc(mg) | 0.14 | 0.42 | 0.53 | 0.16 | 0.23 [3] |
| Vitamins | Thiamin (Vitamin B1)(mg) | 0.02 | 0.03 | 0.02 | 0.04 | - |
| | Riboflavin (Vitamin B2)(mg) | 0.02 | 0.04 | 0.03 | 0.04 | - |
| | Niacin (Vitamin B3)(mg) | 0.39 | 0.6 | 0.65 | 0.42 | - |
| | Pantothenic acid (Vitamin B5) (mg) | 0.13 | 0.33 | 0.28 | 0.12 | - |


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| | Pyridoxine (Vitamin B6) (mg) | 0.05 | 0.06 | 0.03 | 0.05 | - |
| | Folate (Vitamin B9) (µg) | 24 | 21 | 25 | 6 | - |
| | Ascorbic acid (Vitamin C) (mg) | 58.8 | 26.2 | 21 | 9.7 | 600 [4] |
| | A-tocopherol (Vitamin E) (mg) | 0.29 | 0.87 | 1.17 | 0.57 | - |
| | Vitamin K (µg) | 2.2 | 19.3 | 19.8 | 19.3 | - |
| | Carotene, beta (µg) | 7 | 12 | 128 | 32 | - |

Sources:

[1]USDA National Nutrient Database (https://ndb.nal.usda.gov/ndb/);

[2]Gopalan et al., 1980;

[3]Variya et al., 2016;

[4]Jain & Khurdiya, 2004

**Table 2: Phytochemicals present in berries**

| Berry | Phenolics | | | | Vitamins | References |
|---|---|---|---|---|---|---|
| | Flavonoids | Phenolic acids | Tannins | Stilbenes | | |
| Strawberry | **Anthocyanins** | gallic acid, | sanguiin H-6, | resveratrol | vitamin C, | da Silva et al., 2007; |
| | cyanidin-3-glucoside, | p-coumaric acid, | bis-HHDP-glucose, | | vitamin B9 | Aaby et al., 2007; |
| | cyanidin-3-rutinoside, | p-hydroxybenzoic acid, | galloyl-HHDP-glucose, | | | Aaby et al., 2012; |
| | cyanidin-3-malonyl glucoside, | protocatechuic acid, | galloyl-diHHDP-glucose, | | | Huang et al., 2012; |
| | cyanidin-3-malonylglucosyl-5-glucoside, | caffeic acid | galloyl-bis-HHDP-glucose, | | | Giampieri et al., 2012 |
| | pelargonidin-3-glucoside, | | diHHDP-glucose-galloyl-ellagic acid, | | | |
| | pelargonidin-3-galactoside, | | dimer of galloyl-diHHDP-glucose, | | | |
| | pelargonidin-3-rutinoside, | | ellagic acid, | | | |
| | pelargonidin-3-arabinoside, | | ellagic acid deoxyhexoside, | | | |

 

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|---|---|---|---|---|---|---|
| | pelargonidin-3,5-diglucoside, | | ellagic acid pentoside, | | | |
| | pelargonidin-3-malylglucoside, | | methyl-EA-pentose conjugates | | | |
| | pelargonidin-3-malonylglucoside, | | | | | |
| | pelargonidin-3-acetylglucoside, | | | | | |
| | pelargonidin-dissacharide (hexose+pentose) acylated with acetic acid, | | | | | |
| | 5-carboxypyranopelargonidin-3-glucoside | | | | | |
| | 5-pyranopelargonidin-3-glucoside | | | | | |
| | **Flavonols** | | | | | |
| | quercetin-3-glucuronide, | | | | | |


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|---|---|---|---|---|---|---|
| | quercetin-3-malonylglucoside,<br>quercetin-glucoside, | | | | | |
| | quercetin-glucuronide | | | | | |
| | quercetin-rutinoside, | | | | | |
| | kaempferol-3-glucoside, | | | | | |
| | kaempferol-3-malonylglucoside, | | | | | |
| | kaempferol-3-coumaroyl-glucoside, | | | | | |
| | kaempferol-glucunoride | | | | | |
| | **Flavanols** | | | | | |
| | proanthocyanidin B1 (EC-4,8-C), | | | | | |
| | proanthocyanidin trimer<br>(EC-4,8-EC-4,8-C), | | | | | |
| | proanthocyanidin B3 (C-4,8-C), | | | | | |

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|---|---|---|---|---|---|---|
| | (+)-catechin | | | | | |
| Raspberry | **Anthocyanins** | caffeic acid, | sanguiin H-6, | resveratrol | vitamin C | Romero Rodriguez et al., 1992; |
| | cyanidin-3-glucoside, | ferulic acid, | lambertianin C, | | | Mullen et al., 2002; |
| | cyanidin-3-arabinose, | gallic acid, | ellagic acid, | | | Tian et al., 2006; |
| | cyanidin-3-sophoroside, | chlorogenic acid, | ellagic acid acetylxyloside, | | | Probst, 2015 |
| | cyanidin-3-rutinoside, | p-coumaric acid, | ellagic acid acetylarabinoside | | | |
| | cyanidin-3,5-diglucoside, | p-hydroxybenzoic acid | | | | |
| | cyanidin-3-($2^G$-glucosylrutinoside), | | | | | |
| | cyanidin-3-sambubioside, | | | | | |
| | cyanidin-3-xylosylrutinoside, | | | | | |
| | pelargonidin-3-sophoroside | | | | | |
| | pelargonidin-3-($2^G$-gluco- | | | | | |

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| | sylrutinoside) | | | | | |
| | pelargonidin-3-glucoside | | | | | |
| | pelargonidin-3-rutinoside | | | | | |
| | **Flavonols and Flavones** | | | | | |
| | quercetin, | | | | | |
| | quercetin-3-glucuronide, | | | | | |
| | quercetin-3-rutinoside or rutin, quercetin-3-hexoside, | | | | | |
| | quercetin-3-rhamnoside, | | | | | |
| | quercetin-3-glucoside, | | | | | |
| | methylquercetin−pentose conjugate | | | | | |
| | kaempferol-glucuronide, | | | | | |
| | kaempferol-hexoside, | | | | | |
| | catechin, | | | | | |

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|---|---|---|---|---|---|---|
| | epicatechin, | | | | | |
| | apigenin, | | | | | |
| | chrysin, | | | | | |
| | naringenin | | | | | |
| Blackberry | **Anthocyanins** | p-coumaric, | sanguiin H-6, | | vitamin C, | Henning et al., 1981; |
| | cyanidin-3-glucoside, | ferulic acid, | sanguiin H-10 isomer (2), | | vitamin B9 | Mi et al., 2004; |
| | cyanidin-3-galactoside, | caffeic acid, | sanguiin H-6 minus gallic acid moiety, | | | Jakobek et al., 2007; |
| | cyanidin-3-arabinoside, | gallic acid, | sanguiin H-2, | | | Hager et al., 2008; |
| | cyanidin-3-xyloside, | protocatechuic acid, | sanguiin H-6 plus gallic acid moiety, | | | Hassimotto et al., 2008; |
| | cyanidin-3-rutinoside, | p-hydroxybenzoic acid | lambertianin C, | | | Huang et al., 2012; |
| | cyanidin-3-sophoroside, | | lambertianin D, | | | Diaconeasa et al., 2014; |
| | cyanidin-3-glucosylrutinoside, | | lambertianin C minus ellagic acid moiety (4), | | | Probst, 2015 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | cyanidin-3-(3-malonyl) glucoside, | | pedunculagin, | | | |
| | cyanidin-3-(6-malonyl) glucoside, | | galloyl-HHDP glucose, | | | |
| | pelargonidin-3-glucoside, | | galloyl-bis-HHDP glucose | | | |
| | delphinidin 3-galactoside | | ellagic acid, | | | |
| | delphinidin 3-glucoside, | | ellagic acid and its glycosides, | | | |
| | delphinidin 3-arabinoside, | | methyl ellagic acid pentose conjugate (2) | | | |
| | malvidin-3-arabinoside | | castalagin/vescalagin, | | | |
| | **Flavonols** | | | | | |
| | quercetin-3-galactoside, | | | | | |
| | quercetin-3-glucoside, | | | | | |
| | quercetin-3-rutinoside, | | | | | |

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|---|---|---|---|---|---|---|
| | quercetin 3-xyloside, | | | | | |
| | quercetin-3-xylosylglucuronide, | | | | | |
| | quercetin-3-glucosylxyloside, | | | | | |
| | quercetin-3-glucosylpentoside, | | | | | |
| | quercetin 3-glucuronide, | | | | | |
| | quercetin-3-methoxyhexoside,<br>quercetin-3-oxalylpentoside, | | | | | |
| | quercetin-3-O-[6-(3-hydroxy-3-methyl-glutaroyl)-β- d -galactoside, | | | | | |
| | kaempferol-3-glucuronide, | | | | | |
| | kaempferol-3-glucoside, | | | | | |

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|---|---|---|---|---|---|---|
| | kaempferol-3-galactoside, kaempferol-3-xylosylglucuronide, | | | | | |
| | myricetin | | | | | |
| | myricetin-galactoside, | | | | | |
| | myricetin-arabinoside | | | | | |
| Blueberry | **Anthocyanins** | *p*-hydroxybenzoic acid, | | resveratrol | vitamin C | Huang et al., 2012; |
| | cyanidin-3-glucoside, | vanillic acid, | | | | Bunea, et al., 2013; |
| | cyanidin-3-galactoside, | chlorogenic acid, | | | | Brito et al., 2014; |
| | cyanidin-3-arabinoside, | ferulic acid, | | | | Diaconeasa et al., 2014 |
| | cyanidin-3-O-galactoside, | caffeic acid deriivatives | | | | |
| | Cyanidin- 3-O-di-hexoside, | | | | | |
| | Cyanidin 3-O-(6'' acetyl) glucoside | | | | | |

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|---|---|---|---|---|---|---|
| | malvidin-3-O-arabinoside, | | | | | |
| | malvidin-3-galactoside, | | | | | |
| | malvidin-3-glucoside, | | | | | |
| | Malvidin 3-O-(6" acetyl) glucoside, | | | | | |
| | delphinidin-3-O-galactoside, | | | | | |
| | delphinidin-3-O-glucoside, | | | | | |
| | delphinidin-3-O-arabinoside, | | | | | |
| | Delphinidin-3-O-rutinose | | | | | |
| | (6"-p-coumaroyl)-2"-O-glucose, | | | | | |
| | Delphinidin 3-O-(6" acetyl) glucoside, | | | | | |
| | Delphinidin-3-O-(6"caffeoyl)-glucose, | | | | | |


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| | | | | | | |
|---|---|---|---|---|---|---|
| | petunidin-3-O-galactoside, | | | | | |
| | petunidin-3-O-arabinoside, | | | | | |
| | Petunidin-3-O-di-hexoside, | | | | | |
| | Petunidin-3-O-rutinoside, | | | | | |
| | paeonidin-3-O-galactoside, | | | | | |
| | Peonidin 3-O-rutinose, | | | | | |
| | Peonidin-3-O-galactoside, | | | | | |
| | Petunidin 3-O-(6'' acetyl) glucoside, | | | | | |
| | **Flavonols** | | | | | |
| | quercetin, | | | | | |
| | quercetin-3-rutinoside, | | | | | |
| | quercetin-3-rhamnoside, | | | | | |
| | quercetin-3-glucoside, | | | | | |


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|---|---|---|---|---|---|---|
| | quercetin 3-galactoside**,** | | | | | |
| | (+)-catechin, | | | | | |
| | (-)-epicatechin | | | | | |
| Indian gooseberry | **Flavonols** | hydroxycinnamic acid, | ellagic acid, | | vitamin C | Ghosal et al., 1996; |
| | myricetin, | gallic acid, | Glucogallin (1-O-galloyl-beta-D-glucose), | | | Bhattacharya et al., 1999; |
| | quercetin, | | corilagin, | | | Yang et al., 2002; |
| | isoquercitrin, | | pedunculagin, | | | Habib ur et al., 2007; |
| | kaempferol-3-O-alpha L (6" methyl) rhamnopyranoside, | | punigluconin, | | | Puppala et al., 2012; |
| | kaempferol-3-O-alpha L | | chebulic acid, | | | Bansal et al., 2014; |
| | (5"ethyl) rhamnopyranoside | | phyllanemblinins A,B,C,D & F, | | | Olennikov et al., 2015; |
| | | | mucic acid 2-O-gallate, | | | Variya et al., 2016; |
| | | | mucic acid 2-O-gallate 1, 4-lactone, | | | |

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| | | | | | | |
|---|---|---|---|---|---|---|
| | | | mucic acid 5-O-gallate 1,<br>4-lactone, | | | |
| | | | l-malic acid 2-O-gallate, | | | |
| | | | mucic acid 5-O-gallate 1,4-lactone | | | |
| | | | 1,4-di-O-galloyl-3,<br>6-(R)-HHDP-β- D -glucose, | | | |
| | | | 1,2,4-tri-O-galloyl-3,6-(R)-HHDP-β- D -glucose, | | | |
| | | | 1,6-di-O-galloyl- β- D -glucose, | | | |
| | | | 3,6-di-O-galloyl-d-glucose,<br>3,4,6-tri-O-galloyl- E -D-glucose, | | | |

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**Table 3: Oxygen Radical Absorbance Capacity (ORAC) value of berries**

| Berry | ORAC value (μmol TE/100g) | Reference |
|---|---|---|
| Strawberry, raw | 4302 | Haytowitz & Bhagwat, 2010 |
| Raspberry, raw | 5065 | Haytowitz & Bhagwat, 2010 |
| Blackberry, raw | 5905 | Haytowitz & Bhagwat, 2010 |
| Blueberry, raw | 4669 | Haytowitz & Bhagwat, 2010 |
| Indian gooseberry, dried | 261500 | Carlsen et al., 2010 |

 