Rubus occidentalis

Scientific Name

Rubus occidentalis **L.**

Synonyms

Melanobatus neglectus (Peck) Greene, *Melanobatus occidentalis* (L.) Greene, *Rubus idaeus* L. var. *americanus* Torr., *Rubus idaeus* × *occidentalis* Focke, *Rubus michiganus* Greene, *Rubus neglectus* Peck, *Rubus occidentalis* × *strigosus* Rydb.

Family

Rosaceae

Common/English Names

American Black Raspberry, Blackcap, Black Raspberry, Purple Raspberry, Scotch Cap, Thimble Berry.

Vernacular Names

Chinese: Cao Mei;
Czech: Ostružiník Ojíněný, Ostružiník Západní;
Danish: Sort Hindbær, Ontario-Brombær;
Eastonian: Läänevaarikas
French: Framboisier De Virginie, Framboise Noire (Quebec), Framboisier À Fruits Noirs, Framboisier Noir;
German: Schwarze Himbeere, Schwarzfrüchtige Himbeere;
Greek: Rouvos O Dytikos;
Italian: Lampone Americano;
Japanese: Kuro Mirasu Berii, Kuro Miki Ichigo;
Portuguese: Framboesa Negra;
Russian: Malina Zagadochnaia, Malina Zagadočnaja, Malina Zapadnaia;
Slovašcina: Črna Malina;
Spanish: Frambueso Negro;
Swedish: Svarthallon.

Origin/Distribution

Black Raspberry is indigenous to East and central North America: New Brunswick to Minnesota, south to Georgia, west to Nebraska and Colorado.

Agroecology

A cool climate temperate species. Its natural habitats include openings in deciduous woodlands, woodland borders, savannas, thickets, fence rows, overgrown vacant lots, power-line clearances in wooded areas, and partially shaded areas along buildings. It prefers partial sun, moist to mesic conditions, and thrives best on deep, rich, well-drained, sandy-loam soils well supplied with

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organic matter and with high moisture holding capacity. a range of 5.8–6.5 is considered optimum. The canes also fail to set fruit if there is too much shade. In areas that are too sunny and dry, the fruit may not develop properly without adequate rain or supplemental irrigation.

Edible Plant Parts and Uses

Black raspberries are eaten raw, cooked, dried, frozen or made into purées and juices or processed as colorants. They are very versatile and can be made into a wide array of food preparations and recipes. They are excellent for jam, jellies, sauces and preserves. They can be used in bread, cakes, cookies, pastries, pudding, pies, tarts, flan, soufflés, pancakes, waffles, soups, salads, salsa, raspberry vinaigrette, and eaten in ice-cream, yoghurt, sorbets, sherberts and slushes. Some popular common recipes using raspberry are fondue-cheesecake, chocolate raspberry streusel squares, chocolate raspberry cheesecake. Pancakes and waffles goes well with raspberry syrup. Black raspberries can be processed into refreshing beverages, syrup, mead, wine and liquor. Raspberry sac-mead is a sweet alcoholic liquor popular in Poland and is made of fermented honey, water and often with spices and black raspberries. Two well known liqueurs predominantly based on black raspberry fruit include France's Chambord Liqueur Royale de France and South Korea's various manufacturers of *Bokbunja*. *Bokbunja* is made from Korean black raspberries and contain 15% alcohol and is considered by many to be especially good for sexual stamina.

Young black raspberry shoots are eaten raw or cooked like rhubarb. They are harvested as they emerge through the soil in the spring, and whilst they are still tender, and then peeled. A tea is made from the leaves and another from the bark of the root.

Botany

An arching, erect, deciduous, armed shrub reaching 1–2 m with stems rooting at the tips. Twigs are reddish-purple, terete, glaucous; eglandular, sparsely bristly with straight or hooked, stout prickles that is wider at the base. Leaves are alternate, palmately compound, 3–5 foliate. Leaflets are ovate to ovate-lanceolate, 5–19 cm long by 3.8–8.9 cm wide; glabrous above, densely white tomentose beneath; rounded to subcordate at base; margins doubly serrate with occasional shallow lobes; petiole and rachis have many stout prickles. Inflorescence is an umbel of 3–7 monoecious flowers borne on pedicels with stout prickles; sepals are lanceolate, green, tomentose, 6–8 mm long; petals 5, elliptic-oblong, white, less than half the length of the sepals; carpels many, inserted on hypanthium; stamens numerous with filiform filaments and didymous anthers surrounding the carpels; each carpel becomes a drupelet with 1 locule 1 with 1 developed ovule. Fruit is an aggregation of drupelets, 10–15 mm in diameter, hemispherical, yellowish-white to red and purplish-black when ripe (Plate 1), glaucous. Seed is small and pendulous.

Plate 1 Black raspberries

Nutritive/Medicinal Properties

Food value of raw, raspberries, *Rubus* spp. (exclude 4% refuse consisting of caps and spoiled berries) per 100 g edible portion was reported as follows (USDA 2011): water 85.75 g, energy 52 kcal (220 kJ), protein 1.20 g, total lipid (fat) 0.65 g, ash 0.46 g, carbohydrate 11.94 g; total dietary fibre 6.5 g, sugars (total) 4.42 g, sucrose 0.20 g, glucose (dextrose) 1.86 g, fructose 2.35 g; minerals – calcium 25 mg, iron, 0.69 mg, magnesium 22 mg, phosphorus 29 mg, potassium 151 mg, sodium 1 mg, Zn 0.42 g, Cu 0.090 g, Mn 0.670 g, Se 0.2 µg; vitamins – vitamin C (total ascorbic acid) 26.2 mg, thiamin 0.032 mg, riboflavin 0.038 mg, niacin 0.598 mg, pantothenic acid 0.329 mg,vitamin-6 0.055 mg, folate (total) 21 µg, choline (total) 12.3 mg, betaine 0.8 mg, β carotene 12 µg, α carotene 16 µg, vitamin A 33 IU, lutein + zeaxanthin 136 µg, vitamin E (α-tocopherol) 0.87 mg, β-tocopherol 0.06 mg, γ-tocopherol 1.42 mg, δ-tocopherol 1.04 mg, vitamin K (phylloquinone) 7.8 µg; total saturated fatty acids 0.014 g, 16:0 (palmitic acid) 0.016 g, 18:0 (stearic acid) 0.004 g; total monounsaturated fatty acids 0.375 g, 18:1 undifferentiated (oleic acid) 0.059 g, 20:1 (gadoleic acid) 0.005 g; total polyunsaturated fatty acids 0.375 g, 18:2 undifferentiated (linoleic acid) 0.249 g and 18:3 undifferentiated (linolenic acid) 0.126 g.

Flavonoids (kaempferol, quercetin, myricetin) and phenolic acids (p-coumaric, caffeic, ferulic, p-hydroxybenzoic, gallic and ellagic acids) were detected in the fruits of 19 berries (Hákkinen et al. 1999). Ellagic acid was the main phenolic compound in the berries of the genus *Rubus* (red raspberry, Arctic bramble and cloudberry) and genus *Fragaria* (strawberry). The data suggested berries to have potential as good dietary sources of quercetin or ellagic acid.

Berry fruits including black raspberries are widely consumed in our diet and have attracted much attention due to their potential human health benefits. Black raspberries are loaded with nutrients such as vitamins, minerals diverse range of phytochemicals including anthocyanins and phenolic compounds with biological properties such as antioxidant, anticancer, anti-neurodegerative, and antiinflammatory activities. Extensive studies have been conducted on their phytochemical contents, pharmacological activities and anticancerous potential in the United States particularly in Ohio.

Antioxidant Activity

Among the berry fruits analysed, black raspberries and strawberries had the highest ORAC (oxygen radical absorbance capacity) values during the green stages, whereas red raspberries had the highest ORAC activity at the ripe stage (Wang and Lin 2000). Total anthocyanin content increased with maturity for all three species of fruits. Compared with fruits, leaves were found to have higher ORAC values. In fruits, ORAC values ranged from 7.8 to 33.7 µmol of Trolox equivalents (TE)/g of fresh berries (35. 0–162.1 µmol of TE/g of dry matter), whereas in leaves, ORAC values ranged from 69.7 to 182.2 µmol of TE/g of fresh leaves (205.0–728.8 µmol of TE/g of dry matter). As the leaves become older, the ORAC values and total phenolic contents decreased. Of the ripe fruits tested, on the basis of wet weight of fruit, cv. Jewel black raspberry and blackberries had the richest source for antioxidants. On the basis of the dry weight of fruit, strawberries had the highest ORAC activity followed by black raspberries (cv. Jewel), blackberries, and red raspberries.

Separate studies showed caneberries including black raspberries (*Rubus occidentalis*) to be excellent and rich sources of anthocyanins and phenolics and to be high in antioxidant activity (Wada and Ou 2002). Anthocyanin content ranged from 0.65 to 5.89 mg/g, and phenolics ranged from 4.95 to 9.8 mg/g. All berries had high levels of ellagic acid (47–90 mg/g). All of the berries had high oxygen radical absorbance capacity (ORAC) activity ranging from 24 to 77.2 µmol of Trolox equivalent/g of fresh berries. Black raspberries had the highest ORAC and anthocyanin and phenolic contents.

The black raspberry seed oil contained about 35% α-linolenic acid (18:30–3) and 55% to 50% linoleic acid (Parry and Yu 2004). The meal exhibited strong free radical scavenging activities against 2,2-diphenyl-1-plcrylhydrazyl (DPPH) and 2,2′-azinobi(3-ethylbenzothlazoline-6-sulfonic acid) diammonium salt (ABTS.+) radicals and had a total phenolic content (IPC) of 46 mg gallic acid equivalent/g meal. The ABTS scavenging capacity and TPC of the meal were 300 and 290 times greater than that of the oil. The results from this study suggest the possible food application of black raspberry seed and its fractions in improving human nutrition and potential value-adding opportunities in black raspberry production and processing.

Anticancer Activity

In-Vitro Studies

Due to their content of phenolic and flavonoid compounds, berries including black raspberries were found to exhibit high antioxidant potential, exceeding that of many other foodstuffs (Stoner et al. 2008b). Through their ability to scavenge ROS and reduce oxidative DNA damage, stimulate antioxidant enzymes, inhibit carcinogen-induced DNA adduct formation and enhance DNA repair, berry compounds had been demonstrated to inhibit mutagenesis and cancer initiation. Berry constituents also influenced cellular processes associated with cancer progression including signalling pathways associated with cell proliferation, differentiation, apoptosis and angiogenesis. The bioactive phytochemicals in berries namely blackberry, black raspberry, blueberry, cranberry, red raspberry and strawberry reported included phenolic acids (hydroxycinnamic and hydroxybenzoic acids), flavonoids (anthocyanins, flavanols, flavonols), condensed tannins (proanthocyanins), hydrolyzable tannins (ellagitannins and gallotannins), stilbenoids, lignans, triterpenes and sterols (Seeram 2006; Seeram et al. 2006). Ellagitannins were reported to be hydrolysed to ellagic acid which was gradually metabolised by the intestinal mircobiota to produce different types of urolithins (Landete 2011). Urolithins could exert estrogenic and/or anti-estrogenic activity and tissue disposition studies revealed that urolithins were enriched in prostate, intestinal, and colon tissues in mouse, which explained their inhibitory effect on prostate and colon cancer cell growth. Additionally, antiproliferative and apoptosis-inducing activities of ellagic acid and urolithins had been demonstrated by the inhibition of cancer cell growth. Studies by Seeram et al. (2006) showed that with concentration of berry extract from 25 to 200 μg/mL, increasing inhibition of cell proliferation in all of the human oral (KB, CAL-27), breast (MCF-7), colon (HT-29, HCT116), and prostate (LNCaP) tumour cell lines were observed, with different degrees of potency between cell lines. Black raspberry and strawberry extracts showed the most significant pro-apoptotic effects against colon cancer cell line, HT-29.

Black raspberry seed flour significantly inhibited HT-29 colon cancer cell line proliferation (Parry et al. 2006). The ORAC value was significantly correlated to the total phenolic content under the experimental condition, and also differed in its total anthocyanin values and Fe(2+)-chelating capacities. The results suggest the potential of developing the value-added use of fruit seed flour as dietary sources of natural antioxidants and antiproliferative agents for optimal human health. Studies showed that the lack of correlation between growth inhibition of HT-29 colon cancer cells and extract total phenolic and total monomeric anthocyanin assays suggested horticultural parameters namely cultivar, production site, and fruit maturity stage influence bioactivity in a complex manner (Johnson et al. 2011).

Five percent and 10% dietary freeze-dried black raspberries (BRBs) inhibited N-nitrosomethylbenzylamine (NMBA) metabolism in the rat oesophageal explants (26% and 20%) and in liver microsomes (22% and 28%), but the inhibition was not dose dependent (Reen et al. 2006). NMBA metabolism in oesophageal explants was inhibited by individual components of BRBs, maximally by cyanidin-3-rutinoside (47%) followed by EA (33%), cyanidin-3-glucoside (23%), and the extract (11%). Similarly, in liver microsomes, the inhibition was maximal by cyanidin-3-rutinoside (47%) followed by EA (33%) and cyanidin-3-glucoside (32%).

In separate studies, black raspberry (*Rubus occidentalis*) extract was found to be antiangiogenic (0.1% w/v) in the human tissue-based in-vitro fibrin clot angiogenesis assay (Liu et al. 2005). At 0.075% (w/v), the active fraction completely inhibited angiogenic initiation and angiogenic vessel growth. The studies suggested that an active black raspberry fraction containing multiple antiangiogenic compounds, one of which had been identified as gallic acid, may be a promising complementary cancer therapy. The multiple active ingredients in the extracts may be additive or synergistic in their antiangiogenic effects. Angiogenesis-inhibiting agents have the potential for inhibiting tumour growth and limiting the dissemination of metastasis, thus keeping cancers in a static growth state for prolonged periods. Han et al. (2005) found that two major chemopreventive components of black raspberries, ferulic acid and β-sitosterol, and a fraction eluted with ethanol (RO-ET) inhibited the growth of premalignant and malignant but not normal human oral epithelial cell lines. Another fraction eluted with CH2Cl2/ethanol (DM:ET) and ellagic acid inhibited the growth of normal as well as premalignant and malignant human oral cell lines. Their results showed that the growth inhibitory effects of black raspberries on premalignant and malignant human oral cells may reside in specific components that target aberrant signalling pathways regulating cell cycle progression.

Rodrigo et el. (2006) demonstrated that a freeze-dried black raspberry ethanol extract suppressed human oral squamous cell carcinoma without affecting viability, inhibited translation of the complete angiogenic cytokine vascular endothelial growth factor, suppressed nitric oxide synthase activity, and induced both apoptosis and terminal differentiation. The data suggested that a freeze-dried black raspberry ethanol extract may have potential to be used as a chemopreventive agent in persons with oral epithelial dysplasia. Studies by Zikri et al. (2009) concluded that the selective effects of the ethanol extract of freeze-dried black raspberries on growth and apoptosis of highly tumorigenic rat esophageal epithelial cells in-vitro may be due to preferential uptake and retention of its component anthocyanins, and this may also be responsible for the greater inhibitory effects of freeze-dried whole berries on tumour cells in-vivo.

Xue et al. (2001) found that freeze-dried strawberries or black raspberries extracts, fractions and ellagic acid exhibited anti-transformation activity in Syrian hamster embryo (SHE) cell transformation model. Ellagic acid and methanol extract from strawberries and black raspberries displayed chemopreventive activity against benzo[a]pyrene (B[a]P)-induced transformation in SHE cells. The possible mechanism by which these methanol fractions inhibited cell transformation was postulated to involve interference of uptake, activation, detoxification of B[a]P and/or intervention of DNA binding and DNA repair. One molecular mechanism through which black raspberries inhibited carcinogenesis may be mediated by impairing signal transduction pathways leading to activation of activator protein 1 and nuclear factor kappaβ (NFκB). Another mechanism for the chemopreventive effect of black raspberry may involve inhibition of the PI-phosphotidylinositol 3-kinase (PI-3K)/Akt pathway and endothelial growth factor (VEGF) pathway (Huang et al. 2006). Li et al. (2008) found that black raspberry fractions inhibited the activation of AP-1, NF-kappaB, and nuclear factor of activated T cells (NFAT) benzoapyrene diol-epoxide (BaPDE) as well as their upstream PI-3K/Akt-p70(S6K) and mitogen-activated protein kinase pathways. In contrast, strawberry fractions inhibited NFAT activation, but did not inhibit the activation of AP-1, NF-kappaB or the PI-3K/Akt-p70(S6K) and mitogen-activated protein kinase pathways. Consistent with the effects on NFAT activation, tumour necrosis factor-α (TNF-α) induction by BaPDE was blocked by extract fractions of both black raspberries and strawberries, whereas vascular endothelial growth factor (VEGF) expression, which depended on AP-1 activation, was suppressed by black raspberry fractions but not strawberry fractions. The results suggested that black raspberry and strawberry components may target different signalling pathways in exerting their anti-carcinogenic effects. Zhang et al. (2011) found that non-toxic levels of a lyophilized black raspberry ethanol extract significantly inhibited the growth of human cervical cancer cell lines HeLa (HPV16-/HPV18+, adenocarcinoma), SiHa (HPV16+/HPV18-, squamous cell carcinoma) and C-33A (HPV16-/HPV18-, squamous cell carcinoma) in a dose-dependent and time-dependent manner to a maximum of 54%, 52% and 67%, respectively.

In-Vivo Studies

Dietary lyophilized black raspberries (LBRs) suppressed N-nitrosomethylbenzylamine (NMBA)-induced oesophageal tumorigenesis in the F344 rat at both the initiation and promotion/progression stages of carcinogenesis (Kresty et al. 2001). LBR at 5% significantly reduced tumour incidence and multiplicity, proliferation indices and preneoplastic lesion formation. Chen et al. (2006a) found dietary black raspberries (BRB) inhibited tumour multiplicity in F344 rats treated with the oesophageal carcinogen, N-nitrosomethylbenzylamine (NMBA). The results suggested a novel tumour suppressive role of BRB through inhibition of COX-2, iNOS, and c-Jun. BRB inhibited mRNA expression of iNOS and c-*Jun*, but not COX-2, in papillomatous lesions of the esophagus. Prostaglandin E_2 and total nitrite levels were also decreased by BRB in papillomas. The scientists (Chen et al. 2006b) also reported that dietary black raspberry powder (BRB) inhibited N-nitrosomethylbenzylamine (NMBA)-induced tumour development in the rat oesophagus by inhibiting the formation of DNA adducts and reducing the proliferation rate of preneoplastic cells. On a molecular level, BRB downregulated the expression of c-Jun, cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS). The data also suggested that down-regulation of vascular endothelial growth factor (VEGF) wais correlated with suppression of COX-2 and iNOS. As high vascularity is a risk factor for metastasis and tumour recurrence, BRB may have cancer therapeutic effects in human oesophageal cancer.

Over the years, extensive studies have been conducted on the anticancerous properties of berry fruit especially black raspberry in Ohio state, USA (Stoner et al. 2006). Berry fruits like black raspberries (*Rubus occidentalis*), blackberries (*R. fructicosus*), and strawberries (*Fragaria ananas*) contain known chemopreventive agents which include vitamins A, C, and E and folic acid; calcium and selenium; β-carotene, α-carotene, and lutein; polyphenols such as ellagic acid, ferulic acid, p-coumaric acid, quercetin, and several anthocyanins; and phytosterols such as β-sitosterol, stigmasterol, and kaempferol. Studies had examined and demonstrated the potential cancer chemopreventive activity of freeze-dried diets containing freeze-dried black raspberries, blackberries and strawberries suppressed the development of *N*-nitrosomethylbenzylamine (NMBA)–induced tumours in the rat esophagus. Studies showed that feeding rats with diets containing 5% of either black or red raspberries, strawberries, blueberries, noni, açaí or wolfberry were about equally capable of inhibiting N-nitrosomethylbenzylamine – induced tumour progression in the rat esophagus in spite of known differences in levels of anthocyanins and ellagitannins (Stoner et al. 2010). They also reduced the levels of the serum cytokines, interleukin 5 (IL-5) and GRO/KC (growth related oncogene), the rat homologue for human interleukin-8 (IL-8), and this was associated with increased serum antioxidant capacity.

Studies in male Syrian Golden hamsters showed that ingestion of lyophilized black raspberries (LBR) for 2 weeks prior to treatment with 0.2% 7,12-dimethylbenz(a) anthracene in dimethylsulfoxide inhibited tumour formation in the oral cavity (Casto et al. 2002). Lyophilized (freeze-dried) black raspberries, blackberries, and strawberries had been reported to inhibit carcinogen-induced cancer in the rodent esophagus (Stoner et al. 2006). Some of the known chemopreventive agents in berries include vitamins A, C, and E and folic acid; calcium and selenium; β-carotene, α-carotene, and lutein; polyphenols such as ellagic acid, ferulic acid, p-coumaric acid, quercetin, and several anthocyanins; and phytosterols such as β-sitosterol, stigmasterol, and kaempferol. All three berry types were found to inhibit the number of esophageal tumours (papillomas) in N-nitrosomethylbenzylamine (NMBA) treated Fischer 344 rats. In-vivo mechanistic studies with BRBs indicated that they reduced the growth rate of premalignant oesophageal cells, in part, through down-regulation of cyclooxygenase-2 leading to reduced prostaglandin production and of inducible nitric oxide synthase leading to reduced nitrate/nitrite levels in the oesophagus. Dietary freeze-dried berries were shown to inhibit chemically-induced cancer of the rodent esophagus by 30–60% and of the colon by up- to 80%. The berries were effective at both the initiation and promotion/progression stages of tumour development (Stoner et al. 2007). On a molecular level, berries modulated the expression of genes involved with proliferation, apoptosis, inflammation and angiogenesis. Rats were administered diets containing an alcohol/water-insoluble (residue) fraction of fractions of three berry types, that is, black raspberries (BRBs), strawberries (STRWs), and blueberries (BBs), that differed in their content of ellagitannins in the order BRB > STRW > BB prior to treatment with the esophageal carcinogen N-nitrosomethylbenzylamine (NMBA) (Wang et al. 2010). The residue fractions from all three berry types were about equally effective in reducing NMBA tumorigenesis in the rat esophagus irrespective of their ellagitannin content (0.01–0.62 g/kg of diet). The results suggested that ellagitannins may not be responsible for the chemopreventive effects of the alcohol/water-insoluble fraction of berries. In another study, F344 rats were administered diets containing either (a) 5% whole freeze-dried black raspberries (BRB) powder, (b) an anthocyanin-rich fraction, (c) an organic solvent-soluble, (d) an organic-insoluble (residue) fraction containing (0.02 μmol anthocyanins/g diet), (e) a hexane extract, and (f) a sugar fraction, all derived from BRB prior to treatment with NMBA (Wang et al. 2009). Diets a-c each contained approximately 3.8 μmol anthocyanins/g diet and diets e and f had only trace quantities of anthocyanins. The anthocyanin treatments (diet groups a-c) were about equally effective in reducing NMBA tumorigenesis in the esophagus, indicating that the anthocyanins in BRB had chemopreventive potential. The organic-insoluble (residue) fraction (d) was also effective, suggesting that components other than berry anthocyanins may be chemopreventive. The hexane and sugar diets were inactive. Diet groups a, b, and d all inhibited cell proliferation, inflammation, and angiogenesis and induced apoptosis in both preneoplastic and papillomatous esophageal tissues, suggesting similar mechanisms of action by the different berry components.

Wang et al. (2011b) reported on the effects of black raspberries on the expression of genes associated with the late stages of rat oesophageal carcinogenesis. Treatment with 5% black raspberries (BRBs) reduced the number of dysplastic lesions and the number and size of oesophageal papillomas in N-nitrosomethylbenzylamine (NMBA)-treated rats. When compared to oesophagi from control rats, NMBA treatment led to the differential expression of 4,807 genes in preneoplastic oesophagus and 17,846 genes in oesophageal papillomas. Dietary BRBs modulated 626 of the 4,807 differentially expressed genes in preneoplastic esophagus and 625 of the 17,846 differentially expressed genes in oesophageal papillomas. In both preneoplastic oesophagus and in papillomas, BRBs modulated the mRNA expression of genes associated with carbohydrate and lipid metabolism, cell proliferation and death, and inflammation. In these same tissues, BRBs modulated the expression of proteins associated with proliferation, apoptosis, inflammation, angiogenesis, and both cyclooxygenase and lipoxygenase pathways of arachidonic acid metabolism. Additionally, matrix metalloproteinases involved in tissue invasion and metastasis, and proteins associated with cell-cell adhesion, were also modulated by BRBs. Stoner et al. (2008a) found that 462 of the 2,261 NMBA-dysregulated genes in rat esophagus were restored to near-normal levels of expression by BRB. Further, they identified 53 NMBA-dysregulated genes that were positively regulated by both phenylethyl isothiocyanate (PEITC), a constituent of cruciferous vegetables and BRB. These 53 common genes included genes involved in phase I and II metabolism, oxidative damage, and oncogenes and tumour suppressor genes that regulate apoptosis, cell cycling, and angiogenesis.

Dietary administration of lyophilized black raspberries (LBRs) significantly inhibited chemically induced oral, esophageal, and colon carcinogenesis in animal models (Kresty et al. 2006). Interim results from 6-months chemopreventive pilot study showed that daily consumption of LBRs modulated markers of oxidative stress 8-epi-prostaglandin F2α (8-Iso-PGF2) and, to a lesser more-variable extent, 8-hydroxy-2′-deoxyguanosine (8-OHdG), in Barrett's esophagus patients.

Mallery et al. (2007) formulated and characterised a novel mucoadhesive gel containing freeze dried black raspberries for local delivery to human oral mucosal tissues for oral cancer chemoprevention. The study showed anthocyanin stability was dependent upon gel pH and storage temperature and also demonstrated that the gel composition was well-suited for absorption and penetration into the target oral mucosal tissue site. They also showed show that black raspberry gel application modulated oral intraepithelial neoplasia gene expression profiles, ultimately reducing epithelial COX-2 protein (Mallery et al. 2008). In a patient subset, raspberry gel application also reduced microvascular densities in the superficial connective tissues and induced genes associated with keratinocyte terminal differentiation. A highly sensitive and specific LC-MS/MS assay was developed and validated to simultaneously quantify cyanidin 3-glucoside, cyanidin 3-rutinoside, cyanidin 3-sambubioside and cyanidin 3-(2(G)-xylosyl) rutinoside, the four bioactive constituent black raspberry (FBR) anthocyanins in human saliva, plasma and oral tissue homogenates (Ling et al. 2009). This assay was subsequently used in a pilot pharmacology study to evaluate the effects of topical application of a 10% (w/w) FBR bioadhesive gel to selected mucosal sites in the posterior mandibular gingiva. Measurable saliva and tissue levels of the FBR anthocyanins confirmed that gel-delivered anthocyanins were readily distributed to saliva and easily penetrated human oral mucosa. Studies by Mallery et al. (2011) indicated that interpatient differences in oral mucosal tissue, saliva, and oral microflora could impact on intraoral metabolism, bioactivation and capacities for enteric recycling of black raspberry anthocyanins.

Freeze-dried black raspberries (BRB) were found to be highly effective in inhibiting intestinal tumorigenesis in apc1638$^{+/-}$ and Muc2$^{-/-}$ mouse models of colorectal cancer through targeting multiple signalling pathways (Bi et al. 2010). BRB reduce tumour and tumour multiplicity in both models by suppressing β-catenin signalling in the former and by reducing chronic inflammation in the latter. Montrose et al. (2011) found that dietary BRB markedly reduced dextran sodium sulfate DSS-induced acute injury to the colonic epithelium in C57BL/6 J mice. Body mass were maintained and colonic shortening and ulceration were reduced. However, BRB treatment did not affect the levels of either plasma nitric oxide or colon malondialdehyde, biomarkers of oxidative stress that are otherwise increased by DSS-induced colonic injury. BRB treatment suppressed tissue levels of several key pro-inflammatory cytokines, including tumour necrosis factor α and interleukin 1β. The results demonstrated a potent anti-inflammatory effect of BRB during DSS-induced colonic injury, supporting its possible therapeutic or preventive role in the pathogenesis of ulcerative colitis and related neoplastic events. In a phase I pilot study, Wang et al. (2011a) found that BRBs protectively modulated expression of genes and other epigenetic biomarkers associated with Wnt pathway, proliferation, apoptosis, and angiogenesis in the human colon and rectum of some patients with colorectal adenocarcinomas.

In a clinical trial, 45 g of freeze-dried dietary BRB daily for 7 days was found to be well tolerated by healthy volunteers and resulted in quantifiable anthocyanins and ellagic acid in plasma and urine (Stoner et al. 2005). Overall, less than 1% of these compounds were absorbed and excreted in urine.

Traditional Medicinal Uses

Black raspberry root tea was also part of the traditional pharmacopeia for treatment of haemorrhaging and haemophilia. In south USA, blackberry tea was mixed with whiskey to expel gas. The juice of raspberry fruits was used to flavour medicines. The Kiowa and Apache Indians made a tea from the roots to treat stomach ache. The roots are cathartic. A decoction of the roots has been used as a remedy for gonorrhoea, diarrhoea and dysentery. The root has been chewed in the treatment of coughs and toothache. An infusion of the roots has been employed as a wash for sore eyes. The root has been used, combined with *Hypericum* spp, to treat the early stages of consumption. A decoction of the roots, stems and leaves has been used to treat whooping cough. The leaves are highly astringent. A decoction is employed in the treatment of bowel complaints. A tea made from the leaves is administered as a wash for old and foul sores, ulcers and boils.

Other Uses

A purple to dull blue dye is obtained from the fruit. The plant is used as a disease resistance source against the spur-blight disease of the leaves. Crossing of *R. idaeus* × *R. occidentalis* establish very fruitful hybrids, which usually are called *R.* × *neglectus* Peck.

Comments

Occasional mutations in the genes controlling anthocyanin production has resulted in yellow-fruited variants that still retain the species' distinctive flavour.

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