

Disease type/risk	First Author	Study Title Complete Citation	Date	Abstract	Human	Human cell	Animal	Animal cell
Cancer	Atalay, M.	Atalay, M.; Gordillo, G.; Roy, S.; Rovin, B.; Bagchi, D.; Bagchi, M.; Sen, C. K.,  Anti-angiogenic property of edible berry in a model of hemangioma.  <i>FEBS Lett</i> <b>2003</b> , 544, (1-3), 252-7.	2003	<b>Hemangiomas</b> represent a powerful model to study in vivo angiogenesis. Monocyte chemotactic protein 1 (MCP-1) is known to be responsible for recruiting macrophages to sites of infection or inflammation and facilitate angiogenesis. Recently we have demonstrated that edible berry extracts potently suppress inducible vascular <b>endothelial</b> growth factor expression and <b>in vitro</b> angiogenesis. Comparative analysis of several berry extracts led to the observation that wild blueberry and a berry mix were most effective. Our goal was to follow up on our findings with wild blueberry and the <b>berry mix</b> (OptiBerry). The present work rests on our current finding that these two berry powders significantly inhibit inducible MCP-1 expression in endothelioma cells. Therefore, we sought to examine the effects of wild blueberry and berry mix in an in vivo model of experimental angiogenesis. Reporter studies showed that the <b>berry powders significantly inhibited basal MCP-1 transcription and inducible nuclear factor kappaB transcription. Endothelioma cells pre-treated with berry powders showed diminished ability to form hemangioma.</b> Histological analysis demonstrated markedly decreased infiltration of macrophages in hemangioma of treated <b>mice</b> compared to placebo-treated controls. The current results provide the first <b>in vivo evidence substantiating the anti-angiogenic property of edible berries.</b>			X	
	Bagchi, D.	Bagchi, D.; Roy, S.; Patel, V.; He, G.; Khanna, S.; Ojha, N.; Phillips, C.; Ghosh, S.; Bagchi, M.; Sen, C. K.,  Safety and whole-body antioxidant potential of a novel anthocyanin-rich formulation of edible berries.  <i>Mol Cell Biochem</i> <b>2006</b> , 281, (1-2), 197-209.	2006	Edible berry extracts rich in anthocyanins possess a broad spectrum of therapeutic, pharmacologic and <b>anti-carcinogenic</b> properties. Six berry extracts (wild blueberry, bilberry, cranberry, elderberry, raspberry seeds and strawberry), singly and in combination, were studied in our laboratories for antioxidant efficacy, cytotoxic potential, cellular uptake and anti-angiogenic properties. Combinations of edible berry extracts were evaluated to develop a synergistic formula, OptiBerry, which exhibited high oxygen radical absorbance capacity (ORAC) value, low cytotoxicity and superior anti-angiogenic properties compared to the other combinations tested. The current study sought to determine the broad spectrum safety and antioxidant potential of OptiBerry in vivo. Acute oral LD(50) of OptiBerry was greater than 5 g/kg in rats. Acute dermal LD(50) of OptiBerry was greater than 2 g/kg. No changes in the body weight or adverse effects were observed following necropsy. Primary skin and eye irritation studies were conducted in New Zealand albino <b>rabbits</b> . OptiBerry was classified as slightly irritating to the skin (primary skin irritation index 0.3) and minimally irritating to the eye (maximum mean total score 6.0). The antioxidant potential of OptiBerry was investigated in <b>rats and mice</b> by assessing GSH redox status in tissues as well as by a unique state-of-the-art electron paramagnetic resonance (EPR) imaging of whole-body redox status. A clinically relevant hyperbaric oxygen (HBO) exposure system (2 atm, 2 h) was employed to study the antioxidant properties of OptiBerry. OptiBerry feeding (8 weeks) significantly prevented HBO-induced GSH oxidation in the lung and liver of vitamin E-deficient Sprague Dawley rats. Furthermore, OptiBerry-fed mice, when exposed to HBO, demonstrated significant protection in whole-body HBO-induced oxidation compared to the unfed controls by EPR imaging. Taken together, these results indicate that OptiBerry is reasonably safe and possess antioxidant properties.			x	

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	Bagchi, D.	<p>Bagchi, D.; Sen, C. K.; Bagchi, M.; Atalay, M.,</p> <p>Anti-angiogenic, antioxidant, and anti-carcinogenic properties of a novel anthocyanin-rich berry extract formula.</p> <p><i>Biochemistry (Mosc)</i> <b>2004</b>, 69, (1), 75-80, 1 p preceding 75.</p>	2004	<p>Edible berry anthocyanins possess a broad spectrum of therapeutic and <b>anti-carcinogenic</b> properties. Berries are rich in anthocyanins, compounds that provide pigmentation to fruits and serve as natural antioxidants. Anthocyanins repair and protect genomic DNA integrity. Earlier studies have shown that berry anthocyanins are beneficial in reducing age-associated oxidative stress, as well as in improving neuronal and cognitive brain function. Six berry extracts (wild blueberry, bilberry, cranberry, elderberry, raspberry seeds, and strawberry) were studied for antioxidant efficacy, cytotoxic potential, cellular uptake, and anti-angiogenic (the ability to reduce unwanted growth of blood vessels, which can lead to varicose veins and tumor formation) properties. We evaluated various combinations of edible berry extracts and developed a synergistic formula, OptiBerry IH141, which exhibited high ORAC (Oxygen-Radical Absorbing Capacity) value, low cytotoxicity, and superior anti-angiogenic properties compared to the other combinations tested. Anti-angiogenic approaches to treat cancer represent a priority area in vascular tumor biology. OptiBerry significantly inhibited both H2O2- and TNF-alpha-induced VEGF (Vascular <b>Endothelial</b> Growth Factor) expression by human keratinocytes. VEGF is a key regulator of tumor angiogenesis. Matrigel assay using <b>human microvascular endothelial cells</b> showed that OptiBerry impaired angiogenesis. In an in vivo model of angiogenesis, OptiBerry significantly inhibited basal MCP-1 and inducible NF-kappaB transcriptions. Endothelioma cells pretreated with OptiBerry showed a diminished ability to form hemangioma and markedly decreased tumor growth by more than 50%. In essence, these studies highlight the novel anti-angiogenic, antioxidant, and anti-carcinogenic potential of a novel anthocyanin-rich berry extract formula, OptiBerry.</p>		x		
	Balasubramanian, S.	<p>Balasubramanian, S.; Govindasamy, S.,</p> <p>Inhibitory effect of dietary flavonol quercetin on 7,12-dimethylbenz[a]anthracene-induced hamster buccal pouch carcinogenesis.</p> <p><i>Carcinogenesis</i> <b>1996</b>, 17, (4), 877-9.</p>	1996	<p>The inhibitory effect of dietary supplementation with flavonol quercetin on 7,12-dimethylbenz[a]anthracene (DMBA)-induced <b>hamster buccal pouch carcinogenesis</b> was investigated. Dietary <b>quercetin</b> inhibited the incidence of both papillomas and tumors induced by DMBA. The fluorescence spectra of papillomas and tumors showed different prominent maxima and a characteristic peak around 620-630 nm, which could be attributed to the accumulation of porphyrin compounds. Further, the fluorescence intensities at 630 nm (F1630nm) were elevated, whereas the ratio F1530nm/F1630nm was decreased in DMBA-induced lesions. Quercetin treatment significantly decreased F1630nm and increased the ratio F1520nm/F1630nm when compared with DMBA-induced lesions. It is therefore evident that quercetin has an inhibitory effect on DMBA-induced carcinogenesis and further studies will throw more light on its use as a chemopreventive agent against oral cancer.</p>			x	

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	Barch, D. H.	Barch, D. H.; Fox, C. C.,  Selective inhibition of methylbenzyl nitrosamine-induced formation of esophageal O6-methylguanine by dietary ellagic acid in rats.  Cancer Res 1988, 48, (24 Pt 1), 7088-92.	1988	<b>Ellagic acid</b> is a naturally occurring plant phenol which has been shown to reduce the incidence of a number of carcinogen-induced tumors including methylbenzyl nitrosamine (MBN)-induced esophageal carcinoma in the rat. The postulated mechanism of MBN-induced esophageal carcinogenesis is through oxidation of MBN to form benzaldehyde and an activated metabolite which methylates DNA forming a variety of methylated DNA adducts including O6-methylguanine (O6-mGua) and 7-methylguanine (m7Gua). O6-mGua adducts have been shown to induce DNA mutations which can lead to cancer, while m7Gua adducts do not appear to be related to tumor induction. In this study, we examined whether the decreased incidence of MBN-induced esophageal carcinoma observed with dietary ellagic acid was associated with a decrease in the in vivo and in vitro formation of MBN-induced DNA adducts and whether this reduction was specific to O6-mGua or due to a reduction in total methylation. Weanling male Sprague-Dawley <b>rats</b> were fed a nutritionally complete diet with and without the addition of 0.4 g of ellagic acid per kg of diet. This dose of dietary ellagic acid has previously been shown to reduce the incidence of MBN-induced esophageal carcinoma by 30 to 50%. After 3 wk on the diets, rats were given injections of a single dose of MBN (2.0 mg/kg of body weight i.p.) and sacrificed 1 h after injection. <b>Dietary ellagic acid significantly reduced the MBN-induced in vivo formation of esophageal O6-mGua</b> , without significantly reducing the formation of esophageal m7Gua. Examination of this effect in an in vitro methylation assay demonstrated that dietary ellagic acid did not reduce the ability of esophageal microsomes to methylate purified calf thymus DNA; however, pretreatment of the calf thymus DNA with ellagic acid selectively reduced the MBN-induced formation of O6-mGua by microsomes from both ellagic acid-fed and control animals without altering the in vitro formation of m7Gua. These results suggest that ellagic acid bound to DNA selectively blocks methylation of the O6-position of guanine without inhibiting the activation of MBN or the ability of MBN to methylate DNA.			x	
	Barch, D. H.	Barch, D. H.; Rundhaugen, L. M.; Pillay, N. S.,  Ellagic acid induces transcription of the rat glutathione S-transferase-Ya gene.  Carcinogenesis 1995, 16, (3), 665-8.	1995	Induction of glutathione S-transferase (GST) enzymes can increase detoxification of carcinogens and reduce carcinogen-induced mutagenesis and tumorigenesis. To determine if the anticarcinogen <b>ellagic acid</b> induces cellular enzymes which detoxify carcinogens, we examined the effect of ellagic acid on the expression of glutathione S-transferase-Ya. <b>Rats fed ellagic acid demonstrated significant increases in total hepatic GST activity, hepatic GST-Ya activity and hepatic GST-Ya mRNA.</b> To determine if the observed increase in GST-Ya mRNA was due to ellagic acid inducing transcription of the GST-Ya gene, transfection studies were performed with plasmid constructs containing various portions of the 5' regulatory region of the rat GST-Ya gene. The transfection studies demonstrated that ellagic acid increased GST-Ya mRNA by inducing transcription of the GST-Ya gene and demonstrated that this induction is mediated through the antioxidant responsive element of the GST-Ya gene.			x	

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	Barch, D. H.	Barch, D. H.; Rundhaugen, L. M.; Stoner, G. D.; Pillay, N. S.; Rosche, W. A.,  Structure-function relationships of the dietary anticarcinogen ellagic acid.  Carcinogenesis 1996, 17, (2), 265-9.	1996	<b>Ellagic acid</b> is a complex planar molecule which demonstrates a variety of anticarcinogenic activities. Ellagic acid has been shown to inhibit the CYP1A1-dependent activation of benzo[a]pyrene; to bind to and detoxify the diolepoxide of benzo[a]pyrene; to bind to DNA and reduce the formation of O6-methylguanine by methylating carcinogens; and to induce the phase II detoxification enzymes glutathione S-transferase Ya and NAD(P)H:quinone reductase. Chemical analogs of ellagic acid were synthesized to examine the relationship between the hydroxyl and lactone groups of the ellagic acid molecule and its different anticarcinogenic activities. These studies demonstrated that both the 3-hydroxyl and the 4-hydroxyl groups were required for ellagic acid to directly detoxify the diolepoxide of benzo[a]pyrene, while only the 4-hydroxyl groups were necessary for ellagic acid to inhibit CYP1A1-dependent benzo[a]pyrene hydroxylase activity. Induction of glutathione S-transferase Ya and NAD(P):quinone reductase required the lactone groups of ellagic acid, but the hydroxyl groups were not required for the induction of these phase II enzymes. In addition, the lactone groups, but not the hydroxyl groups, were required for the analogs to reduce the carcinogen-induced formation of O6-methylguanine. Thus, <b>different portions of the ellagic acid molecule are responsible for its different putative anticarcinogenic activities.</b>				
	Boukharta, M.	Boukharta, M.; Jalbert, G.; Castonguay, A., Biodistribution of ellagic acid and dose-related inhibition of lung tumorigenesis in A/J mice. Nutr Cancer 1992, 18, (2), 181-9.		<b>Ellagic acid (EA)</b> , derived from fruit ellagitannins, is known to be antimutagenic and anticarcinogenic in various animal tumor models. In this study, EA at a dose of 4 g/kg diet <b>inhibited multiplicity of tumors</b> induced by 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) in A/J mice by 54%. This inhibition was dose related between 0.06 and 4.0 g/kg diet. In contrast, two related compounds, esculin and esculetin, had no effect on lung tumorigenesis. The biodistribution of EA was studied as a function of dose and time after gavage of EA. The levels of EA in the lung were directly proportional to the dose of EA between 0.2 and 2.0 mmol. The maximum level of EA, corresponding to 21.3 nmol/g, was observed 30 minutes after gavage with 2.0 mmol of EA/kg body wt, which corresponds to only 70 ppm of the administered dose. The levels in liver tissues were 10-fold lower and reached a maximum 30 minutes after gavage. At this interval, the blood level of EA was 1 nmol/ml. The inclusion of EA in cyclodextrin doubles the level of EA in lung tissues. These results demonstrate that <b>EA localizes preferentially in lung tissues and confirm that EA administered orally can inhibit lung umorigenesis.</b>			x	

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	Beecher, G. R.	Beecher, G. R.,  Proanthocyanidins: Biological activities associated with human health.  <i>Pharmaceutical Biology</i> <b>2004</b> , 42, 2-20.	2004	<b>Proanthocyanidins</b> , also called condensed tannins, are oligomers and polymers of monomeric flavans linked through specific single (B linkages) and double (A linkages) bonds. These secondary plant metabolites have substantial antioxidant activity. They are prevalent in some foods and dietary supplements including <b>several berries</b> , red grapes and their wines, and seeds, baking chocolate, cinnamon, pycnogenol, and Ginkgo biloba. Calculations based on limited food composition data suggest daily intakes of about 54 mg/day per person in the United States. Similar data are unavailable to estimate intakes from dietary supplements. Studies on digestion of proanthocyanidins indicates only monomers and dimers are absorbed; however, preliminary evidence suggests hydroxylated phenolic acids are important products of gastrointestinal microflora activity that also may be absorbed. Several types of investigations support improved vascular health after short- or long-term consumption of proanthocyanidins or foods and supplements that contain them. These effects include vasodilation, presumably as a result of increased NO production, decreased platelet aggregation, reduced sensitivity of low-density lipoproteins (LDL) to oxidization, and modulation of several reactions associated with inflammation. Studies with cranberries and cinnamon, both of which contain uniquely linked proanthocyanidins, support a role for bacterial antiadhesion and improved glucose metabolism in type 2 diabetics, respectively. Results from a variety of experiments indicate <b>proanthocyanidins may modulate several reactions involved in cancer processes</b> . A crucial research need is to identify further biologically active components of proanthocyanidins so that mechanisms of action at the tissue, cellular, and subcellular levels.				
	Cerda, B.	Cerda, B.; Tomas-Barberan, F. A.; Espin, J. C.,  Metabolism of antioxidant and chemopreventive ellagitannins from strawberries, raspberries, walnuts, and oak-aged wine in humans: identification of biomarkers and individual variability.  <i>J Agric Food Chem</i> <b>2005</b> , 53, (2), 227-35.	2005	<b>Ellagitannins (ETs)</b> are dietary polyphenols, containing ellagic acid (EA) subunits, with antioxidant and cancer chemopreventive activities that might contribute to health benefits in humans. However, little is known about their <b>metabolic fate</b> . We investigate here the metabolism of different dietary ETs and EA derivatives in humans. Forty healthy volunteers were distributed in four groups. Each group consumed, in a single dose, a different ET-containing foodstuff, i.e., strawberries (250 g), <b>red raspberries</b> (225 g), walnuts (35 g), and oak-aged red wine (300 mL). After the intake, five urine fractions (F) were collected at 8 (F1), 16 (F2), 32 (F3), 40 (F4), and 56 (F5) h. Neither ETs nor EA were detected in urine after LC-MS/MS analysis. However, the microbial metabolite 3,8-dihydroxy-6H-dibenzo[b,d]pyran-6-one (urolithin B) conjugated with glucuronic acid was detected along the fractions F3-F5 in all of the subjects, independently of the consumed foodstuff. The mean percentage of metabolite excretion ranged from 2.8 (strawberries) to 16.6% (walnuts) regarding the ingested ETs. Considerable interindividual differences were noted, identifying "high and low metabolite excreters" in each group, which supported the <b>involvement of the colonic microflora in ET metabolism</b> . These results indicate that urolithin B (a previously described antiangiogenic and hyaluronidase inhibitor compound) is a biomarker of human exposure to dietary ETs and may be useful in intervention studies with ET-containing products. <b>The antioxidant and anticarcinogenic effects of dietary ETs and EA should be considered in the gastrointestinal tract</b> whereas the study of potential systemic activities should be focused on the bioavailable urolithin B derivatives.	x			

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	Chen, T.	Chen, T.; Hwang, H.; Rose, M. E.; Nines, R. G.; Stoner, G. D., Chemopreventive properties of black raspberries in N-nitrosomethylbenzylamine-induced rat esophageal tumorigenesis: down-regulation of cyclooxygenase-2, inducible nitric oxide synthase, and c-Jun. <i>Cancer Res</i> <b>2006</b> , 66, (5), 2853-9.	2006	Our laboratory has used a rodent model of human esophageal squamous cell carcinoma to identify putative chemopreventive agents for this disease and to determine their mechanisms of action. In the present study, we treated F344 <b>rats</b> with the esophageal carcinogen, N-nitrosomethylbenzylamine (NMBA), thrice per week for 5 weeks. Beginning 1 week later, they were fed a synthetic diet containing 5% <b>black raspberries</b> (BRB) for the duration of the bioassay (25 weeks). Rats were sacrificed at weeks 9, 15, and 25. Esophageal tissues were collected, and tumor data were recorded. The expression and enzymatic activities of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) as well as the expression of c-Jun in the esophagi, were evaluated to investigate the mechanism(s) by which black raspberries modulate tumorigenesis. At week 25, <b>BRB inhibited tumor multiplicity</b> , the standard end point in this tumor model, from 3.78 +/- 0.41 tumors per rat in NMBA-treated animals to 2.23 +/- 0.21 tumors per rat in animals treated with NMBA plus BRB (P < 0.005). BRB reduced mRNA and protein expression levels of COX-2, iNOS, and c-Jun as well as the level of prostaglandin E(2) in preneoplastic lesions of the esophagus at week 25. The berries 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. These results suggest a novel tumor suppressive role of BRB through inhibition of COX-2, iNOS, and c-Jun.			x	x
	Clifford, M. N.	Clifford, M. N.; Scalbert, A.,  Ellagitannins - nature, occurrence and dietary burden.  <i>Journal of the Science of Food and Agriculture</i> <b>2000</b> , 80, (7), 1118-1125.	2000	The occurrence of <b>ellagitannins</b> in common foodstuffs is limited to a few fruit and nut species. Dietary intake of ellagitannins is largely explained by the consumption of strawberries, raspberries and blackberries. No reliable figures are available for the ellagitannin burden, but it will probably not exceed 5 mg day <sup>-1</sup> . Their bioavailability is not well defined. A fraction of the ellagitannins ingested is hydrolysed in the gut and the resulting ellagic acid absorbed and metabolised, but whether intact ellagitannins are absorbed is not clear. There are apparently conflicting claims for beneficial and toxic effects caused by ellagitannins, ellagic acid or ellagitannin-containing extracts in various animal species including rodents and ruminants. It seems unlikely that normal consumption can cause toxic effects in man, but any attempt to increase the intake significantly in pursuit of the suggested benefits should be resisted until the metabolism and pharmacokinetics are better understood.				

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	Cooke, D.	<p>Cooke, D.; Steward, W. P.; Gescher, A. J.; Marczylo, T.,</p> <p>Anthocyanins from fruits and vegetables--does bright colour signal cancer chemopreventive activity?</p> <p><i>Eur J Cancer</i> <b>2005</b>, 41, (13), 1931-40.</p>	2005	<p>Consumption of fruits and berries has been associated with decreased risk of developing cancer. The most abundant flavonoid constituents of fruits and berries are anthocyanins (i.e. <b>anthocyanins</b>, glycosides, and their aglycons, anthocyanidins) that cause intense colouration. In this review, we describe epidemiological evidence hinting at the cancer preventive activity of anthocyanin-containing foods in humans, results of chemoprevention studies in rodent models with anthocyanins or anthocyanin-containing fruit/vegetable extracts, and pharmacological properties of anthocyanins. Anthocyanidins have been shown to inhibit malignant cell survival and confound many oncogenic signalling events in the 10(-6)-10(-4) M concentration range. Studies of the pharmacokinetics of anthocyanins after their consumption as single agents, anthocyanin mixtures or <b>berry extracts suggest that anthocyanins reach levels of 10(-8)-10(-7) M in human blood</b>. It is unclear whether such concentrations are sufficient to explain anticarcinogenic effects, and whether anthocyanins exert chemopreventive efficacy themselves, or if they need to undergo hydrolysis to their aglyconic counterparts. The currently available literature provides tantalising hints of the potential usefulness of anthocyanins or anthocyanin mixtures as cancer chemopreventive interventions. <b>Nevertheless further studies are necessary to help adjudge the propitiousness of their clinical development.</b></p>				
	De Boer, J. G.	<p>De Boer, J. G.; Yang, H.; Holcroft, J.; Skov, K.,</p> <p>Chemoprotection against N-nitrosomethylbenzylamine-induced mutation in the rat esophagus.</p> <p><i>Nutr Cancer</i> <b>2004</b>, 50, (2), 168-73.</p>	2004	<p>Prevention of esophageal cancer may be possible through dietary modification or supplementation. In this study we have investigated the mutation preventive properties of <b>ellagic acid</b>, green tea, and diallyl sulfide (DAS) against the mutagenicity of the nitrosamine N-nitrosomethylbenzylamine (NMBA) in the esophagus of the rat. In addition, the effect of the consumption of ethanol on the mutagenicity of NMBA was examined. NMBA is specific in inducing tumors in the rat esophagus and has been used in many studies investigating the mechanism and the prevention of this cancer. We found that the type of mutations induced by two 2-mg/kg subcutaneous injections of NMBA in the lacI gene of "Big Blue" rats is consistent with that found previously for nitrosamines in other systems and consists of G:C--&gt;A:T transitions. We report that the addition of ellagic acid to the feed, replacing drinking water with green tea, and gavage with DAS <b>significantly reduced the mutagenicity of NMBA</b>. In contrast, the addition of 5% ethanol to the drinking water increased the mutagenicity of NMBA. This is consistent with findings that these compounds modulate NMBA-induced carcinogenesis in the rat.</p>			x	

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	Erlund, I.	Erlund, I.; Freese, R.; Marniemi, J.; Hakala, P.; Alfthan, G., Bioavailability of quercetin from berries and the diet. <i>Nutr Cancer</i> <b>2006</b> , 54, (1), 13-7.	2006	Berries are a rich source of various polyphenols, including the flavonoid quercetin. In this article, the results of three intervention studies investigating the bioavailability of <b>quercetin from berries</b> are reviewed. In the first study, we investigated the short-term kinetics of quercetin after consumption of black currant juice and showed that quercetin is rapidly absorbed from it. In the second study, we showed that plasma quercetin levels increase up to 50% in subjects consuming 100 g/day of bilberries, black currants, and lingonberries as a part of their normal diets for 2 mo. In the third study, healthy subjects consumed a diet high or low in vegetables, berries, and other fruit for 6 wk. Quercetin concentrations nearly doubled in the high-vegetable, -berry, and -other fruit group and decreased by 30% in subjects consuming less of these foods than normally. The results showed that plasma <b>quercetin is bioavailable from a diet containing berries</b> and indicate that it may be a good biomarker of fruit and vegetable intake in general.				
Colon cancer	Femia, A. P.	Femia, A. P.; Caderni, G.; Buzzigoli, C.; Cocca, E.; Salvadori, M.; Dolara, P., Effect of simple phenolic compounds on azoxymethane-induced aberrant crypt foci in rat colon. <i>Nutr Cancer</i> <b>2001</b> , 41, (1-2), 107-10.	2001	Because complex mixtures of plant polyphenols exert anticancer activity in animal models, we investigated whether low-molecular-weight natural phenolic compounds (2-OH-coumaric acid, 3-OH-coumaric acid, 4-OH-coumaric acid, 3-OH-flavone, 7-OH-flavone, 4-OH-benzoic acid, 3-OH-benzoic acid, and 2,3-OH-benzoic acid) affect azoxymethane (AOM)-induced aberrant crypt foci (ACF), which have been suggested to represent preneoplastic lesions, in the colon of rats. Male Fischer 344 <b>rats</b> were fed diets supplemented with 0.1% (wt/wt) of the different phenolic compounds, and after 2 wk they were treated twice (1 wk apart) with AOM (15 mg/kg s.c.); the dietary treatment continued until sacrifice, 7 wk after the first injection with AOM. The results showed that none of these phenolic compounds exerted chemopreventive activity on the ACF assay. On the contrary, 3-OH-flavone slightly, although significantly, increased ( $P < 0.05$ ), the number of ACF per colon [157 +/- 7 and 198 +/- 14 (SE) in control and 3-OH-flavone groups, respectively, $n = 10$ ]. We also found that the number of "large" ACF was significantly increased in the group treated with 4-OH-benzoic acid. In conclusion, <b>none of the phenolic compounds tested demonstrated a suppressive action on ACF induction by AOM.</b>			x	

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	Feng, R.	<p>Feng, R.; Bowman, L. L.; Lu, Y.; Leonard, S. S.; Shi, X.; Jiang, B. H.; Castranova, V.; Vallyathan, V.; Ding, M.,</p> <p>Blackberry extracts inhibit activating protein 1 activation and cell transformation by perturbing the mitogenic signaling pathway.</p> <p><i>Nutr Cancer</i> <b>2004</b>, 50, (1), 80-9.</p>	2004	<p>Blackberries are natural rich sources of bioflavonoids and phenolic compounds that are commonly known as potential chemopreventive agents. Here, we investigated the effects of fresh blackberry extracts on proliferation of cancer cells and neoplastic transformation induced by 12-O-tetradecanoylphorbol-13-acetate (TPA), as well as the underlying mechanisms of signal transduction pathways. Using electron spin resonance, we found that blackberry extract is an effective scavenger of free radicals, including hydroxyl and superoxide radicals. Blackberry extract inhibited the proliferation of a <b>human lung cancer cell line</b>, A549. Pretreatment of A549 cells with blackberry extract resulted in an inhibition of 8-hydroxy-2'-deoxyguanosine (8-OHdG) formation induced by ultraviolet B (UVB) irradiation. Blackberry extract decreased TPA-induced neoplastic transformation of JB6 P+ cells. Pretreatment of JB6 cells with blackberry extract resulted in the inhibition of both UVB- and TPA-induced AP-1 transactivation. Furthermore, blackberry extract also blocked UVB- or TPA-induced phosphorylation of ERKs and JNKs, but not p38 kinase. Overall, these results indicated that an extract from fresh blackberry may inhibit tumor promoter-induced carcinogenesis and associated cell signaling, and suggest that the chemopreventive effects of fresh blackberry <b>may be through its antioxidant properties</b> by blocking reactive oxygen species-mediated AP-1 and mitogen-activated protein kinase activation.</p>		x		
	Freese, R.	<p>Freese, R.,</p> <p>Markers of oxidative DNA damage in human interventions with fruit and berries.</p> <p><i>Nutr Cancer</i> <b>2006</b>, 54, (1), 143-7.</p>	2006	<p>Diets rich in fruit and vegetables are associated with a decreased risk of several cancers via numerous possible mechanisms. For example, phytochemicals may decrease oxidative DNA damage and enhance DNA repair. Markers of oxidative DNA damage in human dietary intervention trials used most frequently include oxidized nucleosides such as 7-hydro-8-oxo-2'-deoxyguanosine, which can be analyzed from isolated DNA or urine. Single-cell gel electrophoresis has been widely used to measure baseline or H2O2-induced DNA strand breaks or sites of modified bases sensitive to repair enzymes recognizing oxidized purines or pyrimidines. Recently, markers of DNA repair also have been used. <b>Few controlled human dietary interventions have investigated the specific effects of fruit or berries.</b> There are indications that kiwifruit can decrease H2O2 sensitivity of lymphocyte DNA ex vivo and enhance DNA repair. Carefully controlled studies with flavonoid-rich fruit or berry juices found only few significant differences; less rigorously controlled studies gave more optimistic results. Data on the effects of fruit and berries on DNA damage in humans are scarce and inconclusive; adequately controlled studies with validated markers are needed. Because levels of DNA damage are usually low in young healthy volunteers, <b>groups with an enhanced risk of DNA damage should be studied.</b></p>	x			

Disease type/risk	First Author	Study Title Complete Citation	Date	Abstract				
	Funt, R. C.	Funt, R. C., Antioxidants in Ohio berries. <i>Acta Hort. (ISHS) 2003</i>	2003	Strawberries ( <i>Fragaria x ananassa</i> Duch) and <b>raspberries</b> ( <i>Rubus</i> species) contain many compounds that have been shown to inhibit carcinogenic induced cancer in rats. <b>Ellagic acid</b> (C <sub>14</sub> H <sub>6</sub> O <sub>8</sub> ) is a naturally occurring phenolic compound in strawberries and raspberries. It functions as an antioxidant in the human body. Strawberry and raspberry cultivars grown in Ohio were <b>compared for ellagic acid (EA) in the fruit pulp and seeds</b> and in the leaves in 1997 and 1998. Earliglow and Kent strawberry cultivars had similar levels of ellagic acid, but Jewel's level was lower than those of Earliglow and Kent. Caroline, a fall red raspberry cultivar had a higher seed EA content than Heritage or Autumn Bliss. Oxygen Radical Absorbency Capacity (ORAC), another method for measuring antioxidant content, was used to compare red and black raspberries. Black raspberries were higher in ORAC than red raspberries.			x	
	Galvano, F.	Galvano, F.; La Fauci, L.; Lazzarino, G.; Fogliano, V.; Ritieni, A.; Ciappellano, S.; Battistini, N. C.; Tavazzi, B.; Galvano, G., Cyanidins: metabolism and biological properties. <i>J Nutr Biochem</i> <b>2004</b> , 15, (1), 2-11.	2004	Cyanidin and its glycosides belong to the <b>anthocyanins</b> , a widespread class of water-soluble plant compounds that are responsible for the brilliant color (red, orange, blue) of fruits and flowers. They are widely ingested by humans as it has been estimated a daily intake around 180 mg, mainly deriving from fruits and red wines. This paper reviews the literature on the <b>biological activities</b> , absorption and metabolism of cyanidins, with emphasis to the antioxidant, antimutagenic and other protective activities ascribed to these compounds. Their role in contrasting development of cancer and other pathologies is also reviewed. It is concluded that a great deal of work is still necessary to i) definitively clarify the metabolism of cyanidins in human beings; ii) assess the dietary burden and variations within and between populations; iii) evaluate the relationship between cyanidin glycosides-rich food consumption and incidence of given pathologies. The amount of work to be performed is even more significant when considering a possible therapeutic use of cyanidin glycosides-based drugs. With this aim, <b>information on absorption, distribution, metabolism and excretion of cyanidin-glycosides administered by main possible routes are largely insufficient</b> . However, consisting findings allow looking at cyanidins as dietary compounds with a potential beneficial role for human health.				

Disease type/risk	First Author	Study Title Complete Citation	Date	Abstract	Human	Human cell	Animal	Animal cell
Oral, esophageal and colon cancer	Han, C.	Han, C.; Ding, H.; Casto, B.; Stoner, G. D.; D'Ambrosio, S. M.,  Inhibition of the growth of premalignant and malignant human oral cell lines by extracts and components of black raspberries.  <i>Nutr Cancer</i> <b>2005</b> , 51, (2), 207-17.	2005	Black raspberries are a rich natural source of chemopreventive phytochemicals. Recent studies have shown that freeze-dried black raspberries inhibit the development of oral, esophageal, and colon cancer in rodents, and extracts of black raspberries inhibit benzo(a)pyrene-induced cell transformation of hamster embryo fibroblasts. However, the molecular mechanisms and the active components responsible for black raspberry chemoprevention are unclear. In this study, we found that <b>2 major chemopreventive components of black raspberries, ferulic acid and beta-sitosterol</b> , and a fraction eluted with ethanol (RO-ET) during silica column chromatography of the organic extract of freeze-dried black raspberries inhibit the growth of premalignant and malignant but not normal human oral epithelial cell lines. Another fraction eluted with CH <sub>2</sub> Cl <sub>2</sub> /ethanol (DM:ET) and ellagic acid inhibited the growth of normal as well as premalignant and malignant human oral cell lines. We investigated the molecular mechanisms by which ferulic acid and beta-sitosterol and the RO-ET fraction selectively inhibited the growth of premalignant and malignant oral cells using flow cytometry and Western blotting of cell cycle regulatory proteins. There was no discernable change in the cell cycle distribution following treatment of cells with the RO-ET fraction. Premalignant and malignant cells redistributed to the G2/M phase of the cell cycle following incubation with ferulic acid. beta-sitosterol treated premalignant and malignant cells accumulated in the G0/G1 and G2/M phases, respectively. The RO-ET fraction reduced the levels of cyclin A and cell division cycle gene 2 (cdc2) in premalignant cells and cyclin B1, cyclin D1, and cdc2 in the malignant cell lines. This fraction also elevated the levels of p21waf1/cip1 in the malignant cell line. Ferulic acid treatment led to increased levels of cyclin B1 and cdc2 in both cell lines, and p21waf1/cip1 was induced in the malignant cell line. beta-sitosterol reduced the levels of cyclin B1 and cdc2 while increasing p21waf1/cip1 in both the premalignant and malignant cell lines. <b>These results show for the first time that the growth inhibitory effects of black raspberries on premalignant and malignant human oral cells may reside in specific components that target aberrant signaling pathways regulating cell cycle progression.</b>		x	x	
	Harris, G. K.	Harris, G. K.; Gupta, A.; Nines, R. G.; Kresty, L. A.; Habib, S. G.; Frankel, W. L.; LaPerle, K.; Gallaher, D. D.; Schwartz, S. J.; Stoner, G. D.,  Effects of lyophilized black raspberries on azoxymethane-induced colon cancer and 8-hydroxy-2'-deoxyguanosine levels in the Fischer 344 rat.  <i>Nutr Cancer</i> <b>2001</b> , 40, (2), 125-33.	2001	This study examined the effects of <b>lyophilized black raspberries (BRB)</b> on azoxymethane (AOM)-induced aberrant crypt foci (ACF), colon tumors, and urinary 8-hydroxy-2'-deoxyguanosine (8-OHdG) levels in male Fischer 344 rats. AOM was injected (15 mg/kg body wt i.p.) once per week for 2 wk. At 24 h after the final injection, AOM-treated rats began consuming diets containing 0%, 2.5%, 5%, or 10% (wt/wt) BRB. Vehicle controls received 5% BRB or diet only. Rats were sacrificed after 9 and 33 wk of BRB feeding for ACF enumeration and tumor analysis. ACF multiplicity decreased 36%, 24%, and 21% (P < 0.01 for all groups) in the 2.5%, 5%, and 10% BRB groups, respectively, relative to the AOM-only group. Total tumor multiplicity declined 42%, 45%, and 71% (P < 0.05 for all groups). Although not significant, a decrease in tumor burden (28%, 42%, and 75%) was observed in all BRB groups. Adenocarcinoma multiplicity decreased 28%, 35%, and 80% (P < 0.01) in the same treatment groups. Urinary 8-OHdG levels were reduced by 73%, 81%, and 83% (P < 0.01 for all groups). These results indicate that <b>BRB inhibit several measures of AOM-induced colon carcinogenesis and modulate an important marker of oxidative stress in the Fischer 344 rat.</b>			x	

Disease type/risk	First Author	Study Title Complete Citation	Date	Abstract				
	He, J.	<p>He, J.; Magnuson, B. A.; Lala, G.; Tian, Q.; Schwartz, S. J.; Giusti, M. M.,</p> <p>Intact anthocyanins and metabolites in rat urine and plasma after 3 months of anthocyanin supplementation.</p> <p><i>Nutr Cancer</i> <b>2006</b>, 54, (1), 3-12.</p>	2006	<p>Anthocyanins are polyphenols responsible for most red to purple colors in plants. Human consumption of these pigments is increasing because of their potential health benefits and use as natural colorants. With more than 600 different anthocyanins found in nature, the impact of chemical structure on their absorption and metabolism needs to be investigated. Urine and plasma samples were collected from 32 <b>rats</b> receiving control diet or chokeberry-, bilberry-, and grape-enriched (3.85 g cyanidin 3-galactoside equivalent/kg) diet for 14 wk. Below 2 micromol/l of anthocyanins and relatively higher levels of presumable metabolites were detected by high-performance liquid chromatography-photodiode array in the plasma. In the urine the total concentration of intact anthocyanins and methylated derivatives ranged from 17.4 (bilberry) to 52.6 (chokeberry) nmol/l. The type and number of anthocyanin glycosylations affected the absorption remarkably. <b>Detection of an acylated anthocyanin in plasma and urine suggests bioavailability of these anthocyanin derivatives</b> that are commonly found in commercially available colorants.</p>			x	
	Hecht, S. S.	<p>Hecht, S. S.; Huang, C.; Stoner, G. D.; Li, J.; Kenney, P. M.; Sturla, S. J.; Carmella, S. G.,</p> <p>Identification of cyanidin glycosides as constituents of freeze-dried black raspberries which inhibit anti-benzo[a]pyrene-7,8-diol-9,10-epoxide induced NFkappaB and AP-1 activity. <i>Carcinogenesis</i> <b>2006</b>, 27, (8), 1617-26.</p>	2006	<p>Dietary freeze-dried black raspberries inhibit tumor induction by N-nitrosomethylbenzylamine in the rat esophagus, but the constituents responsible for this chemopreventive activity have not been identified. We fractionated freeze-dried black raspberries and used mouse epidermal JB6 Cl 41 cells stably transfected with either a nuclear factor kappa B (NFkappaB)- or an activator protein 1 (AP-1)-luciferase reporter, and treated with racemic anti-benzo[a]pyrene-7,8-diol-9,10-epoxide (BPDE), to assess the inhibitory effects of the fractions. The ethanol and water extracts of the freeze-dried black raspberries had inhibitory activity and these extracts were fractionated by HPLC to give several bioactive fractions. Further HPLC analysis yielded multiple subfractions, some of which inhibited BPDE-induced NFkappaB activity. Major constituents of the most active subfractions were identified by their spectral properties and in comparison with standards as cyanidin-3-O-glucoside, cyanidin 3-O-(2(G)-xylosylrutinoside) and cyanidin 3-O-rutinoside. Analysis of freeze-dried black raspberries indicated that these three components comprised approximately 3.4% of the material by dry weight. Consistent with these results, standard cyanidin-3-O-glucoside and cyanidin chloride were also good inhibitors of BPDE-induced NFkappaB activity. The results of this study demonstrate that <b>cyanidin glycosides of freeze-dried black raspberries are bioactive compounds which could account for at least some of the chemopreventive activity observed in animal models.</b></p>			x	

Disease type/risk	First Author	Study Title Complete Citation	Date	Abstract				
	Horner, N. K.	<p>Horner, N. K.; Kristal, A. R.; Prunty, J.; Skor, H. E.; Potter, J. D.; Lampe, J. W.,</p> <p>Dietary determinants of plasma enterolactone.</p> <p><i>Cancer Epidemiol Biomarkers Prev</i> <b>2002</b>, 11, (1), 121-6.</p>	2002	<p>Enterolactone is a lignan produced by fermentation of dietary precursors in the human gut. Because lignan precursors are uniquely found in plant foods, plasma enterolactone concentration may serve as a biological marker of plant food consumption. This cross-sectional study examined associations of dietary intake with plasma enterolactone concentration. Weight-stable, 20-40-year-old volunteers (<b>115 women and 78 men</b> in Seattle, Washington) reporting intake of &lt; or =2.5 or &gt; or =4.5 fruit and vegetable servings/day and no antibiotic use for &gt; or =3 months completed a food frequency questionnaire and 3-day food record. Time-resolved fluoroimmunoassay was used to measure plasma enterolactone. Based on diet records, plasma enterolactone was positively correlated with daily vegetable servings (r = 0.17; P &lt; 0.05), fiber (r = 0.36; P &lt; 0.0001), alcohol (r = 0.24; P &lt; 0.001), caffeine (r = 0.21; P &lt; 0.001), and daily botanical group servings [Chenopodiaceae (r = 0.15; P &lt; 0.05), Juglandaceae (r = 0.15; P &lt; 0.05), Leguminosae (r = 0.20; P &lt; 0.001), Pedaliaceae (r = 0.20; P &lt; 0.001), and Vitaceae (r = 0.20; P &lt; 0.001)]. Fat-related variables were not correlated with plasma enterolactone. Based on linear regression models, plasma enterolactone increased by 37.0% (SE = 2.3%) for each 10-g increase in fiber and by 6.6% (SE = 0.2%) for each 50-mg serving of caffeine. Participants consuming 0.5-1 alcoholic drink/day had plasma enterolactone concentrations that were 131.4% (SE = 37.6%) higher than those of nondrinkers. Although plasma enterolactone may be useful as a biological measure of exposure to lignan-containing foods, it may be of limited use as a specific biomarker of fruit and vegetable or plant food intake because coffee, tea, and alcoholic beverages also significantly increase its plasma concentration.</p>	x			
	Hou, D. X.	<p>Hou, D. X.,</p> <p>Potential mechanisms of cancer chemoprevention by anthocyanins.</p> <p><i>Curr Mol Med</i> <b>2003</b>, 3, (2), 149-59.</p>	2003	<p><b>Anthocyanins</b> are the chemical components that give the intense color to many fruits and vegetables, such as blueberries, red cabbages and purple sweet potatoes. Epidemiological investigations have indicated that the moderate consumption of anthocyanin products such as red wine or bilberry extract is associated with a lower risk of cardiovascular disease and improvement of visual functions. Recently, there is increasing interesting in the pharmaceutical function of anthocyanins. This review summarizes current knowledge on the various molecular evidences of cancer chemoprevention by anthocyanins. These mechanisms can be subdivided into the following aspects: <b>1) the antioxidation; 2) the molecular mechanisms involved in anticarcinogenesis; 3) the molecular mechanisms involved in the apoptosis induction of tumor cells.</b> Finally, the bioavailability and structure-activity relationship of anthocyanins are also summarized.</p>				

Disease type/risk	First Author	Study Title Complete Citation	Date	Abstract	Human	Human cell	Animal	Animal cell
	Huang, C.	Huang, C.; Huang, Y.; Li, J.; Hu, W.; Aziz, R.; Tang, M. S.; Sun, N.; Cassady, J.; Stoner, G. D.,  Inhibition of benzo(a)pyrene diol-epoxide-induced transactivation of activated protein 1 and nuclear factor kappaB by black raspberry extracts.  <i>Cancer Res</i> <b>2002</b> , 62, (23), 6857-63.	2002	Freeze-dried black raspberries have been shown to inhibit the development of chemically induced esophageal and colon cancer in rodents. In addition, organic extracts of black raspberries inhibit benzo(a)pyrene (BaP)-induced cell transformation in vitro. The molecular mechanisms through which black raspberries inhibit carcinogenesis remain unclear. We investigated the effects of black raspberry extracts on transactivation of activated protein 1 (AP-1) and nuclear factor kappaB (NFkappaB) induced by BaP diol-epoxide (BPDE), the ultimate carcinogen of BaP, <b>in mouse epidermal JB6 Cl 41 (Cl 41) cells</b> . Black raspberries were extracted with methanol, and the methanol extract was partitioned and chromatographed into several fractions designated RU-F003, RU-F004, RU-DM, and RU-ME. Pretreatment of Cl 41 cells with RU-F003, RU-DM, or RU-ME resulted in an inhibition of BPDE-induced AP-1 and NFkappaB activities. The RU-ME fraction was the most potent inhibitor among the fractions tested. In contrast, fraction RU-F004 did not inhibit BPDE-induced AP-1 or NFkappaB activities in Cl 41 cells. The inhibitory effects of RU-ME on BPDE-induced activation of AP-1 and NFkappaB appear to be mediated via inhibition of mitogen activated protein kinase activation and inhibitory subunit kappaB phosphorylation, respectively. Pretreatment of cells with berry fractions did not result in an inhibition of BPDE binding to DNA; thus, this was not a mechanism of reduced AP-1 and NFkappaB activities. None of the fractions was found to affect p53-dependent transcription activity. In view of the important roles of AP-1 and NFkappaB in tumor promotion/progression, these results suggest that the ability of <b>black raspberries to inhibit tumor development may be mediated by impairing signal transduction pathways leading to activation of AP-1 and NFkappaB</b> . The RU-ME fraction appears to be the major fraction responsible for the inhibitory activity of black raspberries.				x
	Huang, C.	Huang, C.; Li, J.; Song, L.; Zhang, D.; Tong, Q.; Ding, M.; Bowman, L.; Aziz, R.; Stoner, G. D., Black raspberry extracts inhibit benzo(a)pyrene diol-epoxide-induced activator protein 1 activation and VEGF transcription by targeting the phosphatidylinositol 3-kinase/Akt pathway. <i>Cancer Res</i> <b>2006</b> , 66, (1), 581-7.	2006	Previous studies have shown that freeze-dried black raspberry extract fractions inhibit benzo(a)pyrene [B(a)P]-induced transformation of Syrian hamster embryo cells and benzo(a)pyrene diol-epoxide [B(a)PDE]-induced activator protein-1 (AP-1) activity in mouse epidermal Cl 41 cells. The phosphatidylinositol 3-kinase (PI-3K)/Akt pathway is critical for B(a)PDE-induced AP-1 activation in mouse epidermal Cl 41 cells. In the present study, we determined the potential involvement of PI-3K and its downstream kinases on the inhibition of AP-1 activation by black <b>raspberry fractions</b> , RO-FOO3, RO-FOO4, RO-ME, and RO-DM. In addition, we investigated the effects of these fractions on the expression of the AP-1 target genes, vascular endothelial growth factor (VEGF) and inducible nitric oxide synthase (iNOS). Pretreatment of Cl 41 cells with fractions RO-F003 and RO-ME reduced activation of AP-1 and the expression of VEGF, but not iNOS. In contrast, fractions RO-F004 and RO-DM had no effect on AP-1 activation or the expression of either VEGF or iNOS. Consistent with inhibition of AP-1 activation, the RO-ME fraction markedly inhibited activation of PI-3K, Akt, and p70 S6 kinase (p70(S6k)). In addition, overexpression of the dominant negative PI-3K mutant delta p85 reduced the induction of VEGF by B(a)PDE. It is likely that the inhibitory effects of fractions RO-FOO3 and RO-ME on B(a)PDE-induced AP-1 activation and VEGF expression are mediated by inhibition of the PI-3K/Akt pathway. <b>In view of the important roles of AP-1 and VEGF in tumor development, one mechanism for the chemopreventive activity of black raspberries may be inhibition of the PI-3K/Akt/AP-1/VEGF pathway.</b>				x

Disease type/risk	First Author	Study Title Complete Citation	Date	Abstract				
	Huetz, P.	Huetz, P.; Mavaddat, N.; Mavri, J.,  Reaction between ellagic acid and an ultimate carcinogen.  Journal of Chemical Information and Modeling 2005, 45, (6), 1564-1570.	2005	The reaction coordinate between a typical ultimate carcinogen benzo[a]pyrene-7,8-diol-9,10-epoxide (BPDE) and <b>ellagic acid</b> , a proven chemopreventive agent active against cancers caused by polycyclic aromatic hydrocarbons (PAHs), was examined by density functional theory (DFT) and semiempirical MO calculations, and activation energy was calculated. The effect of a polar environment was included using Tomasi and the Langevin dipoles methods. The calculated BPDE/ellagic acid reaction free energy of activation is found to be in decent agreement with experimental data (Sayer, J. M. et al. J. Ant. Chem. Soc. 1982,.104, 55625564]. This work sheds light on the mechanism of action of ellagic acid. Quantum chemical calculations of this kind are valuable for the design of ellagic acid derivatives with even lower activation energy and increased reactivity toward ultimate carcinogens as well as controlled reactivity toward DNA.				
	Juranic, Z.	Juranic, Z.; Zizak, Z.,  Biological activities of berries: from antioxidant capacity to anti-cancer effects.  <i>Biofactors</i> 2005, 23, (4), 207-11.	2005	Consumption of berries has been implicated with diverse health benefits, such as prevention of stroke, of age-related degenerative diseases and cancer. Some berry constituents have been proven to have cancer preventive actions on chemically induced tumors in vivo and cancer suppressive effects in in vitro studies. Many of these effects were attributed to certain berry phytochemicals with high antioxidative potential that could contribute to, or enhance by induction, the endogenous antioxidant properties of living cells or organisms. Producers and the consumers of berry products need more comprehensive and accurate information on the type and level of health benefits that can be expected from different products. The choice of the chemical or biological test that best predicts specific health benefits of berries is crucial to provide targets for berry breeding programmes or to improve processing methods. The aim of this review is to examine the chemical and biological tests developed to characterize the impact of berries on consumer health.				
Disease type/risk	First Author	Study Title Complete Citation	Date	Abstract				
	Juranic, Z.	Juranic, Z.; Zizak, Z.; Tasic, S.; Petrovic, S.; Nidzovic, S.; Lepasovic, A.; Stanojkovic, T.,  Antiproliferative action of water extracts of seeds or pulp of five different raspberry cultivars.  <i>Food Chemistry</i> 2005, 93, (1), 39-45.	2005	In many recent publications the importance of various constituents of berries, anthocyanins and polyphenols, is shown in vitro and in vivo to be beneficial in protecting cells from different forms of cancer. As <b>red raspberries</b> are very rich in the in content of ellagic acid, the goal of this work was to study the cancer suppressive action of <b>water raspberry extracts</b> obtained by extracting water soluble constituents from pulp and from seeds, of five different raspberry cultivars: K81-6, Latham, Meeker, Tulameen and Willamette. The further aim was to compare their antiproliferative action to malignant <b>human colon carcinoma LS174 cells</b> and to normal immune competent cells, with the action of ellagic acid alone. Results from this study show that <b>water extracts of raspberries seeds or pulp possess the potential for antiproliferative action against human colon carcinoma cells in vitro</b> . The antiproliferative action of seeds extract was correlated with its content of ellagic acid. The cytotoxic activity of seeds extracts was not pronounced on normal human PBMC.		x		
	Justo, G. Z.	Justo, G. Z.; Ferreira, C. V., Coagulation and cancer therapy: The potential of natural compounds. <i>Current Genomics</i> 2005, 6, (6), 461-469.	2005	In the past few years, it has become clear that the processes of cancer metastasis and invasion are highly dependent on components of the blood coagulation cascade. Metastasis is critically dependent on the formation of new blood vessels and the role of many blood-clotting factors in tumor angiogenesis has been extensively studied. Angiogenesis constitutes an important point in the control of cancer progression and in recent years much attention has been paid to the development of antiangiogenic agents. Natural compounds constitute a promising alternative for application in antiangiogenesis therapy due to their multiple mechanisms of action. Moreover, they can be used as templates for the production of analogues with enhanced activity. In this review, the potential of natural compounds to target blood coagulation cascades and to prevent tumor growth will be highlighted in view of their underlying mechanisms.				

Disease type/risk	First Author	Study Title Complete Citation	Date	Abstract	Human	Human cell	Animal	Animal cell
	Katsube, N.	Katsube, N.; Iwashita, K.; Tsushida, T.; Yamaki, K.; Kobori, M.,  Induction of apoptosis in cancer cells by bilberry ( <i>Vaccinium myrtillus</i> ) and the anthocyanins.  <i>Journal of Agricultural and Food Chemistry</i> <b>2003</b> , 51, (1), 68-75.	2003	Among ethanol extracts of 10 edible berries( <b>including raspberry</b> ), bilberry extract was found to be the most effective at inhibiting the growth of HL60 human leukemia cells and HCT116 human colon carcinoma cells in vitro. Bilberry extract induced apoptotic cell bodies and nucleosomal DNA fragmentation in HL60 cells. The proportion of apoptotic cells induced by bilberry extract in HCT116 was much lower than that in HL60 cells, and DNA fragmentation was not induced in the former. Of the extracts tested, that from bilberry contained the largest amounts of phenolic compounds, including anthocyanins, and showed the greatest 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging activity. Pure delphinidin and malvidin, like the glycosides isolated from the bilberry extract, induced apoptosis in HL60 cells. These results indicate that the bilberry extract and the anthocyanins, bearing delphinidin or malvidin as the aglycon, inhibit the growth of HL60 cells through the induction of apoptosis. Only pure delphinidin and the glycoside isolated from the bilberry extract, but not malvidin and the glycoside, inhibited the growth of HCT116 cells.		X		
Esophageal cancer	Kresty, L. A.	Kresty, L. A.; Frankel, W. L.; Hammond, C. D.; Baird, M. E.; Mele, J. M.; Stoner, G. D.; Fromkes, J. J.,  Transitioning from preclinical to clinical chemopreventive assessments of lyophilized black raspberries: interim results show berries modulate markers of oxidative stress in Barrett's esophagus patients.  <i>Nutr Cancer</i> <b>2006</b> , 54, (1), 148-56.	2006	Increased fruit and vegetable consumption is associated with decreased risk of a number of cancers of epithelial origin, including esophageal cancer. Dietary administration of lyophilized black raspberries (LBRs) has significantly inhibited chemically induced oral, esophageal, and colon carcinogenesis in animal models. Likewise, berry extracts added to cell cultures significantly inhibited cancer-associated processes. Positive results in preclinical studies have supported further investigation of berries and berry extracts in high-risk human cohorts, including patients with existing premalignancy or patients at risk for cancer recurrence. We are currently conducting a 6-mo chemopreventive pilot study administering 32 or 45 g (female and male, respectively) of LBRs to patients with Barrett's esophagus (BE), a premalignant esophageal condition in which the normal stratified squamous epithelium changes to a metaplastic columnar-lined epithelium. BE's importance lies in the fact that it confers a 30- to 40-fold increased risk for the development of esophageal adenocarcinoma, a rapidly increasing and extremely deadly malignancy. This is a report on interim findings from 10 patients. To date, the results support that daily consumption of LBRs promotes reductions in the urinary excretion of two markers of oxidative stress, 8-epi-prostaglandin F2alpha (8-Iso-PGF2) and, to a lesser more-variable extent, 8-hydroxy-2'-deoxyguanosine (8-OHdG), among patients with BE.				x

Disease type/risk	First Author	Study Title Complete Citation	Date	Abstract				
Esophageal cancer	Kresty, L. A.	Kresty, L. A.; Morse, M. A.; Morgan, C.; Carlton, P. S.; Lu, J.; Gupta, A.; Blackwood, M.; Stoner, G. D.,  Chemoprevention of esophageal tumorigenesis by dietary administration of lyophilized black raspberries.  <i>Cancer Research</i> <b>2001</b> , 61, (16), 6112-9.	2001	Fruit and vegetable consumption has consistently been associated with decreased risk of a number of aerodigestive tract cancers, including esophageal cancer. We have taken a "food-based" chemopreventive approach to evaluate the inhibitory potential of <b>lyophilized black raspberries (LBRs)</b> against N-nitrosomethylbenzylamine (NMBA)-induced esophageal tumorigenesis in the F344 <b>rat</b> , during initiation and postinitiation phases of carcinogenesis. Anti-initiation studies included a 30-week tumorigenicity bioassay, quantification of DNA adducts, and NMBA metabolism study. Feeding 5 and 10% LBRs, for 2 weeks prior to NMBA treatment (0.25 mg/kg, weekly for 15 weeks) and throughout a 30-week bioassay, significantly reduced tumor multiplicity (39 and 49%, respectively). In a short-term bioassay, 5 and 10% LBRs inhibited formation of the promutagenic adduct O(6)-methylguanine (O(6)-meGua) by 73 and 80%, respectively, after a single dose of NMBA at 0.25 mg/kg. Feeding 5% LBRs also significantly inhibited adduct formation (64%) after NMBA administration at 0.50 mg/kg. The postinitiation inhibitory potential of berries was evaluated in a second bioassay with sacrifices at 15, 25, and 35 weeks. Administration of LBRs began after NMBA treatment (0.25 mg/kg, three times per week for 5 weeks). LBRs inhibited tumor progression as evidenced by significant reductions in the formation of preneoplastic esophageal lesions, decreased tumor incidence and multiplicity, and reduced cellular proliferation. At 25 weeks, both 5 and 10% LBRs significantly reduced tumor incidence (54 and 46%, respectively), tumor multiplicity (62 and 43%, respectively), proliferation rates, and preneoplastic lesion development. Yet, at 35 weeks, only 5% LBRs significantly reduced tumor incidence and multiplicity, proliferation indices and preneoplastic lesion formation. In conclusion, dietary administration of <b>LBRs inhibited events associated with both the initiation and promotion/progression stages of carcinogenesis, which is promising considering the limited number of chemopreventives with this potential.</b>				x
	Festa, F.	Festa, F.; Aglitti, T.; Duranti, G.; Ricordy, R.; Perticone, P.; Cozzi, R., Strong antioxidant activity of ellagic acid in mammalian cells in vitro revealed by the comet assay. <i>Anticancer Res</i> 2001, 21, (6A), 3903-8.	2001	Oxidative stress due to oxygen and various radical species is associated with the induction of DNA single- and double-strand breaks and is considered to be a first step in several human degenerative diseases, cancer and ageing. Naturally occurring antioxidants are being extensively analysed for their ability to protect DNA against such injury. We studied three naturally occurring compounds, Ascorbic Acid, Melatonin and <b>Ellagic acid</b> , for their ability to modulate DNA damage produced by two strong radical oxygen inducers (H <sub>2</sub> O <sub>2</sub> and Bleomycin) in <b>cultured CHO cells</b> . The alkaline Comet assay was used to measure DNA damage and a cytofluorimetric analysis was performed to reveal the intracellular oxidative species. The data showed a marked reduction of H <sub>2</sub> O <sub>2</sub> - and Bleomycin-induced DNA damage exerted by Ellagic Acid. On the contrary Ascorbic acid and Melatonin appeared to induce a slight increase in DNA damage per se. In combined treatments, they caused a slight reduction of H <sub>2</sub> O <sub>2</sub> -induced damage, but they did not efficiently modulate the Bleomycin-induced one. The Dichlorofluorescein diacetate (DCFH-DA) cytofluorimetric test confirmed the <b>strong scavenging action exerted by Ellagic Acid.</b>				X

Disease type/risk	First Author	Study Title Complete Citation	Date	Abstract				
	Labrecque, L.	Labrecque, L.; Lamy, S.; Chapus, A.; Mihoubi, S.; Durocher, Y.; Cass, B.; Bojanowski, M. W.; Gingras, D.; Beliveau, R.,  Combined inhibition of PDGF and VEGF receptors by ellagic acid, a dietary-derived phenolic compound.  <i>Carcinogenesis</i> <b>2005</b> , 26, (4), 821-6.	2005	The vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) receptors play essential and complementary roles in angiogenesis and combined inhibition of these receptors has been shown to result in potent antitumor activity in vivo. In this study, we report that <b>ellagic acid (EA)</b> , a natural polyphenol found in fruits and nuts, inhibits VEGF-induced phosphorylation of VEGFR-2 in endothelial cell (EC) as well as PDGF-induced phosphorylation of PDGFR in smooth muscle cells, leading to the inhibition of downstream signaling triggered by these receptors. EA also specifically inhibited VEGF-induced migration of ECs as well as their differentiation into capillary-like tubular structures and abolished PDGF-dependent smooth muscle cell migration. Interestingly, EA presents a greater selectivity for normal cells than for tumor cells since the migration of the U87 and HT1080 cell lines were much less affected by this molecule. The identification of EA as a naturally occurring dual inhibitor of VEGF and PDGF receptors suggests that <b>this molecule possesses important antiangiogenic properties that may be helpful for the prevention and treatment of cancer.</b>		X		X
	Lala, G.	Lala, G.; Malik, M.; Zhao, C.; He, J.; Kwon, Y.; Giusti, M. M.; Magnuson, B. A.,  Anthocyanin-rich extracts inhibit multiple biomarkers of colon cancer in rats.  <i>Nutr Cancer</i> <b>2006</b> , 54, (1), 84-93.	2006	The aim of the present study was to investigate the chemoprotective activity of anthocyanin-rich extracts (AREs) from bilberry ( <i>Vaccinium myrtillus</i> L.), chokeberry ( <i>Aronia meloncarpa</i> E.), and grape ( <i>Vitis vinifera</i> ) by assessing multiple biomarkers of colon cancer in male rats treated with a colon carcinogen, azoxymethane. Fischer 344 male rats were fed the AIN-93 diet (control) or AIN-93 diet supplemented with AREs for 14 wk. Biomarkers that were evaluated included the number and multiplicity of colonic aberrant crypt foci (ACF), colonic cell proliferation, urinary levels of oxidative DNA damage, and expression of cyclooxygenase (COX) genes. To assess the bioavailability, levels of anthocyanins in serum, urine, and feces were evaluated. Total ACF were reduced (P<0.05) in bilberry, chokeberry, and grape diet groups compared with the control group. The number of large ACF was also reduced (P<0.05) in bilberry and chokeberry ARE-fed rats. Colonic cellular proliferation was decreased in rats fed bilberry ARE and chokeberry ARE diets. Rats fed bilberry and grape ARE diets had lower COX-2 mRNA expression of gene. High levels of fecal anthocyanins and increased fecal mass and fecal moisture occurred in ARE-fed rats. There was also a significant reduction (P<0.05) in fecal bile acids in ARE-fed rats. The levels of urinary 8-hydroxyguanosine were similar among rats fed different diets. These results support our previous in vitro studies suggesting a <b>protective role of AREs in colon carcinogenesis and indicate multiple mechanisms of action.</b>			X	

Disease type/risk	First Author	Study Title Complete Citation	Date	Abstract	Human	Human cell	Animal	Animal cell
	Lamy, S	Lamy, S.; Blanchette, M.; Michaud-Levesque, J.; Lafleur, R.; Durocher, Y.; Moghrabi, A.; Barrette, S.; Gingras, D.; Beliveau, R.,  Delphinidin, a dietary anthocyanidin, inhibits vascular endothelial growth factor receptor-2 phosphorylation.  <i>Carcinogenesis</i> <b>2006</b> , 27, (5), 989-96.	2006	Epidemiological studies have shown that a diet rich in fruits and vegetables has a beneficial preventive effect on cardiovascular diseases and cancer by mechanisms that have not yet been elucidated. In this work, we investigated the antiangiogenic activities of anthocyanidins, a class of polyphenols present at high levels in fruits. Among the tested anthocyanidins (cyanidin, delphinidin, malvidin, pelargonidin, peonidin and petunidin), delphinidin was the most potent angiogenic inhibitor. In vitro, low concentrations of delphinidin inhibited vascular endothelial growth factor (VEGF)-induced tyrosine phosphorylation of VEGF receptor (VEGFR)-2, leading to the inhibition of downstream signaling triggered by VEGFR-2. Inhibition of VEGFR-2 by delphinidin inhibited the VEGF-induced activation of ERK-1/2 signaling and the chemotactic motility of human EC as well as their differentiation into capillary-like tubular structures in Matrigel and within fibrin gels. In vivo, delphinidin was able to suppress basic fibroblast growth factor-induced vessel formation in the mouse Matrigel plug assay. The identification of delphinidin as a naturally occurring inhibitor of VEGF receptors suggests that this molecule possesses important antiangiogenic properties that may be helpful for the prevention and treatment of cancer.		X	X	
	Larrosa, M.	Larrosa, M.; Tomas-Barberan, F. A.; Espin, J. C., The dietary hydrolysable tannin punicalagin releases ellagic acid that induces apoptosis in human colon adenocarcinoma Caco-2 cells by using the mitochondrial pathway. <i>J Nutr Biochem</i> <b>2006</b> , 17, (9), 611-25.	2006	Polyphenol-rich dietary foodstuffs have attracted attention due to their cancer chemopreventive and chemotherapeutic properties. <b>Ellagitannins (ETs)</b> belong to the so-called hydrolysable tannins found in strawberries, raspberries, walnuts, pomegranate, oak-aged red wine, etc. Both ETs and their hydrolysis product, ellagic acid (EA), have been reported to induce apoptosis in tumour cells. <b>Ellagitannins are not absorbed in vivo but reach the colon and release EA</b> that is metabolised by the human microflora. Our aim was to investigate the effect of a dietary ET [pomegranate punicalagin (PUNI)] and EA on <b>human colon cancer Caco-2 and colon normal CCD-112CoN cells</b> . Both PUNI and EA provoked the same effects on Caco-2 cells: down-regulation of cyclins A and B1 and upregulation of cyclin E, cell-cycle arrest in S phase, induction of apoptosis via intrinsic pathway (FAS-independent, caspase 8-independent) through bcl-XL down-regulation with mitochondrial release of cytochrome c into the cytosol, activation of initiator caspase 9 and effector caspase 3. Neither EA nor PUNI induced apoptosis in normal colon CCD-112CoN cells (no chromatin condensation and no activation of caspases 3 and 9 were detected). In the case of Caco-2 cells, no specific effect can be attributed to PUNI since it was hydrolysed in the medium to yield EA, which entered into the cells and was metabolised to produce dimethyl-EA derivatives. Our study suggests that the <b>anticarcinogenic effect of dietary ETs could be mainly due to their hydrolysis product, EA, which induced apoptosis via mitochondrial pathway in colon cancer Caco-2 cells but not in normal colon cells</b> .		X		

Disease type/risk	First Author	Study Title Complete Citation	Date	Abstract				
	Lazze, M. C.	Lazze, M. C.; Savio, M.; Pizzala, R.; Cazzalini, O.; Perucca, P.; Scovassi, A. I.; Stivala, L. A.; Bianchi, L.,  Anthocyanins induce cell cycle perturbations and apoptosis in different human cell lines.  <i>Carcinogenesis</i> <b>2004</b> , 25, (8), 1427-33.	2004	To investigate the mechanistic basis for the biological properties of anthocyanins, two aglycone anthocyanins [delphinidin (DY) and cyanidin (CY)] were used to examine their effects on cell cycle progression and on induction of apoptosis in <b>human cancer cells</b> (uterine carcinoma and colon adenocarcinoma cells) and in normal human fibroblasts. These compounds differ in the number and position of hydroxyl groups on the beta ring in the molecular structure. Cellular uptake of anthocyanins was confirmed by HPLC analysis and no metabolites were detected. The clonogenic assay showed that CY induces a dose-dependent growth inhibitory effect only in fibroblasts. This effect was confirmed by flow cytometric analysis, showing a significant reduction of cells in S phase. In contrast, DP inhibited cell growth in normal and tumour cell lines. This event is accompanied in fibroblasts by an accumulation of cells in the S phase suggesting a block in the transition from S to G2 phase. On the other hand, in tumour cell lines we observed a reduction of cells in G1 phase, paralleled by the appearance of a fraction of cells with a hypodiploid DNA content, thus demonstrating an apoptotic effect by DP. The occurrence of apoptosis induced by DP was confirmed by morphological and biochemical features, including nuclear condensation and fragmentation, annexin V staining, DNA laddering and poly(ADP-ribose) polymerase-1-proteolysis. Furthermore, the mitochondrial membrane potential of apoptotic cells after treatment with DP was significantly lost. The different effects exerted by DP as compared with CY suggest that the presence of the three hydroxyl groups on the beta ring in the molecular structure of DP may be important for its greater biological activity.		X		
	Liu, M.	Liu, M.; Li, X. Q.; Weber, C.; Lee, C. Y.; Brown, J.; Liu, R. H.,  Antioxidant and antiproliferative activities of raspberries.  <i>J Agric Food Chem</i> <b>2002</b> , 50, (10), 2926-30.	2002	Raspberries are rich in phenolic phytochemicals. To study the health benefits of raspberries, four fresh <b>raspberry varieties</b> (Heritage, Kiwigold, Goldie, and Anne) were evaluated for total antioxidant and <b>antiproliferative activities</b> . The total amount of phenolics and flavonoids for each of the four raspberry varieties was determined. The Heritage raspberry variety had the highest total phenolic content (512.7 +/- 4.7 mg/100 g of raspberry) of the varieties measured followed by Kiwigold (451.1 +/- 4.5 mg/100 g of raspberry), Goldie (427.5 +/- 7.5 mg/100 g of raspberry), and Anne (359.2 +/- 3.4 mg/100 g of raspberry). Similarly, the Heritage raspberry variety contained the highest total flavonoids (103.4 +/- 2.0 mg/100 g of raspberry) of the varieties tested, followed by Kiwigold (87.3 +/- 1.8 mg/100 g of raspberry), Goldie (84.2 +/- 1.8 mg/100 g of raspberry), and Anne (63.5 +/- 0.7 mg/100 g of raspberry). The color of the raspberry juice correlated well to the total phenolic, flavonoid, and anthocyanin contents of the raspberry. Heritage had the highest a/b ratio and the darkest colored juice, and the Anne variety showed the lowest phytochemical content and the palest color. Heritage raspberry variety had the highest total antioxidant activity, followed by Kiwigold and Goldie, and the Anne raspberry variety had the lowest antioxidant activity of the varieties tested. The proliferation of HepG(2) <b>human liver cancer cells was significantly inhibited in a dose-dependent manner after exposure to the raspberry extracts</b> . The extract equivalent to 50 mg of Goldie, Heritage, and Kiwigold fruit inhibited the proliferation of those cells by 89.4 +/- 0.1, 88 +/- 0.2, and 87.6 +/- 1.0%, respectively. Anne had the lowest antiproliferative activity of the varieties measured but still exhibited a significant inhibition of 70.3 +/- 1.2% with an extract equivalent to 50 mg of fruit. The antioxidant activity of the raspberry was directly related to the total amount of phenolics and flavonoids found in the raspberry (p < 0.01). No relationship was found between antiproliferative activity and the total amount of phenolics/flavonoids found in the same raspberry (p > 0.05).		X		

Disease type/risk	First Author	Study Title Complete Citation	Date	Abstract				
	Liu, Z.	<p>Liu, Z.; Schwimer, J.; Liu, D.; Greenway, F. L.; Anthony, C. T.; Woltering, E. A.,</p> <p>Black raspberry extract and fractions contain angiogenesis inhibitors.</p> <p><i>J Agric Food Chem</i> <b>2005</b>, 53, (10), 3909-15.</p>	2005	<p>Targeted therapies, such as agents that inhibit angiogenesis, offer hope as complementary agents in cancer therapy. Angiogenesis-inhibiting agents have the potential for inhibiting tumor growth and limiting the dissemination of metastasis, thus keeping cancers in a static growth state for prolonged periods. Black raspberry (<i>Rubus occidentalis</i>) extract was discovered to be antiangiogenic (0.1% w/v) in a novel human tissue-based in vitro fibrin clot angiogenesis assay. Assay-guided fractionation of a crude black raspberry extract resulted in a highly potent <b>antiangiogenic fraction that accounted for only 1% of the fresh weight of whole black raspberries</b>. At 0.075% (w/v), the active fraction completely inhibited angiogenic initiation and angiogenic vessel growth. Further subfractionation of this active fraction revealed the coexistence of multiple antiangiogenic compounds, one of which has been identified as gallic acid. However, the individual subfractions did not outperform the active whole fraction. These findings suggest that an active black raspberry fraction may be a promising complementary cancer therapy. It is natural and potent enough for manageable dosing regimens. These extracts contain multiple active ingredients that <b>may be additive or synergistic</b> in their antiangiogenic effects. These observations warrant further investigations in animals and human trials.</p>		X		
	Lu, H.	<p>Lu, H.; Li, J.; Zhang, D.; Stoner, G. D.; Huang, C.,</p> <p>Molecular mechanisms involved in chemoprevention of black raspberry extracts: from transcription factors to their target genes.</p> <p><i>Nutr Cancer</i> <b>2006</b>, 54, (1), 69-78.</p>	2006	<p>Berries have attracted attention for their chemopreventive activities in last a few years. Dietary freeze-dried blackberries have been shown to reduce esophagus and colon cancer development induced by chemical carcinogen in rodents. To elucidate molecular mechanisms involved in chemoprevention by berry extracts, we employed <b>mouse epidermal CI 41 cell</b> line, a well-characterized in vitro model in tumor promotion studies. Pretreatment of CI 41 cells with methanol-extracted blackberry fraction RO-ME resulted in a dramatical inhibition of B(a)PDE-induced activation of AP-1 and NFkB, and expression of VEGF and COX-2. The inhibitory effects of RO-ME on B(a)PDE-induced activation of AP-1 and NFkappaB appear to be mediated via inhibition of MAPKs and IkappaBalpha phosphorylation, respectively. In view of the important roles of AP-1, NFkappaB, VEGF and COX-2 in tumor promotion/progression, and VEGF and COX-2 are target of AP-1 and NFkappaB, we anticipate that the ability of black raspberries to inhibit tumor development may be mediated by impairing signal transduction pathways leading to activation of AP-1 and NFkappaB, subsequently resulting in down-regulation of VEGF and COX-2 expression. The RO-ME fraction appears to be the major fraction responsible for the inhibitory activity of black raspberries.</p>				X

Disease type/risk	First Author	Study Title Complete Citation	Date	Abstract	Human	Human cell	Animal	Animal cell
	Lule, S. U.	Lule, S. U.; Xia, W. S.,  Food phenolics, pros and cons: A review.  <i>Food Reviews International</i> <b>2005</b> , 21, (4), 367-388.	2005	Phenolic compounds like simple phenols, flavonoids, and phenolic acids are commonly in foods of plant origin. Several studies, including animal and epidemiological investigations, have demonstrated that phenolic compounds in foods possess <b>positive attributes</b> such as <b>anticarcinogenesis</b> , antioxidant potential, antiviral activity, antimicrobial activity, and antimutagenic activity. However, other studies have shown that the same phenolics have <b>negative attributes</b> such as carcinogenic activity and antinutritional activity, as well as imparting negative attributes to foods. This review summarizes the information about food phenolics and presents the most current knowledge with respect to its role in human health, food attributes, and toxicity among others.				
	Mahadevan, B.	Mahadevan, B.; Mata, J. E.; Albershardt, D. J.; Rodriguez-Proteau, R.; Baird, W. M.,  The effects of red raspberry extract on PAH transport across Calu-3 cell monolayer, an in vitro cell model.  In 2004; Vol. 2004, pp 740-a-	2004	Chemoprevention has been acknowledged as an important and practical strategy for the management of cancer and naturally occurring substances present in the human diet have been identified as a potential chemopreventive agent. We investigated the potential of phytochemicals in <b>red raspberry extracts (RE) to induce a novel mechanism of chemoprevention</b> of cancer induction by environmental carcinogens such as polycyclic aromatic hydrocarbons (PAH). Studies were also performed to examine the levels of PAH-DNA adducts before transport of PAH and RE across Calu-3 cell monolayer and the effect of RE on their nature of genotoxic DNA damage. Initial analysis indicated that Calu-3 cells do form PAH DNA adducts on treatment with BP and DBP respectively. Experiments were conducted using the Calu-3 cell model of <b>lung epithelial cell</b> transport to characterize the effects of RE on PAH absorption. Benzo[a]pyrene (BP) and dibenzo[a,l]pyrene (DBP) permeability (Pe) from the apical (AP) to basolateral (BL) compartments were $3.35 \times 10^{-5}$ $\pm$ $2.47 \times 10^{-6}$ cm/sec and $1.02 \times 10^{-6}$ $\pm$ $1.56 \times 10^{-7}$ cm/sec, respectively (mean $\pm$ SEM). Addition of 50 $\mu$ g/ml RE significantly ( $P < 0.01$ ) reduced the Pe of BaP to $2.12 \times 10^{-5}$ $\pm$ $2.184 \times 10^{-6}$ cm/sec. 100 $\mu$ g/ml of RE further reduced the Pe of BaP to $2.01 \times 10^{-6}$ $\pm$ $2.32 \times 10^{-6}$ cm/sec ( $P < 0.01$ ). Pe of DBP was significantly inhibited by 50 $\mu$ g/ml RE to $2.57 \times 10^{-7}$ $\pm$ $6.43 \times 10^{-8}$ cm/sec ( $P < 0.05$ ) and 100 $\mu$ g/ml RE to $1.87 \times 10^{-7}$ $\pm$ $4.69 \times 10^{-8}$ cm/sec ( $P < 0.01$ ). RE had no significant effect on Pe from the BL to AP compartments for either PAH. Overall, administration of 100 $\mu$ g/ml of RE indicated a reduction in the absorption of BP by 94 $\pm$ 7.4% and DBP by 81.7 $\pm$ 15.3% respectively. The presence of different types of cyanidins in the RE was confirmed by LC-MS/MS and the identification of the individual components of the extracted fractions that indicate high chemopreventive potential, are in progress. Based on our results, we <b>conclude that phytochemicals present in red raspberries inhibit PAH absorption across Calu-3 cell monolayers.</b>		X		

Disease type/risk	First Author	Study Title Complete Citation	Date	Abstract				
	Myhrstad, M. C.	<p>Myhrstad, M. C.; Carlsen, H.; Dahl, L. I.; Ebihara, K.; Glemmestad, L.; Haffner, K.; Moskaug, J. O.; Blomhoff, R.,</p> <p>Bilberry extracts induce gene expression through the electrophile response element.</p> <p><i>Nutr Cancer</i> <b>2006</b>, 54, (1), 94-101.</p>	2006	<p>A number of genes important for detoxification and antioxidant defense induced by mild stress generated by, for example, physical activity/exercise, caloric restriction, or alcohol may provide health benefits by causing the organism to mount such a defense response. More recently, induction of these defenses has also been attributed to phytochemicals or secondary metabolites from dietary plants. Many polyphenols, which constitute a large fraction of these phytochemicals, increase cellular levels of antioxidants, such as glutathione and other components of the detoxification systems, via the transactivation of genes containing electrophile response elements (EpREs) within their promoters. One such gene, gamma-glutamylcysteine synthetase, has previously been shown to be positively regulated by quercetin, a flavonoid found in high concentrations in onions, apples, and bilberries through EpRE transactivation. As a further step, we have investigated whether bilberries and quercetin have the ability to induce transcription of Fos-related antigen 1 (Fra-1), which contains two EpREs in its promoter. Fra-1 is a member of the activator protein 1 (AP-1) family of transcription factors and, due to the lack of transactivation domain Fra-1, can suppress activation of AP-1. We present results demonstrating that extracts from bilberries, and the flavonoid quercetin, abundant in bilberries, induce the fra-1 promoter and the cellular content of Fra-1 mRNA. We further provide evidence that this induction is mediated through EpREs.</p>		X		
	Narayanan, B. A.	<p>Narayanan, B. A.; Narayanan, N. K.; Stoner, G. D.; Bullock, B. P.,</p> <p>Interactive gene expression pattern in prostate cancer cells exposed to phenolic antioxidants.</p> <p><i>Life Sci</i> <b>2002</b>, 70, (15), 1821-39.</p>	2002	<p>Dietary phenolic compounds are known to elicit vital cellular responses such as cell cycle arrest, apoptosis and differentiation by activating a cascade of molecular events. As there is an increasing interest to improve the efficacy of these compounds for use as potential chemopreventive agents, we wanted to understand the impact of phenolic compounds on target genes in prostate cancer. In this study we used human cDNA microarrays with 2400 clones consisting of 17 prosite motifs to characterize alterations in gene expression pattern in response to the phenolic antioxidants ellagic acid (EA) and resveratrol (RE). Over a 48-hr exposure of androgen - sensitive LNCaP cells to EA and RE, a total of 593 and 555 genes respectively, showed more than a two fold difference in expression. A distinct set of genes in both EA-and RE-treated cells may represent the signature profile of phenolic antioxidant-induced gene expression in LNCaP cells. Although extensive similarity was found between effects of EA - and RE - responsive genes in prostate cancer cells, out of 246 genes with overlapping responses, 25 genes showed an opposite effect. Quantitative RT-PCR was used to verify and validate the differential expression of selected genes identified from cDNA microarrays. In-depth analysis of the data from this study provided insight into the alterations in the p53 - responsive genes, p300, Apaf-1, NF-kBp50 and p65 and PPAR families of genes, suggesting the activation of multiple signaling pathways that leads to growth inhibition of LNCaP cells. This is a first study to look for changes in a large number of human genes in response to dietary compounds.</p>		X		

Disease type/risk	First Author	Study Title Complete Citation	Date	Abstract				
Oral, breast, colon and prostate tumor	Seeram, N.P.	Seeram, N.P.; Adams, L.S.; Zhang, Y.; Lee, R.; Sand, D.; Scheuller, H.S.; and Heber, D.  Blackberry, Black Raspberry, Blueberry, Cranberry, Red Raspberry, and Strawberry Extracts Inhibit Growth and Stimulate Apoptosis of Human Cancer Cells In Vitro.  J. Agric. Food Chem. 2006, 54, 9329-9339.	2006	Berry fruits are widely consumed in our diet and have attracted much attention due to their potential human health benefits. Berries contain a diverse range of phytochemicals with biological properties such as antioxidant, anticancer, anti-neurodegenerative, and anti-inflammatory activities. In the current study, extracts of six popularly consumed berries—blackberry, black raspberry, blueberry, cranberry, red raspberry and strawberries—were evaluated for their phenolic constituents using high performance liquid chromatography with ultraviolet (HPLC-UV) and electrospray ionization mass spectrometry (LCESI-MS) detection. The major classes of berry phenolics were anthocyanins, flavonols, flavanols, ellagitannins, gallotannins, proanthocyanidins, and phenolic acids. The berry extracts were evaluated for their ability to inhibit the growth of human oral (KB, CAL-27), breast (MCF-7), colon (HT-29, HCT116), and prostate (LNCaP) tumor cell lines at concentrations ranging from 25 to 200 µg/mL. With increasing concentration of berry extract, increasing inhibition of cell proliferation in all of the cell lines were observed, with different degrees of potency between cell lines. The berry extracts were also evaluated for their ability to stimulate apoptosis of the COX-2 expressing colon cancer cell line, HT-29. Black raspberry and strawberry extracts showed the most significant pro-apoptotic effects against this cell line. The data provided by the current study and from other laboratories warrants further investigation into the chemopreventive and chemotherapeutic effects of berries using in vivo models.		X		
	Nichenametla, S. N.	Nichenametla, S. N.; Taruscio, T. G.; Barney, D. L.; Exon, J. H., A review of the effects and mechanisms of polyphenolics in cancer. <i>Crit Rev Food Sci Nutr</i> 2006, 46, (2), 161-83.	2006	This paper is a comprehensive review of the effects of bioactive polyphenolic compounds commonly found in many fruits and vegetables on cancer. These include the phenolic acids, anthocyanins, catechins, stilbenes and several other flavonoids. We have attempted to compile information from most of the major studies in this area into one source. The review encompasses the occurrence and bioavailability of the polyphenolics, the in vitro and in vivo evidence for their effects on cancer, both positive and negative, and the various mechanisms by which the chemicals may exert their effects. Although most of the work done to date indicates a chemopreventative activity of these compounds, there are some studies that show cancer-inducing or no effects. There are several common mechanisms by which these chemicals exert their effects that could be conducive to additive, synergistic, or antagonistic interactions. These include effects on cellular differentiation, proliferation, and apoptosis, effects on proteins and enzymes that are involved in these processes at a molecular level, and other various effects through altered immune function and chemical metabolism.				

Disease type/risk	First Author	Study Title Complete Citation	Date	Abstract	Human	Human cell	Animal	Animal cell
	Nohynek, L. J.	Nohynek, L. J.; Alakomi, H. L.; Kahkonen, M. P.; Heinonen, M.; Helander, I. M.; Oksman-Caldentey, K. M.; Puupponen-Pimia, R. H.,  Berry phenolics: antimicrobial properties and mechanisms of action against severe human pathogens.  <i>Nutr Cancer</i> <b>2006</b> , 54, (1), 18-32.	2006	Antimicrobial activity and mechanisms of phenolic extracts of 12 Nordic berries were studied against selected human pathogenic microbes. The most sensitive bacteria on berry phenolics were <i>Helicobacter pylori</i> and <i>Bacillus cereus</i> . <i>Campylobacter jejuni</i> and <i>Candida albicans</i> were inhibited only with phenolic extracts of cloudberry, raspberry, and strawberry, which all were rich in ellagitannins. Cloudberry extract gave strong microbicidal effects on the basis of plate count with all studied strains. However, fluorescence staining of liquid cultures of virulent <i>Salmonella</i> showed viable cells not detectable by plate count adhering to cloudberry extract, whereas <i>Staphylococcus aureus</i> cells adhered to berry extracts were dead on the basis of their fluorescence and plate count. Phenolic extracts of cloudberry and raspberry disintegrated the outer membrane of examined <i>Salmonella</i> strains as indicated by 1-N-phenyl-naphthylamine (NPN) uptake increase and analysis of liberation of [ <sup>14</sup> C]galactose-lipopolysaccharide. Gallic acid effectively permeabilized the tested <i>Salmonella</i> strains, and significant increase in the NPN uptake was recorded. The stability of berry phenolics and their antimicrobial activity in berries stored frozen for a year were examined using <i>Escherichia coli</i> and nonvirulent <i>Salmonella enterica</i> sv. Typhimurium. The amount of phenolic compounds decreased in all berries, but their antimicrobial activity was not influenced accordingly. Cloudberry, in particular, showed constantly strong antimicrobial activity during the storage.	X			
	Olsson, M. E.	Olsson, M. E.; Gustavsson, K. E.; Andersson, S.; Nilsson, A.; Duan, R. D.,  Inhibition of cancer cell proliferation in vitro by fruit and berry extracts and correlations with antioxidant levels.  <i>Journal of Agricultural and Food Chemistry</i> <b>2004</b> , 52, (24), 7264-7271	2004	The effects of 10 different extracts of fruits and berries on cell proliferation of colon cancer cells HT29 and breast cancer cells MCF-7 were investigated. The fruits and berries used were rosehips, blueberries, black currant, black chokeberries, apple, sea buckthorn, plum, lingonberries, cherries, and raspberries. The extracts decreased the proliferation of both colon cancer cells HT29 and breast cancer cells MCF-7, and the effect was concentration dependent. The inhibition effect for the highest concentration of the extracts varied 2-3-fold among the species, and it was in the ranges of 46-74% (average = 62%) for the HT29 cells and 24-68% (average = 52%) for the MCF-7 cells. There were great differences in the content of the analyzed antioxidants in the extracts. The level of the vitamin C content varied almost 100-fold, and the content of total carotenoids varied almost 150-fold among the species. Also in the composition and content of flavonols, hydroxycinnamic acids, anthocyanins, and phenolics were found great differences among the 10 species. The inhibition of cancer cell proliferation seen in these experiments correlated with levels of some carotenoids and with vitamin C levels, present at levels that can be found in human tissues. The same inhibition of cell proliferation could not be found by ascorbate standard alone. This correlation might indicate a synergistic effect of vitamin C and other substances. In MCF-7 cells, the anthocyanins may contribute to the inhibition of proliferation.		X		

Disease type/risk	First Author	Study Title Complete Citation	Date	Abstract				
	Paivarinta, E.	Paivarinta, E.; Pajari, A. M.; Torronen, R.; Mutanen, M.,  Ellagic acid and natural sources of ellagitannins as possible chemopreventive agents against intestinal tumorigenesis in the Min mouse.  <i>Nutr Cancer</i> <b>2006</b> , 54, (1), 79-83.	2006	<b>Ellagic acid</b> has been shown to have chemopreventive effects in various experimental cancer models. We wanted to see whether pure ellagic acid and natural ellagitannins from cloudberry ( <i>Rubus chamaemorus</i> ) seed and pulp have any effect on adenoma formation in Apc-mutated Min <b>mice</b> . From the age of 5 wk, the mice were fed either a control diet, a diet containing pure ellagic acid at 1,564 mg/kg, or diets containing 4.7% (wt/wt) cloudberry seeds or 5.3% cloudberry pulp. The concentrations of ellagitannins and free ellagic acid in the seed diet were 807 and 42 mg/kg and in the pulp diet 820 and 34 mg/kg, respectively. After the 10-wk feeding period, <b>ellagic acid had no effect on the number or size of adenomas</b> in the distal or total small intestine, but it increased adenoma size in the duodenum when compared with the control diet (1.50+/-0.29 vs. 1.16+/-0.31 mm; P=0.029). Neither cloudberry seed nor pulp diets had any effect on the adenoma formation. Chemopreventive effects and mechanisms of whole cloudberry and other similar sources of phenolic compounds should, however, be studied, further taking into account food matrix and interactions with other dietary constituents that may be involved in the bioavailability and metabolism of ellagitannins.			X	
	Parry, J.	Parry, J.; Su, L.; Moore, J.; Cheng, Z.; Luther, M.; Rao, J. N.; Wang, J. Y.; Yu, L. L., Chemical compositions, antioxidant capacities, and antiproliferative activities of selected fruit seed flours. <i>J Agric Food Chem</i> <b>2006</b> , 54, (11), 3773-8.	2006	<b>Seed flours from black raspberry, red raspberry, blueberry, cranberry, pinot noir grape, and chardonnay grape</b> were examined for their total fat content, fatty acid composition, total phenolic content (TPC), total anthocyanin content (TAC), radical scavenging capacities against the peroxy (ORAC) and stable DPPH radicals, chelating capacity against Fe(2+), and antiproliferative activities using the HT-29 <b>colon cancer cell line</b> . Significant levels of fat were detected in the fruit seed flours and their fatty acid profiles may differ from those of the respective seed oils. Cranberry seed flour had the highest level of alpha-linolenic acid (30.9 g/100 g fat) and the lowest ratio of n-6/n-3 fatty acids (1.2/1). The ORAC value of the chardonnay seed flour was 1076.4 Trolox equivalents mumol/g flour, and its TPC was 186.3 mg gallic acid equivalents/g flour. These values were 3-12 times higher than the other tested fruit seed flours. Furthermore, the ORAC value was significantly correlated to the TPC under the experimental conditions (P < 0.05). These fruit seed flours also differed in their TAC values and Fe(2+)-chelating capacities. In addition, black raspberry, cranberry, and chardonnay grape seed flour extracts were evaluated for their antiproliferative effects using HT-29 colon cancer cells. <b>All three tested seed flour extracts significant inhibited HT-29 cell proliferation</b> . The data from this study suggest the potential of developing the value-added use of these fruit seed flours as dietary sources of natural antioxidants and antiproliferative agents for optimal human health.		X		

Disease type/risk	First Author	Study Title Complete Citation	Date	Abstract				
	Premier, R.	Premier, R.,  Phytochemical composition: A paradigm shift for food-health considerations.  <i>Asia Pacific Journal of Clinical Nutrition</i> <b>2002</b> , 11, S197-S201.	2002	Foods derived from plants, such as fruits and vegetables, have been the backbone of human nutrition since the beginning of time. Hunting and fishing supplemented diets with protein-rich foods but nutrition was predominantly based on the availability of plant foods. The importance of various plant foods in the development of some civilizations and economies has been well documented: maize in the Americas, potatoes in parts of Europe after their introduction from the Americas, and wheat in Australia. Plant industries are still the backbone of cultures and economies in almost every corner of the world and production figures support the fact that plant industries are still regarded as the most important source of nutrition. Nutrition parameters found in plant foods vary between crops but there is a consensus that plant foods can supply most, if not all, of the essential components for human nutrition. These components were discovered slowly by trial and error during human history, a classic example was the prevention of scurvy in seafarers. When fresh fruit and vegetables were missing from their diet, they learned that products such as pickled cabbages and citrus, rich in vitamin C, could prevent the manifestation of this debilitating dietary disease. As early as the turn of the century scientists learned that diet not only affected nutrition but also had an effect on health and well-being. But it was not until 1933 that a direct relationship between consumption of fruit and vegetables and diseases such as cancer was shown. Fruit and vegetables not only have become the backbone of local agricultural markets but also play a major role in international trade. Competition for local and international markets is driving extensive research and development to produce new cultivars. Until recent times research has concentrated on producing new varieties that store longer, yield better, look better, taste better, suit local climates, display disease and pest resistance and suit processing technologies. A new wave of research is addressing the newly developing interest in health-based foods. Molecular biologists, biochemists, botanists and medical researchers are linking in with plant breeding programmes to develop new varieties of fruit and vegetables that are tailor-made to produce higher levels of health-related phytochemicals. New phytochemical-enhanced products such as broccoli, tomato, oranges and berries are currently being evaluated for commercial exploitation. The present paper will discuss some of the products that are being produced, the driving forces behind their production, the phytochemicals targeted and the problems that must be addressed if this new approach in human nutrition and health is to be of benefit to consumers.				
	Ramos, S.	Ramos, S.; Alia, M.; Bravo, L.; Goya, L.,  Comparative effects of food-derived polyphenols on the viability and apoptosis of a human hepatoma cell line (HepG2).  <i>J Agric Food Chem</i> <b>2005</b> , 53, (4), 1271-80.	2005	Consumption of fruits and vegetables, which are rich in polyphenols, has been associated with a reduced risk of chronic diseases such as cancer. Dietary polyphenols have antioxidant and antiproliferative properties that might explain their beneficial effect on cancer prevention. The aim of this study was to investigate the effects of different <b>pure polyphenols [quercetin, chlorogenic acid, and (-)-epicatechin] and natural fruit extracts</b> (strawberry and plum) on viability or apoptosis of <b>human hepatoma HepG2 cells</b> . The treatment of cells for 18 h with <b>quercetin</b> and fruit extracts reduced cell viability in a dose-dependent manner; however, chlorogenic acid and (-)-epicatechin had no prominent effects on the cell death rate. Similarly, quercetin and strawberry and plum extracts, rather than chlorogenic acid and (-)-epicatechin, induced apoptosis in HepG2 cells. Moreover, quercetin and fruit extracts arrested the G1 phase in the cell cycle progression prior to apoptosis. <b>Quercetin</b> and strawberry and plum extracts may induce apoptosis and contribute to a reduced cell viability in HepG2 cells.		X		

Disease type/risk	First Author	Study Title Complete Citation	Date	Abstract	Human	Human cell	Animal	Animal cell
	Reen, R. K.	Reen, R. K.; Nines, R.; Stoner, G. D.,  Modulation of N-nitrosomethylbenzylamine metabolism by black raspberries in the esophagus and liver of Fischer 344 rats.  <i>Nutr Cancer</i> <b>2006</b> , 54, (1), 47-57.	2006	Dietary <b>freeze-dried black raspberries (BRBs)</b> inhibit N-nitrosomethylbenzylamine (NMBA)-induced tumorigenesis in the Fischer 344 rat esophagus. To determine the mechanistic basis of the anti-initiating effects of BRBs, NMBA metabolism was studied in esophageal explant <b>cultures and in liver microsomes</b> taken from <b>rats</b> fed with AIN-76A diet or AIN-76A diet containing 5% or 10% BRBs. Five percent and 10% dietary BRBs inhibited NMBA metabolism in explants (26% and 20%) and in microsomes (22% and 28%), but the inhibition was not dose dependent. To identify active inhibitory component(s) in BRBs, esophageal explants and liver microsomes from control rats were treated in vitro with an ethanol extract of BRBs or with individual components of BRBs [ <b>ellagic acid (EA)</b> and two anthocyanins ( <b>cyanidin-3-glucoside</b> and cyanidin-3-rutinoside)]. NMBA metabolism in explants was inhibited 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%). Phenylethylisothiocyanate (PEITC), a potent inhibitor of NMBA tumorigenesis in rat esophagus, was a stronger inhibitor of NMBA metabolism in vivo and in vitro than BRBs or their components. Dietary BRBs and PEITC induced glutathione S-transferase activity in the liver.				X
	Rimando, A. M.	Rimando, A. M.; Barney, D. L.,  Resveratrol and naturally occurring analogues in vaccinium species.  <i>Acta Hort. (ISHS)</i> <b>2005</b> , 680, 137-143	2005	In a continuing study, seventeen samples of berries representing varieties and cultivars of nine <i>Vaccinium</i> species collected from Idaho, Washington, and Wyoming were analyzed for their content of resveratrol, pterostilbene and piceatannol. These naturally occurring stilbenes have been reported to have potential cancer chemopreventive and strong antioxidant activities. Analysis by GC/MS showed contents of 0.26-4.67 and 0.12-2.74 µg/g lyophilized berry for resveratrol and pterostilbene, respectively. Piceatannol was found in only three of the species studied at levels of 0.25-0.61 µg/g lyophilized berries. Enzymatic hydrolysis of the extracts using -D-glucosidase increased resveratrol levels up to 63-fold, suggesting and demonstrating for the first time, that resveratrol also occurs as a glycoside in <i>Vaccinium</i> berries.				

Disease type/risk	First Author	Study Title Complete Citation	Date	Abstract				
	Rimando, A. M.	Rimando, A. M.; Cuendet, M.; Desmarchelier, C.; Mehta, R. G.; Pezzuto, J. M.; Duke, S. O., Cancer chemopreventive and antioxidant activities of pterostilbene, a naturally occurring analogue of resveratrol. <i>J Agric Food Chem</i> <b>2002</b> , 50, (12), 3453-7.	2002	Pterostilbene, a natural methoxylated analogue of resveratrol, was evaluated for antioxidative potential. The peroxy-radical scavenging activity of pterostilbene was the same as that of resveratrol, having total reactive antioxidant potentials of 237 +/- 58 and 253 +/- 53 microM, respectively. Both compounds were found to be more effective than Trolox as free radical scavengers. Using a plant system, pterostilbene also was shown to be as effective as resveratrol in inhibiting electrolyte leakage caused by herbicide-induced oxidative damage, and both compounds had the same activity as alpha-tocopherol. Pterostilbene showed moderate inhibition (IC50 = 19.8 microM) of cyclooxygenase (COX)-1, and was weakly active (IC50 = 83.9 microM) against COX-2, whereas resveratrol strongly inhibited both isoforms of the enzyme with IC50 values of approximately 1 microM. Using a <b>mouse mammary organ culture model</b> , carcinogen-induced <b>preneoplastic lesions</b> were, similarly to resveratrol, <b>significantly inhibited by pterostilbene</b> (ED50 = 4.8 microM), suggesting antioxidant activity plays an important role in this process.				X
	Rodrigo, K. A.	Rodrigo, K. A.; Rawal, Y.; Renner, R. J.; Schwartz, S. J.; Tian, Q.; Larsen, P. E.; Mallery, S. R.,  Suppression of the tumorigenic phenotype in human oral squamous cell carcinoma cells by an ethanol extract derived from freeze-dried black raspberries.  <i>Nutr Cancer</i> <b>2006</b> , 54, (1), 58-68.	2006	Despite focused efforts to improve therapy, 5-yr survival rates for persons with advanced-stage oral squamous cell carcinoma (SCC) remain discouragingly low. Clearly, early detection combined with strategies for local intervention, such as chemoprevention prior to SCC development, could dramatically improve clinical outcomes. Previously conducted oral cavity human chemoprevention trials, however, have provided mixed results. Although some therapies showed efficacy, they were often accompanied by either significant toxicities or circulating antiadenoviral antibodies. It is clearly apparent that identification of nontoxic, effective treatments is essential to prevent malignant transformation of oral epithelial dysplasias. This study employed cell lines isolated from human oral SCC tumors to investigate the effects of a freeze-dried black raspberry ethanol extract (RO-ET) on cellular growth characteristics often associated with a transformed phenotype such as sustained proliferation, induction of angiogenesis, and production of high levels of reactive species. Our results demonstrate that RO-ET suppresses cell proliferation without perturbing viability, inhibits translation of the complete angiogenic cytokine vascular endothelial growth factor, suppresses nitric oxide synthase activity, and induces both apoptosis and terminal differentiation. These data imply that RO-ET is a promising candidate for use as a chemopreventive agent in persons with oral epithelial dysplasia.				

Disease type/risk	First Author	Study Title Complete Citation	Date	Abstract				
Cervical cancer	Ross, H. A.	<p>Ross, H. A.; McDougall, G. J.; Stewart, D.,</p> <p>Antiproliferative activity is predominantly associated with ellagitannins in raspberry extracts.</p> <p><i>Phytochemistry</i> In Press, Corrected Proof.</p>		<p><b>Raspberry extracts</b> enriched in polyphenols, but devoid of organic acids, sugars and vitamin C, were prepared by sorption to C18 solid phase extraction matrices and tested for their ability to inhibit the <b>proliferation of human cervical cancer (HeLa)</b> cells in vitro. The raspberry extract <b>reduced proliferation in a dose-dependent manner</b> whether this was judged by cell number or measurements of cell viability. However, measurements based on cell viability were more accurate and gave an EC50 value of 17.5 [µg/ml gallic acid equivalents (GAE) at day 4 of culture. Raspberry extracts were fractionated by sorption to Sephadex LH-20 into an unbound fraction, which was obviously enriched in anthocyanins, and a bound fraction. The unbound <b>anthocyanin-enriched fraction was much less effective in reducing proliferation</b> than the original extract and gave an EC50 value estimated at 67 [µg/ml. The LH-20 bound fraction was more effective than the original raspberry extract (EC50 = 13 [µg/ml) suggesting that the main anti-proliferative agents were retained in the bound fraction. Analysis of the original extract, the unbound and the LH20 bound fractions by LC-MS confirmed that the unbound fraction was enriched in anthocyanins and the <b>bound fraction primarily contained ellagitannins</b>. The ellagitannin-rich bound fraction had the highest antioxidant capacity as measured by the ferric reducing antioxidant potential (FRAP) assay. The mechanism by which the <b>ellagitannins inhibit proliferation of cancer cells</b> is discussed.</p>		x		
	Roy, S.	<p>Roy, S.; Khanna, S.; Alessio, H. M.; Vider, J.; Bagchi, D.; Bagchi, M.; Sen, C. K.,</p> <p>Anti-angiogenic property of edible berries.</p> <p><i>Free Radic Res</i> <b>2002</b>, 36, (9), 1023-31.</p>	2002	<p>Recent studies show that edible berries may have potent chemopreventive properties. Anti-angiogenic approaches to prevent and treat cancer represent a priority area in investigative tumor biology. Vascular endothelial growth factor (VEGF) plays a crucial role for the vascularization of tumors. The vasculature in adult skin remains normally quiescent. However, skin retains the capacity for brisk initiation of angiogenesis during inflammatory skin diseases such as psoriasis and skin cancers. We sought to test the effects of multiple berry extracts on inducible VEGF expression by <b>human HaCaT keratinocytes</b>. Six berry extracts (wild blueberry, bilberry, cranberry, elderberry, raspberry seed, and strawberry) and a grape seed proanthocyanidin extract (GSPE) were studied. The extracts and uptake of their constituents by HaCaT were studied using a multi-channel HPLC-CoulArray approach. Antioxidant activity of the extracts was determined by ORAC. Cranberry, elderberry and raspberry seed samples were observed to possess comparable ORAC values. The antioxidant capacity of these samples was significantly lower than that of the other samples studied. The ORAC values of strawberry powder and GSPE were higher than cranberry, elderberry or raspberry seed but significantly lower than the other samples studied. Wild bilberry and blueberry extracts possessed the highest ORAC values. Each of the berry samples studied significantly inhibited both H2O2 as well as TNF alpha induced VEGF expression by the human keratinocytes. This effect was not shared by other antioxidants such as alpha-tocopherol or GSPE but was commonly shared by pure flavonoids. Matrigel assay using human dermal microvascular endothelial cells showed that edible berries impair angiogenesis.</p>		X		

Disease type/risk	First Author	Study Title Complete Citation	Date	Abstract	Human	Human cell	Animal	Animal cell
	Seifried, H. E.	Seifried, H. E.; McDonald, S. S.; Anderson, D. E.; Greenwald, P.; Milner, J. A., The antioxidant conundrum in cancer. <i>Cancer Res</i> <b>2003</b> , 63, (15), 4295-8.	2003	The health-related effects of interactions between reactive oxygen species (ROS) and dietary antioxidants and the consequences of dietary antioxidant supplementation on human health are by no means clear. Although ROS, normal byproducts of aerobic metabolism, are essential for various defense mechanisms in most cells, they can also cause oxidative damage to DNA, proteins, and lipids, resulting in enhanced disease risk. Dietary antioxidants (e.g., vitamin E, vitamin C, beta-carotene, and selenium), as well as endogenous antioxidant mechanisms, can help maintain an appropriate balance between the desirable and undesirable cellular effects of ROS. However, any health-related effects of interactions between dietary antioxidants and ROS likely depend on the health status of an individual and may also be influenced by genetic susceptibilities. Clinical studies of antioxidant supplementation and changes in either oxidative status, disease risk, or disease outcome have been carried out in healthy individuals, populations at risk for certain diseases, and patients undergoing disease therapy. The use of antioxidants during cancer therapy is currently a topic of heated debate because of an overall lack of clear research findings. Some data suggest antioxidants can ameliorate toxic side effects of therapy without affecting treatment efficacy, whereas other data suggest antioxidants interfere with radiotherapy or chemotherapy. Overall, examination of the evidence related to potential interactions between ROS and dietary antioxidants and effects on human health indicates that consuming dietary antioxidant supplements has pros and cons for any population and raises numerous questions, issues, and challenges that make this topic a fertile field for future research. Overall, <b>current knowledge makes it premature to generalize and make specific recommendations about antioxidant usage for those at high risk for cancer or undergoing treatment.</b>				
	Skupien, K.	Skupien, K.; Oszmianski, J.; Kostrzewa-Nowak, D.; Tarasiuk, J.,  In vitro antileukaemic activity of extracts from berry plant leaves against sensitive and multidrug resistant HL60 cells.  <i>Cancer Lett</i> <b>2006</b> , 236, (2), 282-91.	2006	The aim of the present study was to determine in vitro antileukaemic activity of extracts obtained from selected berry plant leaves ( <i>Fragaria x ananassa</i> Duch. cv Elsanta, raspberry <i>Rubus ideus</i> L. cv Polana and blueberry <i>Vaccinium corymbosum</i> L. cv Bluecrop) against promyelocytic HL60 cell line and its multidrug resistant sublines exhibiting two different MDR phenotypes: HL60/VINC (overexpressing P-glycoprotein) and HL60/DOX (overexpressing MRP1 protein). It was found that the blueberry extract was the most efficient against sensitive HL60 cell line (about 2-fold more active than strawberry and raspberry extracts) but presented much lower activity towards resistant cells. In contrast, strawberry and raspberry extracts exhibited the high cytotoxic activity against sensitive leukaemia HL60 cell line as well as its MDR sublines. The values of resistance factor (RF) found for these extracts were very low lying in the range 0.32/2.0.		x		

Disease type/risk	First Author	Study Title Complete Citation	Date	Abstract				
	Stoner, G. D.	<p>Stoner, G. D.; Chen, T.; Kresty, L. A.; Aziz, R. M.; Reinemann, T.; Nines, R.,</p> <p>Protection against esophageal cancer in rodents with lyophilized berries: potential mechanisms.</p> <p><i>Nutr Cancer</i> <b>2006</b>, 54, (1), 33-46.</p>	2006	<p>For several years, our laboratory has been evaluating the ability of lyophilized (freeze-dried) black raspberries (<i>Rubus occidentalis</i>, BRBs), blackberries (<i>R. fruticosus</i>, BBs), and strawberries (<i>Fragaria ananassa</i>, STRWs) to inhibit carcinogen-induced cancer in the rodent esophagus. To assure "standardized" berry preparations for study, each berry type is of the same cultivar, picked at about the same degree of ripeness, washed and frozen within 2-4 h of the time of picking, and freeze-dried under conditions that preserve the components in the berries. Some of the known chemopreventive agents in berries include vitamins A, C, and E and folic acid; calcium and selenium; beta-carotene, alpha-carotene, and lutein; polyphenols such as ellagic acid, ferulic acid, p-coumaric acid, quercetin, and several anthocyanins; and phytosterols such as beta-sitosterol, stigmasterol, and kaempferol. In initial bioassays, freeze-dried STRW, BRB, and BB powders were mixed into AIN-76A synthetic diet at concentrations of 5% and 10% and fed to Fischer 344 rats before, during, and after treatment with the esophageal carcinogen N-nitrosomethylbenzylamine (NMBA). At 25 wk of the bioassay, <b>all three berry types were found to inhibit the number of esophageal tumors (papillomas) in NMBA-treated animals</b> by 24-56% relative to NMBA controls. This inhibition correlated with reductions in the formation of the NMBA-induced O6-methylguanine adduct in esophageal DNA, suggesting that the berries influenced the metabolism of NMBA leading to reduced DNA damage. Studies are ongoing to determine the mechanisms by which berries influence NMBA metabolism and DNA adduct formation. BRBs and STRWs were also tested in a postinitiation scheme and were found to inhibit NMBA-induced esophageal tumorigenesis by 31-64% when administered in the diet following treatment of the animals with NMBA. Berries, therefore, inhibit tumor promotion and progression events as well as tumor initiation. In vivo mechanistic studies with BRBs indicate that they reduce the growth rate of premalignant esophageal 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 esophagus. Based upon the preclinical data on rodents, <b>we have initiated prevention trials in humans to determine if berries might exhibit chemopreventive effects in the esophagus.</b></p>			x	
	Stoner, G. D.	<p>Stoner, G. D.; Gupta, A.,</p> <p>Etiology and chemoprevention of esophageal squamous cell carcinoma.</p> <p><i>Carcinogenesis</i> <b>2001</b>, 22, (11), 1737-46.</p>	2001	<p>Squamous cell carcinoma (SCC) of the human esophagus has a multifactorial etiology involving several environmental and/or genetic factors. Current modalities of therapy for this disease offer poor survival and cure rates. Although a number of approaches could be undertaken to reduce the occurrence of esophageal SCC, including changes in lifestyle and improved nutrition, such approaches are not easily implemented. Chemoprevention offers a viable alternative that is likely to be effective against this disease. Clinical investigations in areas of high incidence of esophageal SCC have shown that primary chemoprevention of this disease is feasible, if potent inhibitors are identified. Studies in the Fischer 344 rat model of nitrosamine-induced tumorigenesis have proven valuable in understanding the biology of esophageal SCCs and help identify surrogate end-point biomarkers and putative agents that can be useful in human chemoprevention studies. Several compounds that inhibit tumor initiation by suspected human esophageal carcinogens have been identified using this model. These include diallyl sulfide, isothiocyanates and several polyphenolic compounds. Novel biomarkers, including nuclear/nucleolar morphometry using computer-assisted image analysis of preneoplastic lesions, have been developed to measure efficacy of chemopreventive agents against esophageal SCC. The identification of single agents that inhibit the progression of dysplastic lesions, however, has proven difficult. Results from a food-based approach <b>suggest that the use of freeze-dried berry preparations can affect both initiation and promotion/progression of esophageal SCC in an animal model.</b> These observations provide valuable information for future studies on chemoprevention of cancers of the esophagus in a clinical setting. Given the complex etiology of esophageal SCC, it is felt that the most effective chemoprevention strategies would include agents that reduce mutational events associated with carcinogen exposure in combination with agents that inhibit the progression of intraepithelial dysplasia to invasive cancer.</p>			x	

Disease type/risk	First Author	Study Title Complete Citation	Date	Abstract				
Liver cancer	Weber, C.	Weber, C.; Hai, R.,  Antioxidant capacity and anticancer properties of red raspberry.  <i>Acta Hort. (ISHS) 2002, 585, 451-457.</i>	2002	<b>Fruit extracts from four raspberry cultivars</b> , <i>Rubus idaeus</i> L., 'Heritage', 'Kiwigold', 'Goldie', and 'Anne' were evaluated for total antioxidant capacity and cancer cell antiproliferative activity to study the health benefits of raspberries. The total amount of phenolics and flavonoids for each of the raspberry cultivars was determined. 'Heritage' had the highest total phenolic content (512.70±4.66mg/100g fruit) followed by 'Kiwigold' (451.06±4.45mg/100g fruit), 'Goldie' (427.51±7.51mg/ 100g fruit) and 'Anne' (359.19±3.35mg/100g fruit). Similarly, 'Heritage' contained the highest total flavonoids (103.41±2.04 mg/100g fruit) followed by 'Kiwigold' (87.33±1.83mg/100g fruit), 'Goldie' (84.16±1.82mg/100g fruit) and 'Anne' (63.53±0.65mg/100g fruit). The color of the raspberry juice correlated well to the total phenolic/flavonoid content. 'Heritage' had the highest a/b colorimeter ratio and the darkest colored juice with the highest phenolic/flavonoid content, and 'Anne' had the lowest phytochemical content, the palest color, and lowest a/b ratio. 'Heritage' had the highest total antioxidant activity, followed by 'Kiwigold' and 'Goldie'. 'Anne' had the lowest antioxidant activity of the cultivars tested. <b>The proliferation of HepG2 human liver cancer cells was significantly inhibited in a dose-dependent manner after exposure to the raspberry extracts.</b> The extract equivalent to 50 mg 'Goldie', 'Heritage', and 'Kiwigold' fruit inhibited the proliferation of those cells by 89.43±0.11%, 87.96±0.19% and 87.55±0.98, respectively. 'Anne' had the lowest antiproliferative activity of the cultivars measured, but exhibited a significant inhibition of 70.33±1.15% with an extract equivalent to 50 mg of fruit. The antioxidant activity of each of the cultivars was directly related to the total amount of phenolics and flavonoids (p<0.01), but <b>no significant relationship was found between antiproliferative activity and the total amount of phenolics/flavonoids (p&gt;0.05).</b>		x		
	Wedge, D. E.	Wedge, D. E.; Meepagala, K. M.; Magee, J. B.; Smith, S. H.; Huang, G.; Larcom, L. L., Anticarcinogenic Activity of Strawberry, Blueberry, and Raspberry Extracts to Breast and Cervical Cancer Cells. <i>J Med Food</i> <b>2001</b> , 4, (1), 49-51.	2001	Freeze-dried fruits of two strawberry cultivars, Sweet Charlie and Carlsbad, and two blueberry cultivars, Tifblue and Premier were sequentially extracted with hexane, 50% hexane/ethyl acetate, ethyl acetate, ethanol, and 70% acetone/water at ambient temperature. Each extract was tested separately for in vitro anticancer activity on cervical and breast cancer cell lines. Ethanol extracts from all four fruits strongly inhibited CaSki and SiHa cervical cancer cell lines and MCF-7 and T47-D breast cancer cell lines. An unfractionated aqueous extract of raspberry and the ethanol extract of Premier blueberry significantly inhibited mutagenesis by both direct-acting and metabolically activated carcinogens.		x		

Disease type/risk	First Author	Study Title Complete Citation	Date	Abstract	Human	Human cell	Animal	Animal cell
	Whitley, A. C.	Whitley, A. C.; Stoner, G. D.; Darby, M. V.; Walle, T.,  Intestinal epithelial cell accumulation of the cancer preventive polyphenol ellagic acid--extensive binding to protein and DNA.  <i>Biochem Pharmacol</i> <b>2003</b> , 66, (6), 907-15.	2003	<b>Ellagic acid (EA)</b> , a polyphenol present in many berries, has been demonstrated to be preventive of esophageal cancer in animals both at the initiation and promotion stages. To be able to extrapolate these findings to humans we have studied the <b>transcellular absorption</b> and epithelial cell accumulation of [ <sup>14</sup> C]EA in the <b>human intestinal Caco-2 cells</b> . The apical (mucosal) to basolateral (serosal) transcellular transport of 10 microM [ <sup>14</sup> C]EA was minimal with a P(app) of only 0.13 x 10 <sup>-6</sup> cm/s, which is less than for the paracellular transport marker mannitol. In spite of observations of basolateral to apical efflux, Caco-2 cell uptake studies showed high accumulation of EA in the cells (1054+/-136 pmol/mg protein), indicating facile absorptive transport across the apical membrane. Surprisingly, as much as 93% of the cellular EA was irreversibly bound to macromolecules (982+/-151 pmol/mg protein). To confirm the irreversible nature of the binding to protein, Caco-2 cells treated with 10 microM [ <sup>14</sup> C]EA were subjected to SDS-PAGE analysis. This resulted in radiolabeled protein bands trapped in the stacking gel, consistent with [ <sup>14</sup> C]EA-crosslinked proteins. Treatment of Caco-2 cells with 10 microM [ <sup>14</sup> C]EA also revealed irreversible binding of EA to cellular DNA as much as five times higher than for protein (5020+/-773 pmol/mg DNA). Whereas the irreversible binding to protein required oxidation of EA by reactive oxygen species, this did not seem to be the case with the DNA binding. The avid irreversible binding to cellular DNA and protein may be the reason for its highly limited transcellular absorption. Thus, <b>EA appears to accumulate selectively in the epithelial cells of the aerodigestive tract, where its cancer preventive actions may be displayed.</b>		x		
	Xue, H.	Xue, H.; Aziz, R. M.; Sun, N.; Cassady, J. M.; Kamendulis, L. M.; Xu, Y.; Stoner, G. D.; Klaunig, J. E.,  Inhibition of cellular transformation by berry extracts.  <i>Carcinogenesis</i> <b>2001</b> , 22, (2), 351-6.	2001	Recent studies have examined and demonstrated the potential cancer chemopreventive activity of freeze-dried berries including strawberries and black raspberries. Although ellagic acid, an abundant component in these berries, has been shown to inhibit carcinogenesis both in vivo and in vitro, several studies have reported that other compounds in the berries may also contribute to the observed inhibitory effect. In the present study, freeze-dried strawberries ( <i>Fragaria ananassa</i> , FA) or <b>black raspberries (<i>Rubus ursinus</i>, RU)</b> were extracted, partitioned and chromatographed into several fractions (FA-F001, FA-F003, FA-F004, FA-F005, FA-DM, FA-ME from strawberries and RU-F001, RU-F003, RU-F004, RU-F005, RU-DM, RU-ME from black raspberries). These extracts, along with ellagic acid, were analyzed for anti-transformation activity in the Syrian hamster embryo (SHE) cell transformation model. None of the extracts nor ellagic acid by themselves produced an increase in morphological transformation. For assessment of chemopreventive activity, SHE cells were treated with each agent and benzo[a]pyrene (B[a]P) for 7 days. Ellagic acid, FA-ME and RU-ME fractions produced a dose-dependent decrease in transformation compared with B[a]P treatment only, while other fractions failed to induce a significant decrease. Ellagic acid, FA-ME and RU-ME were further examined using a 24 h co-treatment with B[a]P or a 6 day treatment following 24 h with B[a]P. Ellagic acid showed inhibitory ability in both protocols. FA-ME and RU-ME significantly reduced B[a]P-induced transformation only when co-treated with B[a]P for 24 h. These results suggest that a methanol extract from strawberries and black raspberries may display chemopreventive activity. <b>The possible mechanism by which these methanol fractions (FA-ME, RU-ME) inhibited cell transformation appear to involve interference of uptake, activation, detoxification of B[a]P and/or intervention of DNA binding and DNA repair.</b>				x

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Liver cancer	Yi, W.	Yi, W.; Akoh, C. C.; Fischer, J.; Krewer, G.,  Effects of phenolic compounds in blueberries and muscadine grapes on HepG2 cell viability and apoptosis.  <i>Food Research International</i> <b>2006</b> , 39, (5), 628-638.	2006	Although blueberries and muscadine grapes have high contents of polyphenols, few studies have been conducted to assess their potential effects on cancer cells. The objective of this study was to systematically evaluate the effects of different fractions of phenolic compounds in blueberries and muscadine grapes on <b>HepG2 liver cancer cell viability and apoptosis</b> . Three cultivars of blueberries ('Briteblue', 'Tifblue' and 'Powderblue') and four cultivars of muscadine grapes ('Carlos', 'Ison', 'Noble', and 'Supreme') were assessed in this study. Polyphenols were extracted and further separated into phenolic acids, tannins, flavonols, and anthocyanins using a HLB cartridge and LH-20 column. The major compounds of different fractions were characterized. The phenolic acid fractions of muscadine grapes and blueberries showed a 50% inhibition of HepG2 cell population growth at the level of 1-2 mg/mL. The greatest inhibitory effects were observed from the anthocyanin fractions with 50% inhibitions of cancer cell population growth at concentrations of 70150 and 100-300 µg/mL in blueberries and muscadine grapes, respectively. The flavonol and tannin fractions showed intermediate activities. In addition, DNA fragmentation was measured by using a Cell Death Detection ELISA kit to assess the induction of apoptosis. The <b>anthocyanin fraction resulted in a two- to fourfold increase in DNA fragmentation</b> compared to control in both muscadine grapes and blueberries. These findings of inhibition of cancer cell growth and induction of apoptosis suggest that blueberries and muscadine grapes may contribute to reduction in liver cancer risk.		x		
	Zhao, C.	Zhao, C.; Giusti, M. M.; Malik, M.; Moyer, M. P.; Magnuson, B. A.,  Effects of commercial anthocyanin-rich extracts on colonic cancer and nontumorigenic colonic cell growth.  <i>J Agric Food Chem</i> <b>2004</b> , 52, (20), 6122-8.	2004	Commercially prepared grape ( <i>Vitis vinifera</i> ), bilberry ( <i>Vaccinium myrtillus</i> L.), and chokeberry ( <i>Aronia meloncarpa</i> E.) anthocyanin-rich extracts (AREs) were investigated for their potential chemopreventive activity against colon cancer. The growth of colon-cancer-derived HT-29 and nontumorigenic colonic NCM460 cells exposed to semipurified AREs (10-75 µg of monomeric anthocyanin/mL) was monitored for up to 72 h using a sulforhodamine B assay. All extracts inhibited the growth of HT-29 cells, with chokeberry ARE being the most potent inhibitor. HT-29 cell growth was inhibited approximately 50% after 48 h of exposure to 25 µg/mL chokeberry ARE. Most importantly, the growth of NCM460 cells was not inhibited at lower concentrations of all three AREs, illustrating greater growth inhibition of colon cancer, as compared to nontumorigenic colon cells. Extracts were semipurified and characterized by high-pressure liquid chromatography, spectrophotometry, and colorimetry. Grape anthocyanins were the glucosylated derivatives of five different anthocyanidin molecules, with or without p-coumaric acid acylation. Bilberry contained five different anthocyanidins glycosylated with galactose, glucose, and arabinose. Chokeberry anthocyanins were cyanidin derivatives, monoglycosylated mostly with galactose and arabinose. The varying compositions and degrees of growth inhibition suggest that the anthocyanin chemical structure may play an important role in the growth inhibitory activity of commercially available AREs.				x

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	Carlsen, H.	<p>Carlsen, H.; Myhrstad, M. C.; Thoresen, M.; Moskaug, J. O.; Blomhoff, R.,</p> <p>Berry intake increases the activity of the gamma-glutamylcysteine synthetase promoter in transgenic reporter mice.</p> <p>J Nutr 2003, 133, (7), 2137-40.</p>	2003	<p>A diet rich in fruit and vegetables is associated with decreased risk of disease. One possible mechanism for this is that dietary antioxidants positively regulate protective genes. Toward our goal to identify bioactive compounds with such functions in plants, we developed transgenic <b>mice</b> that express luciferase controlled by the gamma-glutamylcysteine synthetase heavy subunit (GCS(h)) promoter. Mice that consumed a nonpurified diet ad libitum were supplemented with <b>juices or extracts of antioxidant-rich berries</b> for 42 h or 3-4 wk. The treatments generally increased luciferase activity in brain and skeletal muscle and decreased it in liver compared with controls fed water. The same overall pattern was also found in mice fed <b>ellagic acid (EA)</b>, a phenolic acid found in many berries. This change in GCS(h) promoter activity after berry treatment occurred in only approximately 50% of the mice, indicating that they were either responders or nonresponders. Our results demonstrate for the first time that berry extracts rich in polyphenols and EA can induce GCS(h) in vivo. <b>The induction of protective enzymes may be important for the chemopreventive effects of fruits and vegetables.</b></p>			x	