Disease type/risk	First Author	Study Title Complete Citation	Date	Abstract	Human	Human cell	Animal	Animal cell
	Anttonen, M. J.	Anttonen, M. J.; Karjalainen, R. O., Environmental and genetic variation of phenolic compounds in red raspberry. Journal of Food Composition and Analysis 2005, 18, (8), 759-769.	2005	Red raspberry (Rubus idaeus L.) is an economically important berry crop that contains numerous phenolic compounds with potential health benefits. It is known that the content of phenolics is affected by processing factors, but limited information is available on the influence of cultural factors or genotype. To clarify this issue, phenolic compounds were analysed from a diverse range of raspberry cultivars grown under northern European conditions, in Finland.The content of phenolic compounds varied widely and significantly between cultivars. The quercetin content ranged from 0.32 (yellow cultivar) to 1.55 mg/100 g fresh weight (fw) (cv. Balder). The ellagic acid content varied from 38 (cv. Gatineau and cv. Nova) to 118 mg/100 g fw (cv. Ville). The total anthocyanin content varied from close to 0 (yellow cultivars) to 51 mg/100 g fw (cv. Gatineau). The content of total phenolics varied from 192 (cv. Gatineau) to 359 mg/100 g fw (cv. Ville). In addition, environment had a significant effect on the content of quercetin. Thus, breeding material should be evaluated for their potential health benefits over several regions in northern raspberry breeding.				
	Beekwilder, J.	Beekwilder, J.; Jonker, H.; Meesters, P.; Hall, R. D.; van der Meer, I. M.; Ric de Vos, C. H., Antioxidants in raspberry: on-line analysis links antioxidant activity to a diversity of individual metabolites. J Agric Food Chem 2005, 53, (9), 3313-20.	2005	The presence of antioxidant compounds can be considered as a quality parameter for edible fruit. In this paper, we studied the antioxidant compounds in raspberry (Rubus idaeus) fruits by high-performance liquid chromatography (HPLC) coupled to an on-line postcolumn antioxidant detection system. Both developmental and genetic factors were assessed by comparing fruits from a single cultivar of different ripening stages and by comparing ripe fruits of 14 raspberry cultivars, respectively. The HPLC-separated antioxidant compounds were identified using HPLC-photodiode array coupled to mass spectrometry (quadrupole time-of-flight tandem mass spectrometry), using a reference lock mass for determining accurate masses. The dominant antioxidants could be classified as anthocyanins, ellagitannins, and proanthocyanidin-like tannins. During fruit ripening, some anthocyanins were newly produced, while others, like cyanidin-3-glucoside, were already present early in fruit development. The level of tannins, both ellagitannins and proanthocyanidin-like tannins, was reduced strongly during fruit ripening. Among the 14 cultivars, major differences (>20-fold) were observed in the levels of pelagonidin type anthocyanins and some proanthocyanidin type tannins. The content of ellagitannins varied approximately 3-fold. The findings presented here suggest that the content of individual health-promoting compounds varies significantly in raspberry, due to both developmental and genetic factors. This information will assist in the future development and identification of raspberry lines with enhanced health-promoting properties.				

Disease type/risk	First Author	Study Title Complete Citation	Date	Abstract	Human	Human cell	Animal	Animal cell
	Chanjirakul, K.	Chanjirakul, K.; Wang, S. Y.; Wang, C. Y.; Siriphanich, J., Effect of natural volatile compounds on antioxidant capacity and antioxidant enzymes in raspberries. *Postharvest Biology and Technology* **2006,** 40, (2), 106-115.	2006	Changes in antioxidant capacity and antioxidant enzyme activities in raspberries (Rubus idaeus L.) treated with methyl jasmonate (W), allyl isothiocyanate (AITC), essential oil of Melaleuca alternifolia (tea tree oil or TTO), and ethanol (EtOH) were studied. All of the natural volatile compounds tested reduced the severity of decay during storage at 10 degrees C compared to the control. Most of these natural volatile treatments promoted the antioxidant capacity and antioxidant enzyme activities except AITC treatment. The MJ treatment had the highest antioxidant capacity expressed as oxygen radical absorbance capacity (ORAC) values after storage for 7 and 14 days. Raspberry extract from the MJ treatment also showed the highest activity in all antioxidant enzymes, including superoxide dismutase (SOD), guaiacol peroxidase (G-POD), ascorbate peroxidase (AsA-POD), glutathione peroxidase (GSH-POD), glutathione reductase (GR), monodehydroascorbate reductase (MDAR), and dehydroascorbate reductase (DHAR). Moreover, the MJ treatment showed the highest amount of ascorbate (AsA), dehydroascorbate (DHAsA), reduced glutathione (GSH), and oxidized glutathione (GSSG) compared to the other treatments. Even though AITC showed the best result for decay inhibition among all the treatments, it did not increase the antioxidant capacity or the antioxidant enzyme activities. These results indicate that MJ may increase the resistance of tissues to decay through enhancing their antioxidant system and their free radical scavenging capability, while AITC may retard the decay directly by its antimicrobial properties.				
	Deighton, N.	Deighton, N., Stewart, D., Davies, H.V., Gardner, P.T., Duthie, G.G., Mullen, W. and Crozier, A. , Soft fruit as sources of dietary antioxidants. *Acta Hort. (ISHS)* **2002,** 585, 459-465.	2002	Antioxidant capacities were determined on a range of soft fruit, including Fragaria, Rubus and Ribes. These covered a wide range although, in general, the most coloured fruit exhibited the greatest antioxidant abilities. The colour was derived from anthocyanin compounds whose antioxidant efficacy depended of the number of hydroxyl groups and the degree and type of glycosylation. However, antioxidant capacity of the fruit did not directly relate to anthocyanin or vitamin C content. A strong correlation with total phenol content suggests that other polyphenols also contribute to the antioxidant capacity of soft fruit. Determination of total phenols may form the basis of a simple screen in breeding programmes aimed at increasing the antioxidant status of fruit.				

Disease type/risk	First Author	Study Title Complete Citation	Date	Abstract	Human	Human cell	Animal	Animal cell
	Hannum, S. M.,	Hannum, S. M., Potential impact of strawberries on human health: a review of the science. *Crit Rev Food Sci Nutr* **2004,** 44, (1), 1-17.	2004	Epidemiological studies have noted a consistent association between the consumption of diets rich in fruits and vegetables and a lower risk for chronic diseases including cancer and cardiovascular disease. There is accumulating evidence that much of the health-promoting potential of these plant foods may come from phytochemicals, bioactive compounds not designated as traditional nutrients. In strawberries, the most abundant of these are ellagic acid, and certain flavonoids: anthocyanin, catechin, quercetin and kaempferol. These compounds in strawberries have potent antioxidant power. Antioxidants help lower risk of cardiovascular events by inhibition of LDL-cholesterol oxidation, promotion of plaque stability, improved vascular endothelial function, and decreased tendency for thrombosis. Furthermore, strawberry extracts have been shown to inhibit COX enzymes in vitro, which would modulate the inflammatory process. Individual compounds in strawberries have demonstrated anticancer activity in several different experimental systems, blocking initiation of carcinogenesis, and suppressing progression and proliferation of tumors. Preliminary animal studies have indicated that diets rich in strawberries may also have the potential to provide benefits to the aging brain.				
	Jiao, Z. G.	Jiao, Z. G.; Liu, J. C.; Wang, S. X., Antioxidant activities of total pigment extract from blackberries. Food Technology and Biotechnology 2005, 43, (1), 97-102.	2005	Total pigment has been extracted from blackberries and its antioxidant activity against lipid peroxidation and scavenging capacities towards superoxide anion radicals, hydroxyl radicals and nitrite in different in vitro systems have been investigated. The total pigment extract from blackberries (TPEB) exhibited strong antioxidant activity against lipid peroxidation in a linoleic acid model system and scavenging capacities towards superoxide anion radicals, generated by a pyrogallol autoxidation system or by an illuminating riboflavin system, hydroxyl radicals generated by Fenton reaction, and nitrite. Furthermore, the antioxidant activities were correlated with the concentrations of the TPEB. In the test concentration range, the maximum inhibition percentage against linoleic acid peroxidation was 98.32% after one week's incubation, and the maximum scavenging percentages for the free radicals and nitrite inhibition in the above reactive systems reached 90.48, 96.48, 93.58 and 98.94%, respectively. The TPEB is a natural, edible colorant with excellent antioxidant activities and health benefits and it seems to be applicable in both healthy food and medicine.				

Disease type/risk	First Author	Study Title Complete Citation	Date	Abstract	Human	Human cell	Animal	Animal cell
	Kim, H.	Kim, H.; Yoon, Y. J.; Shon, J. H.; Cha, I. J.; Shin, J. G.; Liu, K. H., Inhibitory effects of fruit juices on CYP3A activity. Drug Metab Dispos 2006, 34, (4), 521-3.	2006	There have been very limited reports on the effects of commercial fruit juices on human CYP3A activity. Therefore, the inhibitory effects of readily available commercial fruit juices on midazolam 1'-hydroxylase activity, a marker of CYP3A, were evaluated in pooled human liver microsomes. The fruit juices investigated were black raspberry, black mulberry, plum, and wild grape. White grapefruit, pomegranate, and orange juice were used as positive and negative controls. The black mulberry juice showed the most potent inhibition of CYP3A except for grapefruit juice. The inhibition depended on the amount of a fruit juice added to the incubation mixture. The inhibitory potential of human CYP3A was in the order: grapefruit > black mulberry > wild grape > pomegranate > black raspberry. The IC(50) values of all fruit juices tested were reduced after preincubation with microsomes in the presence of the NADPH-generating system, suggesting that a mechanism-based inhibitory component was present in these fruit juices, as in the case of grapefruit. The results suggest that, like grapefruit juice, commercial fruit juices also have the potential to inhibit CYP3A-catalzyed midazolam 1'-hydroxylation. Therefore, in vivo studies investigating the interactions between fruit juices such as black mulberry and wild grape and CYP3A substrates are necessary to determine whether inhibition of CYP3A activity by fruit juices is clinically relevant.		X		
	Laitinen, L. A.	Laitinen, L. A.; Tammela, P. S.; Galkin, A.; Vuorela, H. J.; Marvola, M. L.; Vuorela, P. M., Effects of extracts of commonly consumed food supplements and food fractions on the permeability of drugs across Caco-2 cell monolayers. Pharm Res 2004, 21, (10), 1904-16.	2004	PURPOSE: Extracts made from berries, herbs, and various plant materials, which might possess a range of activities, are used as health promoting products. Because little is known about their effects on the absorption of co-administered drugs, the effects of some food supplements, Finnish berries, and herbs were studied on the permeability of some commonly used drugs. METHODS: The permeabilities of verapamil, metoprolol, ketoprofen, paracetamol, and furosemide were studied across Caco-2 cell monolayers with contemporaneously administered extracts from flax seed, purple loosestrife, and Scots pine bark; bilberries, cowberries, and raspberries; oregano, rosemary, and sage. Toxicological tests were conducted to determine cellular damage. RESULTS: The effects of extracts on drug permeabilities were generally minor. Flax seed decreased the permeability of all drugs except verapamil. Purple loosestrife and pine decreased verapamil and metoprolol permeability. Changes caused by berries were mainly pH-related. Rosemary and oregano enhanced furosemide permeability. CONCLUSIONS: Ingestion of extracts of herbs and berries studied are not expected to markedly change the permeabilities of highly permeable drugs. Harmful effects at sites of or during absorption are unlikely. However, if high doses of extracts are administered with low permeable drugs in vitro, effects on drug permeabilities could not be excluded. Use of such extracts should therefore be evaluated during continuous medication.		X		

Disease type/risk	First Author	Study Title Complete Citation	Date	Abstract	Human	Human cell	Animal	Animal cell
	Marniemi, J.	Marniemi, J.; Hakala, P.; Maki, J.; Ahotupa, M., Partial resistance of low density lipoprotein to oxidation in vivo after increased intake of berries. Nutr Metab Cardiovasc Dis 2000, 10, (6), 331-7.	2000	BACKGROUND AND AIM: The health-promoting effects of fruit- and vegetable-based diets are known to be associated with their antioxidative components. We found in our preliminary in vitro laboratory tests that extracts of many common Finnish edible berries are potent scavengers of peroxyl radicals and inhibitors of lipid peroxidation. We therefore designed the current study to evaluate both the long-term (8 weeks) and short-term (5 hours) effects of increased intake of three berries on antioxidant potential and lipid peroxidation. METHODS AND RESULTS: Healthy 60-year-old men were randomized to berry, supplement and control groups (20 men in each group). The berry group ate, in addition to their normal diet, a 100 g portion of deep-frozen berries (bilberries, lingonberries, or black currants) daily for 8 weeks. The other groups ingested daily 100 mg of alpha-tocopherol and 500 mg of ascorbic acid (supplement group) or 500 mg of calcium gluconate (control group). In the short-term experiment 6 men ate 80 g of each of the three berries in one go. Serum ascorbate concentrations increased significantly in both the berry and the supplement group. Serum alpha-tocopherol levels and the antioxidant potential (TRAP) in low density lipoprotein (LDL) increased in the supplement group only. In the berry group, slightly lowered LDL diene conjugation ($p = 0.074$) and slightly increased total serum TRAP ($p = 0.084$) values were observed. No changes were found in these measures in the supplement or the control group. In the short-term experiment, LDL TRAP showed a small increase (about 10%, $p = 0.039$) during five hours after the intake of 240 g berries. CONCLUSIONS: The effects of consumption of berries on antioxidant potential and diene conjugation in LDL particles in vivo appear to be small.	X			
	McGhie, T. K.	McGhie, T. K.; Ainge, G. D.; Barnett, L. E.; Cooney, J. M.; Jensen, D. J., Anthocyanin glycosides from berry fruit are absorbed and excreted unmetabolized by both humans and rats. J Agric Food Chem 2003, 51, (16), 4539-48.	2003	Anthocyanins, the red/blue pigments found in plants, are polyphenolic compounds consumed by humans and are part of a normal diet. Recent studies have shown that anthocyanins have substantial bioactivity including antioxidant activity and therefore may have beneficial effects on human health. Anthocyanins are a group of over 500 compounds of diverse structures containing different core phenolic aglycons and conjugated with sugars in a variety of glycosylation patterns. In this study, we have investigated the bioabsorption of 15 anthocyanins with structures containing different aglycons and conjugated sugars extracted from blueberry, boysenberry, black raspberry, and blackcurrant in both humans and rats. Intact and unmetabolized anthocyanins were detected in urine of rats and humans following dosing for all molecular structures investigated, thus demonstrating that anthocyanins with diverse molecular structure and from different dietary sources are bioavailable at diet relevant dosage rates. In addition, the relative concentrations of anthocyanins detected in urine following dosing varied, indicating that differences in bioavailability are due to variations in chemical structure. Our results suggest that the nature of the sugar conjugate and the phenolic aglycon are both important determinants of anthocyanin absorption and excretion in rats and humans.	X		X	

Disease type/risk	First Author	Study Title Complete Citation	Date	Abstract	Human	Human cell	Animal	Animal cell
	Martin, L. J.	Martin, L. J.; Matar, C., Increase of antioxidant capacity of the lowbush blueberry (Vaccinium angustifolium) during fermentation by a novel bacterium from the fruit microflora. Journal of the Science of Food and Agriculture 2005, 85, (9), 1477-1484.	2005	Members of the genus Vaccinium, such as blueberry and cranberry, are known to be excellent sources of antioxidant phenolic compounds, for example anthocyanins, flavonols and phenolic acids. The fruit also provides a natural habitat for numerous microorganisms. Interaction between the fruit and the microflora might affect the antioxidant phenolic compounds. The aim of this study was to investigate the effects on phenolic content and antioxidant capacity of wild blueberry fermented by a newly identified bacterium isolated from blueberry-fruit surface microflora, Serratia vaccinii. Increase in the antioxidant capacity following fermentation of blueberries by the novel bacterium, as determined with the 2,2'-diphenyl-1-picrylhydrazyl method, was attributed not only to an increase in total phenolics, but also to a change in the phenolic profile, as demonstrated by the production of gallic acid and of a novel compound of phenolic or phenylpropanoic structure.				
	Nikitina, V. S.	Nikitina, V. S.; Shendel, G. V.; Gerchikov, A. Y.; Efimenko, N. B., Flavonoids from Raspberry and Blackberry Leaves and Their Antioxidant Activities. Pharmaceutical Chemistry Journal 2000, V34, (11), 596-598.	2000	Studies with the aims of finding plants containing flavonoids and developing methods for extracting phytocomplexes of biologically active substances, identifying their biological activities, and creating therapeutic agents are currently of great relevance. The ranges of therapeutic activities of both individual flavonoids and flavonoids overall have led to the creation of many therapeutic forms of plant flavonoids. Data on the chemical structures of a variety of flavonoids have been obtained, and the fundamental mechanisms of action of flavonoids as antioxidants, anti-inflammatories, antisclerotics, cardiotonics, radioprotectors, antitumor agents, hepatoprotectors, and antiviral agents have been identified. The berry plants European raspberry and blackberry, which are grown in many countries because of their medicinal fruits, have leaves containing a rich complex of biologically active substances. Raspberry leaves are known to contain quercetin, kaempferol, hyperoside, isoquercitrine, aphceline, astragaline, and kaempferol rhamnoside; blackberry leaves contain leukoanthocyanidins, and anthocyanins: pelargonidine mono- and diglucosides, cyanidine 3-glucoside, and cyanidine 3-rutinoside]3]. Hypolipidemic, hepatoprotective, and cholagogic activities have been demonstrated for complexes from the leaves of European and Anatolian blackberries. The authors associated the pharmacological properties of the phytocomplexes from these plants with antioxidant properties and demonstrated the need for developing new therapeutic agents. The aims of the present work were to prepare dry extracts of flavonoids from raspberry and blackberry leaves and test them for antioxidant activity, and to study the leaves of different varieties of raspberry and blackberry as raw materials for therapeutic flavonoids.				

Disease type/risk	First Author	Study Title Complete Citation	Date	Abstract	Human	Human cell	Animal	Animal cell
	Pantelidis, G. E.	Pantelidis, G. E.; Vasilakakis, M.; Manganaris, G. A.; Diamantidis, G., Antioxidant capacity, phenol, anthocyanin and ascorbic acid contents in raspberries, blackberries, red currants, gooseberries and Cornelian cherries. Food Chemistry In Press, Corrected Proof.		Raspberry (Rubus idaeus), blackberry (Rubus fructicosus), raspberry x blackberry hybrids, red currant (Ribes sativum), gooseberry (Ribes glossularia) and Cornelian cherry (Cormus mas) cultivars and native populations of varied pigmentation, originally from the Mediterranean area of Northern Greece, were assayed for antioxidant activity (determined as ferric reducing antioxidant power (FRAP) and deoxyribose protection), ascorbic acid, phenol, and anthocyanin contents. FRAP values ranged from 41 to 149 [mu]mol ascorbic acid g-1 dry weight and protection of deoxyribose ranged from 16.1% up to 98.9%. Anthocyanin content ranged from 1.3, in yellow-coloured fruit, up to 223 mg cyanidin-3-glucoside equivalents 100 g-1 fresh weight in Cornelian cherry, whereas phenol content ranged from 657 up to 2611 mg gallic acid equivalents 100 g-1dry weight. Ascorbic acid content ranged from 14 up to 103 mg 100 g-1 fresh weight. The present study outlines that the native Cornelian cherry population is an extremely rich source of antioxidants, demonstrating its potential use as a food additive.				
	Prior, R. L.	Prior, R. L.; Hoang, H.; Gu, L. W.; Wu, X. L.; Bacchiocca, M.; Howard, L.; Hampsch-Woodill, M.; Huang, D. J.; Ou, B. X.; Jacob, R., Assays for hydrophilic and lipophilic antioxidant capacity (oxygen radical absorbance capacity (ORAC(FL))) of plasma and other biological and food samples. Journal of Agricultural and Food Chemistry 2003, 51, (11), 3273-3279.	2003	Methods are described for the extraction and analysis of hydrophilic and lipophilic antioxidants, using modifications of the oxygen radical absorbing capacity (ORAC(FL)) procedure. These methods provide, for the first time, the ability to obtain a measure of "total antioxidant capacity" in the protein free plasma, using the same peroxyl radical generator for both lipophilic and hydrophilic antioxidants. Separation of the lipophilic and hydrophilic antioxidant fractions from plasma was accomplished by extracting with hexane after adding water and ethanol to the plasma (hexane/plasma/ethanol/water, 4:1:2: 1, v/v). Lipophilic and hydrophilic antioxidants were efficiently partitioned between hexane and aqueous solvents. Conditions for controlling temperature effects and decreasing assay variability using fluorescein as the fluorescent probe were validated in different laboratories. Incubation (37 degreesC for at least 30 min) of the buffer to which AAPH was dissolved was critical in decreasing assay variability. Lipophilic antioxidants represented 33.1 +/- 1.5 and 38.2 +/- 1.9% of the total antioxidant capacity of the protein free plasma in two independent studies of 6 and 10 subjects, respectively. Methods are described for application of the assay techniques to other types of biological and food samples.				

Disease type/risk	First Author	Study Title Complete Citation	Date	Abstract	Human	Human cell	Animal	Animal cell
	Prior, R. L	Prior, R. L.; Wu, X. L.; Gu, L. W.; Hoang, H.; Jacob, R., Plasma lipophilic and hydrophilic antioxidant status in human subjects: effects of meals containing different berries or fruits. Faseb Journal 2003, 17, (5), A1114-A1114.	2003	No abstract				
	Rimando, A. M.	Rimando, A. M.; Nagmani, R.; Feller, D. R.; Yokoyama, W., Pterostilbene, a new agonist for the peroxisome proliferator-activated receptor alpha-isoform, lowers plasma lipoproteins and cholesterol in hypercholesterolemic hamsters. *J Agric Food Chem* **2005,** 53, (9), 3403-7.	2005	Resveratrol, a stilbenoid antioxidant found in grapes, wine, peanuts and other berries, has been reported to have hypolipidemic properties. We investigated whether resveratrol and its three analogues (pterostilbene, piceatannol, and resveratrol trimethyl ether) would activate the peroxisome proliferator-activated receptor alpha (PPARalpha) isoform. This nuclear receptor is proposed to mediate the activity of lipid-lowering drugs such as the fibrates. The four stilbenes were evaluated at 1, 10, 100, and 300 microM along with ciprofibrate (positive control), for the activation of endogenous PPARalpha in H4IIEC3 cells. Cells were transfected with a peroxisome proliferator response element-AB (rat fatty acyl CoA beta-oxidase response element)-luciferase gene reporter construct. Pterostilbene demonstrated the highest induction of PPARalpha showing 8- and 14-fold increases in luciferase activity at 100 and 300 microM, respectively, relative to the control. The maximal luciferase activity responses to pterostilbene were higher than those obtained with the hypolipidemic drug, ciprofibrate (33910 and 19460 relative luciferase units, respectively), at 100 microM. Hypercholesterolemic hamsters fed with pterostilbene at 25 ppm of the diet showed 29% lower plasma low density lipoprotein (LDL) cholesterol, 7% higher plasma high density lipoprotein (HDL) cholesterol, and 14% lower plasma glucose as compared to the control group. The LDL/HDL ratio was also statistically significantly lower for pterostilbene, as compared to results for the control animals, at this diet concentration. Results from in vitro studies showed that pterostilbene acts as a PPARalpha agonist and may be a more effective PPARalpha agonist and hypolipidemic agent than resveratrol. In vivo studies demonstrate that pterostilbene possesses lipid and glucose lowering effects.			X	

Disease type/risk	First Author	Study Title Complete Citation	Date	Abstract	Human	Human cell	Animal	Animal cell
	Scalzo, J.	Scalzo, J.; Mezzetti, B.; Hall, H.;McGhie, T. Comparing methods for evaluation of raspberry's quality *Acta Hort. (ISHS)* **2004** 649, 327-330.	2004	Antioxidant activity (AA), Anthocyanin Content (ACY) and other fruit characters including color, Soluble Solids (SS) and Titratable Acidity (TA) were determined for raspberry cultivars, selections and offsprings cultivated at Hortresearch, Nelson Region, New Zealand. Two methods to assess the AA have been used: TEAC (Trolox Equivalent Antioxidant Analysis) and FRAP (Ferric reducing antioxidant power), strongly correlated with each other (r = 0.858). Correlation between AA and ACY was found (data not shown). Our results demonstrate that AA in raspberry is different among cultivars, selections and families and could be improved by a breeding program.				
	Rodriguez-Proteau, R.	Rodriguez-Proteau, R.; Mata, J. E.; Miranda, C. L.; Fan, Y.; Brown, J. J.; Buhler, D. R., Plant polyphenols and multidrug resistance: effects of dietary flavonoids on drug transporters in Caco-2 and MDCKII-MDR1 cell transport models. Xenobiotica 2006, 36, (1), 41-58.	2006	The hypothesis tested was that specific flavonoids such as epicatechin gallate, epigallocatechin gallate, genistein, genistin, naringenin, naringin, quercetin and xanthohumol will modulate cellular uptake and permeability (P(e)) of multidrug-resistant substrates, cyclosporin A (CSA) and digoxin, across Caco-2 and MDCKII-MDR1 cell transport models. (3)H-CSA/(3)H-digoxin transport and uptake experiments were performed with and without co-exposure of the flavonoids. Aglycone flavonoids reduced the P(e) of CSA to a greater extent than glycosylated flavonoids with 30 microM xanthohumol producing the greatest effect (7.2 x 10(-6) to 6.6 x 10(-7) and 17.9 x 10(-6) to 4.02 x 10(-6) cm s(-1) in Caco-2 and MDCKII-MDR1 cells, respectively); while no measurable effects were seen with digoxin. Xanthohumol significantly demonstrated (1) saturable efflux, (2) increased uptake of (3)H-digoxin and (3) decreased uptake of (3)H-CSA in the Caco-2 cells. The transport data suggests that xanthohumol effects transport of CSA in a manner that is distinct from the digoxin efflux pathway and suggests that intestinal transport of these MDR1 substrates is more complex than previously reported.				

Disease type/risk	First Author	Study Title Complete Citation	Date	Abstract	Human	Human cell	Animal	Animal cell
	Rojas-Vera, J.	Rojas-Vera, J.; Patel, A. V.; Dacke, C. G., Relaxant activity of raspberry (Rubus idaeus) leaf extract in guinea-pig ileum in vitro. Phytother Res 2002, 16, (7), 665-8.	2002	Tea made from the leaves of Rubus idaeus L. (raspberry) has been used for centuries as a folk medicine to treat wounds, diarrhoea, colic pain and as a uterine relaxant. Extracts of dried raspberry leaves prepared with different solvents, (n-hexane, ethyl acetate, chloroform and methanol) were tested in vitro for relaxant activity on transmurally stimulated guinea-pig ileum. The methanol (MeOH) extract exhibited the largest response and also indicated that the active compounds are of a relatively polar nature. Hence the bulk of the leaves were extracted with methanol and the dried extract fractionated on a silica gel column, eluting with chloroform, mixtures of chloroform and methanol and finally methanol. Each fraction was examined by thin layer chromatography and tested for relaxant activity in an in vitro transmurally stimulated guinea-pig ileum preparation. The fractions eluted with chloroform (CHCl(3)) lacked relaxant activity. Samples eluted with CHCl(3)/MeOH (95:5) had moderate relaxant activity, while a second distinctive peak of activity eluted with a more polar solvent mixture (CHCl(3)/MeOH 50:50) provided strong dose dependent responses. Evidence was obtained that there are at least two components of raspberry leaf extract which exhibit relaxant activity in an in vitro gastrointestinal preparation.				
	Scalzo, J.	Scalzo, J.; Mezzetti, B.; Battino, M., Total antioxidant capacity evaluation: critical steps for assaying berry antioxidant features. Biofactors 2005, 23, (4), 221-7.	2005	No abstract				

Disease type/risk	First Author	Study Title Complete Citation	Date	Abstract	Human	Human cell	Animal	Animal cell
	Seeram, N. P.	Seeram, N. P.; Momin, R. A.; Nair, M. G.; Bourquin, L. D., Cyclooxygenase inhibitory and antioxidant cyanidin glycosides in cherries and berries. Phytomedicine 2001, 8, (5), 362-9.	2001	Anthocyanins from tart cherries, Prunus cerasus L. (Rosaceae) cv. Balaton and Montmorency; sweet cherries, Prunus avium L. (Rosaceae); bilberries, Vaccinum myrtillus L. (Ericaceae); blackberries, Rubus sp. (Rosaceae); blueberries var. Jersey, Vaccinium corymbosum L. (Ericaceae); cranberries var. Early Black, Vaccinium macrocarpon Ait. (Ericaceae); elderberries, Sambucus canadensis (Caprifoliaceae); raspberries, Rubus idaeus (Rosaceae); and strawberries var. Honeoye, Fragaria x ananassa Duch. (Rosaceae), were investigated for cyclooxygenase inhibitory and antioxidant activities. The presence and levels of cyanidin-3-glucosylrutinoside 1 and cyanidin-3-rutinoside 2 were determined in the fruits using HPLC. The antioxidant activity of anthocyanins from cherries was comparable to the commercial antioxidants, tert-butylhydroquinone, butylated hydroxytoluene and butylated hydroxyanisole, and superior to vitamin E, at a test concentration of 125 microg/ml. Anthocyanins from raspberries and sweet cherries demonstrated 45% and 47% cyclooxygenase-I and cyclooxygenase-II inhibitory activities, respectively, when assayed at 125 microg/ml. The cyclooxygenase inhibitory activities of anthocyanins from these fruits were comparable to those of ibuprofen and naproxen at 10 microM concentrations. Anthocyanins 1 and 2 are present in both cherries and raspberry. The yields of pure anthocyanins 1 and 2 in 100 g Balaton and Montmorency tart cherries, sweet cherries and raspberries were 21, 16.5; 11, 5; 4.95, 21; and 4.65, 13.5 mg, respectively. Fresh blackberries and strawberries contained only anthocyanin 2 in yields of 24 and 22.5 mg/100 g, respectively. Anthocyanins 1 and 2 were not found in bilberries, blueberries, cranberries or elderberries.				
	Stoner, G. D.	Stoner, G. D.; Sardo, C.; Apseloff, G.; Mullet, D.; Wargo, W.; Pound, V.; Singh, A.; Sanders, J.; Aziz, R.; Casto, B.; Sun, X., Pharmacokinetics of anthocyanins and ellagic acid in healthy volunteers fed freeze-dried black raspberries daily for 7 days. J Clin Pharmacol 2005, 45, (10), 1153-64.	2005	Eleven subjects completed a clinical trial to determine the safety/tolerability of freeze-dried black raspberries (BRB) and to measure, in plasma and urine, specific anthocyanins-cyanidin-3-glucoside, cyanidin-3-sambubioside, cyanidin-3-rutinoside, and cyanidin-3-xylosylrutinoside, as well as ellagic acid. Subjects were fed 45 g of freeze-dried BRB daily for 7 days. Blood samples were collected predose on days 1 and 7 and at 10 time points postdose. Urine was collected for 12 hours predose on days 1 and 7 and at three 4-hour intervals postdose. Maximum concentrations of anthocyanins and ellagic acid in plasma occurred at 1 to 2 hours, and maximum quantities in urine appeared from 0 to 4 hours. Overall, less than 1% of these compounds were absorbed and excreted in urine. None of the pharmacokinetic parameters changed significantly between days 1 and 7. In conclusion, 45 g of freeze-dried BRB daily are well tolerated and result in quantifiable anthocyanins and ellagic acid in plasma and urine.	X			

Disease type/risk	First Author	Study Title Complete Citation	Date	Abstract	Human	Human cell	Animal	Animal cell
	Talavera, S.	Talavera, S.; Felgines, C.; Texier, O.; Besson, C.; Gil-Izquierdo, A.; Lamaison, J. L.; Remesy, C., Anthocyanin metabolism in rats and their distribution to digestive area, kidney, and brain. J Agric Food Chem 2005, 53, (10), 3902-8.	2005	Anthocyanins are present in human diet due to their wide occurrence in fruits and beverages. They possess antioxidant activities and could be involved in several health effects. The aim of this study was to investigate anthocyanin metabolism and distribution in the digestive area organs (stomach, jejunum and liver) and kidney, as well as a target tissue (brain) in rats fed with a blackberry (Rubus fruticosus L.) anthocyanin-enriched diet for 15 days. Identification and quantification of anthocyanin metabolites was carried out by HPLC-ESI-MS-MS and HPLC-DAD, respectively. The stomach exhibited only native blackberry anthocyanins (cyanidin 3-O-glucoside and cyanidin 3-O-pentose), while in other organs (jejunum, liver, and kidney) native and methylated anthocyanins as well as conjugated anthocyanidins (cyanidin and peonidin monoglucuronides) were identified. Proportions of anthocyanin derivatives differed according to the organ considered, with the liver presenting the highest proportion of methylated forms. Jejunum and plasma also contained aglycone forms. In the brain, total anthocyanin content (blackberry anthocyanins and peonidin 3-O-glucoside) reached 0.25 +/- 0.05 nmol/g of tissue (n = 6). The urinary excretion of total anthocyanins was low (0.19 +/- 0.02% of the ingested amount). Thus, organs of the digestive area indicated a metabolic pathway of anthocyanins with enzymatic conversions (methylation and/or glucurono-conjugation). Moreover, following consumption of an anthocyanin-rich diet, anthocyanins enter the brain.			X	
	Talavera, S.	Talavera, S.; Felgines, C.; Texier, O.; Besson, C.; Manach, C.; Lamaison, J. L.; Remesy, C., Anthocyanins are efficiently absorbed from the small intestine in rats. J Nutr 2004, 134, (9), 2275-9.	2004	Anthocyanins are natural pigments that possess antioxidant activities and are implicated in various health effects. Recent studies showed that the stomach is a site of anthocyanin absorption. However, the fate of anthocyanins in the small intestine remains unknown. We therefore investigated anthocyanin absorption after in situ perfusion of the jejunum + ileum in rats. The intestine was perfused for 45 min with a physiological buffer supplemented with various anthocyanins. Purified anthocyanin glycosides (9.2 nmol/min) or blackberry (9.0 nmol/min) or bilberry (45.2 nmol/min) anthocyanins were perfused. A high proportion of anthocyanin glycosides was absorbed through the small intestine after perfusion. The rate of absorption was influenced by the chemical structure of the anthocyanin and varied from 10.7 (malvidin 3-glucoside) to 22.4% (cyanidin 3-glucoside). Regardless of the anthocyanins perfused, only glycosides were recovered in the intestinal lumen. After perfusion of a high amount of blackberry anthocyanins (600 nmol/min), native cyanidin 3-glucoside was recovered in urine and plasma from the aorta and mesenteric vein. Methylated and/or glucuronidated derivatives were also identified. Analysis of bile samples revealed that cyanidin 3-glucoside and its methylated derivatives (peonidin 3-glucoside + peonidin glucuronide) quickly appeared in bile. This study demonstrated that anthocyanin glycosides are rapidly and efficiently absorbed from the small intestine. Furthermore, anthocyanins are quickly metabolized and excreted into bile and urine as intact glycosides as well as methylated forms and glucuronidated derivatives.			X	

Disease type/risk	First Author	Study Title Complete Citation	Date	Abstract	Human	Human cell	Animal	Animal cell
	Tian, Q.	Tian, Q.; Giusti, M. M.; Stoner, G. D.; Schwartz, S. J., Urinary excretion of black raspberry (Rubus occidentalis) anthocyanins and their metabolites. J Agric Food Chem 2006, 54, (4), 1467-72.	2006	Anthocyanins are the most abundant phenolic compounds, widely distributed in fruits and vegetables, and exhibit potent antioxidant capacity. Humans ingest a significant amount of anthocyanins in the daily diet. The objective of the current study was to examine human absorption and metabolism of black raspberry anthocyanins when administered at high doses (2.69 +/- 0.085 g/day). Ten healthy men consumed 45 g of freeze-dried black raspberries daily for 1 week. Urine samples were collected over a 12 h period in 4 h intervals at day 1 and day 7. Urinary anthocyanins were analyzed by high-performance liquid chromatography coupled to a photodiode array detector and a tandem mass spectrometer using precursor ion and product ion analyses. Anthocyanins were excreted in intact forms and metabolized into methylated derivatives in human urine. The urinary excretion of anthocyanins reached a maximum concentration (1091.8 +/- 1081.3 pmol/L, n = 10) during the 4-8 h period after black raspberry ingestion. As compared to the anthocyanin distribution in black raspberries, urinary cyanidin 3-xylosylrutinoside was detected at a higher concentration than that of cyanidin-3-rutinoside.				
	Viljanen, K.	Viljanen, K.; Kylli, P.; Kivikari, R.; Heinonen, M., Inhibition of protein and lipid oxidation in liposomes by berry phenolics. J Agric Food Chem 2004, 52, (24), 7419-24.	2004	The antioxidant activity of berry phenolics (at concentrations of 1.4, 4.2, and 8.4 mug of purified extracts/mL of liposome sample) such as anthocyanins, ellagitannins, and proanthocyanidins from raspberry (Rubus idaeus), bilberry (Vaccinium myrtillus), lingonberry (Vaccinium vitis-idaea), and black currant (Ribes nigrum) was investigated in a lactalbumin-liposome system. The extent of protein oxidation was measured by determining the loss of tryptophan fluorescence and formation of protein carbonyl compounds and that of lipid oxidation by conjugated diene hydroperoxides and hexanal analyses. The antioxidant protection toward lipid oxidation was best provided by lingonberry and bilberry phenolics followed by black currant and raspberry phenolics. Bilberry and raspberry phenolics exhibited the best overall antioxidant activity toward protein oxidation. Proanthocyanidins, especially the dimeric and trimeric forms, in lingonberries were among the most active phenolic constituents toward both lipid and protein oxidation. In bilberries and black currants, anthocyanins contributed the most to the antioxidant effect by inhibiting the formation of both hexanal and protein carbonyls. In raspberries, ellagitannins were responsible for the antioxidant activity. While the antioxidant effect of berry proanthocyanidins and anthocyanins was dose-dependent, ellagitannins appeared to be equally active at all concentrations. In conclusion, berries are rich in monomeric and polymeric phenolic compounds providing protection toward both lipid and protein oxidation.				

Disease type/risk	First Author	Study Title Complete Citation	Date	Abstract	Human	Human cell	Animal	Animal cell
	Wu, X.	Wu, X.; Beecher, G. R.; Holden, J. M.; Haytowitz, D. B.; Gebhardt, S. E.; Prior, R. L., Concentrations of anthocyanins in common foods in the United States and estimation of normal consumption. J Agric Food Chem 2006, 54, (11), 4069-75.	2006	Anthocyanins (ACNs) are water-soluble plant pigments that have important functions in plant physiology as well as possible health effects. Over 100 common foods were screened for ACNs, and 24 of them were found to contain ACNs. Concentrations of total ACNs varied considerably from 0.7 to 1480 mg/100 g of fresh weight in gooseberry ('Careless' variety) and chokeberry, respectively. Not only does the concentration vary, but the specific anthocyanins present in foods are also quite different. Only six common aglycones, delphinidin, cyanidin, petunidin, pelargonidin, peonidin, and malvidin, were found in all of these foods. However, their sugar moieties and acylation patterns varied from food to food. Results from this study will add to the available data for the USDA Nutrient Database of flavonoids. On the basis of the concentration data and updated food intake data from NHANES 2001-2002, the daily intake of ACNs is estimated to be 12.5 mg/day/person in the United States. Of the different aglycones, cyanidin, delphinidin, and malvidin were estimated to contribute 45, 21, and 15%, respectively, of the total ACN intake. Nonacylated contributed 77% compared to 23% from acylated ACNs.				
	Wang, C. Y.	Wang, C. Y., Maintaining postharvest quality of raspberries with natural volatile compounds. *International Journal of Food Science and Technology* **2003,** 38, (8), 869-875.	2003	The postharvest quality of raspberries (Rubus idaeus L.) was evaluated after treatment with several natural volatile compounds and storage at 0, 10 or 20 degreesC. At high storage temperature (20 degreesC), raspberries deteriorated rapidly and none of the natural volatile compounds that were used were effective in extending storage life of the fruit. At low storage temperature (0 degreesC), little difference could be discerned among the various volatile treatments. However, at 10 degreesC storage, raspberries treated with methyl jasmonate (MJ), allyl isothiocyanate (AITC), tea tree oil (TTO), or absolute ethyl alcohol had less decay. MJ- and TTO-treated fruit also maintained higher levels of sugars, organic acids and oxygen radical absorbance capacity compared with untreated fruit. Samples treated with acetic acid or vinegar vapour did not differ from control fruit. Measurement of oxygen and carbon dioxide concentrations within the containers during storage revealed that none of the treatments caused accumulation or depletion of these gases to a level that would be harmful to raspberries. Colour measurements of the berries showed that all raspberry fruit became darker and less red after storage, but fruit treated with MJ were found to have the highest intensity of red colour while AITC application caused the berries to appear lighter in colour.				

Disease type/risk	First Author	Study Title Complete Citation	Date	Abstract	Human	Human cell	Animal	Animal cell
	Wu, X.	Wu, X. L.; Beecher, G. R.; Holden, J. M.; Haytowitz, D. B.; Gebhardt, S. E.; Prior, R. L., Lipophilic and hydrophilic antioxidant capacities of common foods in the United States. *Journal of Agricultural and Food Chemistry* **2004,** 52, (12), 4026-4037.	2004	Both lipophilic and hydrophilic antioxidant capacities were determined using the oxygen radical absorbance capacity (ORAC(FL)) assay with fluorescein as the fluorescent probe and 2,2'-azobis(2-amidinopropane) dihydrochloride as a peroxyl radical generator on over 100 different kinds of foods, including fruits, vegetables, nuts, dried fruits, spices, cereals, infant, and other foods. Most of the foods were collected from four different regions and during two different seasons in U.S. markets. Total phenolics of each sample were also measured using the Folin-Ciocalteu reagent. Hydrophilic ORAC(FL) values (H-ORAC(FL)) ranged from 0.87 to 2641 mumol of Trolox equivalents (TE)/g among all of the foods, whereas lipophilic ORAC(FL) values (L-ORAC(FL)) ranged from 0.07 to 1611 mumol of TE/g. Generally, L-ORAC(FL) values were <10% of the H-ORAC(FL) values except for a very few samples. Total antioxidant capacity was calculated by combining L-ORAC(FL) and H-ORAC(FL). Differences of ORAC(FL) values in fruits and vegetables from different seasons and regions were relatively large for some foods but could not be analyzed in detail because of the sampling scheme. Two different processing methods, cooking and peeling, were used on selected foods to evaluate the impact of processing on ORAC(FL). The data demonstrated that processing can have significant effects on ORAC(FL). Considering all of the foods analyzed, the relationship between TP and H-ORAC(FL) showed a very weak correlation. Total hydrophilic and lipophilic antioxidant capacity intakes were calculated to be 5558 and 166 mumol of TE/clay, respectively, on the basis of data from the USDA Continuing Survey of Food Intakes by Individuals (1994-1996).				
	Wu, X.	Wu, X. L.; Gu, L. W.; Holden, J.; Haytowitz, D. B.; Gebhardt, S. E.; Beecher, G.; Prior, R. L., Development of a database for total antioxidant capacity in foods: a preliminary study. Journal of Food Composition and Analysis 2004, 17, (3-4), 407-422.	2004	For the first time, a database of the antioxidant capacities of both the lipophilic and hydrophilic components of foods has been developed using the modified oxygen radical absorbance capacity (ORAC(FL)) assay and a peroxyl radical generator. For lipophilic components, randomly methylated beta-cyclodextrin was used as a solubility enhancer. Four representative samples were extracted directly with the hydrophilic solvent (acetone: water: acetic acid, 70:29.5:0.5). Their ORACFL values were similar to that obtained for hydrophilic ORAC(FL) (H-ORAC(FL)) following lipophilic extraction with hexane:dichloromethane (1:1). Lipophilic ORAC values (L-ORAC(FL)) were relatively low compared to H-ORAC(FL), ranging from 0.11 +/- 0.06 to 154.70 +/- 3.58 mumol TE/g of fresh or dry weight, whereas H-ORAC(FL) ranged from 1.23 +/- 0.17 to 175.24 +/- 10.36 mumol TE/g of fresh or dry weight. Total antioxidant capacity (TAC) was calculated as the sum of the lipophlic and hydrophilic ORACFL values. L-ORAC(FL) as a percentage of TAC ranged from 0.27% to 63.70%. Sampling time during the year significantly influenced lipophilic and/or hydrophilic ORAC(FL) values in some food samples. In order to get an accurate total antioxidant capacity of a given food sample, both lipophilic and hydrophilic fractions need to be measured. Food processing, such as cooking or peeling, need to be considered as additional factors which can introduce variation in antioxidant capacity measurements of foods.				

Disease type/risk	First Author	Study Title Complete Citation	Date	Abstract	Human	Human cell	Animal	Animal cell
	Wu, X.	Wu, X. L.; Pittman, H. E.; Prior, R. L., Pelargonidin is absorbed and metabolized differently than cyanidin after marionberry consumption in pigs. Journal of Nutrition 2004, 134, (10), 2603-2610.	2004	Weaning pigs (7.9 +/- 1.7 kg) were fed a freeze-dried powder of marionberry (MB) by stomach tube to study the absorption and metabolism of anthocyanins. Four major anthocyanins (ACNs) were found in MB: cyanidin-3-glucoside (Cy-3-glc, 78%), cyanidin-3-rutinoside (Cy-3-rutin, 20%), pelargonidin-3-glucoside (Pg-3-glc, 0.4%), and 1 unknown acylated cyanidin-based ACN (UACy, 1.5%). In the urine, the 4 original ACNs and 11 metabolites were identified and quantified. The main metabolites were glucuronidated and/or methylated forms of the original anthocyanins. Total recovery of the 4 original ACNs plus their related metabolites was 0.087 +/- 0.034% for Cy-3-glc, 0.084 +/- 0.026% for Cy-3-rutin, 0.583 +/- 0.229% for Pg-3-glc and 0.036 +/- 0.011% for UACy (mean +/-SD, n = 3), respectively. For the individual ACNs, the amount of metabolites recovered from Cy-3-rutin was lower than that of the original intact Cy-3-rutin, whereas the amounts of metabolites from Cy-3-glc and Pg-3-glc in the urine were much higher than their original forms. In pig plasma, the 2 original ACNs, Cy-3-glc and Cy-3-rutin, and a trace of 1 metabolite (cyanidin monoglucuronide) were detected. The plasma concentration: dose ratio of Cy-3-rutin was higher than that of Cy-3-glc. Different aglycones and/or sugar moieties may influence the absorption and metabolism of ACNs. Cy-3-glc and Cy-3-rutin had similar apparent excretion rates relative to dose, whereas Pg-3-glc had a much higher total urinary excretion than cyanidin-based anthocyanins. Most of Cy-3-glc and Pg-3-glc were excreted in the form of metabolites, whereas most of the Cy-3-rutin was excreted in its original unmetabolized form. Urinary recovery of the acylated anthocyanin was lower than that of nonacylated anthocyanins.				