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Berries and Health: A review of the evidence

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Introduction

Berries already benefit from a "health halo" which is partly associated with a general recognition that fruit is good for us and that they are popular and palatable way to increase intake. In addition soft fruit and health have long established associations steeped in traditions with strong linkages to Scottish[1] and world folklore (see http://www.fruit.cornell.edu/berry/production/pdfs/berryfolklore.pdf). Indeed, many traditional or folk medicines have used berries in remedies for a range of health issues[2]. For example, North American indigenous peoples have used berries from the *Rubus* species as treatments against diarrhoea and for pain relief. However, evidence has accrued over the last twenty years highlighting that components from berries have measurable beneficial effects on health[3]. This report provides a short overview of the current evidence.

In botanical terms, "berries" are defined as a fleshy fruit that arises from the entire plant ovary that surrounds the seeds and therefore true berries include bananas, grapes, blueberries, black currants and coffee beans. In this review, we use the common usage of "berries" and this includes soft fruits with multiple seeds including strawberries, raspberries, blueberries, black currants, blackberries etc. Strawberries are the most popular berries in the UK market but there have been consistent increases in sales of other berries (http://www.internationalsupermarketnews.com/news/4680) and indeed in a range of "berry-plus" products.

The health beneficial components of berries can be split into nutritional and non-nutritional components[4]. Nutritionally-speaking, berries are generally low in calories; fats and sodium but contain essential minerals, dietary fibre (including soluble fibres such as pectins) and vitamin C (see Table 1).

Table 1 Nutritional components in selected berries

COMPONENT	Black currant	Raspberry	Strawberry	Cloudberry	Bilberry	Cranberry	Sea buckthorn
MACRO-COMPONENTS							
Energy kJ (Kcal)	247 (59)	172 (41)	195 (47)	225 (54)	184 (44)	136 (33)	377 (90)
Carbohydrate, available (g)	7.8	4.1	8.4	7.8	6.4	3.5	6.3
Fat, total (g)	0.4	0.8	0.2	0.5	0.6	0.7	5.0
Protein, total	1.1	1.0	0.5	1.4	0.5	0.4	0.7
CARBOHYDRATE COMPONENTS (g)							
Organic acids, total	2.7	2.0	1.6	0	1.4	1.4	2
Starch, total	0	0	0	0	0	0	0
Sugars, total	7.8	4.1	8.4	7.8	6.4	3.5	6.3
Sucrose	0.3	0.3	2.3	< 0.1	0.5	< 0.1	< 0.1
Glucose	3.5	1.6	3.1	4.0	3.0	2.2	3.7
Fructose	4.0	2.2	3.0	3.7	2.9	1.2	2.5
Fibre, total	5.8	3.7	1.9	6.3	3.3	3.3	6
Fibre, water-insoluble	3.0	3.3	1.5	5.8	2.6	2.8	5.1
Non-cellulosic polysaccharides, water-soluble	1.9	0.4	0.9	0.5	0.5	0.5	0.9
FATS							
Fatty acids, total (g)	0.1	0.2	0.2	0.3	0.4	0.3	2.9

Fatty acids, total saturated (g)	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	0.8
Fatty acids, monounsaturated* (g)	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	1.6
Fatty acids, polyunsaturated (g)	< 0.1	0.1	0.1	0.2	0.2	0.3	0.3
Linoleic acid (mg)	45	55	64	84	123	125	250
α-linolenic acid (mg)	27	53	64	75	117	143	90
Cholesterol (mg)	0	0	0	0	0	0	0
Total sterols (mg)	8.8	27.4	10	17.8	26.4	17.8	17.8
MINERALS (mg)							
Sodium	0.5	0.7	0.7	1.5	0.3	0.9	3.5
Salt	1.3	1.8	1.8	3.8	0.8	2.3	8.9
Potassium	340	220	190	170	110	25	133
Magnesium	24	25	15	29	9	8	30
Calcium	72	35	21	16	19	13	42
Phosphorus	58	37	30	36	20	10	8.6
Iron	1.2	1.1	0.5	0.7	0.6	0.7	0.4
Zinc	0.3	0.4	0.1	0.6	0.2	0.2	0.0
Iodide (μg)	1.0	1.0	1.0	1.0	1.0	1.0	0.0
Selenium (μg)	0.1	0.1	0.1	0.1	0.1	0.1	< 0.1
VITAMINS and OTHERS							
Vitamin A [retinol activity equiv. (μg)]	8.2	1.1	0.9	14.4	3.9	1.8	2.6
Vitamin D (μg)	0	0	0	0	0	0	0

Vitamin E [α-tocopherol (mg)]	2.2	0.9	0.6	3.0	1.9	0.9	3.0
Vitamin K (μg)	30	10.2	5.5	9.0	9.0	9.0	11.3
Vitamin C (ascorbic acid, mg)	120	38	60	100	15	20	165
Folate (μg)	7.7	33.0	35.6	30.0	11.5	2.0	10.0
Niacin equivalents (μg)	0.5	0.7	0.7	0.8	0.6	0.2	0.4
Riboflavin	0.07	0.07	0.07	0.07	0.07	0.07	0.07
Thiamin (vitamin B1, mg)	0.05	0.01	0.03	0.06	0.04	0.05	0.18
Pyridoxine vitamers (mg)	0.08	0.09	0.06	0.09	0.06	0.06	0.13
Carotenoids (μg)	542.2	95.9	44.5	240.9	310.5	50.0	158.6

All data was extracted from the FINELI database - http://www.fineli.fi/foodlist.php?foodname=A%&lang=en

*- all monounsaturated FA are in *cis*-form

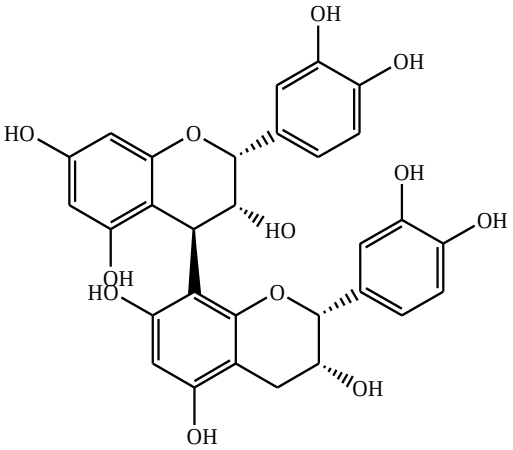
Most berries contain sugars such as glucose, fructose and sucrose which contribute to their sweetness. All berries contain carotenoids, including components that are precursors of vitamin A. The levels of some vitamins are nutritionally-significant e.g. black currants can supply 40 % RDA for vitamin K/100g. In addition, raspberries, strawberries and cloudberries can supply approx. 15-18 % RDA for folate/100g.

Berries are best known for their accumulation of antioxidant components (mainly polyphenols, carotenoids and vitamin C) and have amongst the highest antioxidant capacity of commonly-eaten foods[5]. The amounts of these antioxidant components vary between berry species, between varieties and can be influenced by growing conditions. For example, berry species differ greatly in their vitamin C content with black currants and sea buckthorn containing levels that exceed the RDA in a single 100 g portion (Table 1) whereas some berries (e.g. current commercial blueberries) can have negligible levels[6]. Certain berries, such as sea buckthorn, are rich in carotenoids but also accumulate more fats. The vast majority of these fats are unsaturated. Carotenoids, in addition to those that act as precursors for vitamin A, contribute to the health benefits of berries[7].

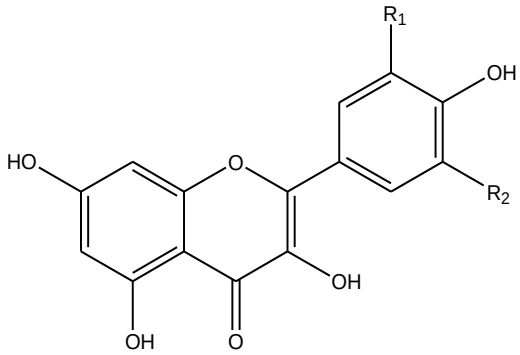
Total polyphenol content also can vary hugely between berry species, varieties and under different growing conditions. Total polyphenol contents of 300-100 mg/100g are common for black currant, raspberry and strawberry[8]. In addition, the levels of these antioxidant components can be heavily influenced by post-harvest treatments and processing[9] so their levels must be validated in any product.

The composition of polyphenols can define the colour and palatability of different berry species and influence their possible beneficial effects on health. Polyphenols are a diverse family of components which differ in structure and potential bioactivity. The red-to-purple-to-blue colouration of berries is due to the presence of polyphenol pigments called anthocyanins (Fig. 1).

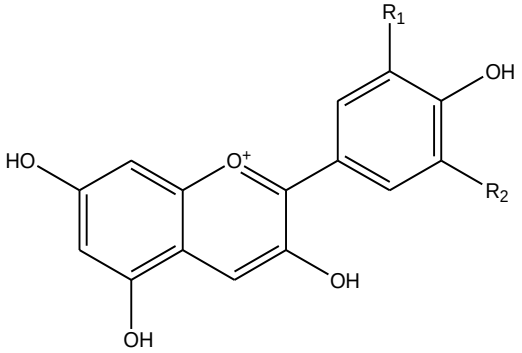
Figure 1 Structures of polyphenols found in berries



The proanthocyanidin dimer B2. Proanthocyanidins are found in a range of berries and are associated with a range of health benefits.

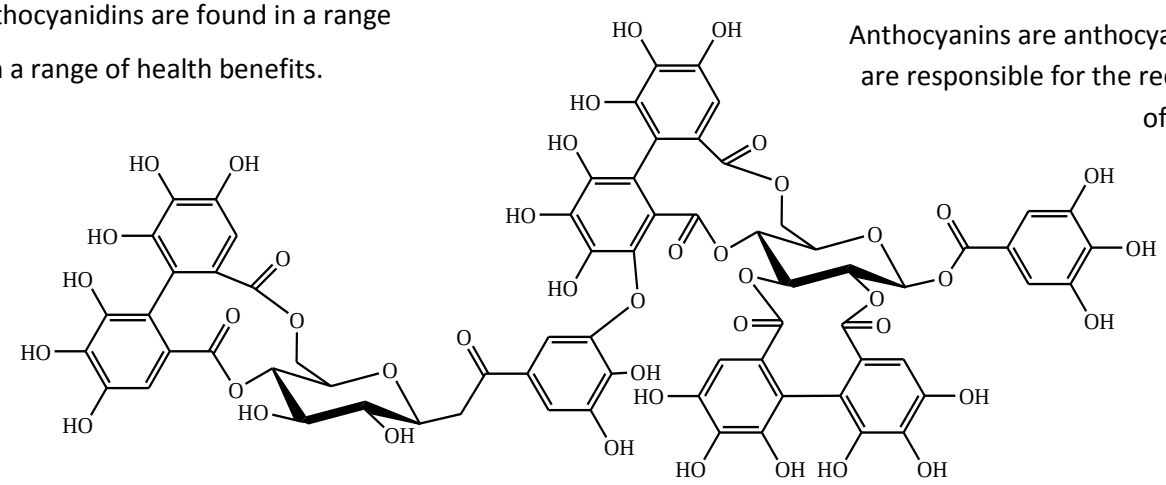


Flavonol	R_1	R_2
Kaempferol	H	H
Quercetin	OH	H
Isorhamnetin	OCH_3	H
Myricetin	OH	OH



Anthocyanidin	R_1	R_2
Pelargonidin	H	H
Cyanidin	OH	H
Delphinidin	OH	OH
Peonidin	OH	H
Petunidin	OCH_3	OH
Malvidin	OCH_3	OCH_3

Anthocyanins are anthocyanidins with attached sugars and are responsible for the red-to-blue-to-purple colouration of berries



The ellagitannin, Sanguiin H-10, is one of the main antioxidant components in raspberry and contributes to its characteristic astringency.

Their composition can vary greatly between berry species – the red-orange colour of strawberries is due to the presence of pelargonidin-type anthoycanins in the flesh and skin whereas the deep purple-black colour of black currants is due to the accumulation of high amounts of delphinidin and cyanidin-type anthocyanins in the skin. The levels and composition of anthocyanins vary between species and varieties, degree of ripening and growing conditions[10].

Although the primary driver for flavour in berries is acid/sugar balance, polyphenol components can influence taste or sensory perception. The presence of tannins, such as ellagitannins in raspberry or ellagitannins and proanthocyanins in strawberry, contributes the characteristic astringency of these berries[11]. Flavonol components may also contribute the bitter undertones of certain berry taste profiles. Berry species and varieties have characteristic compositions of polyphenols largely determined by genetic parameters but these can be influenced by growth conditions.

Over the last twenty years, a concept has developed that the high antioxidant capacity of polyphenol components could contribute to health benefits by acting to ameliorate the detrimental effects of reactive oxygen species (ROS) generated in the body through metabolism with oxygen. It was proposed that the polyphenols could act as chain-breaking agents preventing the ROS from instigating free radical cascades that could damage cells, DNA and membranes and through accumulation causes diseases[12]. However, this simple and attractive precept is not generally tenable and high antioxidant capacity in the test-tube does not automatically translate into *in vivo* effectiveness. Although berry polyphenols may have high antioxidant capacity in the test tube, their effectiveness is limited by their often low uptake into the blood stream. Indeed, the effectiveness of even the small proportion taken up in to the serum is exacerbated by further metabolism in the liver and excretion through the bile or urine[13]. In many cases, the original components are effectively absent and their circulating metabolites may differ greatly in structure and potential function[14]. Again, it should be noted that different polyphenols have different stabilities, bioavailability and therefore potential effectiveness.

Berry polyphenols that are not taken up into the blood stream could still have beneficial functions in the gastrointestinal tract (GIT) as they pass through the digestive system such as preventing the formation of oxidation products from foods in the stomach and GIT[15] or by influencing food digestion, glucose levels and calorie usage[16]. Berry polyphenols that pass through the upper digestive tract and reach the colon are subject to fermentation by bacteria and this produces phenolic metabolites that recirculate in the bloodstream, which could be the causative agents for beneficial effects[14]. Fermentation by colonic bacteria also releases polyphenols tightly bound to the berry flesh or skin and are not released by digestive processes.

Therefore the issue of *bioavailability* overshadows much work carried out in model systems [such as cell lines, *in vitro* models and *ex vivo* (excised tissue) systems]. The issue can be framed as a simple question

“Can the berry polyphenol components reach their supposed targets in the body in sufficient amounts to cause the beneficial effect?”

Nevertheless, many such studies using cell lines or *in vitro* model systems have provided useful information. For example, such studies can precede and inform expensive and time-consuming human studies and, in certain cases, indicate possible mechanisms of actions that underlie health benefits. For example, studies on human cancer cells grown in culture can provide a means to assess possible

mechanisms of anti-cancer effects[17] and *in vitro* assays carried out at physiologically-achievable concentrations can confirm inhibition of key digestive enzymes by berry polyphenols[16].

The following section lays out the current evidence that berry intake can have beneficial effects on cancers, cardiovascular disease (CVD), diabetes, neurodegenerative diseases and other conditions.

Cancers

There is considerable evidence that berry components from raspberries, black currants, strawberries and other less common berries can influence the proliferation of human cancer cell lines grown in model systems. Evidence of this type has been obtained from a range of cancer lines originating from different organs and body locations from prostate to lung, breast to colon and blood to cervical cancers.

Many studies have not adequately defined their source material so making assumptions about effective components is impossible and sometimes certain components are proposed to be causative without sufficient evidence. Previous studies at the James Hutton Institute suggested that ellagitannins from raspberry were particularly effective against cancer cells[18] but others[19] found that hexane extracts from *Rubus* species were more effective than methanol or ethyl acetate extracts against colon, lung, breast and gastric cancer cells. This suggested that non-polar components, such as fats or terpenes extracted from the berry seeds, may also be effective anticancer agents.

Considering the problems of bioavailability outlined above, the use of cell lines derived from GIT cancers which could be in contact with active components in the digestive trait could be more physiologically-relevant models[20]. It is important to tease out that the effects of the berry components are specifically anti-cancer rather than generally cytotoxic. Studies on “normal” versus “tumourigenic” cells can be very relevant in this regard[21].

Cell-based models can be usefully employed to examine new and complex areas. For example, long-term chronic exposure to low levels of environmental carcinogens could cause the transformation of normal human breast epithelial cells into precancerous cells[22] and it was noted that application of proanthocyanidins could ameliorate this transformation. Researchers also noted that anthocyanidins co-administered with paclitaxel, a mitotic inhibitor used in cancer chemotherapy, increased the effectiveness of this anti-cancer drug by 5-8 fold in cell line models[23]. Cell line studies can be very effective in defining possible mechanisms involved in anticancer effects. For example, signal transduction events may be specifically triggered during anti-proliferative effects of berry components[17].

Animal studies

There is substantial evidence that berries can inhibit the development of carcinogen-induced tumours in animals (e.g. [24]). Much work has involved cancers of the oesophagus and freeze-dried powders of strawberries, black raspberries, red raspberries, blueberries, Acai and wolfberry have been shown to be effective[25]. As these berries vary widely in their phytochemical profiles, notably in their polyphenol contents, the nature of the active ingredients remains obscure.

In addition, oral intake of raspberry extracts has been reported to inhibit carcinogen-induced liver tumours[26]. Freeze-dried black raspberries and blueberries reduced β-estradiol-induced mammary tumours in rats[27]. Blueberry and black raspberry inhibited estrogen-induced mammary tumour formation in rats[28]. In a different model, oral administration of blueberry extract could significantly inhibit the development of hemangioendotheliomas caused by injection of spontaneously-transformed murine endothelial cells under the skin[29]. Positive effects have also been noted in the genetically-cancer prone ApxMin/+ mouse model for bilberry extracts[30, 31] but also for freeze-dried bilberry, cloudberry and lingonberry[32].

Human studies

Understandably, there have been fewer studies on the effect of berries on human cancers.

An anthocyanin-rich bilberry extract (*Vaccinium mytillus*) orally-administered to colorectal cancer patients prior to scheduled resection of primary tumour or liver metastases caused non-significant reductions in tumour proliferation. Interestingly anthocyanin-derived metabolites were identified in serum, urine and in colorectal tissues[33]. Other studies suggested that topically-applied bioadhesive gels containing black raspberry could positively influence biomarkers for oral cancers[34]. A randomized phase II trial of freeze dried strawberry in patients with dysplastic precancerous lesion of the oesophagus was reported[35]. Intake at 60 g/day (equivalent to ~750g FWt/day) over six months caused significant improvement in the histological endpoints of the lesions in the majority (29/36) of the patients. The intervention also beneficially altered the expression of other specific biomarkers.

Diabetes

The incidence of type 2 diabetes has reached near-epidemic proportions in the Western world. Following the outline of Hanhineva[36], there are four main areas where berries can beneficially influence glycemic control are

1. *Protection of pancreatic β-cells from glucose-induced toxicity and oxidative stress*
2. *Inhibition of starch digestion and absorption*
3. *Suppression of glucose release from the liver*
4. *Improvement of glucose uptake in peripheral tissues such as muscles*

Protection from glucose-induced toxicity and oxidative stress

In the prediabetic state, the pancreatic β-cells (which secrete insulin) become dysfunctional and decline in number [36]. Considerable evidence has accrued that suggests that polyphenols found in berries can maintain insulin secretion in β-cells grown in culture [37], protect against oxidative damage induced by elevated glucose in rats [38] (which leads to reduced cell numbers) and modulate insulin secretion and function in humans [39, 40].

Inhibition of digestion and absorption

As discussed above, the main part of dietary polyphenols are retained in the gastrointestinal tract and pass through to the colon without substantial absorption. These components can interact and modulate the digestion of crucial carbohydrates, namely starch and sucrose. Polyphenol-rich extracts from berries

inhibit α-amylase and α-glucosidase *in vitro*[41], the key enzymes involved in glucose production from starch in the GIT. The degree of inhibition differed between the berries and was linked to their polyphenol composition. Fractionation studies suggested that tannins (ellagitannins and proanthocyanidins) were potent inhibitors of amylase[42]. However, a range of polyphenols may be capable of inhibition of α-glucosidase[43, 44]. Interestingly, berry extracts acted synergistically with the pharmaceutical inhibitor, acarbose, which is prescribed to control starch digestion and blood glucose levels in type 2 diabetics[42, 44]. Depending on the phytochemical composition of the berries, it is possible that specific berries could inhibit both amylase and glucosidase and synergistically reduce the pool of glucose available for uptake into the blood.

Glucose uptake

Purified polyphenols can influence intestinal absorption of glucose through interaction with sodium-dependent glucose transporter (SGLT1) and the glucose transporter, GLUT2[36] in the human gut. In addition, polyphenols from strawberry[45] decreased glucose transport across gut epithelial cells through inhibition of both SGTL1 and GLUT2.

Effects on glucose uptake by muscle/fat cells

Polyphenols increased basal and insulin-stimulated glucose uptake in muscle cells[46]. Lingonberry extracts stimulated basal glucose uptake by muscle cells through activation of the AMPK system[47]. The common berry anthocyanin, cyanidin-3-glucoside, (and its metabolite protocatechuic acid) exerted insulin-like effects in a human adipocyte model[48].

Effects on liver production of glucose

Polyphenols may interact with the insulin-sensing pathway and modulate glucose release from the liver through reduction in glucose synthesis[36]. Polyphenols appear to act on signal transduction pathways and influence the phosphorylation status of key transcription factors such as FOXO1a[49, 50].

Control of blood glucose levels

Positive effects of berry components on blood glucose levels in animal and human *in vivo* systems have been reported.

Animal studies

Extracts of wild bilberry (*Vaccinium myrtillus*) reduced blood glucose levels and enhanced insulin sensitivity in type 2 diabetic mice[50]. Extracts from *Vaccinium uliginosum* (bog bilberry) and *Empretrum nigrum* (crowberry) reduced serum blood glucose levels in C57BL/6J mice[2] by up to 45 %. An extract from Maqui berry (*Aristotelia chilensis*) improved fasting blood glucose levels and glucose tolerance in hyperglycaemic obese mice and showed positive anti-diabetic effects in a range of other models[51].

Human Studies

Results from human studies have been less consistent. Intake of a berry puree (bilberries, blackcurrants, cranberries and strawberries) altered the glycemic responses in volunteers with similar carbohydrate load[52]. An earlier study on sweetened cranberry juice showed different but not statistically significant alterations in glycemic responses[53]. Sea buckthorn berry (*Hippophae rhamnoides*) caused significant

changes in post-prandial glycemic and insulin responses after glucose intake and different berry formats caused different levels of effect[54]. On the other hand, the addition of raspberries and/or blueberries did not alter glycemic responses to a starch-rich meal in humans[55]. Supplementation of blackcurrant juice with crowberry powder altered the glycemic and insulin responses of healthy subjects after sucrose-sweetened juice intake[56]. In addition, berry intake has been shown to improve glycemic responses after berry intake over controls[57].

Cardiovascular disease (CVD)

Substantial evidence has been provided that berry components can influence parameters relevant to CVD in *in- vitro* studies and animal models. For example, berry extracts modulated endothelial function in endothelial cells *in vitro*[58]. Raspberry juice reduced risk factors for atherosclerosis in hypercholesterolemic hamster models[59].

Retrospective epidemiological reviews suggest that intake of polyphenols commonly found in berries can beneficially affect blood pressure in adults[60]. Polyphenols may aid the muscle layer of blood vessels to relax (i.e. vasodilation). Endothelial cells, which make up the inner layer of blood vessels, produce nitric oxide which regulates blood pressure. Polyphenols found in berries can increase the activity of endothelial nitric oxide synthase (eNOS) to stimulate nitric oxide production and increase vasodilation[61].

A review of human intervention studies with fruit polyphenols[62] found inconsistent but positive effects on CVD risk factors and suggested that the inconsistency was due to differences in experimental design and treatment groups. Since then further evidence has been presented that suggest that berry components may beneficially influence clinical parameters associated with enhanced risk of CVD[63].

Individuals with elevated cholesterol levels improved their endothelium-dependent vasodilation after berry anthocyanin intake along with improved serum lipid profiles and decreased markers of inflammation[64]. Indeed, berry intake has been shown to have anti-inflammatory effects[65] which may underlie beneficial effects in a range of conditions where inflammation is part of the development of disease. Intake of various berries was associated with decreased CVD risk factors in overweight women[66]. However, a randomised trial[67] found no significant effect of berry supplements on endothelial function. Nevertheless, CVD risk factors were decreased after blueberry intake in obese subjects with metabolic syndrome, including significant decreases in blood pressure[68].

In fact, there is substantial overlap in the development of CVD and type 2 diabetes and this has led to the naming of the condition of Metabolic Syndrome which is characterized by a pre-diabetic state with markers of the development of CV risk factors (http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0004546/). As a result, there has also been considerable research directed at the effects of berry intake on this new combination of conditions[69].

Berries have also been implicated in the prevention of obesity[70] perhaps through interference with lipid digestion[71] and/or modulation of lipid metabolism[72]. Obesity is often associated as an underlying risk factor in CVD, metabolic syndrome and diabetes.

Neuroprotective effects

A body of evidence has developed that supports a role for berry polyphenol components in neuroprotection (see[73]). The berry components are proposed to protect against damage induced by ROS, which are known to be implicated in the development of neurological conditions such as Alzheimer's disease[74]. The brain is a particularly active organ: it represents only 2% of the body weight; it receives 15% of the cardiac output, 20% of total body oxygen consumption, and 25% of total body glucose utilization. Consequently this energetic and highly oxygenated environment means that the brain is particularly prone to damage induced by ROS. However, it has innately less-well developed antioxidant mechanisms and brain/nerve cells cannot regenerate by cell division. In most cases, berry components are proposed to mediate in cell signalling pathways that potentiate antioxidant mechanisms and influence inflammatory responses. Once again, initial work on *in vitro* and cell-based models laid the foundations for further work. For example, anthocyanin-rich extracts from black currants protected against dopamine and amyloid-beta-induced oxidative stress in brain cell line models[75]. *In vitro* studies have also been used to support the possibility that polyphenols found in berries can beneficially remodel amyloid-beta aggregation[76] *in vitro*, a process which ultimately causes brain damage in Alzheimer's disease. Blueberry extracts protected against inflammation-induced damage in microglial cells through reduction in inflammatory mediators[77].

Animal studies

Dietary supplementation with blueberry, cranberry or black currant fruit for eight weeks improved indicators of neuronal function in aged rats[78]. Blackberry intake reversed declines in motor and cognitive function in aging rats[79]. Importantly, these effects are accompanied by the detection of small but measurable levels of anthocyanin metabolites which indicates that they cross the blood-brain barrier and enter the brain after anthocyanin-rich blueberry intake in pigs[80].

Human studies

There is some population-based epidemiological evidence that polyphenol intake may be protective against Alzheimer's and Parkinson's disease[81] but the benefit could not be narrowed down to polyphenol over general fruit and vegetable intake. However, intervention studies have shown positive effects[82]. Blueberry intake has been shown to significantly improve memory in older adults[83] which could be beneficial in Alzheimer's disease and other forms of dementia. Similar results have been reported for strawberry intake[84]. Interestingly, many of the protective mechanisms targeted by polyphenols in the amelioration of neurological conditions (stimulation of cell signalling pathways involved in antioxidant and inflammatory responses) are common to those involved in diabetes[85]. In a related study with Concord grape juice, which contains many polyphenol components also found in berries, supplementation improved memory performance in older adults with pre-described mild cognitive impairments, which was supported by studies on brain activity using functional magnetic resonance imaging[86].

Other health effects

Berry preparations have been proposed to improve blood supply to the eye and thereby influence vision[87]. Cranberry juice has been shown to reduce urinary tract infection probably due to its proanthocyanidin content[88] and other berries may have other anti-microbial[89] and anti-viral activities. There have also been suggestions that berry intake may improve sports performance or recovery[90]. The anti-inflammatory effects of berries can also mediate inflammatory responses which directly influence the development of arthritis in model systems[91].

Conclusions

Berries have been implicated in health benefits relevant to a number of disease conditions. Much of the evidence has focused on the polyphenol components but other components (such as carotenoids, fibres and terpenes) may also have roles to play. The mechanisms underlying these health benefits vary from inhibition of digestion in the GIT and stimulation or priming of endogenous antioxidant and anti-inflammatory responses. These may occur at widely different concentrations. Due to metabolism and differential bioavailability, the actual active components may differ greatly from the polyphenols present in berries and metabolites derived from colonic fermentation may also play an important role in long-term effects. It is clear that easy-to-measure criteria such as total antioxidant capacity, total phenolic content or total anthocyanin content may only be linked to efficacy in health benefits. Further research is only likely to extend the evidence for the health benefits associated with berry components.

References

1. Milliken W, Bridgewater S (2004) Flora Celtica – Plants and people of Scotland. Birlinn Books, Edinburgh, UK
2. Kellogg JW, Flint J, C Ribnicky, D Kuhn, P De Mejia, E Gonzalez, Raskin, I, Lila, MA. (2010) Alaskan Wild Berry Resources and Human Health under the Cloud of Climate Change. J. AGRIC. FOOD CHEM. 58: 3884-3900
3. Seeram NP (2012) Emerging research supporting the positive effects of berries on human health and disease prevention. J. AGRIC. FOOD CHEM. 60: 5685-86
4. The fineli food database http://www.fineli.fi/index.php?lang=en
5. Halvorsen BL, Carlsen MH, Phillips KM, Bøhn SK, Holte K, Jacobs DR Jr, Blomhoff R. (2006) Content of redox-active compounds (i.e. antioxidants) in foods consumed in the United States. AM J CLIN NUTR. 84: 95-135
6. Walker PG, Gordon SL, Brennan RM, Hancock RD. (2006) A high-throughput monolithic HPLC method for rapid vitamin C phenotyping of berry fruit. PHYTOCHEMICAL ANALYSIS. 17: 284-90
7. Johnson EJ. (2002) The role of carotenoids in human health. NUTRITION IN CLINICAL CARE 5: 56-65
8. Hancock, R.D. and Stewart, D. (2010) Enhancing the nutritional quality of fruit juices: advanced technologies for juice extraction and pasteurization. In: Biotechnology in Functional Foods and Nutraceuticals (Eds. Bagchi D, Lau FC, Ghosh DK), CRC Press, Florida, USA. pp. 463-482

9. Deighton N, Brennan R, Finn C, Davies HV (2000) Antioxidant properties of domesticated and wild Rubus species. J. SCI. FOOD AGRIC. 80: 1307-13
10. Zheng J, Yang B, Ruusunen V, Laaksonen O, Tahvonen R, Hellsten J, Kallio, H (2010) Compositional differences of phenolic compounds between black currant (*Ribes nigrum* L.) cultivars and their response to latitude and weather conditions. J. AGRIC. FOOD CHEM. 60: 6581−93
11. de Freitas V, Mateus N (2012) Protein/polyphenol interactions: past and present contributions. Mechanisms of astringency perception. CURRENT ORGANIC CHEMISTRY 16: 724-46.
12. Halliwell B. Biochemistry of oxidative stress. (2007) BIOCHEM. SOC. TRANS. 35: 1147-50.
13. Koli R, Erlund I, Jula A, Marniemi J, Mattila P, Alfthan G. (2010) Bioavailability of various polyphenols from a diet containing moderate amounts of berries. J. AGRIC. FOOD CHEM. 58: 3927-32
14. Williamson G, Clifford MN (2010) Colonic metabolites of berry polyphenols: the missing link to biological activity? BRIT. J. NUTR. 104: S48-66
15. Gorelik S, Lapidot T, Shaham I, Granit R, Ligumsky M, Kohen R, Kanner J (2005) Lipid peroxidation and coupled vitamin oxidation in simulated and human gastric fluid inhibited by dietary polyphenols: health implications. J. AGRIC. FOOD CHEM. 53: 3397-402
16. McDougall G.J, Kulkarni NN, Stewart D (2008) Current developments on the inhibitory effects of berry polyphenols on digestive enzymes. BIOFACTORS 34: 73-80
17. Aiyer HS. Warri AM, Woode DR, Hilakivi-Clarke L, Clarke R. (2012) Influence of berry polyphenols on receptor signaling and cell-death pathways: Implications for breast cancer prevention. J. AGRIC. FOOD CHEM. 60: 5693- 708
18. Ross HA, McDougall GJ, Stewart, D (2007) Antiproliferative activity is predominantly associated with ellagitannins in raspberry extracts. PHYTOCHEMISTRY 68: 218-28
19. Bowen-Forbes CS, Zhang YN, Muraleedharan G (2010) Anthocyanin content, antioxidant, anti-inflammatory and anticancer properties of blackberry and raspberry fruits. J. FOOD COMPOSITION & ANALYSIS 23: 554-60
20. Brown EM, Gill CIR, McDougall GJ, Stewart, D (2012) Mechanisms underlying the anti-proliferative effects of berry components in in- vitro models of colon cancer. CURRENT PHARMACEUTICAL BIOTECHNOLOGY 13: 200-209
21. Weaver J, Briscoe T, Hou M, Goodman C, Kata S, Ross H, McDougall GJ, Stewart D, Riches A. (2009) Strawberry polyphenols are equally cytotoxic to tumourigenic and normal human breast and prostate cell lines. INTERNATIONAL JOURNAL OF ONCOLOGY 34: 777-786
22. Song X, Siriwardhana N, Rathore K, Lin D, Wang HC. (2010) Grape seed proanthocyanidin suppression of breast cell carcinogenesis induced by chronic exposure to combined 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone and benzo[a]pyrene. MOLECULAR CARCINOGENESIS. 49: 450-63
23. Kausar H, Jeyabalan J, Aqil F, Chabba D, Sidana J, Singh IP, Gupta RC (2011) Berry anthocyanidins synergistically suppresses non-small-cell lung cancer cell growth and metastasis and enhances sensitivity to the chemotherapeutic drug paclitaxel . J.THORACIC ONCOLOGY 6: S930-S931
24. Carlton PS, Kresty LA, Siglin JC, Morse MA, Lu J, Morgan C, Stoner GD (2001) Inhibition of N-nitrosomethylbenzylamine-induced tumorigenesis in the rat esophagus by dietary freeze-dried strawberries. CARCINOGENESIS 22: 441-6

25. Stoner GD, Wang LS, Seguin C, Rocha C, Stoner K, Chiu S, Kinghorn AD (2010) Multiple berry types prevent N-nitrosomethylbenzylamine-induced esophageal cancer in rats. PHARMACEUTICAL RESEARCH 27: 1138-45
26. Chen HS, Liu M, Shi LJ, Zhao JL, Zhang CP, Lin LQ, Liu Y, Zhang SJ, Jin JC, Wang L, Shen BZ, Liu JR. (2011) Effects of raspberry phytochemical extract on cell proliferation, apoptosis, and serum proteomics in a rat model. J. FOOD SCI. 76: 192-8
27. Aiyer HS, Gupta RC. (2010) Berries and ellagic acid prevent estrogen-induced mammary tumorigenesis by modulating enzymes of estrogen metabolism. CANCER PREVENTION RESEARCH. 3: 727-37
28. Ravoori, SV, Manicka V. Aqil, F, Gupta, RC. (2012) Inhibition of estrogen-mediated mammary tumorigenesis by blueberry and black raspberry. J. AGRIC. FOOD CHEM. 60: 5547-55
29. Gordillo GM, Sen, CK. (2011) Endothelial cell tumor prevention with berry extracts: Clinical problems, molecular mechanisms and therapeutic opportunities. In: Berries and Cancer Prevention. Stoner GD, Seeram NP (eds.) part 3; 117-30. Springer, New York
30. Cooke D, Schwarz M, Boocock D, Winterhalter P, Steward WP, Gescher AJ, Marczylo TH (2006) Effect of cyanidin-3-glucoside and an anthocyanin mixture from bilberry on adenoma development in the Apc/Min mouse model of intestinal carcinogenesis--relationship with tissue anthocyanin levels. INT. J. CANCER. 119: 2213-20
31. Cai H, Marczylo TH, Teller N, Brown K, Steward WP, Marko D, Gescher AJ. (2010) Anthocyanin-rich red grape extract impedes adenoma development in the Apc/Min mouse: Pharmacodynamic changes and anthocyanin levels in the murine biophase. EUROPEAN J. CANCER 46: 811-7
32. Mutanen M, Pajari A-M, Päivärinta E, Misikangas M, Rajakangas J, Marttinen M, Oikarinen. S. (2008) Berries as chemopreventive dietary constituents – a mechanistic approach with the ApcMin/+ mouse. ASIA PACIFIC J. CLIN. NUTR. 17: S123-5
33. Thomasset S, Teller N, Cai H, Marko D, Berry DP, Steward WP, Gescher AJ. (2009) Do anthocyanins and anthocyanidins, cancer chemopreventive pigments in the diet, merit development as potential drugs? CANCER CHEMOTHERAPY & PHARMACOLOGY 64: 201-11
34. Shumway BS, Kresty LA, Larsen PE, Zwick, JC, Lu B, Field HW, Mumper, RJ, Stoner GD, Mallery SR (2008) Effects of a topically applied bioadhesive berry gel on loss of heterozygosity indices in premalignant oral lesions. CLINICAL CANCER RESEARCH 14: 2421-30
35. Chen T, Yan F, Qian J, Guo M, Zhang H, Tang X, Chen F, Stoner GD, Wang X. (2012) Randomized phase II trial of lyophilized strawberries in patients with dysplastic precancerous lesions of the esophagus. CANCER PREVENTION RES. (PHILADELPHIA) 5: 41-50
36. Hanhineva K, Torronen R, Bondia-Pons I, Pekkinen J, Kolehmainen M, Mykkanan, H, Poutanen K. (2010) Impact of dietary polyphenols on carbohydrate metabolism. INTERNATIONAL JOURNAL OF MOLECULAR SCIENCES 11: 1365-1402
37. Martineau LC, Couture A, Spoor D, Benhaddou-Andaloussi A, Harris C, Meddah B, Leduc C, Burt A, Vuong T, Mai Le P, Prentki M, Bennett SA, Arnason JT, Haddad PS (2006) Anti-diabetic properties of the Canadian lowbush blueberry *Vaccinium angustifolium Ait*. PHYTOMEDICINE 13: 612–23
38. Rodrigo R, Miranda A, Vergara L. (2011) Modulation of endogenous antioxidant system by wine polyphenols in human disease. CLIN. CHIM. ACTA. 412: 410-24
39. Seymour EM, Tanone II, Urcuyo-Llanes DE, Lewis SK, Kirakosyan A, Kondoleon MG, Kaufman PB, Bolling SF. (2011) Blueberry intake alters skeletal muscle and adipose tissue peroxisome

proliferator-activated receptor activity and reduces insulin resistance in obese rats. J. MEDICINAL FOOD 14: 1511-8

40. Stull AJ, Cash CK, Johnson WD, Champagne CM, Cefalu WT. (2010). Bioactives in blueberries improve insulin sensitivity in obese, insulin-resistant men and women. J. NUTR. 140: 1764-8
41. McDougall GJ, Shpiro F, Dobson P, Smith P, Blake A, Stewart D. (2005) Different polyphenolic components of soft fruits inhibit α-amylase and α-glucosidase. J. AGRIC. FOOD CHEM. 53: 2760-6
42. Grussu D, Stewart D, McDougall, GJ. (2011) Berry polyphenols inhibit alpha-amylase in vitro: identifying active components in rowanberry and raspberry. J. AGRIC. FOOD CHEM. 59: 2324-31
43. Lo Piparo E, Scheib H, Frei N, Williamson G, Grigorov M, Chou CJ (2008) Flavonoids for controlling starch digestion: Structural requirements for inhibiting human alpha-amylase. J. MED. CHEM. 51: 3555–61
44. Boath AS, Stewart D, McDougall GJ. (2012) Berry components inhibit α-glucosidase in vitro: Synergies between acarbose and polyphenols from black currant and rowanberry. FOOD CHEMISTRY 135: 929–936
45. Manzano S, Williamson G. (2010) Polyphenols and phenolic acids from strawberry and apple decrease glucose uptake and transport by human intestinal Caco-2 cells. MOL. NUTR. FOOD RES. 54: 1773-80
46. Claussnitzer M, Skurk T, Hauner H, Daniel H, Rist MJ. (2011) Effect of flavonoids on basal and insulin-stimulated 2-deoxyglucose uptake in adipocytes. MOL. NUTR. FOOD RES. 1: S26-34
47. Eid HM, Martineau LC, Saleem A, Muhammad A, Vallerand D, Benhaddou-Andaloussi A, Nistor L, Afshar A, Arnason JT, Haddad PS. (2010) Stimulation of AMP-activated protein kinase and enhancement of basal glucose uptake in muscle cells by quercetin and quercetin glycosides, active principles of the antidiabetic medicinal plant *Vaccinium vitis-idaea.* MOL. NUTR. FOOD RES. 54: 991-1003
48. Scazzocchio B, Vari R, Filesi C, D'Archivio M, Santangelo C, Giovannini C, Iacovelli A, Silecchia G, Li Volti G, Galvano F, Masella R. (2011) Cyanidin-3-*O*-beta-glucoside and protocatechuic acid exert insulin-like effects by upregulating PPAR-gamma activity in human omental adipocytes. DIABETES 60: 2234-44
49. Cheng Z, White MF (2011) Targeting Forkhead box O1 from the concept to metabolic diseases: Lessons from mouse models. ANTIOXIDANT & REDOX SIGNALLING 14: 649-61
50. Takikawa M, Inoue S, Horio F, Tsuda T (2010) dietary anthocyanin-rich bilberry extract ameliorates hyperglycemia and insulin sensitivity via activation of AMP-activated protein kinase in diabetic mice. J. NUTR. 140: 527-33
51. Rojo LE, Ribnicky D, Logendra S, Poulev A, Rojas-Silva P, Kuhn P, Dorn R, Grace MH, Lila, MA, Raskin I. (2012) In vitro and in vivo anti-diabetic effects of anthocyanins from Maqui Berry (*Aristotelia chilensis*) FOOD CHEMISTRY 131: 387-96
52. Torronen, R, Sarkkinen, E, Tapola, N, Hautaniemi, E, Kilpi, K, Niskanen, L. (2010) Berries modify the postprandial plasma glucose response to sucrose in healthy subjects. BRITISH J. NUTRITION 103: 1094-7
53. Wilson T, Singh AP, Vorsa N, Goettl CD, Kittleson KM, Roe CM, Kastello GM, Ragsdale FR. (2008) Human glycemic response and phenolic content of unsweetened cranberry juice. J. MED. FOOD 11: 46–54
54. Lehtonen H-M, Suomela J-P, Tahvonen R, Vaarno J, Venojarvi M, Viikari J, Kallio H. (2010) Berry meals and risk factors associated with metabolic syndrome. EUR. J. CLIN. NUTR. 64: 614-21

55. Clegg ME, Pratt M, Meade CM, Henry CJK. (2011) The addition of raspberries and blueberries to a starch-based food does not alter the glycaemic response. BRIT. J. NUTR. 106: 335-338
56. Torronen R, McDougall GJ, Dobson GJ, Stewart D, Hellstrom J, Mattila P, Pihlava J-M, Koskela A, Karjalainen R. (2012) Fortification of blackcurrant juice with crowberry: Impact on polyphenol composition, urinary phenolic metabolites, and postprandial glycemic response in healthy subjects. J. FUNCTIONAL FOODS in press
57. Torronen, R, Sarkkinen, E Niskanen, T, Tapola, N, Kilpi, K, Niskanen, L. (2012) Postprandial glucose, insulin and glucagon-like peptide 1 responses to sucrose ingested with berries in healthy subjects. BRIT. J. NUTR. 107: 1445-51
58. Tulio AZ, Chang C, Edirisinghe I, White KD, Jablonski JE, Banaszewski K, Kangath, A, Tadapaneni RK, Burton-Freeman B, Jackson LS. (2012) Berry fruits modulate endothelial cell migration and angiogenesis via phosphoinositide-3 kinase/protein kinase B pathway in vitro in endothelial cells. J. AGRIC. FOOD CHEM. 60: 5803-5812
59. Suh J-H, Romain C, Gonzalez-Barrio R, Cristol J-P, Teissedre P-L, Crozier A, Rouanet, J-M (2011) Raspberry juice consumption, oxidative stress and reduction of atherosclerosis risk factors in hypercholesterolemic golden Syrian hamsters. FOOD & FUNCTION 2: 400-5
60. Cassidy A, O'Reilly E, Kay C, Sampson L, Franz M, Forman J, Curhan G, Rimm E. (2011) Habitual intake of flavonoid subclasses and incident hypertension in adults. AM. J. CLIN. NUTR. 93: 338-47
61. Galleano M, Pechanova O, Fraga CG. (2010) Hypertension, nitric oxide, oxidants, and dietary plant polyphenols. CURRENT PHARMACEUTICAL BIOTECHNOLOGY. 11: 837-848
62. Chong MF, Macdonald R, Lovegrove JA. (2010) Fruit polyphenols and CVD risk: a review of human intervention studies. BRIT. J.NUTR. 104: S28-S39
63. Basu A, Rhone M, Lyons TJ. (2010) Berries: Emerging impact on cardiovascular health NUTRITION REVIEWS 68: 168-177
64. Zhu Y, Xia M, Yang Y, Liu F, Li Z, Hao Y, Mi M, Jin T, Ling W. (2011) Purified anthocyanin supplementation improves endothelial function via NO-cGMP activation in hyper-cholesterolemic individuals. CLINICAL CHEMISTRY 57: 1524-33
65. Jin Y, Cui X, Singh UP, Chumanevich AA, Harmon B, Cavicchia P, Hofseth AB, Kotakadi V, Stroud B, Volate SR, Hurley TG, Hebert JR, Hofseth LJ. (2010) Systemic inflammatory load in humans is suppressed by consumption of two formulations of dried, encapsulated juice concentrate. MOLECULAR NUTRITION & FOOD RESEARCH 54: 1506-14
66. Lehtonen, H-M Suomela, J-P Tahvonen, R. Yang, B. Venojarvi, M. Viikari, J. Kallio, H. (2011) Different berries and berry fractions have various but slightly positive effects on the associated variables of metabolic diseases on overweight and obese women EUROPEAN JOURNAL OF CLINICAL NUTRITION 65: 394-401
67. Ali A, Yazaki Y, Njike VY, Ma Y, Katz DL (2011) Effect of fruit and vegetable concentrates on endothelial function in metabolic syndrome: A randomized controlled trial. NUTRITION JOURNAL 10: 72-3
68. Basu A, Du M, Leyva MJ, Sanchez K, Betts NM, Wu M, Aston CE, Lyons TJ. (2010) Blueberries decrease cardiovascular risk factors in obese men and women with metabolic syndrome. J. NUTR. 140: 1582-7
69. Basu A, Lyons TJ. (2012) Strawberries, blueberries, and cranberries in the Metabolic Syndrome: Clinical perspectives. J. AGRIC. FOOD CHEM. 60: 5687-5692

70. Tsuda T. (2008) Regulation of adipocyte function by anthocyanins: Possibility of preventing the metabolic syndrome. J. AGRIC. FOOD CHEM. 56: 642-646
71. McDougall GJ, Kulkarni NN, Stewart D. (2009).Berry polyphenols inhibit pancreatic lipase activity in vitro. FOOD CHEMISTRY 115: 193-9
72. Prior R L, Wilkes SE, Rogers TR, Khanal RC, Wu X, Howard LR. (2011) Purified blueberry anthocyanins and blueberry juice alter development of obesity in mice fed an obesogenic high-fat diet. J. AGRIC. FOOD CHEM. 58: 3970-76
73. Miller MG, Shukitt-Hale B. (2012) Berry fruit enhances beneficial signaling in the brain. J. AGRIC. FOOD CHEM. 60: 5709-15
74. Spencer JPE. (2010) The impact of fruit flavonoids on memory and cognition. BRIT. J. NUTR. 104: S40-S47
75. Ghosh D, McGhie TK, Fisher DR, Joseph JA. (2007) Cytoprotective effects of anthocyanins and other phenolic fractions of boysenberry and blackcurrant on dopamine and amyloid beta-induced oxidative stress in transfected COS-7 cells. J. SCI. FOOD AGRIC. 87: 2061-67
76. Ladiwala AR, Mora-Pale M, Lin JC, Bale SS, Fishman ZS, Dordick JS, Tessier PM. (2011) Polyphenolic glycosides and aglycones utilize opposing pathways to selectively remodel and inactivate toxic oligomers of amyloid beta. CHEMBIOCHEM 12: 1749-58
77. Lau FC, Bielinski DF, Joseph JA. (2007) Inhibitory effects of blueberry extract on the production of inflammatory mediators in lipopolysaccharide-activated BV2 microglia. J. NEUROSCIENCE RESEARCH. 85: 1010-7
78. Shukitt-Hale, B, Galli, RL. Meterko, V, Carey A, Bielinski DF, McGhie T, Joseph JA. (2005) Dietary supplementation with fruit polyphenolics ameliorates age-related deficits in behavior and neuronal markers of inflammation and oxidative stress. AGE 27: 49-57
79. Shukitt-Hale B, Cheng V, Joseph, JA. (2009) Effects of blackberries on motor and cognitive function in aged rats. NUTRITIONAL NEUROSCIENCE 12: 135-140
80. Milbury PE, Kalt W. (2010) Xenobiotic metabolism and berry flavonoid transport across the blood-brain barrier. J. AGRIC. FOOD CHEM. 58: 3950-6
81. Gao, X. Cassidy, A. Schwarzschild, M. A. Rimm, E. B. Ascherio, A. (2012) Habitual intake of dietary flavonoids and risk of Parkinson disease. NEUROLOGY 78: 1138-1145
82. Krikorian R, Shidler MD, Nash, TA, Kalt W, Vinqvist-Tymchuk MR, Shukitt-Hale B, Joseph, JA. (2010) Blueberry supplementation improves memory in older adults. J. AGRIC. FOOD CHEM. 58: 3996-4000
83. Devore EE, Kang JH, Breteler MM, Grodstein F. (2012) Dietary intakes of berries and flavonoids in relation to cognitive decline. ANNALS NEUROLOGY 72: 135-43
84. Joseph JA, Shukitt-Hale B, Willis, LM. (2009) Grape juice, berries, and walnuts affect brain aging and behaviour. J. NUTRITION 139: S1813-17
85. de la Monte SM. (2012) Brain insulin resistance and deficiency as therapeutic targets in Alzheimer's disease CURRENT ALZHEIMER RESEARCH 9: 35- 66
86. Krikorian R, Boespflug EL, Fleck DE, Stein AL, Wightman JD, Shidler MD, Sadat-Hossieny S. (2012) Concord grape juice supplementation and neurocognitive function in human aging. J. AGRIC. FOOD CHEM. 60: 5736-42
87. Kalt W, Hanneken A, Milbury P, Tremblay F (2010) Recent research on polyphenolics in vision and eye health. J. AGRIC. FOOD CHEM. 58: 4001-7
88. Howell AB. (2007) Bioactive compounds in cranberries and their role in prevention of urinary tract infections. MOL. NUTR. FOOD RES. 51: 732-7

89. Toivanen M, Huttunen S, Duricová J, Soininen P, Laatikainen R, Loimaranta V, Haataja S, Finne J, Lapinjoki S, Tikkanen-Kaukanen C (2010) Screening of binding activity of *Streptococcus pneumoniae, Streptococcus agalactiae* and *Streptococcus suis* to berries and juices. PHYTOTHERAPY RESEARCH 24: S95-S101
90. Goldfarb AH, Garten RS, Cho CC, Phillip DM, Chambers LA. (2011) Effects of a fruit/berry/vegetable supplement on muscle function and oxidative stress. MEDICINE & SCIENCE IN SPORTS AND EXERCISE 43: 501-8
91. Jean-Gilles D, Li L, Ma H, Yuan T, Chichester CO, Seeram NP (2012) Anti-inflammatory effects of polyphenolic-enriched red raspberry extract in an antigen-induced arthritis rat model. J. AGRIC. FOOD CHEM. 60: 5755−62

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