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FENO-VITIS™

Scientific publications relevant for Feno-Vitis™ line of products

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ANTI-CANCER EFFECTS

Impact of Procyanidins from Different Berries on Caspase 8 Activation in Colon Cancer.

Oxid Med Cell Longev. 2015; 2015:154164. doi: 10.1155/2015/154164. Epub 2015 Jun 9.

SCOPE: The aim of this work is to identify which proapoptotic pathway is induced in human colon cancer cell lines, in contact with proanthocyanidins extracted from various berries.

METHODS AND RESULTS: Proanthocyanidins (Pcys) extracted from 11 berry species are monitored for proapoptotic activities on two related human colon cancer cell lines: SW480-TRAIL-sensitive and SW620-TRAIL-resistant. Apoptosis induction is monitored by cell surface phosphatidylserine (PS) detection. Lowbush blueberry extract triggers the strongest activity. When tested on the human monocytic cell line THP-1, blueberry Pcys are less effective for PS externalisation and DNA fragmentation is absent, highlighting a specificity of apoptosis induction in gut cells. In Pcys-treated gut cell lines, caspase 8 (apoptosis extrinsic pathway) but not caspase 9 (apoptosis intrinsic pathway) is activated after 3 hours through P38 phosphorylation (90 min), emphasizing the potency of lowbush blueberry Pcys to eradicate gut TRAIL-resistant cancer cells.

CONCLUSION: We highlight here that berries Pcys, especially lowbush blueberry Pcys, are of putative interest for nutritional chemoprevention of colorectal cancer in view of their apoptosis induction in a human colorectal cancer cell lines.

Berries as chemopreventive dietary constituents--a mechanistic approach with the ApcMin/+ mouse.

Asia Pac J Clin Nutr. 2008; 17 Suppl 1:123-5.

*Berries contain a number of compounds that are proposed to have anticarcinogenic properties. We wanted to see if pure ellagic acid, natural ellagitannins and three wild berries have any effect on the adenoma formation in Apc- mutated Min/+ mice. Min/+ mice were fed high-fat AIN93-G diets containing 10% (w/w) freeze-dried bilberry (*Vaccinium myrtillus*), lingonberry (*Vaccinium vitis-idaea*), cloudberry (*Rubus chamaemorus*), cloudberry seeds or cloudberry pulp or pure ellagic acid at 1564 mg/kg for 10 weeks. beta-Catenin and cyclin D1 protein levels in the adenomas and in the normal-appearing mucosa were determined by Western blotting and immunohistochemistry. Early changes in gene expression in the normal-appearing mucosa were analyzed by Affymetrix microarrays. Three wild berries significantly reduced tumour number (15-30%, $p < 0.05$), and cloudberry and lingonberry also reduced tumour size by over 60% ($p < 0.01$). Cloudberry resulted in decreased levels of nuclear beta-catenin and cyclin D1 and lingonberry in the level of cyclin D1 in the large adenomas ($p < 0.05$). Affymetrix microarrays revealed changes in genes implicated in colon carcinogenesis, including the decreased expression of the adenosine deaminase, ecto-5f-nucleotidase and PGE2 receptor subtype EP4. Ellagic acid had no effect on the number or size of adenomas in the distal or total small intestine but it increased adenoma size in the duodenum when compared with the control diet ($p < 0.05$). Neither cloudberry seed nor pulp had any effect on the adenoma formation. Berries seem to have great potential as a source of chemopreventive components.*

Berry extracts exert different antiproliferative effects against cervical and colon cancer cells grown in vitro.

J Agric Food Chem. 2008 May 14; 56(9):3016-23. doi: 10.1021/jf073469n. Epub 2008 Apr 16.

Polyphenol-rich berry extracts were screened for their antiproliferative effectiveness using human cervical cancer (HeLa) cells grown in microtiter plates. Rowan berry, raspberry, lingonberry, cloudberry, arctic bramble, and strawberry extracts were effective but blueberry, sea buckthorn, and pomegranate extracts were considerably less effective. The most effective extracts (strawberry > arctic bramble > cloudberry > lingonberry) gave EC 50 values in the range of 25-40 microg/(mL of phenols). These extracts were also effective against human colon cancer (CaCo-2) cells, which were generally more sensitive at low concentrations but conversely less sensitive at higher concentrations. The strawberry, cloudberry, arctic bramble, and the raspberry extracts share common polyphenol constituents, especially the ellagitannins, which have been shown to be effective

antiproliferative agents. However, the components underlying the effectiveness of the lingonberry extracts are not known. The lingonberry extracts were fractionated into anthocyanin-rich and tannin-rich fractions by chromatography on Sephadex LH-20. The anthocyanin-rich fraction was considerably less effective than the original extract, whereas the antiproliferative activity was retained in the tannin-rich fraction. The polyphenolic composition of the lingonberry extract was assessed by liquid chromatography-mass spectrometry and was similar to previous reports. The tannin-rich fraction was almost entirely composed of procyanidins of linkage type A and B. Therefore, the antiproliferative activity of lingonberry was caused predominantly by procyanidins.

Three Nordic berries inhibit intestinal tumorigenesis in multiple intestinal neoplasia/+ mice by modulating beta-catenin signaling in the tumor and transcription in the mucosa.

J Nutr. 2007 Oct; 137(10):2285-90.

Berries contain a number of compounds that are proposed to have anticarcinogenic properties. We studied the effects and molecular mechanisms of wild berries with different phenolic profiles on intestinal tumorigenesis in multiple intestinal neoplasia/+ mice. The mice were fed a high-fat AIN93-G diet (Con) or AIN93-G diets containing 10% (w:w) freeze-dried bilberry, lingonberry (LB), or cloudberry (CB) for 10 wk. All 3 berries significantly inhibited the formation of intestinal adenomas as indicated by a 15-30% reduction in tumor number ($P < 0.05$). CB and LB also reduced tumor burden by over 60% ($P < 0.05$). Compared to Con, CB and LB resulted in a larger ($P < 0.05$) proportion of small adenomas (43, 69, and 64%, respectively) and a smaller proportion of large adenomas (56, 29, and 33%, respectively). Beta-catenin and cyclin D1 in the small and large adenomas and in the normal-appearing mucosa were measured by Western blotting and immunohistochemistry. CB resulted in decreased levels of nuclear beta-catenin and cyclin D1 and LB in the level of cyclin D1 in the large adenomas ($P < 0.05$). Early changes in gene expression in the normal-appearing mucosa were analyzed by Affymetrix microarrays, which revealed changes in genes implicated in colon carcinogenesis, including the decreased expression of the adenosine deaminase, ecto-5'-nucleotidase, and prostaglandin E2 receptor subtype EP4. Our results indicate that berries are potentially a rich source of chemopreventive components.

Antioxidant activity in lingonberries (*Vaccinium vitis-idaea* L.) and its inhibitory effect on activator protein-1, nuclear factor-kappaB, and mitogen-activated protein kinases activation.

J Agric Food Chem. 2005 Apr 20; 53(8):3156-66.

Lingonberry has been shown to contain high antioxidant activity. Fruits from different cultivars of lingonberry (*Vaccinium vitis-idaea* L.) were evaluated for fruit quality, antioxidant activity, and anthocyanin and phenolic contents. The fruit soluble solids, titratable acids, antioxidant capacity, and anthocyanin and phenolic contents varied with cultivars. Lingonberries contain potent free radical scavenging activities for DPPH*, ROO*, *OH, and O₂*- radicals. Pretreatment of JB6 P+ mouse epidermal cells with lingonberry extracts produced a dose-dependent inhibition on the activation of activator protein-1 (AP-1) and nuclear factor-kappaB (NF-kappaB) induced by either 12-O-tetradecanoylphorbol-13-acetate (TPA) or ultraviolet-B (UVB). Lingonberry extract blocked UVB-induced phosphorylation of the mitogen-activated protein kinase (MAPK) signaling members ERK1, ERK2, p38, and MEK1/2 but not JNK. Lingonberry extract also prevented TPA-induced phosphorylation of ERK1, ERK2, and MEK1/2. Results of soft agar assays indicated that lingonberry extract suppressed TPA-induced neoplastic transformation of JB6 P(+) cells in a dose-dependent manner. Lingonberry extract also induced the apoptosis of human leukemia HL-60 cells in a dose-independent manner. These results suggest that ERK1, ERK2, and MEK1/2 may be the primary targets of lingonberry that result in suppression of AP-1, NF-kappaB, and neoplastic transformation in JB6 P(+) cells and causes cancer cell death by an apoptotic mechanism in human leukemia HL-60 cells.

ANTI-MICROBIAL EFFECTS

The Effect of Fermented Lingonberry Juice on *Candida glabrata* Intracellular Protein Expression.

Int J Dent. 2017; 2017:6185395. doi: 10.1155/2017/6185395. Epub 2017 Mar 30.

Lingonberries have a long traditional use in treating fungal infections on mucosal membranes, but very little is known about the exact antifungal mechanisms. We tested the effects of fermented lingonberry juice on Candida glabrata intracellular protein expression. A Candida glabrata clinical strain was grown in the presence of fermented lingonberry juice (FLJ). Also the effect of lowered pH was tested. Intracellular protein expression levels were analyzed by the 2D-DIGE method. Six proteins detected with ≥ 1.5 -fold lowered expression levels from FLJ treated cells were further characterized with LC-MS/MS. Heat shock protein 9/12 and redoxin were identified with peptide coverage/scores of 68/129 and 21/26, respectively. Heat shock protein 9/12 had an oxidized methionine at position 56. We found no differences in protein expression levels at pH 3.5 compared to pH 7.6. These results demonstrate that FLJ exerts an intracellular stress response in Candida glabrata, plausibly impairing its ability to express proteins related to oxidative stress or maintaining cell wall integrity.

Phenolic Compounds Contained in Little-known Wild Fruits as Antiadhesive Agents Against the Beverage-Spoiling Bacteria *Asaia* spp.

Molecules. 2017 Jul 28; 22(8). pii: E1256. doi: 10.3390/molecules22081256.

*The aim of the study was to evaluate antioxidant activity and total phenolic content of juice from three different types of fruits: elderberry (*Sambucus nigra*), lingonberry (*Vaccinium vitis-idaea*) and cornelian cherry (*Cornus mas*), and their action against adhesion of bacterial strains of *Asaia lannensis* and *Asaia bogorensis* isolated from spoiled soft drinks. The antioxidant profiles were determined by total antioxidant capacity (2,2-diphenyl-1-picrylhydrazyl, DPPH), and ferric-reducing antioxidant power (FRAP). Additionally, total polyphenol content (TPC) was investigated. Chemical compositions of juices were tested using the chromatographic techniques: high-performance liquid chromatography (HPLC) and liquid chromatography-mass spectrometry (LC-MS). Adhesion properties of *Asaia* spp. cells to various abiotic materials were evaluated by luminometry, plate count and fluorescence microscopy. Antioxidant activity of fruit juices expressed as inhibitory concentration (IC₅₀) ranged from 0.042 ± 0.001 (cornelian cherry) to 0.021 ± 0.001 g/mL (elderberry). TPC ranged from 8.02 ± 0.027 (elderberry) to 2.33 ± 0.013 mg/mL (cornelian cherry). Cyanidin-3-sambubioside-5-glucoside, cyanidin-3-glucoside, and cyanidin-3-sambubioside were detected as the major anthocyanins and caffeic, cinnamic, gallic, protocatechuic, and p-coumaric acids as the major phenolic acids. A significant linear correlation was noted between TPC and antioxidant capacity. In the presence of fruit juices a significant decrease of bacterial adhesion from 74% (elderberry) to 67% (lingonberry) was observed. The high phenolic content indicated that these compounds may contribute to the reduction of *Asaia* spp. adhesion.*

Characterisation of Antimicrobial Properties of Extracts of Selected Medicinal Plants.

Pol J Microbiol. 2017 Dec 4; 66(4):463-472. doi: 10.5604/01.3001.0010.7002.

*The scope of the experiments included analysis of the antimicrobial activity of ethanolic, methanolic and aqueous extracts against bacterial and fungal cultures and determination of the minimum inhibitory concentration of plant extracts tested microbial growth. Analysis of the antifungal and antibacterial activity was carried out by the disc diffusion method using paper discs. In the experiment 11 species of microorganisms - 8 bacterial and 3 fungal strains were used. The highest antimicrobial activity against the tested strains was demonstrated by black elder (*Sambucus nigra* L.), black locust (*Robinia pseudoacacia* L.) and lingonberry (*Vaccinium vitis-idaea* L.) extracts. The study showed the diverse morphological activity of specific parts of elderberry and quince, which is the effect of different polyphenolic profile of these plants. The yeast *Saccharomyces cerevisiae*, *Escherichia coli*, *Pseudomonas putida* and *Bacillus subtilis* showed the highest sensitivity to the effect of extracts of the*

analysed plants. As a positive control three antibiotics - amphotericin B, vancomycin and amoxicillin with clavulanic acid were used.

Characterization of in vitro antifungal activities of small and American cranberry (*Vaccinium oxycoccos* L. and *V. macrocarpon* Aiton) and lingonberry (*Vaccinium vitis-idaea* L.) concentrates in sugar reduced fruit spreads.

Int J Food Microbiol. 2015 Jul 2; 204:111-7. doi: 10.1016/j.ijfoodmicro.2015.03.017. Epub 2015 Mar 27.

In this study, cranberry and lingonberry concentrates were added to commercial sugar-reduced fruit spreads (raspberry-Aloe vera, strawberry-guava, and strawberry-lime), and tested for their antifungal activities. Selected strains of the species Absidia glauca, Penicillium brevicompactum, Saccharomyces cerevisiae and Zygosaccharomyces bailii, as well as xerophilic environmental isolates of the genera Penicillium and Eurotium were used for challenge testing. Initially, varying concentrations of synthetic antifungal agents, such as sodium benzoate, potassium sorbate and butyl 4-hydroxybenzoate were tested against these fungi on wort agar containing 31% fructose at different pH values. Subsequently, the experiments were conducted in fruit spreads containing different concentrations of cranberry and lingonberry concentrates. The results of this study demonstrate that these concentrates were able to inhibit growth of visible colonies of xerophilic and non-xerophilic fungi. Cranberry and lingonberry concentrates are interesting candidates for natural preservation against fungal growth in sugar reduced fruit spreads.

The antibiofilm activity of lingonberry flavonoids against oral pathogens is a case connected to residual complexity.

Fitoterapia. 2014 Sep; 97:78-86. doi: 10.1016/j.fitote.2014.05.012. Epub 2014 May 29.

*The antimicrobial activity of lingonberry (*Vaccinium vitis-idaea* L.) was evaluated against two oral pathogens, *Streptococcus mutans* and *Fusobacterium nucleatum*. Long-bed gel permeation chromatography (GPC; Sephadex LH-20) yielded purified flavonoids, with the most efficient minimum inhibitory concentrations (MICs) against planktonic cells in the anthocyanin and procyanidin primary fractions against *F. nucleatum* (63-125 µg/ml) and in the procyanidin rich fraction against *S. mutans* (16-31 µg/ml). The purified flavonol glycosides and procyanidins inhibited biofilm formation of *S. mutans* (MICs 16-31 µg/ml), while the corresponding reference compounds showed no activity. Secondary GPC purification yielded flavonol glycosides devoid of antibiofilm activity in the 50% MeOH fraction, while elution with 70% acetone recovered a brownish material with activity against *S. mutans* biofilm (MIC 8 µg/ml). Even after HPLC-PDA, NMR, and MALDI-TOF analyses, the structural identity of this material remained unknown, while its color and analytical characteristics appear to be consistent with flavonoid oxidation products.*

Medicinal plants extracts affect virulence factors expression and biofilm formation by the uropathogenic *Escherichia coli*.

Urol Res. 2012 Dec; 40(6):683-97. doi: 10.1007/s00240-012-0499-6. Epub 2012 Aug 23.

*Medicinal plants are an important source for the therapeutic remedies of various diseases including urinary tract infections. This prompted us to perform research in this area. We decided to focus on medicinal plants species used in urinary tract infections prevention. The aim of our study was to determine the influence of *Betula pendula*, *Equisetum arvense*, *Herniaria glabra*, *Galium odoratum*, *Urtica dioica*, and *Vaccinium vitis-idaea* extracts on bacterial survival and virulence factors involved in tissue colonization and biofilm formation of the uropathogenic *Escherichia coli* rods. Qualitative and quantitative analysis of plant extracts were performed. Antimicrobial assay relied on the estimation of the colony forming unit number. Hydrophobicity of cells was established by salt aggregation test. Using motility agar, the ability of bacteria to move was examined. The erythrocyte hemagglutination test was used for fimbriae P screening. Curli expression was determined using YESCA agar supplemented with congo red. Quantification of biofilm formation was carried out using a microtiter plate assay and a*

spectrophotometric method. The results of the study indicate significant differences between investigated extracts in their antimicrobial activities. The extracts of *H. glabra* and *V. vitis-idaea* showed the highest growth-inhibitory effects ($p < 0.05$). Surface hydrophobicity of autoaggregating *E. coli* strain changed after exposure to all plant extracts, except *V. vitis-idaea* ($p > 0.05$). The *B. pendula* and *U. dioica* extracts significantly reduced the motility of the *E. coli* rods ($p < 0.05$). All the extracts exhibited the anti-biofilm activity.

Antiaggregation potential of berry fractions against pairs of *Streptococcus mutans* with *Fusobacterium nucleatum* or *Actinomyces naeslundii*.

Phytother Res. 2011 Jan; 25(1):81-7. doi: 10.1002/ptr.3228.

Coaggregation is an interspecies adhesion process, which is essential to the development of dental plaque. This is an *in vitro* study of the composition of the soluble solids in the berry juice molecular size fractions (<10 kDa, FI; 10-100 kDa, FII; >100 kDa, FIII) derived from apple, bilberry, blackcurrant, cloudberry, crowberry and lingonberry and their ability to inhibit and reverse coaggregation of the pairs of common species in dental plaque: *Streptococcus mutans* with *Fusobacterium nucleatum* or *Actinomyces naeslundii*. Inhibitory and reversal activity was found in the molecular size fractions FII and FIII of bilberry, blackcurrant, crowberry and lingonberry. The active fractions contained higher amounts of polyphenols (5-12% of soluble solids) than those without activity (<2% of soluble solids). Proanthocyanidins dominated in the active lingonberry juice fractions FII and FIII and also small amounts of anthocyanins were detected. Anthocyanins, proanthocyanidins and flavonol glycosides were prevalent in FII and FIII fractions of bilberry, blackcurrant and crowberry juices. Comparable amounts of sugars and titratable acids were present in the latter three berry juice fractions of different size. The results indicate that the high molecular size fractions of lingonberry, bilberry, blackcurrant and crowberry juices have antiaggregation potential on common oral bacteria, the potential being associated with their polyphenolic content.

Berry phenolics: antimicrobial properties and mechanisms of action against severe human pathogens.

Nutr Cancer. 2006; 54(1):18-32.

Antimicrobial activity and mechanisms of phenolic extracts of 12 Nordic berries were studied against selected human pathogenic microbes. The most sensitive bacteria on berry phenolics were *Helicobacter pylori* and *Bacillus cereus*. *Campylobacter jejuni* and *Candida albicans* were inhibited only with phenolic extracts of cloudberry, raspberry, and strawberry, which all were rich in ellagitannins. Cloudberry extract gave strong microbicidal effects on the basis of plate count with all studied strains. However, fluorescence staining of liquid cultures of virulent *Salmonella* showed viable cells not detectable by plate count adhering to cloudberry extract, whereas *Staphylococcus aureus* cells adhered to berry extracts were dead on the basis of their fluorescence and plate count. Phenolic extracts of cloudberry and raspberry disintegrated the outer membrane of examined *Salmonella* strains as indicated by 1-N-phenyl-naphthylamine (NPN) uptake increase and analysis of liberation of [¹⁴C]galactose-lipopolysaccharide. Gallic acid effectively permeabilized the tested *Salmonella* strains, and significant increase in the NPN uptake was recorded. The stability of berry phenolics and their antimicrobial activity in berries stored frozen for a year were examined using *Escherichia coli* and nonvirulent *Salmonella enterica* sv. Typhimurium. The amount of phenolic compounds decreased in all berries, but their antimicrobial activity was not influenced accordingly. Cloudberry, in particular, showed constantly strong antimicrobial activity during the storage.

Berry phenolics selectively inhibit the growth of intestinal pathogens.

J Appl Microbiol. 2005; 98(4):991-1000.

AIMS: To investigate the effects of berries and berry phenolics on pathogenic intestinal bacteria and to identify single phenolic compounds being responsible for antimicrobial activity.



METHODS AND RESULTS: Antimicrobial activity of eight Nordic berries and their phenolic extracts and purified phenolic fractions were measured against eight selected human pathogens. Pathogenic bacterial strains, both Gram-positive and Gram-negative, were selectively inhibited by bioactive berry compounds. Cloudberry and raspberry were the best inhibitors, and Staphylococcus and Salmonella the most sensitive bacteria. Phenolic compounds, especially ellagitannins, were strong inhibitory compounds against Staphylococcus bacteria. Salmonella bacteria were only partly inhibited by the berry phenolics, and most of the inhibition seemed to originate from other compounds, such as organic acids. Listeria strains were not affected by berry compounds, with the exception of cranberry. Phenolic compounds affect the bacteria in different mechanisms.

CONCLUSIONS: Berries and their phenolics selectively inhibit the growth of human pathogenic bacteria.

SIGNIFICANCE AND IMPACT OF THE STUDY: Antimicrobial properties of berries could be utilized in functional foods. Furthermore, these compounds would be of high interest for further evaluation of their properties as natural antimicrobial agents for food and pharmaceutical industry.

ANTIOXIDATIVE AND ANTI-INFLAMMATORY EFFECTS

Phytochemical Properties and Antioxidant Activities of Extracts from Wild Blueberries and Lingonberries.

Plant Foods Hum Nutr. 2017 Dec; 72(4):360-364. doi: 10.1007/s11130-017-0640-3.

Among Vaccinium species, blueberries (Vaccinium myrtillus L.) and lingonberries (Vaccinium vitis-idaea) are popular in the human diet. In this study, total phenolic, total flavonoid and total monomeric anthocyanin contents in the ethanol-water extracts of blueberry and lingonberry fruits grown wild in the forests in the central region of Poland were assayed. Antioxidant activities of the extracts from each plant were also evaluated for scavenging ability on 1,1-diphenyl-2-picrylhydrazyl (DPPH) radicals and reducing power by cupric reducing antioxidant capacity (CUPRAC) method. Total phenolics in the blueberry extracts ranged from 4.58 to 5.28 mg GAE/CE/g fw. The extracts from lingonberry fruits contained higher total contents of phenolic compounds (5.82-7.60 mg GAE/g fw) as well as total flavonoids (5.22-6.47 μ mol CE/g fw) than those from blueberries (3.74-4.18 μ mol CE/g fw). For the total monomeric anthocyanin contents, the blueberry extracts presented significantly higher values (3.01-3.93 mg cyanidin-3-glucoside (C3G) equivalent/g fw) in comparison to the lingonberry extracts (0.32-0.47). Blueberry extracts exhibited higher antioxidant activity measured by both assays in comparison to lingonberry extracts. Water extracts from fresh and dried fruits also exhibited significant antioxidant activities for both types of berries. Considering the health benefits that have been associated with polyphenolic consumption, these fruits could appear as a good source of this group of phytochemical compounds for their direct consumption or their use as ingredients for the design of new food products or food supplements.

Biochemical Properties and Neuroprotective Effects of Compounds in Various Species of Berries.

Molecules. 2017 Dec 22; 23(1). pii: E26. doi: 10.3390/molecules23010026.

Several species of berries, such as blueberries (Vaccinium angustifolium) and lingonberries (Vaccinium vitis-idaea L.), have attracted much scientific attention in recent years, especially due to their reported antioxidant and anti-inflammatory properties. Berries, as with other types of plants, have developed metabolic mechanisms to survive various environmental stresses, some of which involve reactive oxygen species. In addition, the fruits and leaves of berries have high amounts of polyphenols, such as flavonoids, which act as potent antioxidants. These compounds could potentially be beneficial for brain aging and neurodegenerative disorders. There are now several studies documenting the beneficial effects of various berries in cell models of neurotoxicity as well as in vivo models of neurodegenerative disease. In the current review, we discuss the metabolic strategies that plants and animals have developed in order to combat reactive oxygen species. We then discuss issues of bioavailability of various compounds in mammals and provide a synopsis of studies demonstrating the neuroprotective ability of berries and polyphenols. We also summarize findings from our own research group. For example, we have detected various polyphenols in samples of blueberries and lingonberries and have found that the leaves have a much higher antioxidant capacity than the fruits. Extracts from these species have also demonstrated neuroprotective effects in cellular models of toxicity and inflammation, which are being further pursued in animal models.

Evaluation of Bioactive Compounds, Minerals and Antioxidant Activity of Lingonberry (Vaccinium vitis-idaea L.) Fruits.

Molecules. 2017 Dec 26; 23(1). pii: E53. doi: 10.3390/molecules23010053.

The extraction efficiency of major classes of phenolics from lingonberries grown in the central region of Poland was evaluated. The ethanol-water solution (60:40, v/v) resulted in the highest extraction yields; however, the results obtained for ethyl acetate were only slightly lower. Total phenolics estimated by Folin-Ciocalteu assay ranged from 468 to 661 mg of GA/100 g fresh weight (fw), while total flavonoids were in the range of 53.2-67.8 μ mol/100 g fw. Both solvents exhibited comparable potential for monomeric anthocyanin extraction (26.1-43.0 mg CGE/100 g of fw). The content of several minerals in these fruits and in soil collected from the same places were compared. The essential metal concentrations in all samples increased in the following

order: Cr < Cu < Zn < Fe. The levels of toxic elements (Cd, Pb) were acceptable to human consumption for most tested samples. The ethanol-water extracts exhibited the highest scavenging activity against 1,1-diphenyl-2-picryl-hydrazyl (DPPH) radicals, while the highest reducing capacity evaluated by cupric reducing antioxidant capacity (CUPRAC) was obtained for ethyl acetate extracts.

Antioxidant and cytoprotective properties of partridgeberry polyphenols.

Food Chem. 2015 Feb 1; 168:595-605. doi: 10.1016/j.foodchem.2014.07.103. Epub 2014 Jul 30.

Partridgeberry (Vaccinium vitis-idaea) is a polyphenol-rich berry of the Ericaceae family, grown in Newfoundland and Labrador province of Canada. The aims of this study were to identify extraction solvents for the maximum recovery of polyphenols, to establish fractionation technique for isolation of major sub-classes of polyphenols, and to evaluate antioxidant and cytoprotective properties of the partridgeberry polyphenol preparations. The acidified 70% acetone was identified as the ideal solvent for the maximum recovery of polyphenols from partridgeberry. Further, aqueous two-phase extraction, column chromatography and UPLC-MS/MS were employed to produce three partridgeberry polyphenol fractions, rich in either, anthocyanins, flavan-3-ols or flavonols. All the three PPF were potent antioxidants and displayed cytoprotective activity through the activation of nuclear factor erythroid 2-related factor 2 pathway, scavenging of reactive oxygen species, and inhibition of cellular death. The current study suggests that partridgeberry has numerous potential health implications in both prevention and amelioration of various diseases involving oxidative stress.

Comparative analysis of phenolic content and profile, antioxidant capacity, and anti-inflammatory bioactivity in wild Alaskan and commercial Vaccinium berries.

J Agric Food Chem. 2014 May 7; 62(18):4007-17. doi: 10.1021/jf403810y. Epub 2013 Nov 19.

Wild Alaskan Vaccinium berries, V. vitis-idaea (lowbush cranberry) and V. uliginosum (bog blueberry), were investigated in parallel with their commercial berry counterparts, V. macrocarpon (cranberry) and V. angustifolium (lowbush blueberry). Lowbush cranberry accumulated about twice the total phenolics (624.4 mg/100 g FW) and proanthocyanidins (278.8 mg/100 g) content as commercial cranberries, but A-type proanthocyanidins were more prevalent in the latter. Bog blueberry anthocyanin and total phenolic contents of 220 and 504.5 mg/100 g, respectively, significantly exceeded those of the lowbush blueberry. Chlorogenic acid, however, was quite high in lowbush blueberry (83.1 mg/100 g), but undetected in bog blueberry, and the proanthocyanidins of lowbush blueberry had significantly higher levels of polymerization. Antioxidant capacity (DPPH, APTS, and FRAP) correlated with phenolic content for each berry. A polyphenol-rich fraction from lowbush cranberry exhibited dose-dependent inhibition of LPS-elicited induction of IL-1 β in RAW 264.7 cells, indicative of strong anti-inflammatory activity. These results corroborate the historic use of wild Alaskan berries as medicinally important foods in Alaska Native communities.

Food grade lingonberry extract: polyphenolic composition and in vivo protective effect against oxidative stress.

J Agric Food Chem. 2011 Apr 13; 59(7):3330-9. doi: 10.1021/jf103965b. Epub 2011 Mar 4.

Fractionation of the polyphenols constituting a food grade lingonberry extract (Vaccinium vitis-idaea) highlighted a composition more complex than described until now in the berry. Procyanidins B1, B2, and A2 were identified by UPLC/ESI-MS(2) along with the presence of other flavanol oligomers. Processing induced the release of large amounts of aglycones for ferulic acid, p-coumaric acid, and quercetin. The described anthocyanic composition of lingonberry was completed with hexoside derivatives of peonidin, petunidin, malvidin, and delphinidin. Besides confirmation of in vitro antioxidant activity, in vivo study was performed on rats fed a diet inducing oxidative stress. Supplementation with lingonberry extract significantly decreased the total oxidant status and favorably affected antioxidant defense enzymes in red blood cells and liver. A drop in the serum reduced

glutathione level was also prevented, and uric acid was maintained at low level, confirming the antioxidant activity of the extract (5% proanthocyanidins) from a dosage of 23 mg/kg of body weight.

Lingonberry (*Vaccinium vitis-idaea*) and European cranberry (*Vaccinium microcarpon*) proanthocyanidins: isolation, identification, and bioactivities.

J Agric Food Chem. 2011 Apr 13; 59(7):3373-84. doi: 10.1021/jf104621e. Epub 2011 Mar 3.

*European, small-fruited cranberries (*Vaccinium microcarpon*) and lingonberries (*Vaccinium vitis-idaea*) were characterized for their phenolic compounds and tested for antioxidant, antimicrobial, antiadhesive, and antiinflammatory effects. The main phenolic compounds in both lingonberries and cranberries were proanthocyanidins comprising 63-71% of the total phenolic content, but anthocyanins, hydroxycinnamic acids, hydroxybenzoic acids, and flavonols were also found. Proanthocyanidins are polymeric phenolic compounds consisting mainly of catechin, epicatechin, gallocatechin, and epigallocatechin units. In the present study, proanthocyanidins were divided into three groups: dimers and trimers, oligomers (mDP 4-10), and polymers (mDP > 10). Catechin, epicatechin, A-type dimers and trimers were found to be the terminal units of isolated proanthocyanidin fractions. Inhibitions of lipid oxidation in liposomes were over 70% and in emulsions over 85%, and in most cases the oligomeric or polymeric fraction was the most effective. Polymeric proanthocyanidin extracts of lingonberries and cranberries were strongly antimicrobial against *Staphylococcus aureus*, whereas they had no effect on other bacterial strains such as *Salmonella enterica* sv. *Typhimurium*, *Lactobacillus rhamnosus* and *Escherichia coli*. Polymeric fraction of cranberries and oligomeric fractions of both lingonberries and cranberries showed an inhibitory effect on hemagglutination of *E. coli*, which expresses the M hemagglutinin. Cranberry phenolic extract inhibited LPS-induced NO production in a dose-dependent manner, but it had no major effect on iNOS of COX-2 expression. At a concentration of 100 µg/mL cranberry phenolic extract inhibited LPS-induced IL-6, IL-1β and TNF-α production. Lingonberry phenolics had no significant effect on IL-1β production but inhibited IL-6 and TNF-α production at a concentration of 100 µg/mL similarly to cranberry phenolic extract. In conclusion the phenolics, notably proanthocyanidins (oligomers and polymers), in both lingonberries and cranberries exert multiple bioactivities that may be exploited in food development.*

Catechins and procyanidins in berries of *Vaccinium* species and their antioxidant activity.

J Agric Food Chem. 2005 Nov 2; 53(22):8485-91.

*The fractions of monomeric catechins and the fractions of dimeric and trimeric procyanidins were extracted and concentrated from wild berries of *Vaccinium* species to study their antioxidant activities. The compositions of the fractions were analyzed using high-performance liquid chromatography combined with diode-array and electrospray ionization mass spectrometric detection. Rare A-type dimers and trimers were identified as the predominant procyanidins in wild lingonberry, cranberry, bilberry, and bog whortleberry. Lingonberry and cranberry catechin and procyanidin fractions as well as bog whortleberry catechin fraction were good scavengers of radicals in the 2,2-diphenyl-1-picrylhydrazyl (DPPH) test and more efficient than the respective bilberry fractions. Bog whortleberry procyanidin fraction was less active, this being mainly due to the lower content of these compounds. Fractions from lingonberry, cranberry, and bilberry were equally efficient in inhibiting the oxidation of methyl linoleate emulsion, but differences among the berries were found in their abilities to inhibit low-density lipoprotein (LDL) oxidation. Catechins, the monomers, exhibited comparable activity to the fractions containing dimers and trimers in inhibiting the oxidation of methyl linoleate emulsion and human LDL. Bog whortleberry catechins were excellent antioxidants toward the oxidation of human LDL. Radical scavenging and antioxidant activities of *Vaccinium* berry fractions were attributable to the their composition of catechins and procyanidins. In conclusion, *Vaccinium* catechins as well as dimeric and trimeric procyanidins provide substantial antioxidant protection.*

Oxygen radical absorbing capacity of phenolics in blueberries, cranberries, chokeberries, and lingonberries.

J Agric Food Chem. 2003 Jan 15; 51(2):502-9.

The antioxidant activity of phenolics in fruits of blueberry (*Vaccinium corymbosum* cv. Sierra), cranberry (*Vaccinium macrocarpon* cv. Ben Lear), wild chokeberry (*Aronia melanocarpa*), and lingonberry (*Vaccinium vitis-idaea* cv. Amberland) was determined in this study. The phenolic constituents and contents among the different berries varied considerably. Anthocyanins were found to be the main components in all these berries. Chlorogenic acid in blueberry, quercetin glycosides in cranberry and lingonberry, and caffeic acid and its derivative in chokeberry were also present in relatively high concentrations. Chlorogenic acid, peonidin 3-galactoside, cyanidin 3-galactoside, and cyanidin 3-galactoside were the most important antioxidants in blueberry, cranberry, wild chokeberry, and lingonberry, respectively. The contribution of individual phenolics to the total antioxidant capacity was generally dependent on their structure and content in the berries. Phenolics such as quercetin and cyanidin, with 3',4'-dihydroxy substituents in the B ring and conjugation between the A and B rings, had highly effective radical scavenging structures in blueberries, cranberries, chokeberries, and lingonberries. Phenolic acids such as caffeic acid also showed high antioxidant activity, probably due to its dihydroxylation in the 3,4 positions as hydrogen donors.

Inhibition of protein and lipid oxidation in liposomes by berry phenolics.

J Agric Food Chem. 2004 Dec 1; 52(24):7419-24.

The antioxidant activity of berry phenolics (at concentrations of 1.4, 4.2, and 8.4 µg 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.

Evaluation of anti-inflammatory activity of some Swedish medicinal plants. Inhibition of prostaglandin biosynthesis and PAF-induced exocytosis.

J Ethnopharmacol. 1995 Oct; 48(2):61-76.

Plants used in Swedish traditional medicine to treat inflammatory diseases and/or wounds were selected, based on literature data, for evaluation of inhibitory activity on prostaglandin biosynthesis and platelet activating factor (PAF)-induced exocytosis *in vitro*. Fifty-nine water extracts from 52 different plants in 28 families were tested. A number of plants, e.g. *Calluna vulgaris*, *Corylus avellana*, *Geum urbanum*, *Juniperus communis*, *Polygonum aviculare*, *Potentilla erecta* and *Salix caprea* were found to be active in both assays. The most potent cyclooxygenase inhibitors were extracts of *Calluna vulgaris*, *Potentilla erecta* and *Salix caprea*. None of the extracts inhibited just the prostaglandin biosynthesis. In the PAF-test, high inhibition was obtained by 19 extracts, the most potent of which were from *Geum rivale*, *G. urbanum*, *Solanum dulcamara*, *Symphytum x uplandicum* and *Vaccinium vitis-idaea*. The *in vitro* effects in relation to the traditional use, chemical contents and botanical classification, as well as the possibilities and the limitations of the methods are discussed.

BIOAVAILABILITY

Bioavailability of various polyphenols from a diet containing moderate amounts of berries.

J Agric Food Chem. 2010 Apr 14; 58(7):3927-32. doi: 10.1021/jf9024823.

Berries are a rich source of various polyphenols. The objective of this study was to investigate the bioavailability of polyphenols from berries. Middle-aged subjects (n = 72) consumed moderate amounts of berry or control products for 8 weeks in a randomized, placebo-controlled dietary intervention trial. Average intake of berries was 160 g/day (bilberries, lingonberries, black currants, and chokeberries). Plasma and urine polyphenols were analyzed by GC-MS and HPLC and berry polyphenols by HPLC. The total intake of polyphenols was 837 mg/day. Plasma quercetin, p-coumaric acid, 3-hydroxyphenylacetic acid, caffeic acid, protocatechuic acid, vanillic acid, homovanillic acid, and 3-(3-hydroxyphenyl)propionic acid increased significantly from the baseline in the berry group compared to the control group (p < 0.05). The urinary excretion of quercetin, p-coumaric acid, and 3-hydroxyphenylacetic acid increased significantly in the berry group compared to the control group (p < 0.05). In conclusion, a number of polyphenols are bioavailable from a diet containing moderate amounts of blue and red berries.

Flavonol glycosides of sea buckthorn (*Hippophaë rhamnoides* ssp. *sinensis*) and lingonberry (*Vaccinium vitis-idaea*) are bioavailable in humans and monoglucuronidated for excretion.

J Agric Food Chem. 2010 Jan 13; 58(1):620-7. doi: 10.1021/jf9029942.

Glucuronidation and excretion of sea buckthorn and lingonberry flavonols were investigated in a postprandial trial by analyzing the intact forms of flavonol glycosides as well as glucuronides in plasma, urine, and feces. Four study subjects consumed sea buckthorn (study day 1) and lingonberry (study day 2) breakfasts, and blood, urine, and fecal samples were collected for 8, 24, and 48 h, respectively. Both glycosides and glucuronides of the flavonol quercetin as well as kaempferol glucuronides were detected in urine and plasma samples after the consumption of lingonberries; 14% of flavonols in urine were glycosides, and 86% were glucuronidated forms (wt %). After the consumption of sea buckthorn, 5% of flavonols excreted in urine were detected intact, and 95% as the glucuronides (wt %). Solely glucuronides of flavonols isorhamnetin and quercetin were found in plasma after the consumption of sea buckthorn berries. Only glycosides were detected in the feces after each berry trial. Flavonol glycosides and glucuronides remained in blood and urine quite long, and the peak concentrations appeared slightly later than previously described. The berries seemed to serve as a good flavonol supply, providing steady flavonol input for the body for a relatively long time.

Comparison of in vivo and in vitro digestion on polyphenol composition in lingonberries: potential impact on colonic health.

Biofactors. 2014 Nov-Dec; 40(6):611-23. doi: 10.1002/biof.1173. Epub 2014 Oct 30.

The composition of polyphenols in ileal fluid samples obtained from an ileostomy subject after lingonberry intake was compared with lingonberry extracts obtained after simulated in vitro digestion (IVDL) and subsequent faecal fermentation (IVFL). HPLC-PDA-MS/MS analysis confirmed similar patterns of lingonberry (poly)phenolic metabolism after the in vivo and in vitro digestion, with reduced recovery of anthocyanins and a similar pattern of recovery for proanthocyanidins observed for both methods of digestion. On the other hand, the IVFL sample contained none of the original (poly)phenolic components but was enriched in simple aromatic components. Digested and fermented extracts exhibited significant (P < 0.05) anti-genotoxic (Comet assay), anti-mutagenic (Mutation Frequency assay), and anti-invasive (Matrigel Invasion assay) effects in human cell culture models of colorectal cancer at physiologically-relevant doses (0-50 µg/mL gallic acid equivalents). The ileal fluid induced significant anti-genotoxic activity (P < 0.05), but at a higher concentration (200 µg/mL gallic acid equivalents) than the IVDL. Despite extensive structural modification following digestion and fermentation, lingonberry extracts retained their bioactivity in vitro. This reinforces the need for studies to consider the impact of digestion when investigating bioactivity of dietary phytochemicals.

¹H NMR-based metabolic fingerprinting of urine metabolites after consumption of lingonberries (*Vaccinium vitis-idaea*) with a high-fat meal.

Food Chem. 2013 Jun 1; 138(2-3):982-90. doi: 10.1016/j.foodchem.2012.10.081. Epub 2012 Nov 16.

The use of NMR metabolomics in clinical trials is growing; however, reports of postprandial experiments in humans are scarce. The present study investigated whether consumption of lingonberries as a supplement to an oil-rich meal modifies the postprandial fingerprints of human urine. Urine samples were analysed by (1)H NMR, and untargeted multivariate analysis was applied to the data for comprehensive fingerprinting. A clear separation of postprandial lingonberry meal samples was revealed. To evaluate statistical differences, a targeted approach was applied for the informative spectral areas. Significantly ($p < 0.05$) increased levels of polyphenol metabolites, hippuric acid and 4-hydroxyhippuric acid, and decreased creatinine and dimethylamine levels were the major explanations for the grouping of the postprandial samples after the different meals. Thus, inclusion of polyphenol-rich lingonberry powder in a rapeseed oil-rich meal modifies the metabolic profile of urine which may be used to reveal both consumption of berries and health-promoting changes in the common metabolism.

Bioavailability of quercetin from berries and the diet.

Nutr Cancer. 2006; 54(1):13-7.

Berries are a rich source of various polyphenols, including the flavonoid quercetin. In this article, the results of three intervention studies investigating the bioavailability of quercetin from berries are reviewed. In the first study, we investigated the short-term kinetics of quercetin after consumption of black currant juice and showed that quercetin is rapidly absorbed from it. In the second study, we showed that plasma quercetin levels increase up to 50% in subjects consuming 100 g/day of bilberries, black currants, and lingonberries as a part of their normal diets for 2 mo. In the third study, healthy subjects consumed a diet high or low in vegetables, berries, and other fruit for 6 wk. Quercetin concentrations nearly doubled in the high-vegetable, -berry, and -other fruit group and decreased by 30% in subjects consuming less of these foods than normally. The results showed that plasma quercetin is bioavailable from a diet containing berries and indicate that it may be a good biomarker of fruit and vegetable intake in general.

Analysis and bioactive evaluation of the compounds absorbed into blood after oral administration of the extracts of *Vaccinium vitis-idaea* in rat.

Biol Pharm Bull. 2005 Jun; 28(6):1106-8.

*In order to screen the active constituents of *Vaccinium vitis-idaea* L., the compounds absorbed into the rat blood after oral administration of ethanol extract of the stems and leaves of *V. vitis-idaea* (EEV) have been analyzed. Two compounds were detected in the plasma and identified as arbutin and fraxin, which are originally existed in the crude drug. Furthermore, the pharmacological effects of the two compounds involving EEV for curing acute and chronic respiratory tract infection were tested. The results showed that both arbutin and fraxin have the anti-inflammatory, anti-coughing and phlegm-removing effects. Therefore, it was ascertained that the arbutin and fraxin would be the main active constituents of *V. vitis-idaea* L.*

Consumption of black currants, lingonberries and bilberries increases serum quercetin concentrations.

Eur J Clin Nutr. 2003 Jan; 57(1):37-42.

OBJECTIVE: To study serum quercetin concentrations of subjects consuming berries or habitual Finnish diets.

DESIGN: Randomized parallel dietary intervention.

SUBJECTS: Forty healthy men (age 60 y).



INTERVENTION: Twenty subjects consumed 100 g/day of berries (black currants, lingonberries and bilberries) for 8 weeks. Twenty subjects consuming their habitual diets served as controls. Fasting blood samples were obtained 2 weeks prior to the study, at baseline, and at 2, 4 and 8 weeks. Intake of quercetin was assessed from 3 day food records collected at baseline and at 8 weeks.

RESULTS: The serum quercetin concentrations were significantly higher in the subjects consuming berries compared to the control group ($P=0.039$ ANCOVA with repeated measures). During the berry consumption period the mean serum concentrations of quercetin ranged between 21.4 and 25.3 micro g/l in the berry group, which was 32-51% higher compared with the control group. According to 3 day food records, there was no difference in quercetin intake at baseline, but at 8 weeks the intake was 12.3+/-1.4 mg/day (mean+/-s.e.m.) in the berry group and 5.8+/-0.6 mg/day in the control group ($P=0.001$).

CONCLUSIONS: The results indicate that the berries used in this study are a good source of bioavailable quercetin.

BRAIN HEALTH

Chemical Analysis of Extracts from Newfoundland Berries and Potential Neuroprotective Effects.

Antioxidants (Basel). 2016 Oct 19;5(4). pii: E36.

*Various species of berries have been reported to contain several polyphenolic compounds, such as anthocyanins and flavonols, which are known to possess high antioxidant activity and may be beneficial for human health. To our knowledge, a thorough chemical analysis of polyphenolics in species of these plants native to Newfoundland, Canada has not been conducted. The primary objective of this study was to determine the polyphenolic compounds present in commercial extracts from Newfoundland berries, which included blueberries (*V. angustifolium*), lingonberries (*V. vitis-idaea*) and black currant (*Ribes lacustre*). Anthocyanin and flavonol glycosides in powdered extracts from *Ribes lacustre* and the *Vaccinium* species were identified using the high performance liquid chromatographic (HPLC) separation method with mass spectrometric (MS) detection. The identified compounds were extracted from dried berries by various solvents via ultrasonication followed by centrifugation. A reverse-phase analytical column was employed to identify the retention time of each chemical component before submission for LC-MS analysis. A total of 21 phenolic compounds were tentatively identified in the three species. Further, we tested the effects of the lingonberry extract for its ability to protect neurons and glia from trauma utilizing an in vitro model of cell injury. Surprisingly, these extracts provided complete protection from cell death in this model. These findings indicate the presence of a wide variety of anthocyanins and flavonols in berries that grow natively in Newfoundland. These powdered extracts maintain these compounds intact despite being processed from berry fruit, indicating their potential use as dietary supplements. In addition, these recent findings and previous data from our lab demonstrate the ability of compounds in berries to protect the nervous system from traumatic insults.*

[Effects of lingonberry extraction on the mice cognitive function damaged by chronic stress].

Wei Sheng Yan Jiu. 2015 Nov;44(6):943-8. Article in Chinese.

OBJECTIVE: *To study the effects of lingonberry extraction on mice cognitive impairment caused by chronic stress.*

METHODS: *Kunming mice were randomly divided into six groups, which were control group, stress model group, the fluoxetine group (dose of 4.4 mg · kg(-1) · d(-1)), lingonberry extraction low, medium and high dose group (respectively 50, 100 and 200 mg · kg(-1) · d(-1)). All groups were given chronic uncertainty stress but the control group, and were intragastric administration for 18 days. Then the cognition of the mice was tested by using water maze, the contents of the SOD, GSH-Px, MDA and the activity of the neurotransmitters such as noradrenaline (NE), serotonin (5-HT), glucocorticoids (GC), acetylcholinesterase (AChE) were measured by using kit.*

RESULTS: *Lingonberry extraction improved the cognition and memory of the mice induced by chronic uncertainty stress, increased the content of the SOD and GSH-Px in mice brain, and decreased the content of oxidative damage markers MDA. Lingonberry extraction could also inhibit the increase of GC, inhibit the activity of AChE in blood serum, elevated the content of 5-HT and NE in mice blood serum and brain.*

CONCLUSION: *Lingonberry extraction improved the cognition and memory of the mice induced by chronic uncertainty stress. The possible mechanism was that lingonberry enhanced the antioxidative ability of tissue and improved the disorder of neurotransmitter levels caused by chronic stress.*

Partridgeberry polyphenols protect primary cortical and hippocampal neurons against β -amyloid toxicity.

Food Res Int. 2015 Aug; 74:237-249. doi: 10.1016/j.foodres.2015.05.019. Epub 2015 May 11.

β -Amyloid ($A\beta$) deposition elicits a toxic effect on neurons and plays a crucial role in the etiology and/or progression of Alzheimer's disease (AD). Polyphenols found in fruits are endorsed for nutritional intervention in AD, since they are known to have extensive therapeutic properties apropos of brain health owing to their anti-oxidative effects against $A\beta$ and neural reactive oxygen species (ROS). The present study was aimed to investigate the neuroprotective potential of polyphenols of partridgeberry (*Vaccinium vitis-idaea* L.) and elucidate the mechanism by which they confer protection against $A\beta$ toxicity in rat primary neurons *in vitro*. The pre-treatment of rat primary cortical and hippocampal neurons with partridgeberry polyphenols (10-200 $\mu\text{g mL}^{-1}$) significantly attenuated $A\beta$ -induced cell death and membrane damage. The flavan-3-ol- and flavonol-rich fractions of the partridgeberry exhibited the strongest ability to maintain cell viability (EC_{50} 5.9 $\mu\text{g mL}^{-1}$) and prevent lactose dehydrogenase release (IC_{50} 0.01 $\mu\text{g mL}^{-1}$) ($P \leq 0.05$). Similar to the maintenance of cellular viability, the flavan-3-ol- and flavonol-rich fractions also amplified the greatest activity of SOD and catalase among all polyphenol preparations exposed to neurons ($P \leq 0.05$). All four partridgeberry polyphenol preparations reduced the intracellular $A\beta$ levels by 7-15 folds, and initiated $A\beta$ clearance from neurons as compared to untreated cells ($P \leq 0.05$). Partridgeberry derived polyphenol preparations; especially the flavonol-rich fraction (IC_{50} 97.1 $\mu\text{g mL}^{-1}$) significantly modulated the apoptotic targets and *in vitro* acetylcholinesterase activity ($P \leq 0.05$), indicating potential pharmacotherapy application in AD. Furthermore, the restoration of hyperactive caspases and Bcl2 family of apoptotic architects added to the neuroprotective candidacy of PPFs. These findings suggest that partridgeberry polyphenols, especially flavan-3-ol- and flavonol-rich fractions, could be of importance in prevention and/or treatment of AD.

Partridgeberry polyphenols protect rat primary cortical neurons from oxygen-glucose deprivation reperfusion-induced injury via suppression of inflammatory adipokines and regulation of HIF-1 α and PPAR γ .

Nutr Neurosci. 2015 May 5. [Epub ahead of print].

OBJECTIVES: The aim of this study was to investigate the neuroprotective ability of partridgeberry polyphenols in rat primary cortical neurons against oxygen-glucose deprivation/reperfusion (OGD/R) injury *in vitro* and explore the underlying therapeutic mechanism(s).

METHODS: The OGD/R injury was induced in rat primary cortical neurons by incubation with deoxygenated glucose-free medium in a hypoxia chamber.

RESULTS: The strongest activity in this regard was exhibited by partridgeberry-derived PPF2 and PPF3, i.e. the flavan-3-ol- and flavonol-rich polyphenol fractions of partridgeberry ($P \leq 0.05$). Moreover, partridgeberry polyphenol pre-treatment reduced the membrane damage in primary neurons, as measured by the lactose dehydrogenase (LDH) release assay ($P \leq 0.05$). Furthermore, PPF2 and PPF3 pre-treatment (100 $\mu\text{g mL}^{-1}$) for 24 hours, before OGD/R, resulted in the strongest suppression of interleukin (IL)-6 and tumor necrosis factor- α induction by OGD/R injury, compared with the control group ($P \leq 0.05$). Additionally, the protein levels of hypoxia-inducible factor (HIF-1 α) and PPAR γ , quantified by ELISA presented a significant modulation following PPFs treatment (100 $\mu\text{g mL}^{-1}$), favorably toward neuroprotection, compared with the respective controls after OGD/R injury *in vitro* ($P \leq 0.05$).

CONCLUSION: In summary, partridgeberry polyphenols at concentrations of 1-100 $\mu\text{g mL}^{-1}$, significantly induced a decline in OGD/R injury-triggered apoptosis *in vitro*, suppressed the inflammatory biomarkers in primary neurons, and modulated the activity of HIF-1 α and proliferator-activated receptor gamma (PPAR γ) following hypoxic injury.

CARDIAC HEALTH

Lingonberries reduce atherosclerosis in Apoe(-/-) mice in association with altered gut microbiota composition and improved lipid profile.

Mol Nutr Food Res. 2016 May;60(5):1150-60. doi: 10.1002/mnfr.201500738. Epub 2016 Mar 22.

SCOPE: To investigate the efficacy of lingonberries in prevention of atherosclerosis, using atherosclerosis-prone Apoe(-/-) mice and to clarify whether effects were associated with changes in the gut microbiota, gut metabolites, and lipid metabolism.

METHODS AND RESULTS: Male Apoe(-/-) mice were fed either low-fat diet, high-fat diet, or high-fat diet with 44% lingonberries for 8 weeks. Blood lipid profiles, hepatic gene expression, atherosclerotic plaques in the aortic root region of the heart, bacterial 16S rRNA gene profiles, and cecal short-chain fatty acids (SCFAs) were analyzed. Triglyceride levels and amount of atherosclerotic plaques decreased in the group fed lingonberries in comparison to the high-fat group. Hepatic expression of the bile acid synthesis gene Cyp7a1 was significantly upregulated in the lingonberry group. Lingonberries increased the cecal relative abundance of bacterial genera Bacteroides, Parabacteroides and Clostridium. The cecal levels of total SCFAs were significantly lower in the lingonberry group, while the cecal proportion of propionic acid was higher in mice fed lingonberries.

CONCLUSION: Intake of lingonberries resulted in decreased triglyceridemia and reduced atherosclerosis. The altered gut microbiota composition and SCFA profile was associated with increased hepatic bile acid gene expression in mice fed lingonberries.

Lingonberry anthocyanins protect cardiac cells from oxidative-stress-induced apoptosis.

Can J Physiol Pharmacol. 2017 Aug; 95(8):904-910. doi: 10.1139/cjpp-2016-0667. Epub 2017 Apr 6.

Lingonberry grown in northern Manitoba, Canada, contains exceptionally high levels of anthocyanins and other polyphenols. Previous studies from our lab have shown that lingonberry anthocyanins can protect H9c2 cells from ischemia-reperfusion injury and anthocyanin-rich diets have been shown to be associated with decreased cardiovascular disease and mortality. Oxidative stress can impair function and trigger apoptosis in cardiomyocytes. This study investigated the protective effects of physiologically relevant doses of lingonberry extracts and pure anthocyanins against hydrogen-peroxide-induced cell death. Apoptosis and necrosis were detected in H9c2 cells after hydrogen peroxide treatment via flow cytometry using FLICA 660 caspase 3/7 combined with YO-PRO-1 and then confirmed with Hoechst staining and fluorescence microscopy. Each of the 3 major anthocyanins found in lingonberry (cyanidin-3-galactoside, cyanidin-3-glucoside, and cyanidin-3-arabinoside) was protective against hydrogen-peroxide-induced apoptosis in H9c2 cells at 10 ng·mL⁻¹ (20 nmol·L⁻¹) and restored the number of viable cells to match the control group. A combination of the 3 anthocyanins was also protective and a lingonberry extract tested at 3 concentrations produced a dose-dependent protective effect. Lingonberry anthocyanins protected cardiac cells from oxidative-stress-induced apoptosis and may have cardioprotective effects as a dietary modification.

Lingonberry juice improves endothelium-dependent vasodilatation of mesenteric arteries in spontaneously hypertensive rats in a long-term intervention.

Journal of Functional Foods. 10/2011; 3(4):267-274. DOI: 10.1016/j.jff.2011.05.001.

Phenolic compounds of berries, fruits and vegetables affect vascular health. Endothelium-dependent vasodilatation has an important role in blood pressure development by controlling the vascular tone. Endothelial cells produce and release various relaxing and contracting factors, like nitric oxide (NO), cyclo-oxygenase (COX)-derived prostanoids and endothelium-derived hyperpolarizing factor (EDHF). The purpose of this study was to investigate whether 8 weeks treatment with Finnish berry juices, cranberry (Vaccinium oxycoccos), lingonberry (Vaccinium vitis-idaea) and blackcurrant (Ribes nigrum) affects blood pressure and vascular function of spontaneously hypertensive rats (SHR). After 8 weeks treatment the mesenteric arteries of the rats

were taken for vascular reactivity studies. Lingonberry treatment normalized the impaired endothelium-dependent relaxation seen in the cranberry, blackcurrant and control rats. In the arteries of lingonberry treated rats the relaxation was partly due to NO, but also dependent on EDHF. It can be concluded that long-term lingonberry juice treatment improves endothelium-dependent vasodilatation of SHR.

Lingonberry, cranberry and blackcurrant juices affect mRNA expressions of inflammatory and atherothrombotic markers of SHR in a long-term treatment.

Journal of Functional Foods. 04/2012; 4(2):496–503. DOI: 10.1016/j.jff.2012.02.010.

Flavonoids and other phenolic compounds affect low-grade inflammation related to cardiovascular diseases among other positive health effects. Cardioprotective actions are mainly due to enhanced endothelial function and production of nitric oxide (NO). We investigated vascular anti-inflammatory effects of cranberry (Vaccinium oxycoccos), lingonberry (Vaccinium vitis-idaea) and blackcurrant (Ribes nigrum) juices given as drinking fluid ad libitum to spontaneously hypertensive rats (SHR), a widely used model of human hypertension, in an 8 week intervention study. The animals were sacrificed, the aortas cleaned and RNA was extracted. cDNA was prepared for real-time PCR and blood was collected for biochemical analyses. The mRNA expressions of angiotensin-converting enzyme 1 (ACE1), cyclooxygenase 2 (COX2), monocyte chemoattractant protein 1 (MCP1) and P-selectin were significantly reduced in the cranberry and lingonberry groups. These findings suggest that cranberry and lingonberry cold-compressed juices have anti-inflammatory and anti-atherothrombotic actions in long-term treatment of SHR.

Lingonberry juice lowers blood pressure of spontaneously hypertensive rats (SHR).

Journal of Functional Foods. 07/2013; 5(3):1432-1440. DOI: 10.1016/j.jff.2013.05.012.

Lingonberries (Vaccinium vitis-idaea) are rich in polyphenols, such as proanthocyanidins, anthocyanins, flavonols and flavanols. Polyphenol-rich foods affect vascular health. We previously described improved endothelium-dependent vascular function as well as anti-inflammatory and anti-atherothrombotic effects in spontaneously hypertensive rats (SHR) fed with lingonberry juice. In the present study, we investigated the effects of lingonberry juice dose on blood pressure, vascular function and vascular inflammation in SHR in an 8 weeks' study. Diluted (1:5) cold-compressed lingonberry juice was given as drinking fluid ad libitum to 5 week old SHR for 8 weeks. Control group (SHR) and normotensive reference group (Wistar-Kyoto) received tap water. Systolic blood pressure (SBP) was monitored weekly. Function of mesenteric artery rings was assessed in standard organ-bath chambers after 8 weeks. Biochemical and clinical chemistry variables were measured from plasma and urine. Lingonberry juice lowered SBP of SHR ($p = 0.007$). Endothelium-dependent vascular relaxation was not improved. Lingonberry treatment slightly affected plasma inflammatory markers (reduction of NOx and sICAM-1) and clinical chemistry variables (decreased alkaline phosphatase and increased chloride and calcium levels). In conclusion, Lingonberry juice at small concentrations lowers blood pressure in a long-term treatment in SHR.

Lingonberry juice negates the effects of a high salt diet on vascular function and low-grade inflammation.

Journal of Functional Foods. 2014 March; 7(1). DOI: 10.1016/j.jff.2014.02.005.

High salt in diet elevates blood pressure in man. Berries and fruits are regarded beneficial in antagonizing hypertension and related vascular complications. We aimed to test whether lingonberry juice shows beneficial and anti-inflammatory effects in salt induced hypertension rat model. Male Wistar–Kyoto rats were fed with 8% sodium chloride enriched pellets for 10 weeks having tap water or diluted lingonberry juice as drinking fluid. Blood pressure was recorded weekly and mesenteric artery functions tested ex vivo. Urine was collected in metabolic caging. Salt loading had only minor effects on blood pressure or endothelial function. Increased urine excretion of 8-isoprostane, cGMP and albumin reflected general or renal inflammation. Elevated expression (mRNA) of proinflammatory COX-2 by salt was normalized by lingonberry. Salt increased kidney, heart and



left ventricle masses and changed serum chloride, alkaline phosphatase, albumin and lipid concentrations. Taken together the results show that 10 weeks' high-salt diet impaired kidney function of young rats without clear effect on blood pressure or vascular function. Lingonberry juice moderately reduced biomarkers of low-grade inflammation probably due to its high polyphenol concentrations.

Manitoba Lingonberry (*Vaccinium vitis-idaea*) Bioactivities in Ischemia-Reperfusion Injury.

J Agric Food Chem. 2015 Jun 17; 63(23):5660-9. doi: 10.1021/acs.jafc.5b00797. Epub 2015 Jun 9.

*Evidence for the efficacy of dietary interventions in protecting against cardiovascular disease has grown significantly, with flavonoids and anthocyanins receiving special attention. Lingonberry (*Vaccinium vitis-idaea* L.) is a good source of these compounds, and this study examined the protective effects of wild lingonberry found in Manitoba, Canada, against ischemia-reperfusion (IR) injury. Manitoba lingonberry contained 3793 ± 27 mg gallic acid equiv, $120,501 \pm 7651$ μ mol trolox equiv, and 575 ± 20 mg cyanidin-3-glucoside equiv per 100 g dry weight, which correspond with high total phenolic content, antioxidant activity, and anthocyanin content, respectively. A complete methanolic extract and both anthocyanin-rich and phenolic-rich fractions inhibited apoptosis in H9c2 cells during simulated IR. Lingonberry extract and fractions significantly inhibited several markers of apoptosis induced by IR, including nuclei condensation, caspase-3 activation, and MAP kinase signaling. These results provide the first analysis of Manitoba lingonberry and highlight the mechanistic importance of dietary berry compounds for cardiovascular health.*

EYE HEALTH

Protective effects of bilberry and lingonberry extracts against blue light-emitting diode light induced retinal photoreceptor cell damage in vitro.

BMC Complement Altern Med. 2014 Apr 2; 14:120. doi: 10.1186/1472-6882-14-120.

BACKGROUND: Blue light is a high-energy or short-wavelength visible light, which induces retinal diseases such as age-related macular degeneration and retinitis pigmentosa. Bilberry (Vaccinium myrtillus L.) and lingonberry (Vaccinium vitis-idaea) contain high amounts of polyphenols (anthocyanins, resveratrol, and proanthocyanidins) and thus confer health benefits. This study aimed to determine the protective effects and mechanism of action of bilberry extract (B-ext) and lingonberry extract (L-ext) and their active components against blue light-emitting diode (LED) light-induced retinal photoreceptor cell damage.

METHODS: Cultured murine photoreceptor (661 W) cells were exposed to blue LED light following treatment with B-ext, L-ext, or their constituents (cyanidin, delphinidin, malvidin, trans-resveratrol, and procyanidin B2). 661 W cell viability was assessed using a tetrazolium salt (WST-8) assay and Hoechst 33342 nuclear staining, and intracellular reactive oxygen species (ROS) production was determined using CM-H2DCFDA after blue LED light exposure. Activation of p38 mitogen-activated protein kinase (p38 MAPK), nuclear factor-kappa B (NF-κB), and LC3, an ubiquitin-like protein that is necessary for the formation of autophagosomes, were analyzed using Western blotting. Caspase-3/7 activation caused by blue LED light exposure in 661 W cells was determined using a caspase-3/7 assay kit.

RESULTS: B-ext, L-ext, NAC, and their active components improved the viability of 661 W cells and inhibited the generation of intracellular ROS induced by blue LED light irradiation. Furthermore, B-ext and L-ext inhibited the activation of p38 MAPK and NF-κB induced by blue LED light exposure. Finally, B-ext, L-ext, and NAC inhibited caspase-3/7 activation and autophagy.

CONCLUSIONS: These findings suggest that B-ext and L-ext containing high amounts of polyphenols exert protective effects against blue LED light-induced retinal photoreceptor cell damage mainly through inhibition of ROS production and activation of pro-apoptotic proteins.

The protective effects of bilberry and lingonberry extracts against UV light-induced retinal photoreceptor cell damage in vitro.

J Agric Food Chem. 2013 Oct 30; 61(43):10345-53. doi: 10.1021/jf402772h. Epub 2013 Oct 16.

Bilberry extract (B-ext) and lingonberry extract (L-ext) are currently used as health supplements. We investigated the protective mechanisms of the B-ext and L-ext against ultraviolet A (UVA)-induced retinal photoreceptor cell damage. Cultured murine photoreceptor (661W) cells were exposed to UVA following treatment with B-ext and L-ext and their main constituents (cyanidin, delphinidin, malvidin, trans-resveratrol, and procyanidin). B-ext, L-ext, and constituents improved cell viability and suppressed ROS generation. Phosphorylation of p38 mitogen-activated protein kinase (p38 MAPK), c-Jun N-terminal kinase (JNK), and protein kinase B (Akt) were analyzed by Western blotting. B-ext and cyanidin inhibited phosphorylation of p38 MAPK, and B-ext also inhibited phosphorylation of JNK by UVA. L-ext, trans-resveratrol, and procyanidin alleviated the reduction of phosphorylated Akt levels by UVA. Finally, a cotreatment with B-ext and L-ext showed an additive effect on cell viability. Our findings suggest that both B-ext and L-ext endow protective effects against UVA-induced retinal damage.



KIDNEY HEALTH

Supplementing diet with Manitoba lingonberry juice reduces kidney ischemia-reperfusion injury.

J Sci Food Agric. 2017 Jul; 97(9):3065-3076. doi: 10.1002/jsfa.8200. Epub 2017 Feb 6.

BACKGROUND: Lingonberry (Vaccinium vitis-idaea L.) contains high levels of anthocyanins which are bioavailable in the kidney and may be protective against ischemia-reperfusion (IR)-induced acute kidney injury. This study investigated the effect of lingonberry juice on the IR-induced stress-activated signalling pathway and inflammatory response in the kidney.

RESULTS: Sprague-Dawley rats subjected to kidney IR had significantly impaired kidney function, with increased activation of the JNK signalling pathway and increased inflammatory response, measured using a multiplex panel containing an extensive array of inflammatory biomarkers. In rats fed 1 mL lingonberry juice daily for 3 weeks prior to IR, kidney function was protected and attenuation of inflammatory response and JNK signalling was reflected in the reduction of the measured biomarkers. In vitro results in cultured HK-2 cells confirmed that lingonberry anthocyanins reduced JNK signalling and inflammatory gene expression after IR.

CONCLUSION: This study shows, for the first time, that daily supplementation with lingonberry juice may protect against loss of kidney function induced by IR injury by modulating JNK signalling and inhibiting the subsequent inflammatory response. © 2017 Her Majesty the Queen in Right of Canada. Journal of the Science of Food and Agriculture © 2017 Society of Chemical Industry.

METABOLIC HEALTH

Alterations in the plasma metabolite profile associated with improved hepatic function and glycemia in mice fed lingonberry supplemented high-fat diets.

Mol Nutr Food Res. 2017 Mar;61(3). doi: 10.1002/mnfr.201600442. Epub 2016 Dec 5.

SCOPE: Lingonberries have been shown to reduce the detrimental effects of high-fat diet (HFD) on weight gain, plasma glucose, and inflammation. However, the extent of effects was recently shown to vary between different batches of berries. Here, we examine the metabolic response to two independent batches of lingonberries.

METHODS AND RESULTS: Alterations in the phenotype and circulating metabolome elicited by three matched HFDs, two of which containing lingonberries (L1D and L2D) from different sources, were investigated. Glycemia was improved only in mice fed L1D, whereas liver function was improved and inflammation reduced in mice fed both L1D and L2D, compared to mice fed HFD. The unique improvement in glycemia elicited by L1D was associated with a 21% increase in circulating levels of fatty acids. Increased levels of phosphatidylcholines (62%) and lysophosphatidylcholines (28%) and decreased levels of serine (-13%) and sphingomyelins (-26%) were observed in mice fed L1D and L2D, as compared to HFD.

CONCLUSION: The unique improvement in glycemia in mice fed L1D was associated with a normal metabolic control with an altered set point. Moreover, the batch-independent reduction in liver steatosis and inflammation, was associated with an altered sphingomyelin metabolism.

Lingonberries alter the gut microbiota and prevent low-grade inflammation in high-fat diet fed mice.

Food Nutr Res. 2016 Apr 27; 60:29993. doi: 10.3402/fnr.v60.29993. eCollection 2016.

BACKGROUND: The gut microbiota plays an important role in the development of obesity and obesity-associated impairments such as low-grade inflammation. Lingonberries have been shown to prevent diet-induced obesity and low-grade inflammation. However, it is not known whether the effect of lingonberry supplementation is related to modifications of the gut microbiota. The aim of the present study was to describe whether consumption of different batches of lingonberries alters the composition of the gut microbiota, which could be relevant for the protective effect against high fat (HF)-induced metabolic alterations.

METHODS: Three groups of C57BL/6J mice were fed HF diet with or without a supplement of 20% lingonberries from two different batches (Lingon1 and Lingon2) during 11 weeks. The composition and functionality of the cecal microbiota were assessed by 16S rRNA sequencing and PICRUSt. In addition, parameters related to obesity, insulin sensitivity, hepatic steatosis, inflammation and gut barrier function were examined.

RESULTS: HF-induced obesity was only prevented by the Lingon1 diet, whereas both batches of lingonberries reduced plasma levels of markers of inflammation and endotoxemia (SAA and LBP) as well as modified the composition and functionality of the gut microbiota, compared to the HF control group. The relative abundance of Akkermansia and Faecalibacterium, genera associated with healthy gut mucosa and anti-inflammation, was found to increase in response to lingonberry intake.

CONCLUSIONS: Our results show that supplementation with lingonberries to an HF diet prevents low-grade inflammation and is associated with significant changes of the microbiota composition. Notably, the anti-inflammatory properties of lingonberries seem to be independent of effects on body weight gain.

Enhanced Glucose Uptake in Human Liver Cells and Inhibition of Carbohydrate Hydrolyzing Enzymes by Nordic Berry Extracts.

Molecules. 2017 Oct 24;22(10). pii: E1806. doi: 10.3390/molecules22101806.

A Western lifestyle with low physical activity and a diet rich in sugar, fat and processed food contribute to higher incidences of diabetes and obesity. Enhanced glucose uptake in human liver cells was observed after treatment with phenolic extracts from different Nordic berries. All berry extracts showed higher inhibition against α -amylase and α -glucosidase than the anti-diabetic agent acarbose. Total phenolic content and phenolic profiles in addition to antioxidant activities, were also investigated. The berries were extracted with 80% methanol on an accelerated solvent extraction system (ASE) and then purified by C-18 solid phase extraction (SPE). Among the ASE methanol extracts, black chokeberry, crowberry and elderberry extracts showed high stimulation of glucose uptake in HepG2 cells and also considerable inhibitory effect towards carbohydrate hydrolyzing enzymes. SPE extracts with higher concentrations of phenolics, resulted in increased glucose uptake and enhanced inhibition of α -amylase and α -glucosidase compared to the ASE extracts. Crowberry and cloudberry were the most potent 15-lipoxygenase inhibitors, while bog whortleberry and lingonberry were the most active xanthine oxidase inhibitors. These results increase the value of these berries as a component of a healthy Nordic diet and have a potential benefit against diabetes.

Arctic berry extracts target the gut-liver axis to alleviate metabolic endotoxaemia, insulin resistance and hepatic steatosis in diet-induced obese mice.

Diabetologia. 2017 Dec 21. doi: 10.1007/s00125-017-4520-z. [Epub ahead of print]

AIMS/HYPOTHESIS: There is growing evidence that fruit polyphenols exert beneficial effects on the metabolic syndrome, but the underlying mechanisms remain poorly understood. In the present study, we aimed to analyse the effects of polyphenolic extracts from five types of Arctic berries in a model of diet-induced obesity.

METHODS: Male C57BL/6 J mice were fed a high-fat/high-sucrose (HFHS) diet and orally treated with extracts of bog blueberry (BBE), cloudberry (CLE), crowberry (CRE), alpine bearberry (ABE), lingonberry (LGE) or vehicle (HFHS) for 8 weeks. An additional group of standard-chow-fed, vehicle-treated mice was included as a reference control for diet-induced obesity. OGTTs and insulin tolerance tests were conducted, and both plasma insulin and C-peptide were assessed throughout the OGTT. Quantitative PCR, western blot analysis and ELISAs were used to assess enterohepatic immunometabolic features. Faecal DNA was extracted and 16S rRNA gene-based analysis was used to profile the gut microbiota.

RESULTS: Treatment with CLE, ABE and LGE, but not with BBE or CRE, prevented both fasting hyperinsulinaemia (mean \pm SEM [pmol/l]: chow 67.2 \pm 12.3, HFHS 153.9 \pm 19.3, BBE 114.4 \pm 14.3, CLE 82.5 \pm 13.0, CRE 152.3 \pm 24.4, ABE 90.6 \pm 18.0, LGE 95.4 \pm 10.5) and postprandial hyperinsulinaemia (mean \pm SEM AUC [pmol/l \times min]: chow 14.3 \pm 1.4, HFHS 31.4 \pm 3.1, BBE 27.2 \pm 4.0, CLE 17.7 \pm 2.2, CRE 32.6 \pm 6.3, ABE 22.7 \pm 18.0, LGE 23.9 \pm 2.5). None of the berry extracts affected C-peptide levels or body weight gain. Levels of hepatic serine phosphorylated Akt were 1.6-, 1.5- and 1.2-fold higher with CLE, ABE and LGE treatment, respectively, and hepatic carcinoembryonic antigen-related cell adhesion molecule (CEACAM)-1 tyrosine phosphorylation was 0.6-, 0.7- and 0.9-fold increased in these mice vs vehicle-treated, HFHS-fed mice. These changes were associated with reduced liver triacylglycerol deposition, lower circulating endotoxins, alleviated hepatic and intestinal inflammation, and major gut microbial alterations (e.g. bloom of Akkermansia muciniphila, Turicibacter and Oscillibacter) in CLE-, ABE- and LGE-treated mice.

CONCLUSIONS/INTERPRETATION: Our findings reveal novel mechanisms by which polyphenolic extracts from ABE, LGE and especially CLE target the gut-liver axis to protect diet-induced obese mice against metabolic endotoxaemia, insulin resistance and hepatic steatosis, which importantly improves hepatic insulin clearance. These results support the potential benefits of these Arctic berries and their integration into health programmes to help attenuate obesity-related chronic inflammation and metabolic disorders.

Postprandial glycaemic response to berry nectars containing inverted sucrose.

J Nutr Sci. 2017 Jan 26;6:e4. doi: 10.1017/jns.2016.44. eCollection 2017.

*Sucrose is commonly used for sweetening berry products. During processing and storage of berry products containing added sucrose, sucrose is inverted to glucose and fructose. We have previously shown that postprandial glycaemic response induced by intact sucrose is attenuated when sucrose is consumed with berries rich in polyphenols. It is not known how inversion of sucrose affects glycaemic response. We investigated postprandial glycaemic and insulinaemic responses to blackcurrant (*Ribes nigrum*) and lingonberry (*Vaccinium vitis-idaea*) nectars and a reference drink (water) sweetened with glucose and fructose, representing completely inverted sucrose. The nectars and reference drink (300 ml) contained 17.5 g glucose and 17.5 g fructose. Polyphenol composition of the nectars was analysed. A total of eighteen healthy volunteers participated in a randomised, controlled, cross-over study. Blood samples were collected at fasting and six times postprandially during 120 min. Inverted sucrose in the reference drink induced glycaemic and insulinaemic responses similar to those previously observed for intact sucrose. In comparison with the reference, the blackcurrant nectar attenuated the early glycaemic response and improved glycaemic profile, and the lingonberry nectar reduced the insulinaemic response. The responses induced by inverted sucrose in the berry nectars are similar to those previously observed for berry nectars containing intact sucrose, suggesting that inversion has no major impact on glycaemic response to sucrose-sweetened berry products. The attenuated glycaemic response after the blackcurrant nectar may be explained by inhibition of intestinal absorption of glucose by blackcurrant anthocyanins.*

Influence of polyphenols from lingonberry, cranberry, and red grape on in vitro digestibility of rice.

Int J Food Sci Nutr. 2015; 66(4):378-82. doi: 10.3109/09637486.2015.1042849. Epub 2015 May 26.

Dietary polyphenols are abundant antioxidants in the human diet and are associated with lower rates of diabetes and cardiovascular disease. This study aims to determine the effects of cooking white rice (WR) added with lingonberry (WRLB), cranberry (WRCB), and red grape (WRRG) on in vitro digestibility. There was significantly lower level of glucose release for WRRG compared with WR ($p < 0.05$). WRLB and WRCB showed no effect on glucose release compared with WR ($p > 0.05$). Increasing concentrations of red grape polyphenol decreased digestibility of white rice ($p < 0.05$). A positive correlation between the red grape phenolic content and the resistant starch was observed ($R = 0.9854$). Red grape polyphenol had the greatest impact on reducing in vitro digestibility of white rice. The addition of polyphenols in carbohydrate-rich foods may be a practical means to reduce the high glycemic response of rice eaten around the world.

Evaluation of Beneficial Metabolic Effects of Berries in High-Fat Fed C57BL/6J Mice.

J Nutr Metab. 2014; 2014:403041. doi: 10.1155/2014/403041. Epub 2014 Jan 14.

OBJECTIVE: The aim of the study was to screen eight species of berries for their ability to prevent obesity and metabolic abnormalities associated with type 2 diabetes.

METHODS: C57BL/6J mice were assigned the following diets for 13 weeks: low-fat diet, high-fat diet or high-fat diet supplemented (20%) with lingonberry, blackcurrant, bilberry, raspberry, açai, crowberry, prune or blackberry.

RESULTS: The groups receiving a high-fat diet supplemented with lingonberries, blackcurrants, raspberries or bilberries gained less weight and had lower fasting insulin levels than the control group receiving high-fat diet without berries. Lingonberries, and also blackcurrants and bilberries, significantly decreased body fat content, hepatic lipid accumulation, and plasma levels of the inflammatory marker PAI-1, as well as mediated positive effects on glucose homeostasis. The group receiving açai displayed increased weight gain and developed large, steatotic livers. Quercetin glycosides were detected in the lingonberry and the blackcurrant diets.

CONCLUSION: Lingonberries were shown to fully or partially prevent the detrimental metabolic effects induced by high-fat diet. Blackcurrants and bilberries had similar properties, but to a lower degree. We propose that the beneficial metabolic effects of lingonberries could be useful in preventing obesity and related disorders.

Berries reduce postprandial insulin responses to wheat and rye breads in healthy women.

J Nutr. 2013 Apr; 143(4):430-6. doi: 10.3945/jn.112.169771. Epub 2013 Jan 30.

Starch in white wheat bread (WB) induces high postprandial glucose and insulin responses. For rye bread (RB), the glucose response is similar, whereas the insulin response is lower. In vitro studies suggest that polyphenol-rich berries may reduce digestion and absorption of starch and thereby suppress postprandial glycemia, but the evidence in humans is limited. We investigated the effects of berries consumed with WB or RB on postprandial glucose and insulin responses. Healthy females (n = 13-20) participated in 3 randomized, controlled, crossover, 2-h meal studies. They consumed WB or RB, both equal to 50 g available starch, with 150 g whole-berry purée or the same amount of bread without berries as reference. In study 1, WB was served with strawberries, bilberries, or lingonberries and in study 2 with raspberries, cloudberry, or chokeberries. In study 3, WB or RB was served with a mixture of berries consisting of equal amounts of strawberries, bilberries, cranberries, and blackcurrants. Strawberries, bilberries, lingonberries, and chokeberries consumed with WB and the berry mixture consumed with WB or RB significantly reduced the postprandial insulin response. Only strawberries (36%) and the berry mixture (with WB, 38%; with RB, 19%) significantly improved the glycemic profile of the breads. These results suggest that when WB is consumed with berries, less insulin is needed for maintenance of normal or slightly improved postprandial glucose metabolism. The lower insulin response to RB compared with WB can also be further reduced by berries.

Lingonberry (*Vaccinium vitis-idaea* L.) Exhibits Antidiabetic Activities in a Mouse Model of Diet- Induced Obesity.

Evid Based Complement Alternat Med. 2014; 2014:645812. doi: 10.1155/2014/645812. Epub 2014 Jun 10.

Vaccinium vitis-idaea, commonly known as lingonberry, has been identified among species used by the Cree of Eeyou Istchee of northern Quebec to treat symptoms of diabetes. In a previous study, the ethanol extract of berries of V. vitis-idaea enhanced glucose uptake in C2C12 muscle cells via stimulation of AMP-activated protein kinase (AMPK) pathway. The purpose of this study was to examine the effect of plant extract in a dietary mouse model of mild type 2 diabetes. C57BL/6 mice fed a high-fat diet (HFD, ~35% lipids) for 8 weeks that become obese and insulin-resistant (diet-induced obesity, DIO) were used. Treatment began by adding V. vitis-idaea extract to HFD at 3 different concentrations (125, 250, and 500 mg/Kg) for a subsequent period of 8 weeks (total HFD, 16 weeks). The plant extract significantly decreased glycemia and strongly tended to decrease insulin levels in this model. This was correlated with a significant increase in GLUT4 content and activation of the AMPK and Akt pathways in skeletal muscle. V. vitis-idaea treatment also improved hepatic steatosis by decreasing hepatic triglyceride levels and significantly activated liver AMPK and Akt pathways. The results of the present study confirm that V. vitis-idaea represents a culturally relevant treatment option for Cree diabetics and pave the way to clinical studies.

The glycaemic and C-peptide responses of foods rich in dietary fibre from oat, buckwheat and lingonberry.

Int J Food Sci Nutr. 2013 Aug; 64(5):528-34. doi: 10.3109/09637486.2013.763914. Epub 2013 Jan 30.

Dietary fibre has a beneficial effect on metabolic syndrome, e.g. by influencing the absorption of glucose. The source and structure of fibre affect the glucose response. In this study, the glycaemic and insulinaemic response to oat bread, oat bread with lingonberry fibre, oat-buckwheat bread and buckwheat porridge were tested in a small-scale clinical study (KHSHP E514/09). Nine healthy volunteers consumed test foods after overnight fasting. Serum glucose and C-peptide levels were determined by colorimetric and ELISA methods, respectively, from samples taken at seven time points during 120 min. The mean glycaemic and C-peptide indexes (C-pepls) were 32 and 100 for oat bread, 47 and 119 for oat-lingonberry fibre bread, 58

and 105 for oat-buckwheat bread and 71 and 77 for buckwheat porridge. Similar to rye, buckwheat porridge having a relatively high glycaemic index (GI) tended to have a low C-pept. Buckwheat and lingonberry fibres provide new alternatives for low GI foods.

The fiber and/or polyphenols present in lingonberries null the glycemic effect of the sugars present in the berries when consumed together with added glucose in healthy human volunteers.

Nutr Res. 2012 Jul; 32(7):471-8. doi: 10.1016/j.nutres.2012.06.004. Epub 2012 Jul 18.

*This study was undertaken on the broad hypothesis that lingonberry (*Vaccinium vitis-idaea* L.) has potential to reduce postprandial glycemic and lipemic response. More specifically, 2 postprandial crossover studies with healthy normal-weight male subjects were conducted to study the influence of commercial lingonberry powder on postprandial glycemia and lipemia. The test meals contained fat-free yoghurt with either glucose (50 g) or triacylglycerols (35 g) with or without (control) the lingonberry powder. The lingonberry powder provided the meals with a known amount of fiber and a known amount and composition of sugars, and it was a rich source of polyphenols. Postprandial glucose, insulin, and triacylglycerol responses were analyzed. There were no significant differences in the postprandial glucose concentration between the meals in the glycemia trial despite the fact that the lingonberry meal contained more glucose and fructose. When the meal did not contain added sugar but, instead, added triacylglycerol, no glycemia or lipemia-lowering effect was detected. On the contrary, there were indications of higher glycemic and insulinemic effect after the lingonberry meal. The results of this study indicate that the fibers and/or polyphenols present in lingonberries null the glycemic effect of the sugars present in the berries when consumed together with added glucose. By contrast, the lingonberry powder did not affect the postprandial lipemic response.*

Postprandial glucose, insulin, and free fatty acid responses to sucrose consumed with blackcurrants and lingonberries in healthy women.

Am J Clin Nutr. 2012 Sep; 96(3):527-33. doi: 10.3945/ajcn.112.042184. Epub 2012 Aug 1.

BACKGROUND: Sucrose induces high postprandial glucose and insulin responses. In vitro studies suggest that berries may reduce the digestion and absorption of sucrose and thereby suppress postprandial glycemia, but the evidence in humans is limited.

*OBJECTIVE: We investigated the effects of sucrose ingested with blackcurrants (*Ribes nigrum*) and lingonberries (*Vaccinium vitis-idaea*) on postprandial glucose, insulin, and free fatty acid responses.*

DESIGN: Twenty healthy women participated in a randomized, controlled, crossover meal study. They consumed whole blackcurrants or lingonberries (150 g served as purées) or blackcurrant or lingonberry nectars (300 mL), each with 35 g added sucrose. Sucrose alone (35 g in 300 mL water) was used as a reference. Blood samples were collected at 0, 15, 30, 45, 60, 90, and 120 min.

RESULTS: In comparison with sucrose alone, ingestion of sucrose with whole berries resulted in reduced glucose and insulin concentrations during the first 30 min and a slower decline during the second hour and a significantly improved glycemic profile. Berries prevented the sucrose-induced late postprandial hypoglycemic response and the compensatory free fatty acid rebound. Nearly similar effects were observed when sucrose was consumed with berry nectars. The improved responses were evident despite the higher content of available carbohydrate in the berry and nectar meals, because of the natural sugars present in berries.

CONCLUSIONS: Blackcurrants and lingonberries, as either whole berries or nectars, optimize the postprandial metabolic responses to sucrose. The responses are consistent with delayed digestion of sucrose and consequent slower absorption of glucose.

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. 2010 Jul; 54(7):991-1003. doi: 10.1002/mnfr.200900218.

*Several medicinal plants that stimulate glucose uptake in skeletal muscle cells were identified from among species used by the Cree of Eeyou Istchee of northern Quebec to treat symptoms of diabetes. This study aimed to elucidate the mechanism of action of one of these products, the berries of *Vaccinium vitis idaea*, as well as to isolate and identify its active constituents using a classical bioassay-guided fractionation approach. Western immunoblot analysis in C2C12 muscle cells revealed that the ethanol extract of the berries stimulated the insulin-independent AMP-activated protein kinase (AMPK) pathway. The extract mildly inhibited ADP-stimulated oxygen consumption in isolated mitochondria, an effect consistent with metabolic stress and the ensuing stimulation of AMPK. This mechanism is highly analogous to that of Metformin. Fractionation guided by glucose uptake activity resulted in the isolation of ten compounds. The two most active, quercetin-3-O-glycosides, enhanced glucose uptake by 38-59% (50 μ M; 18 h treatment) in the absence of insulin. Quercetin aglycone, a minor constituent, stimulated uptake by 37%. The quercetin glycosides and the aglycone stimulated the AMPK pathway at concentrations of 25-100 μ M, but only the aglycone inhibited ATP synthase in isolated mitochondria (by 34 and 79% at 25 and 100 μ M, respectively). This discrepancy suggests that the activity of the glycosides may require hydrolysis to the aglycone form. These findings indicate that quercetin and quercetin 3-O-glycosides are responsible for the antidiabetic activity of *V. vitis* crude berry extract mediated by AMPK. These common plant products may thus have potential applications for the prevention and treatment of insulin resistance and other metabolic diseases.*

Inhibitory effect of the Cree traditional medicine wiishichimanaan (*Vaccinium vitis-idaea*) on advanced glycation endproduct formation: identification of active principles.

Phytother Res. 2010 May; 24(5):741-7. doi: 10.1002/ptr.3025.

*Like many aboriginal populations, First Nations communities such as the Cree of Eeyou Istchee are facing continuously increasing rates of diabetes and related complications. Advanced glycation endproducts (AGEs), which readily form and accumulate with sustained hyperglycemia, contribute to the development of diabetic complications and, as such, are considered a potential therapeutic target. In the present study, the inhibition of AGE formation by ethanolic extracts of the Cree medicinal plant *Vaccinium vitis-idaea* L. was assessed by fluorometric detection of fluorescent AGEs and immunodetection of N(epsilon)-(carboxymethyl)lysine adducts of albumin. Extracts from *V. vitis-idaea* berries demonstrated a concentration-dependent inhibition of AGE formation in both measures. High performance liquid chromatography mass spectrometry (HPLC/MS) identified nine main phenolic constituents. Four were selected for further testing, of which catechin, quercetin-3-O-galactoside and cyanidin-3-O-glucoside but not para-coumaric acid displayed antiglycation activities. These results demonstrate that the flavonoid components of the berry extract are potent antiglycation agents and provide pharmacological validation for the traditional use of *V. vitis-idaea* as an antidiabetic remedy.*

URINARY TRACT HEALTH

Prevention of urinary tract infections with vaccinium products.

Phytother Res. 2014 Mar; 28(3):465-70. doi: 10.1002/ptr.5047. Epub 2013 Aug 6.

Cranberries exert a dose-dependent inhibition of the adherence of E. coli fimbriae to uroepithelial cells. This was demonstrated in vitro but also ex vivo in vitro with urine from cranberry consumers. The active principle has not been identified in detail but type-A proanthocyanidins (PAC) play an important role in the mechanism of action. Since the three species, American cranberry (Vaccinium macrocarpon), European cranberry (Vaccinium oxycoccus) and/or lingonberry (Vaccinium vitis-idaea), have different patterns of type-A PACs, results from one species cannot be transferred to the others. It seems likely that most of the studies with monopreparations from V. macrocarpon were underdosed. Whereas photometric PAC quantification may overestimate the true content on co-active compounds, reversed phase high-performance liquid chromatography may underestimate them. Recent studies with PAC doses in the upper range (DMAC method) or declared type-A PAC content in the daily dose reveal a dose-dependent trend of clinical effectiveness, however, with a possible ceiling effect. In order to clarify this, future three-arm studies should investigate Vaccinium preparations with higher type-A PAC doses than previously used. We analysed two popular European vitis-idaea products, a mother juice and a proprietary extract. Both preparations may be appropriate to confirm the Vaccinium urinary tract infection-preventive effect beyond doubt.

Cranberries for preventing urinary tract infections.

Cochrane Database Syst Rev. 2008 Jan 23; (1):CD001321. doi: 10.1002/14651858.CD001321.pub4.

BACKGROUND: Cranberries have been used widely for several decades for the prevention and treatment of urinary tract infections (UTIs). This is the third update of our review first published in 1998 and updated in 2004 and 2008.

OBJECTIVES: To assess the effectiveness of cranberry products in preventing UTIs in susceptible populations.

SEARCH METHODS: We searched MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL in The Cochrane Library) and the Internet. We contacted companies involved with the promotion and distribution of cranberry preparations and checked reference lists of review articles and relevant studies. Date of search: July 2012

SELECTION CRITERIA: All randomised controlled trials (RCTs) or quasi-RCTs of cranberry products for the prevention of UTIs.

DATA COLLECTION AND ANALYSIS: Two authors independently assessed and extracted data. Information was collected on methods, participants, interventions and outcomes (incidence of symptomatic UTIs, positive culture results, side effects, adherence to therapy). Risk ratios (RR) were calculated where appropriate, otherwise a narrative synthesis was undertaken. Quality was assessed using the Cochrane risk of bias assessment tool.

MAIN RESULTS: This updated review includes a total of 24 studies (six cross-over studies, 11 parallel group studies with two arms; five with three arms, and two studies with a factorial design) with a total of 4473 participants. Ten studies were included in the 2008 update, and 14 studies have been added to this update. Thirteen studies (2380 participants) evaluated only cranberry juice/concentrate; nine studies (1032 participants) evaluated only cranberry tablets/capsules; one study compared cranberry juice and tablets; and one study compared cranberry capsules and tablets. The comparison/control arms were placebo, no treatment, water, methenamine hippurate, antibiotics, or lactobacillus. Eleven studies were not included in the meta-analyses because either the design was a cross-over study and data were not reported separately for the first phase, or there was a lack of relevant data. Data included in the meta-analyses showed that, compared with placebo, water or not treatment, cranberry products did not significantly reduce the occurrence of symptomatic UTI overall (RR 0.86, 95% CI 0.71 to 1.04) or for any the subgroups: women with recurrent UTIs (RR 0.74, 95% CI 0.42 to 1.31); older people (RR 0.75, 95% CI 0.39 to 1.44); pregnant women (RR 1.04, 95% CI 0.97 to 1.17); children with recurrent UTI (RR 0.48, 95% CI 0.19 to 1.22); cancer patients (RR 1.15 95% CI 0.75 to 1.77); or people with neuropathic bladder or spinal injury (RR 0.95, 95% CI: 0.75 to 1.20). Overall heterogeneity was

moderate ($I^2 = 55\%$). The effectiveness of cranberry was not significantly different to antibiotics for women (RR 1.31, 95% CI 0.85, 2.02) and children (RR 0.69 95% CI 0.32 to 1.51). There was no significant difference between gastrointestinal adverse effects from cranberry product compared to those of placebo/no treatment (RR 0.83, 95% CI 0.31 to 2.27). Many studies reported low compliance and high withdrawal/dropout problems which they attributed to palatability/acceptability of the products, primarily the cranberry juice. Most studies of other cranberry products (tablets and capsules) did not report how much of the 'active' ingredient the product contained, and therefore the products may not have had enough potency to be effective.

AUTHORS' CONCLUSIONS: Prior to the current update it appeared there was some evidence that cranberry juice may decrease the number of symptomatic UTIs over a 12 month period, particularly for women with recurrent UTIs. The addition of 14 further studies suggests that cranberry juice is less effective than previously indicated. Although some of small studies demonstrated a small benefit for women with recurrent UTIs, there were no statistically significant differences when the results of a much larger study were included. Cranberry products were not significantly different to antibiotics for preventing UTIs in three small studies. Given the large number of dropouts/withdrawals from studies (mainly attributed to the acceptability of consuming cranberry products particularly juice, over long periods), and the evidence that the benefit for preventing UTI is small, cranberry juice cannot currently be recommended for the prevention of UTIs. Other preparations (such as powders) need to be quantified using standardised methods to ensure the potency, and contain enough of the 'active' ingredient, before being evaluated in clinical studies or recommended for use.

Cranberries for preventing urinary tract infections.

Cochrane Database Syst Rev. 2004; (2):CD001321.

BACKGROUND: Cranberries (particularly in the form of cranberry juice) have been used widely for several decades for the prevention and treatment of urinary tract infections (UTIs). The aim of this review is to assess the effectiveness of cranberries in preventing such infections.

OBJECTIVES: To assess the effectiveness of cranberry juice and other cranberry products in preventing UTIs in susceptible populations.

SEARCH STRATEGY: Electronic databases and the Internet were searched using English and non English language terms; companies involved with the promotion and distribution of cranberry preparations were contacted; reference lists of review articles and relevant trials were searched. Cochrane Central Register of Controlled Trials (CENTRAL - the Cochrane Library, issue 1, 2003) was searched in February 2003.

SELECTION CRITERIA: All randomised or quasi randomised controlled trials of cranberry juice/products for the prevention of urinary tract infections in susceptible populations. Trials of men, women or children were included.

DATA COLLECTION AND ANALYSIS: Two reviewers independently assessed and extracted information. Information was collected on methods, participants, interventions and outcomes (urinary tract infections (symptomatic and asymptomatic), side effects and adherence to therapy). RR were calculated where appropriate, otherwise a narrative synthesis was undertaken. Quality was assessed using the Cochrane criteria.

MAIN RESULTS: Seven trials met the inclusion criteria (four cross-over, three parallel group). The effectiveness of cranberry juice (or cranberry-lingonberry juice) versus placebo juice or water was evaluated in six trials, and the effectiveness of cranberries tablets versus placebo was evaluated in two trials (one study evaluated both juice and tablets). In two good quality RCTs, cranberry products significantly reduced the incidence of UTIs at twelve months (RR 0.61 95% CI:0.40 to 0.91) compared with placebo/control in women. One trial gave 7.5 g cranberry concentrate daily (in 50 ml), the other gave 1:30 concentrate given either in 250 ml juice or in tablet form. There was no significant difference in the incidence of UTIs between cranberry juice versus cranberry capsules (RR 1.11 95% CI:0.49 to 2.50). Five trials were not included in the meta-analyses due to methodological flaws or lack of available data. However, only one reported a significant result for the outcome of symptomatic UTIs. Side effects were common in all trials, and dropouts/withdrawals in several of the trials were high.

REVIEWERS' CONCLUSIONS: There is some evidence from two good quality RCTs that cranberry juice may decrease the number of symptomatic UTIs over a 12 month period in women. If it is effective for other groups such as children and elderly men and women is not clear. The large number of dropouts/withdrawals from some of the trials indicates that cranberry juice may not be acceptable over long periods of time. In addition it is not clear what is the optimum dosage or method of administration (e.g. juice or tablets). Further properly designed trials with relevant outcomes are needed.

Regular drinking of cranberry-lingonberry juice concentrate reduced recurrent urinary tract infections in women.

Evid Based Nurs. 2002 Apr; 5(2):43.

No abstract available for this publication.

Randomised trial of cranberry-lingonberry juice and Lactobacillus GG drink for the prevention of urinary tract infections in women.

BMJ. 2001 Jun 30; 322(7302):1571.

OBJECTIVE: To determine whether recurrences of urinary tract infection can be prevented with cranberry-lingonberry juice or with Lactobacillus GG drink.

DESIGN: Open, randomised controlled 12 month follow up trial.

SETTING: Health centres for university students and staff of university hospital.

PARTICIPANTS: 150 women with urinary tract infection caused by Escherichia coli randomly allocated into three groups.

INTERVENTIONS: 50 ml of cranberry-lingonberry juice concentrate daily for six months or 100 ml of lactobacillus drink five days a week for one year, or no intervention.

MAIN OUTCOME MEASURE: First recurrence of symptomatic urinary tract infection, defined as bacterial growth $\geq 10^5$ colony forming units/ml in a clean voided midstream urine specimen.

RESULTS: The cumulative rate of first recurrence of urinary tract infection during the 12 month follow up differed significantly between the groups ($P=0.048$). At six months, eight (16%) women in the cranberry group, 19 (39%) in the lactobacillus group, and 18 (36%) in the control group had had at least one recurrence. This is a 20% reduction in absolute risk in the cranberry group compared with the control group (95% confidence interval 3% to 36%, $P=0.023$, number needed to treat=5, 95% confidence interval 3 to 34).

CONCLUSION: Regular drinking of cranberry juice but not lactobacillus seems to reduce the recurrence of urinary tract infection.