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## List of references supporting the assessment of *Vaccinium myrtillus* L., fructus recens and *Vaccinium myrtillus* L., fructus siccus

Final

**The European Medicines Agency acknowledges that copies of the underlying works used to produce this monograph were provided for research only with exclusion of any commercial purpose.**

Aktaş C, Şenkal V, Sarikaya S, Karti S. Bilberry potentiates warfarin effect? *Turk J Geriatr* 2011, 14(1):79-81

Alfieri R, Sole P. Influence des anthocyanosides administrés par voie oro-perlinguale sur l'adapto-electroretinogramme (AERG) en lumière rouge chez l'Homme. [Influence of anthocyanosides, in oral-perlingual administration, on the adapto-electroretinogram (AERG) in red light in humans.] *C R Seances Soc Biol Fil* 1966, 160(8):1590-1593

Allegra C, Pollari G, Criscuolo A, Bonifacio M. Antocianosidi e sistema microvascolotessutale. *Minerva Angiol* 1982, 7:39-44

Anderson KG, Anderson A, Connor CG. Potential use of bilberry for dry eye relief. *Optometry* 2011, 82(6):380

Anthocyanins. Available at: <http://www.inchem.org/documents/jecfa/jecmono/v17je05.htm>. Accessed 25/07/2012

Anthony JP, Fyfe L, Stewart D, McDougall GJ, Smith HV. The effect of blueberry extracts on *Giardia duodenalis* viability and spontaneous excystation of *Cryptosporidium parvum* oocysts, *in vitro*. *Methods* 2007, 42(4):339-348

Anthony JP, Fyfe L, Stewart D, McDougall GJ. Differential effectiveness of berry polyphenols as anti-giardial agents. *Parasitology* 2011, 138(9):1110-1116

Aura AM. Microbial metabolism of dietary phenolic compounds in the colon. *Phytochem Rev* 2008, 7(3):407-429

Aura AM, Martin-Lopez P, O'Leary KA, Williamson G, Oksman-Caldentey KM, Poutanen K, *et al*. *In vitro* metabolism of anthocyanins by human gut microflora. *Eur J Nutr* 2005, 44(3):133-142



- Barnes J, Anderson LA, Philipson JD. Herbal Medicines: a guide for healthcare professionals. Pharmaceutical Press, London 2002
- Bell DR, Gochenaur K. Direct vasoactive and vasoprotective properties of anthocyanin-rich extracts. *J Appl Physiol* 2006, 100(4):1164-1170
- Belleoud L, Leluan D, Boyer Y. Etude des effets des glucosides d'anthocyane sur la vision nocturne du personnel navigant. *Rev Med Aeronaut Spat* 1967, 6:5-10
- Bertuglia S, Malandrino S, Colantuoni A. Effect of *Vaccinium myrtillus* anthocyanosides on ischaemia reperfusion injury in hamster cheek pouch microcirculation. *Pharmacol Res* 1995, 31(3-4):183-187
- Bettini V, Guerra B, Martino R, Ton P, Tegazzini V. Contractile responses of isolated rat stomach to stimulation of postganglionic cholinergic fibers in the presence of *Vaccinium myrtillus* anthocyanosides. *Fitoterapia* 1986, 57:211-216
- Bettini V, Mayellaro F, Ton P, Zanella P. Effects of *Vaccinium myrtillus* anthocyanosides on vascular smooth muscle. *Fitoterapia* 1984a, 55:265-272
- Bettini V, Mayellaro F, Ton P, Zogno M. Interactions between *Vaccinium myrtillus* anthocyanosides and serotonin on splenic artery smooth muscle. *Fitoterapia* 1984b, 55:201-208
- Bettini V, Mayellaro F, Patron E, Ton P, Terribile Wiel VM. Inhibition by *Vaccinium myrtillus* anthocyanosides of barium-induced contractions in segments of internal thoracic vein. *Fitoterapia* 1984c, 55:323-327
- Bettini V, Mayellaro F, Pilla I, Terribile Wiel VM. Mechanical responses of isolated coronary arteries to barium in the presence of *Vaccinium myrtillus* anthocyanosides. *Fitoterapia* 1985a, 56:3-10
- Bettini V, Aragno R, Bettini MB, Bettini V, Fiori A, Martino R, et al. Study of the mechanism whereby anthocyanosides potentiate the effect of catecholamines on coronary vessels. *Fitoterapia* 1985b, 56:67-72
- Bettini V, Aragno R, Bettini M, Braggion G, Calore L, Concolato MT, et al. Vasodilator and inhibitory effects of *Vaccinium myrtillus* anthocyanosides on the contractile responses of coronary artery segments to acetylcholine: role of the prostacyclins and of the endothelium-derived relaxing factor. *Fitoterapia* 1991, 62:15-28
- Bettini V, Aragno R, Bettini MB, Braggion G, Calore L, Morimando L, et al. Facilitating influence of *Vaccinium myrtillus* anthocyanosides on the acetylcholine-induced relaxation of isolated coronary arteries: role of the endothelium-derived relaxing factor. *Fitoterapia* 1993, 64:45-57
- Bhargava SK. Anti-spermatogenic activity of malvidin chloride in langur monkeys (*Presbytis entellus entellus* Dufresne). *Int J Androl* 1990, 13(3):207-215
- Biedermann L, Mwinyi J, Scharl M, Frei P, Zeitz J, Kullak-Ublick GA, et al. Bilberry ingestion improves disease activity in mild to moderate ulcerative colitis - an open pilot study. *J Crohns Colitis* 2013, 7(4):271-279
- Bilberry Fruit Extract. Summary of data for chemical selection. Available at: [http://ntp-server.niehs.nih.gov/ntp/htdocs/Chem\\_Background/ExSumPdf/Bilberry\\_508.pdf](http://ntp-server.niehs.nih.gov/ntp/htdocs/Chem_Background/ExSumPdf/Bilberry_508.pdf). Accessed 20/10/2013
- Bomser J, Madhavi DL, Singletary K, Smith MA. *In vitro* anticancer activity of fruit extracts from *Vaccinium* species. *Planta Med* 1996, 62(3):212-216

- Boniface R, Robert AM. Einfluss von Anthocyanen auf den Bindegewebsmetabolismus beim Menschen. [Effect of anthocyanins on human connective tissue metabolism in the human.] *Klin Monbl Augenheilkd* 1996, 209(6):368-372
- Bornsek SM, Ziberna L, Polak T, Vanzo A, Ulrich NP, Abram V, *et al.* Bilberry and blueberry anthocyanins act as powerful intracellular antioxidants in mammalian cells. *Food Chem* 2012, 134(4):1878-1884
- Bottecchia D, Bettini V, Martino R, Camerra G. Preliminary report on the inhibitory effect of *Vaccinium myrtillus* anthocyanosides on platelet aggregation and clot retraction. *Fitoterapia* 1987, 58:3-8
- Brenneisen VR, Steinegger E. Zur Analytik der Polyphenole der Früchte von *Vaccinium myrtillus* L. (Ericaceae)" *Pharm. Acta Helv* 1981a, 56:180-185
- Brenneisen VR, Steinegger E. Quantitativer Vergleich der Polyphenole in Früchten von *Vaccinium myrtillus* L. unter verschiedenen Reifegraden. *Pharm Acta Helv* 1981b, 56:341-343
- Brown EM, Gill CI, McDougall GJ, Stewart D. Mechanisms underlying the anti-proliferative effects of berry components in *in vitro* models of colon cancer. *Curr Pharm Biotechnol* 2012, 13(1):200-209
- Burdulis D, Ivanauskas L, Dirse V, Kazlauskas S, Razukas A. Study of diversity of anthocyanin composition in bilberry (*Vaccinium myrtillus* L.) fruits. *Medicina (Kaunas)* 2007, 43(12):971-977
- Cahyana Y, Gordon MH. Interaction of anthocyanins with human serum albumin: influence of pH and chemical structure on binding. *Food Chem* 2013, 141(3):2278-2285
- Camire ME. Phytochemicals in the *Vaccinium* Family: bilberries, blueberries, and cranberries. In: Meskin MS, Bidlack WR, Davies AJ, Omaye ST, editors. *Phytochemicals in Nutrition and Health*. CRC Press, Boca Raton FL 2002
- Campbell FM, Nicol PF, Moar KM, Cruickshank M, Hoggard N. Lower levels of damaged protein biomarkers in the plasma of overweight type 2 diabetic men following supplementation with a standardised bilberry extract. *Proc Nutr Soc* 2012, 71:E130
- Canter PH, Ernst E. Anthocyanosides of *Vaccinium myrtillus* (bilberry) for night vision - a systematic review of placebo-controlled trials. *Surv Ophthalmol* 2004, 49(1):38-50
- Capasso F, Gaginella TS, Grandolini G, Izzo AA. *Phytotherapy*, Springer Verlag, Berlin 2003
- Cerutti R, Ferruzzi BE, Balbi E, Santelli F, Sbrignadello C. Utilità degli antocianosidi del mirtillo nella profilassi degli effetti collaterali minori nella contraccezione con dispositivi intrauterine medicate al rame. [Value of *Vaccinium myrtillus* anthocyanosides in the prophylaxis of minor side effects with copper intrauterine device contraception.] *Ginecol Clin* 1984, 3-4:244-249
- Clifford MN. Anthocyanins - nature, occurrence and dietary burden. *J Sci Food Agric* 2000, 80:1063-1072
- Cluzel C, Bastide P, Wegman R, Tronche P. Activités enzymatiques de la rétine et anthocyanosides extraits de *Vaccinium myrtillus*. *Biochem Pharmacol* 1970, 19:2295-2302
- Cluzel C, Bastide P, Tronche P. Activités phosphoglucomutase et glucose-6-phosphatase de la rétine et anthocyanosides extraits de *Vaccinium myrtillus* (étude *in vitro* et *in vivo*). [Phosphoglucomutase and glucose-6-phosphatase activities of the retina and anthocyanoside extracts from *Vaccinium myrtillum* (study *in vitro* and *vivo*)]. *C R Seances Soc Biol Fil* 1969, 163(1):147-50

Coget PJ, Merlen JF. Étude clinique d'un nouvel agent de protection vasculaire, le Difrarel 20, composé d'anthocyanosides extraits du *Vaccinium myrtillus*. *Phlébologie* 1968, 21(2):221-228

Commission E. Aufbereitungsmonographie Myrtilli fructus. *Bundesanzeiger* (Nr. 76) vom 23/04/1987, amended in *Bundesanzeiger* (Nr. 50) vom 13/05/1990

Contestabile M, Appolloni R, Suppressa F, D'Alba E, Pecorelli B. Trattamento prolungato con antocianosidi del mirtillo ad alto dosaggio: risposte elettrofisiologiche nel paziente miope. [Prolonged treatment with blueberry anthocyanosides administered in high doses: electrophysiological response in myopic patients.] *Boll Ocul* 1991, 70:1157-1169

Cristoni A, Magistretti MJ. Antiulcer and healing activity of *Vaccinium myrtillus* anthocyanosides. *Farmaco Prat* 1987, 42(2):29-43

Dall'Asta M, Calani L, Tedeschi M, Jechiu L, Brighenti F, Del Rio D. Identification of microbial metabolites derived from *in vitro* fecal fermentation of different polyphenolic food sources. *Nutrition* 2012, 28(2):197-203

Delgado-Vargas F, Jiménez AR, Paredes-López O. Natural Pigments: Carotenoids, Anthocyanins, and Betalains — Characteristics, Biosynthesis, Processing, and Stability. *Crit Rev Food Sci Nutr* 2000, 40:173-289

Djuv A, Nilsen OG, Steinsbekk A. The co-use of conventional drugs and herbs among patients in Norwegian general practice: a cross-sectional study. *BMC Complement Altern Med* 2013, 13:295

Eandi M. Relazione dell'esperto sullo documentazione farmacologica e tossicologica relative alla specialità Tegens<sup>®</sup>, 1987; cited in Morazzoni P, Bombardelli E. *Vaccinium myrtillus* L. *Fitoterapia* 1996, 67(1)3-29

Edenharder R., von Petersdorff I. Rauscher R. Antimutagenic effects of flavonoids, chalcones and structurally related compounds on the activity of 2-amino-3-methylimidazo[4,5-f]quinoline (IQ) and other heterocyclic amine mutagens from cooked food. *Mutat. Res.* 1993, 287(2), 261- 274

Ek S, Kartimo H, Mattila S, Tolonen A. Characterization of phenolic compounds from lingonberry (*Vaccinium vitis-idaea*). *J Agric Food Chem* 2006, 54(26):9834-9842

ESCOP Monographs 2<sup>nd</sup> ed. Myrtilli fructus – Bilberry fruit. European Scientific Cooperative on Phytotherapy, editor. Thieme, Stuttgart 2003, 345-350

Esselen M, Fritz J, Hutter M, Teller N, Baechler S, Boettler U, et al. Anthocyanin-rich extracts suppress the DNA-damaging effects of topoisomerase poisons in human colon cancer cells. *Mol Nutr Food Res* 2011, 55(Suppl 1):S143-153

European Pharmacopoeia 8<sup>th</sup> ed. Bilberry fruit, dried - Myrtilli fructus siccus. Council of Europe. 01/2008:1588

European Pharmacopoeia 8<sup>th</sup> ed. Bilberry fruit, fresh - Myrtilli fructus recens. Council of Europe. 01/2008:1602

European Pharmacopoeia 8<sup>th</sup> ed. Bilberry fructus dry extract prepared from fresh bilberry fruit – Myrtilli fructus recentis extractum siccum raffinatatum et normatum. Council of Europe. 07/2008:2394

Felgines C, Talavera S, Texier O, Gil-Izquierdo A, Lamaison JL, Remesy C. Blackberry Anthocyanins Are Mainly Recovered from Urine as Methylated and Glucuronidated Conjugates in Humans. *J Agric Food Chem* 2005, 53(20):7721-7727

- Felgines C, Talavera S, Texier O, Besson C, Fogliano V, Lamaison JL, *et al.* Absorption and metabolism of red orange juice anthocyanins in rats. *Br J Nutr* 2006, 95(5):898-904
- Felgines C, Texier O, Besson C, Vitaglione P, Lamaison JL, Fogliano V, *et al.* Influence of glucose on cyanidin 3-glucoside absorption in rats. *Mol Nutr Food Res* 2008, 52(8):959-964
- Fleischhut J, Kratzer F, Reckemmer G, Kulling SE. Stability and biotransformation of various dietary anthocyanins *in vitro*. *Eur J Nutr* 2006, 45(1):7-18
- Fossen T, Cabrita L, Andersen EM. Colour and stability of pure anthocyanins influenced by pH including the alkaline region. *Food Chem* 1998, 63:435-440
- Friedrich H, Schönert J. Untersuchungen über einige Inhaltsstoffe der Blätter und Früchte von *Vaccinium myrtillus*. *Planta Med* 1973, 24:90-100
- Frohne D. Heilpflanzenlexikon. Ein Leitfaden auf wissenschaftlicher Grundlage. *Vaccinium myrtillus* 8<sup>th</sup> ed. Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart 2006 [Polish Translation]
- Fuchikami H, Satoh H, Tsujimoto M, Ohdo S, Ohtani H, Sawada Y. Effects of herbal extracts on the function of human organic anion-transporting polypeptide OATP-B. *Drug Metab Dispos* 2006, 34(4):577-582
- Galvano F, Vitaglione P, Li Volti G, Di Giacomo C, Gazzolo D, Vanella L, *et al.* Protocatechuic acid: the missing human cyanidins' metabolite. *Mol Nutr Food Res* 2008, 52(3):386-387
- Garcia V, Diban N, Gorri D, Keiski R, Urtiaga A, Ortiz I. Separation and concentration of bilberry impact aroma compound from dilute model solution by pervaporation. *J Chem Technol Biotechnol* 2008, 83:973-982
- Gardner Z, McGuffin M. Botanical Safety Handbook. *Vaccinium myrtillus* L. American Herbal Products Association, CRC Press, Boca Raton (FL) 2013
- Gatta L. *Vaccinium myrtillus* anthocyanosides in the treatment of venous stasis: controlled clinical study on sixty patients. *Fitoterapia* 1988, 59:19-26
- Gloria E, Perla A. Effetto degli antocianosidi sulla soglia visiva assoluta. [Effect of anthocyanosides on the absolute visual threshold.] *Ann Oftalmol Clin Ocul* 1966, 92:595-607
- Grismondi G. Contributo al trattamento delle flebopatie da stasi in gravidanza. [Treatment of pregnancy induced phleboopathies.] *Minerva Gin* 1981, 33:221-230
- Gruenwald J, Brendler T, Jaenicke C, editors. PDR for Herbal Medicines. 4<sup>th</sup> ed. Medical Economics Co., Inc., Montvale 2000
- Hansel R, Keller K, Rimpler H, Schneider G, editors. Hagers Handbuch der Pharmazeutischen Praxis. Drogen P-Z. Vol 6. Springer-Verlag, Berlin 1994
- Heinonen M. Antioxidant activity and antimicrobial effect of berry phenolics--a Finnish perspective. *Mol Nutr Food Res* 2007, 51:684-691
- Hou DX, Yanagita T, Uto T, Masuzaki S, Fujii M. Anthocyanidins inhibit cyclooxygenase-2 expression in LPS-evoked macrophages: structure-activity relationship and molecular mechanisms involved. *Biochem Pharmacol* 2005, 70(3):417-25
- Huttunen S, Toivanen M, Arkko S, Ruponen M, Tikkanen-Kaukanen C. Inhibition activity of wild berry juice fractions against *Streptococcus pneumoniae* binding to human bronchial cells. *Phytother Res* 2011, 25(1):122-127

- Ichiyanagi T, Hatano Y, Matsugo S, Konishi T. Structural dependence of HPLC separation pattern of anthocyanins from Bilberry (*Vaccinium myrtillus* L.). *Chem Pharm Bull* 2004a, 52:628–630
- Ichiyanagi T, Kashiwada Y, Ikeshiro Y, Hatano, Y Shida Y, Horie M, *et al.* Complete assignment of bilberry (*Vaccinium myrtillus* L.) anthocyanins separated by capillary zone electrophoresis. *Chem Pharm Bull* 2004b, 52(2):226–229
- Jayle GE, Aubert L. Action des glucosides d'anthocyanes sur la vision scotopique et mésopique du sujet normal. *Therapie* 1964, 19:171–185
- Johnson J, Maher P, Hanneken A. The flavonoid, eriodictyol, induces long-term protection in ARPE-19 cells through its effects on Nrf2 activation and phase 2 gene expression. *Invest Ophthalmol Vis Sci* 2009, 50(5):2398-2406
- Kahle K, Kraus M, Scheppach W, Ackermann M, Ridder F, Richling E. Studies on apple and blueberry fruit constituents: Do the polyphenols reach the colon after ingestion? *Mol Nutr Food Res* 2006, 50(4-5):418–423
- Kalt W, McDonald JE, Ricker RD, Lu X. Anthocyanin content and profile within and among blueberry species. *Can J Plant Sci* 1999, 79:617–623
- Kalt W, Hanneken A, Milbury P, Tremblay F. Recent research on polyphenolics in vision and eye health. *J Agric Food Chem* 2010, 58(7):4001-4007
- Karlsen A, Paur I, Bøhn SK, Sakhi AK, Borge GI, Serafini M, *et al.* Bilberry juice modulates plasma concentration of NF-kappaB related inflammatory markers in subjects at increased risk of CVD. *Eur J Nutr* 2010, 49(6):345-355
- Katsube N, Iwashita K, Tsushida T, Yamaki K, Kobori M. Induction of apoptosis in cancer cells by Bilberry (*Vaccinium myrtillus*) and the anthocyanins. *J Agric Food Chem* 2003, 51(1):68-75
- Kay CD. Aspects of anthocyanin absorption, metabolism and pharmacokinetics in humans. *Nutr Res Rev* 2006, 19(1):137–146
- Kay CD, Mazza GJ, Holub BJ. Anthocyanins exist in the circulation primarily as metabolites in adult men. *J Nutr* 2005, 135(11):2582-2588
- Kähkönen MP, Hopia AI, Heinonen M. Berry phenolics and their antioxidant activity. *J Agric Food Chem* 2001, 49(8):4076-4082
- Kähkönen MP, Heinämäki J, Ollilainen V, Heinonen M. Berry anthocyanins: isolation, identification and antioxidant activities. *J Sci Food Agric* 2003, 83:1403-1411
- Kemperman RA, Bolca S, Roger LC, Vaughan EE. Novel approaches for analysing gut microbes and dietary polyphenols: challenges and opportunities. *Microbiology* 2010, 156:3224-3231
- Keppler K, Humpf H-U. Metabolism of anthocyanins and their phenolic degradation products by the intestinal microflora. *Bioorg Med Chem* 2005, 13(17):5195-5205
- Kim ES, Yu SY, Kwon SJ, Kwon OW, Kim SY, Kim TW, *et al.* Clinical Evaluation of Patients with non proliferative diabetic retinopathy following medication of anthocyanoside: Multicenter Study. *Korean Ophthalmol Soc* 2008, 49:1629-1633
- Kolehmainen M, Mykkänen O, Kirjavainen PV, Leppänen T, Moilanen E, Adriaens M, *et al.* Bilberries reduce low-grade inflammation in individuals with features of metabolic syndrome. *Mol Nutr Food Res* 2012, 56(10):1501-1510

- Kong JM, Chia LS, Goh NK, Chia TF, Brouillard R. Analysis and biological activities of anthocyanins. *Phytochemistry* 2003, 64(5):923-933
- Kramer JH. Anthocyanosides of *Vaccinium myrtillus* (Bilberry) for Night Vision—A Systematic Review of Placebo-controlled Trials. *Surv Ophthalmol* 2004, 49(6):618
- Laaksonen O, Sandell M, Kallio H. Chemical factors contributing to orosensory profiles of bilberry (*Vaccinium myrtillus*) fractions. *Eur Food Res Techn* 2010, 231:271-285
- Lamy S, Lafleur R, Bédard V, Moghrabi A, Barrette S, Gingras D, et al. Anthocyanidins inhibit migration of glioblastoma cells: structure-activity relationship and involvement of the plasminolytic system. *J Cell Biochem* 2007, 100(1):100-111
- Laplaud PM, Lelubre A, Chapman MJ. Antioxidant action of *Vaccinium myrtillus* extract on human low density lipoproteins *in vitro*: initial observations. *Fundam Clin Pharmacol* 1997, 11(1):35-40
- Lätti AK, Riihinen KR, Kainulainen PS. Analysis of anthocyanin variation in wild populations of bilberry (*Vaccinium myrtillus* L.) in Finland. *J Agric Food Chem* 2008, 56(1):190-196
- Levy Y, Glovinsky Y. The effect of anthocyanosides on night vision. *Eye (Lond)* 1998, 12:967-969
- Lietti A, Forni G. Studies on *Vaccinium myrtillus* anthocyanosides. II. Aspects of anthocyanins pharmacokinetics in the rat. *Arzneimittelforschung* 1976, 26:832-835
- Määttä-Riihinen KR, Kamal-Eldin A, Mattila PH, González-Paramás AM, Törrönen AR. Distribution and contents of phenolic compounds in eighteen Scandinavian berry species. *J Agric Food Chem* 2004, 52(14):4477-4486
- Magnasco A, Zingirian M. Influenza degli antocianosidi sulla soglia retinica differenziale mesopica. [Influence of anthocyanosides on the mesopic differential threshold of the retina.] *Ann Ottalmol Clin Ocul* 1966, 92(3):188-193
- Maher P, Hanneken A. Flavonoids Protect Retinal Ganglion Cells from Oxidative Stress-Induced Death. *Invest Ophthalmol Vis Sci* 2005, 46(12):4796-4803
- Maher P, Hanneken A. Flavonoids protect retinal ganglion cells from ischemia *in vitro*. *Exp Eye Res* 2008, 86(2):366-374
- Malaveille C, Hautefeuille A, Pignatelli B, Talaska G, Vineis P, Bartsch H. Dietary phenolics as anti-mutagens and inhibitors of tobacco-related DNA adduction in the urothelium of smokers. *Carcinogenesis* 1996(10), 17:2193-2200
- Manach C, Williamson G, Morand C, Scalbert A, Rémésy C. Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. *Am J Clin Nutr* 2005, 81(1 Suppl):230S-242S
- Martín-Aragón S, Basabe B, Benedí JM, Villar AM. Antioxidant Action of *Vaccinium myrtillus* L. *Phytother Res* 1998, 12:104-106
- Martín-Aragón S, Basabe B, Benedí JM, Villar AM. *In vitro* and *in vivo* Antioxidant Properties of *Vaccinium myrtillus*. *Pharm Biol* 1999, 37:109-113
- Matsumoto H, Nakamura Y, Tachibanaki S, Kawamura S, Hirayama M. Stimulatory Effect of Cyanidin 3-Glycosides on the Regeneration of Rhodopsin. *J Agric Food Chem* 2003, 51(12):3560-3563
- Matuschek MC, Hendriks WH, McGhie TK, Reynolds GW. The jejunum is the main site of absorption for anthocyanins in mice. *J Nutr Biochem* 2006, 17(1):31-36

- Mayser HM, Wilhelm H. Effects of anthocyanosides on contrast vision (abstract). *Invest Ophthalmol Vis Sci* 2001, 42(Suppl):63
- Mazza G, Kay CD, Cottrell T, Holub BJ. Absorption of anthocyanins from blueberries and serum antioxidant status in human subjects. *J Agric Food Chem* 2002, 50(26):7731-7737
- McGhie TK, Walton MC. The bioavailability and absorption of anthocyanins: towards a better understanding. *Mol Nutr Food Res* 2007, 51:702-713
- Mian E, Curri SB, Lietti A, Bombardelli E. Anthocyanosides and the walls of the microvessels: further aspects of the mechanism of action of their protective effect in syndromes due to abnormal capillary fragility. *Minerva Med* 1977, 68(52):3565-3581
- Mills S, Bone K. Bilberry fruit (*Vaccinium myrtillus*). In: Principles and Practice of Phytotherapy. Churchill Livingstone, Edinburgh 2000
- Morazzoni P, Bombardelli E. *Vaccinium myrtillus* L. *Fitoterapia* 1996, 67:3-29
- Morazzoni P, Magistretti MJ. Activity of Myrtocyan®, an anthocyanoside complex from *Vaccinium myrtillus* (VMA), on platelet aggregation and adhesiveness. *Fitoterapia* 1990, 61:13-21
- Morazzoni P, Livio S, Scilingo A, Malandrino S. *Vaccinium myrtillus* anthocyanosides pharmacokinetics in rats. *Arzneimittelforschung* 1991, 41(2):128-131 Može S, Polak T, Gasperlin L, Koron D, Vanzo A, Poklar Ulrih N, et al. Phenolics in Slovenian bilberries (*Vaccinium myrtillus* L.) and blueberries (*Vaccinium corymbosum* L.). *J Agric Food Chem* 2011, 59(13):6998-7004
- Muth ER, Laurent JM, Jasper P. The effect of bilberry nutritional supplementation on night visual acuity and contrast sensitivity. *Altern Med Rev* 2000, 5(2):164-173
- Nielsen IL, Dragsted LO, Ravn-Haren G, Freese R, Rasmussen SE. Absorption and excretion of black currant anthocyanins in humans and Watanabe heritable hyperlipidemic rabbits. *J Agric Food Chem* 2003, 51(9):2813-2820
- Nohynek LJ, Alakomi HL, Kähkönen MP, Heinonen M, Helander IM, Oksman-Caldentey KM, et al. Berry phenolics: antimicrobial properties and mechanisms of action against severe human pathogens. *Nutr Cancer* 2006, 54(1):18-32
- Nurmi T, Mursu J, Heinonen M, Nurmi A, Hiltunen R, Voutilainen S. Metabolism of berry anthocyanins to phenolic acids in humans. *J Agric Food Chem* 2009, 57(6):2274-2281
- Ogawa K, Oyagi A, Tanaka J, Kobayashi S, Hara H. The protective effect and action mechanism of *Vaccinium myrtillus* L. on gastric ulcer in mice. *Phytother Res* 2011, 25(8):1160-1165
- Paoletti A, Gallo E, Benemei S, Vietri M, Lapi F, Volpi R, et al. Interactions between Natural Health Products and Oral Anticoagulants: Spontaneous Reports in the Italian Surveillance System of Natural Health Products. *Evid Based Complement Alternat Med* 2011, 612150:1-5
- Passamonti S, Vrhovsek U, Vanzo A, Mattivi F. The stomach as a site for anthocyanins absorption from food. *FEBS Lett* 2003, 544(1-3):210-213
- Patras A, Brunton NP, O'Donnell C, Tiwari BK. Effects of thermal processing on anthocyanin stability in foods, mechanisms and kinetics of degradation. *Trends Food Sci Techn* 2010, 21:3-11
- Pennarola R, Roco P, Matarazzo G, De Martino F, Mormile A, Labate L. L'azione terapeutica degli antocianosidi nelle alterazioni microcircolatorie da polinevrite da collanti. [The therapeutic action of the



anthocyanosides in microcirculatory changes due to adhesive-induced polyneuritis.] *Gazz Med Ital* 1980, 139:485-491

Peris J, Pascual B, Garcia L, Muro N, Surra G, Vinuesa T. Drug herb interactions with oral anticoagulants. *Pharm World Sci* 2008, 30:677-678 Abstr. DI-81, No 5. Published in: Reactions Weekly 2008, 1229:5

Perossini M, Chiellini S, Guidi G, Siravo D. Diabetic and hypertensive retinopathy therapy with *Vaccinium myrtillus* anthocyanosides (Tegens) double-blind placebo-controlled clinical trial. *Ann Ottalmol Clin Ocul* 1987, 113:1173-1190

Pourrat H, Bastide P, Dorier P, Tronche P. Préparation et activité thérapeutique de quelques glycosides d'anthocyanes, *Chim Thérap* 1967, 2:33-38

Prior RL, Cao G, Martin A, Sofic E, McEwen J, O'Brien C, et al. Antioxidant capacity as influenced by total phenolic and anthocyanin content, maturity, and variety of *Vaccinium* species. *J Agric Food Chem* 1998, 46:2686-2693  
Prior RL, Cao G. Antioxidant Phytochemicals in Fruits and Vegetables: Diet and Health Implications. *Hort Science* 2000, 35(4):588-592

Pulliero G, Montin S, Bettini V, Martino R, Mogno C, Lo Castro G. *Ex vivo* study of the inhibitory effects of *Vaccinium myrtillus* anthocyanosides on human platelet aggregation. *Fitoterapia* 1989, 60:69-75

Puupponen-Pimiä R, Nohynek L, Alakomi HL, Oksman-Caldentey KM. Bioactive berry compounds – novel tools against human pathogens. *Appl Microbiol Biotechnol* 2005a, 67(1):8-18

Puupponen-Pimiä R, Nohynek L, Hartmann-Schmidlin S, Kähkönen M, Heinonen M, Maatta-Riihinen K, et al. Berry phenolics selectively inhibit the growth of intestinal pathogens. *J Appl Microbiol* 2005b, 98(4):991-1000

Puupponen-Pimiä R, Nohynek L, Alakomi HL, Oksman-Caldentey KM. The action of berry phenolics against human intestinal pathogens. *Biofactors* 2005c, 23(4):243-251

Rauha JP, Remes S, Heinonen M, Hopia A, Kähkönen M, Kujala T, et al. Antimicrobial effects of Finnish plant extracts containing flavonoids and other phenolic compounds. *Int J Food Microbiol* 2000, 56(1):3-12

Reposi P, Malagola R, De Cadilhac C. The role of anthocyanosides on vascular permeability in diabetic retinopathy. *Ann Ottalmol Clin Ocul* 1987, 113:357-361

Riihinen K, Ryynänen A, Toivanen M, Könönen E, Törrönen R, Tikkanen-Kaukanen C. Antiaggregation potential of berry fractions against pairs of *Streptococcus mutans* with *Fusobacterium nucleatum* or *Actinomyces naeslundii*. *Phytother Res* 2011, 25(1):81-87

Rivas-Gonzalo JC. Analysis of anthocyanins. In: Santos-Buelga C, Williamson G, editors. *Methods in Polyphenol Analysis*. The Royal Society of Chemistry, Cambridge 2003

Rotblatt M, Ziment I. Evidence-Based Herbal Medicine. Bilberry (*Vaccinium myrtillus*). In: Hanley and Belfus Inc, Philadelphia 2002

Sakakibara H, Ogawa T, Koyanagi A, Kobayashi S, Goda T, Kumazawa S, et al. Distribution and excretion of bilberry anthocyanins [corrected] in mice. *J Agric Food Chem* 2009, 57(17):7681-7686

Sala D, Rolando M, Rossi PL, Pissarello L. Effetto degli antocianosidi sulle "performances" visive alle basse luminanze. [Effect of anthocyanosides on visual performances at low illumination.] *Minerva Oftalmol* 1979, 21:283-285

- Scharrer A, Ober M. [Anthocyanosides in the treatment of retinopathies.] *Klin Monbl Augenheilkd* 1981, 178(5):386–389 [German]
- Schilcher H. Phytotherapie in der Kinderheilkunde. Wissenschaftliche Verlagsgesellschaft, Stuttgart 1992 [Polish Edition PZWL, Warszawa 1998]
- Schimmer O, Krüger A, Paulini H, Haefele F. An evaluation of 55 commercial plant extracts in the Ames mutagenicity test. *Pharmazie* 1994, 49(6):448-451
- Selma MV, Espín JC, Tomás-Barberán FA. Interaction between phenolics and gut microbiota: role in human health. *J Agric Food Chem* 2009, 57(15):6485-6501
- Shim SH, Kim JM, Choi CY, Kim CY, Park KH. *Ginkgo biloba* extract and bilberry anthocyanins improve visual function in patients with normal tension glaucoma. *J Med Food* 2012, 15(9):818-823
- Slosse P, Hootelé C. Structure and absolute configuration of myrtine, a new quinolizidine alkaloid from *Vaccinium Myrtillus*. *Tetrahedron Lett* 1978, 4:397
- Song J, Li Y, Ge J, Duan Y, Sze SC, Tong Y, et al. Protective effect of bilberry (*Vaccinium myrtillus* L.) extracts on cultured human corneal limbal epithelial cells (HCLEC). *Phytother Res* 2010, 24(4):520-524
- Steinert RE, Ditscheid B, Netzel M, Jahreis G. Absorption of black currant anthocyanins by monolayers of human intestinal epithelial Caco-2 cells mounted in ussing type chambers. *J Agric Food Chem* 2008, 56(13):4995-5001
- Stoner GD, Wang LS, Casto BC. Laboratory and clinical studies of cancer chemoprevention by antioxidants in berries. *Carcinogenesis* 2008, 29(9):1665–1674
- Su Z. Anthocyanins and Flavonoids of *Vaccinium* L. *Pharm Crops* 2012, 3:7-37
- Svobodová A, Rambousková J, Walterová D, Vostalová J. Bilberry extract reduces UVA-induced oxidative stress in HaCaT keratinocytes: a pilot study. *Biofactors* 2008, 33(4):249-266
- Svobodová A, Zdarilová A, Vostálová J. *Lonicera caerulea* and *Vaccinium myrtillus* fruit polyphenols protect HaCaT keratinocytes against UVB-induced phototoxic stress and DNA damage. *J Dermatol Sci* 2009, 56(3):196-204
- Szakiel A, Paczkowski C, Huttunen S. Triterpenoid content of berries and leaves of bilberry *Vaccinium myrtillus* from Finland and Poland. *J Agric Food Chem* 2012, 60(48):11839-11849
- Talavéra S, Felgines C, Texier O, Besson C, Lamaison JL, Rémésy C. Anthocyanins are efficiently absorbed from the stomach in anesthetized rats. *J Nutr* 2003, 133(12):4178-4182
- Talavéra S, Felgines C, Texier O, Besson C, Manach C, Lamaison JL, et al. Anthocyanins are efficiently absorbed from the small intestine in rats. *J Nutr* 2004, 134(9):2275-2279
- Tangen O, Berman HJ, Marfey P. Gel Filtration. A New Technique for Separation of Blood Platelets from Plasma. *Thromb Diath Haemorrh* 1971, 25(2):268-278
- Tirupula KC, Balem F, Yanamala N, Klein-Seetharaman J. pH-dependent interaction of rhodopsin with cyanidin-3-glucoside. 2. Functional aspects. *Photochem Photobiol* 2009, 85(2):463-70
- Toivanen M, Ryyänen A, Huttunen S, Duricová J, Riihinen K, Törrönen R, et al. Binding of *Neisseria meningitidis* pili to berry polyphenolic fractions. *J Agric Food Chem* 2009, 57(8):3120-3127

- Toivanen M, Huttunen S, Lapinjoki S, Tikkanen-Kaukanen C. Inhibition of adhesion of *Neisseria meningitidis* to human epithelial cells by berry juice polyphenolic fractions. *Phytother Res* 2011, 25(6):828-832
- Triebel S, Trieu HL, Richling E. Modulation of inflammatory gene expression by a bilberry (*Vaccinium myrtillus* L.) extract and single anthocyanins considering their limited stability under cell culture conditions. *J Agric Food Chem* 2012, 60(36):8902-8910
- Trumbeckaitė S, Burdulis D, Raudonė L, Liobikas J, Toleikis A, Janulis V. Direct effects of *Vaccinium myrtillus* L. fruit extracts on rat heart mitochondrial functions. *Phytother Res* 2013, 27(4):499-506
- Upton R, Graff A, Länger R, Sudberg S, Sudberg E, Miller T, *et al.* Bilberry Fruit, *Vaccinium myrtillus* L. American Herbal Pharmacopoeia and Therapeutic Compendium: Standards of Analysis, Quality Control, and Therapeutics. Santa Cruz (CA), 2001
- Valentová K, Ulrichová J, Cvak L, Šimánek V. Cytoprotective effect of a bilberry extract against oxidative damage of rat hepatocytes. *Food Chem* 2007, 101:912-917
- Vannini L, Samuelli R, Coffano M, Tibaldi L. Studio del comportamento pupillare in seguito a somministrazione di anticianosidi. [Study of the pupillary reflex after anthocyanoside administration.] *Bollett Ocul* 1986, 65(Suppl 6):569-577
- Viljanen K, Kylli P, Kivikari R, Heinonen M. Inhibition of protein and lipid oxidation in liposomes by berry phenolics. *J Agric Food Chem* 2004, 52(24):7419-7424
- Vitaglione P, Donnarumma G, Napolitano A, Galvano F, Gallo A, Scalfi L, *et al.* Protocatechuic acid is the major human metabolite of cyanidin-glucosides. *J Nutr* 2007, 137(9):2043-2048
- Wang LS, Stoner GD. Anthocyanins and their role in cancer prevention. *Cancer Lett* 2008, 269(2):281-290
- Wichtl M, editor. Herbal drugs and phytopharmaceuticals. 3<sup>rd</sup> ed. Medpharm Scientific Publishers GmbH, Stuttgart 1994
- Wichtl M, editor. Teedrogen: Ein handbuch für Apotheker und Ärzte Herbal drugs and phytopharmaceuticals. Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart 1984
- Williamson G, Clifford MN. Colonic metabolites of berry polyphenols: the missing link to biological activity? *Br J Nutr* 2010, 104(Suppl 3):S48-66
- Williamson G, Manach C. Bioavailability and bioefficacy of polyphenols in humans. II. Review of 93 intervention studies. *Am J Clin Nutr* 2005, 81(Suppl 1):243S-255S
- Yamamoto M, Yamaura K, Ishiwatari M, Shimada M, Kado S, Seki H, *et al.* Degradation Index for Quality Evaluation of Commercial Dietary Supplements of Bilberry Extract. *J Food Sci* 2013a, 78(3):S477-483
- Yamamoto M, Yamaura K, Ishiwatari M, Ueno K. Difficulty for consumers in choosing commercial bilberry supplements by relying only on product label information. *Pharmacognosy Res* 2013b, 5(3):212-215
- Yanamala N, Tirupula KC, Balem F, Klein-Seetharaman J. pH-dependent Interaction of Rhodopsin with Cyanidin-3-glucoside. 1. Structural Aspects. *Photochem Photobiol* 2009, 85(2):454-462
- Yue X, Xu Z. Changes of anthocyanins, anthocyanidins, and antioxidant activity in bilberry extract during dry heating. *J Food Sci* 2008, 73(6):C494-499

Zadok D, Levy Y, Glovinsky Y. The effect of anthocyanosides in a multiple oral dose on night vision. *Eye (Lond)* 1999, 13 (Pt 6):734-736

Zanetti-Ripamonti G. Piante Medicinali Nostre. Mirtillo (*Vaccinium myrtillus* L.). Istituto Editoriale Ticinese, Lugano-Belinzona 1940

Zhang Z, Kou X, Fugal K, McLaughlin J. Comparison of HPLC methods for determination of anthocyanins and anthocyanidins in bilberry extracts. *J Agric Food Chem* 2004, 52(4):688-691

Ziberna L, Lunder M, Tramer F, Drevenšek G, Passamonti S. The endothelial plasma membrane transporter bilitranslocase mediates rat aortic vasodilation induced by anthocyanins. *Nutr Metab Cardiovasc Dis* 2013, 23(1):68-74

#### **References assessed, but not cited in the assessment report**

Govindaraghavan S. Pharmacopoeial HPLC identification methods are not sufficient to detect adulterations in commercial bilberry (*Vaccinium myrtillus*) extracts. Anthocyanin profile provides additional clues. *Fitoterapia* 2014, 99:124-138

Heinonen IM, Meyer AS, Frankel EN. Antioxidant activity of berry phenolics on human low-density lipoprotein and liposome oxidation. *J Agric Food Chem* 1998, 46:4107-4112

Jayle GE, Aubry M, Gavini H, Braccini G, De la Baume C. Etude concernant l'action sur la vision nocturne des anthocyanosides extrait du *Vaccinium myrtillus*. *Ann Ocul* 1965, 198(6):556-62

Milbury PE, Graf B, Curran-Celentano JM, Blumberg JB. Bilberry (*Vaccinium myrtillus*) anthocyanins modulate heme oxygenase-1 and glutathione S transferase-pi expression in ARPE-19 cells. *Invest Ophthalmol Vis Sci* 2007, 48(5):2343-2349