



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

This document was valid from 24 January 2012 until January 2018.
It is now superseded by a [new version](#) adopted by the HMPC on 30
January 2018 and published on the EMA website.

24 January 2012
EMA/HMPC/573461/2009 Rev.1
Committee on Herbal Medicinal Products (HMPC)

List of references supporting the assessment of *Arctostaphylos uva-ursi* (L.) Spreng., folium

Final

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

Adesunloye BA. Acute renal failure due to the herbal remedy CKLS. *Am J Med* 2003, 115(6):506-7.

Ahn KS, Moon KY, Lee J, Kim YS. Downregulation of NF-kappaB activation in human keratinocytes by melanogenic inhibitors. *J Dermatol Sci* 2003, 31(3):193-201.

Albrecht J, Kreyes G. Langzeitbehandlung von Dauerkatheterpatienten: Chemoprophylaxe oder Phytotherapie? *Extr Urol* 1988, 11(5):277-80.

Alvarado F. The relationship between Na⁺ and the active transport of arbutin in the small intestine. *Biochim Biophys Acta* 1965, 109:478-94.

Alvarado F, Monreal J. Na⁺-Dependent active transport of phenylglucosides in the chicken small intestine. *Comp Biochem Physiol* 1967, 20:471-88.

Annuk H, Hirno S, Türi E, Mikelsaar M, Arak E, Wadström T. Effect on cell surface hydrophobicity and susceptibility of *Helicobacter pylori* to medicinal plant extracts. *FEMS Microbiol Lett* 1999, 172:41-5.

Assaf MH, Makboul MA, Beck JP, Anton R. Preliminary study of phenolic glycosides from *Origanum majorana*; quantitative estimation of arbutin, cytotoxic activity of hydroquinone. *Planta Med* 1987, 53(4):343-5.

Barnes J, Anderson L, Phillipson D. Herbal Medicines: A guide for healthcare professionals. 3rd ed. Pharmaceutical Press, London 2002, 577-9.

Bartleby J. Effects of Bearberry: Uva ursi for urinary infections. Potent herbal for pee problems. Associated content. 2006. Available at:

www.associatedcontent.com/article/19953/effects_of_bearberry_uva_ursi_for_urinary_infections.htm

Accessed 3/9/2009.



Beaux D, Fleurentin J, Mortier F. Effects of extracts of *Ortosiphon stamineus* Benth., *Hieracium pilosella* L., *Sambucus nigra* L. and *Arctostaphylos uva-ursi* (L.) Spreng. in rats. *Phytother Res* 1999, 13:222-5.

Beeko R, Schneider EM, Schneeberger W, Hesse A. Häufige Harnwegsinfekte: nur im Akutstadium Antibiotika! *Ärztl Praxis* 1983, 35:2196-97.

Blumenthal M, Busse WR, Goldberg A, Gruenwald J, [et al.], editors. The Complete German Commission E Monographs. American Botanical Council, Austin Texas 1998, 224-5.

Borkowski B. Diuretische Wirkung einiger Flavondrogen. *Planta Med* 1960, 8:95-104 - abstract.

Bradley PR, editor. Uva ursi. In: British Herbal Compendium. Volume 1. British Herbal Medicine Association 1992, 211-3.

British Herbal Pharmacopoeia. 4th ed. British Herbal Medicine Association, Bournemouth 1996, 211-12.

Britton G, Haslam E. Gallotanins. Part XII. Phenolic constituents of *Arctostaphylos uva-ursi*. (L.) Spreng. *J Chem Soc* 1965, 7312-9.

Brusch JL. Urinary Tract Infections in Males. Medscape Reference, Drugs, Diseases & Procedures, 2011 Available at <http://emedicine.medscape.com/article/231574-overview>. Accessed 3/10/2011

Československý lékopis (Pharmacopoeia Bohemoslovenica), 1st ed. Folia uvae ursi. Státní Tiskárna 1947, 192-93.

Český lékopis (Pharmacopoeia Bohemica MMV), Vol. 3. Uvae ursi folium – Medvědicový list. Grada Publishing 2005, 5.0: 1054.

Chauhan B, Yu C, Krantis A, Scott I, Arnason JT, Marles RJ, Foster BC. In vitro activity of uva-ursi against cytochrome P450 isoenzymes and P-glycoprotein. *Can J Physiol Pharmacol* 2007, 85(11):1099-107.

Clifford GM, Farmer RD. Medical therapy for benign prostatic hyperplasia: a review of the literature. *Eur Urol* 2000, 38:2-19

Choi S, Park YI, Lee SK, Kim JE, Chung MH. Aloesin inhibits hyperpigmentation induced by UV radiation. *Clin Exp Dermatol* 2002, 27(6):513-15.

DeCaprio AP. The toxicology of hydroquinone – relevance to occupational and environmental exposure. *Critical Rev Toxicol* 1999, 29(3):283-330.

Deisinger PJ, Hill TS, English JC. Human exposure to naturally occurring hydroquinone. *J Toxicol Environ Health* 1996, 47(1):31-46.

Deutsches Arzneibuch. 6th ed. Folia uvae ursi. Druckerei des Protektorates Böhmen und Mähren, Prague 1926, 207-8.

Deutsches Arzneibuch. 9th ed. Bärentraubenblätter – Uvae ursi folium. Deutscher Apotheker Verlag, Stuttgart 1986, 539-41.

Deysson G, Truhaut R. Influence of glucoside formation on radiomimetic activity; comparison of hydroquinone and its glucoside, arbutoside. *Comp Rendus Seanc Soc Biol Fil* 1957, 151:1719-22.

Dorsch W, Loew D, Meyer-Buchtela E, Schilcher H. Kinderdosierungen von Phytopharmaka: Uvae ursi folium. Kooperation Phytopharmaka, Bonn 1998, 139-140.

Dykes GA, Amarowicz R, Pegg RB. Enhancement of Nisin antibacterial activity by a bearberry (*Arctostaphylos uva-ursi*) leaf extract. *Food Microbiol* 2003, 20:211-16.

English JC, Deisinger PJ. Metabolism and disposition of hydroquinone in Fischer 344 rats after oral or dermal administration. *Food Chem Toxicol* 2005, 43:483-93.

ESCOP Monographs 2nd ed. Uvae ursi folium – Bearberry leaf. European Scientific Cooperative on Phytotherapy, editor. Thieme, Stuttgart 2003, 536-37.

European Pharmacopoeia 6.5. 6th ed. Bearberry Leaf – Uvae ursi folium. Council of Europe 2009, 04/2008: 1054.

Foxman B. Epidemiology of urinary tract infections: incidence, morbidity, and economic costs. *Am J Med* 2002, 113 Suppl 1A:5S-13S.

Frerichs G, Arends G, Zörnig H, editors. Hagers Handbuch der Pharmazeutischen Praxis, Volume 1. 2nd ed. Arctostaphylos. Springer-Verlag, Berlin 1938, 521-24.

Frohne D. Untersuchungen zur Frage der harndesinfizierenden Wirkungen von Bärentraubenblatt-Extrakten. *Planta Med* 1970, 18:1-25.

Frohne D. Arctostaphylos uva-ursi (L.) Spreng. (Bärentraube). Kooperation Phytopharmaka. Unpublished review, Bonn 1977.

Frohne D. Bearberry leaf. In: Wichtl M, editor. Herbal drug and Phytopharmaceuticals. 3rd ed. MedPharm Scientific Publishers GmbH, Stuttgart 2004, 626-29.

Gad-El-Karim MM, Sadagopa Ramanujam VM, Ahmed AE, Legator MS. Benzene myeloclastogenicity: a function of its metabolism. *Am J Ind Med* 1985, 7:475-84.

Glöckl I, Blaschke G, Veit M. Validated methods for direct determination of hydroquinone glucuronide and sulfate in human urine after oral intake of bearberry leaf extract by capillary zone electrophoresis. *J Chromatogr B Biomed Sci Appl* 2001, 761:261-66.

Gottshall RY, Lucas EH, Lickfeldt A, Roberts M. The occurrence of antibacterial substances active against *Mycobacterium tuberculosis* in seed plants. *J Clin Invest* 1949, 920-23.

Grases F, Melero G, Costa-Bauzá A, Prieto R, March JG. Urolithiasis and phytotherapy. *Int Urol Nephrol* 1994, 26:507-11.

Gruenwald J, Brendler T, Jaenicke C, editors. PDR for herbal medicines. 3rd ed. Arctostaphylos uva-ursi. Thomson PDR, Montvale 2004, 847-51.

Guay DR. Contemporary management of uncomplicated urinary tract infections. *Drugs* 2008, 68(9):1169-205.

Hänsel R, Keller K, Rimpler H, Schneider G, editors. Arctostaphylos. In: Hagers Handbuch der Pharmazeutischen Praxis, 5th ed. Volume 4: Drogen A-D. Springer-Verlag, Berlin 1993, 328-38.

Hard GC, Seely JC. Recommendations for the interpretation of renal tubule proliferative lesions occurring in rat kidneys with advanced chronic progressive nephropathy (CPN). *Toxicol Pathol* 2005, 33:641-49.

Hard GC, Whysner J, English JC, Zhang E, Williams GM. Relationship of hydroquinone-associated rat renal tumors with spontaneous chronic progressive neuropathy. *Toxicol Pathol* 1997, 25:132.

Herbal Medicines. Uva-ursi. Pharmaceutical Press 2008 [electronic version]. Available at: www.medicinescomplete.com/mc/herbals/current/1000738619.htm. Accessed 11/3/2009.

Holopainen M, Jahodář L, Seppänen-Laakso T, Laakso I, Kauppinen V. Antimicrobial Activity of Some Finnish Ericaceous Plants. *Acta Pharm Fenn* 1988, 97:197-202.

- IPCS Environmental Health Criteria 157. Hydroquinone. WHO, Geneva 1994. Available at: <http://www.inchem.org/documents/ehc/ehc/ehc157.htm>. Accessed 3/9/2009.
- IPCS Health and Safety Guide. Hydroquinone: Health and safety guide No.101. WHO, Geneva 1996. Available at: <http://www.inchem.org/documents/hsg/hsg/hsg101.htm>. Accessed 3/9/2009.
- Jahodář L, Leifertová I, Lisá M. Investigation of iridoid substances in *Arctostaphylos uva-ursi*. *Pharmazie* 1978, 33:536-7.
- Jahodář L, Leifertová I, Lisá M. Elimination of arbutin from the organism. *Pharmazie* 1983, 38:780-1.
- Jahodář L, Jílek P, Pátková M, Dvořáková V. Antimikrobiální působení arbutinu a extraktu z listů medvědice léčivé in vitro. [Antimicrobial Action of Arbutin and the Extract from the Leaves of *Arctostaphylos uva-ursi* in vitro.] *Českoslov Farm* 1985, 34(5):174-180.
- Joksic G, Stankovic M, Novak A. Antibacterial medicinal plants *Equiseti herba* and *Ononidis radix* modulate micronucleus formation in human lymphocytes in vitro. *J Environ Pathol Toxicol Oncol* 2003, 22:41-8.
- Kamei H, Koide T, Kojima T, Hashimoto Y, Hasegawa M. Inhibition of cell growth in culture by quinones. *Cancer Biother Radiopharm* 1998, 13:185-88.
- Kedzia B, Wrocinski T, Mrugasiewicz K, Gorecki P, Grzewinska H. Antibacterial action of urine containing arbutin metabolic products. *Med Dosw Mikrobiol* 1975, 27:305-14.
- Kubo M, Ito M, Nakata H, Matsuda. Pharmacological studies on leaf of *Arctostaphylos uva-ursi* (L.) Spreng. I. Combined effect of 50% methanolic extract from *Arctostaphylos uva-ursi* (L.) Spreng. (bearberry leaf) and prednisolone on immuno-inflammation. *Yakug Zasshi* 1990, 110(1):59-67 abstract.
- Larsson B, Jonasson A, Pianu S. Prophylactic effect of UVE E in women with recurrent cystitis: A preliminary report. *Curr Ther Res* 1993, 53(4):441-443.
- Lee M Tamsulosin for the treatment of benign prostatic hypertrophy. *Ann Pharmacother* 2000, 34:188-199.
- Li S, Liu G, Zhang Y, Xu J. Experimental study on antitussive effect of arbutin (Chin.). *Yaoxue Tongbao* 1982, 17(12):720-22.
- Lim SS, Joo WK, Jung SH, Cho S, Shin KH. Effects of *Vaccinium koreanum* on rat lens aldose reductase and platelet aggregation (Korean with English summary). *Korean J Pharmacogn* 2003, 34(4):314-17.
- Martindale. The Extra Pharmacopoeia. 34th ed. The Pharmaceutical Press, London 2004, 1659.
- Matsuda H, Nakata H, Tanaka T, Kubo M. [Pharmacological study on *Arctostaphylos uva-ursi* (L.) Spreng. II. Combined effects of arbutin and prednisolone or dexamethazone on immuno-inflammation]. *Yakug Zasshi* 1990, 110(1):68-76. 111(4-5):253-8. [Japanese, abstract]
- Matsuda H, Tanaka T, Kubo M. [Pharmacological study on *Arctostaphylos uva-ursi* (L.) Spreng. III. Combined effect of arbutin and indomethacin on immuno-inflammation]. *Yakug Zasshi* 1991, 111(4-5):253-8. [Japanese with English summary, abstract]
- Matsuda H, Nakamura S, Shiimoto H, Tanaka T, Kubo M. [Pharmacological studies on leaf of *Arctostaphylos uva-ursi* (L.) Spreng. IV. effect of 50% methanolic extract from *Arctostaphylos uva-ursi* (L.) Spreng. (Bearberry Leaf) on melanin synthesis]. *Yakug Yasshi* 1992a, 112(4) 276-82. [Japanese with English summary, abstract]

- Matsuda H, Nakamura S, Tanaka T, Kubo M. [Pharmacological studies on leaf of *Arctostaphylos uva-ursi* (L.) Spreng. V. Effect of water extract from *Arctostaphylos uva-ursi* (L.) Spreng. (Bearberry Leaf) on the Antiallergic and Antiinflammatory Activities of Dexamethasone Ointment]. *Yakug Zasshi* 1992b, 112(9): 673-77. [Japanese with English summary, abstract]
- May G, Willuhn G. Antiviral activity of aqueous plant extracts in tissue cultures. *Arzneimittel-Forschung* 1978, 28(1):1-7.
- McGregor D. Hydroquinone: An evaluation of the human risks from its carcinogenic and mutagenic properties. *Crit Rev Toxicol* 2007, 37:887-914.
- Moreira RR, Carlos IZ, Vilega W. Release of intermediate reactive hydrogen peroxide by macrophage cells activated by natural products. *Biol Pharm Bull* 2001, 24:201-4.
- Morimoto I, Watanabe F, Osawa T, Okitsu T. Mutagenicity screening of crude drugs with *Bacillus subtilis* rec-assay and *Salmonella*/microsome reversion assay. *Mutat Res* 1982, 97:81-102.
- Moskalenko SA. Preliminary screening of far eastern ethnomedical plants for antibacterial activity. *J Ethnopharmacol* 1986, 15:231-59.
- Müller L, Kasper P. The mutagenic potential of arbutine, a naturally occurring hydroquinone glycoside. *Mutat Res* 1996, 360:291-292. Abstract.
- Namba T, Tsunozuka M, Hwan Bae K, Hattori M. Studies on dental caries prevention by traditional Chinese medicines. Part I. Screening of crude drugs for antibacterial action against *Streptococcus mutans*. *Shoyakugaku Zasshi* 1981, 35:295-302.
- NTP (U.S. National Toxicology Program) Toxicology and carcinogenesis studies of hydroquinone (CAS No. 123-31-9) in F344/N rats and B6C3F1 mice (Technical Report Series No. 366; NIH Publ. No.90-2821) 1989. Research Triangle Park, NC. Available at: http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/tr366.pdf.
- NTP (National Toxicology Program). Chemical information review document for arbutin [CAS No. 497-76-7] and extracts from *Arctostaphylos uva-ursi*. Integrated Laboratory Systems, Inc. 2006. Available at: <http://ntp.niehs.nih.gov/files/Arbutin.pdf>. Accessed 1/9/2009.
- Österreichisches Arzneibuch, 9th ed. Volume 2. Folium Uvae-ursi – Bärentraubenblatt. Österreichische Staatsdruckerei, Wien 1960, 748-49.
- Österreichisches Arzneibuch, 9th ed. Volume 2. Species urologicae – Blasentee. Österreichische Staatsdruckerei, Wien 1960, 1393.
- Paper DH, Koehler J, Franz G. Bioavailability of drug preparations containing a leaf extract of *Arctostaphylos uva-ursi* (L.) Spreng. (Uvae ursi folium). *Pharm Pharmacol Lett* 1993, 3:63-6.
- Pharmacopoea Helvetica V. 5th German ed. Folium uvae ursi; Species anticystiticae. Eidgenössisches Drucksachen- und Materialzentrale, Bern 1953, 481-82; 964.
- Pharmacopoeia Helvetica VII. 7th German ed. Species anticystiticae. Eidgenössisches Departement des Innern, Bern 1993.
- Quintus J, Kovar KA, Link P, Hamacher H. Urinary excretion of arbutin metabolites after oral administration of bearberry leaf extracts. *Planta Med* 2005, 71:147-52.
- Ríos JL, Recio MC, Villar A. Antimicrobial activity of selected plants employed in the Spanish Mediterranean area. *J Ethnopharmacol* 1987, 21:139-52.

Robertson JA, Howard LA. Effect of carbohydrates on growth of *Uroplasma urealyticum* and *Mycoplasma hominis*. *J Clin Microbiol* 1987, 25:160-1.

Schindler G, Patzak U, Brinkhaus B, Nieciek A, Wittig J, Krahmer N, Glockl I, Veit M. Urinary excretion and metabolism of arbutin after oral administration of *Arctostaphylos uvae ursi* extract as film-coated tablets and aqueous solution in healthy humans. *J Clin Pharmacol* 2002, 42:920-27.

Semenza G, Bircher J, Mülhaupt E, Koide T, Pfenninger E, Marthaler TH, Gmünder U, Haemmerli UP. Arbutin absorption in human small intestine: a simple procedure for the determination of active sugar uptake in peroral biopsy specimens. *Clinic Chim Acta* 1969, 25:213-19.

Shipochliev T. Uterotonic action of extracts from group of medicinal plants. *Veterinarno-meditsinski Nauki* 1981, 18(4):94-8.

Siegers CP, Siegers JP, Pentz R, Bodinet C, Freudenstein J. Metabolism of arbutin from *Uvae Ursi*-extracts in humans. *Pharm Pharmacol Lett* 1997, 7:90-2.

Siegers C, Bodinet C, Ali SS, Siegers CP. Bacterial deconjugation of arbutin by *Escherichia coli*. *Phytomedicine* 2003, 10(4):58-60.

Slovenský farmaceutický kódex (Codex Pharmaceuticus Slovacus). 1st ed. Urologicae species. Herba, Bratislava 1997, 345.

Standard Zulassungen für Fertigarzneimittel, Volume 1. Bärentraubenblätter. Govi-Verlag Pharmazeutischer Verlag, Frankfurt am Main 1996, Lfd.-Nr. 68.

Strapkova A, Jahodář L, Nosáľová G. Antitussive effect of arbutin. *Pharmazie* 1991, 46:611-12.

Türi M, Türi E, Köljalg S, Mikelsaar M. Influence of aqueous extracts of medicinal plants on surface hydrophobicity of *Escherichia coli* strains of different origin. *APMIS* 1997, 105(12):956-62.

Varga JM, Kalchschmid G, Klein GF, Fritsch P. Mechanism of allergic cross-reactions—I. Multispecific binding of ligands to a mouse monoclonal anti-DNP IgE antibody. *Mol Immunol* 1991, 28(6):641-54.

Wade A, editor. Martindale. The Extra Pharmacopoeia. 27th ed. The Pharmaceutical Press, London 1977, 1725.

Weiss RF. In: Lehrbuch der Phytotherapie. 6th ed. Hippokrates Verlag, Stuttgart 1985, 304-6.

WHO Monographs on Selected Medicinal Plants, Volume 2. Folium *Uvae ursi*. World Health Organization, Geneva 2002, 342-51.

Wilde MI, Goa KL. Finasteride: an update of its use in the management of symptomatic benign prostatic hyperplasia. *Drugs* 1999, 57: 557-581

Woodard G, Hagan CE, Radomski JL. Toxicity of hydroquinone for laboratory animals. *Fed Proc* 1949, 8:348.

Workowski KA, Berman SM. Sexually transmitted diseases treatment guidelines, 2006. MMWR Recomm Rep. 2006, 55:1-94.