



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

30 January 2018  
EMA/HMPC/750270/2016  
Committee on Herbal Medicinal Products (HMPC)

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

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.**

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

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

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

Annik 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. 3<sup>rd</sup> ed. Pharmaceutical Press, London 2002, 577-9

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

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 1983. British Herbal Medicine Association, Bournemouth 1983, 29 – 30
- British Herbal Pharmacopoeia. 4<sup>th</sup> 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 18/01/2017
- Československý lékopis (Pharmacopoeia Bohemoslovenica), 1<sup>st</sup> 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, et al. In vitro activity of uva-ursi against cytochrome P450 isoenzymes and P-glycoprotein. *Can J Physiol Pharmacol* 2007, 85(11):1099-107
- 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
- Clifford GM, Farmer RD. Medical therapy for benign prostatic hyperplasia: a review of the literature. *Eur Urol* 2000, 38:2-19
- Cybulska P, Thakur SD, Foster BC, Scott IM, Leduc RI, Arnason JT, et al. Extracts of Canadian first nations medicinal plants, used as natural products, inhibit *Neisseria gonorrhoeae* isolates with different antibiotic resistance profiles. *Sex Transm Dis* 2011, 38(7):667-71
- 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. 6<sup>th</sup> ed. Folia uvae ursi. Druckerei des Protektorates Böhmen und Mähren, Prague 1926, 207-8
- Deutsches Arzneibuch. 9<sup>th</sup> 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
- DiVincenzo GD, Hamilton ML, Reynolds RC, Ziegler DA. Metabolic Fate Disposition of [<sup>14</sup>C] Hydroquinone Given Orally to Sprague-Dawley Rats. *Toxicology* 1984, 33:9-18
- Dorsch W, Loew D, Meyer-Buchtela E, Schilcher H. Kinderdosierungen von Phytopharmaka: Uvae ursi folium. Kooperation Phytopharmaka, Bonn 1998, 139-40
- 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

- English JC, Hill T, O'Donoghue JL, Reddy MV. Measurement of nuclear DNA modification by <sup>32</sup>P-postlabeling in the kidneys of male and female Fischer 344 rats after multiple gavage doses of hydroquinone. *Fund Appl Toxicol* 1994, 23(3):391-96
- ESCOP Monographs 2<sup>nd</sup> ed. Uvae ursi folium – Bearberry leaf. European Scientific Cooperative on Phytotherapy, editor. Thieme, Stuttgart 2003, 536-37
- European Pharmacopoeia 9.0. 9<sup>th</sup> ed. Bearberry Leaf – Uvae ursi folium. Council of Europe 2017, 07/2013:1054
- 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. 2<sup>nd</sup> 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. 3<sup>rd</sup> ed. MedPharm Scientific Publishers GmbH, Stuttgart 2004, 626-29
- Gad-EI-Karim MM, Sadagopa Ramanujam VM, Ahmed AE, Legator MS. Benzene myeloclastogenicity: a function of its metabolism. *Am J Ind Med* 1985, 7:475-84
- Garcia de Arriba S, Naser B, Nolte KU. Risk assessment of free hydroquinone derived from *Arctostaphylos Uva-ursi* folium herbal preparations. *Int J Toxicol* 2013, 32(6):442-53
- 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. 3<sup>rd</sup> 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
- Hänzel R, Keller K, Rimpler H, Schneider G, editors. *Arctostaphylos*. In: Hagers Handbuch der Pharmazeutischen Praxis, 5<sup>th</sup> 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

- 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
- IARC. IARC Monographs on the Evaluation of Carcinogenic Risk to Humans, Hydroquinone, Vol. 71, part 2, WHO International Agency for Research of Cancer, 1999. Available at: <http://monographs.iarc.fr/ENG/Monographs/vol71/mono71-30.pdf>. Accessed 10/11/2016
- IPCS Environmental Health Criteria 157. Hydroquinone. WHO, Geneva 1994. Available at: <http://www.inchem.org/documents/ehc/ehc/ehc157.htm>. Accessed 18/01/2017
- 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 18/01/2017
- Itabashi M, Aihara H, INOUE T, Yamate J, Sannai S, Tajima M, Tanaka C, Wakisaka Y. Reproduction study of arbutin in rats by subcutaneous administration. *Iyakuin Kenkyu* 1988, 19(2):282-297 [Japanese with English summary]
- 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
- Kern W, List PH, Hörhammer L. Hagers Handbuch der Pharmazeutischen Praxis. 4<sup>th</sup> ed. Volume 3: Chemikalien und Drogen AM-CH. Springer-Verlag, Berlin 1972, 177 – 184
- 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
- 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
- Li H, Jeong YM, Kim SY, Kim MK, Kim DS. Arbutin inhibits TCCSUP human bladder cancer cell proliferation via up-regulation of p21. *Pharmazie* 2011, 66(4):306-9
- 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

Management of Chronic Kidney Disease, SelectHealth and Intermountain Healthcare, Care Process Model, 2015. Available at: <https://intermountainhealthcare.org/ext/Dcmnt?ncid=521395847>. Accessed 16/1/2017

Martindale. The Extra Pharmacopoeia. 34<sup>th</sup> 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 Zasshi* 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](http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/tr366.pdf). Accessed 10/11/2016

NTP Supporting Information for Toxicological Evaluation by the National Toxicology Program. Hydroquinone [CAS 123-31-9], 2009, Available at: [https://ntp.niehs.nih.gov/ntp/noms/support\\_docs/hydroquinone\\_may2009.pdf](https://ntp.niehs.nih.gov/ntp/noms/support_docs/hydroquinone_may2009.pdf). Accessed 10/11/2016.

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: [https://ntp.niehs.nih.gov/ntp/htdocs/chem\\_background/exsumpdf/arbutin\\_508.pdf](https://ntp.niehs.nih.gov/ntp/htdocs/chem_background/exsumpdf/arbutin_508.pdf). Accessed 18/01/2017

OECD/SIDS Organization for Economic Cooperation and Developments/Screening Information Data (2002). Hydroquinone (CAS No. 123-31-9), UNEP Publication 2002, <http://webnet.oecd.org/hpv/UI/handler.axd?id=7ca97271-99ed-4918-90e0-5c89d1ce200c>. Accessed 9/10/2016

Österreichisches Arzneibuch, 9<sup>th</sup> ed. Volume 2. Folium Uvae-ursi – Bärentraubenblatt. Österreichische Staatsdruckerei, Wien 1960, 748-49

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

Pečivová J, Nosál' R, Svitekova K, Mačičková T. Arbutin and decrease of potentially toxic substances generated in human blood neutrophils. *Interdiscip Toxicol* 2014, 7(4):195-200

Pharmacopoea Helvetica V. 5<sup>th</sup> German ed. Folium uvae ursi; Species anticystiticae. Eidgenössisches Drucksachen- und Materialzentrale, Bern 1953, 481-82; 964

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

Saeed F, Mehjabeen S, Sikandar K S, Jahan N, Ahmad M. Diuretic & Anti-urolithic activity of Some Crude Extracts. *Int J Pharmacogn Phytochem Res* 2015, 7(1):128-131

Saeed F, Mehjabeen S, Jahan N, Ahmad M. *In vivo* evaluation & safety profile evaluation of *Arctostaphylos uva-ursi* (L.) Spreng. extract in rabbits. *Pak J Pharm Sci* 2014, 27(6):2197-2205

Schindler G, Patzak U, Brinkhaus B, Nieciek A, Wittig J, Krahmer N, et al. 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, et al. 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

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

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

- Tolmacheva AA, Rogozhin EA, Deryabin DG. Antibacterial and quorum sensing regulatory activities of some traditional Eastern-European medicinal plants. *Acta Pharmaceut* 2014, 64(2):173-86
- Topping DC, Bernard LG, Donoghue JL, English JC. Hydroquinone: Acute and sunchronic toxicity studies with emphasis on neurobehavioral and nephrotoxic effects. *Food Chem Toxicol* 2007, 45: 70-78
- 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
- Vučić DM, Petković MR, Rodić-Grabovac BB. Vasić SM, Čomić LR. In vitro efficacy of extracts of arctostaphylos uva-ursi l. On clinical isolated escherichia coli and enterococcus faecalis strains. *Kragujevac J Sci* 2013, 35:107-13
- Wade A, editor. Martindale. The Extra Pharmacopoeia. 27<sup>th</sup> 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
- Williams GM, Iatropoulos MJ, Jeffrey AM, Duan J-D. Inhibition by dietary hydroquinone of acetylaminofluorene induction of initiation of rat liver carcinogenesis, *Food Chem Toxicol* 2007, 45:1620-25
- 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
- Wu LH, Li P, Zhao QL, Piao JL, Jiao YF, Kadowaki M, et al. Arbutin, an intracellular hydroxyl radical scavenger, protects radiation-induced apoptosis in human lymphoma U937 cells. *Pez Fdn Sym* 2014, 19(11):1654-63. abstract