



23 September 2020
EMA/HMPC/509104/2019
Committee on Herbal Medicinal Products (HMPC)

List of references supporting the assessment of *Achillea millefolium* L., herba

Final – Revision 1

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.

Ahmadi-Dastgerdi A, Ezzatpanah H, Asgary S, Dokhani S, Rahimi E. Phytochemical, Antioxidant and Antimicrobial Activity of the Essential Oil from Flowers and Leaves of *Achillea millefolium* subsp. *Millefolium*. *J Essent Oil Bear Pl* 2017, 20:395-409

Ali SI, Gopalakrishnan B, Venkatesalu V. Pharmacognosy, Phytochemistry and Pharmacological Properties of *Achillea Millefolium* L.: A Review. *Phytother Res* 2017, 31(8):1140-116

Anonymous. Final Report on the Safety Assessment of Yarrow (*Achillea Millefolium*) Extract. *Int J Toxicol* 2001, 20 (Supplement 2):79-84

Augustin B, Javorka S, Giovannini R, Rom P. Magyar gyógynövények [Hungarian Herbal Drugs] I. Általános és leíró rész (I. General and describing part). Földművelésügyi Minisztérium Budapest, 1948 [Hungarian]

Baggio CH, Otofuji Gde M, Freitas CS, Mayer B, Marques MC, Mesia-Vela S. Modulation of antioxidant systems by subchronic exposure to the aqueous extract of leaves from *Achillea millefolium* L. in rats. *Nat Prod Res* 2015, 30:613-615

Barnes J, Anderson LA, Philipson JD. Herbal Medicines Third edition. Pharmaceutical Press London, Chicago 2007

Benedek B, Geisz N, Jäger W, Thalhammer T, Kopp B. Choleretic effects of yarrow (*Achillea millefolium* s.L.) in the isolated perfused rat liver. *Phytomedicine* 2006, 13(9-10):702-706

Benedek B, Gjoncaj N, Saukel J, Kopp B. Distribution of phenolic compounds in Middle-European taxa of the *Achillea millefolium* L. aggregate. *Chem Biodivers* 2007 (a), 4(5):849-857 (abstract only)

Benedek B, Kopp B, Melzig MF. *Achillea millefolium* L. s.l.-Is the anti-inflammatory activity mediated by protease inhibition? *J Ethnopharmacol* 2007(b), 113(2):312-317



Benedek B, Rothwagli-Wiltschnigg K, Rozema E, Gjoncaj N, Reznicek G, Jurenitsch J, et al. Yarrow (*Achillea millefolium* L. s.l.): pharmaceutical quality of commercial samples. *Pharmazie* 2008, 63(1):23-26

Bisset NG, ed. *Herbal Drugs and Phytopharmaceuticals: A Handbook for Practice on a Scientific Basis* (translated from Wichtl, ed. Teedrogen 2nd ed.). Medpharm Scientific Publishers, Stuttgart, 1994, 342-344

Blumenthal M, Busse WR, Goldberg A, Gruenwald J, Hall T, Riggins CW, et al. editors. The complete German Commission E monographs. American Botanical Council, Austin Texas 1998, 233-234

Blumenthal M, Goldberg A, Brinckmann J. editors. *Herbal medicine, Expanded Commission E monographs*. The American Botanical Council, Austin Texas, 2000, 419-423

Boswell-Ruys CL, Ritchie HE, Brown-Woodman PD. Preliminary screening study of reproductive outcomes after exposure to yarrow in the pregnant rat. *Birth Defects Res B Dev* 2003, 68(5):416-420

Bozin B, Mimica-Dukic N, Bogavac M, Suvajdzic L, Simin N, Samoljik I, et al. Chemical Composition, Antioxidant and Antibacterial Properties of *Achillea collina* Becker ex Heimerl s.l. and *A. pannonica* Scheele Essential oils. *Molecules* 2008, 13:2058-2068

Bradley PR editor. *British Herbal Compendium*. Vol.1. British Herbal Medicine Association, Bournemouth 1992, 227-229

British Herbal Pharmacopoeia 1974: Section One, Two and Three. *Millefolium - Achillea millefolium*. British Herbal Medicine Association, London 1974

British Herbal Pharmacopoeia 4th ed. *Yarrow, Millefolii herba*. British Herbal Medicine Association, Exeter 1996, 190-191

Budavari S. (ed.) *The Merck Index: an Encyclopedia of Chemicals, Drugs, and Biologicals*, 12th ed. Whitehouse Station, N.J.: Merck & Co, Inc. 1996 (cited in Blumenthal M, et al. 2000)

Candan F, Unlu M, Tepe B, Daferera D, Polissiou M, Sökmen A, et al. Antioxidant and antimicrobial activity of the essential oil and methanol extracts of *Achillea millefolium* subsp. *millefolium* Afan. (Asteraceae). *J Ethnopharmacol* 2003, 87(2-3):215-220

Cavalcanti AM, Baggio CH, Freitas CS, Rieck L, de Sousa RS, Da Silva-Santos JE, et al. Safety and antiulcer efficacy studies of *Achillea millefolium* L. after chronic treatment in Wistar rats. *J Ethnopharmacol* 2006, 107:277-284

Chou ST, Peng HY, Hsu JC, Lin CC, Shih Y. *Achillea millefolium* L. essential oil inhibits LPS-induced oxidative stress and nitric oxide production in RAW 264.7 Macrophages. *Int J Mol Sci* 2013, 14(7):12978-12993

Compes E, Bartolome B, Fernandez-Nieto M, Sastre J, Cuesta J. Occupational asthma from dried flowers of *Carthamus tinctorius* (safflower) and *Achillea millefolium* (yarrow). *Allergy* 2006, 61:1239-1240

Csupor-Löffler B, Hajdú Zs, Zupkó I, Réthy B, Falkay G, Forgo P, et al. Antiproliferative effect of flavonoids and sesquiterpenoids from *Achillea millefolium* s.l. on cultured human tumour cell lines. *Phytother Res* 2009, 23(5):672-676 (abstract only)

Dalsenter PR, Cavalcanti AM, Andrade AJ, Araújo SL, Marques MC. Reproductive evaluation of aqueous crude extract of *Achillea millefolium* L. (Asteraceae) in Wistar rats. *Reprod Toxicol* 2004, 18(6):819-823

de Sant'anna JR, Franco CC, Milyamoto CT, Cunico MM, Miguel OG, Cocco LC, et al. Genotoxicity of *Achillea millefolium* essential oil in diploid cells of *Aspergillus nidulans*. *Phytother Res* 2009, Feb; 23(2):231-235 (abstract only)

de Souza P, Gasparotto A Jr, Crestani S, Stefanello MÉ, Marques MC, da Silva-Santos JE, et al. Hypotensive mechanism of the extracts and artemetin isolated from *Achillea millefolium* L. (Asteraceae) in rats. *Phytomedicine* 2011, 18:819-825

Deutsches Arzneibuch, 10th ed. Schafgarbenkraut – Millefolii herba. Deutscher Apotheker Verlag, Stuttgart, 1997

Dornberger K, Lich H. Screening nach antimikrobiell sowie potentiell cancerostatisch wirksamen Pflanzeninhaltsstoffen. *Pharmazie* 1982, 37:215-221 (cited in ESCOP Supplement 2009)

Ebadollahi A, Jalali-Sendi J, Razmjou J. Toxicity and phytochemical profile of essential oil from Iranian *Achillea millefolium* L. against *Tetranychus urticae* Koch (Acari: Tetranychidae). *Toxin Reviews* 2016, 35:24-28.

El-Kalamouni C, Venskutonis PR, Zebib B, Merah O, Raynaud C, Talou T. Antioxidant and Antimicrobial Activities of the Essential Oil of *Achillea millefolium* L. Grown in France. *Medicines (Basel)* 2017, 4(2):30.

ESCOP Monographs 2nd edition Supplement 2009. Millefolii herba-Yarrow. European Scientific Cooperative on Phytotherapy, editor. Thieme, Stuttgart 2009, 175-183

European Pharmacopoeia 9th ed. Yarrow-Millefolii herba. Council of Europe, 2016:1564-5

Falconieri D, Piras A, Porcedda S, Marongiu B, Goncalves MJ, Cabral C, et al. Chemical composition and biological activity of the volatile extracts of *Achillea millefolium*. *Nat Prod Commun* 2011, 6:1527-1530

Fintelmann V, Weiss RF. Lehrbuch der Phytotherapie 10th ed. Dysmenorrhö. Hippokrates Verlag, Stuttgart 2002, 355-356

Gadgoli C, Mishra SH. Preliminary screening of *Achillea millefolium*, *Cichorium intybus* and *Capparis spinosa* for antihepatotoxic activity. *Fitoterapia* 1995, 66:319-323 (cited in ESCOP 2009)

García-Risco MR, Mouhid L, Salas-Pérez L, López-Padilla A, Santoyo S, Jaime L, et al. Biological Activities of Asteraceae (*Achillea millefolium* and *Calendula officinalis*) and Lamiaceae (*Melissa officinalis* and *Origanum majorana*) Plant Extracts. *Plant Foods Hum Nutr* 2017, 72:96-102

German Commission E Monograph. *Achillea millefolium* (Schafgarbe). Bundesanzeiger Nr.22 a vom 01.02.1990 [German]

Gharibi S, Tabatabaei BES, Saeidi G. Comparison of Essential Oil Composition, Flavonoid Content and Antioxidant Activity in Eight *Achillea* Species. *J Essent Oil Bear Pl* 2015, 18:1382-1394

Graf U, Moraga AA, Castro R, Díaz Carrillo E. Genotoxicity testing of different types of beverages in the *Drosophila* wing Somatic Mutation and Recombination Test. *Food Chem Toxicol* 1994, 32(5):423-430

Guin JD. Compositae dermatitis in Childhood, *Arch Dermatol* 1987, 123(4):500-502 (abstract only)

Guz L, Adaszek L, Wawrzynkowsky J, Zietek J, Winiarczyk S. In vitro antioxidant and antibabesial activities of the extracts of *Achillea millefolium*. *Polish J Vet Sci* 2019, 22:369-376

Haidara K, Zamir L, Shi Q-W, Batist G. The flavonoid casticin has multiple mechanism of tumor cytotoxicity action. *Cancer Letters* 2006, 242:180-190

Hajhashemi M, Ghanbari Z, Movahedi M, Rafieian M, Keivani A, Haghollahi F. The effect of *Achillea millefolium* and *Hypericum perforatum* ointments on episiotomy wound healing in primiparous women. *J Matern Fetal Neonatal Med* 2018, 31:63-69

Hänsel R, Keller K, Rimpler H, Schneider G, editors. *Hagers Handbuch der Pharmazeutischen Praxis. Drogen: A-D.* 5th ed. Springer-Verlag, Berlin Heidelberg 1992, 48-53

Hasanzadeh A. K. Hasanzadeh S, Shalizar A. J: Ameliorative effects of *Achillea millefolium* inflorescences alcoholic extract on nicotine-induced reproductive toxicity in male rat: Apoptotic and biochemical evidences. *Veterinary Research Forum*. 2017; 8(2):97-104

Hausen BM, Breuer J, Weglewski J, Rücker G. alpha-Peroxyachifolid and other new sensitizing sesquiterpene lactones from yarrow (*Achillea millefolium* L., Compositae). *Contact Dermatitis* 1991, 24(4):274-280

Hausen BM. A 6-year experience with Compositae mix. *Am J Contact Dermat* 1996, 7(2):94-99 (abstract only)

Hoerhammer L. Flavone concentration of medicinal plants with regard to their spasmolytic action. *Congr Sci Farm Commun 21st Pisa* 1961; 578-588. (cited in Barnes J, Anderson LA, Philipson DJ. *Herbal Medicines* Third edition. Pharmaceutical Press London, Chicago 2007)

Howyzeh MS, Aslani S, Pooraskari O. Essential Oil Profile of an Iranian Yarrow (*Achillea millefolium*). *J Essent Oil Bear Pl* 2019, 22:295-300

Innocenti G, Vegeto E, Dall`Acqua S, Ciana P, Giorgetti M, Agradi E, et al. *In vitro* estrogenic activity of *Achillea millefolium* L. *Phytomedicine* 2007, 14:147-152

Jaenson TG, Palsson K, Borg-Karlson AK. Evaluation of extracts and oils of mosquito (Diptera: Culicidae) repellent plants from Sweden and Guinea-Bissau. *J Med Entomol* 2006, 43:113-119

Kahvand M, Malecky M. Dose-response effects of sage (*Salvia officinalis*) and yarrow (*Achillea millefolium*) essential oils on rumen fermentation *in vitro*. *Ann Anim Sci* 2018, 18:125-142

Karnick CR. *Pharmacopoeial Standards of Herbal Plants Vol. 2.* Delhi: Sri Satguru Publications. 1994, 150 (cited in Blumenthal M, et al. 2000)

Kern W. *Hagers Handbuch der Pharmazeutischen Praxis, Substancen and Drogen A-AL Vol 2.* 4th ed. Springer-Verlag, Berlin, Heidelberg, New York 1969 [German]

Khan AU, Gilani AH. Blood pressure lowering, cardiovascular inhibitory and bronchodilatory actions of *Achillea millefolium*. *Phytother Res* 2011, 25:577-83

Kocak A, Bagci E, Bakoglu A. Chemical Composition of Essential Oils of *Achillea teretifolia* Willd. and *A. millefolium* L. subsp. *millefolium* Growing in Turkey. *Asian J Chem* 2010, 22:3653-3658

Ladan Moghadam AR. New compound from the aerial parts of *Achillea millefolium*. *Int J Food Properties* 2017, 20:2041-2051

Lemmens-Gruber R, Marchart E, Rawnduzi P, Engel N, Benedek B, Kopp B. Investigation of the spasmolytic activity of the flavonoid fraction of *Achillea millefolium* s.l. on isolated guinea-pig ilea. *Arzneimittel-Forsch* 2006, 56:582-588

Lin LT, Liu LT, Chiang LC, Lin CC. *In vitro* anti-hepatoma activity of fifteen natural medicines from Canada. *Phytother Research* 2002, 16(5):440-444 (abstract only)

Madaus G. *Lehrbuch der biologischen Heilmittel.* Georg Thieme Verlag, Leipzig 1938 [German]

Mahady GB, Pendland SL, Stoia A, Hamill FA, Fabricant D, Dietz BM, et al. *In vitro* susceptibility of *Helicobacter pylori* to botanical extracts used traditionally for the treatment of gastrointestinal disorders. *Phytother Res* 2005, 19(11):988-91

Mascolo N, Autore G, Capasso F, Menghini A, Fasulo MP. Biological screening of Italian medicinal plants for anti-inflammatory activity. *Phytother Res* 1987, 1:28-31 (cited in ESCOP 2009)

Mazandarani M, Mirdeilami SZ, Pessarakli M. Essential oil composition and antibacterial activity of *Achillea millefolium* L. from different regions in North east of Iran. *J Med Plants Res* 2013, 7:1063-1069

Mutagenicity study of dry extract from yarrow (70% native) in *Salmonella typhimurium* reverse mutation assay (*in vitro*)-according to Regulation (EC) No. 440/2008 method B.13/14 and OECD Guideline 471 -, LPT Report No. 32134, 2015. Unpublished study provided by Finzelberg GmbH & Co. KG.

Newal AC, Anderson LA, Philipson JD. *Herbal Medicines A Guide for Health-care Professionals*. The Pharmaceutical Press, London 1996, 271-273

Nilforoushzadeh MA, Shirani-Bidabadi L, Zolfaghari-Baghbaderani A, Saberi S, Siadat AH, Mahmoudi M. Comparison of *Thymus vulgaris* (Thyme), *Achillea millefolium* (Yarrow) and propolis hydroalcoholic extracts versus systemic glucantime in the treatment of cutaneous leishmaniasis in balb/c mice. *J Vector Borne Dis* 2008, 45(4):301-306

Noureddini M, Rasta V. Analgesic Effect of Aqueous Extract of *Achillea Millefolium* L. on Rat's Formalin Test. *Pharmacologyonline* 2008, 3:659-664

O'Donnell SA. Yarrow: the new cold stopper. *Prevention* 1999, 51:44

Orav A, Arak E, Raal A. Phytochemical analysis of the essential oil of *Achillea millefolium* L. from various European Countries. *Nat Prod Res* 2006, 20(12):1082-1088

Parejo I, Viladomat F, Bastida J, Rosas-Romero A, Flerlage N, Burillo J, et al. Comparison between the Radical Scavenging Activity and Antioxidant Activity of Six Distilled and Nondistilled Mediterranean Herbs and Aromatic Plants. *J Agric Food Chem* 2002, 50(23):6882-6890 (abstract only)

Pharmacopoeia Hungarica Editio VI. Tomus III. Medicina könyvkiadó, Budapest 1967 [Hungarian]

(English version: Hungarian Pharmacopoeia VIth ed. Volume III. Akademia Kiadó, Budapest 1970)

Polish Herbal Compendium 1978

Raal A, Orav A, Arak E. Essential Oil Content and Composition in Commercial *Achillea millefolium* L. Herbs from Different Countries. *J Essent Oil Bear Pl* 2012, 15:22-31

Rácz G, Rácz-Kotilla E, Laza A. Gyógynövényismeret [Pharmacognosy]. Ceres Könyvkiadó 1984, 95-96 [Hungarian]

Rahchamani R, Mokhberdezfoli MR, Hadjiakhoondi A, Raoofi A, Rezazadeh SH, Banihasan E, et al. Para clinical studies of ethanol extract of *Achillea millefolium* L. on electrocardiogram, cardiac enzymes and serum electrolytes in sheep. *Journal of Medicinal Plants* 2008, 7(26); 63-69+96 (abstract only)

Roncada T, Vicentini VE, Mantovani MS. Possible modulating actions of plant extracts on the chromosome breaking activity of MMC and Ara-C in human lymphocytes *in vitro*. *Toxicol In Vitro* 2004, 18(5):617-622

Sahari Moghadam A, Mehrafarin A, Naghdi Badi H. Chemical Composition and Antioxidant Activity *Achillea millefolium* L. Essential Oils. *J Essent Oil Bear Pl* 2017, 20:293-297

Scott IM, Leduc RI, Burt AJ, Marles RJ, Arnason JT, Foster BC. The inhibition of human cytochrome P450 by ethanol extracts of North American botanicals. *Pharmaceut Biol* 2006, 44:315-327

Sellerberg U, Glas LH. Pharmacognostical examination concerning the hemostyptic effect of *Achillea millefolium* aggregate. *Sci Phar* 2000, 68(2):201-206 (cited in Escop Monograph 2009)

Sevindik E, Abaci ZT, Yamaner C, Ayvaz M. Determination of the chemical composition and antimicrobial activity of the essential oils of *Teucrium polium* and *Achillea millefolium* grown under North Anatolian ecological conditions. *Biotechnol Biotech Equip* 2016, 30:375-380

Stevanovic ZD, Pljevljakusic D, Ristic M, Sostaric I, Kresovic M, Simic I, et al. Essential Oil Composition of *Achillea millefolium* agg. Populations Collected from Saline Habitats in Serbia. *J Essent Oil Bear Pl* 2015, 18:1343-1352.

Stojanović G, Radulović N, Hashimoto T, Palić R. *In vitro* antimicrobial activity of extracts of four *Achillea* species: the composition of *Achillea clavennae* L. (Asteraceae) extract. *J Ethnopharmacol* 2005, 101(1-3):185-190

Tadić V, Arsić I, Zvezdanović J, Zugić A, Cvetković D, Pavkov S. The estimation of the traditionally used yarrow (*Achillea millefolium* L. Asteraceae) oil extracts with anti-inflammatory potential in topical application. *J Ethnopharmacol* 2017, 199:138-148

Takzaree N, Mortazavi H, Safaie S, Hosseini SJ. Assessment the effect of *Achillea millefolium* L. extract on spermatogenesis and its reversibility. *Toxicol Lett* 2008, 180 (Sup1): S203-S204

Todd RG editor. Extra Pharmacopoeia Martindale 25th edition. The Pharmaceutical Press London 1967

Trouillas P, Calliste C-A, Allais D-P, Simon A, Marfak A, Delage C, et al. Antioxidant, anti-inflammatory and antiproliferative properties of sixteen water plant extracts used in the Limousin countryside as herbal teas. *Food Chem* 2003, 80(3):399-407

Tunón H, Olavsdotter C, Bohlin L. Evaluation of anti-inflammatory activity of some Swedish medicinal plants. Inhibition of prostaglandin biosynthesis and PAF-induced exocytosis. *J Ethnopharmacol* 1995, 48(2):61-76

Verma RS, Joshi N, Padalia RC, Goswami P, Singh VR, Chauhan A, et al. Chemical composition and allelopathic, antibacterial, antifungal and *in vitro* acetylcholinesterase inhibitory activities of yarrow (*Achillea millefolium* L.) native to India. *Ind Crops Prod* 2017, 104:144-155

WHO monographs on selected medicinal plants. Vol. 4. *Herba millefolii*. World Health Organisation. Geneva 2009, 179-191

Wren RC. Potter's New Cyclopaedia of Botanical Drugs and Preparations. Completely revised by Williamson EM, Evans FJ. C. W. Daniel Company Ltd, Saffron Walden, Essex 1988, 290

Yaeesh S, Jamal Q, Khan AU, Gilani AH. Studies on hepatoprotective, antispasmodic and calcium antagonist activities of the aqueous-methanol extract of *Achillea millefolium*. *Phytother Res* 2006, 20(7):546-551

Zeylstra H. Just Yarrow? *Brit J Phytother* 1997, 4(4):184-189 (cited in Blumenthal M, et al. 2000)