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List of references supporting the assessment of *Tanacetum parthenium* (L.) Schultz Bip., 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.

ABC Clinical Guide 2003 – American Botanical Council. Available at:

<http://cms.herbalgram.org/ABCGuide/GuidePDFs/Feverfew.pdf>

Al-Fatlawi AnA, Al-Fatlawi AtA, Irshad M, Rahisuddin, Ahmad A. Effect of parthenolide on growth and apoptosis regulatory genes of human cancer cell lines. *Pharm Biol* 2015, 53(1):104-109

Anderson D, Jenkinson PC, Dewdney RS, Blowers SD, Johnson ES, Kadam NP. Chromosomal aberrations and sister chromatid exchanges in lymphocytes and urine mutagenicity of migraine patients: a comparison of chronic feverfew users and matched non-users. *Hum Toxicol* 1988, 7:145-152

Anderson KN, Bejcek BE. Parthenolide induces apoptosis in glioblastomas without affecting NF-kappaB. *J Pharmacol Sci* 2008, 106:318-320

Aviram A, Tsoukias NM, Melnick SJ, Resek AP, Ramachandran C. Inhibition of Nitric Oxide Synthesis in Mouse Macrophage Cells by Feverfew Supercritical Extract. *Phytother Res* 2012, 26:541-545

Awang D. Parthenocide: The demise of a facile theory of feverfew activity. *J Herbs Spices Med Plants* 1998, 5(4):95-8

Bamford CC, Tepper SJ. Daily pharmacologic prophylaxis of episodic migraine. *Tech Reg Anesth Pain Manag* 2009, 13:20-27

Barnes J, Anderson LA, Philipson JD. Herbal Medicines. 3rd ed. Pharmaceutical Press, London 2007

Barsby RW, Knight DW, McFadzean I. A chloroform extract of the herb feverfew blocks voltage-dependent potassium currents recorded from single smooth muscle cells. *J Pharm Pharmacol* 1993, 45:641-645

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- Barsby RW, Salan U, Knight DW, Hoult JR. Feverfew extracts and parthenolide irreversibly inhibit vascular responses of the rabbit aorta. *J Pharm Pharmacol* 1992, 44:737-740
- Bejar E. Parthenolide inhibits the contractile responses of rat stomach fundus to fenfluramine and dextroamphetamine but not serotonin. *J Ethnopharmacol* 1996, 50:1-12
- British Herbal Pharmacopoeia. British Herbal Medicine Association, Bournemouth 1990
- Brown AM, Edwards CM, Davey MR, Power JB, Lowe KC. Pharmacological activity of feverfew (*Tanacetum parthenium* (L.) Schultz-Bip.): assessment by inhibition of human polymorphonuclear leukocyte chemiluminescence in-vitro. *J Pharm Pharmacol* 1997, 49:558-561
- Capasso F. The effect of an aqueous extract of *Tanacetum parthenium* L. on arachidonic acid metabolism by rat peritoneal leucocytes. *J Pharm Pharmacol* 1986, 38:71-72
- Chen CF, Leung AY. Gene response of human monocytic cells for the detection of antimigraine activity of feverfew extracts. *Can J Physiol Pharmacol* 2007, 85:1108-1115
- Curry III EA *et al.* Phase I dose escalation trial of feverfew with standardized doses of parthenolide in patients with cancer. *Invest New Drugs* 2004, 22(3):299-305
- Cutlan AR, Bonilla LE, Simon JE, Erwin JE. Intra-specific variability of feverfew: correlations between parthenolide, morphological traits and seed origin. *Planta Med* 2000, 66:612-617
- De Weerd CJ, Bootsma HPR, Hendricks H. Herbal medicines in migraine prevention: Randomized double-blind placebo-controlled crossover trial of feverfew preparation. *Phytomedicine* 1996, 3:225-230
- Dennis V, Awang DVC. Prescribing therapeutic feverfew (*Tanacetum parthenium* (L.) Schultz bip., syn. *Chrysanthemum parthenium* (L.) Bernh.). *Elsevier Science Inc* 1998, 1:11-13
- Di Cesare-Mannelli *et al.* Widespread pain reliever profile of a flower extract of *Tanacetum parthenium*. *Phytomedicine* 2015, 22:752-758
- Diener HC, Pfaffenrath V, Schnitker J, Friede M, Henneicke-von Zepelin HH. Efficacy and safety of 6.25 mg t.i.d. feverfew CO₂-extract (MIG-99) in migraine prevention--a randomized, double-blind, multicentre, placebo-controlled study. *Cephalalgia* 2005, 25:1031-1041
- El-Shazly A, Dorai G, Wink M. Composition and antimicrobial activity of essential oil and hexane-ether extract of *Tanacetum santolinoides* (dc.) Feinbr. and Fertig. *Z Naturforsch C* 2002, 57:620-623
- Ernst E, Pittler MH. The efficacy and safety of feverfew (*Tanacetum parthenium* L.): an update of a systematic review. *Public Health Nutr* 2000, 3:509-514
- ESCOP Monographs 2nd ed. *Tanacetum Parthenii Herba - Feverfew*. European Scientific Cooperative on Phytotherapy, editor. Thieme, Stuttgart 2003
- European Pharmacopoeia 9th ed. *Feverfew - Tanacetum parthenii herba* 01/2008:1516
- Ferro EC, Biagini AP, Fuchs da Silva IE, Silva ML, Torres Silva JR. The combined effect of acupuncture and *Tanacetum parthenium* on quality of life in women with headache: randomised study. *Acupunct Med* 2012, 30:252-257
- Foster BC, Vandenhoek S, Hana J, Krantis A, Akhtar MH, Bryan M, Budzinski JW, Ramputh A, Arnason JT. *In vitro* inhibition of human cytochrome P450-mediated metabolism of marker substrates by natural products. *Phytomedicine* 2003, 10: 334-342

- Fukuda K, Hibiya Y, Mutoh M, *et al.* Inhibition by parthenolide of phorbol ester-induced transcriptional activation of inducible nitric oxide synthase gene in a human monocyte cell line THP-1. *Biochem Pharmacol* 2000, 60:595-600
- Ghantous A, Sinjab A, Herceg Z, Darwiche N. Parthenolide: from plant shoots to cancer roots. *Drug Discov Today* 2013, 18(17-18):894-905
- Groenewegen WA, Heptinstall S. A comparison of the effects of an extract of feverfew and parthenolide, a component of feverfew, on human platelet activity in-vitro. *J Pharm Pharmacol* 1990, 42:553-557
- Groenewegen WA, Knight DW, Heptinstall S. Progress in the medicinal chemistry of the herb feverfew. *Prog Med Chem* 1992, 29:217-238
- Gromek D, Kisiel W, Stojakowska A, Kohlmunzer S. Attempts of chemical standardizing of *Chrysanthemum parthenium* as a prospective antimigraine drug. *Pol J Pharmacol Pharm* 1991, 43:213-217
- Guilbot A, Bangratz M, Ait Abdellah S, Lucas C. A combination of coenzyme Q10, feverfew and magnesium for migraine prophylaxis: a prospective observational study. *BMC Complementary and Alternative Medicine* 2017, 17:433
- Guzman ML, Rossi RM, Karnischky L, *et al.* The sesquiterpene lactone parthenolide induces apoptosis of human acute myelogenous leukemia stem and progenitor cells. *Blood* 2005, 105:4163-4169
- Hay AJ, Hamburger M, Hostettmann K, Hoult JR. Toxic inhibition of smooth muscle contractility by plant-derived sesquiterpenes caused by their chemically reactive alpha-methylenebutyrolactone functions. *Br J Pharmacol* 1994, 112:9-12
- Hayes NA, Foreman JC. The activity of compounds extracted from feverfew on histamine release from rat mast cells. *J Pharm Pharmacol* 1987, 39:466-470
- Hendriks H, Bos R, Woerdenbag J. The essential oil of *Tanacetum parthenium* (L.) Schultz-Bip. *Flav Frag J* 1996, 11:367-371
- Hendricks H, Anderson-Wildeboer Y, Engels G, Bos R, Woerdenbag HJ. The content of parthenolide and its yield per plant during the growth of *Tanacetum parthenium*. *Planta Med* 1997, 63:356-359
- Heptinstall S, White A, Williamson L, Mitchell JR. Extracts of feverfew inhibit granule secretion in blood platelets and polymorphonuclear leucocytes. *Lancet* 1985, 1:1071-1074
- Heptinstall S. Feverfew - an ancient remedy for modern times? (Editorial). *J R Soc Med* 1988, 81:373
- Heptinstall S, Awang DV, Dawson BA, Kindack D, Knight DW, May J. Parthenolide content and bioactivity of feverfew (*Tanacetum parthenium* (L.) Schultz-Bip.). Estimation of commercial and authenticated feverfew products. *J Pharm Pharmacol* 1992, 44:391-395
- Hwang D, Fischer NH, Jang BC, Tak H, Kim JK, Lee W. Inhibition of the expression of inducible cyclooxygenase and proinflammatory cytokines by sesquiterpene lactones in macrophages correlates with the inhibition of MAP kinases. *Biochem Biophys Res Commun* 1996, 226:810-818
- Izumi E, Morello LG, Ueda-Nakamura T, *et al.* Trypanosoma cruzi: antiprotozoal activity of parthenolide obtained from *Tanacetum parthenium* (L.) Schultz Bip. (Asteraceae, Compositae) against epimastigote and amastigote forms. *Exp Parasitol* 2008, 118:324-330
- Jadad AR, Moore RA, Carrol D, Jenkinson C, Reynolds DJM, Gavaghan DJ, *et al.* Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Controlled Clinical Trials* 1996, 17:1-12

- Jain NK, Kulkarni SK. Antinociceptive and anti-inflammatory effects of Tanacetum parthenium L. extract in mice and rats. *J Ethnopharmacol* 1999, 68:251-259
- Jin P, Madieh S, Augsburger LL. The solution and solid state stability and excipient compatibility of parthenolide in feverfew. *AAPS Pharm Sci Tech* 2007, 8(4):105
- Johnson ES, Kadam NP, Hylands DM, Hylands PJ. Efficacy of feverfew as prophylactic treatment of migraine. *Br Med J (Clin Res Ed)* 1985, 291:569-573
- Kalodera Z, Pepeljnjak S, Blazevic N, Petrak T. Chemical composition and antimicrobial activity of Tanacetum parthenium essential oil. *Pharmazie* 1997, 52:885-886
- Kang BY, Chung SW, Kim TS. Inhibition of interleukin-12 production in lipopolysaccharide-activated mouse macrophages by parthenolide, a predominant sesquiterpene lactone in Tanacetum parthenium: involvement of nuclear factor-kappaB. *Immunol Lett* 2001, 77:159-163
- Kang SN, Kim SH, Chung SW, Lee MH, Kim HJ, Kim TS. Enhancement of 1 alpha,25-dihydroxyvitamin D(3)-induced differentiation of human leukaemia HL-60 cells into monocytes by parthenolide via inhibition of NF-kappa B activity. *Br J Pharmacol* 2002, 135:1235-1244
- Killoran CE, Crawford GH, Pedvis-Leftick A. Two cases of compositae dermatitis exacerbated by moisturizer containing feverfew. *Dermatitis* 2007, 18:225-229
- Kim MJ. FDA perspectives on supplement use by patients on antithrombotic therapy. *Thromb Res*. 2005, 117(1-2):197-200 Available at: <https://pubmed.ncbi.nlm.nih.gov/16188297/>
- Kisiel W, Stojakowska A. A Sesquiterpene coumarin ether from transformed roots of Tanacetum Parthenium. *Phytochemistry* 1997, 46:515-516
- Knight DW. Feverfew: chemistry and biological activity. *Nat Prod Rep* 1995, 12:271-276
- Kwok BH, Koh B, Ndubuisi MI, Elofsson M, Crews CM. The anti-inflammatory natural product parthenolide from the medicinal herb Feverfew directly binds to and inhibits IkappaB kinase. *Chem Biol* 2001, 8:759-766
- Loder E, Burch R, Rizzoli P. The 2012 AHS/AAN Guidelines for Prevention of Episodic Migraine: A Summary and Comparison With Other Recent Clinical Practice Guidelines. *Headache* 2012, Jun; 52(6):930-45
- Loesche W, Mazurov AV, Voyno-Yasenetskaya TA, Groenewegen WA, Heptinstall S, Repin VS. Feverfew-an antithrombotic drug? *Folia Haematol Int Mag Klin Morphol Blutforsch* 1988, 115:181-184
- Long C, Sauleau P, David B, et al. Bioactive flavonoids of Tanacetum parthenium revisited. *Phytochemistry* 2003, 64:567-569
- Magni P, Ruscica M, Dozio E, Rizzi E, Beretta G, Maffei Facino R. Parthenolide Inhibits the LPS-induced Secretion of IL-6 and TNF-a and NF-kB Nuclear Translocation in BV-2 Microglia. *Phytother. Res*. 2012, 26:1405-1409
- Mahmoodzadeh Y, Mazani M, Rezagholizadeh L. Hepatoprotective effect of methanolic Tanacetum parthenium extract on CCl4-induced liver damage in rats. *Toxicol Rep* 2017, 4:455-462
- Maizels M, Blumenfeld A, Burchette R. A combination of riboflavin, magnesium, and feverfew for migraine prophylaxis: a randomized trial. *Headache* 2004, 44:885-890
- Martin K, Sur R, Liebel F, et al. Parthenolide-depleted Feverfew (Tanacetum parthenium) protects skin from UV irradiation and external aggression. *Arch Dermatol Res* 2008, 300:69-80

- Materazzi S *et al.* Parthenolide inhibits nociception and neurogenic vasodilatation in the trigeminovascular system by targeting TRPA1 channel. *Pain* 2013, 154(12):2750-8
- Milbrodt M, Schröder F, König W. 3,4- β -Epoxy-8-Deoxycumambrin B, a sesquiterpene lactone from *Tanacetum Parthenium*. *Phytochemistry* 1997, 44:471-474
- Mitra S, Datta A, Singh SK, Singh A. 5-Hydroxytryptamine-inhibiting property of Feverfew: role of parthenolide content. *Acta Pharmacol Sin* 2000, 21:1106-1114
- Murch SJ, Simmons CB, Saxena PK. Melatonin in feverfew and other medicinal plants. *Lancet* 1997, 350:1598-1599
- Murphy JJ, Heptinstall S, Mitchell JR. Randomised double-blind placebo-controlled trial of feverfew in migraine prevention. *Lancet* 1988, 2:189-192
- Nelson MH, Cobb SE, Shelton J. Variations in parthenolide content and daily dose of feverfew products. *Am J Health Syst Pharm* 2002, 59:1527-1531
- O'Neill LA, Barrett ML, Lewis GP. Extracts of feverfew inhibit mitogen-induced human peripheral blood mononuclear cell proliferation and cytokine mediated responses: a cytotoxic effect. *Br J Clin Pharmacol* 1987, 23(1):81-3
- Pajak B, Orzechowski A, Gajkowska B. Molecular basis of parthenolide-dependent proapoptotic activity in cancer cells. *Folia Histochem Cytobiol* 2008, 46:129-135
- Palevitch D, Earon G, Carasso R. Feverfew (*Tanacetum parthenium*) as a prophylactic treatment for migraine: A placebo-controlled double-blind study. *Phytother Res* 1997, 11:508-511
- Parada-Turska J, Mitura A, Brzana W, Jablonski M, Majdan M, Rzeski W. Parthenolide inhibits proliferation of fibroblast-like synoviocytes in vitro. *Inflammation* 2008, 31:281-285
- Parada-Turska J, Paduch R, Majdan M, Kandefer-Szerszen M, Rzeski W. Antiproliferative activity of parthenolide against three human cancer cell lines and human umbilical vein endothelial cells. *Pharmacol Rep* 2007, 59:233-237
- Pareek A, Suthar M, Rathore GS, Bansal V. Feverfew (*Tanacetum parthenium* L.): A systematic review. *Pharmacognosy Reviews* 2011, 5(9):103-110
- Patrick M, Heptinstall S, Doherty M. Feverfew in rheumatoid arthritis: a double blind, placebo controlled study. *Ann Rheum Dis* 1989, 48:547-549
- PDR for Herbal Medicines. 3rd edition. Thomson PDR 2004, G-11:306
- Pfaffenrath V, Diener HC, Fischer M, Friede M, Henneicke-von Zepelin HH. The efficacy and safety of *Tanacetum parthenium* (feverfew) in migraine prophylaxis-a double-blind, multicentre, randomized placebo-controlled dose-response study. *Cephalalgia* 2002, 22:523-532
- Piela-Smith TH, Liu X. Feverfew extracts and the sesquiterpene lactone parthenolide inhibit intercellular adhesion molecule-1 expression in human synovial fibroblasts. *Cell Immunol* 2001, 209:89-96
- Pittler MH, Ernst E. Feverfew for preventing migraine. *Cochrane Database Syst Rev* 2004, Issue 1. Art. No: CD002286
- Pugh WJ, Sambo K. Prostaglandin synthetase inhibitors in feverfew. *J Pharm Pharmacol* 1988, 40:743-745
- Pugh WJ. What is the drug (if any) in the plantfeverfew (*Pyrethrum parthenium*)? What are its therapeutic benefits? *BMJ* 1985, 290:925

- Rateb MEM, El-Gendy A-NAM, El-Hawary SS, El-Shamy AM. Phytochemical and biological investigation of *Tanacetum parthenium* (L.) cultivated in Egypt. *J Med Plant Res* 2007, 1:18-26
- Reuter U, Chiarugi A, Bolay H, Moskowitz MA. Nuclear factor-kappaB as a molecular target for migraine therapy. *Ann Neurol* 2002, 51:507-516
- Ross JJ, Arnason JT, Birnboim HC. Low concentrations of the feverfew component parthenolide inhibit in vitro growth of tumor lines in a cytostatic fashion. *Planta Med* 1999, 65:126-129
- Se Lim K *et al.* Parthenolide exerts inhibitory effects on angiogenesis through the downregulation of VEGF/VEGFRs in colorectal cancer. *International Journal of Molecular Medicine* 2014, 33:1261-1267
- Shrivastava R, Pechadre JC, John GW. *Tanacetum parthenium* and *Salix alba* (Mig-RL) combination in migraine prophylaxis: a prospective, open-label study. *Clin Drug Investig* 2006, 26:287-296
- Somes J, Donatelli NS. Strange medication reactions. *Journal of Emergency Nursing* 2011, 37(4):388-390
- Sumner H, Salan U, Knight DW, Hoult JR. Inhibition of 5-lipoxygenase and cyclo-oxygenase in leukocytes by feverfew. Involvement of sesquiterpene lactones and other components. *Biochem Pharmacol* 1992, 43:2313-2320
- Tassorelli C, Greco R, Morazzoni P, Riva A, Sandrini G, Nappi G. Parthenolide is the component of *tanacetum parthenium* that inhibits nitroglycerin-induced Fos activation: studies in an animal model of migraine. *Cephalalgia* 2005, 25:612-621
- Taylor FR. Lifestyle changes, dietary restrictions, and nutraceuticals in migraine prevention. *Tech Reg Anesth Pain Manag* 2009, 13:28-37
- Thakkar JK, Sperelakis N, Pang D, Franson RC. Characterization of phospholipase A2 activity in rat aorta smooth muscle cells. *Biochim Biophys Acta* 1983, 750:134-140
- Tiuman TS, Ueda-Nakamura T, Garcia Cortez DA, *et al.* Antileishmanial activity of parthenolide, a sesquiterpene lactone isolated from *Tanacetum parthenium*. *Antimicrob Agents Chemother* 2005, 49:176-182
- Unger M, Frank A. Simultaneous determination of the inhibitory potency of herbal extracts on the activity of six major cytochrome P450 enzymes using liquid chromatography/mass spectrometry and automated online extraction. *Rapid Commun Mass Spectrom*. 2004, 18(19):2273-81
- Vogler BK, Pittler MH, Ernst E. Feverfew as a preventive treatment for migraine: a systematic review. *Cephalalgia* 1998, 18:704-708
- WHO monographs on selected medicinal plants. Vol. 2. *Herba tanacetii parthenii*. World Health Organization. Geneva 2004
- Wider B, Pittler MH, Ernst E. Feverfew for preventing migraine (Review). *Cochrane Database of Systematic Reviews* 2015, Issue 4. Art. No.: CD002286
- Williams CA, Hoult JR, Harborne JB, Greenham J, Eagles J. A biologically active lipophilic flavonol from *Tanacetum parthenium*. *Phytochemistry* 1995, 38:267-270
- Won YK, Ong CN, Shen HM. Parthenolide sensitizes ultraviolet (UV)-B-induced apoptosis via protein kinase C-dependent pathways. *Carcinogenesis* 2005, 26:2149-2156
- Won YK, Ong CN, Shi X, Shen HM. Chemopreventive activity of parthenolide against UVB-induced skin cancer and its mechanisms. *Carcinogenesis* 2004, 25:1449-1458

- Wu C, Chen F, Wang X, *et al.* Antioxidant constituents in feverfew (*Tanacetum parthenium*) extract and their chromatographic quantification. *Food Chem* 2006a, 96:220-227
- Wu C, Chen F, Rushing JW, *et al.* Antiproliferative activities of parthenolide and golden feverfew extract against three human cancer cell lines. *J Med Food* 2006b, 9:55-61
- Wu C, Chen F, Wang X, *et al.* Identification of antioxidant phenolic compounds in feverfew (*Tanacetum parthenium*) by HPLC-ESI-MS/MS and NMR. *Phytochem Anal* 2007, 18:401-410
- Wyrebska A *et al.* Apoptosis-mediated cytotoxic effects of parthenolide and the new synthetic analog MZ-6 on two breast cancer cell lines. *Mol Biol Rep* 2013, 40:1655-1663
- Yao H, Tang X, Shao X, Feng L, Wu N, Yao K. Parthenolide protects human lens epithelial cells from oxidative stress-induced apoptosis via inhibition of activation of caspase-3 and caspase-9. *Cell Res* 2007, 17:565-571
- Yao M, Ritchie HE, Brown-Woodman PD. A reproductive screening test of feverfew: is a full reproductive study warranted? *Reprod Toxicol* 2006, 22:688-693
- Yu Chuan L, Se Lim K, Young Ran P, Soo-Teik L, Sang Wook K. Parthenolide promotes apoptotic cell death and inhibits the migration and invasion of SW620 cells. *Intest Res* 2017, 15(2):174-181
- Zhang X, Fan C, Xiao Y, Mao X. Anti-Inflammatory and Antiosteoclastogenic Activities of Parthenolide on Human Periodontal Ligament Cells *In Vitro*. *Evid Based Complement Alternat Med* 2014
- Zunino SJ, Ducore JM, Storms DH. Parthenolide induces significant apoptosis and production of reactive oxygen species in high-risk pre-B leukemia cells. *Cancer Lett* 2007, 254:119-127