

6 May 2010  
EMA/HMPC/587580/2009  
Committee on Herbal Medicinal Products (HMPC)

## List of references supporting the assessment of *Tanacetum parthenium* (L.) Schulz Bip.

Tanaceti parthenii herba  
(Feverfew)

Draft

**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.**

Abourashed EA, Khan IA. GC determination of parthenolide in feverfew products. *Pharmazie* 2001; 56: 971-2.

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: 145-52.

Anderson KN, Bejcek BE. Parthenolide induces apoptosis in glioblastomas without affecting NF-kappaB. *J Pharmacol Sci* 2008; 106: 318-20.

Bamford CC, Tepper SJ. Daily pharmacologic prophylaxis of episodic migraine. *Techniques in Regional Anesthesia and Pain Management* 2009; 13: 20-27.

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: 641-5.

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: 737-40.

Bejar E. Parthenolide inhibits the contractile responses of rat stomach fundus to fenfluramine and dextroamphetamine but not serotonin. *J Ethnopharmacol* 1996; 50: 1-12.

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: 558-61.



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: 71-2.

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: 1108-15.

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: 612-7.

Awang DVC. Prescribing therapeutic feverfew (*Tanacetum parthenium* (L.) Schultz bip., syn. *Chrysanthemum parthenium* (L.) Bernh.). Elsevier Science Inc. 1998; 1(1): 11-3

Diener HC, Pfaffenrath V, Schnitker J, Friede M, Henneicke-von Zepelin HH. Efficacy and safety of 6.25 mg t.i.d. feverfew CO<sub>2</sub>-extract (MIG-99) in migraine prevention--a randomized, double-blind, multicentre, placebo-controlled study. *Cephalgia* 2005; 25: 1031-41.

Heptinstall S.: Feverfew - an ancient remedy for modern times? (Editorial). *Journal of the Royal Society of Medicine* 1988; 81: 373.

Ernst E, Pittler MH. The efficacy and safety of feverfew (*Tanacetum parthenium* L.): an update of a systematic review. *Public Health Nutr* 2000; 3: 509-14.

EUROPEAN PHARMACOPOEIA 6th edition FEVERFEW *Tanaceti parthenii* herba 01/2008:1516

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.

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: 553-7.

Groenewegen WA, Knight DW, Heptinstall S. Progress in the medicinal chemistry of the herb feverfew. *Prog Med Chem* 1992; 29: 217-38.

Gromek D, Kisiel W, Stojakowska A, Kohlmueller S. Attempts of chemical standardizing of *Chrysanthemum parthenium* as a prospective antimigraine drug. *Pol J Pharmacol Pharm* 1991; 43: 213-7.

Guin JD, Skidmore G. Compositae dermatitis in childhood. *Arch Dermatol* 1987; 123: 500-2.

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: 4163-9.

Hausen BM, Osmundsen PE. Contact allergy to parthenolide in *Tanacetum parthenium* (L.) Schulz-Bip. (feverfew, Asteraceae) and cross-reactions to related sesquiterpene lactone containing Compositae species. *Acta Derm Venereol* 1983; 63: 308-14.

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: 466-70.

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: 356-9.

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: 391-5.

Heptinstall S, White A, Williamson L, Mitchell JR. Extracts of feverfew inhibit granule secretion in blood platelets and polymorphonuclear leucocytes. *Lancet* 1985; 1: 1071-4.

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: 810-8.

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: 324-30.

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: E105.

Johnson ES, Kadam NP, Hylands DM, Hylands PJ. Efficacy of feverfew as prophylactic treatment of migraine. *Br Med J (Clin Res Ed)* 1985; 291: 569-73.

Kalodera Z, Pepelnjak S, Blazevic N, Petrank T. Chemical composition and antimicrobial activity of *Tanacetum parthenium* essential oil. *Pharmazie* 1997; 52: 885-6.

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: 159-63.

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: 1235-44.

Killoran CE, Crawford GH, Pedvis-Leftick A. Two cases of compositae dermatitis exacerbated by moisturizer containing feverfew. *Dermatitis* 2007; 18: 225-9.

Kisiel W, Stojakowska A. A Sesquiterpene coumarin ether from transformed roots of *Tanacetum Parthenium*. *Phytochemistry* 1997; 46: 515-6.

Knight DW. Feverfew: chemistry and biological activity. *Nat Prod Rep* 1995; 12: 271-6.

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: 759-66.

Loesche W, Groenewegen WA, Krause S, Spangenberg P, Heptinstall S. Effects of an extract of feverfew (*Tanacetum parthenium*) on arachidonic acid metabolism in human blood platelets. *Biomed Biochim Acta* 1988; 47: 241-3.

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: 181-4.

Long C, Sauleau P, David B, et al. Bioactive flavonoids of *Tanacetum parthenium* revisited. *Phytochemistry* 2003; 64: 567-9.

Maizels M, Blumenfeld A, Burchette R. A combination of riboflavin, magnesium, and feverfew for migraine prophylaxis: a randomized trial. *Headache* 2004; 44: 885-90.

- 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.
- Milbrodt M, Schröder F, König W. 3,4- $\beta$ -Epoxy-8-Deoxycumambrin B, a sesquiterpene lactone from *Tanacetum Parthenium*. *Phytochemistry* 1997; 44: 471-4.
- Mittra S, Datta A, Singh SK, Singh A. 5-Hydroxytryptamine-inhibiting property of Feverfew: role of parthenolide content. *Acta Pharmacol Sin* 2000; 21: 1106-14.
- Murch SJ, Simmons CB, Saxena PK. Melatonin in feverfew and other medicinal plants. *Lancet* 1997; 350: 1598-9.
- Murphy JJ, Heptinstall S, Mitchell JR. Randomised double-blind placebo-controlled trial of feverfew in migraine prevention. *Lancet* 1988; 2: 189-92.
- Naveen K, Jain, Shrinivas K, Kulkarni .Antinociceptive and anti inflammatory effects of *Tanacetum parthenium* L. extract in mice and rats. *Journal of Ethnopharmacology* 1999; 68: 251-59.
- Nelson MH, Cobb SE, Shelton J. Variations in parthenolide content and daily dose of feverfew products. *Am J Health Syst Pharm* 2002; 59: 1527-31.
- 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: 81-3.
- Pajak B, Orzechowski A, Gajkowska B. Molecular basis of parthenolide-dependent proapoptotic activity in cancer cells. *Folia Histochem Cytobiol* 2008; 46: 129-35.
- 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: 281-5.
- 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: 233-7.
- Patrick M, Heptinstall S, Doherty M. Feverfew in rheumatoid arthritis: a double blind, placebo controlled study. *Ann Rheum Dis* 1989; 48: 547-9.
- Paulsen E, Christensen LP, Andersen KE. Compositae dermatitis from airborne parthenolide. *Br J Dermatol* 2007; 156: 510-5.
- 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. *Cephalgia* 2002; 22: 523-32.
- 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.
- Pryse-Phillips WE, Dodick DW, Edmeads JG, et al. Guidelines for the nonpharmacologic management of migraine in clinical practice. Canadian Headache Society. *CMAJ* 1998; 159: 47-54.
- 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: 018-26.
- Reuter U, Chiarugi A, Bolay H, Moskowitz MA. Nuclear factor-kappaB as a molecular target for migraine therapy. *Ann Neurol* 2002; 51: 507-16.

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: 126-9.

Sharma VK, Sahoo B. Prurigo-nodularis-like lesion in parthenium dermatitis. *Contact Dermatitis* 2000; 42: 235.

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: 287-96.

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: 2313-20.

Taylor F.R., MD, FAHS. Lifestyle changes, dietary restrictions, and nutraceuticals in migraine prevention. *Techniques in Regional Anesthesia and Pain Management* 2009; 13: 28-37.

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. *Cephalgia* 2005; 25: 612-21.

Thakkar JK, Sperelakis N, Pang D, Franson RC. Characterization of phospholipase A2 activity in rat aorta smooth muscle cells. *Biochim Biophys Acta* 1983; 750: 134-40.

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: 176-82.

Vogler BK, Pittler MH, Ernst E. Feverfew as a preventive treatment for migraine: a systematic review. *Cephalgia* 1998; 18: 704-8.

WHO monographs 1998

Williams CA, Harborne JB, Geiger H, Hoult JR. The flavonoids of Tanacetum parthenium and *T. vulgare* and their anti-inflammatory properties. *Phytochemistry* 1999; 51: 417-23.

Won YK, Ong CN, Shen HM. Parthenolide sensitizes ultraviolet (UV)-B-induced apoptosis via protein kinase C-dependent pathways. *Carcinogenesis* 2005; 26: 2149-56.

Won YK, Ong CN, Shi X, Shen HM. Chemopreventive activity of parthenolide against UVB-induced skin cancer and its mechanisms. *Carcinogenesis* 2004; 25: 1449-58.

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* 2006; 9: 55-61.

Wu C, Chen F, Wang X, et al. Antioxidant constituents in feverfew (Tanacetum parthenium) extract and their chromatographic quantification. *Food Chem* 2006; 96: 220-7.

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: 401-10.

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: 565-71.

Yao M, Ritchie HE, Brown-Woodman PD. A reproductive screening test of feverfew: is a full reproductive study warranted? *Reprod Toxicol* 2006; 22: 688-93.

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: 119-27.