# Feverfew

## Species (Family)

*Tanacetum parthenium* (L.) Schultz Bip. (Asteraceae/Compositae)

## Synonym(s)

Altamisa, *Chrysanthemum parthenium* (L.) Bernh., *Leucanthemum parthenium* (L.) Gren & Godron, *Pyrethrum parthenium* (L.) Sm.

## Part(s) Used

Leaf, aerial parts

## Pharmacopoeial and Other Monographs

BHC 1992[G6]
BHP 1996[G9]
ESCOP 1996[G52]
Martindale 32nd edition[G43]
Mills and Bone[G50]
PDR for Herbal Medicines[G36]
USP24/NF19[G61]

## Legal Category (Licensed Products)

Feverfew is not included in the GSL.[G37]

## Constituents[G6,G22,G49,G64]

*Terpenoids* Sesquiterpene lactones: germacranolides (GE), guaianolides (GU) and eudesmanolides (EU). The structural feature common to all three types is an α-unsaturated γ-lactone moiety, and examples of each type include parthenolide, 3-β-hydroxy-parthenolide, costunolide, 3-β-hydroxycostunolide, artemorin, 8-α-hydroxyestafiatin and chrysanthemonin (novel dimeric nucleus) (GE); artecanin, chrysanthemin A (canin) and B (stereoisomers), chrysanthemolide, partholide, two chlorine-containing sesquiterpene lactones (GU); magnolialide, reynosin, santamarine, 1-β-hydroxyarbusculin and 5-β-hydroxyreynosin (EU).[1–5]

*Volatile oils* (0.02–0.07%). Various monoterpene and sesquiterpene components (e.g. camphor, borneol, α-pinene derivatives, germacrene, farnesene and their esters).

*Other constituents* Pyrethrin, flavonoids, tannins (type unspecified) and melatonin.[6]

## Food Use

Feverfew is not generally used in foods.

## Herbal Use[G6,G8,G32,G43,G49,G52,G64]

Feverfew has traditionally been used in the treatment of migraine, tinnitus, vertigo, arthritis, fever, menstrual disorders, difficulty during labour, stomachache, toothache and insect bites. Modern use of feverfew is focused on its effects in the prevention and treatment of migraine.

## Dosage

Limited information is available regarding the traditional dose of feverfew. The doses that have been recommended for migraine prophylaxis are as follows.

*Leaf (fresh)* 2.5 leaves daily with or after food.

*Leaf (freeze-dried)* 50 mg daily with or after food.

*Aerial parts (dried)* 50–200 mg daily; equivalent to 0.2–0.6 mg parthenolide daily.[G6,G52]

Clinical trials of feverfew for the prevention of migraine have assessed the effects of, for example, 143 mg of a dried alcoholic extract of feverfew daily (equivalent to 0.5 mg parthenolide),[7] and capsules containing powdered feverfew leaf 50 mg daily,[8,9] for one to six months.

## Pharmacological Actions

### *In vitro* and animal studies

Feverfew extracts have been documented to inhibit platelet aggregation and prostaglandin, thromboxane and leukotriene production, although feverfew has also been reported to have no effect on cyclooxygenase (the mechanism by which non-steroidal anti-inflammatory drugs inhibit prostaglandin production).[10–12] Instead, feverfew is thought to act by inhibiting the enzyme phospholipase $A_2$, which facilitates the release of arachidonic acid

from the phospholipid cellular membrane.[11–13] The clinical significance of this action has been questioned.[14] In addition, *in vitro* experiments have shown that feverfew extracts inhibit the interaction of human platelets with collagen substrates.[15,16] Feverfew has been shown to inhibit granule secretion in blood platelets and neutrophils, which has been associated with the aetiology of migraine and rheumatoid arthritis, respectively.[17] Feverfew was also found to inhibit the release of vitamin $B_{12}$-binding protein from polymorphonuclear leukocytes, but to be ineffective against platelet and polymorphonucleocyte secretion induced by calcium ionophore A2318.[17] Sesquiterpene lactone constituents of feverfew containing an α-methylene butyrolactone unit are thought to be responsible for the antisecretory activity.[18] Their inhibitory effect on platelet aggregation is thought to involve neutralisation of sulfhydryl groups on specific enzymes of proteins that are necessary for platelet aggregation and secretion.[19] A similar mode of action has been proposed for the inhibitory action of feverfew on polymorphonuclocyte secretion.[20] In addition, feverfew extracts have been reported to produce a dose-dependent inhibition of anti-IgE-induced histamine release from mast cells.[21] The authors concluded that the mechanism of action of the feverfew extract was different to that of both cromoglycate and quercetin.

Parthenolide markedly interfered with contractile and relaxant mechanisms in blood vessels.[G52] An aqueous extract of feverfew administered intravenously significantly inhibited collagen-induced bronchoconstriction in guinea-pigs.[G52]

The presence of large numbers of lymphocytes and monocytes in the synovium is considered to be of significance in rheumatoid arthritis.[22] Feverfew extract and parthenolide have been documented to inhibit mitogen-induced proliferation of human peripheral blood mononuclear cells and mitogen-induced prostaglandin $E_2$ ($PGE_2$) production by synovial cells.[22] The feverfew extract and parthenolide also proved to be cytotoxic to mitogen-treated peripheral blood mononuclear cells and the authors considered that this cytotoxicity was responsible for the actions observed.[22] *In vitro* studies using crude feverfew extracts and parthenolide have documented other activities that may contribute to the reported anti-inflammatory effects of feverfew. Pretreatment of human synovial fibroblasts with feverfew extract and with purified parthenolide inhibited cytokine-induced expression of intercellular adhesion molecule 1 (ICAM-1) expression.[23] A reduction in T cell adhesion to the treated fibroblasts also occurred. In other *in vitro* studies, parthenolide inhibited lipopolysaccharide-induced interleukin-12 (IL-12) production by mouse macrophages in a concentration-dependent manner.[24] Parthenolide has also been shown to inhibit promoter activity of the inducible nitric oxide synthase gene in a human monocyte cell line, THP-1, in a concentration-dependent manner.[25] (Excessive nitric oxide production in inflammatory cells is thought to be a causative factor in cellular injury in inflammatory disease.) Anti-inflammatory activity of feverfew has also been attributed to the presence of flavonoids, e.g. santonin.[26]

Anti-inflammatory properties have also been documented for feverfew extract and parthenolide *in vivo*. Oral administration of feverfew extract (10, 20 and 40 mg/kg) reduced carrageenan-induced oedema in rat paw in a dose-dependent manner.[27] Intraperitoneal parthenolide (1 and 2 mg/kg) also demonstrated anti-inflammatory effects in this model.

Parthenolide has been documented to have cytotoxic activity in Eagle's 9KB carcinoma of the nasopharynx cell culture system, the activity being associated with the presence of an α-methylene-γ-lactone moiety in the molecule.[28] *In vitro*, parthenolide has been shown to inhibit growth of mouse fibrosarcoma (MN-11) and human lymphoma (TK6) cell lines.[29] The effect appeared to be reversible.

Antinociceptive properties have been reported for feverfew and parthenolide *in vivo*. Oral administration of feverfew extract (10, 20 and 40 mg/kg) and intraperitoneal administration of parthenolide (1 and 2 mg/kg) led to reductions in acetic acid-induced writhing in mice.[27]

Antimicrobial properties against Gram-positive bacteria, yeasts and filamentous fungi *in vitro* have been documented for parthenolide.[30] Gram-negative bacteria were not affected.

## Clinical studies

*Migraine* Several placebo-controlled clinical trials have assessed the effects of preparations of feverfew in the prevention of migraine.[7–9,31]

A randomised, double-blind, placebo-controlled trial involved 17 patients who had been successfully controlling their migraine by eating raw feverfew leaves for at least three months.[8] Patients either continued to receive feverfew (50 mg daily) or were given placebo for six periods of four weeks. The authors reported that the placebo group experienced a significant increase in the frequency and severity of headache. Those given feverfew showed no change. It was suggested that the placebo group was in fact suffering withdrawal symptoms from feverfew and a 'post-feverfew syndrome' was described (*see* Side-effects, Toxicity).

Another study, a randomised double-blind, placebo-controlled, crossover trial involved 72 adults who had experienced migraine for more than two years and who had at least one attack per month.[31] The only concurrent medication allowed was the oral contraceptive pill. Patients completed a one-month, single-blind, placebo run-in phase, followed by four months' administration of placebo/active and four months' crossover. It was reported that patients experienced a 24% reduction in the number of attacks during feverfew treatment (one capsule daily; 70–114 mg feverfew equivalent to 2.19 µg parthenolide) although the duration of each individual attack was not significantly affected. Patients allocated to the active and then placebo group did not experience the withdrawal symptoms documented in another study,[8] although patients involved in the previous study had used feverfew over a longer period of time.

In a randomised, double-blind, placebo-controlled trial, 57 patients received capsules of dried, powdered feverfew leaves (parthenolide 0.2%) 100 mg daily for 60 days (open-label phase), followed by randomisation to feverfew or placebo (ground parsley) for 30 days then crossover to the other arm for 30 days.[9] There was no washout between crossover. At the end of the open-label phase (i.e. during which all participants received feverfew), there was a significant reduction in pain intensity and symptoms, such as vomiting and sensitivity to light, compared with baseline values ($p < 0.001$). At the end of the double-blind, crossover phase, it was reported that pain intensity was significantly lower during feverfew administration, compared with placebo administration ($p < 0.01$).

Thus, these three studies reported beneficial effects for feverfew, as demonstrated by fewer and/or less severe migraine episodes and/or reductions in pain intensity, compared with placebo.[8,9,31] However, one double-blind, placebo-controlled trial involving 50 feverfew-naïve patients who experienced migraine attacks at least once a month reported no difference in the number of migraine attacks between placebo recipients and participants who received capsules containing a dried alcoholic extract of feverfew equivalent to 0.5 mg parthenolide daily for nine months.[7] Another randomised, double-blind, placebo-controlled, crossover trial involving 20 patients with migraine assessed the effects of feverfew 100 mg daily for two months on serotonin uptake and platelet activity.[32] This trial found no effect for feverfew in the prevention of migraine attacks and also reported that feverfew administration had no effect on the uptake of serotonin by platelets.

The authors of a Cochrane systematic review of six randomised, double-blind, placebo-controlled trials (the five studies mentioned above, plus one another) concluded that although data suggest that feverfew preparations are superior to placebo in preventing migraine, further well-designed clinical trials are required to establish the beneficial effects of feverfew for migraine prophylaxis.[33]

*Rheumatoid arthritis* A double-blind, placebo-controlled, non-crossover trial studying the use of feverfew in rheumatoid arthritis has also been documented.[34] Forty-one female patients with inflammatory joint symptoms inadequately controlled by non-steroidal anti-inflammatory drugs were given either one feverfew capsule (70–86 mg equivalent to 2–3 µmol parthenolide) daily, or one placebo capsule, for six weeks. Current non-steroidal therapy was maintained. It was concluded that patients in the trial had experienced no additional benefit from feverfew.[34] The authors commented that while concomitant non-steroidal anti-inflammatory drug therapy has been stated to reduce the effectiveness of feverfew, the majority of rheumatoid arthritis sufferers will use feverfew to supplement existing therapy.

## Side-effects, Toxicity

Randomised, double-blind, placebo-controlled trials have documented the following adverse effects during feverfew administration, although most effects were also reported (sometimes more frequently) during placebo administration: mouth ulcers (reported more frequently during placebo administration in one study[31]), sore mouth, abdominal pain and indigestion, diarrhoea, flatulence, nausea, dizziness and skin rash.[7,8,31] On balance, adverse effects reported for feverfew are mild and transient, are similar to those reported during placebo administration and occur with a similar frequency.

A 'post-feverfew syndrome' has been described on stopping feverfew administration[8] (*see* Clinical studies) with symptoms such as nervousness, tension headaches, insomnia, stiffness/pain in joints and tiredness.

The onset of side-effects with feverfew is reported to vary, with symptoms becoming apparent within the first week of treatment, or appearing gradually over the first two months.

Sesquiterpene lactones that contain an α-methylene butyrolactone ring are known to cause allergic reactions.[35,G51] Compounds with this structure are present in feverfew and reports of contact dermatitis

have been documented.[36–39] No documented allergic reactions following oral ingestion were located.

An $LD_{50}$ value for feverfew has not been estimated. No adverse effects were reported for rats and guinea-pigs receiving feverfew at doses 100 and 150 times the human daily dose, respectively.[40] No chronic toxicity studies have been reported. However, detailed haematological analysis of 60 feverfew users, some of whom had used feverfew for more than one year, did not show any significant differences when compared with analysis of controls.[40] A human toxicity study has investigated whether the sesquiterpene lactones in feverfew induce chromosomal or other changes in normal human cells of individuals who have taken the herb.[41] The study compared 30 chronic female feverfew users (leaves, tablets or capsules taken daily for more than 11 consecutive months) with matched non-users. The results of lymphocyte cultures established from blood samples taken over a period of several months were stated to indicate that feverfew affects neither the frequency of chromosomal aberrations nor the frequency of sister chromatid exchanges in the circulating peripheral lymphocytes.

## Contra-indications, Warnings

Feverfew is contra-indicated in individuals with a known hypersensitivity to other members of the family Compositae (Asteraceae), such as chamomile, ragweed and yarrow. Feverfew should not be ingested by individuals who develop a rash on contact with the plant.

Feverfew should only be considered as a treatment for migraine that has proved unresponsive to conventional forms of medication. Although traditionally recommended as a remedy for rheumatic conditions, self-medication with feverfew should not be undertaken without first consulting a doctor.

*Pregnancy and lactation* Feverfew is contra-indicated during pregnancy. It is reputed to be an abortifacient and to affect the menstrual cycle. It is documented to modify menstrual flow, cause abortion in cattle and induce uterine contraction in full-term women.[G30]

## Pharmaceutical Comment

Feverfew is characterised by the sesquiterpene lactone constituents, in particular by parthenolide which is thought to be the main active component. *In vitro* studies provide some evidence to support the reputation of feverfew as a herb used to treat migraine and arthritis. Clinical studies have suggested that feverfew may be a useful prophylactic remedy against migraine,[42,43] although further research is deemed necessary to establish the benefits.[33] It has been recommended that feverfew should only be used by sufferers who have proved unresponsive to conventional forms of migraine treatment. Those using feverfew as a remedy for migraine should preferably do so under medical supervision.

Results of a study that investigated the usefulness of feverfew in treating rheumatoid arthritis were less encouraging: feverfew provided no additional benefit when added to existing non-steroidal anti-inflammatory treatment. Feverfew products currently available are unlicensed and vary in their recommended daily doses.[44] Furthermore, variation between the stated and actual amount of feverfew in commercial products (based on their ability to inhibit platelet secretion) has been reported.[16]

## References

*See also* General References G5, G6, G9, G18, G19, G22, G29, G31, G32, G36, G43, G49, G50, G51, G52, G55, G61 and G64.

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