The Longwood Herbal Task Force

(http://www.mcp.edu/herbal/default.htm) and

The Center for Holistic Pediatric Education and Research

(http://www.childrenshospital.org/holistic/)

Feverfew (*Tanacetum parthenium*)

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Principal Proposed Uses: Prevention of migraine headaches; treatment of rheumatoid arthritis and menstrual cramps

Other Proposed Uses: Antipyretic; occasional remedy for asthma, dermatitis

Overview

Feverfew is a member of the daisy family; it is used primarily to prevent migraine headaches and to treat rheumatoid arthritis. The active ingredients are sesquiterpene lactones, primarily parthenolide. Case series and randomized controlled trials support its use as a prophylactic agent for migraine, but have not compared it with other medications, biofeedback or hypnosis. No trials support its use in the treatment of rheumatoid arthritis, asthma, skin rashes, fever or menstrual cramps. Allergic reactions have been reported. Oral ulceration has been reported in 10% - 15% of those who chew the leaves; rebound headaches have been reported in patients who suddenly stopped taking feverfew. Because of its *in vitro* effects on platelet aggregation, feverfew should be used only cautiously by patients taking anticoagulants or those planning elective surgery; no adverse effects on clotting in humans have been reported. There are no data on its use in children or during pregnancy or lactation.

Historical and Popular Uses

Feverfew was used by the ancient Greeks and early Europeans to treat fevers, repel insects and treat bites and stings[1]. Its botanical name, *Tanacetum parthenium*, was derived in part from a Greek story about a workman who fell during construction of the Parthenon but was saved by the timely administration of this healing plant. A different version suggests that the name was derived from the Greek word, *parthenos* (virgin), referring to the plant's use in treating menstrual problems[2].

Historically, feverfew was considered too bitter to take orally; instead it was applied topically to the wrists or head to treat headaches. Medieval healers used it as an antipyretic. It was also planted in house gardens to keep malaria at bay. It has been used as an insect repellent[3]. In Chinese medicine it is described as having a bitter-cooling, sour-cooling flavor, acting as a fire or wood yang element[4].

In 1978, a British health magazine reported that a 68-year-old woman who had suffered from chronic migraines since the age of 16 tried feverfew leaves with complete relief of her headaches within a few months[5]. Since the 1980's feverfew has become a highly popular British, French and Canadian phytomedicine used to prevent migraine headaches, relieve menstrual cramps and treat painful joints[6,7,8]. It also became a top-selling American phytopharmaceutical in the late 1990's. Feverfew has not been reviewed by the German Commission E. A thorough review of feverfew and migraine headaches, written for a consumer audience is: D. Baranov (ed. S Bratman and D Kroll). *Everything you need to know about Feverfew and Migraines*. Prima Publishing. 1998.

Botany

Medicinal species: Tanacetum parthenium, also known as *Chrysanthemum parthenium, Leucanthemum parthenium, Matricaria parthenium*, or *Pyrethrum parthenium*

Common names: Altamisa, featherfew, featherfoil, febrifuge plant, feverfew, midsummer daisy, grande camomille (Fr), Santa Maria (Sp)[9,10]

Botanical family: Compositate (Asteraceae, Matricaria or daisy)

Plant description: Feverfew looks like a small daisy and has an appearance very similar to chamomile and tansy, to which it is closely related. It is a short perennial plant that grows 15 – 60 cm tall in poor soils along roadsides and abandoned fields. It has small flowers and feathery yellow-green leaves. The flowers bloom from July through October. The leaves are the part used medicinally[11].

Where it's grown: Originally a native of Europe's Balkan mountains, feverfew now grows in North and South America, Europe, North Africa, China, Japan and Australia. Plants from the US, Mexico and Serbia appear to be nearly devoid of parthenium[8,12].

Biochemistry

Feverfew: Potentially Active Chemical Constituents

- Sesquiterpene lactones: parthenolides, canin, artecanin, santamarin
- Flavonoid glycosides: luteolin, tanetin, apigenin, 6-hydroxy-flavanols
- Sesquiterpenes and monoterpenes: camphor, borneol, germacrene, and pinenes
- Other: polyacetylenes, pyrethrin, melatonin, tannins

Feverfew contains sesquiterpene lactones, flavonoid glycosides, pinenes and other compounds[2,5,13,14,15]. *Parthenolide* is the most abundant sesquiterpene lactone and is thought to be the most active chemical constituent in the plant[16]. However, the flavonoid glycosides have vasodilating and anti-inflammatory effects, and pinenes have mild sedative characteristics[13,17,18,19,20]. Minute amounts (1.75 mcg/gram) of melatonin are found in feverfew as well as in St. Johns wort and other herbs[21].

Parthenolide is found in at least 34 different plant species, some of which (e.g. tansy) are easily mistaken for feverfew, some of which (e.g. bay leaves) are found in the kitchen garden and some of which (e.g. the roots of the Himalayan plant, champaca) are fairly exotic[22,23]. Even within the feverfew species, there is enormous variation in the amount of parthenolide. American-grown plants contain from none to less than half the concentrations of British and French-grown plants[24]. The leaves, flowers and seeds contain higher concentrations than the stalks and roots. Harvesting the plants in spring yields a much higher concentration of parthenolide than harvesting in the fall[25]. Processing and storage can also affect the concentration of active ingredients in the final product[26,27,28]. A review published in 1993 concluded that there was enormous variation in the amount of parthenolide in different products marketed in Great Britain, with some products containing no parthenolide at all[29]. Also, the different lactones in the different preparations may result in completely opposite effects[28]. Commercial products should be standardized to contain at least 0.2% parthenolide. During storage at room temperature, concentrations of parthenolide drop by 20% - 25% in six months and by 50% in two years[29,30].

The whole, dried leaf appears to be more effective than feverfew extracts[33]. Two clinical studies failed to demonstrate benefits of alcoholic extracts of feverfew (which did contain parthenolide, but not other constituents), while products based on whole fresh or powdered leaves did show clinical benefits. This has led to speculation that parthenolide is not the most active constituent, but that other compounds such as flavonoids might provide a greater anti-inflammatory clinical effect[19,20,31,32].

Experimental Studies

Feverfew: Potential Clinical Benefits

1. Cardiovascular: none
2. Pulmonary: none
3. Renal and electrolyte balance: none
4. Gastrointestinal/hepatic: none
5. Neuro-psychiatric: Prevention of migraine headaches
6. Endocrine: none
7. Hematologic: none
8. Rheumatologic: Rheumatoid arthritis
9. Reproductive: Menstrual cramps
10. Immune modulation: Anti-inflammatory
11. Antimicrobial: none
12. Antineoplastic: Antineoplastic
13. Antioxidant: none
14. Skin and mucus membranes: none
15. Other/miscellaneous: none

1. **Cardiovascular:** none
2. **Pulmonary:** none
3. **Renal and electrolyte balance:** none
4. **Gastrointestinal/hepatic:** none
5. **Neuro-psychiatric:** Prevention of migraine headaches. Feverfew appears to work through four different mechanisms: reducing inflammation, reducing platelet activation, minimizing damage to endothelium, and modulating vasoconstriction[34].
   i. *In vitro data:* Sesquiterpene lactones, including parthenolide, have known anti-inflammatory effects[35]. Parthenolide and other sesquiterpene lactones in feverfew inhibited granular release from human platelets and neutrophils of pro-inflammatory compounds such as arachidonic acid and serotonin[17,36,37,38,39]. Feverfew appears to

inhibit both uptake and secretion of arachidonic acid from the cell membrane[40]. In aortic smooth muscle, a feverfew extract inhibited aortic smooth muscle phospholipase(s) A2, which functions at the beginning of the arachidonic acid cascade to pro-inflammatory prostaglandins[41,42]. In peritoneal leukocytes from rats, aqueous extracts of feverfew blocked the cyclooxygenase and lipoxygenase products of arachidonic acid metabolism[43,44].

Feverfew extracts inhibited ADP-, thrombin-, and collagen-induced aggregation of human platelets, presumably by interfering with cellular phospholipases and preventing the release of arachidonic acid[45]. Feverfew extracts also interfered with platelet aggregation and the deposition of platelets on mildly injured epithelium[46,47]. In rabbit tissues, feverfew extracts inhibited both platelet spreading and formation of thrombus-like platelet aggregates on the collagen surface and protected mildly injured epithelial cells from platelet deposition[48].

Feverfew extracts and parthenolide strongly inhibited responses of rabbit aortic rings to phenylephrine, 5-hydroxytryptamine, thromboxane mimetic U46619 (9,11-dideoxy-11 alpha,9 alpha-epoxy-methano-PGF2 alpha), and angiotensin II; the inhibition was concentration- and time-dependent, non-competitive, and irreversible[49,50,51]. Similar effects were observed in studies of smooth muscle from rats' stomachs: parthenolide inhibited serotonin-mediated smooth muscle contraction[52]. In smooth muscle, feverfew extracts reduced the voltage-dependent potassium current in a concentration-related manner[53]. In another study, different effects were found from different types of feverfew extracts. Extracts of fresh leaves (which contain parthenolide) caused dose- and time-dependent inhibition of the contractile responses of aortic rings to receptor-acting agonists; in contrast, chloroform extracts of dried powdered leaves (which did not contain parthenolide) were not inhibitory but instead elicited potent and sustained contractions of aortic smooth muscle[28].

ii. *Animal data:* none

iii. *Human data:* Case series suggest that ingesting as few as two to three fresh feverfew leaves daily effectively prevents migraine headaches[42].

Two clinical trials of patients with migraine headaches reported that 25 - 90 milligrams daily of dried feverfew leaves (standardized to contain at least 0.66% parthenolide) provided significant protection against recurrent headaches[54,55]. These studies were small and only one was prospective and controlled[56]. In an Israeli trial of 57 adult patients with migraines, taking feverfew leaves (50 mg twice daily of a product standardized to contain 0.2% parthenolide) for two months provided significant benefit in terms of the severity of headache and nausea symptoms[57].

In contrast, in a randomized, double-blind, placebo-controlled crossover trial of 50 Dutch migraineurs, a daily capsule containing a dried, alcoholic extract of feverfew (which contained 0.5 milligrams parthenolide) provided no significant benefit in preventing migraine symptoms; this is the only trial using a feverfew *extract* rather than feverfew leaves[58,59].

Feverfew must be taken daily for several weeks before the effects become noticeable; its effectiveness has not been established in the acute treatment of headaches. A meta-analysis published in 1998 concluded that although the majority of studies support the effectiveness of feverfew in preventing migraines, larger studies with longer follow-up times and comparisons with modern migraine medications are needed to definitively establish feverfew's role[60].

6. **Endocrine:** none
7. **Hematologic:** none
8. **Rheumatologic:** Rheumatoid arthritis
   i. *In vitro data:* See **Immune modulation**
   ii. *Animal data:* See **Immune modulation**
   iii. *Human data:* In one double-blind randomized, controlled clinical trial of 41 women with rheumatoid arthritis, feverfew treatment over six weeks provided no statistically significant benefit over placebo[61].

9. **Reproductive:** Menstrual cramps. Despite the popular use of feverfew as an anti-inflammatory remedy for painful menstrual cramps, no clinical trials have evaluated its effectiveness for this indication.
10. **Immune modulation:** Anti-inflammatory
    i. *In vitro data:* In rat peritoneal mast cells, parthenolide blocked the IgE-stimulated release of histamine in a dose-dependent fashion; it also blocked the synthesis of pro-inflammatory prostaglandins by up to 88%[62,63,64]. Unlike aspirin, neither the whole plant nor leaf extracts inhibited cyclo-oxygenation of arachidonic acid, but they did inhibit prostaglandin synthesis[42,62]. Feverfew inhibited both the uptake and secretion of arachidonic acid from cell membranes, preventing ADP-stimulated and thrombin-stimulated platelet aggregation[40]. It is thought to work by inhibiting phospholipase A2, a critical enzyme in the release of arachidonic acid from cell membranes. Both extracts and dried leaves produced dose-dependent inhibition of the generation of thromboxane B2 (TXB2) and leukotriene B4 (LTB4) by ionophore- and chemoattractant-stimulated rat peritoneal leukocytes and human polymorphonuclear leukocytes[65]. Feverfew extracts effectively inhibited the release of serotonin from both platelets and polymorphonuclear leukocyte granules.
    ii. *Animal data:* In guinea pigs, pretreatment with feverfew inhibited collagen-induced bronchoconstriction, presumably by interfering with phospholipase A2[66].
    iii. *Human data:* see **Rheumatologic**
11. **Antimicrobial:** none
12. **Antineoplastic:** Antineoplastic
    i. *In vitro data:* Sesquiterpene lactones, including parthenolide, have demonstrated cytotoxicity against different human (human lymphoma TK6) and animal (mouse fibrosarcoma) tumor lines[67,68,69,70,71].
    ii. *Animal data:* none
    iii. *Human data:* none
13. **Antioxidant:** none
14. **Skin and mucus membranes:** none

15. **Other/miscellaneous:** none

Toxicity and Contraindications

All herbal products carry the potential for contamination with other herbal products, pesticides, herbicides, heavy metals and pharmaceuticals.

Allergic reactions can occur to any natural product in sensitive persons.

Allergic reactions (including contact dermatitis) to feverfew have been reported, particularly among gardeners and others with intense occupational exposure[72,73,74,75,76,77,78,79,80]; there is potential cross-reactivity to other members of the Compositae family including ragweed[81].

Potentially toxic compounds in feverfew: Unknown

Acute side effects and toxicity: Reported acute side effects include mouth ulcers and lip and tongue swelling in 10% -15% of those who chewed fresh leaves in one study[54]; these effects have not been reported in studies in which capsules were used. Other reported side effects include upset stomach, tachycardia, insomnia and skin rashes[5,80,82,83]. However, some clinical trials have not reported more frequent side effects with feverfew than with placebo[54,55]. Animal studies have not shown significant toxicity at doses up to 100 times the usual human dose[84].

Chronic toxicity: In one study, rebound headaches were reported when feverfew was discontinued after chronic use[54]; no other studies have reported this effect, and no other chronic adverse effects have been noted with use up to 10 years[54]. There appear to be no toxic effects on DNA or risk of mutations or carcinogenesis with feverfew use over several months[85,86].

Limitations during other illnesses or in patients with specific organ dysfunction: None reported[16,54]. Because parthenolide affects platelet aggregation in some *in vitro* studies, caution may be appropriate for patients with bleeding disorders or anticipating surgery. On the other hand, in a study of 10 patients who had been taking feverfew for between

three and eight years, there was no significant impact on platelet aggregation compared to control patients who had not used feverfew within the previous six months[16,34].

Interactions with other herbs or pharmaceuticals: Because parthenolide affects platelet aggregation in some *in vitro* studies, caution may be appropriate for patients using anticoagulant or antiplatelet medications.

Safety during pregnancy, lactation and/or childhood: No clinical studies or systematic surveillance. However, herbalists have classified it as an emmenagogue and recommended avoiding it during pregnancy to avoid miscarriage[87,88]. It is not typically recommended for lactating women or for children less than two years old[7].

Typical Dosages

Provision of dosage information dose NOT constitute a recommendation or endorsement, but rather indicates the range of doses commonly used in herbal practice.

Doses are given for single herb use and must be adjusted when using herbs in combinations.

Doses may also vary according to the type and severity of the condition treated and individual patient conditions.

Adult doses of feverfew:

Fresh leaves: 2 - 3 daily

Dried, powdered leaves: 50 - 250 mg daily; most experts recommend 125 - 250 mg daily divided into two doses.

Alcoholic extracts are not recommended due to potential loss of active ingredients.

Pediatric dosages: Unknown

Availability of standardized preparations: In the UK and Canada, products are standardized to contain at least 0.2% parthenolide. In France, standardized products must contain at least 0.1% parthenolide[29,24].

Dosages used in herbal combinations: Variable

Proprietary names: Herbal Headache Relief, Partenelle (FM), Tanacet, Presselin Stoffwechseltee (FM)

See Also:

Clinician Information Summary: http://www.mcp.edu/herbal/feverfew/feverfew.cis.pdf

Patient Fact Sheet: http://www.mcp.edu/herbal/feverfew/feverfew.ph.pdf

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