

Feverfew

Tanacetum parthenium (L.) Sch. Bip. (syn. *Chrysanthemum parthenium* [L.] Bernh.)

[Fam. Asteraceae]

OVERVIEW

Feverfew is ranked 19th among herbal supplements sold in mainstream retail outlets in the U.S. It is used primarily for migraine prophylactic effects, and for concomitant nausea and vomiting. Many commercial feverfew preparations are standardized based on 0.1% to 0.2% parthenolide content. However, different commercial preparations can vary widely in parthenolide content depending upon the geographical location from which the seeds were derived, the vegetative cycle of the plant at the time of harvest, the parts of the plant used, and the duration and conditions of storage. Parthenolide, once believed to be the primary active constituent, is no longer considered principal; other, unknown compounds are believed to be responsible for feverfew's anti-migraine activity.

PRIMARY USES

- Migraine prophylaxis
- Nausea and vomiting associated with migraine

PHARMACOLOGICAL ACTIONS

Anti-nociceptive; anti-inflammatory; inhibits collagen-induced bronchoconstriction; anti-thrombotic potential; inhibits prostaglandin synthesis; inhibits serotonin release; inhibits mast cell release of histamine.

DOSAGE AND ADMINISTRATION

Optimal doses of feverfew for therapeutic benefits have not been established. However, an adult dose equivalent to 0.2–0.6 mg of parthenolide is recommended for migraine prophylaxis.

DRIED LEAVES: 50–150 mg per day, as indicated by the clinical studies.

FRESH LEAVES: 2.5 leaves per day, with or after food.

TINCTURE: (1:5, 25% ethanol) 5–20 drops per day.

NOTE: Clinical experience suggests that the beneficial effects of feverfew for migraine prophylaxis can usually be seen within 4–6 weeks of initiating treatment. However, the duration of treatment will vary for individual migraine sufferers. There are no long-term safety data because clinical studies showing positive results for the effects of feverfew on migraine prophylaxis have

been conducted for a brief duration of only 4–6 months. Therefore, it is recommended that patients on long-term therapy discontinue using feverfew for at least one month per year to evaluate efficacy and determine if continued treatment is necessary. The feverfew dose should be tapered gradually over the preceding month to prevent potential withdrawal symptoms.

CONTRAINDICATIONS

Feverfew is contraindicated for persons who are allergic to feverfew (*Tanacetum parthenium*) and other members of the family Asteraceae, including ragweed (*Ambrosia* spp.), chrysanthemums (*Chrysanthemum* spp.), marigolds (*Calendula officinalis*), chamomile (*Matricaria* spp.), yarrow (*Achillea* spp.), and daisies. Feverfew is not recommended for children under two years of age.

PREGNANCY AND LACTATION: Not for use in pregnancy and lactation. Feverfew is contraindicated during pregnancy because it may act as an emmenagogue in early pregnancy.

ADVERSE EFFECTS

Allergic contact dermatitis can result from handling fresh feverfew. Mouth ulceration and swelling of the tongue, lips, and oral mucosa have also been reported. Abdominal pains and indigestion have been reported for feverfew users who chewed the leaves over a period of years. Diarrhea, flatulence, nausea, and vomiting were rare, but important enough to discontinue treatment. Although long-term toxicity data are presently unavailable, no serious side effects have been noted in patients taking the plant for several years.

DRUG INTERACTIONS

No adverse side effects were noted in a large number of individuals taking feverfew in combination with other medications. Pharmacological studies suggest that, in theory, feverfew should not be ingested with anticoagulants or antiplatelet agents such as aspirin or warfarin. However, this recommendation is speculative and has yet to be substantiated by pharmacological or clinical data.



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CLINICAL REVIEW

In six trials that included a total of 279 participants, 5 demonstrated positive effects in treating migraine. However, 1 trial examining feverfew's effects on arthritis found no apparent benefit. Three of the 5 migraine studies were randomized, double-blind, and placebo-controlled. In one of these studies, the participants used a feverfew extract, but did not experience a reduction in the number of migraine attacks; however, they were able to use fewer drugs during the period in which they took the feverfew. It has been theorized that the therapeutic effect of feverfew is due to an unidentified plant constituent that may have been lost or

degraded in the extract made from feverfew material used in a study that did not produce positive results. In addition, the leaves of the plant used in the latter study were not cultivated from certified seeds. By comparison, the studies using dried feverfew leaf found a reduction in number and severity of migraine attacks. Feverfew consistently reduced vomiting and nausea associated with migraine. A recently published literature review concluded that the efficacy of feverfew for the prevention of migraine has not been established beyond reasonable doubt. In addition, one trial found that feverfew did not benefit women with rheumatoid arthritis.



Feverfew

Tanacetum parthenium (L.) Sch. Bip. (syn. *Chrysanthemum parthenium* [L.] Bernh.)

[Fam. Asteraceae]

OVERVIEW

Feverfew is usually collected when the plant is in bloom. However, different commercial preparations can vary widely in active ingredients depending on where the plant was growing, its condition at the time of harvest, and the parts of the plant used. Parthenolide is an active ingredient in feverfew that may be partly responsible for its effects in preventing and treating migraine headache, although scientists now believe that some other unidentified compound(s) may be responsible. Many feverfew products are standardized to contain between 0.1–0.2% parthenolide. Feverfew is ranked 19th among herbal supplements sold in mainstream retail outlets in the U.S.

USES

Migraine prevention; nausea and vomiting associated with migraine.

DOSAGE

To prevent migraine, take adult dose equal to 0.2–0.6 mg of parthenolide. Benefits usually begin within 4–6 weeks after starting treatment. The length of treatment will vary for individual migraine sufferers.

DRIED LEAVES: 50–150 mg per day, as indicated by clinical studies.

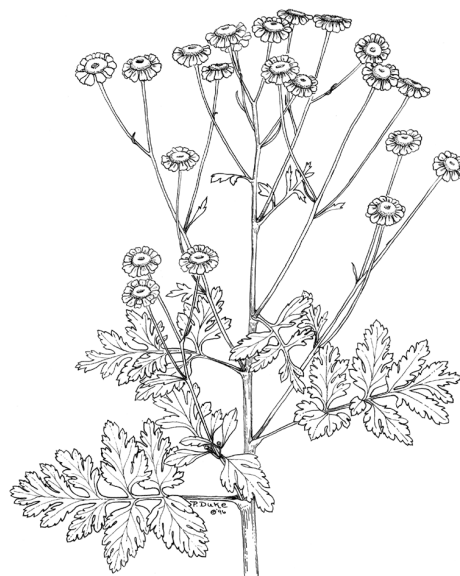
FRESH LEAVES: 2.5 leaves per day, with or after food.

TINCTURE: 5–20 drops per day [1:5, 25% ethanol].

CONTRAINDICATIONS

Consult a healthcare provider before using feverfew if you are allergic to this or other plants in the family *Asteraceae* such as ragweed, chrysanthemums, marigolds, chamomile, yarrow, and daisies. Feverfew is not recommended for children under 2 years of age.

PREGNANCY AND LACTATION: Feverfew should not be used during pregnancy or while breast-feeding.



ADVERSE EFFECTS

No serious side effects have been noted in individuals taking feverfew for a period of years. Skin inflammation can result from handling fresh feverfew. Mouth ulcers and swelling of the tongue, lip, and the mucous membrane of the mouth may occur. Abdominal pains and indigestion have been reported for feverfew users who chewed the leaves over a period of years. Diarrhea, flatulence, nausea, and vomiting occur rarely.

DRUG INTERACTIONS

There are no known drug interactions. Theoretically, feverfew should not be ingested at the same time as blood-thinning (anticoagulant or antiplatelet) medications like aspirin or warfarin. However, this has not been scientifically proven in human studies.

Comments

When using a dietary supplement, purchase it from a reliable source. For best results, use the same brand of product throughout the period of use. As with all medications and dietary supplements, please inform your healthcare provider of all herbs and medications you are taking. Interactions may occur between medications and herbs or even among different herbs when taken at the same time. Treat your herbal supplement with care by taking it as directed, storing it as advised on the label, and keeping it out of the reach of children and pets. Consult your healthcare provider with any questions.



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Feverfew

Tanacetum parthenium (L.) Sch. Bip.

[Fam. Asteraceae]

OVERVIEW

Traditionally, feverfew was used for a wide range of disorders including psoriasis, toothache, insect bites, rheumatism, vertigo, colic, cleansing the kidneys and bladder, stomach pain, menstrual problems, inflammation, and fever (Hobbs, 1989; Groenewegen *et al.*, 1992). The ancient Greeks called feverfew “parthenium” because, according to legend, it was used to save the life of someone who had fallen from the Parthenon, the Doric temple of the virgin goddess Athena on the Acropolis in Athens (Hobbs, 1989). However, its name may be more likely based on feverfew’s traditional use for alleviating menstrual cramps in young girls (*parthenos* = virgin in Greek). Currently, feverfew is used primarily for migraine prophylactic effects, and for concomitant nausea and vomiting (Brown, 1995; ESCOP, 1996; Johnson *et al.*, 1985; Murphy *et al.*, 1988). Feverfew is ranked 19th among herbal supplements sold in mainstream retail outlets in the U.S. (Blumenthal, 2001).



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DESCRIPTION

Feverfew preparations consist of the aerial parts or leaves of *Tanacetum parthenium* (L.) Sch. Bip. (syn. *Chrysanthemum parthenium* (L.) Bernh.) [Fam. Asteraceae], collected when the plant is in flower (Bradley, 1992; Reynolds, 1993; Newall *et al.*, 1996). The fresh leaves can also be chewed to obtain the purported therapeutic benefits (Newall *et al.*, 1996). Many commercial feverfew preparations are standardized based on parthenolide content (0.1% [French regulatory authorities] to 0.2% [Canadian authorities] are suggested as minimum contents for quality control purposes) (Bruneton, 1999; Evans, 1998). However, different commercial preparations can vary widely in parthenolide content depending upon the geographical location from which the seeds were derived, the vegetative cycle of the plant at the time of harvest, the parts of the plant used, and the

duration and conditions of storage (Bruneton, 1999; Evans, 1998; Heptinstall, 1992). No parthenolide was detected in feverfew grown in Mexico or Yugoslavia, and the feverfew in both countries contained eudesmolides and guaianolides as the primary constituents (Heptinstall *et al.*, 1992). Recent evidence indicates that the pharmacological activity of feverfew in the treatment and prophylaxis of migraines is not attributed to parthenolide content as was previously thought, but to other unidentified constituents (Awang, 1998a; de Weerd *et al.*, 1996). In addition, parthenolide is not a unique constituent of feverfew (Heptinstall *et al.*, 1992); parthenolide is detected in 34 plant species (25 from Asteraceae, nine from Magnoliaceae) (Heptinstall *et al.*, 1992; Heptinstall and Awang, 1998). Therefore, parthenolide is used to ensure that the correct chemotype of *T. parthenium* is used, but it is not an assurance of the botanical identity or efficacy of feverfew products (Awang, 1998b). Since the active constituents are unknown, it is recommended that preparations containing the whole leaf (dried or fresh) should be used (Awang, 1998b; Heptinstall and Awang, 1998). Since parthenolide stability can vary with storage conditions, feverfew should be stored in a cool, dry, dark environment (Heptinstall *et al.*, 1992; Heptinstall and Awang, 1998).

PRIMARY USES

- Migraine prophylaxis (de Weerd *et al.*, 1996; Palevitch *et al.*, 1997; Anderson *et al.*, 1988; Murphy *et al.*, 1988; Johnson *et al.*, 1985)
- Nausea and vomiting associated with migraine (Palevitch *et al.*, 1997; Murphy *et al.*, 1988; Johnson *et al.*, 1985)

DOSAGE

Optimal doses of feverfew for therapeutic benefits have not been established; however, an adult dose equivalent to 0.2–0.6 mg of parthenolide is recommended for migraine prophylaxis (ESCOP, 1996; Johnson *et al.*, 1985; Murphy *et al.*, 1988).

Internal

Crude Preparations

DRIED LEAF: 50–150 mg daily (Palevitch *et al.*, 1997; Murphy *et al.*, 1988; Johnson *et al.*, 1985).

FRESH LEAF: 2.5 leaves daily, with or after food (Newall *et al.*, 1996).

TINCTURE: 1:5, 25% ethanol, 5–20 drops daily (Bradley, 1992).

DURATION OF ADMINISTRATION

Internal

Crude Preparations

Prophylaxis benefit for migraine can usually be seen within four to six weeks of the initiation of treatment (Brown, 1995; Palevitch *et al.*, 1997). However, the duration of treatment will vary for individual migraine sufferers (Brown, 1995). Successful clinical studies involving feverfew for migraine prophylaxis have been conducted for durations of up to 46 months;

longer-term safety data are not presently available (Johnson *et al.*, 1985; Murphy *et al.*, 1988; Palevitch *et al.*, 1997). It is recommended that patients continuing long-term use should discontinue therapy for at least one month per year to evaluate efficacy and determine whether continuation is necessary (ESCO, 1996; Baldwin *et al.*, 1987). The feverfew dose should be tapered gradually over the preceding month to prevent potential withdrawal symptoms (ESCO, 1996; Baldwin *et al.*, 1987).

CHEMISTRY

The constituents of feverfew can vary depending upon the chemotype and the geographical location from which the seeds were derived (Heptinstall *et al.*, 1992). Constituents include sesquiterpene lactones including germacranolides—parthenolide (Bohlmann and Zdero, 1982; ESCO, 1996; Hausen, 1992), eudesmolides—reynosin, and santamarin (Awang, 1989; Bohlmann and Zdero, 1982; Leung and Foster, 1996), guaianolides—canin and articanin (Bohlmann and Zdero, 1982; Bradley, 1992; Hausen, 1992; Leung and Foster, 1996). Parthenolide is usually the primary sesquiterpene lactone, but it is lacking in samples from Mexico and Yugoslavia (Heptinstall *et al.*, 1992). Additional sesquiterpenes and monoterpenes include camphor, β -farnesene, germacrene, chrysanthenyl acetate, α -pinene derivatives, bornyl acetate, bornyl angelate (Bohlmann and Zdero, 1982; Bradley, 1992; Newall *et al.*, 1996), pyrethrin (Newall *et al.*, 1996), flavonoids (Bruneton, 1999; Newall *et al.*, 1996; Williams *et al.*, 1995), tannins (Newall *et al.*, 1996), and melatonin (Murch *et al.*, 1997).

PHARMACOLOGICAL ACTIONS

Human

Antimigraine (Johnson *et al.*, 1985; Murphy *et al.*, 1988; Palevitch *et al.*, 1997); however, more information is needed. Although past studies have focused upon parthenolide as the active component responsible for antimigraine activity, a recent Dutch study determined an alcoholic feverfew leaf extract (containing an appropriate level of parthenolide) to be ineffective in migraine prophylaxis, challenging previous hypotheses (Awang, 1998b; de Weerd *et al.*, 1996). The Dutch researchers suggest that another compound such as chrysanthenyl acetate, detected in significantly reduced amounts in the extract compared with the dried, whole plant material, may contribute to the antimigraine activity due to its prostaglandin inhibition (de Weerd *et al.*, 1996; Heptinstall and Awang, 1998).

Animal

Anti-nociceptive (Jain and Kulkarni, 1999); anti-inflammatory (Jain and Kulkarni, 1999); inhibits collagen-induced bronchoconstriction (Keery and Lumley, 1986).

In vitro

Anti-inflammatory (Williams *et al.*, 1995; Brown *et al.*, 1997); inhibits mast cell release of histamine (Hayes and Foreman, 1987); inhibits blood platelet secretion of serotonin (Heptinstall *et al.*, 1985; Groenewegen and Heptinstall, 1990); anti-thrombotic potential (Voyno-Yasenetskaya *et al.*, 1988; Groenewegen and Heptinstall, 1990; Loesche *et al.*, 1987); inhibits prostaglandin synthesis (Pugh and Sambo, 1988); inhibits serotonin release (Béjar, 1996; Marles *et al.*, 1992); inhibits eicosanoid synthesis (Sumner *et al.*, 1992); alters vascular responses (Barsby *et al.*, 1992, 1993a, 1993b); inhibits neutrophil phagocytosis (Williamson *et al.*, 1988); antibacterial (Hayes and Foreman, 1987); cytotoxic (O'Neill *et al.*, 1987).

MECHANISM OF ACTION

- May inhibit platelet behavior through the neutralization of sulphhydryl groups on enzymes of proteins implicated in platelet aggregation and secretion (Heptinstall *et al.*, 1987).
- Sesquiterpene lactones and non-sesquiterpene lactones inhibit eicosanoid synthesis by inhibiting 5-lipoxygenase and cyclo-oxygenase in leukocytes (Sumner *et al.*, 1992). Tanetin may contribute to anti-inflammatory properties by inhibiting the generation of pro-inflammatory eicosanoids (Williams *et al.*, 1995; Hoult *et al.*, 1995).
- Parthenolide and other sesquiterpene lactones in extracts of fresh leaves appear to irreversibly and nonspecifically inhibit smooth muscle contractions (Barsby *et al.*, 1993a). In contrast, chloroform extracts of dried feverfew leaves, containing no parthenolide, produce reversible smooth muscle contractions via a selective open-channel block of voltage-dependent potassium channels (Barsby *et al.*, 1993b).
- Inhibits collagen-induced bronchoconstriction by inhibiting phospholipase A2 activity (Keery and Lumley, 1986).
- Parthenolide, and other sesquiterpene lactones inhibit serotonin release from bovine platelets. Serotonin has been implicated in the pathogenesis of migraines (Marles *et al.*, 1992).
- Parthenolide, michefuscalide, and chrysanthenyl acetate can inhibit prostaglandin synthetase, which catalyzes the conversion of arachadonic acid to prostaglandins (Pugh and Sambo, 1988).
- Extract inhibits histamine release from rat peritoneal mast cells (Hayes and Foreman, 1987).
- Blocks secretory activity in blood platelets and polymorphonuclear leukocytes (PMNs) (Heptinstall *et al.*, 1985).
- Inhibits the release of serotonin from platelets and platelet aggregation (Heptinstall *et al.*, 1985).
- Inhibits neutrophil phagocytosis and degranulation (Williamson *et al.*, 1988).
- Extract inhibits mitogen-induced, human peripheral-blood mononuclear cell proliferation and cytokine-mediated responses (O'Neill *et al.*, 1987).

CONTRAINDICATIONS

Feverfew is contraindicated when the patient is allergic to members of family *Asteraceae* (*Compositae*), which includes feverfew (*Tanacetum parthenium*), ragweed (*Ambrosia* spp.), chrysanthemums (*Chrysanthemum* spp.), marigolds (*Calendula officinalis*), chamomile (*Matricaria* spp.), yarrow (*Achillea* spp.), and daisies (ESCO, 1996; Hausen and Osmundsen, 1983; Newall *et al.*, 1996). Not recommended for children under two years old (Awang, 1993). Contraindicated for presurgical patients due to possible anti-PAF activity (Brinker, 2001).

PREGNANCY AND LACTATION: Not for use in pregnancy or lactation (Awang, 1993). Contraindicated during pregnancy because it may act as an emmenagogue in early pregnancy (Brinker, 2001).

ADVERSE EFFECTS

Allergic contact dermatitis can occur when feverfew is handled (Brinker, 2001). Mouth ulceration and swelling of the tongue, lips, and oral mucosa have also been reported (Hausen, 1992;

Murphy *et al.*, 1988). Abdominal pains and indigestion have been reported for feverfew users who have chewed the leaves over a period of years (Hausen, 1992; Murphy *et al.*, 1988). Diarrhea, flatulence, nausea, and vomiting were rare, but resulted in the discontinuation of treatment (ESCOP, 1996; Hausen, 1992). Although long-term toxicity data are presently unavailable, no serious side effects have been noted in patients taking the plant for a period of years (Hausen *et al.*, 1992; Johnson *et al.*, 1985; Murphy *et al.*, 1988).

DRUG INTERACTIONS

No adverse side effects were noted in a large number of individuals taking feverfew together with other medications (ESCOP, 1996). Due to the pharmacology, speculative theories suggest that feverfew should not be consumed with anticoagulants or antiplatelet agents like aspirin or warfarin (Brinker, 2001; Bratman and Kroll, 1999). However, these theories have not been proven in a clinical or scientific setting (Boon and Smith, 1999).

AMERICAN HERBAL PRODUCTS ASSOCIATION (AHPA) SAFETY RATING

CLASS 2B: Not to be used during pregnancy (McGuffin *et al.*, 1997). NOTE: Mouth ulceration and gastric disturbances have been reported in 6–15% of users, usually in the first week of use (McGuffin *et al.*, 1997).

REGULATORY STATUS

CANADA: The Canadian Health Protection Branch has issued Drug Identification Numbers (DIN) to dried-leaf products containing a minimum of 0.2% parthenolide with certification of botanical identity. The Feverfew Leaf Labeling Standard permits the following indications: “Traditional Herbal Medicine (THM) to help prevent recurring migraine headaches and associated nausea and vomiting” (Awang, 1998b; Health Canada, 1997; Leung and Foster, 1996).

EUROPEAN UNION: Dried aerial part, containing not less than 0.2% of parthenolide, is official in the *European Pharmacopoeia* 3rd ed. Supplement 2001 (Ph.Eur., 2001).

FRANCE: THM approved for specific indications (Bradley, 1992). Fresh or dried aerial parts are official in the *French Pharmacopoeia* (ESCOP, 1996).

GERMANY: Not reviewed by the German Commission E. No monograph in the *German Pharmacopoeia* (DAB).

SWEDEN: Classified as a natural product (De Smet *et al.*, 1993). As of January 2001, no feverfew products are listed in the Medical Products Agency (MPA) “Authorised Natural Remedies” (MPA, 2001).

SWITZERLAND: No feverfew products are licensed herbal medicines. No monograph in the *Swiss Pharmacopoeia*.

U.K.: Not on the *General Sale List* and no product licenses granted (Bradley, 1992).

U.S.: Dietary supplement (USC, 1994). Dried leaf and dried powdered leaf are official in the *United States National Formulary* (USP, 2002).

CLINICAL REVIEW

Six trials are outlined in the following table “Clinical Studies on Feverfew”, including a total of 279 participants. All five of the trials examining feverfew’s effects on migraine demonstrate some positive effects, but one trial examining feverfew’s effects on

arthritis found no apparent benefit. Three of the five migraine studies were randomized, double-blind, and placebo-controlled (R, DB, PC) (de Weerd *et al.*, 1996; Murphy *et al.*, 1988; Johnson *et al.*, 1985). In one of these studies the participants used a feverfew extract but did not experience a reduction in the number of migraine attacks; however, they were able to use fewer drugs during the period they took the feverfew (de Weerd *et al.*, 1996). Awang (1998b) has theorized that the therapeutic effect of feverfew is due to an unidentified plant constituent that may have been lost or degraded in the extract made from the feverfew material used in the de Weerd (1996) study. Further, the leaves of the plant used in the study were not cultivated from certified seeds (Awang, 1998b). By comparison, the studies using dried feverfew leaf found a reduced number and severity of migraine attacks (Palevitch *et al.*, 1997; Murphy *et al.*, 1988; Johnson *et al.*, 1985). Feverfew consistently reduced vomiting and nausea associated with migraine (Palevitch *et al.*, 1997; Murphy *et al.*, 1988; Johnson *et al.*, 1985). A recently published literature review concludes that the efficacy of feverfew for the prevention of migraine has not been established beyond reasonable doubt (Pittler *et al.*, 2000). One trial found that feverfew did not benefit women with rheumatoid arthritis (Patrick *et al.*, 1989).

BRANDED PRODUCTS

Studies conducted were based on generic, not specific products.

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Clinical Studies on Feverfew (*Tanacetum parthenium* [L.] Schultz Bip.)

Migraine Prophylaxis

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
de Weerd et al., 1996	Migraine	R, DB, PC, CO n=44 men and women with migraine at least 1x/month	9 months: 1 placebo capsule/day for 1 month; 4 months feverfew, and 4 months placebo	One, 143 mg capsule/day	Dried alcoholic extract of feverfew leaves providing 0.5 mg of parthenolide per capsule, prepared by investigators	Feverfew did not reduce the number of migraine attacks. However, patients taking feverfew had a tendency to use fewer symptomatic drugs during the period they took feverfew. Note: It is very likely that this extract and/or its method of preparation caused degradation of active constituents.
Palevitch et al., 1997	Migraine	R, DB, CO (there was also an O phase for the first 2 months) n=57 men and women with migraine	4 months (Group A: 3 months feverfew followed by 1 month placebo. Group B: 2 months feverfew followed by 1 month placebo, then an additional 1 month feverfew. No washout periods.)	One, 50 mg capsule 2x/day or placebo (chopped parsley)	50 mg of dried powdered leaves packed in gelatin capsules. 0.2% parthenolide content, prepared by investigators	Feverfew caused a significant ($p<0.01$) reduction in pain intensity ($p<0.001$). There was a significant ($p<0.017-0.001$) reduction in vomiting, nausea, sensitivity to noise, and sensitivity to light.
Anderson et al., 1988	Migraine	O, C, RS n=60 women with history of common or classical migraine for at least 2 years	30 of the patients had been using feverfew daily for at least 11 consecutive months; 30 of the patients were non-users	Varied, patients were self-dosing	This study examined blood and urine, and did not dispense feverfew. Patients self-administered raw feverfew leaves, or dried leaves in capsules or tablets	Prophylactic use of feverfew by migraine sufferers did not result in increases in chromosomal aberrations or sister chromatid exchanges in peripheral lymphocytes, nor did it produce mutagenic urine. The effect of feverfew on migraine was not examined.
Murphy et al., 1988	Migraine	R, DB, PC, CO n=60 men and women with migraine	9 months (1 month single-blind placebo-run-in, 4 months feverfew, 4 months placebo)	70–114 mg capsule/day (mean 82 mg) (amount of powder varied with the strength of the preparation, as judged by its anti-secretory activity) or placebo (dried cabbage)	Dried feverfew leaves in capsules (2.19 mmol parthenolide) prepared by investigators, or placebo	Feverfew was associated with reduced number and severity of attacks. However, the duration of the attacks was unaltered. Feverfew caused a significant reduction in nausea and vomiting ($p<0.02$). No serious side effects were reported.
Johnson et al., 1985	Migraine	R, DB, PC n=17 patients with migraine who had been self-administering raw feverfew leaves daily for at least 3 months	6 months	One, 25 mg capsule 2x/day	Capsules contained 5 freeze-dried feverfew leaflets weighing 25.7 mg, prepared by investigators	Feverfew taken prophylactically reduced the frequency and severity of symptoms of migraine ($p<0.02$), but not the duration of attacks. Feverfew also reduced incidence of nausea/vomiting ($p<0.05$). During months 3–6 the patients taking dried feverfew had the same number of attacks as when they were taking fresh feverfew. In contrast, the patients taking the placebo had a relapse and experienced a significant increase in the frequency and severity of migraines and associated symptoms of nausea and vomiting.

Arthritis

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Patrick et al., 1989	Rheumatoid arthritis	R, DB, PC n=41 women with classical or definite rheumatoid arthritis (ages 28–65 years)	6 weeks	70–86 mg/day (mean 76 mg) or placebo (cabbage)	Dry, powdered leaf (equivalent to 2–3 μ mol parthenolide), prepared by investigators	No differences observed between the groups. No apparent benefit from oral feverfew for rheumatoid arthritis.

KEY: C – controlled, CC – case-control, CH – cohort, CI – confidence interval, Cm – comparison, CO – crossover, CS – cross-sectional, DB – double-blind, E – epidemiological, LC – longitudinal cohort, MA – meta-analysis, MC – multi-center, n – number of patients, O – open, OB – observational, OL – open label, OR – odds ratio, P – prospective, PB – patient-blind, PC – placebo-controlled, PG – parallel group, PS – pilot study, R – randomized, RC – reference-controlled, RCS – retrospective cross-sectional, RS – retrospective, S – surveillance, SB – single-blind, SC – single-center, U – uncontrolled, UP – unpublished, VC – vehicle-controlled.