

The efficacy and safety of feverfew (*Tanacetum parthenium* L.): an update of a systematic review*

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Abstract

Objective: Feverfew (*Tanacetum parthenium* L.) is a popular herbal remedy often advocated for the prevention of migraine. The aims of this systematic review are to update the evidence from rigorous clinical trials for or against the efficacy of feverfew for migraine prevention and to provide a safety profile of this herbal remedy.

Design: Literature searches were performed using the following databases: Medline, Embase, Biosis, CISCOM and the Cochrane Library (all from their inception to December 1999). Only randomized, placebo-controlled, double-blind trials of feverfew mono-preparations for the prevention of migraine in human subjects were included. All articles were read by two independent reviewers. Data were extracted in a pre-defined, standardized fashion. The methodological quality of the trials was evaluated by the Jadad score. For the assessment of safety issues, major reference texts were also consulted.

Results: Six trials met the inclusion/exclusion criteria. The majority favour feverfew over placebo. Yet important caveats exist. The data also suggest that feverfew is associated with only mild and transient adverse effects and few other safety concerns.

Conclusions: Feverfew is likely to be effective in the prevention of migraine. There are no major safety problems.

Keywords
Feverfew
Migraine
Herbal medicine
Prevention
Alternative medicine

The usage of herbalism by the general US population increased by a staggering 480% between 1990 and 1997; in 1990 the 1-year prevalence was 2.5% while in 1997 it had risen to 12.1%. Herbalism is most commonly employed for allergies, insomnia, respiratory problems and digestive problems. The out-of-pocket expenditure amounted in 1997 to \$5.1 billion¹. Faced with this remarkable revival of medical herbalism, mainstream healthcare professionals feel the need to familiarize themselves with this subject. The most pressing questions are whether herbal medicinal products (HMPs) are effective and safe.

Feverfew (*Tanacetum parthenium* L.) has traditionally been used as an HMP for fever, women's ailments, inflammatory conditions, psoriasis, toothache, insect bites, rheumatism, asthma and stomach-ache. During the last decades, it has been increasingly employed as a

remedy for migraine prophylaxis. The sesquiterpene lactone parthenolide has been suggested as its main active component. Its role in migraine prophylaxis was supported by *in vitro* studies suggesting inhibition of serotonin release from blood platelets (e.g. Ref. 2). A recent study, however, seems to contradict this notion³.

Regardless of these and other uncertainties, the crucial questions are, does feverfew work and is it safe? This systematic review is aimed at updating the current evidence from randomized controlled trials (RCTs) for or against the clinical efficacy of feverfew for migraine prophylaxis and at assessing the safety profile of this herbal remedy.

Methods

Systematic literature searches were performed to identify all RCTs of feverfew. Independent searches were conducted in the following electronic databases: Medline, Embase, Biosis, CISCOM and the Cochrane Library (all from their respective inception to December 1999). The

*A previous version of a similar paper was first published in 1998 (Vogler BK, Pittler MH, Ernst E. Feverfew as a preventive treatment for migraine: a systematic review. *Cephalalgia* 1998; **18**: 704–8).

Table 1 Double-blind, placebo-controlled RCTs of feverfew for migraine prevention

First author [reference]	Jadad score (max: 5)	Design	Patients entered/sample size (age; years)	Medication	Length of medication (months)	Main outcome measures	Result	Comments
Johnson <i>et al.</i> [5]	4	Two parallel groups	17/17 (n.r.)	Two capsules (25 mg) of powdered feverfew per day	6	Frequency of headache Incidence of nausea and vomiting	Frequency of headache increased significantly ($P < 0.02$) in patients receiving placebo compared with baseline values Significant inter-group differences in favour of feverfew ($P < 0.05$) for the incidence of nausea, vomiting	All patients had taken feverfew daily for the previous 3–4 years Small sample size
Murphy <i>et al.</i> [6]	4	Crossover	72/59 (24–72)	One capsule (mean weight: 82 mg) of powdered feverfew per day	4	Frequency, duration and severity of headache Incidence of nausea and vomiting	24% reduction ($P < 0.005$) in attack frequency Significant reduction ($P < 0.002$) of nausea and vomiting No change in duration and severity of headache	Inhomogeneous patients sample with respect to former use of feverfew One-month placebo run-in No wash-out period Subgroup analysis in classical/common migraine
Kuritzky <i>et al.</i> [8]	*	Crossover	20/n.r. (18–60)	100 mg feverfew per day	2	Effect of feverfew on serotonin uptake and platelet activity	No effect	Reported only as abstract Small sample size No mention of details of feverfew preparations, further outcome measures or withdrawals
Weerdts <i>et al.</i> [3]	5	Crossover	50/44 (18–64)	One capsule (143 mg) of granulated feverfew per day	4	Severity of headache attacks Number of work days lost	No significant effect in either outcome measure	Different drug preparation One month placebo run-in period No wash-out periods
Palevitch <i>et al.</i> [7]	3	Crossover	57/57 (9–65)	Two capsules (50 mg) of powdered feverfew per day	1	Pain intensity Severity of nausea, vomiting Sensitivity to noise and light	Significant reduction ($P < 0.01$) in each outcome measure	Both groups were treated with feverfew in the preliminary period for 60 days No wash-out period No mention of the patients' migraine history, inclusion criteria or withdrawals
Pfaffenrath <i>et al.</i> [9]	*	Four parallel groups	147/49	A. 2.08 B. 6.25 C. 18.75 mg extract 3×/day D. placebo	3	Frequency of migraine attacks	Significant reduction	Dose–response relationship observed

n.r., not reported.

* Cannot be calculated (abstract only).

search terms were feverfew, *Tanacetum parthenium*, *Chrysanthemum parthenium*, Mutterkraut (the German common name), headache and migraine. A manual search was performed using the bibliographies of articles located through the computer search and through scanning our own files. In addition, leading manufacturers of feverfew preparations were contacted and asked to contribute published and unpublished material.

Only double-blind, placebo-controlled RCTs of feverfew for migraine prophylaxis were included. Studies were excluded if not performed on feverfew mono-preparations. There were no restrictions regarding publication language. Data were extracted independently by two reviewers following a standardized, predefined procedure. Methodological quality was assessed using the Jadad score⁴. A meta-analysis was considered but proved to be infeasible due to the lack of a common outcome measure across the studies.

Results

Efficacy

Six clinical studies met the above inclusion/exclusion criteria (Table 1). All trials scored at least 2 of 5 points on the Jadad score. Four studies reporting positive results favouring feverfew scored 3–4 points on the quality scale^{5–7,9}. One of the two negative trials scored 5 points³ (Table 1).

Johnson *et al.*⁵ conducted a trial including 17 patients who had consumed raw feverfew leaves every day for the previous 3–4 years. Patients were randomized to receive either two capsules of freeze-dried feverfew leaves daily (50 mg) or identical placebo for 24 weeks. During the trial period all patients graded severity and frequency of headache, visual disturbance, incidence of nausea and vomiting on diary cards. A significant increase of mean attack frequency per month was observed in the placebo group compared with baseline measurements ($P < 0.02$), while this parameter remained constant in patients receiving feverfew. Five of eight patients from the feverfew group reported good to excellent effectiveness, while this was reported by only one patient in the placebo group.

Murphy *et al.*⁶ randomized 72 patients to receive either one capsule of feverfew or placebo for 4 months after a 1-month placebo run-in period. Patients were subsequently crossed over into the other group for the second 4-month period. Feverfew treatment was associated with a 24% reduction ($P < 0.005$) in attack frequency and a significant decrease ($P < 0.02$) in migraine-associated nausea and vomiting compared with placebo. In patients with common migraine, feverfew reduced the number of attacks by 21% ($P = 0.06$) while it was reduced by 32% ($P < 0.05$) in patients with classical migraine.

Kuritzky *et al.*⁸ assessed the effect of feverfew on serotonin uptake and platelet activity in 20 migraine patients. Each patient received 100 mg of feverfew or placebo daily for 2 months. No effect on serotonin uptake and platelet activity was found. Without providing details

of clinical data, the authors concluded: '100 mg of feverfew a day was found to be ineffective in the prophylaxis of migraine'.

Weerdt *et al.*³ administered either one capsule of an alcoholic feverfew extract or placebo to 50 patients in a crossover RCT. A 1-month placebo run-in phase was followed by two treatment periods of 2 months each. The frequency of headache attacks and the number of work days lost were reported in a daily calendar. The results showed no statistically significant beneficial effect of feverfew compared with placebo.

A crossover trial conducted by Palevitch *et al.*⁷ included 57 migraine patients. During the preliminary phase of this study each patient was treated with 100 mg feverfew daily for 2 months. Thereafter, one group received placebo for an additional 30 days while the other group continued taking feverfew. In the third phase, the treatment group was crossed over to the placebo arm and *vice versa*. Pain intensity and severity of the accompanying symptoms such as nausea, vomiting and sensitivity to noise and light were reported. The results of the preliminary phase showed a significant decrease in pain intensity after the treatment with feverfew compared with baseline ($P < 0.001$). In the crossover phase, a significant reduction of pain intensity was reported in the treatment group compared with the placebo group ($P < 0.01$). There was also a significant reduction in the severity of nausea and vomiting in favour of feverfew.

Pfaffenrath *et al.*⁹ conducted a double-blind, placebo-controlled, multicentre RCT which, so far, has only been published as an abstract (for this reason no Jadad score was attributed to this study). Three dosage regimens (2.08 mg vs. 6.25 mg vs. 18.75 mg, each 3 times per day administered for 12 weeks) of a novel CO₂ feverfew extract were compared with placebo. One hundred and forty seven patients with migraine (according to International Headache Society criteria) were enrolled. The primary endpoint had been pre-defined as the total number of migraine attacks during the last 28 days of treatment compared with the 4-week baseline period. The results showed significant effects compared with placebo and a dose-response relationship. The optimal effectiveness was noted with 3 × 6.25 mg extract per day. The authors concluded that this extract was 'particularly effective in migraine prophylaxis in patients with at least 4 attacks during 28 days prior to onset of prophylaxis'.

Safety

Adverse effects, as reported in the above trials, are summarized in Table 2. Feverfew was generally well tolerated and adverse effects were usually mild and reversible. Two studies^{5,6} reported a higher and one trial⁹ a similar incidence of adverse effects in the placebo group compared with the feverfew group. In total, three withdrawals were necessitated by adverse effects in the feverfew groups compared with five in the placebo groups.

Table 2 Adverse effects of feverfew as reported in RCTs

First author [reference]	Type of adverse effect	Withdrawals (feverfew/placebo)	Comments
Johnson <i>et al.</i> [5]	Nervousness, tension headache, insomnia, stiffness in joints, tiredness, nausea, heavier or lighter periods, palpitations, colicky abdominal pain	(0/2)	All patients taking placebo reported one event with adverse effects, whereas four patients taking feverfew reported none
Murphy <i>et al.</i> [6]	Mouth ulceration, indigestion, heartburn, dizziness, skin rash, diarrhoea, abdominal bloating, sore mouth, weight gain, flatulence, nausea, constipation	(2/3)	Mouth ulceration was more common with placebo
Kuritzky <i>et al.</i> [8]	n.r.	n.r.	Only reported in abstract form
Weerd <i>et al.</i> [3]	Diarrhoea	(1/0)	None
Palevitch <i>et al.</i> [7]	n.r.	n.r.	None
Pfaffenrath <i>et al.</i> [9]	Minor GI symptoms	n.r.	Only reported in abstract form

n.r., not reported.

A 'post-feverfew syndrome' has been described after allocating patients who previously were taking feverfew to placebo treatment⁵. Feverfew did not appear to affect blood pressure, heart rate, body weight, or the results of haematological and biochemical safety parameters.

Sources other than the above-mentioned RCTs need to be consulted to generate reliable information on the safety of feverfew. Information from several recent reference texts^{10–15} has been extracted and is summarized in Table 3. These cumulative data suggest that feverfew is not entirely free of risks but that adverse effects are usually transient and mild.

Discussion

In view of the popularity of feverfew, the paucity of the existing RCTs on the subject is disappointing. Most of the studies that exist are not fully satisfactory in terms of methodological quality. Collectively, however, the data do

imply that feverfew is effective in preventing migraine attacks.

While the study with the highest Jadad score³ showed no beneficial effects, four of the six trials^{5–7,9} favoured feverfew. Amongst the four trials with an acceptable sample size¹⁶, three studies^{6,7,9} reported feverfew to be superior to placebo while one³ did not. The frequency of migraine was positively affected by feverfew in three trials^{5,6,9}. Feverfew reduced the severity of migraine in one trial⁷ while two studies^{3,6} reported no such effect. The incidence of nausea and vomiting was positively affected in two^{5,6} of four trials, while severity was reduced in one study⁷.

It is often assumed that parthenolide represents the active principal of feverfew. This hypothesis is supported by *in vitro* experiments demonstrating that feverfew has inhibitory effects on platelet aggregation as well as release of serotonin from blood platelets and leucocytes^{8,17}. Feverfew also inhibits prostaglandin biosynthesis¹⁸ by interfering with phospholipase A¹⁹. However, a definitive

Table 3 Risks of feverfew – information from major recent reference texts

Adverse effects	Cautions and contraindications	Drug interactions
Abdominal pain	Children under 12 years	Enhanced effects of platelet inhibitors
Bitter taste*	Not longer than for 4 months	Effect reduced when taken with NSAIDs
Contact dermatitis	Known hypersensitivity	
Diarrhoea	Pregnancy/lactation	
Dry, sore tongue*	Feverfew is not effective in treating acute migraine attacks	
Fatigue†		
Flatulence		
GI symptoms		
Indigestion		
Inflammation of lips or tongue*		
Joint pain†		
Loss of taste*		
Mouth ulceration*		
Nausea/vomiting		
Nervousness†		
Swollen lips*		
Tension†		

* Not when taken in capsules.

† During feverfew withdrawal.

link between the aetiology of migraine and parthenolide or any other feverfew constituent has not been established beyond reasonable doubt. One trial using an extract of feverfew with a standardized concentration of parthenolide did not show any beneficial effect³. This lack of effectiveness may be due to the absence of essential therapeutic components of the granulated feverfew leaves³. A divorce from the serotonin inhibition theory might lead to more attention being given to the other components of the feverfew leaf²⁰. This is supported by a study²¹ that states a secondary role of serotonin in the aetiology of migraine. The results of the Dutch study³ suggested that the essential oil constituent of feverfew, chrysanthemyl acetate, may be important. This component inhibits prostaglandin synthetase *in vitro* and seems to possess analgesic properties¹⁸. Other investigators also agree that parthenolide is not the only pharmacological active constituent in feverfew^{22,23}. A link between the relatively high concentration of melatonin in different feverfew varieties²⁴ and a decrease in melatonin excretion during migraine attacks has been suggested²⁵. An alternative explanation for negative trial results is offered by the fact that some commercial preparations are underdosed, possibly due to the instability of the active constituents in these extracts²⁶.

How safe is feverfew? Chronic prophylactic use of feverfew did not affect the frequency of chromosomal aberration in lymphocytes or urine mutagenicity²⁷. Anecdotal reports relate to contact dermatitis (e.g. Refs. 28 and 29). In the RCTs reviewed here, adverse effects were generally mild and reversible. Mouth ulceration and gastrointestinal symptoms were the most frequent adverse effect, also experienced by long-term feverfew users³⁰. Obviously such problems can be avoided through adequate galenic design of the HMP. A 'post feverfew syndrome' including a rebound of migraine symptoms, anxiety, insomnia, and muscle and joint stiffness was reported by long-term consumers after discontinuation of feverfew⁵.

How useful are systematic reviews? SRs minimize selection and random biases, yet they are not totally bias-free. The tendency for negative trials to remain unpublished is well known³¹. Conversely, in journals of complementary or alternative medicine positive studies may be over-represented^{32,33}. Such publication biases may distort the overall result of SRs. Other problems of SRs of HMPs pertain to the heterogeneity of extracts and the often low methodological quality of the original trials. Nevertheless, at my department we firmly believe that SRs of HMPs do offer a valuable step forward and have therefore conducted numerous SRs similar to the one presented here. This work has been recently summarized elsewhere³⁴.

In conclusion, the results of RCTs favour feverfew over placebo as a preventive treatment for migraine. However, several caveats prevent firm conclusions as to the efficacy of feverfew. Major safety problems do not seem to exist.

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