Drugs of the Future 1999, 24(12): 1339-1343

CCC: 0377-8282/99

Review Article

Feverfew: ancient remedy for multiple disorders

S.K. Kulkarni *** and N.K. Jain***

Pharmacology Division, University Institute of Pharmaceutical Sciences, Panjab University, Chandigarh 160014, India.
**Correspondence*

CONTENTS

Introduction 1339
Pharmacognosy 1339
Chemical constituents 1340
Pharmacology 1340
Antimigraine activity 1340
Antiinflammatory activity 1340
Miscellaneous activities 1341
Dose and administration 1341
Side effects and toxicity 1342
Contraindications 1342
Future perspectives 1342
Conclusions 1342
References 1342

Introduction

Herbal pharmacology is gaining importance as more and more age-old remedies are being introduced on the international market. In the last decade, there has been increased interest in the ancient herb *Tanacetum parthenium* (L.) Sch. Bip. (Asteraceae family), which is also known as *Chrysanthemum parthenium*, *Leucan themum parthenium*, *Pyrethrum parthenium* and, more commonly, feverfew (Fig. 1). Feverfew is widely used as a herbal remedy especially for the prophylactic treatment of migraine headache (1). Because of its beneficial medicinal properties seen since ancient times, the plant is also known as the “medieval aspirin” (2, 3).

The origin of the word *parthenium* has been ascribed to the ancient Greek author Plutarch in reference to an incident where feverfew was used to save the life of someone who had fallen from the Parthenon during its construction in the 5th century (4). The term also may come from the Greek word *parthenios* meaning “virgin”, presumably because of the herb’s use as a treatment for women’s ailments such as threatened miscarriage, regulation of menses and difficulties in labor. Historically, the herb has been claimed to cure a wide variety of ailments including psoriasis, toothache, insect bites, rheumatism, asthma, stomachache and menstrual problems (2, 5, 6). In recent years, feverfew has been extensively investigated in Canada and Europe (7). The present review describes the pharmacological properties of this traditional herb in the treatment of various disorders.

Pharmacognosy

The botanical features of feverfew have been reviewed by Berry (5). Feverfew is a common perennial herb growing to a height of 14-45 cm with an erect, ridged downy stem and strong smelling greenish-yellow leaves; the plant grows in hedges and waste areas throughout much of Europe and has long been cultivated both as an ornamental and medicinal plant. The upper leaves have short stalks and the lower cauline leaves are more or less ovate, long stalked and pinnate. The plant has a flower head with a common axis bearing several daisy-like, stalked flowers which are elongated so that the top of the flower head is nearly flat. Each flower has yellow central disc florets and a single layer of outer white ray florets. Ray florets are short and broad with 2-7 mm ligules, and female or disc flowers are tubular and hermaphrodite. Feverfew can be easily identified microscopically by the presence of characteristic glandular trichomes which are not found in other species but are similar to those found in the Asteraceae family (8). Also present are nonglandular trichomes which are large, multicellular and uniseriate with a dome-shaped basal cell. Both types of trichomes are found on the interneural lamina and above the veins of both epidermis (9).

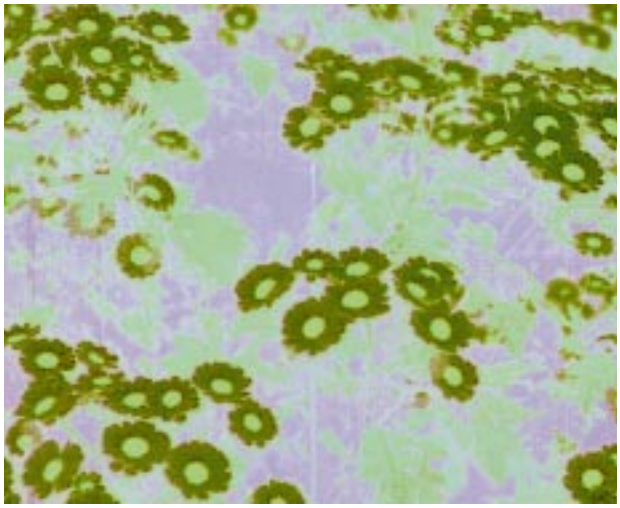

Fig. 1. *Tanacetum parthenium* (feverfew).

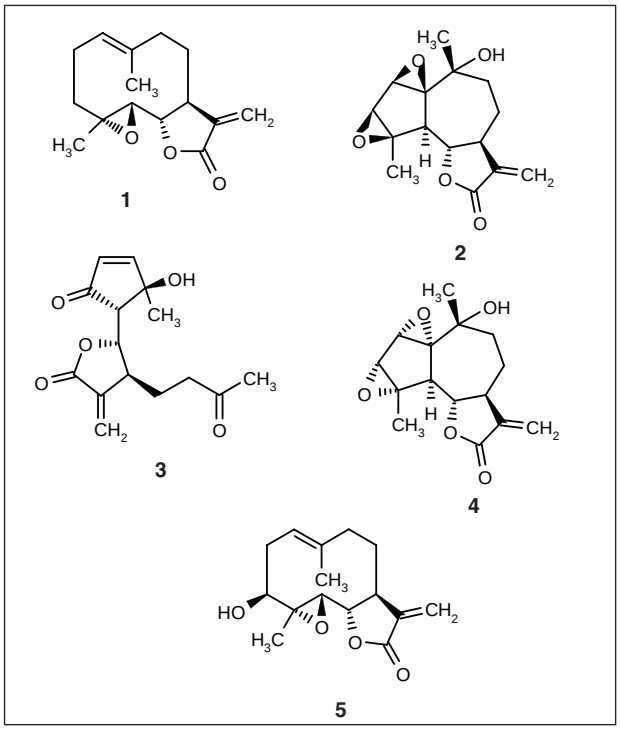

Fig. 2. Active components isolated from feverfew (5).

Chemical constituents

The phytochemistry of feverfew has been studied by several different groups (10, 11). Bohlman and Zdero (11) reported the presence of 39 terpene derivatives, 3 pinene derivatives, 2 spirochetal and enoletherpolyines, 4 germacranolides and 6 guainolides of which 2 are endoperoxides and another 2 are secoguainolides.

The aerial parts of feverfew are a source of many types of sesquiterpene lactones such as parthenolide (**1**), canin (**2**), secotanapartholide (**3**), artecanin (**4**) and 3β-hydroxyparthenolide (**5**) having α-methylene butylrolactone moiety (Fig. 2). These components are also present in the roots of the plant (5). Parthenolide is considered to be the most important biologically active component of feverfew (1, 12, 13) and was first isolated by Vivar (14). Concentrations of parthenolide can be as high as 1% in dried leaves and are highest at an early stage, just before formation of the stem. The yield of parthenolide per individual plant gradually increases from about 10 mg to 20 mg when the plant is in full bloom (15) (Fig. 3).

Recently, Murch *et al.* (16) reported the presence of melatonin in various feverfew samples (*T. parthenium*, 2.45 mcg/g) and commercial preparations (Tanacet tablet; 70-80 ng/tablet). A biologically active lipophilic flavonol, tanetin (6-hydroxykaempferol 3,7,4'-trimethyl ether), has been characterized in the leaf, flower and seeds of feverfew. It co-occurs with the known 6-hydroxykaempferol 3,7-dimethyl ether, quercetangetin 3,7- dimethyl ether and quercetagetin 3,7,3'-trimethyl ether (17).

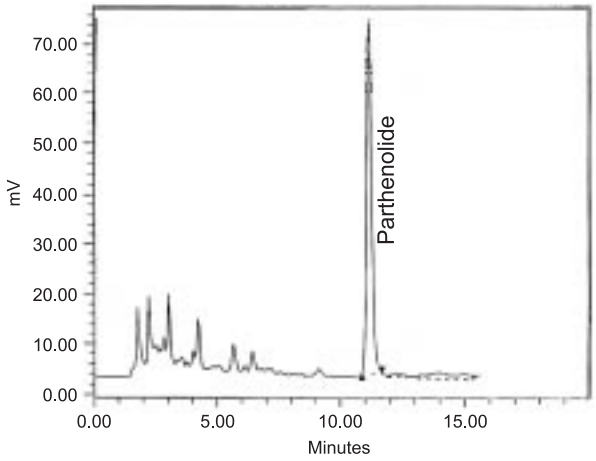

Fig. 3. HPLC pattern of feverfew extract.

Pharmacology

Antimigraine activity

The beneficial effects of feverfew in migraine prophylaxis have been demonstrated in various clinical studies (12, 13, 18) and several mechanisms have been proposed for its therapeutic effect on migraine (19). Migraine is a complex neurovascular disorder and several studies have suggested that 5-HT and its receptor systems play key roles in its pathophysiology (20, 21). Feverfew has been shown to inhibit human blood platelet aggregation and secretory activity in platelets and polymorphonuclear leukocytes (22, 23). Sesquiterpene lactones containing an α-methylene butyrolactone moiety such as parthenolide and feverfew extract caused significant depletion of intracellular reduced glutathione which resulted in a change in arachidonic acid metabolism and alkylation of protein sulphydryl group through Michael-type nucleophilic addition (24, 25). Groenewegen *et al.* (26, 27) reported that parthenolide and feverfew extract inhibited 5-HT secretion but not phorbol-12-myristate-13-acetate-induced platelet aggregation, suggesting that there may be interactions between parthenolide and protein kinase C. Weber *et al.* (1) have reported that parthenolide has 5-HT_{2A} antagonistic activity which may contribute to its prophylactic potential in migraine therapy. Parthenolide was also shown to nonselectively render smooth muscle less responsive to endogenous substances such as noradrenaline, acetylcholine, bradykinin, prostaglandins, histamine and serotonin in a noncompetitive manner (28). These antagonistic properties are consistent with an antimigraine effect occurring via inhibition of extracellular calcium influx into vascular smooth muscle cells.

Antiinflammatory activity

Feverfew has been reputed to be beneficial in inflammatory conditions and to have fever reducing properties.

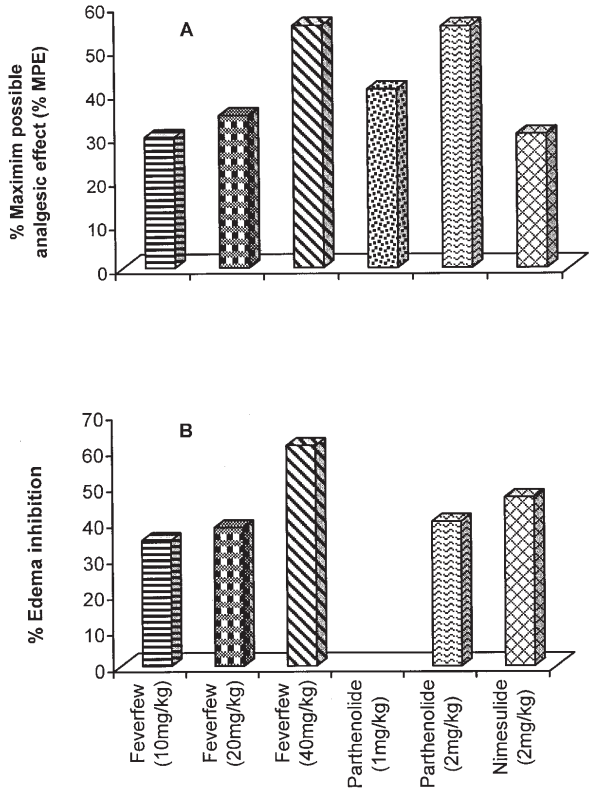

Fig. 4. (A) Analgesic effect (% MPE) of feverfew extract (10, 20 and 40 mg/kg p.o.), parthenolide (1 and 2 mg/kg p.o.) and nimesulide (2 mg/kg p.o.) against acetic acid-induced chemonociception in mice. (B) Antiinflammatory effect (1% edema inhibition) of feverfew extract (10, 20 and 40 mg/kg p.o.), parthenolide (2 mg/kg p.o.) and nimesulide (2 mg/kg p.o.) in carrageenan-induced paw edema in rats.

Thus, several studies have been carried out examining the effects of feverfew extract on prostaglandin biosynthesis. Collier *et al.* showed that an aqueous extract of the plant blocked prostaglandin production derived from arachidonic acid metabolism *in vitro* without blocking the cyclooxygenase pathway (29). Hall *et al.* reported that sesquiterpene lactones with an α-methylene butyrolactone moiety showed good antiinflammatory action against carrageenan-induced inflammation and analgesic activity against writhing reflux (24). Their study was supported by a recent one in which parthenolide and feverfew were shown to exert analgesic and antiinflammatory activity in mice and rats, respectively (30) (Fig. 4).

Parthenolide and other sesquiterpene lactones in feverfew produce the compound's antiinflammatory activity due to alpha-methylene butylrolactone moieties which undergo Michael-type nucleophilic addition with L-cysteine, glutathione and a number of sulphydryl bearing cell enzymes (biological nucleophiles) (26, 31-33).

Pugh and Sambo (34) showed that the aqueous extract of feverfew inhibited cyclooxygenase and lipoxygenase controlled pathways and 5-HT secretion from polymorphonuclear leukocytes and platelets in inflamed joints. This would account for the beneficial effects of feverfew seen in arthritis since cyclooxygenase and lipoxygenase are found in synovial fluid. Tanetin could also contribute to the antiinflammatory properties of feverfew by inhibiting the generation of proinflammatory eicosanoids (17). The inhibitory effects of feverfew on secretion of enzymes by polymorphonuclear leukocytes have been shown to be significantly more pronounced than those of nonsteroidal antiinflammatory drugs such as indomethacin (5). Hwang *et al.* (35) reported that sesquiterpene lactones (*i.e.*, parthenolide) have an inhibitory effect on the expression of cyclooxygenase-2 and cytokines, which could explain the antiinflammatory effects of feverfew.

Miscellaneous activities

Sesquiterpenes lactones have been reported to possess antitumor and cytotoxic activities (36). Their cytotoxicity is due to the presence of an α-methylene-γ-lactone and α,β-unsaturated ketonic moiety. Parthenolide was reported to be cytotoxic at 0.45 μg/ml in nasopharynx carcinoma (37), whereas dihydroparthenolide was not effective. Recently, Ross *et al.* (38) reported that parthenolide at low concentrations inhibited tumor cell growth *in vitro* (mouse fibrosarcoma MN-11 and human lymphoma TK-6) in a cytostatic manner over multiple cell generations. Parthenolide has also been shown to be antimicrobial in studies in which it inhibited growth of Gram-positive bacteria, yeasts and filamentous fungi *in vitro* (39, 40).

Feverfew extract was shown to protect the endothelial cell monolayer of aorta segments from perfusion-induced injury which led to a reversible increase in the cAMP content. Furthermore, feverfew inhibited platelet deposition on collagen substrate, indicating that it may have antithrombotic potential as well (41).

Dose and administration

Feverfew can be given either as the fresh leaf or dried powder in capsule or tablet formulations. The daily recommended dose for migraine prophylaxis is two and one-half leaves or 50 mg of powder (4, 12). Canada's Health Protection Branch recommends a daily dosage of 125 mg of authenticated dried feverfew leaf preparation containing at least 0.2% parthenolide for the prevention of migraine (42). However, studies have reported that various feverfew formulations differ in parthenolide content (42). Moreover, appropriate duration of treatment has not been established and users who have taken feverfew continuously for more than 3 years are advised to discontinue treatment for at least 1 month per year (4).

Table I: Side effects documented for feverfew.

Symptoms	Incidence %
Mouth ulcers/sore tongue	6.4
Abdominal pain/indigestion	3.9
Unpleasant taste	3.0
Tingling sensation	0.9
Urinary problems	0.9
Headache	0.9
Swollen lips/mouth	0.4
Diarrhea	0.4
Nausea/vomiting	2.4
Allergy	0.6
Disturbance of vision	0.6
Flatulence	0.6
Menstrual disorders	0.6
Skin rash	0.6
"Post-feverfew syndrome"	
Nervousness/tension	55.6
Tension headaches	33.3
Insomnia	22.2
Stiffness/pain in joints	33.3
Fatigue	22.2

Side effects and toxicity

No major adverse effects have been documented for feverfew. Side effects occurred in 17.9% (48/270) of the migraine patients surveyed by Johnson (4, 12), with mouth ulcers, abdominal pain and unpleasant taste being the most frequent (Table I). The onset of side effects can vary between 1 week and 2 months. A "post-feverfew syndrome" upon withdrawal, characterized by nervousness, tension, insomnia, tiredness, joint stiffness and pain has also been reported (7). Hypersensitivity reactions to feverfew resulting from repeated external contact and manifested as allergic contact dermatitis have also been frequently reported. This reaction may be due to alpha-methylene butyrolactones since it is a common feature of this group following Michael-type addition mechanisms (43).

No adverse effects were demonstrated in experimental animals after the administration of feverfew at 100-150 times the comparable human daily dose (4). No chronic toxicity studies have been reported.

Contraindications

Canadian authorities have advised consumers not to take feverfew for more than 4 months without the advice of a physician due to lack of precise information regarding potential long-term toxicity (42). Feverfew is contraindicated in pregnant and lactating mothers based on the traditional view that it acts as an abortifacient and emmenagogue (7). It was recently reported that feverfew may alter bleeding time, so it should not be used concomitantly with anticoagulants such as warfarin (44).

Future perspectives

It is well established from several clinical studies (12, 13, 18) that feverfew has therapeutic value in migraine prophylaxis. The pharmacotherapy of migraine is being investigated in order to determine a definitive chemical link between mediators and their receptors involved in its pathophysiology. Studies on the therapeutic use of feverfew in the management of migraine and its mechanism of action and possible interactions are warranted. Other indications for feverfew remain to be fully established. Since the parthenolide content of feverfew products varies (45), analytical validation of parthenolide content should be performed as a means of standardization and quality control.

Conclusions

Parthenolide, a principle sesquiterpene lactone containing α-methylene butyrolactone moiety, is responsible for the effect of feverfew in migraine prophylaxis. The pharmacological action of feverfew is due to inhibition of 5-HT release from platelets, possibly via neutralization of sulphydryl groups on specific enzymes that are fundamental to platelet aggregation and secretion. Extended pharmacodynamic studies on feverfew should elucidate new indications for its therapeutic use.

References

1. Weber, J.T., 0'Connor, M.F., Hayataka, K., Colson, N., Medora, R., Russo, E.B., Parker, K.K. *Activity of parthenolide at 5-HT$_{2A}$ receptors.* J Nat Prod 1997, 60: 651-3.

2. Groenwegen, W.A., Knight, D.W., Heptinstall, S. *Progress in the medicinal chemistry of feverfew.* Prog Med Chem 1992, 29: 217-36.

3. Heptinstall, S. *Feverfew - An ancient remedy for modern times.* J Roy Soc Med 1988, 81: 373-4.

4. Johnson, S. (Ed.). Feverfew - A Traditional Herbal Remedy for Migraine and Arthritis. Sheldon Press: London 1984.

5. Berry, M. *Feverfew.* Pharm J 1994, 253: 806-8.

6. Berry, M.I. *Feverfew faces the future.* Pharm J 1984, 232: 611-4.

7. Baldwin, C.A., Anderson, L.A., Phillipson, J.D. *What pharmacists should know about feverfew.* Pharm J 1987, 239: 237-8.

8. Metcalfe, C.R., Chalk, L. (Eds.). Anatomy of the Dicotyledons. Oxford University Press: London 1950.

9. British Herbal Pharmacopoeia. Keighley: British Herbal Medicine Association, Keighley 1979, Part-II: 117.

10. Romo, J., Vivar, A., Trevino, R., Nathan, J.P., Diaz, E. *Constituents of artemisia and chrysanthemum species - The structure of chrystartemins A and B.* Phytochemistry 1970, 9: 1615-21.

11. Bohlman, F., Zdero, C. *Sequiterpene lactones and other constituents from Tanacetum parthenium.* Phytochemistry 1982, 21: 2543-49.

12. Johnson, E.S., Kadam, N.P., Hylands, D.M., Hylands, P.J. *Efficacy of feverfew as prophylactic treatment of migraine.* Br Med J 1985, 291: 569-73.

13. Murphy, J.J., Heptinstall, S., Mitchell, J.R.A. *Randomised double-blind placebo-controlled trial of feverfew in migraine prevention.* Lancet 1988, 2: 189-92.

14. Vivar, A., Jimenez, H. *Structure of santamarine a new sesquiterpene lactone.* Tetrahedron 1965, 21: 1741-5.

15. Hendriks, H., Wildeboer, Y.A., Engels, G., Bos, R., Woerdenbag, H.J. *The content of parthenolide and its yield per plant during the growth of Tanacetum parthenium.* Planta Medica 1997, 63: 356-9.

16. Murch, S.J., Simmons, C.B., Saxena, P.K. *Melatonin in feverfew and other medicinal plants.* Lancet 1997, 350: 1598-9.

17. Williams, C.A., Hoult, J.R., Harborne, J.B., Greenham, J., Eagles, J. *A biologically active lipophilic flavonol from Tanacetum parthenium.* Phytochemistry 1995, 38: 267-70.

18. DeWeerdt, C.J., Bootsma, H.P.R., Hendriks, H. *Herbal medicines in migraine prevention.* Phytomedicine 1996, 3: 225-30.

19. Marles, R.J., Kaminski, J. *A bioassay for inhibition of serotonin release from bovine platelets.* J Nat Prod 1992, 55: 1044-56.

20. Peroutka, S.J. *Antimigraine drug interactions with serotonin receptor subtypes in human brain.* Ann Neurol 1988, 23: 500-4.

21. Olesen, J. *Understanding the biological basis of migraine.* N Engl J Med 1994, 25: 1713-4.

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

23. Makheja, A.N., Bailey, J.M. *A platelet phospholipase inhibitor from the medicinal herb feverfew (Tanacetum parthenium).* Prostaglandins Leukotr Med 1982, 8: 653-60.

24. Hall, I.H., Lee, K.H., Starnes, C.O. et al. *Anti-inflammatory activity of sesquiterpene lactones and related compounds.* J Pharm Sci 1979, 68: 537-42.

25. Hewlett, M.J., Begley, M.J., Groenewegen, W.A. et al. *Sesquiterpene lactones from feverfew, Tanacetum parthenium: Isolation, structural revision, activity against human blood platelet function and implications for migraine therapy.* J Chem Soc Perkin Trans 1996, 1: 1979-86.

26. Groenewegen, W.A., Knight, D.W., Heptinstall, S. *Compounds extracted from feverfew that have anti-secretory activity contain an α-methylene butyrolactone unit.* J Pharm Pharmacol 1986, 38: 709-12.

27. Groenewegen, W.A., 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, 43: 553-7.

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

29. Collier, H.O.J., Buft, N.M., McDonald-Gibson, W.J., Saeed, S.A. *Extracts of feverfew inhibit prostaglandin synthesis.* Lancet 1980, 1: 922.

30. Jain, N.K., Kulkarni, S.K. *Antinociceptive and anti-inflammatory effects of Tanacetum parthenium L. extract in mice and rats.* J Ethnopharmacol, in press.

31. Hayes, N.A., Foreman, J.C. *The activity of compounds extracted from feverfew on histamine release from mast cells.* J Pharm Pharmacol 1987, 39: 466-70.

32. Heptinstall, S., Groenewegen, W.A., Spangeberg, P., Loesche, W. *Extracts of feverfew may inhibit platelet behaviour via neutralization of sulphydryl groups.* J Pharm Pharmacol 1987, 39: 459-65.

33. Sumner, H., Salan, U., Knight, D.W., Hoult, J.R. *Inhibition of 5-lipoxygenase and cyclooxygenase in leucocytes by feverfew. Involvement of sesquiterpene and other components.* Biochem Pharmacol 1992, 43: 2313-20.

34. Pugh, W.J., Sambo, K. *Prostaglandin synthetase inhibitors in feverfew.* J Pharm Pharmacol 1988, 40: 743-5.

35. Hwang, D., Fischer, N.H., Jang, B.C., Tak, H., Kim, J.K., 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.

36. Robles, M., Aregullin, M., West, J., Rodriguez, E. *Recent studies on the zoopharmacognosy, pharmacology and neurotoxicology of sesquiterpene lactones.* Planta Med 1995, 61: 199-203.

37. Ogura, M., Cordell, G.A., Farnsworth, N. R. *Anticancer sesquiterpene lactones of Michelia compressa (Magnoliaceac).* Phytochemistry 1978, 17: 957-96.

38. Ross, J.J., Arnason, J.T., Birnboim, H.C. *Low concentrations of the feverfew component parthenolide inhibit in vitro growth of tumor lines in cytostatic fashion.* Planta Med 1999, 65: 126-9.

39. Blakeman, J.P., Atkinson, P. *Antimicrobial properties and possible role in host pathogen interaction of parthenolide, a sesquiterpene lactone isolated from glands of Chrysanthemum parthenium.* Physiol Planta Pathol 1979, 15: 183-92.

40. Kalodera, Z., Pepaljnjak, S., Petrak, T. *The antimicrobial activity of Tanacetum parthenium.* Pharmazie 1996, 51: 995-6.

41. Losche, W., Mazurov, A.V., Heptinstall, S., Groenewegen, W.A., Repin, V.S., Till, U. *An extract of feverfew inhibits interactions of human platelets with collagen substrates.* Thromb Res 1987, 48: 511-8.

42. Awang, D.V.C. *Feverfew fever - A headache for the consumer.* Herbalgram 1993, 29: 217-36.

43. Knight, D.W. *Feverfew: Chemistry and biological activity.* Nat Prod Rep 1995, 271-6.

44. Miller, L.G. *Herbal medicinals: Selected clinical considerations focussing on known or potential drug-herb interactions.* Arch Intern Med 1998, 158: 2211-20.

45. Heptinstall, S., Awang, D.V.C., Dawson, B.A., Kindack, D., Knight, D.W., 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.