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A Systemic Review on Parthenolide

Om BabaraoKalyankar, Surekha Khamkar
Late N. B. Chabada Institute of Pharmacy, Satara, Maharashtra, India.

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ABSTRACT;
Feverfew (Tanacetumparthenium L.) (Asteraceae) is a medicinal plant traditionally used for the treatment of fevers, migraine headaches, rheumatoid arthritis, stomach aches, toothaches, insect bites, infertility, and problems with menstruation and labor during childbirth. The feverfew herb has a long history of use in traditional and folk medicine, especially among Greek and early European herbalists. Feverfew has also been used for psoriasis, allergies, asthma, tinnitus, dizziness, nausea, and vomiting. The plant contains a large number of natural products, but the active principles probably include one or more of the sesquiterpene lactones known to be present, including parthenolide. Other potentially active constituents include flavonoid glycosides and pinenes. It has multiple pharmacologic properties, such as anticancer, anti-inflammatory, cardiotonic, antispasmodic, an emmenagogue, and as an enema for worms. In this review, we have explored the various dimensions of the feverfew plant and compiled its vast pharmacologic applications to comprehend and synthesize the subject of its potential image of multipurpose medicinal agent. The plant is widely cultivated to large regions of the world and its importance as a medicinal plant is growing substantially with increasing and stronger reports in support of its multifarious therapeutic uses.

Keywords: Anti-inflammatory, migraine, parthenolide, Tanacetumparthenium

I. INTRODUCTION :

Feverfew (Tanacetum parthenium L.) belonging to the family Asteraceae (daisies) is a daisy-like perennial plant found commonly in gardens and along roadsides. The name stems from the Latin word febrifugia, “fever reducer.” The first-century Greek physician Dioscorides prescribed feverfew for “all hot inflammations.” Also known as “featherfew,” because of its feathery leaves. [1–2] It is a short, bushy, aromatic perennial that grows 0.3–1 m in height. Its yellow-green leaves are usually less than 8 cm in length, almost hairless, and pinnate–bipinnate (chrysanthemum-like). Its yellow flowers bloom from July to October, are about 2 cm in diameter. They resemble those of chamomile (Matricaria chamomilla), for which they are sometimes confused, and have a single layer of white outer-ray florets. [3–4] This aromatic plant gives off a strong and bitter odor. Its yellow-green leaves are alternate (in other words the leaves grow on both sides of the stem at alternating levels), and turn downward with short hairs. The small, daisy-like yellow flowers are arranged in a dense flat-topped cluster [Figure 1].

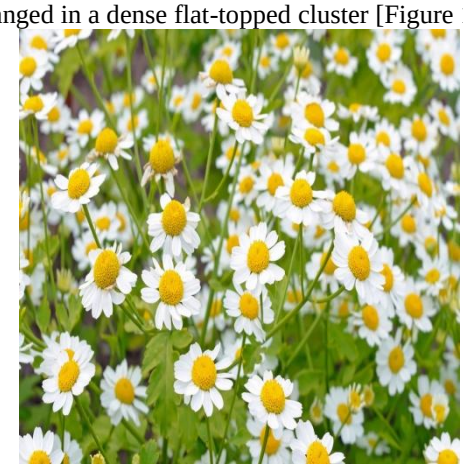

Fig.no-1 1

Botanical classification:
Kingdom: Plantae (Plants)
Subkingdom:Trachiobionta (Vascular plants)
Super division: Spermatophyta (Seed plants)
Division:Mangliophyta (Flowering plants)
Class: Magnoliopsida (Dicotyledons)
Subclass: Asteriidae
Order: Asterales
Family: Asteraceae (Aster family)
Genus: Tanacetum (tansy)
Species: Tanacetum parthenium (feverfew)

PHARMACOLOGICAL USES OF PARTHENOLIDE:
Anti-inflammatory activity:

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A proposed mechanism of action involves parthenolide specifically binding to and inhibiting IκB kinase complex (IKK)β. IKKβ plays an important role in pro-inflammatory cytokine-mediated signaling.[5]

Feverfew appears to be an inhibitor of prostaglandin synthesis. Extracts of the above ground portions of the plant suppress prostaglandin production; leaf extracts inhibit prostaglandin production to a lesser extent. Neither the whole plant nor leaf extracts inhibit cyclooxygenation of arachidonic acid, the first step in prostaglandin synthesis. Chloroform leaf extracts, rich in sesquiterpene lactones, inhibit production of inflammatory prostaglandins in rat and human leukocytes. Inhibition was irreversible and the effect was not caused by cytotoxicity. Studies have shown that lipophilic compounds other than parthenolide may be associated with anti-inflammatory activity, particularly with reducing human neutrophil oxidative burst activity. [10,24,25]

Tanetin, a lipophilic flavonoid found in the leaf, flower, and seed of feverfew, blocks prostaglandin synthesis. Aqueous extracts do not contribute to feverfew's anti-inflammatory activity, but do prevent the release of arachidonic acid and inhibit in vitro aggregation of platelets stimulated by adenosine 5″-diphosphate (ADP) or thrombin. Whether or not these extracts block the synthesis of thromboxane, a prostaglandin involved in platelet aggregation, is controversial. Results suggest that feverfew's inhibition of prostaglandin synthesis differs in mechanism from that of the salicylates. [26–28]

Phospholipase inhibition in platelets has been documented. Inhibition of prostaglandin synthetase also has been documented for parthenolide. [29,30]

The anti-inflammatory effects of feverfew may be caused by a cytotoxic effect. Feverfew extracts were found to inhibit mitogen-induced tritiated thymidine uptake by human peripheral blood mononuclear cells, interleukin-2-induced tritiated thymidine uptake by lymphoblasts, and prostaglandin release by interleukin-1-stimulated synovial cells. Parthenolide also blocked tritiated thymidine uptake by mitogen-induced human peripheral blood mononuclear cells.[31]

Effects on vascular smooth muscle

Chloroform leaf extracts of feverfew inhibited the contraction and relaxation of rabbit aorta. The inhibition was concentration and time-dependent, noncompetitive, and irreversible, occurring with or without the presence of endothelium. The leaf extracts inhibited contractions induced by potassium depolarization much less. Only fresh leaf extracts as compared with dried powdered leaves (available commercially) inhibited the effects on smooth muscle, which was likely because of a higher concentration of parthenolide. Experiments in rat and rabbit muscle using chloroform extract from fresh leaves suggest feverfew may inhibit smooth muscle spasm by blocking open potassium channels. [32–34]

Researchers have demonstrated that parthenolide noncompetitively inhibited serotonin (5-HT)-mediated spasmogenic response of indirect-acting 5-HT agonists in isolated rat stomach fundus preparation. Parthenolide noncompetitively antagonized the contractions elicited by the serotonergic drugs fenfluramine and dextroamphetamine on the fundal tissue. The mechanism of action associated with parthenolide does not involve the inhibition of 5-HT2 receptors directly, but rather occurs at the level of 5-HT stored in vesicles of the intramural neurons of fundal tissue.[35]

Effects on platelets

Extracts of feverfew inhibit platelet 5-HT secretion via neutralization of sulfhydryl groups inside or outside the cell. The sesquiterpenes in feverfew contain the alpha-methylenebutyrolactone unit capable of reacting with sulfhydryl groups. Feverfew extracts are not only potent inhibitors of serotonin release from platelets but also of polymorphonuclear leukocyte granules, providing a possible connection between the claimed benefit of feverfew in migraines and arthritis.[5,23,28,36–39]

Inhibition of histamine release

A chloroform extract of feverfew inhibited histamine release from rat peritoneal mast cells in a different manner from established mast cell inhibitors, such as cromoglycate and quercetin. The exact mechanism of action has not been determined but may be mediated by entry of calcium into mast cells.[40]

Chemotherapeutic activity

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Parthenolide inhibited the growth of gram-positive bacteria, yeast, and filamentous fungi.[5] A hydroalcoholic extract of feverfew inhibited the growth of Leishmania amazonesis at an IC50 of 29 µg/mL, whereas a dichloromethane fraction inhibited growth at an IC50 of 3.6 µg/mL.Parthenolide has also inhibited Mycobacterium tuberculosis and Mycobacterium avium at a minimum inhibitory concentration of 16 and 64 µg/mL, respectively.[41]

Anticancer activity

Mechanisms of action may include cytotoxic action associated with interruption of DNA replication by the highly reactive lactone ring, epoxide, and methylene groups of parthenolide through inhibition of thymidine into DNA; oxidative stress, intracellular thiol depletion, endoplasmic reticulum stress, and mitochondrial dysfunction.[5,42,43]

Parthenolide and similar lactones displayed anticancer activity against several human cancer cell lines, including human fibroblasts, human laryngeal carcinoma, human cells transformed with simian virus, human epidermoid cancer of the nasopharynx, and anti-Epstein–Barr early antigen activity. One study document how parthenolide may influence and enhance the effectiveness of paclitaxel. [44–46]

Migraine headache, prophylactic treatment

Feverfew action does not appear to be limited to a single mechanism. Plant extracts affect a wide variety of physiologic pathways. Some of these mechanisms have been discussed previously, including inhibition of prostaglandin synthesis, decrease of vascular smooth muscle spasm, and blockage of platelet granule secretion.

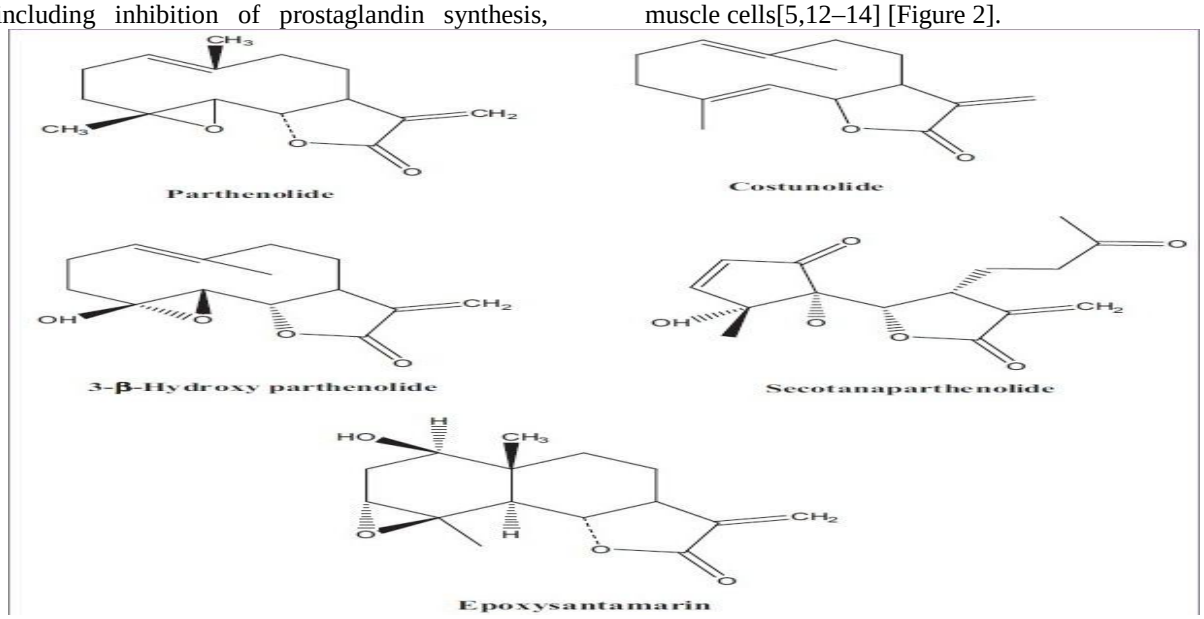
CHEMISTRY:

The chemistry of feverfew is now well defined. The most important biologically active principles are the sesquiterpene lactones, the principal one being parthenolide. Parthenolide is found in the superficial leaf glands (0.2%–0.5%), but not in the stems, and comprises up to 85% of the total sesquiterpene content. [5,7,11]

Sesquiterpene lactones

More than 30 sesquiterpene lactones have been identified in feverfew. In general, there are 5 different types of sesquiterpene lactones, which may be classified by chemical ring structures. Feverfew contains eudesmanolides, germacranolides, and guaianolides. Parthenolide is a germacranolide.[5]

Researchers have also isolated the following sesquiterpene lactones: artecanin, artemorin, balchanin, canin, costunolide, 10-epicanin, epoxyartemorin, 1-beta-hydroxyarbusculin, 3-beta-hydroxycostunolide, 8-alpha-hydroxyestagiatin, 8-beta hydroxyreynosinn, 3-beta-hydroxyparthenolide, manolialide, reynosin, santamarine, epoxysantamarine, secotanaparthenolide A, secotanaparthenolide B, tanaparthin-alpha-peroxide, and 3,4-beta-epoxy-8-deoxycumambrin B.[8] Other members of this class have been isolated and possess spasmolytic activity, perhaps through an inhibition of the influx of extracellular calcium into vascular smooth muscle cells[5,12–14] [Figure 2].



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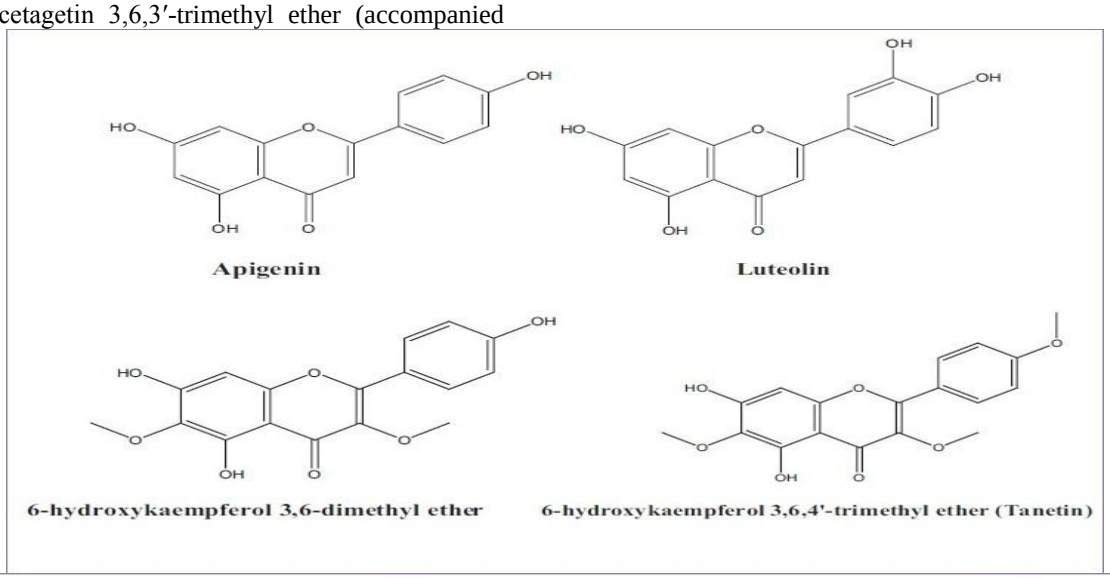
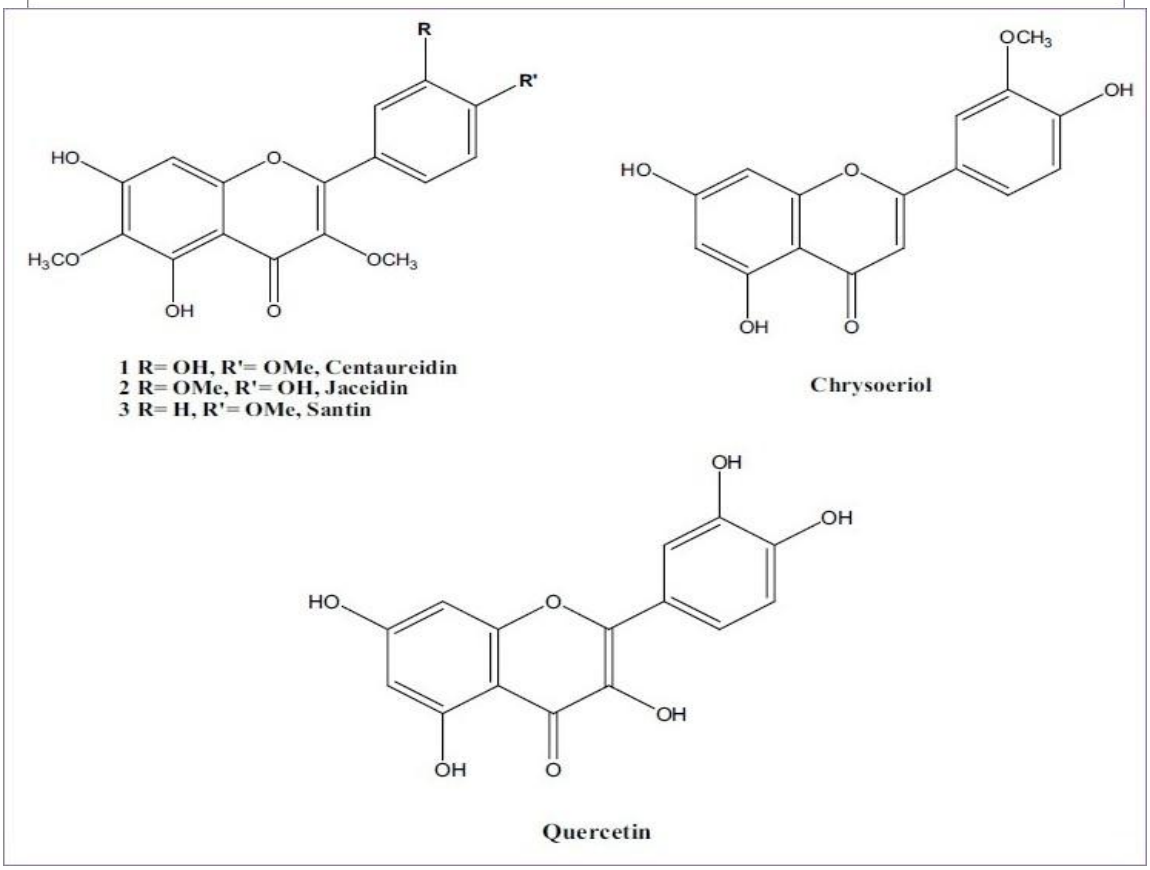
Flavonoids

The following flavonoids have been isolated: 6-hydroxykaempferol 3,6-dimethyl ether, 6-hydroxykaempferol 3,6,4′-trimethyl ether (tanetin), quercetagetin 3,6-dimethyl ether, quercetagetin 3,6,3′-trimethyl ether (accompanied by isomeric 3,6,4′-trimethyl ether), quercetin, apigenin (also apigenin 7-glucuronide), luteolin (also luteolin 7-glucuronide), chrysoeriol, santin, jaceidin, and centaureidin[15–19] [Figures [Figures33 and and44].





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Habitat:

Native to the Balkan Peninsula, feverfew is now found in Australia, Europe, China, Japan, and North Africa. In the mid-19th century, feverfew was introduced in the United States. The plant grows along roadsides, fields, waste areas, and along the borders of woods from eastern Canada to Maryland and westward to Missouri.

ADVERSE REACTIONS:

Adverse effects of patients administered feverfew 50 mg/day (roughly equivalent to 2 leaves) during 6 months of continued treatment were mild and did not result in discontinuation. Four of 8 patients taking the plant had no adverse effects. Heart rate increased dramatically (by up to 26 beats/min) in 2 treated patients. There were no differences between treatment groups in laboratory test results. Patients who switched to placebo after taking feverfew for several years experienced a cluster of nervous system reactions (eg, headaches, insomnia, joint pain, nervousness, poor sleep patterns, stiffness, tension, tiredness) along with muscle and joint stiffness, often referred to as "postfeverfew" syndrome.[48,60]

In a larger series of feverfew users, 18% reported adverse effects, the most serious being mouth ulceration (11%). Feverfew can induce more widespread inflammation of the oral mucosa and tongue, often with lip swelling and loss of taste. Dermatitis has been associated with this plant.[40,47,61]

TOXICOLOGY:

No studies of chronic toxicity have been performed on the plant and the safety of long-term use has not been established. Pregnant women should not use the plant because the leaves have been shown to possess potential emmenagogue activity. It is not recommended for lactating mothers or for use in children. [54]

One study evaluated the potential genotoxic effects of chronic feverfew ingestion in 30 migraine sufferers. Analysis of the frequency of chromosomal aberrations and sister chromatid exchanges in circulating lymphocytes from patients who ingested feverfew for 11 months found no unexpected aberrations, suggesting that the plant does not induce chromosomal abnormalities.[62]

II. CONCLUSION

The broadest conclusion of this review is that parthenolide itself remains a drug of great scientific interest, despite its identified limitations for clinical use. It is an active compound that become a very promising drug in terms of combating a wide range of human health problems, such as cancer, inflammation, bone loss, neuropathy, gout, parasite infections, and hypoadiponectinemia.

In the tables and literature review presented, we have shown that parthenolide is considered to be a potential treatment for inflammation and many other diseases.this review suggests that parthenolide could become a promising and stable new anti-inflammatory drug.

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