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Review on feverfew, a valuable medicinal plant

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ABSTRACT

Background and Aims: Feverfew (*Tanacetum parthenium*) is a valuable medicinal plant from Asteraceae family with various pharmacological and therapeutic properties. In this article we reviewed the various aspects of feverfew including botanical characteristics, cultivation and production and medicinal and clinical uses.
Material and Methods: Google Scholar, PubMed, EBSCO, Directory of open access journals (DOAJ), EMBASE, and Web of Science were searched using the keywords feverfew and parthenolide.
Results: The essential oil of feverfew is frequently used in pharmaceutical and cosmetic industries. Parthenolide is the most important active component of feverfew that is used for the treatment of a wide variety of diseases such as fever, migraine headache, and rheumatoid arthritis.
Conclusion: Feverfew has several positive clinical uses and has the potential to be considered as a new drug for the treatment of some diseases.

Implication for health policy/practice/research/medical education:
Feverrfew has several positive clinical uses. The main active ingredients in feverfew are sesquiterpene lactones, predominantly parthenolide. The parthenolide has multiple pharmacologic properties such as anticancer, anti-inflammatory and cardiotonic. It has the potential to be considered as a new drug for these purposes.
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Introduction

Feverfew (*Tanacetum parthenium*) is a perennial plant which is herbaceous in habit. This plant is native to Kazakhstan, Central Asia and Mediterranean region and has a wide distribution in Europe, Asia and America (1,2). It is distributed in various regions of north, west, east and central Iran and is found in the provinces of Golestan, Mazandaran, Gilan, East and West Azarbaijan. Tehran, Hamedan, Markazi and Yazd as a wild herb (3). The environmental conditions have a great effect on phytochemical composition of feverfew including sesquiterpene lactones content, flavonoid content, volatile oil and lipid content of different organs of the plant cultivated in Egypt (4). Feverfew has been reported to contain many sesquiterpene lactones as major secondary metabolites, of which parthenolide is considered the major active component of the plant (5). The sesquiterpene lactones biosynthetic pathway is influenced by environmental conditions (6). This plant has been investigated mainly for its traditional uses in medicine, such as treatment of fever, headache, migraine, stomachache, insect bites, bronchitis, arthritis, cold, abortifacient property and menstruation-related problems (7).
Previous studies on the antimicrobial properties of plants from Asteraceae family have shown that their antimicrobial activity is moderate to strong. Saharkhiz et al reported antimicrobial activity of feverfew against some bacteria (8).
Pareek et al reported that feverfew has been used for psoriasis, allergies, asthma, tinnitus, dizziness and vomiting (9). Given the importance of feverfew plant and its medicinal properties, the aim of this review article is to investigate the medicinal and clinical uses of feverfew in relevant clinical studies.

Historical and popular uses

Feverfew was used by the ancient Greeks and early Europeans to treat fever, to repel insects and to treat bites and stings (10). The first-century Greek physician, dioscorides, used feverfew as an antipyretic. Feverfew was known as "medieval aspirin" or the "aspirin" of the 18th century (11). Its botanical name, *Tanacetum parthenium*,

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was partially derived from a story about a worker who fell during building of the Parthenon but was saved by this plant administration. The name may be derived from the Greek word, Parthenos (virgin), implying the plant's use for treating menstrual problems (12). In central and south America, the plant has been used to treat a variety of disorders. The Kallaway Indians of the Andes Mountains consider this plant valuable for treating colic, kidney pain, morning sickness and stomachache. In Venezuela, it is used for treating earaches (13).

Feverfew has been used as an abortifacient and an insecticide, and for treating coughs and cold. Traditionally, feverfew has been used as antipyretic, for which it is commonly named (14).

Botanical

T. parthenium is a gramineous plant from Asteraceae which has scattered crack and a short and direct root. It has a straight stem with longitudinal grooves in brown-red color. It is 30-80 cm high depending on climatic conditions. The leaves have a long petiole, divided and oval-shaped lamina. Flowers are in two genera and appear during June-August. Flowers have white color and are 0.6 -1 cm in diameter (15).

Leaves have bright green color and blade shape as egg and their surface is covered with crack. Flowers are seen at the end of main stem and branches. They are hermaphrodite and self-fertile. *T. parthenium* is a diploid (2n = 18) plant. Vegetative sections contain essence (16).

Ecology

T. parthenium is a long-day plant and needs sufficient light in the vegetative period of growth (17). *T. parthenium* is resistant to chilling but high temperature plays an important role in increasing yield of its vegetative organs (18). Also, this plant is resistant to drought stress that increases content of total parthenolide and simultaneously decreases phenol components (19). This plant can grow in every soil but has better yield in medium texture soils containing Ca components (8).

T. parthenium is sensitive to heavy irrigation, and in flood irrigation conditions, it will wither. Supplemental irrigation in drought season caused increase in yield of vegetative organs (20).

Cultivation

Propagation of this plant is both sexual and asexual via direction or indirection methods. In indirection method, seeds grown in outdoor bed at suitable period. Light is necessary for germination. After regular irrigation and weeding in outdoor bed, seedlings should be transfer to the main land at suitable time. The best time for vegetative propagation is in the fall. In asexual propagation, plants are propagated by crown division (21). *T. parthenium* is a long day plant, which means that 12 or more hours of light will induce the formation of flower buds.

Environmental conditions could be modified throughout the cultivation to maximize the accumulation of key compounds. Regulation of stress in plants results in the changes in level of secondary metabolites. When growth is reduced due to stress, more carbon becomes available for secondary metabolism, inducing the production of some phytochemicals (22). It is known that in various plants environmental stress increases the accumulation of phenolic compounds (23).

Exposure to high visible radiation may increase the xanthophyll cycle activity and therefore production of various secondary metabolites (24).

Under low light intensities, ABA increases, which regulates some processes in secondary metabolism (25).

During cultivation and especially at the initial stage, watering is required and is very important for *T. parthenium*. Water stress is another factor that can potentially alter concentration of key compounds in medicinal plants. The plants under water stress normally show increased accumulation of ABA (26,27), which triggers changes in content of other secondary metabolites such as phenolic, tannins, proline, polyamines and terpenoid compounds (28-30).

T. parthenium can be susceptible to aphids, miners, caterpillar and mildew. Controlling weeds in vegetative period has important role in increasing yield, so in the first season weeds are weeding mechanically two or three times. So far, there has not been any pest or disease observed on this plant (20). Fertilization has an effective role in increasing yield and improves qualitative and quantitative characteristics of the extract. Nitrogen has an important role in increasing sesquiterpenes lactones. Adding 100 kg nitrogen per hectare causes increase in yield and content of parthenolide. Use of parthenolide also affected the qualitative and quantitative characteristics of extract. So firstly, the nutritive needs should be studied in the cultivation conditions. Usage of micro elements such as Mg, Na, Mn and Cu is recommended to increase yield (31).

Harvest and postharvest

Harvesting is possible as soon as two-thirds of the buds are open; time and the method of harvesting are important for increasing quality and quantity of extract as harvesting in the summer has the highest content of parthenolide than in the fall. The effect of light was evaluated by harvesting plants at different times of the day. The lowest amount of parthenolide was observed in plants harvested at night and maximum level was observed in those harvested during late afternoon (32).

An effect of water stress was increase in the production of jasmonic acid and ABA, which led to stomata closure (33) and accumulation of sesquiterpene (34) and tannins (29). Under water stress plants had higher parthenolide levels compared to when they received water daily (32).

In flowering period the yield has the highest level than other times. As harvest time delayed (up to fruit set), the content of parthenolide decreased (35).

Leaf tissue contains significantly more parthenolide than stem tissue. Succulent stems contain significantly more parthenolide than more mature and tougher stems (36).

Increase in drying temperatures causes a decrease in parthenolide in both leaves and stems. Rushing showed that drying feverfew plants at temperatures higher than 60°C decreased parthenolide. Also, parthenolide levels decreased 30% after 11-month storage (32).

Phytochemicals

Potentially active chemical components of feverfew are as follows:

1- Sesquiterpen lactones: parthenolides, canin, artecanin, santamarin;
2- Flavonoid glycosides: luteolin, tanetin, apigenin, 6-hydroxy-flavanols;
3- Sesquiterpenes and monoterpenes: camphor, borneol, germacrene and pinenes; and
4- Other components including polyacetylenes, pyrethrin, melatonin and tannins (37).

Parthenolide is the most abundant sesquiterpene lactone and is considered the most active chemical component in feverfew (38).

Sesquiterpenes

The most important components in feverfew leaves are a complex series of sesquiterpene α-methylene butyrolactones stored in the glandular trichomes on leaves, seeds and flowers. Some of the identified sesquiterpene lactones have biological actions such as cytotoxicity, antimicrobial effects and growth regulation, and cause allergic contact dermatitis (39).

Flavonoids

Lipophilic flavonoids in the leaf and flower of feverfew have been identified as methyl ethers of the flavonols 6-hydroxykaempferol and quercetagetin. Two flavone glucuronides and apigenin are found in glandular trichomes on the flowers' lower epidermis (40).

Volatile oils

Twenty-three compounds, comprising 90% of the volatile oils, have been identified in feverfew. The main components include camphor (56.9%), camphene (12.7%), p-cymene (5.2%) and bornyl acetate (4.6%) (40).

Other chemical components:

Coumarin, isofraxidin and isofraxidin drimenyl ether (9-epipectachol B) have been isolated from the roots of the plant (42,43).

Uses

Feverfew has been used as herbal drug to relieve fever and to treat headaches, arthritis and digestive problems.

Anti-inflammatory activity

Feverfew seems to inhibit prostaglandin synthesis. Extract of the above ground parts of the plant suppresses prostaglandin production and leaf extracts to a lesser extent inhibit prostaglandin production. Chloroform leaf extract, rich in sesquiterpene lactones, inhibits production of inflammatory prostaglandin in rat and human leukocytes (18,44).

Parthenolide has been also demonstrated to inhibit prostaglandin syntheses (45). The anti-inflammatory effect of feverfew may be due to a cytotoxic effect (46).

Effect on vascular smooth muscle

Fresh leaf extracts compared to dried pulverized leaves inhibited the effect on smooth muscle, which could be due to a higher concentration of parthenolide. Studies of rat and rabbit muscle using chloroform extract of fresh leaves suggested that feverfew could inhibit smooth muscle spasm through blocking open potassium channel (47).

Effect on platelets

The sesquiterpenes in feverfew contain the α-methylene butyrolactone unit which is able to react with sulfhydryl groups. Feverfew extract is not only a potent inhibitor of serotonin release from platelets but also of polymorph nuclear leukocyte granules, causing a possible link between the potential beneficial effect of feverfew on migraine and arthritis (13).

Anticancer activity

Mechanism of action could be a cytotoxic action related to interruption of DNA replication by the highly reactive lactone ring, epoxide and methylene groups of parthenolide via inhibiting thymidine into DNA, intracellular thiol depletion, oxidative stress, endoplasmic reticulum stress and mitochondrial dysfunction (13). Parthenolide and similar lactones have shown anticancer activity against several human cancer cell lines, such as human fibroblasts, human cells transformed with simian virus, human laryngeal carcinoma, anti-Epstein-Barr early antigen activity and human epidermoid cancer of nasopharynx (48).

Migraine headache and prophylactic treatment

Feverfew activity does not seem to be exerted through a single mechanism. The plant extract affects a wide variety of physiologic pathways, some of which have been already discussed, such as decrease in vascular smooth muscle spasm, inhibition of prostaglandin synthesis and blockage of platelet granule secretion (9).

Conclusion

Medicinal plants respond to environmental conditions and different environmental conditions affect medicinal plants' quality. The active ingredients in feverfew are sesquiterpene lactones, mainly parthenolide. The highest parthenolide levels were seen in the plants that received low-water regimens and light enhanced accumulation of parthenolide immediately before harvest. The parthenolide has multiple pharmacologic properties such as anticancer, anti-inflammatory and cardiotonic. In Iran, this plant needs to be cultivated because of its importance as a medicinal plant and various therapeutic uses.

Authors' contributions

All authors contributed in the collection of data and MM

edited the final version. All read and confirmed the final version.

Conflict of interests

The authors declared no competing interests.

Ethical considerations

Ethical issues (including plagiarism, misconduct, data fabrication, falsification, double publication or submission and redundancy) were completely observed by the authors.

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