



A REVIEW ON THE THERAPEUTIC POTENTIALS OF PARTHENOLIDE: A SESQUITERPENE LACTONE

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Article Received on: 12/12/11 Revised on: 18/01/12 Approved for publication: 19/02/12

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ABSTRACT

Medicinal plants have been widely employed in treating various diseases for centuries and are still a major resource and repository that can be further exploited for a variety of infectious and non-infectious ailments. The popularity of medicinal herbs has grown significantly in recent years despite a dearth of information regarding their modes of action and continuing concerns over their efficacy. Hence there is a necessity to study various plants meticulously with respect to their biological properties. Recent efforts to elucidate the mechanisms of action of several anti-inflammatory herbs have focused on a class of compounds, sesquiterpene lactones, which are believed to be the active components of these herbal medicines. At present, the pharmacokinetics of sesquiterpene lactones is not well known. Parthenolide is a major sesquiterpene lactone isolated from medical herbs *Tanacetum parthenium* (commonly known as feverfew) and from *Magnolia grandiflora*. Feverfew has been traditionally used as a herbal medicine for the treatment of fever, arthritis, and migraine in Asia and Europe for centuries. Hence, the present study discusses various biological properties of parthenolide and its mode of action which can be used in drug designing processes to maximize efficacy and minimize side-effects.

KEYWORDS: Sesquiterpene lactones, Feverfew, Parthenolide, Therapeutic potentials, Mechanism of action.

INTRODUCTION

Natural products from plants has been used for thousands of years and found to be vital in curing various deadly diseases including cancer. Several plants have already been employed for its diverse medicinal properties. Isolation of pure compounds from plants opened a new era, for treating human ailments by using it alone or in combinations. For the last fifteen years, researchers have focused on drug development strategies to isolate and purify active principles from plant sources, since these drugs, in general, have lesser side effects in comparison with those synthesized chemically.

Tanacetum parthenium is a medicinal herb which is found in many old gardens¹ and is also occasionally grown for ornamental purposes. The plant grows into a small bush, around 46 cm (18 inch) high, with citrus-scented leaves and is covered by flowers, reminiscent of daisies. It spreads rapidly and will cover a wide area after a few years. Feverfew has been used in folk medicine for the treatment of migraines, tinnitus, giddiness, arthritis, fever, menstrual disorders, stomachaches, toothaches, and insect bites^{2,3}. Sesquiterpene lactones (SQLs) are secondary metabolites found in most species of *Compositae* and in at least 14 angiosperm families. There are more than 4,000 SQLs reported with known structures⁴. In 1960, Parthenolide (PN) was first reported as a new SQL from feverfew (*Tanacetum parthenium*), with the initial structure later revised as shown in Figure 1. PN was believed to be the primary bioactive compound in feverfew⁵ which was used in prophylactic treatment for migraine with positive therapeutic effects in clinical trials⁶. Its pharmacological action is similar to that of aspirin. PN helps to prevent excessive clumping of platelets and inhibits the release of certain chemicals, including serotonin and some inflammatory mediators⁷. So it is clearly evident that PN has good therapeutic potential and can be developed to be a drug for several ailments. Hence, this review is aimed at providing the reader with recent information about the therapeutic

potential as well as the mode of action of PN and its multiple applications. Even though a recent review article⁸ has discussed the molecular aspects of the anticancer and anti-inflammatory properties of PN, our review is broader in scope and also includes the other therapeutic potentials of this compound.

Extraction yield and phytochemical screening

The highest content of PN was found in flower heads (1.38%) followed by leaves (0.95%) and with only 0.08% in stalks and 0.01% in roots⁹. Methanol was the solvent of choice in terms of maximizing the yield (763.6 mg/100 g dry material) of PN using conventional extraction methodologies¹⁰. Major phytochemicals from leaves and flowers of *Tanacetum parthenium*, were isolated and identified which includes four flavonoids isolated from the aerial part, four sesquiterpene lactones isolated from the leaves, two sterols isolated from the roots¹¹. A comparative study of the essential oil content of the leaves and the flower heads using GC/MS have revealed the presence of 42 components in the leaves and 30 components in the flower heads with camphor constituting 37.7 and 48.4% respectively. Further, chrysanthenyl acetate constituted 33.8% in leaf extracts while the flower heads contained 26.3% of this compound¹².

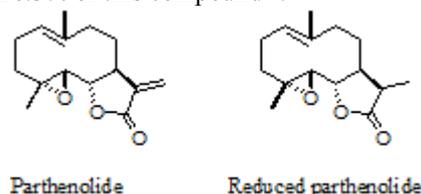


Fig. 1 Chemical structure of the sesquiterpene lactone- parthenolide and reduced parthenolide from *T. parthenium*.

Anti-inflammatory activity

Acute anti-inflammatory effects of PN were evaluated using the yeast-induced rat paw edema test¹³. Groups of male albino rats, weighing 100-125 g, were separately

administered (ethanolic and aqueous extracts of *Tanacetum parthenium* - doses of 1 g/kg body weight) and PN at doses of 10 mg/kg body weight. Ethanolic extracts of leaves and flowers of *Tanacetum parthenium* and PN showed significant anti-inflammatory activity¹¹. A target has been identified for PN, which provided a possible molecular basis for its anti-inflammatory properties¹⁴. PN specifically binds and inhibits IKK (a multi-subunit complex that inhibits NF- κ B activation) in HeLa cells. PN is a powerful anti-inflammatory agent in cellular and animal models of cystic fibrosis (CF)¹⁵. All these findings validate the anti-inflammatory activity of PN.

Antileishmanial and antiprotozoal Activity

Leishmaniasis is a group of infectious diseases caused by organisms of the genus *Leishmania* and is a significant cause of morbidity and mortality in several countries. PN has been isolated from areal parts of *Tanacetum parthenium*¹⁶. This compound was found to have antileishmanial activity. The extract was filtered, evaporated under vacuum, and lyophilized; and the residue (the hydroalcoholic extract) was directly assayed for its activity against *L. amazonensis*. The hydroalcoholic extract of this plant inhibited promastigote growth with an IC₅₀ of 29 μ g/ml which clearly suggested its antileishmanial activity. The dichloromethane fraction showed a greater inhibitory effect than the hydroalcoholic extract, with the IC₅₀ of 3.6 μ g/ml. Antiprotozoal activity of PN was reported¹⁷ in two forms of the parasite *Trypanosoma cruzi*. The pure compound (PN) showed IC_{50/96h} and IC_{90/96h} values of 0.5 μ g/ml and 1.25 μ g/ml, respectively.

Antimyelomic activity

Multiple myeloma, a chronic untreatable blood cancer and is one of causes for cancer-induced mortality. The interaction of multiple myeloma (MM) cells with the bone marrow microenvironment contributes to the heterogeneous response and drug resistance. NF- κ B is central to the pathogenesis of MM both within the MM cells, as well as the biological consequence of the interaction between MM cells and the bone marrow. The p65/p50 heteromer is the most prevalent form in cancers, including MM¹⁸. PN inhibits NF- κ B indirectly by blocking IKK and directly by inhibiting p65 at the cysteine residue in its activation loop^{19,20}. The ability of PN which inhibits the growth of MM cell lines and primary cells were also studied²¹. After a 72-hour treatment of MM

cells with PN (0-10 μ mol/L), a dose-dependent inhibition of proliferation in all cell lines, including the dexamethasone-resistant MM.1R cells and the doxorubicin resistant RPMI-8226/Dox6 cells were observed. The IC₅₀ for all cell lines and primary cells ranged from 1-3 μ mol/L. These results imply the ability of PN to inhibit NF- κ B, induce apoptosis in MM cell lines and primary cells, and also be effective against MM cells in the context of the bone marrow microenvironment.

Anticancer activity

Antiproliferative effect of PN was studied against A549, TE67, HT-29 and human umbilical vein endothelial cells²². The IC₅₀ value of PN against A549, TE671 and HT-29 was 4.3 μ M, 6.5 μ M and 7.0 μ M, respectively. PN decreased the viability of HUVEC in a concentration-dependent manner with an IC₅₀ value was 2.8 μ M. PN also showed anticancer activity against human melanoma cells *in vitro*²³. PN inhibited cell proliferation and killed various cancer cells mainly by inducing apoptosis. The cytotoxicity of PN was also tested in melanoma cell lines and melanocytes, as well as melanoma cells directly derived from a surgical excision. PN reduced the number of viable adherent cells in melanoma cultures. Pre-incubation of PN with the thiol nucleophile N-acetyl-cysteine protected melanoma cells from PN-induced cell death suggesting the reaction with intracellular thiols as the mechanism responsible for PN activity²⁴.

Chemopreventive activity of PN against UVB-induced skin cancer, the most common type of cancer among Caucasians²⁵, was also studied. Skin cancer in mice fed with PN (1 mg/day) showed a delayed onset of papilloma incidence, a significant reduction in papilloma multiplicity (papilloma/mouse) and sizes when compared to the UVB-only group. Non-cytotoxic concentrations of PN significantly inhibited UVB-induced AP-1 DNA binding and transcriptional activity. In addition, PN pre-treatment also inhibits c-Jun-N-terminal kinase (JNK) and p38 kinase activation. *In vitro* studies in JB6 murine epidermal cells showed that synergistic effects of PN and UVB in sensitizing cells for apoptosis. Such sensitization appears to be mediated through inhibition of AP-1, JNK and p38 signalling pathways and these effects may contribute to the anticancer activity of PN²⁶.

Table 1: IC₅₀ values for various biological activities of *Tanacetum parthenium* and PN in different organism/ cell lines.

Activity	Organism/cell lines	Extracts/PN	IC ₅₀ value	Ref
Anticancer	A549	PN	0.5 μ g/ml	22
	TE671		4.3 μ g/ml	
	HT-29		7.0 μ g/ml	
	HUVEC		2.8 μ g/ml	
Antileishmanial	<i>L. amazonensis</i>	Dichloromethane	29 μ g/ml	16
		Hydroalcoholic	3.6 μ g/ml	
Antiprotozoal	<i>Trypanosoma cruzi</i>	PN	0.5 μ g/ml	17

Microtubule-interfering activity

PN may be related to a tubulin/microtubule-interfering activity²⁷. PN exerted *in vitro* stimulatory activity on tubulin assembly, by inducing the formation of well-organized microtubule polymers. Light microscopy-based studies showed that PN-induced alterations of either microtubule network or nuclear morphology happened only after combination treatment with paclitaxel. In addition, the growth of MCF-7 cells was significantly inhibited by PN, which enhanced the effectiveness of paclitaxel. The anti-

microtubular and antiproliferative effects of PN, well known microtubule-stabilizing anticancer agent, may influence paclitaxel activity. The tubulin/microtubule system may represent a novel molecular target for PN, to be utilized in developing new combinational anticancer strategies²⁸.

Antioxidant property

The strong intracellular antioxidant activity of the sesquiterpene lactone- PN in the hippocampal HT22 cells were observed²⁹. The redox state of the cell has been shown to be involved in cell cycle regulation and cell

death/survival³⁰. GSH (total glutathione) is the main intracellular antioxidant and plays an important role in these processes. GSH depletion can lead to cell death²⁹. Intracellular free radicals measurements, total levels of glutathione, *in vitro* lipid and protein oxidation assays showed that PN, at sub-lethal concentrations (5 μ M), strikingly decreased DCF (2',7'-dichlorofluorescein) fluorescence, indicating its powerful antioxidant potential in the aforesaid HT22 cells (60%) while the higher dose (10 μ M) decreased intracellular ROS nearly completely (80%). An increase of GSH in a non-tumoral liver cell line after treatment with 10 μ M PN therefore, further confirms GSH regulation by this chemical, in both normal and tumoral cell lines. PN also increases the activation of the antioxidant/electrophile response element. Since this response element is on the promoter regulating the enzyme involved in GSH synthesis, its PN-mediated activation may account for the observed increase of this protective thiol.

Antimigraine activity

5-Hydroxytryptamine-inhibiting property of Feverfew was reported³¹. This inhibition of the release of serotonin (5-hydroxytryptamine) from blood platelets by PN was attributed to be the basis for feverfew's antimigraine activity³². Contradictory results were reported³³. In this study, an extract of feverfew leaf, with ample (more than 4%) PN content was found ineffective in mitigating the symptoms of migraine. PN effects on 5-HT storage and release, and stimulation of 5-HT_{2B} and 5-HT_{2A} receptor were studied for elucidating its possible mechanism as an antimigraine agent. Antimigraine drugs interact predominantly with receptors of 5-HT₁ and 5-HT₂ classes. 5-HT_{2B} and 5-HT_{2A} receptor antagonists such as methysergide, cyproheptadme, and mianserin have been shown to be effective in migraine prophylaxis. Furthermore, effectiveness of Feverfew in migraine prophylaxis has been demonstrated in several clinical trials³⁴. Subsequent studies conducted by researchers, demonstrated the effectiveness in migraine prophylaxis of a supercritical carbon dioxide extract of feverfew leaf, although in only a small subset of patients with a minimum of 4 migraine headache attacks per month^{35,36}.

Parthenolide as cocaine antagonists

PN preventing the expression of withdrawal-like behaviors in planarians (model for chronic cocaine exposure) was studied³⁷. Several studies have been carried out in planaria to analyze the morphological and behavioral effects of cocaine^{38,39,40,41}. The experiments indicated that the putative binding sites for cocaine and PN in planarian worms are related and this may provide innovative directions in the search for cocaine antagonists.

Depression effect of PN in rodents

Sepsis is a common cause of death and drug resistance is becoming a major medical problem and preventive measures are scarce. Recent *in vitro* studies shown that PN can inhibit NF- κ B. The effect of PN in endotoxic shock in rodents was studied⁴². Endotoxic shock was induced by administration of *E. coli* endotoxin in rats. Various doses of PN were given to rats and northern blotting results showed an increase in mRNA expression for inducible nitric-oxide synthase (iNOS) in thoracic aortas. *In vivo* pre-treatment and post-treatment with PN improved the hemodynamic profile, reduced plasma nitrate/nitrite and lung neutrophil infiltration in a dose-dependent fashion. In a separate set of experiments, pre-

treatment or post-treatment with PN significantly improved survival in mice challenged with endotoxin.

Curative properties of PN in phase I clinical trial

Phase I clinical studies with PN were studied⁴³. Feverfew was administered as a daily oral tablet in a 28-day cycle. A starting dose of 1 mg per day was given with subsequent dose escalations to 2, 3, and 4 mg. Assessment of plasma pharmacokinetics was performed on patients accrued to the trial. However, at doses up to 4 mg as a daily oral capsule, there was no detectable concentration in the plasma. Feverfew, with up to 4 mg of PN, given daily as an oral tablet is well tolerated without dose-limiting toxicity, but does not provide detectable plasma concentrations. Hence, further purification studies are needed to evaluate the effect of PN probably with higher doses.

CONCLUSION

Although current research focuses on the isolation of major compounds from plant sources, it is still not clear which mechanism of action of the various sesquiterpene lactones is important in the treatment of diseases. Further, the various medicinal properties of natural herbs are still known only to indigenous people and can be exploited for its beneficial therapeutic properties. Here, we discussed the therapeutic potential of PN isolated from *Tanacetum parthenium* attributing its anti-inflammatory, antileishmanial, antimyelomic, microtubule-interfering, anticancer, antioxidant, antimigraine and its preventive medicinal activities. PN has already undergone a preliminary phase I safety clinical trial. More *in vivo* and clinical studies have to be carried out to explore the action of PN for its biological efficacies and safety in humans.

ACKNOWLEDGMENT

We are thankful to the management of VIT University, Vellore, Tamil Nadu, India, for providing the necessary infrastructure for successful accomplishment of this research work.

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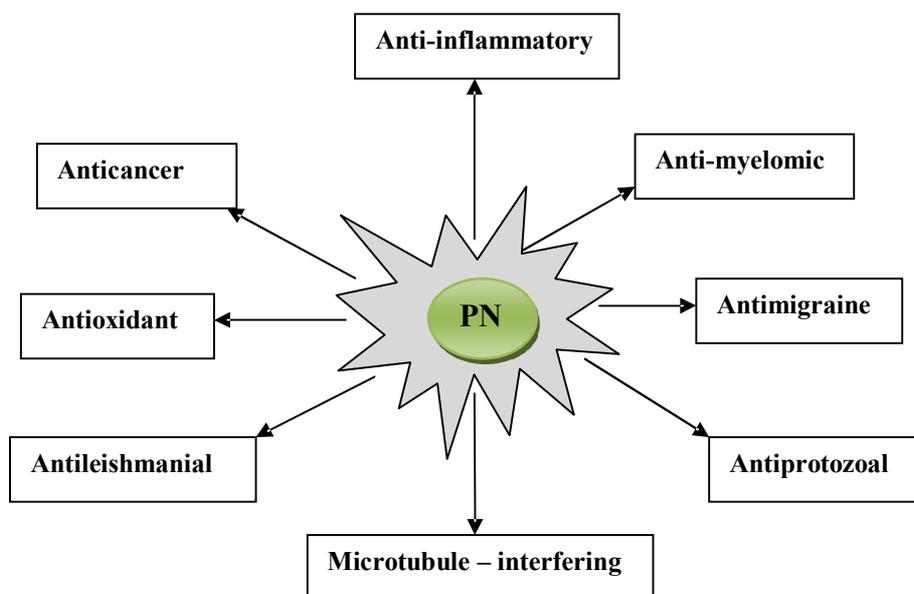


Fig. 2 Various biological properties of PN