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PHYTOCHEMICAL INVESTIGATION AND THERAPEUTIC POTENTIAL OF PHYLLIS ANGULATE - A REVIEW

M. Sakthivel[1]*, C. Kalaiselvi[2], C. Jothimanivannan[3], V. Kalaiyarasan[4], A. Prameshwaran[5], M. Srinivasan[6] and T. Sarankumar[7]

[1]Student, SS Institute of Pharmacy-Sankari.

[2]Department of Pharmaceutics, SS Institute of Pharmacy-Sankari.

[3]Department of Pharmaceutical Analysis, SS Institute of Pharmacy-Sankari.

[4]Student, SS Institute of Pharmacy- Sankari.

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***Corresponding Author**
M. Sakthivel
Student, SS Institute of Pharmacy-Sankari.
sakthivel312001@gmail.com

ABSTRACT

Phyllis angulate plant is very well known for its therapeutics benefits in Indian systems of medicine including Ayurveda and Siddha and in other forms of traditional medicine worldwide for the treatment of several ailments. It observed that many traditional utilities of Phyllis angulata got their authentication when tested using different disease-based pharmacological models taking various extracts of roots, leaves, and root oil as test samples. Our review article focusses to Pharmacological studies, phytochemical screening & pharmacological activites are anti-hepatoma, Immunomodulatory, Genotoxicity, antieishmanial, anti-parasitic, anti-inflammatory, anti-nociceptive, anti-asthmatic, anti-bacterial, antimycobacterial, antiulcer, analgesic, anti-diabetic, anticancer, anti-microbial, anti-oxidant, anti-tumor. This article can give potential research areas to explore next, and to formulate new formulation in allopathy and some traditional medicine system.

KEYWORDS: Phyllis angulate, Solanaceae, Darkgreen, Cape gooseberry, antiasthmatic, antimycobacterial, antidiabetic, anticancer.

INDRODUCTION

Phyllis angulata is an erect, herbaceous, annual plant belonging to the nightshade family Solanaceae. It reproduces by seed. Its leaves are dark green and roughly oval, often with tooth shapes around the edge. The flowers are five-sided and pale yellow; the yellow-orange fruits are born inside a balloon-like calyx. It is native to the Americas, but is now widely

distributed and naturalized in tropical and subtropical regions worldwide. It is related to, but not to be confused with Phyllis peruviana, the Cape gooseberry, a fruit native to, and cultivated in the western Andes, and exported worldwide. The plant produces fruit and is edible. Can be eaten raw, cooked, jammed, etc. English common names include: angular winter cherry, balloon cherry, cutleaf groundcherry, gooseberry, hogweed, wild tomato, camapu, and occasionally other common names for the genus Phyllis. In Malayalam it is known as njottanjodiyan and mottaampuli In Indonesian it is known as ceplukan or ciplukan. In Suriname it is known as batoto wiwiri. In Meru it is known as Nkabakabu.[1]

PHARMACOGNOSTIC & PHYTOCHEMICAL SCREENING

Taxonomy

Family Solanaceae Species Phyllis angulata L. Common name bunchy sedge, field sedge. Details Eppo code PHYAN Family Solanaceae Species Phyllis angulata L. Weed type Broadleaf. Terrestrial, annual, erect herb. Roots fibrous, brown or white. Stems quadrangular, hollow, hairy. Stipules absent. Leaves simple, lobed or entire, alternate spiral, stalked, ovate, more than 2 cm long/wide, hairy on both sides, margin entire, undulate or coarsely dentate, apex acute, base acute, pinnately veined. Flowers bisexual, solitary, axillary, petals 5, white or yellow. Fruits a berry, surrounded by calyx. Cotyledons First leaves. General habit Erect plant, the plant forms a small bush profusely branched. Underground system Tap root.

Stem

The stem is hollow and polygonal. It is completely hairless.

Leaf

The leaves are simple and alternate. They are carried by a petiole along 3 to 5 cm. The lamina is oval to elliptical, apiculate at the top and bottom corner attenuated acute. Its length is 7 to 12 cm and a width of 3 to 6 cm. The margin is sinuous and irregularly toothed, with few short white hairs. The blade is marked with 4 to 6 pairs of veined pinnate. Both sides are smooth, although some short white hairs are present along the veins of the lower face.

Inflorescence

The flowers are solitary and axillary, located at the intersection of the branches of the plant.

Flower

They are carried by a glabrous stalk from 7 to 10 mm long. The calyx, 3 mm long, consists of 5 sepals fused at the base section and ending with 5 triangular teeth. Corolla campanulate, composed of 5 petals fused. It is large of 7 to 8 mm and creamy white with a purple spot at the base of the petals. The five stamens are inserted in the corolla tube alternate with the petals. The ovary consists of two boxes with numerous ovules.

Fruit

It is traversed by longitudinal ribs 8 or 9, connected by a network of fine ribs.

Seed

The seeds are flat and lenticular, with a diameter of 1 mm. The seed coat is orange and finely honeycombed.

Biology

P. angulata is an annual species. It reproduces by seeds only.

Ecology

Sunny to somewhat shaded, not too dry, fertile spots in fields, gardens, wastelands, dunes, fallow fields, along roads, in open forests, forest margins; from 0-1500 m alt. Upland rice fields.

Origin

This species is native to tropical America. Now widespread throughout tropical, subtropical and warmer temperate regions of the world (almost cosmopolitan).

Local weediness

Benin: Frequent but not abundant.

Burkina Faso: Rare and not abundant.

Cote d'Ivoire: Frequent but not abundant.

Mali: Rare but abundant when present

Nigeria: Rare and not abundant.

Ghana: Rare but abondant when present

Senegal: Rare and not abundant.

Uganda: Frequent and usually abundant

Control

Chemical control: Pre-emergence application of diuron, simazine (in sugarcane, USA); post-emergence aapplication of 2.4-DB (S.Africa); 2.4.5-T (USA); in E.Africa both 2.4-D and MCPA were found to be ineffective.

Use

The fruits are edible, but poisonous when they are consumed in large quantities.[2]

Phytochemical

The main objective of this mini-review was to synthesize recent data about the phytochemical composition, the nutritional properties, and the biological and pharmacological activities of a now cosmopolitan genus, Phyllis(Solanaceae), being in the focus of intensive research over the last two decades. Six Phyllis species with nutritional and pharmacological promise are considered in particular – P. peruviana L., P. philadelphica Lam., P. ixocarpa Brot. ex Horm., P. angulata L., P. pubescens L., and P. alkekengi L. Summarized contemporary data on the metabolite profile and the biological activities of Phyllis species support their century-long use in traditional medicine and human nutrition. The fruit represent a rich source of minerals, vitamins, fibers, carotenoids, proteins, fructose, sucrose esters, pectins, flavonoids, polyphenols, polyunsaturated fatty acids, phytosterols and many other beneficial nutrients. Individual phytochemicals and complex fractions isolated from Phyllis plants demonstrate various biological and pharmacological activities, the most promising of which include antimicrobial, antioxidant, anti-diabetic, hepatorenoprotective, anti-cancer, anti-inflammatory, immunomodulatory and others. Most of these activities are associated with the presence of flavonoids, phenylpropanoids, alkaloids, physalins, withanolides, and other bioactive compounds. The accumulated data disclose the potential of Phyllis spp. as highly functional foods, as profitable crops for many regions over the world, and as sources of valuable secondary metabolites for phytopharmacy, novel medicine and cosmetics. Information provided by this review is also important for a more intensive promotion of Phyllis species in Bulgaria and for future studies on their composition and benefits.[3]

PHARMACOLOGICAL ACTIVITIES

1) Antihepatoma activity

Phyllis angulata and P. peruviana are herbs widely used in folk medicine. In this study, the aqueous and ethanol extracts prepared from the whole plant of these species were evaluated for their antihepatoma activity. Using XTT assay, three human hepatoma cells, namely Hep G2, Hep 3B and PLC/PRF/5 were tested. The results showed that ethanol extract of P. peruviana (EEPP) possessed the lowest IC50 value against the Hep G2 cells. Interestingly, all extracts showed no cytotoxic effect on normal mouse liver cells. Treatment with carbonyl cyanide m-chlorophenyl hydrazone, a protonophore, caused a reduction of membrane potential ($\Delta\psi m$) by mitochondrial membrane depolarization. At high concentrations, EEPP was shown to induce cell cycle arrest and apoptosis through mitochondrial dysfunction as demonstrated by the following observations: (i) EEPP induced the collapse of $\Delta\psi m$ and the depletion of glutathione content in a dose dependent manner; (ii) pretreatment with the antioxidant (1.0 µg/ml vitamin E) protected cells from EEPP-induced release of ROS; and (iii) at concentrations 10 to 50 µg/ml, EEPP displayed a dose-dependent accumulation of the Sub-G1 peak (hypoploid) and caused G0/G1-phase arrest. Apoptosis was elicited when the cells were treated with 50 µg/ml EEPP as characterized by the appearance of phosphatidylserine on the outer surface of the plasma membrane. The results conclude that EEPP possesses potent antihepatoma activity and its effect on apoptosis is associated with mitochondrial dysfunction.[4]

2) Immunomodulatoty activity

The immunomodulatory effects of Phyllis angulata L. extract fraction VII (PA-VII), PA-VII-A, PA-VII-B and PA-VII-C were investigated in this study. The results showed that PA-VII and PA-VII-C strongly enhanced blastogenesis response, PA-VII-B had moderate activity, and PA-VII-A exerted only slight effect on cell proliferation. A synergistic effect was observed when the suboptimal dosage of phytohemagglutinin (PHA) or lipopolysaccharide (LPS) was added to the culture. Furthermore, PA-VII and PA-VII-C possessed stimulatory activity on B cells and less effect on T cells. The antibody responses were also augmented by PA-VII, PA-VII-B and PA-VII-C, but not by PA-VII-A. The enhancement of antibody response could be observed both in BALB/c and C3H/HeJ mice.[5]

3) Genotoxicity and Antieishmanial activity

Antileishmanial in vitro tests, as well as Ames and micronucleus assays were performed with a concentrated ethanolic extract of Phyllis angulata (EEPA).EEPA did not present mutagenic effect in Salmonella typhimurium strains at concentration reaching 3000 µg/plate and did not

induce mutagenic effects after two oral administrations with a 24 h interval at a dose level of 2000 mg/kg. EEPA presented antileishmanial activity and presented an IC50 value of 5.35 ± 2.50 µg/mL and 4.50 ± 1.17 µg/mL against Leishmania amazonensis and Leishmania braziliensis promastigotes, respectively. In the cytotoxicity test against macrophages, the EEPA had a LC50 of 6.14 ± 0.59 µg/mL. Importantly, the IC50 against L. amazonensis intracellular amastigotes was 1.23 ± 0.11 µg/mL. EEPA extract is non-mutagenic and presented a promising pharmacological effect against Leishmania parasites.[6]

4) Antiparasitic activity

The current treatment of Chagas disease, endemic in Latin America and emerging in several countries, is limited by the frequent side effects and variable efficacy of benznidazole. Natural products are an important source for the search for new drugs. Considering the great potential of natural products as antiparasitic agents, we investigated the anti-Trypanosoma cruzi activity of a concentrated ethanolic extract of Phyllis angulata (EEPA).Cytotoxicity to mammalian cells was determined using mouse peritoneal macrophages. The antiparasitic activity was evaluated against axenic epimastigote and bloodstream trypomastigote forms of T. cruzi, and against amastigote forms using T. cruzi-infected macrophages. Cell death mechanism was determined in trypomastigotes by flow cytometry analysis after annexin V and propidium iodide staining. The efficacy of EEPA was examined in vivo in an acute model of infection by monitoring blood parasitaemia and survival rate 30 days after treatment. The effect against trypomastigotes of EEPA and benznidazole acting in combination was evaluated. EEPA effectively inhibits the epimastigote growth (IC50 2.9 ± 0.1 µM) and reduces bloodstream trypomastigote viability (EC50 1.7 ± 0.5 µM). It causes parasite cell death by necrosis. EEPA impairs parasite infectivity as well as amastigote development in concentrations noncytotoxic to mammalian cells. In mice acutely-infected with T. cruzi, EEPA reduced the blood parasitaemia in 72.7%. When combined with benznidazole, EEPA showed a synergistic anti-T. cruzi activity, displaying CI values of 0.8 ± 0.07 at EC50 and 0.83 ± 0.1 at EC90.EEPA has antiparasitic activity against T. cruzi, causing cell death by necrosis and showing synergistic activity with benznidazole. These findings were reinforced by the observed efficacy of EEPA in reducing parasite load in T. cruzi-mice. Therefore, this represents an important source of antiparasitic natural products.[7]

5) Antiinflammatory and Wound healing properties

The leaf of Phyllis angulata L. is widely used in Ghana by rural and urban dwellers for the treatment of wounds. This study sought to evaluate the anti-inflammatory and wound healing activities of methanol leaf extract of Phyllis angulata L. (PAL). Preliminary phytochemical screening was used to determine the phytochemical constituents in this plant material. Anti-inflammatory activity of extract concentrations at doses of 30, 100 and 300 mg/kg body weight of the rats, were determined by carrageenan-induced foot oedema model in rats. The wound healing activity was studied using the excision wound model in rats with concentrations of 1.25, 2.5, 5, 10% w/w. The progression and microscopic bedding of wound healing was determined by the periodic assessment of the contraction of excision wounds and histological studies. Preliminary phytochemical screening of the PAL and its pulverized leaves revealed the presence of saponins, tannins, flavonoids, reducing sugars, anthracenosides and carbohydrates in the extracts. The anti-inflammatory activity of the extract at 100 and 300 mg/kg caused a significant ($p<0.001$) decrease in paw thickness when administered both therapeutically and prophylactically. The PAL formulated into cream (1.25, 2.5, 5, 10% w/w) showed significant ($p<0.001$) increase in the rate of wound contraction from day 3 to 15 after injury with increased fibroblast proliferation and collagenation as well as re-epithelialisation compared with the untreated wounds. The methanol leaf extract of P. angulata possesses anti-inflammatory and wound healing activity which may justify the medicinal uses of this plant in the treatment of wounds.[8]

6) Antiasthmatic activity

In this study the methanolic leaves extract of Phyllis angulata Linn (Solanaceae) (PAL) was investigated for anti-histaminic activity by usingisolated animal smooth muscle models (guinea pig ileum preparation, guinea pig trachea and rat fundus strip), where the plants extract possess inhibitory efficacy against histamine and 5 – HT. Acute toxicity study of the plant extract was also performed to measure the safety prospective. In smooth muscle models, PAL possesses inhibitory efficacy by 100% (1 µg), 133% (2 µg) and 126% (4 µg) in guinea pig ileum preparation (GPIP) against 1 µg histamine; 86% (1 µg), 100% (2 µg) and 106% (4 µg) in guinea pig tracheal chain preparation(GPTCP) against 1 µg histamine; and 50% (1 µg), 75% (2 µg) and 100% (4 µg) in fundus strip preparation (FSP) against 1 µg 5HT. A survey by the National Asthma Campaign found that 60% of the people with moderate asthma and 70% with severe asthma used complementary and alternative medicine to treat their conditions. Herbal medicine is the third most popular choice of both adults (11%) and children (6%) suffering from asthma, although P. angulata is used for the treatment of

antihyper glycemic, anti-inflammatory, antimicrobial, antiseptic, antiviral, diuretic, expectorant and febrifuge. In traditional systems, there was only one claim for asthma. The present study will help the industry to produce herbal drug with less side effect, less cost and more effectiveness in the treatment of asthma.[9]

7) Anti-inflammatory and Anti-nociceptive activity

The anti-inflammatory activities of Piper cubeba (fruit), Phyllis angulata (flower) and Rosa hybrida (flower) were determined by carrageenan-induced paw edema, arachidonic acid-induced ear edema and formaldehyde-induced arthritis in mice. The anti-allergic and analgesic activities of these plants were also studied by using 2,4-dinitrofluorobenzene (DNFB)-induced contact hypersensitivity reaction (type IV) and hot plate test in mice, respectively. These plant extracts clearly exhibited inhibitory effects against acute and subacute inflammation by oral administration (200 mg/kg). Also, administration (200 mg/kg, p.o.) of plant extracts for 1 week significantly inhibited type IV allergic reaction in mice ($P<0.05$). Rosa hybrida showed an analgesic effect against hot plate-induced thermal stimulation at a dose of 200 mg/kg. These results provide support for the use of Rosa hybrida in relieving inflammatory pain, and insight into the development of new agents for treating inflammatory diseases.[10]

8) Antibacterial activity

The inhibitory activity of zinc oxide-ointment formulation as well as the unformulated crude extract of fruits of Phyllis angulata was investigated against clinical wound isolates of Staphylococcus aureus and Pseudomonas aeruginosa. The zinc oxide-ointment formulation and the unformulated P. angulata crude extract were found to be ineffective against P. aeruginosa at all concentrations used, but potent against S. aureus at varying degrees. The zinc oxide-ointment (100 mg g-1, 125 mg g-1 and 150 mg g-1) and P. angulata crude extract/zinc oxide-ointment (100 mg g-1, 125 mg g-1 and 150 mg g-1) formulations were only slightly active against S. aureus at the highest concentration of 150 mg g-1. The unformulated P. angulata crude extract alone exhibited the highest inhibitory activity against S. aureus at all concentrations used with zones of inhibition between 34.5 mm and 50.5 mm, followed by a formulation of the extract with only oleaginous base (ointment), with zones of inhibition between 12.8 mm and 20.3 mm. A one-way analysis of variance (ANOVA) of these values compared with the activity of Chloramphenicol (positive control) indicated significant inhibitory activity by the unformulated P angulata crude extract and the extract

and ointment for-mulation against S. aureus thus suggesting their efficacy in treating staphylococcal infections.[11]

9) Antimycobacterial activity

The HIV-tuberculosis co-infection has caused an impact on tuberculosis epidemiology all over the world and the efficacies of the therapeutic schemes traditionally prescribed in the treatment of tuberculosis, such as isoniazid, rifampicin and pyrazinamide, have decreased due to the appearance of multidrug-resistant M. tuberculosis strains (MDR). This work is part of research on natural antimicrobial agents from plant extracts through bioassay-guided fractionation, by in vitro determination of the minimum inhibitory concentration (MIC) using the microdilution method with Alamar blue oxidation-reduction dye. Crude CHCl3Physalis angulata extracts and physalin-containing fractions displayed antimycobacterial activity against Mycobacterium tuberculosis, Mycobacterium avium, Mycobacterium kansasii, Mycobacterium malmoense and Mycobacterium intracellulare.[12]

10) Antiulcer activity

The present study was designed to investigate the antiulcer effect of ethanolic extract of Phyllis angulata leaves (EEPAL) using different models of gastric ulceration in rats. Acute gastric ulceration in rats is induced by oral administration of noxious chemicals like aspirin and ethanol. Anti-secretory studies and total gastric acid output were studied using pylorus ligation technique. EEPAL was administered at the doses of 250 and 500 mg/kg orally to the respective experimental groups. Omeprazole was used as a reference drug. The antiulcer activity was assessed by determining and comparing the ulcer index in the test groups with that of the control group and standard group animals. EEPAL at the dose of 500mg/kg showed a significant reduction in the ulcer index and also significantly inhibited gastric mucosal damage induced by aspirin and ethanol. In pylorus ligated rats, EEPAL significantly reduced the basal gastric acid secretion. The present study suggested that the protective effect of EEPAL might be mediated by anti secretory and cytoprotective mechanisms. Moreover, further insight into the precise mechanism of action is essential to explore the complete potency of EEPAL and increase its usage in contemporary medicine.[13]

11) Analgesic and Anti inflammatory activity

Phyllis angulata is a medicinal plant used for the treatment of malaria, ulcer, pains and other diverse ailments. The present study evaluated the analgesic and anti-inflammatory activity of methanolic leaf extract of the plant. Acetic acid-induced abdominal contraction or writhing analgesic models in Swiss albino mice (13-23g) were used for studying analgesic activity of the leaf extract. 200, 300 and 400 mg/kg body weight of the extract were administered intraperitoneally. Analgesic activities of the extract were compared with standard reference drug ibuprofen (100 mg/kg) and negative control. The plant extract showed a significant dose dependent analgesic effect, with 72.7% inhibition at 400 mg/kg compared to that of the 100 mg/kg standard drug ibuprofen which showed 21.2% inhibition ($P< 0.05$). The anti-inflammatory activity of the extract against carrageenan-induced paw edema was also dose-dependent with 62.71% inhibition at 400 mg/kg when compared to that of the standard drug with 34.31% inhibition. The study showed that P. angulata was effective in pain reduction (analgesia) and acted as a good anti-inflammatory agent, which supports the claim in traditional medicine.[14]

12) Antidiabetic activity

Phyllis angulata L. is a plant applied in traditional treatment as a remedy for numerous ailments, which include diabetes mellitus. This study examines the antidiabetic effects of P. angulata fruit extract on streptozotocin-induced type-2 diabetes mellitus in rats. Rats were sorted randomly into five clusters, which are a normal cluster, a diabetic cluster, two diabetic clusters administered with the fruit extract of P. angulata, and a diabetic cluster administered with metformin. The diabetic rats were treated orally using 1 mL and 2 mL of P. angulata fruit extract every day for two weeks. The effects of P. angulata fruit juice were studied by measuring the body weight, Fasting Blood Glucose level, GLUT-4 genes expression and histopathological changes. P. angulata fruit juice significantly decreased the blood glucose level, therefore there is no significant changes of the body weight and upregulate GLUT4 gene expression in the soleus muscle. Histopathological analysis showed significant improvement results of pancreatic tissues that were treated with 2 mL/day compared to 1 mL/day. Furthermore, P. angulata fruit juice contains high concentration of vitamin C and phenolic compounds that could effectively attenuate diabetes. The results obtained provides important information that supports the use of P. angulata fruit in management of diabetes.[15]

13) Cytotoxic, Antimicrobial and Antioxident activity

Phyllis angulata L. belongs to the family Solanaceae and is distributed throughout the tropical and subtropical regions. Phyllis angulata leaf and fruit extracts were assessed for in vitro anticancer, antioxidant activity, and total phenolic and flavonoid content. The GC-MS technique investigated the chemical composition and structure of bioactive chemicals reported in extracts. The anticancer activity results revealed a decrease in the percentage of anticancer cells' viability in a concentration- and time-dependent way. We also noticed morphological alterations in the cells, which we believe are related to Phyllis angulata extracts. Under light microscopy, we observed that as the concentration of ethanolic extract (fruit and leaves) treated HeLa cells increased, the number of cells began to decrease.[16]

14) Antitumor activity

We have evaluated the in-vitro and in-vivo antitumour activity of physalin B and physalin D isolated from the aerial parts of Phyllis angulata. In-vitro, both compounds displayed considerable cytotoxicity against several cancer cell lines, showing IC50 values in the range of 0.58 to 15.18 μg mL−1 for physalin B, and 0.28 to 2.43 μg mL−1 for physalin D. The antitumour activity of both compounds was confirmed in-vivo using mice bearing sarcoma 180 tumour cells. The in-vivo antitumour activity was related to the inhibition of tumour proliferation, as observed by the reduction of Ki67 staining in tumours of treated animals. Histopathological examination of the kidney and liver showed that both organs were affected by physalin treatment, but in a reversible manner. These compounds were probably responsible for the previously described antitumour activity of ethanol extracts of P. angulata, and their identification and characterization presented here could explain the ethnopharmacological use of this species in the treatment of cancer.[17]

CONCLUSION

This review paper shows the Pharamacognostical studies(Taxonomy, Phytochemical of Phyllis angulate and the pharmacological activities like anti-bacterial, anti-cancer, anti-ulcer etc. Extract of Phyllis angulate leaves contains more bioactive principles, which act against the representative human pathogens. Moreover, this reviewed article showed more pharmacological applications and Pharmacological studies helps to developing the allopathy and traditional formulations.

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