ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Polyalthia longifolia Sonn: an Ancient Remedy to Explore for Novel Therapeutic Agents

Subramanion L Jothy[1], Yee Siew Choong[1], Dharmaraj Saravanan[2], Subramanian Deivanai[3], Lachimanan Yoga Latha[1], Soundararajan Vijayarathna[1], Sreenivasan Sasidharan[1]*

[1] Institute for Research in Molecular Medicine (INFORMM), University Sains Malaysia, 11800 USM, Penang, Malaysia
[2] Faculty of Medicine and Health Sciences, University Sultan Zainal Abidin, Kota Kampus, 20400 Kuala Terengganu, Terengganu, Malaysia
[3] Department of Biotechnology, Faculty of Applied Sciences, AIMST University, Jalan Bedong Semeling, Batu 3½, Bukit Air Nasi, Bedong 08100, Kedah, Malaysia

ABSTRACT

Polyalthia longifolia (Sonn.) Thwaites (PL) (Family: Annonaceae) is a tall handsome evergreen tree and it is cultivated all over India. The plant has been commonly used in traditional system of medicine for the treatment of fever, skin diseases, diabetes, hypertension and helminthiasis. In view of the immense medicinal importance of P. longifolia, this review was aimed at compiling all currently available botanical, phytochemical, pharmacological, and toxicological and ethnomedical information on P. longifolia's including its mechanisms of action. Information in the biomedical literature has indicated the presence of a variety of medicinally-important chemical constituents in P. longifolia. Pharmacological studies by various groups of investigators have shown that P. longifolia possesses significant biological and pharmacological activities, such as antibacterial, antifungal, antitumor, anti-ulcer and antioxidant properties. Beside this, toxicity studies of this plant have revealed no toxic effect on mice. P. longifolia can be considered as an ancient remedy to be explored for the development of various novel therapeutic agents.

Keywords: Polyalthia longifolia, pharmacological properties, ethnomedicinal uses, phytochemistry

Corresponding author

ISSN: 0975-8585

INTRODUCTION

Medicinal plants play vital role in the sustainability of the human race in this earth planet. Plants continuously provide us oxygen for breathing, nutrient through edible plants and bioactive ingredients as medicine for our health through phythochemicals. Therefore we cannot deny the important role of the medicinal plant in human life especially the medicinal uses of plants, has provided many important drugs of modern day [1-3]. Even at present day medicinal plants play important roles despite the tremendous scientific development and holds much more hidden treasure to be explored as almost 80% of the human population in developing countries is dependent on plant resources for their primary healthcare [4]. Medicinal plants used in traditional medicine in developing countries contain a wide range of phythochemicals that can be used to treat chronic as well as infectious diseases in the treatment of present or future diseases [5]. One such plant belonging to the genus Polyalthia and known to have curative value is Polyalthia longifolia (Sonn.) Thwaites (PL) from Annonaceae family (Figure 1). Polyalthia is the Greek word for poly, meaning much or many and althia from àltheo, meaning to cure, which showed its multiple health benefit. The genus Polyalthia includes about 120 species occurring mainly in Africa, South and South-Eastern Asia, Australia, and New Zealand [6]. P. longifolia is one of the most important indigenous medicinal plants in Indian medicinal Literature is found throughout Malaysia and widely used in traditional medicine as febrifuge and tonic. Almost all parts of this plant are used in Indian traditional system for the treatment of various ailments and the significant medicinal properties was further reported through scientific investigation. However, detailed information on P. longifolia is lacking. Keeping this in view the present review was focused on the botany, phytochemistry, pharmacology, toxicity, safety and ethnomedicinal uses of P. longifolia.

BOTANY

Scientific Name: Polyalthia longifolia (Sonn.) Thwaites (PL) (Figure 1 and Figure 2).

Common Names : False Ashoka, Buddha Tree, Green champa, Indian mast tree, and Indian Fir tree.

Synonyms: Uvaria longifolia Sonn., Guatteria longifolia (Sonn.) Wallich, Unona longifolia (Sonn.)

ISSN: 0975-8585

Figure 1. Polyalthia longifolia . F, fruit and L, leaf

Classification of Polyalthia longifolia

Kingdom	Plantae
Division	Magnoliophyta
Class	Magnoliopsida
Subclass	Magnoliidae
Order	Mognoliids
Family	Annonaceae
Tribe	Annoneae
Genus	Polyalthia
Species	Longifolia

Distribution of Polyalthia longifolia

Native to India and Sri Lanka and it has been introduced in gardens of many tropical countries across the world.

ISSN: 0975-8585

Figure 2: The Polyalthia longifolia herbarium

Botanical Description of Polyalthia longifolia

Evergreen tree can grow up to a height of 15-20 meters tall. Young plants have straight trunks and weeping pendulous branch. The longest branch is seen at the base and shorter at the end of the trunk, giving an appearance of conical crown. Leaves are long, narrow dark green and glossy. Leaf blades are ovate-oblong to ovate-lanceolate with wavy margins. Reticulate veins rose on both surfaces of leaf. Transverse section of the leaf through the midrib showed bowl shaped abaxial parts and straight adaxial side. Both the adaxial and abaxial epidermal layers were single layered thin walled cubical cells. The epidermal cells wide, polygonal, thin walled and the walls were straight or slightly wavy. The epidermal cells followed by four to six layers of angular collenchyma cells on both the sides. In the midrib region, vascular bundle is encircled by a schlerenchymatous ring (Figure 3). Bundle sheath, xylem and phloem are clearly visible Inflorescences axillary, fasciculate and shortly pedunculate, racemose, or umbelliform and sessile, mostly many flowered. Flowers are delicate pale green with wavy petals. The flowers last for a short period, usually two to three weeks and are not conspicuous due to their color. Sepals are ovate-triangular, outside it is tomentulose but inside glabrous. Petals are greenish yellow, narrowly triangular-lanceolate. Stamens are; connectives apically convex. Carpels are 20-25 in number with one ovule per carpel; stigmas are sessile. Fruits are borne in clusters of 10-20, usually ovoid in shape. Initially fruits are green in color but turns purple or black when ripe. Seeds are pale brown, ovoid, with a longitudinal groove [7].

Propagation of Polyalthia longifolia

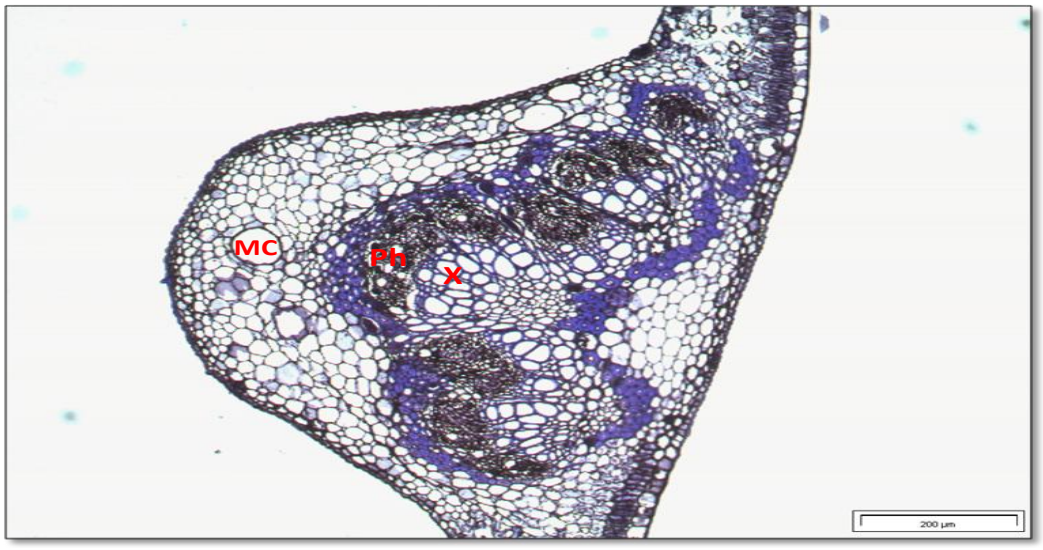
It is generally propagated through seeds, but occasionally through soft wood cuttings and air layering.

ETHNOMEDICINAL USES OF POLYALTHIA LONGIFOLIA

Enthnobotany is a conception of conscientious use of natural resources. Ages ago, these resources had rendered the rudimentary essence of every medicinal folk culture throughout the world. In contemplating the folk culture, one should be able to translate, interpret, and amalgamate these native concepts and beliefs pertaining to illness, its signs and symptoms. In uniformity, it may beget a better practical biomedical image of therapeutic study [8]. It follows that, the plant Polyalthia longifolia had long served the purpose of being medically important as per Ayurveda.

ISSN: 0975-8585

Figure 3: Transverse section of P. longifolia leaf midrib view. X: xylem; Ph: phloem; MC: mucilage cavity.



P. longifolia bark is the most common serving part of this plant as it had been use to treat pyrexia [9], rheumatism, menorrhagia, scorpion sting and diabetes [10], meanwhile the decoction is widely used for curing mouth ulcer in many parts of India [11]. For instance, the Eastern Ghats culture use the stem bark as a combination ingredient to Sesamum indicum and Piper nigrum seeds to treat bone fractures. Similarly, a different mixture of Mimosa intsia root bark, Tridax procumbens leaves and stem bark of P. longifolia is also prepared and bandaged daily till the fractures cured [12]. The bark is bitter, acrid, cooling and febrifuge. Beside from being a good febrifuge agent, it is believed also to relieve skin disease, hypertension, helminthiasis and vitiate conditions of vata and pitta. Likewise, the bark embraces the treatment for digestive system, constipation, circulatory system, urinary system, and antipyretic activity [13]. The herb healers from Uthiramerur, use the stem bark extract orally for indigestion [14] plus the traditional healers of Trinulveli, as treatment for diarrhoea and dysentery [15]. The Kavirajes practitioners administer the bark or crushed whole plant as antiseptic for most fungal infections [16-18].

The Kavirajes also have an unfamiliar way in exerting the benefits from the roots of P. longifolia. The roots are cooperated with the roots of Morinda citrifolia and rhizomes of Curcuma longa for treating snake bites [16]. Coterminously, healersfrom Sylhet, Bangladesh accompany crushed leaves and barks of P. longifolia in recuperating coughs and mucus formation [18]. As a whole, the plant had been traditionally used to lower blood pressure, stimulate respiration, and recover uterus ailment, gonorrhoea, leucorrhoea and menorrhagia [19].

PHYTOCHEMISTRY OF POLYALTHIA LONGIFOLIA

Phytochemical studies of P. longifolia have been carried mainly since 1980s and often have resulted in the isolation of diterpenoids and alkaloids. Most of the studies involve the use

of stem and bark of stem but a few report work done on leaves and berries. Samples are often from the Indian subcontinent but some studies have used Chinese samples. Literature report few phytochemical screening tests on this plant and the study of Malairajan et al. [20] report only the presence of alkaloid and terpenoids. However, chromatographic screening with spray reagents revealed the presence of steroids, alkaloids, terpenoids, phenolics and flavonoids as major phytochemicals [21, 22].

Initial isolation studies were carried out to obtain antifeedant compounds from this plant led to discovery of 16α-hydroxy-cleroda-3,13(14)Z-dien-15,16-olide (Figure 4) and 16-oxocleroda-3,13(14)E-dien-15-oic acid from leaves of the plant [23] . Two new clerodane diterpenes were later isolated from bark by others [24] and these were γ-methoxybutenolide and γ-hydroxybutenolide. Later, another γ-hydroxybutenolide with an oxiran ring were isolated also from bark [25]. Three new clerodanes were obtained from stem by Hara et al. [26] and these were 16-hydroxycleroda-4(18),13-dien-16,15-olide, 16-oxocleroda-4(18),13E-dien-15-oic acid, cleroda-4(18),-13-dien-16,15-olide. Other clerodanes obtained by other researchers were 6α,16-dihydroxycleroda-3,13-dien-15-oic acid, 6α,16-dihydroxycleroda-4(18),13-dien-15-oic acid, and 4α,18β-epoxy-16-hydroxyclerod-13-en-15-oic acid from stem [27] as well as 16-hydroxycleroda-13-ene-15,16-olide-3-one from bark [28].

Bioassay monitored isolation work on the methanol extract of leaves and berries lead to three new clerodane diterpene from this plant; methyl-16-oxo-cleroda-3,13(14)E-dien-15-oate, 3β,16α-dihydroxy-cleroda-4(18), 13(14)Z-dien-15,16-olide, and solidagonal acid [29]. Later, two other clerodane diterpenes were obtained from leaves and these were 3α,16 α-dihydroxycleroda-4(18),13(14)Z-dien-15,16-olide and 3β,16 α-dihydroxycleroda-4(18),13(14)Z-dien-15,16-olide [30]. The dimeric clerodane diterpene has also been isolated and two examples of this bisclerodane compound are Longimide A and Longimide B (Figure 4). These compounds were isolated together with a cycloartane triterpene. The triterpene was named longitriol [31].

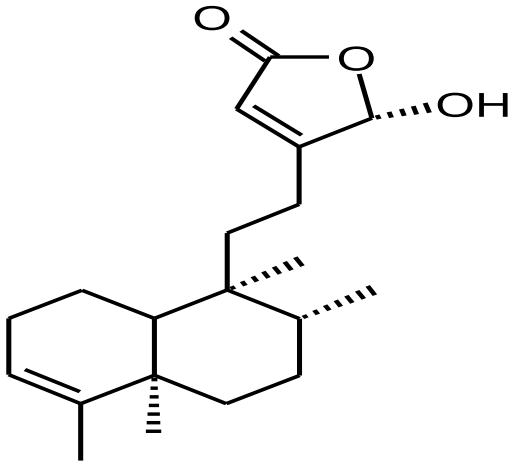
Another group of diterpenes with quite similar structure to the clerodanes have also been isolated from this species and these compounds are the ent-halimanes. These compounds were initially isolated from these species by Hara et al [26] and they are 16-hydroxy-ent-halima-5(10),13-dien-16,15-olide, ent-halima-5(10),13E-dien-15-oic acid, ent-halima-1(10),13E-dien-15-oic acid, 16-oxo-ent-halima-5(10),13E-dien-15-oic acid, ent-halima-5(10),13-dien-16,15-olide and ent-halima-1(10),13-dien-16,15-olide. Later another compound of this type was isolated and it was 3β,5β,16α-trihydroxyhalima-3(14)en-15,16-olide [32].

Other than terpenoids the other major group of chemical from this plant was alkaloid. Two structurally different groups of Alkaloids from this plant are azafluorene, aporphine and protoberberine alkaloids. Examples of azafluorene alkaloids from this plant are polylongine [33]; polyfothine (Figure 4), isooncodine, and darienine [34] using samples from Taiwan whereas samples from Pakistan showed presence of penduline and isoursuline. The earlier group of researchers also obtained aporphine alkaloids and examples of this type are (+)-O-methylbulbocapnine-β-N-oxide, (+)-O-methylbulbocapnine-α-N-oxide, (+)-N-

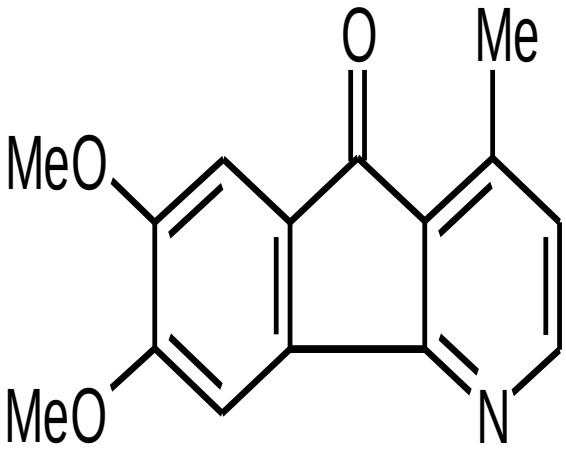
ISSN: 0975-8585

methylnandigerine-β-N-oxide [33] as well as liriodenine, noroliveroline (Figure 4) and oliveroline-β-N-oxide [34]. The protoberberine compounds obtained were (-)-8-oxo-polyalthiaine by Chen et al. [32]; pendulamine A (Figure 4), pendulamine B [35] as well as (-)-8-Oxo-10- hydroxy-2,3,9-trimethoxyberberine, (-)-8-Oxo-2,11-dihydroxy-3, 10-dimethoxyberberine, (-)-8-Oxo-11-hydroxy- 2,3,9,10-tetramethoxyberberine and (-)-8-Oxo-2,10-dihydroxy-3,9,11-trimethoxyberberine by Lee et al. [27].

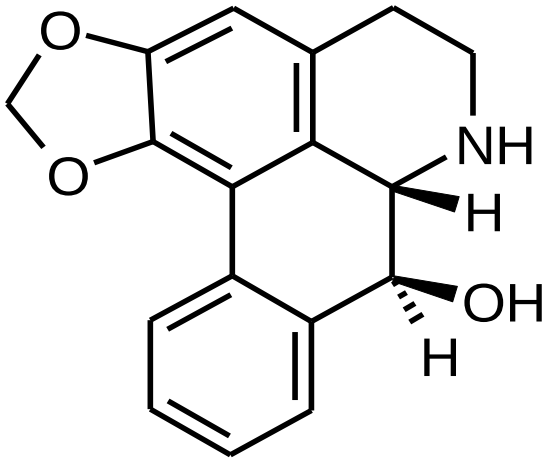
Figure 4: Various phytochemicals isolated from Polyalthia longifolia



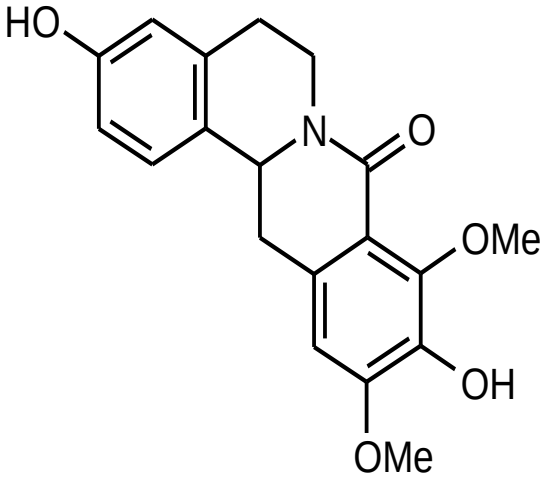
16α-hydroxy-cleroda-3,13(14)Z-dien-15,16-olide



Polyfothine

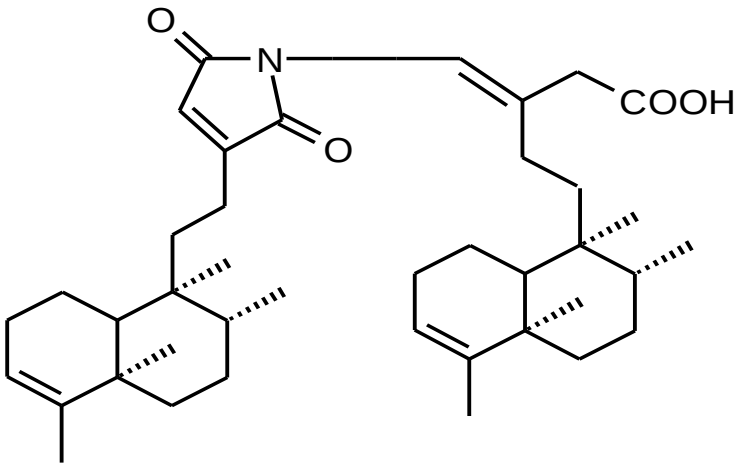


Noroliveroline



Pendulamine A

ISSN: 0975-8585



Longimide B

Although flavonoids were detected in the phytochemical screening mentioned earlier, they were not isolated in the above studies. The essential oils of the leaf and stem bark of P. longifolia Thw., (Annonaceae) have been studied for their constituents by means of gas chromatography and gas chromatography/mass spectrometry. Similar approach could be used for flavonoids using liquid chromatography/mass spectrometry and such a profile could be analysed by chemometric methods for quality control as done for the traditional chinese medicine, Scutellaria barbata by Pan et al. [36].

PHARMACOLOGICAL ACTIVITIES OF POLYALTHIA LONGIFOLIA

Pharmacognostic studies and physicochemical properties of the P. longifolia leaf

Standardization of P. longifolia leaf was reported by Dave et al. [37] with respect to authenticity, macroscopic and microscopic, and physiochemical analysis. They had done various pharmacognostic studies including examinations of macroscopic and microscopic characters, and powder analysis were determined on leaf of P. longifolia. The physiochemical properties such as loss on drying, total ash value, acid insoluble ash value, water soluble ash value, pH, boiling point, melting point and extractive values of leaf were carried out. The solubility of methanolic extract of leaves was carried out in various polar and nonpolar solvents. Their studies provided crucial information for correct identification and standardization of P. longifolia leaf material.

Antibacterial activity

The preliminary antibacterial activity of various solvent extract (petroleum ether, chloroform ethyl acetate, ethanol and aqueous) of Polyalthia longifolia leaves was studied against six different bacteria by disc diffusion method [22]. The study revealed that all the extract possesses potent antimicrobials against all the test pathogenic organisms. The antibacterial activity was screened by measuring the zone of inhibition. Among various extracts,

chloroform extract showed the higher degree of inhibition followed by ethylacetate, ethanol, and petroleum ether. The aqueous extract showed minimum inhibitory effect compared to all other extracts. The diameter of inhibition zones for each samples were compared with standard antibiotic positive control chloramphenicol (30 mcg/disc). The highest antibacterial activity was reported against Bacillus subtilis (26 mm) in chloroform extract, followed by Staphylococcus aureus (25 mm), Escherichia coli (24 mm), Pseudomonas aeruginosa (24 mm), Proteus vulgaris (23 mm) and Salmonella typhi (21 mm). Meanwhile, similar phenomena were observed in all other extract with an average zone of inhibition. In another study by Uzama et al. [38], the antibacterial activity of methanolic leaf extract of P. longifolia showed highest degree of inhibition against Bacillus subtilis (24 mm), which was comparable with standard positive control chloramphenicol (22.3 mm) and ciprofloxacin (24 mm) followed by Staphylococcus aureus (22.6 mm). Meanwhile, the leaf extract did not show any inhibitory effect against Klebsiella pneumonia and Escherichia coli. In addition to the disc diffusion method the P. longifolia leaf extract was also further subjected to determine the minimum inhibitory concentration (MIC) and Minimum bactericidal concentration (MBC) to evaluate its potency as an antimicrobial agent. The leaf extract shows favourable antibacterial activity with minimum inhibitory concentration (MIC) against Bacillus subtilis (0.01 mg/ml) and Staphylococcus aureus (0.01 mg/ml). Meanwhile, Minimum Bactericidal Concentration (MBC) of leaf extract was ranged between 0.01 and 1.3 mg/ml. Apart from that, the stem bark of P. longifolia was also reported for its antibacterial activity against Gram positive and Gram negative bacteria [39]. The inhibitory activity of the extract was compared with the standard antibiotics Ciprofloxacin, Roxithromycin and Cefuroxime. The extract shows significant antibacterial activity against all the tested bacteria which was suggested as potential antibacterial agent. In addition, Chanda & Nair [40] also tested the methanol, acetone and 1,4-dioxan fractions of leaf of P. longifolia were evaluated for antibacterial and antifungal activity. They were used 91 clinically important strains for their study which were both clinical isolates as well as identified strains. They reported that the extract and fraction was showed more pronounced antimicrobial activity against gram positive bacterial and fungal strains and poor activity was shown against gram negative bacterial strains studied. Shazid et al. [41] also reported antibacterial activity of 90% ethanol extract from barks of P. longifolia. They reported that ethanol extract from barks of P. longifolia showed significant (21 - 32 and 30 -44 mm in diameter zone of inhibition) antibacterial activity against all the test bacteria at 400 and 600 µg/ml.

Antioxidant activity

The in vitro antioxidant potential of ethanolic stem bark extract of P. longifolia was evaluated for its role on reactive oxygen species in tumor initiation and progression [42]. The extract scavenged DPPH radicals, reduced ferric ions and inhibited lipid peroxidation with IC_{50} values of 18.14, 155.41 and 73.33 microg/mL, respectively. In addition, the methanolic stem bark extract of P. longifolia was evaluated for its radical scavenging potential [43]. The extract at 100 µg/ml concentration showed maximum scavenging of the radical cation in ABTS observed up to 54.79 % followed by scavenging of stable radical DPPH (75.36 %), Nitric oxide (57.25 %) and Super oxide dismutase (78.40 %) at the same concentration. The IC_{50} values of this extract in these models were calculated as 77.07, 46.84, 88.54 and 40.91 respectively at 1

mg/ml concentration. Another study by Vijaya et al. [44], was to evaluate the antioxidant activity of seed extracts of P. longifolia. Petroleum ether, chloroform, methanol and aqueous extracts of seeds of P. longifolia were evaluated for preliminary antioxidant activity using DPPH and FRAP assays. Among the various extracts methanol and petroleum ether extracts showed good antioxidant activity with IC_{50} 98.43 and 62.52 for DPPH assay while 1.40 and 0.81 for FRAP assay. Whereas, aqueous extract showed very low activity in both of the antioxidant assays tested. The antioxidant activity of ethanol extract of the seeds and leaves of P. longifolia was determined by measuring the radical scavenging activity against 2, 2 – Diphenyl– 1-picryl hydrazyl radical (DPPH) [45]. The highest radical scavenging effect was observed in leaves with IC_{50} 0.5824mg/ml than in seeds with IC_{50} 1.4677 mg/ml. Phenolic compounds and flavonoid contribute to this activity.

Anti-inflammatory activity

The anti-inflammatory activity of various solvent extract (petroleum ether, hexane, toluene, chloroform, acetone and methanol) of P. longifolia leaf was evaluated using acute inflammatory studies in Wistar albino rats [46]. Methanolic extract revealed most potential ant-inflammatory effect hence; three doses of methanolic extract (300, 600, 900 mg/kg) were used to evaluate its potential as an anti-inflammatory agent. The three doses of methanolic extract showed anti-inflammatory activity comparable to that of the standard (Diclofenac sodium). Thus the results indicates the methanolic leaves extract of P. longifolia possess a significant anti-inflammatory activity. Another study by Sharma et al. [47], as evaluated the anti-inflammatory potential of ethanolic and aqueous extracts of P. longifolia leaf in albino wister rats. Anti-inflammatory activity was also reported using Cotton pellet granuloma study which is a sub-acute anti-inflammatory model. Where the weight of cotton pellet was determined at the end of the study and the percentage decrease in granuloma tissue weight was also found out. All the extracts were found to produce significant ($P<0.001$) decrease in the granuloma tissue as evident by the decrease in the weight of cotton pellet when compared to the disease control. Both ethanolic and aqueous leaf extracts revealed anti-inflammatory activity comparable ($P<0.05$) with indomethacin and at dose 300 mg/kg being the most active, exhibited maximum anti-inflammatory activity. However, the aqueous extracts showed better ($P<0.05$) anti-inflammatory activity when compared to the ethanolic extracts at dose of 200mg/kg body weight.

Anticancer activity

The in vitro and in vivo antitumor activity of ethanolic stem bark extract of P. longifolia was evaluated by Manjula et al. [42]. The extract was reported for in vitro cytotoxicity using murine cancer cells and human cancer cells by Trypan blue exclusion assay and MTT assay, respectively. The extract showed concentration-dependent cytotoxicity in Ehrlich's ascites carcinoma (EAC) and Dalton's ascites lymphoma (DLA) cells with IC_{50} values of 45.77 and 52.52 microg/mL, respectively. In the MTT assay, the IC_{50} values of extract against HeLa and MCF-7 cells were 25.24 and 50.49 μg/mL, respectively. The extract was further subjected for in vivo antitumor activity against Ehrlich's ascites tumor and Dalton's solid tumor models by

administering 50 and 100 mg/kg extract, i.p., for 7 consecutive days. Stem bark extract of P. longifolia at a dose of 100 mg/kg, significantly enhanced mean survival time (MST) and marginally improved hematological parameters when compared to EAC control mice. And the same dose significantly reduced the tumor volume as compared to control DLA inoculated mice. Positive control, cisplatin (3.5 mg/kg, i.p., single dose), significantly enhanced MST and improved hematological parameters when compared to EAC and significantly reduced the tumor volume when compared to DLA control. Apart from that, another study by Rajesh et al. [48] was further evaluated the P. longifolia extract for its in vitro anticancer activity using various cancer cell lines namely HeLa-B75, HEP-3B and PN-15. The potential anticancer activity towards cancer cell lines determine based on IC_{50} values 68.22, 39.15 and 55.21 respectively. Verma et al. [49] also reported for the first time the anticancer potential of P. longifolia leaf extract (A001) and its chloroform fraction (F002). They reported that both inhibited cell proliferation of various human cancer cell lines in which colon cancer cells SW-620 showed maximum inhibition with IC(50) value 6.1 microg/ml. Furthermore, F002 induce apoptosis in human leukemia HL-60 cells as measured by several biological end points. F002 induce apoptotic bodies formation, DNA ladder, enhanced annexin-V-FITC binding of the cells, increased sub-G(0) DNA fraction, loss of mitochondrial membrane potential (DeltaPsi(mt)), release of cytochrome c, activation of caspase-9, caspase-3, and cleavage of poly ADP ribose polymerase (PARP) in HL-60 cells. They concluded that all the parameters they evaluated revealed that F002-induced apoptosis through the mitochondrial-dependent pathway in HL-60 cells.

Hepatoprotective activity

The hepatoprotective activity of extracs (petroleum ether, hexane, toluene, chloroform, acetone and methanol) of P. longifolia leaf was evaluated using Wistar albino rats [46]. The methanolic leave extract showed a significant hepatoprotective activity. Therefore, the extract was further subjected into three different concentrations (300, 600, 900 mg/kg) to determine its potential as an hepatoprotective agent. Diclofenac sodium was used as the toxicant in hepatoprotective studies, in which various serum biochemical parameters and liver glycogen were assessed. All the serum biochemical parameters studied revealed the hepatoprotective nature of the methanol extract, but a concentration effect was not observed. Another study was undertaken by Jain et al. [50], to ascertain the hepatoprotective effect of dried leaf of P. longifolia. Ethanolic leaf extract of P. longifolia was evaluated and subjected for hepatoprotective activity in Wistar strain of albino rats of either sex against CCl_4 induced hepatic damage. SGOT, SGPT, ALP and total bilirubin were used as biochemical marker for assessment of the activity. The increased serum level of enzymes SGOT, SGPT, ALP and bilirubin were monitored in rats administered carbon tetrachloride, which were very much reduced in the animals treated with the ethanolic fraction. In recent reports Jothy et al [51], reported in vivo hepatoprotective activity of P. longifolia methanol extract in paracetamol intoxicated mice. They found that the therapy of P. longifolia showed the liver protective effect on biochemical and histopathological alterations. Moreover, in their histological studies also supported the biochemical finding that is, the maximum improvement in the histoarchitecture of the liver. Their results revealed that the P. longifolia leaf extract could protect the liver against

paracetamol-induced oxidative damage by possibly increasing the antioxidant protection mechanism in mice.

Antihyperglycemic activity

Nair et al. [52] reported the hypoglycemic and antihyperglycemic activity of various solvent extracts of P. longifolia leaf extracts which was evaluated in alloxan induced experimental diabetes in rats. Diabetes was induced by them using 180 mg/kg i.p. of alloxan consecutively two times at an interval of 24 h. The test drugs were administered for 7 days. On 8th day various biochemical parameters like serum cholesterol, serum urea, serum creatinine, serum triglyceride, total serum protein, serum alkaline phosphatase, blood glucose and glycogen from liver were estimated. The authors reported that P. longifolia extracts and powder produced glucose lowering activity. However, the extracts did not modify any of the biochemical parameter significantly. Hence they concluded that the extracts and crude powder are devoid of anti-diabetic properties, but has gross glucose lowering properties. The presence of anti-hyperglycemic effect against sucrose loading induced hyperglycemia is a significant finding and they considered that this effect is most important property in a drug used in diabetes treatment.

Biological activity of the isolated compounds from P. longifolia

Hypotensive activity

Saleem et al. [53] was repoted the hypotensive activity and toxicology of constituents isolated from root bark of P. longifolia. They observed a defatted extract of P. longifolia from root bark in 50% methanol showed a significant ability to reduce blood pressure in their experiment. It caused a 22% and 47% fall in mean arterial blood pressure (MABP) in rats at doses of 3 mg/kg and 30 mg/kg, respectively. They also purified compounds from this extract included kolavenic acid, clerodane and its isomer, liriodenine, lysicamine and bisclerodane imide and its isomer. Of these isolated compounds, only kolavenic acid produced a 22% fall in MABP, at a dose of 30 mg/kg. Extract of P. longifolia from root bark showed a decrease in blood pressure of normotensive and egg yolk induced hypertensive rats. The LD50 of extract of P. longifolia from root bark was determined as 100 mg/kg in mice in their study.

Antimicrobial activity

Murthy et al. [54] isolated two compound namely diterpenoids 16α-hydroxy-cleroda-3,13 (14)-Z-diene-15,16-olide (1) and 16-oxo-cleroda-3, 13(14)-E-diene-15-oic acid (2) from the hexane extract of the seeds of P. longifolia, and reported antibacterial and antifungal activities of this compounds. Compounds (1) and (2) demonstrated very good activity against Gram negative and Gram positive bacteria. Of the two, compound (1) is highly active against Gram negative bacteria such as E. coli, K. aerogenes, Pseudomones species and S. lutea with MICs 0.78–1.5 Ag. Amongst Gram positive bacteria Bacillus species are highly active with less than 2

Ag of MIC. In general, they reported that the compound (1) is highly active against Gram negative bacteria and compound (2) against all the bacteria tested. Compound (1) exhibited more activity than standard gentamycin. Compound (2) showed higher activity against fungi than compound (1) with MIC values of 25 to 50 Ag. The activity is compared with fungicide Dithane M-45. Candida and Saccharomyces species recorded MIC values of 12.5–25 Ag comparable with standard Nystatin. Furthermore, Bose et al. [55] also reported the antimicrobial activity of isolated flavonoid fractions of P. longifolia bark namely F1 and F2. In antimicrobial activity, they used six microorganisms, which included two Gram positive, two Gram negative bacteria and two fungi. In their antimicrobial test, the compound F1 showed highly significant result against B.subtilis. It showed moderately significant result against B. thuringiensis, E. coli and P. aeruginosa. Similarly, they reported that the compound F2 showed moderately significant results against B. subtilis, B. thuringiensis, E. coli and P. aeruginosa. They also found that the isolated compounds showed promising results against various micro-organisms in comparison with standard drugs such as Penicillin, Gentamicin and Ketoconazol.

Antioxidant activities

Bose et al. [55] reported the antioxidant activity of isolated flavonoid fractions of P. longifolia bark namely F1 and F2. Their preliminary phytochemical investigation of various extracts of the bark of P. longifolia showed the presence of flavonoids, alkaloids, steroids and carbohydrates. After that they attempted to isolate flavonoids and perform antioxidant activity of the isolated compounds. They carried out DPPH radical scavenging assay, nitric oxide scavenging assay, metal chelating activity and reducing power activity in antioxidant activity. They found that the both of the isolated flavonoids exhibited a concentration-dependant free radical scavenging capacity.

DOSAGE/MODE OF USAGE

Stem bark, flower, leaf, root and fruit can be used as potential herbal samples in pharmacy as decoction.

TOXICOLOGICAL ASSESSMENT

Chanda et al recently reported the acute oral toxicity of P. longifolia leaf extract in Wistar albino rats. The parameters they evaluated daily after oral drug administration of the extract (540, 1080, 2160 and 3240 mg/kg body weight) were mortality, signs of toxicity, feed and water consumption and body weight changes up to 14 days. The effect of different doses of the extract on organ weight, biochemical and hematological parameters also were evaluated on the 15th day. They found that the methanol extract of P. longifolia leaf up to the dose level 3240 mg/kg body weight did not produce any toxic effect or death; the extract was well tolerated by the rats. They also reported that the extract did not alter body weight, feed and water consumption. The organ weight, biochemical and hematological analysis did not show any dose-dependant changes in any of the parameters examined in animals of both sexes. They concluded that the acute oral administration of the methanolic extract of P. longifolia leaf was

not toxic and safe in a single dose [56]. Oral acute toxicity of P. longifolia leaf also reported by Nair et al. [57] in mice. They were administered orally (p.o.) five different dose levels of P. longifolia leaf extract to the animals. The 5 dose levels studied were 400 mg, 800 mg, 1200 mg, 1600 mg and 3200 mg/kg. From safety assessment in acute condition and gross behavioral studies it is concluded that all extracts produced mild to moderate hypo activity and also exhibited analgesic activity to some extent. They concluded that crude powder and the extracts of P. longifolia leaf are considered as safe in acute condition up to 3.2 g/kg dose level. Further more, Shazid et al. [41] as well reported toxicity of 90% ethanol extract from barks of P. longifolia by using brine shrimps lethality assay. The researcher reported that extract from barks of P. longifolia showed a very low level of general toxicity in the brine shrimps lethality assay with a LC50 of 20 µg/ml and LC_{90} value of 70.80 µg/ml.

PRECAUTIONS/SAFETY FOR USAGE

Although medicinal plants are natural, and some have been in use for thousands of years in the traditional medicinal practices, this does not necessarily mean that they are always safe and without side effects. Therefore the safe use of the medicinal plants is of major importance since many herbal plants are self prescribed and patients usually do not inform their doctors that herbal medicines are being consumed. Hence, the consumer should tell their doctor that they may be considering using P. longifolia preparations. In addition, the consumer also must always tell their doctor when and why they have stopped taking an herbal medicine, especially if it is due to allergic or adverse reaction. Moreover, precautions should be taken to ensure collection of P. longifolia that has not been sprayed with weed killer. The samples are to be washed thoroughly or soaked with water to remove unwanted pollution.

CONCLUSIONS

In this review, we attempted to bring together the botanical, Phytochemical, pharmacological, toxicological and ethnomedicinal information on P. longifolia, a medicinal herb used in the traditional medicine and an ancient remedy to be explored for novel therapeutic uses. The survey of the literature revealed the presence of various phytochemicals in P. longifolia, which will be lead compound for novel therapeutic agents. It also revealed a broad spectrum of pharmacological activities and traditional uses of the P. longifolia.

ACKNOWLEDGEMENTS

Subramanion L Jothy was supported by MyPhD fellowship from the Ministry of Higher Education, Government of Malaysia, Malaysia.

REFERENCES

[1] Anonymous. Ethnobotany in the search for new drugs. Ciba Foundation Symposium188, John Wiley and Sons, New York, USA, 1994.
[2] Cox PA, Ballick MJ. Sci Am 1994; 270: 82-87.

[3] Fabricant DS, Farnsworth NR. Health Perspect. 2001; 109: 69-75.
[4] Farnsworth NR, Akerele O, Bingel AS. Bull WHO 1985; 63: 965-981.
[5] Duraipandiyan V, Ayyanar M, Ignacimuthu S. BMC Complement Altern Med. 2006; 6: 35.
[6] Katkar KV, Suthar AC, Chauhan VS. Pharmacogn Rev. 2010; 4: 62-68.
[7] Lemmens RHMJ, Bunyapraphatsara N. (Eds.). Plant Resources of South-East Asia No. 12(3). In Medicinal and Poisonous Plants 3, Backhuys Publishers: Leiden, Netherlands, 2003.
[8] Elisabetsky E, Posey DA. Anais do 10 Symposio do Tropico Umido. 1986; 2: 85-93.
[9] Krishnamurthi A. The wealth of India, Publication and Information Directorate CSIR: New Delhi, India, 1969, Volume VIII, pp. 187-188.
[10] Savithramma N, Linga Rao M, Suhrulatha D. MEJSR. 2011; 8 579-84.
[11] Pradhan P, Jhajharia M, Chulet R, Yagnik D. Pharmacologyonline 2011; 2: 11-15.
[12] Sunnetha J, Prasanthi S, Ramarao Naidu BVA, Seetharami Reddi TVV. Indian J Tradit Know. 2011; 10: 550-553.
[13] Katkar KV, Suthat AC, Chauhan VS. Pharmacog Rev. 2010; 4:, 62-68.
[14] Sugumaran M, Bharathi V, Hemachander R, Lakshmi M. J Chem Pharm Res. 2010; 2: 463-470.
[15] Vanila D, Ghanthikumar S, Manickam VS. Ethnobotanical Leaflets 2008; 12: 1198-1205.
[16] Rahmatullah M, Ferdausi D, Mollik MAH, Azam MNK, Taufiq-Ur-Rahman M, Jahan R. Am-Eurasian J Sustain Agric. 2009; 3: 534-541.
[17] Hasan MM, Annay MEA, Sintaha M, Khleque HN, Noor FA, Nahar A, Seraj S, Jhan R, Chowdhury MH, Rahmatullah M. Am-Eurasian J Sustain Agric. 2010; 4: 326-333.
[18] Rahmatullah M, Khatun MA, Morshed N, Neogi PK, Khan SUA, Hossan MS, Mahal MJ, Jahan R. Adv Nat Appl Sci. 2010; 4: 52-62.
[19] Danlami U, Rebecca A, Machan DB, Asuquo TS. JAPS. 2011; 1: 174-176.
[20] Malairajan P, Gopalakrishnan G, Narasimhan S, Veni KJ. Indian J Pharmacol. 2008; 40: 126-128.
[21] Ghosh A, Das BK, Chatterjee SK, Chandra G. South Pac J Nat Sci. 2008; 26: 68-72.
[22] Thenmozhi M, Sivaraj R. Int J Pharma Bio Sci. 2010; 1: 1-7.
[23] Phadnis AP, Patwardhan SA, Dhaneshwar NN, Tavale SS, Row TNG. Phytochem. 1988; 27: 2899-2901.
[24] Chakrabarty M, Nath AC. J Nat Prod. 1992; 55: 256-258.
[25] Ghosh G, Subudhi BB, Banerjee M, Mishra SK. Ind J Chem. 2011; 50B: 1510-1512.
[26] Hara N, Asaki H, Fujimoto Y, Gupta YK, Singh AK, Sahai M. 1995; 38: 189-194.
[27] Lee TH, Wang MJ, Chen P-Y, Wu T-Y, Wen W-C, Tsai F-Y, Lee CK. J Nat Prod. 2009; 72: 1960-1963.
[28] Chang FR, Hwang TL, Yang YL, Li CE, Wu CC, Issa HH, Hsieh WB, Wu YC. Planta Med. 2006; 72: 1344-1347.
[29] Faizi S, Khan RA, Mughal NR, Malik MS, Sajjadi K-E-S, Ahmad A. Phytother Res. 2008; 22: 907-912.
[30] Sashidara KV, Singh SP, Sarkar J, Sinha S. Nat Prod Res. 2010; 24: 1687-1694.
[31] Sashidara KV, Singh SP, Kant R, Maulik PR, Sarkar J, Kanojiya S, Kumar KR. Bioorg Med Chem Lett. 2010; 20: 5767-5771.

[32] Chen CY, Chang FR, Shih YC, Hsieh TJ, Chia YC, Tseng HY, Chen HC, Chen SJ, Hsu MC, Wu YC. J Nat Prod. 2000; 63: 1475-1478.
[33] Wu YC. 1989; 49: 263-275.
[34] Wu YC, Duh CY, Wang SK, Chen KS, Yang TH. J Nat Prod. 1990; 53: 1327-1331.
[35] Faizi S, Khan RA, Azher S, Khan SA, Tauseef S, Ahmad A. Planta Med. 2003; 69: 350-355.
[36] Pan R, Guo F, Lu H, Feng WW, Iiang YZ. J Pharm Biomed Anal. 2011; 55: 391-396.
[37] Dave R, Nagani K, Chanda S. Phcog. J 2010; 2: 572-576.
[38] Uzama, D, David MB, Ahmadu R, Thomas SA. Asian J Pharm Biol Res. 2011; 1: 480-485.
[39] Tripta J, Kanika S. J Pharm Res. 2011; 4: 815-817.
[40] Chanda S, Nair R. Chin Med. 2010; 1: 31-38.
[41] Shazid S, Shahid IJ. Afr J Pharm Pharacol. 2010; 4: 66-69.
[42] Manjula SN, Kenganora M, Parihar VK, Kumar S, Nayak PG, Kumar N, Ranganath Pai K.S, Rao CM. Pharm Biol. 2010; 48: 690-696.
[43] Ghosh G, Kar DM, Subudhi BB, Mishra SK. Der Pharmacia Lettre 2010; 2: 206-216.
[44] Dasari VN, Rupachandra S, Dinesh MG, Chandrasekharam HR, Sidambaram RR. Int J Pharm Pharm Sci. 2011; 3: 311-314.
[45] Mundhe KS, Kale AA, Gaikwad, SA, Deshpande NR, Rajashree RV. J Chem Pharm Res. 2011; 3: 764-769.
[46] Tanna A, Nair R, Chanda S. J Nat Med. 2009; 63: 80-85.
[47] Sharma RK, Mandal S, Rajani GP, Gupta N, Srivastava DP. Int J Drug Dev Res. 2011; 3: 351-359.
[48] Gacche RN, Shaikh RU, Pund MM. Asian J Trad Med. 2011; 6: 127-133.
[49] Verma M, Singh SK, Bhushan S, Sharma VK, Datt P, Kapahi BK, Saxena AK. Chem Biol Interact. 2008; 171: 45-46.
[50] Jain AK, Jain A, Jain A, Jain S, Sikarwar MS, Dubey SK. Plant Arch. 2006; 6: 841-842.
[51] Jothy SL, Azlan A, Chen Y, Sasidharan S. Evid Based Complement Alternat Med. 2012; Volume 2012: Article ID 561284, 10 pages.
[52] Nair R, Shukla V, Chanda S. J Clin Diag Res. 2007; 1: 116–121.
[53] Saleem R, Ahmed M, Ahmed SI, Azeem M, Khan RA, Rasool N, Saleem H, Noor F, Faizi S. Phytother Res. 2005; 19: 881-884.
[54] Marthanda Murthya M, Subramanyama M, Hima Bindub M, Annapurna J. Fitoterapia 2006; 76: 336-339.
[55] Bose S, Byahatti VV, D'Souza M, Bose A. Int J Green Pharm. 2010; 4:93-97.
[56] Chanda S, Dave R, Kaneria M, Shukla V. Pharm Biol. 2012; 50: 1408-1415.
[57] Nair R, Shukla V, Chanda S. Indian Drugs 2009; 46: 116–123.