

The chemistry, pharmacologic, and therapeutic applications of *Polyalthia longifolia*

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ABSTRACT

Medicinal plants are nature's gift to human beings to lead a disease-free, healthy life. They play a vital role in preserving our health. India is one of the most medicoculturally diverse countries in the world, where the medicinal plant sector is part of a time-honored tradition that is respected even today. Medicinal plants are believed to be much safer and proved as elixir in the treatment of various ailments. In our country, more than 2000 medicinal plants are recognized. *Polyalthia longifolia* cv. *pendula* (Annonaceae) is native to the drier regions of India and is locally known as "Ashoka" and is commonly cultivated in Pakistan and Sri Lanka. This plant is used as an antipyretic agent in indigenous systems of medicine. Pharmacologic studies on the bark and leaves of this plant show effective antimicrobial activity, cytotoxic function, antiulcer activity, hypoglycemic activity, and hypotensive effect. The present article includes the detailed exploration of pharmacologic properties of *P. longifolia* in an attempt to provide a direction for further research.

Key words: *Polyalthia longifolia*, phytochemicals, pharmacologic action

INTRODUCTION

Plant and plant products are being used as a source of medicine since long. According to the World Health Organization, more than 80% of the world's population, mostly in poor and less developed countries depend on traditional plant-based medicines for their primary health care needs.^[1] Medicinal plants are nature's gift to human beings to lead a disease-free, healthy life. It plays a vital role in preserving our health. India is one of the most medicoculturally diverse countries in the world, where the medicinal plant sector is part of a time-honored tradition that is respected even today.^[2]

Traditions are dynamic entities of unchanging knowledge. Traditional medicine is in an evolutionary process as communities and individuals continue to discover new techniques that can transform practices.^[3] Ethnopharmacology and drug discovery using natural products remain important issues in the current target-rich, lead-poor scenario.^[4] Many modern drugs have their origin in ethnopharmacology. However, despite technologic advances, the drug discovery process is facing a major innovation deficit that is adversely affecting the pharmaceutical industry.^[5,6]

Polyalthia longifolia cv. *pendula* (Annonaceae) is native to the drier regions of India and is locally known as "Ashoka" and is commonly cultivated in India, Pakistan, and Sri Lanka. *P. longifolia*, although an ornamental tree, finds its reference in Indian medicinal literature owing to its popular Hindi name Ashoka.^[7] Ashoka (Latin name: *Saraca asoka* (Roxb) De Wilde) is also a Sanskrit name in Ayurveda of a drug used for the treatment of uterine disorders.^[8] However, the bark of *P. longifolia* is available as one of the adulterant and used as Ashoka due to its easy availability in nature.

PHARMACOLOGIC ACTIVITY OF THE PLANT *P. LONGIFOLIA*

This plant is used as an antipyretic agent in indigenous systems of medicine.^[9] Pharmacologic studies on the bark and leaves of this plant display effective antimicrobial activity,^[10-12] cytotoxic function,^[13,14] and hypotensive effects.^[15] The aim of the present review is to highlight the traditional uses, phytochemical and pharmacologic investigations carried out on the plant, and to explain the multifaceted role of this medicinal plant.

The genus *Polyalthia* belongs to the family Annonaceae. The *Polyalthia* genus is considered to be of medicinal importance because of the presence of clerodane diterpenoids and alkaloids in various parts of the plant.^[16-18] *Polyalthia* is the Greek word for poly, meaning much or many and althia from *altho*, meaning to cure. The genus *Polyalthia* includes about 120 species occurring

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mainly in Africa, South and South-Eastern Asia, Australia, and New Zealand. According to Mitra,^[19] India has 14 species of *Polyalthia*. The distribution of major *Polyalthia* species in India are *Polyalthia cerasoides* Bedd.—a shrub or small tree, found throughout India, *Polyalthia fragrans* Benth. and Hk. —a large tree found in Western Ghats and *P. longifolia* (Sonn.) Thw. found under cultivation in India. There are 2 distinct varieties of this species, both found in Maharashtra and elsewhere. One of them is with spreading perpendicular branches that are generally known as the typical variety. The other variety is with drooping pendulous branches and it is used as an avenue tree and is sometimes known as *P. longifolia* cv. *pendula*.^[20] Based on their phytochemical investigations, *P. longifolia* and *P. longifolia* cv. *pendula* are considered to be 2 distinct species.^[21] Among the several species of “*Polyalthia*”, *P. longifolia* cv. *pendula*, grown in India, is most commonly used in indigenous medicine. *P. longifolia* var. *pendula* is the one most commonly used in traditional medicine.^[22,23]

SCIENTIFIC CLASSIFICATION

Kingdom: Plantae; Division: Magnoliophyta; Class: Magnoliopsida; Order: Magnoliales; Family: Annonaceae; Genus: *Polyalthia*; Botanical name: *Polyalthia longifolia* cv. *pendula*

VERNACULAR NAME

P. longifolia cv. *pendula* is commonly called Ashoka, Deodari in Hindi; Ulkatakah, Kastadaru in Sanskrit; Debdaru in Bengali; Unboi in Assamese; Asopalov in Gujarati; Nara maamidi, Asokamu in Telugu; Nettiilongam assothi, Asogu in Tamil; Aranamaram, Assoti in Malayalam; Kambadomara, Assoti in Kanarese [Figures 1-3].^[24]

TAXONOMY

The plant grows throughout the tropical and subtropical parts of India up to an altitude of 1500 m. A tall, evergreen, handsome, pyramid-like, columnar, tree: main stem straight, undivided, growing up to 12 m or more. Branches slender, short, about 1-2 m long, glabrous, and pendulous. Leaves alternate, exstipulate, distichous, mildly aromatic, 7.5-23 by 1.5-3.8 cm, shining, glabrous, narrowly lanceolate, tapering to a fine acuminate apex, margin markedly undulate, pinnately veined, leathery or subcoriaceous, shortly petiolate; petiole about 6 mm long. Flowers arise from branches below the leaves, nonfragrant, 2.5-3.5 cm across, yellowish to green, in fascicles or shortly pendunculate umbels; petals 6, 2 seriate, flat, from a broad base, lanceolate, long acuminate, spreading; and sepals 3, broad, short, triangular, the tips reflexed. Stamens many, cuneate; connective truncately dilated beyond the cells. Ovaries indefinite; ovules 1-2; style oblong. Ripe fruits ovoid, 1.8-2 cm long, numerous, stalked, glabrous, 1 seeded; stalk 1.3 cm long, short, glabrous. Seeds smooth, shining. Flowering and fruiting: February-June.^[25,26]



Figure 1: Leaves of *P. longifolia*

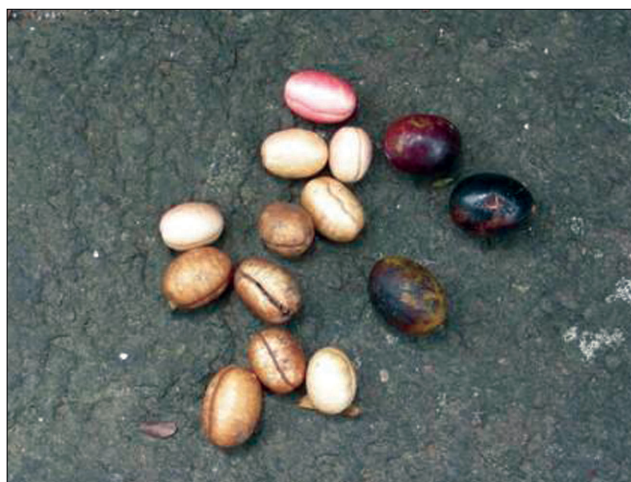


Figure 2: Seeds of *P. longifolia*



Figure 3: The whole tree of *P. longifolia*

PHYTOCHEMISTRY

P. longifolia mainly contains diterpenoids,^[27] alkaloids,

tannins, and mucilage. The chief components of the plant are O-methylbulbocapnine-*N*-oxide (1), polyfothine (2), *N*-methylnandigerine-*N*-oxide (3), oliveroline-*N*-oxide (4), pendulamine A (5), *N*-pendulamine B (6), 8-oxopolyalthiane (7), 16-oxo-5 (10), 13-halimadien-15-oic acid (8), 16-Oxo-3, 13-clerodadien-15-oic acid (9), 16-hydroxycleroda-3, 13-dien-16, 15-olide (10) [Figure 2].

Two clerodane-type diterpenoids, with antifeedant properties have been isolated from *P. longifolia* and identified as 16 α -hydroxycleroda-3,13(14)*Z*-dien-15,16-olide and 16-oxo-cleroda-3,13(14)*E*-dien-15-oic acid on the basis of spectral properties. Configuration of the olide at C-16 was established by X-ray crystallographic analysis.^[28] A new γ -methoxybutenolide clerodane diterpene 2 has been isolated from the petroleum ether extract of the bark of *P. longifolia*. Its structure has been deduced by spectral analyses and by chemical correlation with the corresponding γ -hydroxybutenolide diterpene 1, isolated earlier from this plant.^[29]

Aporphine and azafluorene alkaloids, proanthocyanidins, h-sitosterol, and leukocyanidin, clerodane, and ent-helimane, diterpenoids were isolated from the leaves, stem, and stem bark. Carbohydrate was isolated from the seeds. A novel azafluorene alkaloid, polylongine (5-hydroxy-6-methoxy-1-methyl-4-azafluoren-9-ol), and 3 new aporphine *N*-oxide alkaloids named (+)-O-methylbulbocapnine- β -*N*-oxide, (+)-O-methylbulbocapnine- α -*N*-oxide, and (+)-*N*-methylnandigerine- β -*N*-oxide were isolated from the leaves of *P. longifolia* (Sonn.) Thwaites (Annonaceae).^[17,18]

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. The leaf oil was almost exclusively composed of sesquiterpene derivatives, being represented by allo-aromadendrene (19.7%), caryophyllene oxide (14.4%), β -caryophyllene (13.0%), β -selinene (7.9%), α -humulene (7.0%) and ar-curcumene (6.8%). However, α -copaene and α -muurolol (approx 8.7%), β -selinene (8.6%), viridiflorene (8.1%), α -guaiene (7.8%), allo-aromadendrene (7.4%), and δ -cadinene (7.0%) were the major constituents in the oil of the bark sample. All the other sesquiterpenoid compounds were observed in amount greater than 1%. α -Pinene (0.5%) and camphene (tr), which are the 2 monoterpenoids present in the leaf oil, could not be detected from the bark essential oil [Figure 4].^[30]

MEDICINAL VALUE OF THE FAMILY ANNONACEAE

The Annonaceous plants are well known as folk medicines for the treatment of septic infections, coughing, hepatomegaly, hepatosplenomegaly, diarrhea, and cancers.^[31]

P. LONGIFOLIA IN AYURVEDA

Part used: Bark

Sanskrit names: Kasthadaru

Ayurvedic properties, Action and Uses

Kula: Sitaphala Kula (Annonaceae), Kaphapitashamak, Anulomak (purgative), Krimighna (Anthelminthic) and pramehahara (Antidiabetic) properties.

Rasa: Tikta (bitter), Katu (pungent); Guna: Lagu (light), rooksha (dry); Veerya: Ushna (hot); Vipaka: Katu (pungent).

MEDICINAL VALUE OF *P. LONGIFOLIA*

Almost all parts of the plant are used in the Indian traditional system of medicine for the treatment of various ailments in human beings. In Ayurveda, particularly, the bark of *P. longifolia* has significant medicinal properties as described in the following.

TRADITIONAL USES

Action: Febrifuge

It is having Javaranaashaka (reducing fever) action. Bark is useful in fever. In some places, it is a substitute for Ashoka (*Saraca asboka*) bark, but it is not advisable. The bark is bitter, acrid, cooling, febrifuge, and anthelminthic. It is useful in fever, skin disease, diabetes, hypertension, helminthiasis, and vitiated conditions of vata and pitta.^[32]

1. Digestive system: Aam dosha, Constipation and Krimiroga; 2. Circulatory system: It is used in hypertension; 3. Urinary system: Pramehaghna; 4. Skin: Kusthaghna; 5. Antipyretic activity: It reduces fever.

Dose: Decoction of bark (50-100 mL).

THERAPEUTIC APPLICATIONS OF *P. LONGIFOLIA*

Anticancer activity

Plants of Annonaceae family contain antitumor and anticancer active principles and hence, the medicinal potential of alcoholic extract and its chloroform fraction obtained from *P. longifolia* leaves were studied for their anticancer potential. The chloroform fraction was further studied for its mechanism of action of apoptosis in HL-60 cells. Deregulation of apoptosis is the hallmark of all cancer cells, and agents that activate programmed cell death in cancer cells could be valuable anticancer therapeutics. Anticancer drugs act through different pathways converging ultimately into the activation of apoptosis in cancer cells, leading to cell cytotoxicity.

A new halimane diterpene, 3 β ,5 β ,16 α -trihydroxyhalima-13(14)-en-15,16-olide, and a new oxoprotoberberine alkaloid, (-)-8-oxopolyalthiane, along with 20 known compounds, were isolated from a methanolic extract of *P. longifolia* var. *pendula*. The structures of compounds 3 β ,5 β ,16 α -trihydroxyhalima-13(14)-en-15,16-olide and (-)-8-oxopolyalthiane were established

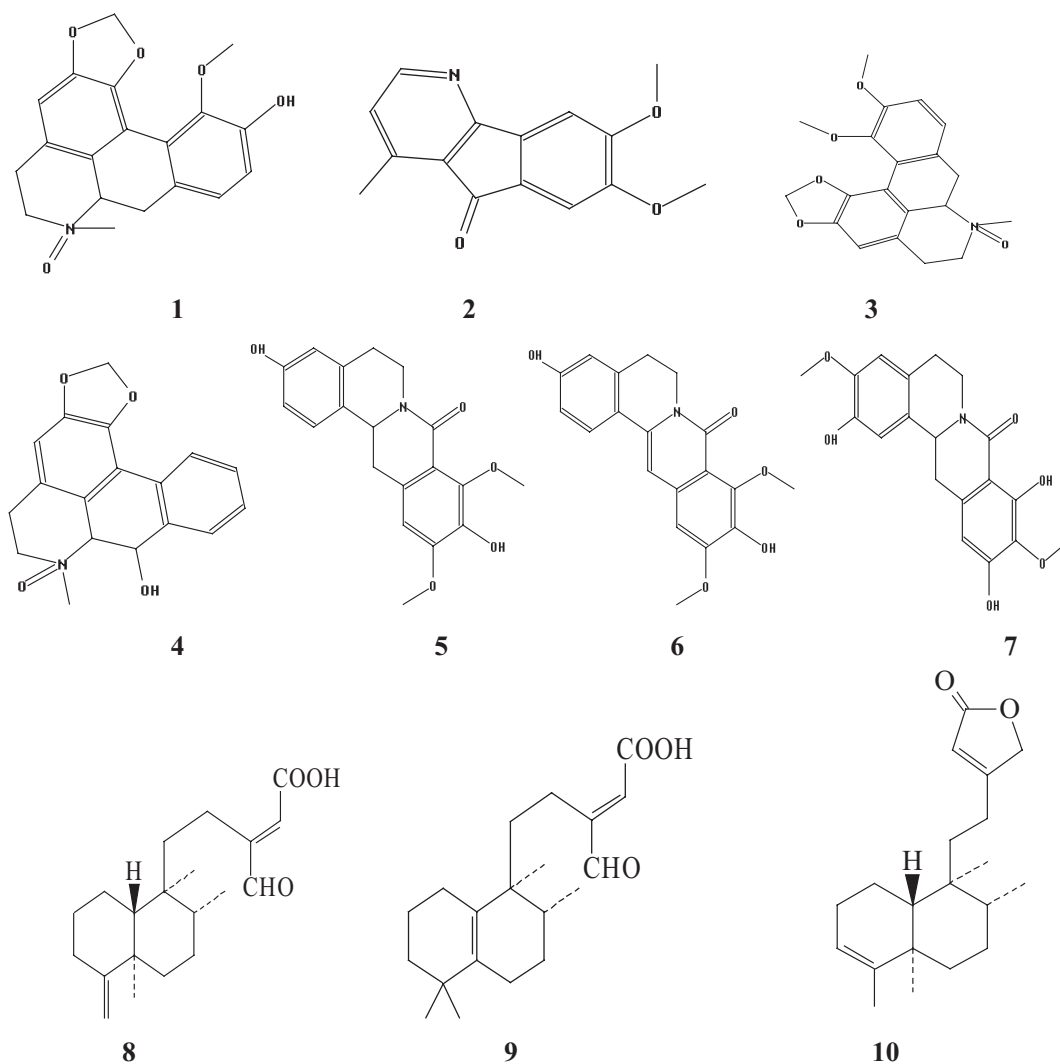


Figure 4: Chemical Constituents of *P. longifolia*

by spectroscopic analysis. These compounds were evaluated for cytotoxicity toward a small panel of human cell lines.^[13] The stem and stem bark of *P. longifolia* afforded the cytotoxic aporphine alkaloid liriodenine, as well as 2 aporphine alkaloids, noroliveroline and oliveroline- β -*N*-oxide and 3 azafuorene alkaloids, darienine, polyfothine, and isooncodine, which are not bioactive.^[13]

The anticancer potential of *P. longifolia* leaves extract and its chloroform fraction was observed when the extract and chloroform fraction 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 μ g/mL. Chloroform fraction induced apoptosis in human leukemia HL-60 cells as measured by several biological endpoints. Chloroform fraction induced apoptotic bodies formation, DNA ladder, enhanced annexin-V-FITC binding of the cells, increased sub-G₀ DNA fraction, loss of mitochondrial membrane potential, release of cytochrome *c*, activation of caspase-9, caspase-3, and cleavage

of poly-ADP ribose polymerase (PARP) in HL-60 cells. All the above parameters revealed that chloroform fraction induced apoptosis through the mitochondrial-dependent pathway in HL-60 cells.^[34]

Bioassay-directed chemical investigation of the stem bark of *P. longifolia* Thw. (Annonaceae) has led to the identification of clerodane diterpene, 16-oxo-cleroda-3,13(14)*Z*-dien-15-oic acid, which was named polyalthialdoic acid. The bioassays also led to the identification of the previously known related diterpene, kolavenic acid, which has not been reported as a constituent of this plant, and 16 α -hydroxy-cleroda-3,13(14) *Z*-dien-15,16-olide, which is previously known to be in this plant. These structures were identified by chemical and spectroscopic methods. All the 3 compounds were significantly bioactive in the brine shrimp bioassay; they strongly inhibited the growth of crown gall tumors on potato discs; and they were cytotoxic in 3 human tumor cell lines. These activities suggest potential antitumor applications. Polyalthialdoic acid was the most active (ED_{50} values ca. 6×10^{-1}

μg/mL in the human tumor cell culture systems).^[35]

Antiproliferative activity of the extracts from the medicinal plants *Hemidesmus indicus*, *P. longifolia*, *Aphanamixis polystachya*, *Moringa oleifera*, *Lagerstroemia speciosa*, *Paederia foetida*, *Cassia sophera*, *Hygrophila auriculata*, and *Ocimum sanctum* were analyzed on different human cell lines, including erythroleukemia K562, B-lymphoid (Raji), T-lymphoid (Jurkat), and erythroleukemia (HEL) cell lines. The electrophoretic mobility shift assay as a suitable technique was employed for the identification of plant extracts altering the binding between transcription factors and the specific DNA elements. Low concentrations of *H. indicus*, *P. longifolia*, *M. oleifera*, and *L. speciosa*, and very low concentrations of *A. polystachya* extracts inhibit the interactions between nuclear factors and target DNA elements, mimicking sequences recognized by the nuclear factor-κB (NF-κB). On the contrary, high amount of extracts from *P. foetida*, *C. sophera*, *H. auriculata*, or *O. sanctum* were unable to inhibit NF-κB/DNA interactions. Extracts inhibiting both NF-κB-binding activity and tumor cell growth might be a source for antitumor compounds, whereas extracts inhibiting NF-κB-DNA interactions with lower effects on cell growth could be of interest in the search of compounds active in inflammatory diseases, for which inhibition of NF-κB-binding activity without toxic effects should be obtained.^[36]

Antimicrobial activity

Methanol extracts of leaves, stem, twigs, green berries, flowers, roots, root-wood, and root-bark of *P. longifolia* var. *pendula*, were tested for their antibacterial and antifungal properties. Bioassay monitored isolation work on the methanol extract of leaves and berries, which possess promising antibacterial activity, led to the isolation of 7 clerodane diterpenoids, 16(R and S)-hydroxy-cleroda-3,13(14)Z-dien-15,16-olide (1), 16-oxo-cleroda-3,13(14)E-dien-15-oic acid (2), methyl-16-oxo-cleroda-3,13(14)E-dien-15-oate (3), 2-oxokolavenic acid (4), 16(R and S)-hydroxy-cleroda-3,13(14)Z-dien-15,16-olide-2-one (5), (4→2)-abeo-16(R and S)-hydroxy-cleroda-2,13(14)Z-dien-15, 16-olide-3-al (6), 3β,16α-dihydroxy-cleroda-4(18), 13(14)Z-dien-15,16-olide (7), whereas kolavenic acid (8) and solidagonal acid (9) were obtained from the root-wood. Diterpenoids 1 and 8 were also obtained from the root-bark. Clerodanes 1, 2, 5, 6, and 7 were found to be active antimicrobial agents with minimum inhibitory concentration values ranging between 7.8 and 500 μg/mL. Diterpenoid 16(R and S)-hydroxy-cleroda-3,13(14)Z-dien-15,16-olide emerged as the most active antimicrobial agent. The acetyl derivative of 16(R and S)-hydroxy-cleroda-3,13(14) Z-dien-15,16-olide and the methyl derivative of 16-oxo-cleroda-3,13(14) E-dien-15-oic acid were found to be less active than the parent compounds.^[10]

The diterpenoids 16α-hydroxy-cleroda-3,13(14)-Z-diene-15,16-olide and 16-oxo-cleroda-3,13(14)-E-diene-15-oic acid, isolated from the hexane extract of the seeds of *P. longifolia*, demonstrated significant antibacterial and antifungal properties.^[37] The antimicrobial activities of the petroleum ether extract of the stem bark of *P. longifolia* var. *pendula* as well as the diterpenes isolated

from it were studied. Among the diterpenoids, 16-oxocleroda-3,13E-dien-15-oic acid showed the highest activities against most of the bacteria and the kanamycin-resistant fungal strains, *Aspergillus fumigatus*, *Saccharomyces caulbequence*, *Saccharomyces cerevaceae*, *Candida albicans*, and *Hensila californica* compared with those of kolavenic acid and 16β-hydroxycleroda-3,13-dien-15,16-olide. The minimum inhibitory concentrations for all of these compounds were determined and were found to be 8-64 μg/mL.^[38] Bioassay-guided fractionation of the ethanolic extract of *P. longifolia* var. *pendula* stem, which showed promising antibacterial activity against 13 Gram-positive and 9 Gram-negative organisms, furnished (3*S*,4*R*)-3,4,5-trihydroxypentanoic acid-1,4-lactone as the active principle. The structure of (3*S*,4*R*)-3,4,5-trihydroxypentanoic acid-1,4-lactone was established by UV, IR, mass, 1H and 13C NMR, as well as 2D NMR spectral studies and the formation of its acetate. On acetylation activity of (3*S*,4*R*)-3,4,5-trihydroxypentanoic acid-1,4-lactone was markedly reduced. The extract, fractions, and pure compounds did not show any remarkable activity against the fungi *Mycobacterium fortuitum* and *Mycobacterium smegmatis*.^[11]

Bioassay-guided isolation studies on the root extract of *P. longifolia* var. *pendula* possessing significant antibacterial activity led to the isolation of 3 new alkaloids pendulamine A and B and penduline, along with stigmaterol 3-O-β-D-glucoside, allantoin, the known diterpenoid kolavenic acid, and the azafluorene alkaloid isoursuline. Compounds pendulamine A and B, which are the only protoberberine alkaloids having a monosubstituted A ring with a hydroxy group at C-3, were found to be the active antibacterial principles of the roots. Their MIC values ranged between 0.02 and 20 μg against the tested bacteria.^[12]

Antiinflammatory activity

The methanolic extract of the root at doses 20 and 400 mg/kg showed a maximum inhibition of edema of 18.6% and 33.7% at 3 h with carrageenin and 22.2% and 40.5% at 5 h with serotonin-induced rat paw edema, respectively. The antiinflammatory activity of *P. longifolia* extract was comparable with that of phenylbutazone.^[4] 16-Oxo-cleroda-3,13E-dien-15-oic acid has been isolated from petroleum ether extract of twigs of *P. longifolia* by bioactivity monitored purification. 16-Oxo-cleroda-3,13E-dien-15-oic acid shows good IKKβ kinase inhibitory activity with an IC₅₀ of 14.9 μM.^[39]

Hypotensive activity

A defatted extract of *P. longifolia* var. *pendula* root bark in 50% methanol showed a significant ability to reduce blood pressure. Compounds purified from this extract include kolavenic acid, clerodane and its isomer, liriodenine, lysicamine, and bisclerodane imide and its isomer; of these, only kolavenic acid produced a 22% fall in the mean arterial blood pressure, at a dose of 30 mg/kg. The extract showed a decrease in blood pressure of normotensive and egg yolk-induced hypertensive rats.^[15]

Antiulcer activity

The ethanol extract of *P. longifolia* (Sonn.) Thw. leaves was

investigated for its antiulcer activity against aspirin plus pylorus ligation-induced gastric ulcer in rats, HCl-ethanol-induced ulcer in mice, and water immersion stress-induced ulcer in rats at 300 mg/kg body weight p.o. A significant ($P < 0.01$) antiulcer activity was observed in all the models. Pylorus ligation showed significant ($P < 0.01$) reduction in the gastric volume, free acidity, and ulcer index as compared with those of control. It also showed 89.71% ulcer inhibition in HCl-ethanol-induced ulcer and 95.3% ulcer protection index in stress-induced ulcer.^[40]

ANTIOXIDANT PROPERTIES

A cellular model in isolated human neutrophils was established to elucidate the antiinflammatory functions of 16-hydroxycleroda-3,13(14)E-dien-15-oic acid, a clerodane diterpenoid from *P. longifolia* var. *pendula*. 16-Hydroxycleroda-3,13(14)E-dien-15-oic acid significantly inhibited the generation of superoxide anion and the release of elastase in formyl-L-methionyl-L-leucyl-L-phenylalanine (FMLP)-activated human neutrophils in a concentration-dependent fashion with IC_{50} values of 3.06 ± 0.20 and 3.30 ± 0.48 μ M, respectively. 16-Hydroxycleroda-3,13(14)E-dien-15-oic acid did not affect cAMP-dependent pathway, and the inhibitory effect of 16-hydroxycleroda-3,13(14)E-dien-15-oic acid was not reversed by protein kinase A inhibitor. 16-Hydroxycleroda-3,13(14)E-dien-15-oic acid concentration-dependently inhibited calcium mobilization caused by FMLP but not thapsigargin. Furthermore, 16-hydroxycleroda-3,13(14)E-dien-15-oic acid attenuated the FMLP-induced protein kinase B (AKT) and p38 mitogen-activated protein kinase phosphorylation. However, 16-hydroxycleroda-3,13(14)E-dien-15-oic acid had no effect on FMLP-induced phosphorylation of extracellular-regulated kinase and c-Jun N-terminal kinase. These results indicate that the suppressive effects of 16-hydroxycleroda-3,13(14)E-dien-15-oic acid on human neutrophil respiratory burst and degranulation are at least partly mediated by the inhibition of calcium, AKT, and p38 signaling pathways.^[41]

Hypoglycemic activity

The hypoglycemic and antihyperglycemic activities of various solvent extracts of *P. longifolia* var. *pendula* leaf extracts were evaluated in alloxan-induced experimental diabetes in rats. *P. longifolia* extracts and powder produced glucose-lowering activity. However, the extracts did not modify any of the biochemical parameters significantly. Hence the extracts and crude powder are devoid of antidiabetic properties, but have gross glucose lowering properties. The presence of antihyperglycemic effect against sucrose loading-induced hyperglycemia is a significant finding. Now a days, it is considered that this effect is the most important property in a drug used in diabetes treatment.^[42]

CONCLUSION

The therapeutic efficacy of *P. longifolia* extensively used in Indian System of Medicine has been established through modern

testing and evaluation (preclinical and clinical trials) in different disease conditions. These studies place this indigenous drug as a novel candidate for bioprospection and drug development for the treatment of diseases, such as cancer, infectious diseases, diabetes, and various inflammatory conditions. The medicinal applications of this plant and the countless possibilities for investigation still remain in relatively newer areas of its function. Hence, phytochemicals of these plants will enable to exploit its therapeutic use.

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