International Journal of Scientific and Innovative Research 2014; 2(1): 17-25,
P-ISSN 2347-2189, E- ISSN 2347-4971

POLYALTHIA LONGIFOLIA AND ITS PHARMACOLOGICAL ACTIVITIES : REVIEW

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ABSTRACT

Polyalthia longifolia var. angustifolia is a member of the Annonaceae family and is a small medium-sized tree distributed in many tropical countries around the world, commonly used as ornamental street tree due to its effectiveness in combating noise pollution. In traditional and indigenous systems of medicine *Polyalthia longifolia* has been commonly used in the treatment of fever, helminthiasis, diabetes and in cardiac problems. Various pharmacological investigations have shown that *Polyalthia longifolia* posseses significant biological and pharmacological activities such as antibacterial, antifungal, antitumor, anti-ulcer, antidiabetic and antioxidant properties. In context of various medicinal importance of *P. longifolia,* this review is an attempt to compile detailed exploration of all currently available botanical, phytochemical, pharmacological and other ethnomedicinal properties of *P. longifolia* in an attempt to provide a direction for further research work.

Keywords: *Polyalthia longifolia,* Phytochemistry, Pharmacological Actions.

INTRODUCTION

Herbs and the humans have a great relationship with each other. Plants have been known to be used for alleviation and management of diseases since the very beginning of human civilization. Even at present day medicinal plants play important roles despite the tremendous scientific development and hold much more hidden treasure to be explored as almost 80 percent of the human population in developing countries is dependent on plant resources for their primary healthcare [1]. Plant-based therapy has been used as a vital component in traditional medicine systems and also serves as the main source of inspiration for several major pharmaceutical drugs used in the defence against various diseases. One such plant *Polyalthia longifolia* (Order: Magnoliales ; Family : Annonaceae) is an evergreen plant commonly used as an ornamental street tree due to its effectiveness in combating noise pollution. *Polyalthia longifolia* is also known as false Ashoka, Buddha Tree, Green champa, Indian mast tree, and Indian Fire tree. It exhibits symmetrical pyramidal growth with willowy weeping pendulous branches and long narrow lanceolate leaves with undulate margins. The tree is known to grow over 30 ft in height. In traditional medicines various herbal preparations are being used for treating dueodenal ulcers. The plant has been used in traditional system of medicine for the treatment of fever, skin diseases, diabetes, hypertension and helminthiasis. A number of biologically active compounds have been isolated from the plant [2]. The leaves of the plant are aromatic and are generally used for decoration, while the bark is used as a folk medicine for the treatment of pyrexia and other bleeding disorders in India [3]. Ethanomedically *Polyalthia longifolia* is a versatile plant which is used to treat rheumatism, menorrhagia, scorpion sting, diabetes, skin disease, hypertension, helminthiasis and also in treatment for the digestive system [4].

DISTRIBUTION

The genus *Polyalthia* includes about 120 species occurring mainly in Africa, South and South Eastern Asia, Australia, and New Zealand. India has 14 species of *Polyalthia* [5]. The distribution of major *Polyalthia* species in India are *Polyalthia cerasoides* Bedd.; a shrub or small tree, found throughout India, *Polyalthia fragrans* Benth ; a large tree found in Western Ghats and *P. longifolia* (Sonn.) Thw ; found under cultivation in India. There are two distinct varieties of this species, both found in Maharashtra and elsewhere [6].

PHYTOCHEMISTRY OF *POLYALTHIA LONGIFOLIA*

Polyalthia longifolia is very versatile plant due to its chemical constituents which are responsible for its various pharmacological actions. Literature report of few phytochemical screening tests on this plant shows the presence of saponins, carbohydrates, alkaloids, tannins, resins, steroids, glycosides and flavonoids as major phytochemical constituents. Previous studies on its leaves, bark, roots, root bark, and seeds have revealed various types of diterpenoids and alkaloids with numerous biological activities such as anti-inflammatory, antihypertensive, antimicrobial, and cytotoxic effects.

A new halimane diterpene, 3â,5â,16á-trihydroxyhalima- 13(14)-en-15,16-olide, and a new oxoprotoberberine alkaloid, (-)-8-oxopolyalthiaine, along with 20 known compounds, were isolated from a methanolic extract of *Polyalthia longifolia* var. *pendula*. These compounds were evaluated for cytotoxicity toward a small panel of human cell lines [7].

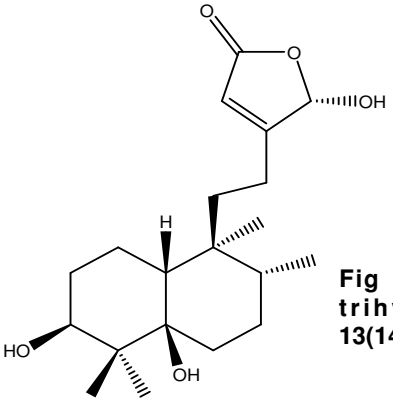
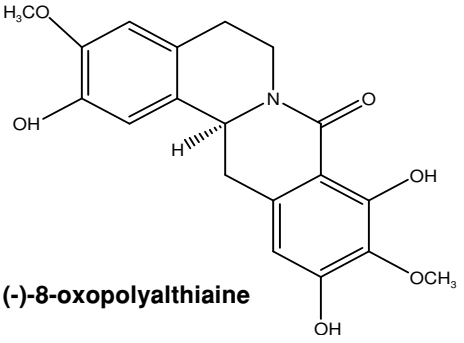


Fig 1. 3β,5β,16α-trihydroxyhalima-13(14)-en-15,16-olide



(-)-8-oxopolyalthiaine

Ethanolic extract of the leaves of P. longifolia var. pendula showed the presence 16a-hydroxycleroda-3,13(14) Z-dien-15,16-olide as the active principle, and its metabolite 16-oxocleroda-3, 13(14) Z-dien-15-oic acid as a novel antidyslipidemic agent [8].

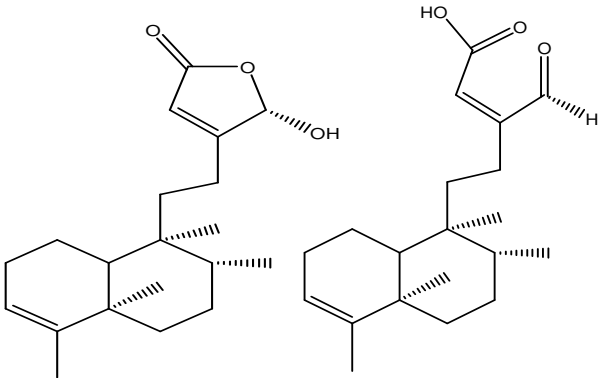


Fig. 2: 16a-hydroxycleroda-3,13(14)Z-dien-15,16-olide & its metabolite

Other clerodanes like compounds also reported from stem of P.longifolia by other researchers are 6á,16-dihydroxycleroda-3,13-dien-15-oic acid, 6á,16-dihydroxycleroda-4(18),13-dien-15-oic acid, and 4á,18â-epoxy-16-hydroxyclerod-13-en-15-oic acid [9] as well as 16-hydroxycleroda-13-ene-15,16-olide-3-one from bark [10]. Isolation of the methanol extract of leaves and berries shows the presence of three new clerodane diterpene from this plant i.e. methyl-16-oxo-cleroda-3,13(14)E-dien-15-oate, 3â,16á-dihydroxy-cleroda-4(18), 13(14)Z-dien-15,16-olide, and solidagonal acid [11]. Later, two other clerodane diterpenes were obtained from leaves and these were 3á,16 á-dihydroxycleroda-4(18),13(14)Z-dien-15,16-olide and 3â,16 á-dihydroxycleroda-4(18),13(14)Z-dien-15,16-olide [12].

The bark of *Polyalthia longifolia* has also been reported to contain a new clerodane-type

gamma hydroxylbutenolide diterpene i.e. (Z)-4-hydroxy-3-(2"6"-hydroxy-5"-(hydroxymethyl)-5",8"a-dimethyloctahydro-1*H*-spiro[naphthalene-2",2"-oxiran]-1"-yl) ethylidene)dihydro-furan-2(3*H*)-one [13].

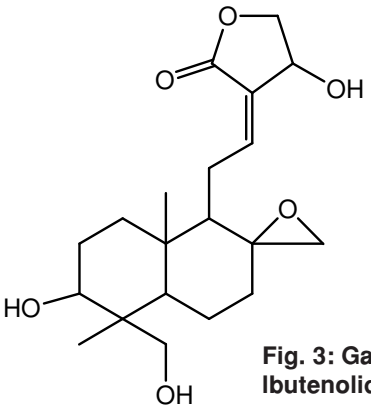


Fig. 3: Gamma hydroxy-lbutenolide

The dimeric clerodane diterpene has also been isolated and two examples of this bisclerodane compound are Longimide A and Longimide B [14].

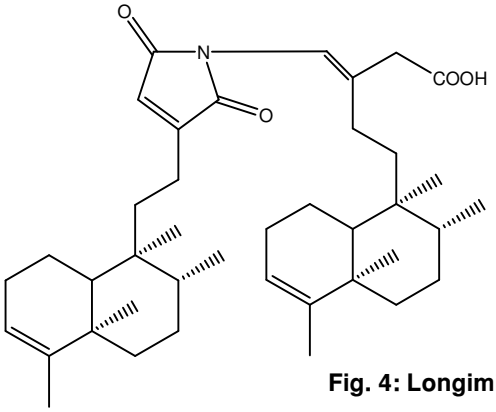


Fig. 4: Longimide B

Other than these compounds this plant has also been reported to have 5-hydroxy-6-methoxyonychine [15,16], (-)-anonaine [17], (-)-norboldine [18], (+)-norboldine, (-)-norpallidine [19], (-)-asimilobine, p-hydroxybenzoic acid [20], beta-sitosterol and stigmasterol.

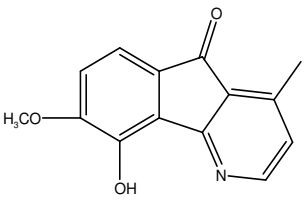
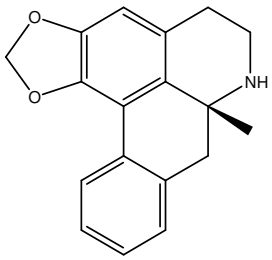


Fig [5] 5-hydroxy-6-methoxyonychine,



(-)-anonaine

Other than terpenoids the other major group of chemical from this plant was alkaloid. Azafluorene type of alkaloids are majorly found in this plant which includes polylongine and polyfothine [21]. Aporphine alkaloids were also obtained which include methylnandigerine-â-N-oxide as well as liriodenine, noroliveroline and oliveroline-â-N-oxide [21, 22].

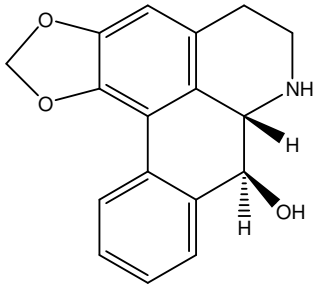
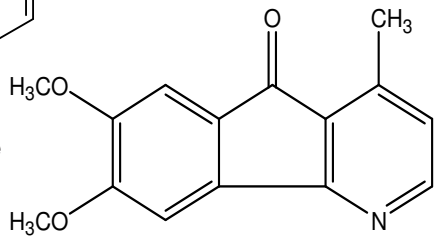


Fig [6] polyfothine

noroliveroline



The protoberberine compounds obtained has also been identified as (-)-8-oxo-polyalthiaine [23], pendulamine A and pendulamine B [24].

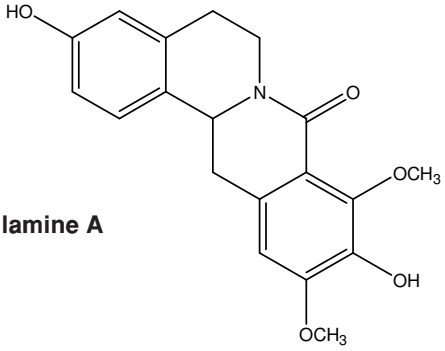


Fig [7] Pendulamine A

PHARMACOLOGICAL ACTIVITIES OF *POLYALTHIA LONGIFOLIA*

(A) Antibacterial activity

Silver nanoparticles of *Polyalthia longifolia* leaves extract were synthesized along with D-sorbitol. These silver nanoparticles exhibited excellent antibacterial activity against the bacterial pathogens *Staphylococcus aureus* (Gram positive), *Escherichia coli,* and *Pseudomonas aeruginosa* (Gram negative) [25] and indicated that the synthesized silver nanoparticles have good antibacterial action against Gram-positive organism than Gram-

negative organisms. Results showed that the effect of antibacterial activity against test organisms (*Escherichia coli, Pseudomonas aeruginosa and Staphylococcus aureus*) is higher in the case of silver nanoparticles synthesized at 60 C (8mm-16.4 mm) compared to 25 C (7.3-14 mm) because of being smaller in size [26].

Leaf extracts of *Polyalthia longiflia* (Debdaru) treated with different solvents like hexane, methanol and chloroform were subjected to *in vitro* determination of antibacterial activity against six tested pathogenic bacteria viz. *Bacillus subtilis*, *Sarcina lutea*, *Xanthomonas compestris*, *Escherichia coli*, *Klebsiella pneumonia and Pseudomonas* sp. using agar disc diffusion method and MIC determination test. The zone of inhibition against the tested bacteria was found ranging from 21.00 to 44.20mm. The highest zone of inhibition produced by the hexane, methanol and chloroform extracts of *Polyalthia longiflia* at a concentration of 500ìg/10ìl against pathogenic bacteria i.e. *Sarcina lutea* were found 41.80mm, 44.20mm and 43.50mm respectively. The MIC values of all extracts against six tested bacteria were almost 15.625 ìg/ 10ìl [27].

Polyalthia longifolia var. *angustifolia* stem bark extracts were evaluated against six important pathogenic bacteria *viz. Escherichia coli, Bacillus subtilis, Salmonella typhi, Proteus mirabilis, Pseudomonas aeruginosa, Klebsiella sp.and Staphylococcus aureus*. The powdered stem bark extracts were successively extracted with petroleum ether, chloroform, methanol and water using Soxhlet apparatus. The antibacterial activity study was performed by both agar well diffusion and serial dilution methods. The petroleum ether extract was found to exhibit highest activity against all tested bacteria [28]

(B) Antioxidant activity:

The antioxidant activities of the ethanolic extract of *Polyalthia longifolia* seeds were assayed using rat liver homogenate. Nitric oxide, ferrous sulphate and carbon tetrachloride-induced lipid scavenging activities were carried out and showed significant free radical scavenging activity. The percentage inhibition of peroxide formation increased in a dose-dependent manner [29].

Methanolic leaf extracts from *Polyalthia longifolia* were evaluated for *in vitro* antioxidant activity for free radical scavenging capacity, using established *in vitro* models such as ferric-reducing antioxidant power (FRAP), 2,2-diphenyl-1-picryl-hydrazyl (DPPH), hydroxyl radical (OH), nitric oxide radical (NO) scavenging, metal chelating, and antilipidperoxidation activities. The methanolic extracts of *P. longifolia* exhibited concentration dependent antiradical activity by inhibiting DPPH radical with inhibitory concentration 50% (IC50) values of 2.721 0.116 mg/mL [30].

The active constituents like quercetin, quecetin-3-O-ß-glucopyranoside and rutin were isolated from the ethanolic extract of the leaves of the *P. Longifolia and* shows the antioxidant capacity determined by their ability to scavenge $ABTS^{+}$ radical cation which was expressed using Trolox Equivalent Antioxidant Capacity (TEAC) assays [31].

(C) Anti-inflammatory activity

A clerodane diterpenoid 16-hydroxycleroda-3,13(14)E-dien- 15-oic acid from P. longifolia 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 IC50 values of 3.06±0.20 and 3.30±0.48 ìM, respectively [32].

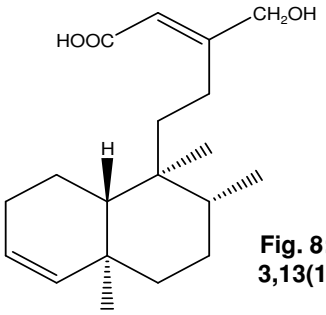


Fig. 8: 16-hydroxycleroda-3,13(14)E-dien-15-oic acid.

The anti-inflammatory potential of ethanolic and aqueous extracts of *P. longifolia* leaf in albino wister rats was evaluated using Cotton pellet granuloma which is a sub-acute anti-inflammatory model. All the extracts were found to produce significant 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 with indomethacin and at dose 300 mg/kg being the most active, exhibited maximum anti-inflammatory activity. However, the aqueous extracts showed better anti-inflammatory activity when compared to the ethanolic extracts at dose of 200mg/kg body weight [33].

The anti-inflammatory activity of various solvent extracts (petroleum ether, hexane, toluene, chloroform, acetone and methanol) of *P. longifolia* leaf was evaluated using acute inflammatory studies in Wistar albino rats. 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) [34].

(D) Anti-leishmanial Activity

A clerodane diterpene; 16a-Hydroxycleroda-3,13(14)Z-dien-15,16-olide from *Polyalthia longifolia* was found to be a potential antileishmanial and non-cytotoxic, as evidenced by long-term survival (>6 months) of treated animals. A very rapid and dose-dependent death occurred with Compound 1 at concentrations between 2 and 50 mg/ml. The IC50 was calculated to be 8.04 mg/mL against the reference drug miltefosine [35].

The *in vitro* antileishmanial activity of methanolic extract from *P.longifolia* leaf was evaluated against *Leismania donovani* promastigotes by *in vitro* promastigote cell toxicity assay by using MTT [3-4,5-dimethylthiazol-2-yl)-2,5 diphenyltetrazolium bromide]. The extract markedly inhibited the growth of *L.donovani* promastigotes *in vitro* in a dose dependent manner and demonstrated IC_{50} value of 4.18 µg/ml [36].

(E) Antimicrobial Activity

Previously reported clerodane diterpene (16á-hydroxycleroda-3, 13 (14) Z-dien-15, 16-olide) was isolated from *Polyalthia longifolia* against methicillin-resistant S. aureus through *in vitro* and *in vivo* assays. Minimum inhibitory concentration (MIC) of this compound exhibited significant antimicrobial activity (15.625 31.25 mg/ml) against reference strain [37].

Methanol extracts of leaves, stem, twigs, green berries, flowers, roots, root-wood and root-bark of *Polyalthia longifolia* var. *pendula*, were tested for their antibacterial and antifungal potentials. Bioassay monitored isolation work on the methanol extract of leaves and berries which possesses promising antibacterial activity with MIC values ranging between 7.8 and 500 ìg/ml [11].

Different *P. longifolia* leaf extracts like 1, 4-dioxan, methanol and acetone extracts were investigated at two different concentrations for their antimicrobial potentiality against 91 clinically important microbial strains. All the three extracts at 500 ìg/disc concentration were active against 95% of the total gram positive bacterial strains. 1, 4-Dioxan extract was active against 18.18% of the total gram negative bacterial strains while methanolic and acetone extracts were active against 12.72% of the total gram negative bacterial strains [38].

(F) Antifungal Activity

Different solvent extracts viz., petroleum ether, benzene, chloroform, methanol and ethanol extracts of *Polyalthia longifolia* were tested for their antifungal activity where petroleum ether extract showed highly significant antifungal activity than other solvent extracts [39].

Antifungal activity of aqueous (10-50% concentration) of *Polyalthia longifolia* were tested against ten seed borne fungi of paddy (*Oryza sativa.* L) *in vitro* condition. The fungus strain *A. alternata* recorded a maximum inhibition of 92.88% followed by *F. solani* (87.10%), *F. moniliforme* (86.40%), *D. Halodes* (86.07%), *F. oxysporum* (85.14%), *C. lunata* (83.33%) *and D. tetramera* (83.02%) at 50% concentration compared to synthetic fungicide, Dithane M-45, Captan, Benlate, Thiram and Bavistin at 2% recommended dosage [40].

The leaf and pericarp aqueous extracts of *P. longifolia* were assessed *in vitro* for inhibitory activity against *Fusarium oxysporium* and *Pythium aphanidermatum* which were isolated from rhizome rot specimen of ginger. The extract

was found to be active and showed dose dependent antifungal activity [41].

(G) Anti-diabetic activity

Ethanol and chloroform extracts of *Polyalthia longifolia* showed *in vitro* inhibitory activity of the two enzymes viz. á-amylase and á-glucosidase and *in vivo* anti-diabetic activity against streptozotocin-induced type 1 diabetes mellitus in rats. The IC50 of ethanolic extract for á-amylase was found to be 154.3±2.42 ìg/ml whereas chloroform was 180.3± 1.35 ìg/ml. While the IC50 values of the ethanol for á- glucosidase inhibition was found to be 208.7±2.54 ìg/ml and chloroform showed at 271.6±0.85 ìg/ml. Acute toxicity studies showed that the extracts were safe at 2000 mg/kg b.w. Both the extracts dose dependently reversed the abnormal changes observed in untreated diabetic rats and the effect produced by the ethanol extract was slightly higher than the chloroform extract [42].

The petroleum ether extract from *Polyalthia longifolia* leaves (50, 100, 200 and 300 mg/kg) produced a significant decrease in the blood glucose level in the model of alloxan-induced diabetes in rabbits on oral administration [43].

Different solvent n-hexane, ethyl acetate and methanolic extracts of *Polyalthia longifolia* bark showed markedly improved the glucose tolerance in alloxan- induced diabetes in rats when compared to normal control and these extracts at 300mg/kg dose showed reduction in glucose level [44].

The hypoglycemic and antihyperglycemic activity of various solvent extracts of *Polyalthia longifolia* var. pendula leaf extracts was evaluated in alloxan- induced experimental diabetes in rats. *Polyalthia longifolia* extracts and powder produced glucose lowering activity. However, the extracts did not modify any of the biochemical parameter significantly [45].

(H) Antipyretic activity

Polyalthia longifolia methanolic extracts of the leaves, stem bark and root were tested for their antipyretic activities at doses of 30, 100 and 300 mg/kg body weight using LPS-induced antipyretic activity model. All extracts showed significant dose-dependent antipyretic activity. At 300 mg/ kg, all extracts exhibited activities higher than that of Acetylsalicyclic acid (Aspirin) whose percentage inhibition of pyrexia was 86%. The root extract was the most active with a percentage inhibition of 127.5%, followed by the leaf extract (123.0%) and the stem bark extract (99.2%) [46].

(I) Anti-ulcer activity

The ethanolic extract of *polyalthia longifolia* was investigated for anti-ulcer activity against aspirin plus pylorous ligation induced gastric ulcer in rats, HCl – ethanol induced ulcer in mice and water immersion stress induced ulcer at 300 mg/kg body weight which showed a significant reduction in gastric volume, free acidity and ulcer index as compared to control. It also showed 89.71 % and 95.3% inhibition in ulcer inhibition in HCl- ethanol induced ulcer and ulcer protection index in stress induced ulcer respectively [47].

Methanolic extract of *Polyalthia longifolia* showed gastroprotective potential on ethanol and ethanol/HCl induced ulcers at 270 mg/kg and 540 mg/kg body weight. The reduction of ulcer index in treated animals was found to be statistically significant with respect to control animals [48].

(J) Anticancer activity

The ethanolic extract of stem bark of *Polyalthia longifolia* was screened for its *in vitro* and *in vivo* antitumor activity and extract showed concentration-dependent cytotoxicity in Ehrlich's Ascites Carcinoma (EAC), Dalton's ascites lymphoma (DLA), HeLa and MCF-7 cells with IC50 values of 45.77 and 52.52, 25.24 and 50.49 ìg/ml respectively [49].

The two new clerodane diterpenes were isolated from the leaves of *Polyalthia longifolia* viz polyalthialdoic acid and 16 á-hydroxy-cleroda-3,13(14)Z-diene-15,16-olide and evaluated for their apoptotic potential against human leukemia HL-60 cells. These compounds inhibited cell proliferation with IC_{50} values of 21.8 and 13.7 µM, respectively [50].

The rare bisclerodane imides Longimide A and Longimide B were isolated from ethanolic extract of the leaves of *Polyalthia longifolia* and evaluated for their cytotoxic effects against four human cancer cell lines and found to be most

active against cervical carcinoma cell lines with IC50 value of 10.03 and 4.12 lg/ml, respectively [51].

(K) Termiticidal activity

Polyalthia longifolia showed termiticidal activity in comparison to their respective solvent extract viz. chloroform, methanol, ethyl acetate, n- hexane, distilled water, at various concentrations (0.5%-5% solution). Methanolic extract showed potent termiticidal activity [52].

A significant mortality rate was recorded with 5 % chloroform extract of *Polyalthia longifolia* along with *Samanea saman, Cassia siamea, Pithecellobium dulce, Eucalyptus camaldulensis,* at various concentrations viz 75, 75, 55, 50 and 45% mortality occurred respectively [53].

(L) Hepatoprotective activity

Methanolic extract of fruits of *Polyalthiya longifolia* was investigated as the potent hepatoprotective agent by *in vitro* and *in vivo* methods. In the *in vitro* study, freshly isolated rat primary hepatocytes and HepG2 cells were exposed with CCl_4 along with/without various concentrations of methanolic extract (125, 250, 500 ìg/kg). In the *in vivo* studies, CCl_4 intoxication method was used and aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin and total proteins were estimated and supported with histopathological studies [54].

The methanolic leaf extract of *Polyalthiya longifolia* showed a significant hepatoprotective activity when subjected to 300, 600, 900 mg/kg concentrations and determined its potential as an hepatoprotective agent against diclofenac sodium as the toxicant [55].

CONCLUSION

In this review, we attempted to bring together the phytochemical, pharmacological, toxicological and ethnomedicinal information on *Polyalthiya longifolia*, a medicinally important herb used in the traditional system of medicine and an ancient remedy to be explored for novel therapeutic uses. The survey of the literature revealed the presence of various phytochemicals in *Polyalthiya longifolia*, which will be lead compound for novel therapeutic agents. 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 this plant will enable to exploit its therapeutic use.

ACKNOWLEDGEMENTS

The authors are thankful to the Director, CSIR-National Botanical Research Institute, Lucknow, India for facilities and encouragements. The authors are also thankful to the Director, CSIR-Central Drug Research Institute, Lucknow for the encouragements and allowing us to the anticancer activity. The financial support received from Council and Scientific and Industrial Research, New Delhi under the project 'Bio-prospection PR (BSC0106)' is duly acknowledged

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