Review Article

Pharmacological Profiles of Ethno-Medicinal Plant: *Plumbago zeylanica* l.- A Review

Paras Jain*, H. P. Sharma, Fauziya Basri, Binit Baraik, Soni Kumari, Chanchala Pathak
Laboratory of Plant Physiology and Biotechnology, University Department of Botany, Ranchi University, Ranchi, India.
***Corresponding author's E-mail:** paras.jain42@yahoo.in

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ABSTRACT

Plumbago zeylanica L. (also known as Doctorbush) is a shrub, widely distributed throughout the tropical and sub-tropical regions of the world. The literature reveals its wide application in traditional system of medicines against various diseases, as anti-inflammatory, anti-malarial, anti-fertility, anti-microbial, anti-oxidant, blood coagulation, wound healing, memory enhancer and anti-cancer. The therapeutic uses of the plant have been attributed to the presence of number of bioactive compounds, such as elliptinone, zeylanone, sistosterol and plumbagin. The objective of the present review is to give a comprehensive information; taxonomical description, phytochemistry, pharmacological properties and traditional uses.

Keywords: *Plumbago zeylanica,* plumbagin, bioactive compound, cancer, therapeutic uses.

INTRODUCTION

Historically plants have provided a source of inspiration for novel drug compounds. Ayurveda is time tested science of treating disease with natural products derived from plants, animals and minerals. Atharveda (around 1200 BC), Charak Samhita and Sushrut Samhita (1000-5000 BC) are the main classics that give detailed description of over 700 herbs. India has about 45,000 plant species. According to the World Health Organization (WHO), approximately 80% of the world's population currently uses herbal traditional system of medicine for their primary health care.

Plumbago zeylanica L. (chromosome number 2n=24) is a multipurpose medicinal herb of family Plumbaginaceae. *P. zeylanica* is the most common plant used in Indian traditional system of medicine. A native of South Asia, the species is distributed throughout most of the tropics and subtropics; growing in deciduous woodland, savannas' and scrub lands from sea level up to 2000 m altitude.[1-3] The root is used as laxative, expectorant, astringent, abortifacient and in dysentery. Tincture of root bark is used as antiperiodic. The leaves are caustic and used in treatment of scabies. Plumbago are chemically characterized by the presence of naphthoquinones, flavonoids, terpenoids and steroids, many of them being responsible for several biodynamic activities.

Popular name of *Plumbago zylanica* is lead wort. This plant is also known by several names in different parts of the world. In India its common name is "Chitrak".

BOTANICAL DESCRIPTION

The family Plumbaginaceae consists of 10 genera and 280 species. In India *Plumbago zeylanica* grows in different parts as wild species but it is also cultivated due to its wide therapeutic applications. It is used in indigenous system of medicine, and commonly known as "Chitthra mulam".

Classification

Kingdom:	Plantae
Order:	Caryophyllales
Family:	Plumbaginaceae
Genus:	*Plumbago*
Species:	*zeylanica*

MORPHOLOGICAL DESCRIPTION

Habit: A rambling sub-scandent perennial herb or under shrub with green branches.

Roots: 30 cm or more in length, 6 mm or more in diameter, stout, cylindrical, friable, blackish red in colour, light yellow coloured when fresh, reddish brown when dry, straight unbranched or slightly branched with or without secondary roots, with uniform and smooth texture. It has characteristic odour with acrid and bitter taste.

Stems: somewhat woody, spreading, terate, striate, glabous. It attains a height of about 0.5–2 m (1.6–6.6 ft) (Figure 1A). Bark is thin and brown in colour.

Leaf: simple, alternate, 8 cm long and 3 cm broad, ovate or oblong, petiole narrow, amplexicaul at the base and often dilated into stipule like auricles.

Inflorescence: terminal raceme-type about 6–30 cm long and many-flowered.

Flowers: white in colour, 10-25 cm long, inodorous, inbracteate, axillary and terminal elongated spikes, and bisexual. Calyx densely covered with stalked, sticky glands. Corolla is white, very slender, and tubular and Stamens 5, free. Ovary superior, 5-gonous, one celled, ovule one basal.

Fruit: Oblong (7.5–8 mm long) five-furrowed capsule containing single seed. Each seed is oblong in structure, 5–6 mm long and reddish- brown to dark brown in colour.

Microscopic description

Transverse section of the **root** shows the following structure:

***Cork*:** outer most tissue of cork consisting of 5 -7 row, of cubical to rectangular dark brown cells.

***Secondary cortex*:** secondary cortex consists of 2-3 rows of thin walled rectangular, light brown cells; most of the cortex cells contain starch grains.

***Cortex*:** Composed of large polygonal to tangentially elongated parenchymatous cells varying in size and shape, containing starch grains and some cells with yellow contents, fibres scattered singly or in groups of 2-6.

***Phloem*:** A narrow zone of polygonal, thin-walled cells, consisting of usual elements and phloem fibres, similar to cortical zone, phloem fibres usually in groups of 2-5 or more but occasionally occurring singly, lignified with pointed ends and narrow lumen, similar in shape and size to those of secondary cortex.

***Cambium*:** indistinct.

***Xylem*:** Light yellow to whitish; xylem vessels arranged in single or radial rows; tracheids are also filled with starch grains.

Medullary ray: Single to multilayered loaded with simple to compound starch grains, radially elongated, stone cells absent.

Leaves: It has Dicotyledonous organization; irregular in shape. T.S. of leaf shows the following structure:

Lamina: One palisade layer; two to three spongy layers.

***Mesophyll*:** Idioblast cells were occasionally found in intercellular spaces containing lesser amount of tannins than *P. indica*.

Trichomes: Not found.

PHYTOCHEMISTRY

Stem: Stem contain plumbagin, zeylanone, isozeylanone, sitosterol, stigmasterol, campesterol, and dihydroflavinol-plumbaginol.

Leaves: Leaves contain plumbagin, chitanone.

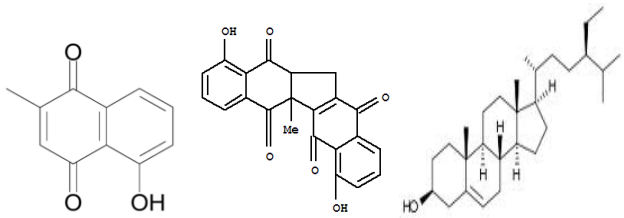
Flower: Flowers contain plumbagin, zeylanone, and glucose.

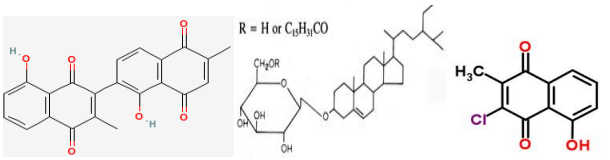
Fruit: It contains plumbagin, glucopyranoside and sitosterol.

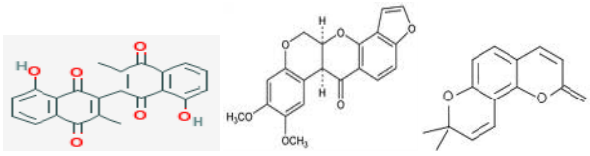
Seeds: Seeds contain plumbagin.

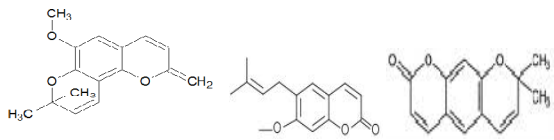
Roots: The root bark of *P. zeylanica* contains plumbagin. The root yield new pigment, viz, 3-chloroplumbagin, 3, 3-biplumbagin, binaphthoquinone identify as 3', 6'-biplumbagin, and four other pigments identify as isozeylanone, zeylanone, elliptinone, and droserone 2, 3**.** The isolation of plumbagin, droserone, isoshinanolone and a new napthalenone i.e., 1, 2 (3)-tetrahydro-3, 3'-plumbagin is reported from the phenolic fraction of the light petrol extract of the roots**.**

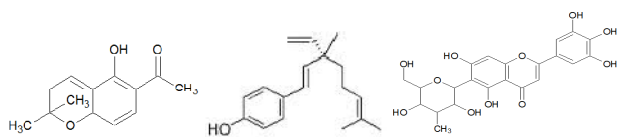
Two plumbagic acid glucosides; 3'o-beta-glucopyranosyl plumbagic acid and 3'-o-beta- glucopyranosyl plumbagic acid methyl ester along with five naphthaquinones (plumbagin, chitranone, maritinone, elliptinone and isoshinanolone), and five coumarins (seselin, methoxyseselin, suberosine, xanthyletin and xanthoxyletin) were isolated from the roots**.**[4]

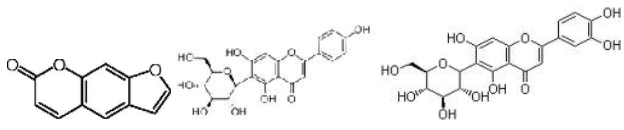

Plumbagin zeylanone β-sitosterol


Chitranone β-sitosteryl-glucoside 3-Chloroplumbagin


Biplumbagin Elliptone Seselin

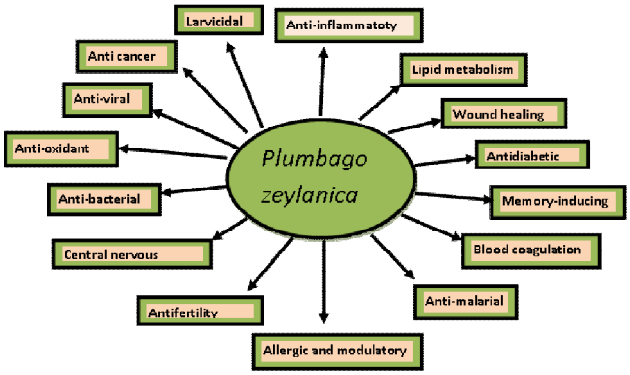

5-methoxyseselin Suberosin Xanthyletin


2,2-dimethyl-5-hydroxy-6-acetylchromene Bakuchiol Isoaffinetin


Psoralen Saponaretin Isoorientin

PHARMACOLOGICAL ACTIVITIES

The plant *P. zeylanica* exhibits large numbers of medicinal properties which are describes as under



Anti-inflammatoty activity

Plumbago species are one of the most important medicinal plants which are used for anti-inflammatory diseases. The root of *P. zeylanica* extracted with methanol was used for determining the anti inflammatory effects. The methanolic extracts at 300 and 500 mg/kg produced 31.03 and 60.3% inhibition of acute inflammation, respectively, in Carrageenin induced raw paw oedema confirming that *P. zeylanica* roots are effective against acute inflammation.

In Ethiopia, the powdered bark, root or leaf is used to treat gonorrhea, syphilis, and tuberculosis. The Zambians make use of the roots boiled in milk as a remedy for inflammation of the mouth, throat and chest.

Sheeja *et al*.,[5] studied the anti-inflammatory of various leaf extracts of *P. zeylanica* using *in vivo* experimental models. The acetone extract significantly ($p < 0.01$) reduced inflammation in the carrageenan induced rats when compared to the control group.

Yedapo[6] investigated the phosphate buffered saline extract of the roots of *P. zeylanica* for anti-inflammatory activity.

The plant has been used for anti-inflammatory properties.[7,8] Three medicinal plants namely *Phyllanthus emblica*, *P. zeylanica* and *Cyperus rotundus* were used to analyse two models of acute inflammation and result showed that *P. zeylanica* reduce the oedema while the combination of *P. emblica* compared to aspirin.[9] Also *P. zeylanica* brought to suppress the activation of NF-kappa B in tumor cells and prevented Graft Versus Host Disease-induced mortality in mice.[10]

Lipid metabolism activity

Plumbagin (2-methyl-5-hydroxy, 1:4naphthoquinone) isolated from the roots of *P. zeylanica* when administered to hyperlipidaemic rabbits, reduced serum cholesteroland. Plumbagin was reported to reduce serum cholesterol and LDL-cholesterol by 53% - 86% and 61%-91 % respectively; lower cholesterol/ phospholipid ratio by 45.8%; elevates decreased HDL-cholesterol significantly in rabbits.[11]

Wound healing activity

The wound healing activity of *Plumbago zeylanica* was investigated by Devender Rao Kodati *et al*[12] and Reddy *et al*[8] in rat. Significant wound healing activity of methanolic root extract of *Plumbago zeylanica* was observed.

Antidiabetic activity

Olagunju *et al.*[13] investigate antihyperglycemic effect of *P. zeylanica* on induced diabetic animals.

Zarmouh *et al.*[14] shows that oral administration of ethanolic root extract of *P. zeylanica* (100 mg, 200 mg/kg/p.o), tolbutamide (250 mg/kg/p.o) increased the activity of hexokinase and decreased the activity of glucose-6-phosphatase ($P < 0.001$) in streptozotocin treated diabetic rats.

Christudas Sunil and *et al.*[15] also evaluated the antidiabetic effects of plumbagin isolated from *P. zeylanica* root and its effect on GLUT4 translocation in STZ-induced diabetic rats.

Memory-inducing activity:

Mittal *et al*[16] reported the effect of *P. zeylanica* roots on scopolamine induced amnesia for learning and memory of mice. The chloroform extract of plant at dose 200 mg/kg has shown promising memory enhancing effect in mice. The extract significantly reversed the amnesia induced by scopolamine (0.4 mg/kg i.p.).

Blood coagulation activity

The structure of *Plumbago zeylanica* active principle compound is similar to that of vitamin K. The *P. zeylanica* extract (2 mg/kg body weight) and napthoquinone (2 mg/kg body weight) given to individual groups were screened for its effect on bleeding time (BT), clotting time (CT), prothrombin time (PT), platelet count and platelet adhesion in albino rats after 1-day, 15-day and 31-day treatment. There was no change observed in treated groups and control group but the platelet adhesion was significantly decreased in *Plumbago zeylanica* and napthaquinone-treated animals.[17]

Anti-malarial activity

Malaria is normally transmitted to people by mosquitoes infected with the malaria parasite.

Avoiding the bites of *Anopheles* mosquitoes is the best way to prevent malaria. Plants are traditionally used in India for the treatment of malarial fever since time immemoral. *Plumbago* spp have been tested for mosquito larvicidal activity. The crude extracts which been show highest larvicidal activity against *Anopheles gambiae* were hexane (LC50 = 6.4 µg/mL) and chloroform(LC50 = 6.7 µg/mL) extracts.[18] Patil *et al*. tested extracts of *P. zeylanica* and *C. nocturnum* for larvicidal activity against second, third, and fourth instar larvae of *Aedes aegypti*. The LC (50) values of all the extracts in different solvents of both the plants were less than 50 ppm (15.40 to 38.50 ppm) against all tested larval

instars. Plant extracts also affected the life cycle of *A. aegypti* by inhibition of pupal development and adult emergence with increasing concentrations.[19]

Simonsen *et al*.[20] carried out *in vitro* screening of Indian medicinal plants for anti-plasmodial properties against *Plasmodium falciparum*. Out of 80 analyzed ethanol extracts, from 47 species, significant effects were found for 31 of the extracts and only 5 plant extract show special interest for further study, one of that was *P. zeylanica*.

Plumbagin shows anti-malarial effects on *Plasmodium falciparum* enzyme, the succinate dehydrogenase (SDH). It also inhibited the in vitro growth of the parasite with a 50% inhibitory concentration of 0.27mM.[21]

Allergic and modulatory effects

Plumbagin, derived from *P. zeylanica* modulates cellular proliferation, carcinogenesis and radio resistance. All these reactions should be regulated by the activation of the transcription factor NF-kappa B activation pathway. Plumbagin inhibits NF-kappa B activation induced by TNF, other carcinogens and inflammatory stimuli like phorbol myristate acetate.[22]

The modulatory ability of plumbagin from *P. zeylanica* was studied on peritoneal macrophages of BALBC mice. The functions of macrophages are anti-bactericidal activity, against *staphylococcus aureus*. Study shows that plumbagin augments the macrophage antibactericidal activity at low concentrations and inhibits it at higher concentrations.[23]

Allergic reactions of ethanolic extracts (70 %) from *P. zeylanica* stems were investigated. The extracts (500, 1000mg/kg orally) inhibited dose-dependently systemic anaphylactic shocks, induced by compound 48/80 in mice, reduced homologous passive cutaneous anaphylaxis and skin reactions, induced by histamine or serotonin in rats. Significant differences were observed at the dose of 1000mg/kg.[24]

Antifertility activity

Some worker reported that *Plumbago zeylanica* treatment during first 7 days of pregnancy abolished uterine proteins of 13, 000, 19, 000 and 26, 000 and 75, 000 Da molecular weights resulting in preimplantationary loss. Proteins having molecular weights 55,000 and 65, 000 Da were absent in aborted rats, that were given *P. zeylanica* root powder since day 6 to day 17 of pregnancy.[25] In another study, Inclusion complex of plumbagin with hydroxyl propyl betacyclodextron (HPßCD) was prepared with a view to increase the efficacy and solubility. The complex was entrapped in the aqueous layer of niosomes and evaluated for antifertility activity. Given intraperitoneally, at a dose of 5 mg/kg the niosomes of the complex showed promising anti-fertility activity when compared to the control and niosomes with lipid layer entrapment.[26] Some worker reported the significant anti-implantation and abortifacient activity in albino rats without any teratogenic effect of plumbagin in the doses of 1mg/100g.[27] The roots of *Plumbago zeylanica* has been reported to be a powerful poison when given orally or applied to ostium uteri, causes abortion.[28]

Hydroalcoholic extract of *Plumbago zeylanica* leaves showed highly potent (95.167 %) anti-implantation activity because of anti-estrogenic activity, which antagonizes the action of estrogen, causes structural and functional changes in uterus. The antiestrogenic effect is also supported by decrease in glycogen content, diameter, thickness of endometrium, myometrium, reduced uterine lumen with decreased pits and folds, decreased in the number and size of the uterine glands, vaginal opening and cornification.[29]

Azad Chowdhury *et al*.[28] and Edwin *et al*.[30] investigated that the acetone and ethanol extracts of *P. zeylanica* were most effective to interrupt the estrous cycle and exhibited a prolonged diestrous stage of the estrous cycle resulting to a temporary inhibition of ovulation. Also in human, *P. zeylanica* acts as family planning agents[27,31] and anti-implantation agents that appear to interfere with progesterone synthesis or utilization.[32,25]

Central nervous system activity

Bopaiah *et al*[33] investigated the effects of a 50% ethanol extract of the root of *P. zeylanica* on locomotor behaviour and central dopaminergic activity in rats. The extract significantly increased the spontaneous motility in animals. The stereotypic behaviour which is characteristic of a dopamine agonist showed biphasic effects. They observed the extract of the root of *P. zeylanica* specifically enhanced the spontaneous ambulatory activity without inducing stereotypic behaviour. Hydroalcoholic extract of *Plumbago zeylanica* leaf were evaluated by Vishnukanta and Rana AC[34] for central nervous system activities. They reported that the extract showed significant CNS depressant activity, with muscle relaxant properties. It also showed anxiolytic activity.

Microbiological activity

Infectious diseases account for a high proportion of the health problems in developing countries. Claims of effective therapy for the treatment of these diseases have prompted the interest in scientific investigation. Extracts from roots of *Plumbago zeylanica* showed microbiological properties.

Anti-bacterial activity

82 plants were evaluated for antibacterial activity, among them only alcoholic extract of *Plumbago zeylanica, Emblica officinalis, Terminalia chebula, Terminalia belerica* showed potential antibacterial activity.[35] The alcoholic extract from roots of *Plumbago zeylanica* was tested against multi-drug resistant of clinical origin (*Salmonella paratyphi, Staphylococcus aureus, Escherichia coli* and *Shigella dysenteriae*). The extract exhibited strong antibacterial activity against all tested bacteria.[23]

The chloroform extract of *Plumbago zeylanica* L. root showed antibacterial activity against *Escherichia coli* (16.7 }0.14 mm), *Salmonella typhi*(14.3 }0.04 mm) and *Staphylococcus aureus* (12.0 }0.54 mm). Moderate inhibition is shown against *Klebsiella pneumonia* (9.2}0.73 mm), *Serratia marcescens* (8.6}0.07 mm) and *Bacillus subtilis*(8.0 }0.61 mm), and lowest against *Proteus vulgaris* (5.9}0.55mm) and *Pseudomonas aeruginosa* (4.8}0.87mm). The methanolic extract exhibited moderate activity while aqueous extract has been found weak against the bacterial strains.[36] The synergistic activity of antimycobacterial constituents from *Plumbago zeylanica* was evaluated in combination with isonicotinic acid hydrazide (INH) against four atypical organisms, namely, *Mycobacterium intracellulare, M. smegmatis, M. xenopei* and *M. chelonei.* The potency of INH was increased four-fold, The MIC values of plumbagin (from *Plumbago zeylanica*) were thus lowered from 1.25-2.5 to 0.15-0.3 µg/ml due to synergism with INH.[37]

Anti-viral activity

Chen[38] examined the antiviral activities of the 80% methanolic extracts of *Plumbago zeylanica* against coxsackievirus B3 (CVB3), influenza A virus and herpes simplex virus type1 Kupka (HSV-1) using cytopathic effect (CPE) inhibitory assays in HeLa, MDCK, and GMK cells, respectively. The antiviral activity of the most active compound was confirmed with plaque reduction assays. *Plumbago zeylanica* L had marked inhibition effects on HBeAg and HBsAg which is expressed by cells. In addition, CVB3 was inhibited by the extracts of *Plumbago zeylanica*.[39]

Anti-oxidant activity

Antioxidant effects of the aqueous/alcoholic extracts of root, corresponding to medicinal preparations, and the active ingredient, plumbagin, were studied by Tilak *et al*.[40] Methods used included: ferric reducing/antioxidant power (FRAP), radical scavenging of 1,1-diphenyl- 2-picryl hydrazyl (DPPH) and 2,2'-azobis-3- ethylbenzthiazoline-6-sulfonic acid (ABTS), lipid peroxidation in rat liver mitochondria induced by different agents, and estimating phenolic and flavonoid content. In FRAP/DPPH assays, boiled ethanolic extracts was the most effective, while in the ABTS assay boiled aqueous extracts was the most efficient. These extracts also significantly inhibited lipid peroxidation induced by cumene hydroperoxide, ascorbate-Fe^{2+} and peroxynitrite and contained high amounts of polyphenols and flavonoids. In conclusion, various studies reveal that extracts of *P. zeylanica* and its active ingredient plumbagin have significant antioxidant abilities that may possibly explain some of the reported therapeutic effects.

The isolation and spectral data for new flavonoid 2-(2,4-Dihydroxy-phenyl)-3,6,8 trihydroxy chromen-4-one from the roots of *P. zeylanica* were determined and in the other studies carried out by Nile *et al*.[41] the antioxidant activity was studied by free radical scavenging and superoxide radical scavenging methods. The antioxidant activity by DPPH was found to be 96µg/ml and by NBT as 4.6µg/ml which were greater than that of standard (quercetin) 45µg/ml by DPPH and 10 µg/ml by NBT assay.

Zahin *et al*.[42] carried out *in vitro* antioxidant activity and total phenolic content of methanolic extracts of *P. zeylanica*(root), *A. calamus* (rhizome), *H. indicus* (stem) and *H. antidysenterica* (bark). The order of antioxidant potential according to FTC assay was found to be highest in *P. zeylanica.*

Anti cancer activity

It was observed that the plant *Plumbago zeylanica* show anti cancer activity agains various cancer cell lines. There are so many report that show the anti cancer activity of the plant *Plumbago zeylanica.*

Sachin Hiradeve *et al*.[43] carried out the preliminary phytochemical screening and anticancer evaluation of *Plumbago zeylanica* L. against Ehrlich Ascites Carcinoma in animal model.They observed that the ethanolic extract of *Plumbago zeylanica* L. possess significant anticancer activity and also reduce elevated level of lipid peroxidation due to higher content of terpenoids and flavonoids.

Zhao YL and Lu DP[44] investigated the effects of plumbagin on the proliferation, cell cycle and apoptosis of APL cell line NB4 Cells. The results demonstrated that 2-15 micromol/L plumbagin inhibited the proliferation of NB4 cells in a dose-dependent manner. The morphologic changes of cell apoptosis, such as chromsome condensation and apoptotic body formation, were observed by light microscope and transmission electron microscope. Cell cycle analysis showed that NB4 cells were blocked in G2/M phase of cell cycle. Plumbagin induced annexin V+/PI- cell increase and DNA fragmentation. There was a correlation between cell apoptosis rates and the concentrations of plumbagin in dose-dependent manner ($P < 0.05$. The study show that plumbagin can inhibit cell proliferation, block cell cycle and induce apoptosis of APL cell line NB4 cells.

Nguyen *et al*.[45] isolatet betasitosterol, beta-sitosteryl-3beta-glucopyranoside, beta-sitosteryl-3beta-glucopyranoside-6'-Opalmitate (1), lupenone, lupeol acetate, plumbagin and trilinolein from the dichloromethane extract of aerial parts of *Plumbago zeylanica*. Compound 1 showed cytotoxic activity against MCF7 and Bowes cancer cell lines (IC50 113 microM and 152 microM, respectively), beta-sitosterol inhibited Bowes cell growth (IC50 36.5 microM) and plumbagin was cytotoxic against MCF7 and Bowes cells (IC50 1.28 microM and 1.39 microM, respectively).

Anticancer evaluation of *Plumbago zeylanica* L. leaves against Ehrlich Ascites Carcinoma was done by Hiradeve S in animal model. Administration of the ethanolic extract of the leaves at concentration 200mg/kg reduced the tumour volume (3.42 }0.082), packed cell volume (1.05 }0.092) and viable tumour cell count % 107 cells/ml (4.85 }0.23) in a dose dependent manner.[46]

Larvicidal activity

Larvicidal activity of extract from *Plumbago zeylanica* were observed by some author.

Barasa M Maniafu *et al.*[47] tested three *Plumbago spp.* for mosquito larvicidal activity. The crude extracts exhibiting the highest larvicidal activity against *An. gambiae* were hexane and chloroform extracts from *P. zeylanica* exhibited LC50 6.4 and 6.7 µg/ml respectively.

The methanolic extract of *P. zeylanica* roots possesses larvicidal activity against two mosquito species, *Aedes aegypti* and *Anopheles stephensi*. The LC50 concentration against fourth instar larvae of *Aedesaegypti* and *Anopheles stephensi* was found to be 169.61 }7.99mg/lit and 222.34} 8.65 mg/lit, respectively.[48]

CONCLUSION

This article briefly reviews the traditional knowledge, ethnomedicinal, pharmacological and therapeutic applications of the plant *Plumbago zeylanica* L. This is an attempt to compile and document information on different aspects of *P. zeylanica* and highlight the need for research and development. It is evident from the review of the research that *P. zeylanica* is used for centuries in Ayurvedic medicine for the treatment of various disease. It is the most important medicinal plant extensively used in herbal formulations. It is chemically rich with its diverse content of active compounds, such as plumbagin, chitranone, zeylanone and many useful naphthaquinone constituents as a multi-purpose medicinal agents. The evidence presented in this review has showed that *Plumbago zeylanica* L. has great potential to be integrated into conventional medical practice for the treatment and management of various metabolic syndromes, hepatotoxic, diabetes, inflammation, cancer and other disease complications. It is anticipated that this review will provide some valuable information for ongoing explorations of this fascinating species and its phytochemicals. Future research on *P. zeylanica* would not only provide much needed knowledge on this popular herbal medicine, but would also offer a noticeable socio-economic impact in turning a common weed into beneficial nutraceutical and pharmaceutical products.

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