ANNALS OF MULTIDISCIPLINARY RESEARCH, INNOVATION AND TECHNOLOGY (AMRIT)

(A peer-reviewed open access multidisciplinary journal)

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REVIEW ARTICLE

ETHNOMEDICINAL PLANT

Potential Therapeutic impact of *Plumbago auriculata* Lam: A brief review

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Article Chronicle: Received: 30.06.24 Accepted: 14.12.24 Published: 31.12.24

Abstract

Plants with herbal properties and their extracts have long been used in medicine. A well-known flowering plant species in the Plumbaginaceae family, *Plumbago auriculata* is sometimes referred to as cape leadwort, blue plumbago, or Cape plumbago. Along with being useful for gardening and aesthetics, it offers noteworthy advantages in the treatment of a variety of ailments. There is no better medicinal plant than *Plumbago auriculata*, which is grown commercially and has been shown to have positive therapeutic effects. With its many therapeutic qualities, the plant is a valuable source of medicinal chemicals. These qualities include tannins, fixed oils, lipids, proteins, tri-terpenoids, glycosides, steroids, flavonoids, and alkaloids. The plumbagins are the main bioactive components of this plant. Historically, this plant has been used to treat a wide range of illnesses, including warts, fractured bones, wounds, and black water fever. The roots of the plant in powdered form have been used to treat headaches and stop bad nightmares. The root is also used as an emetic and as a textile dye. But this plant is in danger of being extinct, therefore there is a need to find a new way to grow it to solve the issue. The goal of this review is to present a thorough analysis of *Plumbago auriculata*, covering its taxonomy, phytochemistry, pharmacological characteristics, and traditional uses.

Keywords: *Therapeutic applications, antimicrobial, antioxidant, bioactive compound, Plumbago auriculata, plumbagin*

1 Introduction

Plumbago auriculata, a perennial plant or small shrub, features an upright, trailing, or ascending stem reaching up to 2 meters in height. Its simple leaves are elliptic to obovate, 3-41.5 cm long, with a petiole up to 1 cm in length and a sharp to attenuate base. The compact inflorescence boasts a broadly obovate flower tube, 1 cm long, with blue to violet hues, measuring 3 cm in length. It bears five unattached stamens with three-centimeter-long filaments and an additional three-millimeter filament. The ovary is superior, filiform, 1 celled, measuring 4 cm by 2 cm. The fruit is membranous, present in a dehiscent capsule, 1-seeded, rectangular (7mm long), somewhat flattened, dark brown or black, up to 8mm in length, tapering to an apex encased in the persistent calyx. *Plumbago auriculata* produces flowers and fruits year-round (1-8).

Figure 1: *Plumbago auriculata* Lam

Botanical Classification: Kingdom: Plantae, Division: Magnoliophyta, Class: Magnoliopsida, Order: Plumbaginales, Family: Plumbaginaceae, Genus: *Plumbago*, Species: *auriculata*

Orange jasmine, or *Murraya exotica* L., is a perennial plant in the Rutaceae family that has long been utilized in Chinese medicine. Although it is widely grown in Taiwan, it has recently been reported to have symptoms similar to witches' broom (WB), including stunted foliage, yellowing of the leaves, and probable infection. A phytoplasma that is closely linked to those that cause diseases in other plants was found in the plants that were exhibiting symptoms, according to DNA analysis. This strain of phytoplasma is linked to aster yellows; it was identified as a member of the 16SrI group. This discovery implies that *M. exotica* may serve as a reservoir host for this phytoplasma, which may have an impact on roselle, wax apple, and periwinkle plants. This is the first time that a phytoplasma belonging to the aster yellows group has been documented to have infected *M. exotica* (9). The Plumbaginaceae family's grouping of *L. sinense* and *Plumbago auriculata* is confirmed by phylogenetic analysis, providing a basis for further phylogenomic research (10). This investigation assessed the phytochemical makeup and antimicrobial and cytotoxic characteristics of the leaves and flowers of three Mexican ornamental plants viz, *Callistemon citrinus*, *Hibiscus rosa-sinensis*, and *Plumbago auriculata*. Although these plants have different uses in different countries, their therapeutic potential was the main focus of this study. Compared to the other plants, *C. citrinus* ethanol extracts showed higher antibacterial activity, especially against Gram-positive and Gram-negative bacteria. Furthermore, the leaf of *C. citrinus* demonstrated minimal cytotoxicity, suggesting its potential for use in the management of microbial diseases. Notably, lupeol triterpene and lupeol acetate which had not before been described in this genus were found in the ethanol extract of *P. auriculata* leaf, indicating that its pharmacological characteristics warrant further investigation (11).

2 Traditional Uses

There are several historical applications of *Plumbago auriculata* root powder. It has been used as a headache and nightmare preventive snuff. It has historically been used to cure warts, wounds, and broken bones. It is said that putting the stick of the plant in thatched-roof cottages will keep lightning from striking. Its parts are decoction to treat nausea and black water fever, among other ailments. The roasted, powdered root helps mend fractures and stitches when applied topically. It is grown as attractive plants in tropical climates and as live fences in temperate gardens. In East Africa, it is also used as a fabric dye. Tribes in Maharashtra drink the root juice for stomach acidity. Tattoos are made from the gray-blue sap that comes from its roots (9, 10).

3 Phytochemical Constituents

Plumbago auriculata is known to possess diverse secondary metabolites, particularly plumbagin, a hydroxylnaphthoquinone compound offering a varied and significant biological activity. Alongside plumbagin, it contains epi-isoshinanolone, sitosterol, 3-0 glucosylsitosterol, palmitic acid, and plumbagic acid. Plumbagin exhibits a broad spectrum of pharmacological actions, present throughout the different plant parts. Flowers possess capensinidin, azalein, and capensinidin-3-rhamnoside, while leaves contain apigenin, luteolin, and their glycosides. Higher plumbagin content in leaves and stems are found compared to other related species. The methanolic root extract contain compounds like amyrin acetate, amyrin, sitosterol, diomuscinone, capensisone, isoshinanolone, and sitosterol glucopyranoside, with capensisone being a newfound natural substance. Various solvent extractions yield different compound profiles, as evident in TLC analysis (11, 12, 13, 14, 15, 16).

4 Pharmacological Activity

Anti-inflammatory activity

A study found that a hydro-alcoholic extract of *P. auriculata* roots, given at a dose of 250 mg/kg, had a peak inhibitory impact of 46.88% on carageenan-induced paw edema and also, in a dose-dependent manner, reduced leukocyte migration (17).

Antifungal activity

The crude antifungal protein 20 KDA was prepared from young leaves, isolated, and tested for toxicity against the pathogen *Macrophomina phaeolina*. Inhibiting the pathogen's spore germination is the activity that is being explained (18).

Antioxidant activity

Several methods were employed to investigate *P. auriculata* leaf extract's antioxidant capacity. The TBARS and NBT tests were used to quantify antioxidant activity. Ethanol acetate and crude extract had much better antioxidant activity than petroleum ether and dichloromethane extract. The NBT assay showed that, at the highest concentration ranges of 0.625-2.5 mg/ml (KeN), the ethyl acetate and ethanol extract exhibited the best (p0.001) superoxide scavenging activity in relation to the toxin. The ethyl acetate and petroleum ether extract dramatically decreased the proliferation of HeLa cells by 11.52% (p0.05) and 27.3% (p0.001), respectively, as compared to the control at 10 mg/ml. Results from the plant's ferric reducing antioxidant (FRAP) and oxygen radical absorbance capacity (ORAC) show that ethanolic leaf extracts have the highest antioxidant values. The ethyl acetate extract with the most promising antioxidant activity, at a concentration of 10 mg/ml, was shown to be hazardous according to the findings of the 20 MTT experiments (19).

Anti-ulcer and gastro protective activity

The DPPH scavenging assay, the lipid peroxide inhibition assay, the acid neutralizing capability test, and the ethanol-induced ulcer model were used to assess the anti-ulcer activity of plants. MTT results indicated that plumbagin has cytotoxic activity at 40.18 g/ml. *P. auriculata* is the species that is least cytotoxic. Even so, all plumbaginales had significant anti-ulcer activity. In a study including the popular drug ranitidine, *P. auriculata* was shown to have both ulcer-healing and gastroprotective properties (20).

Larvicidal Activity

Using bioassay-guided fractionation and chemical analysis of a chloroform extract of Plumbagocapensis roots, two novel napthaquine derivatives and six other recognized compounds were identified and characterized. By carefully analyzing spectroscopic (IR, MS, 1D, and 2D NMR) data and comparing the findings to information from the literature, their structure was determined. Plumbagin demonstrated excellent toxicity with LC50 values of 1.26 and 5.43 g/mL, outperforming all other substances in the examination of their efficiency against *Aedes aegypti* mosquito larvae in their fourth instar. A novel chemical proved to be somewhat harmful when tested on several types of mosquitoes (21).

Chitin Synthesis Activity

Using integument derived from Trichopulsiani larvae, Kubo conducted an *in vitro* study (22) on chitin synthetase (UDP-N-chitin Nacetylglucosamine: chitin N=acetyl-glucosaminyltransferase, EC 2.4.1.16) to investigate the effects of plumbagin, a material isolated from crude aqueous methanol extract from *P. auriculata* roots. The results indicate that plumbagin inhibits the isolated T chitin synthase by approximately 30%. in integument at a concentration of 3x10=4 M (22).

Antileishmanial Activity

This study evaluates the effectiveness of plumbagin, extracted from *P. auriculata* roots, against the Leishmania Major infection. Leishmanial activity was found in the study, although no overt cytotoxicity was found. Here, the plumbagin extract's purity is evaluated using NMR spectroscopy and HPLC. Based on available data, plubagin has a variety of antibacterial, dermatological, and cytological effects against protozoan parasites (23).

5 Reported other research works

The hepatoprotective qualities and chemical makeup of *Plumbago indica* L. and *P. auriculata* were examined in this study. Lam's LC-MS/MS analysis identified 25 compounds in *P. auriculata* extracts and 30 in *P. indica* extracts. Rats with TAA-induced liver fibrosis that received the extracts for 15 days displayed corrected liver histology, increased antioxidant levels, decreased inflammatory cytokines, and restored liver function biomarkers. *P. indica* showed much higher hepatoprotective effect, especially at 200 mg/kg. Additionally, the extracts showed antifibrotic qualities by reducing the amount of collagen deposited in the liver. Further research is needed to identify particular compounds, assess toxicity, and understand the processes of action (21).

An alcoholic extract from the flowering aerial portions of *Plumbago auriculata* Lam was used to create Zinc oxide nanoparticles, or ZnO NPs. The extract contained significant phenolic components that were discovered by HPLC analysis, such as gallic acid, chlorogenic acid, and catechin. Tests against the avian metapneumovirus (aMPV) subtype B revealed strong antiviral activity; the plant extract-mediated uncalcinated Nano-ZnO displayed a cytotoxic concentration (CC50) and inhibition, respectively (22).

Infected by *Trypanosoma cruzi*, Chagas disease (CD) affects more than six million people worldwide. The two available therapies are hazardous and have limited use: benznidazole (Bz) and nifurtimox (Nf). The Plumbaginaceae family's Plumbago sp. exhibits potential against CD. We evaluated Plumbagin (Pb) and root and aerial component extracts of *P. auriculata* both *in vitro* and *in silico*. Strong activity was shown by root extract against several strains and types of *T. cruzi*. Pb demonstrated low toxicity, excellent oral absorption, and permeability. Pb performed better against circulatory forms and equaled Bz's potency against intracellular forms. On *T. cruzi*, Pb's cellular targets suggested autophagic insults. Mammalian cells were moderately toxic to Pb and root extracts. The combination of Bz and root extract or Pb had cumulative effects that decreased host toxicity. This work (23) demonstrates *in vitro* the potential anti-parasitic effects of *P. auriculata* extracts and Pb against different strains and types of *T. cruzi*. In this work, *Plumbago auriculata* alcoholic extract was used to create silver nanoparticles. The UV-Visible absorption spectroscopy was used to optimize the reaction conditions. X-Ray diffraction investigations, transmission electron microscopy, and infrared spectroscopy were used to characterize the nanoparticles. The nanoparticles had face-centered cubic geometry and a spherical form, with sizes varying from 15 to 45 nm. They demonstrated strong antioxidant and antitubercular properties. They also effectively decreased organic dyes like malachite green (in 40 minutes) and congo red (in 2 hours). The work demonstrates *P. auriculata's* capacity to produce silver nanoparticles and suggests uses for them in the creation of antitubercular drugs, antioxidant therapy, and water filtration in the textile industry (24).

Tetraploid recretohalophyte *P. auriculata* has higher salt tolerance, which can be attributed to increased Na+ and Cl- secretion from leaf glands, leaf vacuolar sequestration of Na+, or root retention of Cl- in conjunction with K+ retention. Plant growth is threatened by salt stress, however, polyploids such as *P. auriculata* usually show more tolerance. When *P. auriculata* under salt stress was compared to diploid and autotetraploid, the results showed that tetraploids maintained superior morphology, photosynthetic efficiency, and chloroplast structure. Additionally, tetraploids had lower concentrations of harmful compounds like H_2O_2 and malondialdehyde (MDA) and more organic osmoregulatory molecules (proline and soluble carbohydrates). Tetraploids also showed less K+ loss in roots than diploids, and they acquired more Na+ in stems and leaves and more Cl- in roots. Additionally, tetraploids had reduced rates of K+, Mg2+, and Ca2+ secretion from leaf surfaces but greater rates of Na+ and Cl- secretion. Different Na+ accumulation locations were identified by X-ray microanalysis: vacuoles in tetraploids and cytoplasm in diploids. According to this study, polyploid recretohalophytes succeed in preserving ion homeostasis in high salinity environments by selectively secreting Na+ and Cl- and storing them while avoiding K+ loss (25).

In this work, *Plumbago auriculata* aqueous extract is used to synthesize silver nanoparticles (AgNPs), and their antibacterial and larvicidal characteristics were examined. FTIR, XRD, TEM, EDX, Zeta potential, and DLS were among the several spectroscopic methods that were used to completely analyze the produced AgNPs. They showed notable antibacterial activity against a variety of pathogens, including *Escherichia coli*, *Bacillus subtilis*, *Staphylococcus aureus*, and *Klebsiella pneumoniae*. Furthermore, even at low concentrations, the AgNPs demonstrated dose-dependent activity as they successfully suppressed the larvae of *Aedes aegypti* and *Culex quinquefasciatus* in their fourth instar, at concentrations of 45.1 and 41.1 µg/mL, respectively. Plumbagin, a substance in the plant extract, demonstrated a substantial binding affinity to the mosquitoes' salivary protein and odorant-binding protein, according to molecular docking tests. These findings imply that the plant extract and its nanoparticles could be viable substitutes for traditional insecticides in the management of mosquitoes (26).

In order to comprehend the metabolic alterations involved in this process, the study concentrated on heteromorphic self-incompatibility (HetSI), which is regulated by sporophytes. Growth behavior and structural differences in self-incompatible (SI) and self-compatible (SC) pollination of the pin and thrum flowers of *Plumbago auriculata* were observed using fluorescence and scanning electron microscopy. Energy deprivation as a cause of HetSI was refuted by UPLC-MS/MS/MS identification of metabolites, which showed higher amounts of energy-related nutrients in SI pollinations compared to SC, suggesting physiological differences in pollen-stigma interactions in pin/thrum styles and SC/SI pollinations (27).

The study explores the defense mechanism known as "Heteromorphic self-incompatibility" (HetSI), which plants use to inhibit self-pollination and promote outcrossing. Researchers used RNA-seq to study *plumbago auriculata* Lam. flowers for self-compatible (SC) and self-incompatible (SI) pollination. They discovered genes that were differentially expressed (DEGs) across the pollination types of SC and SI, enhancing processes such as plant-pathogen interaction, MAPK signaling, and plant hormone signaling. It's interesting to note that different gene regulation was seen in HetSI, indicating that *P. auriculata* has distinct processes similar to sporophytic self-incompatibility (SSI), but with different mechanisms in thrum and pin flowers. The results offer fresh theories that are advantageous for crop breeding and production (28).

It has been found that *Plumbago auriculata* Lam mediated metallic nanoparticles are potential anti-cancer candidates. All cancer cell types investigated showed that *Plumbago auriculata* Lam - synthesized silver nanoparticles were more lethal than gold nanoparticles. Although the majority of plant-mediated metallic nanoparticles demonstrated cytotoxicity, more study is required to fully understand their pharmacological and toxicological effects in order to successfully treat cancer (29).

In this work, *Plumbago auriculata* leaf extract (PALE), an extract from a medicinal plant, was used to create nanoparticles of different sizes and shapes that may be used in photocatalytic dye degradation. By varying the amounts of zinc acetate and silver nitrate, zinc oxide particles (ZnOPs) and silver mixed zinc oxide particles (ZnOAg1Ps, ZnOAg10Ps, and ZnO10Ag1Ps) were created. PALE showed high amounts of many substances that helped with the green synthesis and capping of the nanoparticles, such as flavonoids, reducing sugar, and polyphenols. The resultant particles were irregular, spherical, hexagonal, and rod-like in shape, and they displayed polydispersity. Energy dispersive spectra verified the constituent composition, while UV absorption spectra displayed distinctive peaks. The synthesis and capping processes involved particular functional groups, as revealed by the

Fourier transform infrared spectra. Excellent photocatalytic degradation of methylene blue dye was shown by the composites; ZnOAg10Ps showed the best efficiency, with a degradation rate of 95.7%. These results point to the possibility of using PALE-synthesized Ag mixed ZnOPs as an environmentally benign alternative for pollution remediation by treating harmful dyes in wastewater from the textile and dye industries (30).

The first whole chloroplast genome of *Plumbago zeylanica* L. a prominent herb in the Plumbaginaceae family, has been presented in a recent work (31). A big single-copy section, a small single-copy region, and two inverted repeat regions made up the 169,178 bp long plastome. It included 124 genes, comprising 37 tRNA genes, 8 rRNA genes, and 79 protein-coding genes. Within the Plumbago genus, phylogenetic research showed a close relationship between *P. zeylanica* and *P. auriculata*. This thorough genome study provides information on genetic diversity and facilitates the identification of species and conservation initiatives.

Another study (32) used GC-MS and NMR techniques to do a comparative metabolomic profiling of the roots of three Plumbago species: *P. zeylanica, P. auriculata,* and *P. indica*. Antioxidant activity was assessed and multivariate statistical analyses were carried out. Furthermore, *P. indica* yielded two alkylated phenols that had not been previously described in this taxon. Eighteen of the twenty-five metabolites that were discovered were quantified. The three species were identified via principal component analysis. Using a free radical scavenging approach, antioxidant potential was evaluated. All species showed noteworthy activity, with *P. indica* showing the lowest IC50 value. These results highlight the potential of *P. indica* to mitigate oxidative stress, especially in foods that have undergone fermentation (32).

Plumbbago scandens L., which grows all throughout Brazil, is known to be harmful to goats and cattle, and because of its high plumbagin concentration, it causes caustic sores in their digestive tracts. Although there isn't much information on *Plumbago auriculata* Lam.'s toxicity, it is thought to be possibly harmful. Thin layer chromatography (TLC) and high-performance liquid chromatography (HPLC) are two analytical techniques that were validated in this work in order to identify plumbagin levels in leaves, stems, and rumen contents. Rumen content and popular forages had little effect on either technique. While HPLC has a quantification limit of 0.05 μg/mL and a detection limit of 0.01 μg/mL, TLC is straightforward to use and cost-effective while being qualitative. While *P. auriculata* samples revealed low quantities (up to 0.000114%) in some stems and no detectable toxin in leaves, *P. scandens* samples showed substantial levels of plumbagin in leaves (0.261 ± 0.087%) and stems (0.327 ± 0.055%). In situations when poisoning is suspected, these techniques can help confirm or rule out *P. scandens* intake (33). This study revealed that more and elaborate research work needs to be done to standardize the plant materials and development of therapeutic natural products development.

Conclusion

The ethnomedical, pharmacological, and therapeutic uses of *Plumbago auriculata* are briefly reviewed and summarized in this article. The scientific evaluation demonstrates that this plant has been used for many years in Ayurvedic medicine to treat a variety of ailments. Due to its wide spectrum of active ingredients, which contain several advantageous naphthaquinone components that are multifunctional therapeutic agents including plumbagin, chitranone, zeylanone, and many more, it is an essential medicinal plant which is commonly used in herbal medicines. The review revealed that *P. auriculata* may be used to treat a number of metabolic syndromes, hepatotoxic illnesses, diabetes, cancer, inflammation, and side effects encountered while treating diseases in conventional medicine. This intriguing plant species and its phytochemicals warrant further investigation, and this review provides useful information for ongoing studies. Future research on *P. auriculata* would not only add to the body of knowledge necessary for understanding this well-known herbal remedy but also have a significant economic impact by transforming a common weed into valuable nutraceutical and pharmaceutical products.

Conflict of Interest

The authors have declared no conflict of interest.

Acknowledgement

All the authors extend thanks to their concerned institutions for providing facilities for the work.

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