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Plumbago indica L.: A review of its medicinal uses, phytochemistry, pharmacology, and toxicology

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Abstract
The biggest genus of flowering plants in the Plumbaginaceae family is called *Plumbago indica* L. This plant is regarded as toxic and is used mostly for external applications to cure skin conditions. The root is thought to be the most active component of the plant. It is regarded as an emmenagogue, abortifacient, alterative, carminative, stimulant, tomachic, and vesicant. The root is used internally to improve menstrual flow, cleanse the blood, stimulate digestion, and induce abortion. Leprosy, rheumatism, paralysis, tumors, headaches, toothaches, hemorrhoids, and swollen glands can all be treated with a poultice made from the roots. A vesicant is created using the root-bark. The leaves are applied as a poultice to cure headaches and rheumatism. With regard to taxonomy, morphology, medicinal applications, phytochemistry, pharmacology, and toxicity, *Plumbago indica* research has made significant strides in recent years. This study seeks to provide full information on such advances. Studies on its phytochemistry and pharmacology are the key areas of interest. Scientific databases such Web of Science, Pub Med, Google Scholar, Google, Sci. Finder, Science direct, Springer Link, and Wiley were used to find pertinent material. Many phytochemical and pharmacological investigations on *Plumbago indica* have been conducted in the last ten years. The naphthoquinone plumbagin is the plant's main active ingredient. Leucodelphinidin, plumbaginol (a flavonol), 6-hydroxyplumbagin, and steroids are further substances that have been identified from the aerial portions. Plumbagin has a range of pharmacological properties, including as anti-implantation, abortifacient, anti-microbial, anti-cancer, cardiotonic, and anti-fertility effects. Moreover, it is a potent irritant. To inspire further research, this review paper included empirically supported information on its therapeutic applications, photochemistry, pharmacology, and toxicological actions.

Keywords: *Plumbago indica*, medicinal uses, pharmacology, toxicology

1. Introduction
Human health issues have been getting worse at an alarming rate over time and are now potentially fatal. Traditional medicine, which is used to manage health issues, is frequently overpriced and has several adverse effects. As a result, many individuals have started using medicinal plants to cure and manage their health issues. Ailments have been treated using plant extracts for hundreds of years [1]. It is still unknown how many therapeutic plants there are and how they might benefit human health. In a time of rising worldwide expenses for western medicine and increased demand for drug manufacture, using traditional medical systems has shown to be a beneficial strategy. Many plants are known to naturally create secondary metabolites, also known as phytochemicals or biologically active substances, which are crucial for plant metabolism but also, play a significant part in the plants' defence system [2]. Due to their medicinal and aromatic qualities, these bioactive chemicals also serve as precursors for the creation of natural, ecologically friendly, low-toxicity medications, flavorants, perfumes, cosmetics, and insecticides in addition to protecting plants. In specialized cells known as secretory structures, such as salt glands, trichomes, resin ducts, idioblasts, laticifers, colleters, and nectaries found in various reproductive and vegetative parts of the plant, bioactive substances are either generated, expelled, or stored in minute amounts [3]. Understanding the shape, location, and secretory processes of the primary secretory structures involved is essential in order to comprehend the biological activity and composition of the produced exudate.
The biggest genus of flowering plants in the Plumbaginaceae family is called *Plumbago indica* L. This plant, formerly known as *Plumbago rosea*, may flourish in a variety of climates. One of the most significant medicinal herbs is *Plumbago indica*. Ayurveda, Siddha, Unani, and homeopathy all employ the upright or spreading, half-woody plant known as *Plumbago indica*. The Sikkim and Khasi highlands of India are where this species originated, and it has since nations including Sri Lanka [4].

It is dispersed across Dhaka, Chittagong, and the Chittagong hills tracts [5]. Across the tropics and the temperate zone, *Plumbago indica* is grown both as a decorative plant and as a medicine [6]. For the aim of extracting its tuberos roots for therapeutic purposes, *Plumbago indica* is widely planted in South India, the Philippines, Kenya, Tanzania, Zimbabwe, Mozambique, Madagascar [4], Africa, Europe, Indonesia, China, Malaysia, and Arabian Peninsula [7]. With regard to taxonomy, morphology, medicinal applications, phytochemistry, pharmacology, and toxicity, *Plumbago indica* research has made significant strides in recent years. This study seeks to provide full information on such advances. Studies on its phytochemistry and pharmacology are the key areas of interest.

1.1 Synonyms
Plumbago rosea, *Plumbago coccinea*, *Thela coccinea*.

1.2 Common name
Chitraka (In Ayurvedic), Sheetraj, Chita (in Unani), Chitraka, Chitrakamool (Trade Name).

1.3 Others name
English: Rosy-flowered Leadwort; Tamil: Akkini; Hindi: Chitra, Lal-Chitra; Sanskrit: Agni, Atidipya, Chitraka; Bengali: Lalchitra; Marati: Lal; Malay: Nilavaka; Gujarati: Nat-ki-Sana.

1.4 Taxonomic profile
Kingdom: Plantae
Division: Magnoliophyta
Class: Magnoliopsida
Order: Caryophyllales
Family: Plumbaginnaceae
Genus: Plumbago
Species: *Plumbago indica* L. [8].

Fig 1: *Plumbago indica* L.

2. Morphology
Plumbago indica is a tiny shrub or perennial plant that thrives in warm, tropical climates. These little shrubs can reach heights of 1.0 to 1.5 m, and their stems can be upright, trailing, or ascending. From the base, the stem is either straight or branched [9]. The leaves are simple, ovate-elliptic in form, and about 10 cm long. They have an alternating arrangement with an entire edge and are exstipulated. The leaf's base tapers into a short petiole that resembles a clasp [10]. The inflorescence of bisexual, regular, and pentamery flowers is red and grows on an elongated, glabrous spike or raceme that is 10–30 cm long. Bracts on the flowers are 8–9 mm long, tubular, glandular, and crimson, and have an oval form. The calyx is made up of five united sepals [9].

To produce the 2.5 cm long, spreading, apiculate, tubular silverform corolla, five petals are fused together. Stamen filaments are the same length as the corolla tube. A little bit above the neck, anthers are active. Superior ovary with one anatropous ovule, five carpellary, unilocular, basal placenta, and five carpellary. In a style that is roughly 2.2 cm long, there are five stigmas. Flowers that have been pollinated develop a membrane circumscissile capsule that is encased in a persistent calyx [10]. While blossoming, several plumbago species exhibit carnivorous behavior. Plumbago sepal glands secrete a resinous substance that aids in catching tiny insects. When exposed to stimuli like insects or decaying insects, *Plumbago indica* can produce proteases [11].

This species doesn't produce fruit or seeds. Since vegetative propagation is the primary means of multiplication, this species exhibits little genetic diversity in nature [12]. *Plumbago indica* has a robust cylindrical root system with small transverse cracks at the locations of the bents. The smooth, light yellowish brown surface of the roots exudes fluid when they are freshly cut. 18–20 strong roots may be produced by a healthy *Plumbago indica* plant per plant [13]. When dried, roots change from dark brown to blackish brown and have a distinctively strong odor [14].

2.1 Medicinal Uses
Indian leadwort, also known as *Plumbago indica*, is a well-liked traditional remedy in India as well as in several regions of Africa and Southeast Asia - particularly in areas with a sizable Indian population. It is a toxic plant that is largely used topically to treat skin conditions, with the root being thought of as the plant's most active component. The plant is regarded as an emmenagogue, abortifacient, alterative, carminative, stimulant, tomachic, and vesicant. Excessive dosages are risky and can be fatal. The naphthoquinone plumbagin is the plant's main active ingredient. Leucodelphinidin, 6-hydroxyplumbagin, plumbaginol (a flavonol), and steroids (Such as -itosterol, stigmasterol, and campesterol) are other chemicals identified from the aerial portions. The pharmacological properties of plumbagin include antibacterial, anticancer, cardiotonic, and antifertility effects. Moreover, it is a potent irritant. The substance encourages perspiration and activates the central nervous system in modest quantities; excessive dosages may result in respiratory failure and paralysis, which can result in death. The anti-implantation and abortifacient properties of plumbago have been observed. Plumbagin significantly inhibited Ehrlich ascites carcinoma tumor growth at low dosages. The leaves' ethanol extract has anti-herpes simplex virus type 1 activity (HSV-1). The root is used internally to improve menstrual flow, cleanse the blood, stimulate digestion, and induce abortion. Leprosy, rheumatism, paralysis, tumors, headaches, toothaches, hemorrhoids, and swollen glands can all be treated with a poultice made from the roots. A vesicant is created using the root-bark. To do this, extremely thin slices of the fresh root are cut and fastened to the skin. Similar to how they may be used on the forehead to treat headaches. The leaves are applied as a poultice to cure headaches and rheumatism [15].

2.2 Phytochemistry
Several kinds of alkaloids, flavonoids, saponins, glycosides,

and tannins are prominent in *Plumbago indica* [16]. Apigethenin, cuteolin, 7-0 gencides, amyrin, palmistic acid, sitostrol, plumbaginol, campesterol, plumbagin, stigmasterol, and 6-hydroxy plumbagin are all present in the leaves and stem. Pelargonidin, cyanidin, delphinidin [17-20]; kaempferol, mono galloy lglucose, and digalloylglucose are all present in the inflorescence. Roots contain plumbagin, 6-hydroxy plumbagin, droserone, elliptinone, plumbagic acid, 3, 3 - biplumbagin, lactone, ayanin, azaleatin, arachidyl alcohol [21-22], myricetin-3, 3′, 5′, 7-tetra methyl ether, ampelopsin 3′, 4′, 5′, 7- tetramethylether, plumbagic acid, roseanoic acid [23], αnaphthylamine, myricyl palmitate, palmitic acid and β-sitosterol [21].

2.3 Pharmacology

2.3.1 Anti-fungal activity

The greatest antifungal activity was found against *C. albicans*, *B. blastomeres* dermatitides, *Trichophyton* spp., and *Microsporum* spp. *C. albicans* the more sensitive against fungal strain with the methanol extract of *Plumbago indica* L. [24]. Methanol extract demonstrated strong antifungal activity with zone inhibition of (10.0-27.0) mm.

Aspergillus niger and *Candida albicans* are resistant to the antifungal effects of ethanol-based *Plumbago indica* root extract [25].

With MIC and MFC values of 0.78 and 1.56 g/mL, respectively, the active ingredient Plumbagin was described as fungicidal against *Candida albicans* [26].

2.3.2 Anti-Acne Activity

Plumbago indica roots were reported to have MICs of 600, 200, and 300 g/mL against *P. acnes*, *S. epidermidis*, and *M. furfur*, respectively [27].

The *Plumbago indica* (In gel formulation) acetone extract shown anti-acne action against *P. acnes*, *S. epidermidis*, and yeast by well diffusion technique, suggesting potential activity against acne-causing bacteria [28].

2.3.3 Antimicrobial activity

When using ciprofloxacin as a reference drug, methanolic extracts of *Plumbago indica* shown antibacterial efficacy with zones of inhibition ranging from 7.0 to 25.0 mm against *Staphylococcus aureus*, *Salmonella typhi*, and *Salmonella paratyphi* [29].

PPE (Plumbago derivative-rich *Plumbago indica* extracts) was not less than 13.0%w/w contains and exhibits antimicrobial effects against *Propionibacterium acnes*, *Staphylococcus aureus*, and *Staphylococcus epidermidis* by micro-dilution assay method. Its stability was determined quarterly when stored in a well-closed container at temperature 42 °C in dried powder form, which is to be protected from light [30].

Plumbago releases dynamic antibacterial activity against methicillin-resistant *Staphylococcus aureus* using the Disc Diffusion Assay technique. During molecular docking, Plumbago demonstrated good selectivity with the DNA gyrase binding site, high affinity, and a minimal energy barrier of - 7.651 kcal/mol [31].

2.3.4 Antifertility Activity

At dosages of 200 and 400 mg/kg b/w, *Plumbago indica* demonstrated a percentage pre-implantation loss of 40% and 50% compared to control. With a focus of 10%, *Plumbago indica* and *A. lanata* have not demonstrated any motility. In rats, neither *Plumbago indica* nor *A. lanata* had spermatozoa that move within 60 seconds at a 10% concentration [32].

At dosages of 200 and 400 mg/kg, acetone extracts of *Plumbago indica* stem exhibit action in female albino rats. When the extract was stopped, the anti-ovulatory effect was reversible and demonstrated strong estrogenic and anti-estrogenic activity [33].

2.3.5 Analgesic Activity

Using the acetic acid-induced writhing technique, methanolic extract of *Plumbago indica* has been demonstrated to significantly reduce the pain response in young Swiss albino mice at dosage concentrations of 250 mg/kg and 500 mg/kg [34].

With a dosage of 300 mg/kg body weight, *Plumbago indica* aqueous extracts were calculated; the Eddy's hot plate method revealed that carrageenan-induced paw volume exhibited analgesia in 68.29% and 45.2% of cases [35].

2.3.6 Antimalarial activity

In a mouse model infected with *Plasmodium berghei*, *Plumbago indica* L. was reported to have *in vitro* antimalarial activity at a dosage level of 25 mg/kg BW administered daily for up to 4 days was both safe and generated antimalarial activity [36].

2.3.7 Antibacterial activity

While aqueous extract had a Microbial Inhibitory Concentration of 10 and 20 g/mL of *Escherichia coli* and *Klebsiella pneumonia*, methanolic extract was found to have a MIC of 20 g/mL on both *Escherichia coli* and *Klebsiella pneumonia* [37].

Bacillus subtilis, *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa* are all susceptible to ethanol extracts (80%), with MICs of 6.25 mg/mL for *Bacillus subtilis* and 12.5 mg/mL for *Staphylococcus aureus*, *Es Times New Roman cherichia coli*, and *Pseudomonas aeruginosa*. 10 When tested against *Staphylococcus aureus*, plumbagin showed activity with MIC and MBC/MFC values of 1.56 and 25.0 g/mL.11 Mycobacterial resistance Using the recombinant form of MtbThyX, which is pure and harmless, a structural arrangement of the linked molecule inhibits its action and causes cell death. Plumbago destroys mycobacterial cells by using an essential enzyme called ThyX, which is necessary for their survival [38].

2.3.8 Antioxidant Activity

Using utilizing 2,2-diphenyl-1-picrylhydrazyl in a test design using the technique Oyaizu, methanolic extracts of *Plumbago indica* exhibited *in vitro* antioxidant activity in addition to hydroxyl radical scavenging activity [39].

2.3.9 Hepatoprotective Activity

With reference medication Silymarin (100 mg/kg), the alcoholic root extract of *Plumbago indica* was found to be astonishingly safe against paracetamol-induced hepatocellular damage [40].

2.3.10 Anti-influenza Activity

At concentrations of 10 mg/mL, 5 mg/mL, and 1 mg/mL, methanolic and ethanolic extracts of *Plumbago indica* showed 100% depletion in both contemporaneous and post treatment assessment [41].

2.3.11 Cardioprotective Activity

Animals treated with plumbago regained their body weight

and heart weight after being protected from doxorubicin-induced damage by plumbago [42].
By oral treatment, plumbagin raised cardiac troponin and creatine kinase activities, restored the level of lipid peroxide indicators, boosted anti-oxidative enzymes, and reduced pro-inflammatory cytokines [43].
By lowering ROS and lipid peroxide levels in animals with cardiac injuries and redox imbalance caused by damage by transcription factors NF-kB and Nfr-2, plumbagin was able to manage free radical scavenging (Oxidative stress). Treatment with plumbagin substantially reduced pro-inflammatory cytokine expressions [44].

2.3.12 Macrofilaricidal Property
The effectiveness of *Plumbago indica* against *Setaria Digitata*, a cow filarial parasite, was observed to range between 0.02 and 0.05 mg/mL [45].

2.3.13 Antifertility Activity
When used at concentrations of 200 mg/kg and 400 mg/kg body weight, an ethanolic extract of *Plumbago indica* roots exhibits an anti-implantation effect with losses of 40% and 50% compared to the control dose, whereas the recommended percentage defeat was 30% and 40% [32]. With dosages of 200 and 400 mg/kg assessed on estrogenic activity in rats and verified by histopathology analysis of the uterus, acetonic and ethanolic extracts exhibit antifertility action [33]. Female rats exposed to the acetone extract plumbagin at doses of 200 and 400mg/kg body weight had considerable estrogenic and anti-estrogenic action (p 0.05) (p 0.001) [46].

2.3.14 Anti-inflammatory Activity
Plumbagin blocks cell cycle progression-induced IL-2, IL-4, IL-6, and IFN- cytokines, which are responsible for suppressing T cell growth in response to the polyclonal mitogen concanavalin A. In activated T cells, CD25 and CD69 were also reduced [47].

2.3.15 Genotoxic Effect
The ethanolic extract of the roots of *Plumbago indica* (EEPIR) has the potential to have therapeutic benefits at doses of 25 to 100 g/mL, which induce cell death, and 500 g/mL or more, which have cytotoxic effects [48].

2.3.16 Anticancer Activity
The LC_{50} and LC_{90} values for *Plumbago indica* L.'s Methanolic extraction against brine shrimp nauplii were 5.0 g/mL and 12 g/mL, respectively [49]. Using the MTT test, ethanol extract (50–250 g/mL) reveals cytotoxicity in HE-17 cell lines [50].
The feasibility of human prostate cancer cells (PC-3, LNCaP, and C4-2) was reduced by superoxide dismutase 2 (Mn-SOD), ROS origination, and decreased intracellular GSH levels [51].
Plumbagin performed as a strong ROS inducer, suppressing cellular glutathione and generating DNA double-strand breaks through oxidative DNA base damage [52].
In Pten-KO mice, plumbagin suppresses the growth of tumors and, at doses of 200 or 500 ppm, shows minimal toxicity while lowering Stat3, AKT, PKCE, and COX2 in both primary and castration-resistant prostate cancer, compared to the control group [53].

2.3.17 Antiproliferative effect
By labeling the nucleus, *Plumbago indica* L. and *P. zeylanica* L. demonstrated cell death in breast and stomach cancer cell lines [54].

2.3.18 Antidiarrhoeal Effect
With the inhibition of CaCC-calcium-activated Cl-channels and cystic fibrosis, plumbagin can treat CT-induced, rotaviral diarrhea, travelers' diarrhea, and delayed intestinal motility. It also inhibits both cAMP-activated and Ca2+ Cl-channels according to its mechanism. Both HT-29 cells and the mouse colon have a transmembrane conductance regulator [55].

3. Toxicology
When administered to mice in high doses, plumbago induces adverse reactions such as diarrhea, skin rashes, leukocytosis, and elevated blood phosphatase levels [56]. To determine the safe dose for therapies, it is necessary to assess the extract's harmful effects. Mice administered extracts orally demonstrated higher tolerance than those administered intraperitoneally. The extract's LD_{50} when administered orally was 1148.15 mg/kg, whereas it was 239.88 mg/kg when administered intraperitoneally. Male rats showed dark patches on the liver, green thyroid, increased weight of the spleen, and decreased weight of the liver, thymus, testes, and kidneys. When female rats were autopsied, the thymus weighed less and the uterus weighed more [57]. Using the brine shrimp lethality experiment to assess the cytotoxic activity of the extract, *Plumbago indica*, the LD_{50} was determined to be 4.57 g/ml [58]. When under oxidative stress, the non-enzymatic intracellular antioxidant GSH oxidizes to GSSG. By decreasing the amount of hepatic GSH while increasing the amount of hepatic GSSG, plumbagin and the extract of *Plumbago indica* L. cause an imbalance of oxidant-antioxidant substances in the liver. Chronic inflammation and cellular damage in the liver are results of this elevated hepatic oxidative stress [56]. The cytotoxicity of *Plumbago indica* was evaluated using the MDCK cell line and the MTT test. The CC_{50} value for the cold-macerated extract was 20.66 mg/ml, while the CC_{50} value for the 15-hour Soxhlet extract was 14.17 mg/ml [59].
Plumbago indica root extract has an IC_{50} of 178.29 g/ml on HGE-17 cell lines. *Plumbago indica* root extract's cytotoxicity was less hazardous than that of *P. zeylanica* (199.94 g/ml) and *P. auriculata* (278.59 g/ml) [60]. The EC_{50} values of *Plumbago indica* root bark extracts in aqueous and methanol on the HeLa cell line were 781.9 0.23 g/ml and 42.5 0.13 g/ml, respectively. Comparing niosomal plumbagin to free plumbagin, reduced toxicity has been observed. When BALB/c mice were intravenously injected with 10 mg kg-1 free plumbagin, there was a 70% death rate, compared to a 30% mortality rate for niosomal plumbagin [61].

4. Agronomy
Agronomic research on *Plumbago indica* is the subject of certain studies. However, many medicinal species are able to flourish in environments with very low light levels. They are *Adhatoda vasica* and *Plumbago rosea*. There may be ways to intercrop these species in mature Hevea strands profitably without harming the latex production of rubber plants. Plants cultivated beneath coconut trees produce more fruit than those growing in open spaces [62].

4.1 Management
Using nodal explants, callus societies, cell suspension societies, or root societies, *Plumbago indica* may be bulk produced *in vitro*. The plumbagin content of the roots of the

plants given in this way is basically greater than that of control plants. Tests on the root yield of *Plumbago indica* in India showed that the best harvesting stage occurred between 12 and half years after field planting. Being a short-day plant, *Plumbago indica* requires a protracted dull period treatment in the mild zone to produce conservative plants and blooms. Drilling is used to micro propagate fruitful plant recovery using a variety of growth mediums. Knowing more about *Plumbago indica* and its traits has made it much evident that this plant is significant and useful in many fields, particularly the field of medicine. This publication is a valuable resource for botanists to study this plant's characteristics, management etc. [63].

5. Conclusion

Numerous therapeutic benefits can be derived from Genera Plumbago. Among them, *Plumbago indica* has a wide variety of phytochemicals that can treat a variety of illnesses in people and other animals. *Plumbago indica* is widely utilized in Ayurveda, Siddha, Unani, and Homeopathy, as well as other conventional medical systems. It is now the focus of several experimental studies to see whether it has the capacity to treat cancer. Over the past few decades, there has been a sharp increase in demand for dry *Plumbago indica* plant parts. Therefore, due to overexploitation for commercial purposes, it is rapidly disappearing from its natural environment. This plant grows slowly and does not generate seeds. To keep it in its natural habitat and to ensure that there is a sufficient supply of raw materials for pharmaceutical compositions. To inspire more research, this page included data regarding its pharmacological, photochemical, and therapeutic uses that has been supported by science.

6. Acknowledgement

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7. Conflict of Interest

The author declares that there is no conflict of interest.

8. References

1. Balunas MJ, Kinghorn AD. Drug discovery from medicinal plants. Life sciences. 2005;78:431-441.
2. Ascensao L, Marques N, Pais MS. Peltate glandular trichomes of *Leonotis leonurus* leaves Ultrastructure and histochemical characterization of secretions. International Journal of Plant Sciences. 1997;158:249-258.
3. Thomas V. Structural, functional and phylogenetic aspects of the collector. Annals of Botany. 1991;68:287-305.
4. Jose B, Dhanya BP, Silja PK, Krishnan PN, Satheeshkumar K. *Plumbago rosea* L. A review on tissue culture and pharmacological research. International Journal of Pharmaceutical Sciences Review and Research. 2014;25(1):246-56.
5. Porandla R, Kumar Dr. CH. P. A review on different activities of medicinal plants of *Plumbago indica* L. World Journal of Pharmaceutical Research. 2018;7(14):473-478.
6. Schmelzer GH, Gurib-fakim A. Plant resources of Tropical Africa. 1st ed. Prota Foundation; Netherlands; 2008.
7. Sharma K, Yadav P. Forensic analysis of roots of an abortifacient plant *Plumbago rosea* L. International Journal of Scientific Research and Review. 2019;7(5):1156-59.
8. Arambewela L, Silva R. Sri Lankan medicinal plant monographs and analysis – *Plumbago indica*. Industrial Technology Institute (CISIR) & National Science Foundation; Colombo; 1999.
9. Jose B, Dhanya BP, Silja PK, Krishnan PN, Satheeshkumar K. *Plumbago rosea* L. A review on tissue culture and pharmacological research. International Journal of Pharmaceutical Sciences Review and Research. 2014;25(1):246-256.
10. Jayaweera DMA. Medicinal plants (Indigenous and exotic) used in Ceylon. 4th ed. The national science council of Sri Lanka: Colombo; 1982.
11. Stoltzfus A, Suda J, Kettering R, Wolfe A, Williams S. Secretions of digestive enzymes in Plumbago. The 4t6. Schmelzer GH, Gurib-fakim A. Plant resources of Tropical Africa. 1st ed. Prota Foundation; Netherlands; 2008.
12. Schmelzer GH, Gurib-fakim A. Plant resources of Tropical Africa. 1st ed. Prota foundation; Netherlands; 2008.
13. Sala AV. Indian medicinal plants. 6th ed. Sangam books Limited; London; 1955.
14. Babu LK, Austin A. Macro and Micromorphological studies on roots of *Plumbago indica* L. and *Plumbago zeylanica* L. Journal of Pharmacognosy and Phytochemistry. 2016;5(5):351-53.
15. Devi A, Sharma Dr. MK. An Analysis and Study of *Plumbago indica* Linn and its Concerning Issues and Characteristics. Published in International Journal of Trend in Scientific Research and Development (ijtsrd).2019;3(4):1703-1704.
16. Eldhose B, Notario V, Latha MS. Evaluation of phytochemical constituents and *In vitro* antioxidant activities of *Plumbago indica* root extract. Journal of Pharmacognosy and Phytochemistry. 2013;2(4):157-61.
17. Kumar SG, Joseph LH, Thangavel K. *In vitro* propagation of *Plumbago rosea*. Journal of Applied Biology and Biotechnology.2014;2(2):1-7.
18. Dinda B, Chel G, Achari B. A Dihydroflavonol from *Plumbago indica*. Phytochemistry, 1994;31(10):1083-84.
19. Dinda B, Chel G. 6-hydroxy plumbagin, A naphthoquinone from *Plumbago indica* Phytochemistry. 1992;35(4):1083-1084.
20. Harborne JB. Plant polyphenols: Occurrence of azalein and related pigments in flowers of Plumbago and Rhododendron species. Archives of Biochemistry and Biophysics. 1962;96:171-178.
21. Jose B, Dhanya BP, Silja PK, Krishnan PN, Satheeshkumar K. *Plumbago rosea* L. A review on tissue culture and pharmacological research. International Journal of Pharmaceutical Sciences Review and Research.2014; 25(1):246-256.
22. Kaewbumrunga S, Panichayupakarananta P. Isolation of three antibacterial naphthoquinones from *Plumbago indica* roots and development of a validated quantitative HPLC analytical method. Natural Product Research. 2012;26(21):2020-2023.
23. Ariyanathan S, Saraswathy A, Rajamanickam GV Connolly JD. Polyphenol from the roots of *Plumbago rosea*. Indian Journal of Chemistry. 2010;49B:386-389.
24. Saha D, Paul S. in-vitro screening of antifungal activity of methanol extract of *Plumbago indica* L. against some pathogenic species of fungi. Asian J Res Pharm Sci.

2012;2(2):55-57.
25. Valsaraj R, Pushpangadan P, Smitt UW, Adsersen A, Nyman U. Antimicrobial screening of selected medicinal plants from India. J Ethno. 1997;58(2):75-83.
26. Paiva SRD, Figueiredo MR, Aragão TV. Kaplan MAC. Antimicrobial activity in-vitro of plumbagin isolated from Plumbago species. Memorias do Instituto Oswaldo Cruz. 2003;98:959-961.
27. Kaur D, Prasad SB. The anti-acne activity of acetone extract of *Plumbago indica* root. Asian J Pharm Cli Res. 2016;9(2):285-287.
28. Kaur D, Prasad SB, Verma S. Formulation and evaluation gel from extract of *Plumbago indica* for acne. Int J Drug Del Tech. 2016;6(03):95-98.
29. Saha D, Paul S. Antibacterial activity of *Plumbago indica*. Turk J Pharm Sci. 2014;11(2):217-222.
30. Kaewbumrung S, Panichayupakaranant, P. Antibacterial activity of plumbagin derivative-rich *Plumbago indica* root extracts and chemical stability. Nat pro res. 2014;28(11):835-837.
31. Dissanayake DMIH, Perera DDBD, Keerthirathna LR, Heendeniya S, Anderson R., Williams DE, *et al*. Antimicrobial activity of *Plumbago indica* and ligand screening of plumbagin against methicillin-resistant Staphylococcus aureus. J Biomo Str Dyn. 2020, 1-12.
32. Savadi RV, Alagawadi KR. Antifertility activity of ethanolic extracts of *Plumbago indica* and Aerva lanata on albino rats. Int. J Green Pharma. 2009, 3(3).
33. Sheeja E, Joshi SB, Jain DC. Anti-ovulatory and estrogenic activity of *Plumbago rosea* leaves in female albino rats. Ind. J Pharma. 2009;41(6):273.
34. Paul S, Saha D. Analgesic activity of methanol extract of *Plumbago indica* (L.) by acetic acid-induced writhing method. Asi J Pharm Tech. 2012;2(2):74-76.
35. Ittiyavirah S, Jobin KV, Jissa MS, Jomy M, Josmi TJ, Littin B. Anti-inflammatory and analgesic activities of *Plumbago capensis* and *Plumbago indica*. Adv Pharma Toxi. 2012, 13(1).
36. Sumsakul W, Plengsuriyakarn T, Chaijaroenkul W, Viyanant V, Karbwang J, NaBangchang K. Antimalarial activity of plumbagin in-vitro and in animal models. BMC comps alter med. 2014;14(1):1-6.
37. Bashir SF, Kumar G. Preliminary phytochemical screening and in-vitro antibacterial activity of *Plumbago indica* (Laal chitrak) root extracts against drug-resistant *Escherichia coli* and *Klebsiella pneumonia*. Open Agri. 2021;6(1):435-444.
38. Sarkar A, Ghosh S, Shaw R, Patra MM, Calcuttawala F, Mukherjee N. Mycobacterium tuberculosis thymidylate synthase (ThyX) is a target for plumbagin, a natural product with anti-mycobacterial activity. PloS one. 2020;15(2):e0228657.
39. Eldhose B, Notario V, Latha MS. Evaluation of phytochemical constituents and in-vitro antioxidant activities of *Plumbago indica* root extracts. J Pharma Phyto. 2013, 2(4).
40. Rajasekaran A, Periasamy M. Protective effect of ethanolic root extract of *Plumbago indica* L. on paracetamol-induced hepatotoxicity in rats. African J Pharma Pharmacology. 2011;5:2330-4.
41. Chavan RD, Shinde P, Girkar K, Madage R, Chowdhary A. Assessment of anti-influenza activity and hemagglutination inhibition of *Plumbago indica* and *Allium sativum* extracts. Pharma Res. 2016;8(2):105.
42. Li Z, Chinnathambi A, Ali Alharbi S, Yin F. Plumbagin protects the myocardial damage by modulating the cardiac biomarkers, antioxidants, and apoptosis signaling in the doxorubicin-induced cardio-toxicity in rats. Env Toxi. 2020;35(12):1374-1385.
43. Zhang G, Ni X, Zhou Y. Cardio-protective effect of plumbagin and amelioration of pro-inflammatory cytokines through suppression of Na+/K+-ATPase on myocardial ischemia. Pharma Maga. 2021;17(75):643.
44. Wang SX, Wang J, Shao JB, Tang WN, Zhong JQ. Plumbagin mediates cardio protection against myocardial ischemia/reperfusion injury through Nrf-2 signaling. Medical science monitor: Int. Med J Exp clinical Res. 2016; 22:1250.
45. Mathew N, Paily KP, Vanamail P, Kalyanasundaram M, Balaraman K. Macrofilaricidal activity of the plant *Plumbago indica/rosea* in-vitro. Drug Dev Res. 2002;56(1):33-9.
46. Sheeja E, Joshi SB, Jain DC. Antifertility activity of stems of *Plumbago rosea* in female albino rats. Pharma Bio. 2008;46(12):920-27.
47. Checker R, Sharma D, Sandur SK, Khanam S, Poduval TB. Anti-inflammatory effects of plumbagin are mediated by inhibition of NF-kappa B activation in lymphocytes. Int. Immuno Pharma. 2009;9(7-8):949-958.
48. Thitiorul S, Ratanavalachai T, Tanuchit S, Itharat A, Sakpakdeejaroen I. Genotoxicity and interference with cell cycle activities by an ethanolic extract from thai *Plumbago indica* roots in human lymphocytes in-vitro. Asian Pacific J Cancer Prev. 2013;14(4):2487-2490.
49. Saha D, Paul S. Cytotoxic activity of methanolic extract of *Plumbago indica* L. (Family: Plumbaginaceae). Asian J Pharma Tech. 2012;2(2);59-61.
50. Paul AS, Islam A, Yuvaraj P. Anti-Helicobacter pylori and cytotoxic activity of detoxified root of *Plumbago auriculata*, *Plumbago indica*, and *Plumbago zeylanica*. J Phyto. 2013;2(3):4-8.
51. Powolny AA, Singh SV. Plumbagin-induced apoptosis in human prostate cancer cells is associated with modulation of cellular redox status and generation of reactive oxygen species. Pharma Res. 2008;25(9):2171-2180.
52. Yin Z, Zhang J, Chen L, Guo Q, Yang B, Zhang W, *et al*. Anticancer effects and mechanisms of action of plumbagin: Rev Res adv Bio Med Res Int. 2020.
53. Hafeez BB, Fischer JW, Singh A, Zhong W, Mustafa A, Meske L, *et al*. Plumbagin inhibits prostate carcinogenesis in intact and castrated PTEN knockout mice via targeting PKCε, Stat3, and epithelial-to-mesenchymal transition markers. Cancer Prev Res. 2015;8(5):375-386.
54. Jayanthi M, Gokulanathan A, Haribalan P, Ashakiran K, Kumar CD, Kamal D. Plumbagin from two Plumbago species inhibits the growth of stomach and breast cancer cell lines. Indl Crops Pro. 2020;146:112-147.
55. Yu B, Zhu X, Yang X, Jin L, Xu J, Ma T, *et al*. Plumbagin prevents secretory diarrhoea by inhibiting CaCC and CFTR channel activities. Frontiers in Pharma. 2019;10:1181.
56. Sukkasem N, Chatuphonprasert W, Tatiyaaphiradee N, Jarukamjorn K. Imbalance of the antioxidative system by plumbagin and *Plumbago indica* L. extract induces hepatotoxicity in mice. Journal of Intercultural Ethnopharmacology. 2016;5(2):137-145.
57. Solomon FE, Sharada AC, Devi PU. Toxic effect of crude root extract of *Plumbago rosea* (Rakta chitraka) on mice and rats. Journal of Ethnopharmacology.

1993;38:79-84.
58. Rafa ZT, Ashrafudoulla M, Fuad F, Islam R, Hasan M, Kafi MAH, *et al*. Phytochemical and pharmacological investigation of *Plumbago indica* L. Journal of Medicinal Plants Studies. 2016;4(2):115-118.
59. Chavan RD, Shinde P, Girkar K, Madage R, Chowdhary A. Assessment of anti-influenza activity and hemagglutination inhibition of *Plumbago indica* and *Allium sativum* Extracts. Pharmacognosy Research. 2016;8(2):106-11.
60. Paul AS, Islam A, Yuvaraj P. Antihelicobacter pylori and cytotoxic activity of detoxified root of *Plumbago auriculata*, *Plumbago indica* and *Plumbago zeylanica*. The Journal of Phytopharmacology. 2013;2(3):4-8.
61. Naresh RAR, Udupa N, Devi PU. Niosomal plumbagin with reduced toxicity and improved anticancer activity in BALB/C Mice. Journal of Pharmacy and Pharmacology. 1996;48:1128-1132.
62. Arambewela L, Silva R. Sri Lankan medicinal plant monographs and analysis – *Plumbago indica*. Industrial Technology Institute (CISIR) and National Science Foundation; Colombo; 1999.
63. Anju Devi, Dr. Mukesh Kumar Sharma. An Analysis and Study of *Plumbago indica* Linn and its Concerning Issues and Characteristics. International Journal of Trend in Scientific Research and Development (IJTSRD), 2019;3(4):1703-1704.