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Review Article

EXPLORATION OF THERAPEUTIC POTENTIAL OF PLUMBAGO AURICULATA: TRANSITIONING FROM TRADITIONAL MEDICINE TO PHARMACOLOGICAL USES

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Abstract

Plumbago auriculata, often known as Cape leadwort, is a pharmacologically significant plant that has long been prized in traditional medicinal systems for its numerous therapeutic applications. The pharmacological potential of the plant's roots, stem, flower, and leaves—including their antibacterial, hepatoprotective, anticancer, antifertility, antiulcer, antifungal, and wound-healing properties—has been evaluated in a number of research. The goal of this paper is to provide a succinct overview of the ethnobotanical applications, phytochemistry, putative pharmaceutical actions, facts, and phytoconstituents of this precious plant. A thorough review of the literature was conducted using a variety of online resources, including PubMed, Science Direct, Springer, and Google Scholar. All of the papers were based on pharmacological characteristics and traditional therapeutic applications. According to the detailed findings, *P. auriculata* has great potential for treating serious illnesses like diabetes, heart disease, ulcers, liver issues, obesity, wound healing, cancer, and more. This analysis also highlights current limitations, including toxicity concerns, a lack of comprehensive clinical trials, and the need for standardized phytochemical profiling.

Keywords: *Plumbago auriculata,* Cape leadwort, Pharmacology, Tradition, Antioxidant, Anti-inflammatory, Antimicrobial, Anticancer, Neuroprotective

1. Introduction

1.1 Botanical Overview of Plumbago auriculata

Conventional medicine to combat the human health problems and life-threatening diseases is not only expensive but also has several side effects. Medicinal plants that are used since ancient times to treat and cure deadly diseases can serve as potential complementary and alternative medicine. Formulations developed from plant-derived secondary metabolites have broad-spectrum therapeutic applications with negligible or no adverse effects. Plants can either produce and secrete or store these bioactive principles in their tissues[1]. *Plumbago auriculata* is a medicinal plant from the family *Plumbaginaceae* (Leadwort family) that was first described by Antoine Laurent De Jussieu in 1789. *Plumbaginaceae* with 24 genera and 400 species includes herbs, lianas, and shrubs which occur even in saline habitats. *P. auriculata* is a perennial, evergreen shrub that is mostly native to South Africa. Due to its widespread distribution

in South Africa's Cape regions, it is also found in tropical and subtropical areas. It is also referred to as Cape Plumbago or Cape Leadwort. *P. auriculata* is tolerant of high temperatures and humidity. With upright and climbing stems, the plant can reach a height of three meters. The leaves have a thin texture, elliptic, greyish green underneath with a whitish scale, and tiny glandular dots. The leaves have salt glands on both surfaces. *P. auriculata* flowers can be sky blue, deep blue, or white. The salver-shaped, 2.5–3 cm long flowers bloom all year long. The calyx has glandular and nonglandular hairs called trichomes, and the corolla is blue. The seed is 7 mm long and dark brown, and the fruit has a long beak. Plumbagin is a major compound produced by P. auriculata. Proteins, sugars, alkaloids, tannins, phenols, and saponins are abundant in the plant[2].

1.2 Traditional and Ethnomedicinal Uses

Research in the field of ethnopharmacology has great promise as a means of discovering alternative and complementary medicine (CAM) solutions to common health problems and the negative effects of mainstream pharmaceuticals[3]. Medicinal plants have a wide variety of unique phytochemicals that have a long history of usage in traditional medicine as a means of illness treatment. Herbal remedies are preferred because they are safer, less expensive, and have less negative side effects. Plumbago auriculata, a perennial herb belonging to the Plumbaginaceae family, is described in detail in this chapter along with its phytochemical variety and related therapeutic potential. Since its blossoms are blue, this attractive plant is also known as Nila Chitrak, which means "Blue Plumbago" in Sanskrit. *P. auriculata* is primarily comprised of plumbagin, its primary bioactive component[4]. The plant may contain a wealth of medicinally useful substances, including phenols, alkaloids, saponins, flavonoids, steroids, carbs, and proteins. Wounds, fractured bones, warts, and black water sickness have all traditionally been treated with plant components, including roots and leaves. Paracoccus auriculata has a wide range of medicinal uses, including fighting infections, viruses, diabetes, cancer, inflammation, ulcers, and leishmanial parasites. One example of the nano-biotechnological potential of *P. auriculata* is the biofabrication of zinc oxide and silver nanoparticles using extracts from the plant's leaves, roots, and stems. It is worth noting that *P. auriculata* contains a wide variety of phytochemicals, which can aid in the development of safe and effective drugs derived from plants [5].

1.3 Objectives and Scope of the Review

The objective of this review is to provide a comprehensive and up-to-date synthesis of the pharmacological and medicinal properties of *Plumbago auriculata*. This article aims to summarize the traditional and ethnomedicinal uses of *P. auriculata* across different cultures. This paper also highlight the phytochemical constituents responsible for its biological activities. This paper Critically evaluate the existing preclinical and clinical pharmacological studies and discuss the mechanisms of action underlying its therapeutic effects. This review aims to identify gaps in current research and suggest future directions for scientific exploration and potential drug development. By consolidating available data, this review seeks to support the rational use of *P. auriculata* in modern medicine and promote further investigations into its pharmacological potential.

1.4 Phytochemical Composition

Plumbago auriculata, also known as Cape leadwort, is a medicinal plant known for its traditional use in various therapeutic applications. Its phytochemical composition includes a range of bioactive compounds that contribute to its pharmacological properties.

Table 1: Key Phytochemicals Identified in Plumbago *auriculata*

S.No.	Phytochemical	Example	Medicinal Properties	Reference
1.	Naphthoquinones	Plumbagin	Antimicrobial, Anticancer, Anti-inflammatory, Antioxidant activities	44
2.	Flavonoids	Quercetin, Kaempferol, Luteolin	Antioxidant and anti-inflammatory effects	53
3.	Tannins	Gallic acid, Ellagic acid	Exhibit astringent properties and contribute to antimicrobial activity	19
4.	Saponins	Oleanolic acid-based saponins, Hederagenin derivatives	These compounds can have immune-modulating and cholesterol-lowering effects.	2
5.	Alkaloids	Indole alkaloids, Plumbaginine	Potential neurological and antimicrobial activities have been detected.	41
6.	Phenolic compounds	Caffeic acid, p-Coumaric acid, Ferulic acid, Quercetin (also a flavonoid), Kaempferol, Luteolin	Contributes to the overall antioxidant capacity of the plant.	19
7.	Steroids and Terpenoids	β-Sitosterol, Lupeol, α/β-Amyrin	Contribute to anti-inflammatory and analgesic effects.	41

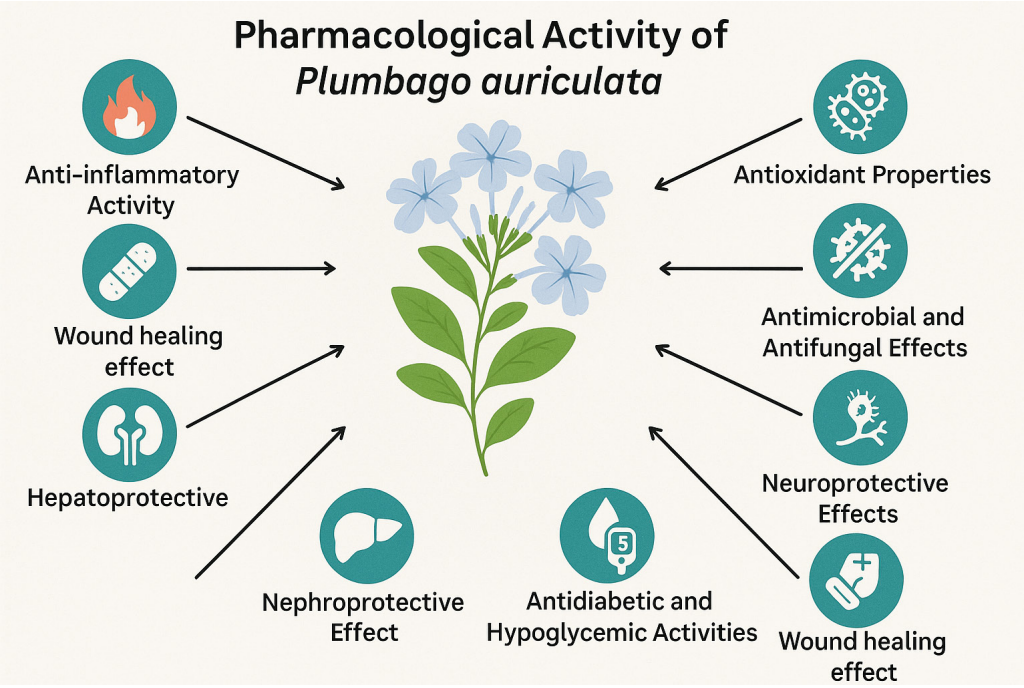

Figure 1: Pharmacological activity of Plumbago auriculata

1.5 Pharmacological Activities

One kind of perennial flowering plant is *Plumbago auriculata* Lam., often known as Cape Leadwort. You can find this plant anywhere in the world, from subtropical gardens in Florida to warm winter climates in South Africa[6]. Malaria, wounds, GERD, fractured bones, and wart removal are all common uses for *P. auriculata* in traditional medicine in South Africa and Arabia[7-8]. From P. auriculata, scientists were able to extract steroid-like phytoestrogens, plumbagin naphthoquinones, epi-isoshinanolone, palmitic acid, and plumbagic acid[9–10].

1.6 Anti-inflammatory Activity

The presence of several metabolites in *Plumbago auriculata* Lam. extract, which have strong anti-inflammatory properties, is responsible for its anti-inflammatory effects[11,12]. An anti-inflammatory effect with a percentage inhibition of 92.6 ± 1.7% at 100 mg/Kg was demonstrated by the whole methanolic extract of the aerial portions of *P. auriculata* Lam. in rats utilising a carrageenan-induced paw oedema model. The extract was subsequently bio-guided fractionated using the same methodology that had previously shown that the pet. ether-soluble and ethylacetate-soluble fractions were the most effective across the board[13,14]. Analysis of the active fractions chemically yielded sixteen compounds. They were identified as trilinolein, β-amyrin, β-sitosterol, palmitic acid, umbelliferone, oleanolic acid, β-sitosterol-3-O-β-D-glucoside, cis-isoshinanolone, p-cumic acid (4-isopropylbenzoic acid), diosmetin, luteolin , isoorientin (luteolin 6-C-β-D-glucoside), isovitexin (apigenin 6-C-β-D-glucoside), quercitrin (quercetin 3-O-α-L-rhamnopyranoside), biflorin (6-β-C-glucopyranosyl-5,7-dihydroxy-2-methylchromone) and chlorogenic acid. This study reports the first occurrences of several compounds from the species under study, including umbelliferone, oleanolic acid, p-cumic acid, isoorientin, isovitexin, quercitrin, biflorin, and chlorogenic acid[15–18].

1.7 Antioxidant Properties

There has been a dramatic uptick in the study of medicinal plants, particularly those with a history of usage in folk medicine, in recent years. Reasons for this upsurge in curiosity include the growing number of resistant microorganisms, the negative consequences of chemical chemicals, and the dearth of effective medicinal agents for the treatment of chronic disorders. Metabolic diseases including diabetes mellitus, hypercholesterolaemia, overweight, and obesity may respond positively to natural plant products that include polyphenolic chemicals such tannins, anthocyanins, flavonoids, and phenolic acids[19]. The pharmacological properties of natural compounds, such as their antioxidant and anti-lipase effects, have been the subject of multiple investigations[20].

1.8 Antimicrobial and Antifungal Effects

Scientists tested *Plumbago auriculata* leaf extracts against several commonly used antibiotics to determine their antibacterial capabilities. Comparing the crude extract to the gold standard medicines, researchers looked at their antibacterial activity in vitro and determined their minimum inhibitory concentration (MIC). Extracts from the leaves were shown to have the highest level of inhibition when compared to the conventional antibiotics[21]. Another study looked at the antibacterial properties of methanolic stem and leaf extracts against nine fungus species and six bacterial species. The antibacterial activity of both extracts was dose-dependent. In addition, the zones of inhibition were used to test the antibacterial properties. The stem extract was found to have greater antibacterial activity against Pseudomonas aeruginosa and Penicillium expansum species, whilst the leaves extract exhibited the highest antimicrobial activity against Staphylococcus aureus and Fusarium oxysporum. Research indicates that *Plumbago auriculata* stem methanolic extract has potent antibacterial properties[22]. The antibacterial activity of an ethanolic extract of *Plumbago auriculata* root bark was tested against seven bacteria

isolated from two dumpsites in Akure in another study. The antimicrobial activity of the extract is found to increase as the concentration increases, according to the study[23]. Four pathogenic fungal species—Fusarium oxysporum, Rhizoctonia solanii, Alternaria sp., and Sclerotium rolfsii—were tested for antifungal capability. The study found that it had the best inhibitory effects against Alternaria spp. at concentrations of 62.5 µg/ml, but the weakest against S. rolfsii[24].

1.9 Anticancer Potential

The primary ingredient in Plumbago indica root extract, plumbagin, has anticancer properties against a variety of cancer cell lines. Its root extract decreased cervical cancer cells' migration, colony formation, and cell viability in a dose-and time-dependent manner. Increased ROS, induced apoptosis, and depolarised mitochondrial membrane potential are all part of the mechanism[25]. Cancer remains one of the leading causes of death globally. In pursuit of alternative treatments, nature-based ones are especially in demand due to the perceived lesser toxicity and cost-effectiveness. Plumbagin, a naphthoquinone compound derived from the *Plumbaginaceae* family, has demonstrated significant anticancer properties. It is a yellow crystalline phytochemical that exhibits potent cytotoxic effects against various cancer cells in vitro and in vivo. Its distinct anticancer mechanisms include modulating signaling pathways, such as NF-kβ, STAT3, MMP-9, VEGF, and Akt, induction of apoptosis, autophagy, cell cycle regulation etc[26]. Furthermore, plumbagin also induces reactive oxygen species (ROS) generation and causes oxidative DNA damage. An exciting feature of plumbagin is its ability to sensitize chemo and radio resistant cancer cells[27]. Even with significant anticancer potential, plumbagin is yet to be used in clinics due to its high lipophilicity, insolubility in water, short half-life, and low melting point[28]. To conquer these limitations and possible exploitation of this potent natural compound, the scientific community has used several nano-based delivery systems, such as liposomes, niosomes, micelles, microparticles etc. Despite all these promising attributes, rigorous preclinical and clinical evaluations are essential to validate its actual anticancer potential before considering it as one of the mainstream phytotherapeutic agents.

1.10 Neuroprotective Effects

Plumbago auriculata, particularly its active compound plumbagin, has shown neuroprotective effects, primarily by mitigating oxidative stress and inflammation in the brain. Plumbagin has been investigated as a possible treatment for behavioural disorders because of its demonstrated binding affinity to the neurotransmitter enzyme acetylcholinesterase[29]. In brain tissue models, plumbagin has been demonstrated to lower oxidative stress, a major contributing factor to neurodegenerative diseases. Additionally, it has anti-inflammatory qualities, which are essential for preventing neuronal damage[30]. According to in-silico research, plumbagin attaches itself to the active site of acetylcholinesterase, an enzyme that degrades acetylcholine, a neurotransmitter crucial for memory and learning. In situations where acetylcholine is lacking, this binding may raise acetylcholine levels, which could be advantageous. Plumbagin's neuroprotective effects are believed to be mediated through a variety of pathways, such as the modulation of neurotransmitter systems and the inhibition of inflammation and oxidative stress[31]. Plumbagin's neuroprotective qualities point to its potential as a treatment for a number of neurological conditions, such as Parkinson's disease, Alzheimer's disease, and other neurodegenerative diseases[32].

1.11 Antidiabetic and Hypoglycemic Activities (32-35)

The presence of plumbagin, the principal active ingredient, is responsible for *Plumbago auriculata*'s delicious inactivation characteristic. *Plumbago auriculata* has been shown in multiple studies to have an antidiabetic effect. Researchers found that an ethanolic extract from *Plumbago auriculata* roots had antidiabetic effects. Rats with diabetes that had been generated by streptozotocin were studied for six

weeks using dosages of 100-200 mg/kg. The results demonstrated a drastic decrease in levels of serum acid phosphatase (ACP), lactate dehydrogenase (LDH), and a considerable rise in hepatic hexokinase activity[32]. In addition, a study was conducted to assess the effects of plumbagin, a compound produced from *Plumbago auriculata* root, on GLUT4 translocation in rats that had been induced to develop diabetes by STZ. Rats with diabetes caused by STZ were given plubagin orally at doses of 15 and 30 mg/kg of body weight for a duration of 28 days. Someone has to take an oral glucose tolerance test on the twenty-first day. Plumbagin shown a significant decrease in blood glucose levels. Every other biochemical parameter was found to be within the normal range. Furthermore, treated diabetic rats showed reduced levels of glucose-6-phosphatase and fructose-1,6-bisphosphatase and enhanced activity of hexokinase. Plumbagin therapy increased the expression of GLUT4 mRNA and protein in diabetic rats. According to the findings, plumbagin has a very effective anti-diabetic effect[33]. Another study used a STZ-induced diabetes rat model to examine the possible synergistic effects of aqueous extracts of Murraya koenigii (MK) leaves, Annona squamosa (AS), and *Plumbago auriculata* roots[34]. Each capsule included the following substances, which were combined in the appropriate amounts with the appropriate excipients. When compared to Glibenclamide, the study outcomes with the polyherbal formulation were more significant[35].

1.12 Hepatoprotective

The petroleum ether extract of *Plumbago auriculata* roots showed hepatoprotective effect against paracetamol-induced liver injury, according to the researchers[36]. In order to assess the hepatoprotective activity, several biochemical indicators were investigated. Animals given paracetamol showed signs of significant liver damage, as indicated by elevated marker levels[37]. After the extract was given, the serum indicators dropped significantly, showing that the extract had the desired impact of getting the hepatocytes back to normal functioning ability. Results show that *Plumbago auriculata* root petroleum ether extract may significantly reduce paracetamol-induced hepatocellular damage[38].

1.13 Nephroprotective Effects

Scientists looked at the preventive effects of a *Plumbago auriculata* root hydroalcoholic extract on the kidneys of Swiss albino mice that had been exposed to cisplatin-induced nephrotoxicity. Research shown that *Plumbago auriculata* exhibited a renoprotective effect when administered at a high dose (400 mg/kg) of extracts, thereby reversing the negative effects of cisplatin on kidney weight, blood urea, and creatinine[39]. *Plumbago auriculata* hydroalcoholic extract has a nephroprotective effect, according to the study's results[40].

1.14 Wound healing effect

According to conventional wisdom, *Plumbago auriculata* can speed the healing of wounds. Scientists found that a methanolic extract of *Plumbago auriculata* roots significantly aided in the healing of wounds in wistar rats. Applying a 10% (w/w) extract ointment to the wound surface allowed for the measurement of wound healing activities. Results showed that beginning on day six, rats given the extract showed substantial improvement in their wound-contracting abilities. With the extract, both the time it took for the wound to close and the percentage of contraction were increased. In addition, after 16 days of treatment with the extract, the wounds were completely healed, while the control group took almost 20 days to exhibit any signs of epithelization[41]. Additionally, the ethanolic root extract of *Plumbago auriculata* was examined for its wound healing capabilities in a separate study. Researchers found that phytoconstituents (such as alkaloids, terpenoids, flavonoids, etc.) in the ethanolic root extract may have an additive or individual impact on the extract's wound-healing capabilities.

1.15 Biosynthetic pathway for Plumbagin: Major Source of *Plumbago auriculata*

It was found by labelled tests that plumbagin does

not include shikimate-7-C, L-14CH3-methionine, DL-tyrosine-β-14C, DL-phenylalanine (ring-1-14C), and DL-mevalonic acid-5-14C. Contrarily, plumbagin has been found to be biosynthesised via the polyacetate-malonate pathway due to the incorporation of acetate-1-14C, 2-14C, and malonate-2-14C-labeled molecules[42]. By first feeding Ancistrocladus heyneanus suspension cultures 13C2-acetate and then using 13C NMR studies, Bringmann et al.[43] were able to explore the plumbagin route. They showed that plumbagin folds into polyketides during biogenesis and that it comes from acetate, elucidating its acetogenic origin. Contrarily, plumbagin has labelled alanine integrated into it, whereas other glycoside molecules, such as plumbaside A, do not. This suggests that the C2 carbon atom of alanine is utilised by Nepenthes. It can be inferred that alanine is a precursor for plumbagin production in N. insignis because none of the secondary metabolites have labelled sodium acetate. Plumbagin can also be made by various plants using the acetate and polymalonate routes. The divergent opinions reach the conclusion that various taxa may use either the alanine or the acetate-malonate routes for plumbagin production. A sequence of processes transform tyrosine into homogentisate, acetate, and finally plumbagin[44]. Condensation of aldoles, cyclisation of aldoles, dehydration, hydration, hydroxylation, and oxidation processes make up its production. There were just a handful of essential genes and enzymes linked to the plumbagin biosynthesis pathway that were uncovered by the transcriptome and metabolome analyses. Important genes in P. zeylanica include aldoketoreductase, polyketide cyclase, CYP81B140, and CYP81B141. With the help of the enzyme polyketide synthase, this species is able to produce hexaketide backbones by combining one molecule of acetyl coenzyme A (Co-A) with five molecules of malonyl Co-A[45]. Two enzymes, Pzcyclase 1 and Pzaldo-keto reductase 1, decarboxylate, aldol-cyclize, and reduce the hexaketide backbone to produce 3-methyl-1,8-naphthalenediol. The plumbagin isoshinanolone precursor is formed via oxidation and hydroxylation of the molecule 3-methyl-1,8-naphthalenediol. According to the findings, plumbagin production relies heavily on the methylvaleric acid route. In addition, Muralidharan et al. uncovered a crucial enzyme, naphthoate synthase, which facilitates the conversion of O-malonyl benzoyl CoA to an unidentified intermediate that could have two distinct structures, through the use of molecular dynamic simulations[46]. Although these in silico studies do not fully decipher the route, the thioesterase enzyme catalyses the production of plumbagin from this intermediate[47].

1.16 Need to Explore Biotechnological Methods to Produce Plumbagin

Plumbago species are known for their sluggish growth rates and protracted root production cycles, which might take years. It is common practice to uproot entire plants in order to harvest the bioactive chemical plumbabin because it is mostly synthesised in the root cortex and epidermal cells. According to estimates, the demand for roots in India increased by 10% annually between 2004 and 2006, reaching around 1,285 tonnes. Due to its possible pharmacological effects, plumbagin is experiencing a surge in demand. As a result of habitat loss, the availability of raw materials is decreasing. Many pharmaceutical businesses are requesting that plumbagin be produced. On top of that, it has a limited supply, produces low yields, and uses up all of the natural resources it has. This has prompted the search for methods to increase plumbagin production without harming the environment. In addition, factors such as age, developmental stage, season, geographical location, and extraction method will affect the concentration of plumbagin in intact plants[49]. Contrarily, regardless of the season or place, plant tissue, cell, and hairy root cultures can potentially produce bioactive chemicals on a huge scale and all year round. In addition, genetic engineering and genome editing do not yet have a full understanding of the genes and pathways involved in its biosynthesis. At this time, we also don't know what epigenetic mechanisms regulate

plumbagin production[50]. Although plumbagin can be chemically synthesised, this process uses a lot of carbon. Although synthetic biology enables the production of secondary metabolites, the availability of appropriate host species and gene modifications is not guaranteed. In light of the pressing need to reduce carbon emissions in response to climate change, it is prudent to resume biosynthesis using cultured plant cells and hairy roots, as these methods are significantly more energy and carbon efficient than their natural counterparts[51]. We must use biotechnological approaches, such as genome editing technology, to produce plumbagin on a big scale under these circumstances[52]. Shikonin, berberine, taxol, and a slew of other cosmetics have all been mass-produced using cell and organ cultures. Many secondary plant compounds, including α-tocopherol, ajmaline, flavonoids, paclitaxel, reserpine, resveratrol, serpentine, and others, have been mass-produced using callus cultures[53]. These days, a lot of scientists think that hairy root cultures and callus/suspension cultures are good ways to get medicinal metabolites. It is possible to produce suspensions and to use bioreactors to further exploit single cell clones derived from callus for commercial manufacturing[54]. The in vitro development of pharmaceutically relevant chemical accumulation has also made use of shoots, adventitious roots, and hairy roots in addition to callus and suspension cultures. In addition to ensuring genetic stability in long-term cultures, hairy roots are a multipurpose instrument for high production. Consequently, there is an urgent need to investigate the potential of using hairy roots and suspensions to produce pharmaceutically significant chemicals from uncommon, endangered, and endemic plants on a commercial scale.

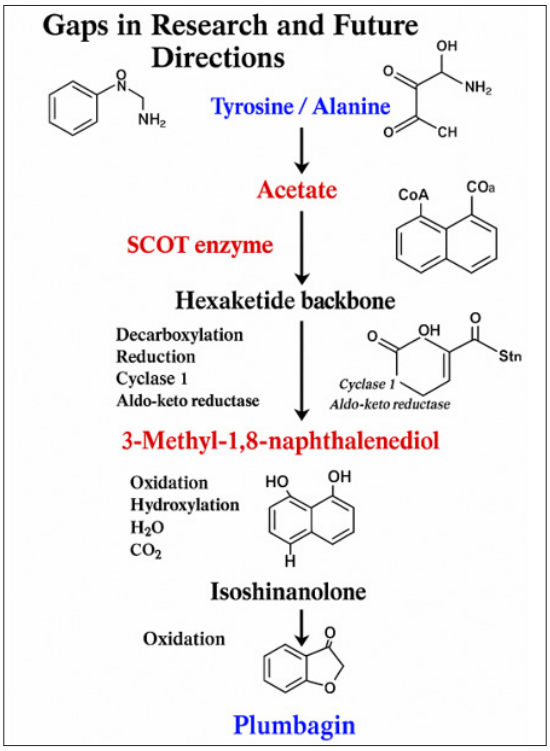

Figure 1: This figure shows the proposed plumbagin biosynthesis process. ("SCOT" stands for succinyl-CoA: 3-ketoacid CoA transferase), "cytochromes" for cytochromes, "CO2" for carbon dioxide, and "CoA" for coenzyme A. There is still a lack of information regarding the pathway and the genes that are associated with it. Isoshinanoline is the immediate precursor to plumbagin production, but the aromatic amino acid tyrosine seems to be the distant precursor. The precise mechanisms and enzymes involved in the transformation of isoshinanolone to plumbagin are not yet known, as shown by the dotted lines. But the last stage of the process involves an oxidation reaction. Some plants that produce plumbagin may also include alanine, an additional amino acid that isn't represented in the route. [55]

1.17 Nanoparticle Formulations and Drug Delivery Approaches loaded with *P. auriculata* extract

Researchers biosynthesised zinc oxide nanoparticles (ZnO NPs) from an alcoholic extract of *P. auriculata* and studied their antiviral activities against aMPV subtype B. This study suggests that ZnO nanoparticles and/or *P. auriculata* extract, when combined with vaccination, could help restrict the transmission of the virus in afflicted birds. Environmental pollution and the subsequent danger of viral transmission can be mitigated in societies where this disease is endemic. Due to the complexity of the poultry digestive tract, additional in vivo trials are needed to confirm the antiviral activity observed in vitro and determine the optimal concentration of *P. auriculata* and Nano-ZnO needed in bird diets for antiviral effectiveness. However, our in vitro results indicate that supplementing the poultry diet with ZnO nanoparticles and *P. auriculata* extract could be useful for controlling aMPV enteric infections [56]. Antibacterial activity against several species was shown in the synthesised AgNPs derived from *Plumbago auriculata* Lam. extract. Plant components, namely secondary metabolites, that were bound to AgNPs may have amplified this effect [57]. In addition to their antibacterial properties, the AgNPs produced by the plant extract showed strong larvicidal action against Aedes aegypti and Culex quinquefasciatus fourth instar larvae. Research using molecular docking with Aedes aegypti salivary protein and Culex quinquefasciatus odorant-binding protein demonstrated that the naphthoquinone compound plumbagin had a strong binding affinity for both enzymes[58]. All things considered, these findings point to the possibility of further optimisation of the synthesis process for metal nanoparticles using plant extracts, allowing for the production of nanoparticles with the appropriate active properties. This technology could be useful for producing similar metallic nanomaterials on a wide scale because these nanoparticles are environmentally friendly and have several useful applications, such as wound healing, targeted drug delivery systems, and bactericidal effects[59].

1.18 Gaps in Research and Future Directions

Despite the promising pharmacological potential of *Plumbago auriculata*, several research gaps persist, limiting its full therapeutic exploitation. While *Plumbago auriculata* has been traditionally employed in ethnomedicine, rigorous scientific validation of its efficacy against various diseases remains inadequate. Studies are mostly limited to preliminary in vitro and in vivo evaluations. Recent research is primarily focused on anti-inflammatory, antioxidant, and antimicrobial effects. Exploration into its efficacy against chronic and complex diseases such as cancer, diabetes, neurodegenerative disorders (e.g., Alzheimer's, Parkinson's), and autoimmune conditions is sparse. There is a lack of detailed mechanistic studies explaining how individual or synergistic phytochemicals exert biological activity. There is a paucity of dose-standardized data for various extracts and isolated compounds, making efficacy comparison and replication difficult. Most studies isolate single bioactive compounds like plumbagin, neglecting the synergistic interactions among the phytoconstituents that may enhance therapeutic activity.

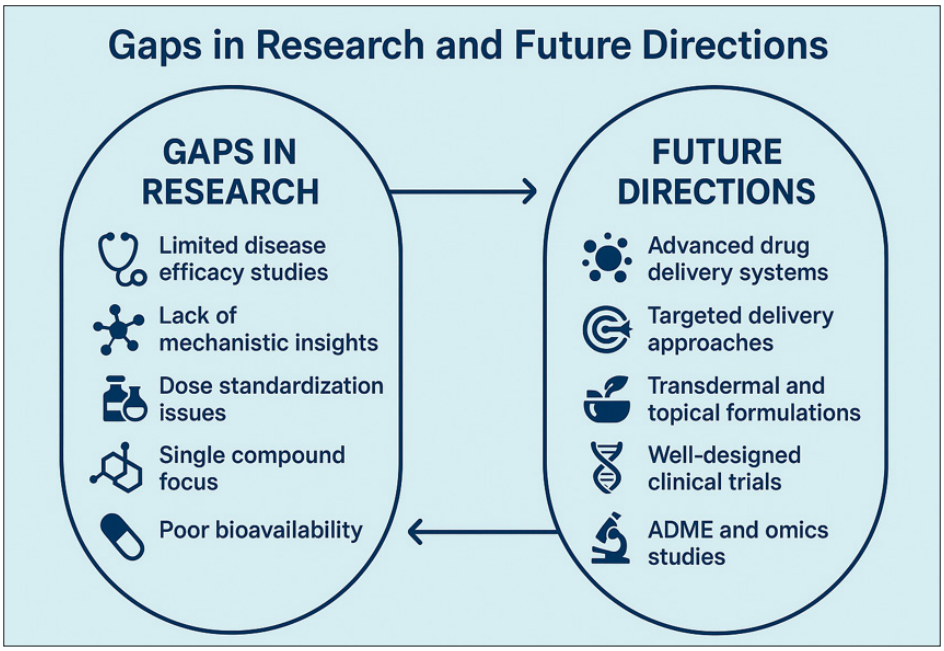

Figure 2: Research gaps persist, limiting the full therapeutic exploitation of *Plumbago auriculata*

Research should focus on whole extract vs isolated compound analysis followed by investigating the comparative efficacy and toxicity profiles. The delivery of bioactive compounds such as plumbagin is hampered by poor solubility, low bioavailability, and rapid metabolism. Innovative drug delivery systems have not been sufficiently explored for *P. auriculata* phytochemicals. Future research should explore: Utilization of nanoparticles, liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs) to enhance delivery and therapeutic efficacy. Targeted Delivery Approaches includes employing ligand-based targeting or stimuli-responsive carriers for site-specific drug release (e.g., tumor-targeted delivery). Transdermal and Topical Systems for skin conditions, more studies should focus on gels, creams, or patches for localized delivery. Currently, there is an absence of well-designed clinical trials to confirm the safety, efficacy, and tolerability of *P. auriculata* preparations in humans. Research must expand to establish comprehensive safety profiles across different administration routes and doses. Pharmacokinetics and Metabolism studies are needed to evaluate absorption, distribution, metabolism, and excretion (ADME) properties of bioactive constituents. Emerging tools such as transcriptomics, proteomics, and metabolomics are underutilized in the study of *P. auriculata*. These can uncover biosynthetic pathways, regulatory genes, and novel compounds. Elucidating genes responsible for biosynthesis of pharmacologically important compounds like plumbagin. Metabolic Engineering may enhance yield of active phytochemicals through biotechnology.CRISPR/Cas and Synthetic Biology Tools can potentiate the use in manipulating biosynthetic pathways for targeted compound production.

2. Conclusion

Plumbago auriculata holds untapped therapeutic promise, but realizing its full potential requires a multidisciplinary approach combining phytochemistry, pharmacology, nanotechnology, and molecular biology. Future research should emphasize not only broad-spectrum biological efficacy but also advanced drug delivery systems to transform it into a viable candidate for clinical application.

3. Conflicts of Interest

The authors declare no competing financial interests or personal relationships that could have influenced this work.

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