

REVIEW

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Phytochemistry and pharmacological studies of *Plumbago zeylanica* L.: a medicinal plant review

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Abstract

Plumbago zeylanica L. (Plumbaginaceae) commonly known, as chitrak is pharmacologically important plant. Various studies have been undertaken to assess the pharmacological potential of different parts of the plant namely like roots, stem, flower, and leaves as antimicrobial, hepatoprotective, anticancer, antifertility, antiulcer, antifungal and wound healing. The intention of the present review is to deliver a concise account on its ethnobotanical uses, phytochemistry with an in-depth study of its phytoconstituents, facts and prospects of its potential pharmacological activities of this golden plant. An extensive literature survey was undertaken through different online platforms viz. Google Scholar and online databases namely PubMed, Science Direct and Springer. All papers based on traditional medicinal uses and pharmacological properties were included. Sixty three research articles and review articles were found to be apt for inclusion into the review. About 150 articles were retrieved for the purpose. The elaborative results vindicated that *Plumbago zeylanica* L. holds significant prospects in major health conditions such as diabetes, cardiovascular disorders, ulcer, liver problems, obesity, wound healing, cancer etc.

Keywords: *Plumbago zeylanica* L, Plumbagin, Antioxidant, Antimicrobial, Wound healing, Anticancer

Introduction

Plants have been extensively exploited for varied pharmacological activities since prehistoric times and gaining thrust in the current scenario. Many of the presently available drugs have been obtained from some or other natural resources [1]. They have been the basis of many traditional medicinal systems for thousands of years and continue to provide humankind with new remedies for each disease. Most practitioners formulate and dispense their own recipes, which necessitates proper documentation and utmost attention to research oriented services [2]. This attempts to prove scientific insight behind the traditional adaptation. Less toxicity and increased therapeutic effect leading to better patient compliance are the few main reasons for adhering to drugs from natural origin [3]. Although, there lies a prevalent use of herbs in traditional systems of medicines, despite the fact that written

documentation is missing from historic times. Therefore, it is of utmost importance to document all such data for systematic regulation and appropriate application. This may lead to development of significant number of synthetic drugs having sound background of literature with actual origin from plant/isolated ingredient through derivatization [4]. An intensive study of the naturally occurring molecules known as 'therapeutically active' is need of the hour to come up with novel therapeutic moieties [5]. Active constituents present in many plants species are isolated for direct use as drugs, lead compounds, or as pharmacological agents.

The ethnopharmacological and chemotaxonomic importance of the genus *Plumbago* became the driving force, which led us to investigate the infochemicals present in its species.

The genus *Plumbago* belonging to the family Plumbaginaceae, comprises 10 genera and 280 species [5, 6]. Three main species included in genus *Plumbago* namely,

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Plumbago indica L., *Plumbago auriculata* L. and *Plumbago zeylanica* L. (Fig. 1). Among these species, *Plumbago zeylanica* L. is more popular due to its therapeutic properties. *Plumbago zeylanica* L. usually referred to as Ceylon leadwort, doctor bush and wild leadwort, is one of the well-known herbal plant. It also named as chitramula and chitrak in Ayurveda. Chitrak is a perennial herb cultivated in shady places in the garden for its brilliant inflorescence [6, 8, 9]. It is widely distributed throughout India and Sri Lanka [6].

The present compilation aimed to highlight the phytochemicals present in *Plumbago zeylanica* L. and provide a comprehensive data regarding its pharmacological potentials.

Taxonomy

Morphological studies

Plumbago zeylanica L., is an abundantly branched perennial herb with alternate leaves (Fig. 2) [9]. It an annual plant. The plant grows up to height of 3–4 ft. Leaves are thick, fleshy, sessile, oval and lance-elliptic in shape. Flowers of this plant are 10–25 cm long and arranged in terminal and axillary elongated spikes [6].

Taxonomic classification and common names [10]

| Kingdom | Plantae |
|---------------|---------------------------|
| Subkingdom | Tracheobionta |
| Class | Magnoliopsida |
| Subclass | Caryophyllidae |
| Superdivision | Spermatophyta |
| Division | Magnoliophyta |
| Order | Caryophyllales |
| Family | Plumbaginaceae |
| Genus | <i>Plumbago</i> |
| Species | <i>Plumbago zeylanica</i> |

Traditional perspective

Plant parts of *Plumbago zeylanica* L. have been utilized since centuries for its wide variety of medicinal properties. It is a very potent medicinal herb. In Ayurveda, it is considered as rasayan. Root and root bark of this herb utilized in preparation of varied ayurvedic medicines. In traditional system of medicine, it has been indicated for its significant protective role in enlarged liver and spleen. It is a bitter tonic and suggested as a rejuvenator, well known for its use in chronic colds and cough. It also finds its use in correcting chronic menstrual disorders, viral warts and chronic diseases of nervous system. Extract of chitramula are reported as anticancer drugs. Root bark additionally considered beneficial in obesity [6, 9]. It has

been described for its potential use in digestive disorders such as loss of appetite and indigestion. Also recommended in piles, worms, colitis, ascites and liver diseases. Flowers of this plant are used as digestant [11]. Leaves possess aphrodisiac property. They are used in treatment of scabies, in sore and swelling. Leaves have shown their effective role in treatment of infections and digestive problems such as dysentery. They are also used as stimulant. Paste of leaves are topically applied in painful rheumatic areas or in chronic and itchy skin conditions [12]. Roots of this plant are demonstrated as laxative, expectorant, tonic, abortifacient, good appetizer. Roots are also reported to be beneficial in treatment of rheumatism, laryngitis, scabies and disease of spleen. Decoction of seeds are used for reducing muscular pain [13, 14].

Methodology adopted

Literature search

Substantial literature survey was undertaken to abridge the traditional medicinal uses of *Plumbago zeylanica* L. and its therapeutic properties comprising information from previous couple of decades. The information retrieval was carried out through various online platforms viz. Google scholar and other online databases such as PubMed, Springer and Science Direct, using keywords *Plumbago zeylanica* L., its traditional Medicine uses and pharmacological activities. The acceptability criteria of the included studies and execution of study design was based on PICOS model (Population, Intervention, Comparison, Outcome, Study design), to report the retrieved relevant articles, and to explain data collection process comprehensively.

Study design

Well-explained and most suitable research articles based on in-vitro and in-vivo studies on pharmacological properties and clinical studies were covered in study design. If articles were, unpublished works or communications, letters, case reports or if they were unavailable as full-length papers, they were excluded. The study outcomes were assessed if there was outcome information on the nutritional composition of the plant and its application or clinical benefits and harms. An extensive literature survey was undertaken by screening sources with title and abstract. Eligible studies with full text were selected. Unrelated and identical articles were eliminated during sorting. The exploration of articles was concluded through a reference list sorting and assessed considering the criteria articulated above. The included articles were heterogeneous considering both the outcomes and the quality, which made the comparison quite difficult. The quality of the retrieved papers was analyzed and evaluated based on the GRADE (Grading of



a. *Plumbago indica* L.

b. *Plumbago auriculata* L.

c. *Plumbago zeylanica* L.

Fig. 1 Genus *Plumbago* Species [7]

Recommendations, Assessment, Development and Evaluation) approach.

Screening

As per GRADE system, reviews on the single studies relevant to the topic were sorted and covered in the review. The incorporated studies were evaluated and the results were explicated based on the nature of evidence such as in-vitro studies, animal activities, patents and investigation. Total 150 articles were identified. The literature review was completed through 63 full-length research articles (reference lists which include research

articles on traditional and medicinal properties, studies on pharmacological activities both in-vitro and in-vivo. No randomized controlled trials investigated on the human population were identified.

Phytochemical profiling

Plumbago zeylanica L. is a most substantially used plant in the traditional medicine due to the variety of pharmacological activities obtained by its active constituents.

Several researches have made various investigations to reveal the presence of phytoconstituents in its plant parts. Ganesan and Gani reported the presence of four



Fig. 2 Morphological description of the *Plumbago zeylanica* L. [7]

macroelements (Na, K, Ca and Mg) in adequate proportion, five critical microelements (Zn, Fe, Mn, Cr, and Co) and eight other elements (Mo, Sb, Bi, Cd, Sr, Pb, Cd, and As) in leaves, stems and roots of *Plumbago zeylanica* L. Many anticancer and antioxidant compounds normally have these elements [11]. Ravikumar and Sudha investigated the presence of various constituents in ethanol, petroleum ether and aqueous extract of *Plumbago zeylanica* L. From the investigation, they confirmed the presence of alkaloids, carbohydrates, triterpenoids, flavonoids, gums, mucilage, protein, fatty acids and saponins [15]. Jijhotiya and team carried a study to evaluate scientific data for presence of various phytochemicals in the leaves extract of methanol, aqueous and petroleum benzene. All the three different extracts of leaves were found to contain triterpenoids, flavonoids, phenolic tannins, saponins & carbohydrate. Study suggested the importance of these reported secondary metabolites for the pharmacological properties of the plant [11]. Recently Roy et.al, studied fatty acid methyl ester profile of five different accession of *Plumbago zeylanica* L. The fatty acid methyl ester analysis revealed the presence of several types of fatty acids in the plant. They found that these accessions are affluent in octadecadienoic acid (8–22%), octadecatrienoic acid (7–24%), pentadecanoic acid (11–22%) fatty acids [16].

Phytoconstituents present in various plant parts

Different researchers report phytochemicals from different parts of the plant (Table 1). Large range of therapeutic activities possessed by this plant are due to presence of this valuable constituent. Number of secondary metabolites such as naphthoquinones flavonoids, alkaloids, glycosides, saponins, steroids, tannins, triterpenoids, coumarins, carbohydrates, phenolic compounds, fixed oils, fats and proteins reported to be present in *Plumbago zeylanica* L. [12, 13]. Major naphthoquinones present in the plant are plumbagin, chitranone, 3-biplumbagin, chlorplumbagin, elliptone, coumarins includes seselin, 5-methoxy seselin, xanthyletin, suberosin. Other phytoconstituents present in the plant includes plumbagic acid, β sitosterol, 2-dimethyl-5-hydroxy-6-acetylchromene, saponaretin, and isoaffinetin [14]. Several other naphthoquinones, difuranonaphthoquinones binaphthoquinones, coumarins, di-phenyl sulfone, carboxylic acids and esters, monoterpenes, tri-terpenoids, amino acids, anthraquinones, steroids, steroid glucosides, sugars and other compounds are also reported to be present [17–21].

The roots of the plant contains plumbagin, and other constituents such as 3-chloroplumbagin, binaphthoquinone named as 3', 6'-biplumbagin, 3,3'-biplumbagin and four other pigments reported as isozeylanone, zeylanone, elliptone, and droserone. Isoshinanolone and a new naphthalenone i.e., 1, 2(3)-tetrahydro-3, 3'-biplumbagin isolated from the phenolic fraction of the light petrol

extract of the roots has also been identified. Two plumbagic acid glucosides; 3'-O-beta-glucopyranosyl plumbagic acid and 3'-o-beta-glucopyranosyl plumbagic acid methylester along with five naphthoquinones (plumbagin, chitranone, maritnone, elliptone and isoshinanolone), and five coumarins (seselin, methoxyseselin, suberosine, xanthyletin and xanthoxyletin) are reported to be isolated from the roots [21–23].

Stem contains plumbagin, campesterol, sitosterol, stigmasterol, isozeylanone and zeylanone. The leaves of *Plumbago zeylanica* L. reported to contain chitanone, plumbagic acid and plumbagin. The presence of alkaloids, glycoside, reducing sugars, simple phenolics, tannins, lignin, saponins and flavonoids are reported from the qualitative phytochemicals analysis of leaves [17, 18]. Seeds mainly contain plumbagin. Stem revealed the presence of plumbagin, zeylanone, isozeylanone, sitosterol, stigmasterol, campesterol, and dihydroflavonol. Plumbagin, zeylanone and sitosterol identified in the flowers of the plant. Fruit confirmed the presence of plumbagin, glucopyranoside and sitosterol [22–24].

Since plumbagin is one of the pharmaceutically important phytoconstituent of *P. zeylanica*. However, the productivity of this constituent is very low, which is insufficient to meet the demand. Keeping this view, in a recent study Andhale and his coworkers attempted an investigation to study the effect of fungal endophytes on increment of plumbagin content in the plant. They assume fungal endophytes have the potential to synthesize various secondary metabolites and influence the synthesis of the secondary metabolites in plants [25].

Pharmacological and therapeutic activities

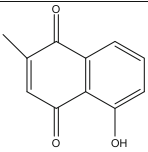
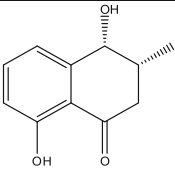
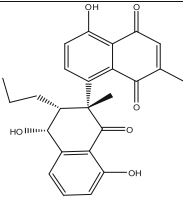
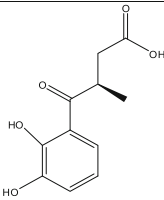
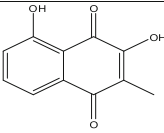
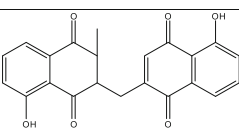
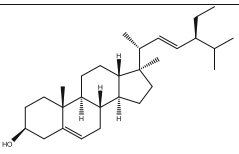
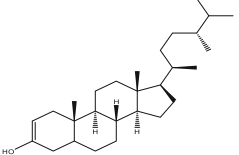
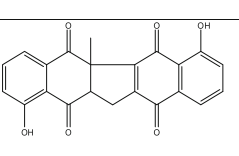
Plumbago zeylanica L., is a pharmaceutically important plant. It exhibits broad range of pharmacological activities, which includes antibacterial, antifungal, anti-inflammatory, antidiabetic, anticancer, antioxidant, hepatoprotective, cytotoxic and wound healing.

The reported pharmacological activities of various parts of *Plumbago zeylanica* L. are detailed below:

Antimicrobial activity

Shweta and Dubey studied antimicrobial properties of the leaves extracts of the plant against some known drugs. The in-vitro antimicrobial activity and the minimum inhibitory concentration (MIC) of the crude extract and the standard antibiotics were studied. Maximum inhibition was reported with leaves extracts as compared to the standard antibiotics [26]. In another study, Singh and colleagues investigated methanolic extracts of the stem and the leaves against six bacterial species and nine fungal species for antimicrobial studies. Both the extracts showed antimicrobial activity in a dose-dependent manner. Moreover, the antimicrobial

Table 1 Phytoconstituents present in different plant parts and their structure.

| Phytoconstituent isolated from various plant parts | Chemical structure | Plant part | Reference |
|--|---|-----------------------------------|--------------------|
| Plumbagin, |  | Leaves, Root, Stem, Seed & Flower | 17, 21, 22, 23, 24 |
| Isoshinanolone |  | Root | 21, 22, 23 |
| Chitanone |  | Leaves | 23, 24 |
| Plumbagic acid |  | Leaves | 22, 23 |
| Zeylanone, |  | Stem & Flower | 17, 22, 23, 24 |
| Isozeylanone |  | Stem | 17, 18 |
| Stigmasterol |  | Stem | 17, 18 |
| Campesterol |  | Stem | 17, 18 |
| Sitosterol |  | Flower & Fruit | 23, 24 |

activities assayed from the zones of inhibition. Leaves extract indicated maximum antimicrobial activity against both *Staphylococcus aureus* and *Fusarium oxysporum* whereas the stem extract was noted to be more antimicrobial against the *Pseudomonas aeruginosa* and the *Penicillium expansum* species. Study suggests that the methanolic extract of *Plumbago zeylanica* L. stem possess significant antibacterial activity [27]. In another study, Ogunleye and coworkers carried an investigation to evaluate the antibacterial activity of the ethanolic extract of *Plumbago zeylanica* L. root bark against seven bacteria extracted from two dumpsites within the city of Akure. Study revealed, antibacterial activity of the extract enhances with increasing concentration [28].

In a recent experiment Jain et al., investigated *Plumbago zeylanica* L. for its antifungal activity. Antifungal potential was studied against four pathogenic fungal species *Fusarium oxysporum*, *Rhizoctonia solanii*, *Alternaria* sp. and *Sclerotium rolfsii*. Study suggested excellent inhibitory activities against *Alternaria* spp. whereas least against *S. rolfsii* at 62.5 µg/ml [29].

Anti-inflammatory activity

Sheeja et al., investigated anti-inflammatory activities of acetone and petroleum ether extracts of *Plumbago zeylanica* L. leaves using in vivo experimental models at two dose levels (200 and 400 mg/kg, p.o.). The acetone extract significantly decreased inflammation in rats induced by carrageenan compared to the control group. Study revealed anti-inflammatory activity of the extract may be linked to reduction in prostaglandin synthesis and release, rather than preformed inflammatory agents [30–32]. In another study Thanigavelan et al., investigated the anti-inflammatory activity of hydroalcoholic extract of *Plumbago zeylanica* L. root bark through in-vitro human red blood cell membrane protective activity, and in-vivo through carrageenan induced rat paw oedema and complete Freund's adjuvant induced chronic inflammatory model in rat. In both acute and chronic model of inflammation, hydroalcoholic extract of root bark of *Plumbago zeylanica* L. showed moderate anti-inflammatory response at the dosage of 250 mg/kg b.w comparable with standard indomethacin. Carrageenan injection is the biphasic occurrence that contributes to the development of paw oedema in the rat. Study indicated, the mechanism of anti-inflammatory activity might be due to prostaglandins inhibition [33]. Further Nile et al., studied anti-inflammatory activity of root and shoot extracts of *Plumbago zeylanica* L. at a concentration of 25, 50, 75, and 100 mg/mL using diene-conjugate and β-glucuronidase assays [34]. Later on, Subramaniyan et al., investigated dichloromethane extract of *Plumbago zeylanica* L. against carrageenan-induced paw oedema at the doses of 250 mg/kg and 500 mg/kg. Study showed

inhibition effect of oedema was comparable to diclofenac (standard drug). Study suggested that the inhibition effect may be attributed to its free radical scavenger activity and protection of apoptosis [35]. In another research Poosarla et al., investigated a freeze-dried ethyl acetate fraction (PZE-6) of *Plumbago zeylanica* L., roots for the management of joint inflammation. Study showed PZE-6 substantially suppressed arthritis by reducing paw volume, clinical score and delayed-type hypersensitivity reaction. In addition, PZE-6 was found to inhibit the development of inflammation in adjuvant-induced arthritis rats [36]. As reported by Zaki et al., plumbagin prominently hampered high mobility group box 1 expression and subsequently quelled inflammatory cascades, as nuclear factor κB (NF-κB), tumour necrosis factor-alpha (TNF-α) and myeloperoxidase (MPO) activity [37].

Antioxidant activity

Plumbago zeylanica L. has been widely investigated for its anti-oxidant properties. Tilak and coworkers studied antioxidant activity of the aqueous and alcoholic root extracts against known medicinal preparations and the active constituent, plumbagin. Ferric reducing/anti-oxidant power (FRAP), radical scavenging of 1,1-diphenyl-2-picrylhydrazyl (DPPH) and 2,2'-azobis-3-ethylbenzthiazoline-6-sulfonic acid (ABTS), lipid peroxidation, phenolic and flavonoid content was assessed for evaluation of its antioxidant potential. In FRAP/DPPH assays, ethanolic extracts were shown to be most efficient, whereas in the ABTS assay aqueous extracts were reported to be the more effective. These extracts also demonstrated significant lipid peroxidation inhibition and augmented proportion of polyphenols and flavonoids. Antioxidant and pulse radiolysis studies were performed to examine the detailed mechanisms of action [38].

In a recent study, Gabriel and colleagues investigated free radical scavenging activity of methanolic root extract (ME) and ethylacetate extract (EA) by using 1,1-diphenyl-2-picrylhydrazyl (DPPH). Study showed ME extract possess highest antioxidant activity in comparison to EA extract [39].

Hair growth promoter and regulation

Androgenetic alopecia (AGA) is a common type of baldness characterized by progressive hair loss. Yamada et al., investigated the potential of *Plumbago zeylanica* L. roots extract in the prevention AGA. Study examined the inferences of cellular senescence of DP cells in prevention of AGA. Quantitative RT-PCR and Western blotting analysis in DP cells examined the expression of the 5α-reductase type II (SRD5A2) gene. In addition, DP cells were cultured with the herbal extract of *P. zeylanica* roots. Study demonstrated up-regulation in the expression of the

SRD5A2 in senescent DP cells whereas, the herbal extract of *Plumbago zeylanica* L. root enhanced the growth of DP cells and showed down-regulation in expression of SRD5A2 in DP cells. Observations confirmed the role of senescent DP cells in the development of AGA through up-regulating SRD5A2 expression, and suggested the potential of *Plumbago zeylanica* L. extract and role of plumbagin in suppressing its development through enhancing the growth of DP cells and down-regulating SRD5A2 expression in DP cells [40].

Antidiabetic activity

Plumbago zeylanica L. account for its sweet inactivation property to the presence of its chief active constituent plumbagin. Experimental trials confirmed the antidiabetic effect of *Plumbago zeylanica* L. in various studies. Zarmouh et al., reported antidiabetic activity of ethanolic extract of *Plumbago zeylanica* L. roots. The study was conducted in streptozotocin induced diabetic rats at the doses of 100–200 mg/kg for six weeks. Results showed marked increase in hepatic hexokinase activity and reduction in hepatic glucose-6-phosphatase, serum acid phosphatase (ACP), alkaline phosphatase (ALP) and lactate dehydrogenase (LDH) levels [41]. Furthermore, an investigation to determine the antidiabetic activity of plumbagin derived from the root of *Plumbago zeylanica* L. and its implication on GLUT4 translocation in STZ-induced diabetic rats was performed by Christudas et al. Plumbagin orally administered to STZ-induced diabetic rats for 28 days in the dose concentration of 15 and 30 mg/kg body weight. On 21st day, oral glucose tolerance test was performed. Plumbagin showed remarkable reduction in the blood glucose. All the other biochemical parameters were observed to near normal. In addition, increased activity of hexokinase and reduction in glucose-6-phosphatase and fructose-1,6-bisphosphatase was indicated in treated diabetic rats. The GLUT4 mRNA and protein expressions found raised in diabetic rats after treatment with plumbagin. The obtained results concludes that plumbagin exhibit remarkable antidiabetic activity [42].

In another research Khatwani et al., investigated potential synergistic activity of aqueous extracts of leaves of *Murraya koenigii* (MK), *Annona squamosa* (AS), and roots of *Plumbago zeylanica* L. (PZ) using STZ induced diabetic rat model. All the ingredients of the capsules were mixed together in required proportion with suitable excipients and filled into the capsules. Study results with the polyherbal formulation was noted to be more significant as compared to Glibenclamide [43].

Antiulcer activity

Falang and coworkers investigated aqueous extract of *Plumbago zeylanica* L. root against aspirin and indomethacin induced acute gastric ulceration in albino rats. They determined and compared ulcer score, ulcer

index and percentage protection of the extract with negative and positive control groups. The extract showed significant dose dependent inhibition of aspirin induced gastric mucosal damage at the doses of 25, 50 and 100 ml/kg whereas in case of indomethacin-induced ulcer, extract showed inhibition at doses of 50 and 100 mg/kg respectively [44].

Antiobesity

Kotecha and Rao investigated anti-obesity activity of *Plumbago zeylanica* L. A clinical study was conducted on obese patients taken from I.P.G.T & R. Hospital at Jamnagar, Gujarat. During the investigation, an intervention of *Plumbago zeylanica* L. and haridra powder within the dose of 500 mg and 1 g (4 times a day) respectively administered in a capsule form to the patients for 45 days with restricted diet schedule of low calorie diet. Proposed intervention of *Plumbago zeylanica* L. and haridra powder showed potential reduction in the weight of the patient as compared to the haridra alone [45].

Antihyperlipidemic activity

Pendurkar and Mengi evaluated the antihyperlipidemic activity of aqueous extract of *Plumbago zeylanica* L. roots in diet-induced hyperlipidemic rats. Ameliorated effect in hyperlipidemic condition was displayed by lowering of cholesterol and triglyceride levels on oral administration of the extract at the doses of 20, 40, and 80 mg kg⁻¹. Similar effects were also obtained with standards fenofibrate (20 mg kg⁻¹) and atorvastatin (8 mg kg⁻¹). In addition, significant reduction in the total lipid content in the liver was also noted with the extract. Results obtained demonstrated the beneficial role of aqueous extract of *Plumbago zeylanica* L. roots in hyperlipidemic condition [46].

Hepatoprotective activity

Kanchana et.al, reported hepatoprotective activity of petroleum ether extract of *Plumbago zeylanica* L. roots against paracetamol induced liver damage. Various biochemical parameters were studied to evaluate the hepatoprotective activity. Elevated levels of markers in the animals treated with paracetamol confirmed the severe hepatic damage by paracetamol. Following the administration of extract, significant reduction was noted in the serum markers indicating the effect of the extract in restoring the normal functional ability of the hepatocytes. The study concludes the petroleum ether extract of *Plumbago zeylanica* L. root could provide a significant protection against paracetamol-induced hepatocellular injury [47].

Wound healing activity

Plumbago zeylanica L. has been widely recommended for its wound healing potential in the traditional system

of medicine. Kodati et al., reported significant wound healing activity of methanolic extract of *Plumbago zeylanica* L. roots in wistar rats. For the evaluation of wound healing activity, 10% (w/w) extract ointment was applied on the wound surface. It was found that the wound contracting ability of the extract treated rats displayed significant wound healing from the sixth day onwards. The wound closure time was lesser, as well as the percentage of wound contraction was more with the extract. Moreover, the extract treated groups demonstrated complete healing of wound in 16 days whereas the control group showed epithelization in more than 20 days [48].

Furthermore, in another study Jyothi and colleagues investigated wound healing potential of the ethanolic root extract of *Plumbago zeylanica* L. Study indicated the increased wound healing activity of the ethanolic root extract might be attributed to the presence of phytoconstituents (alkaloids, terpenoids, flavonoids etc.) which may act individually or have additive effect [49].

Nephroprotective activity

Rajakrishnan and coworkers studied the nephroprotective effect of hydroalcoholic extract of *Plumbago zeylanica* L. (HAPZ) roots in cisplatin-induced nephrotoxicity in Swiss albino mice. Study revealed that, high dose (400 mg/kg) administration of HAPZ significantly reversed the adverse effect of cisplatin on kidney weight, serum urea and creatinine, and displayed the renoprotective effect of HAPZ. The results of the study supports nephroprotective effect of hydroalcoholic extract of *Plumbago zeylanica* L. [50].

Antifertility activity

Edwin and co-workers assessed antifertility potential of extracts of *Plumbago zeylanica* L. leaves. They studied the effect of petroleum ether, chloroform, acetone, ethanol and aqueous extracts on the estrous cycle of rats at the doses of 200 and 400 mg/kg. The acetone and ethanol extracts were found to be more promising in interrupting the estrous cycle of the rats. It was observed that, the anti-ovulatory activity reversed on discontinuation of treatment. Therefore, the study suggests the antifertility potential of acetone and ethanolic extracts of *Plumbago zeylanica* L. leaves [51].

In another study, Vishnukanta and Rana evaluated antiimplantation activity of hydroalcoholic extract of *Plumbago zeylanica* L. leaves. The estrogenic/antiestrogenic activity of the extract was studied on immature ovariectomized female wistar rats for 1–7 days of post-coitum. Significant antiimplantation activity was noted at the dose of 200 mg/kg. Extract showed antiestrogenic activity and caused overall structural and functional changes in uterus [52].

Anticancer and cytotoxic activity

Plumbago zeylanica L. reported to possess number of phytoconstituents that have cytotoxic activity. Plumbagin is one of the major bioactive widely investigated for anticancer and cytotoxic potential. Eldhose et.al, studied the potential of plumbagin against colon cancer cells. Study examined the proliferation and survival of colon cancer cells in attached culture conditions i.e. experimental conditions resembling the environment in primary tumors and in unattached conditions i.e. circulating tumor cells. Observations showed the exposure of HCT116 cells to plumbagin in the low micromolar concentrations in both the experimental conditions resulted in cell cycle arrest at the G1 phase, apoptosis via the mitochondrial cell death pathway, and enhanced production of reactive oxygen species. The cell cycle effects were more significant in attached cells, whereas the induction of cell death was more noticeable in unattached cells. Study findings displayed that plumbagin lacks toxicity on normal colon cells and showed its striking anti-survival effect on colon cancer cells [53].

Many researchers have also reported in-vitro anticancer activities of extracts derived from *Plumbago zeylanica* L. In an experimental study, Mani and Jayachitra investigated anticancer effect of ethanolic extract of *Plumbago zeylanica* L. (EEPZ) leaves against the standard 5-Fluorouracil (20 mg/kg). The EEPZ was administered orally to the tumor-bearing group at doses of 200 mg/kg and 400 mg/kg body weight for 14 consecutive days. It was found that both doses of EEPZ evidentially reduced average body weight, decreased viable tumor cell count for packed cell volume (PCV), and increased mice's lifetime for DAL treatment, with a reduction in blood flows, serum enzymes and lipid profile close to normal values [54]. Furthermore, Kumar et.al evaluated cytotoxicity activity and compared the toxicity potential of the *Plumbago zeylanica* L. roots petroleum ether (PZPE), acetone (PZAC) and hydroalcoholic (PZHA) extracts in rodents. According to OECD guidelines 425 and 407, acute and sub-acute toxicities of the extracts in female rats was evaluated. Study revealed PZPE was more toxic than PZAC and PZHA, based on LD₅₀ values. The observed difference was attributed to the plumbagin content of extracts. Sub-acute toxicity study displayed significant increase in organ weights (liver, adrenal glands, and/or heart) in PZPE and PZAC treated groups. Whereas all the extracts showed significant rise in serum aspartate aminotransferase and urea. PZAC produced a remarkable increase in serum creatinine as compared to control. Moreover, reduction in hematocrit was observed in the highest dose PZPE group, and a decrease in leukocytes was observed in all PZAC groups. Hepatic and renal changes were also noticed in all

extract treated groups. Study suggests liver and kidney are the primary organs being adversely affected following sub-acute administration of *Plumbago zeylanica* L. root extract [55]. In a recent study, Tokarz et.al, investigated survival strategy of *Plumbago zeylanica* L. to the lead toxicity via photosynthetic apparatus acclimatization. Study revealed the plants acclimate to lead toxicity by Pb accumulation in roots [56].

Anthelmintic activity

Desai and associates evaluated anthelmintic effects of aqueous and methanolic extract of *Plumbago zeylanica* L. roots at the concentrations of 5, 10, 15 and 20 mg/ml against the standard Piperazine citrate. Results were assessed in respect of time for paralysis and time for death of worms. Significant effect was recorded with methanolic extract as compared to aqueous extract [57]. Furthermore, in another study Weldemariam et.al, investigated anthelmintic potential of chloroform and ethanolic extracts of *Plumbago zeylanica* L. roots in both crude and fractions. Both crude and fractions paralyse and killed the worms in lesser time than that of the positive control. Chloroform extracts demonstrated significant results as compared to ethanolic extract. These significant findings suggests the long lasting use of this plant for helminthes [58].

Discussion

Plumbago zeylanica L. contain a wide range of phytoconstituents like flavonoids, alkaloids, glycosides, saponins, steroids, tannins, triterpenoids, coumarins and phenolic compounds which have been found to be beneficial in the prevention and treatment of various diseases, including cancer, and also to have antimicrobial [26], antihyperlipidemic [46], antiulcer [44], hepatoprotective [47], antioxidant [38], anti-inflammatory [36], antihyperglycemic [42] and wound healing properties [48]. Encouragingly, current review discusses several promising pharmacological activities, which are intrigued by extensive variety of potential phytoconstituents of *Plumbago zeylanica* L.

Plumbago zeylanica L. was reported to possess protective effects against hepatotoxicity [47]. Treatment with paracetamol is potentially ascribe to hepatic injury inducing necrosis and inflammatory reactions due to the disruption of hepatocyte [59]. *Plumbago zeylanica* L. was found to maintain membrane integrity and limit the leakage of hepatic enzymes [41]. Scientists discovered that flavonoids, among the plant metabolites have an effect on cancer cells and inhibit their proliferation [60]. Assuredly, having ample flavonoids would possibly lead *Plumbago zeylanica* L. to exhibit antiproliferative activity.

Phytoconstituent showing toxicity may be a major concern of researchers and our reviewed plant was

found to indicate cytotoxicity that is most frequently associated with chemoprevention. The cytotoxic activity of this plant may be mainly attributed to the plumbagin, which was previously reported as anticancer agent [55]. Some of the phytoconstituents, viz. tannins, flavonoids, terpenoids, and alkaloids, are indicated for antimicrobial activity [26, 27]. Noteworthy, the reviewed plant contains plumbagin, which is a pharmacologically active naphthoquinones that has displayed antimicrobial property earlier [28, 61]. Besides, it is profoundly enriched with terpenoids and henceforth may be leading to a remarkable antibacterial activity.

Several investigations disclosed hypoglycemic potentials of *Plumbago zeylanica* L. Moreover, stem bark of this plant contains two promising phytoconstituents; specifically, β -sitosterol and stigmasterol, which could be the contributive to hypoglycemic potential [17–23]. Presence of these two constituents, β -sitosterol and stigmasterol, which play a significant role in glucose metabolism, might be accountable for the degradation of incretins like glucagon-like peptide. Earlier reports recommend that the reviewed plant exhibit potent antioxidant activity. It is well established that oxidative damage to biomolecules, due to the overproduction of free radical plays a vital role in the etiology of various diseases such as atherosclerosis, cancer, diabetes, rheumatoid arthritis etc. [62]. Scavenging of a large range of free radicals including the most active hydroxyl radicals, which initiate lipid peroxidation process also displayed by the *Plumbago zeylanica* L. [63].

Admittedly, *Plumbago zeylanica* L. can be considered as a versatile plant having a plethora of medicinal activities. This plant is distinctive source of a large range of compounds having diverse therapeutic properties. The current information relating to this medicinal plant could serve as the baseline knowledge to enforce to do in depth studies for the discovery of new potent compounds and more investigations for their biological activities.

Conclusion and future perspectives

The present review investigated the traditional medicinal uses, phytochemical profile and pharmacological properties of *Plumbago zeylanica* L. The retrieved data documented that *Plumbago zeylanica* L is a good source of diverse phytoconstituents and has tremendous therapeutic properties. Major constituents reported in the plant were flavonoids, alkaloids, glycosides, saponins, steroids, tannins, triterpenoids, coumarins and phenolic compounds. Literature indicates its huge utility towards numerous diseases including cardiovascular disorders, ulcer, liver problems, diabetes, obesity, wound healing, cancer etc. The work reviewed substantiated most of the traditional claims on its health benefits. But as seen during literature search it was found that major work has been done on extracts therefore, there is need for future investigations to isolate

and characterize pharmacologically active agents that confer medicinal properties on *Plumbago zeylanica* L., as well as elucidate the structures of these agents, their pathways by which they exert their healing properties and to scientifically validate the prevailing ancient practices regarding its health benefits. Besides, the isolation studies can help to leverage the pharmacological attributes while reducing the side effects.

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Authors' contributions

PK make substantial contribution to conception and design. PK and SU participated in the analysis and interpretation of data. BS carried out acquisition of data and wrote the paper with input from all authors. All authors read and approved the final manuscript

Competing interests

There is no conflict of interest.

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