Review Article

Ethnomedical and Pharmacological Potentials of *Plumbago zeylanica* L- A Review

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ABSTRACT

Plumbago zeylanica L. (Plumbaginaceae) (PZ) commonly called as Doctorbush is a semi climbing sub shrub used to effective against anaemia, rheumatic pain, dysmenorrhoea, leprosy, ulcers and elimination of intestinal parasites. In Ayurvedic system of medicine, the roots of the plant and its constituents are credited with potential therapeutic properties including cardiotonic, neuroprotective and CNS stimulating properties. The aim of this review is to provide comprehensive information on the traditional uses, phytochemistry, pharmacological actions and toxicity study of Plumbago zeylanica L to explore their therapeutic potential and future research opportunities. All the relevant information of PZ was collected through MEDLINE/PUBMED. The evidence presented in this review has showed that PZ has great potential to be integrated into conventional medical practice for the treatment of various metabolic diseases, hepatotoxic, diabetes, inflammation, cancer and other disease complications. Future research on PZ would provide much knowledge about pharmacological uses and socio-economic impact.

Keywords: *Plumbago zeylanica*, Pharmacology, Phytochemistry, Toxicity, Bioactive compounds.

INTRODUCTION

The usage of medicinal plants is increasing worldwide. According to the World Health Organization (WHO), approximately 80% of the world's population currently uses herbal medicines directly as teas, decocts or extracts with easily accessible liquids such as water, milk, or alcohol.[1] In fact, most of the plants produce a various bioactive molecules making them for various types of diseases.
The medicinal plants and its active principles have been continued to play a

dominant role in the maintenance of human health since ancient times.[2] Over 50% of all modern clinical drugs are synthesised from natural product origin.[3] Natural products play on important role in drug development in the pharmaceutical industry.[4] There are many reports on the use of medicinal plants in traditionally used by either tribal people or indigenous population.[5-9]

BOTANICAL DESCRIPTION

Plumbago is a genus of 15-20 species of Angiosperms in the family Plumbaginaceae. The family Plumbaginaceae consists of 10 genera and 280 species. The genus *Plumbago* includes 3 species, namely *Plumbago indica* L. (*P. rosea* L.), *P. capensis* L., and *P. zeylanica* L., which are distributed in several parts of India. Among these species *Plumbago zeylanica* grows all districts of plains in Tamilnadu, Andra Pradesh, Karnataka and Kerala, common, wild or in cultivation due to its more therapeutic uses.[10]

Plumbago zeylanica (PZ) commonly called as Doctorbush or Ceylon Leadwort is a semi climbing sub shrub that grows throughout Asia, Australia, Africa and Ceylon and widely used in ethnomedicine.[11] It is used in indigenous system of medicine, and commonly known as “Chitthra mulam”. It is branched evergreen shrub growing up to 2 meters. The leaves are dark-green, ovate 30 cm long and 15 cm wide. The flowers are white in thick racemes, individuals around 1cm across, flowering throughout the year.[12]

Classification

Kingdom: Plantae
Order: Caryophyllales
Family: Plumbaginaceae
Genus: *Plumbago*
Species: **Z***eylanica*
Sanskrit Synonyms: Agni, Vahini

Regional names:

English: Lead wort, Ceylon lead wort
Hindi: Chira, Chitra
Gujarati: Chitrakmula
Kannada: Chitrakmula, Bilichitramala
Malayalam: Vellakeduveli
Punjabi: Chitra
Bengali: Chita
Tamil: Kodiveli, Chitramoolam
Telugu: Chitramulam

ETHNOPHARMACOLOGICAL & TRADITIONAL USES

In Ayurvedic and Unani system of medicines the whole plant has been described for significant effective against anaemia, rheumatic pain, sprains, dysmenorrhoea, carbuncles, scabies, leprosy, contusion of the extremities, inflammation, ulcers and elimination of intestinal parasites.[13-19] The roots of the plant and its constituents are credited with potential therapeutic properties including antiatherogenic, cardiotonic, neuroprotective and central nervous system stimulating properties.[20-23]

In Indian system of medicine, the plant has been recommended for the treatment of various ailments such as dyspepsia, piles, diarrhoea, skin diseases and used in formulations of a number of ayurvedic compounds.[24] It is said to increase digestive power and improve appetite.[25] The roots of *Plumbago* species have been demonstrated to possess immunosuppressive and antitumor activities.[26]

Ethnopharmacological studies carried out by many studies have indicated that PZ has an effect of antidiarroheal activities;[27] antiallergic;[28] insecticidal;[29] antidiabetic;[30] hepatoprotective;[20,31] hypolipidaemic;[32,33] anti-inflammatory;[34,35] antitumour activity;[36,37] antibacterial, antifungal;[38,39] antimicrobial[19,40,41] and oral treatment for complaints related to infections of the urinary tract.[42] PZ has been extensively studied for the inhibition of proliferation of variety of cell

lines and animal models[43] and cytotoxic for tumor cell activities[37].

The present review aims to describe PZ has been pharmacologically tested and shown to be proving as potential healer and highlight the main medicinal properties with a view to focus future studies on this plant.

PHARMACOLOGICAL ACTIONS

Pharmacological studies on PZ has been reviewed and a detailed information of dose range tested, type of extract used, the model used, controls, duration of the study as well as their pharmacological results are given in the **table 1.**

Antidiabetic Activity

Pharmacological studies carried out by Olagunju *et al.*[30] have indicated that PZ has antihyperglycemic effect on diabetic induced animals. The ethanol extract of PZ root on key enzymes of glycolysis and muscle hexokinase, phosphofructokinase, pyruvate kinase lactate dehydrogenase activities were diminished in diabetic rats.[44-46]

Hypocholesterolemic Action

Pharmacological and Clinical studies carried out by Sharma *et al.* [32] indicated that PZ extract has hypolipidaemic and antiatherosclerotic activities. Plumbagin, an active principle isolated from PZ brings about a definite regression of atherosclerosis and prevents the accumulation of cholesterol and triglycerides in liver and aorta. ‘‘Panchcole’’ an Ayurvedic formulation containing PZ as one of its chief ingredients has been advocated to produce hypolipidaemic effect.[33]

Anti-Inflammatory Activity

The plant has been used for anti-inflammatory properties.[34,35] Three medicinal plants namely Phyllanthus emblica, PZ and Cyperus rotundus were used to analyse two models of acute inflammation and result showed that PZ reduce the oedema while the combination of P. emblica compared to aspirin.[47,48] Also PZ brought to suppress the activation of NF-kappa B in tumor cells and prevented Graft Versus Host Disease-induced mortality in mice.[49]

Anticancer Activity

The methanolic extract of PZ root and pure compound 3β-hydroxylup-20(29)-ene-27, 28-dioic acid (PZP) isolated from PZ have anti-invasive properties[50] and antitumour activity.[36,37] Both compounds were noted to have the ability to induce apoptosis and found to release of cytochrome c, activation of caspase-3 and cleavage of PARP leading to DNA fragmentation,[51,52] followed by effectiveness in human promyelocytic leukemia cells, NB4.[53] This action inhibits STAT3 activation pathway through the induction of SHP-1 and mediate the sensitization of STAT3 [54] and chronically activate ERK1/2 and inhibit Akt activity in cancer cells.[55]

Cu(PLN)(2)].2H(2)O (1) and Cu(PLN)(bipy)(H(2)O)](2)(NO(3))(2).4H(2) O (2), active principles obtained from reaction of Cu(II) salt with plumbagin, isolated from methanolic extract of PZ root and identified inhibition of topoisomerase I (TOPO I) [56] and GST activity[57] in the cancer cells and inhibition of proliferation of variety of cell lines and animal models[43].

Antimicrobial Activity

The plant has been used for antibacterial, antifungal[38,39,58,59] and antimicrobial activities.[19,40,41,60] The ethanol, ethyl acetate and acetone extracts of PZ have the highest inhibitory effects against *Helicobactor pylori* using the agar diffusion and dilution methods at the pH 1-7,[62-64] having synergistic and action against *Mycobacterium intracellulare, M. smegmatis, M. xenopei and M. Chelonei.*[65] The antimicrobial potential of PZ have been described in various pathogenic

bacteria[40,42,58,59] like Staphylococcus aureus[66] and E.coli[61]and regulate gastrointestinal flora.[67]

Aqil and Ahmad[68] & Ahmad and Aqil[69] investigated a broad-spectrum antibacterial activity against different bacteria and the most promising plant fraction of PZ (ethyl acetate fraction) confirmed killing of test bacteria at the lower level compared to its Minimum Inhibitory Concentration. In addition the root contains Anti-methicillin-resistant Staphylococcus aureus (MRSA) activity.[70] The antimicrobial properties of compounds such as neoisoshinanolone and 1-epineo-isoshinanolone separated from the crude petroleum ether extract of roots of PZ.[71]

Antimalarial Activity

The root of the PZ has been used for a potential of antiplasmodial properties and to treat fever or malaria.[72,73] The study was examined in vitro for antiplasmodial properties against *Plasmodium falciparum.* Malaria is normally transmitted to people by mosquitoes infected with the malaria parasite. Avoiding the bites of *Anopheles* mosquitoes is the best way to prevent Malaria. On the other hand, the highest Larvicidal potential was found in methanol extracts of PZ roots against *Anopheles aegypti* and *A.stephensi*.[74,75] The hexane and chloroform extracts of PZ also found to have highest larvicidal activity against Anopheles gambiae.[76] It shows that the plant has high larval mortality of mosquito species.

Abortifacient & Antifertility Activity

Azad Chowdhury *et al.*[77] and Edwin *et al.*[78] investigated that the acetone and ethanol extracts of PZ were most effective to interrupt the estrous cycle and exhibited a prolonged diestrous stage of the estrous cycle resulting to a temporary inhibition of ovulation. Also in human, PZ acts as family planning agents[79,80] and anti-implantation agents that appear to interfere with progesterone synthesis or utilization.[81,82]

PHYTOCHEMISTRY

A raw phytochemical analysis with thin layer chromatography of crude extracts of PZ showed the presence of alkaloids, phenols and flavonoids.[70] Phytochemical screening of various parts of PZ revealed to produce lineleic acid, palmitic acid, nonylnonanoate, stigmasterol acetate, lupeol acetate, friedelinol, lupeol, lupanone, sitosterone and stigmasterol.[42,83-86]

The leaves, stems and roots of PZ exists with abundant amounts of elements like four macro-elements (Na, K, Ca and Mg), five essential microelements (Zn, Fe, Mn, Cr and Co), and eight other elements (Mo, Sb, Bi, Cd, Sr, Pb, Cd and As) respectively were detected by inductively Coupled plasma atomic emission spectrometry (ICP-AES). Many anticancer and antioxidant drugs usually possess these elements.[87] The aerial parts contain plumbagin, isoshinanolone, plumbagic acid, beta-sitosterol, 4-hydroxybenzaldehyde, trans-cinnamic acid, vanillic acid, 2, 5-dimethyl-7-hydroxychromone, indole-3-carboxaldehyde isolated by column chromatography.[88] The dichloromethane extract of aerial parts contain beta-sitosterol, beta-sitosteryl-3beta-glucopyranoside, beta-sitosteryl-3-beta-glucopyranoside-6'-O-palmitate, lupenone, lupeol acetate, plumbagin and trilinolein.[59] In addition, the natural active compound Plumbagin isolated from different plant part of PZ by RP-HPLC[89] along with synthesis of the binaphthoquinone, 3, 3'-biplumbagin [90]. Plumbagin was quantified by reverse phase HPLC and UV detection,[91] liquid chromatography coupled with tandem mass spectrometric.[92]

The root of PZ contains a numerous bioactive products such as two plumbagic acid glucosides [3'-O-beta-glucopyranosyl

plumbagic acid and 3'-O-beta-glucopyranosyl plumbagic acid methylester][93] along with five naphthoquinones (plumbagin[94], chitranone,[95] maritinone,[96] elliptinone and isoshinanolone[94]), and five coumarins (seselin,[97] 5-methoxyseselin,[98] suberosin,[99] xanthyletin[100] and xanthoxyletin[101,102]) respectively.

Kamal *et al.*[103] isolated a number of compounds such as plumbagin, droserone, isoshinanolone and a new naphthalenone, 1,2(3)-tetrahydro-3,3'-biplumbagin from the phenolic fraction of PZ. A variety of compounds have been isolated from various parts of PZ includes naphthoquinones, such as plumbagin,[19,94] droserone, isoshinanolone and the new variant, 1,2(3)-tetrahydro- 3,30-biplumbagin;[94] metroterpenes, such as bakuchiol and 12-hydroxyisobakuchiol;[102] C-glucosylflavonoids and saponaretin.[103]

The various fractions of petroleum ether, chloroform, ethyl acetate and n-butanol extracts of PZ root provided Difuranonaphthoquinones, analysed by MS and ^{1}H and ^{13}C NMR spectroscopic data.[104] Plumbagin reacted with lanthanide salts to produce five new lanthanide (III) complexes, characterized by different physicochemical methods such as elemental analyses, UV-visible, IR and ^{1}H NMR, Electro Spray Ionization Mass Spectrum) and Thermogravimetric analysis.[105] Neo- and 1-epineo-isoshinanolones along with plumbagin separated from the crude petroleum ether extract of PZ roots, analysed by using NMR, IR and Mass Spectroscopy.[71]

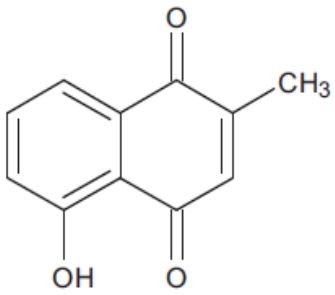
TOXICITY STUDY

The root of PZ has been reported to be a powerful poison when given orally or applied to ostium uteri, causes abortion.[77,79] But the methanol root extract of PZ in rabbits produced a limited toxic effect and did not produce any overt signs of toxicity in skin[28] and possible in vivo protective effect against cyclophosphamide-induced genotoxicity and oxidative stress in mice.[106-108]Moreover the acute toxicity studies of PZ in albino rats revealed that the oral LD_{50} of the drug is 65mg/kg body weight and in the dead animals, the post mortem revealed a profuse bleeding in the viscera.[79,106,110]The active compound of PZ, Plumbagin may have potential as a compound in synthetic insecticides.[28]

BIOACTIVE COMPOUNDS

Plumbagin

Plumbagin (2-methyl-5-hydroxy-1,4-naphthoquinone) is a yellow crystalline bioactive phytoconstituent present in the roots isolated from PZ by soxhlet apparatus followed by silica gel column chromatography[104] cold maceration followed by preparative Thin layer chromatography techniques;[110] Thin Layer Chromarography and column chromatography;[111] normal-phase liquid chromatography;[112] reverse-phase liquid chromatography;[113] and liquid chromatography-tandem mass spectroscopy (LC-MS/MS).[114]



Structure of Plumbagin

Plumbagin, an active compound have a potential of anticarcinogenic and antioxidant,[115-117] cardioprotective,[118] antimicrobial,[66,119] antibacterial,[120] antifungal,[121] antimalarial,[122] antifertility,[109] anti HIV activity,[123] anti-atherosclerotic [32,124] and potentiate phagocytosis in the human white blood cells.[125]Plumbagin has a potential of anticancer properties[126,127] and studies on mouse embryonic fibroblast cells suggest that

the cytotoxic action of plumbagin may be due to apoptotic cascade through the generation of reactive oxygen species (ROS).[128]

Plumbagin is known to produce reactive oxygen species (ROS) such as superoxide anion and hydrogen peroxide. [129-133] Plumbagin generates ROS through multiple mechanisms depending upon cell types, can produce ROS via the redox cycling,[130] the leakage of the mitochondrial respiratory chain,[134] or the depletion of intracellular glutathione levels.[132,133] The generation of ROS by plumbagin may account for its cytotoxic or apoptotic effects.[135]

Plumbagin can also as a radio-sensitizer modulate the effects of radiation in the treatment of tumor.[136] The anticancer effect of plumbagin has been postulated to come true by disrupting microtubule polymerization through tubulin binding and inducing apoptosis.[137,138] In addition, plumbagin does not exert an apoptotic effect on normal cells and therefore may have potential as a chemotherapeutic agent.[139,117,140]

Plumbagin has also observed to have oxidative effects in prokaryotic cells lacking superoxide dismutase (SOD), due to its antimicrobial activity[141] and prevent the development of antibiotic resistant mutants in bacteria through mutagenic mechanisms,[61] but plumbagin itself did not have mutagenic effect; it rather reduced the mutagenic effects of other mutagens in *Salmonella typhimurium* suggesting a plumbagin associated antimutagenic activity.[120] Indeed, the fact that plumbagin acts as an antigenotoxic and antioxidative agent[142,22,143]as well as anticarcinogenic agent.[124, 117, 132]

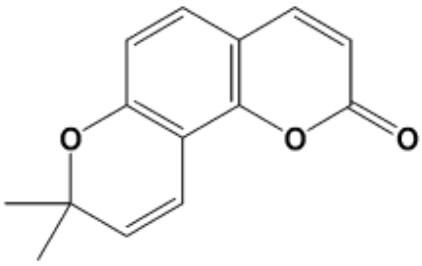
In addition, Plumbagin is a potential beneficial for the treatment of various diseases like diarrhoea, skin rashes, hepatic toxicity, reproductive toxicity and also involved in white blood cell counts enhancement, increase in serum phosphate and acid phosphate level.[144, 127, 79, 109,145]

Also the research showed that the plumbagin doesn't have any mutagenic effects in different E. coli strains,[146,52] Salmonella typhimurium[147] and reported to induce clastogenic effects in a micronucleus assay[57] and somatic mutations.[148]

The anticancer and antiproliferative activity of plumbagin tested in either *in vivo* or *in vitro* models are listed in the **Table-2.** The structure of the plumbagin has been reported to closely resemble the vitamin K and the anticoagulant property of PZ might be similar to coumarin derivative, the haemorrhage may be due to the competitive inhibition of vitamin K activity, needed for the synthesis of clotting factors.[149] The anticoagulant activity of the PZ was reported after an hour exposure and the effect of PZ on platelets and coagulation profile lead to the development of an antithrombotic drug.[150,151]

Seselin

Seselin (2,2-Dimethyl-1,5-dioxaphenanthrene-6(2H)-one;8,8-Dimethyl-2H,8H-benzo[1,2-b:3,4-b']dipyran-2-one) is an angular pyranocoumarin[37,152] isolated from PZ.



Structure of Seselin

Several biological activities of seselin have been reported as antinociceptive activities *in* vivo;[152,153] antibacterial activity[154] and antiproliferative effects on several cancer cell lines such as leukemia and lymphoma cells.[155-157, 37]Also it has been blocked the ear and paw edema in murine[158, 159] and inhibitory

effects on Ca2+ influx in mast cells and smooth muscle cells.[160, 161]

CONCLUSION

The evidence presented in this review has showed that Plumbago zeylanica L. has great potential to be integrated into conventional medical practice for the treatment and management of various metabolic syndromes, hepatotoxic, diabetes, inflammation, cancer and other disease complications. Development and research on PZ through modern pharmaceutical technologies and analytical protocols is essential to assure its quality, safety and efficacy. It is anticipated that this review will provide some valuable information for ongoing explorations of this fascinating species and its phytochemicals. Future research on PZ would not only provide much needed knowledge on this popular herbal medicine, but would also offer a noticeable socio-economic impact in turning a common weed into beneficial nutraceutical and pharmaceutical products.

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Table 1. Pharmacological studies and review on *Plumbago zeylanica* L.

Type of plant extract	Dose ranges	Negative Control	Animal model/Microorganisms	Duration of the study	Results	References
Methanolic extract of leaves	25, 50 and 100 mg	-	Indian earth worms (*Pheretima posthuma*)	2 days	Anthelmintic activity	162
Methanolic extract of root	50, 100, and 150 µg/ml	-	*Helicobacter pylori*	1day	Anti- bacterial activity	62
ethanol, acetone or ethyl acetate of Rhizome	30µl	-	*Helicobacter pylori*	3 days	Anti- bacterial activity	64
Ethanolic extract of root	0.64-10.24 mg/ml	Ethanol	E. coli and Shigella	2 days	Anti- bacterial activity	68
chitraka root	100mg/kg	-	Human study	14days	Anti- hypercholesterolemic activity	73
Ethanolic extract of stems	500, 1000mg/kg	48/80	Wistar Mice	2 days	Antiallergic activity	28
Methanol, chloroform and alcoholic extracts of leaves	50, 100 mg/ ml	-	Staphylococcus aureus, Bacillus subtilis, Echerichia coli , Pseudomonas aeruginosa	1 day	Antibacterial activity	41
Methanol, Chloroform and aqueous extract of root	1mg/ml	-	*E.coli, Salmonella typhi, Klebsiella pneumoniae,Serratia marcescens, Proteus*	2days	Antibacterial activity	163

			vulgaris, Pseudomonas aeruginosa, Staphylococcus aureus, Bacillus cereus			
Petroleum ether, ethanol and aqueous extract of root	1200µg/ml	-	*Staphylococcus aureus and Micrococcus luteus*	2 days	Antibacterial activity	164
Methanolic extract of leaves	50, 100 mg/ml	-	*Bacillus subtilis, Staphylococcus aureus, Escherichia coli* and *Salmonella typhi*	2 days	Antibacterial activity	162
Ethanolic extract of root	100, 200 mg/kg	Cancer cell line	Male Swiss albino mice	14days	Anticancer activity	165
Ethanolic extract of root	250mg/kg bw	3-methyl-4-dimethyl aminoazobenzine	Wistar Albino rats	7 days	Anticarcinogenic activity	116
Hydroalcoholic extract of leaves	250, 500 mg/kg	Pentylene tetrazole	Wistar albino rats	1hour	Anti-convulsion activity	166
Methanolic extract of root	4–10 mg/ml	occluded dermal irritation	Albino rabbits, Swiss mice and Albino rats	1 day	Anti-dermatotoxicity	26
Ethanolic extract of root	250mg/kg bw	Alloxan	Wistar Albino rats	21days	Antidiabetic activity	30
Aqueous extract of root	100, 200mg/kg	STZ	Wistar albino rats	42 days	Antidiabetic activity	167
Aqueous extract of leaves	100, 200mg/kg	STZ	Wistar albino rats	28 days	Antidiabetic activity	45

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Aqueous extract of leaves	100, 200mg/kg	STZ	Wistar albino rats	28 days	Antidiabetic activity	168
Methanol, chloroform extract of whole plant	50µl	-	*Rhizoctonia solani Kuhn, Bipolaris spp., Ustilago maydis and Alternaria alternate*	2days	Antifungal activity	169
Ethanolic extract of root	250, 500 mg /kg bw	cyclophosphamide	Swiss Albino mice	7 days	Antigenotoxic activity	106
Petroleum ether extract of root	300 mg/kg	Paracetamol	Wistar Albino rats	7days	Antihepatotoxic activity	31
Methanolic extract of aerial parts	35, 70 mg/kg	CCl_4	Wistar albino rats	14 days	Antihepatotoxic activity	170
Aqueous extract of root	20, 40, and 80 mg/kg	diet-induced hyperlipidemic rats	Wistar albino rats	7days	Antihyperlipidemic effect	171
Methanol, extract of root	300, 500mg/kg	Carrageenin	Wistar albino rats	7days	Anti-inflammatory activity	172
Petroleum ether, chloroform and acetone extract of root	0.1ml	-	*Salmonella typhi, Staphylococcus aureus, Escherichia coli, Aspergillus niger, Pencillium sp. and Fusarium oxysporum*	2 days	Antimicrobial activity	173
Methanolic extract of root	7.5mg/ml	RPMI & Dimethyl Sulfoxide	male Sprague–Dawley rats	3 hours	Antimutagenic effect	107
Root powder	7.5 mg/kg bw	Phenylhydrazine	Male Wistar Albino rats	21days	Antioxidant activity	174

Ethanolic extract of root	1mg/L	DPPH (1, 1-Diphenyl-2-picrylhydrazyl), ABTS (2, 2-azinobis-3-ethyl benzothiazoline-6-sulfonic acid diammonium salt	In-vitro study	1hour	Antioxidant activity	175
Ethanolic extract of root	100mg/kg	-	Invitro	2hours	Antioxidant activity	176
Methanolic extract of leaves	50,100 mg/ml	Butylated hydroxyanisole	In-vitro	2hours	Antioxidant actvity	162
Methanolic extract of root	0.8–200µg/ml	Guanidine hydrochloride, amantadine, and phosphonoformic acid	coxsackievirus B3 Nancy (CVB3), influenza A virus Hong Kong/1/68 (H3N2), and herpes simplex virus type 1 Kupka (HSV-1)	2 days	Antiviral activity	177
Aqueous extract of plant	0.5 µg/ml	-	Hepatitis B-virus	2 days	Antiviral activity	178
Ethanolic extract of root	250mg/kg	Cholesterol	Rabbit	28days	Hypolipidaemic activity	179
Ethanolic extract of root	250mg/kg	diet-induced hyperlipidemic rats	Rabbit	28days	Hypolipidaemic activity	180
Ethanolic extract of root	250mg/kg bw	-	BALB/C mice	6 weeks	Immunomodulatory activity	66

aqueous root extract	4mg/ml	Turkey egg albumin	Balb/c mice	56days	Immunosuppressive activity	181
Chloroform extract of root	100, 200 and 400 mg/kg.	Scopolamine	Swiss albino mice	10days	Memory Enhancing effect	182

Table 2. List of studied plumbagin with putative anticancer and antiproliferative tested in either *in vivo* or *in vitro* models (source: PUBMED, English language).

Cancer cell	Results	References
Human Prostate cancer cell (PC-3, LNCaP, and C4-2)	Decrease in cell viability, apoptosis induction, Generation of ROS, depletion of intra cellular GSH	132
Human Melanoma A375.S2	Reduced amounts of cyclin B1, cyclin A, Cdc2, and Cdc25C and enhanced the levels of inactivated phosphorylated Cdc2 and Cdc25C, increased the activation of apoptosis signal-regulating kinase 1, JNK and extracellular signal-regulated kinase 1/2 (ERK1/2) and finally blocking ERK and JNK	133
Human nonsmall cell lung cancer cells, A549	Activation of JNK and SP600125 (Aanthra [1,9-cd]pyrazol-6(2H)-one-1,9-pyrazoloanthrone), a specific inhibitor of JNK, decreased apoptosis by inhibiting the phosphorylation of p53 and subsequent increased in the interaction of p53 and MDM2. SP6000125 also inhibited the	117

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	phosphorylation of Bcl-2 (Ser70)	
Human Peripheral blood lymphocytes	Effective cell growth inhibition, induces apoptosis, generates single-strand of DNA breaks and cytotoxic action	183
Human Prostate Cancer	Inhibition of both cultured Prostate Cancer cells and DU145 xenografts (a) the expression of protein kinase Cepsilon (PKCepsilon), phosphatidylinositol 3-kinase, phosphorylated AKT, phosphorylated Janus-activated kinase-2, and phosphorylated signal transducer and activator of transcription 3 (Stat3); (b) the DNA-binding activity of transcription factors activator protein-1, nuclear factor-kappaB, and Stat3; and (c) Bcl-xL, cdc25A, and cyclooxygenase-2 expression	139
Human acute promyelocytic leukemia cells	Inhibition of proliferation of NB4 cells, chromosomes condensation and apoptotic body formation, cell proliferation and induce apoptosis of APL cell line NB4 cells.	184
MCF7 and Bowes cancer cell lines	Inhibition of the proliferation of MCF7 and Bowes cells	59
Human hepatoma	Inhibition of the certain glycolytic enzymes and gluconeogenesis.	116
Human peripheral blood mononuclear cells	involve the regulation of cell cycle progression, interleukin-2 and interferon-production	153

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MDA-MB-231 cells	inhibitory effect on the protein levels of p-PI3K, p-Akt, p-JNK, p-ERK1/2, MMP-2, MMP-9, VEGF and HIF-1α	50
Human breast cancer cells	Inactivation of NF-kappaB and Bcl-2	185
Lung A549 cells	Increased the expression of p53 and phosphorylated p53 (Ser15 and Ser392) and regulates the levels of cell cycle-related molecules in A549 and activates JNK	117
Human ovarian cancer cells	Bound to the active site of ER-α and inhibit classical ER-α signaling pathways	186
Cervical cancer cells	Lower dose of radiation in combination with plumbagin could induce apoptosis more effectively and activation of caspase 3 in C33A cells. Induction of apoptosis by irradiation and involves caspase-dependent pathways.	136
Human promyelocytic leukemia cells	Induced apoptotic cell death and inhibits tumor growth without obvious toxicity and triggering the mitochondria-dependent apoptosis of tumor cells by increasing ROS	53
Ovarian cancer cells	Induced loss of mitochondrial membrane potential, nuclear condensation, DNA fragmentation, and morphological changes	131
Human cervical cancer	Induced cell death is through the generation of ROS and subsequent induction of apoptosis caused loss of mitochondrial membrane potential and morphological changes characteristic of	128

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	apoptosis, such as the translocation of phosphatidyl serine, nuclear condensation, and DNA fragmentation.	
Human breast cancer cells	inhibit Akt activity and enhanced the activation of Chk2, resulting in increased inactive phosphorylation of Cdc25C and Cdc2.	134
sarcoma-180	Ehrlich ascites model was evaluated and identified as less toxic, justified with the help of LD50 survival studies and study of tumour volume doubling time	126
Azoxymethane induced intestinal carcinogenesis	promising chemopreventive agents for human intestinal neoplasia	187
3T3-L1 cells	activated PI3-kinase and/or PDK1 stimulate Akt activity with Ras–Raf–MEK1/2–ERK1/2 pathway	55

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