



Review on Plumbagin Obtained from *Plumbago Zeylanica* Linn

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ABSTRACT

Plumbago zeylanica Linn belong to family Plumbagenaceae a perennial herb, distributed throughout India. *Plumbago zeylanica* is one of the important herbs in Indian traditional medicine commonly known as Chitramula, Chitraka or Chitrak. The root and its bark are bitter, hot and used in treatment of leucoderma, bronchitis and liver disorder. The root has a bitter taste and laxative, expectorant, stomachic, tonic, abortifacient and appetizer property. The leaves are caustic and use in treatment of scabies. A tincture of the root – barks has been employed as an antiperiodic. This review contains detail information about isolation method, some standardization method and some pharmacological activity of plumbagin, a major phytoconstitutes present *Plumbago zeylanica* Linn.

Keywords: *Plumbago zeylanica*, Chitraka, Phytochemical, Pharmacological, Plumbagin.

INTRODUCTION

Ayurveda is a medical system primarily practiced in India that has been known for nearly 5000 years. It includes diet and herbal remedies, while emphasizing the body, mind and spirit in disease prevention and treatment. During the latter part of the twentieth century, increasing interest in self-care resulted in an enormous growth in popularity of traditional healing modalities, including the use of herbal remedies. The World Health Organization (WHO) estimates that 4 billion people, 80% of the world population, presently use herbal medicine for some aspect of primary health care. Herbal medicine is a major component in all indigenous traditional medicine and a common element in ayurvedic, homeopathic and naturopathic medicine. WHO notes that of 119 plant-derived pharmaceutical medicines, about 74% are used in modern medicine in ways that correlated directly with their traditional uses as plant medicines by native cultures. Major pharmaceutical companies are currently conducting extensive research on plant materials gathered from forests and other places for their potential medicinal value.

Plumbago zeylanica is one of the important herbs in Indian traditional medicine commonly known as Chitramula, Chitraka or Chitrak. The plant growing wild in Bengal, Uttar Pradesh, Sothern India and Ceylon. The root and its bark are bitter, hot and used in treatment of leucoderma, bronchitis and liver disorder. The root has a bitter taste and laxative, expectorant, stomachic, tonic, abortifacient and appetizer property. The leaves are caustic and use in treatment of scabies. A tincture of the root – barks has been employed as an antiperiodic. The aim of the present review contains detail information about isolation method, standardization method and

some pharmacological activity of plumbagin, a major phytoconstitutes present *Plumbago zeylanica* Linn. ^{1,2}

ISOLATION METHOD

Rapid method for isolation of plumbagin by cold maceration process

Chellampillai Bothiraja and et al used cold maceration process for extraction and isolation of plumbagin, from *Plumbago zeylanica* root. The roots of *P. zeylanica* were cold macerated with a mixture of chloroform/dichloromethane (1:1) and the extract was successively washed with water, saturated sodium bicarbonate and water. The cold maceration yielded 1.2% (w/w) fine crystalline orange needle of plumbagin. It showed melting point at 78.4 °C, Rf value at 0.64 in n-hexane:benzene (1:9) solvent system, UV absorption maxima at 417 nm and molecular peak [M+H]⁺ at 188.20 m/z. Mass spectra and ¹³C NMR confirmed the isolated compound structure which was supported by P-NMR.³

Novel solvent free extract of *Plumbago zeylanica* using hydrophilic lipid Gelucire

Chellampillai Bothiraja and et al used a single step technique using hydrophilic lipid Gelucire 44/14 for extraction and isolation of plumbagin from *Plumbago zeylanica*. Gelucire extract of *P. zeylanica* (GPZ) was prepared and evaluated for extraction efficiency, High-performance thin layer chromatography (HPTLC) and thermal analysis. The GPZ showed significantly higher extraction efficiency (3.24±0.12% w/w). GPZ displayed significantly higher Q30min (cumulative percentage absorption of plumbagin in 30 min) and lower t40% (time required for 40% w/w drug absorption). The flux and apparent permeability coefficient in duodenum and ileum was 2, 3 and 6 fold higher. Improved therapeutic efficacy of plumbagin may be due to the micellar solubilization



and consequent enhanced partitioning of plumbagin through intestinal by Gelucire.⁴

STANDARDIZATION METHOD

Reverse phase HPLC-UV and HPTLC method for determination plumbagin in *Plumbago indica* and *Plumbago zeylanica*

K.P.Unnikrishnan and et al develop a reverse phase HPLC method with UV detection has been developed and validated in order to quantify plumbagin, the bioactive marker of *Plumbago indica* and *Plumbago zeylanica*. A quantitative HPTLC method was also developed using Hexane: Ethyl Acetate as a mobile phase. The plumbagin content in the root was determined using both methods. *Plumbago indica* was found to content higher amount of plumbagin than *Plumbago zeylanica*. The HPLC and HPTLC method described here are simple, rapid, accurate and sensitive.⁵

UV-Visible Spectrophotometric Method for the Estimation of Plumbagin

Israni S A and et al develop spectrophotometric method for estimation of plumbagin. The proposed spectrophotometric method is based on formation of magenta pink colored phenolate ion by reaction of naphthoquinones with alkalis. A graph of absorbance versus concentration shows that Beer's law is obeyed in the concentration range of 40µg/ml-240µg/ml. The pink colored chromogen is measured at maximum wavelength of 520nm. The results of analysis have been validated statistically and by recovery studies. The study revealed that the bioactive marker was found to be maximum in *P. rosea* (1.68%) followed by *P. zeylanica* (0.413%), *P. capensis* (0.33%), *P. capensis* (0.297%) and *V. indica* (0.13%).⁶

HPLC Analysis of Plumbagin *Plumbago europaea*

Hazhar M and et al, extracted *Plumbago europaea* were by Soxhlet apparatus using ethyl acetate and plumbagin was characterized by spectroscopic analysis (IR, 1H-NMR, and 13C-NMR). Quantitative and qualitative study of plumbagin in the roots and leaves extracts was carried out by HPLC technique using analytical column (Eurospher 100, C18, 5 µm, 250 x 4.6 mm) with 10% solvent (B) isocratic elution of methanol (solvent A) and water (solvent B) at flow rate 0.75 ml/min and detection wave length of 270 nm. The percentage of plumbagin in the root and leaf extracts was recorded to be (1.9 %) and (1.5 %) respectively.⁷

Plumbagin quantification in roots of *Plumbago scandens*

Selma R. De Paiva extract Plumbagin from roots of *Plumbago scandens* L. using static maceration, dynamic maceration, with assistance of ultrasonic waves and in Soxhlet apparatus. Four compounds were qualitatively detected in all extracts: the naphthoquinones plumbagin and epi-isoshinanolone, palmitic acid and sitosterol. Plumbagin was always the major component in all

analyzed extracts and it was quantitatively determined by gas chromatograph coupled with mass spectrometer. Soxhlet was the most efficient extraction technique however, prolonged heating time promoted plumbagin degradation.⁸

PHARMACOLOGICAL ACTIVITY

Anti-inflammatory and Analgesic Effect of Plumbagin through Inhibition of Nuclear Factor- B Activation

Pei Luo and et al study anti-inflammatory and analgesic effects of PL orally administrated in a range of dosages from 5 to 20 mg/kg and also examined the role of nuclear factor κB (NF-κB) and proinflammatory cytokines mediators in this effect. The results showed that PL significantly and dose-dependently suppressed the paw edema of rats induced by carrageenan and various proinflammatory mediators, including histamine, serotonin, bradykinin, and prostaglandin E2. PL reduced the number of writhing episodes of mice induced by the intraperitoneal injection of acetic acid, but it did not reduce the writhing episode numbers induced by MgSO4 in mice or prolong the tail-flick reaction time of rats to noxious thermal pain. Mechanistic studies showed that PL effectively decreased the production of the proinflammatory cytokines interleukin 1β, interleukin 6 and tumor necrosis factor α. It also inhibited the expression of the proinflammatory mediator's inducible nitricoxide synthase and cyclooxygenase-2, whereas it did not inhibit the expression of cyclooxygenase-1. Further studies demonstrated that PL suppressed inhibitor of κB phosphorylation and degradation, thus inhibiting the phosphorylation of the p65 subunit of NF-κB. This study suggests that PL has a potential to be developed into an anti-inflammatory agent for treating inflammatory diseases.⁹

Apoptosis Inducing Effect of Plumbagin on Colonic Cancer Cells Depends on Expression of COX-2

Bharathi R S and et al investigated the anti-proliferative and apoptotic activity of plumbagin by using two human colonic cancer cell lines, HT29 and HCT15. IC50 of Plumbagin for HCT15 and HT29 cells (22.5 mM and 62.5 mM, respectively) were significantly different. To study the response of cancer cells during treatment strategies, cells were treated with two different concentrations, 15 mM, 30 mM for HCT15 and 50 mM, 75 mM for HT29 cells. Though activation of NFκB, Caspases-3, elevated levels of TNF-α, cytosolic Cytochrome C were seen in both HCT15 cells HT29 treated with plumbagin, aberrant apoptosis with decreased level of pEGFR, pAkt, pGsk-3β, PCNA and Cyclin D1 was observed only in 15 mM and 30 mM plumbagin treated HCT15 and 75 mM plumbagin treated HT29 cells. This suggests that plumbagin induces apoptosis in both HCT15 cells and HT29 treated, whereas, proliferation was inhibited only in 15 mM and 30 mM plumbagin treated HCT15 and 75 mM plumbagin treated HT29 cells, but not in 50 mM plumbagin treated HT29 cells. Expression of COX-2 was decreased in 75 mM



plumbagin treated HT29 cells when compared to 50 mM plumbagin treated HT29 cells, whereas HCT15 cells lack COX. Hence the observed resistance to induction of apoptosis in 50 mM plumbagin treated HT29 cells are attributed to the expression of COX-2. Plumbagin induces apoptosis in colonic cancer cells through TNF- α mediated pathway depending on expression of COX-2 expression.¹⁰

Cytotoxicity of naphthoquinones and their capacity to generate reactive oxygen species is quenched when conjugated with gold nanoparticles

Priya Srinivas and et al demonstrate the fabrication and characterization of gold nanoparticles conjugated with plumbagin (AuPB). The anticancer activity and ability of plumbagin to produce reactive oxygen species was studied and compared with that of bromoderivatives of 1,4 naphthoquinones such as 2-bromo-1,4-naphthoquinone (2-BNQ) and 2,3-dibromo-1, 4-naphthoquinone (2,3-DBNQ) and their gold nanoconjugates. Plumbagin and bromoderivatives of 1,4 naphthoquinones in the form of gold nanoconjugates showed reduced cytotoxicity and apoptosis compared with the pristine compounds, ie, plumbagin, 2-BNQ, and 2,3-DBNQ. Observation shows that the gold nanoparticles could quench the reactive oxygen species generating capacity of plumbagin, 2-BNQ and 2, 3-BNQ, which is one of the main mechanisms of action of the naphthoquinones. Therefore, it can be concluded that conjugation with gold nanoparticles can reduce the cytotoxicity of these compounds.¹¹

Plumbagin induces cell death through a copper-redox cycle mechanism in human cancer cells

Nazeem S and et al study whether plumbagin induces apoptosis in human cancer cells. Using 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, inner salt assay, 3-(4,5-B-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay for cell growth inhibition, histone/DNA ELISA, homogeneous caspase-3/7 assay for apoptosis as well as alkaline comet assay for DNA single-strand breaks detection in this report, we confirm that plumbagin causes effective cell growth inhibition, induces apoptosis and generates single-strand breaks in cancer cells. Incubation of cancer cells with scavengers of ROS and neocuproine inhibited the cytotoxic action of plumbagin proving that generation of ROS and Cu(I) are the critical mediators in plumbagin-induced cell growth inhibition. Study investigate the copper-mediated anticancer mechanism of plumbagin in human cancer cells and these properties of plumbagin could be further explored for the development of anticancer agents with higher therapeutic indices, especially for skin cancer. 12

Plumbagin Promotes the Generation of Astrocytes from Rat Spinal Cord Neural Progenitors Via Activation of the Transcription Factor Stat

Yongquan Luo and et al study whether plumbagin could modify the developmental fate of rat E14.5 embryonic

neural progenitor cells (NPC). Plumbagin exhibited no cytotoxicity when applied to cultured NPC at concentrations below 1 μ M. At a concentration of 0.1 μ M, plumbagin significantly enhanced the proliferation of NPC as indicated by a 17% increase in the percentage of cells incorporating bromo-deoxyuridine. Plumbagin at a concentration of 0.1 pM (but not 0.1 μ M), stimulated the production of astrocytes as indicated by increased GFAP expression. Plumbagin selectively induced the proliferation and differentiation of glial progenitor cells without affecting the proliferation or differentiation of neuron-restricted progenitors. Plumbagin (0.1 pM) rapidly activated the transcription factor Stat3 in NPC, and a Stat 3 inhibitor peptide prevented both plumbagin-induced astrocyte formation and proliferation. These findings demonstrate the ability of a low molecular weight naturally occurring phytochemical to control the fate of glial progenitor cells by a mechanism involving the Stat3 signaling pathway.¹³

Plumbagin suppresses NF- κ B activation and NF- κ B-regulated gene products through modulation of p65 and I κ B κ kinase activation, leading to potentiation of apoptosis induced by cytokine and chemotherapeutic agents

Santosh K. Sandur and et al found that plumbagin inhibited NF- κ B activation induced by TNF, and other carcinogens and inflammatory stimuli. Plumbagin also suppressed the constitutive NF- κ B activation in certain tumor cells. The suppression of NF- κ B activation correlated with sequential inhibition of the tumor necrosis factor (TNF)-induced activation of I κ B κ kinase, I κ B κ phosphorylation, I κ B κ degradation, p65 phosphorylation, p65 nuclear translocation, and the NF- κ B-dependent reporter gene expression activated by TNF, TNFR1, TRAF2, NIK, IKK- β , and the p65 subunit of NF- κ B. Plumbagin also suppressed the direct binding of nuclear p65 and recombinant p65 to the DNA, and this binding was reversed by dithiothreitol both in vitro and in vivo. However, plumbagin did not inhibit p65 binding to DNA when cells were transfected with the p65 plasmid containing cysteine 38 mutated to serine. Plumbagin down-regulated the expression of NF- κ B-regulated anti-apoptotic (IAP1, IAP2, Bcl-2, Bcl-xL, cFLIP, Bfl-1/A1, and survivin), proliferative (cyclin D1 and COX-2), and angiogenic (matrix metalloproteinase-9 and vascular endothelial growth factor) gene products. This led to potentiation of apoptosis induced by TNF and paclitaxel and inhibited cell invasion. Overall, our results indicate that plumbagin is a potent inhibitor of the NF- κ B activation pathway that leads to suppression of NF- κ B-regulated gene products.¹⁴

Inhibition of Lysine Acetyltransferase KAT3B/p300 Activity by a naturally Occurring Hydroxynaphthoquinone, Plumbagin

Kodihalli C R and et al, describe plumbagin (RTK1), isolated from *Plumbago rosea* root extract, that inhibits histone acetyltransferase activity potently *in vivo*.



Interestingly, RTK1 specifically inhibits the p300-mediated acetylation of p53 but not the acetylation by another acetyltransferase, p300/CREB-binding protein-associated factor, PCAF, *in vivo*. RTK1 inhibits p300 histone acetyltransferase activity in a noncompetitive manner. Docking studies and site-directed mutagenesis of the p300 histone acetyltransferase domain suggest that a single hydroxyl group of RTK1 makes a hydrogen bond with the lysine 1358 residue of this domain. In agreement with this, we found that indeed the hydroxyl group-substituted plumbagin derivatives lost the acetyltransferase inhibitory activity.¹⁵

Plumbagin, a medicinal plant-derived naphthoquinone, is a novel inhibitor of the growth and invasion of hormone refractory prostate cancer

Moammir H. Aziz and et al presented that plumbagin (PL), may be a potential novel agent in the control of hormone refractory PCa. Specific observations are the findings that PL inhibited PCa cell invasion and selectively induced apoptosis in PCa cells but not in immortalized non-tumorigenic prostate epithelial RWPE-1 cells. Also, intraperitoneal administration of PL (2mg/kg body weight), beginning 3 days after ectopic implantation of hormone refractory DU145 PCa cells, delayed tumor growth by 3 weeks and reduced both tumor weight and volume by 90%. Discontinuation of PL treatment in PL-treated mice, for as long as 4 weeks did not result in progression of tumor growth. PL, at concentrations as low as 5 μ M, inhibited both in cultured PCa cells and DU145 xenografts the expression of: 1) PKC ϵ , PI3K, pAKT, pJAK-2 and pStat3; 2) the DNA-binding activity of transcription factors AP-1, NFkB, and Stat3 and 3) Bcl-xL, cdc25A and COX-2 expression. The results indicate for the first time, using both in vitro and in vivo preclinical models, that PL inhibits the growth and invasion of PCa. PL inhibits multiple molecular targets including PKC ϵ , a predictive biomarker of PCa aggressiveness. PL may be a novel agent for therapy of hormone refractory PCa.¹⁶

Modulation of T cell proliferation and cytokine response by Plumbagin, extracted from Plumbago zeylanica in collagen induced arthritis

Aparanji Poosarla and et al observed effect of Plumbagin on Con-A induced T cell proliferation was studied in spleen cells from collagen induced arthritic DBA/1 mice. The DBA/1 mice (five per each group) were immunized with 0.1 mL of collagen (emulsified in CFA) by intradermal injection at the base of the tail. On day 20, mice were given a booster dose of collagen (emulsified in IFA) through the same route. Plumbagin was given at different concentrations (3.3, 6.6, 13.3 mg/kg body weight) intraperitoneally. Control mice received olive oil alone. The Con-A induced T cell proliferative responses of arthritic and Plumbagin treated mice were studied by cell culture experiments using tritiated Thymidine. In addition the cytokine levels were estimated from the in vitro spleen culture supernatants of arthritic mice primed with different concentrations of Plumbagin by ELISA.

Plumbagin enhanced the decreased Con-A induced T cell proliferation and Interleukin-2 production in arthritic mice. Moreover elevated levels of IFN- γ were found to be decreased in Plumbagin treated spleen cell culture supernatants. Subclasses of IgG were found to be decreased by Plumbagin treatment, IgG2a reduction seems to be more prominent. The results obtained in the study indicate that Plumbagin is very effective in the mechanism based treatment of Rheumatoid arthritis.¹⁷

Amelioration of Experimental Autoimmune Encephalomyelitis by Plumbagin through Down-Regulation of JAK-STAT and NF- κ B Signaling Pathways

Yan Jia and et al reported that Plumbagin (PL) is a potent novel agent in control of encephalitogenic T cell responses and amelioration of mouse experimental autoimmune encephalomyelitis (EAE), through down-regulation of JAK-STAT pathway. PL was found to selectively inhibit IFN- γ and IL-17 production by CD4⁺T cells, which was mediated through abrogated phosphorylation of JAK1 and JAK2. Consistent with IFN- γ and IL-17 reduction was suppressed STAT1/STAT4/T-bet pathway which is critical for Th1 differentiation, as well as STAT3/ROR pathway which is essential for Th17 differentiation. In addition, PL suppressed pro-inflammatory molecules such as iNOS, IFN- γ and IL-6, accompanied by inhibition of I κ B degradation as well as NF- κ B phosphorylation.¹⁸

Antidiabetic effect of plumbagin isolated from Plumbago zeylanica L. root and its effect on GLUT4 translocation in streptozotocin-induced diabetic rats

Christudas Sunil and et al evaluated the antidiabetic effects of plumbagin isolated from *P. zeylanica* L. root and its effect on GLUT4 translocation in STZ-induced diabetic rats. Plumbagin (15 and 30 mg/kg b wt) was orally administered to STZ-induced diabetic rats for 28 days. An oral glucose tolerance test was performed on 21st day. The effect of plumbagin on body weight, blood glucose, plasma insulin, total protein, urea, ceratinine, liver glycogen, plasma enzymes (SGOT, SGPT and ALP) and carbohydrate metabolism enzymes (glucose-6-phosphatase, fructose-1,6-bisphosphatase and hexokinase) were investigated. GLUT4 mRNA and protein expression in skeletal muscles were also studied. Plumbagin significantly reduced the blood glucose and significantly altered all other biochemical parameters to near normal. Further, plumbagin increased the activity of hexokinase and decreased the activities of glucose-6-phosphatase and fructose-1,6-bisphosphatase significantly in treated diabetic rats. Enhanced GLUT4 mRNA and protein expression were observed in diabetic rats after treatment with plumbagin.¹⁹

Genotoxicity of plumbagin and its effects on catechol and NQNO-induced DNA damage in mouse lymphoma cells

Jemal Demma and et al study genotoxicity and antigenotoxicity of plumbagin in mouse lymphoma



L5178Y cells, using the comet assay. Without affecting the cell viability, plumbagin itself was found to induce significant DNA damage at concentrations as low as 0.25 ng/ml. When the cells were exposed to non-DNA damaging concentrations of plumbagin, together with NQNO (known to interact with DNA in many different ways) or catechol (known to induce oxidative DNA damage), plumbagin was found to significantly reduce the catechol-induced DNA damage, but to be without protective effect against the NQNO-induced damage.²⁰

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