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ANTICANCER POTENTIAL OF *PLUMBAGO ZEYLANICA* LINN. AND ITS ISOLATED CONSTITUENT PLUMBAGIN: A REVIEW

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ABSTRACT: Varieties of natural products have been proved as a rich source of phytoconstituents which are reported for a wide range of therapeutic potential. *Plumbago zeylanica* L. Is one of the herbs which are traditionally used for its therapeutic value. It is reported for several bioactive chemical constituents like naphthoquinones, flavonoids, alkaloids, glycosides, steroids, tri-terpenoids, tannins, fixed oils, fats, proteins, etc. in its chemical composition. Plumbagin is one of the most bioactive compounds of *Plumbago zeylanica* L., which is reported for a wide range of pharmacological activities such as anti-cancer, anti-diabetic, anti-malarial, anti-microbial, *etc*. It is a naphthoquinone derived yellow crystalline phytochemical constituent which is well proven for cytotoxicity against various cancer cell lines both *in-vitro* and *in-vivo*. This study is aimed to review and highlight the anticancer potential of plumbagin, formulation development approaches, and issues in the dosage form design of *Plumbago zeylanica* L. and its isolated constituent plumbagin.

INTRODUCTION: *Plumbago zeylanica* L., commonly known as white chitraka, belongs to family Plumbaginaceae. It serves as a weed all through the tropical and subtropical nations of the world. It is an enduring sub scandent bush, develops all through India, particularly in Bengal, Uttar Pradesh, South India, and Sri Lanka [1]. The family Plumbaginaceae includes 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 regions of India. Various chemical constituents have been reported, which includes naphthoquinones, flavonoids, terpenoids, and steroids, *etc*.

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It is reported for various pharmacological activities such as stimulant, digestant, expectorant, diuretic, abortifacient, and in the treatment of strong torment and rheumatic malady traditionally in Ayurveda [1]. The name chitraka signifies one which renders staining to the skin when applied topically. Leaves of *P. zeylanica* are dark green in shading and have basic, circular with bristly edges alongside exchange situation on the stem with the separation of up to 3 inches and thickness of 1.5 inches.

Petioles are flimsy and with an estimated length of 0.5 mm, and local stipules are available. Plants produce white blooms with a distance across of 1/2 to 3/4 inch having a stalk estimating 4 to 12 crawls alongside a terminal raceme kind of the inflorescence [2, 3]. The shade of the flowers is white or yellow, and roots generally appear as light yellow **Fig. 1** and **2** when the plant is naturally culled out of the ground and changes to rosy dark-colored in shading when it is dried, which regularly starts as hard pieces [2, 4].

Various auxiliary metabolites like flavonoids, alkaloids, glycosides, saponins, steroids, tannins, tri-terpenoids, coumarins, starches, phenolic mixes, fixed oils, fats, proteins, and naphthoquinones have been reported as chemical constituents in *P. Zeylanica* [2, 5].

FIG. 1: *PLUMBAGO ZEYLANICA* LINN. (FLOWERS AND ROOT MORPHOLOGY)

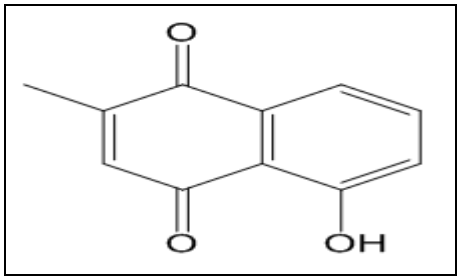

FIG. 2: CHEMICAL STRUCTURE OF PLUMBAGIN

Napthoquinones present in the plant are plumbagin, chitranone, 3-biplumbvagin, chloroplumbagin, elliptone. Coumarins are seselin, 5-methoxy seselin, xanthyletin, suberosin. Other compounds present in the plant are Plumbagin acid, β sitosterol, 2, 2-dimethyl-5-hydroxy-6-acetylchromene, sapo-naretin, isoaffinetin, *etc*. Among all these Plumbagin, is bioactive compounds present in *P. zeylanica*. *P. zeylanica* has been reported for various pharmacological activities like anti-diabetic, memory-actuating, lipid digestion, hostile to malarial, hypersensitive and modulatory, against fruitfulness, against bacterial, hostile to viral, hostile to disease, against oxidant and larvicidal [2]. The IUPAC name of the Plumbagin is 5-hydroxy-2-methyl-1,4-naphthoquinone. Plumbagin is well known for antineoplastic movement in the number of malignancy cells like breast cancer cells, lung malignant growth cells, pancreatic cells, prostate disease cells, colon malignant growth cells, and malignant ovarian growth. Plumbagin has been accounted for to dominatingly initiate apoptosis in disease cells.

Plumbagin has shown antibacterial activity against both gram-positive (*e.g., Staphylococcus, Streptococcus, Pneumococcus sp.)* and gram-negative (*e.g., Salmonella, Neisseria*) bacteria. It is also active against certain yeasts and fungi (C*andida, Trichophyton, Epidermophyton,* and *Microsporum* spp.) and protozoa (Leishmania). A wide range of medicinal properties of *P. zeylanica* are attributed to Plumbagin and other secondary metabolites [8-12].

Anticancer Potential: *P. zeylanica* reported to possess various bioactive compounds that have cytotoxic potential against various cancer cell lines. Plumbagin is one of the chemical constituent widely reported for cytotoxic potential. The plumbagin modulates cellular proliferation, radioresistance, and carcinogenesis. All these reactions are regulated by the activation of the NF-κB activation pathway. An examination additionally uncovers that plumbagin can restrain cell multiplication, square cell cycle, and incite apoptosis of APL cell line NB4 cells. Ethanolic extract of *P. zeylanica* is reported to inhibit malignant growth movement against Ehrlich Ascites Carcinoma, and it additionally diminishes the raised degree of lipid peroxidation having a nearness of higher terpenoids and flavonoids [2, 6, 7]. Plumbagin also reported for cell apoptosis in human gastric cancer cells, and that impact might be connected with its capacity to stifle phosphorylation of STAT3 and Akt and might be a promising moiety in the treatment of gastric malignant growth [13, 14].

The literature review reported that plumbagin, a bioactive naphthoquinone obtained from three noteworthy plant families *viz.* Plumbaginaceae, Ebenceae and Droseraceae, possess anticancer

potential in differing malignant growth cells both *in-vitro* and *in-vivo*. Plumbagin shows anti-neoplastic impacts by means of multi-channel subatomic components, including the acceptance of apoptosis and autophagy, the disturbance of the cell cycle, the hindrance of intrusion, and metastasis, and hostile to angiogenesis. Plumbagin represses the development of malignant growth cells primarily through the regulation of the sign of PI3K/Akt/mTOR, AMPK, Ras, *etc*. The pharmaceutical uses of plumbagin are incorporated in nano-carriers like liposomes, nanoparticles, micro-spheres, micelles, and niosomes to accomplish better remedial effectiveness in malignancy treatment [15].

Zhao and Lu *et al*., (2006) explored the impacts of plumbagin on the multiplication, cell cycle, and apoptosis of APL cell line NB4 Cells. Cell inhibitory rates were recognized by MTT colorimetric measure; morphologic changes were seen under light magnifying lens and transmission electron magnifying instrument; apoptosis-prompting impacts were dictated by DNA gel electrophoresis, annexin V/PI twofold recolored, and PI single-recolored stream cytometry. The results demonstrated that 2-15 mmol/L of plumbagin hindered the multiplication of NB4 cells in a portion subordinate way. The morphologic changes of cell apoptosis, such as chromosome condensation and apoptotic body formation, were observed by light microscope and transmission electron microscope. Cell cycle examination demonstrated that NB4 cells were obstructed in the G2/M period of cell cycle [16].

Jamal *et al.*, (2014) reported that Plumbagin (5-hydroxy- 2- methyl- 1, 4- naphthoquinone) is a naphthoquinone subsidiary from the underlying foundations of plant *Plumbago zeylanica* and has a place with one of the biggest and assorted gatherings of plant metabolites. The anticancer and anti-proliferative activity of plumbagin has been seen in creature models just as in cell societies. Plumbagin applies inhibitory consequences for different malignant growth flagging proteins [17].

Sandur *et al*. (2006) determined Plumbagin, from *Plumbago zeylanica*, adjusts cell expansion, carcinogenesis, and radioresistance, all known to be controlled by the actuation of the translation factor NF-kB, proposing plumbagin may influence the NF-kB initiation pathway. They found that plumbagin hindered NF-kB actuation prompted by TNF, and different cancer-causing agents and incendiary boosts (*e.g.,* PMA, H2O2, tobacco smoke condensate, IL-1b, LPS, and OA). Plumbagin also suppressed the constitutive NF-kB activation in certain tumor cells. The suppression of NF-kB activation correlated with sequential inhibition of the TNF-induced activation of IkBa kinase, IkBa phosphorylation, IkBa degradation, p65 phosphorylation, p65 nuclear translocation, and the NF-kB-dependent reporter gene expression activated by TNF, TNFR1, TRAF2, NIK, IKKb, and the p65 subunit of NF-kB [18].

Wei Yan *et al*., (2013) reported the impacts of plumbagin on the attack and relocation of human bosom disease cells. Human bosom malignant growth MDA-MB-231SArfp cells were treated with various convergences of plumbagin for 24 h. *In-vitro* outcomes demonstrated that plumbagin could stifle the relocation and intrusion of bosom malignant growth cells and down-manage mRNA articulations of IL-1α, TGF-β, MMP-2, and MMP-9 [19].

***In-vitro* Anticancer Activities:** *In-vitro* anticancer activities of extracts derived from roots of *Plumbago zeylanica* Linn. Collected from two distinctive geological zones of India (Himalayas-Jammu and the Western Ghats- Belgaum district) against five distinctive malignant growth, cell lines were analyzed. Alcoholic, hydroalcoholic, and aqueous fractions of *P. zeylanica* were studied by Sulphorhodamine B(SRB) assay.

Hydroalcholic concentrates showed better effects on HCT-15 cell line Colon malignancy cells, whereas aqueous extract showed better potential on MCF-7 Breast disease cells at 50, 70, and 100 µg/ml. In terms of correlation of IC_{50} Northern area (Jammu) sample was found to be with promising outcomes compared with Southern zone sample [20].

In-vitro treatment of plumbagin showed potential activity against malignancy [21, 22]. Despite this, the *in-vivo* organization in xenograft mouse models isn't demonstrating any symptoms in treated mice with a huge decrease in tumor development [23]. The detail system study uncovered that plumbagin

prompted cytotoxicity in malignancy cells through tweaking the qualities engaged with angiogenesis (counting STAT3, TGF-b, interleukin-1a, NF-kB, and VEGF), expansion, cell cycle capture (p53, p21, cyclin A, Cdk2, and cyclin D1), age of reactive oxygen species (ROS), and so forth and their downstream managed pathways [24, 25]. Concentrates additionally proposed that plumbagin can be utilized in mix with the existing enemy of malignant growth sedates that would be useful in the treatment of radiotherapy and chemotherapy-safe patients [26-31].

The plumbagin was reported in terms of proliferative and invasion effects on L9981 and NL9980 cells by MTT and Boyden chamber assays, respectively. Plumbagin showed significant inhibition in both cell lines by the mechanism of IL-6/STAT3 signaling pathway [32].

***In-vivo* Anticancer Activities:** MDA-MB-231S Arfp cells were injected intracardially into BALB/c nude mice to construct a breast cancer bone metastatic model. Plumbagin was injected in mice intraperitoneally. Non-invasive *in-vivo* monitoring, X-ray imaging, and histological staining were performed to investigate the effects of plumbagin on the invasion and migration of breast cancer cells *in-vivo*. *In-vivo* investigations demonstrated that plumbagin repressed the metastasis of breast cancer cells and diminished osteolytic bone metastases, just as the discharge of MMP-2 and MMP-9 by tumor cells at metastatic lesions [19].

Literature also showed the ethanolic extract of *Plumbago zeylanica* (EEPZ) after administering intra-peritoneal reduces the tumor volume in Ehrlich Ascites Carcinoma (EAC) control male Swiss albino mice shows favorable effects in terms of hematological parameters [13, 7].

In-vivo investigations proposed that plumbagin diminishes the tumor weight and volume with no symptoms in tried model creatures. Another energizing part of plumbagin is the capacity to resensitize the chemo and radioresistant malignant growth cells when utilized in the blend or alone. Nano epitome of plumbagin beats the poor water solvency and bioavailability snags, upgrading the pharmaceutical importance with better restorative adequacy [21].

Xu and Lu *et al*., (2010) reported the anticancer effect of plumbagin was investigated *in-vivo* using NB4 xenograft in NOD/SCID mice. The mitochondrial pathway engaged with plumbagin-initiated apoptosis. It was found that the age of ROS was a basic middle person dressed in plumbagin-actuated apoptosis, which would be repealed totally by cell reinforcement, NAC [13, 28].

Plumbagin has demonstrated inhibition of glioma genesis and tumor cell growth *via* the inactivation of FOXM1 in glioma cell xenografts mice model. Also, it has been reported as a potential down regulator of FOXM1 and could be useful in the treatment of malignant gliomas [33]. Plumbagin, is also reported for inhibition of malignant growth operator and development of ovarian disease cells through the hindrance of expansion as angiogenesis [34].

Anticancer Formulation Development Approaches: Stable plumbagin nanoparticles from *Plumbago zeylanica* root extract were explored as a potential natural drug against prostate cancer. Inhibitory effect of the nanoparticles on the migration properties of prostate cancer cells revealing its therapeutic potentials for prostate cancer. It is also reported that plumbagin nanoformulation was found to be superior to crude extract in terms of controlling the toxicity profile to the normal cells and in inducing dose-dependent toxicity for prostate cancer cells [35].

Bothiraja *et al*., (2013) investigated Phospholipid and Tween® 80 mixed micelles as injectable nanocarriers for the natural anticancer compound, plumbagin (PBG), with the aim to improve anticancer efficiency. PBG-loaded mixed micelles were fabricated by self-assembly, the composition being optimized using 3^2 factorial designs. The results were obtained as optimized mixed micelles were spherical and 46 nm in size. Zeta potential, drug loading, and encapsulation efficiency were 5.04 mV, 91.21 and 98.38%, respectively. Micelles demonstrated sustained release of PBG. Micelles caused a 2.1-fold enhancement *in-vitro* antitumor activity of PBG towards MCF-7 cells. Micelles proved safe for intravenous injection as PBG was stable at high pH; micelle size and encapsulation efficiency were retained upon dilution. The overall study concluded that the developed mixed micelles

proved potential nanocarriers for plumbagin in cancer chemotherapy [36].

Sunil Kumar Mandala Rayabandla *et al*., (2010) developed chitosan-based plumbagin microspheres to assess the tumor viability and fundamental lethality of plumbagin microspheres in contrast with free plumbagin. The streamlined definition had a mean molecule size of 106.35 µm, with embodiment effectiveness of 80.12%. Pharmaco-kinetic studies demonstrated a 22.2-overlay increment in end half-life of plumbagin from chitosan microspheres when contrasted with free plumbagin. The organization of plumbagin microspheres brought about a noteworthy tumor development hindrance and diminished fundamental harmfulness. These outcomes recommend that chitosan-based microspheres could be a promising methodology for plumbagin [37].

Issues in Development as Dosage Form: Despite the great therapeutic interest, PBG showed low oral bioavailability (39%) due to its high lipophilicity (log P = 3.04) and poor aqueous solubility (79.3 ± 1.7 µg/ml); factors considered as major challenges for design formulations to improve therapeutic efficacy [11]. Besides, a high/frequent dose is needed to achieve optimum therapeutic efficacy, which often causes severe side effects, including diarrhea, skin rashes, an increase in white blood cells, and neutrophil count [9]. To overcome these problems, several pharmaceutical carriers such as liposomes, microspheres, nanoparticles, and metal complexes have been investigated [12–15]. These approaches, although advantageous, seem to be complicated, expensive, and demonstrate low drug-loading (DL) capacities. They are unable to control drug release, increased hemolysis, and poor stability of plumbagin. This juncture demands a new carrier system that ensures sufficient solubility, stability, bioactivity, and biosafety of *Plumbago zeylanica* L. and plumbagin [38-43].

Also, a detailed investigation is needful in terms of dosage form design with a systematic formulation development approach by the design of the experiment, which gives a detailed analysis of material and process attributes.

CONCLUSION: Natural products have been well established as a rich source of nutritional as well as therapeutic potential [44]. Various drugs obtained from medicinal plants/natural resources have great advantages such as fewer side effects, easy availability, and cost-effectiveness so as to make them more desirable therapeutic agents [45]. Literature reveals the tremendous nutritional and therapeutic value of *Plumbago zeylanica* L. and plumbagin. Despite this fact, its pharmacological effects are limited because of its high lipophilicity, low bioavailability, and high toxicity. Some conventional formulations development approaches are reported for *Plumbago zeylanica* L. and plumbagin, but the study is limited in terms of targeted drug delivery system by systematic formulation development approach within detail characterization to improve its biopharmaceutical properties and therapeutic efficacy.

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