A Review on Anti-Cancerous Activity of a Bioactive Compound Plumbagin

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Abstract
Cancer is one of the major problems in both the developing and developed countries. Treatment of cancer using chemotherapy and radiotherapy induces several problems which include vomiting, nausea, unpleasant side effects, etc. In this context, there is a requirement of an alternative source of the drug to treat cancer. Herbal products that are derived from the plants have been used for the treatment of various cancers due to their non-toxic nature. Medicinal plants contain various phytochemicals which play an important role in elimination of different types of diseases. Plumbagin is one such important bioactive compound that has been investigated for its anticancer activity. It is present in the three different families i.e. Plumbaginaceae, Ebenceae and Droseraceae. Plumbagin possesses anticancer activity by the inactivation of Akt/NF-κB signaling pathway as well as inactivation of MMP-9 and VEGF pathways which are considered as important for the invasion, metastasis, and angiogenesis processes. This review provides an insight to the anticancer activity of plumbagin in various cancers such as breast, lung, colon, etc.

Keywords
Plumbagin; Breast Cancer; Lung Cancer; Colon Cancer

Introduction
Cancer is one of the leading cause of disease worldwide accounting for 12.7 million new cases every year and this number is expected to rise to 26 million by 2030 [1]. The main cause behind the increase cancer cases is change in lifestyle of population across the world. Jemal et al., [2] reported that breast cancer is the most prevalent cancer among females and lung cancer in case of males which accounts about 23% 17% of total cancer cases respectively. In developing countries, survival rate of cancer patient is very less due to the lack of limited facilities and proper diagnosis process. Cancer is a major challenge to the scientific world and there is a necessity to discover novel agents for the treatment of this disease, it could be possible with the use of naturally occurring compounds. Medicinal plants contains wide range of bioactive compounds which posses variety of therapeutic effect. In Ayurveda they have been utilized for the treatment of various diseases such as cancer, tumour, malaria, neurological disorders, etc. Several studies have been done on naturally occurring compounds which are known to possess cytotoxic effects and have the potential for destroy cancer cells [3]. The compounds isolated from plants are natural and have advantage over synthetic chemical compounds as they are readily available in the nature, since they are natural products so the problem of acquiring resistance against these compounds is minimized to a very great extent. Pharmaceutical research...
has done in countries like USA, Germany, France, Japan, etc. to enhance the herbal medicines quality for the cancer treatment. Some herb suppresses the growth of cancer by modulating the activity of specific enzymes and hormones and some protects body by enhancing detoxification function. Till now pharmaceutical companies screened more than 25000 plants for their potential as anti-cancer agents.

Plumbagin is one such important compound which possesses anti-cancer activity. Plumbagin possesses anti-cancer activity in both animal models as well as in cell cultures [4]. Plumbagin (5-hydroxy-2-methyl-1, 4-naphthoquinone- C_{11}H_{8}O_{3}) was first isolated in 1829 [5] and it was successfully synthesized through chemical process [6]. Plumbagin is a naphthoquinone and yellow crystals having melting point ranging 78-79°C. It is a simple molecule with double benzene ring structure. Colour, solubility and molecular weight of plumbagin were reported by Budavari et al.,[7]. It is soluble in chloroform, acetone, alcohol, benzene, and acetic acid and slightly soluble in hot water [7]. Plumbagin shows a spectrum with absorption bands at 212, 266, 410 and 423 nm [8]. Harborne [9] reported the λ max of plumbagin in ethanol is 220 or 226 nm in the UV range and 418 nm in the visible range (526nm). Amount of plumbagin synthesized in plants varies according to growth, flowering and age as well as its locality, conditions of soil and season of the year. Plumbagin content is high in the roots of older plants grown in dry soil [10]. Origin and distribution of plumbagin was obtained from the report on isolation and identification of plumbagin from Diospyros olen (Ebenaceae). While the original plant source of plumbagin, Diospyros, is indigenous to the old world it is still retained in related plants after a possible period of 350 million years [11]. India owns two process patents for the production of plumbagin [12, 13]. Emergence of natural anti-cancer agents requires more research and experimental work for the development of successful therapeutic compound to treat this disease. This review focuses on the anti-cancer potential of plumbagin and provides an insight to the research progress in the application plumbagin in cancer treatment, which may provide some reference for further research of plumbagin.

Plumbagin in Anti-Cancer Activity

Various reports state that plumbagin shows anti-cancer activity against various types of cancer cell lines. Santhakumari et al., [14] reported that plumbagin in low concentration inhibit cell mitosis and in higher concentrations exhibited radiomimetic, cytotoxic and nucleotoxic effects. Imlay and Fridovich [15] reported that plumbagin is toxic in nature as it generates superoxide anion reactive oxygen species which can damage various kinds of biomolecules. Shen et al., [16] reported that plumbagin inhibits the platelet aggregation in in vitro and in vivo studies by suppressing the binding of activated platelets to neutrophils and also increased intact neutrophils inhibition on platelet reactivity. Plumbagin possesses anticancer activity by the inactivation of Akt/ NF-κB signaling pathway as well as inactivation of MMP-9 and VEGF pathways which are considered as important for the invasion, metastasis, and angiogenesis processes [17]. The anti-cancer activity of plumbagin have been reported in different cancer models such as ovarian [18], lung [19], prostate [20], cervical [21], melanoma [22] and breast cancer [23]. Plumbagin possess selectivity towards cancer cells and does not damage normal epithelial, lung and cervical cells which is a desirable attribute [24, 17, 25, 26].

a) Role of Plumbagin in Breast Cancer

A study reported that plumbagin showed inhibition of breast cancer cells growth (Her2/neu) without affecting the normal breast cells and it also induces apoptosis by inactivating the Bel 2 and DNA binding activity of NF-kB [26]. Manu et al., [27] investigated that plumbagin down regulates CXCR4 expression in breast cancer cells and declination in the CXCR4 expression was not specific to cell type as inhibition also occurred in gastric, renal, oral, lung, and hepatocellular tumor cell lines. Kawiak and Domachowska, [28] reported that plumbagin could suppress breast cancer cell (MDA-MB-231SArfp) invasion and migration and down regulates mRNA expression of MMP-2,MMP-9, IL-1α, and TGF-β, it also inhibited the activation of STAT3 signaling in the cells. Domachowska [28] reported that plumbagin suppress the invasion of HER 2 over-expressing breast cancer cells and inhibits the cell invasion due to the ability of plumbagin to inhibit NF-κB transcriptional activity. Sakumranqit et al., [29] investigated the effect of plumbagin on growth of human endocrine resistant breast cancer cell and found that at micro-molar concentration plumbagin exhibits cytotoxic effect and it was also found that combination of plumbagin and tamoxifen at fixed low concentration showed increase in inhibition of growth in endocrine resistant cells. In addition plumbagin also suppressed
mesenchymal biomarker expression which governs the epithelial mesenchymal transition and result in attenuated metastatic capabilities. Sameni and Hande [30] reported that in human breast cancer cells plumbagin induces cytotoxicity and arrest cell cycle, cell death and DNA damage which lead to apoptosis.

b) Role of Plumbagin in Lung Cancer

Hsu et al., [24] reported that plumbagin possesses effective cell growth inhibition by inducing the cancer cells to undergo G2 phase in human lung cancer A549 cells, it enhanced the levels of inactivated Cdc25C and Cdc2. Plumbagin also triggered the mitochondrial apoptotic pathway. Activation of Jun NH2-terminal kinase by plumbagin increased the p53 gene stability by decreasing the p53 and MDM2 interaction. Gomathinayagam et al., [19] studied the role of plumbagin in two lung cancer cell line (H460 and H549) and found that plumbagin inhibits the H460 cell line growth as compared to the A549 cells where it down regulated the EGFR/Neu expression in H460 cells. Plumbagin also unregulated the p53 and p21 expression which caused the cell cycle arrest in G2 phase by down regulating the G2 regulatory proteins and it also activate JNK/p38 signalling which lead to caspase-3 activation and finally apoptosis induction. Xu et al., [31] reported that lung cancer cells proliferation was inhibited by plumbagin in a dose dependent manner and the concentration of plumbagin induce apoptosis in all the three cell lines (A549, H292 and H460). Plumbagin increases the level of intracellular reactive oxygen species and inhibits NK-kB activation. Rattarom et al., [32] reported that ethanolic extract of Benjakul which is a thai traditional herbal preparation comprise of five different plants:–, Piper chaba, Piper sarmentosum Plumbago indica Piper interrumptum, and Zingiber officinale showed cytotoxicity against human lung cancer cell line NCI-HI 688 where plumbagin exhibits maximum cytotoxic activity and IC50 value was 1.41±0.01.

c) Role of Plumbagin in Colon Cancer

A study reported the apoptotic activity of plumbagin in human colon cancer cell lines HCT29 and HCT15 [33]. In this study it was found that the IC 50 of plumbagin for HCT15 was 22.5mM and for HCT29 was 62.5 mM. Further study has been conducted to observed the impact of different concentration of plumbagin (i.e 15mM and 30mM in case of HCT15 and 50mM and 75mM in case of HCT29) and it was found that apoptosis occur with decreased level of pEGFR, pAkt, PCNA, pGsk-3b and Cyclin D1 in case of 15mM and 30mM plumbagin treated HCT15 and 75mM plumbagin treated HCT29 cell lines which suggested that plumbagin induces apoptosis in both the cell lines [33]. Lai et al., [34] reported that plumbagin suppressed tumour growth and tumour angiogenesis in human colon carcinoma mouse models and it blocked the Ras/Rac/cofilin and Ras/MEK signaling pathways by VEGF receptor 2 in human umbilical vein endothelial cells. Eldhose et al., [35] reported that low micro-molar concentration of plumbagin in HCT116 cells results in cell cycle arrest at G1 phase and increases reactive oxygen species production and this shows that plumbagin can be used for the treatment of colon cancer.

d) Role of Plumbagin in Prostate Cancer

Powolny and Singh [20] reported that plumbagin decreased human prostate cancer cells (PC-3, C4-2, and LNCaP) viability. It decreased the cell viability which is correlated with the apoptosis induction which was followed by generation of reactive oxygen species and decline of intracellular glutathione levels and it also altered the gene expression which is responsible for the reactive oxygen species metabolism, including superoxide dismutase 2. Another study reported the effect of plumbagin on apoptosis and autophagy in human prostate cancer cell lines PC-3 and DU145 [36]. They found that plumbagin had potential to pro-autophagic and pro-apoptotic effect on both the cell lines. Plumbagin induced the apoptosis and autophagy in concentration and time dependent manners. It also inhibits phosphatidylinositol-3-kinase and p38 mitogen activated protein kinase pathways and activates the 5-AMP dependent kinase pathway which activates the 5-AMP dependent kinase which indicates that plumbagin promotes autophagy and apoptosis in prostate cancer cells. Reshma et al., [29] investigated the effect of plumbagin on BRCA1/2 silenced prostate cancer and the study reveals that DU 145 and PC-3 cells were sensitive to plumbagin and induced mitochondrial potential loss, DNA fragmentation and morphological changes. Gene expression profiling after treatment with plumbagin in BCRA1/2 silenced cells revealed that plumbagin showed effective role in tumor suppression in BRCA defective cancer. This study suggested that plumbagin has an anti-tumor property and holds promise for the novel therapeutic development against BRCA mutated cancers.

e) Role of Plumbagin in Other Cancers

Plumbagin arrests cell cycle and induces apoptosis
through reactive oxygen species in human melanoma A375.S2 cells, cell cycle arrest due to the increased level of p21 and reduced level of cyclin B1, cyclin A, Cdc2 and Cdc25C [22].

Gowda et al., [37] reported that plumbagin destroys the the melanoma cells by STAT3 and COX-2 pathways inhibition which are constitutively activated in 70% of melanomas, it also retarded the vascular development of tumor and decreases the level of cyclins on which melanoma cells are dependent for their survival. Okeyo [38] reported the tumour inhibitory effects against Ehrlich ascites carcinoma in mice were studied and low doses of plumbagin have significant tumour inhibitory effects. This leads for development of drugs using plumbagin, especially for cancers. Plumbagin also shows anticancer activity in human osteosarcoma (MG-63) cells by S-phase cell cycle inhibition and by down regulating the cyclin A and CDK2 protein levels. It also triggered DNA damage in MG-63 cells and down regulated the c-myc protein expression [39]. Li et al., [40] reported that plumbagin suppressed the BAX, BCL-2, pro-caspase-3 expression and cleaved caspase-3 in gastric cancer cells. Plumbagin inhibits the apoptosis in human gastric cancer cells that may be due to its ability to suppress the STAT3 and Akt phosphorylation.

Conclusion

Medicinal plants are the prime source of effective conventional drugs for the treatment of different forms of cancers. Medicines from plant origin have been used for the past decade. They have provided opportunities to the researchers for future research and development in this field. In modern cancer treatment, chemotherapy is an important option, plant drive agents used in chemotherapy provides less side effects to the patients as compared to the chemical agents. To cure the cancer there is a need to find a better way to treat this disease by finding anti-cancer compounds from herbal sources. Compounds isolated from plants are natural and have advantage over synthetic chemical compounds as they are readily available in the nature, since they are natural products so the problem of acquiring resistance against these compounds is minimized to a very great extent. Medicinal plants synthesize variety of bioactive compounds which poses anticancer activity. They inhibit the growth of cancer by modulating the activity of specific enzymes and hormones and some protects body by enhancing detoxification function. Plumbagin is one of the important compounds which show potential towards treatment of several cancers like breast, lung, colon, prostate, liver, etc. in cell culture as well as in animal models. Due to the importance of plumbagin in anti-cancer activity there is need for large production of it. In-vitro cultures provide an alternative for the large production of this compound. Hairy root and cell suspension cultures were utilized by several researches for this purpose and they have found increases production of plumbagin as compared to the normal conditions. For the development of new drug, plumbagin need to be subjected to clinical trials to figure out its effectiveness and safety. In this review, an effort has been made to summarise the role of plumbagin in different cancers and their mode of action. Naturally drive product offers great opportunity to evaluate new compounds as potential anticancer agents. There is no such report available which shows the use of drug containing plumbagin for the treatment of cancer. More till now the investigations which were done in plumbagin for its anticancer activity are on laboratory scale. So there is a requirement of further investigation to obtain a successful drug available in the market.

References

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