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Therapeutic Potential of Plumbagin: Redox Modulation and Pathway Inhibition in Cancer and Neuroinflammation

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Abstract : Aim of this research review is to explore anti-microbial and anti-inflammatory properties of Plumbagin which is a naturally occurring secondary metabolite which is derived from Naphthoquinone which resembles vitamin-K in chemical structure and to observe common challenges currently being faced with plumbagin which ranges from low bio-availibilty to moderate toxicity. In current day Plumbagin is the new red hot frontier in fields of pharmaceutics as latest research has shown its extensive therapeutic activities, including anticancer, anti-inflammatory, antimicrobial, activities and PLB exerts potent antitumor activity by inducing reactive oxygen species (ROS), triggering cell cycle arrest, apoptosis, and autophagy across multiple cancer types such as breast, brain, and hepatocellular carcinoma.

Keywords: **Plumbagin, Naphthoquinone, Anticancer activity ,anti-inflammatory Reactive oxygen species (ROS)**

INTRODUCTION

Plumbagin is a naturally potent bioactive naphthoquinone primarily found in the Plumbaginaceae family, and it was mainly investigated for its anticancer, antioxidant, anti-inflammatory, antimicrobial, antiviral properties.1 Naphthoquinone is structurally similar to vitamin K and shows antioxidant properties. Plumbagin shows short half-life and poor water solubility (79mg/ml), which lowers its bioavailability (39%) when it is administered orally. It exhibits moderate toxicity, need for strict dosage and advanced delivery methods for careful dose optimization for therapeutic use of plumbagin.2 It shows redox balance in microbial system, so it also known to enhance superoxide generation via diaphorase-mediated reduction, disrupting microbial oxidative homeostasis and contributing to its antimicrobial effects.4 Plumbagin (PLB) triggers its anticancer effects by activating reactive oxygen species (ROS), causing cell cycle arrest, and triggering apoptotic signaling. In Lewis lung carcinoma (LLC) cells, PLB inhibits Thioredoxin Reductase (TrxR) and Glutathione Reductase (GR), leading to increased ROS levels and apoptosis. These mechanisms highlight its potential in targeting redox-regulated pathways in cancer therapy.3 Recent studies reveal that plumbagin (PLB) inhibits cancer progression across various cancer cell lines by targeting critical signaling pathways. Key pathways affected include the Akt/NF-κB signaling pathway, which regulates cell survival and inflammation, and the MMP-9 pathway, which is crucial for tumor invasion and metastasis.3.

Researchers have highlighted the anti-inflammatory effects of plumbagin (PLB) in neurodegenerative diseases like Parkinson's disease (PD). Studies have shown that PLB provides neuroprotection in PD mouse models by suppressing inflammation through the TLR/NF-κB signaling pathway. This inhibition results in reduced expression of pro-inflammatory markers, including IL-1β, TNF-α, and IL-6 mRNA levels.6 Apart from its applications in cancer treatment, plumbagin (PLB) has demonstrated notable anti-viral properties against RNA viruses, including Hepatitis C Virus (HCV) and SARS-CoV-2. This effectiveness is attributed to PLB's capacity to induce ROS-mediated oxidative stress, which specifically targets the highly susceptible single-stranded RNA genomes of

these viruses.5This review explores the antitumor anti-inflammatory, cytoprotective, and anti-senescent properties of plumbagin (PB), offering a clear and comprehensive overview.

Figure-1

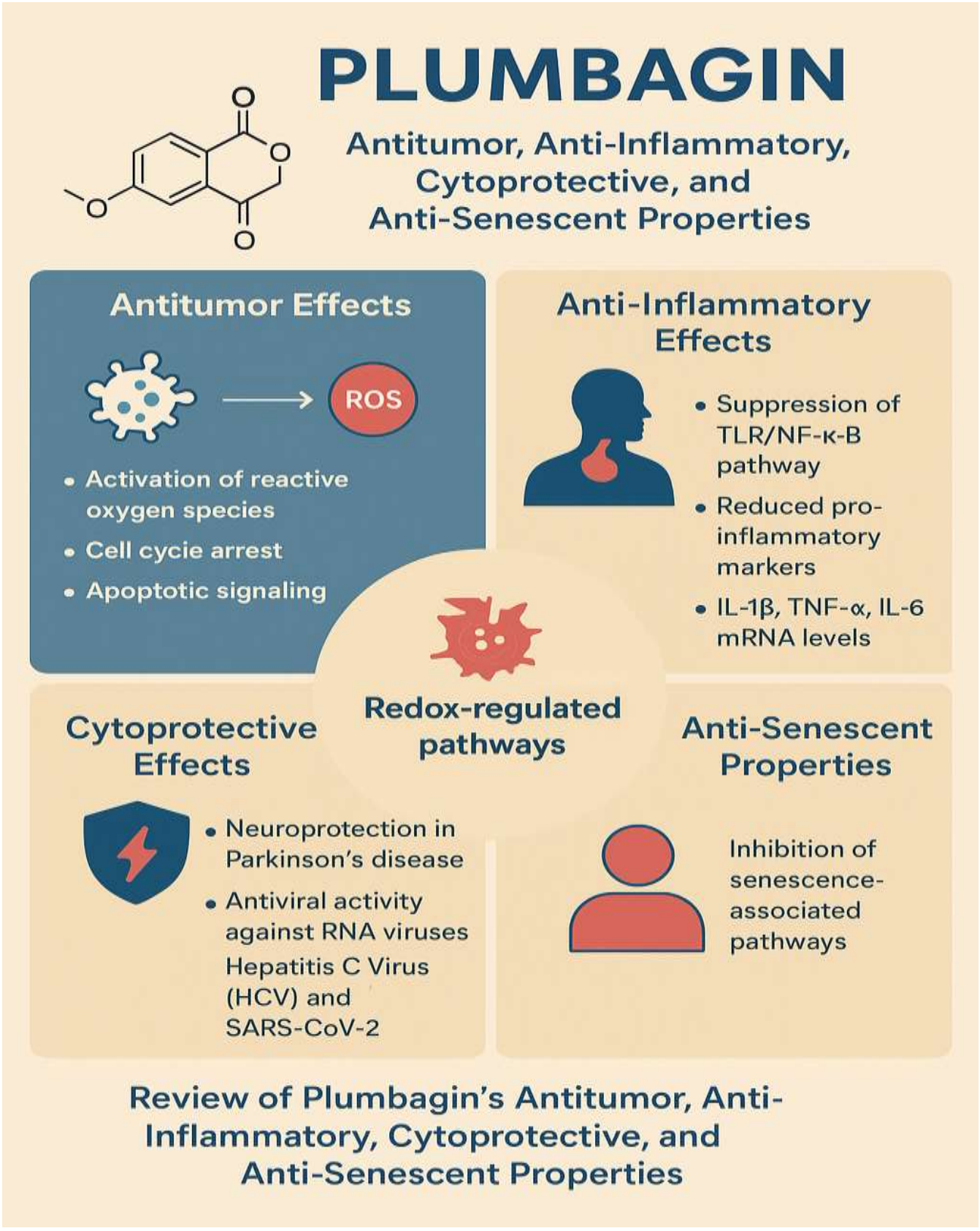


Figure-1

Antitumor Activity

Cancer is the primary cause of death in economically developed countries and the second leading cause of death in developing nations.23 Cancer is a rapidly progressing group of diseases characterized by uncontrolled cell growth, often culminating in fatal outcomes. Common types of cancer in men include colorectal, liver, lung, prostate, and stomach cancers, while in women, breast, cervical, colorectal, lung, stomach, and uterine cancers are prevalent. Treatment typically involves chemotherapy, radiotherapy, or surgery, applied either individually or in combination. Among these, chemotherapy is considered the most effective; however, it is not without limitations. Current chemotherapeutic drugs fail to provide a permanent cure and are associated with significant drawbacks, including severe side effects, high costs, and the development of drug resistance.8

This highlights the urgent need for novel, potent anti-cancer agents with minimal adverse effects. Natural compounds offer promising alternatives due to their high therapeutic efficacy, lower toxicity, and reduced side effects on healthy cells. This review explores plumbagin, a natural naphthoquinone derivative, recognized for its strong therapeutic potential, pharmacological importance, and minimal side effects, positioning it as a promising candidate in cancer treatment.**7**

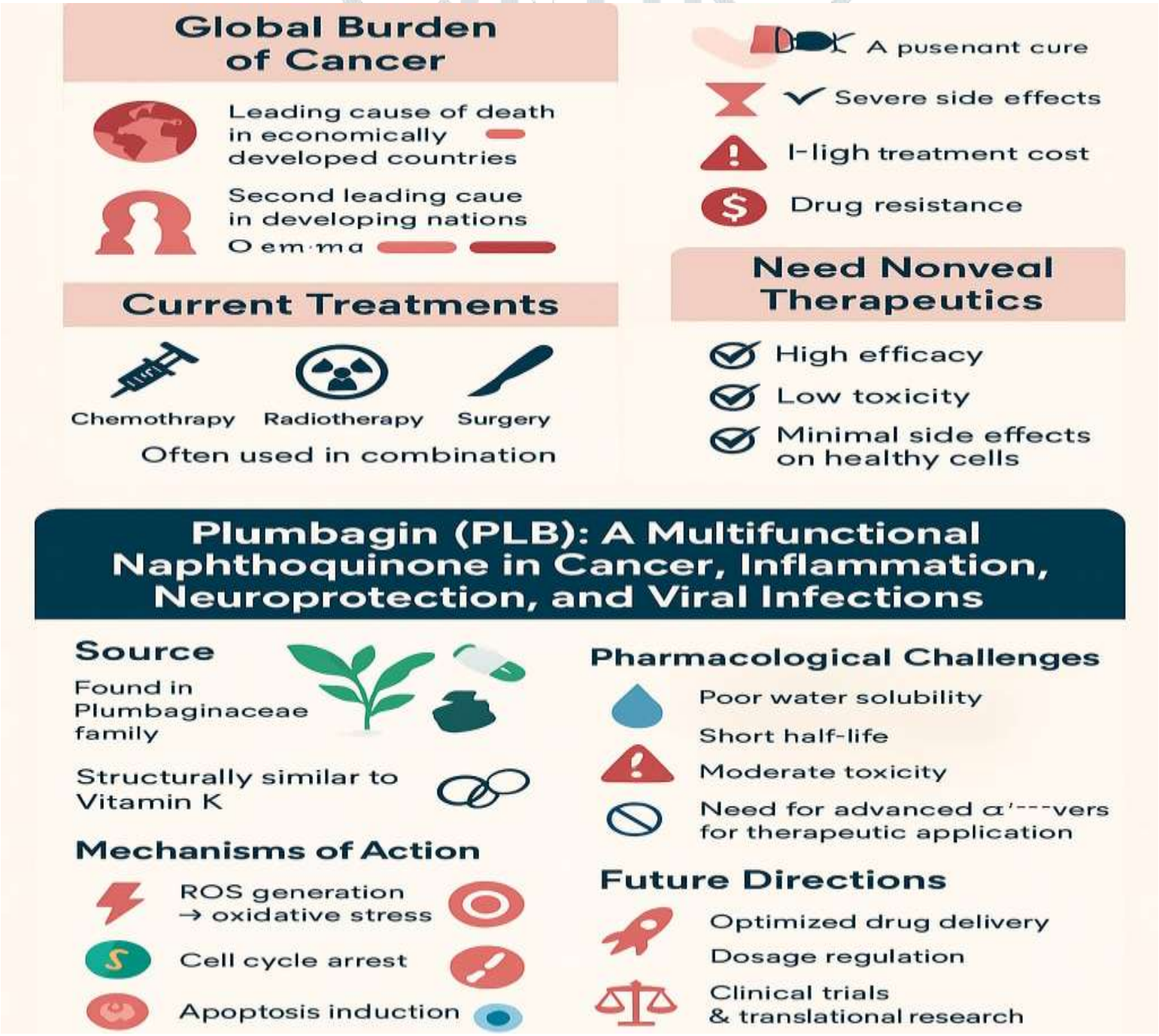


Figure 2

Antibreast Tumor Activity

Plumbagin (PLB) shown significant anti-breast cancer activity by inducing mechanisms such as cell cycle arrest**,** autophagy, and apoptosis, making it a promising candidate for breast cancer therapy. Plumbagin has been shown to induce cell cycle arrest at the G2/M phase and promote autophagy by inhibiting the AKT/mammalian target of rapamycin (mTOR) pathway. Additionally, it inactivates NF-κB and Bcl-2, thereby triggering apoptosis in breast cancer cells.9 In endocrine-resistant breast cancer cells (MCF-7/LCC2 and MCF-7/LCC9), PLB effectively inhibited growth, invasion, and metastasis by downregulating Snail and modulating the expression of key epithelial-mesenchymal transition (EMT) markers.10 In endocrine-resistant breast cancer cells (MCF-7/LCC2 and MCF-7/LCC9), PLB effectively inhibited growth, invasion, and metastasis by downregulating Snail and modulating the expression of key epithelial-mesenchymal transition (EMT) markers. 11

The nuclear factor kappa-B (NF-κB) is often overexpressed in a subset of HER2-positive breast cancers, with its upregulation linked to the metastatic potential of HER2-overexpressing tumors. Kawiak et al. [12] demonstrated that PLB effectively inhibited the invasion of HER2-overexpressing breast cancer cells, BT474 and SKBR3, by suppressing IKKα-mediated NF-κB activation and downregulating NF-κB-regulated MMP-9 expression. 12 PLB exhibited distinct anticancer effects on racially diverse triple-negative breast cancer cells, including MDA-MB-231 (MM-231) and MDA-MB-468 (MM-468), which represent Caucasian Americans and African Americans, respectively. These effects were mediated through the NF-κB pathway and the modulation of CCL2 release. 13,10 Plumbagin is a ROS inducer.3 The generation of intracellular ROS can induce apoptosis through the activation of the p53-dependent pathway.14 As a ROS inducer, PLB triggered apoptosis in defective BRCA1-mutant triple-negative breast cancer cells and mouse models through ROS-mediated DNA double-strand breaks (DSBs). 15 Additionally, PLB induced apoptosis in MCF-7 cells by increasing ROS production and causing a loss of mitochondrial membrane potential.16

Plumbagin influenced the expression of five additional genes in MM-231 cells, including BCL2A1, ICAM1, IKBKE, IL1β, and LTA. These findings suggest that the quinone compound PL has potential as a novel cancer therapeutic agent.13

TABLE-1

Mechanism / Target	Cell Lines / Models	Effects
Cell Cycle Arrest & Autophagy	**Breast cancer cells**	**Arrest at G2/M phase; Autophagy via AKT/mTOR inhibition**
Apoptosis via NF-κB & Bcl-2	**Breast cancer cells**	**NF-κB inactivation; Bcl-2 downregulation → apoptosis**
Endocrine-resistant Breast Cancer	**MCF-7/LCC2, MCF-7/LCC9**	**Inhibits growth, invasion, metastasis; Snail downregulation; EMT modulation**
HER2-positive Breast Cancer	**BT474, SKBR3**	**Invasion inhibition; Suppresses IKKα-mediated NF-κB activation; ↓ MMP-9**
Triple-Negative Breast Cancer (TNBC)	**MDA-MB-231 (Caucasian), MDA-MB-468 (African American), BRCA1-mutant TNBC**	**NF-κB modulation; CCL2 suppression; ROS induction → p53 pathway apoptosis; ROS-mediated DNA DSBs**
Mitochondrial Dysfunction	**MCF-7**	**↑ ROS; Loss of mitochondrial membrane potential → apoptosis**
Gene Expression Modulation	**MDA-MB-231**	**Altered genes: BCL2A1, ICAM1, IKBKE, IL1β, LTA**

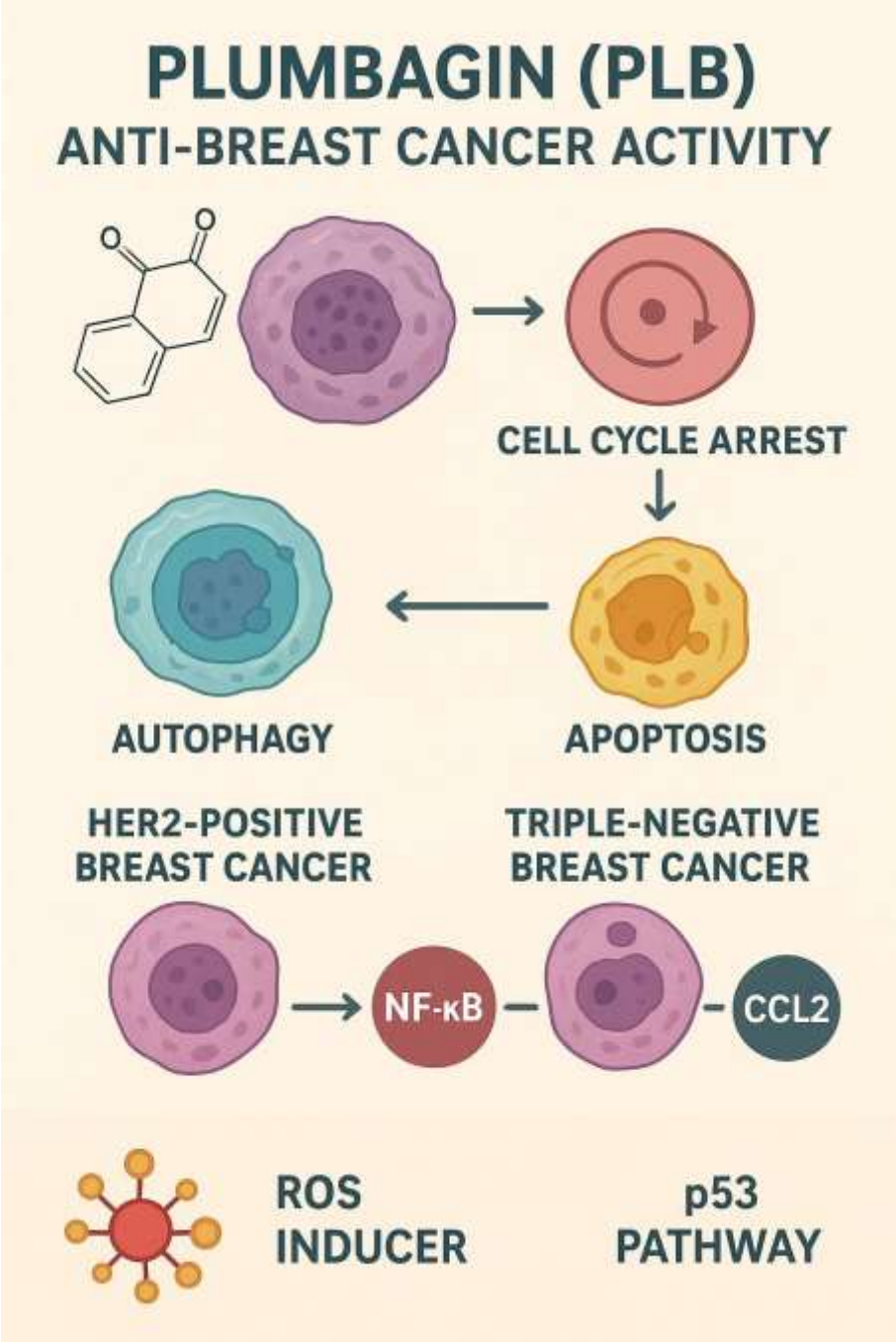

PLUMBAGIN (PLB)
ANTI-BREAST CANCER ACTIVITY
CELL CYCLE ARREST
AUTOPHAGY
APOPTOSIS
HER2-POSITIVE BREAST CANCER
TRIPLE-NEGATIVE BREAST CANCER
NF-κB
CCL2
ROS INDUCER
p53 PATHWAY

FIGURE-3

Mechanism / Target	Cell Lines / Models	Effects
Apoptosis via p53 & ROS	Various cancer cells	Upregulates p53, alters Bax/Bcl-2 ratio, ↑ ROS, activates mitochondrial pathway (caspase-3).
Telomerase Inhibition	Cancer cells (general)	Inhibits telomerase → induces cancer cell death.
DNA Damage & Cell Cycle Arrest	Glioblastoma multiforme (A172, KNS60, U251MG (KO)); Medulloblastoma (ONS76)	DNA damage; G2/M phase arrest; apoptosis; suppressed colony formation.
Gene/Protein Modulation	Glioblastoma & medulloblastoma cells	↑ E2F1 & TNFRSF1A; ↓ MDM2, cyclin B1, surviving, BCL2; Caspase-3/7 activation.
FOXM1 Suppression	Glioma cells	↓ FOXM1 (mRNA & protein); inhibits proliferation, migration, invasion; apoptosis induction.
Redox Pathway Modulation	Glioma & other models	Inhibits NADPH oxidase 4 (NOX4); alters redox signaling.
Neuroprotection	Rat cerebral infarction-reperfusion model	Protects neurons by suppressing apoptosis; inhibits NF-κB activation.

Antitrain Tumor Activity:

TABLE-2

The anticancer activity of plumbagin is attributed to its multifaceted effects on various cellular processes. It induces apoptosis by upregulating p53 expression, altering the Bax/Bcl-2 ratio, generating reactive oxygen species (ROS), and activating the mitochondrial pathway through caspase 3 activation.17 Some researchers have discovered that inhibiting telomerase can lead to the death of human cancer cells, as telomerase is abnormally expressed in cancer cells compared to normal somatic cells.18

PLB demonstrated significant anticancer effects on brain tumor cells, including human glioblastoma multiforme cells (A172, KNS60, U251MG (KO)) and medulloblastoma cells (ONS76), by inducing DNA damage, cell cycle arrest, and apoptosis. It also suppressed colony-forming ability. These effects were linked to the upregulation of E2F1 and TNFRSF1A, downregulation of specific E2F1 genes, and reduced expression of MDM2, cyclin B1, surviving, and BCL2 proteins. Additionally, PLB treatment resulted in elevated caspase-3/7 activity, further confirming its apoptotic mechanism.17

The oncogenic transcription factor Forehead Box M1 (FOXM1) has recently attracted significant attention as a potential target for glioma prevention and therapeutic intervention. However, information on FOXM1 inhibitors remains limited. This study demonstrates that plumbagin effectively suppresses glioma cell proliferation, migration, and invasion while inducing apoptosis. 19 Cell cycle analysis revealed that plumbagin causes G2/M phase arrest.20 Notably, plumbagin was found to reduce FOXM1 expression at both the mRNA and protein levels, highlighting its potential as a therapeutic agent for glioma. 19 Researchers also studied have plumbagin plays a role in inhibiting NADPH oxidase 4 (NOX4) and modulating redox signaling pathways 21 and protective effects against cerebral infarction-reperfusion-induced neurogenic injury in rats by suppressing apoptosis and inhibiting NF-κB activation.22

Antihepatoma Activity:

Hepatocellular carcinoma (HCC) ranks as the fifth most prevalent malignant tumor globally and stands as the third leading cause of cancer-related mortality.[15] Plumbagin exhibits antiproliferative and pro-apoptotic activities, suppresses invasion and metastasis, and enhances chemosensitivity in cancer cells.[16] Plumbagin has been observed to arrest cells in the G2/M phase of the cell cycle and increase reactive oxygen species (ROS) levels. It inhibits the phosphatidylinositol 3-kinase (PI3K)/Akt/mTOR signaling pathway by reducing the phosphorylation of Akt and mTOR. Furthermore, plumbagin induces autophagy in a dose-dependent manner, highlighting its potential as an anticancer agent.[16,17]

PLB suppressed the proliferation of the SMMC-7721 cell line in a dose- and time-dependent manner. It enhanced the expression levels of autophagy-related genes and proteins, including LC3, Beclin1, Atg7, and Atg5, which are linked to tumor apoptosis and autophagy in HCC cells. Additionally, PLB facilitated apoptosis and autophagic cell death in these cells.[17] In addition, PLB induced apoptosis in human HCC SMMC-7721 cells undergoing epithelial-mesenchymal transition by elevating caspase-3 protein levels and promoting vimentin cleavage. Plumbagin shown its cytotoxic against the HEPA-3B hepatoma cell line, inhibiting liver cancer cell migration and invasion by downregulating MMP-2 and uPA. [18]

Therefore, PLB could inhibit proliferation and induce apoptosis in HCC by suppressing the SIVA/mTOR signaling pathway.[18] SIVA (Skeletal Inhibitory V-type ATPase-associated protein) an apoptosis regulator protein that binds to CD27 and regulates cell death, has been reported to play a crucial role in activating mTOR signaling and contributing to tumorigenesis. Inhibiting SIVA expression can induce apoptosis and autophagy.[18,19]

2 Anti-inflammatory Activity of plumbagin

Inflammation is characterized by an imbalance between reactive oxygen species (ROS), reactive nitrogen species (RNS), and pro-inflammatory cytokines. The equilibrium between pro-oxidant molecules (ROS/RNS) and antioxidant defence mechanisms including catalase (CAT), glutathione peroxidase (GPx), and superoxide dismutase (SOD) plays a crucial role in maintaining cellular redox homeostasis. This balance is closely linked to cellular metabolism and respiration.30 ROS can directly activate signaling pathways, particularly the NF-κB pathway, driving the transcription of pro-inflammatory genes, including cytokines and chemokines, they lead to inflammation.

Plumbagin, known for its anti-inflammatory and growth-modulatory effects, also exhibits antibacterial activity by inducing the generation of pro-oxidants.29 PLB downregulated pro-inflammatory markers, highlighting its potential as a therapeutic agent for neurodegenerative diseases.

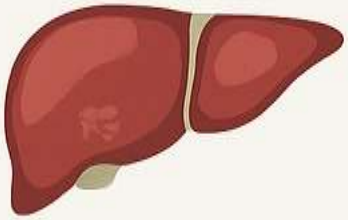
In H_2O_2-induced chondrocytes, PLB effectively mitigated oxidative stress, regulated redox balance, modulated inflammation-associated transcription factors, and strengthened antioxidant defences.31 Plumbagin can suppress TNF-α levels by activating nuclear factor (erythroid-derived 2)-like 2 (Nrf-2), thereby alleviating oxidative stress and inflammation in H_2O_2-stimulated chondrocytes.[19]

Plumbagin also suppresses the secretion of IL-1 and IL-6 in microglial cells following lipopolysaccharide (LPS) stimulation.32 IL-1 activates NF-κB and MAPK pathways, leading to the production of other inflammatory mediators which plays a key role in arthritis, neuroinflammation, and cancer.34 IL-6 drives the JAK/STAT3 signaling pathway and contributes to autoimmune diseases, cardiovascular disorders, and cancer progression.35

Plumbagin has been shown to inhibit HMGB1 release, reducing TLR4 and RAGE-mediated inflammatory signaling. By modulating these pathways, plumbagin may help suppress oxidative stress, reduce cytokine production, and alleviate chronic inflammation in diseases such as arthritis, neurodegenerative disorders, and cancer.[19,20]

ANTI-CANCER AND ANTI-INFLAMMATORY ACTIVITY OF PLUMBAGIN

ANTI-CANCER ACTIV



Hepatocellular carcinoma (HCC) is the fifth most common malignant tumor and the third leading cause of cancer mortality worldwide

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Plumbagin

↓

Inhibits proliferation
Induces apoptosis
Suppresses invasion and metastasis

↓

Increases chemosensitivity

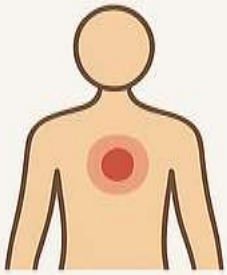
↓

Arrests cells in the G2/M phase

Increases reactive oxygen species (ROS)

Inhibits PI3K/Akt/mTOR signaling pathway

ANTI-INFLAMMATORY ACTIVITY



Inflammation is characterized by an imbalance between reactive oxygen species (ROS). reactive nitrogen species (RNS), and pro-inflammatory cytokines

↓

Plumbagin

↓

Reduces pro-inflammatory cytokines
Mitigates oxidative stress
Regulates redox balance
Modulates inflammation-associated transcription factors

↓

Suppresses secetion of IL-1 and IL-6

Inhibits HMGB1 release

Conclusion:

Plumbagin (PLB), a natural naphthoquinone, exhibits diverse pharmacological activities including anticancer, anti-inflammatory, antimicrobial, and antiviral effects. Its therapeutic action is largely attributed to modulation of redox balance, induction of apoptosis and autophagy, and regulation of key signaling pathways such as PI3K/Akt/mTOR, NF-κB, and MAPK. PLB has shown strong antitumor potential in breast, liver, and brain cancers by suppressing proliferation, invasion, and metastasis while enhancing chemosensitivity. In addition, it demonstrates anti-inflammatory benefits by downregulating cytokines (IL-1β, TNF-α, IL-6) and inhibiting NF-κB signaling, as well as antiviral activity against RNA viruses like HCV and SARS-CoV-2.

Despite these promising effects, clinical application of PLB is limited due to its poor solubility, low bioavailability, and dose-related toxicity. Future advances in nanoformulations and drug delivery approaches are essential to overcome these barriers. Overall, PLB holds significant promise as a natural therapeutic candidate for cancer, neurodegenerative, inflammatory, and viral diseases.

References:

1. Roy, A. (2021). Plumbagin: a potential anti-cancer compound. Mini reviews in medicinal chemistry, 21(6), 731-737.
2. Petrocelli, G., Marrazzo, P., Bonsi, L., Facchin, F., Alviano, F., & Canaider, S. (2023). Plumbagin, a natural compound with several biological effects and anti-inflammatory properties. Life, 13(6), 1303.
3. Sharma, B., Dhiman, C., Hasan, G. M., Shamsi, A., & Hassan, M. I. (2024). Pharmacological features and therapeutic implications of plumbagin in cancer and metabolic disorders: A narrative review. Nutrients, 16(17), 3033.
4. Nadhan, R., Patra, D., Krishnan, N., Rajan, A., Gopala, S., Ravi, D., & Srinivas, P. (2021). Perspectives on mechanistic implications of ROS inducers for targeting viral infections. *European journal of pharmacology*, *890*, 173621.
5. Nadhan, R., Patra, D., Krishnan, N., Rajan, A., Gopala, S., Ravi, D., & Srinivas, P. (2021). Perspectives on mechanistic implications of ROS inducers for targeting viral infections. *European journal of pharmacology*, *890*, 173621.
6. Wang, T., Wu, F., Jin, Z., Zhai, Z., Wang, Y., Tu, B., ... & Tang, T. (2014). Plumbagin inhibits LPS-induced inflammation through the inactivation of the nuclear factor-kappa B and mitogen activated protein kinase signaling pathways in RAW 264.7 cells. *Food and chemical toxicology*, *64*, 177-183.
7. Tripathi, S. K., Panda, M., & Biswal, B. K. (2019). Emerging role of plumbagin: Cytotoxic potential and pharmaceutical relevance towards cancer therapy. *Food and Chemical Toxicology*, *125*, 566-582.
8. Urruticoechea, A., Alemany, R., Balart, J., Villanueva, A., Vinals, F., & Capella, G. (2010). Recent advances in cancer therapy: an overview. *Current pharmaceutical design*, *16*(1), 3-10.
9. Sameni, S., & Hande, M. P. (2016). Plumbagin triggers DNA damage response, telomere dysfunction and genome instability of human breast cancer cells. Biomedicine & Pharmacotherapy, 82, 256-268.
10. Yin, Z., Zhang, J., Chen, L., Guo, Q., Yang, B., Zhang, W., & Kang, W. (2020). Anticancer effects and mechanisms of action of plumbagin: review of research advances. *BioMed Research International*, *2020*(1), 6940953.
11. Sakunrangsit, N., Kalpongnukul, N., Pisitkun, T., & Ketchart, W. (2016). Plumbagin enhances tamoxifen sensitivity and inhibits tumor invasion in endocrine resistant breast cancer through EMT regulation. *Phytotherapy Research*, *30*(12), 1968-1977.
12. PLOS ONE Editors. (2019). Retraction: Plumbagin Suppresses the Invasion of HER2-Overexpressing Breast Cancer Cells through Inhibition of IKKα-Mediated NF-κB Activation.
13. De, U., Son, J. Y., Jeon, Y., Ha, S. Y., Park, Y. J., Yoon, S., ... & Kim, H. S. (2019). Plumbagin from a tropical pitcher plant (Nepenthes alata Blanco) induces apoptotic cell death via a p53-dependent pathway in MCF-7 human breast cancer cells. *Food and Chemical Toxicology*, *123*, 492-500.
14. Somasundaram, V., Hemalatha, S. K., Pal, K., Sinha, S., Nair, A. S., Mukhopadhyay, D., & Srinivas, P. (2016). Selective mode of action of plumbagin through BRCA1 deficient breast cancer stem cells. *BMC cancer*, *16*(1), 336.
15. Khaw, A. K., Hande, M. P., Kalthur, G., & Hande, M. P. (2013). Curcumin inhibits telomerase and induces telomere shortening and apoptosis in brain tumour cells. *Journal of cellular biochemistry*, *114*(6), 1257-1270.
16. Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R. L., Torre, L. A., & Jemal, A. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: a cancer journal for clinicians*, *68*(6), 394-424.
17. Hwang, G. H., Ryu, J. M., Jeon, Y. J., Choi, J., Han, H. J., Lee, Y. M., ... & Lee, M. Y. (2015). The role of thioredoxin reductase and glutathione reductase in plumbagin-induced, reactive oxygen species-mediated apoptosis in cancer cell lines. *European journal of pharmacology*, *765*, 384-393.
18. Van Nostrand, J. L., Brisac, A., Mello, S. S., Jacobs, S. B., Luong, R., & Attardi, L. D. (2015). The p53 target gene SIVA enables non–small cell lung cancer development. *Cancer discovery*, *5*(6), 622-635.
19. Checker, R., Sharma, D., Sandur, S. K., Subrahmanyam, G., Krishnan, S., Poduval, T. B., & Sainis, K. B. (2010). Plumbagin inhibits proliferative and inflammatory responses of T cells independent of ROS generation but by modulating intracellular thiols. *Journal of Cellular Biochemistry*, *110*(5), 1082-1093.
20. Haddad, J. J., & Harb, H. L. (2005). l-γ-Glutamyl-l-cysteinyl-glycine (glutathione; GSH) and GSH-related enzymes in the regulation of pro-and anti-inflammatory cytokines: a signaling transcriptional scenario for redox (y) immunologic sensor (s)?. *Molecular immunology*, *42*(9), 987-1014.