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PIPERINE: PHYSICOCHEMICAL ASPECTS FOR LUNG CANCER

TANDI DY, SAHU P, SHARMA H, NEMA RK AND SAHU GK*

Rungta Institute of Pharmaceutical Sciences, Bhilai

***Corresponding Author: Dr. Gyanesh Kumar Sahu: E Mail: gyanesh.sahu23@gmail.com**

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ABSTRACT

Alkaloids are a group of chemical compounds root in nature that are chiefly made up of basic nitrogen atoms. Piperine is an alkaloid found in black pepper (*Piper nigrum*), one of the most often used spices, as well as long pepper (*Piper longum*) and other Piperaceae species fruits. Piperine is culpable for the distinctive biting quality of black pepper. Piperine provide a heterogeneity of pharmacological effects and health advantages, including the reduction of insulin resistance, anti-inflammatory properties, and the alleviation of hepatic steatosis. Piperine has been shown to limit the growth and survival of many different types of cancer cells by activating apoptotic signals and inhibiting cell cycle progression. Piperine is known to have a number of additional effects on cancer cells, including altering redox homeostasis, limiting CSC self-renewal, and modulating ER stress and autophagy. Piperine inhibits invasion, metastasis, and angiogenesis via altering the activity of numerous enzymes and transcription factors. Piperine is a powerful p-glycoprotein (P-gp) inhibitor that has a considerable impact on the drug metabolising enzyme (DME) system. Piperine can overcome multidrug resistance (MDR) in cancer cells and functions as a bioavailability enhancer for many chemotherapeutic drugs due to its negative effect on P-gp activity. The purpose of this review is to summarise the effects of piperine in chronic conditions, either alone or in combination with other medications and phytochemicals. In this review, we will discuss the concept of cancer chemoprevention and analyse recent advances in piperine's chemopreventive action at the molecular, cellular, and organism levels, which can aid in the design of future studies and the exploration of new molecular targets for therapeutic intervention.

Keywords: Piperine, antidepressant effects, bioavailability booster, insulin resistance

1. INTRODUCTION:

Herbal medicines have become more important as plant medicines in recent years due to their indisputable effectiveness. The active ingredients or principles contained in these natural products act as templates or intermediates for synthetic drugs **[1]**. Piperine is a white crystalline alkaloid $C_{17}H_{19}NO_3$ that is the chief active constituent of pepper and a colorless, crystalline alkaloid, $C_{17}H_{19}NO_3$, found in pepper **[2]**.

A pungent alkaloid that is concentrated in the outer skin of pepper berries (which gives pepper much of its bite) and is found in other spices and vegetables including jalapeno peppers **[3]**. Piperine is used as a flavouring and as an insecticide. The word is derived from the Latin piper, pepper.

Piperine ($C_{17}H_{19}NO_3$) is an alkaloid found in the fruits and roots of Piperaceae and Piperaceae species. This alkaloid is responsible for the pungent taste of black pepper (P. nigrum) and the isomer of piperine, long pepper (P. longum) **[4]**. Fluckiger and Hanbury discovered that the "long pepper" species P. longum and P. officinarum also contained this alkaloid. In addition to the above species, this compound is also found in West African pepper species **[5]**. The pungent taste of piperine is caused by activation of the heat on nociceptors and the transient receptor potential vanilloid (TRPV) ion channel TRPV1 of the acid sensor **[6]**.

Piperine forms a white prism that melts at 128 A°-219 A°. It is almost insoluble or slightly soluble in water (40 mg / l at 18°C), but more soluble in alcohol (1 g / 15 ml) and ether (1 g/1.7 ml). It's a very weak foundation **[7]**. It forms salts only with mineral acids, which are dissociated by water. Piperine was first hydrolyzed to bases and acids using alkali[i] and later called piperidine and piperic acid, respectively **[8]**. This alkaloid was synthesized by the action of piperoyl chloride on piperidine. There are more than 1000 species in the genus Piper, but the most well-known species are P.nigrum, P.longum and P.betel. Of these, P.nigrum is known as Spice King because of its exciting quality. P.nigrum is a flowering vine grown primarily for its fruits **[9]**. Its fruits are used to produce black, white and green peppers and have been evaluated for the presence of alkaloids, piperines and their isomers **[10]**.

1.1 Chemical structure of Piperine:

Piperine is a N-acylpiperidine in which the nitrogen atom is replaced by a (1E,3E)-1-(1,3-benzodioxol-5-yl)-5-oxopenta-1,3-dien-5-yl group. It's an alkaloid derived from the *Piper nigrum* plant **[11]**. It functions as an NF-kappaB inhibitor, a

plant metabolite, a dietary component, and a metabolite in human blood serum. It is a N-acylpiperidine, a piperidine alkaloid, and a tertiary carboxamide that belongs to the benzodioxole family. It's made up of (E,E)-piperic acid **[12]**.

1.2 Cancer Development:

A genetically changed cell undergoes malignant transformation to generate a mass of neoplastic cells, which is a slow and dynamic process. Cancer has at least three distinct but interconnected stages: initiation, promotion, and progression (malignant conversion), all of which can be slowed or stopped with the use of pharmacologically active medicines **[13]**. Cancer is a difficult disease to treat, but it can be avoided. In reality, 30–40% of all cancer deaths can be avoided by making suitable dietary changes and limiting exposure to dietary and environmental carcinogens **[14]**. The majority of cancer chemopreventive chemicals can influence cancer cells in a number of ways and are found in fruits, vegetables, and spices **[15]**. However, before these components can be prescribed for inclusion in dietary portions or tested in human intervention studies, the mechanisms by which they reduce cancer must be validated. The chemopreventive qualities of piperine, a pharmacologically safe alkaloid, have been extensively explored **[16]**.

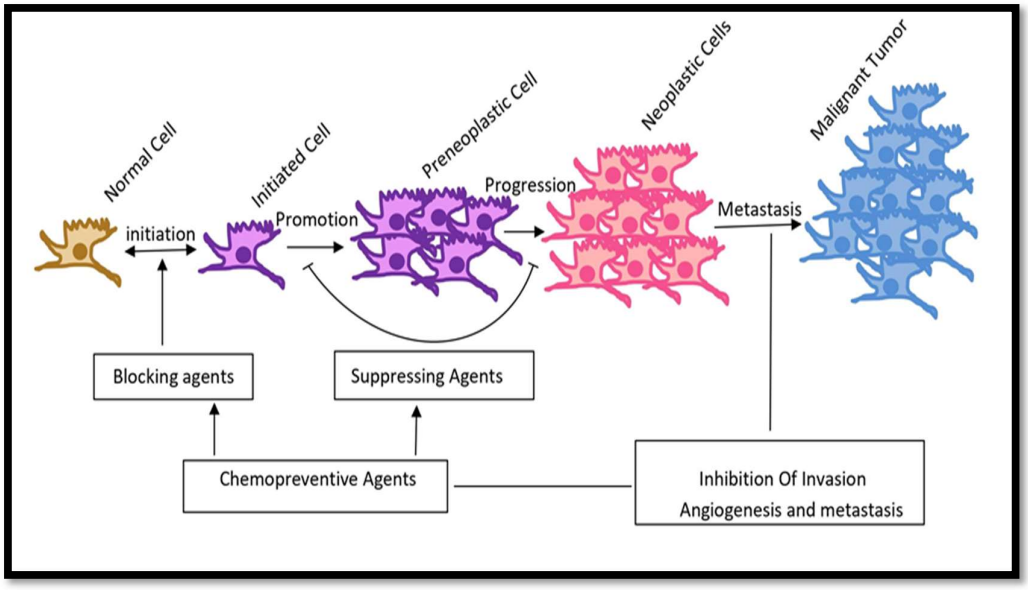

Fig 1.1: Steps that is crucial in the genesis of cancer. Cancer begins when a normal cell transforms into an initiated cell, which then undergoes tumour promotion to generate preneoplastic cells, which then advance to neoplastic cells. Chemopreventive drugs for cancer can obstruct the commencement (blocking agents) or later stages of this multi-step process (suppressing agents) [17]

1.3 Piperine for Lung cancer:

Many studies have investigated the effects of piperine on lung cancer and found very

promising results. Piperine is selective cytotoxic to the lung cancer cell line (A549) by arresting the G2 / M phase of the cell cycle and inducing apoptosis by activating the caspase 3 and caspase 9 cascades of cancer cells. In addition, the Bcl_2 protein expression decreased and the Bax protein increased, resulting in a higher Bax / Bcl2 ratio **[18]**. Benzo (a) pyrene induces lung carcinogenesis by reducing glutathione transferase (GST), quinone reductase (QR), UDPGT and increasing hydrogen peroxide levels. In a study in a Swiss albino mouse study, piperine (50 mg / kg body weight) was orally administered with benzo (a) pyrene (BaP) for 16 weeks. Reduced levels of lipid peroxidation, protein carbonyl, nucleic acid content, and polyamine synthesis were observed in piperine-treated animals compared to controls, demonstrating the BaP-induced lung carcinogenesis protective effect of this compound **[19]**. Piperine exhibits BaP-induced cytotoxicity in V79 lung fibroblasts by reducing GST and UDPGT. Piperine administration reduces DNA damage and DNA-protein cross-linking in animals with lung cancer.

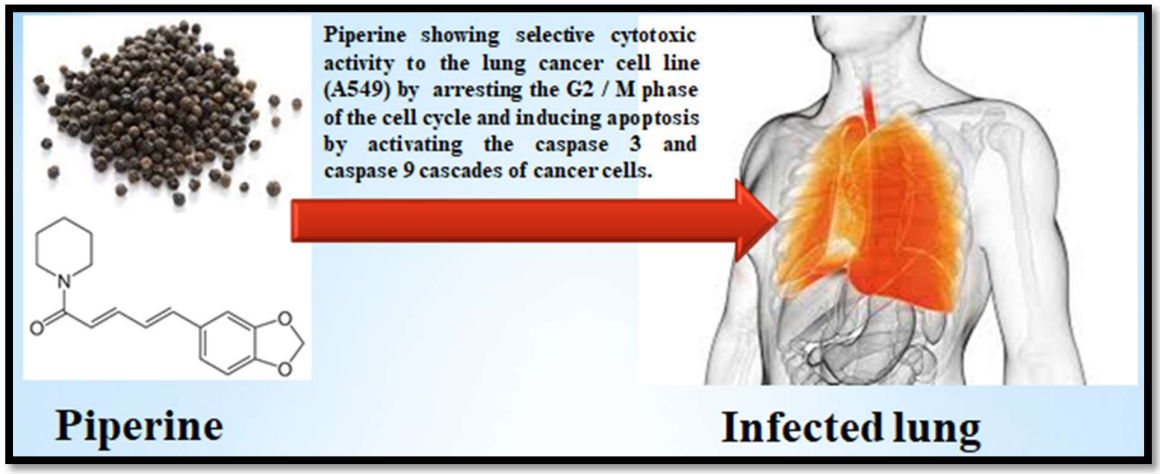

Fig 1.2: Piperine activity against lung cancer

Db *et al*., in this work shown that, mitochondrial enzymes (isocitrate dehydrogenase (ICDH), ketoglutarate dehydrogenase (KDH), succinate dehydrogenase (SDH), malate dehydrogenase (MDH)), glutathione metabolizing enzymes GPx, GR, and glucose-6-phosphodehydrogenase.

(G6PDH) NADPH Chito chrome reductase (NADPHC reductase), Chito chrome P450 (cytp450) and chitochrome b5 (cytb5) showed increased levels in piperin-treated mice. In addition, in these animals, ATPase enzymes were shown to increase in erythrocyte membranes and tissues and sodium /potassium /magnesium ATPase enzyme activity to decrease, demonstrating the chemo-preventive effect of piperine.

When piperine was co-administered with tumor induction, lung metastases induced by B16F10 melanoma cells in C57BL/6 mice were significantly suppressed. The results showed a decrease in lung collagen hydroxyproline, uronic acid and hexosamine content, a significant decrease in tumor nodule formation and lung size, and a decrease in serum sialic acid and serum glutamiltranspeptidase activity, a very promising anti-piperin. It shows metastatic activity **[20]**.

Yi Lin *et al*., evaluate the cytotoxic and apoptotic effects of piperine on human lung cancer A549 cells and to explore its mechanisms. Piperine was found to exert the greatest cytotoxic effect against A549 cells in a dose-dependent manner, whereas it showed no effect on WI38 human lung fibroblasts. This cell growth-inhibitory effect might be attributed to cell DNA damage and cytotoxic effects. Besides, piperine had the ability to cause cell cycle arrest in G2/M phase and to activate caspase-3 and caspase-9 cascades in A549 cells. Furthermore, piperine-induced apoptosis could be blocked by the broad caspase inhibitor z-VAD-fmk in majority. In addition, piperine treatment decreased Bcl-2 protein expression, but increased Bax protein expression in A549 cells, which were positively correlated with an elevated expression of p53 compared to control. Taken together, these results suggested that piperine could induce p53-mediated cell cycle arrest and apoptosis via activation of caspase-3 and caspase-9 cascades, as well as increasing the Bax/Bcl-2 ratio. Thus, piperine could be developed as an effective antitumor agent in the prevention and treatment of lung cancer without toxicity to the host **[21]**.

Pradeep *et al*., showed the effect of piperine on the inhibition of lung metastasis induced by B16F-10 melanoma cells was studied in C57BL/6 mice. Simultaneous administration of the compound with tumor induction produced a significant reduction (95.2%) in tumor nodule formation. Increased lung collagen hydroxyproline (22.37 µg/mg protein) in the metastasized lungs of the control animals compared to normal animals (0.95 µg/mg protein) was significantly reduced (2.59 µg/mg protein) in the piperine-treated animals. The high amount of uronic acid (355.83 µg/100 mg tissue) in the metastasized control animals was significantly reduced (65 µg/100 mg tissue) in the animals treated with piperine. Lung hexosamine content was also significantly reduced in the piperine-treated animals (0.98 mg/100 mg lyophilized tissue) compared to the untreated tumor-bearing animals (4.2 mg/100 mg lyophilized tissue). The elevated levels of serum sialic acid and serum gamma glutamyl transpeptidase activity in the untreated control animals was significantly

reduced in the animals treated with piperine. The piperine-treated animals even survived the experiment (90 days). Histopathology of the lung tissue also correlated with the lifespan of the drug-treated animals. The results of this study demonstrate the antimetastatic activity of piperine, an alkaloid present in plants such as *Piper nigrum* and *Piper longum* **[22]**.

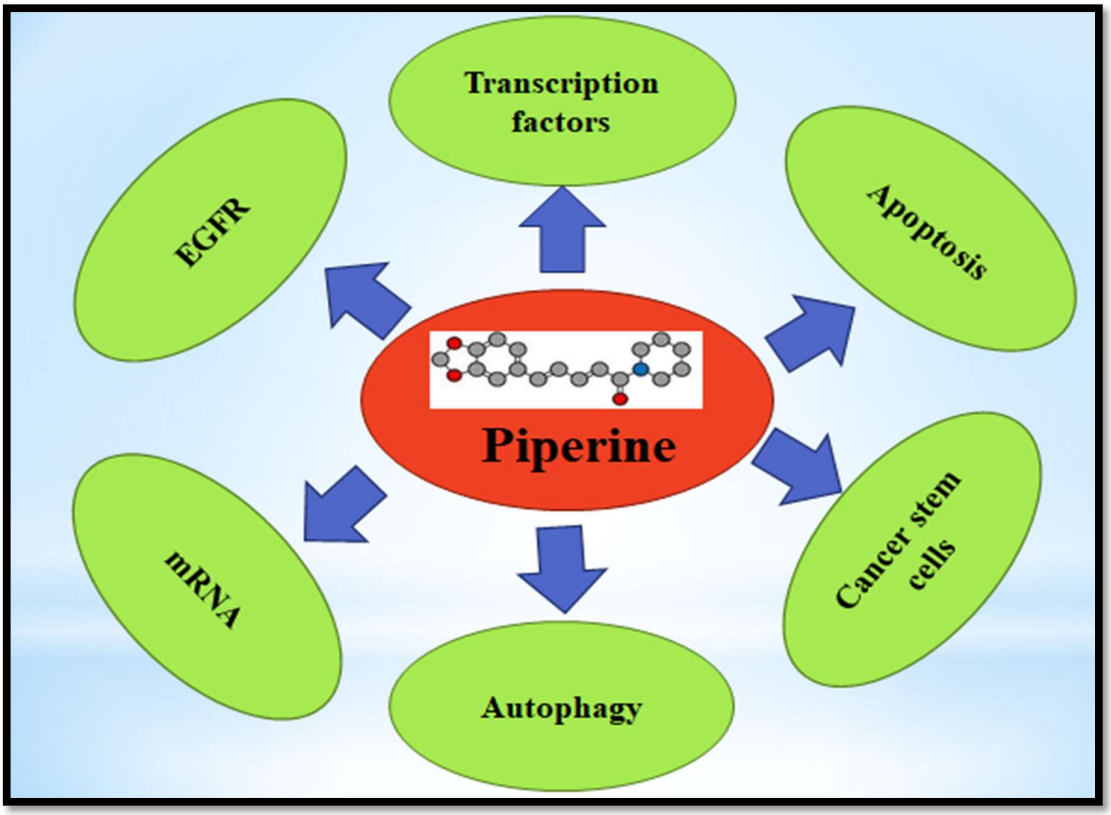

Fig 1.3: Targets and potential novel targets for piperine in human lung cancer

1.4 Piperine Enhances the Bioavailability of Drugs

Because of its inhibitory influence on P-gp activity, piperine acts an efficient bioavailability enhancer for a series of chemotherapeutic agents. Piperine is regarded as the world's first scientifically validated bioavailability enhancer **[23, 24]**. Different mechanisms have been postulated to explain the bioenhancer activity of piperine. For example, piperine inhibits P-gp and cytochrome P450 3A4 (CYP3A4), both of which contribute to first-pass elimination of many drugs. CYP3A4 alone metabolizes ~50% of marketed drugs [25]. Other DMEs influenced by piperine include CYP1A1, CYP1B1, CYP1B2, CYP2E1, CYP3A4, etc. Therefore, all the drugs that are metabolized by these enzymes are affected by the administration of piperine, making piperine a non-specific inhibitor of different forms of cytochrome P-450 enzyme system **[26]**. Piperine is an inhibitor of UDP-glucuronosyltransferase.

Piperine substantially enhanced the bioavailability of many chemopreventive agents such as resveratrol mostly through the inhibition of glucuronidation. Therefore, when resveratrol is administered along with piperine, the plasma concentration of resveratrol is significantly enhanced **[27, 28]**. Piperine is the first and most potent bioenhancer to this date. Piperine increases bioavailability of various anticancerous drugs and reduces dosage, cost and toxicity of drugs such as methotrexate, paclitaxel, etc. **[29]**. The bioenhancing effects of piperine have been demonstrated in several other studies showing that piperine can improve the absorption of many nutrients **[30]**. The benefits of adding a bioenhancer include reduced drug dosage, reduced cost of the drug, reduced incidence of drug resistance and reduced risk of adverse drug reaction/side effects **[31]**. Moreover, efficacy is enhanced by increased bioavailability. Secondary beneficial effects include reduced requirement of raw material for drug manufacture **[32]**. For example, this is especially beneficial and evident in anti-cancer drugs like Taxol used to treat breast cancer **[33]**. This drug is obtained from the Yew tree, one of the slowest growing trees in the world, and to obtain taxol for one patient, six trees of 25–100 years need are to be chopped **[34]**. Simply adding a bioenhancer to Taxol means that fewer trees need to be sacrificed. The great reduction in raw material is an added, ecological, benefit **[35]**. With the discovery of the first bioavailability enhancer piperine in 1979, a new class of drug and a new concept was introduced into science **[36]**. This revolutionary discovery opened up a new field, that of increasing drug bioavailability. Piperine still remains the most effective bioenhancer **[37, 38]**.

2. CONCLUSION:

The information collected by us in this review has revealed that piperine can target lung cancer cells specifically and manifest specific mechanisms of action in accordance with the type of cancer it acts on. However, the exact mechanism involved in the chemopreventive effects of piperine against the cancer development is not fully understood. Therefore, the precise mechanism of action of piperine must be validated before final recommendations on the clinical use of this natural molecule can be made. The hope is that piperine could be administered with minimum risk to human subjects and that it would produce a significant chemopreventive effect as well as it has been piperine can act as a bioenhancer for increasing the bioavailabilty of anticancer drugs and reducing their toxicity.

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