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Review Article

Examining Piperine's Potential for Cancer Chemoprevention

Prof Dr Sheetal Asutkar[1], E. Lakshmi[2] and Dr. Gurmeet Singh Chhabra[3*]

[1] *Head Dept of Shalya Tantra, Mahatma Gandhi Ayurveda College Hospital and Research Centre DMIHER Sawangi Wardha*

[2] *Associate Professor, Clinical Nutrition and Dietetics, SRM Medical College hospital and Research Centre, SRM IST, kattankulathur, chengalpattu district, India*

[3] *Professor, Pharmaceutical Chemistry, Indore institute of pharmacy, Pithampur road, Opposite Indian institute of management Rau, indore (M.P)*

Abstract: Cancer is a major global health issue that raises morbidity and death rates everywhere. It is distinguished by the unchecked growth, survival, and dissemination of cancerous cells. Complex genetic, molecular, and metabolic changes that facilitate the conversion of healthy cells to malignant cells characterize the multi-stage process of cancer formation. Cancer chemoprevention, which uses pharmaceutically active drugs to stop, slow, postpone, or reverse the progression of cancer at various stages, is one of the innovative ways needed to treat this complex illness. Black pepper (Piper nigrum) contains piperine, a naturally occurring alkaloid that has garnered a lot of attention due to its several therapeutic applications, which include immunomodulatory, antibacterial, anti-inflammatory, and antioxidant properties. Piperine can inhibit important signaling pathways and molecular processes associated with carcinogenesis, including inflammation, oxidative stress, and the control of apoptosis. These processes are all essential for the development, progression, and spread of cancer. It has been demonstrated that piperine dramatically modulates many pathways, such as MAPK, PI3K/Akt, STAT3, and NF-κB, which are frequently dysregulated in various cancer types. Piperine has shown promise in enhancing the therapeutic effectiveness of traditional cancer treatments by increasing the sensitivity of cancer cells to UV phototherapy and TRAIL-based treatments and reducing resistance. Synergistic effects with chemotherapeutic medications may result in combination therapy that improves clinical results. This review assesses the potential effects, and long-term safety of drugs based on piperine, highlighting the urgent need for comprehensive preclinical and clinical research to confirm the drugs' safety profile and therapeutic efficacy.

Keywords: Antioxidant and Anti-Inflammatory Effects, Piperine, Cancer Chemoprevention, Molecular Signaling Pathways, Combination Cancer Therapy.

***Corresponding Author**

Dr. Gurmeet Singh Chhabra , Professor, Pharmaceutical Chemistry, Indore institute of pharmacy, Pithampur road, Opposite Indian institute of management Rau, indore (M.P)

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1. INTRODUCTION

Recent statistics indicates a concerning rise in cancer incidence and mortality worldwide demonstrating the urgent need for more aggressive cancer prevention efforts. After colon, stomach, prostate, and lung cancers, breast cancer is the second most common malignancy in women. Colorectal, liver, stomach, and female breast cancers are the next most common causes of cancer-related fatalities, after lung cancer. Global death rates are significantly impacted by these malignancies. Cancer incidence is much greater in transitioned nations, particularly for both sexes, whereas mortality rates are less variable, particularly for women. Researchers' attention on chemo preventive medications manufactured from both natural and synthetic components to improve cancer therapy has led to the identification of potential prospects. Because of its several ways of action, piperine has garnered a lot of attention among natural compounds. Piperine is a nitrogenous alkaloid that has long been used medicinally. Early in the 19th century, Danish scientist Hans Christian Ørsted isolated it for the first time from dried pepper fruit extracts. Piperine's unique structural features and biological activity are facilitated by a conjugated aliphatic chain that joins a piperidine ring to a methylenedioxyphenyl group. Among the many benefits of piperine are its capacity to lower inflammation, encourage cellular death, and deter cancer stem cells, which are crucial for preventing the growth and spread of cancer since they interfere with the cell cycle. Because it may specifically target sick cells while protecting healthy ones, piperine is an alluring possibility for treating cancer. This successfully resolves the problem of distinguishing between healthy and diseased cells, which is a frequent obstacle for conventional therapies. By improving medication absorption, reducing side effects, and boosting effectiveness, piperine may improve conventional cancer treatment. Its versatility in oncological therapy is further demonstrated by its capacity to overcome multidrug resistance, enhance the sensitivity of radiation resistance in cancer cells, and collaborate with therapies such as TRAIL-based treatments. Using both *invitro* and *invivo* models, this review investigates the potential of piperine in the prevention and treatment of a number of malignancies, including those of the breast, cervix, prostate, lung, skin, stomach, liver, colon, and bone. A literature search was conducted using reliable databases, such as Google Scholar, Elsevier Science Direct, PubMed, Springer, and Web of Science, to ensure a comprehensive and accurate investigation. The primary objective was to locate relevant research that had been published in the recent several decades; background information about earlier works was provided. Only English-language papers were analyzed using keyword searches that contained terms such as piperine, cancer chemoprevention, cellular apoptosis, antitumor, in vitro testing, in vivo studies, and combination cancer therapy. Before carefully evaluating original research and reviewing papers that met preset inclusion conditions, a rigorous selection procedure was employed, which included removing publications that were redundant or irrelevant. This ensured that the data used in this evaluation was reliable and accurate.

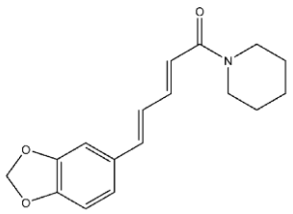

Fig 1: Piperine

1.1 The Dual Role of Piperine in Preventing and Treating Cancer

The use of bioactive compounds, either natural or synthetic to prevent, slow, or even reverse the progression of cancer is known as cancer chemoprevention. Usually, these substances fall into one of two groups: suppressive agents and blocking agents. While suppressive drugs function by stopping the development of aberrant cells into preneoplastic, neoplastic, or malignant states, blocking agents function by inhibiting the start of tumor formation. To further boost their protective effects, several chemopreventive drugs can further improve the body's antioxidant defense systems or alter immunological responses. Black pepper contains a substance called piperine, which has a unique role in the prevention and treatment of cancer because it acts as a suppressive and blocking agent. By disrupting important biochemical processes implicated in carcinogenesis, including inflammation and oxidative stress, piperine acts as a blocking agent, preventing the development of cancer [1]. By altering gene expression, signaling pathways, and apoptotic mechanisms, it can act as a suppressor and stop started cells from progressing into advanced stages of cancer. Piperine is a useful adjuvant in combination therapy as it has also been demonstrated to improve the therapeutic effectiveness and bioavailability of other anticancer medications. Because of its dual action, piperine can target several routes and stages of cancer growth, increasing the overall efficacy of chemopreventive measures and perhaps leading to better patient outcomes.

1.2 Piperine's Anti-Inflammatory Properties in Cancer

The anti-inflammatory properties of piperine, which are essential for both preventing and treating cancer, have been the subject of several research. Several isolated cell types have been used to evaluate its anti-inflammatory qualities *invitro*. In a model of inflammation using LPS-induced nucleus pulposus cells, piperine markedly reduced the expression of genes linked to inflammation and oxidative stress. Furthermore, piperine prevented human peripheral blood mononuclear cells (PBMCs) from producing IL-2 and interferon-gamma (IFN-γ) [2]. Piperine inhibited the production of reactive oxygen and nitrogen species (ROS/RNS) in a UV-B-induced oxidative stress model using HaCaT keratinocyte cells [3]. This resulted in a reduction of inflammatory mediators such p38, JNK, AP-1, iNOS, and COX-2 proteins. Piperine prevented BV2 microglial cells from producing prostaglandin E2 [4] (PGE2), IL-6, IL-1β, and tumor necrosis factor (TNF)-α. By down-regulating the IL-1β and nuclear factor-κB (NF-κB) pathways, activating the Nrf2/keap1 pathway, and blocking TNF-α-induced production of cell adhesion molecules such ICAM-1, VCAM-1, and E-

selectin, piperine decreased neutrophil adherence to the endothelium in a time- and concentration-dependent manner [5]. Studies conducted *invivo* under a range of acute and chronic settings have demonstrated the dose-dependent anti-inflammatory effects of piperine [6]. Piperine treatment dramatically decreased inflammation in models such as cotton pellet-induced granuloma, croton oil-induced granuloma pouch, formalin-induced arthritis, and carrageenan-induced paw edema. Piperine suppressed AP-1, MMP-13, and IL-6 in a dose-dependent way while also lowering PGE2 levels in an animal model of arthritis employing fibroblast-like synoviocytes treated with IL-1β from rheumatoid arthritis patients [7]. Piperine treatment significantly reduced the nociceptive and arthritic symptoms in rats. Piperine continuously exhibited strong anti-inflammatory qualities in a variety of animal models, showing that it inhibit inflammatory factors, alter the generation of cytokines, and down-regulate important pathways [8]. Piperine's promise for future studies into the treatment of inflammation-related illnesses is highlighted by the dose-dependent decrease of inflammation shown in these animals.

1.3 Mechanisms of Piperine-Induced Cell Death

(1) Apoptosis

There are two main methods to trigger apoptosis: intrinsic and extrinsic. Apoptosis is triggered by a wide range of events, but the signalling ultimately converges on a single execution pathway. Numerous cellular alterations follow, including DNA breakage, nuclear and cytoskeletal protein degradation, protein cross-linking, apoptotic body formation, and the synthesis of ligands that draw phagocytic cells to devour the apoptotic bodies. Overall, apoptosis is a highly regulated process that is crucial for maintaining tissue homeostasis and eliminating damaged or unnecessary cells. The intrinsic pathway is often activated by internal stress signals, such as DNA damage or low oxygen levels, while the extrinsic pathway is triggered by external signals, such as binding of death ligands to cell surface receptors. Both pathways ultimately lead to the activation of caspases, which are proteases that carry out the destruction of the cell in a controlled and organized manner. Through these mechanisms, apoptosis plays a vital role in development, immune response, and the prevention of diseases such as cancer. Apoptosis may be induced by a number of chemopreventive drugs, and piperine has demonstrated the ability to start both innate and extrinsic apoptotic pathways. Piperine's toxic effects on a variety of human cancer cell lines, including those from the breast, liver, cervix, and prostate, emphasize apoptotic characteristics such DNA fragmentation, externalization of membrane phosphatidylserine, and condensation of the cytoplasm and nucleus [9]. Piperine has been shown to inhibit the growth of tumors in animal models, further highlighting its potential as a promising anticancer agent. Its ability to specifically target cancer cells while sparing normal cells makes it a valuable candidate for further research and potential clinical applications in the future. In conclusion, the induction of apoptosis by piperine represents a promising strategy for the treatment and prevention of various types of cancer. Moreover, it has been shown that piperine can interact with human G-quadruplex DNA sequences that control cellular functions linked to the development of cancer [10]. The induction of apoptosis by piperine was verified by an independent investigation. In a dose-dependent manner, piperine promotes nuclear condensation, DNA fragmentation, loss of mitochondrial membrane potential, reactive oxygen species (ROS) generation, and caspase-3 activation [11]. In an osteosarcoma xenograft mouse model, in vivo investigations showed that piperine suppressed tumor development by upregulating p53 and Bax expression and downregulating Bcl-2 expression [12].

(2) Autophagy

One important biological mechanism via which several chemopreventive drugs work is autophagy. This process, which helps maintain homeostasis, differentiation, development, and survival, entails the lysosomal breakdown of molecules and subcellular constituents. Autophagy is crucial for eliminating damaged organelles and proteins, as well as for recycling nutrients during times of stress or nutrient deprivation. This process plays a key role in the clearance of intracellular pathogens and in the regulation of inflammation. Research has shown that dysregulation of autophagy can contribute to various diseases, including cancer, neurodegenerative disorders, and metabolic conditions. Therefore, targeting autophagy with chemopreventive drugs can have significant implications for disease prevention and treatment. By reducing tissue damage and cellular death, two factors that might promote the development and spread of cancer, autophagy acts as a defense mechanism in the field of oncology. One important autophagy modulator is the PI3K/Akt/mTOR signaling pathway [13]. Piperine, have been shown to help cancer cells go through autophagy by lowering the activity of mTORC kinase and increasing the formation of autophagosomes [14]. This modulation of autophagy by substances like piperine could potentially be utilized in combination with traditional cancer treatments to enhance their effectiveness and reduce harmful side effects. Targeting the PI3K/Akt/mTOR pathway through autophagy modulation may also have implications for other diseases beyond cancer, such as neurodegenerative disorders and metabolic conditions. Further research into the use of autophagy modulators in various disease treatments could lead to innovative therapeutic strategies with significant clinical impact. Piperine also increases oxidative stress, hurts the potential of the mitochondria, stops thioredoxin reductase from working, and changes proteins related to autophagy to help autophagy [15]. These findings suggest that piperine could potentially be used as an autophagy modulator in the treatment of various diseases, not just cancer. By targeting the PI3K/Akt/mTOR pathway, piperine could offer a new avenue for therapeutic intervention with potentially fewer side effects. Further studies are needed to completely understand the implications of piperine on autophagy and its role in disease treatment. According to *invivo* research, piperine reduces tumor growth in oral cancer via increasing autophagy through PI3K signaling modulation [16].

(3) Ferroptosis

Ferroptosis's function in controlling cell death via iron and lipid peroxidation makes it a promising target for chemopreventive treatments. This process is marked by an imbalance between the production of reactive oxygen species (ROS) and the antioxidant defenses of cells, especially those that depend on glutathione (GSH). There is also an accumulation of ROS or peroxides derived from iron and lipids, which is aided by the Fenton reaction [17]. Targeting ferroptosis as a means of preventing cancer development and progression has shown

promise in preclinical studies. By disrupting the delicate balance between ROS production and antioxidant defenses, researchers hope to exploit this pathway for therapeutic purposes. Ferroptosis is different from other types of cell death like apoptosis and necrosis because it is caused by lipid peroxidation and iron dysregulation. This makes it a precise target for cancer treatment. In some cases, piperine can speed up the Fenton reaction by increasing the amount of calcium and ROS that build up inside cancer cells. This shows promise in controlling ferroptosis [18]. This method make tumor cells more likely to go through ferroptosis when used with other medicines that weaken cellular iron metabolism or antioxidant systems even more. One possible way to do this is to use piperine with other chemicals, like ferrostatins or liproxstatins, that target specific pathways in ferroptosis [19]. By strategically combining these agents, researchers hope to enhance the efficacy of ferroptosis induction in cancer cells while minimizing potential off-target effects. Researchers are also looking into use of nanoparticles that are loaded with piperine to improve its delivery and bioavailability. This would make it even more useful for treating cancer. Manipulation of ferroptosis pathways holds great promise as a novel strategy for combating cancer and overcoming resistance to traditional therapies. Apart from its function in encouraging ferroptosis, piperine may also decrease the production of proteins that prevent ferroptosis, such glutathione peroxidase 4 (GPX4), a crucial enzyme that shields cells from lipid peroxidation, or ferritin, which accumulates excess iron [20]. By inhibiting these proteins, piperine could potentially enhance the effectiveness of ferroptosis in destroying cancer cells. The use of nanoparticles loaded with piperine could help target specific cancer cells more effectively, increasing the overall efficacy of treatment. Overall, the combination of piperine and nanoparticle technology shows great promise in revolutionizing cancer therapy and overcoming traditional treatment limitations. Piperine not only causes ferroptosis, but it also makes chemopreventive treatments work better, to stop cancer cells. Piperine can work with other chemopreventive drugs due to its capacity to influence a variety of molecular targets, including as ROS generation, iron homeostasis, and antioxidant defense mechanisms. This multifaceted approach makes piperine a valuable addition to cancer treatment regimens, potentially leading to better outcomes and fewer side effects for patients. The use of nanoparticle technology enhances the delivery of piperine to cancer cells, increasing its effectiveness and reducing the risk of systemic toxicity [21]. As research in this area continues to advance, the combination of piperine and nanoparticle technology holds great promise for improving the overall success of cancer therapy. This comprehensive strategy may enhance treatment results, lower the chance of cancer recurrence, and offer fresh methods for focusing on cancer cells that are resistant to therapy.

(4) Anoikis

Anoikis, a unique form of regulated cell death, is essential for stopping the separation and spread of cancer cells. Anoikis is a process that eliminates misplaced or disconnected cells under both normal and pathological situations, therefore promoting tissue homeostasis. Anoikis in cancer cells inhibits metastasis to other locations; however, this is often not seen since cancer cells develop resistance to anoikis [22]. This resistance allows cancer cells to survive and thrive in distant tissues, leading to the formation of secondary tumors. Scientists are currently researching ways to overcome this resistance in order to prevent metastasis and improve cancer treatment outcomes. By understanding the mechanisms of anoikis resistance, new targeted therapies may be developed to specifically address this challenge in cancer management. Cell detachment from its original location causes changes in the external environment, which lead to anoikis. ECM components and membrane proteins associated with cell adhesion function as sensors to convey intracellular signals. These signals can activate survival pathways within the cell, allowing it to evade anoikis and survive in a detached state. This survival mechanism is crucial for cancer cells to metastasize and spread to other parts of the body. By targeting these specific pathways and disrupting the signals that promote anoikis resistance, researchers hope to develop more effective treatments that can prevent the spread of cancer and ultimately improve patient outcomes. There are several ways that cancer cells become resistant to anoikis. They can change the integrin repertoire so they can grow in different places, turn on too many pro-survival signals from many receptors because of persistent autocrine loops, turn on oncogenes, overexpress growth factor receptors, or change or increase the activity of key enzymes that are involved in integrin or growth factor receptor signaling. Piperlongumine, a chemically related molecule to piperine, has been shown to successfully cause anoikis in melanoma cells in vitro [23]. This stimulation is made possible by blocking the STAT3 signaling pathway, which is often linked to cancer growth and resistance to apoptosis. As a possible therapeutic drug in melanoma treatment techniques, piperlongumine blocks this route, impairing cellular adhesion processes and causing death.

1.4 Using Piperine to Target Cancer Stem Cells

Tumor-derived cancer stem cells (CSCs) have the ability to self-renew and differentiate into different kinds of cancer cells. These cells are essential for the development of malignancies as well as their recurrence. Characteristics of CSCs include resistance to apoptosis, evasion of immune detection, altered metabolism, increase of inflammation associated with malignancies, and resistance to cancer therapies. Important biochemical pathways that control CSC development and self-renewal include TGF/SMAD signaling, PI3K/Akt/mTOR, NF-κB, JAK-STAT, Notch, Hedgehog, and Wnt/β-catenin [24]. Certain medications that target these pathways may be able to stop tumor development. It has been established that piperine interacts with a number of pathways, such as blocking the Wnt/β-catenin pathway in breast and colorectal cancer cells and perhaps modifying the PI3K/Akt/mTOR pathway. Furthermore, it has been demonstrated that piperine and mitomycin-C together efficiently suppress the STAT3/NF-κB pathway in cervical cancer, therefore disrupting the Bcl-2 signaling pathway [25].

1.5 The Function of Piperine in Cell Cycle Control and Arrest

Initiation of cancer is frequently associated with the breakdown of cell cycle control, which is necessary to sustain appropriate cell growth and function. At several checkpoints, cyclins and cyclin-dependent kinases (CDKs) are essential for controlling the cell cycle. It has been demonstrated that piperine disrupts important checkpoints and regulatory proteins involved in this process. According to Fofaria et al., piperine injection stops melanoma cells' cell cycle in the G1 phase, which results in decreased cyclin D1 levels and

increased p21 expression [26]. H2AX phosphorylation at Ser139 indicates DNA damage and the start of apoptosis brought on by the generation of intracellular ROS [27]. By inhibiting cyclins D1 and D3 and their associated CDKs 4 and 6, piperine demonstrated antiproliferative effects in colon cancer, stopping cells in the G1 phase. Reduced phosphorylation of the retinoblastoma protein and increased p21/WAF1 and p27/KIP1 levels further corroborated this. By downregulating G2 phase proteins such cyclin B, CDK1, and Cdc25C, increasing p21 expression, and encouraging the phosphorylation of CDK1 and checkpoint kinase 2 (Chk2), piperine also prevented the cancer cells' cell cycle during the G2/M phase [28].

1.6 Piperine's Selective Growth Inhibition of Cancer Cells

The advancement of cancer is frequently associated with the disruption of cell cycle control, which is essential for cell integrity and proliferation. At several checkpoints, cyclins and cyclin-dependent kinases (CDKs) are crucial for controlling the cell cycle. It has been shown that piperine can block important regulatory proteins and checkpoints involved in this process. Piperine injection stops melanoma cells' cell cycle in the G1 phase, which raises p21 expression and lowers cyclin D1 levels [29]. DNA damage is shown by the phosphorylation of H2AX at Ser139, which implies that the generation of intracellular ROS caused apoptosis. By inhibiting cyclins D1 and D3, as well as the cyclin-dependent kinases 4 and 6, piperine caused G1 phase arrest in colon cancer cells, demonstrating antiproliferative properties. This was further corroborated by increased levels of p21/WAF1 and p27/KIP1 and reduced phosphorylation of retinoblastoma protein. By downregulating G2-phase proteins such cyclin B, CDK1, and Cdc25C, causing p21 expression, and encouraging the phosphorylation of CDK1 and checkpoint kinase 2 (Chk2), piperine has also been shown to stop the cell cycle in cancer cells during the G2/M phase.

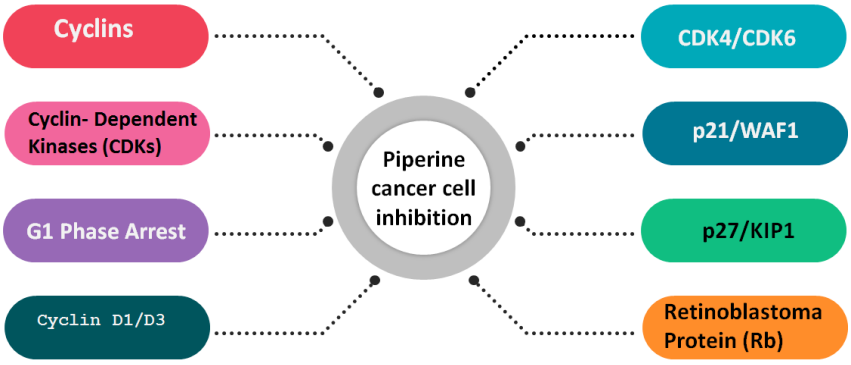

Fig 1: Piperine inhibits CDK4/6 and upregulates CKIs, leading to G1 phase arrest and cancer cell death.

1.7 The Inhibition of Cancer Metastasis and Invasion by Piperine

Metastasis, the spread of cancer cells to distant organs, is a primary contributor to cancer-related death. Piperine demonstrates anti-metastatic properties via many methods, such as the modification of signaling pathways, suppression of matrix metalloproteinases (MMPs), and prevention of epithelial-to-mesenchymal transition (EMT) [30]. Piperine inhibits the production of MMP-2 and MMP-9, enzymes vital for the destruction of the extracellular matrix, which is crucial for tumor invasion. It also disrupts essential signaling pathways, including PI3K/Akt, NF-κB, and Wnt/β-catenin, which are critical for cell migration and survival. Furthermore, piperine prevents epithelial-mesenchymal transition (EMT), a process in which cancer cells forfeit epithelial properties and acquire mesenchymal ones, therefore diminishing their motility and invasiveness [31]. Moreover, piperine's antioxidant and anti-inflammatory characteristics foster a milieu that is less favourable for metastasis. It also sensitizes neoplastic cells to chemotherapeutic drugs, increasing their efficiency while perhaps reducing negative effects. Preclinical studies and *invitro* models have repeatedly shown piperine's capacity to suppress metastasis in numerous cancer types, including breast, lung, and colorectal malignancies, establishing it as a prospective option for anti-metastatic therapy.

1.8 Piperine's Anti-Angiogenic Effects on Cancer

Angiogenesis and cell motility are activated during tumor development, allowing tumor cells to proliferate by secreting angiogenic chemicals such as vascular endothelial growth factor (VEGF). Piperine can decrease collagen-induced angiogenic activity in breast cancer cells and obstruct tubule formation, a crucial step in angiogenesis [32]. Piperine blocks certain phosphorylation pathways linked to angiogenesis and endothelial cell regulation. Piperine reduces VEGF expression levels in a dose-dependent fashion, emphasizing its role in blocking this crucial growth factor in cancer cell migration. Studies on how piperine affects angiogenic factors in breast cancer cells showed that it decreased the expression of MMP-9 and VEGF mRNA while increasing the levels of E-cadherin, which is necessary for preserving the integrity of the extracellular matrix and cell adhesion [33]. These results demonstrate piperine's anti-angiogenic and anti-metastatic properties.

1.9 Anti-Metastatic Properties

The main cause of cancer-related death is metastasis, which is the process by which cancer cells spread from their initial location and infiltrate other tissues. Piperine's anti-metastatic efficacy has been shown in experimental tests using a mouse lung metastasis model [34]. Treatment with piperine significantly lowered tumor growth and reduced uronic acid and hexosamine, two indicators linked to metastasis pathways [35]. Its function in preventing metastasis was further demonstrated by the reduction of hydroxyproline levels, a collagen metabolite connected to tumor cell infiltration into bones. In studies using human gastric cancer cells, piperine has been shown to inhibit the production of IL-6, a cytokine essential for cancer invasion and metastasis via the c-Src/RhoA/ROCK

signaling cascade [36]. By downregulating matrix metalloproteinases (MMPs), specifically MMP-13 and MMP-9, piperine inhibited tumor migration and growth. These results demonstrate piperine's potential as an anti-metastatic drug and its capacity to affect pathways linked to metastasis.

1.10 UV-Phototherapy and Radiosensitization

Radiation treatment destroys cancerous cells by exposing them to high-energy radiation. However, its efficacy in treating cancer is limited by the damage it does to healthy tissue and the radioresistance of some tumors. By producing free radicals from ionized or excited water molecules, radiation can cause direct or indirect molecular DNA damage. Pharmaceuticals that protect healthy cells from radiation damage and increase radiation-induced cytotoxicity in neoplastic cells without producing systemic toxicity are thus required. Because of their therapeutic and cancer-preventive qualities, a wide variety of chemopreventive phytochemicals fulfill this function. While piperine has prooxidant effects on cancer cells, it has antioxidant qualities in healthy cells [37]. This differential effect preserves healthy cells while increasing the radiosensitivity of malignant cells. By altering the potential of the mitochondrial membrane, piperine promotes the production of ROS, which leads to cellular death. The combination of piperine with UVB in melanoma cells increases cell death by increasing ROS levels and upsetting intracellular calcium balance.

1.11 The Function of Piperine in TRAIL-Based Therapeutic Approaches

Apo2L, also known as tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), is a type 2 membrane protein that belongs to the TNF superfamily [38]. It is one of the few tumor-selective therapeutic drugs that may specifically cause cancer cells to undergo apoptosis via a signaling route linked to the innate immune system. However, the development of resistance in many cancer cells, which enables them to avoid immune system identification, limits the efficacy of TRAIL-based treatment. The combined effects of several medications with TRAIL on triple-negative breast cancer (TNBC) cell lines, including both TRAIL-sensitive and TRAIL-resistant varieties, were investigated by Abdelhamed et al. Key signaling molecules involved in cell survival were reduced among the tested treatments as a result of piperine's synergistic actions with TRAIL in both cell lines. Piperine, has attracted interest for its potential to augment TRAIL-based cancer therapies. Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is a potential anti-cancer therapy since it selectively induces apoptosis in cancer cells while preserving normal cells [39]. The therapeutic effectiveness of TRAIL is often limited by the emergence of resistance in certain cancer types. Piperine functions as a chemosensitizer, mitigating TRAIL resistance via the modulation of several cellular pathways [40]. It increases the expression of death receptors (DR4 and DR5) on the surface of cancer cells, which are essential for TRAIL-induced apoptosis. Piperine inhibits anti-apoptotic proteins, including Bcl-2 and survivin, while enhancing the function of pro-apoptotic molecules such as Bax and caspases, thereby intensifying the apoptotic signaling cascade [41]. Piperine has anti-inflammatory and antioxidant characteristics, which may alleviate the tumor-promoting effects of the tumor microenvironment, hence augmenting TRAIL effectiveness. Piperine enhances TRAIL sensitivity and diminishes the probability of cancer recurrence by targeting numerous pathways.

1.12 Improving Drug Bioavailability

The release of the drug from its dosage form, stability in the gastrointestinal tract, solubility, translocation over the intestinal barrier, and the degree of pre-systemic metabolism are some of the variables that affect the bioavailability of cancer treatments. Piperine is recognized as the first bioavailability enhancer to be scientifically validated. There are several reasons for the improvement in bioavailability. Piperine facilitates the passage of many substances across cellular membranes by interacting with transporter proteins, including ATP-binding cassette (ABC) transporters [42]. ABC transporters facilitate the efflux of anticancer medications and are frequently seen in intestinal wall epithelial cells and neoplasms. However, piperine is able to overcome this limitation. According to studies, piperine inhibits cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) [43]. When taken combined, piperine raises the plasma levels of resveratrol by blocking glucuronidation, which enhances the bioavailability of chemopreventive natural compounds like curcumin and resveratrol [44]. Adverse effects are seldom reported in human trials, despite these findings. However, a number of issues restrict this research's applicability to thorough risk evaluations. There are gaps in the knowledge of piperine's overall effects and safety as a result of this, including a lack of attention to safety beyond drug interactions, a failure to consider possible negative effects observed in animal studies, and a lack of analysis of piperine's concurrent administration with other substances.

2. CONCLUSION

In-depth analysis of piperine's anticancer properties is provided in this review, along with information on its therapeutic advantages and modes of action. It illustrates piperine cancer prevention by limiting cell division, triggering apoptosis, and altering signaling pathways linked to cancer. Through boosting bioavailability, blocking drug transporters, and reducing drug resistance, piperine shows potential as a supplement to traditional cancer therapies. In order to enable more individualized treatment approaches, the review looks at the need for more research to identify the specific biological targets and pathways that piperine influences. To improve therapeutic efficacy, it is essential to look into possible synergistic interactions with other medications and optimize delivery systems for increased bioavailability. To assess piperine's efficacy and safety in a range of patient groups, clinical studies are crucial. The study emphasizes how important it is to investigate piperine's chemopreventive qualities, especially for high-risk populations, in order to lower the incidence of cancer and its impacts on society. By advancing piperine-based treatments, these initiatives will increase patient survival rates and provide better cancer therapy alternatives.

3. AUTHORS CONTRIBUTION STATEMENT

Prof Dr Sheetal Asutkar wrote the initial draft. E. Lakshmi contributed to critical revision and supervision. Finally, Dr. Gurmeet Singh Chhabra has reviewed the article. All authors reviewed the manuscript.

4. CONFLICT OF INTEREST

Conflict of interest declared none.

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