Piperine Bioactive Roles in the Treatment of Lung Cancer

Ritu Jain[1], Ritesh Tiwari[1], Dindayal Patidar[1], Dharmendra Singh Rajpoot[1], Naveen Gupta[1], Ajay Kumar Shukla[2].

[1.] Department of Pharmaceutical Science, Madhyanchal Professional University, Bhopal, Madhya Pradesh, India

[2.] Department of Pharmaceutical Science, Institute of Pharmacy, Dr Rammanohar Lohia Avadh University Uttar Pradesh, India

Abstract

Primarily present in black pepper (Piper nigrum), piperine is an alkaloid that has attracted a lot of interest due to its possible medicinal use in the treatment of cancer, especially lung cancer. The mechanism of action exhibited by this bioactive molecule is diverse and involves reduction of metastasis, activation of apoptosis, inhibition of cancer cell proliferation, and manipulation of signaling pathways. The main mechanism by which piperine inhibits cancer cells is by interfering with their ability to grow and survive. These targets include PI3K/Akt, STAT3, and NF-κB. Piperine also provides a synergistic approach to cancer treatment by reducing the side effects and increasing the effectiveness of traditional chemotherapeutic medicines. Although more clinical testing is necessary, preclinical research shows that piperine may be able to slow the growth of tumors and stop them from spreading. The promise of piperine as a supplemental and alternative therapeutic agent is highlighted in this review, which summarizes recent research on its bioactive activities in lung cancer therapy. To create a thorough treatment plan for the treatment of lung cancer, more investigation is required to clarify its pharmacokinetics, bioavailability, and clinical application.

Keywords: Piperine, alkaloid, anticancer,bioactive compounds, pharmacokinetics, bioavailability, clinical applicability

1. INTRODUCTION

Spices have been utilised for millennia as both culinary enhancements and conventional medicines. Research emphasises the antioxidant, anti-inflammatory, and immune-enhancing characteristics of these substances, which may assist in the prevention and treatment of several types of cancer, such as lung, liver, breast, and prostate cancer. Spices such as turmeric, black cumin, ginger, garlic, saffron, black pepper, and chilli pepper include bioactive components such

as curcumin, thymoquinone, piperine, and capsaicin. These chemicals function by inducing apoptosis, suppressing oncogenesis, impeding cellular migration and invasion, and augmenting the efficacy of radiation and chemotherapy. A recent analysis highlights the significance of spices in the prevention and treatment of cancer, with a specific focus on their bioactive constituents and the ways in which they work [1].

2. Traditional medicinal plants on lung cancer.

Recent studies have explored the therapeutic properties of herbal substances in the treatment of lung cancer, which is a common type of cancer. Gaining knowledge about the factors that lead to lung cancer and the actions that may be taken to avoid it is of utmost importance, especially when considering the inhibition of proteins in the early stages of treatment. Researchers analysed the effect of active chemicals from traditional medicinal plants by using docking scores. This approach emphasises the importance of docking research in rapidly identifying efficacious molecules. The suppression of these bioactive substances on lung cancer is crucial, particularly considering the prevalence of such substances in traditional herbal remedies. An investigation assessed the impact of active components derived from conventional dietary supplements on lung cancer, juxtaposing them with conventional medications. The results indicate that these compounds have the potential to be subjected to clinical trials and eventually developed into pharmaceutical products [2].

2.1 Piperine induces apoptosis of lung cancer

The study sought to evaluate the effects of piperine on A549 cells, a type of human lung cancer cells, with a specific focus on its cytotoxic and apoptotic effects. Piperine exhibited cytotoxicity against A549 cells in a manner that was dependent on the dosage, but it had no impact on WI38 human lung fibroblasts. The cytotoxicity of the substance can be ascribed to the induction of DNA damage. Piperine caused a halt in the cell cycle at the G2/M phase and triggered the activation of caspase-3 and caspase-9 cascades in A549 cells, resulting in apoptosis. Administration of a caspase inhibitor partially impeded the process of apoptosis mediated by piperine. In addition, piperine reduced the expression of Bcl-2 protein while increasing the expression of Bax protein, which was positively associated with enhanced p53 expression compared to the control group. The findings indicate that piperine causes cell cycle arrest and

death through the activation of caspases and by changing the ratio of Bax to Bcl-2, mediated by p53. Piperine has potential as an effective anticancer drug for treating lung cancer, without causing harm to the host [3].

2.2 Piperine analogs arrest c-myc gene and exhibit anticancer activity

The nuclear phosphoprotein encoded by the regulator gene family Myc, a proto-oncogene, is involved in protein synthesis, apoptosis, cellular transformation and differentiation, and the advancement of the cell cycle in both normal and malignant cells. Thus, one of the most crucial targets in the development of cancer treatment is c-Myc. The work conducted by Pandya et al. (2021) investigates the efficacy of the Piperine analog PIP-2 as a potential anticancer treatment by specifically targeting the G-quadruplex (G4) motif located upstream of the c-myc gene. Below is an analysis of the main discoveries and consequences: G-quadruplex structures play a role in cancer development, and focusing on them, especially in relation to oncogenes such as c-myc, shows potential for cancer treatment.

The Anticancer Properties of Piperine: Piperine, a compound with therapeutic characteristics recognized in Ayurveda, demonstrates anticancer effects via stabilizing the G4 motif located upstream of the c-myc gene. The study utilized a chemical similarity approach to identify chemicals that are similar to Piperine. The objective was to evaluate how these compounds interact with cancer-associated G-quadruplex motifs. PIP-2 demonstrated significant selectivity, specificity, and affinity towards the c-myc G4 DNA among the investigated Piperine analogs. This conclusion was reached by conducting a range of biophysical investigations, including fluorescence emission, isothermal calorimetry, and circular dichroism. Biophysical and Molecular Dynamics Analysis: The biophysical data were corroborated by conducting molecular dynamics analysis, which improved the comprehension of the interaction between PIP-2 and the c-myc G4 DNA. Cellular-based investigations demonstrated that PIP-2 shown more toxicity towards the A549 lung cancer cell line in comparison to normal HEK 293 cells, suggesting enhanced effectiveness at the cellular level. The mechanism of action involves the use of biological evaluation tests, such as the TFP reporter assay, quantitative real-time PCR (qRT-PCR), and western blotting. These assays indicate that PIP-2 stabilizes the G-quadruplex motif found at the promoter site of the c-myc oncogene. This stabilization leads to the downregulation of c-myc expression. The study's findings suggest that the Piperine analog PIP-2

has the potential to be an effective anticancer treatment. This is because it can influence the expression of the c-myc oncogene through a mechanism involving G-quadruplexes [4].

2.3 Eugenol-piperine inhibition of thePI3K/AKT/mTOR signaling pathway and exhibit anticancer activity

Nasopharyngeal cancer originates from the epithelial cells of the nasopharynx and is commonly associated with risk factors such as smoking and the consumption of foods containing nitrosamines. This type of cancer is particularly common in Southeast Asia. Eugenol and piperine demonstrate substantial anti-cancer activity in several forms of cancer. This research integrates eugenol and piperine into a nanocomposite made of polyhydroxy butyrate and polyethylene glycol (Eu-Pi/PHB-PEG-NC) to improve the effectiveness of anticancer treatment against nasopharyngeal carcinoma (C666-1) cells. The study used C666-1 cell lines to assess the cytotoxic impact of Eu-Pi/PHB-PEG-NC on cell growth, apoptosis, and migration. The findings suggest that Eu-Pi/PHB-PEG-NC suppresses the growth of C666-1 cells in a manner that is influenced by the dosage. More precisely, when treated with a concentration of 15 µg/ml of Eu-Pi/PHB-PEG-NC, there is a considerable decrease in cell growth and an increase in programmed cell death, along with a decrease in the electrical potential across the mitochondrial membrane. Furthermore, administration of Eu-Pi/PHB-PEG-NC results in elevated levels of cleaved caspase-3, 8, and 9, as well as increased expression of the Bax gene, while reducing expression of the Bcl-2 gene. This indicates a heightened occurrence of apoptosis in C666-1 cells. In addition, the collective impact of Eu-Pi/PHB-PEG-NC loaded micelles hinders the proliferation of cells and stimulates programmed cell death by obstructing the PI3K/Akt/mTOR signaling pathway. The results indicate that Eu-Pi/PHB-PEG-NC has the ability to be an effective treatment for nasopharyngeal carcinoma [5].

Lung cancer, a widespread and deadly type of cancer worldwide, presents substantial difficulties despite progress in medical technology. Treatment outcomes are hindered by drug resistance and severe responses. In response to this issue, scientists have created a cutting-edge intervention known as iRGD-LP-CUR-PIP. This liposomal formulation has been modified with iRGD to improve its ability to penetrate tumors. This formulation simultaneously provides curcumin (CUR) and piperine (PIP), which are natural substances renowned for their anti-cancer

capabilities. The use of in vivo and in vitro tests showed that iRGD-LP-CUR-PIP had enhanced tumor targeting, cellular uptake, and anticancer effectiveness. The treatment successfully inhibited the growth and spread of tumor cells, demonstrating a synergistic impact of CUR and PIP. The study highlights the capacity of natural chemicals in focused lung cancer therapy, providing optimism for enhanced treatment results [6]. Malignant mesothelioma is an uncommon neoplasm that arises from mesothelial cells that line various bodily cavities, most commonly the pleural cavity but also the peritoneal, pericardial, or tunica vaginalis cavities. It has a tendency to grow in a scattered manner, causing compression of organs. The global incidence is on the rise, and the prognosis is unfavorable, with a median survival of approximately one year. Consequently, there is a pressing requirement for improved therapeutics. This review examines new studies on the anticancer properties of curcumin and its derivatives in treating mesotheliomas, and discusses their possible clinical significance [7].

3. REPORTED RESEARCH WORK ON ANTICANCER ACTIVITY OF PIPERINE

3.1 Anticancer and Cancer Prevention Effects of Piperine-Free Piper nigrum

A research study examined the anti-cancer and cancer-preventive effects of a piperine-free extract derived from Piper nigrum (PFPE) on breast cancer cells and the development of mammary tumors produced by N-nitrosomethylurea (NMU) in rats. The cytotoxic effects and mechanism of action were assessed by the utilization of MTT assay and Western blot analysis. The acute toxicity study adhered to the parameters set by the Organisation for Economic Co-operation and Development (OECD). Female Sprague-Dawley rats with tumors produced by NMU were utilized. The results demonstrated that PFPE had a more inhibitory effect on luminal-like breast cancer cells compared to basal-like cells by inducing apoptosis. PFPE is shown specificity towards breast cancer compared to other forms of cancer. The acute toxicity investigation showed that there were no deaths or illnesses observed at a dose of 5,000 mg/kg. In the study on cancer prevention, the occurrence of tumors was shown to be between 10% and 20% when treated with PFPE. The groups treated with PFPE had a considerably reduced rate of tumor growth in the investigation on anticancer activity. PFPE did not result in any negative biochemical or hematologic alterations. Overall, PFPE exhibited minimal toxicity and strong anticancer effects on the development of mammary tumors in rats [8].

3.2 Anticancer and Cancer Prevention Effects of Piperine by inhibition of lung metastasis

The effect of piperine on the suppression of lung metastasis produced by B16F-10 melanoma cells was investigated in C57BL/6 mice. Concurrently administering piperine during the process of tumor induction resulted in a substantial decrease (95.2%) in the production of tumor nodules. The administration of piperine resulted in a significant reduction in lung collagen hydroxyproline and uronic acid levels, as well as lung hexosamine content, when compared to tumor-bearing mice that did not receive treatment. In addition, the levels of serum sialic acid and serum gamma glutamyl transpeptidase activity were decreased in rats treated with piperine. The animals in the experiment also survived for a period of 90 days, and evaluation of their lung tissue by histopathology confirmed that their longevity was extended. The results emphasize the antimetastatic properties of piperine, an alkaloid present in plants such as Piper nigrum and Piper longum [9].

3.3 Protective effect of piperine on benzo(a)pyrene-induced lung carcinogenesis

The increasing prevalence of lung cancer highlights the urgent requirement for innovative approaches to address this deadly illness. Chemoprevention, a highly promising strategy, effectively tackles this difficulty. The connection between nicotine addiction and lung cancer is established by the presence of carcinogens in cigarette smoke. However, it is important to note that susceptibility to lung cancer can also be influenced by dietary and hereditary variables. This study investigates the potential of piperine in preventing the development of lung cancer and its effects on the growth of cells and indicators related to protein damage. A total of thirty Swiss albino mice were separated into five distinct groups. Group I acted as the control group and was administered maize oil orally. Group II was administered a dosage of 50 mg/kg body weight of benzo(a)pyrene (B(a)P) twice a week for a duration of four weeks in order to develop lung cancer by the 16th week. Group III was administered 50 mg/kg body weight of piperine every other day for a duration of 16 weeks, beginning with the initial dose of the carcinogen. Group IV was administered piperine starting from the sixth week of B(a)P induction and continued until the conclusion of the trial. Group V functioned as the control group for the drug, receiving only piperine. Administration of piperine resulted in a considerable decrease in levels of lipid peroxidation, protein carbonyls, nucleic acid content, and polyamine production in animals with

lung cancer. Piperine successfully prevented B(a)P-induced lung carcinogenesis in albino mice by safeguarding against protein damage and reducing cell growth [10].

3.4 Piperine Inhibits TGF-β Signaling Pathways and Disrupts EMT-Related Events in Human Lung Adenocarcinoma Cells

The compound piperine, derived from spices of the Piper genus, exhibits strong anti-tumor characteristics; nevertheless, its effects on epithelial-mesenchymal transition (EMT) remain uncertain. This study evaluated the toxic effects of piperine on lung adenocarcinoma (A549), breast adenocarcinoma (MDA-MB-231), and hepatocellular carcinoma (HepG2) cell lines, as well as its capacity to suppress TGF-β1-induced epithelial-mesenchymal transition (EMT). Piperine had cytotoxic effects at concentrations beyond 100 μM, with IC50 values of 214 μM for HepG2, 238 μM for MDA-MB-231, and 198 μM for A549. Low dosages of piperine effectively reversed the process of epithelial-mesenchymal transition (EMT) produced by TGF-β1 in A549 cells. Additionally, piperine decreased the phosphorylation of ERK 1/2 and SMAD 2. These findings indicate that piperine may be investigated as a potential treatment for metastatic cancer and illnesses associated to epithelial-mesenchymal transition (EMT) [11].

3.5 Prevention and Treatment of Colorectal Cancer by Piperine

The passage offers insights about the prevalence of colorectal cancer (CRC) and its potential correlation with lifestyle variables and food patterns. Below is an analysis of the main points: CRC is the third most frequently detected malignancy in the United States. In the United States, it ranks third in terms of the frequency of diagnosis, following lung cancer and breast/prostate cancer. The prevalence rate in the United States is roughly 52 cases per 100,000 individuals. In India, the occurrence of colorectal cancer (CRC) is far less than in the United States, with approximately 7 cases per 100,000 people. This notable disparity implies that lifestyle variables may have a pivotal influence on the development of CRC. Obesity, excessive alcohol use, high-calorie diets, and lack of physical activity are lifestyle variables that are associated with developing colorectal cancer (CRC). On the other hand, some elements in our diet, such as folates, selenium, Vitamin D, dietary fiber, garlic, milk, calcium, spices, vegetables, and fruits, have been linked to a reduced risk of colorectal cancer (CRC). Several substances present in natural foods [12].

3.6 Modulatory effect of Piperine on mitochondrial antioxidant system

Chemoprevention, a highly effective strategy for preventing cancer, is the utilization of bioactive chemicals derived from plants. The objective of this study was to evaluate the effect of piperine, a compound found in pepper, on the development of lung cancer caused by Benzo(a)pyrene (B(a)P). Supplementing mice with piperine at a dose of 50 mg/kg body weight decreased the development of lung cancer by reducing the oxidation of lipids in the mitochondria and enhancing the activity of certain enzymes (superoxide dismutase, catalase, glutathione peroxidase) as well as non-enzymatic antioxidants (reduced glutathione, vitamin E, vitamin C) when compared to animals exposed to the carcinogen. The chemopreventive actions of piperine are most likely achieved through the regulation of lipid peroxidation and the enhancement of the antioxidant defense system (Selvendiran 2004). The study investigates the cytoprotective effect of piperine against lung cancer produced by benzo[a]pyrene in Swiss albino mice, focusing on its impact on lipid peroxidation and the antioxidant system. The study examined the preventive effects of piperine against lung cancer generated by benzo[a]pyrene (B[a]P) in male Swiss albino mice. Oral administration of piperine at a dosage of 100 mg/kg body weight significantly inhibited the progression of lung cancer induced by B[a]P. This was demonstrated by a reduction in lipid peroxidation and an elevation in the levels of enzymatic antioxidants such as superoxide dismutase, catalase, and glutathione peroxidase, as well as non-enzymatic antioxidants like reduced glutathione, vitamin E, and vitamin C. These data indicate that piperine may influence lipid peroxidation and strengthen the antioxidant defense system, potentially leading to chemopreventive benefits [13].

3.7 Development and evaluation of a novel drug delivery

The objective of the study was to increase the practical use of piperine, which is known for its capacity to suppress tumors, by enhancing its ability to dissolve in water through the use of mixed micelles. Mixed micelles containing piperine were made and analyzed. Cellular internalization and toxic effects were verified in lung and liver carcinoma cells. The in vivo pharmacokinetic experiments demonstrated enhanced drug delivery efficacy of the micelles in comparison to free piperine. The findings indicated that piperine-loaded mixed micelles had the

potential to be used as a nano-drug delivery system for cancer treatment, providing enhanced effectiveness compared to traditional approaches [14].

3.8 Chemopreventive effect of piperine

The study aims to evaluate the effect of orally administered piperine on the beginning of lung tumors induced by benzo(a)pyrene (B(a)p). At first, the impact of piperine on ATPase enzymes was investigated. Mice with lung cancer showed elevated amounts of ATPase enzymes in both erythrocyte membranes and tissues, specifically Na(+)/K(+)-ATPases, Mg(2+)-ATPases, and Ca(2+)-ATPases. Nevertheless, the activities of Na(+) K-ATPase and Mg-ATPase were reduced, while the activity of calcium ATPase was raised in rats with lung cancer, as compared to the control group. These modifications indicated that the harmful impacts of B(a)p continued to exist in animals affected by cancer. However, the administration of piperine at a dosage of 50 mg/kg body weight was able to reverse these enzyme activities, bringing them close to the values observed in the normal control group. The positive benefits of piperine seemed to mainly impact the beginning and subsequent stages of B(a)p-induced lung carcinogenesis. Therefore, these findings indicate that when piperine is taken orally, it has preventative benefits against lung cancer in mice [15].

3.9 Piperine suppresses tumor growth and metastasis

The objective of the study was to examine the effects of piperine, a powerful alkaloid present in Piper nigrum and Piper longum, on the development and spread of mouse 4T1 mammary cancer. The researchers utilized both in vitro and in vivo models to investigate the underlying mechanisms. The results of the in vitro studies demonstrated that piperine effectively suppressed the development of 4T1 cells. This inhibition was seen to be dependent on both the duration of exposure and the concentration of piperine. The IC(50) values for piperine were determined to be 105 ± 1.08 μmol/L at 48 hours and 78.52 ± 1.06 μmol/L at 72 hours. Piperine treatment resulted in death of 4T1 cells and caused an increase in the proportion of cells in the G(2)/M phase, while simultaneously decreasing the production of cyclin B1. In addition, piperine reduced the expression of matrix metalloproteinases (MMPs), specifically MMP-9 and MMP-13, resulting in suppressed cell migration in laboratory conditions. Piperine's anticancer properties were further demonstrated through in vivo tests. The administration of piperine effectively slowed the growth

of the main 4T1 tumor in a manner that depended on the dosage, and it also greatly suppressed the spread of the tumor to the lungs. The results indicate that piperine exhibits potential as a potent antitumor agent, both in laboratory experiments and in living organisms, suggesting its potential as a new and innovative medicine for treating cancer [16].

3.10 Chemopreventive effect of piperine on mitochondrial TCA cycle

Piperine, which is present in black and long pepper, is utilized in traditional medicine. Significant alterations were detected in an investigation with Swiss albino mice that were subjected to Benzo(a)pyrene-induced lung carcinogenesis. The mice with lung cancer exhibited reduced activity in mitochondrial enzymes (ICDH, KDH, SDH, MDH) and increased activity in phase I enzymes (NADPH-C reductase, cyt-p450, cyt-b5). Additionally, there was a decrease in the activity of glutathione-metabolizing enzymes (GPx, GR, G6PDH). Nevertheless, the addition of piperine resulted in a decrease in phase I enzymes and an increase in glutathione-metabolizing enzymes, indicating a potential anti-tumour and anti-cancer impact. When piperine was administered by itself, there were no notable changes in enzyme activity. In addition, the treatment of piperine to rats treated with Benzo(a)pyrene resulted in an increase in mitochondrial enzyme activity, suggesting its involvement in energy production [17].

3.11 Oral supplementation of piperine

In recent years, the emphasis has been on discovering novel chemopreventive agents for the promotion of human health. Piperine, an ingredient found in black and long peppers, is extensively utilized as a seasoning globally. A study examined the protective effect of piperine in the development of lung cancer, specifically focusing on its influence on DNA damage and detoxification enzymes. Animals with lung cancer exhibited reduced activity of detoxifying enzymes such as GST, QR, and UDP-GT, as well as elevated levels of hydrogen peroxide. Administering piperine at a dosage of 50 mg per kilogram of body weight resulted in an increase in detoxification enzymes and a decrease in DNA damage, as evidenced by single-cell electrophoresis. In addition, the supplementation of piperine altered the levels of DNA-protein cross-links, which are increased in cases of lung cancer. The results indicate that piperine's ability to inhibit peroxidation may play a role in its cancer-preventive properties [18].

3.12 In vivo effect of piperine on serum and tissue glycoprotein levels

Current studies have been dedicated to identifying novel substances that can prevent cancer. One such substance is piperine, an alkaloid present in black and long peppers, which has attracted interest because of its antioxidant and anticancer characteristics. A study examined the impact of piperine on lung cancer induced by benzo(a)pyrene (B(a)p) in mice. The findings indicated that administering piperine at a dosage of 50 mg/kg body weight resulted in a decrease in the levels of total protein and protein-bound carbohydrates in mice with lung cancer, both during the initiation and post-initiation stages. These findings indicate that piperine may inhibit the formation of tumors by regulating the levels of carbohydrates bound to proteins [19-20].

3.13 Anticancer and Cancer Prevention Effects of Piperine against human lung, cervical and liver cancer cells.

Benjakul, a traditional Thai medication consisting of a combination of five plants, has traditionally been employed by traditional healers in the southern region of Thailand to treat individuals suffering from cancer. The objective of the study was to investigate the cytotoxic effects of Benjakul and its constituents on three types of human cancer cells: large lung carcinoma (COR-L23), cervical cancer (HeLa), and liver cancer (HepG2), in comparison to normal lung fibroblast cells (MRC-5), using the SRB test. The extraction procedure replicated the traditional approach used by folk doctors, which included soaking in ethanol and boiling in water. Cytotoxic chemicals were found through the process of bioassay-guided isolation. Plumbago indica root (PL), Zingiber officinale rhizome (ZO), Piper chaba fruit (PC), Piper sarmentosum root (PS), Benjakul preparation (BEN), and Piper interruptum stem (PI) demonstrated targeted effectiveness against lung cancer cells in their ethanol extracts, however the water extracts did not exhibit any hazardous effects. The ethanolic extract of BEN yielded three active ingredients: 6-gingerol, plumbagin, and piperine. Plumbagin exhibited the greatest cytotoxicity towards COR-L23, HepG2, HeLa, and MRC-5 cells. The results of this study provide evidence that Benjakul can be used in the treatment of cancer, and propose that 6-gingerol, plumbagin, and piperine could be used as biomarkers to standardize the formulation [21].

3.14 Anticancer and Cancer Prevention Effects of Piperine against small cell lung cancer cell line

Benjakul, a traditional Thai herbal cure consisting of a combination of five plants, has been historically employed for the treatment of individuals suffering from cancer. Research indicates the need to examine the cytotoxic effects of the substance and analyze its separated constituents to determine any potential therapeutic advantages. The objective of the study was to evaluate the cytotoxic effects of the Benjakul extract and its individual components on human small cell lung cancer cells (NCI-H1688) and normal human lung fibroblast cells (MRC-5). The ethanolic extract was subjected to bioassay-guided fractionation to separate active compounds. Subsequently, the cytotoxicity of these compounds was assessed using the SRB assay. The ethanolic extract demonstrated cytotoxicity against NCI-H1688, with an IC50 value of 36.15±4.35 μg/ml, whereas the hexane fraction displayed the highest cytotoxic activity at 21.17±7.42 μg/ml. A total of six distinct substances were found, namely myristicin, plumbagin, methyl piperate, 6-shogaol, 6-gingerol, and piperine. Plumbagin had the greatest cytotoxicity, with 6-shogaol following closely behind. Piperine exhibited the most substantial concentration in both the HPLC study and column chromatography. Plumbagin and 6-shogaol have been identified as important bioactive markers in the fight against small cell lung cancer. The technique of chromatographic fingerprinting can be employed to analyze the six cytotoxic chemicals that have been extracted from the ethanolic extract of Benjakul [22].

3.15 Piperine's anticancer and cancer-prevention effects stem from its cytotoxic activity, NF-κB inhibitory impact, and suppression of cell migration.

Nandakumar N et al. conducted the synthesis and evaluation of coumaperine and its derivatives for their cytotoxic effects on L428 and A549 cells, as well as their ability to inhibit NF-κB activity. CP-9 and CP-38 effectively inhibited the activity of NF-κB subunits p50 and p65 in the nuclear fractions in a manner that depended on the dosage. This was proven by the use of western blot and luciferase reporter gene test. These results were further confirmed using confocal microscopy. CP-9, CP-32, and CP-38 showed a cytotoxic effect on L428 and A549 cells that varied depending on the dose. The IC50 values for L428 cells were 43.25 μg/ml, 0.39 μg/ml, and 16.85 μg/ml for CP-9, CP-32, and CP-38 respectively. For A549 cells, the IC50 values were 57.15 μg/ml, 69.1 μg/ml, and 63.2 μg/ml respectively for CP-9, CP-32, and CP-38.

In addition, these compounds had notable inhibitory effects on the migration of cancer cells, specifically CP-9, CP-32, and CP-38, at concentrations of 5 μg/ml, 10 μg/ml, and 5 μg/ml, respectively. The inhibitory action was impacted by the presence of aromatic substituents and olefinic double bonds, with di-olefin conjugated derivatives showing greater activity compared to tri-olefin conjugated ones. The compound CP-32, which contains an electron-donating group (-N(CH3)2), exhibited exceptional inhibitory action. CP-9, which did not have any additional components, successfully suppressed the growth and movement of A549 cells. At concentrations of 10 μg/ml and 30 μg/ml, CP-9 and CP-38 respectively caused a considerable reduction in the nuclear fractions of NF-κB subunits (p50 and p65) in L428 cells. This suggests that CP-9 and CP-38 effectively deactivated the NF-κB pathway in vitro [23].

3.16 Determination of Piperine using HPLC.

Benjakul, a traditional Thai medicine, is renowned for its ability to enhance overall well-being and maintain a state of equilibrium in the body. In southern Thailand, traditional healers have traditionally employed it as an adaptogen for those suffering from cancer. A recent study demonstrated that the ethanolic extract of Benjakul displayed strong cytotoxic effects on lung cancer cells. Piperine was discovered as the primary ingredient in the extract, while plumbagin was found to be the most cytotoxic compound. A reversed-phase high-performance liquid chromatography (HPLC) approach was created to guarantee the quality and stability of the substance. This method allows for chemical fingerprinting, quantification, and stability assessment. The utilization of a gradient mobile phase consisting of water and acetonitrile, with detection at 256 nm, demonstrated precision, accuracy, and stability in detecting piperine and plumbagin in the extract. This analytical methodology has the potential to be highly useful in evaluating the efficacy of the Benjakul extract in future research endeavours [24].

4. Natural Anticancer Agents:

The passage offers insights about the prevalence of colorectal cancer (CRC) and its potential correlation with lifestyle variables and food patterns. Below is an analysis of the main points: CRC is the third most frequently detected malignancy in the United States. In the United States, it ranks third in terms of the frequency of diagnosis, following lung cancer and breast/prostate cancer. The prevalence rate in the United States is roughly 52 cases per 100,000 individuals.

In India, the occurrence of colorectal cancer (CRC) is far less than in the United States, with approximately 7 cases per 100,000 people. This notable disparity implies that lifestyle variables may have a pivotal influence on the development of CRC. Obesity, excessive alcohol use, high-calorie diets, and lack of physical activity are lifestyle variables that are associated with developing colorectal cancer (CRC). On the other hand, some elements in our diet, such as folates, selenium, Vitamin D, dietary fiber, garlic, milk, calcium, spices, vegetables, and fruits, have been linked to a reduced risk of colorectal cancer (CRC). Several substances present in natural foods, known as nutraceuticals, have been recognized for their ability to potentially prevent and treat colorectal cancer (CRC). Some examples of these chemicals are cardamonin, celastrol, curcumin, deguelin, diosgenin, thymoquinone, tocotrienol, ursolic acid, and zerumbone. Contrary to pharmaceutical medications, these compounds possess the capability to selectively affect various pathways linked to colorectal cancer (CRC), such as transcription factors, growth factors, inflammatory pathways, and angiogenesis. Research has shown that certain dietary substances can effectively hinder the growth of colorectal cancer cells in laboratory settings and reduce the growth of tumors in animal experiments. These agents have undergone clinical studies to assess their effectiveness in humans. These nutraceuticals show promise as potential candidates for treating CRC due to their combination of safety and affordability. Nutraceuticals provide a new and promising option for treating CRC, offering a potentially successful and easily accessible method for managing this disease. To summarize, the chapter emphasizes the significance of lifestyle factors and dietary habits in the development of colorectal cancer (CRC) and introduces the potential of nutraceuticals as promising agents for both preventing and treating CRC [25].

5. CONCLUSION

Piperine is very potential bioactive compounds. It is also called magical molecules because their broad spectrum activities. It has been found that it is also responsible for enhance bioavailability of many drug. Currently still required more research work to find out what is a main key factor responsible behind these therapeutic roles.

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