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Therapeutic Potential of Piper longum: A Review of Piperine and Piperlongumine in Human Health

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ABSTRACT

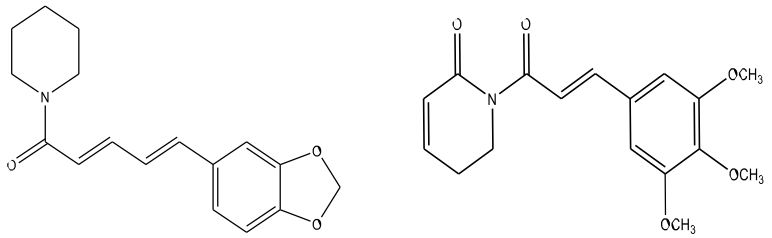
In the contemporary context, research on plant alkaloids, plant-based products, and nutraceuticals is crucial. Scholars and scientists are focusing more on this area because there is a lot of medication available today to address conditions including kidney disease, cancer, hypertension, and hyperlipidemia, but the side effects of these medications have not yet been regulated. Therefore, research on plants and plant-based products is crucial. The primary bioactive components of the medicinal plant Piper longum are piperlongumine (PL) and piperine (PP). These compounds have a wide range of medicinal effects, including anti- cancer, analgesic, antipyretic, antioxidant, antimicrobial, antifertility, promoter of permeability, cardioprotective, immune-stimulating, and many more. The primary bioactive components of the medicinal plant Piper longum, piperine (PP) and longumine (PL), are the phytochemicals we will examine in this review along with their diverse therapeutic effects on the healthcare system of humans.

Keywords: *Piperlongumine, Piperine, Anti-cancer, Anti-inflammatory*

1. INTRODUCTION

Piper Longum Linn., also known as Indian Long Pepper, is a perennial herb in the Family of Piperaceae. *P. longum* is a small shrub with a massive piney base and many trickling, fused branches, Branches with enlarged endpoints. The leaflets include shears of varying diameters, are dispersed, alternate, and lack stipules. In comparison, the upper leaves are 23% longer than the lower leaves, which are 57% longer. Flowers grow in solitary spikes. The blackish- green, blunt, rectangular fruits grow on spongy spikes. Length of 3–4 cm and thickness of 4-5 mm [1].The plant is native to South Asia and can also be found in both forests and farmed all across the hot and humid areas of India, from the center towards the northeastern Himalayan region. The herb can also be found growing wild in Malaysia, Singapore, Nepal, Bhutan, Sikkim as well as Myanmar [2]. The main bioactive compounds present in *P. longum* seem to be an amide alkaloid that contains 5-9 percent piperine [3]. The above root oil contains citral, β –Caryophyllene, terpenes sabinene, alpha-pinene and beta-pinene, limonene, phellandrene, and linalool, as well as other compounds, piperine and piperlongumine are the main compound of this plant Shown in figure 1 and 2 [4]. *P. longum* contains antioxidants compound including lauric, palmitic acids, myristic, and beta carotene, as well as piperine. Piperine has elicited a variety of therapeutic properties in olden history, according to widespread physiological activities. The Spikes, as well as Stalks parts of P. longum, are also the primary sources of piperlongumine as well as piperine. Several studies have been published on such piperine content of long pepper spikes, but still, only a few have been published on the piperine content of the root parts [5]. Long pepper seems to be an autoicous and ornamental vine grown as well as collected throughout the tropical region in India, Bangladesh, Sri-lanka and Nepal. Long pepper is among the most popular spices, and its spiciness has been indicative of the presence of piperine, an alkaloid, active chemical components, as well as essential oils. Piperine is identified within Piperaceae family's long pepper, white pepper as well as black pepper

piperine as well as piperlongumine have a variety of natural activities, including antioxidant, antitumor, bioenhancer, analgesic, anti- inflammatory, hepatoprotective, antithyroid, antihypertensive, anti-pyretic, antiasthmatic, as well as CNS-depressant properties (Shown in figure 3). Piperine as well as piperlongumine are anti-Alzheimer's, antidepressant, anti-larvicidal, and also most notably, bioavailability enhancers. In this review, we have used PubMed, Science Direct and other resources to locate and critically evaluate 30 years' worth of studies that concentrated on various clinically significant and related conditions involving active ingredients from piperine and Piperlongumine and their plant-based products.



(A) **(B)**

Figure: 1 Chemical structure of piperine and piperlongumine

2. ABSORPTION AND METABOLISM-

Piperine accumulation and biochemical conversion have been thoroughly researched throughout to track their prospective effects on various healthy life abnormalities. Piperine has been assimilated (97%) and discovered to be self-reliant in administration mode once given to albino mice via tube feeding or intraperitoneal injection at dose levels of 170 and 85 mg/kg, correspondingly. Despite this, only 3% of the total administered dose has been removed from the body as piperine in feces, without a remnant detected in the urine. Additionally, when 100-1,000 g of piperine was administered to the everted sacs of rodent intestines, 45-64 percent of the piperine faded away from the mucosal side, resulting in the greatest amount of absorption (60-63%). Biological effects of piperine shown in Table 1. Furthermore, when compared to systemic spice contemporaries like curcumin, the ultimate quantities of piperine assimilated have been substantially greater [7]. Even though, recent research has shown that piperine rate of absorption through the use of orally administered is improved by nano-encapsulation as well as the eventual results piperine-loaded nanostructures [8]. During absorption, piperine does not experience any alterations in metabolism. Since evidenced by its presence in both colon tissue as well as sub mucosal fluid, which further endorses scientific evidence that this remains unaffected Structures of piperine and its analogs during the adsorption step. Furthermore, once piperine has been blended into micelles, it enhanced absorption of dietary, as illustrated by such an in vitro everted digestive model.

Table: 1 Piperine and also its Biological Effects

Disorders	Mechanisms of Action
Allergy	▪ Leads to the inhibition of cytokine activity as well as the secretion of -hexosaminidase and inflammatory mediators. ▪ Piperine and Piperlongumine, which reveals it as a possible therapeutic target in ocular anti-inflammation. The data also demonstrates that the anti-inflammatory effects of Ac2-26 and PL when provided separately are nullified when combined. ▪ Decrease IL-1β, IL-6, as well as IgE expression. ▪ Impedes leucocyte infiltration as well as hyperplasia.
Anti- Inflammatory	▪ This leads to a reduction in Interleukins 1β, TNF-, as well as IL-6 overexpression while increasing IL-10 expression ▪ Blocks the action of Nuclear factor- B and Mitogen-activated- protein kinase, p65, I-B, ERK, p38, as well as JNK.
Anti-cancer	▪ Piperine inhibited the growth of human follicular thyroid cancer cells by inducing apoptosis and autophagy and preventing the cells from dividing in the G2/M phase of the cell cycle. ▪ Piperlongumine induces apoptosis via reactive oxygen species (ROS)-mediated

	oxidative stress, making it a selective cytotoxic agent against cancer cells.
Type 2 diabetes	▪ Reduces alanine but also aspartate aminotransferases and serum enzyme levels, as well as renal (urinary protein) disorder. ▪ Reduces blood sugar while increasing insulin release
Cardiovascular diseases	▪ Provides protection against pyruvate dehydrogenase as well as Kreb's cycle enzyme decrease.
	▪ Changes in mitochondrial structure, inflammation, di-tyrosine level, as well as Damage to DNA in mitochondria. ▪ Inhibits cardiovascular action potential irregularities.
Obesity	▪ Inhibits changes in physical mass, muscle tone, fat percentage, visceral fat indicator, blood volume, leptin, adiponectin, erythrocytes, as well as tissue lipid levels caused by the HFD. ▪ SREBP-1c, as well as C/EBP mRNA expression decrease
Aging	▪ Reduces the effects of MPTP on motor control as well as cognitive performance. ▪ Protects against MPTP-induced lowering in tyrosine hydroxylase- positive cells. ▪ Piperine To rejuvenate the body and delay the onset of cancer and other age-related disorders in humans, as well as to extend their lifespan, selective depletion of senescent cells (SCs) has been proposed as a novel anti-aging therapy.

3. PERSPECTIVES ON THE TOXICOLOGY OF PIPERINE AND PIPERLONGUMINE-

The main way that humans take piperine is through their food. Because of this, exposure to this material varies substantially based on dietary practices and the total amount of foods containing piperine consumed. Black pepper is one of the staple elements found in many Asian countries, whether they are made at home or bought from food sources, marketing malls, or small-time vendors. Recent sources state that piperine's dry mass comprises 5.35 percent piper nigrum. [9]. However, the amounts of piperine in food and drink might vary from 0.5 to 7 ppm in caramels to 640 ppm in dried items. [10]. The amount of P. Nigrum consumed through a range of meals may be used to determine an individual's exposure to this chemical, as piperine accounts for 40% of Piper nigrum oleoresins. One pg kg1 of piperine is consumed daily by a person using this method. Additionally, it is known that the piperine NOAEL (no identifiable adverse impacts) is five mg kg1 day [11] . Piperine has been shown in carcinogenicity studies to inhibit the formation of micronuclei in rodents exposed to both cyclophosphamide and benzo[a]pyrene. [12]. However, a conflict between investigations conducted both in vivo and in vitro has found that high ingestion of piperine produces positive results. In both in vitro CHO Cell as well as in vivo research, piperine was established to be non-genotoxic [13]. Particularly potent are piperine's inhibitory effects against breast cancer (BC), the most prevalent cancer in women worldwide. PIP influences numerous signaling pathways that are important for treating BC cells.[14].

4. HEALTH CONSIDERATIONS.

4.1 Antidiabetic-

The P. longum plant's ethyl alcohol crude was demonstrated to have anti-diabetic effects in diabetic rats. By altering adipokines, piperine and curcuminoids have also been demonstrated to control energy metabolism in type II diabetes mellitus. [15]. The antihyperlipidemic and antidiabetic properties of piperine were found in rats with diabetes produced by streptozotocin, respectively. [16]. It was found that ingesting the extract raised blood glucose levels again, which in turn triggered liver processes to maintain blood glucose levels within typical ranges of homeostasis. The plant's aqueous extract showed significant anti-diabetic effects in rats, with a dose of 200 mg/kg b.w. after 6 hours of treatment with the eluent in various studies on streptozotocin-influenced diabetic mice. [17].

4.2 Anticancer-

Malignancy is a terrible disease that kills several thousand people each year in addition to is the world's second most common cause of death. Treatment is ongoing and a major therapeutic option for various cancers, even though rebellion, toxicity, and target mutation are significant reasons why chemotherapy fails. As a result, more research is needed to identify and create novel anticancer agents capable of preventing that kind of cause of chemotherapeutic failure. Without a doubt, natural anticancer agents are being approved for clinical trials these days [18]. Therefore in context, the antineoplastic effect of various natural molecules, such as piperlongumine and piperine, has been extensively researched, with several publications and journal articles published in recent decades. These studies are in favor of using natural compounds as cancer treatment and prevention agents [19]. Piperine must have recently been discovered as a substantial antineoplastic agent, regulating a potential antineoplastic agent that regulates autophagy. It exhibited improved antineoplastic effectiveness in vivo and could be an effective anticancer drug contender [20]. According to recent research, piperine was used both alone and in conjunction with other drugs to improve cytotoxic activity and effectively control tumorigenesis. When compared to free DTX, co-treatment with piperine and docetaxel (DTX) had a stimulating impact on the catalytic activity and anticarcinogenic function in cell lines (HepG2) [21].

4.3 Immunomodulatory-

The *P. longum* alcoholic extract was used to demonstrate the extract's immunomodulatory properties. The alcoholic fruit extract and piperine component were administered to the rat animal. By replenishing inflammation markers and halting glutathione decrease, piperine enhances antioxidant activity. Additionally, piperine increases cell viability and reduces the generation of reactive oxygen species (ROS) as well as caspase-3 (Kumar et al. 2015). A

notable rise within WBC numbers and plaque-forming cells that contribute to the manufacture of antibodies was seen, and these changes eventually stimulated the hematopoietic system, suggesting stem cell propagation and the body's immune system as a whole [22]. Furthermore, piperine significantly influenced the immune response to metal (cadmium) influenced immunotoxicity in mice, implying that piperine has immunoprotective properties [23]. N-(p-nitrophenyl) acetamide-piperine, a piperine-like compound, has low toxicity and anticancer effects via Th1-mediated immunomodulation [24].

4.4 Antioxidant

The antioxidant properties of such isolate are determined by the ROS activity of the DPPH free radical [25]. Phenolic chemicals and flavonoids have antioxidant effects against oxidative damage caused by free radicals. In addition, petroleum ether extract and piperine components of roots reduced lipid peroxide levels while maintaining glutathione levels [26]. The extract therefore had hepatoprotective, antiviral, and anticancer effects. Piperine from the roots and petroleum ether extract from P. longum roots lower lipid peroxide levels while preserving glutathione levels, indicating antioxidant activity. Together with anticancer qualities, the extract also possessed hepatoprotective and antiviral qualities. [27].

4.5 Hepatoprotective activity.

The hepatoprotective effect of plant fruit solvent extract against carbon tetrachloride-induced severe, chronic, reversible, and irreversible damage was investigated in mouse models using morphological, biochemical, and histological characteristics. The extract inhibits fibrosis to aid in healing, but it provides little defense against genuine illness or liver disease. Piperine has been demonstrated in vitro to protect against hepatic injury caused by carbon tetrachloride and tertiary butyl hydroperoxide by lowering lipid oxidation [28].

4.6 Antifertility

To study the antifertility effects of benzene derived from P. longum root, female mice were used as a model. In the female rat model, it was discovered that the oral bioavailability of the bioactive component in a mixture through E. ribes berries inhibited the pregnancy rate by 80%. *P. longum* solvent extract contains an immobility component that reduces sperm quality and mobility by disrupting the outer layer of sperm cells [29].

4.7 Antiplatelet

It has been demonstrated that the fruit P. longum contains the antiplatelet agent's piperine, pipernonaline, piperlongumine, and piperoctadecalidine, which inhibit the aggregation of washed rabbit platelets. Depending on the dose, polyunsaturated lipids (arachidonic acid), thrombin factor, and collagen all reduced washed platelet activation [30].

4.8 Antiulcer

The antiulcer potential of *P. longum* extract was examined. When compared to doxycycline, it was shown that giving the extract to animals under stress caused by foot shock reduced ulcer severity by up to 90. Piperine, a *P. longum* alkaloid, inhibited stomach emptying (GE) as well as alimentary tract in rats and mice as in dose- as well as the time-dependent way. The inhibiting action of piperine on GE is unaffected by stomach acid or pepsin secretion [31].

4.9 Antimicrobial activity

Antimicrobial activity was tested on bacterial pathogens such as Salix alba, Salmonella typhi, E. coli, and one fungus,

Aspergillus niger, using various extracts such as fruit and root extracts. The plant extract has high antibacterial action when compared to Streptomycin. N-Hexane extract and separated components exhibited variable degrees of antibacterial activity against all of the microorganisms tested .*P. longum* extracts in organic solvents such as petroleum ether as well as ethyl acetate were reported to have antibacterial properties against a variety of microorganisms [32]. Researchers investigated the antimicrobial activity of Piperine and mupirocin be effective against S. aureus strains, counting methicillin-resistant S. aureus. Even though piperine is shown in the direction of impede efflux in the wild as well as mutant strains as a potential method of mupirocin activity stimulatory effects, such scientists showed that the combination greatly decreased the MIC of mupirocin and reduced the mutation incidence [33].

4.10 Anti-Inflammatory Effect

In acetaminophen-challenged rats, piperine reduces the action of enzymes that produce liver such as alkaline phosphatase, alanine transaminase, and aspartate transaminase, indicating hepatoprotective as well as antioxidant effect, Physiological activities of piperine include anti-asthmatic, anti-tumor and immunomodulatory, cytoprotective, and hepatoprotective effects, as well as other notable properties such as anti-apoptotic, anti- inflammatory, and bioavailability enhancing abilities. These abilities make piperine an excellent choice for treating pathological conditions affecting the central nervous system (CNS), cardiovascular system (CVS), gastrointestinal tract (GIT), bone, and other tissues. [23].

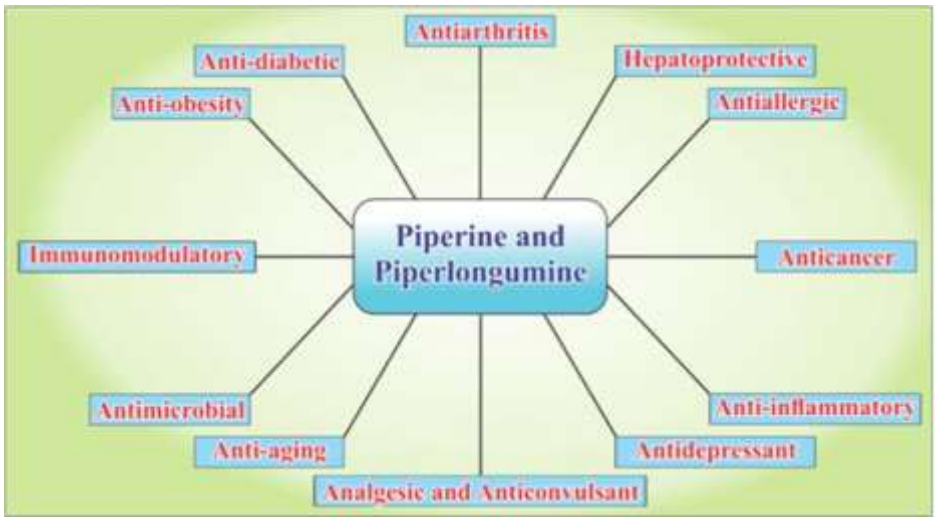


Figure 2: Health prospective piperine and piperlongumine

5. COMBINATIONAL THERAPY USING PIPERLONGUMINE AND PIPERINE

Piperine exhibits satisfactory anticancer efficacy (forward into tumor cells) against a wide range of malignancies, including lung, cervical, breast, prostate, and other cancers, according to in vitro research on various malignancy cells. When Kumar and colleagues 20 used rotenone and iron dietary supplements to stimulate animals with Parkinson's disease, they discovered that piperine significantly enhanced quercetin's neuroprotective, anti-inflammatory, and ROS scavenging effects. Piperine and piperlongumine affect Bcl- 2 to promote apoptosis in the cancer cells shown in Figure 3 [34].

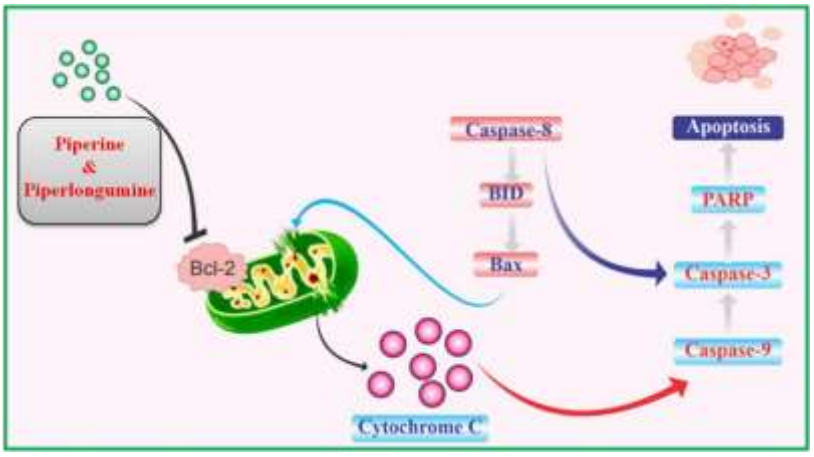


Figure 3: Role of piperine and piperlongumine in apoptosis

Piperine significantly increased the degree of lipid peroxidation during the DMBA- induced carcinogenesis of the buccal pouch in hamsters. The chemo preventive efficacy of piperine was demonstrated by FT-IR spectroscopic analysis, which revealed reduced protein and nucleic acid levels in cancer cells with an unknown etiology (Krishnakumar et al. 2009). In AGS adult gastric cancer cells, piperine decreases transcription factor, XIAP (anti-apoptotic), Bcl-2, and Akt while raising p53, Bax (pro-apoptotic), cleaved caspase-9, and cleaved-PARP. According to Xia et al. (2015), piperine inhibits Interleukin-1 from initiating STAT3 and p38 MAPK, which in turn stops IL-1 from triggering the synthesis of Interleukin-6 in TMK-1 intestinal cancer cells.

As well lessens survivin (inhibitor of apoptosis protein) Bcl-2, and levels while increasing Fas levels, inhibiting the growth of human colorectal tumor cells lineHT-29. In some cancer cell lines like HT-29 colon cancer cells, alkaloids piperine decreases the expression of cyclins such as D1 as well as D3 along with cyclin-dependent kinases (CDK-4 and 6), in addition to enhancing the appearance of kinase inhibitors p21/WAF1 as well as p27/KIP1 [35]. Discovered to facilitate this normal product reduced about development of human rectal adenocarcinoma cell line (HRT-18) through process of apoptosis. Similar research showed that a piperine-treated cancer cell's production of reactive oxygen species (ROS) increased, at least in part, as a result of these effects. Chronic inflammation and the development of colorectal cancer have been connected to the stimulation of the mechanism of action target of rapamycin complex 1 (mTORC1). Piperine, either alone or in combination with curcumin, inhibits TNF but also mTORC1 on human gastrointestinal epithelial cells, inhibiting the development of colon cancer. A fluorometric imaging plate reader (FLIPR) assay using Chinese hamster oocyte cells transfected with the 12 subunits of the GABAA receptor was used to confirm the effects of bioactive components and plant extracts on GABAA receptor modulation. This assay was created to detect various plant crude extracts and various active compounds (Biswas et al. 2022).

5.1 In a cervical cancer cell line, piperlongumine (PL) enhances the anticancer activity of doxorubicin and paclitaxel.

The fact that PL by itself caused cell death in cell lines must have been found. When doxorubicin and paclitaxel were coupled, the combined action of PL increased cell death compared to the single cytotoxic drugs. [37]. In pancreatic cancer cell lines, PPLGM appears to function, at least in part, through the JNK and MEK/ERK pathways by triggering JNK and ERK, which may induce apoptosis-inducing enzymes or phosphorylate regulatory proteins that regulate the expression of pro-apoptotic genes [38]. Previous investigations have shown that PPLGM raises the expression of several proteins, such as Bax and p53, in addition to p21, in colorectal cancer, oral cervical carcinoma, and myeloid leukemia, including both [39].

5.2 Piperlongumine and breast cancer.

Piperlongumine-induced ROS helps facilitate the downregulation of such receptor proteins in breast cancer cells. Even when compared to decreased HER2 along with MCF 7 cell expression, the responsiveness to piperlongumine appears to be a little bit stronger in HER2-overexpressing BT474 and SkBr3 breast cancer cells [40]. Additionally, compared to human breast epithelial MCF-10A cell lines, piperlongumine is substantially more harmful to breast cancer cell lines MCF-7 [41]. In addition, Breast cancer (triple- negative breast cancer MDA-MB-231 and MDA-MB-453 cell lines)/ (female nude mice bearing MDA-MB-231 tumor xenografts) Doxorubicin in addition to piperlongumine (peritoneal administration every other day for 3 weeks). By impairing the JAK2-STAT3 signalling pathway in vitro and in vivo, piperlongumine and doxorubicin anticancer medication co-treatment promote apoptotic cell death in breast cancer cells. Doxorubicin (0.8 mg/kg) or piperlongumine (4 mg/kg) administration alone resulted in a significant reduction in the growth rate of breast tumors, but combined treatment with piperlongumine (4 mg/kg) and doxorubicin (0.8 mg/kg) results in an additive reduction the rate of cell proliferation. No discernible difference in body mass has been found between the groups receiving treatment and those who have not, indicating that the therapy is not being adversely affected by the treated patients [42].

5.3 Piperlongumine and oral cancer

Mouth cancer is the eighth leading cause of death worldwide and remains one of the major subtypes of hepatocellular carcinoma (Biswas et al. 2022). Piperlongumine uses enhanced ROS production to induce apoptosis in adult oral squamous cell carcinoma cells. [43]. Piperlongumine induced the release of the cyclin-dependent potent inhibitors p21, which usually causes OSCC cells to arrest within in G0/G1 phase. Furthermore, piperlongumine stimulates the free radical release, influencing caspase-dependent pathways as well as conducting apoptotic cell death in OSSC cells. Piperlongumine as well as cisplatin (the use of intraperitoneal medication Cisplatin once a week for a minimum of 21 days and piperlongumine once a day) By accumulating ROS while also activating apoptotic pathways counting-Jun N-terminal kinase (JNK) and Poly(ADP-ribose) polymerase-1, cisplatin and piperlongumine co-treatment increases cisplatin-increased cytotoxicity in vitro and in vivo. Additionally, piperlongumine dose of 2.5 mg/kg along with cisplatin 5 mg/kg co-treatment does have a higher tumor -inhibitory action than piperlongumine or oxaliplatin alone. Then there's no notable change in body weights between both the treated and untreated groups of transgenic mice, implying that the therapy has no apparent adverse reactions [44].

5.4 Piperlongumine and pancreatic cancer.

Under oxidative stress, JNK is induced, which has a negative impact on cancer genesis and progression. According to new research, piperlongumine therapy activated JNK pathways in pancreatic cancer cells by disabling the JNK-GSTP1 connection. In pancreatic cancer cells, piperlongumine enhances JNK severance, which causes JNK, c-Jun, and early ERK

activation. This is preceded by repression, the nuclear movement of c-Myc, and the stimulation of intrinsic pathway proteins, including the death of malignant cells (Mohammad et al. 2019). Overall, our findings suggest that piperlongumine may have anticancer properties in pancreatic cancer cells by increasing oxidative stress.

5.5 Piperlongumine and Gastric cancer.

Piperlongumine reduces TrxR1, which increases intracellular ROS, damages DNA, and activates the protein p38 along with JNK signalling pathways both in vitro and in vivo (BGC-823, AGS, SGC-7901, as well as HCT116 cells)/ (female athymic BALB/c nu/nu mice bearing HCT-116 or SGC -7901 tumor xenografts). This enhances the anticancer effect. Furthermore, when piperlongumine with oxaliplatin are given together, the tumor-inhibiting impact is larger than when piperlongumine or oxaliplatin are given separately. Piperlongumine, interestingly, reduces oxaliplatin-induced adverse impact in the treated rats, such as weight loss [45].

Pictilisib alone has a cytotoxic IC50 of 0.16 M against NCIH1925 cells, but piperlongumine Pictilisib's cytotoxic IC50 for NCI-H1925 is reduced. This suggests piperlongumine boosts pictilisib's anticancer efficacy against lung cancer cells by a factor of ten. Similarly, piperlongumine enhances pictilisib's anticancer effectiveness against leukemia cells by 18 times. Furthermore, when both medications are used together, there is an increase in intracellular ROS generation, as well as an expansive range of synergistic anticancer impact [46].

5.6 Piperlongumine and prostat cancer.

When piperlongumine and doxorubicin are used in tandem, urinary tract cancer cell growth, invasion, and migration are suppressed, and the proapoptotic effect is enhanced, as compared to when either drug is used alone (CBR1). Prostate cancer is a type of cancer that affects men (DU-145 cells). [47]. According to Jeong et al., reactive oxygen exhibits anti-proliferative and anti-itinerant effects on an estrogen receptor (ER)-positive breast cancer cell line. MC-7 [48]. Additionally, piperlongumine influences the presence of proliferating cell nuclear antigen messenger RNA (PCNA), cyclin-dependent kinases (CDK) 1/4/6, cyclins B1/D1, and p21. Piperlongumine also inhibits NF-B's nuclear translocation in MCF-7 cells by blocking IKK, which has an anticancer effect. Piperlongumine, whether used in combination with TRAIL (25 ng/mL) or at low concentrations (10 M), inhibited cell proliferation and reduced cyclooxygenase activity. Furthermore, piperlongumine was able to potentiate TRAIL-induced apoptosis in tumor cells by upregulating the expression of death receptors, but not decoy receptors. Piperlongumine suppressed individual or collective colony development and translocation of tumor cells in conjunction through TRAIL, as well as down-regulating tumor cell survival pathways. It was discovered that TRAIL and piperlongumine worked in concert. [49].

5.7 Piperlongumine is like a cancer-fighting combination therapy.

There has been increasing resistance to traditional chemotherapy treatments, suggesting that single-agent chemotherapy may not be effective in treating cancer. In recent decades, combination therapy has gained prominence as a successful anticancer treatment. [50]. When combined with traditional anti-cancer medications, treatment with phytoconstituents like piperlongumine may improve the efficacy of cancer therapy. Remarkably, several in vitro and in vivo studies have demonstrated the therapeutic benefits of piperlongumine as a combinatorial anticancer medication. For example, piperlongumine stimulates the death of breast cancer cells by the CHOP + activation mediated by reactive oxygen species. [51]. Furthermore, by controlling the expression of the DR5 protein, piperlongumine in combination with TRAIL significantly enhances the apoptosis induced by TRAIL in cells harboring malignant mammary cells. [52]. It was found that piperlonguminine and dihydropiperlonguminine together significantly regulate the expression of APP (Amyloid Precursor Protein). Alzheimer's patients benefit from attempts to regulate this protein's development.

6. FUTURE PROSPECTS

The review states that the plant has a significant amount of phytochemical components. Piper longum contains a variety of health benefits, including anti-cancer, anti-asthmatic, liver- protective, anti-allergic, antifertility, laxative , aphrodisiac, hypoglycemic, antihypertensive, and antiviral qualities. As previously mentioned, the breakthrough method for isolating piperine has been found to involve the use of glacial acetic acid for isolation, followed by condensation using an organic solvent like ether following a hydroxide wash. This approach also makes use of opportunities throughout the process to yield a much higher yield and purity of piperine. Chemical analyses using M.P., TLC, UV, and IR have been performed to examine isolated piperine, producing more pure piperine crystals than actual piperine modes of action. From the discussion above, we can infer that plant-derived

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