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Black Pepper Being A Potent Anti-Carcinogen- A Short Review

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Abstract

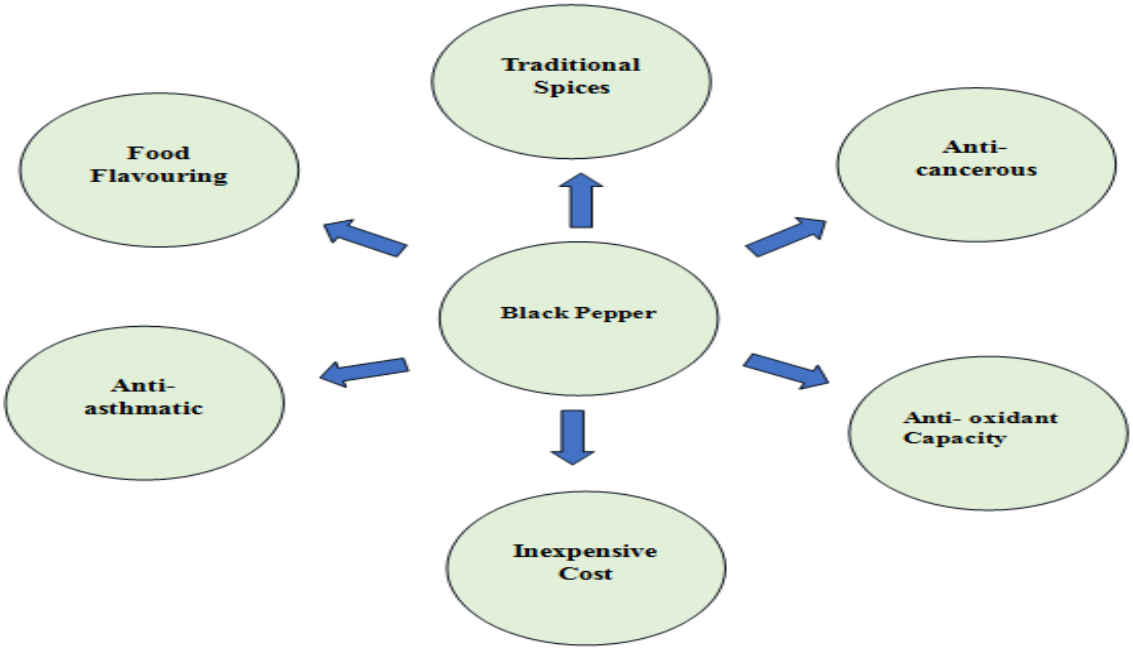
Black pepper (*Piper nigrum*), sometimes referred to as the "King of Spices" in India, is a natural product that is well-known for its capacity to target cancer cells and serve as a source of bioactive chemicals. For several cancer cell lines, animal models, human leukaemia cell lines, K-562 cells, and other cancer cell lines, the two main active ingredients, piperine and piperidine, have anti-cancer potential. According to reports, piperine has the ability to treat cancers of the breast, ovary, stomach, lung, prostrate, rectal, cervical, and leukemic types. Black pepper's main component, piperidine, a possible therapeutic drug, has also been linked to ovarian, breast, colon, lung, and prostate cancer prevention. These two plant chemicals, piperine and piperidine, prevent cell migration, which aids in cell cycle arrest and prevents the proliferation of cancer cells. According to reports, piperine's interaction with DNA causes a decrease in mutagens. The anti-cancer effects of black pepper and the likely processes by which it functions as an anti-carcinogen, as well mentioned in the literature, are the subjects of the current review.

KeyWords: Piper nigrum, cancer cell lines, piperine, piperidine, anti-cancer properties.

Introduction:

Both industrialised and developing nations are currently dealing with the serious health issue of cancer. After heart disease, cancer ranks as the second largest cause of death in people. Leukaemia, a cancer of the blood and bone marrow that alone claims 0.62% of all cancer deaths each year, is one of the most lethal tumours (Banerjee et al. 2021). Black pepper and star anise are two traditional spices and food flavourings that have been used for thousands of years. Due to their advantageous medicinal use, powerful pharmacological action, antioxidant capacity, and inexpensive cost, they played significant roles in clinical therapy and the food sector (Li et al. 2021). Black pepper (Piper nigrum L. family Piperaceae) is one of the most popular home spices in the world. Black pepper is used for more than just flavouring food; it is also a preservative, an insecticide, and a medicine. The perennial climber plant known as Piper nigrum is indigenous to India's Malabar Coast. Through the use of its aerial roots, the herb can reach heights of up to 10 metres. The dried green unripe drupe from which black pepper fruits are made and its seeds have long been used to treat a variety of ailments in folk medicine, from epilepsy to gastrointestinal disorders. The alkaloid piperine is primarily responsible for pepper's medicinal benefits. Piperine has anti-inflammatory, cardioprotective, neuroprotective, immunomodulatory, and

anticancer properties (Turrini et al. 2020). It has been shown to have a variety of pharmacological actions, including antihypertensive, anti-asthmatic, anti-bacterial, anti-oxidant, anti-cancer, anti-inflammatory, and immunomodulatory effects. Several phytochemicals have been extracted from black pepper, but phenolic acids are thought to be the most effective molecule and to offer therapeutic properties against a variety of illnesses, including cancer (de Almeida et al. 2020).



The biological actions of piperine and piperidine include the generation of ROS, activation of mitochondrial cytochrome C, release of the Bax protein from mitochondria, and downregulation of the Bcl-2 protein, which results in a high Bax:Bcl-2 ratio. These procedures also cause cancer cells to undergo caspase-3/9/8-induced cell death. The anticancer effects of these two phytochemicals have also been demonstrated against ovarian cancer, prostate cancer, lung cancer, and many other cancers, which are further covered in this review study. Additionally, earlier research have demonstrated that the signalling pathways essential for controlling cancer can be activated or inhibited by piperine and piperidine (Mitra et al. 2022). The complex process of mutagenesis, which involves DNA damage produced by many forms of ROS, is thought to be the first step in the development of several types of cancer. This resulted in the identification and characterization of numerous anti-mutagenic and antioxidant compounds (Zahin et al. 2021).

Discussion:

Anti cancer properties of Piperine on cell lines

It was found in this study that MDR leukemic cell lines were more responsive to piperine than parental cell line. The metabolic activity and viability of the parental cell line, K562, as well as the MDR cell lines, Lucena-1 and FEPS, were examined as the initial step in the analysis of piperine's impact. To measure cellular metabolic activity, samples were subjected to varied doses of piperine for 48 hours (Figure 1), 72 hours (Figure 2), and 96 hours (Figure 3) and analysed using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide (MTT) reduction assays. After 72 hours of piperine treatment (50 or 100 µM), a viability test using trypan blue was also carried out (Figure 4).The results showed that, in a dose-dependent manner, piperine decreased the metabolism and cell survival of K562, Lucena-1, and FEPS cells. The MDR celllines Lucena-1 and FEPS were demonstrated to be more affected by piperine than the parental cellline K562, indicating the presence of the CS phenomenon (Quarti et al. 2021).

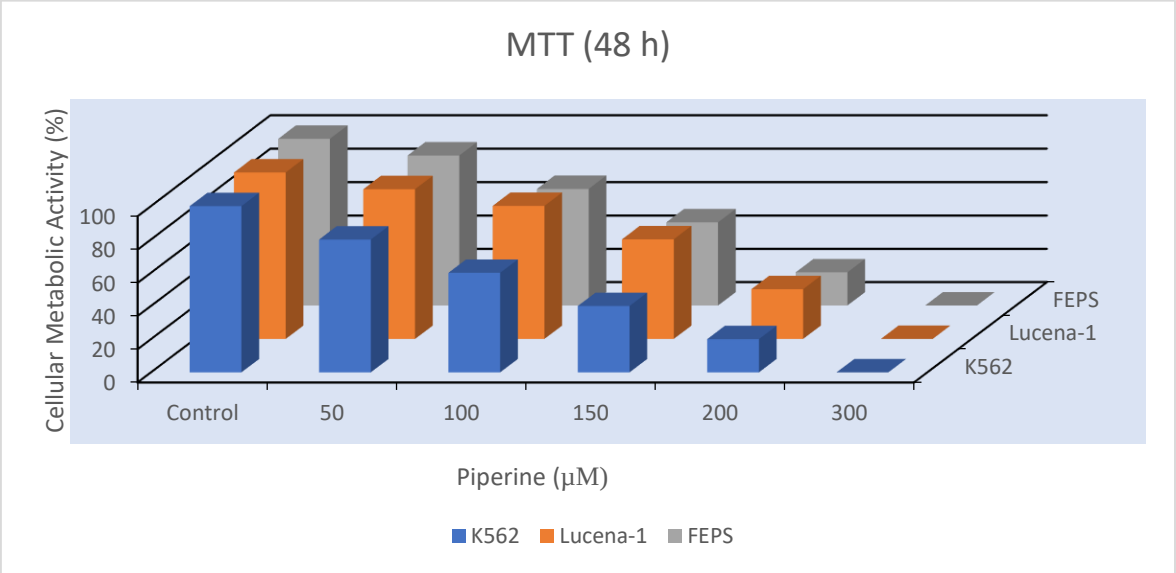


Figure 1: Chart showing MTT reduction assay after 48 hours

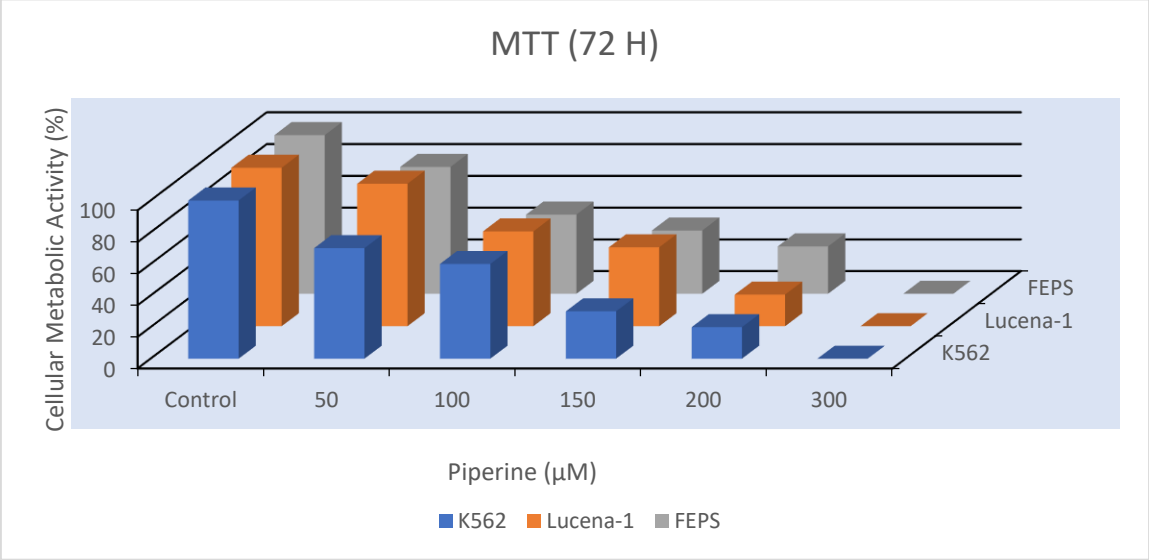


Figure 2: Chart showing MTT reduction assay after 72 hours.

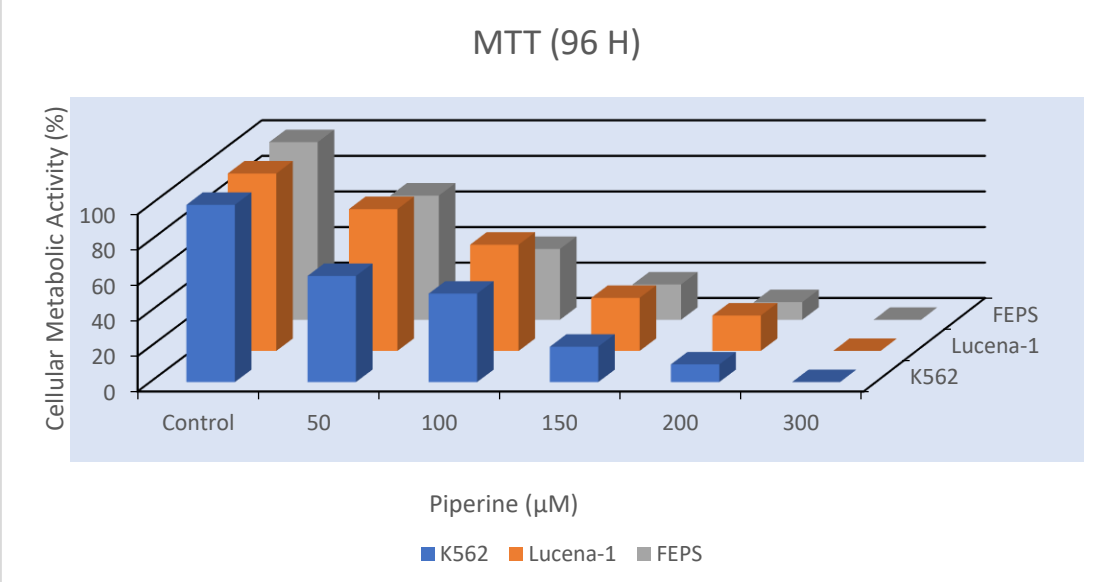


Figure 3: Chart showing MTT reduction assay after 96 hours.

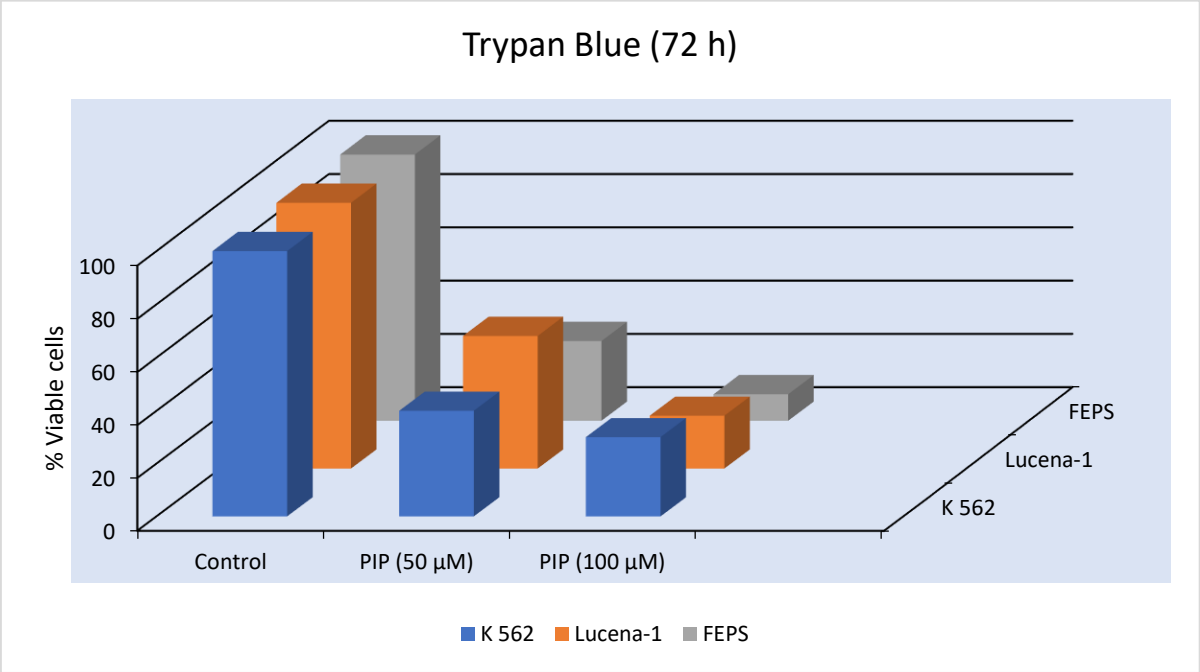


Figure 4: Chart showing cell viability determined by Trypan blue staining after 72 hours

Effect of piperine on different types of cancer:

In case of breast cancer this study shows thatby blocking the G1-S transition of the cell cycle, piperine administration prevents the development of p53-deficient cell lines. It also increases the expression of p21Waf1/Cip1, further reducing CDK activity. Apoptosis was brought on by piperine because it reduced the phosphorylation of the Ser473 site in Akt. Release of mitochondrial Smac/DIABLO by piperine inhibits IAP (inhibitor of apoptosis) and cytochrome c, which triggers the development of apoptosomes and results in cell death. The lowered gene expression of MMP-2 and MMP-9 caused by piperine also inhibits the migration of cancer cells (Mitra et al. 2022). In case of ovarian cancer it was seen that, A 48-hour piperine administration enhanced mitochondrial cytochrome c release, which in turn boosted caspase-9 and caspase-3 activity (intrinsic route), but there was no corresponding change in caspase-8 concentration. Additionally, Caspase-9/3 starts the apoptosis of cells. A2780 cells that were treated with piperine similarly saw an increase in the rate of apoptosis as a result of the phosphorylation of JNK and p38 MAPK.In case of gastric cancer, the c-Src/RhoA/ROCK signalling pathway can be downregulated by piperine therapy to reduce IL-6 expression. Additionally, piperine has the ability to prevent STAT3 activation. Piperine can therefore prevent the TML-1 cell lines' gastric characteristics by blocking STAT3 activation and p38 expression (Mitra et al. 2022). In case of lung cancer the study shows that, piperine treatment causes the expression of p53 to increase, which stops the cell cycle in phase G2-M. Piperine also decreases Bcl-2 and increases Bax-2, and this high Bax:Bcl-2 ratio aids in the further induction of caspase 9/3 dependent apoptosis in A549 cells. In case of prostate cancer it was seen that, the caspase-3-dependent apoptotic pathway can be successfully activated in these cell lines by piperine administration. In DU145, PC-3, and LNCaP cells, piperine inhibited cell proliferation by decreasing the activation of phosphorylated STAT-3. Treatment with piperine can also stimulate PARP-1 cleavage and down-regulate Nf-B expression in DU145, PC-3, and LNCaP (Mitra et al. 2022).

Anti-cancer properties of Piperidine derivatives on cell proliferation and cell cycle:

In this study 2-Amino-4-(1-piperidine) pyridine (APP) had reduced DLD-1 and HT29 cell proliferation and also arrests cell cycle. The CCK-8 assay results demonstrated that 2-amino-4-(1 piperidine) pyridine reduced the growth of DLD-1 and HT29 cells in a dose-dependent manner (Figure 5). At 72 hours, 2-amino-4-(1-piperidine) pyridine significantly reduced the proliferative capacity of DLD-1 and HT29 cells. 2-Amino-4-(1-piperidine) pyridine treatment decreased the proliferation of DLD-1 cells to 93, 84, 71, 58, 45, and 30%, respectively. HT29 cell growth was reduced by the 2-amino-4-(1-piperidine) pyridine to 91, 80, 69, 54, 42, and 27% at 10, 20, 30, 40, 50, and 100 µM, respectively (Wang et al. 2019).

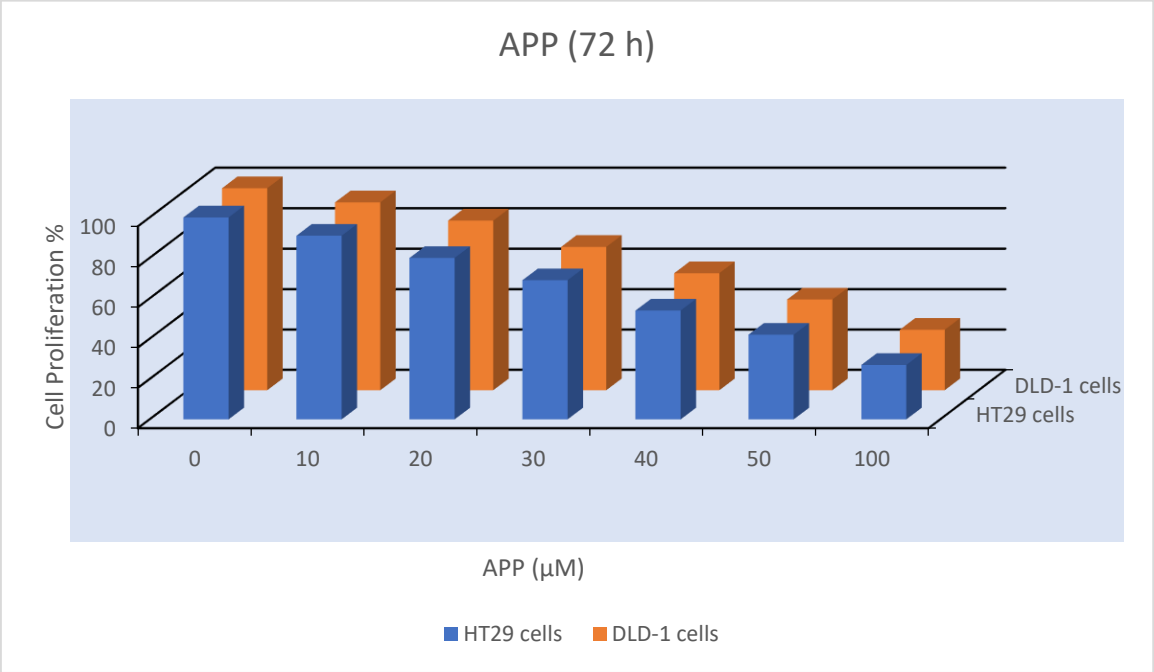


Figure 5: Chart showing effect of APP after 72 hours

Effect of piperidine derivativeson different types of cancer:

In case of breast cancer the study shows that, both MDA-MB-231 and MCF-7 cell lines were treated with DTPEP (1-(2-(4-(Dibenzo[b,f]thiepin-10-yl)phenoxy)ethyl)piperidine)-a piperidine derivative, causing cell cycle arrest in phase G0/G1 and an increase in ROS production.A high Bax:Bcl-2 ratio was discovered to cause cell death, associated with the release of mitochondrial cytochrome c, up-regulation of Bax, and down-regulation of Bcl-2. Treatment with DTPEP increased the level of ERß expression while decreasing the expression of ER, which is essential for the development of breast cancer. Piperidine has a significant anti-breast cancer potential, as evidenced by the MDA-MB-231 cell line's suppression of the PI3K/AKT signalling pathway and subsequent down-regulation of phosphorylation at Tyr485 of PI3k and Ser473 of AKT after treatment with DTPEP.(Mitra et al. 2022)In case of ovarian cancer it was observed that, cotreatment with piperidine derivatives TPL (Tempol) and DPP (cisplatin) on OVCCAR3 cells had a few key anticancer effects, including a reduction in cell proliferation, an increase in apoptosis, and an increase in ROS production. The release of mitochondrial cytochrome c and induction of a high Bax:Bcl-2 ratio as a result of further ROS buildup by TPL and DPP trigger the caspase 9/3 dependent apoptotic signalling pathway in OVCAR3 cells.In case of colon cancer, piperidine derivative 2-amino-4-(1 piperidine) pyridine blocks cell cycle progression past phase S in DLD-1 and HRT29 cells, stopping the cell cycle at phase G1/G0. The recommended treatment lowers the level of FOXA2 mRNA expression in DLD-1 and HT29 cells. It also suppresses the epithelial-mesenchymal transition (EMT) and down-regulates E-cadherin, both of which prevent the capacity of DLD-1 and HT29 cells to migrate (Mitra et al. 2022). In case of lung cancer the study shows that, piperidine derivative CELFMA induces redox homeostasis and activates the caspase 9/3 pathway by cleaving PARP, both of which result in cell apoptosis. Additionally, CELFMA boosted the release of Bax while decreasing the release of Bid, maintaining a high Bax:Bid ratio, which is essential for the death of cancer cells. Another effect of CELFMA treatment-induced cell death is P53 phosphorylation. Degradation of phosphorylated I-B was likewise prevented by proteasome inhibitors, preventing NF-B from translocating into the nucleus. By lowering the levels of COX-2 and pro-inflammatory cytokines, CELFMA decreased cellular inflammation. The G1/S phase transition of the cell cycle, ICAM1, which is important for cell adhesion, and downregulation of CD31 expression were all blocked by CELFMA administration. In case of prostate cancer this study shows that, by increasing the expression of the Bax protein while decreasing the expression of Bcl-2 and Bax, treatment of PC3 cells with the piperidine derivative compound 17a maintains a high Bax:Bcl-2 ratio.These occurrences cause PC3 cells to apoptose. The epithelial-mesenchymal transition is similarly impacted by compound 17a therapy, which prevents PC3 cells from migrating by upregulating E-cadherin and downregulating N-cadherin and Vimentin (Mitra et al. 2022).

Conclusion:

This study shows the anti-cancerous properties of the main components (piperine and piperidine) of black pepper on different types of cancers, such as, breast cancer, lung cancer, prostate cancer, ovarian cancer, colon cancer, etc. and their role in supressing different cell line cancers, cell proliferation and cell cycle.

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Conflict of interest:

The authors disclose no potential conflict of interest.

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