# Molecular basis for the pharmacological activities of piperlongumine against breast cancer: Role of glucose import, ROS, NF-κB and lncRNAs.

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**Background:** Piperlongumine (PL, piplartine) is an alkaloid derived from the *Piper longum* L. (long pepper) root. The activities PL against breast cancer and the underlying mechanism is not thoroughly investigated. **Aim:** We examined the anti-cancer activities of PL against breast cancer cells. The molecular basis for the pharmacological activities of this alkaloid was also examined. **Methods**: The breast cancer cell lines such as MCF-7, T-47D, MDA-MB-231, MDA-MB-468 and MDA-MB-453 were used during the study. We used MTT assay, clonogenic and soft agar colony formation assay for cytotoxicity. The cell cycle analysis, phosphatidylserine externalization assay, measurement of mitochondrial membrane potential, AO/PI and DAPI staining, and DNA laddering was used for apoptosis. The western blot analysis was performed to examine the expression pattern of tumorigenic proteins. Other parameters used were the intracellular detection of ROS, immunocytochemistry for NF-κB and GLUT-1 activation, wound healing assay for cell migration, and real-time PCR for lncRNA expression. We also evaluated if PL can enhance the efficacy of doxorubicin in swiss albino mice implanted with Ehrlich Ascites Carcinoma (EAC) cells and metabolic parameters were also examined in serum of mice. **Results:** PL inhibited proliferation and suppressed the long-term as well as soft agar colony formation of breast cancer cells in a dose dependent manner. PL induced ROS generation and accumulation of cells in sub-G1 phase, mitochondria mediated apoptosis in cancer cells as revealed by the presence of fragmented nuclei, PARP activation, loss of mitochondrial membrane potential, chromatin condensation, DNA laddering and suppression in the expression of cell survival proteins. PL reduced glucose import and modifies the expression of glucose and lactate transporter in breast cancer cells. The amide alkaloid suppresses the TNF-α induced NF-κB activation and modulate the lncRNAs such as MEG-3, GAS-5 and H19 expression in breast cancer. In mice model, PL was found to synergize with doxorubicin by reducing the size, volume and weight of the tumor. With an increase in the concentration of PL, the serum cholesterol and triglyceride levels were decreased while there was increase in the serum level of glucose in EAC bearing mice. **Conclusion:** PL exhibit potential against breast cancer. Further, PL enhances the efficacy of doxorubicin in EAC mice model. The modulation of lncRNAs, NF-κB and glucose import may contribute to the activities of PL against breast cancer.