ABSTRACT

Breast cancer is the second leading cause of death in women worldwide. Cancer begins when the cells undergo rapid multiplication and DNA damage. The major causes of cancer include late first pregnancy, early menarche and late menopause along with westernized lifestyle, obesity, alcohol, environmental factors and genetic disorders, which directly or indirectly contribute to breast cancer. The survival rate has been continuously increasing since 1989 due to a combination of factors, including early detection with the use of mammogram, improved surgical techniques, a better understanding of the disease, awareness about the cancer symptoms and wide use of adjuvant therapy.

The treatment strategies are planned according to the clinicopathological features of breast cancer such as age, nodal status, hormonal receptor status, tumor grade and size. Lymphatic and blood vessel invasion are the most powerful prognostic factor in evaluating the patients with breast cancer. Advances in life-saving treatment options in the medical field have led to increasing survival rates of breast cancer patients. Breast cancer treatment includes surgery, radiation therapy, hormonal therapy and chemotherapy. The treatment may result in many side effects and some of them include abdominal pain, anemia, anxiety, nausea, fever, pain and weakness. Despite available treatment options, breast cancer is considered to be fatal and life threatening. Thus the search for novel drugs is still an ongoing process in order to enhance the survival rates.

The ultimate goal of this work is to develop potent inhibitors for molecular targets. Cancer cells undergo innumerable pathological changes prior to solid tumor formation and this is evident from overexpression of oncogenes and enzymes. One such enzyme is Phospholipase A2 (PLA₂), which cleaves the phospholipids at sn-2 position to produce fatty acids and lysophospholipids. Also, PLA₂ enzyme is one of the important mediators of pain & inflammation. There are several subfamilies of PLA₂ including secretory PLA₂.
The enzyme is over expressed in breast cancer cells than in stromal cells and thus making the survival of cancer cells for a longer period. To overcome this scenario, researchers have focused on identifying novel bioactive compounds from both natural and synthetic sources.

Initial part of the work deals with identifying and isolating a potent bioactive compound from a natural source. *Myristica fragrans* Houtt (Mace) was chosen for our study due to its wide range of applications in traditional medicine. Sequential extracts of mace (Hexane, Dichloromethane, Ethyl acetate and Ethanol) were obtained and tested for its cytotoxic activity against breast cancer cell lines (MCF-7). The extracts were also tested for *in vitro* PLA$_2$ inhibition. The extracts were shown to exhibit PLA$_2$ inhibition and found to be cytotoxic for breast cancer cell lines. Furthermore, the extracts displayed good antioxidant property, which was evident from dot blot, DPPH and hydrogen peroxide assays. When compared with other mace extracts, ethyl acetate extract shown to posses good antioxidant, cytotoxic and PLA$_2$ inhibitory property and hence the extract was chosen for compound isolation and characterization procedure. The isolation was performed by repeated column chromatography and this resulted in the isolation of a phenylpropene, Elemicin/Isoelemicin. Further, the isolated compound was also found to be cytotoxic against breast cancer cell lines and also inhibited PLA$_2$ enzyme effectively. A molecular docking study was performed to identify the binding mode of the compound towards the protein target (sPLA$_2$).

The second part of the work aims in identifying a potent compound from a series of hydrazine carbothioamide derivatives. A series of 11 new hydrazine carbothioamide derivatives were synthesized and three-dimensional crystal structure of four compounds was determined. All 11 compounds were studied for its antioxidant property, cytotoxicity and PLA$_2$ inhibitory potentials (*in vitro* and *in silico*).

**Keywords:** *Myristica fragrans*, compound isolation, column chromatography, biochemical assays, synthetic compounds, X-ray crystal structures & molecular docking.