CHAPTER 4

CONCLUSION

Inflammation has long been known as a localized protective reaction of tissue to injury or infection and there has been a new realization about its role in a wide variety of diseases, including cancer. Recent studies indicate chronic inflammation can lead to cancer, diabetes, cardiovascular, pulmonary, and neurological diseases. Inflammatory cells and cytokines found in tumours are more likely to contribute to tumour growth, progression, and immunosuppression than acting as an effective host antitumour response. Moreover cancer susceptibility and severity may be associated with functional polymorphisms of inflammatory cytokine genes, and deletion or inhibition of inflammatory cytokines inhibits development of experimental cancer.

Cancer is a disease in which abnormal cells divide without control and are able to invade other tissues through the blood and lymph systems. Elimination of known carcinogens from the environment is one way to reduce the incidence of cancer, alternatively, a few changes in lifestyle could reduce the incidence of cancer. Traditionally, cancer chemoprevention has been defined as an intervention in the carcinogenic process facilitated by blocking induction of the neoplastic process, or preventing transformed cells from progressing to malignant phenotypes by understanding the sequence of events encompassing the process of carcinogenesis.
Breast cancer remains the major cause of cancer-related deaths in women world-wide with the heterogeneity of the disease further complicating the progress of target-based therapies. Chemoprevention strategies include development of drug compounds based their interaction with tissue-specific signal transduction molecules, screening and selection of natural products containing novel compounds that can interact with known or new molecular targets. Once the activity of a newly identified chemical or a class of chemicals is established, an ideal drug can be confirmed using structure-activity studies, molecular modeling, or combinatorial chemistry and developed using in vivo studies and clinical trials. Phytoprinciples have been reported to exhibit a significant impact in breast cancer prevention and/or therapy by targeting both receptor-positive and negative cancer cells. Natural products and traditional medicines are rich source of leads for the pharmaceutical industry. The compounds derived from medicinal plant extracts are often stereochemically complex, with multi or macrocyclic molecules tending to possess interesting biological properties. Despite these advantages, the path from traditional medicines/natural products to synthetic pharmaceuticals poses great challenges in the isolation of active component, elucidation of molecular mechanism, and pharmaceutical development. In the current study, *Alpinia officinarum* has been studied extensively for its multifunctional activities. The salient observations from the investigations include:

1. Among the extracts of *Alpinia officinarum*, AOHE showed a significant anti-proliferative effect in both MCF-7(ER+ve) and MDA-MB-231(ER-ve) Breast cancer cell lines. Bioactivity based purification led to the isolation of 1-(4-Hydroxyphenyl)-7-phenyl-hept-4-en-3-one, an Diarylheptanoid (DAH).

2. Anti-estrogenic effect of AOHE and DAH investigated using estrogen induced cell proliferation assay, pS2 gene expression level and ER binding assay suggesting the binding of AOHE and DAH towards ER in MCF-7. Docking analysis of DAH
illustrated the binding with ERα, confirming that DAH may act as ERα antagonist for estrogen dependent breast cancer cells.

3. DAH inhibits the constitutive activation of NF-κB through blocking the transcriptional activity of NF-κB and its signaling pathway in both hormone dependent and independent breast cancer cells.

4. Reduced level of Nitrite release in LPS treated RAW264.7 cells and a downregulation of pro-inflammatory cytokine gene level expression revealed the anti-inflammatory effect of DAH, concordantly inhibiting the activation of NF-κB through blocking the transcriptional activity of NF-κB.

5. FACS analysis revealed AOHE and DAH in the regulation of cell cycle arrest, confirming the G₀ phase arrest in MCF-7 and S-phase arrest in MDA-MB-231 cell lines. Protein level expression of CDKs, Cyclins and CDKs inhibitors further confirmed the arrest in their respective phases.

Thus, the Diarylheptanoid (DAH) isolated from Alpinia officinarum can serve as a potential drug candidate since it exhibits multiple mechanism of action for inflammation associated cancer treatment.

4.1 SCOPE FOR FUTURE STUDY

The present study focused on the multifunctional activity of a DAH in breast cancer cells and RAW264.7 cells. The data clearly shows the molecular mechanism of DAH in the inhibition of activation of NF-κB, suggesting that DAH is a potent bioactive molecule and could play a major role in the treatment for inflammation to cancer sequence. Further Molecular dynamics simulation can be applied to verify the stability of DAH on ER. Further, In vivo studies may ascertain whether this cell growth inhibitory effect of DAH might contribute its overall chemotherapy effects in the fight against breast cancer and its possible future therapeutic applications.