CONCLUSIONS AND STUDY LIMITATIONS

Conclusions:

In conclusion, results of this Ph.D. dissertation demonstrate that (a) Nrf2 is expressed at a high level in poorly differentiated lung carcinomas, hence, Nrf2 could be a good therapeutic target; (b) screening of extracts collected from plants using Nrf2 expressing A549 cells identified Anacyclus pyrethrum and Glycyrrhiza glabra as the potential candidates for further testing in cells (for elucidating the mechanism of action) and in animals (for measuring the efficacy in vivo); (c) Among hexane (APH), chloroform (APC) and ethanol (APE) extracts of Anacyclus pyrethrum root APE found to modulate the expression of Nrf2 in a dose dependent manner to inhibit the survival of A549 cells; Ethanolic extract of Glycyrrhiza glabra also showed better Nrf2 inhibitory potential; (d) In animals, APE alone and in combination with cisplatin (a known antitumor agent) increased the Nrf2 expressing EAC bearing mice life span significantly compared to untreated mice. However, either APE or GGE did not change the levels of Nrf2 expression or activity, indicating that the inhibition of tumor cells proliferation exerted by APE and GGE is due to mechanisms other than Nrf2 regulation. Further studies are warranted to determine these mechanisms and also to isolate the anti-tumor components from these extracts.

Study limitations:

Even though the presented data in this Ph.D. thesis demonstrated (a) elevated expression of Nrf2 in lung cancers with metastasis and poor differentiation, emphasizing that Nrf2 is a potential therapeutic target; (b) preliminary data about the isolation and in vitro characterization of identified plant extracts that inhibited A549 lung cancer cell line with high Nrf2 expression and activity; (c) efficacy of plant extracts from Anacyclus pyrethrum and Glycyrrhiza glabra for inhibiting EAC tumor cells growth in mice; many studies are still warranted to bring the identified extracts to clinical testing stage. For example, further studies are required to test the identified extracts (a) on multiple lung cancer cell lines expressing Nrf2 and not expressing Nrf2; (b) for target inhibition in the xenografted tumors’ (c) for pharmacodynamic behavior in animal studies. In addition, experiments purifying and characterizing the key active ingredients present in the extracts are also warranted, as his information is required to develop better combination agents for effective treatment of lung cancers.