CHAPTER 7

CONCLUSION

The bi-directional communication between the neuroendocrine system and immune system is essential to the maintenance of cellular and systemic homeostasis and in the prevention of the development of disease. However, the roles played by the active mediators of the neuroendocrine-immune network have not been fully explored. Although there are several key regulatory molecules in the neuroendocrine-immune network that we have examined in this study, we have chosen neural and growth factors as the neural mediator, corticosterone and testosterone as the endocrine counterparts and activated lymphocytes and their molecules (cytokines) as the immune parameters of the network. These key mediators have been chosen to examine their roles in the dysregulation of the neuroendocrine-immune network as demonstrated by age-related decline in sympathetic noradrenergic innervation of secondary lymphoid organs and immunosuppression that facilitates the development of age-associated diseases such as Alzheimer’s disease, Parkinson’s disease, and cancer. To investigate our hypothesis, studies were conducted on the four specific objectives as detailed earlier and the conclusions for obtained results are discussed below:

In summary, results from the preliminary study conducted on young male Wistar rats demonstrated that Noni fruit juice (NFJ, NSL, and NWS) had differential effects on immune function and antioxidant enzyme activities. Noni fruit juice contributed to increased immune functions by enhancing compensatory mechanisms such as the activities of antioxidant enzymes in the splenocytes of young Wistar rats.

Results from in vitro study showed that Noni fruit juices (NWS and NSL) exerted their differential effects on immune function, antioxidant enzyme activities and inflammatory markers in the lymphocytes isolated from the spleens of young, early middle-aged, and old male F344 rats by modulating intracellular signaling pathways. Differential effects of NSL and NWS on immune function and ERK expression were due to the presence of damncanthal, ursolic acid and myricetin in Noni fruit juice with seed (NWS).
**In vivo** treatment with Noni (*Morinda citrifolia*) fruit juice (NFJ) reversed the age-associated decline in immune system by increasing the IL-2 and IFN-γ production, decreasing the expression of inflammatory markers and free radical formation, and enhancing neural-immune interactions by upregulating the expression of TH, and NGF through intracellular signal transduction pathways in the spleen of old F344 rats. Findings from our study provide an understanding of its modulatory role in neural-immune interactions that can be used as a therapeutic intervention in the aged population to promote healthy aging.

Noni (*Morinda citrifolia*) fruit juice (NFJ) showed beneficial effects on the endocrine functions by regulation the hormone levels in old F344 rats. NFJ may have beneficial effects on cognitive function through an increase in the level of neural growth factor, signaling markers, decreased APP levels and cholinesterase activity, and enhanced nitric oxide-mediated neuronal activity in the brain areas of old rats.

**Figure 7.** An overview of the results depicting the probable intracellular pathways involved in mediating immunomodulatory and neuroprotective effects of Noni fruit juice in spleen and brain areas of F344 rats.
Although there were some discrepancy in the effects of Noni fruit juices in immune function and intracellular signaling pathways, but results examining the effects of NSL and NWS on antioxidant enzymes were consistent in old rats showing the beneficial effect of Noni fruit juice in improving the age-associated decline in antioxidant enzyme activities. Based on the results from *in vitro* and *in vivo* studies, superoxide dismutase (SOD) and glutathione s transferase (GST) were the most critical antioxidant enzymes, as SOD is the primary antioxidant defense mechanism of the body and boost the body’s primary antioxidant defense system. GST is another crucial antioxidant enzyme that plays an important role in the elimination of xenobiotics, recycling of glutathione, as well as the detoxification of peroxidized lipids. Thereby acting as a compensatory mechanism by increasing the antioxidant enzyme activities *Morinda citrifolia* fruit juice enhanced neural-immune interactions and cell survival pathways while inhibiting inflammatory processes that may be useful in the treatment of age-associated diseases. Altered immunomodulatory effects of Noni fruit juice with seeds may be attributed to alter phytochemical and protein profiles of seed components that needs to be investigated further. Although it is a preliminary study involving *in vitro* methods examining the effects of whole fruit juice, further studies have to be undertaken to investigate the effect of individual phytochemicals of Noni fruit juice *in vitro and in vivo* in animals to get more insight about the variability of the differences in immune function and intracellular signaling pathways.

**In conclusion, findings from our studies shed light on the role of** *Morinda citrifolia* **fruit juice in improving in neuroendocrine-immune interactions, which can be used as an intervention therapy in the aged population to promote healthy aging. Further studies are needed to explore the mechanisms of** *Morinda citrifolia* **fruit juice-mediated improvement in immunity and in cognitive function by examining the role of phytochemicals in different subsets of immune cells and brain areas of old rats.**