

# **Chapter-6**



# **Conclusion**

## CONCLUSION

The present work was designed to evaluate standardised hydro-methanolic *Andrographis paniculata* leaves extract (AP) and isolated pure andrographolide for their neuropsychopharmacological activity. Additionally, the effects of both the tested drugs on diabetes associated comorbid brain disorders were also investigated in rodents. The ultimate goal of the experiments and observations discussed in this thesis was to obtain evidence based pharmacological activities and to identify neuro- and bio-chemical processes potentially involved in its observed activities. Observations made and inferences possible from these efforts strongly suggest that its broad spectrum of neuropsychopharmacological activity profile of AP and andrographolide is due to its ability to protect animals against mental stress induced central sensitivity syndromes. Salient findings of the present work are as follows:

- ❖ Results of the pilot experiments reported in this thesis strongly suggest that repeated dose studies with AP and andrographolide are necessary for such purposes.
- ❖ AP was found effective in rat models of diabetes and obesity. AP significantly reversed the overt hyperglycemia induced by streptozotocin and histopathological examinations of pancreas of diabetic rats were revealed regeneration of beta cells. Cytoprotective and anti-oxidant activities of tested extract are further supported the observed anti-diabetic activity. AP is beneficial in management of dyslipidemia and insulin dysfunction induced by high fat diet and fructose feeding. These observations strongly suggest that the effects of AP treatments on insulin level and body weight depend largely on metabolic status of animals.
- ❖ AP showed significant anti-depressant and anxiolytic activity in nondiabetic and diabetic rats. Brain monoaminergic and oxidative defence mechanisms are involved in observed effects of tested drugs. In addition, possible involvement of central cholinergic function modulating effects of AP and that of pure andrographolide in their modes of actions are indicated by the

observation made in the morris water-maze test. Deteriorated memory function observed in diabetic rats was accompanied with elevated acetylcholinesterase (AChE) activity in their brains, and both these pathologies were dose dependently antagonised by treatments with AP as well as andrographolide. Piracetam like memory function improving effects of both AP and andrographolide were also apparent in nondiabetic rats. In view of this, tested extract and andrographolide may be potentially beneficial for the patients suffering with diabetes and its co-morbid CNS disorders.

- ❖ Our observations not only reconfirm hyperalgesia in diabetic rodents, but also reveal dose dependant central analgesic and anti-inflammatory efficacies of both AP and andrographolide in nondiabetic as well as diabetic animals. Their beneficial effects on blood glucose level also accompanied these effects of both the test agents in diabetic rodents. Such efficacies of both of them in diabetic as well as nondiabetic animals were qualitatively similar to those of that of the centrally acting analgesic pentazocine or that of the anti-inflammatory drug indomethacin.
- ❖ Almost all observed effects of AP or andrographolide treatments in chronically stressed animals were quite analogous to that of the tested root extract of another well-known adaptogenic Rasayana herb *Withania somnifera*. However, both AP and andrographolide treatments suppressed the chronic unpredictable foot shock stress triggered over expressions of both anti-inflammatory (IL-10) and inflammatory cytokines (TNF- $\alpha$  and IL-1) in blood as well as in the brain tissue with almost equal efficacy, whereas the effects of tested dose of the *Withania somnifera* root extract on blood IL-10 expression were somewhat lower than those for its suppressing effects on blood and all the three cytokine expressions quantified in their brain. This could as well be due to different cellular sites of action of the tested *Withania somnifera* extract and those of AP and andrographolide.
- ❖ Results of the *in vitro* experiments using HL-60 cell lines also revealed that andrographolide is indeed the quantitatively major bioactive constituent of AP involved in unspecific suppression of cytokine expression of the extract. In

addition, they also revealed that expressions of Toll-like receptors TLR-7 and TLR-8 are suppressed by non-cytotoxic concentration of andrographolide, whereas the expression of that of TLR-3 is not altered after its tested concentration (10  $\mu$ M). These observations strongly suggest that modulation of cellular processes involved not only in expressions of inflammatory and anti-inflammatory cytokines but also in those of TLR-7 and TLR-8 are involved in the modes of actions of this extremely bitter secondary metabolite of *Andrographis paniculata*.

*Andrographis paniculata* is another adaptogenic Rasayana herb with a uniquely broad psychopharmacological activity profile and could be herbal lead for prevention and treatments of diverse spectrums of psychopathologies and other comorbidities commonly associated with diabetes. Andrographolide is quantitatively the major stress response modulating secondary metabolite of the plant. However, further efforts to identify the roles of diverse other known bioactive secondary metabolites of the plant are necessary for understanding its Ayurvedic pharmacology. The bioassay procedure used in the pilot study in this thesis could be a useful one for such purposes.