PART V
SYNOPSIS
(Summary and Conclusions)

"It's what we learn, after we know it all- that counts!"

- Anonymous -
V: SYNOPSIS

8. Summary and conclusions

1. The key features of morphology and other parameters evaluated in the present study revealed that the herbal extracts were in confirmation with the standards compared and thus the standardized extracts were utilized in the present studies.

2. The analytical profile checked; that of the conventional antidepressants, namely, fluoxetine, imipramine and reboxetine complied as per the USP specifications and utilized in the present studies.

3. Acute and sub acute toxicity tests on the animal revealed that the dose of *Bacopa monniera* extracts (BME), *Centella asiatica* extracts (CAE) and *Curcuma longa* extracts (CLE) were safe up to the dose 2g/kg and did not produce any lethality in the experimental animals; so the same was considered to be safe and the three mentioned doses of aforementioned three herbal extracts, ranging from minimum, moderate and maximum were administered alone and in combinations with the conventional antidepressants, orally as per body weight of the animals in the studies.

4. In first regimen of BME and fluoxetine combinations evaluated in rats, BM emerged as a tranquillizer or sedative antidepressant which potentiated the antidepressant action of conventional drug fluoxetine as that was apparent from a significant reductions in time of immobility observed in rats in forced swim test (FST), tail suspension test (TST) and chronic fatigue test (CFT). The same was corroborated with the increased serotonin concentrations as estimated in rat brain homogenates of the groups of rats treated with the combinations of BME and fluoxetine compared to that of control group treated with vehicle alone and the groups administerd with either of the BME or fluoxetine alone. The combinations were also proved to be therapeutically synergistic in improving chronic fatigue syndrome (CFS).
The doses of BME-40 mg/kg and 80 mg/kg in combinations with fluoxetine were proved to be more potent than the highest dose of BME-80 mg/kg utilized in the study. While the effects on general motor learning and motor coordination were improved in the groups of rats receiving the combinations of BME and fluoxetine, the sedation was very apparent in the same groups. The effect on locomotor activity was found to be independent from motor coordination or from the effects observed on time of immobility in animals in both FST and TST. The neurotransmitters like serotonin (5-HT), noradrenalin (NA) and \(\gamma\)-amino butyric acid (GABA) were implicated majorly in mediating the actions.

5. In second regimen, the groups of mice treated with the combination of *Centella asiatica* extracts (CLE) and imipramine too, showed synergistic actions in relieving depressive like state in behaviour despair tests like FST and in CFT. The reductions in duration of immobility were more pronounced in the groups receiving combinations than the groups treated with either of three doses of CLE or imipramine alone. While the above combinations showed reduced hyperactivity, irritability and straub tall incidence in gross behaviour test along with the reduced locomotor activity in mice, the same groups, also showed improved ambulation and stereotypy phenomenon along with reduced freezing time and reduced frequency of defecation in open field test. At the same time, the motor coordination was significantly reduced in the groups of mice treated with the combinations especially that consisting of the highest dose of CAE-300 mg/kg along with imipramine. The results indicated that, while the aforesaid combinations could be therapeutically synergistic in depression and chronic fatigue test; it may also be useful in relieving anxiety like status. Though, these combinations can help reduce the dose of a drug, the same may lead to the alterations in the ANS activity and may potentiate the side effects like loss of motor coordination or unwarranted sedation.
The potentiation observed in central NA in groups of mice receiving these combinations compared to the groups treated with CLE or imipramine alone was thought to be majorly responsible for the antidepressant effect, though other mechanisms may be involved.

6. In third regimen, the combinations of *Curcuma longa* extract (CLE) and reboxetine were also found to be highly synergistic in reducing time of immobility in FST and TST as well as in the CFT on groups of mice. The extracts clearly showed potent additive effects when used in combinations with reboxetine which was corroborated with increased NA concentrations estimated in mice brain. While the data regarding gross behaviour as well as open field activity were mostly inconsistent and non significant, the hyperactivity observed while checking the gross behaviour of mice was apparent in the groups treated with combinations and also the time of initiation to explore new environment in open field, that was increased compared to that of control and groups treated with either reboxetine or CLE alone. On the other hand, the significant reductions found in locomotor activity and “fall off” time in mice indicated the effect on the ANS. Therefore, it was speculated that the aforementioned combinations may help in reducing the dose of the drug but can also results in combined side effects like reduced muscle tone/relaxation and sedation.

In conclusion, BME, CAE and CLE utilized in present study showed significant antidepressant-like activity through interaction with adrenergic and serotonergic systems in CNS in animals. A dopaminergic and GABAergic systems is also implicated. The antidepressant-like actions of the herbal extracts utilized in the present studies were clearly augmented with the simultaneous use of fluoxetine, imipramine and reboxetine respectively. Hence, it was contemplated that the respective combinations may have potential therapeutic value for the management of depressive and anxiety disorders as well as in management of a chronic fatigue syndrome.
This could be important in reducing the dose of the drugs to achieve enhanced therapeutic effects with minimal adverse effects. However, the respective combinations have potential for other side effects also, like sedation or muscle incoordination, which could be compounded on concurrent use of the both.

Today, the concomitant consumption of drugs from different disciplines is a common finding. Very few studies however, address the problem of potential herb-drug interactions or herb-herb interactions. The studies such as this, documenting the herbal drug interactions with modern medicine may be very important from the clinician’s point of view. As the documented data on adverse drug reactions of plant drugs are sparse, further research in this area seems prudent. The additional studies on behavioural and biochemical estimations to further substantiate the results in this study are the need of the hour.

In the last two decades, information regarding the interactions between herb and drug has been piling up and the complexities of these interactions are remarkable. Future studies will probably divulge even more complex associations. The clinically most relevant advance will be the investigations of these interactions in humans.

The present studies not only demonstrated the possibilities of interactions between aqueous BME, CAE and CLE with that of respective conventional antidepressants, but also attempted to suggest the rationale behind the potential interactions.