ABSTRACT

Anxiety and depression are the most common behavioral disorders encountered. Anxiety is a state of universal feeling that is part of the everyday human life. Feelings of anxiety and fear are often unpleasant emotions commonly caused by the perception of potential danger that threatens the security of the individual and results in various somatic and autonomic effects, restlessness and agitation, tachycardia, sweating, weeping, gastrointestinal disorders, sleep disturbances, interference with normal.

Depression is considered as an affective disorder, characterized primarily by change of mood (depression and mania) rather than thought disturbances.

Epidemiological studies reveal that 25% individuals develop one or more mental or behavioral disorders at some stage in their life. At present about 4 million adult Americans suffer from Generalized Anxiety Disorder (GAD). Phobia is the most commonly seen anxiety disorder, and 49.5% of people reporting an unreasonably strong fear and 22.7% of those people meeting criteria for simple phobia. The prevalence of major depression in the general population is estimated at 5%.

Despite the advent of new molecules in pharmacotherapy of anxiety and depression, it is however unfortunate that both these disorders go undrilled, undiagnosed and untreated and such drugs come with the burden of adverse events.

On the other hand drugs obtained from natural origin are perceived to have least risk and side effect profiles and yet claim to cure psychiatric disorders much the same way as their synthetic counterparts. Some of the examples of the drugs employed for this purpose are, St. Jonh’s wort, Ginseng, Ginko biloba, kava, Saw palmetto, Euphorbia hirta, Shilajit, Valerian, Convulvulus etc. They are used either as monoextracts or as polyherbal preparations combining two or three plant based medications. Among the polyherbal preparations the popularly used are Mentat, GS-02, Lipon, Panvita, Androcare, Live 52 etc. The mechanism of action of herbal drugs and their extract preparations differ in many respects from that of the synthetic drugs or single substances.

The investigational drug Trans-01 is such a polyherbal formulation claimed to be beneficial in managing anxiety, depression, stress and insomnia, with the following
composition, *Valeriana wallichii* (45%), *Convolvus microphyllus* (30%), *Plumbago zylanica* (7.5%), *Boswellia serrata* (15%) and *Acorus calamus* (3.5%). The aqueous extract of the formulation was used in the study.

In view of the importance of the medicinal properties attributed to drugs of plant origin and non compliance of the most of synthetic drugs, we undertook an investigation related to the usefulness or beneficial effects of a polyherbal formulation, Trans-01, for its psychopharmacological activities using various animal models depicting psychological aberrations. The study was carried with the following objectives,

- To ascertain its short and long term toxicity profiles
- To assess the effect of Trans-01 in various anxiety models
- To extend the activity profile of the Trans-01 in depression models
- Since most of the commonly used antianxiety drugs especially benzodiazepines are laden with side effects like sedation, muscle incoordination, addiction liability etc. Therefore, studies were also carried which are indicative of sedative and/or muscle incoordination liability for the herbal formulation, Trans-01.

- Attempt was also made to understand the mode of action of Trans-01 by exploiting the use of various antagonists (Flumazenil, Bicuculine Picrotoxin and yohimbine) and biochemical estimation to unearth its mechanism.

*Anxiolytic activity* was assessed by using different animal models like, Elevated plus maze (EPM), Open field (OFT), Staircase test, Mirror chamber test (MC), Hole board (HB) test and Light-Dark test (LDT) in mice. Various doses of Trans-01 were selected (100, 200, 400 and 800 mg/kg, b.w) for the study. Trans-01 exhibited significant dose dependent Anxiolytic profile in different models following oral administration for varying periods of time in different paradigms like increased time spent in open arms of EPM, mirror chamber, central platform of OF, light arena of LDT enhanced climbings of steps in staircase, head poking in HB etc. Among them 200 and 400 mg/kg were more effective. Their probable mechanism study showed to be through interaction with GABA_A-benzodiazepine (BZD) receptor-chloride channel receptor complex as evident from the blockade of Trans-01 (400 mg/kg) action by Flumazenil (GABA_A-benzodiazepine (BZD) receptor antagonist) and Picrotoxin (GABA_A receptor chloride...
channel complex antagonist). However blockade of action by bicuculine (GABA\_A-GABA binding receptor antagonist) was not statistically significant.

Antidepressant activity was evaluated by using following models, Loco motor Activity, Tail suspension test (TST), Forced Swimming test (FST) in rats, Forced swimming stress (FSS) induced changes in plasma corticosterone levels and yohimbine potentiation test. Doses of Trans-01 selected for the study were (25, 50, 75 and 100 mg/kg, b.w). Trans-01 exhibited dose dependent significant Antidepressant effect as indicated by reduced immobility time in TST and FST, normalization of swim induced aggravated corticosterone levels. The mechanism of Trans-01 in eliciting its antidepressant effect might be through inhibition of HPA axis activation as revealed from the reduced corticosterone levels. However involvement of serotonergic component cannot be ruled out as there were significant changes observed in the swimming but not the climbing behavior in rats during FST and non potentiation of yohimbine lethality in mice.

Trans-01 at the highest dose tested did produce sedation and muscle incoordination as clear from potentiation of alcohol and pentobarbitone sleeping time and shortened fall off time in rota rod and inclined tests respectively. These actions can be attributed to the involvement of interaction with GABA\_A receptors.

In conclusion, Trans-01 showed varied activity profile depending on dose, at lowest doses behaved as antidepressant, medium doses as antianxiety and at highest dose as sedative.