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ANTI DEPRESSANT ACTIVITY OF FRESH LEAVES OF *TINOSPORA CORDIFOLIA* MIERS (AMRUTHABALLI) IN ALBINO MICE

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ABSTRACT: Objectives: To evaluate the antidepressant activity of fresh leaves of *Tinospora cordifolia* in albino mice. **Materials and Methods:** Swiss albino mice weighing 25-30grams of either sex were selected for the study. Six animals were allocated to each experimental group. Animals were divided into 4 groups of 6 mice each. Group 1 - Control group treated with normal saline (0.1ml/10gm), Group 2 received standard group treated with 15mg/kg of imipramine, Group 3 - T1 treated with *Tinospora cordifolia* fresh leaves (100 mg/kg) and Group 4 – T2 treated with *Tinospora cordifolia* fresh leaves 50 mg/kg and 10 mg/kg of imipramine. Decrease in total immobility period denoted antidepressant activity in both tail suspension method & forced swim test in albino mice. **Results:** The test drug that is 50mg/kgp.o of *Tinospora cordifolia* fresh leaves along with 10mg/kg p.o of imipramine significantly decreased the total immobility period in both forced swim test and tail suspension method in albino mice. In forced swim test the percentage decrease in the immobility period was 38.68% when compared to control while in tail suspension method the percentage decrease in the immobility period was 29.06% when compared to control group. **Conclusion:** Fresh leaves of *Tinospora cordifolia* exhibits antidepressant activity in albino mice.

INTRODUCTION: Depression is considered as an affective disorder characterized primarily by change of mood. It is associated with significant morbidity and mortality. The prevalence of major depression in the general population is estimated at 5 % in world population. Prevalence ranges from 9% in ambulatory medical patients to 30% in hospitalized patients. According to the World Health report approximately 450 million people suffer from a mental or behavioral disorder, yet only a small minority of them receives even the most basic treatment.

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This amounts to 12.3% of the global burden of disease, and expected to rise to 15% by 2020 [1]. Essential feature of depression is a period of at least 2 weeks during which there is either depressed mood or the loss of interest or pleasure in all the activities. Additional symptoms are changes in appetite or weight, sleep, psychomotor activity, decreased energy, feeling of worthlessness and suicidal ideation. [2]

Natural products with medicinal value are gradually gaining importance in clinical research due to their well-known property of no side effects as compared to drugs. *Tinospora cordifolia* commonly named as "Guduchi" in Sanskrit belonging to family Menispermaceae is a genetically diverse, large, deciduous climbing shrub with greenish yellow typical flowers, found at higher altitude. A variety of active components derived from the plant like alkaloids, steroids,

diterpenoid lactones, aliphatics, and glycosides have been isolated from the different parts of the plant body, including root, stem, and whole plant [3]. Recently, the plant is of great interest to researchers across the globe because of its reported medicinal properties like anti-diabetic, anti-periodic, anti-spasmodic, anti-inflammatory, anti-arthritic, anti-oxidant, anti-allergic, anti-stress, anti-leprotic, anti-malarial, hepato-protective, immunomodulatory and anti-neoplastic activities. *T. cordifolia* has also been claimed to possess learning and memory enhancing activity [4].

MATERIALS AND METHODS:

Animals: Albino mice (25-30g) of either sex were randomly selected from central animal facility, JSS Medical college, Mysore. Animals were housed into groups of 6-8 per cage at a temperature of $25^0 \pm 1^0$ and relative humidity of 45-55 %. Animals had free access to food and water. Animals were provided free access to tap water and commercial food, and maintained under standard laboratory conditions with a natural light and dark cycle, under room temperature. The study was carried out after obtaining the approval of Institutional Animal Ethical Committee (IAEC/13/5670).

Drugs and Chemicals:

Imipramine (15 mg/kg& 10mg/kg), Normal saline, fresh leaves of *T. cordifolia* were taken at doses of 50 and 100mg/kg.

Methodology:

24 swiss albino mice weighing around 25 g – 30 g of either sex were randomly selected from central animal facility and were acclimatized for 2 days before the start of experimentation.

Animals were divided into 4 groups of 6 mice each.

Group 1 - Control group treated with normal saline (0.1ml/10gm)

Group 2 - Standard group treated with 15mg/kg of imipramine.

Group 3 - T1 treated with *Tinospora cordifolia* fresh leaves (100 mg/kg)

Group 4 - T2 treated with *Tinospora cordifolia* fresh leaves 50 mg/kg and 10 mg/kg of imipramine.

Assessment of Antidepressant Activity:

1. Forced Swim Test (FST) [5, 6]:

Principle: Behavioral despair is a standard proposed model to test for antidepressant activity. It is suggested that mice or rats forced to swim in a restricted space from which they cannot escape are induced to a characteristic behavior of immobility. This behavior reflects a state of despair which can be reduced by agents which are therapeutically effective in human depression.

Procedure: Mice weighing 25 g – 30 g of either sex will be used. The experiment will be carried out 30 min after the oral drug administration. Mice are individually forced to swim inside a vertical cylinder (height: 25cm, diameter: 12cm, containing 15cm of water maintained at room temperature). Mice placed in the cylinder first time are initially highly active, vigorously swim in circles, trying to climb the wall or diving to the bottom. After 2-3 minutes activity begins to subside and interspersed with phases of immobility or floating of increasing length. After 2-4 minutes, immobility reaches a plateau where the mice remain immobile for 80% of the time. A mouse is considered immobile when floating motionless or making only those movements necessary to keep its head above water surface. Time of immobility is recorded in seconds every minute from 3 minute to 6 minute. After 6 min mice are taken out, dried by a towel or tissue paper. The water is changed after each test because urine and the other chemicals released by the first mouse will affect the swimming pattern of the next mouse.

Tail Suspension Test (TST) [7, 8]

Principle: This test has been a facile means of evaluating potential antidepressants. The immobility displayed by mice when subjected to an unavoidable and inescapable stress has been hypothesized to reflect behavioral despair which in turn may reflect depressive disorders in humans. Clinically effective antidepressants reduce the immobility that mice display after active and unsuccessful attempts to escape when suspended by the tail.

Procedure: Mice weighing 25 g – 30 g of either sex are used. Groups of 6 animals are treated orally

with the drugs 30 min prior to the testing. For the test mice are suspended from metal rod

50 cm above the ground or table by adhesive tape placed approximately 1 cm from the tip of the tail. Mice are initially highly active, making vigorous movement to escape. After 2-3 minutes activity begins to subside and interspersed with phases of immobility. The duration of immobility is recorded for a period of 4 minutes from 3 to 6 minutes. Mice are considered immobile when they hang passively and completely motionless.

Statistical Analysis:

The effects of different drugs under study were calculated by taking the mean and SD of the outcome parameters. ANOVA (Analysis of Variance) was applied to compare the effects of drugs under the study. The data were analysed using ANOVA followed by post hoc Bonferroni's test. Differences were considered significant at 5 % level (*p value < 0.05).

RESULTS:

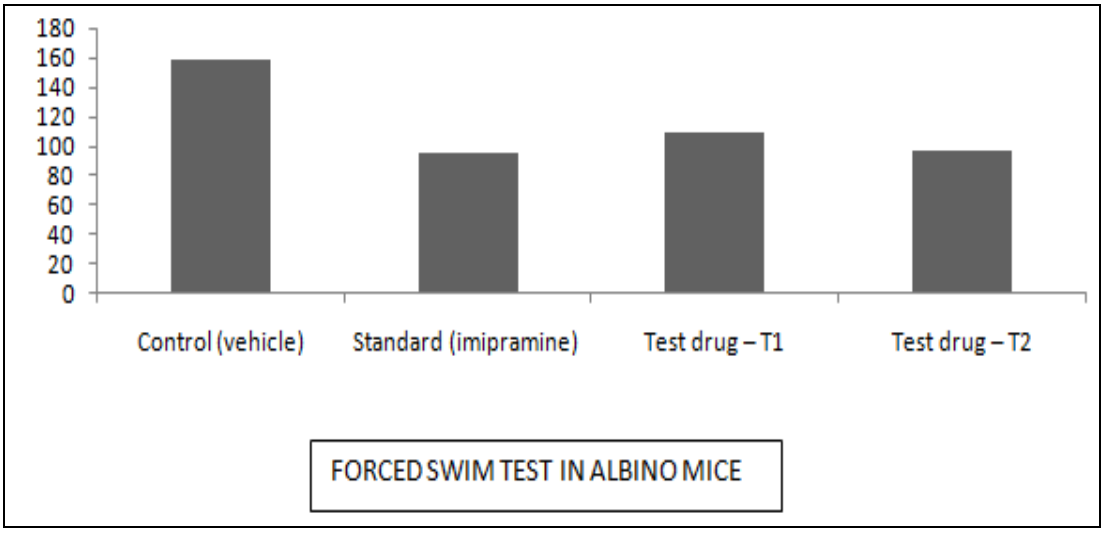
Forced Swim Test Method:

In this method the animals receiving test drug 2 which contained a combination of 50mg of fresh leaves of *T. cordifolia* and 10 mg of imipramine showed significant decrease in the immobility period when compared to control group. The percentage decrease in the immobility period of test drug 2 was 38.68% when compared to control while the standard drug&100mg of fresh leaves *T. cordifolia* reduced the immobility period by 39.63% and 30.59% respectively when compared to control.

TABLE 1: DEPICTS IMMOBILITY PERIOD IN FORCED SWIM TEST IN ALL GROUPS

Group	Treatment for 14 days p.o	Dose (Kg^{-1})	Immobility period (secs)
1	Control (vehicle)	Normal saline- 10ml	158.2 ± 5.1
2	Standard	Imipramine- 15mg	95.5 ± 8.4
3	Test drug – T1	Fresh leaves of *T.cordifolia*	109.8 ± 7.7*
4	Test drug – T2	10mg/kg Imipramine + 50mg/kg of fresh leaves of *T.cordifolia*	97.0 ± 7.6*

n=6 in each group, values are represented as mean + SD. *p value was < 0.05 when compared to control group.

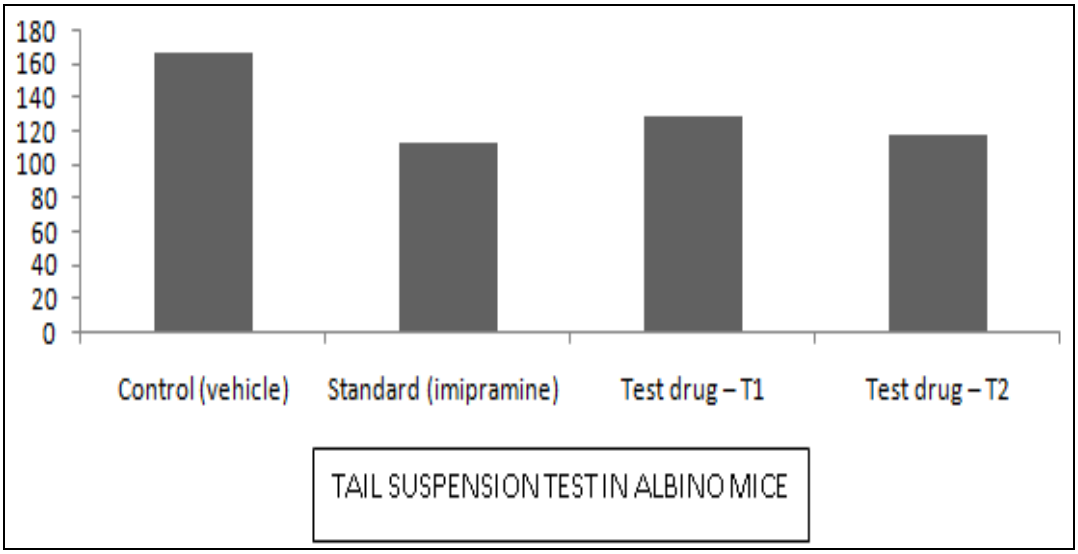


GRAPH 1: DEPICTS IMMOBILITY PERIOD IN FORCED SWIM TEST IN ALL GROUPS.

TABLE 2: DEPICTS IMMOBILITY PERIOD IN TAIL SUSPENSION TEST IN ALL GROUPS.

Group	Treatment for 14 days p.o	Dose (Kg^{-1})	Immobility period (secs)
1	Control (vehicle)	Normal saline- 10ml	166.5 ± 7.9
2	Standard	Imipramine- 15mg	112.8 ± 3.9
3	Test drug – T1	Fresh leaves of *T.cordifolia*	129.3 ± 4.6*
4	Test drug – T2	10mg/kg Imipramine + 50mg/kg of fresh leaves of *T.cordifolia*	117.2 ± 6.6*

n=6 in each group, values are represented as mean + SD. *p value was < 0.05 when compared to control group



GRAPH 2: DEPICTS IMMOBILITY PERIOD IN FORCED SWIM TEST IN ALL GROUPS

Tail Suspension method in Mice:

In this method the animals receiving test drug 2 which contained a combination of 50mg of fresh leaves of *T. cordifolia* and 10 mg of imipramine showed significant decrease in the immobility period when compared to control group. The percentage decrease in the immobility period of test drug 2 was 29.06% when compared to control while the standard drug &100mg of fresh leaves *T. cordifolia* reduced the immobility period by 32.25% and 22.34% respectively when compared to control.

DISCUSSION: Since the incidence of depression in the country is on the raise and is also associated with significant morbidity& mortality rates, it is very important to address these problems and find effective remedies. Though several medications are available, all of these are associated with some limitations and there is an constant need for alternative medications for treating these disorders. [9] Natural products with medicinal value are gradually gaining importance in clinical research due to their well-known property of no side effects as compared to drugs.

Despite the widely popular use of *T. cordifolia* for treating various disorders, there are only few studies carried out for the evaluation of its pharmacological action & effects on nervous disorders. In this study, it was demonstrated that the administration of different doses of the fresh leaves of *T. Cordifolia* in mice was able to induce antidepressant effects**.**

On the basis of the clinical association of depressive episodes and stressful life events, many of the animal models for the evaluation of antidepressant drug activity assess stress-precipitated behaviors. [8] The two most widely used animal models for antidepressant screening are the forced swimming and tail suspension tests. These tests are quite sensitive and relatively specific to all major classes of antidepressants. In TST, immobility reflects a state of despair which can be reduced by several agents which are therapeutically effective in human depression. Similarly in the FST, mice are forced to swim in restricted space from which they cannot escape. This induces a state of behavioral despair in animals, which is claimed to reproduce a condition similar to human depression.

It has been seen that the TST is less stressful and has higher pharmacological sensitivity than FST.[10] It has been established that the shortening of immobility time in the forced swimming and the tail suspension tests depends mainly on the enhancement of central 5-HT and catecholamine neurotransmission.[11]

The present study was conducted for 14 days with administration of all the control, standard and test drugs to study the antidepressant activity. Results showed that the administration of the fresh leaves of *T. cordifolia* produced a diminution of immobility time in mice which were exposed to both forced swimming and tail suspension tests.

In this study, fresh leaves of *T. cordifolia* (100 mg/kg, po) and fresh leaves of *T. cordifolia* (50 mg/kg, po) along with imipramine 10mg/kg administered to mice, produced significant antidepressant-like effect in both TST and FST when compared to control group.

A variety of phytoconstituents have been isolated from *T. cordifolia* plant. They contain various constituents such as alkaloids like tinosporin, diterpenoid lactones like tinosporon & columbin, glycosides like tinocordisides & syringin, steroids, sesquiterpenoid like tinocordifolin, phenolics, aliphatic compounds and polysaccharides.

Three major groups of compounds; protoberberine alkaloids, terpenoids and polysaccharides are considered as putative active constituents of Tcordifolia. [12] *T. cordifolia* has been referred as an herbal psychotropic drug which possibly acts as a nootropic involving cholinergic and GABAergic modulation.[13, 14] The antidepressant activity of *T. cordifolia* is mostly due to increased levels of brain monoamines by its inhibition of metabolism of monoamines particularly serotonin and noradrenaline.[15, 16]

CONCLUSION: Thus fresh leaves of *Tinospora cordifolia* has significant antidepressant activity in albino mice when compared to control group. Further studies would be necessary to evaluate the contribution of active chemical constituents for the observed antidepressant activity.

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