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ANTI DEPRESSANT ACTIVITY OF ETHANOLIC EXTRACT OF *DENDROPTHOE FALCATA LINN IN MICE*

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ABSTRACT

The objective was to investigate the anti depressant activity of ethanolic extract of Dendropthoe Falcata Linn [EEDF] in albino mice. In this studys rats were separated into 4 groups 1st group was denoted as control group in which only distilled water was used, 2nd group was denoted as standard group in which desimpramine hydrochloric acid [20mg/kg] was used as standard and rest 2 groups were denoted as test groups [T1, T2]. Two doses of the ethanolic extract of dendropthoe falcata [200 and 400 mg/kg] were used as T1 and T2 respectively. Control, standard and test samples [Desimpramine and ethanolic extract of Dendropthoe Falcata] were administered via gavage through oral route [p. o]. The outcomes demonstrated that a dose dependent antidepressant activity FOB and MTD. In the Functional Observational Battery of Drug [FOB] the behaviour of mice can be identified by the effect of the drug. In the determination of MTD [Maximum Tolerance Dose] the early citation and main study were done. The present outcomes obviously show that the EEDF has antidepressant activity in FOB and MTD. The current study could be of therapeutic interest for using in the treatment of patients with depression.

KEYWORDS: Dendropthoe Falcata, Anti-depressant activity, Determination of Maximum Tolerance Dose, Functional observational Battery of Drug.

INTRODUCTION

Depression is a state of low mood and aversion to activity that can affect a pervon's thoughts, behavior, felings and sense of well-being The term depression was derived from the Latin verb “Depremere”, “press down”.

According to the World Health report, approximately 450 million people suffer from a mental or behavioral disorder. This amounts to 12.3% of the global burden of disease, and will rise to 15% by 2020., Psychiatric illnesses is also often associated with suicide and there are between 10 and 20 million suicide attempts every year.

One of the carliest forms of depression specific treatment was psychoanalysis, a method developed by Sigmund Freud in the late 1 800's In the 1930's clectroconvulsive therapy was utilized, but again, there was not always a distincti between pensistent mental disorders. In 1949 the National Institute of Mental Health (NIMH) was founded to conduct research into mind, brain and behavior which they reduce mental illness.

There are now several major types of anti depressant drugs, but the carliest found to successfully trear depression were the monoamine oxidase inhibitors (MAO-I) and tricyclic antidepressants. Like many pharmacological breakthroughs, the first major antidepressant was discovered by accident. Iproniarid (the first MAO Inhibitor) it was originally developed to fight tuberculosis In addition to efectively treating tuberculosis, Iproniazid was observed to clevate mood and stimulate activity in many patients. These eflects led rescarchers to investigate the ability of Iproniazid to treat the symptoms of depression.

Depressed mood is not nocessarily a psychiatric disonder. It may be a normal reaction to certain life events, a symptom of some medical conditions, or a side effect of some drugs or medical treatments. Depressed mood is also a primary or associated feature of certain psychiatrie syndromes sach as clinical depressicn.

Depressed people may feel sal, anxious, CImpty, hopeless, Womed, helples, worthless, guilty, imitable hur, or restless. They may lost interest in activities that once were pleasurable, experience loss of appetite or overating, have problems concentrating. remembering details, or making decisions, and many contemplate or attempt suicide,

Insomnia, Cxcessive sleeping, fatigue, loss of energy, or achies, pains, or digestive problems that are Sistant to treatment may also be present '

India is regarded as the treasure trove of herbs in the world. Herbs demonstralc Treal vCTsatility for the treatment of 11 brotid variety of health needs, Medicinal plans are of great value in the field of railiment and cur of diseases. It has now been universally accepted that tulie herbal medicines are fir safer than that of synthetic medicines for curing of many of complex diseaae.

These are many number of plants viz IIyperictim perforatum, Areca catechita, Apocynut Chiettum, Bacopa noneri, Curcuma longa, Chella asiatica, Clitoria termarea, Crous sativus, Mimosa pudica, Morinda offeInalis, Mimosa pudica, OcInitum sancturn 107thania sontrifera, Zingiber officinalis, Passiflora foetida,Perilla frutescens etc Having antidepressant activity.

"Deridrophthoe falcata (L) locally called as Badanika and Jiddu, belonging to the family, Loranthacea is a large parasitic shrub. Dendrophthoe galatta is reported to contain biological active substances such as favonoid, quercetin, kerniplcrol, rutin, tannis, itosterol, stigmasterol, Amyrin. Ileanolic acid.

As per literature review, no antidepressant work has been reported till now: for this plan. So, the present study is designed to evaluate this antidepressant activity of Dendropthoe flacata (L) Using different animal models in mice.

MATERIALS AND METHODS

Chemical and Drugs

Fluoxetine (Sigma Life Sciences, Bangalore), Desipramine (Sigma LifeSciences, Bangalore), Apomorphine (Sigma Life Sciences, Bangalore), Reserpine (Sigma Life Sciences, Bangalore), 5-HTP (Sigma Life Sciences, Bangalore). Glacial acetic acid, IN Sodium hydroxide (Sigma Life Sciences, Bangalore) 5.1.0.

Plant Collection and Authentication

The leaf part of Dendropthoe falcatal(L) was collected from local distributor in tirupathi in the month of February. The leaf (D.Falcata) was identified and authenticated by K.Madhava chetty, assistant professor from Sri Venkateswara University, Tirupathi, chittoor district, Andhrapradesh.

Preparation of The Extract

The dried leaves of Dendropthoe falcata were crushed into fine particles (powder) using a mixer. The Powdered leaves were packed in a soxhlet apparatus and subjected to continuous hot Perrcolation at temperature 50°c using ethanol as solvent till clear solvent was observed in siphon tube Extract was concentrated in water bath at 40° extract was dried and packed in an air tight container.

Animals

Albino mice of either sex weighing between 18-25 gm were used in this study Il the animals were acclimatized in the quarantine room at NATCO Animal house NATCO Pharma Limited, Sanathnogar, Hyderabad), for 7 days and housed in groups ve under standard husbandry conditions like room temperature 23+2°C, relative humidity 30-70% and light / dark cycle of 12 hrs.

All the animals were fed with synthetic standard diet (National Institute for Nutrition, Hubsiguda, and Hyderabad) and water was supplied ad libitum under strict hygienic condition Animal Ethical Committee (IAEC) of Sree Krishna chaitanya College of Pharmacy All the animal studies were performed as per the rules and regulations in accordance to the guidelines of CPCSEA with registered number as PG/COL/12-13/03 s.

All the experimental protocols were approved by Institutional All the animals were fasted 3hrs prior to oral administration of vehicle/standard/test compounds during the experiment. All the experiments were carried out during the light period (9:00 to 17:00 hrs) to avoid circadian rhythms.

METHODS

The Ethanolic root extract of Dendropthoe falcata (L) was subjected to the following investigations.

i) preminary Phytochemical screening

ii) Pharmacological activities

1) Acute Oral Toxicity

2) Functional Observation Battery

3) Assesment of Antidepressant activity

PHARMACOLOGICAL STUDY

Acute Oral Toxicity Study (Aot Study)

1) Dermination of Maximum Tolerance Dose (Mtd)

An OECD guidelines (425) states that, before establishing pharmacological vity of the New Chemical Enity, it was mandatory to establish Maximum erated Dose in mice. The purpose of the citing study was to allow selection of agpropriate starting dose for the main study. The citing study was completed when a ision on the starting dose for the main study was made. The starting dose for a iting study was selected from the fixed dose levels or S, 50, 200, 300, 1000 and 2000 kg as a dose expected to produce evident toxicity, when possible, from in vivo and Tolcralc decis vitro data from the same chemical and from structurally related chemicals. in vitro data tfr.

a) EARLY CITATION

Two male and three female mice were taken for each dose. Before administering compound by oral route, mice were fasted by withdrawing food for 3-4 hours and water should be given ad libitum, Animals were administered with single dose of the drug by oral route according to the body weight. Observations were taken every 1/2he, Ihr, 2hr and 4hr after oral administration. Mortality was recorded for 72hrs. After completion of 72hrs, the survived animals were sacrificed so as to ascertain the absorption of the compound and the changes in the vital organ due to drug.

b) MAIN STUDY

Five Mice (2males and 3 females) were taken for each dose. Mice were fasted istration by withdrawing food for 3-4hrs and water should be given ad libitum. The selected dose of the test substance was administered orally to the animals according to the body weight. The animals were observed for behavioral changes for every 1/2hr, Ihr, 2hr and 4hr after oral administration. The mortality should be observed ill 14days. After completion of 14days, the survived animals were sacrificed so as to ascertain the absorption of the compound and the changes in the vital organ due to drug. From this, $1/10^{th}$ & $1/5^{th}$ doses were selected for pharmacological activity.

2) Functonal Observational Battery of Drug (Fob)

The Functional Observational Battery was a non-invasive procedure designe d to detect gross behavioral observations resulting from expose to chemicals and to better quantify neurotoxic effects. A group of 5 mice of either sex were used to study the effect on behavioral pattern.

The mice were fasted for 3hrs prior to single dose of oral administration. Gross behavioral observations were taken at 1/2hr, Ihr, 2hr and hr intervals. The various parameters listed below and scorings were made as per the standard method.

3) Apomorphine Induced Hypothermia

Animals were divided into 4 groups of 5 animals each weighing between 18-25 gms

Group -Control (Vehicle treated group, p.o)

Group II-Standard (Desipramine 20 mgkg. p.o)

Group III- dose of EEDF (200 mg/kg. P.o)

Group IV-High dose of EEDF (400 mg/kg, p.o)

Apomorphine induces hypothermia antagonism aginst apomorphine induced hypothermia can be regarded as a hint for anti-depressant activity for noradrenalin uptake. Compounds with a marked nor-adrenaline or dopaminergic components antagonize apomorphine induced hypothermia but not antidepressants acting mainly through seratoninergic system.

All the animals were fasted for 3 hrs prior to oral administration of vehicle/standard/test compounds. One hour after oral administration of the test compounds or the vehicle, 16 mg/kg apomorphine was injected s.c to the animals. The rectal temperature of each mouse was measured by an electronic thermometer prior to apomorphine administration and 10, 20, 30 & 60 minutes after apomorphine administration. During the entire experiment, animals were housed in groups in glass jar at room temperature.

Statistical Analysis

Results were presented as mean ± SEM. The data was subjected for statical analysis by One way analysis of variance (ANOVA) followed by Dunnett's test and P.05*, 0.01** and 0.001*** were considered as significant, considered as non-singnificant (ns) Vs Control group.

RESULTS

Preliminary Phytochemical Screening

The Ethanolic root extract of Dendropthoe falcat (L) was subjected to Preliminary Phytochemical Screening and the results were tabulated in Table No.2.The results showed the presence of alkaloids, carbohydrates, polyphenols, glycosides, di & tri terpenes, proteins and amino acids.

Table No.2: Preminary Phytochemical.

S.no	Phytochemical tests	Inference
1	Test for Alkaloids	**+ve**
2	Test for Flavanoides or polyphenols	**+ve**
3	Test for Streoids	**-ve**
4	Test for Glycosides	**+ve**
5	Test for Phenols	**-ve**
6	Test for Terpens	**+ve**
7	Test for Saponins	**-ve**
8	Test for Carbohydrates	**+ve**
9	Test for Proteins	**+ve**
10	Test for amino acids	**+ve**

Ve indicates the presence of compound

-ve indicates the absence of compounds

Acute Oral Toxicity Study (Aot)

The Ethanolic extract of Dendropthoe falcata was administered orally to different groups of mice at different dose levels and was found to be safe up to the dose level of 2000 mg/lkg, p.o, and did not produce any toxic symptoms. The survived animals were sacrificed and complete absorption of drug through GIT was observed Hence l/10 and 1/5 of Maximum Therapeutic Doss (2000 mg/kg) seleted for the pharmacologic-al models.

Functional Observational Battery (Fob)

The Ethanol extract of Dendropthoe falcata was subjected to FOB, which is a non-invasive procedure to detect gross functional deficits basing upon various of various behavioral parameters. The scoring of various parameters was shown in Table. The results showed an increase in stereotypic behaviors like rearing und neurological symptoms of EEDF on pharmacological models.

The various parameters observed in Functional observational battery for control group and EEDF at doses of 200 & 400 mg/kg, po were tabulated as follows.

Table: Functional observation battery of control group.

S.No	Behavirol Parameters	Normal Score	30 Min	60 Min	120 Min	240 Min
1	Spontaneous Motor Activity	4	4	4	4	**4**
2	Respiration	4	4	4	4	**4**
3	Atasis	0	0	0	0	**0**
4	Inclined plane	0	0	0	0	**0**
5	Body tremor	0	0	0	0	**0**
6	convulsions	0	0	0	0	**0**
7	Reactivity of sound & touch	0	0	0	0	**0**
8	Pinna reflex. corneal reflex. Righiting reflex	4	4	4	4	**4**
9	Analgesia	4	4	4	4	**4**
10	Writinng	0	0	0	0	**0**
11	Stereotype behavior	0	0	0	0	**0**
12	Body tone	4	4	4	4	**4**
13	Limb tone	4	4	4	4	**4**
14	Urination	0	0	0	0	**0**
15	Salibvation	0	0	0	0	**0**
16	diaarrhoea	0	0	0	0	**0**
17	Piloerection	0	0	0	0	**0**
18	Pupil size	4	4	4	4	**4**
19	Ptosis	0	0	0	0	**0**
20	Strub tail	0	0	0	0	**0**
21	Catalepsy	0	0	0	0	**0**
22	Hypothermia	0	+0.9	+0.5	+0.9	**+0.3**
23	Stratle responce	0	0	0	0	**0**
24	Cyanosis	0	0	0	0	**0**
25	Lacrination	0	0	0	0	**0**
26	**Exopthalmus**	**0**	**0**	**0**	**0**	**0**

ASSESSMENT OF ANTI DEPARESSANT ACTIVITY (ADA)

Forced Swim Test Model In Mice

S.no	Group	Immobility time (mean ± sem) ;n=5			
		30 Min	**60 Min**	**120 Min**	**240 Min**
1	Control	140 ± 11.6	139.2 ±7.94	114.6 ± 6.51	**110 ± 3.53**
2	Flouxetine (25 mg/kg, p.o)	82.4 ± 25.38*	42.2 ± 14.22**	60.4 ±17.91*	**55.8 ± 14.50****
3	**EEDF(test-2) (400 mg /kg, p.o)**	**63 ± 13.60****	**56.6 ± 19.09****	**60.2 ± 20.42***	**54.4 ± 10.11****

In this model started drug Fluoxetine (25 mg/kg,p.o and EEDF (200 mg/kg, p.o) showed significant decrease in the mobility time of mice when compared to control group.

N=5 in each group; results were analysed by one-way ANOVA usinmg dunnetts multiple comparision test; Significance at **< 0.01, *p<0.05, Non Significance (ns) at p<0.05 Vs control.

DISCUSSION

Depression is "a mental state or chronic mental disorder characterized by feelings of sadness, loneliness, despair, low self-esteem, and self-reproach accompanying signs include psychomotor retardation (or less frequently agitation). withdrawal from social contact, and vegetative states such as loss of appetite and insomnia". According to world health report, approximately 450 million people suffer from a mental or behavioral disorder. This amounts to 12.3% of the global burden of disease, and will rise to 15% by 2020, Psychiatric illness is also often associated with suicide and there are between 10 and 20 million attempts every year.

The current therapy of depression with modern antidepressant drugs is associated with side effects, dose-related and chronic toxicity as well as teratogenic effects. A review of trials involving over four thousand children revealed that 4% of children and adolescents who took antidepressants thought about or attempted suicide, compared to 2% of those on a placebo (a dummy drug). However, nobody did commit suicide. The warning also said that those taking antidepressants should be watched closely by their doctors during the first weeks of treatment. As a result of this, many investigations have been geared towards finding new antidepressant drugs which are effective and have better safety profiles.

Medicinal plants play a valuable role in the drug discovery process as they have been believed to be an important source of new chemical substances with potential therapeutic effects. Many rural dwellers of the developing countries still depend largely on traditional herbal remedies for the management of depression. Although there are available scientific reports to support the folkloric use of some of the herbs used traditionally in the management of depression, many of them are still without documented evidence. Dendropthoe falcata (L) is one of such plant used in depression.

The present work was subjected to investigation for the evaluation of the antidepressant activity of Ethanolic root extract of Dendropthoe falcata (L) in mice The extract was primarily subjected to phytochemical investigation and acute oral toxicity study.

In Acute Oral Toxicity study, EEDF did not show any lethal effect even up to the doses of 2000 mg/kg, p.o and complete absorption of drug through GIT was observed. The Functional Observational Battery is a non-invasive procedure designed to quantify neurotoxic effects. It is used for assessing the behavioral parameters in the mice when exposed to chemicals. The behavioral parameters observed in EEDF(200&400 mg/kg, p.o) were showed an increase in spontancous motor activity, Respiration and stereotypic behavior like scratching, grooming and limb tone as compared to control group.

The effect of EEDF was investigated for its putative antidepressant activity models in mice viz. Tail Suspension test, Forced Swim test, Apomorphine induced Hypothermia, Reserpine induced Hypothermia and by using various experimental SHTP potentiation of Head twitches in mice.

Forced Swim test & Tail Suspension test are the most commonly used preliminary sereening tests for characterizing potential antidepressant drugs. In these models EEDF at doses of 200 mgkg, p.o and 40group mg/kg, p.o showed significant increase in the motor activity of mice which elevate depressed mood by decreasing immobility time of mice. The parameters observed in this model are immobility time of mice. Drugs which decrease immobility time leads to increase in the motor activity of mice which inhibit depression developed due to swimming and tail suspension of mice in these tests and offer protection against depression induced by methods. In the present study, EEDF (200 & 400 mgkg. p.o) has shown a significant dose dependent activity ie. increase in the dose of the drug proportional to decrease in the immobility time threshold and offers good percentage protection as compared to control group. Similarly, the standard drug Fluoxetine (25 mg/kg o) had significant percentage protection. Fluoxetine was selective serotonin work on the serotonin balance by inhibiting a transporter that reuptake inhibitor selectively pumps serotonin back into the neurons.

In Apomorphine induced hypothermia model, Apomorphine induces hypothermia which cannot be antagonized by the EEDF (200&400 mp/kg, p.o) but desipramine (Standard-20 mg/Kg-p.o), antagonized hypothermia revealed that the component might be acting through

Serotonin reuptake inhibition. The are rectal temperature readings of the mice. In this test component parameters observed in this model are rectal temperature Readings of the mice.In this model. Desipramine and EEDF (200 & 400 mg/kg. p.o) had significantly showed opposite actions against hypothermia induced by Apomorphine.

In Reserpine induced hypothermia model, Reserpine induces hypothermia which cannot antagonized by the EEDF (200 & 400 mgkg. p.o) and Fluoxethine (Standard-25 mg/kg-p.o) which revealed that EEDF might be acting Serotonin reuptake inhibition like Fluoxetine. The parameters observed in this model are rectal temperature readings and Ptosis Score.

In 5-HTP model, EEDF at doses of 200 mg/kg and 400 mg/kg, Standard drug, Fluoxetine (25 mgkg, p.o) had significant effect in potentiation of head twitches in mice compared to control group.

The action of EEDF in Apomorphine, Reserpine induced hypothermia and S- HTP potentiation of head twitches models showed that the extract might have affect on the Serotonin reuptake inhibition like Serotonin reuptake inhibitors to exert its antidepressant activity.

CONCLUSION

In the present y. EEDE was evaluated by using various experimental models. EEDF at dos increase in the motor activity of immobility time of mice in Forced Swim test and Tail Suspension tes es of 200 mg/kg, p.o and 400 mg/kg, po showed significant nice which elevate depressed mood by decreasing t. In in & Reserpine induced hypothermia model, EEDF didn't show any ngainst hypothermia produced by the Apomorphine and Reserpine. showed significant potentiation of head twitches in mice in 5-HTP model. From all the above findings, the present investigation suggests that the Ethanolic extract of Dendropthoe falcata may possess antidepressant activity by inhibiting reuptake of Serotonin which acts through Serotonergic receptors (G-protein EEDF coupled receptors) as mood elevator. Therefore lend pharmacological credence to the traditional use of this plant in the treatment of depression.

However, an extensive Pharmacological study of this plant is required for complete understanding of the antidepressant activity of Ethanolic extract of Dendropthoe falcate.

Further investigation should be carried out to isolate and identify the chemical constituent which is responsible for its antidepressant activity.

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