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Research Article.....!!!

**PHARMACOLOGICAL EVALUATION OF ANTIDEPRESSANT ACTIVITY OF
AQUEOUS EXTRACTS OF *TERMINALIA BELLIRICA* FRUITS USING RODENT
MODELS OF DEPRESSION**

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ABSTRACT

Depression is a disorder often manifested with symptoms at the psychological, behavioral and physiological levels. Herbal medicine holds a valuable place in the treatment of depression. It is also a reasonable alternative for developing novel drugs. The present study was to investigate the effect of aqueous extracts of *Terminalia Bellirica* on depression in mice using force swim test (FST) and tail suspension test (TST). The extracts were administered by oral route for 7 days in separate group of mice. Mice of either sex were divided into 6 groups of 5 animals in each group. Group were vehicle of aqueous extracts, Imipramine (15mg/kg), *Terminalia Bellirica* aqueous extract 100mg/kg and 200mg/kg, *Terminalia Bellirica* aqueous extract 100mg/kg + Imipramine (15mg/kg) and *Terminalia Bellirica* aqueous extract 200mg/kg + Imipramine (15mg/kg). Aqueous extracts of *Terminalia Bellirica* (100mg/kg and 200mg/kg) in a dose dependent manner significantly reduced the immobility time of mice. The efficacies of aqueous extract (200mg/kg) were found to be similar to that imipramine (15mg/kg, p.o.) administered for 7 days. The aqueous extracts of *Terminalia Bellirica* give a significant anti-depressant like effect in mice by interaction with adrenergic, dopaminergic and serotonergic systems.

INTRODUCTION:

Depression is a chronic mental disorder that causes changes in mood, thoughts, behaviour and physical health. It's a common but serious disease that can take away a person's ability to enjoy life and cause decline in capacity to undertake even the simplest daily tasks. Other than its chronic nature, symptoms associated with this mental disorder are often recurring and life threatening. According to the World Health Organization (WHO) unipolar depression is one of the leading causes of disability-adjusted life year (DALY) and approximately 350 people worldwide are said to suffer from this mental disorder.¹

Types of depression : Depression is a heterogeneous disorder often mistaken for a single clinical mental illness Diagnosis of this disorder is complicated because of the co-occurrence of many other mental conditions such as anxiety disorders, including panicagoraphobia syndrome, severe phobias, generalized anxiety disorder, social anxiety disorder, post-traumatic stress disorder (PTSD) and obsessive-compulsive disorder (OCD).

Terminalia bellirica Roxb. (Family: Combretaceae) also known as Bahera in Hindi, is one of the important constituents of Indian preparation Triphala (the other two constituents being *Terminalia chebula* and *Embllica officinalis*). Fruits of *Terminalia bellirica* (TB) contain about 17% tannin and β-sitosterol, gallic acid, ellagic acid, ethyl gallate, galloyl glucose and chebulagic acid². The fruits are useful in cough, hoarseness, eye disease, scorpion sting etc. when given along with salt and long pepper². The fruit is bitter, astringent, laxative, antipyretic, analgesic and brain tonic. It is chiefly used in piles, dropsy, diarrhoea and leprosy³. It cures tuberculosis, nose, throat, heart diseases and impurity of blood and fat⁴. The fruits exhibited bronchodilator, antispasmodic, antiasthmatic⁵, hepatoprotective⁶ and spermicidal activities⁷. Alcoholic extract of the fruits showed antistress and endurance promoting properties in hypoxia test in mice and swimming performance test in rats⁸. Ethanolic extract of fruits possessed hypoglycemic activity in alloxan-induced diabetes in rats⁹ and amoebicidal activity *in vitro*¹⁰. Aqueous extract of the fruits showed negative chronotropic, negative inotropic, hypotensive¹³, hypolipidemic¹⁴ and antioxidant activities¹⁵.

In light of above information, the present study has been undertaken (i) to study the effect of the aqueous of fruits of TB on depression in mice employing forced swim test and tail suspension test. Standard antidepressant drug like, imipramine, a tricyclic antidepressant were employed to standardize the animal models of depression and to compare the antidepressant efficacy of the extracts.

Material and Methods:

Preparation of extracts of fruits of *T. Bellirica*: Coarse powder (450 g) of fruits was extracted with distilled water by double maceration for 48 hr. The extract was filtered through muslin cloth. The filtrate was evaporated to dryness in vacuum and kept in a refrigerator. The yield of extract was

26.63%. The aqueous extract of TB was dissolved in 0.25% w/v carboxymethylcellulose.

Animals: Animals used for this study were mice (6–8 weeks, 20–30 g). A total of 30 animals were used for this study. Rodent models were used for acute toxicity test and male rats were used for activity testing. The animals used for this study were I.V.R.I Bareilly. The animals were housed in groups of 6 and were allowed to acclimatize to laboratory conditions for a minimum of 5 days before the time of experimentation. The experimental protocol was approved by the Institutional Animals Ethics Committee (IAEC) and care of laboratory animals was taken as per the guidelines of Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA).

Drug and Chemical: The dried fruits of *Terminalia bellirica* Roxb. were purchased from commercial source. The crude drug was authenticated by Raw Materials, Herbarium and Museum, Department of Botany, MJP Rohilkhnad University, Bareilly (voucher specimen number 478/84). The dried fruits were crushed to make coarse powder.

Sodium hydroxide pellets (Hi-Media, Mumbai, India), Tween 80 (Loba Chemie, Mumbai, India), carboxy methyl cellulose (Hi-Media, Mumbai, India) and imipramine hydrochloride (Sigma-Aldrich, St. Louis, USA) were used in the present study.

Tests for evaluating antidepressant activity:

Forced swim test (FST): Forced swim test was proposed as a model to test for antidepressant activity by Porsolt *et al*¹⁷. The procedure was same as followed earlier^{18,19}. Mice were forced to swim individually in a glass jar (25 × 12 × 25 cm³) containing fresh water of 15 cm height and maintained at 25°C (± 3°C). After an initial 2 min period of vigorous activity, each animal assumed a typical immobile posture. A mouse was considered to be immobile when it remained floating in the water without struggling, making only minimum movements of its limbs necessary to keep its head above water. The total duration of immobility was recorded during the next 4 min of a total 6 min test. The changes in immobility periods were studied after administering drugs in separate groups of animals. Each animal was used only once.

Tail suspension test (TST): The total duration of immobility induced by tail suspension was measured according to the method described earlier¹⁸⁻²⁰ as a means of evaluating potential antidepressants. Mice were suspended on the edge of a table 50 cm above the floor by the adhesive tape placed approximately 1 cm from the tip of the tail. Immobility time was recorded during a 6 min period²¹. Animal was considered to be immobile when it did not show any movement of body and hanged passively.

Drug treatment and Experimental procedure:

Animals were divided into 6 groups and each group comprised of 5 animals. All the test solutions were freshly prepared daily and administered in animals for 7 days by oral route, 60 minutes prior to experimentation. Group I- vehicle of aqueous extracts (0.25% w/v carboxy methyl cellulose (CMC), Group II- Imipramine (15mg/kg), Group III- *Terminalia Bellirica* aqueous extract 100mg/kg, Group IV- *Terminalia Bellirica* aqueous extract 200mg/kg, Group V- *Terminalia Bellirica* aqueous extract 100mg/kg + Imipramine (15mg/kg) Group VI- *Terminalia Bellirica* aqueous extract 200mg/kg + Imipramine (15mg/kg). On seventh day, each animal of each group was checked for depression by forced swim test and tail suspension test.

Statistical Analysis: All results were expressed as mean \pm SEM. Data was analyzed using one-way ANOVA followed by Dennett's test and Student t-test. P < 0.05 was considered to be statistically significant.

Result:

Aqueous extract (100 and 200mg/kg, p.o.) administered for 7 successive days to mice decreased the immobility periods significantly in a dose-dependent manner in both TST and FST, indicating significant antidepressant-like activity. Among two doses administered for 7 days, a dose of 200 mg/kg, p.o. of aqueous extract showed most potent antidepressant- like activity as indicated by highest decrease in immobility period. On the other hand, low dose (100 mg/kg) of aqueous extract administered for 7 successive days to mice did not show significant effect on immobility period when compared to control group. While the highest dose (200 mg/kg) of the aqueous extract with imipramine (15mg/kg) decrease in the immobility period, significantly in both TST and FST as compared to imipramine (15mg/kg) treated groups. The efficacy of aqueous extract (200mg/kg) was found to be comparable to imipramine (15mg/kg) in both FST and TST.

Table: 1 Effect of *T. bellirica* (TB) extract on immobility period of mice using forced swim test (FST) [Values are mean \pm SE].

Group Number	Treatment for 7 days (p.o)	Immobility Period (sec)
I	Vehicle of aqueous extracts (0.25% w/v carboxy methyl cellulose (CMC)	175.5 \pm 3.5
II	Imipramine (15mg/kg)	116.4 \pm 3.3*
III	<i>Terminalia Bellirica</i> aqueous extract 100mg/kg	161.0 \pm 2.8*
IV	<i>Terminalia Bellirica</i> aqueous extract 200mg/kg	119.2 \pm 3.3*
V	<i>Terminalia Bellirica</i> aqueous extract 100mg/kg + Imipramine (15mg/kg)	118.2 \pm 2.3 [#]
VI	<i>Terminalia Bellirica</i> aqueous extract 200mg/kg + Imipramine (15mg/kg)	109.2 \pm 1.5 [#]

[Values are expressed as mean \pm SEM. *P \leq 0.05 as compared to vehicle, #P \leq 0.05 as compared to Imipramine (15mg/kg) group]

Table: 2 Effect of TB extract on immobility period of mice using tail suspension test (TST) [Values are mean \pm SE].

Group Number	Treatment for 7 days (p.o)	Immobility Period (sec)
I	Vehicle of aqueous extracts (0.25% w/v carboxy methyl cellulose (CMC)	195.5 \pm 2.5
II	Imipramine (15mg/kg)	126.4 \pm 3.3*
III	<i>Terminalia Bellirica</i> aqueous extract 100mg/kg	181.0 \pm 2.6*
IV	<i>Terminalia Bellirica</i> aqueous extract 200mg/kg	132.2 \pm 3.3*
V	<i>Terminalia Bellirica</i> aqueous extract 100mg/kg + Imipramine (15mg/kg)	128.2 \pm 2.3 [#]
VI	<i>Terminalia Bellirica</i> aqueous extract 200mg/kg + Imipramine (15mg/kg)	114.2 \pm 1.5 [#]

[Values are expressed as mean \pm SEM. *P \leq 0.05 as compared to vehicle, #P \leq 0.05 as compared to Imipramine (15mg/kg) group]

Discussion:

In the present study, aqueous extract (200 mg/kg) of TB produced significant antidepressant-like effect in mice in both TST and FST and its efficacy was found to be similar to imipramine. Both the models of depression are widely used to screen new antidepressant drugs^{17,20}. These tests are quite sensitive and relatively specific to all major classes of antidepressant drugs^{17,20,22}. 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 depression²³. It has been seen that the TST is less stressful and has higher pharmacological sensitivity than FST²⁴.

The aqueous extract of TB fruits has antioxidant activity due to the presence of phenolic compounds, particularly gallic acid¹⁵. There is evidence of derangement of oxidant and antioxidant defense systems in depression²⁶. Thus, antidepressant-like activity of TB extracts might be due to its antioxidant activity. The present results suggest that aqueous extracts of *Terminalia bellirica* produced antidepressant-like effect in mice in both FST and TST, and it was found to be similar to that of imipramine. The antidepressant-like effects of the extracts seem most likely to be mediated through an interaction with adrenergic, dopaminergic and serotonergic systems. Thus, extracts of *Terminalia bellirica* may have potential therapeutic value for the management of depressive disorders.

CONCLUSION:

It may be concluded that, aqueous extracts of *Terminalia bellirica* (200mg/kg) is give antidepressant effect might be due to an interaction with adrenergic, dopaminergic and serotonergic systems in mice. The aqueous extracts of *Terminalia bellirica* (200mg/kg) with imipramine give synergetic antidepressant effect in mice.

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