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EVALUATION OF ANTI-DEPRESSANT ACTIVITY OF AQUEOUS EXTRACT OF *AVERRHOA BILIMBI* IN MICE

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ABSTRACT
Objective: To evaluate the antidepressant activity of aqueous extract of *Averrhoa bilimbi* (AEAB) fruits in mice. **Methods:** The antidepressant activity of aqueous extract of *Averrhoa bilimbi* was evaluated using tail suspension test, forced swim test and hole board test. The test was carried out at two different doses of AEAB (0.5ml and 1ml). The treatment was given for 11 days and the antidepressant activity was tested on 0^{th} and 11^{th} day of the treatment. Imipramine (10 mg/kg) was served as standard in all the models. **Results:** AEAB treatment showed a significant antidepressant activity compared to control. The duration of immobility reduced significantly in case of TST and FST and a increase in number of head dips were observed in case of hole board test. *Averrhoa bilimbi* showed dose dependent antidepressant action with better action at higher dose. **Conclusion:** The present study suggested that the aqueous extract of *Averrhoa bilimbi* is effective against depression.

KEYWORDS: Averrhoa bilimbi, FST, TST, Hole board Test.

INTRODUCTION
Depression is a chronic mental disorder that causes changes in mood, thoughts, behavior and physical health. There are indeed diverse forms of depression that can either be mild or extremely severe conditions like psychotic depression in which the patients show symptoms such as hallucinations and delusions.[1]

Major depressive disorder (MDD) is the most common psychiatric disorder. According to the World Health Organization (WHO), it is also the most important precursor of suicide and will be the second cause of Global Disease Burden by the year 2020. The symptoms of minor depression are similar to major depression and dysthymia, but they are less severe and/or usually have a shorter term.[2] Depressive disorders are currently estimated to affect 350 million people worldwide with approximately 1 in 20 people reporting an episode of depression each year.[3]

The main biochemical theory of depression is monoamine hypothesis, which states that depression is caused by functional deficit of monoamines (norepinephrin serotonin and dopamine) at certain parts of the brain.[4]

In this study, *Averrhoa bilimbi* was screened for its potential in treatment of depression in experimental animal model.

MATERIALS AND METHODS
Plant material and extraction[5]
50g of the fresh fruits were cut into halves and blended with 100ml of water. To obtain clear juice, the blended fruit was filtered through a muslin cloth or stainless steel filter with small porosity. The filtered fruit extract was immediately stored in freezer at 4^0C for further use.

Priliminary phytochemical test: The aqueous extract of Averrhoa bilimbi was subjected to phytochemical screening tests for various phytoconstituents.

EXPERIMENTAL ANIMAL
Wistar Albino mice (20 to 25 g) of either sex were used for the experiment were procured from the animal house of Srinivas College of Pharmacy, Mangalore. They were maintained under standard conditions (temperature 22 ± 2°C, relative humidity 60±5% and 12 h light/dark cycle) and had free access to standard pellet diet and water *ad libitum*. The animals were housed in sanitized polypropylene cages containing sterile paddy husk as bedding. The Institutional Animal Ethics Committee reviewed and approved the experimental protocol (approval no **SCP/IAEC/F150/P117/2017**).

Experimental Design
Dose[6]
The mice were randomly allocated to four experimental groups each containing 6.

- Group I: (Control group)Vehicle.
- Group II: (Standard group) Imipramine, 10 mg/kg, oral
- Group III: (Test group) *Averrhoa bilimbi* fruit extract (0.5ml).
- Group IV: (Test group) *Averrhoa bilimbi* fruit extract (1ml).

Forced swim test[7]: Mice of either sex (22-25 g) were divided into 4 groups of six animals. Mice were forced to swim individually for 6 min, in a glass beaker of 11cm diameter, 15cm height containing fresh water up to a height of 6cm, at a temperature of 27±2°c. This constituted the "pre-test" session. The test-session was conducted before (0th day) and after the drug treatment (on 11th day). The mouse is considered immobile when it floats motionlessly or makes only those movements necessary to keep its head above the water surface.

Evaluation: The total duration of the immobility during the 6 min test was recorded on 0th and 11th day.

Tail suspension test[7]

Mice were suspended by tail from a height of 75cm. The mouse makes attempts to regain upright posture, but continues in a motion less state (immobility phase). Baseline immobility was measured for a period of 6 min. Then the drug is administered for 11 days.

Evaluation: Immobility was recorded for a period of 6min on 0th and 11th day.

Hole board test for mice[8]: Drugs were administered for 10 days. Hole board consists of a wooden board having dimensions of 40 × 40 × 25 cm^3 along with uniformly dispersed 16 holes each having constant diameter of 3 cm. Mice was placed at the center of hole board before (0th day) and after (11th day) the administration of given treatments and its activity was observed.

Evaluation: The number of head dips were recorded for a period of 6min on 0th and 11th day.

RESULTS

Preliminary Phytochemical Screening

Table 1: preliminary phytochemical analysis

Sl. No.	Test	Results
1	Tannins	+
2	Glycosides	+
3	Flavonoids	+
4	Saponins	+
5	Carbohydrates	+
6	Proteins	+
7	Alkaloids	-
8	Terpinoids	-
9	steroids	-

Table. 2: effect of AEAB on duration of immobility in forced swim test.

Group	Dose	No. of animals	Duration of immobility (seconds)	
			Before treatment	After treatment
Control (normal saline)	1ml	6	155.61±6.185	156.70±5.442
Imipramine	10mg/kg	6	156.52±5.012	72.50±5.423***
AEAB (Low dose)	0.5ml	6	156.74±5.149	133.56±6.256*
AEAB (high dose)	1ml	6	157.25±5.332	123.00±5.467**
Values are expressed as the mean ± SEM. n=6. Data were analyzed by one-way ANOVA followed by Tukey's comparision test. *p<0.05, **p<0.01, ***p<0.001, as compared to depressive control mice.				

Table. 3: effect of AEAB on duration of immobility in tail suspension test.

Group	Dose	No. of animals	Duration of immobility (seconds)	
			Before treatment	After treatment
Control	1ml	6	143.82±5.160	144.30±5.535
Imipramine	10mg/kg	6	144.23±5.900	65.83±5.535***
AEAB (Low dose)	0.5ml	6	143.36±5.243	124.30±5.122*
AEAB (high dose)	1ml	6	144.37±5.342	119.20±5.639**
Values are expressed as the mean ± SEM. n=6. Data were analyzed by one-way ANOVA followed by Tukey's comparision test. *p<0.05, **p<0.01, ***p<0.001, as compared to depressive control mice.				

Table. 4: effect of AEAB on number of head dips in hole board test.

Group	Dose	No. of animals	No of head dips	
			Before treatment	After treatment
Control	1ml	6	57.67±5.637	56.83±5.935
Imipramine	10mg/kg	6	56.00±5.842	127.00±5.121***
AEAB(Low dose)	0.5ml	6	56.67±5.852	78.83±5.012*
AEAB(high dose)	1ml	6	57.33±5.869	87.17±5.130**
Values are expressed as the mean ± SEM. n=6. Data were analyzed by one-way ANOVA followed by Tukey's comparision test. *p<0.05, **p<0.01, ***p<0.001, as compared to depressive control mice.				

DISCUSSION

It is estimated that by the year 2020, depression will result in the second greatest increase in morbidity after cardiovascular disease, presenting a significant socioeconomic burden. Depressed mood, lack of interest and reduced energy are considered as the core symptoms of depression and at least two of them have to be present to confirm the diagnosis of major depressive disorder.[9]

Scientific understanding of psychoactive plants has significantly advanced over the last two centuries. Research into psychoactive plants that may affect the central nervous system (CNS) has flourished, with an abundance of pre-clinical in vitro and in vivo studies validating many phytotherapies as having an array of biopsychological effects. Both at the cellular and whole organism level, a plethora of molecular processes are involved in stress responses mediated by the CNS.

Mechanisms of action for herbal medicines used for treatment of psychiatric disorders primarily involve modulation of neuronal communication, via specific plant metabolites binding to neurotransmitter/neuromodulator receptors, and via alteration of neurotransmitter synthesis and general function. Other actions may involve stimulating or sedating CNS activity, and regulating or supporting the healthy function of the endocrine system. Several herbal medicines revealed an array of pre-clinical antidepressant activity.[10]

Moreover, in many countries of the world, natural medicine remains the most available and sometimes the only form of medical care, also as far as mental health is concerned. According to some studies, post-industrial societies reveal an increasing interest in alternative medicine, including herbal therapy, despite the achievements of conventional medicine. It seems that for many people the „natural" model best meets their expectations concerning effective and safe treatment.[11]
The present study was designed to elucidate the effect of aqueous extract of *Averrhoa bilimbi* in the treatment of depression using forced swim test, Tail Suspension Test, Hole board test in mice .These tests are quite sensitive and relatively specific to all major classes of antidepressant drugs.[12]

Preliminary phytochemical analysis of aqueous extract of *Averrhoa bilimbi* revealed the presence of flavonoids, tannins, glycosides, carbohydrates and proteins. The effective components of herbs that have antidepressant-like effect includes flavonoid, oligosaccharide, polysaccharide, organic acid.[13]

Tail suspension test (TST) is a common behavioural paradigm used to evaluate the antidepressant activity of experimental drugs. Like the forced swimming test, in this test the animals are set in an inescapable yet modestly distressing circumstance. . In this test the mice are suspended by their tails. Every mouse remains suspended for 6 minutes. The behaviour of the mouse to escape this aversive situation is recorded during this time. Mice, suspended by their tails, intrinsically endeavour to get away from this aversive circumstance. However, as a result of the fizzled endeavour to get away, the mice experience despair and become immobile. In the tail suspension test, the extent of immobility is thought to be associated with the depressive-like condition of the animal and is significantly diminished by antidepressant drugs.[14]

During the FST an animal is placed in a container filled with water from which it cannot escape. The animal will first try to escape but eventually will exhibit immobility (i.e. floating with the absence of any movement except for those necessary for keeping the nose above water). The FST is a very popular model in animal research for a number of reasons. First, it involves the exposure of the animals to stress, which was shown to have a role in the tendency for major depression. Moreover depression is often viewed as a lack of ability to handle with stress. Second, pharmacological treatment with antidepressants prior to the test has been shown to reduce immobility in the FST. Therefore, it is often used as a screening assay for novel compounds with potential antidepressant properties.[15]

In both FST and TST there was a decrease in immobility time after 11 days of treatment which was comparable to standard drug group that is Imipramine indicating the antidepressant activity of aqueous extract of *Averrhoa bilimbi.* It showed a dose dependent action with higher action at 1ml compared to lower dose 0.5ml.

The same is proved even in hole board test as there was significant increase in number of head dips in case of *Averrhoa bilimbi* treated mice which was comparable to the Imipramine. Depression has been associated with lowered concentrations of several endogenous

antioxidant compounds. Oxidative damage to lipids and decreased antioxidant enzyme activity have been reported in patients with major depressive disorder and preclinical studies have suggested that antioxidants may have antidepressant properties.[16] *Averrhoa bilimbi* is also a very good antioxidant agent.[17] So its antioxidant property might be the reason behind its antidepressant activity.

As the extract used for the study was a crude one, it is not possible to point out that the particular compound is responsible for antidepressant property shown by the fruit. It may be better assumed that the biologically active principles present in the extract act in synergetic fashion.

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