Research Article

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ACUTE ANTIDEPRESSANT ACTIVITY OF AQUEOUS EXTRACT OF *TERMINALIA BELERICA* FRUIT IN MICE IN EXPERIMENTAL PARADIGMS

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ABSTRACT
Depression is a common symptom in today's scenario, which is a widespread psychiatric disorder. The aqueous extract of *Terminalia belerica* fruit (AETB) contains phenol and tannin compounds which have shown promising therapeutic potential in neurological diseases. The study was undertaken to evaluate the antidepressant activity of AETB using Forced Swim Test (FST) and Tail Suspension Test (TST). Adult male Swiss Albino mice weighing about 25-30 g were used. The animals were divided into five groups, each group containing six animals (n = 6). Group I was control that received gum acacia (10 ml/kg, per oral), group II standard imipramine (10 mg/kg, per oral) and group III, IV and V were test groups that received AETB (9 mg/kg, 18 mg/kg and 36 mg/kg, per oral respectively). All the drugs were administered one hour prior to the study. The results were analyzed using one way ANOVA followed by Dunnett's t-test, $p < 0.05$ was considered significant. The effect of AETB on immobility periods of mice were assessed in Forced Swim Test (FST) and Tail Suspension Test (TST). The effects of AETB were compared with that of control. The AETB showed significant reduction in immobility time of mice in both FST and TST at the doses of 9 mg/kg, and 36 mg/kg and 9 mg/kg, 18 mg/kg respectively on acute administration. The present study suggests the possible antidepressant like activity of AETB in mice on acute administration.
Keywords: Depression, Forced Swim Test, Tail Suspension Test, *Terminalia belerica*.

INTRODUCTION

Depression, a mood disorder which has knocked down several lives in the current scenario. Globally, more than 350 million people from all age groups suffer from depression. In India the prevalence of depression is 31.2 per 1000 population. Depression is a common mental disorder that presents with depressed mood, loss of interest or pleasure, decreased energy, feelings of guilt or low self-worth, disturbed sleep or appetite and poor concentration. It can range from a mild scale to major depressive disorder. The cause is neither a predictable one nor is the treatment, as the origin is multifactorial[1,2]. The most commonly used antidepressants, although provide a significant symptomatic relief, often cause adverse effects and difficulty in tolerating these drugs is the prime factor for their noncompliance among patients. The Selective Serotonin Reuptake Inhibitor (SSRIs) produces nausea, diarrhea, agitation, headache and sexual dysfunction. The Food and Drug Administration (FDA) has stamped a Black Box warning on all SSRIs, which state that they double suicidal rates (from 2 in 1,000 to 4 in 1,000) in children and adolescents. Tricyclic Antidepressants (TCA's) exhibit an array of side effects like drowsiness, anxiety, emotional blunting (apathy/anhedonia), confusion, restlessness, dizziness, akathisia, hypersensitivity, changes in appetite and weight, sweating, sexual dysfunction, muscle twitches, weakness, nausea and vomiting, hypotension, tachycardia, and rarely irregular heart rhythms[3]. Hence it is essential to develop new molecules with similar therapeutic benefits with no or negligible side effects. Traditional medicine paves its path; Ayurveda which reigned from the Indian subcontinent provided several medications that can be utilized in psychiatry. *Terminalia belerica* derived from the plant kingdom is a large deciduous tree found on the plains and lower lying hilly regions of Southeast Asia[3]. As per the traditional norms in Indian Ayurvedic medicine, *Terminalia belerica* is known as "Bibhitaki". In Sanskrit it is called Vibhidaka[4]. The grey to dark brown oval fruit is 1-2 cm in diameter. Pulp of the fruit extract has astringent, antiseptic, rejuvenating, brain tonic, expectorant and laxative properties hence used to alleviate asthma, piles and cough[5]. *Terminalia belerica* has been reported to promote digestion, wound healing, and ulcer healing and is used in the treatment of local swelling, anemia and chronic recurrent fever. *Terminalia belerica* also exhibits anti-diabetic[6], anti-cancer[7], anti-mutagenic[8] and anti-viral activity[9]. "Triphala" which comprises of *Emblica officinalis*, *Terminalia chebula* and *Terminalia belerica* has been proved to have antidepressant activity. Individually, *Emblica officinalis*[10] as well as *Terminalia chebula*[4] has also been proved to have antidepressant activity. Hence this study was undertaken to evaluate the acute antidepressant activity of aqueous extract of *Teminalia belerica* fruit pulp.

MATERIALS AND METHODS

Animals

The experimental protocol was approved by the Institutional Animal Ethics Committee (Approval No. IAEC/02/2013/CPCSEA) dated 05/10/2013. Adult male Swiss Albino mice weighing 25-30 g from our college animal house breeding stock were taken in the study. The animals were housed at 24 ± 2^0C with 12:12 hour light

and dark cycle. They had free access to food and water *ad libitum*. The animals were acclimatized for a period of 7 days before the study. The study was conducted according to CPCSEA guidelines.

Drugs and chemicals

The standard antidepressant drug Imipramine was procured from Himedica laboratory. The test drug *Terminalia belerica* was provided by Shri Lakshmi Ayurvedic Dispensary, Mangalore, India and 1 % gum acacia (vehicle) was used[4].

Authentication

Terminalia Belerica fruit was authenticated by Dr. Krishna Kumar. G, Chairman, Department of Applied Botany, Mangalore University, Mangalore, Karnataka, India.

Extraction

About 1000 g of air dried crude powder of *Terminalia belerica* fruit pulp was extracted with water in Soxhlet extractor for 36 hours. It was dried and reduced under controlled pressure and temperature (40-50^{0}C) using a rotatory evaporator. The aqueous extract yielded a brownish mass weighing 145 g. The yield obtained was 14.5 % w/w with respect to dried powder[4].

Experimental design

On the day of the experiment, the animals were divided randomly into control and experimental groups (n = 6). Group I received the vehicle, 1 % gum acacia (10 ml/kg) and served as the control group, group II received the standard drug imipramine (10 mg/kg) , group III, group IV and group V received the test drug (AETB) in doses of 9, 18 and 36 mg/kg respectively per orally. The above drugs were dissolved in 1 % gum acacia. Vehicle/Drugs were administered to the animals 60 minutes prior to the behavioral evaluation. The antidepressant activity of the test drug was evaluated using Forced Swim Test and Tail Suspension Test[3].

Forced Swim Test (FST)

Each animal was placed individually in a 5 litre glass beaker, filled with water up to a height of 15 cm and were observed for duration of 6 minutes. The duration of immobility was recorded during the last 4 minutes of the observation period. The mouse was considered immobile when it floated motionlessly or made only those moments necessary to keep its head above the water surface. The water was changed after each test[11].

Tail Suspension Test (TST)

Mice were hung on a plastic string 38 cm above the table top with an adhesive tape placed approximately 1 cm from the tip of the tail. Duration of immobility time was recorded for 8 minutes. The duration of immobility was recorded during the last 6 minutes of the observation period. Mice were considered immobile only when they hung passively and completely motionless[12].

Statistical analysis

The mean ± SEM values were calculated for each group. The data was analyzed using one-way ANOVA followed by Dunnett's multiple comparison test, $p < 0.05$ was considered to be statistically significant.

RESULTS

As shown in Table 2, during FST on acute administration of AETB at the dose of 9 mg/kg (group III) and 36 mg/kg (group V), the duration of immobility in mice was decreased as compared to the control (1 % Gum Acacia) and was highly significant. AETB in a dose of 18 mg/kg (group IV) was significant but less as compared to the other doses in FST. As shown in Table 3, on acute administration, AETB at the dose of 9 mg/kg (group III) and 18 mg/kg (group IV) decreased the duration of immobility when compared to the control (1 % Gum Acacia) and was highly significant in TST.

Table 1: Groups and dose of the drug and route of administration

Group (n = 6)	Administered drug	Route of administration
I – CONTROL	1 % gum acacia (10 ml/kg)	PER ORAL
II – STANDARD	Imipramine (10 mg/kg)	PER ORAL
III – TEST GROUP	AETB (9 mg/kg)	PER ORAL
IV – TEST GROUP	AETB (18 mg/kg)	PER ORAL
V – TEST GROUP	AETB (36 mg/kg)	PER ORAL

AETB - Aqueous Extract of *Terminalia Belerica*

Table 2: Effect of Aqueous Extract of *Terminalia belerica* (AETB) on immobility time in FST

Group	Mean Duration of immobility (in seconds)
I - (1 % gum acacia 10.0 ml/kg))	110.830 ± 12.595
II - (Imipramine 10.0 mg/kg)	36.500 ± 12.748**
III - (AETB 9 mg/kg)	19.333 ± 9.109**
IV - (AETB 18 mg/kg)	50.667 ± 19.913*
V - (AETB 36 mg/kg)	36.500 ± 5.824 **

All data are expressed as Mean ± SEM.*p < 0.05, **p < 0.01 as compared to control (ANOVA followed by Dunnett's multiple comparison test) control. AETB - Aqueous Extract of *Terminalia belerica*

Table 3: Effect of Aqueous Extract of *Terminalia belerica* on immobility time in TST

Group	Mean Duration of immobility (in seconds)
I - (1 % gum acacia 10.0 ml/kg))	228.50 ± 18.749
II - (Imipramine 10.0 mg/kg)	139.00 ± 8.274**
III - (AETB 9 mg/kg)	116.50 ± 16.223**
IV - (AETB 18 mg/kg)	142.67 ± 15.928**
V - (AETB 36 mg/kg)	177.00 ± 24.870

All data are expressed as Mean ± SEM.*p < 0.05, **p < 0.01 as compared to control (ANOVA followed by Dunnett's multiple comparison test) control. AETB - Aqueous Extract of *Terminalia belerica*

DISCUSSION

A decrease in the level of brain neurotransmitters has been theorized to be a core pathogenic factor in depression for half a century. The newer inventions suggest the involvement of oxidative stress in the development of depression[13,14]. Evidence based medicine, suggests that depression may be associated with neurodegeneration and reduction in the neurogenesis in the hippocampus[15,16]. Probing a little further into the issue, despite the stacks of newer medications, the health care professionals afford a mere relief in depression. Relief of symptoms in depressive patients has however been over powered by the various adverse effects. In the current experimental paradigms, the immobility displayed by the rodents when subjected to an unavoidable and inescapable stress, has been hypothesized to reflect the behavioral despair which in turn may reflect depressive disorders in humans. The drop in the duration of immobility after the administration of the drug expresses the antidepressant activity. Current study suggested, acute administration of AETB in the dose of 9 mg/kg (group III) and 36 mg/kg (group V) significantly decreased the immobility duration in FST and AETB in a dose of 9 mg/kg (group III) and 18 mg/kg (group IV) showed a significant decrease in the duration of immobility in mice subjected to TST. The antidepressant activity may be attributed to the presence of tannic acid and polyphenols in the extract[17]. Tannic acid is considered to be a non selective inhibitor of monoamine oxidase, thereby increasing the levels of monoaminergic neurotransmitters in the brain[10]. Another suggestive mechanism could be attenuation of oxidative stress produced during depression due to polyphenols and tannic acid[10].

CONCLUSION

The current study suggests the antidepressant like activity of aqueous extract of *Terminalia belerica* in adult male Swiss Albino mice on acute administration utilising Forced Swim Test and Tail Suspension Test experimental paradigms. However, further research is required to establish the exact underlying mechanism and also to assess potential of developing aqueous extract of *Terminalia belerica* as an antidepressant drug used in clinical practice for the future.

REFERENCES

1. Marina Marcus M, Taghi Yasamy, Mark Van Ommeren and Dan Chisholm, Saxena Shekhar. Depression; A Global Crisis; World Mental Health Day, World Federation for Mental Health; 2012. p. 6.
2. Aakanksha, Kumar Vinay, Singh Bhulan Kumar, Nagarajan K, Machawal Lalit, Bajaj UK. Attenuating depression behavior by *Centella asiatica* extract and venlafaxine in mice induced through forced swim and tail suspension test: International Journal of Pharmacology and Toxicology 2013; 2: 29-35.
3. Chandra Shekar R, Manohar VR, Dr Rao SN. Antidepressant Activity Of Aqueous Extract of Fruits of *Terminalia chebula* in Rats, Int J Pharm Sci 2012; 4 Suppl 4: 449-451.
4. Manohar VR, Chandrashekar R, Rao SN. Phytochemical Analysis of *Terminalia Belerica* Fruit Pulp Extracts, World Journal Of Pharmacy And Pharmaceutical Sciences 2012; 4(1): 1376-1383.
5. Chatterjee S, Pakrasi SC. The Treatise on Indian Medicinal Plants, National Institute of Science Communication and Information Resources 2000; 3: 203–204.
6. Sabu MC, Kuttan R. Anti-diabetic activity of medicinal plants and its relationship with their anti oxidant property. J. Ethanopharmacol 2002; 81: 155–160. http://dx.doi.org/10.1016/S0378-8741(02)00034-X
7. Saleem A, Husheem M, Harkonen P, Pihalaja K. Inhibition of cancer cell growth by crude extract and the phenolics of *Terminalia chebula* Retz. fruit. J. Ethnopharmacol 2002; 81: 327–336. http://dx.doi.org/10.1016/S0378-8741(02)00099-5
8. Kaur S, Arora S, Kaur K, Kumar S. The *in vitro* antimutagenic activity of Triphala – an Indian herbal drug. Food Chem. Toxicol 2002; 40: 527–534. http://dx.doi.org/10.1016/S0278-6915(01)00101-6
9. Ahn MJ, Kim CY, Lee JS, Kim TG, Kim SH, Lee CK *et al*. Inhibition of HIV-I integrase by galloyl glucose from *Terminalia chebula* and flavonol glycoside gallates from *Euphorbia pekinensis*, Planta Med 2002; 68: 457–459. http://dx.doi.org/10.1055/s-2002-32070
10. Pemminati Sudhakar, Gopalakrishna HN, Shenoy Ashok K, Sahu Sudhanshu Sekhar, Mishra Shishir *et al*. Antidepressant Activity of Aqueous Extract of Fruits of *Emblica officinalis* in Mice, International Journal of Applied Biology and Pharmaceutical Technology 2010; 2: 449-452.
11. RD Porsolt, A Bertin and M Jalfre. Behavioral despair in mice, A primary screening test for antidepressant, Archint Pharmacodyn 1967; 229: 327-336.
12. Stenu L, Chermat R, Thierry B, Simon P. The tail suspension test: a new model sensitive to antidepressants in mice, Psychopharmacology 1985; 85: 367-370. http://dx.doi.org/10.1007/BF00428203
13. Sarandol A, Sarandol E, Eker SS, Erdinc S, Vatansever E, Kirli S. Human Psychopharmacol, Clin Exp 2007; 22(1, Suppl 2): 67-73.
14. Eren I, Naziroğlu M, Demirdaş A, Celik O, Uğuz AC, Altunbaşak A *et al*. Venlafaxine modulates depression-induced oxidative stress in brain and medulla of rat, Neurochem Res 2007; 32(Suppl 3): 497-505. http://dx.doi.org/10.1007/s11064-007-9289-x
15. Baldessarini RJ. Fifty years of biomedical psychiatry and psychopharmacology in America. In: American psychiatry after World War II: (1944–1994), Menninger R, Nemiah, J, editors. Washington DC: American Psychiatric Press; 2000. p. 371–412.
16. Musselman DL, De Battista C, Nathan KI. Biology of mood disorders. In: The American psychiatric press textbook of psychopharmacology. Schatzberg AF, Nemeroff CB, editors. Washington DC: American Psychiatric Press; 1998. p. 549-88.
17. Rice Evans CA, Miller NJ, Paganga G. Structure-antioxidant activity relationships of flavonoids and phenolic acids. Free Radical Biology and Medicine 1996; 20 Suppl 7: 933–956. http://dx.doi.org/10.1016/0891-5849(95)02227-9

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