

ANTIDEPRESSANT ACTIVITY OF AQUEOUS EXTRACT OF FRUITS OF *TERMINALIA CHEBULA* IN RATS

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ABSTRACT

Depression is a common symptom of the present day world which is widespread psychiatric disorder affecting a large number of population. It is often difficult to predict the cause and also to treat depression. In the traditional systems of medicine, many plants and formulations have been used to treat depression for thousands of years. The water extract of *Terminalia chebula* (TC) contains total phenolic and tannin content. The water extract appeared to have good antioxidant activities. It is believed that tannins have neuroprotective functions capable of reversing 6-hydroxydopamine-induced toxicity. The tannins has shown promise as a potential therapeutic agent, which may be beneficial in patients with neurological disease

Therefore, the present study was undertaken to evaluate the antidepressant potential of acute of TC in forced swim test (FST). Inbred adult male Swiss Albino rats weighing 150-200g were used in the study. Standard drug (imipramine) and aqueous extract of test drug (TC). The vehicle (10ml/kg, p.o), imipramine (10mg/kg, p.o) and TC (9mg/kg, 18mg/kg, 36mg/kg, p.o. respectively) were administered 1hour prior to acute study. Duration of immobility was noted. In our study, both imipramine and TC significantly reduced the duration of immobility forced swim test (FST) as compared to the animals in the control group. The antidepressant activity of TC was comparable to that of standard drug imipramine. The results of the present study indicate the potential for use of TC as an adjuvant in the treatment of depression.

Keywords: Depression, *Terminalia chebula*, Forced swim test.

INTRODUCTION

Mental depression is a chronic illness that affects a person's mood, thoughts and physical and behaviour and may range from very mild condition, bordering on normality to severe depression¹. Depression is an affective disorder, defined as disorders of mood rather than disturbances of thought or cognition; it may range from a very mild condition, bordering on normality, to severe psychotic depression accompanied by hallucinations and delusions². The primary clinical manifestations of major depression are significant depression of mood and impairment of function. Some features of depressive disorder overlap those of the anxiety disorders, including panicagoraphobia syndrome, severe phobias, generalized anxiety disorder, social anxiety disorder, posttraumatic stress disorder, and obsessive-compulsive disorder³.

Along with the classical theory of decrease in the neurotransmitter levels in the brain leading to the pathogenesis of clinical depression, recent studies have also shown the involvement of oxidative stress in the phenomenon^{4,5}. Recent evidence suggests that depression may be associated with neurodegeneration and reduced neurogenesis in the hippocampus^{6,7}. Despite the development of new molecules for pharmacotherapy of depression, it is unfortunate that this disorder goes undiagnosed and untreated in many patients. Although the currently prescribed molecules provide some improvement in the clinical condition of patients, it is at a cost of having to bear the burden of their adverse effects.⁸

Ayurveda, the Indian traditional system of medicine, mentions a number of single and compound drug formulations of plant origin that are used in the treatment of psychiatric disorders^{9,10}. *Terminalia chebula* an important medicinal plant is distributed in the sub-Himalayan tracks, and the eastern, western and southern parts of India. Its fruits are extensively used as an adjuvant in medicines for various diseases with special reference to Ayurvedic medicaments. The pericarp of the dried ripe fruit is used in the preparation of many Ayurvedic formulations for infectious diseases¹¹.

T. chebula is reported to promote digestive power, wound healing, and is curative of ulcers, local swelling, anemia, diabetes, and chronic and recurrent fever. The fruits are astringent, purgative,

laxative, gastro protective and are used to alleviate asthma, piles and coughing¹². *T. chebula* has been reported to exhibit a variety of biological activities, such as anti-diabetic¹³ anti-cancer¹⁴ anti-mutagenic¹⁵ and anti-viral activity¹⁶. The water extract of *Terminalia chebula* (TC) contains total phenolic and tannin content. The water extract appeared to have good antioxidant activities¹⁷. It is believed that tannins have neuroprotective functions capable of reversing 6-hydroxydopamine-induced toxicity. The tannic acid has shown promise as a potential therapeutic agent, which may be beneficial in patients with neurological disease¹⁸.

Since oxidative stress and neurodegeneration is known to play a key role in depression and *T.Chebula* has antioxidant property and neuroprotective function, the present study was undertaken to evaluate the antidepressant potential of acute and chronic administration of TC in forced swim test (FST) in rats.

MATERIALS & METHODS

Animals

The experimental protocol was approved by the Institutional Animal Ethics Committee (IAEC) of Yenepoya Medical College, Yenepoya University, and Mangalore, India. Adult male Swiss Albino rats weighing 150-200 gm from our breeding stock were used in this study. The animals were housed at 24±2°C with 12:12 hr 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 obtained from our institutional pharmacy. The test drug TC was standardized and provided by Al Thary Enterprises, Mangalore. 1% gum acacia (vehicle)¹⁹

Experimental design

On the day of the experiment, the animals were divided randomly into control and experimental groups (n=6). Group 1 received the vehicle, 1% gum acacia(10ml/kg) and served as the control group, groups 2, 3 and 4 received the test drug (TC) in doses of 9,18,36mg/kg, and group 5 received the standard drug imipramine

(10mg/kg) per orally. Drugs/vehicle was administered to the animals 60 minutes prior to the behavioural evaluation in acute study. For chronic study, a new set of animals were used. They were grouped as in acute study and were administered the drugs/vehicle for a period of 10 days. Behavioural evaluation was carried out 60 minutes post drug/vehicle administration on 10th day. The antidepressant activity of the test drug was evaluated using the following experimental model of depression FST.

Forced Swim Test (FST): Each animal was placed individually in a 5 litre glass beakers, filled with water upto 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 test²⁰.

Statistical analysis

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

Table: Effect of TC on immobility time in the Forced Swim Test (FST) using rats

Group (Drug treatment)	Duration of Immobility (sec)	Duration of Immobility (sec)
	Acute Study	Chronic Study
Group 1 (1% gum acacia 10.0 ml/kg)	116.2±1.58	199.61±12.59
Group 2 (TC 9mg/kg)	37.09±4.33**	144.09±8.15**
Group 3 (TC 18mg/kg)	58.46±13.65**	178.90±12.31*
Group 4 (TC 36mg/kg)	128.28±7.59*	170.29±14.99*
Group 5 (Imipramine 10.0 mg/kg)	57.39±0.97**	147.22±1.79**

Test solutions were administered orally 60 min prior to the test. Values represented mean±SEM. (n=6), *P>0.05, **P<0.01 vs. control

RESULTS

Results were given in table. A significant (P<0.01) decrease in the duration of immobility was seen with the standard drug imipramine. Whereas TC showed a significant (P<0.01) decrease in the duration of immobility at the dose of 9mg/kg and 18mg/kg as compared to the control in the acute study. In chronic study, TC in a dose of 9mg/kg has shown decrease in the duration of immobility compared to control.

DISCUSSION

Mood disorders are one of the most common mental illnesses, with a lifetime risk of 10% in general population. Prevalence of depression alone in general population is estimated to be around 5% with suicide being one of the most common outcomes.^{21,22}. Commonly used Antidepressants often cause adverse effects, and difficulty in tolerating these drugs is the most common reason for discontinuing an effective medication, for example the side-effects of Selective Serotonin Reuptake Inhibitor (SSRIs) include: nausea, diarrhea, agitation, headaches. Sexual side-effects are also common with SSRI's. The Food and Drug Administration requires Black Box warnings on all SSRIs, which state that they double suicidal rates (from 2 in 1,000 to 4 in 1,000) in children and adolescents.²³. Side effects of Tricyclic Antidepressants (TCA's) include 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. *Terminalia chebula* fruit is an important constituent of "Triphala", an Ayurvedic formulation known for its rejuvenating properties.

In the present study we have evaluated the antidepressant activity of TC in FST. The development of immobility when rodents are placed in an inescapable cylinder of water during FST reflects the cessation of their persistent escape-directed behavior. Conventional drugs reliably decrease the duration of immobility in animals during this test. This decrease in duration of immobility is considered to have a good predictive value in the evaluation of potential antidepressant agents.

In the present study, TC in the dose of 9mg /kg and 18mg /kg was superior to imipramine in acute and 9mg/kg in chronic study. Exact mechanisms underlying the antidepressant action cannot be concluded at the moment due to the presence of large number of Phytochemicals in the TC. However, the antidepressant activity may be attributed to the presence of tannic acid in the extract. Tannic acid has been shown to be a non selective inhibitor of monoamine oxidase, thereby increasing the levels of monoaminergic neurotransmitters in the brain. Another possible mechanism of

action is the attenuation of oxidative stress produced during depression, by the polyphenols and tannic acid present in TC.

REFERENCES

- Gold,P.W., Goodwin, F.K. and Chrousos, G.P. Clinical and biochemical manifestation of depression in relation to the neurobiology of stress. *N.Eng. J.Med.*, 1998;319:348-353
- Rang HP, Dale MM, Ritter JM, and Flower RJ. Pharmacology. London: Churchill Livingstone Elsevier; 2008.
- American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Washington, DC: APA Press; 2000.
- Sarandol A, Sarandol E, Eker SS, Erdinc S, Vatanserver E, Kirli S. Human Psychopharmacol: Clin Exp: 2007; 22(2) 67-73.
- Ibrahim E, Mustafa N, Arif D. Neurochem Res: 2007; 32(3) 497-505.
- Baldessarini RJ. Fifty years of biomedical psychiatry and psychopharmacology in America. In: American psychiatry after World War II: (1944-1994). Menninger R, Nemiah, J, eds. Washington DC: American Psychiatric Press; 2000:371-412.
- Musselman DL, DeBattista C, Nathan KI. Biology of mood disorders. In: The American psychiatric press textbook of psychopharmacology. Schatzberg AF., Nemeroff CB, eds. Washington DC: American Psychiatric Press: 1998:549-88
- Tripathi KD. Essentials of medical Pharmacology. 6th ed. Medical Publishers (P) Ltd: New Delhi, India; 2008
- Hardman JG, Limbird LE, Goodman Gilman A. Goodman Gilman's; The Pharmacological Basis Of Therapeutics. 11th ed .The McGraw Hill Companies, Inc: New York; 2007.
- Sembulingam K, Sembulingam P, Namasiyam A (1997). Indian J Physiol Pharmacol: 41 139-143
- Sharma RK, Dash B Charaka Samhita: Volume II. Chowkamba Sanskrit Series Office, Varanasi, India 1998.
- Chatterjee S, Pakrasi SC: The Treatise on Indian Medicinal Plants, Vol. 3, National Institute of Science Communication and Information Resources, 2000, pp. 203-204
- Sabu MC, Kuttan R: Anti-diabetic activity of medicinal plants and its relationship with their antioxidant property. J. Ethnopharmacol. 81:155-160, 2002.
- Saleem A, Husheem M, Harkonen P, Pihlaja K: Inhibition of cancer cell growth by crude extract and the phenolics of *Terminalia chebula* Retz. fruit. J. Ethnopharmacol. 81:327-336, 2002.
- 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,
- Ahn MJ, Kim CY, Lee JS, Kim TG, Kim SH, Lee CK, Lee BB, Shin GG, Huh H, Kim J: Inhibition of HIV-1 integrase by galloyl glucose from *Terminalia chebula* and flavonol glycoside gallates from *Euphorbia pekinensis*. Planta Med. 68:457-459, 2002.

17. Chia Lin Chang, Che San Lin. Phytochemical Composition, Antioxidant Activity, and Neuroprotective Effect of Terminalia chebula Retzius Extracts. Evidence-Based Complementary and Alternative Medicine. 2012; 2012:125247
18. Nobre-Junior, Helio V. et al. "Neuroprotective Actions of Tannins from Myracrodruon urundeuva on 6-Hydroxydopamine-Induced Neuronal Cell Death". Journal of Herbs, Spices & Medicinal Plants (Haworth Press) 2007; 13 (2).
19. S. Pemminati and Nair, V. and *, P. Dorababu and *, H.N. Gopalakrishna and Pai, MRSM Effect of the ethanolic extract of Ocimum sanctum on haloperidol induce catalepsy in mice. Indian Journal of pharmacology, 2007; 39 (2). pp. 87-89.
20. Porsolt R.D, Bertin A, Jalfre M. Arch Int Pharmacodyn Ther: 1997; 229 327-336.
21. WHO. Mental and Neurological Disorders.1998 Fact sheet No.25. World Health Organization.
22. Stahl SM. Essential Psychopharmacology: Neuroscientific basis and Practical; Applications. Cambridge University Press; Cambridge; 1998.
23. Lenzer, Jeanne. "Antidepressants double suicidality in children, says FDA". BMJ 2006; 332 (7542):626
24. Nair NP, Ahmed SK, Kin NM, West TE. "Reversible and selective inhibitors of monoamine oxidase A in the treatment of depressed elderly patients". Acta Psychiatr Scand Suppl 1995; 386: 28-35.