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Evaluation of Antidepressant Activity of Gallic Acid in Mice.

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ABSTRACT

Depression is characterized by disturbances in sleep, appetite, deficits in cognition and energy. Gallic acid is a chemical constituent of *Emblica officinalis* (EO). We have reported antidepressant activity of EO. Therefore, the present study was undertaken to evaluate the antidepressant potential of acute and chronic administration of gallic acid in forced swim test (FST) and tail suspension test (TST). Mice weighing 25-30g were used in this study. Standard drug (imipramine) and test drug gallic acid were suspended in normal saline. The vehicle (10ml/kg, p.o), imipramine (10mg/kg, p.o) and gallic acid (0.8mg/kg, 2.0 mg/kg, 4.0 mg/kg, p.o. respectively) were administered one hour prior to acute study. In chronic study, all drugs were given for 10 days and the last dose was given one hour before the experiment. Duration of immobility was noted in both the models. In our study, both imipramine and gallic acid were significantly reduced the duration of immobility in both experimental models as compared to the animals in the control group. The antidepressant activity of gallic acid was comparable to that of standard drug imipramine. The results of the present study indicate the potential for use of gallic acid as an adjuvant in the treatment of depression.

Keywords: Forced swim test, Tail suspension test, Gallic acid, Depression

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INTRODUCTION

Major depressive disorder is characterized by depressed mood most of the time for at least two weeks and or loss of interest or pleasure in most activities. In addition, depression is characterized by disturbances in sleep and appetite as well as deficits in cognition and energy. Thoughts of guilt, worthlessness, and suicide are common. Coronary artery disease, diabetes, and stroke appear to be more common in depressed patients, and depression may considerably worsen the prognosis for patients with a variety of co morbid medical conditions [1]. The prevalence of depression in general population is estimated to be around 5%. At present 121 million people are estimated to suffer from depression. An estimated 5.8% of men and 9.5% of women experience a depressive episode in their lifetime with suicide being one of the most common outcomes of depression [2, 3].

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 [4]. Furthermore, it is difficult to predict which patient will respond to any given treatment. It has been reported in earlier studies that only two out of three patients responds to any given antidepressant treatment, and of these, one would probably have responded to placebo alone [5]. 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 [6,7].

Plant products have been claimed to be free from side effects and less toxic than synthetic drugs [8]. Gallic acid is a trihydroxybenzoic acid found in emblica, gallnuts, sumac, witch hazel, tea leaves, oak bark, and other plants. Various plants having gallic acid as an active ingredient has shown antiviral, antimicrobial and cytotoxic action against cancer [9]. Gallic acid has been implicated in attenuation of platelet activation and platelet- leukocyte aggregation. It also has antileukemic effects on human leukemia K562 cells as well as cardio protective effects in diabetes induced myocardial dysfunction in rats [10]. Gallic acid is reported to exhibit antioxidant property and anti inflammatory action [11]. From our laboratory, we have reported the antianxiety and anticaltaleptic and antidepressant acitivities of *Emblica* officinalis [12-14] and anxiolytic effect of gallic acid [15]. *Emblica officinalis* antidepressant activity prompted us to study antidepressant activity its chemical constituent gallic acid by employing two validated experimental models; forced swim test (FST) and tail suspension test (TST) in mice.

MATERIAL AND METHODS

Animals

The experimental protocol was approved by the Institutional Animal Ethics Committee (IAEC) of Kasturba Medical College, Manipal University, Mangalore, India. Adult male Swiss Albino mice weighing 25-35 gm from our breeding stock were used in this study. The animals were housed at 24±2^{o}C with 12:12 h 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 the Indian National Science Academy Guidelines for the use and care of experimental animals.

Drugs and Reagents

The test drug, gallic acid (Sigma Aldrich Chemicals Pvt. Ltd, United Kingdom) and standard antidepressant drug imipramine (Ranbaxy Ltd, India) were dissolved in 1% gum acacia. Each drug solution was prepared freshly just before the administration. Drugs and vehicle were administered orally 60 minutes prior to the experiment. The doses of each drug were selected on the basis of earlier findings with *Emblica officinalis* [14]. Drugs, dosage and number of animals used per treatment were shown in table 1.

Table 1: The rats groups for experimentation.

Groups	Drug dosage	Route of administration
Gum acacia (1%)	10ml/kg	oral
Imipramine	10mg/kg	oral
Gallic acid	0.8mg/kg	oral
Gallic acid	2.0mg/kg	oral
Gallic acid	4.0mg/kg	oral

Acute Study

Imipramine (10.0 mg/kg) and gallic acid (0.8, 2 & 4 mg/kg) were given orally single dose, 60 minutes prior to the experiment.

Chronic Study

Imipramine (10.0 mg/kg) and gallic acid (0.8, 2 & 4 mg/kg) were administered once a day for 10 days. The last dose was given 60 minutes prior to the exposure to the tests.

Forced swim test

The experiment was carried out according to the method of Porsolt *et al* [16]. Animals were forced to swim individually in a glass jar (25 cm height x 12 cm diameter) containing fresh water of 15 cm height and maintained at 23°C ± 2°C for six minutes. Animal was considered to be immobile when it remained floating in water without struggling and making only minimum movements in the limbs necessary to keep the head above the water. Because little immobility is observed during the first two minutes, only that occurring during the last four minutes of the observed six minutes was counted. Each animal was used only once.

Tail suspension test

The test was carried out according to the method described by Steru *et al* [17]. Each animal was suspended on the horizontal rod 50 cms above the surface of a table by adhesive tape placed approximately one cm from the tip of the tail. Immobility was

recorded during the six minutes of observations. Mice were considered immobile when they hung passively and were completely motionless.

STATISTICAL ANALYSIS

The results were expressed as mean ± SEM and analyzed for statistical significance using one-way ANOVA followed by Dunnet's test. The results were considered to be statistically significant if P< 0.05.

RESULTS

Tail suspension test

Gallic acid at the doses 0.8 mg/kg & 2 mg/kg; significantly (P<0.01) reduced the duration of immobility in a dose dependent manner when compared with vehicle treated group. This reduction of immobility was comparable to that produced by imipramine (10.0 mg/kg) in both acute as well as chronic study. (Table 2)

Table 2: Effect of gallic acid on immobility time in the Tail Suspension Test (TST) using mice

Group (Drug Treatment)	Duration of Immobility (sec)	
	Acute Study	Chronic Study
Group 1 (gum acacia 10.0 ml/)	71.33 ± 15.00	149.50 ± 19.92
Group 2 (gallic acid 0.8 mg/kg)	35.83 ± 18.57*	80.33 ± 8.68*
Group 3 (gallic acid 2.0 mg/kg)	44.50 ± 38.17*	100.16 ± 20.08*
Group 4 (gallic acid 4.0 mg/kg)	91. 16 ± 12.85	118.33 ± 49.48
Group 5 (Imipramine 10.0 mg/kg)	39.66 ± 12.06*	32.00 ± 15.59*

Test solutions were administered orally 60 min prior to the test. Values represented mean±S.E.M (n=6), *P<0.05, vs. control (group 1).

Forced swim test

At all the doses tested (0.8, 2 & 4 mg/kg) gallic acid significantly (P<0.01) reduced the immobility when compare to vehicle treated control group. The reduction was dose related .The effect gallic acid was comparable to that produced by the standard drug imipramine in both acute as well as chronic study. (Table 3)

Table 3: Effect of gallic acid on immobility time in the Forced Swim Test (FST) using mice

Group (Drug Treatment)	Duration of Immobility (sec)	
	Acute Study	Chronic Study
Group 1 (gum acacia 10.0 ml/)	87.00 ± 16.25	79.00 ± 42.70
Group 2 (gallic acid 0.8 mg/kg)	36.83 ±30.98*	31.66 ± 28.48*
Group 3 (gallic acid 2.0 mg/kg)	42.33 ±11.87*	31.66 ± 28.48*
Group 4 (gallic acid 4.0 mg/kg)	53.16 ± 20.79*	18.16 ±9.86*
Group 5 (Imipramine 10.0 mg/kg)	32.16 ± 20.38*	39.50 ± 23.12*

Test solutions were administered orally 60 min prior to the test. Values represented mean±S.E.M. (n=6), *P<0.05, vs. control (group 1).

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DISCUSSION

Depression is a chronic mental disorder affecting more than 10% of population [18]. The World Health Organization revealed that depression is the fourth leading cause of disability worldwide [2]. Stressful life events facilitate the evolution of depressive illness [19] as the stress can influence the function of central nervous system by altering a number of neurotransmitters, endocrine and neuroendocrine systems [20]. In animals restraint stress is being used as a model of depression. The two rodent models, forced swim test and tail suspension test, in which the animals are exposed to unavoidable stress that produce behavioural despair which reflect a condition similar to human depression [21]. These models are widely used for screening antidepressants and are sensitive to all major classes of antidepressants.

Most of the drugs that are currently being used in the treatment of depression have adverse effects that affect the quality of life of the patient. This leads to patient's non-compliance to medication, which further complicates the problem [4]. Ayurveda mentions a number of single and compound drug formulations of plant origin that are used in the treatment of psychiatric disorders [22] and are claimed to have a better side-effect profile than conventional drugs.

The development of immobility when rodents are suspended by their tail during TST and when they 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 these tests. This decrease in duration of immobility is considered to have a good predictive value in the evaluation of potential antidepressant agents [16].

In the present study, gallic acid the highest dose tested (4mg/kg) was superior to imipramine in forced swim test experimental models in chronic study. Exact mechanisms underlying the antidepressant action cannot be concluded at this moment. However, the antidepressant activity may be attributed to the chronic use of gallic acid has been shown to have a neurotropic action on the hypothalamus [23] and GABAergic properties; through inhibition of gamma amino butyric acid transaminase (GABA-T) activity; and nitriergic modulation [24] . We believe that gallic acid has the potential to be used as an adjuvant in the treatment of depression and other mood disorders. Further studies may help to elucidate the possible mechanisms of action of gallic acid.

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