Available online at www.ijpsdr.com

International Journal of Pharmaceutical Sciences and Drug Research 2015; 7(1): 68-71

Research Article

ISSN: 0975-248X
CODEN (USA): IJPSPP

Evaluation of Antidepressant Activity of Ethanolic Extract *Momordica charantia* Unripen Fruit

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ABSTRACT

The aim of the present study was to investigate the antidepressant activity of *Momordica charantia* in swiss albino mice. In this study ethanolic extract of unripen fruit along with seeds of this plant was investigated by using animal models like Despair Swim Test (DST) and Tail Suspension Test (TST) along with 100, 300 and 500 mg/kg (*p.o.*) doses and distilled water as a vehicle for 14 days of treatment and imipramine as a standard drug was administered orally on the test days. During dosing period test was carried out on 1st, 7th and 14th day of treatment. The results showed a significant decrease in immobility time of treated mice as compared to control group.

Keywords: Swiss albino mice, Ethanolic extract of *Momordica charantia* unripe fruit, antidepressant activity.

INTRODUCTION

According to World Health Report, about 450 million people suffer from a mental or behavioural disorder. [1-2] This amounts to 12.3% of the global burden of disease, and predicated to rise up to 15% by 2020. [1, 3] Depression is a burdensome psychiatric disorder that affects a person's mood, physical health and behaviour. Patients with major depression have symptoms that reflect changes in brain, monoamine neurotransmitters, specifically nor, epinephrine, serotonine, dopamine. [4] The disorder is also often associated with suicide and there are between 10 and 20 million suicide attempt every years. Depression is the most prevalent disorder and it is recognised to be symptomatically, psychologically and biologically heterogeneous. [5]

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Received: 25 October, 2014; **Accepted:** 02 November, 2014

Some features of depressive disorder overlap those of the anxiety disorder, including severe phobias, generalized anxiety disorder, social anxiety disorder, post traumatic stress disorder, and obsessive-compulsive disorder. [6] The major disorders of mood or affect include the syndromes of major depression (melancholia) and bipolar disorder (manic-depressive disorder). Major depression is characterized by feelings of intense sadness and despair, mental slowing and loss of concentration, pessimistic worry, lack of pleasure, self-deprecation, and variable agitation or hostility. Physical changes also occur, particularly in severe, vital, or melancholic depression. These include insomnia or hypersomnia; altered eating patterns, with anorexia and weight loss or something overeating; decreased energy and libido; and disruption of the normal circardian and ultradian rhythms of activity, body temperature, and many endocrine functions. [7] Dysthymic disorder, also called dysthmia, psychotic depression, postpartum depression [8], and seasonal affective disorder are also kinds of depression. [9] There is no single known cause of depression. Rather, it likely

results from a combination of genetic, biochemical, environmental, and psychological factors. Some types of depression tend to run in families, suggesting a genetic link. However, depression can occur in people without family histories of depression as well. [10]

Today, a number of synthetic antidepressant drugs are available for treatment, however their effectiveness does not hold true with the entire range of population suffering from this disorder. Moreover the side effects and the drug interactions are major restrictions in its clinical utility. On the other hand, herbal medicines are widely used across the globe due to their wide applicability and therapeutic efficacy along with least side effects and lower price, which in turn has increased the scientific research regarding the antidepressant activity. [11-12]

Momordica charantia, a member of the cucurbitaceae family, is known as bitter melon, bitter gourd, balsam pear, karela, and pare. It grows in tropical areas of the Amazon, East Africa, Asia, India, South Africa, and the Caribbean and is used traditionally as both food and medicine. The plant is a climbing perennial with elongated with elongated fruit that resembles a warty gourd or cucumber. The unripe fruit is white or green in colour and has a bitter taste [13-14] and its phytochemicals are alkaloids, flavonoids, glycosides, triterpenoids, steroids, phenols, tannins, oils and fats. [15-17] The fruit and leaves of *M. charantia* have different activities like antibacterial, antidiabetes, antileprotic, antioxidant, hypocholestorolemic, hypotensive, hypotensive, immunostimulant, insecticide, in jaundice and snake-bite, etc. In traditional medicinal system, like Ayurveda, *M. charantia* has also been already documented as antidepressant, antianxiety herb. [1, 12, 15] Yet, very less data available on systematic biological investigation about leaves, seeds and root [1, 12, 15] of this plant and fruit has never been subjected to systematic biological investigation. Therefore, the present investigation has been designed to evaluate antidepressant activity of unripe fruit along with seeds of *M. charantia* by stress induced depression models like despair swim test and tail suspension test. [18-19]

MATERIALS AND METHODS

Plant materials and Preparation of Drug Solution

The ethanolic extract of *Momordica charantia* was used for antidepressant activity. Stock solution was freshly prepared daily in distilled water before dosing from which the different doses were administered by selecting the appropriate concentration.

Experimental Animals and housing conditions

Healthy Swiss albino female mice (20-25 g) were used. They were maintained at 25 ± 2°C, relative humidity of 45 to 55% and under standard environmental conditions with 12:12 h light/dark cycle in polypropylene cages. The animals were fed with standard pellet feed (Nutrivet life sciences, Pune) and water was given *ad libitum*. The Institutional Animal Ethics Committee approved the protocol (257/CPCSEA). All the experiments were carried out between 9:00 h to 16:00 h.

Acute Oral Toxicity Study

All female mice were free of any toxicity as per acceptable range given by the OECD guideline-423 up to the dose of 2000 mg/kg. From this data and pilot study reports; three different doses 100, 300 and 500 mg/kg were selected for further study.

Antidepressant activity

Despair Swim Test

Behaviour despair test was performed in five groups of 6 Swiss albino mice. Distilled water as vehicle administered to control group (10 ml/kg, *p.o.*); 100, 200 and 500 mg/kg of ethanolic extract of unripe fruit along with seeds of *Momordica charantia* were administered orally to the group I to III respectively for 14 days of treatment and imipramine 15 mg/kg as a standard was administered orally on 1st, 7th and 14th test day. On zero day, in training session, mice were forced to swim individually in a vertical Plexiglas cylinder (height: 40 cm; diameter: 18 cm) containing fresh water up to 15 cm maintained at 25°C for 15 minutes and the animals were observed for 5 minutes. In this test, after a brief spell of vigorous activity, animals show a posture of immobility which is characterized by floating motionless in the water making only those movements necessary to keep the head above the water. This immobility reflects the state of depression. Each mouse was subjected to this 24 h prior and 1 h after administration of vehicle, extract and standard drug for 5 minutes in the test session, and the duration of immobility during the 5 minutes was recorded. Actual test recording was done on 1st, 7th and 14th day of treatment. After recording of immobility time, the mice were removed, wiped with dry cloth and allowed to dry before being returned to their home cages. [15, 18-20]

Tail Suspension Test

TST was done as described by Steru *et al.* [21] After 1 h of dosing of distilled water as vehicle administered to control group (10 ml/kg, *p.o.*); 100, 300, 500 mg/kg of ethanolic extract of unripe fruit along with seeds of *Momordica charantia* and imipramine 15 mg/kg (orally) to group I to IV respectively, mice were suspended on a string held by a metal stand, by an adhesive tape placed 1 cm from the tip of the tail. This string was 58 cm above the table top. The duration of immobility of the mice was recorded for a period of 5 minutes. Mice were considered immobile when they hang passively and completely motionless. During the experiment, each animal under test was both acoustically and visually isolated from other animals. Mice were considered immobile when they hang passively and completely motionless. Dosing of extract was done for 14 days and imipramine as a standard drug administered on test days. Readings were taken on 1st, 7th and 14th day of treatment.

Statistical Analysis

The result of immobility time expressed as mean ± SEM (n=6). The data was analysed using one way

analysis of variance (ANOVA) followed by Dunnett test. Significance set at **P*<0.05, ***P*<0.01, ****P*<0.001.

RESULT

Despair Swim Test

The results of the antidepressant effect of ethanolic extract of *Momordica charantia* unripe fruit and imipramine drug presented in Table 1 and figure 2. The extract showed no any change after 1 day treatment, and had the tendency to significantly reduce the immobility time after 7 and 14 days of treatment. After 14 days of treatment, dose 500 mg/kg of extract showed almost nearly same significant reduction immobility time of imipramine.

Tail Suspension Test

The results of the antidepressant effect of ethanolic extract of *Momordica charantia* unripe fruit and imipramine drug presented in Table 2 and figure 2. The extract showed no any change after 1 day treatment, and had the tendency to significantly reduce the immobility time after 7 and 14 days of treatment. After 14 days of treatment, dose 500 mg/kg of extract showed almost very less difference with significant reduction immobility time of imipramine.

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. [22] The pathophysiology of major depressive disorder (MDD) is a complex, and it appears that a variety of overlapping biological causations exists. [23] In the as several decades, the main premise concerning the biopathophysiology of MDD has focused on monoamine impairment (dysfunction in monoamine expression and receptor activity), lowering of monoamine production, or secondary messenger (e.g. G proteins or cyclic AMP) system malfunction. [24-25] In recent years, added attention has also focused on the role of neuroendocrinological abnormalities involving cortisol excess and its impeding effects on neurogenesis via reducing brain-derived neurotropic factor, as well as impaired endogenous opioid function, changes in GABAergic and/or glutamatergic transmission, cytokine or steroidal alterations, and abnormal circadian rhythm. [12, 24-29]

Modern day life style leads to numerous stress conditions, among which anxiety and depression are general and widely prevalent senile neurological disorders. Physical or Psychological stress activates Hypothalamohypophyseal system, whose goal is to release cortisol from the adrenal cortex, to cope up with stressful situations. [30]

A number of drugs are available for the treatment of stress disorder like depression, and anxiety but clinical evaluation of these drugs has shown incidence of relapses, side effects, and drug interactions and also these medicines have high cost. Tricyclic antidepressants routinely produce adverse autonomic responses, in part related to their relatively potent antimuscarinic effects. These include dry mouth and a sour or metallic taste, epigastric distress, constipation, dizziness, tachycardia, palpitations, blurred vision and urinary retention. Cardiovascular effects include orthostatic hypotension, sinus tachycardia, and variable prolongation of cardiac conduction times with the potential for arrhythmias, particularly with overdoses. [12, 31-32] MAO inhibitors can induce sedation or behavioral excitation and have a high risk of inducing postural hypotension, sometimes with sustained mild elevations of diastolic blood pressure. Newer antidepressants generally present lesser or different side effects and toxic risks than older tricyclics and MAO inhibitors. As a group, the SSRIs have a high risk of nausea and vomiting, headache, and sexual dysfunction, including inhibited ejaculation in men and impaired orgasm in women. Some SSRIs and perhaps fluoxetine in particular, have been associated with agitation and restlessness that resembles akathisia. [12, 33]

Table 1: Effects of the ethanolic extract of *M. charantia* on the immobility time in the mouse forced swimming test

Group Name	Dose	Immobility Time (s)		
		Day 1	Day 7	Day 14
Control	Distilled water (vehicle)-10 ml/kg	206.33 ± 8.83	205 ± 4.72	206.33 ± 7.17
Group I	Extract-100 mg/kg	182.66 ± 5.48	173.33 ± 6.36	157.66 ± 6.36**
Group II	Extract-300 mg/kg	171.33 ± 5.36*	156 ± 8.88**	142.66 ± 10.17**
Group III	Extract-500 mg/kg	141.66 ± 11.62**	135.33 ± 11.89**	126.66 ± 11.02**
Std.	Imipramine-15 mg/kg	127 ± 9.07**	123 ± 8.96**	116.66 ± 7.88**

Results are expressed as mean ± SEM (n=6). Data was analyzed by one way analysis of variance (ANOVA) followed by Dunnett test.
*, *P*<0.05; **, *P*<0.01; ***, *P*<0.001 when compared with control groups.

Table 2: Effects of the ethanolic extract of *M. charantia* on the immobility time in the mouse tail suspension test

Group Name	Dose	Immobility Time (s)		
		Day 1	Day 7	Day 14
Control	Distilled water (vehicle)-10 ml/kg	201.33 ± 11.85	197.33 ± 11.28	194.66 ± 9.56
Group I	Extract-100 mg/kg	177.33 ± 2.90	167.33 ± 4.63*	160.33 ± 2.66**
Group II	Extract-300 mg/kg	169.66 ± 4.80*	151.66 ± 1.85**	136.33 ± 4.25**
Group III	Extract-500 mg/kg	144.33 ± 4.63**	129.66 ± 9.93**	115 ± 6.80**
Std.	Imipramine-15 mg/kg	120 ± 4.04**	109.33 ± 2.33**	107.66 ± 2.96**

Results are expressed as mean ± SEM (n=6). Data was analyzed by one way analysis of variance (ANOVA) followed by Dunnett test.
*, *P*<0.05; **, *P*<0.01; ***, *P*<0.001 when compared with control groups.

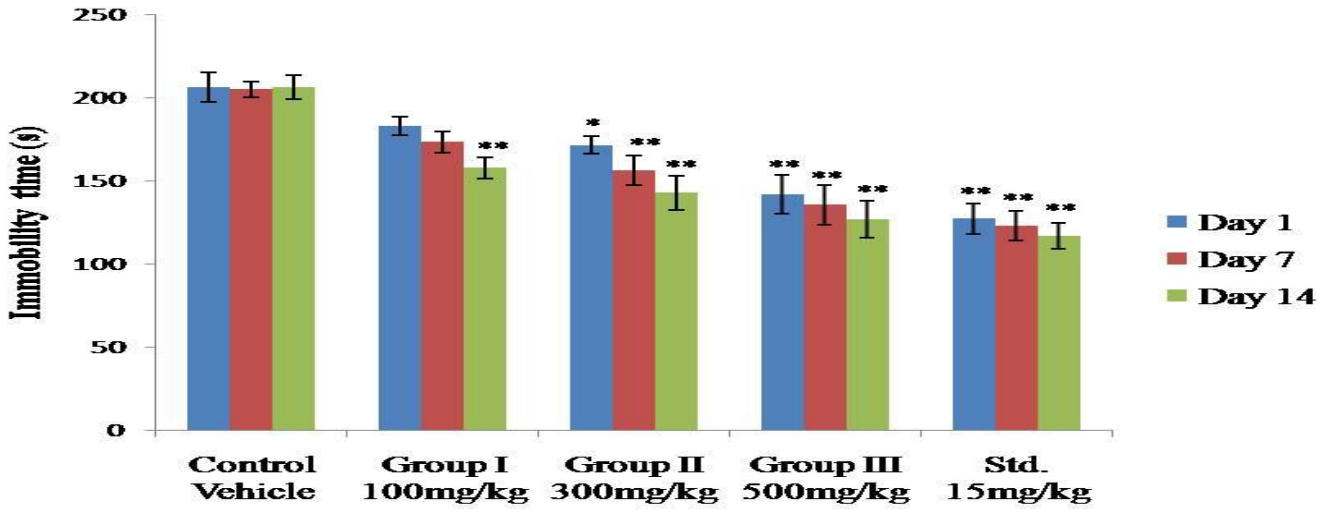

Fig. 1: Effects of the ethanolic extract of *M. charantia* on the immobility time in the mouse forced swimming test
Results are expressed as mean ± SEM (n=6). Data was analyzed by one way analysis of variance (ANOVA) followed by Dunnett test. *, *P*<0.05; **, *P*<0.01; ***, *P*<0.001 when compared with control groups.

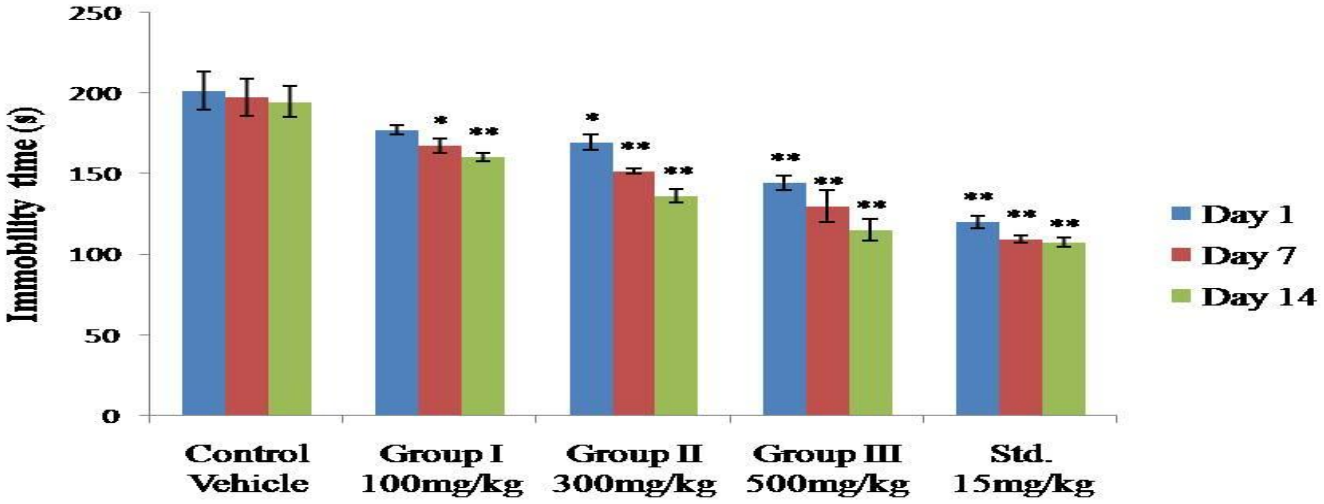

Fig. 2: Effects of the ethanolic extract of *M. charantia* on the immobility time in the mouse tail suspension test
Results are expressed as mean ± SEM (n=6). Data was analyzed by one way analysis of variance (ANOVA) followed by Dunnett test. *, *P*<0.05; **, *P*<0.01; ***, *P*<0.001 when compared with control groups.

Because of the shortcomings of the available antidepressant drugs, attempts are underway to explore plants with antidepressant activity. Herbal medicines are therefore, given attention because of their low price and fewer side effects.

The widely used animal models for assessing antidepressant like activity in small animals are forced swimming test and tail suspension test. It is expected that immobility occurs in these two tests will reflect a state of behavioural despair or unable to adapt the stress as seen in human. [34-35] The basic concept of forced swimming test is animal will get immobile posture when subjected to the short-term or inescapable stress. The methanol extract of *Momordica charantia* produced significant antidepressant effect in forced swimming test, as is evident from the reduction in the immobility time and the effect was comparable to the standard drug, Imipramine. Numerous neural pathways are involved in the pathophysiology of depression state. Therefore, a great number of neurotransmitters are thought to involve in underlying mechanisms of these diseases, as evident by the antidepressant drugs. [36] By performing tail suspension test, the reduced immobility time directed the antidepressant effect.

The antidepressant effect of ethanolic extract of *Momordica charantia* along with seeds may be due to a combination of different biological constituents rather than any single compound, being the most interesting the alkaloids, steroids, glycosides, triterpenoids, etc. However, further studies are required to identify the phytoconstituents responsible for the observed antidepressant effect and chronic administration is also necessary.

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Source of Support: Nil, Conflict of Interest: None declared.