Print ISSN: 2319-2003 | Online ISSN: 2279-0780

IJBCP International Journal of Basic & Clinical Pharmacology

DOI: http://dx.doi.org/10.18203/2319-2003.ijbcp20181184

Original Research Article

Antidepressant activity of aqueous extract of *Momordica charantia* leaves

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Received: 05 February 2018
Accepted: 07 March 2018

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ABSTRACT

Background: Depression is a common debilitating illness contributing to increase in morbidity and mortality worldwide. 20% of all depressed patients are refractory to treatment with available antidepressants at adequate doses. *Momordica charantia* commonly known as Karela is widely used in Indian cuisine. This study was carried out to evaluate its lesser known Antidepressant activity. The objective of this study is to evaluate the Antidepressant activity of Aqueous extract of *Momordica charantia* leaves.
Methods: This study was done in Department of Pharmacology, JNMC, AMU. Tail Suspension test and 5-Hydroxytrytophan induced Head Potentiation was evaluated in Swiss Albino mice. Forced swim test, Learned Helplessness test and Spontaneous motor activity was noted in Albino Wistar rats respectively at doses of AEMC (Aqueous extract of *Momordica charantia* leaves) 100mg/kg, 200mg/kg and 300mg/kg.
Results: AEMC at all three doses 100mg/kg, 200mg/kg and 300mg/kg exhibited antidepressant activity by significantly decreasing the immobility time in Tail Suspension test and except 100mg/kg. In forced swim test psychostimulant activity of AEMC was ruled out in Spontaneous motor activity. Number of Escape failures was decreased in Learned Helplessness test at doses of AEMC 200mg/kg and 300 mg/kg. Increase in Head twitches was seen only with AEMC 300mg/kg in 5-Hydroxytrytophan induced Head Potentiation in mice.
Conclusions: Aqueous Extract of *Momordica Charantia* leaves exhibits Antidepressant activity in animal models of Depression.

Keywords: Depression, Forced swim test, Learned helplessness test, *Momordica charantia*, Tail suspension test, 5-Hydroxytrytophan induced head potentiation in mice

INTRODUCTION

Depression is a common debilitating illness contributing to increase in morbidity and mortality worldwide. It is the fourth leading cause of morbidity and economic loss, exceeded by lower respiratory tract infections, perinatal conditions and AIDS. Furthermore, the World Health Organization predicts that depression will be the second leading cause of disability burden, by the year 2020.[1] In 2002, depression accounted for 4.5% of the worldwide total burden of disease in terms of disability-adjusted life years.[2]

Depression is a disorder of thought presenting with emotional symptoms like misery, apathy, pessimism, low self-esteem, feelings of guilt, inadequacy, indecisiveness and loss of motivation. It is also characterized by biological symptoms like retardation of thought and action, loss of libido, sleep disturbance and loss of appetite.[3]

Depression can affect all the age groups. It usually starts from early adulthood and affects the individual over the life time. Depressed individuals of older age group are more likely to suffer from comorbid conditions like Angina, Myocardial infarction, Diabetes mellitus, Cancer, Parkinson's disease and Alzheimer's disease. 20% of all depressed patients are refractory to treatment with available antidepressants at adequate doses. There is a "therapeutic lag" lasting 3-4 weeks before a measurable therapeutic response becomes evident.[4] Antidepressant drugs are associated with wide range of unwanted side effects and interactions with the drugs used for the treatment of comorbid conditions.[5,6]

Momordica charantia commonly known as Karela is widely used in Indian cuisine. Pharmacological studies on leaves of *Momordica charantia* have demonstrated antidiabetic, antioxidant, hepatoprotective, nephroprotective, antimicrobial and antiviral activity.[7-12]

Inspite of best efforts, search of literature could reveal only one study on the antidepressant activity of *Momordica charantia* leaves.[13] Hence this study was carried out to evaluate the antidepressant effect of leaves of *Momordica charantia*.

METHODS

The leaves of *Momordica charantia* were collected from fields of Pannipur village, near AMU law faculty, Aligarh district, Uttar Pradesh. The leaves were identified and authenticated by Prof. S. H. Afaq, Department of Pharmacognosy, Ilmul Advia, A.K. Tibbya College, A.M.U. Aligarh. Specimen was deposited and Voucher number (SC-0135/12) was obtained. Leaves were shade dried. The leaves were finely powdered in a grinder and stored in air-tight bottles till further use. The powder obtained was extracted in distilled water using Soxhlet's apparatus.

The study protocol was approved by the Institutional Animal Ethics Committee (IAEC) on 13.04.2012. All animal experiments were carried out as per the rules and regulations of IAEC and CPCSEA (Committee for the Purpose of Control and Supervision of Experiments on Animals) under the "Guidelines for Care and Use of Animals in Scientific Research".

Animals used

- Wistar Albino rats of either sex (150-200gm).
- Swiss Albino mice of either sex (20-40gm).

The animals were procured from the Central Animal House, JNMC, Aligarh Muslim University. They were housed in polypropylene cages bedded with paper strips in the Pharmacology section of Central Animal House under standard conditions and fed with pellet diet (Ashirwad Industries) and water ad libitum. They were acclimatized to laboratory conditions for 1 week prior to experimental use.

Acute toxicity testing

Acute toxicity testing was done to find out LD50 of aqueous extract. Testing was done according to OECD 423 guidelines for testing of chemicals for acute oral toxicity by acute class method.[14]

Starting dose was selected as 2g/kg. After dosing, animals were observed at every 30 minutes for first 4 hours, intermittently for 24 hours, then daily for 14 days.

Grouping of animals

Experimental design

The animals were divided into 5 groups, consisting of normal control group, positive control group and 3 test groups. Each group consisted of 6 animals of either sex (n=6). Fresh animals were taken for each group in each screening method (Table 1).

Table 1: Experimental design for each screening method.

Groups	Name	Treatment received
I.	Normal control	Distilled water 1ml/kg, orally
II.	Positive control	Imipramine/Fluoxetine*
III.	Test group-1	Aqueous extract 100mg/kg, Orally
IV.	Test group-2	Aqueous extract 200mg/kg, Orally
V.	Test group-3	Aqueous extract 300mg/kg, Orally

*Imipramine 15 mg/kg was used in all screening tests except 5-Hydroxytryptophan potentiation in mice in which Fluoxetine 20mg/kg was used.

Screening of antidepressant activity

Tail suspension test[15]

Mice were treated with Standard drug/ Vehicle/ Aqueous extracts for 7 days. Test was carried out on 7th day, 1 hour after Drug/Vehicle/Aqueous extracts was administered. Mice were suspended by woollen thread secured with adhesive tape placed approximately 1cm from the tip of the tail. The duration of immobility was recorded for a period of 6 mins.

Mice were considered immobile when they hung passively and completely motionless. Intermittent periods of immobility during 6 mins of time period were recorded and their sum showed the total period of immobility.

Forced swim test[16]

Rats were treated with Drug/Vehicle/ Aqueous extracts for 8 days. Rats were individually forced to swim inside a vertical Plexiglass cylinder (height: 28cm; diameter: 20cm, containing 20cm of water maintained at 25°C). Pre test session was conducted for 15 mins, one day prior to the test (7th day of drug administration). Test was conducted on 8th day 1 hr after drug administration for 5 min. An animal was judged to be immobile whenever it remained floating passively in water, its nose just above the surface. Duration of immobility was recorded.

Spontaneous motor activity[17]

Rats were given Drug/Vehicle/Aqueous extracts for 7 days. Spontaneous motor activity test was done on day 0 (pre drug) and day 7 (7th day of drug administration). Rats were acclimatized with Actophotometer before experiment. They were placed in Actophotometer and the light beam interruptions were recorded as activity counts. Activity counts were assessed on day 0 for a duration of 10 mins. Test was conducted 60 mins after drug administration for 10 mins on day 7. Results of day 7 were compared with that of day 0.

Learned helplessness test[18]

Rats were treated with Drug/Vehicle/ Aqueous extracts for 7 days. Rats were acclimatized in the conditional apparatus on day 5 and day 7 of drug administration before experiment. Rats were exposed to electric shock (30 V) on a schedule of 10 s of shock/min for 1 h on day 5. Gate was not opened during this period.

At the beginning of a trial on 7th day, the gate was opened, and a 30 V shock initiated. Shock was terminated in 10 s if the animal had not escaped to the other side through the gate. If an escape response occurred, the animal was allowed to remain on the other side for the duration of 10 s, then returned to the same chamber. Ten such trials with an intertrial interval of 20 s were given. Number of escape failures was noted.

5-Hydroxytryptophan potentiation in mice[19]

Mice were treated with Drug/ vehicle/ Aqueous extracts for 7 days. Single dose of 5-Hydroxytryptophan was given at a dose of 200mg/kg i.p. on 7th day after 1 hour of drug administration. After 15 mins, characteristic symptom of head-twitches was observed for 6 mins duration intermittently at 2 min intervals (19-21, 23-25, 27-29 mins).

Statistical analysis

Values were expressed as Mean±SEM. Statistical significance was calculated by paired Student's t test, one way ANOVA followed by post hoc Dunnett's multiple comparison test using SPSS-17 software. P<0.05 was considered to be statistically significant.

RESULTS

Plant extracts

Brown coloured semi solid mass of 15.10% yield was obtained.

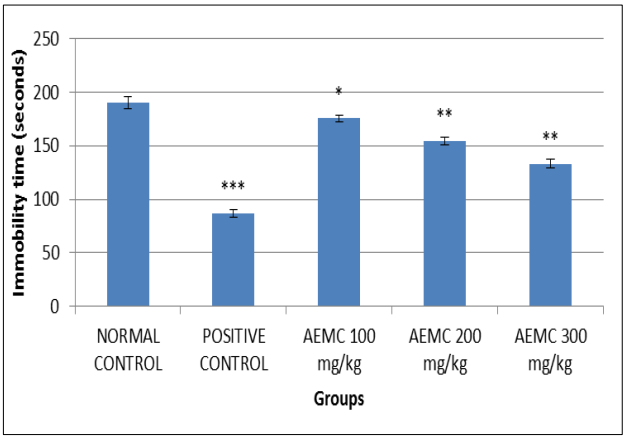
Acute toxicity testing

Acute toxicity testing was done to find out LD50 of the extract. Testing was done according to OECD 423 guidelines. All the animals treated with aqueous extract 2g/kg survived after 14 days of observation. No change in behaviour was seen and all animals were active at the end of observation. Therefore, the LD50 dose was of category 5 i.e. 2000- 5000mg/kg.

Tail suspension test

Immobility time was significantly decreased (p<0.001) in positive control group compared to normal control group. Significant decrease in Immobility time was noted in AEMC 100mg/kg (p<0.05), AEMC 200mg/kg (p<0.01) and AEMC 300mg/kg (p<0.01) received groups.

Aqueous extract of *Momordica charantia* leaves in all the three doses decreased Immobility time in Tail suspension test with varying significance (Figure 1).



AEMC: Aqueous extract of *Momordica charantia* leaves, n = 6 mice in each group.* - p<0.05, ** - p <0.01, *** - p <0.001. Level of significance compared to normal control group. Values are expressed as mean±SEM.

Figure 1: Effect of AEMC and Control drugs on Immobility time in Tail suspension test.

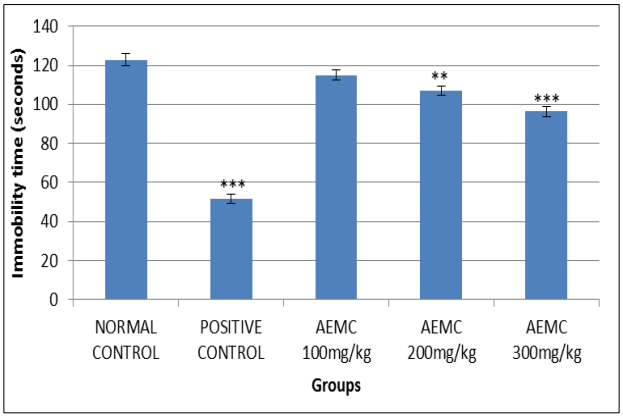
Forced swim test

Imipramine (15mg/kg) treated rats decreased the duration of immobility (p<0.001). Duration of immobility was not significantly decreased in Aqueous extract 100mg/kg (p=0.223) treated groups. Aqueous extract at a dose of 200

mg/kg and 300 mg/kg decreased duration of immobility with a significance value of p<0.01 and p<0.001 respectively. Dose dependent effect was seen (Figure 2).

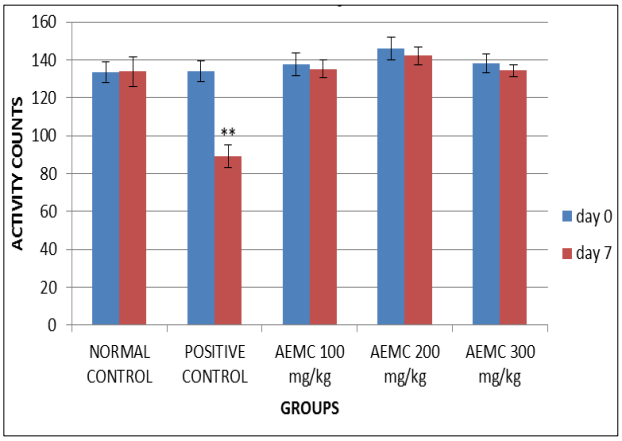
Spontaneous motor activity

In normal control group there was no significant change in Spontaneous motor activity on day 7 compared to day 0, while in Imipramine (15mg/kg) treated rats in positive control group showed decrease in activity counts (p<0.01). This is due to its sedative effect.[21]



AEMC: Aqueous extract of Momordica charantia leaves, n = 6 rats in each group. *- p<0.05, ** - p <0.01, *** - p <0.001. Level of significance compared to normal control group.Values are expressed as mean±SEM.

Figure 2: Effect of AEMC and Control drugs on Immobility time in Forced Swim test.

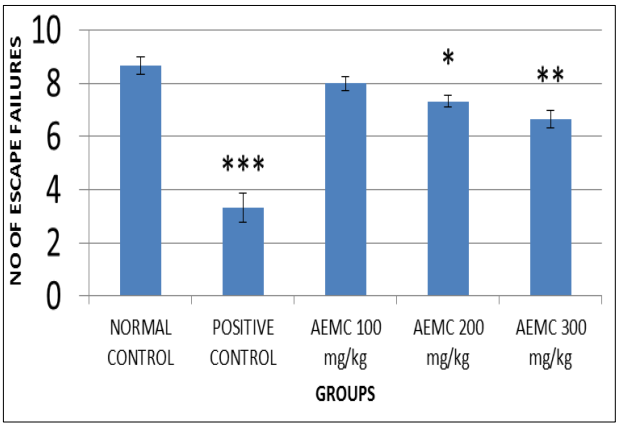


AEMC: Aqueous extract of *Momordica charantia* leaves, n = 6 rats in each group*- p<0.05, **- p <0.01. Level of significance compared to normal control group. Values are expressed as mean±SEM.

Figure 3: Effect of AEMC and Control drugs on Activity counts on day 0 and day 7.

Learned helplessness test

Significant decrease in Escape failures was seen in positive control (p<0.001) group. No Significant decrease in Escape failures was seen in AEMC 100mg/kg received group. Significant decrease in Escape failures was seen in AEMC 200mg/kg (p<0.05) and AEMC 300mg/kg (p<0.01) received groups (Figure 4).

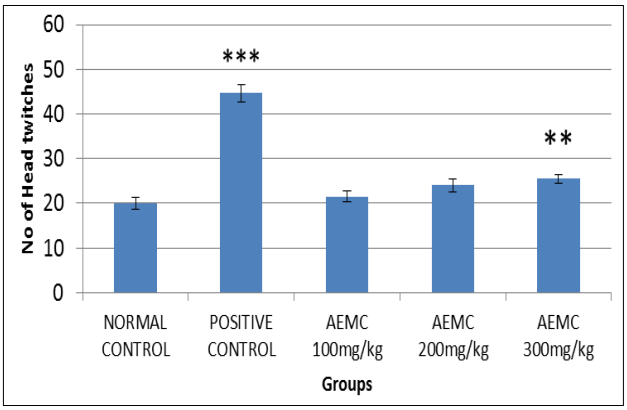


AEMC: Aqueous extract of *Momordica charantia* leaves, n = 6 rats in each group. *- p<0.05, ** - p <0.01, *** - p <0.001. Level of significance compared to normal control group.Values are expressed as mean±SEM.

Figure 4: Effect of AEMC and Control drugs on Escape failures in Learned Helplessness test.

5-Hydroxytryptophan potentiation in mice

Mice treated with Fluoxetine 20mg/kg and Aqueous extract 300mg/kg showed significant increase in the number of head twitches, while Aqueous extract 100mg/kg and 200mg/kg did not show significant results (Figure 5).



AEMC: Aqueous extract of *Momordica charantia* leaves, n = 6 rats in each group. *- p<0.05, ** - p <0.01, *** - p <0.001. Level of significance compared to normal control group. Values are expressed as mean±SEM.

Figure 5: Number of head twitches in normal control, positive control and AEMC treated groups.

DISCUSSION

Depression is a heterogenous clinical disorder with diverse aetiology. Depressive symptoms are subjective and varies from person to person. Animal models of depression does not resemble pathologically similar to human depression

as aetiology of human depression is diverse. Instead the symptomatic profile of humans is developed in animals.[20]

Tail suspension test is a behaviour despair test. It is based on the hypothesis that when an animal is subjected to an aversive situation, animal either goes into state of "agitation" or state of "immobility". Drugs with antidepressant activity shifts the balance towards "agitation". Mice are suspended by tail and duration of immobility is noted.[15]

Forced swim test is a behaviour despair test. It is based on the hypothesis that when an animal is forced to swim in a restricted space, it adopts a state of immobility after few attempts. This state of immobility is a state of despair in rats. Antidepressant drugs decrease the duration of immobility. This test is applied to screen new antidepressants.[16]

Tail suspension test is more sensitive test compared to Forced swim test.[15] This may be the reason why the lower dose (100mg/kg) of extract is showing significant result in Tail suspension test and non significant result in Forced swim test.

Tail suspension test and Forced swim test are common screening tests employed in the evaluation of antidepressant activity. Apart from compounds with antidepressant effect, Psychostimulants also decrease the duration of immobility. To differentiate between antidepressants and Psychostimulants, their effect on Spontaneous motor activity in normal rats is seen. Psychostimulants increase the Spontaneous motor activity, whereas antidepressants do not do so in normal rats.[15,16] To rule out the possibility of Psychostimulant activity of the aqueous extract, its effect on Spontaneous motor activity is seen.

Aqueous extract at the doses of 100mg /kg, 200mg/kg and 300mg/kg did not show significant increase in on motor activity as their significance value was $p=0.446$, $p=0.461$ and $p=0.269$ respectively, thereby ruling out the possibility of Psychostimulant effect of aqueous extract (Figure 3).

Learned helplessness test is a test for screening antidepressants. Animals are subjected to electric shock, later on when the rats are subjected to same strength of electric shock with a chance to avoid it, they fail to do it. This "Helpless" situation is overcome by the administration of antidepressants. This principle is applied to screen new antidepressants.[22]

Rats were subjected to electric shock of 30 volts on day 5, in a space in which there was no scope for escape. On 7th day, rats were subjected to same strength of shock and their ability to overcome the "Helpless" situation was observed in presence of way to escape. Those rats which showed decrease in the number of escape failures were the ones which overcame the state of "Helpless" situation. Antidepressants decrease the number of escape failures. Significant decrease in Escape failures was seen in AEMC 200 mg/kg ($p<0.05$) and AEMC 30mg/kg ($p<0.01$) received groups.

There is 5-Hydroxytryptophan potentiation in mice, an antidepressant model which delineates the mechanism of action of potential antidepressants. Antidepressants which increase serotonergic neurotransmission increase the potentiation of 5-HTP in mice.[19] Increase in serotonergic transmission in mice leads to development of Hallucinogenic effect which presents as Head twitches (wet dog shakes). This is due to loss of cortical inhibition exerted by the inhibitory neurons of brainstem, which are in turn depressed by the serotonergic transmission.[21]

Aqueous extract was evaluated to delineate the antidepressant activity which is exhibited by these extracts in the models mentioned earlier.

Mice treated with Fluoxetine 20mg/kg and Aqueous extract 300mg/kg showed significant increase in the number of head twitches, while Aqueous extract 100mg/kg and 200mg/kg did not show significant results (Figure 5).

Aqueous extract 300mg/kg showed significant effect in all the screening models tested in the study. Aqueous extract 100 mg/kg showed significant effect in Tail suspension test but did not show significant effect in other screening methods. This may be due to the fact that Tail suspension test in more sensitive test than other screening tests.[15] Aqueous extract 200mg/kg showed significant effect in all the screening tests except 5-HTP potentiation in mice. The reason for this needs to be elucidated.

Aqueous extract exhibited antidepressant activity in this study. This activity can be attributed to the phytochemicals present in the extract. Leaves of *Momordica charantia* contain phenolic compounds like Tannic acid, Gallic acid and Catechin.[8] Antidepressant activity of Emblica officinalis evaluated by Tail suspension test and Forced swim test was attributed to the presence of Tannic acid (30%) and Gallic acid (10%). Antidepressant activity of Tannic acid was attributed to its action of non-specific MAO inhibition.[23]

Gallic acid exhibited antidepressant activity, which was evaluated by Forced swim test in mice. The antidepressant effect shown by Gallic acid is by inhibiting MAO-A enzyme, thereby increasing the levels of monoamines in the synapse.[24]

Rocha et al, studied the antidepressant activity of Catechin rich Butanolic fraction in Forced swim test. Its action on Hippocampal synaptosomes showed decreased uptake of serotonin, Noradrenaline and Dopamine, thereby increasing the monoamine levels in the hippocampus and expressing antidepressant effects.[25]

Deficiency of Zinc is associated with depression.[26] Zinc supplementation with antidepressant therapy is effective in

overcoming the treatment resistant depression.[27] Sethi P et al, reported the concentration of Zinc in leaves to be 350mg/kg of dry weight of leaves.[11] This may be aiding the action of antidepressant in animal models. However this cannot conclude that it is the main mechanism of action as none of the screening models have reports of depleting the concentration of zinc.

Momordica charantia leaves contain Tryptophan which is the precursor of serotonin.[28] The antidepressant effect of the extracts seen in the study may be due to Tryptophan present in the leaves.

Momordica charantia leaves contain phenolic compounds Naringin and Rutin.[29] Naringin has shown to be effective in post stroke depression by acting through nitric oxide mechanism by preventing the oxidative damage.[30] Rutin is also known to have antidepressant activity.[31]

Alkaloids, Flavonoids, Tannic acid and Gallic acid contribute to its antioxidant activity. In *Momordica charantia*, among all parts of the plant, leaves show highest antioxidant power as shown by DPPHl (1,1-diphenyl-2-picrylhydrazyl free radical) radical-scavenging activity, Hydroxyl radical-scavenging activity, β-Carotene–linoleate bleaching assay, Ferric reducing/antioxidant power (FRAP) assay. This antioxidant activity may be responsible for prevention and reversal of oxidative stress leading to depression.[8]

CONCLUSION

From this study it can be concluded that *Momordica charantia* leaves possess antidepressant activity, probably by increasing 5-HT levels in brain. Further studies are needed to delineate the other mechanisms of action.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Animal Ethics Committee

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Cite this article as: Haseeb AM, Ahmad F, Kumar A. Antidepressant activity of aqueous extract of *Momordica charantia* leaves. Int J Basic Clin Pharmacol 2018;7:767-73.