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A Study on Assessment of Antidepressant Activity of *Momordica charantia* (Bitter Gourd)

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Abstract
Momordica charantia (bitter gourd) also called Karela is well-known for its medicinal qualities. The antidepressant activity of bitter gourd is least studied. All age groups are susceptible to depression, a common psychiatric illness. Antidepressants that are currently on the market have their own drawbacks. Hence, the present study was carried out with main purpose to evaluate the antidepressant activity of methanolic fruit extract of bitter gourd. Antidepressant activity of methanolic fruit extract of bitter gourd at doses of 250 mg/kg, 500 mg/kg and 750 mg/kg was evaluated in female Swiss albino mice in tail suspension test. After 1 h of dosing of distilled water as vehicle administered to normal control group (10 ml/kg, *p.o.*); 250 mg/kg (Group-A), 500 mg/kg (Group-B), 750 mg/kg (Group-C) methanolic extract of bitter gourd fruit and imipramine 15 mg/kg (positive control) was administered orally respectively, Results inferred that there was statistically significant reduction in immobility time (s) in positive control on day 7 ($p<0.001$) and day 14 ($p<0.001$). In Group-A (250 mg/kg) significant reduction in immobility time (sec) was observed on day 14 ($p<0.05$). However, statistically significant reduction in immobility time (s) was observed in Group-B (500 mg/kg) on day 1 ($p<0.05$), day 7 ($p<0.05$), and day 14 ($p<0.01$). Similarly, in Group-C (750 mg/kg) significant reduction in immobility time (s) was observed on day 1 ($p<0.01$), day 7 ($p<0.01$) , and day 14 ($p<0.001$). The effect of bitter gourd treatment at the dose level of 750 mg/kg was comparable with that of positive control (imipramine). In conclusion, results of the present study clearly demonstrated that methanolic fruit extract of bitter gourd exhibited antidepressant activity. Therefore, methanolic extract of bitter gourd could be considered for development natural antidepressant drugs.

Keywords: Bitter gourd, Fruit, Methanolic extract, Antidepressant

Introduction

Depression accounts for 4.5% of the worldwide total burden of disease in terms of disability-adjusted life years.[1] Mortality due to depression reaches 87 lacs annually in the age range of 15–29.[2] The COVID-19 pandemic saw a further increase in the number of cases of depression. Depression affects all age groups. Depressed individuals of older age group also likely to suffer from comorbid conditions like angina, myocardial infarction, diabetes mellitus, cancer, Parkinson's disease, and Alzheimer's disease. 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, serotonin, dopamine.[3] 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 recognized to be symptomatically, psychologically and biologically heterogeneous.[4] 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.[5]

The major disorders of mood or affect include the syndromes of major depression (melancholia) and bipolar disorder (manic-depressive disorder).

Physical changes also occur, particularly in severe, vital, or melancholic depression. These include insomnia or hypersomnia, altered eating patterns with anorexia, weight loss or something overeating, decreased energy and libido; disruption of the normal circadian, ultradian rhythms of activity, body temperature, and many endocrine functions.[6] Dysthymic disorder also called dysthymia, psychotic depression, postpartum depression,[7,] and seasonal affective disorder are also kinds of depression.[8] 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.[9]

Based on the therapeutic guidelines from the American Psychological Association, the first-line drugs for the treatment of depression include tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors, or dopamine agonists, depending on the patient's clinical condition, drug side effects, and therapy costs.[10] A good number (20%) of all depressed patients are refractory to the available antidepressants at adequate doses. It is compounded with a "therapeutic lag" lasting 3-4 weeks before therapeutic response becomes evident in them.[11] Antidepressant drugs are associated with many adverse effects[12] and interactions with the drugs prescribed for the treatment of comorbid conditions.[13] 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.[14,15]

Momordica charantia, (Bitter gourd) a member of the Cucurbitaceae family, commonly known as bitter melon, bitter gourd, balsam pear, karela, and pare. It grows in tropical areas of the East Africa, Asia, India, South Africa, and the Caribbean and it is used traditionally as both food & medicine. The plant is a climbing perennial with elongated fruit that resembles a warty gourd or cucumber. The unripe fruit is white or green in colour and has a bitter taste[16,17] and it is rich in phytochemicals like alkaloids, flavonoids, glycosides, triterpenoids, steroids, phenols, tannins, oils and fats.[18,19] The studied biological activities include antihyperglycemic, antibacterial, antiviral, antitumor, immunomodulatory, antioxidant, antidiabetic, anthelmintic, antiulcer, antifertility, hepatoprotective, anticancer, and anti-inflammatory activities.[20] Yet, very less data available on systematic biological investigation about this fruit has never been subjected to systematic biological investigation.

Herbal drugs may attract people to consume it due to their effectiveness, relatively low cost and have potential in therapeutic applications without concerning about the toxicity effects it might cause. Investigation on the toxicity profile of bitter gourd fruit in any applications is very important to ensure the safety of the public upon consuming this plant. [21,22] Therefore, the present investigation has been designed to evaluate antidepressant activity of bitter gourd fruit in stress induced depression animal model study.

Materials and Methods

Collection of Plant Materials

The bitter gourd fruits were purchased from the local market of Chikkaballapura. The fruits were sprayed with ethanol, and then shade dried at room temperature for 10 days. The dried stem were crushed to fine powder with help of electric grinder and stored in airtight containers for further analysis.

Extraction

Approximately 50 g of dried and coarsely powdered bitter gourd fruit was subjected to successive solvent extraction by continuous hot extraction (Soxhlet) with 550 mL of methanol. All the extracts were concentrated by distilling the solvent in a rotary flash evaporator. The extracts were preserved in airtight containers and stored at room temperature until further use.[23,24]

Drug Solution

The methanolic extract of bitter gourd 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.

Ethical Approval

The study was conducted by authorized, qualified and trained scientists & technicians in compliance with the guidelines laid down by the Institutional Animal Ethics Committee (IAEC) approved by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), India. All applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

Experimental Animals

Healthy Swiss albino female mice weighing between 20-25g were used. They were maintained at 25ºC with relative humidity of 45 to 50% and under standard environmental conditions with 12:12 h light/dark cycle in polypropylene cages. The animals were fed with standard pellet feed and water was given *ad libitum*.

Acute Oral Toxicity

All female Swiss Albino mice were free of any toxicity as per acceptable range given by the OECD guideline-423 up to the dose of 2000 mg/kg.[25] From this data and pilot study reports; three different doses 250, 500 and 750 mg/kg were selected for further study.

Antidepressant Activity

Tail Suspension Test

Tail suspension test was carried out according procedure described by Steru *et al.*[26] After 1 h of dosing of distilled water as vehicle administered to normal control group (10 ml/kg, *p.o.*); 250 mg/kg (Group-A), 500 mg/kg (Group-B), 750 mg/kg (Group-C) methanolic extract of bitter gourd fruit and imipramine 15 mg/kg was administered orally 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 (positive control). Recordings were taken on treatment day 1, day 7, and day 14.

Statistical Analysis

The data are expressed as Mean ± S.E.M. Data were subjected to statistical analysis using one-way ANOVA followed by Dunnett's multiple comparison *post-hoc* tests. $p \leq 0.05$ was considered as statistically significant.

Results

The results of the antidepressant effect of methanolic extract of bitter gourd fruit and positive control drug was as represented in Figures 1, 2, and 3. Results depicted that there was statistically significant reduction in immobility time (s) in positive control on day 7 ($p<0.001$) and day 14 ($p<0.001$). In Group-A (250 mg/kg) significant reduction in immobility time (sec) was observed on day 14 ($p<0.05$). However, statistically significant reduction in immobility time (s) was observed in Group-B (500 mg/kg) on day 1 ($p<0.05$), day 7 ($p<0.05$) , and day

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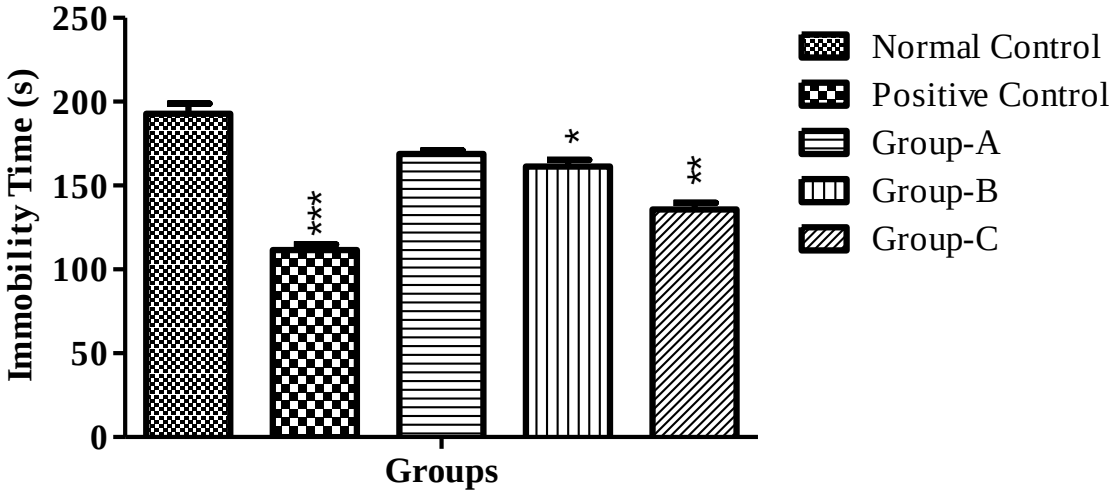
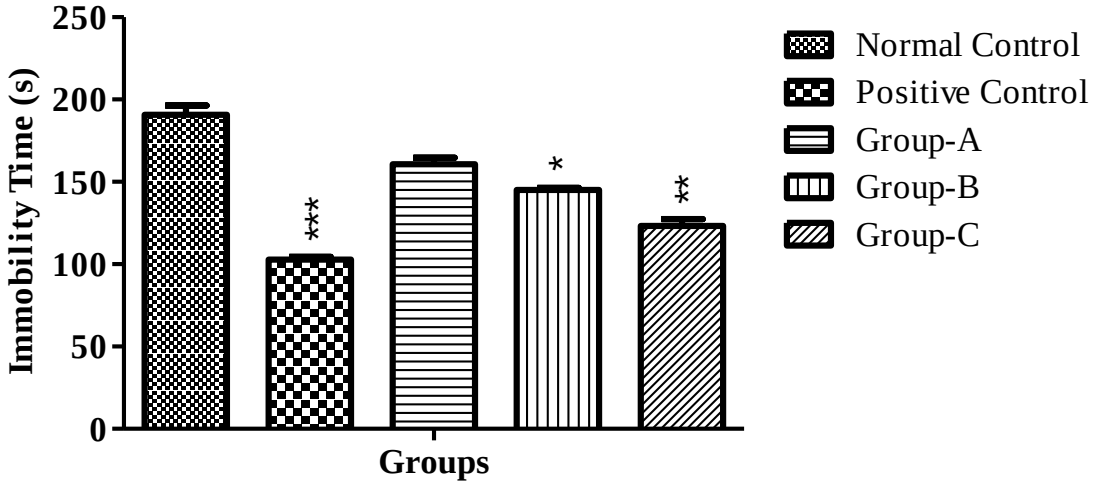
14 ($p<0.01$). Similarly, in Group-C (750 mg/kg) significant reduction in immobility time (s) was observed on day 1 ($p<0.01$), day 7 ($p<0.01$) , and day 14 ($p<0.001$). The effect of bitter gourd treatment at the dose level of 750 mg/kg was comparable with that of positive control (imipramine).

Figure 1: Effect of methanolic fruit extract of bitter gourd on the immobility time (s) of the mouse in tail suspension test on day 1



*p<0.05, **p<0.01, ***p<0.001, as compared to normal control group based on one-way ANOVA followed by Dunnett's multiple comparison *post-hoc* test

Figure 2: Effect of methanolic fruit extract of bitter gourd on the immobility time (s) of the mouse in tail suspension test on day 7



*p<0.05, **p<0.01, ***p<0.001, as compared to normal control group based on one-way ANOVA followed by Dunnett's multiple comparison *post-hoc* test

Figure 3: Effect of methanolic fruit extract of bitter gourd on the immobility time (s) of the mouse in tail suspension test on day 14

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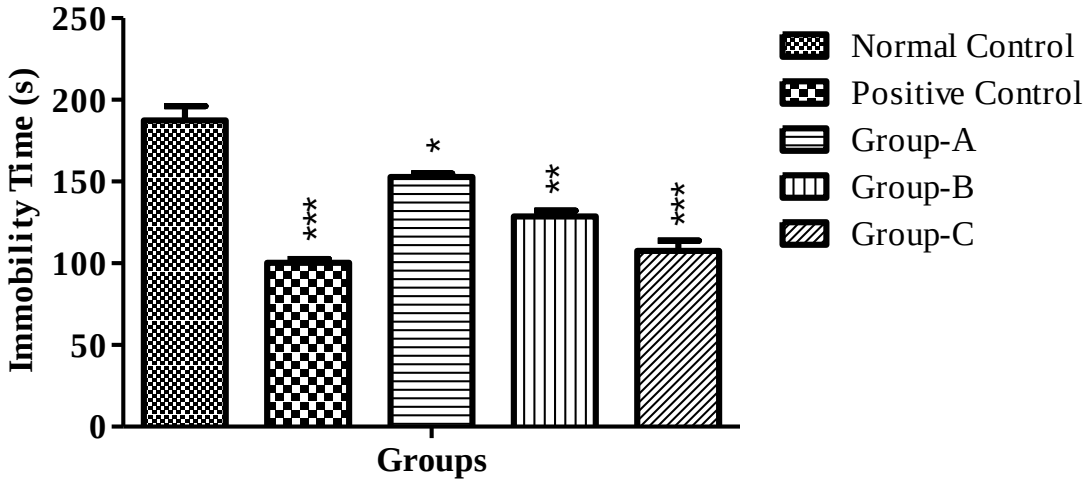

*p<0.05, **p<0.01, ***p<0.001, as compared to normal control group based on one-way ANOVA followed by Dunnett's multiple comparison *post-hoc* test

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.[27] The pathophysiology of depressive disorder is a complex, and it appears that a variety of overlapping biological causations exists.[28] The main premise concerning the bio pathophysiology of depression disorder 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.[29,30] 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.[32]

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.[32] 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 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.

Monoamine oxidase inhibitors (MAO) inhibitors can induce sedation, 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 selective serotonin reuptake inhibitors (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, have been associated with agitation and restlessness that resembles akathisia.[33] 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 is tail suspension test. It is expected that immobility occurs in these tests will reflect a state of behavioral despair or unable to adapt the stress as seen in human. Tail suspension test is based on the hypothesis that when an animal is subjected to an untoward situation, animal either goes into state of "agitation" or state of "immobility." Antidepressant drugs shifts the balance towards "agitation." Mice are suspended by tail and duration of immobility is noted.

The methanol extract of *M. charantia* fruit produced significant antidepressant effect in tail suspension test, as is evident from the reduction in the immobility time and the effect was comparable to the positive control. Numerous neural pathways are involved in the pathophysiology of depression state. The antidepressant effect has been shown in a number of plants of the family Cucurbitaceae, to which bitter melon also belongs. Randawa et al., demonstrated that methanol extract of *Coccinia indica* at 400 mg/kg produced behavioral improvement in an animal model using FST.[34] Meanwhile, methanol extract of *Cucurbita pepo* at 100 mg/kg lowered immobility time in an FST experiment, and the effect was comparable to imipramine at 30 mg/kg.[35] In addition, methanol extract of *Benincasa hispida* at 100 mg/kg was shown to significantly decrease the immobility time, with MAO-A inhibition as a possible mechanism.[36] Hydroalcoholic extract of *Benincasa hispida* was studied for its effect on head twitch, a behavioral model associated with the serotoninergic activity. At the dose of 30 mg/kg, the extract was found to dampen the increase in head twitch.[37] Another study on a plant from the family Cucurbitaceae was carried out by Rahman *et al*., showing that the n-hexane extract *Citrullus lanatus* at 250 and 500 mg/kg given for 7 days lowered immobility times as tested by FST and tail suspension test (TST), which was comparable to a dose of 10 mg/kg of imipramine.[38] The methanol extract of *Lagenaria siceraria* at 100 and 200 mg/kg was demonstrated to decrease immobility time which was stronger than the reference drug imipramine at 12.5 mg/kg.[40] Aqueous extract of *Cucurbita maxima* at 100 mg/kg was demonstrated to blunt immobility time in FST and TST, the activity which was comparable to imipramine at 30 mg/kg.[41] Lastly, *Cucurbita moschata* water extract was also reported to produce an improvement in the behavioral index in the FST model, which was in line with the increase in blood serotonin, a neurotransmitter essentially affected by depression.[42] Therefore, a great number of neurotransmitters are thought to involve in underlying mechanisms of these diseases, as evident by the antidepressant drugs.[43] By performing tail suspension test, the reduced immobility time directed the antidepressant effect of methanolic fruit extract of bitter gourd.

Conclusion

The results of present study clearly demonstrated that methanolic fruit extract of bitter gourd exhibited antidepressant activity. These results could be accredited to phytochemicals mainly alkaloids, steroids, glycosides, triterpenoids present in bitter gourd. Hence, methanolic extract of bitter gourd could be considered for development natural antidepressant drugs. However, further studies are recommended to elucidate the exact mechanism of action of particular phytochemical responsible for antidepressant activity of bitter gourd fruit.

References

1. Molla A, Mekuriaw B, Kerebih H. Depression and associated factors among patients with tuberculosis in Ethiopia: a cross-sectional study. Neuropsychiatr Dis Treat. 2019; (15):1887-93.
2. Depressive disorder. WHO; 2023.
3. Gold PW, Goodwin FK, Chrousos GP. Clinical and biochemical manifestations of depression. Relation to the neurobiology of stress. N Engl J Med. 1988;319(7):413-20.
4. Thase ME, Howland RH. Biological Processes in Depression: an Update and Integression. 2nd ed Bekham EE, Leber WR, editors [handbook] of Depression. Guilford; 1995. pp. 213-79.
5. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Washington, DC: American Psychological Association Press; 2000.
6. Tondo L, Isacsson G, Baldessarini RJ. Suicidal behaviour in bipolar disorder: risk and prevention. CNS Drugs. 2003;17(7):491-511.
7. Altshuler LL, Hendrick V, Cohen LS. Course of mood and anxiety disorders during pregnancy and the postpartum period. J Clin Psychiatry. 1998;59(2); Suppl 2:29-33.
8. Rohan KJ, Lindsey KT, Roecklein KA, Lacy TJ. Cognitive-behavioral therapy, light therapy, and their combination in treating seasonal affective disorder. J Affect Disord. 2004;80(2-3):273-83.
9. Tsuang MT, Faraone SV. The genetics of mood disorders. Johns Hopkins University Press; 1990.
10. American Psychological Association, 2019.
11. O'Donnell JM. Drug therapy of depression and anxiety disorders. Goodman & Gilman's the pharmacological basis of therapeutics; 2011. p. 397-415.
12. Nutt DJ. Treatment of Depression. Clin Pharmacol, 10. 2008:331-41.
13. Horn L, Pao W, Johnson DH, Kasper DL, Jameson JL, Fauci AS et al. Loscalzo: Harrison's principles of internal medicine.
14. Ishaq H. Anxiolytic effect of herbal medicine, Khamira Gaozaban Ambri Jadwar Ood Salib Wala (KGJ) in experimental rat models. Pak J Pharm Sci. 2014;27(2):289-94.
15. Rajput MS, Sinha S, Mathur V, Agrawal P. Herbal antidepressants. IJPFR. 2011;1(1):159-69.
16. T. Momordica charantia (Bitter melo n). ALT Rev. 2007; 12:360-3.
17. Taylor L. Technical data report for bitter melon (Momordica charantia), 1 - 101. 2nd ed. Austin: Herbal Secrets of the Rainforest. SAGE Press; 2002.
18. Arunachalam G, Subramanian N, Pazhani GP, Ravichandiran V, Karunanithi M, Nepolean R. Anxiolytic, antidepressant and anti-inflammatory activities of methanol extract of *Momordica charantia* Linn Leaves (Cucurbitaceae). Iran J Pharmacol Ther. 2008;7(1).
19. Patil SA, Patil SB. Toxicological studies of *Momordica charantia* Linn. Seed extracts in male mice. Int J Morphol. 2011;29(4):1212-8.
20. Jia S, Shen M, Zhang F, Xie J. Recent advances in *Momordica charantia*: functional components and biological activities. Int J Mol Sci. 2017;18(12):2555.
21. Porsolt RD, Bertin A, Jalfre MJ. Behavioral despair in mice: a primary screening test for antidepressants. Arch Int Pharmacodyn Ther. 1977;229(2):327-36.
22. Vogel HG. Drug discovery and evaluation: pharmacological assays. 2nd ed. Springer - Verlag Berlin Heidelberg New York. Germany; 2002. p. 559-61.
23. Rauf A, Khan A, Uddin N, Akram M, Arfan M, Uddin G et al. Preliminary phytochemical screening, antimicrobial and antioxidant activities of *Euphorbia milii*. Pak J Pharm Sci. 2014;27(4):947-51.
24. Kamurthy H, Dontha S, Rajani K. Phytochemical screening on *Euphorbia milii* red flowers-isolation of terpenoids, flavone and phenols. Am J Ethnomed. 2015; 6:322-32.

25. Schlede E. Oral acute toxic class method: OECD Test Guideline 423. Rapport Istisan. 2002;41:32-6.
26. Steru L, Chermat R, Thierry B, Simon P. The tail suspension test: a new method for screening antidepressants in mice. Psychopharmacology. 1985;85(3):367-70.
27. WHO. Mental and Neurological Disorders 'Depression'; 2006.
28. Belmaker RH, Agam G. Major depressive disorder. N Engl J Med. 2008;358(1):55-68.
29. Hindmarch I. Expanding the horizons of depression: beyond the monoamine hypothesis. Hum Psychopharmacol. 2001;16(3):203-18.
30. Ressler KJ, Nemeroff CB. Role of serotonergic and noradrenergic systems in the pathophysiology of depression and anxiety disorders. Depress Anxiety. 2000;12; Suppl 1:2-19.
31. Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression. Trends Immunol. 2006;27(1):24-31.
32. Ziegler DR, Herman JP. Neurocircuitry of stress integration: anatomical pathways regulating the hypothalamo-pituitary-adrenocortical axis of the rat. Integr Comp Biol. 2002;42(3):541-51.
33. Belmaker RH, Agam G. Major depressive disorder. N Engl J Med. 2008;358(1):55-68.
34. Randhawa MA, Khan AA, Javed MS, Sajid MW. Green leafy vegetables: a health promoting source. InHandbook of fertility 2015 (pp. 205-20). Academic Press.
35. Umadevi P, Murugan S, Suganthi J, Subakanmani S. Evaluation of antidepressant like activity of *Cucurbita pepo* seed extracts in rats. Int J Curr Pharm Res. 2011;3(1):108-13.
36. Dhingra D, Joshi P. Antidepressant-like activity of *Benincasa hispida* fruits in mice: possible involvement of monoaminergic and GABAergic systems. J Pharmacol Pharmacother. 2012;3(1):60-2.
37. Shakya A, Bhat HR, Ghosh SK. Assessment of Neurobehavioral properties of hydroalcoholic extract of *Benincasa hispida* (Thunb.) Cogn. fruit pulp in mice. J Biol Act Prod Nat. 2019;9(4):299-310.
38. Rahman AHMM. Systematic studies on Cucurbitaceae family at Rajshahi division, Bangladesh. Sci PG. 2013;1(2):10-5.
39. Prajapati R, Umbarkar R, Parmar S, Sheth N. Antidepressant like.
40. Prajapati R, Umbarkar R, Parmar S, Sheth N. Antidepressant like activity of *Lagenaria siceraria* (Molina) Standley fruits by evaluation of the forced swim behavior in rats. Int J Nutr Pharmacol Neurol Dis. 2011;1(2):152-6.
41. George S, Nazni P. Antidepressive activity of processed pumpkin (*Cucurbita maxima*) seeds on rats. Int J Pharm Med Biol Sci. 2012;1(2):225-31.
42. Kim NR, Kim HY, Kim MH, Kim HM, Jeong HJ. Improvement of depressive behavior by Sweetme Sweet Pumpkin™ and its active compound, β-carotene. Life Sci. 2016; 147:39-
43. Pałucha A., Pilc A. A. On the role of metabotropic glutamate receptors in the mechanisms of action of antidepressants. Pol J Pharmacol. 2002;54(6):581-6.