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Original Article

Anti-depressant Potentials of Some Bioactive Components of *Basella alba* Leaves in Chronic Unpredictable Stress Rat Model

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ABSTRACT

Bioactive components of *Basella alba* leaves are responsible for their antidepressant-like activity. However, the component with the greatest anti-depressant activity is unknown. This study investigated the antidepressant-like activities of the bioactive components (phenols, flavonoids, and glycosides) in *Basella alba* leaves. Forty-two male Wistar rats weighing 50–200 g were randomly divided into six groups (n=7). All the groups, except for the control, were subjected to chronic unpredictable stress (CUS) for five weeks. The rats in the CUS groups were treated with normal saline (1 mL/kg), escitalopram (5 mg/kg), and each of the phenol-, flavonoid-, and glycoside-rich *Basella alba* extracts (200 mg/kg) orally for twenty-one days. The tail suspension, sucrose preference, light-dark box, and hole-board tests were carried out before and after the induction of depression. In the CUS groups, reduced mobility time on tail suspension, increased percentage sucrose consumption, frequency of head dips on the hole board, and line-cross frequency in the light-dark box were observed. The latency on the hole board was reduced with *Basella alba* components, while there was a significant ($p<0.05$) decrease in serum brain-derived neurotrophic factor and an increase in serum IL-6 in the CUS animals not treated with extracts. The phenol-rich *Basella alba* extract showed the most potent antidepressant-like activity, followed by the flavonoid-rich extract. The bioactive components of *Basella alba,* particularly phenols, were effective in ameliorating the depressive features of CUS and should be further studied for use as an adjunct or stand-alone antidepressant.

Keywords
Basella alba, Brain-derived neurotrophic factor, Chronic unpredictable stress, Depression, Interleukin-6

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INTRODUCTION

Depression refers to a wide range of mental health problems characterized by the absence of a positive affect (a loss of interest and enjoyment in ordinary things and experiences), low mood, and a range of associated emotional, cognitive, physical, and behavioural symptoms (Lewinsohn et al. 2000; Abhinayani et al. 2016).
According to the World Health Organization (WHO), depression is one of the leading causes of disability worldwide and is a major contributor to the overall global burden of disease (Biala et al. 2018). Depression affects an estimated one in fifteen adults (6.7%) in any given year, and one in six people (16.6%) will experience depression at some point in their lives (Cai et al. 2020). Women are more likely than men to experience depression, and there is a high degree of heritability (approximately 40%) when first-degree relatives have depression (Cartwright et al. 2016). In recent years, the prevalence of depression in teens and young adults has increased. Trends in prevalence point to a rising number of young people with untreated depression in the sense of little progress in

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mental health treatments (Carniel and da Rocha 2020). Clinically, depression presents with inflammation and/or a reduction in neurotrophic factors, such as the brain-derived neurotrophic factor (BDNF), in the brain (Ahmadi and Khaledi 2020). It is depicted in various physical, emotional, and mental signs and symptoms, some of which are: low self-esteem, over- or under-eating, weight gain or loss, pain without a known cause, loss of interest, and social isolation (Alshawwa et al. 2019). Although several synthetic drugs are being used as the standard treatment for clinically depressed patients, they have adverse effects that can compromise the treatment, which include dry mouth, fatigue, gastrointestinal or respiratory problems, anxiety, agitation, drowsiness, and cardiac arrhythmias (Bahar and Rahman 2020). The long duration before improvement of symptoms is also a drawback (Comai et al. 2020). Several drug-drug interactions can also occur (Bahar and Rahman 2020). These conditions create an opportunity for alternative treatment of depression through the use of medicinal plants. With the use of herbal plants, many of these side effects can be prevented since all the synthetic drugs available for the treatment of depression have various adverse effects associated with problematic interactions. Among animal models, the chronic unpredictable stress model is the most frequently used and considered one of the most perfect models of depression and stress-related disorders (Duman et al. 2021). These disorders occur as a result of hypothalamic-pituitary-adrenal axis dysregulation (Cartwright et al. 2016). Similar to other stress models, CUS has mostly been validated and replicated in adult rodents, with the knowledge obtained in juvenile animals being surprisingly scarce. Behavioural tests to assess stress and depression-like symptoms include the tail suspension test (TST), sucrose preference, light-dark box, and hole-board tests (Katiyar and Kumar 2021).

Escitalopram is a standard drug for the treatment of common depressive disorders. It is a selective inhibitor of serotonin reuptake. It is, in fact, the most selective of all serotonin reuptake inhibitors (Sanchez et al. 2014). In this study, the drug escitalopram was used as a standard antidepressant to constitute a positive control in the experiment.

Basella alba (commonly known as Malabar spinach) leaf is an important vegetable found commonly in tropical regions of the world. It is an underutilized green leafy vegetable rich in vitamins, minerals, dietary fibre, phenols, and antioxidants (Kumar et al. 2022). Numerous bioactive compounds such as flavonoids, phenols, saponins, glycosides, ferulic acid, gallic acid, caffeic acid, lutein, zeaxanthin, and beta-carotene have been isolated from the leaves of *Basella alba* (Mao et al. 2019). However, their potential as ingredients for the development of functional foods has not been fully explored. Some of these bioactive compounds have been worked out for one or more medicinal attributes, including antidepressant activity (Mohammed et al. 2020). In previous research done to investigate the antidepressant effect of *Basella alba* extracts, the specific bioactive compounds that produce its antidepressant effect were not convincingly stated (Abhinayani et al. 2016). This study aimed to explore the potential of some bioactive components of *Basella alba* in the management of depression and compare the antidepressant effects of phenol-, flavonoid-, and glycoside-rich *Basella alba* extracts in CUS-induced depression in male Wistar rats.

MATERIALS AND METHODS

Ethical Considerations

This study was carried out according to the University of Ilorin guidelines and regulations and was assigned the approval number UERC/ASN/2019/1551 by the University Ethical Review Committee.

Study Design

This was a comparative study among normal, healthy rats, CUS-depressed rats untreated or treated with escitalopram, as well as phenol-, flavonoid-, and glycoside-rich *Basella alba* extracts.

Animals

Forty-two adult male Wistar rats weighing 150–200 g were used for the study. The rats were housed in the animal house of the Faculty of Basic Medical Sciences, University of Ilorin, where they were maintained in plastic cages with net covers under standard conditions and fed with rat pellets and distilled water *ad libitum.* The animals were acclimatized for two weeks and randomly divided into six groups of seven animals each.

Identification and Processing of Plant Materials

Fresh leaves of *Basella alba* (Malabar spinach) were obtained from a local farmer in Mopa town, Kogi State. They were identified at the Department of Plant Biology, University of Ilorin, Ilorin, Nigeria, and assigned the identification number UILH/001/1416/2020. After identification, 3.5 kg of the leaves were air-dried and pounded using a mortar and pestle, which yielded 250 g. The powdered leaves were freeze-dried for 48 h, and the various bioactive compounds were extracted.

Extraction of Bioactive Components

Phenol (PHE): Sodium hydroxide pellets (40 g) were dissolved in a litre of methanol, and the solution was added to 83 g of the powdered *Basella alba* leaves. The mixture was stirred and left for 24 h. After which, the extract was filtered twice using a muslin cloth. The filtrate was then dried with a rotary evaporator (to remove the alcohol content). A solid, PHE-rich extract (29 g) was obtained (Alara et al. 2019).

Flavonoid (FLV): Sodium nitrite (3.2 g) was dissolved in 70 mL of distilled water in a beaker, and the solution was added to 83 g of powdered *Basella alba* leaves. Ethanol (30%) was then added to the mixture. A solution containing 700 mL of distilled water and 70 g of aluminium chloride ($AlCl_3$) was prepared separately in another beaker and

added to the previous mixture in the plastic container. The new mixture was stirred and left for 24 h, after which it was filtered twice using a muslin cloth. A 20-gram sodium hydroxide pellet was dissolved in distilled water, added to the filtered extract, and stirred. A deep brown layer was seen precipitating gradually at the base of the container. After about one and a half hours, the upper layer was decanted, leaving behind the lower brown layer of FLV-rich extract. The remaining water content was removed using a freeze dryer. FLV-rich extract (28 g) was obtained in the end (Alara et al. 2021).

Glycoside (GLY): Powdered *Basella alba* leaves (83 g) were dissolved in one litre of 70% ethanol and allowed to stand for 24 h, after which it was filtered twice using a muslin cloth. The filtrate was dried with a rotary evaporator to remove the alcohol content. 5 g of a paste-like GLY-rich extract was obtained (Alara et al. 2019).

Induction of Depression

Depression was induced using the chronic unpredictable stress (CUS) model. This involved exposing the experimental rats to any two random stressors daily for five weeks: 1) bed-wetting (200 mL of water was poured onto the bedding (wood shavings) and it remained unchanged for 24 h); 2) overcrowding (the number of rats in each cage was doubled for 24 h); 3) water deprivation (rats were deprived of water for 24 h); and 4) food deprivation (rats were given water but were deprived of feed for 24 h) (Naveen Kumar 2016).

Animal Grouping and Treatment

After acclimatization, the rats were randomly grouped and received treatment orally, once daily for twenty-one days after the induction of depression, as follows: Control group (normal, healthy rats); CUS group, CUS-depressed rats treated with normal saline (1 mL/kg); CUS + escitalopram (ESC), CUS-depressed rats treated with ESC (5 mg/kg); CUS + PHE, CUS-depressed rats treated with PHE-rich *Basella alba* extract (200 mg/kg); CUS + FLV, CUS-depressed rats treated with FLV-rich *Basella alba* extract (200 mg/kg); CUS + GLY, CUS-depressed rats treated with GLY-rich *Basella alba* extract (200 mg/kg).

Behavioural Tests

The following: tail suspension, sucrose preference, light-dark box, and hole-board tests were carried out before and after induction of depression, as well as after treatment.

Tail Suspension Test

Each animal was suspended from a rod by its tail and, with the aid of masking tape, approximately 10 cm above the ground. The animal would try to escape and reach for the ground. This test lasted for 5 min, and the time it took each rat to remain immobile was measured as the time of mobility (Nishuty et al. 2019).

Sucrose Preference Test

A 2% sucrose solution was prepared by dissolving 20 g of sugar in a bowl containing a litre of distilled water. Each rat was placed in a single cage containing two drinking bottles: One contained 150 mL of sucrose solution, and the other contained 150 mL of distilled water. After 12 h, the positions of the sucrose- and water-containing bottles were changed to eliminate any positional preference. The test lasted for 24 h. At the end of the test, the sucrose preference (SP) was calculated as SP = volume of sucrose consumed/total fluid taken (sucrose + water) ×100% (Ozbeyli et al. 2019).

Light-Dark Box Test

A square box made up of four chambers: two light chambers and two dark chambers was used. Two rats were placed in the box at a time, one in each of the light compartments. The total number of transitions between the light and dark chambers was noted. This test lasted for 5 min.

Hole-Board Test

Each rat was placed one at a time in a box with regularly arranged holes on its floor. Both the number of head dips and latency (time taken before the first head dip) were measured within 5 min (Rabiei and Rabiei 2017).

Blood Sample Collection

Rats were euthanized with intramuscular ketamine/xylazine (87.5/12.55 mg/kg b.w.). Five millilitre of blood samples were collected through cardiac puncture, put in plain sample bottles, and centrifuged at 4,500 rpm for 5 min. The sera were then collected and assayed for the biomarkers interleukin-6 (Il-6) and brain-derived neurotrophic factor (BDNF).

Statistical Analysis

All data were expressed as mean ± standard error of the mean (SEM). Statistical group analysis was performed with the GraphPad Prism software version 5.0. A one-way ANOVA was used to compare the mean values of variables among the groups. Bonferroni's test was used for post-hoc analysis. Statistically significant differences were accepted at $p < 0.05$, $n = 7$.

RESULTS

Body Weight

The mean body weight of rats in all the groups was similar at baseline. However, post-induction of depression, there was a significant ($p<0.05$) decrease in body weight in the CUS, ESC-, PHE-, FLV-, and GLY-treated groups compared to the control group. Post-treatment, there was a significant ($p<0.05$) increase in body weight in the treated groups compared to the control group.

Behavioural Tests

Tail Suspension Test

At baseline, there was no significant difference in the time of mobility. In post-induction depression, there was a significant ($p<0.05$) decrease in mobility time. However, upon treatment, there was a significant ($p<0.05$) increase

in the time of mobility on the tail suspension test in the ESC, PHE, FLV, and GLY groups compared to the CUS group (Fig. 1A).

Sucrose Preference Test

After treatment, there was a significant ($p<0.05$) increase in the percentage of sucrose consumed in the ESC, PHE, FLV, and GLY groups compared to the CUS group (Fig. 1B).

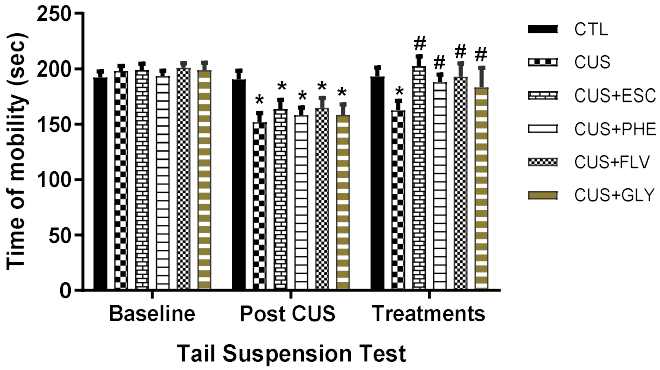

Fig. 1A: Effects of ESC and PHE-, FLV-, and GLY-rich *Basella alba* extract on time of immobility of CUS-depressed male Wistar rats. One-way ANOVA and Bonferroni's test: n=6; *p < 0.05 vs control; #p < 0.05 vs CUS (chronic unpredictable stress). ESC (escitalopram), PHE (phenol), FLV (flavonoid), GLY (glycoside)

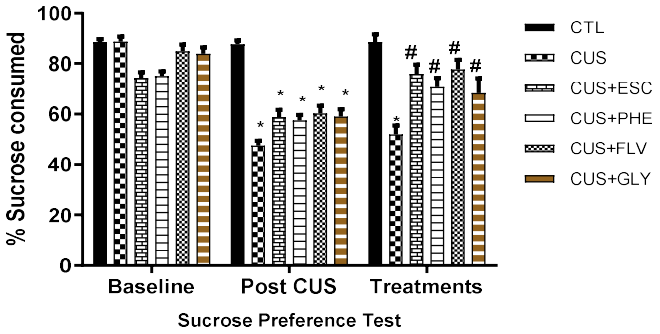

Fig. 1B: Effects of ESC and PHE-, FLV-, and GLY-rich *Basella alba* extract on sucrose preference in male CUS-depressed Wistar rats. One-way ANOVA and Bonferroni's test: n=6; *p < 0.05 vs control; #p < 0.05 vs CUS; αp< 0.05 vs Baseline; βp < 0.05 vs post CUS (chronic unpredictable stress). ESC (escitalopram), PHE (phenol), FLV (flavonoid), GLY (glycoside)

Light-Dark Box Test

After treatment, there was a significant ($p<0.05$) increase in the head dip in the ESC, PHE, FLV, and GLY groups (#) when compared to the CUS group (Fig. 1c).

Hole Board Test

Latency: After treatment, there was a significant ($p<0.05$) decrease in the latency across the ESC, PHE, FLV, and GLY groups compared to the CUS group (Fig. 1di).

Head Dips: After treatment, there was a significant ($p<0.05$) increase in the head dip in the ESC, PHE, FLV, and GLY groups when compared to the CUS group (Fig. 1dii).

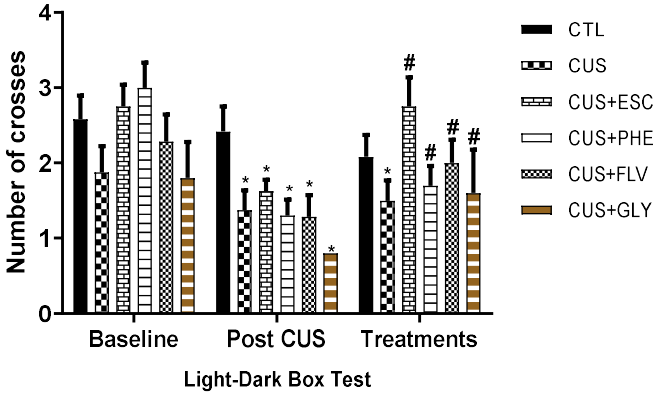

Fig. 1c: Effects of ESC and PHE-, FLV-, and GLY-rich *Basella alba* extract on the number of crosses in CUS-depressed male Wistar rats. One-way ANOVA and Bonferroni's test: n=6; *p < 0.05 vs Control; #p < 0.05 vs CUS (chronic unpredictable stress). ESC (escitalopram), PHE (phenol), FLV (flavonoid), GLY (glycoside)

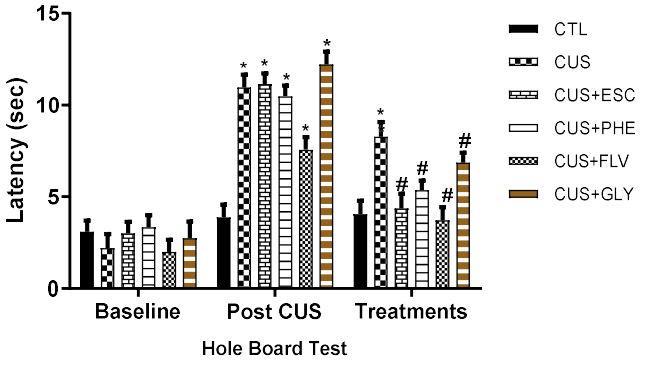

Fig. 1di: Effects of ESC and PHE-, FLV-, and GLY-rich *Basella alba* extract on latency in CUS-depressed male Wistar rats. One-way ANOVA and Bonferroni's test: n=6; *p < 0.05 vs control; #p < 0.05 vs CUS (chronic unpredictable stress). ESC (escitalopram), PHE (phenol), FLV (flavonoid), GLY (glycoside)

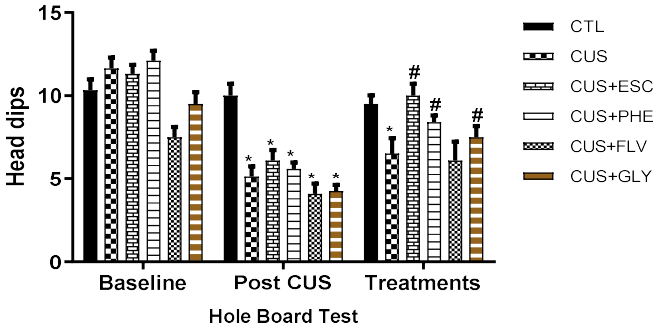

Fig. 1dii: Effects of ESC and PHE-, FLV-, and GLY-rich *Basella alba* extract on the number of head dips in CUS-

depressed male Wistar rats. One-way ANOVA and Bonferroni's test: n=6; *p < 0.05 vs control; #p < 0.05 vs (chronic unpredictable stress). ESC (escitalopram), PHE (phenol), FLV (flavonoid), GLY (glycoside)

Serum Biomarkers

Brain-Derived Neurotrophic Factor (BDNF)

There was a significant increase in the serum BDNF level in the *Basella alba* PHE-treated group more than in the ESC-treated group, which was also more than in the *Basella alba FLV-treated group* and more than in the *Basella alba* glycoside-treated groups compared to the CUS-exposed untreated group (Fig. 2a).

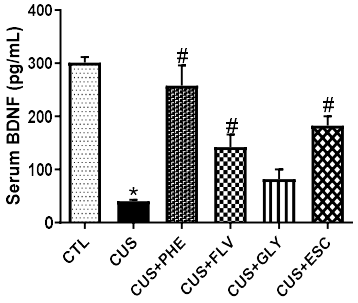

Fig. 2A: Effects of ESC and PHE-, FLV-, GLY-rich *Basella alba* extracts on serum BDNF in CUS-depressed male Wistar rats. One-way ANOVA and Bonferroni's test: n=6; *p < 0.05 vs control; #p < 0.05 vs CUS (chronic unpredictable stress). ESC (escitalopram), PHE (phenol), FLV (flavonoid), GLY (glycoside)

Interleukin-6 (Il-6)

There was a significant decrease in the serum IL-6 level in the *Basella alba* PHE-treated group, which was more than in the ESC-treated group, more than in the *Basella alba FLV-treated group*, and more than in the *Basella alba* GLY-treated group compared to the CUS-exposed untreated group (Fig. 2b).

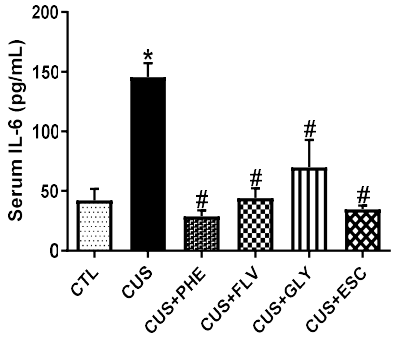

Fig. 2B: Effects of ESC and PHE-, FLV-, and GLY-rich *Basella alba* extract on serum IL-6 in CUS-depressed male Wistar rats. One-way ANOVA and Bonferroni's test: n=6; *p < 0.05 vs control; #p < 0.05 vs CUS (chronic unpredictable stress). ESC (escitalopram), PHE (phenol), FLV (flavonoid), GLY (glycoside)

DISCUSSION

This study was carried out to assess the effect of PHE-, FLV-, and GLY-rich *Basella alba* extracts on CUS-induced depression in male Wistar rats. The results showed that all the extracts have antidepressant activity, with the effect being highest in the PHE-rich, followed by the FLV-rich, and the least in the GLY-rich *Basella alba* extract.

CUS induces a cognitive deficit and anxiety-like behaviour in rats (Romanczuk-Seiferth et al. 2014). CUS has also been reported to induce significant weight loss in rats (Sadaf et al. 2020). Thus, the significant weight loss seen in the groups subjected to CUS can be attributed to the stressors they were exposed to, especially the starvation stressor. Post-treatment, a trend of increased body weight was noticed in both the treated groups and the CUS group. This can be said to be a result of the cessation of the CUS paradigm.

After the induction of depression, a significant decrease was observed in the mobility time in the CUS, ESC-, PHE-, FLV-, and GLY-treated groups when compared with the normal control group. This suggests a successful induction of depression because decreased mobility time is a depression-like symptom (Bahar and Rahman 2020). Post-treatment, the ESC-treated group showed a marked increase in mobility time compared to the CUS group. There was also an increase in mobility time in the PHE-, FLV-, and GLY-treated groups compared to the CUS group. Increased mobility time suggests the absence of stress and, hence, the absence of depression (Bahar and Rahman 2020). This shows that the standard drug ESC and the PHE, FLV, and GLY components of *Basella alba* extract have antidepressant activity.

The high level of sucrose preference at baseline in all the groups also signifies the absence of depression during this stage. Another indication of successful depressive condition modelling is the significant decrease in sucrose preference seen in all the groups subjected to CUS procedures. Decreased sucrose preference represents anhedonia, which is one of the core symptoms of depression in rats (Tongco et al. 2015). A significant increase in sucrose preference was observed in all the test groups after treatment in the CUS group, which suggests that both ESC and *Basella alba* extracts have antidepressant effects. Among the extracts, the antidepressant effects regarding sucrose preference were comparable.

The high mean number of crosses (between the light and dark chambers) and head dips by all the rats in the light-dark box test and hole-board test, respectively, in the baseline show that the rats were normal during this period. The subsequent marked decrease in these parameters in all the groups subjected to depression suggests that the induction of depression was successful in these groups. Stress has been shown to reduce the number of crosses between the two chambers of the light-dark box (Van Bodegom et al. 2017). Anxiety has also been said to reduce the head-dipping behaviour of rats in the hole-board test (Wernecke and Fendt 2015). Therefore, after treatment, the subsequent increase in the number of crosses and number of head dips in the light-dark box test

and hole board test, respectively, by all the treatment groups except the CUS group depicts that ESC and the *Basella alba* extracts are true antidepressants. Likewise, the course of the latency graph also supported the fact that depression was successful in the rats subjected to it and that both ESC and the *Basella alba* extracts functioned as antidepressants. It has been reported that exposure to chronic stress could cause an increase in latency to the first head dip in rats in the hole-board test (Xu et al. 2020). Some medicinal plants exert their antidepressant effects through synaptic regulation of serotonin, noradrenaline, and dopamine, regulating the activity of the hypothalamo-pituitary-adrenal axis, reinforcing the antioxidant defence system, and decreasing inflammatory mediators (Yousuf-Rather et al. 2019).

There was a significant decrease in the BDNF level in the CUS group compared to the normal control group. This finding supports clinical studies that have indicated that serum or plasma BDNF levels are decreased in untreated depressed patients (Sekita-Krzak et al. 2016). Although BDNF is not a classical biomarker of neurodegenerative disease, its reduction is an indication of memory dysfunction in health and disease, which is part of the symptoms of neurodegenerative disease. Here, CUS, plausibly via epigenetic mechanisms, caused a reduction in BDNF levels (Johnson et al. 2021). Nevertheless, a significant increase was seen in serum BDNF levels in the ESC-, PHE-, FLV-, and GLY-treated groups compared with the CUS group. This signifies that both the standard drug and the extracts showed antidepressant effects because it has been shown that antidepressant drugs raise the levels of serum BDNF (Sekita-Krzak et al. 2016). The similar level of BDNF in the ESC- and PHE-treated groups suggests that the standard drug ESC and the PHE-rich extract have similar potencies. Among PHE-, FLV-, and GLY-treated groups, BDNF levels were highest in the PHE-treated group, followed by the FLV- and then GLY-treated groups, showing that PHE is the most potent micronutrient regarding augmentation of BDNF and, by extension, memory functions, followed by FLV and then GLY.

The significant increase in serum Il-6 levels in the CUS group compared with the normal control represents successful modelling of CUS-induced depression. Conversely, the significant decrease in serum Il-6 levels in ESC-treated, PHE-treated, FLV-treated, and GLY-treated groups compared to the CUS group also suggests that both the standard drug and *Basella alba* extracts are potent enough to suppress the pro-inflammatory condition associated with stress-induced depression. This effect is capable of preventing complications and providing considerable neuroprotection. IL-6 is known to be a pro-inflammatory biomarker, with its serum level significantly increased in depressed individuals but very low in normal individuals (Serchov et al. 2016). Insignificant differences in serum IL-6 levels among the ESC-treated and *Basella alba*-treated groups indicate that they may all have similar potencies.

Conclusion

This study shows that PHE, FLV, and GLY-rich *Basella alba* extracts have antidepressant activities. These bioactive compounds may be considered cheaper adjuncts or stand-alone antidepressants in the treatment of depression.

Grants and Financial Support

No funding was received.

Conflict of Interest

None declared.

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Authors' Contribution

HOJA and EDA wrote the paper draft. HOJA, EDA, OSJ, and LSO corrected the draft. HOJA supervised the experimenters. ATS, VTA, AOB, DII, OO, SOY, and JOE performed the experiments. All authors agree to be accountable for all aspects of work ensuring integrity and accuracy.

REFERENCES

Abhinayani, G., Goud, G.N., Nagamani, K.C. and Kaur, D. (2016) Antidepressant and the skeletal muscle relaxant activity of methanolic extracts of *Basella alba* L. Asian J Biomed Pharm Sci. 6(55):7-10.

Ahmadi, S. and Khaledi, S. (2020) Anxiety in rats with bile duct ligation is associated with the activation of JNK3 mitogen-activated protein kinase in the hippocampus. Metab Brain Dis. 35(4):579-588. doi: 10.1007/s11011-020-00542-1.

Alara, O.R., Abdurahman, N.H. and Ukaegbu, C.I. (2019) Soxhlet extraction of phenolic compounds from *Vernonia cinerea* leaves and its antioxidant activity. J Applied Res Med Aromatic Plants. 11:12-17.

Alara, O.R., Abdurahman, N.H. and Ukaegbu, C.I. (2021) Extraction of phenolic compounds: A review. Curr Res Food Sci. 4:200-214.

Alshawwa, I.A., Elkahlout, M., El-Mashharawi, H.Q. and Abu-Naser, S.S. (2019) An expert system for depression diagnosis. Int J Acad Health Med Res. 3(4):20-27.

Bahar, T. and Rahman, S. (2020) Depression in physicians: An overlooked issue in mental health. J Enam Med Coll. 10(1):39-42. https://doi.org/10.3329/jemc.v10i1.45065

Biala, G., Pekala, K., Boguszewska-Czubara, A., Michalak, A., Kruk-Slomka, M., Grot, K., et al. (2018) Behavioral and biochemical impact of chronic unpredictable mild stress on the acquisition of nicotine conditioned place preference in rats. Mol Neurobiol. 55(4):3270-3289.

Cai, Z., Ye, T., Xu, X., Gao, M., Zhang, Y., Wang, D., et al. (2020) Antidepressive properties of microglial stimulation in a mouse model of depression induced by chronic un-

predictable stress. Prog Neuropsychopharmacol Biol Psychiatry. 101:109931. Doi:10.1016/j.pnpbp.2020.109931

Carniel, B.P. and da Rocha, N.S. (2020) Brain-derived neurotrophic factor (BDNF) and inflammatory markers: Perspectives for the management of depression. Prog Neuropsychopharmacol Biol Psychiatry. 108:110151.

Cartwright, C., Gibson, K., Read, J., Cowan, O. and Dehar, T. (2016) Long-term antidepressant use: Patient perspectives of benefits and adverse effects. Patient Prefer Adherence.10:1401-1407.

Comai, S., De Gregorio, D., Posa, L., Ochoa-Sanchez, R., Bedini, A. and Gobbi, G. (2020) Dysfunction of serotonergic activity and emotional responses across the light-dark cycle in mice lacking melatonin MT2 receptors. J Pineal Res. 69(1):12653.

Duman, R.S., Deyama, S. and Fogaça, M.V. (2021) Role of BDNF in the pathophysiology and treatment of depression: Activity-dependent effects distinguish rapid-acting antidepressants. *Eur J Neurosci*. 53(1):126-139.

Johnson, D., Thurairajasingam, S., Letchumanan, V., Chan, K.G. and Lee, L.H. (2021) Exploring the role and potential of probiotics in the field of mental health: Major depressive disorder. Nutrients. 13(5):1728.

Katiyar, R. and Kumar, N. (2021). An updated review on Malabar spinach (Basella alba and Basella rubra) and their importance J Pharmacogn Phytochem 10(2):1201-1207.

Kumar, P.C., Oberoi, H.S. and Azeez, S., (2022) Basella-an underutilized green leafy vegetable with a potential for functional food development. Food Rev Int. 38(s1):456-473.

Lewinsohn, P.M., Solomon, A., Seeley, J.R. and Zeiss, A. (2000) Clinical implications of "subthreshold" depressive symptoms. J Abnorm Psychol. 109(2):345–351.

Mao, M., Li, S., Zong, M., Qiu, L., Yang, J., Xia, J., et al. (2019) Two-hit model of post-intensive care syndrome induced by lipopolysaccharide challenge and subsequent chronic unpredictable stress in mice. Int immunopharmacol.70:446-458.

Mohammed, A., Hamdy, H., Abdelrady, G., Seliman, M. and Mahmoud, U., (2020) Effect of zinc oxide nanoparticles on anxiety-related behaviors in male rats. *SVU*-IJVS. 3(1):123-132. http://dx.doi.org/10.21608/svu.2020.22360.1041

Naveen Kumar, S. (2016) Prevalence of depression among post-myocardial infarction patients attending cardiology outpatient department. Doctoral dissertation, PSG Institute of Medical Sciences and Research, Coimbatore.

Nishuty, N.L., Khandoker, M.M.H., Karmoker, J.R., Ferdous, S., Shahriar, M., Qusar, M.S., et al. (2019) Evaluation of serum interleukin-6 and C-reactive protein levels in drug-naïve major depressive disorder patients. *Cureus*.11(1):e3868. Doi: 10.7759/cureus.3868

Ozbe*yli, D., Aykac, A., Alaca, N., Hazar-Yavuz, A.N., Ozkan, N and Sener, G. (2019) Protective effects of vortioxetine in predator scent stress model of post-traumatic stress disorder in rats: Role on neuroplasticity and apoptosis. J Physiol Pharmacol. 70(4): https://doi.org/10.26402/jpp.2019.4.07

Rabiei, Z.and Rabiei, S. (2017) A review on antidepressant effect of medicinal plants. Bangladesh J Pharmacol. 12(1):1-11. http://dx.doi.org/10.3329/bjp.v12i1.29184

Romanczuk-Seiferth, N., Pöhland, L., Mohnke, S., Garbusow, M., Erk, S., Haddad, L., et al. (2014) Larger amygdala volume in first-degree relatives of patients with major depression. NeuroImage Clin. 5:62-68.

Sadaf, R., Younus, I., Maqbool, S., Fayyaz, T.B., Khan, S.J., Siddique, S. et al. (2020) Evaluation of the anxiolytic activity of Pulsatilla nigricans L. in Wistar rats by using elevated plus maze and hole board paradigms. Pakistan J Zool. 52(3):1201-1204.

Sekita-Krzak, J., Żebrowska-Łupina, I., Łupina, T., Czajkowski, L., Cichacz-Kwiatkowska, B. and Robaczewska, J. (2016) Effects of chronic stress on the brain–the evidence from morphological examinations of hippocampus in a chronic unpredictable stress (CUS) model in rats. J Educ Health Sport. 6(12):384-399.

Sanchez C., Reines E.H. and Montgomery S.A. (2014) A comparative review of escitalopram, paroxetine, and sertraline: Are they all alike? Int Clin Psychopharmacol. 29(4):185-96.

Serchov, T., van Calker, D. and Biber, K. (2016) Sucrose preference test to measure anhedonic behavior in mice. Bio-protocol. 6(19):e1958-e1958.

Tongco, J.V.V., Añis, A.D. and Tamayo, J.P. (2015) Nutritional analysis, phytochemical screening, and total phenolic content of Basella alba leaves from the Philippines. Int J Pharmacogn Phytochem Res. 7:1031-1033.

Van Bodegom, M., Homberg, J.R. and Henckens, M. J. (2017) Modulation of the hypothalamic-pituitary-adrenal axis by early life stress exposure. Front Cell Neurosci.11: 87.

Wernecke, K.E. and Fendt, M. (2015) The olfactory hole-board test in rats: a new paradigm to study aversion and preferences to odors. Front Behav Neurosci. 9:223.

Xu, H.X., Lin, S.X., Gong, Y., Huo, Z.X., Zhao, C.Y., Zhu, H.M., et al. (2020) Chaiyu-Dixian formula exerts protective effects on ovarian follicular abnormal development in chronic unpredictable mild stress (CUMS) rat models. Front Pharmacol. 11:245.

Yousuf Rather, J., Younis Raja, W., Ahmad Dar, M., Gani, R. and Bhat, A.Z. (2019) Herbs as antidepressants: A review. J Nat Ayurvedic Med. 3(2):000182.