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Original Article

Anti-depressant-Like Effect of Ethanolic Leaves Extract of *Anthocephalus cadamba* in CUMS Model of Depression in Swiss Albino Mice

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ABSTRACT

Background: *Anthocephalus cadamba* owe their family name to 'runiaceae'. The plant's primary constituents include triterpenes, glycosides, saponins, flavonoids and indole alkaloids, including isocadambine, cadambine and isodihydrocadambine, cadamine. Literature survey reveals reports on pharmacological effects of anti-inflammatory, antioxidant, cytotoxic, anti-genotoxic, sedative and antiepileptic, anti-convulsant activity, anti-cancer, Anti-helminthic activity and anti-microbial, Anti-fungal activity and anti-pyretic. *Anthocephalus cadamba* has been reported to possess anti-epileptic property and have a neuroprotective effect. So that the present work is designed for anti-depressant activity in experimental animals. The effects of an ethanol leaf extract from *Anthocephalus cadamba* (AC) leaves on depression in Swiss albino mice CUMS models. **Materials and Methods:** Mice were stressed by repeatedly subjecting them to moderate stress for 21 days in succession. Imipramine (15 mg/kg) and EEAC (200 and 400 mg/kg) were administered orally to different groups of stressed and unstressed mice for a period of 21 days. In order to evaluate the mice's propensity towards depressive-like behaviour, they conducted the Forced Swim Test (FST) and the Tail Suspension Test (TST) one hour after receiving an oral administration of EEAC at doses of either 200 or 400 mg/kg. **Results:** The immobility length of both stressed and unstressed mice was dramatically shortened after 21 days of treatment with EEAC (200 and 400 mg/kg) and imipramine (15 mg/kg). The aforementioned impact was observed in both TST and FST. Ethanol leaf Extract of *Anthocephalus cadamba* (EEAC) significantly decreased MDA level and increased catalase level. Both relaxed and anxious mice showed a considerable rise in their serotonin levels after receiving EEAC (200 mg/kg and 400 mg/kg) treatment in contrast to their respective vehicle-treated counterparts. **Conclusion:** In mice that were both relaxed and stressed, the EEAC showed strong antidepressant-like action, perhaps reducing oxidative stress.

Keywords: Depression, Serotonin, Antioxidant, Tail suspension test, Neuroprotective effect.

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INTRODUCTION

Anthocephalus cadamba (https://en.wikipedia.org/wiki/Roxb.) (AC) Bosserowes their family name to 'runiaceae'.[1] Many Indian medical literatures have provided descriptions of the ayurvedic treatment comprising of *Anthocephalus cadamba*.[2] It is used in the treatment of certain diseases like hemoptysis, cough, nausea, injuries, pustules, hindrance and anti-microbial activity.[3] Triterpenes, glycosides, saponins, triterpenoid flavonoids and indole alkaloids (isocadambine, isodihydrocadambine and cadambine) makeup the majority of the plant's constituents. Literature survey reveals reports on pharmacological effects of anti-inflammatory,[4] antioxidant,[5] cytotoxic, antigenotoxic,[6] sedative and anti-epileptic,[7] anti-convulsant activity, anti-cancer,[8] anti-helminthic activity and anti-microbial,[9] anti-fungal activity,[10] anti-tumor activity,[11] anti-hepatotoxic,[12] anti-diabetic,[13] and anti-pyretic activity. *Anthocephalus cadamba* has been reported to possess anti-epileptic properties and have a neuroprotective effect as well. Thus, the present work is designed to assess the anxiolytic and anti-depressant activity of AC in experimental animals.

Depression disorder is a frequent mental illness with symptoms that can be minor to severe. Loss of interest, sorrow, restlessness,

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poor appetite, difficulty doing everyday duties and in more severe instances, a propensity to attempt suicide, are characteristics that define depressive disorders.[14] The etiology of anxiety and depression is significantly influenced by reactive oxygen species. The global prevalence of depression as a mental illness has increased nowadays. Over 300 million individuals around the world suffer from depression and by 2023, WHO projects that it will overtake all other causes of disability (WHO, 2018). According to recent research, depression prevalence rates among young people in India range from 31% to 57% and they are rising.[15] The etiology of anxiety and depression is significantly influenced by reactive oxygen species. It might be challenging for individuals to continue taking their prescribed antidepressant medication because many of the currently available antidepressant drugs have undesirable side effects.[16] This has been linked to a rise in interest in safer alternative medicines using medicinal herbs.[17] Many plants have the potential to be anti-depressive,[18] and they contain a variety of phytoconstituents that might be used to create novel pharmaceuticals to treat these conditions,[19,20] The current study looked at the potential of ethanolic leaf extract of AC for the treatment of anxiety and depression.

MATERIALS AND METHODS

Drugs and chemicals

Methyl alcohol, Spirit, EDTA, Distilled water, Glucose, Phosphate buffer, Trichloroacetic acid, Ethyl alcohol 20% Sodium Hydroxide, Sulphuric acid, Concentrated Hydrochloric Acid. The study employed exclusively analytical-grade chemicals and biochemical reagents of the highest purity. Imipramine was purchased from Likem Pharmaceuticals Pvt. Ltd.

Animal Housing

The experiment was conducted in accordance with the principles laid out by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) and the study proposal was authorized by the Institutional Animal Committee (RAP/7537/IAEC/2023/05).

Plant Material Collection

The plant parts were collected from the Mathura region and Dr. Sunita Garg of the CSIR-NIScPR in Delhi certified them (authentication number: NIScPR/RHMD/Consult/2023/4421-22). The leaves were collected from the plant and then cleaned, dried in the shade at room temp, mechanically grounded and sieved using a 40-no-mesh sieve. Until usage, this fine leaf powder was kept in an air tight container.

Preparation of Ethanol extract of *A. cadamba* (EEAC)

About 1 kg of powdered materials was extracted utilizing ethanol (50°C) as a Soxhlet apparatus. The extraction process continued until the extractive turned colorless. A rotary flask evaporator was used to concentrate the extract. The solvent-free semisolid mass thus obtained was used for the experiment. The mixture was then strained using Whatman filter paper and a cotton plug. A concentrated extract was produced by drying the filtrate in a Heidorph rotating evaporator at 45°C. A solid was created by air drying the leftover material.

Phytochemical analysis of prepared extract

For the phytochemical screening of significant bioactive compounds, all the prepared extracts were exposed to a variety of qualitative assays.[21] Himedia and Merck in India provided the chemicals utilized in the biochemical study. Qualitative tests were conducted to determine the existence of flavonoids, polysterols, tannins, saponins, alkaloids, phenolics and carbohydrates.

Experimental Animals

In this investigation, we employed “Swiss" albino mice weighing between 25-30 g. The Rajiv Academy for Pharmacy in Mathura provided the mice with animal housing that had a 12 hr cycle of light and dark, room temperature, controlled humidity, as well as the necessary food and water. Each animal was subjected to an identical experimental condition to reduce the variability of the animal's behavioral responses to the minor stress caused by handling and injection.

Acute toxicity study of extracts

“For the evaluation of the oral acute toxic effects of the ethanol leaf extract, Swiss albino mice were utilised, which was agreed upon in accordance with OECD guidelines (423). Following 12 hr fast, oral dosages of 100, 200, 500, 1000 and 2000 mg/kg were administered to animal groups. Immediately following administration, all animals were checked for any indications of toxicity throughout the following 12 hr period and every 24 hr period for the following 14 days.[22]

Induction of depression caused by Chronic Unpredictable Mild Stress (CUMS)

A variety of stressors were used to induce depressive-like behaviors in animals, including food and lack of water for 24 hr, stress control for 2 hr, 5 min of tail-clipping, 3 hr of noise stress, 24 hr of wet bedding, 12 hr without any sleep, 45°C of heat stress for 5 min, of 5°C cold stress, tilting the cage for 12 hr, shaking the cage for 10 min and reversal of the cycle of light and dark. These situations were chosen at random each day for 35 days.[23]

Experiment Design

For this research, we utilized adult male "Albino" Swiss mice that weighed 25-30 g. The groups were as follows:

Group 1: Normal control (saline 0.9%, orally),

Group 2: Negative control Group (CUMS),

Group 3: CUMS+Standard (15 mg/kg imipramine),

Group 4: CUMS+EAC (200 mg/ kg),

Group 5: CUMS+EAC (400 mg/kg).

From the 3rd week of the CUMS, Imipramine (15 mg/kg) and EEAC (200 mg/kg and 400 mg/kg) were administered for 21 consecutive days as previously described.[24]

Evaluation of Behavior Observation

Tail Suspension Test (TST)

The mice were suspended from a stable metal rod by their tails at a distance of 50 cm from the ground with their bodies looking downward. Many times, animals would try to climb the rod to get away from uncomfortable circumstances, but depressed animals would give up and stay still. The time was measured when the subject remained immobile during the 5 min of this test, which suggested depressive-like behavior.[25]

Forced Swim Test (FST)

The experiment was completed in accordance with the reference rules, with a few minor adjustments.[26,27] Swimming practice was done in cylinders made of transparent glass that were 30 cm deep, 46 cm in height and 20 cm in width with a water temperature of 23-25°C. Each swim evaluation took place between 10:00 and 16:00 and it consisted of a pre-test that lasted 15 min and a post-test that lasted 5 min. Following each swimming session, the mice were taken out from the cylinders and paper towels were used to dry them off and then maintained in a heated cage for around 15 min prior to becoming returned to their regular cages. Climbing behavior describes the forepaw movements along the swim cylinder's side that are upward-directed. Swimming activity is defined as motion that occurs within the swim cylinder's four quadrants and throughout its whole surface. The behaviors that featured immobility-described as the absence of any additional movement that required maintaining a mouse's head above water-were the ones that were chosen for examination in the modified FST. The sampling approach keeps track of how often each activity is displayed throughout the test time once every 5 sec.[28]

Brain biochemical estimation

Preparation of brain homogenate

On the final day of the investigation, mice were killed by cervical dislocation. The complete brain was removed from the mice after dissection. Weighed tissue was homogenized for about one minute in a 5 mL HCl-butanol solution. After that, at 2000 rpm, the material was centrifuged for 10 min. A 1 mL aliquot of a centrifuge tube was used to collect the supernatant phase with 2.5 mL heptane and 0.31 mL 0.1 M HCl. The organic phase that was on top was removed after the centrifuge tube's contents were separated into two phases after 10 min of spinning at 2000 rpm. Serotonin, catalase and malondialdehyde levels were estimated using the aqueous phase (0.2 mL).[29,30]

Estimation of Malondialdehyde

To a solution containing 1 mL of brain homogenate with a concentration of 10% weight/volume in pH 7.4 buffer with 0.1 molar phosphates, 2 mL of TBA was added. The hydrochloric acid reagent, consisting of 0.25 N hydrochloric acid, 15% trichloroacetic acid with 0.37% thiobarbituric acid in a 1:1:1 ratios, was introduced to the sample. The mixture was then heated to 90°C and boiled for duration of 40 min. After cooling the solution, Centrifugation was performed on it at 5,000 rpm for 10 min at 4°C. Absorbance at 535 nm was determined of the recovered supernatant and compared to a reagent blank.[31]

Estimation of Catalase

In a nutshell, the test mixture of 3.0 mL of post-mitochondrial filtrate with a volume-to-volume ratio of 10%, 0.05 mL of hydrogen peroxide with a concentration of 0.019 mm/L and 1.95 mL of phosphate buffer with a pH of 7.0. The differences in absorbance were observed at 240 nanometers. For the purpose of determining the catalase activity, the extinction coefficient of H_2O_2 (43.6 M-1 cm^{-1}) and its conversion to mol of H_2O_2 degraded per minute per milligram of protein were utilised.[32]

Estimation of Serotonin

High-Performance Liquid Chromatography with electrochemical detection was utilised in order to find out the levels of serotonin (5-HT) and its metabolite, 5-Hydroxyindoleacetic Acid (5-HIAA), that have been detected in the human brain.[33] Both in published works and in the supplementary techniques that were supplied by Pronexus Analytical AB, the approach that was utilised for this particular analysis has previously been disclosed. The detection limit, which is characterised by a signal-to-noise ratio that is greater than two, was established to be 10 femtomoles per 10. This was determined based on the fact that the signal-to-noise ratio was greater than 2.[34]

Statistical analysis

Tukey's test and Analysis of Variance (ANOVA) were used to analyse the data. In statistics, (p<0.05) was selected as the threshold of significance.

RESULTS

Evaluation of behavioural parameters of depression

Tail Suspension test

Figure 1 summarized the acute effects of EEAC (200 mg/kg and 400 mg/kg) on immobility time in the tail suspension test. During the final 4 min of the testing session, the amount of time spent immobile was recorded. When we compared the negative control group to the normal control group, we discovered that

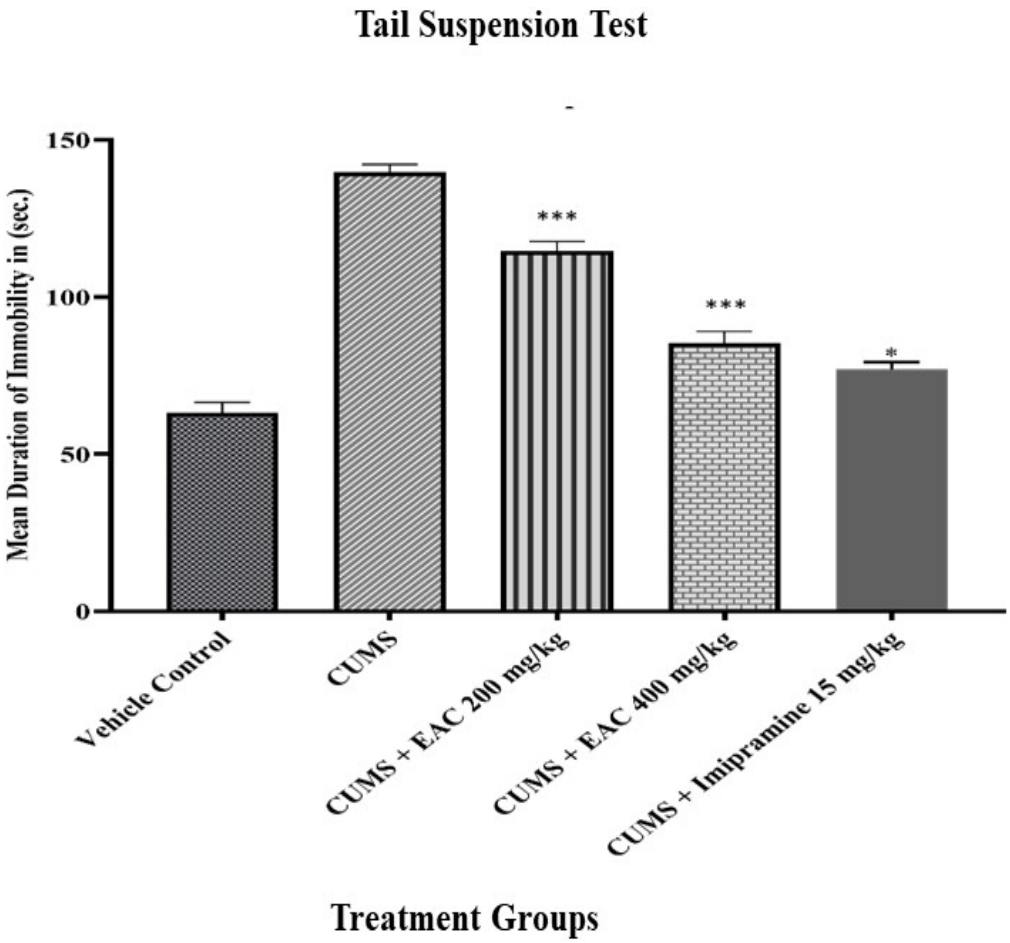

Figure 1: EEAC on immobilization in tail suspension test. One-way ANOVA and Tukey's test were utilised for multiple assessments on the data sets, *p<0.05 and ***p<0.001 against a negative control group.

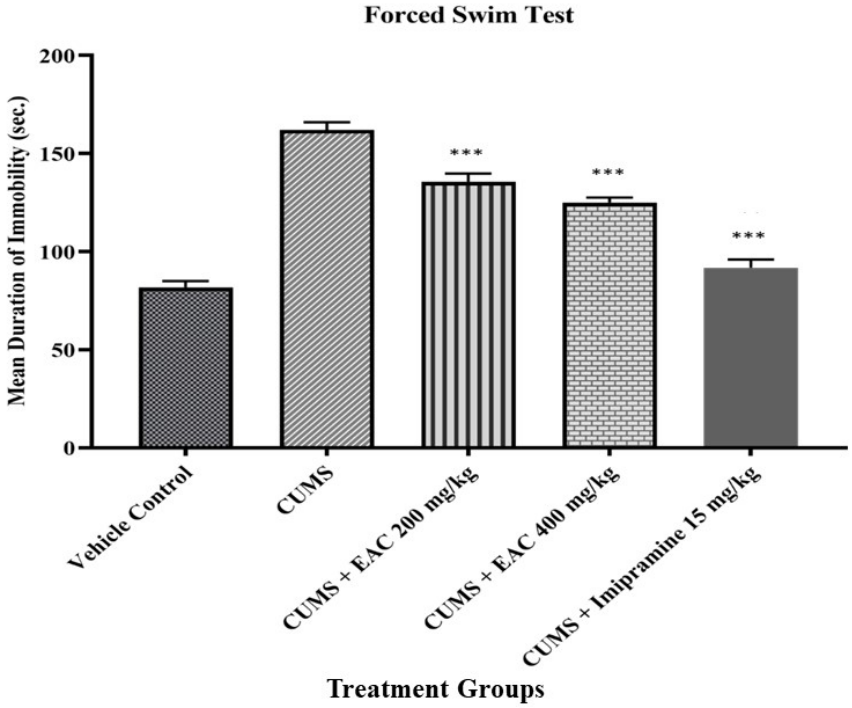

Figure 2: EEAC on immobilization in the force swim test. One-way ANOVA and Tukey's test were utilized for multiple assessments on the data sets, ***p<0.001 vs negative control group.

the immobilization period in the negative control group was substantially greater. The groups that were given imipramine (15 mg/kg) showed significantly (p<0.001) less immobility. When EEAC (200 mg/kg and 400 mg/kg) was given for 21 days, the treatment group's duration of immobility time was significantly (p<0.001) lower than that of the negative control group. The dosage of 400 mg/kg of EEAC exhibited a greater effect than the 200 mg/kg of EEAC.

Forced swim test

Figure 2 showed an increased immobilization in the negative control group. When compared to the negative control group, the groups of mice given EEAC at 200 and 400 mg/kg orally showed a substantial (p<0.001) decrease in the length of immobility time. Additionally, the imipramine (15 mg/kg) group demonstrated a significant (p<0.001) reduction in the length of immobility time compared to negative control groups. It was proposed that both test groups determined the effects on immobility time are comparable to the effects of standard drugs. The administration of extracts at the dosages of 200 mg/kg and 400 mg/kg yielded a reduction in the duration of immobility time.

Estimation of antioxidant enzyme level in the brain

Estimation of Malondialdehyde (MDA)

Oxidative stress is a crucial factor that contributes to depressive-like behaviour and it also promotes inflammation. The hippocampus and the prefrontal cortex, or prefrontal cortex, are the two regions of the brain that are affected by this. When compared to the group served as the normal control, the MDA level in the group used as the negative control was significantly greater. Imipramine (15 mg/kg) showed a significantly decreased MDA level when compared with the negative control group. The MDA level was dramatically decreased (p<0.001) by administration of EEAC at doses of 200 mg/kg and 400 mg/kg (Figure 3). Based on these data, it appeared that EEAC therapy reduced the amount of oxidative stress in both the hippocampus and the prefrontal cortex. In comparison to the group that served the negative control, those who received EEAC treatment exhibited a dose-dependent and statistically significant reduction in MDA levels.

Estimation of Catalase

When oxidative stress occurs, the hippocampus and the prefrontal cortex are both subject to oxidative damage. This type of damage is a significant factor to the stimulation of inflammation. There was a significant reduction in the concentration of catalase. The levels of catalase were dramatically raised by EEAC when

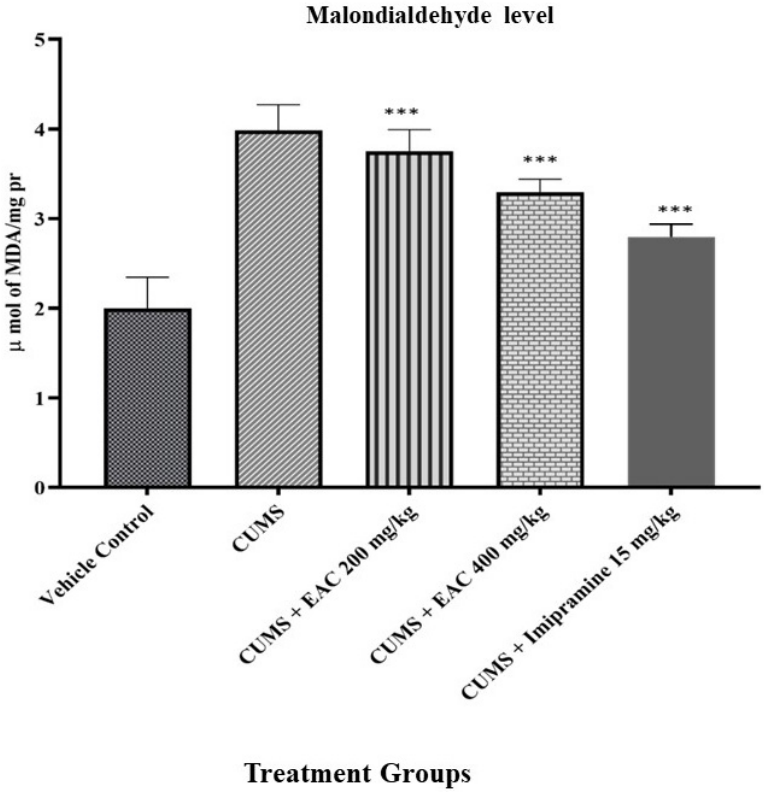

Figure 3: EEAC on immobilization in Malondialdehyde. One-way ANOVA and Tukey's test were utilized for multiple assessments on the data sets, ***p<0.001 vs. negative control group.

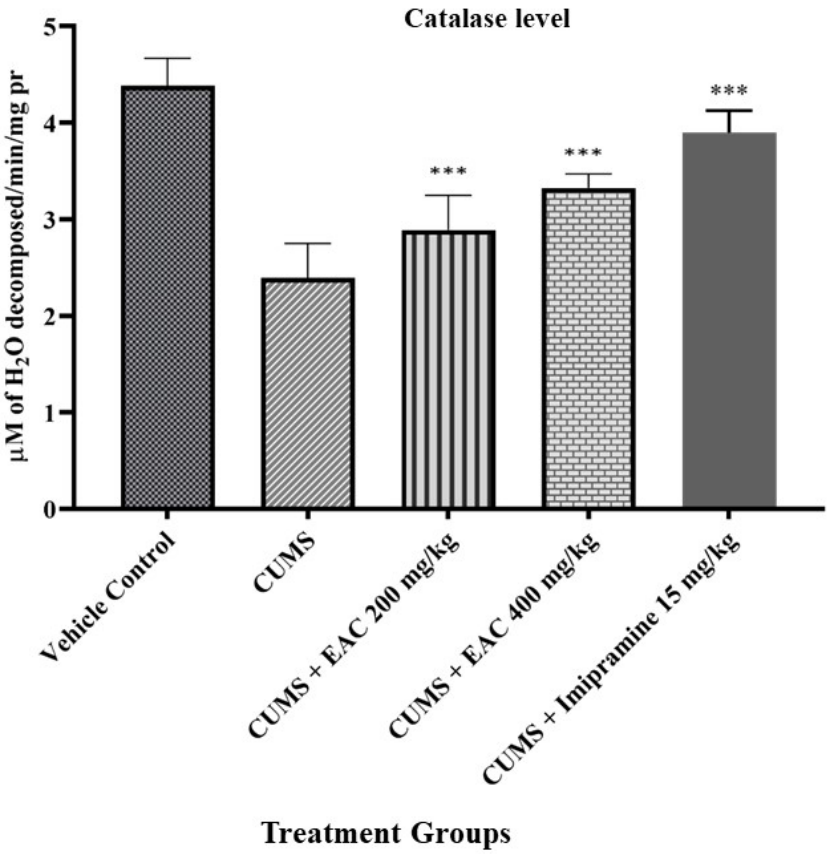

Figure 4: EEAC on immobilization in Catalase. One-way ANOVA and Tukey's test were utilized for multiple assessments on the data sets, ***$p<0.001$ vs. negative control group.

administered at either 200 or 400 mg/kg (Figure 4). Furthermore, those treated with EEAC showed a dose-dependent increase in the concentration of catalase when compared to the group that served as the negative control. According to these findings, EEAC treatment brought about a reduction in oxidative.

Estimation of Serotonin

The results of the 5-HT levels are shown in Figure 5. It showed that the stressed mice had lower amounts of 5-HT in their brains than the normal control group. Treatment with imipramine (15 mg/kg, p.o) and EEAC (200 mg/kg and 400 mg/kg, p.o) significantly ($p<0.001$) elevated 5-HT levels in the brain compared to stressed animals. Moreover, EEAC (200 mg/kg and 400 mg/kg) demonstrated a dose-dependent significant increase in serotonin levels vs. the negative control group.

DISCUSSION

The most reliable animal model for conducting the anti-depressant studies is depression induction with CUMS. FST and TST were used to assess the extract's efficacy on depression-like behavior in mice.[35] Chronic stress alters the levels and turnover of 5-HT as well as how their receptors are regulated. It also disrupts the HPA axis, raises cortisol levels, stimulates several pro-apoptotic processes and generates ROS, which leads to neurodegeneration and makes depressive symptoms worse.[36] The current study attempted to evaluate EEAC's antidepressant effects in a CUMS depressive model. The behavioral and antioxidant results clearly demonstrated that EEAC (200 mg/kg and 400 mg/kg, p.o.) has the potential to improve the neurochemical and behavioral responses Because of its neuroprotective and antioxidant qualities, it is related to the pathophysiology of depression and maybe through modifying the oxidative stress, it can help in treating the depression.

FST and TST are the most dependable behavioral models of depression in mice. The immobility seen in FST and TST is associated with a bad feeling or futility and is comparable to human sadness.[37] Because EEAC usage exponentially lowered FST and TST immobility times; any drop in this indicator implies antidepressant action.

Neurodegeneration is mostly caused by oxidative stress as well as the fact that depression and its symptoms are becoming more severe. Chronic stress causes the overproduction of ROS and the activation of many pro-apoptotic proteins; this causes neurodegeneration and significantly contributes to the pathophysiology of depression. An indication of oxidative stress is the availability of antioxidants in brain homogenate. A decrease in free radical scavengers like catalase and an increase in the development of free radicals like lipid peroxidation are

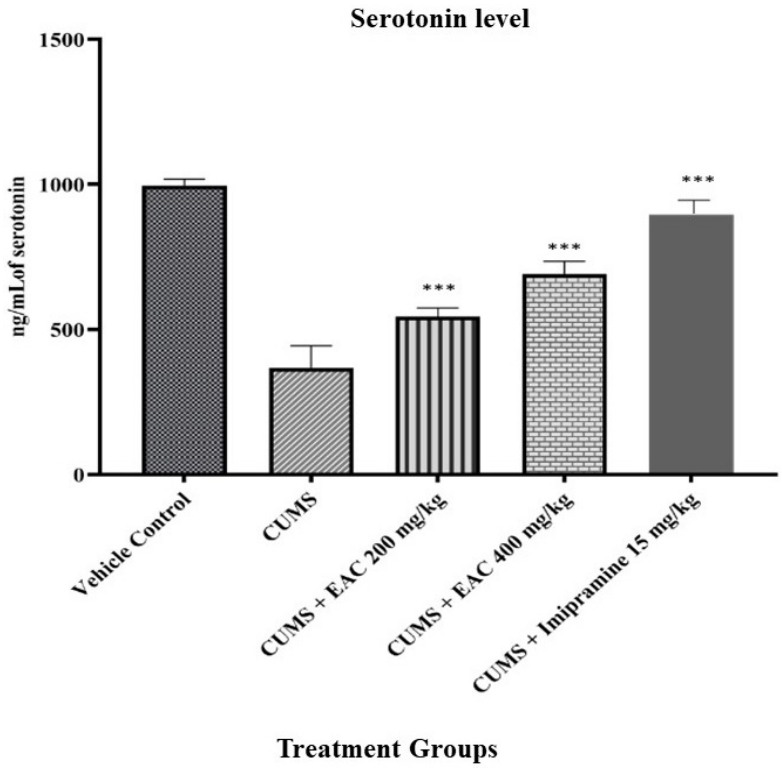

Figure 5: EEAC on immobilization in Serotonin. One-way ANOVA and Tukey's test were utilised for multiple assessments on the data sets, ***p<0.001 vs. negative control group.

both indicators of the development of oxidative stress.[38] Based on our results, the ethanolic extract of AC significantly enhanced the amount and endogenous antioxidant activity in the brain, contains catalase and significantly lowered the MDA level, avoiding brain lipid peroxidation.

Serotonin (5-hydroxytryptamine) is a powerful neurotransmitter whose levels in the CNS are associated with emotional disorders such as depression.[39] Following 3 weeks of restraint stress, brain serotonin levels fell in this research, but these levels significantly and swiftly rose in the EEAC and imipramine-treated groups. Thus, ethanol extract of *Anthocephalus cadamba* leaves may be investigated further for the treatment of depression in people.

CONCLUSION

In the current study, AC was found to have an antidepressant-like effect when used chronically to treat behavioral and neurochemical reactions implicated in the pathophysiology of depression. Since depression is a stress-related condition, the ethanolic leaf extract of AC may be a beneficial therapeutic component for developing substitute medications to treat it as it helps in reducing oxidative stress. In order to cure depression disorders in individuals, ethanol extract from *Anthocephalus cadamba* leaves may be further researched.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

AC: *Anthocephalus cadamba*; **EEAC:** Ethanol leaf Extract *Anthocephalus cadamba*; **TST:** Tail Suspension Test; **FST:** Forced Swim Test; **WHO:** World Health Organisation; **EDTA:** Ethylene Diamine Tetraacetic Acid; **CPCSEA:** Committee for the Purpose of Control and Supervision of Experiments on Animals; **OECD:** Organisation for economic co-operation and development; **CUMS:** Chronic Unpredictable Mild Stress; **5-HIAA:** 5-Hydroxyindoleacetic Acid; **ROS:** Reactive Oxygen Species; **HPA:** Hypothalamic-Pituitary-Adrenal (axis); **MDA:** Malondialdehyde; **p.o.:** Per os (by mouth); **ANOVA:** Analysis of Variance.

SUMMARY

The article explores the antidepressant-like effects of the Ethanolic Extract of *Anthocephalus cadamba* (EEAC) in a Chronic Unpredictable Mild Stress (CUMS) model of depression

using Swiss Albino mice. It emphasizes the role of oxidative stress in the pathophysiology of depression, noting that oxidative damage in the brain contributes to depressive behaviors. The study found that EEAC administration significantly increased endogenous antioxidant activity and catalase levels while reducing Malondialdehyde (MDA) levels, indicating a decrease in oxidative stress. Additionally, the extract positively influenced serotonin levels, crucial for mood regulation, showing a significant increase in serotonin in the EEAC-treated groups compared to the control. Behavioral assessments, including the Forced Swim Test and Tail Suspension Test, demonstrated that EEAC exhibited antidepressant-like effects, as evidenced by reduced immobility time in the treated mice. The study concludes that *Anthocephalus cadamba* has potential as a natural antidepressant, suggesting further investigation for its therapeutic applications in treating depression in humans.

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