Repeated Ascorbic Acid Administration Alleviates Motor Impairment, Anxiety-Related Behaviors, and Sociability Deficits in Fluoxetine-Treated Juvenile Male Rats

Ojo Foluso Olamide[1], Hassan Luqman Adepoju[1*], Adewole Ayodeji Oluwasegun[2], Edward Tolulope Adefola[1], Folorunso Kolade Pelumi[1], Afolabi Olayemi[3], Onaolapo Mary Tolulope[4], Ogundiran Reuben Jesulayomi[5]

[1]Department of Anatomy, Faculty of Basic Medical Sciences, University of Ilesa, Ilesa, Nigeria.

[2]Department of Surgery, Obafemi Awolowo University Teaching Hospital, Ile-Ife, Nigeria.

[3]Department of Human Nutrition and Dietetics, Faculty of Basic Medical Sciences, University of Ilesa, Ilesa, Nigeria.

[4]Department of Nursing Science, Faculty of Nursing Sciences, Saint Peters University, New Jersey, United States of America.

[5]Department of Anatomy, Faculty of Basic Medical Sciences, Ladoke Akintola University of Technology, Ogbomoso, Nigeria.

[6]Department of Biochemistry, Faculty of Sciences, University of Ilesa, Ilesa, Nigeria.

***Corresponding Author**

DOI: https://doi.org/10.51244/IJRSI.2025.12110069

Received: 20 November 2025; Accepted: 27 November 2025; Published: 09 December 2025

ABSTRACTS

Background: The debilitating impact of fluoxetine usage has been established in both animal studies and clinical trials.

Objective: This study aimed to evaluate the ameliorative impacts of ascorbic acid against fluoxetine-induced behavioral despair and social deficits in juvenile rats.

Methods: Thirty-two Juvenile male Wistar rats (80-100 grams) were randomly assigned into four groups of eight animals per group (n=8). Group A served as a normal control and had only access to feed and water; groups B and D received Ascorbic acid orally at 10mg/kg. Additionally, groups C and D received fluoxetine at 10mg/kg orally by gavage. The substances were administered five days per week for eight weeks. After the last administration, rats underwent neurobehavioral tests [motor coordination using the catalepsy bar test, anxiety-related behaviors with the elevated plus maze model, and sociability test (three-chamber social interaction paradigm)]. The analysis was performed using one-way analysis of variance (ANOVA) in Windows (version 0.98), followed by a post-hoc test (Tukey HSD) for inter-group comparisons. Results were presented as mean ± standard error of mean (S.E.M). The intergroup significant difference was accepted as $p < 0.05$.

Results: The feed intake, relative change in body weight, time spent in the open arm, and with the social stimulus results show a statistically significant decrease ($p< 0.05$) in group C compared to group A. Compared to group C, a statistically significant increase ($p < 0.05$) was observed in group D. In contrast, the catalepsy score, time spent in the closed arm, and in the empty chamber results show a statistically significant increase ($p < 0.05$) in group C compared to the control group A. Compared to group C, a statistically significant decrease ($p < 0.05$) was seen in group D.

Conclusion: The debilitating effects of fluoxetine administration, as confirmed in this study, warrant more rigorous monitoring of its use; further research is needed to establish these effects in humans.

Keywords: Behavioral-despair, Ascorbic Acid, Sociability, Fluoxetine, anti-depressants

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XII Issue XI November 2025

INTRODUCTION

Fluoxetine, a well-known selective serotonin reuptake inhibitor (SSRI) commonly used in the management of depressive disorder, has received wide acceptance in clinical trials (1). The expected outcome has been observed through its ability to modulate mood by regulating neurotransmitters such as serotonin and dopamine, which are responsible for mood regulation.

However, in the last few decades, preclinical and clinical trials have established an association between fluoxetine usage and some adverse effects, such as sexual dysfunction, tremor, anxiety, sociability disparity, loss of appetite, and weight loss (2,3), among others. These adverse effects have often called for a careful watch on patients undergoing treatment using fluoxetine. In fact, the onset of fluoxetine usage has been proven to have a strong association with suicidal ideation (4). While its sexual dysfunctional effects have attracted more attention, little or no attention has been considered worthy concerning its other adverse effects. Probably because of their minimal deleterious impact on the population using it. Interestingly, recent studies have established an increased prevalence of social interaction deficit and anxiety, particularly among young male adults undergoing fluoxetine treatment (5). Moreover, Tremor, loss of appetite, and weight loss are also established as associated adverse effects with its usage (6). It is therefore important not to overlook its adverse effects that are considered minimal, but rather search for other possible supplements that will not impede its efficacy in the treatment of depressive disorder, but will mitigate its adverse effects on the stated conditions.

Ascorbic acid, commonly known as vitamin C, is a water-soluble vitamin that plays an essential role in brain health and function due to its antioxidant properties (7). Studies have established its significant reversal effects on some behavioral deficits in rodents (8). Travica et al. (2017) in their study also reported its beneficial effects on brain health (9), the ameliorative effects of ascorbic acid on memory and attention deficit, anxiety, depressive behaviors, motor and social change (10,11, 12). Its ability to scavenge reactive oxygen species and mitigate oxidative stress, as well as its effects on the hypothalamic-pituitary-adrenal (HPA) axis modulation, is the commonly reported mechanism of action in the expression of these effects. Despite the reported beneficial impact of ascorbic acid on brain health and behaviors, there is a paucity of scientific information regarding its effects on the debilitating impact of fluoxetine usage in this shady area. The current study aims to evaluate its mitigating impacts on the adverse depilating effects of fluoxetine usage.

MATERIALS AND METHODS

Drugs

Fluoxetine (Bristol Laboratories Ltd., Berkhamsted, Herts, HP4 1EG, UK), Ascorbic acid (100 mg, BIORAJ Pharmaceuticals LTD, Nigeria), Distilled water, Elevated Plus Maze, Three chambers social interaction paradigm, and Catalepsy rods.

Animals

Healthy Juvenile Male Wistar rats whose weight ranged between 70–90g each used in this study were procured from the animal breeder at Iwo, Osun State, Nigeria. The rats were transported in the cool hour of the day to the research animal house of the Anatomy Department, University of Ilesa, Ilesa, Osun State, Nigeria. The rodents were housed in metal cages with dimensions 25 × 10 × 10 inches under a temperature-controlled (22.5°C ± 2.5°C) arena with switched-on lights at 7.00 in the morning. Animals were allowed to feed and drink clean water ad libitum. Animals were acclimatized for seven days before the commencement of the study. Research ethical approval was obtained from the research ethical committee of the Faculty of Basic Medical Sciences, Obafemi Awolowo University, Ile-Ife, Nigeria, with approval number (IPH/OAU/12/3121). All procedures were carried out in compliance with the approved protocols of the same and within the guidance for animal care and use prescribed in the scientific procedures on living animals, European Council Directive (EU2010/63). Ethical approval.

Diets

From weaning and throughout the experimental period, rats in all groups were fed rodent pellets (29% protein,

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XII Issue XI November 2025

11% fat, 58% carbohydrate) procured from a commercial vendor in Ilesa, Osun State, Nigeria.

EXPERIMENTAL METHODOLOGY

Thirty-two (32) Juvenile male Wistar rats were randomly assigned into four groups of eight (n=8) animals per group. Group A served as a normal control and had only access to feed and water; groups B and D received Ascorbic acid orally at 10mg/kg b.w. of rats as previously administered by Salami et al., 2023 (13) Additionally, groups C and D received fluoxetine at 10mg/kg body weight (14) orally by gavage using an oral cannula. The substances were administered for five (5) days a week for eight (8) weeks. Twenty-four (24) hours after the last administration in the eighth week, the rats were transferred to the neurobehavioral room within the research animal house for assessment of motor coordination using the catalepsy bar test, anxiety-related behaviours using the elevated plus maze model, and sociability using the three-chamber social interaction paradigm.

Feed intake and Body weight assessment

Relative feed intake and Body weight were measured daily and weekly, respectively, by an electronic weighing balance as previously done by García et al. (2013) (15) and Ojo et al. (2025) (16). The relative change in body weight as measured in this study was calculated for each of the animals using the following equation. The values for all animals were computed to determine the statistical mean.

$$\frac{\text{Final body weight} - \text{Initial body weight}}{\text{Initial body weight}}$$

Behavioral tests

The behavioral tests were done as follows: The catalepsy test, the anxiety-related behaviors with the elevated plus maze, and the Sociability test using the three-chamber social interaction paradigm. The behavioral assays were done under a dim light in a room temperature of 25 ± 2°C within the period of 4 days consecutively, running each assay on each day in the order stated above. Animals were habituated to the assay room 30 minutes before the evaluation (17).

The Catalepsy Measurement

As previously discussed by Onaolapo et al. (2012) (18) and Luciani et al. (2020) (19), the catalepsy was measured by lifting the animals and placing their front paws on an elevated steel bar measuring 15cm long, 15mm in diameter, 5.5cm above the surface, with the hind limb above the surface. The centre of the steel bar was marked to ensure rats were placed at the same position throughout the test. For many rats that refused to stay in position, the tests were repeated three times, and the cataleptic score was recorded as zero for rats that were unable to move after several trials. Sixty (60) seconds was considered the end time for animals that remained on a spot for a longer time. Generally, the experiment is terminated for each animal when one or two of its forelimbs are removed from the bar. The time of such events was documented, after which the rats were returned to their respective home cage in preparation for the next test

Anxiety-related Behaviors

The anxiety-related behavior was assessed using the elevated plus-maze, a plus-shaped paradigm that has two open arms measuring 50 × 10 × 0 cm transversing one another and right-angled to two closed arms that measure 45 × 10 × 25 cm, with a midpoint area measuring 10 × 10 × 1 cm. The closed arms have two enclosed walls measuring 30 cm high. Each rat was placed at the midpoint of the maze, facing the closed arm, and the time spent in either of the closed or open arms was measured for 10 minutes per animal, as previously done by Onaolapo et al. (2023) (18). The animal is considered to be in the closed arm when the fore and hind limbs cross into the closed chamber and vice versa.

Sociability Test

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XII Issue XI November 2025

The sociability test was carried out using the three-chamber social interaction paradigm as previously reported by Szabó et al. (2024) (17) and Onaderu et al. (2025) (20). The sociability paradigm is made of a plastic container measuring 60 cm × 40 cm × 20 cm with an exposed upper surface; the chamber is compartmentalized into three chambers measuring 20 cm × 40 cm × 20 cm. The three chambers were connected by an entryway through which the experimental animals could freely move from one chamber to the other. Each of the experimental animals was habituated to the paradigm for five (5) minutes before the commencement of the test. A new rat of the same strain and sex (social stimulus) was positioned in a 10 cm diameter wire cylinder-shaped cup on a side in one of the chambers. The 10 cm diameter wire cylinder-shaped cup was alternated per trial to avoid bias of a side. A similar but empty diameter wire cylinder-shaped cup (Non-social stimulus) was positioned in an opposite chamber. The experimental rats were left to explore the apparatus without obstacles for ten (10) minutes. The total time spent interacting with either the empty wire cylinder-shaped cup, the neutral middle chamber, or the diameter wire cylinder-shaped cup containing the social-stimulus rat was recorded and scored. A proximity of less than one cm (< 1 cm) of the experimental animal's nose oriented towards the diameter of the wire cylinder-shaped cup is considered an interaction**.**

Statistical analysis

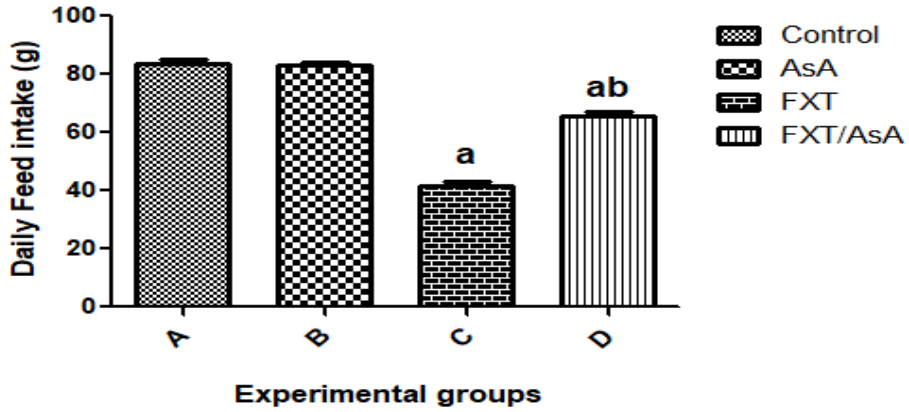
Chris Rorden's ANOVA for Windows (version 0.98) was used to analyze data. The analysis was done by One-way analysis of variance (ANOVA) followed by post-hoc test (Tukey HSD) for intra- and inter-group comparisons. Results were presented as mean ± S.E.M. The significant difference from the control group was accepted as $p < 0.05$.

RESULTS

Effects of Ascorbic Acid on Feed Intake in Fluoxetine-Treated Rats.

Figure 1 shows the effects of ascorbic acid on the daily feed intake in rats treated with fluoxetine. A statistically significant decrease ($p < 0.05$) was observed in the group that received fluoxetine compared to the control group. Compared to the fluoxetine-treated group (C), a statistically significant increase ($p < 0.05$) was observed in the group co-administered fluoxetine and ascorbic acid (D).

Figure 1: Effect of ascorbic acid on the daily feed intake in rats treated with fluoxetine. Each bar represents Mean ± S.E.M., with $p < 0.05$ against control. bp < 0.05 represents a significant difference from FXT; the number of rats per treatment group, n=8. FXT: fluoxetine, AsA: ascorbic acid.

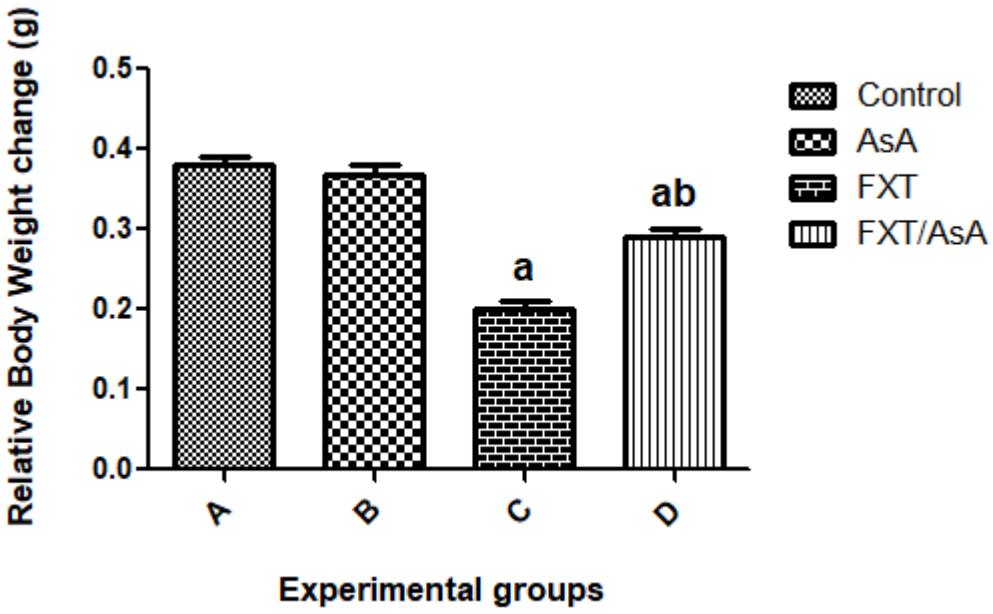


Effects of Ascorbic Acid on Body Weight in Fluoxetine-Treated Rats.

Figure 2 shows the effects of ascorbic acid on the relative change in body weight in rats treated with fluoxetine. A statistically significant decrease ($p < 0.05$) was observed in the group that received fluoxetine alone (C) compared to the control group (A). Compared to the fluoxetine-treated group (C), a statistically significant increase ($p < 0.05$) was seen in the group co-administered fluoxetine and ascorbic acid (D).

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XII Issue XI November 2025

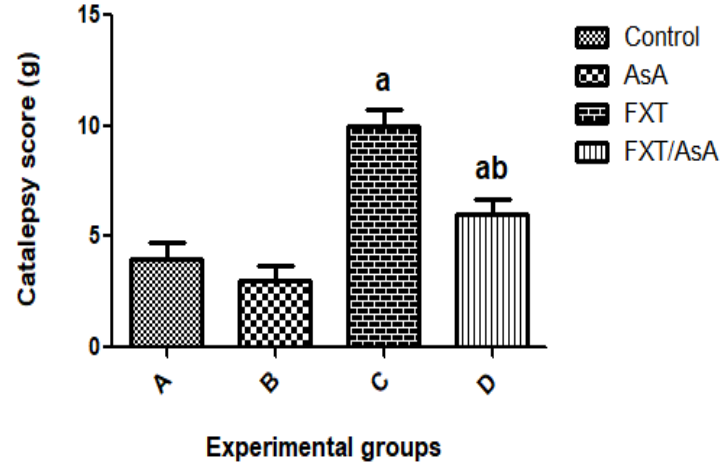
Figure 2: Effect of ascorbic acid on the relative body weight change in rats treated with fluoxetine. Each bar represents Mean ± S.E.M., with $p < 0.05$ against control. $^{b}p < 0.05$ represents a significant difference from FXT; the number of rats per treatment group = 8. FXT: fluoxetine, AsA: ascorbic acid.



Effects of Ascorbic Acid on Motor Coordination on the Catalepsy Bar Test in Fluoxetine-Treated Rats.

Figure 3 shows the effects of ascorbic acid on motor coordination on the catalepsy bar test in rats treated with fluoxetine. A statistically significant increase ($p < 0.05$) was noted in the group that received fluoxetine alone (C) compared to the control group (A). Compared to the fluoxetine-treated group (C), a statistically significant decrease ($p < 0.05$) was seen in the group co-administered fluoxetine and ascorbic acid (D).

Figure 3: Effect of ascorbic acid on catalepsy in rats treated with fluoxetine. Each bar represents Mean ± S.E.M., with $^{a}p < 0.05$ against control. $^{b}p < 0.05$ represents a significant difference from FXT; the number of rats per treatment group = 8. FXT: fluoxetine, AsA: ascorbic acid.



Effects of Ascorbic Acid on Anxiety-Related Behaviors in Fluoxetine-Treated Rats.

Figure 4 shows the effects of ascorbic acid on time spent in the open arm in rats treated with fluoxetine. Sole administration of ascorbic acid in group B was associated with a statistically significant increase ($p < 0.05$) compared to the control group. A statistically significant decrease was observed in the fluoxetine-treated group (C) compared to the control (A) and the ascorbic acid-administered group (B). Moreover, co-administration of fluoxetine and ascorbic acid in group D was associated with a statistically significant increase ($p < 0.05$) in the time spent in the open arm compared to group D.

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XII Issue XI November 2025

Figure 4: Effect of ascorbic acid on the time spent in the open arm in rats treated with fluoxetine. Each bar represents Mean ± S.E.M., with $^{a}p < 0.05$ against control. $^{b}p < 0.05$ represents a significant difference from FXT; the number of rats per treatment group n=8. FXT: fluoxetine, AsA: ascorbic acid.

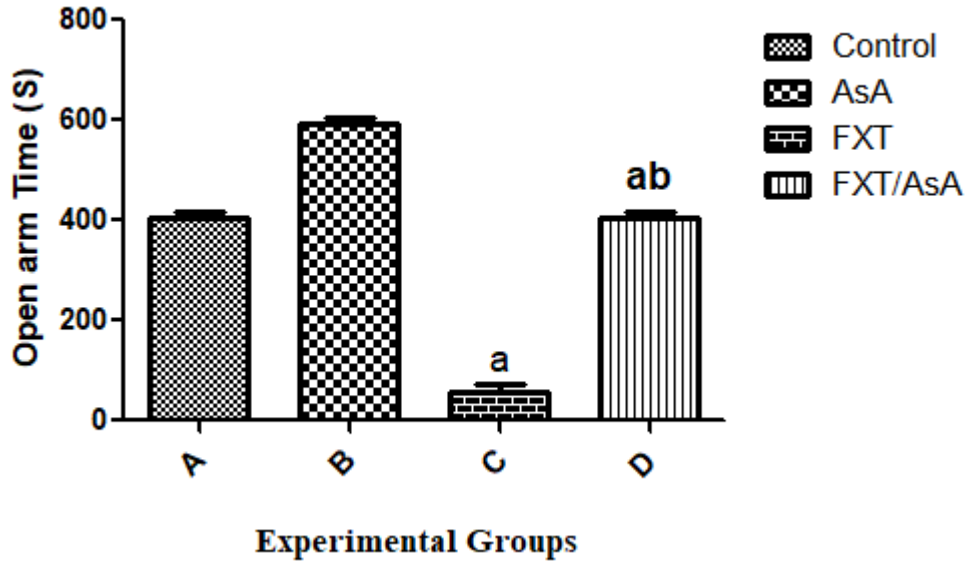
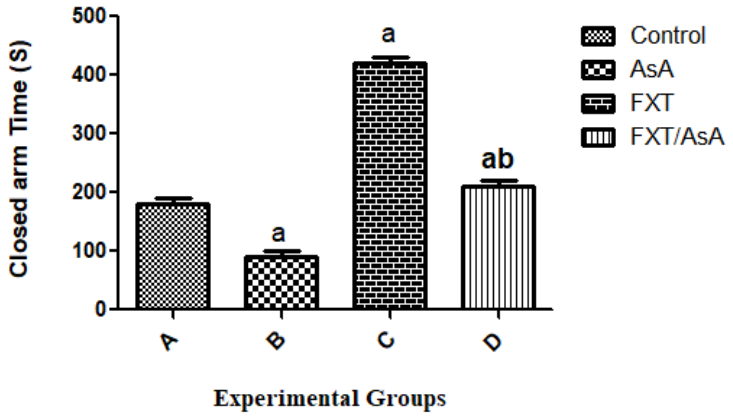


Figure 5 shows the effects of ascorbic acid on time spent in the closed arm in rats treated with fluoxetine. Sole administration of ascorbic acid in group B was associated with a statistically significant decrease ($p < 0.05$) compared to the control group. A statistically significant increase was observed in the fluoxetine-treated group (C) compared to the control (A) and the ascorbic acid-administered group (B). Moreover, co-administration of fluoxetine and ascorbic acid in group D was associated with a statistically significant decrease ($p < 0.05$) in the time spent in the open arm

Figure 5: Effect of ascorbic acid on the time spent in the closed arm in rats treated with fluoxetine. Each bar represents Mean ± S.E.M., with $^{a}p < 0.05$ against control. $^{b}p < 0.05$ represents a significant difference from FXT; the number of rats per treatment group, n=8. FXT: fluoxetine, AsA: ascorbic acid.



Effects of Ascorbic Acid on sociability in fluoxetine-treated rats.

Figure 6 shows the effects of ascorbic acid on the interaction time in seconds (s) with the empty chamber and social stimulus (a strange rat) in rats treated with fluoxetine. On the empty chamber interaction, a statistically significant increase ($p < 0.05$) was observed in the fluoxetine-treated group (C) compared to the control (A), while the co-administration of fluoxetine and ascorbic acid in group D was associated with a statistically significant decrease ($p < 0.05$) in the interaction time with the empty chamber. Moreover, during the time spent with the social stimulus, a statistically significant decrease was observed in the fluoxetine-treated group (C) compared to the control (A) and the ascorbic acid-administered group (B). However, the co-administration of fluoxetine and ascorbic acid in group D was associated with a statistically significant increase ($p < 0.05$) in the interaction time with social stimulus compared to group C.

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XII Issue XI November 2025

Figure 6: Effect of ascorbic acid on the interaction time with the empty chamber and the social stimulus in fluoxetine treated rats. Each bar represents Mean ± S.E.M. The number of rats per treatment group, n=8. FXT: fluoxetine, AsA: ascorbic acid.

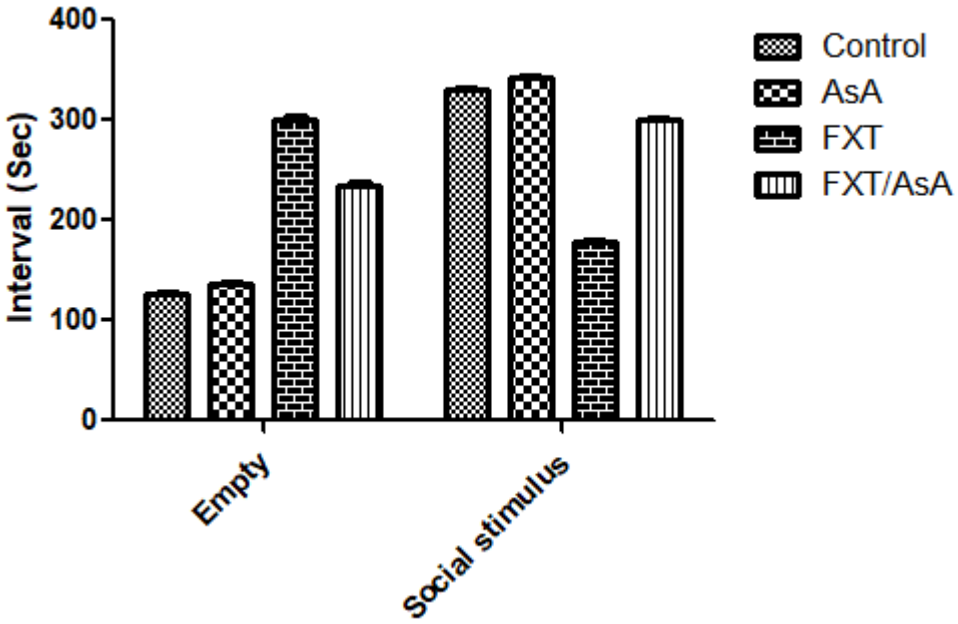
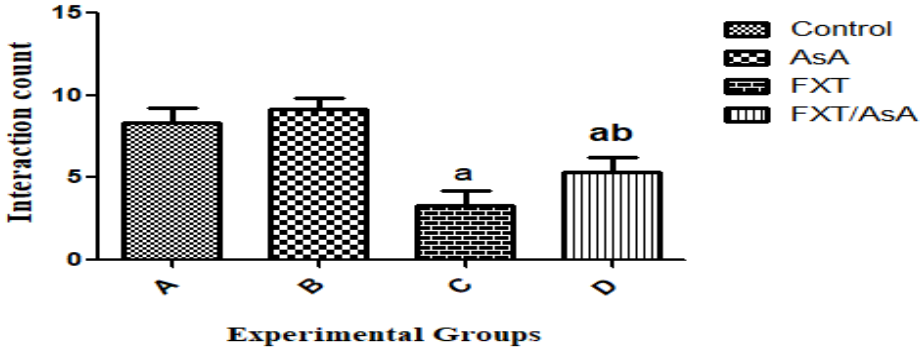


Figure 7 shows the effects of ascorbic acid on the number of interactions between the rats treated with fluoxetine and the social stimulus. A statistically significant decrease ($p < 0.05$) was observed in the fluoxetine-treated group (C) compared to the groups A and B, while the co-administration of fluoxetine and ascorbic acid in group D was associated with a statistically significant increase ($p < 0.05$) compared to group C.

Figure 6: Effect of ascorbic acid on the interaction time with the empty chamber and the social stimulus in fluoxetine treated rats. Each bar represents Mean ± S.E.M. with $^{a}p < 0.05$ against control. $^{b}p < 0.05$ represents a significant difference from FXT. The number of rats per treatment group, n=8. FXT: fluoxetine, AsA: ascorbic acid.



DISCUSSION

The impact of fluoxetine on daily feed intake, relative change in body weight, catalepsy score (a measure of muscular rigidity and the inability to correct an externally imposed abnormal posture), time spent in the open arm, and closed arm of the elevated plus maze, as well as the sociability, was evaluated.

Administration of the commonly prescribed antidepressant drug in this study shows some debilitating effects, as seen with the significant decrease in daily feed intake and loss of body weight in the group solely administered fluoxetine. While this result is in corroboration with clinical trials that reported similar effects (21), it has not been documented as a threat to human health in clinical trials. However, an extended and unmonitored significant loss of appetite and weight loss could further result in other complications, such as fatigue and dizziness, as well

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XII Issue XI November 2025

as other psychological effects (22). The calorie deficit, often resulting from loss of appetite, is a justification for the accompanied weight loss in the same group. Interestingly, the ameliorative effects of ascorbic acid were observed in this study, with both the daily feed intake and relative change in body weight being significantly increased in the group that was co-administered fluoxetine and Ascorbic acid.

Furthermore, the catalepsy score, a measure of muscular rigidity as examined in this study, reveals an association between the fluoxetine usage and muscular rigidity, with the catalepsy score significantly increasing with its sole administration. Fluoxetine's ability to inhibit calcium entry further interferes with the calcium signal, which alters muscle tone and contractility (23). While fluoxetine does not directly deplete striatal dopamine levels, its usage is known to exacerbate decreased striatal dopamine activities (24). A bidirectional relationship exists between dopamine metabolism and oxidative stress; dopamine metabolism generates reactive oxygen species, a hallmark of oxidative stress (25). While fluoxetine is commonly known to reverse oxidative stress in clinical trials and animal studies (26), its chronic administration is shown to induce oxidative stress in animal studies (27). However, the alleviating impact of Ascorbic acid was appreciated with the decreased catalepsy score in the group that received both fluoxetine and Ascorbic acid. Study done by Zylinska. (2023) (28) shows that Ascorbic acid can modulate calcium signaling, a major process that was deregulated by fluoxetine usage. It is known that Ascorbic acid can inhibit and facilitate calcium signaling depending on beneficial calcium levels. Furthermore, ascorbic acid, a dopamine β-hydroxylase cofactor, indirectly enhances dopamine synthesis and also modulates dopamine levels through its antioxidant properties (29). The results of the anxiety-related behaviours as observed with the time spent in the open and closed arms in this study contrast with some studies that reported the anxiolytic effects of fluoxetine. (30) Acute fluoxetine administration rapidly blocks serotonin reuptake, spiking extracellular 5-HT within one hour in animal models, eliciting anxiogenic effects before adaptations (31). Panicogenic effects observed with chronic fluoxetine administration in this study contrast with the established anxiogenic effects that are associated with its acute administration. On the other hand, the result of this study is in tandem with the findings that established an anxiogenic effect of fluoxetine usage as a symptom of its onset of action, although in acute administration (32). Administration of fluoxetine was associated with a significant decrease in the time spent in the open arm, while the increases significant in time spent in the closed arm; these effects were reversed with Ascorbic acid usage. This result raises a controversy as regards the beneficial effects of fluoxetine in this context. Loss of appetite and weight loss observed with fluoxetine usage could be a contributing factor to the anxiogenic traits seen with its administration, as studies have continued to establish a linkage between loss of appetite and psychological derailment, such as emotional distress and depression (33,34).

Although it was interesting to note that depression is not solely a result of loss of appetite, but an outcome of multiple interplays between decreased feed intake and some biological mechanisms that exacerbate wellness. A complex multifactorial impact on sociability test has been documented concerning the fluoxetine usage; (3) their study shows that acute administration of fluoxetine was associated with social avoidance and vigilance, and conversely increases sociability under acute administration, particularly under stress conditions. The time spent with the social stimulus, empty chamber, and the interaction count with the social stimuli all reveal exacerbated effects of fluoxetine on social interaction. On the other hand, ascorbic acid mitigated these effects by enhancing the sociability in rats co-administered ascorbic acid and fluoxetine.

CONCLUSION

This study reveals the debilitating effects of fluoxetine administration on daily feed intake, relative change in body weight, catalepsy test, anxiety-related behaviors, and sociability in the treatment of depressive disorder. Although its usage is generally considered safe in clinical trials, except about its well-established adverse effects on sperm health. Several instances have been seen where a drug that has been considered safe was banned due to repeated reports of its adverse effects. Could there be a complex interplay that underlies its yet-approved adverse effects as seen in this study?

Further research is necessary to evaluate and ascertain the chronic and acute administration of fluoxetine, particularly on the anxiety-related behaviours; such findings will be more precise if the levels of some key oxidative stress markers and the histomorphology of brain regions for mood and sociability are evaluated. Moreover, translation of these effects to humans will require further studies.

Conflict of Interest

The authors declared none

ACKNOWLEDGEMENTS

None

REFERENCES

1. Ajose, O., & Olofinjana, O. (2023). Fluoxetine in children and adolescents with major depressive disorder: A systematic meta-analysis of randomized controlled trials. Journal of Child and Adolescent Psychopharmacology, 33(1), 12-22. https://doi.org/10.1089/cap.2022.0017
2. Beasley, C. M., Jr, Koke, S. C., Nilsson, M. E., & Gonzales, J. S. (2000). Adverse events and treatment discontinuations in clinical trials of fluoxetine in major depressive disorder: an updated meta-analysis. Clinical therapeutics, 22(11), 1319–1330. https://doi.org/10.1016/s0149-2918(00)83028-3
3. Grieb, Z. A., Voisin, D. A., Terranova, J. I., Norvelle, A., Michopoulos, V., Huhman, K. L., & Albers, H. E. (2022). Acute administration of fluoxetine increases social avoidance and risk assessment behaviors in a sex- and social stress-dependent manner in Syrian hamsters (Mesocricetus auratus). Pharmacology, biochemistry, and behavior, 214, 173353. https://doi.org/10.1016/j.pbb.2022.173353
4. Garlow, S. J., Kinkead, B., Thase, M. E., Judd, L. L., Rush, A. J., Yonkers, K. A., Kupfer, D. J., Frank, E., Schettler, P. J., & Rapaport, M. H. (2013). Fluoxetine increases suicide ideation less than placebo during treatment of adults with minor depressive disorder. Journal of psychiatric research, 47(9), 1199–1203. https://doi.org/10.1016/j.jpsychires.2013.05.025
5. Flores-Ramirez, F. J., Themann, A., Sierra-Fonseca, J. A., Garcia-Carachure, I., Castillo, S. A., Rodriguez, M., Lira, O., Preciado-Piña, J., Warren, B. L., Robison, A. J., & Iñiguez, S. D. (2021). Adolescent fluoxetine treatment mediates a persistent anxiety-like outcome in female C57BL/6 mice that is ameliorated by fluoxetine re-exposure in adulthood. Scientific reports, 11(1), 7758. https://doi.org/10.1038/s41598-021-87378-6
6. Plevin, D., & Galletly, C. (2020). The neuropsychiatric effects of vitamin C deficiency: a systematic review. BMC psychiatry, 20(1), 315. https://doi.org/10.1186/s12888-020-02730-w
7. Innocent Effiom Offiong, Adeshina John Ajibade, Foluso Olamide Ojo, Kehinde Busuyi David & Folorunso Kolade Pelumi. (2024). Effects of Vitamin C on Aluminum Chloride- Induced Neurotoxicity on the Hippocampal Cortex of Adult Wistar Male Rats. Asian Journal of Medicine and Health, 22(10), 80–101. https://doi.org/10.9734/ajmah/2024/v22i101106
8. Travica, N., Ried, K., Sali, A., Scholey, A., Hudson, I., & Pipingas, A. (2017). Vitamin C Status and Cognitive Function: A Systematic Review. Nutrients, 9(9), 960. https://doi.org/10.3390/nu9090960
9. Kumar, R. S., Narayanan, S. N., & Nayak, S. (2009). Ascorbic acid protects against restraint stress-induced memory deficits in Wistar rats. Clinics (Sao Paulo, Brazil), 64(12), 1211–1217. https://doi.org/10.1590/S1807-59322009001200012
10. Matisz, C. E., Badenhorst, C. A., & Gruber, A. J. (2021). Chronic unpredictable stress shifts rat behavior from exploration to exploitation. Stress (Amsterdam, Netherlands), 24(5), 635–644. https://doi.org/10.1080/10253890.2021.1947235
11. Matallah, A., Guezi, R., & Bairi, A. (2022). Repeated restraint stress induced neurobehavioral and sexual hormone disorders in male rats. AIMS neuroscience, 9(2), 264–276. https://doi.org/10.3934/Neuroscience.2022014
12. Salami, S. A., Oreagba, F. O., Salahdeen, H. M., Olatunji-Bello, I. I., & Murtala, B. A. (2023). Vitamin C supplementation modulates crude oil contaminated water induced gravid uterine impaired contractile mechanism and foetal outcomes in Wistar rats. Journal of complementary & integrative medicine, 20(3), 548–555. https://doi.org/10.1515/jcim-2023-0081
13. Jayakumar, S., Raghunath, G., Ilango, S., Vijayakumar, J., & Vijayaraghavan, R. (2017). Effect of Fluoxetine on the Hippocampus of Wistar Albino Rats in Cold Restraint Stress Model. Journal of clinical and diagnostic research : JCDR, 11(6), AF01–AF06. https://doi.org/10.7860/JCDR/2017/26958.9953
14. García, J., López-Ibor, J., & Sánchez, S. (2013). How to weigh wild animals without causing stress. PLoS ONE, 8(2), e56302. https://doi.org/10.1371/journal.pone.0056302

15. Ojo F.O., Hassan L.A., Olaniyi O.S., Adetoro E.K., Lawal R.T. and Lawal M.B. Zingiber Officinale supplemented diet reversed lead-induced oxidative stress and cerebral cortex injuries in adult female Wistar rats. J Exp Clin Anat 2025; 22(1):22-26. https://dx.doi.org/10.4314/jeca.v22i1.3
16. Szabó, J., Renczés, E., Borbélyová, V., Ostatníková, D., & Celec, P. (2024). Assessing sociability using the Three-Chamber Social Interaction Test and the Reciprocal Interaction Test in a genetic mouse model of ASD. Behavioral and brain functions : BBF, 20(1), 24. https://doi.org/10.1186/s12993-024-00251-0.
17. Onaolapo, O. J., Olopade, J. O., & Onaolapo, A. Y. (2012). Effect of sertraline on 6-hydroxydopamine-induced catalepsy in hemiparkinsonian rats. Annals of Biological Research, 3(6), 3062-3066.
18. Luciani, K. R., Frie, J. A., & Khokhar, J. Y. (2020). An open source automated bar test for measuring catalepsy in rats. eNeuro, 7(3), ENEURO.0488 19.2020. https://doi.org/10.1523/ENEURO.0488-19.2020
19. Onaderu TA, onaolapo OJ, onaolapo AY Post-conceptional melatonin administration mitigates changes in neurobehaviour and cerebral cortex histomorphology in prenatal sodium valproate-exposed rats. Acta Bioscientia 2024:1(1);38-45 https://doi.org/10.71181/actabioscientia
20. Tong, G., Zhang, C., Li, H., Gao, X., Velu, P., Safargar, M., Prabahar, K., Xie, H., & Wang, X. (2025). The impact of fluoxetine on obesity and diabetes-related biomarkers in overweight and obese individuals: a systematic review and meta-analysis of randomized controlled trials. BMC psychiatry, 25(1), 977. https://doi.org/10.1186/s12888-025-07441-8
21. Liu, L., Zhang, X., Xue, J., Zhao, L., Tang, P., Tian, Y., Fan, H., Hao, M., Zhao, X., Geng, F., Mo, D., Xia, L., & Liu, H. (2025). Associations between appetite loss and clinical features as well as inflammatory cytokines in adolescents with major depressive disorder. Frontiers in psychiatry, 16, 1583060. https://doi.org/10.3389/fpsyt.2025.1583060
22. Serralde-Zuñiga, A. E., González-Garay, A. G., Rodríguez-Carmona, Y., & Meléndez-Mier, G. (2022). Use of Fluoxetine to Reduce Weight in Adults with Overweight or Obesity: Abridged Republication of the Cochrane Systematic Review. Obesity facts, 15(4), 473–486. https://doi.org/10.1159/000524995
23. Kobayashi, K., Haneda, E., Higuchi, M., Suhara, T., & Suzuki, H. (2012). Chronic fluoxetine selectively upregulates dopamine D_1-like receptors in the hippocampus. Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology, 37(6), 1500–1508. https://doi.org/10.1038/npp.2011.335
24. Weng, M., Xie, X., Liu, C., Lim, K. L., Zhang, C. W., & Li, L. (2018). The Sources of Reactive Oxygen Species and Its Possible Role in the Pathogenesis of Parkinson's Disease. Parkinson's disease, 2018, 9163040. https://doi.org/10.1155/2018/9163040
25. Novío, S., Núñez, M. J., Amigo, G., & Freire-Garabal, M. (2011). Effects of fluoxetine on the oxidative status of peripheral blood leucocytes of restraint-stressed mice. Basic & clinical pharmacology & toxicology, 109(5), 365–371. https://doi.org/10.1111/j.1742-7843.2011.00736.x
26. Ganguly, R., Kumar, R., & Pandey, A. K. (2022). Baicalin provides protection against fluoxetine-induced hepatotoxicity by modulation of oxidative stress and inflammation. World journal of hepatology, 14(4), 729–743. https://doi.org/10.4254/wjh.v14.i4.729
27. Zylinska, L., Lisek, M., Guo, F., & Boczek, T. (2023). Vitamin C Modes of Action in Calcium-Involved Signaling in the Brain. Antioxidants (Basel, Switzerland), 12(2), 231. https://doi.org/10.3390/antiox12020231
28. Harrison, F. E., & May, J. M. (2009). Vitamin C function in the brain: vital role of the ascorbate transporter SVCT2. Free radical biology & medicine, 46(6), 719–730. https://doi.org/10.1016/j.freeradbiomed.2008.12.018
29. Farhan, M., & Haleem, D. J. (2016). Anxiolytic profile of fluoxetine as monitored following repeated administration in animal rat model of chronic mild stress. Saudi pharmaceutical journal : SPJ : the official publication of the Saudi Pharmaceutical Society, 24(5), 571–578. https://doi.org/10.1016/j.jsps.2015.03.006
30. Suzuki, Y., Yamaguchi, Y., & Okabe, S. (2023). An exploratory study of behavioral traits and the establishment of social relationships in laboratory rats. PLoS ONE, 18(12), e0295280. https://doi.org/10.1371/journal.pone.0295280
31. Grieb, Z. A., Voisin, D. A., Terranova, J. I., Norvelle, A., Michopoulos, V., Huhman, K. L., & Albers, H. E. (2022). Acute administration of fluoxetine increases social avoidance and risk assessment behaviors in a sex- and social stress-dependent manner in Syrian hamsters (Mesocricetus auratus). Pharmacology, biochemistry, and behavior, 214, 173353. https://doi.org/10.1016/j.pbb.2022.173353

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XII Issue XI November 2025

32. Simmons, W. K., Burrows, K., Avery, J. A., Kerr, K. L., Bodurka, J., Savage, C. R., & Drevets, W. C. (2016). Depression-Related Increases and Decreases in Appetite: Dissociable Patterns of Aberrant Activity in Reward and Interoceptive Neurocircuitry. The American journal of psychiatry, 173(4), 418–428. https://doi.org/10.1176/appi.ajp.2015.15020162
33. Simmons, W. K., Burrows, K., Avery, J. A., Kerr, K. L., Taylor, A., Bodurka, J., Potter, W., Teague, T. K., & Drevets, W. C. (2020). Appetite changes reveal depression subgroups with distinct endocrine, metabolic, and immune states. Molecular psychiatry, 25(7), 1457–1468. https://doi.org/10.1038/s41380-018-0093-6