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*Research Article*

# Antidepressant-Like Effects of *Cinnamomum verum* on Open-Space Forced Swim-Induced Depression in Mice

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**Summary:** Depression is a mental disorder characterized by depressive episodes, such as low mood, low self-esteem, feeling of guilt, and poor concentration. Depression has a high comorbidity with cognitive impairments. Studies have shown that cinnamon has anti-inflammatory antiviral, antihypertensive, antioxidant and anti-diabetic potentials. Therefore, the aim of the research was to assess the antidepressant effect of cinnamon on open-space forced swim-induced depression in mice. Twenty-five (25) Swiss albino mice were grouped into five groups (n=5). Group I: control (negative control) exposed to open-space forced swim test (OSFST) without any treatment, Groups II, III and IV received graded doses of Cinnamon 12.5, 25, and 50 mg/kg, group 5 (positive control) received fluoxetine 20 mg/kg orally. The animals were subjected to OSFST, Open Field Test (Line Crossing) and Novel Object Recognition Test (NORT). Administration of cinnamon showed decreased immobility time (behavioural despair) in OSFST compared to control and fluoxetine groups ($p < 0.05$). However, no statistically significant effect was observed in line crossing (locomotor activity) and the discrimination ratio of NORT (non-spatial short-term memory) between cinnamon administered groups and the control group. In conclusion, cinnamon has shown antidepressant-like effect in open-space forced swim-induced depression in mice.

**Keywords***: Cinnamon, Depression, Cognitive impairment, Immobility time, Behavioural despair*

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## INTRODUCTION

Depression is a common mental disorder, characterized by persistent sadness and also loss of interest in pleasurable activities that the individual once enjoyed as well as behavioural despair (WHO,2017; Yusha'u *et al.*., 2017). It also affects sleep and appetite together with extreme fatigue (Calheiros *et al.*., 2016; Yusha'u *et al.*., 2021). One in four people in the world is affected by mental disorders or neurological disorders at some point in their lives (Simplice *et al.*., 2014). Almost 450 million people currently suffer from such conditions, this makes mental disorders to be among the leading cause of ill-health and disability worldwide (Simplice *et al.*., 2014). In Africa, about 29.19 million people suffer from depression, with over 7 million in Nigeria (Gbadamosi *et al.*., 2022). Furthermore, a comorbid condition associated with depression is anxiety, together, these two are debilitating conditions that greatly impair psychological, social, and emotional wellbeing (Kalin, 2020).

Depression often leads to cognitive impairment due to a reduced level of neurotransmitters like acetylcholine and increased levels of cytokines such as interleukin (IL)-1, IL-6 and tumour necrosis factor alpha (TNF-α) that control mood in the brain (Mustapha *et al.*., 2021). It was found that prolonged therapy with some antidepressants like SSRI's may be associated with cognitive side effects in adult subjects with MDD (Bortolato *et al.*., 2016). Several oxidative disturbances in depression have been reported in clinical and preclinical studies, including lipid peroxidation, decrease catalase (CAT) and superoxide dismutase (SOD) activities which were often associated with serotonergic and noradrenergic systems dysfunctions (Calheiros *et al.*., 2016). In depressed patients peripheral blood sample, increase in granulocytes and macrophage have been reported which was associated with the increase in pro-inflammatory cytokines levels commonly seen in depressed patients (Dowlati *et al.*., 2010).

*Cinnamomum verum* (Cinnamon) the eternal tree of tropical medicine, belongs to the Lauraceae family. Cinnamon is one of the most important spices used daily by people all over the world is commonly found in cooking ingredients worldwide and is believed to provide health benefits. Cinnamon contains various chemical compounds like flavonoid and terpenoid that work as an antidepressant via influencing BDNF synthesis and secretions, and exerting anti-inflammatory and anti-oxidant effects (Jana *et al.*., 2013). The most common and effective class of antidepressants used is the selective serotonin reuptake inhibitors (SSRI's) which include fluoxetine, paroxetine and

citalopram. They replaced the tricyclic antidepressants class due to less toxicity and other side effects(Khawam, 2006; Brent, 2016;). However, side effects reduce compliance to SSRI's usage; some of these side effects include ideation of suicide, anxiety, insomnia, erectile dysfunction and nightmares (Yaseen and Mohammed, 2020). Scientific reports showed that cinnamon extract has neuro-protective, hepato-protective, cardio-protective, gastro-protective, and anti-inflammatory properties due to its phenolic acid and flavonoid compounds (Santos and Guilherme, 2018; Prabhashini *et al.*., 2019).

Cinnamaldehyde is the major component of cinnamon amongst other components. Cinnamaldehyde metabolism in the body produces sodium benzoate (NaB) metabolite, where NaB is thought to be able to increase BDNF expression in rat (Jana *et al.*., 2013). Proanthocyanidin is proved to be protective against depression and anxiety, where it has antidepressant activity by increasing BDNF expression in the hippocampus and frontal cortex of chronically stressed mice (Martinowich and Lu, 2008). Hence, the aim of this study is to assess the effects of aqueous bark extract of cinnamon on depression and non-spatial short-term memory in mice.

## MATERIALS AND METHODS

**Drugs and Reagents:** *Cinnamomum verum* was purchased from Arabian-Syrian Company, South City Plaza, Selangor, Darul-Ehsan, Malaysia. Fluoxetine was purchased from VS International Private Limited Plot Number 17 and 18, Golden Indl estate Somnath Road, Dabhel, Daman-396215, India. Marketed by Fidson Healthcare Private Limited Company, 268, Ikorodu Road, Obanikoro, Lagos-Nigeria. NAFDAC registration number: 04-8881.

**Aqueous bark extraction of Cinnamomum verum:** The aqueous bark extract of *Cinnamomum verum* was prepared according to the method of Abdeen *et al.*. (2018), with some modifications. Cinnamon bark 500 g was grinded to powder form to reduce its size. The powder form of cinnamon bark was dissolved in 3 litres of water for 24 hours to avoid fermentation. The dissolved *Cinnamomum verum* bark was then filtered and the residue was removed. The water content was evaporated so as to get the solid aqueous form of cinnamon.

**Experimental Design;** Twenty-five (25) healthy Swiss albino mice (18-26 g) of both sexes aged 6-8 weeks were purchased from the Animal House, Department of Human Physiology, Faculty of Basic Medical Sciences, Ahmadu Bello University (A.B.U) Zaria-Nigeria. They were housed in plastic cages containing sawdust bedding and fed with pellets made from grower's mash, maize offal as binder and water ad libitum. Ethical clearance was obtained from Ahmadu Bello University Committee on Animal Use and Care with Approval Number: ABUCAUC/2021/008. The animals were grouped into five groups. Each group consisting of five mice (n=5). Daily administration of aqueous bark extract of cinnamon was carried for 2 weeks via oral route. Group I were exposed to OSFST without any treatment (Negative control). Groups II, III and IV were administered graded doses of aqueous bark extract of cinnamon 12.5 mg/kg, 25 mg/kg and 50 mg/kg respectively (Parisa *et al.*., 2020), While Group V, were treated with fluoxetine 20 mg/kg (Positive control) (Hu *et al.*., 2016).

### Neurobehavioural Assays

**Open-space forced swim test:** The open space forced swim test was conducted as described in Figure 1 (Yusha'u *et al.*., 2021)

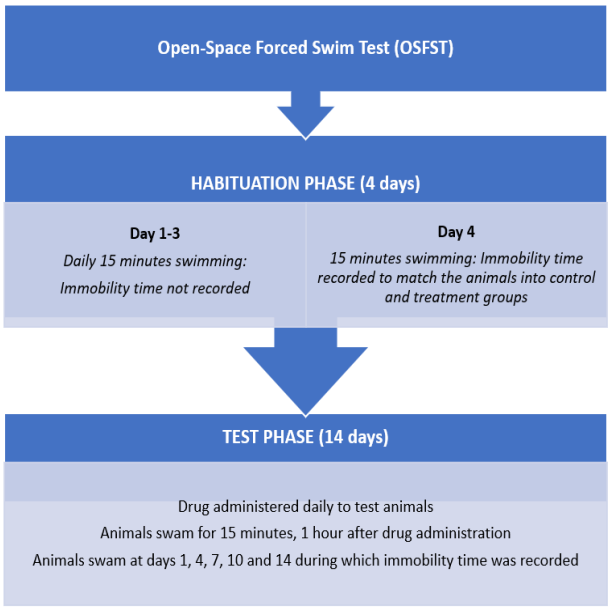


**Figure 1:**
Schedule for open-space forced swim test (Yusha'u *et al.*., 2021)

**Determination of Line crossing using open field test:** Line crossing (an index of locomotor activity) occurs when the mouse crosses one of the grid lines which separate the squares in the open field with all four limbs (Bagewadi *et al.*., 2015). This is a parameter observed by conducting the open field test with an open field test apparatus (50-L × 50-W × 30-H cm). The floor of the apparatus is compartmentalized into 5 × 5 = 25 square areas (10 cm square × 25) and central 4 × 4 = 16 square areas are considered as the central part. Before the testing phase, the mouse was placed at the centre of the floor space and allowed to acclimatize to the surrounding area for 2 minutes. Thereafter, mice were placed into the apparatus from the left-hand corner and allowed to move freely to explore the open field arena (test session) individually for 5 min (Bagewadi *et al.*., 2015).

**Measurement of non-spatial short-term memory using novel object recognition test:** The novel object recognition test (NORT) apparatus is used in the assessment of non-spatial short-term memory. The apparatus is a rectangular arena that is made up of opaque plastic and measures 42 cm × 52 cm. The walls are 40 cm high. It involves two phases: training and testing (Zhang *et al.*., 2012). The mouse is placed in the arena for 5 minutes, where it encountered two identical sample objects (testing phase). At the end of the training phase, the mouse was placed back in its home cage for a 5minutes delay (±15 seconds) and the NORT apparatus with the objects wiped with 70% ethanol to avoid olfactory cue. For the testing phase, animals were returned to the arena for 3 minutes where one of the familiar objects was replaced with a novel object. Successful novel object

recognition is indexed by greater exploration of the novel object compared to the familiar object. The discrimination ratio was calculated as the total time spent exploring the recently seen object (novel object) divided by the time exploring both objects sampled at the test (familiar objects) (Thur *et al.*., 2014).

**Statistical analysis:** Results were expressed as Mean ± SEM. All analysis were done using one way analysis of variance (ANOVA), except data for OSFST which was analysed by two-way repeated measures ANOVA and time spent on familiar and novel objects in NORT analysed by independent sample T-test. Where significance, Tukey's post-hoc test was conducted for multiple comparison using GraphPad prism version 8.0.2. for windows. Values of $p < 0.05$ were considered statistically significant.

## RESULTS

**Depression analysis using open space forced swim test:** Two-way repeated measures ANOVA was conducted to access the effects of treatments and time on immobility time as a depression index. There was no statistically significant effect of time on the different treatment groups [F (3.004, 60.07) =2, p = 0.05]. There was interaction between the treatments and time [F (16,80) = 8.05, $p < 0.001$]. Similarly, significant effects were observed between treatment groups [F (4,20) = 21.0, $p < 0.001$]. At day 1, the immobility time was decreased in CN 50 mg/kg group when compared with untreated negative control group. At day 4, the immobility time was decreased in CN 12.5 mg/kg and fluoxetine group when compared with the negative control group. At day 14 all the treatment groups had less immobility time when compared with the negative control group.

**Assessment of locomotor activity with open field test:** As shown in Figure 3, one-way ANOVA revealed no statistically significant ($p > 0.05$) difference in frequency of line crossing (an index of locomotor activity) between all the treatment groups when compared with the OSFST untreated negative control group.

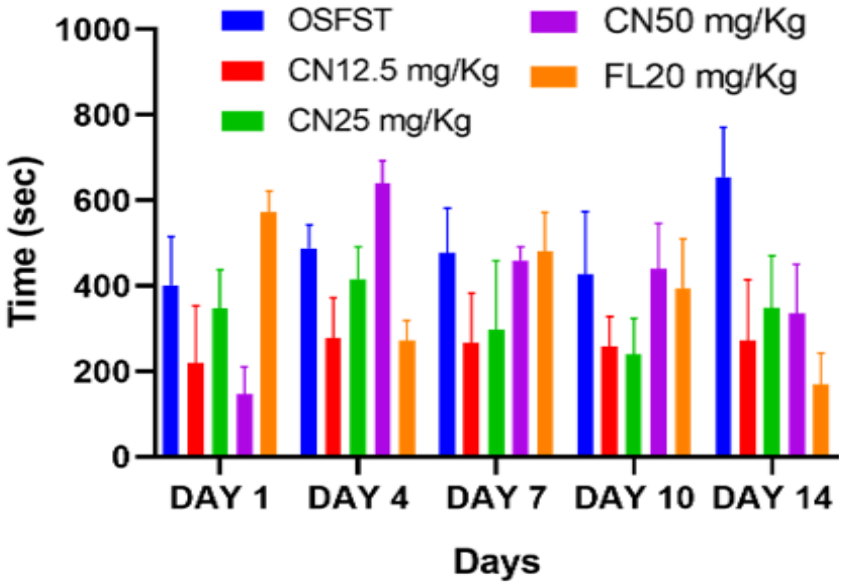


**Figure 2**: Effects of aqueous bark extract of cinnamon on depression in mice exposed to open-space forced swim test. Results expressed as mean ± SEM, (n=5), * showed statistically significant difference compared to control. # Showed statistically significant different when compared with fluoxetine, CN= Cinnamon, Flu= fluoxetine.

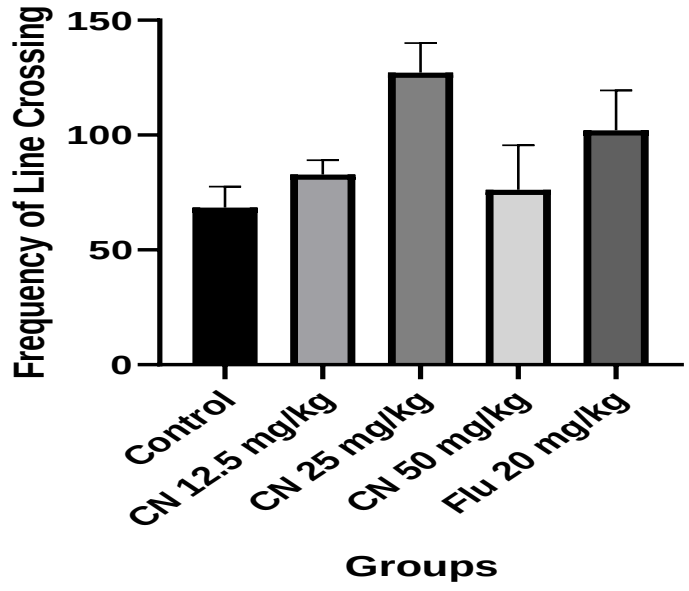


**Figure 3:** Effects of aqueous bark extract of cinnamon on locomotor activity in mice exposed to open-space forced swim test using open field test. Results presented as mean SEM: The mean difference was not statistically significant different $p > 0.5$ (n=5), using one-way ANOVA, Graph pad prism version 8.0.2, CN: Cinnamon, Flu: Fluoxetine.

**Table 1:**
Effects of aqueous bark extract of cinnamon on time spent on familiar and novel objects using novel object recognition task in mice subjected to open-space forced swim test

| Groups | Time Spent on Familiar Object (Seconds) Mean ± SEM | Time Spent on Novel Object (Seconds) Mean ± SEM | P-value | t-value |
|---|---|---|---|---|
| Control | 2.8 ± 0.97 | 4.0 ± 1.38 | 0.497 | 0.712 |
| CN 12.5 mg/kg | 5.8 ± 2.44 | 3.2 ± 0.73 | 0.337 | 1.021 |
| CN 25 mg/kg | 5.2 ± 2.44 | 9.0 ± 1.70 | 0.237 | 1.278 |
| CN 50 mg/kg | 2.0 ± 2.00 | 3.6 ± 1.47 | 0.537 | 0.645 |
| Flu 20 mg/kg | 2.4 ± 0.51 | 3.0 ± 0.71 | 0.511 | 0.688 |

Results presented as mean ± SEM, (n=5) using independent sample t-test, Graph pad prism version 8.0.2. CN: Cinnamon, Flu: Fluoxetine, OSFST: Open-Space Forced Swim Test

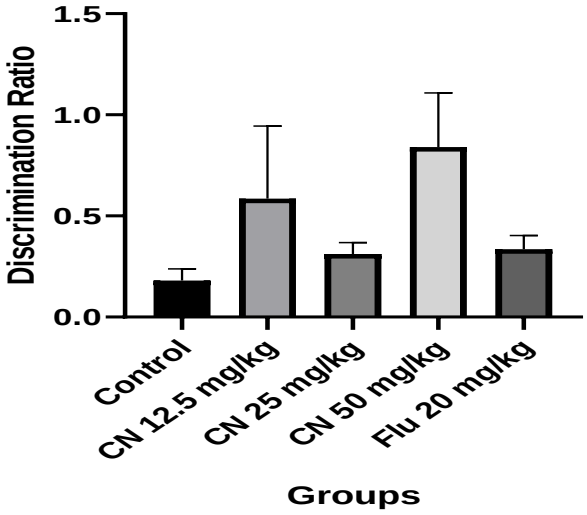


**Figure 4:**
Effect of aqueous bark extract of cinnamon on discrimination ratio in mice exposed to open-space forced swim test using novel object recognition task.
*Results presented as mean ± SEM, (n=5), the mean difference is not statistically significant compared to the control group using one-way ANOVA, Graph pad prism version 8.0.2, CN: Cinnamon, Flu: Fluoxetine.*

**Assessment of non-spatial short-term memory:** The discrimination ratio (an index of short-term memory) did not differ significantly ($p > 0.05$) between the treatment groups and the untreated OSFST group as revealed by one-way ANOVA (Figure 4). Similarly, as shown in Table 1, independent sample T-test showed no statistically significant ($p > 0.05$) difference between time spent on the novel object when compared with the familiar object of the NORT in all the treatment groups as well as the OSFST negative control group.

## DISCUSSION

Depression is a common mental disorder, characterized by persistent sadness and also loss of interest in pleasurable activities that the individual once enjoyed as well as behavioural despair (WHO,2017; Yusha'u *et al.*., 2017). This study observed a decreased in immobility time (an index of depression) in OSFST induced-depressed mice treated with CN 12.5 mg/kg, CN 50 mg/kg and Flu 20 mg/kg in swimming days 1, 4, 7 and 14 when compared with control. The findings of this study is in conformity with the study of Parisa *et al.*., (2020) that stated cinnamon possessed the potential to reduce the duration of immobility and potentially reduce symptoms of depression. The main compound contained in cinnamon is cinnamaldehyde, which is a phenol group. Phenols have anti-inflammatory effects, which are believed to be able to inhibit the inflammatory cascade that forms the basis of the pathogenesis of depressive disorders (Partan *et al.*., 2018). Furthermore, Sohrabi *et al.*. (2017) conducted a depressive-like behaviour test using cinnamon essential oil. They observed significant improvements in the immobility time during forced swim test (FST) and tail suspension test (TST).

The study also showed no difference in frequency of line crossing (an index of locomotor activity) between all the treatment groups when compared with the OSFST untreated negative control group. The locomotor activity was used to screen out antidepressants from psychotonics or psychostimulants. Antidepressants do not significantly improve line crossing in OFT while psychotonics or psychostimulants like amphetamine does so. This is in conformity with the study of Yusha'u *et al.*. (2021) and previous report of Cryan *et al.*. (2005) who reported that psychotonics are clinically ineffective antidepressants. They show anti-immobility effects in the TST but increase locomotor activity. Psychostimulants are a broad class of sympathomimetic drugs (Wood *et al.*., 2014). Psychostimulants are the most used psychotropic substances over the world. A psychostimulant can be defined as a psychotropic substance with the capacity to stimulate central nervous system. It causes excitation and elevated mood, as well as increased alertness and arousal. Its global effect is to speed up signals into the brain. Some examples of psychostimulants include amphetamine, cocaine, nicotine, caffeine (Favrod-coune & Broers, 2010).

The result of discrimination ratio showed that cinnamon and fluoxetine did not differ significantly with the OSFST only group. Contrary to (Kawatra and Rajagopalan, 2015; Kelestemur *et al.*., 2016) findings which states that cinnamon also exerts strong brain protective and pro-cognitive effects in various models of neurodegeneration. In addition, according to Modi *et al.*. (2016), oral administration of cinnamon and sodium benzoate (NaB) increased memory consolidation-induced activation of cAMP- response element binding protein (CREB) and expression of plasticity-related molecules in vivo in the hippocampus of poor learning mice and improved their memory and learning almost to the level observed in untreated good learning ones.

In conclusion aqueous bark extract of cinnamon shows an antidepressant-like effect on depressed mice exposed to OSFST but did not significantly affect non-spatial short-term memory and locomotor activity of the mice subjected to NORT and OFT respectively. However, there is need for further research on the effect of cinnamon on the brain biomarkers of depression and cognition.

## REFERENCES


Abdeen, A., Abdelkader, A., Abdo, M., Wareth, G., Aboubakr, M., Aleya, L., and Abdel-Daim, M. (2018). Protective effect of cinnamon against acetaminophen-mediated cellular damage and apoptosis in renal tissue. *Environmental Science and Pollution Research*, 26(1): 240-249. https://doi.org/10.1007/s11356-018-3553-2

Bagewadi, H. G., Ak, A. K., & Shivaramegowda, R. M. (2015). An Experimental Study to Evaluate the Effect of Memantine in Animal Models of Anxiety in Swiss Albino Mice. 2–6. https://doi.org/10.7860/JCDR/2015/13233.6287

Bortolato, B., Miskowiak, K. W., Köhler, C. A., Maes, M., Fernandes, B. S., Berk, M., & Carvalho, A. F. (2016). Cognitive remission : a novel objective for the treatment of major depression ? *BMC Medicine*, 1–18. https://doi.org/10.1186/s12916-016-0560-3

Brent, D. A. (2016). A n t i d e p re s s a n t s a n d Suicidality. *Psychiatric Clinics of NA*, 39(3), 503–512. https://doi.org/10.1016/j.psc.2016.04.002

Calheiros, M., Silva, C., Nádia, C., Sousa, S. De, Xavier, P., Gomes, L., Valente, G., Oliveira, D., Yvelize, F., Araújo, R., Coelho, N., Calheiros, J., Silva, G., Kalyne, L., Moreira, A., Macêdo, D., Maria, S., & Vasconcelos, M. (2016). Progress in Neuro-Psychopharmacology & Biological Psychiatry Evidence for protective effect of lipoic acid and desvenlafaxine on oxidative stress in a model depression in mice. *Progress in Neuropsychopharmacology & Biological Psychiatry*, 64,142–148. https://doi.org/10.1016/j.pnpbp.2015.08.002

Dowlati, Y., Herrmann, N., Swardfager, W., Liu, H., Sham, L., Reim, E. K., & Lanctôt, K. L. (2010). A Meta-Analysis of Cytokines in Major Depression. BPS, 67(5), 446–457. https://doi.org/10.1016/j.biopsych.2009.09.033

Favrod-coune, T., & Broers, B. (2010). The Health Effect of Psychostimulants: A Literature Review. 2333–2361. https://doi.org/10.3390/ph3072333

Hu, B., Doods, H., Treede, R., & Ceci, A. (2016). Neuroscience Letters Duloxetine and 8-OH-DPAT , but not fluoxetine , reduce depression-like behaviour in an animal model of chronic neuropathic pain. *Neuroscience Letters,* 619, 162–167. https://doi.org/10.1016/j.neulet.2016.03.019

Jana, A., Modi, K. K., Roy, A., Anderson, J. A., & Breemen, R. B. Van. (2013). Up-Regulation of Neurotrophic Factors by Cinnamon and its Metabolite Sodium Benzoate : Therapeutic Implications for Neurodegenerative Disorders. 739–755. https://doi.org/10.1007/s11481-013-9447-7

Kalin, N. H. (2020). The Critical Relationship Between Anxiety and Depression. May, 365–367. https://doi.org/10.1176/appi.ajp.2020.20030305

Kawatra, P., & Rajagopalan, R. (2015). Cinnamon : Mystic powers of a minute ingredient. 7, 1–6. https://doi.org/10.4103/0974-8490.157990

Kelestemur, T., Yulug, B., Burak, A., & Caglar, M. (2016). Neuroscience Letters Targeting different pathophysiological events after traumatic brain injury in mice : Role of melatonin and memantine. *Neuroscience Letters*, 612, 92–97. https://doi.org/10.1016/j.neulet.2015.11.043

Khawam, E. A. (2006). Side effects of antidepressants : An overview. 73(4).

Martinowich, K., & Lu, B. (2008). Interaction between BDNF and Serotonin : Role in Mood Disorders. 73–83. https://doi.org/10.1038/sj.npp.1301571

Mustapha, S., Oshafu, M. Y., Adam, U. M., Yusha'u, Y., & Daku, A. B. (2021). Influence of Antidepressant Medication on Short Term Memory in Chronic Mild Stress Mouse Model of Depression. 12(1), 22–28.

Parisa, N., Tamzil, N. S., Arroyantri, B., & Maritska, Z. (2020). Antidepresant effects of Cinnamon (*Cinnamomum burmannii*) extract in depressed induced rats using 3-minutes Tail Suspension method Antidepresant effects of Cinnamon ( Cinnamomum burmannii ) extract in depressed induced rats using 3-minutes Tail Suspension method. August 2019. https://doi.org/10.32539/bsm.v3i3.91

Partan, R. U. M. I., Hidayat, R., Saleh, M. G. S. I., Parisa, N., & Tanzil, N. I. A. S. (2018). Effect Of Supplementation Kayu Manis ( Cinnamomum Burmannii ) Extract In Neuronal Cell Death Protection In Wistar Rats Lir-Psychotic On Haloperidol Therapy. 11(2).

Santos, H. O., & Guilherme, A. R. (2018). Clinical Nutrition ESPEN To what extent does cinnamon administration improve the glycemic and lipid pro fi les ? Clinical Nutrition ESPEN, 1–9. https://doi.org/10.1016/j.clnesp.2018.07.011

Simplice, F. H., Emery, T. D., Abaissou, N., & Hervé, H. (2014). Enhancing Spatial Memory : Anxiolytic and Antidepressant Effects of Tapinanthus dodoneifolius ( DC ) Danser in Mice. 2014.

Thur, K. E., Nelson, A. J. D., & Cassaday, H. J. (2014). Ro 04-6790-induced cognitive enhancement : No effect in trace conditioning and novel object recognition procedures in adult male Wistar rats Pharmacology , Biochemistry and Behavior Ro 04-6790-induced cognitive enhancement : No effect in trace conditioning and novel object recognition procedures in adult male Wistar rats. November. https://doi.org/10.1016/j.pbb.2014.10.006

Wood, S., Sage, J. R., Shuman, T., & Anagnostaras, S. G. (2014). Psychostimulants and Cognition : A Continuum of Behavioral and Cognitive Activation. 15261(January), 193–221.

Yusha'u, Y., Muhammed, U. A., Nze, M., Egwuma, J. M., Igomu, O. J., and Abdulkadir, M. (2017). Modulatory Role of Rutin Supplement on Open Space Forced Swim Test Murine Model of Depression. 32(December), 201–205.

Yusha'u, Y, Mustapha, S., Umar, A. H., Imam, M. I., & Umar, B. (2021). Alpha-lipoic acid attenuates depressive symptoms in mice exposed to chronic unpredictable mild stress . 9(July), 58–68.

Yusha'u, Yusuf, Adam, U. M., Wahab, A. A., Ibrahim, M., & Saleh, A. (2021). OPEN ACCESS | RESEARCH NOTES Alpha-lipoic acid enhances short-term spatial memory of mice in open-space forced swim-induced depression mouse model.

Zhang, R., Xue, G., Wang, S., Zhang, L., Shi, C., & Xie, X. (2012). Novel Object Recognition as a Facile Behavior Test for Evaluating Drug Effects in A ␣ PP / PS1 Alzheimer ' s Disease Mouse Model. 31, 801–812. https://doi.org/10.3233/JAD-2012-120151.