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Research Article

Neuroprotective Effects of Sesame Oil on Depressive-Like Behaviours in Mice Subjected to Open-Space Forced Swim Test

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ABSTRACT
Depression is a mood disorder that causes a persistent feeling of sadness and loss of interest. This study investigated the neuroprotective effects of sesame oil on depressive-like behaviours in mice subjected to the open-space forced swim test (OSFST). This study was carried out using thirty (30) adult mice; the animals were randomly divided into six (6) groups of five (5) animals each. Group I received normal saline (10 ml/kg) only, group II received normal saline (10 ml/kg) + OSFST, group III, IV and V were subjected to OSFST and received Sesame oil (100, 200 and 400 mg/kg), respectively and group VI received Fluoxetine (20 mg/kg) + OSFST. All administrations were carried out through the oral route and lasted for twenty-one days. Neurobehavioural assessments were carried out at the end of the twenty-one days of the experiment. Brain tissues were collected for neurochemical determination of serotonin levels. The results showed that administration of sesame oil (100, 200 and 400 mg/kg) significantly ($p < 0.05$) decreased immobility time (behavioural despair) and increased sucrose index (an indicator of anhedonia). Administration of Sesame oil (SO) improved cognitive performance compared to the normal saline (10 ml/kg) + OSFST group. Sesame oil 100, 200, and 400 mg/kg) significantly ($p < 0.05$) increased serotonin level when compared to the normal saline (10 ml/kg) + OSFST group. These findings suggest that SO may be beneficial in attenuating OSFST-induced depression and cognitive dysfunction mediated via modulation of serotonin.

Keywords: Antidepressant-like effects; Behavioural despair; Depression; Open-space forced swim test (OSFST); Sesame oil

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INTRODUCTION

Depression is considered among the most common mental disorders worldwide, requiring the attention of over 322 million people, resulting in a prevalence of 4.4% globally, 5.4% in Africa, and 3.1% in Nigeria (WHO, 2019; Suraj *et al*., 2021). Between 1990 and 2017, the rise in the incidence of this disorder was 49.29%, causing the prevalence to rise from 162 to 241 million, reflecting an increase of 42% in Western sub-Saharan Africa (Liu *et al*., 2019; Jain *et al*., 2022). Clinically, depression is defined by feelings of sadness, anhedonia, insomnia, changes in appetite, fatigue, and problems with concentrating, also playing an essential part in deficits of everyday function and quality of life (WHO, 2025). Moreover, it is often found alongside conditions of chronic stress, memory loss, and hyperactivity of the hypothalamic-pituitary-adrenal axis, resulting in an increase in cortisol levels through corticotropin-releasing hormone over secretions (CRH) having increased cortisol levels secreted in the body (Grosso *et al*., 2014; Liu *et al*., 2018; Zhao *et al*., 2019).

The existing pharmacotherapeutic approach for depression, consisting of selective serotonin reuptake

inhibitors (SSRIs) such as fluoxetine, as well as serotonin/norepinephrine reuptake inhibitors (SNRIs), acts through the inhibition of the reuptake of serotonin (5-HT) and norepinephrine (NE) (Braund *et al*., 2021). Unfortunately, these therapies are associated with side reactions such as headaches, weight change, agitation, confusion, sexual dysfunction, nausea, somnolence, and increased cardiovascular risks, which in many instances require a dosage change or switch, potentially hindering their efficacy (Zhao *et al*., 2019; Thurfah *et al*., 2022). The aforementioned limitations highlight the important need for a safer and more effective alternative, especially in light of the constantly rising prevalence as well as the less-than-optimal management (Wang *et al*., 2025).

Sesame (*Sesamum indicum* L.), one of the four major oil plants in China, together with soybeans and peanuts, has been planted for more than 5,000 years and remains one of the largest producers of this crop in India, Sudan, Myanmar, China, and Tanzanian countries (Wei *et al*., 2022). Sesame seeds contain unsaturated fatty acids, proteins, vitamins, mineral substances, and fibers, which can be extracted into sesame oil (SO) by traditional methods (Thurfah *et al*., 2022). Sesame oil and its lignans, mainly sesamin and sesamol, possess diversified bioactivities, including antioxidant, anti-inflammatory, and lipid-lowerers (Wei *et al*., 2022). More specifically, sesamin suppresses the overexpression of cytokines (e.g., TNF-α, IL-6, IL-1β) induced by lipopolysaccharides in microglial cells, protects against the disruption of the blood-brain barrier, and crosses the blood-brain barrier, and sesamol regulates the gut microbiota to abate the state of anxiety-like behaviours (Fitwi & Tadesse, 2013; Wang *et al*., 2019). Current findings make SO a promising potential antidepressant (Wei *et al*., 2022). This compound can decrease serum cholesterol and regulate the composition of neuronal membrane (Kesmati *et al*., 2014). Correcting the inappropriate functions in the HPA axis and the levels of neurotransmitters without the side effects associated with drug treatments makes SO possess the potential for the promotion of neuron growth for an inexpensive and natural drug (Liu *et al*., 2018; Thurfah *et al*., 2022). This study investigates the neuroprotective effects of sesame oil on depressive-like behaviours in mice subjected to the open-space forced swim test.

MATERIALS AND METHODS

Chemicals and drugs

Fluoxetine (Bristol Laboratories Ltd, Berkhamsted, Herts, HP4 1EG, UK, Batch Number PL 17907/0374). Sesame oil was commercially obtained (NAFDAC No: A-100437), ELISA biochemical assay kits were used in the study (EM1465) and were purchased from Wuhan, Fine Biotech Co., Ltd. (FineTest) Wuhan, China.

Experimental Animals

Thirty (30) adult albino mice both sexes of 12-14 weeks old weighing 18-26 g were used for the study and housed in different cages for 21 days. The animals were obtained from the Animal House in the Department of Human Physiology, Faculty of Basic Medical Sciences, Ahmadu Bello University Zaria. They were kept in plastic cages with bedding material (saw dust) and provided with food and water *ad libitum*.

Ethical approval

Ethical approval was sort from Ahmadu Bello University Committee on Animal Use and Care (ABUCAUC/2024/060).

Experimental groupings

The experimental animals were divided into six (6) groups of five (5) animals each in separate cages. The animals received treatments as follows:

Group I: Normal saline (10 ml/kg) only
Group II: Normal saline (10 ml/kg) + OSFST
Group III: Sesame oil (100 mg/kg) + OSFST
Group IV: Sesame oil (200 mg/kg) + OSFST
Group V: Sesame oil (400 mg/kg) + OSFST
Group VI: Fluoxetine 20 mg/kg (Yusha'u *et al.,* 2021).

All administrations were carried out orally (oral route) using oral cannula for mice.

Open-space forced swim test

This protocol outlines an optimized approach for producing the chronic depression-like state in mice, based on earlier work performed by Stone and Lin in 2011. The apparatus used consisted of plastic boxes measuring 24 × 43 × 23 cm, filled to a height of 13 cm with tap water at 32–34 °C and placed in an environment heated to 32–34 °C. The open-space forced swim test (OSFST) had both habituation and testing sessions. During the habituation session, each mouse was given three consecutive days of 15 minutes of swimming at 32–34 °C water temperature, verified using a thermometer, and replenished periodically using hot water. Swimming was again performed on two consecutive days, and on the fourth day, the mouse immobility time was measured in order to split the animals into an experiment and control group. In the testing phase, daily oral administration of normal saline, sesame oil, and fluoxetine was administered 24 hours after the

fourth-day swim and was continued for two weeks. Immobility time was recorded during 15-minute test sessions on days 1, 4, 7, 10, and 14 using a digital camera. All sessions were recorded digital camera for subsequent analysis, with immobility operationally defined as the absence of limb or body movements, except for respiration.

Sucrose preference test

Mice were separated (single mice per cage) and presented to two drinking bottles. One contained 1% sucrose and the other water, for 3 days in their home cage (Primo *et al*., 2023). It was carried out according to the method described by Serchov *et al*. (2016).

Y-Maze test

The Y-maze test was conducted to assess short-term spatial memory. The Y-maze apparatus featured three arms with dimensions of two equal arms (15 cm length × 7 cm width × 12 cm height) and one extended arm (20 cm length × 7 cm width × 12 cm height). In phase one, mice were placed into the apparatus at the start arm. The mice had access to two arms, while the entrance to the third arm was blocked. In phase 2, the block in arm three was removed, the mouse was placed into the start arm and then allowed to access all three arms of the maze (Wolf *et al*., 2016).

Novel object recognition Test

This behavioural test consists of three stages of habituation, training, and testing in 10 minutes. Two similar objects were placed in the chamber. Mice were permitted to detect both objects. Object exploration was monitored as placing the nose to the object at a distance of < 1 cm and/or touching it with the nose. A new object was replaced with the previous object. This test includes a video recording system and a cubic open space (40 × 43× 35 cm). The discrimination index (DI) was calculated by dividing the time spent exploring a new object (N) by the total time spent exploring both objects $(N + F) \times 100$. Increased memory is expressed as an increase in DI (Thur *et al.*, 2014; Rustaei *et al.,* 2023).

Brain tissues collection

The animals were sacrificed and mice brain tissues were collected following the method outlined by Zatta *et al.* (2002) & Habila *et al*. (2012). Euthanasia was performed by decapitation under anaesthesia, with scissors inserted anteriorly to the olfactory bulb to rupture the skull. The brain tissue was immediately extracted using a brain spatula and placed on an inverted Petri dish on ice. The brain was dissected, weighed, and homogenized in a medium containing a 0.1 M sodium phosphate solution (10 % W/V, pH 7.5). The resulting total homogenate was centrifuged at 1500 × g for 7 minutes, and brain homogenates was stored at -20°C until use.

Biochemical Analysis

Brain concentration of serotonin (5-HT)

Mouse serotonin assay kit EM1465 (Wuhan, Fine Biotechnology (FineTest)) ELISA, China were used to detect serotonin concentrations, according to the manufacturer's protocol.

Data Analyses

Results were expressed as Mean ± SEM. All analyses were done using one-way analysis of variance (ANOVA) followed by Tukey's *post-hoc* test for multiple comparisons, except data from OSFST that were analyzed using 2-way mixed ANOVA followed by Bonferoni *post-hoc* test for multiple comparisons using SPSS version 23 and Graphpad Prism version 8 was used to create figures. Values with $p<0.05$ were considered statistically significant.

RESULTS

Effects of Sesame Oil on Immobility Time in mice Subjected to Open-space Forced Swim Test (OSFST)

The effects of treatments and time on immobility time as a depression index. There were statistically significant effects of treatments and but not of time on the different treatment groups [$F (16,95) = 936.7$, $p<0.0001$], no interaction was found between the treatment and time [$F (4,95) = 2.161$, $p >0.05$]. however, we found significant effects of treatment between the groups [$F (16,95) =33.07$, $p<0.0001$]. at day 7 the immobility time is decreased in SO 400 mg/kg, and fluoxetine group when compared with untreated normal saline group. At day 10 and 14 all treatments groups had decreased immobility time when compared with normal saline group. Overall, the administration of different doses SO in depressed mice model decreases their depressive-like symptoms as assessed using immobility time in Figure 1.

Effects of Sesame Oil on Sucrose Index in mice Subjected to Open-space Forced Swim Test (OSFST)

The results obtained from the effect of sesame oil on anhedonic behaviour using sucrose preference test in Figure 2 showed the OSFST group was significantly lower (37.58%) compared to the normal control group (55.59%) ($p < 0.05$), indicating the presence of anhedonia. Fluoxetine-treated groups showed a significant increase in sucrose preference to 54.19% compared to the OSFST group controls ($p < 0.05$). Additionally, administration of SO at 100 mg/kg (55.01%), 200 mg/kg (64.99%), and 400 mg/kg

(83.27%) significantly increased sucrose preference compared to the OSFST group controls ($p < 0.05$). The highest dose elicited a higher response rate that exceeded the normal controls.

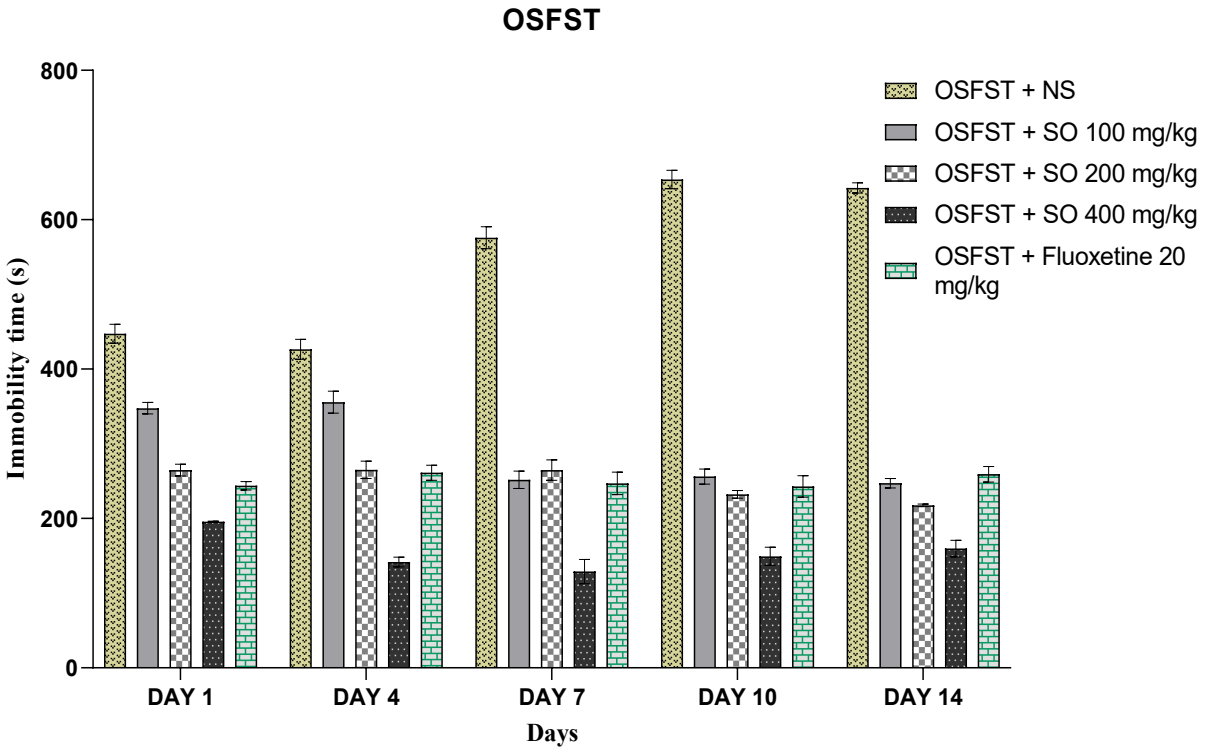

Figure 1: Effects of Sesame Oil on Depressive-Like Behaviours in Mice Subjected to Open-Space Forced Swim Test
Results expressed as mean ± SEM. GraphPad. NS: normal saline, SO: sesame oil, OSFST: Open-Space Forced Swim Test

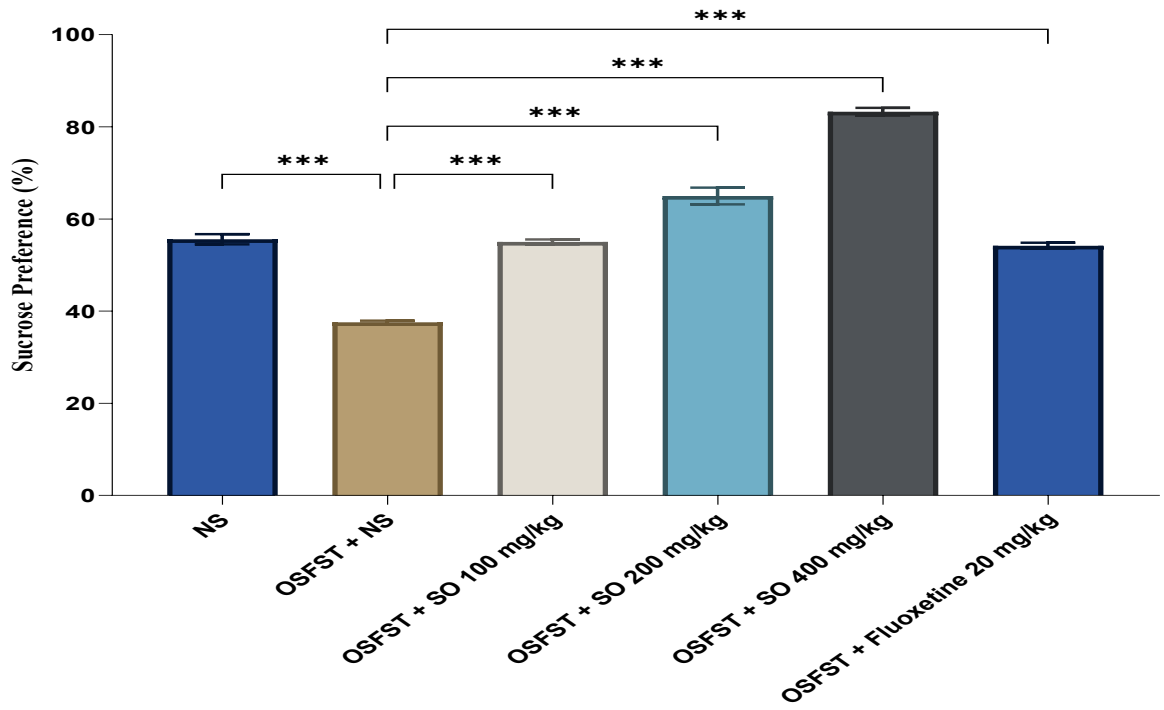

Figure 2: Effect of Sesame oil on sucrose index in mice subjected to open-space forced swim test

Results expressed as mean ± SEM, *** Mean difference is statistically significant at p<0.05. GraphPad Prism. NS: normal saline, SO: sesame oil, OSFST: Open-Space Forced Swim Test

Effect of Sesame oil on Spatial Short-term Memory using Y-maze Test in Mice Subjected to Open-space Forced Swim Test (OSFST)

The results obtained from the effect of sesame oil on spatial and non-spatial short-term memory using Y maze test is represented in Figure 3. Spatial working memory performance was also significantly affected in the OSFST control group (15.79%), as the preference score for spontaneous alternation was significantly ($p < 0.05$) lower than in the normal control group (22.07%). However, fluoxetine significantly increased spontaneous alternation behaviour to 20.47% compared with the OSFST control group ($p < 0.05$). Similarly, SO administration significantly and dose-dependently increased alternation behaviour at 100 mg/kg (21.44%), 200 mg/kg (27.83%), and 400 mg/kg (30.58%) compared with the OSFST control group ($p < 0.05$).

Effect of Sesame oil on Non-spatial Short-term Memory using Novel Object Recognition Test in mice Subjected to Open-space Forced Swim Test (OSFST)

The results obtained from the effect of sesame oil on spatial and non-spatial short-term memory using novel object recognition test is represented in Figure 4. Recognition memory was attenuated in the OSFST control group with a mean of 41.72% as compared to normal controls at 59.84% ($p < 0.05$). Fluoxetine treatment showed significant ($p < 0.05$) improvement in recognition memory to 55.18% (compared to OSFST controls). On the other hand, SO treatment showed similar patterns of improvement in recognition memory at all dosages of 100 mg/kg, 200 mg/kg, and 400 mg/kg with mean values of 65.55%, 75.28%, and 84.93%, respectively, compared to OSFST controls ($p < 0.05$).

Biochemical Test Effects of Sesame Oil on Brain Serotonin Level in mice Subjected to Open-space Forced Swim Test (OSFST)

The results obtained from the effect of sesame oil on brain concentration of serotonin in Figure 5. Serotonin level of 16.78 (ng/mL) was recorded in normal control with no exposure to OSFST. However, exposure to OSFST significantly ($p < 0.05$) decreased serotonin levels to 4.04 (ng/mL) compared to normal controls ($p < 0.05$). Administration of SO at 100, 200 and 400 mg/kg (14.36 ng/mL, 15.53 ng/mL, 19.38 ng/mL, respectively), significantly ($p < 0.05$) increased serotonin when compared to OSFST group and control group. Additionally, treatment with fluoxetine at 20 mg/kg, serotonin levels (14.86 ng/mL) were significantly ($p < 0.05$) increased compared to OSFST group.

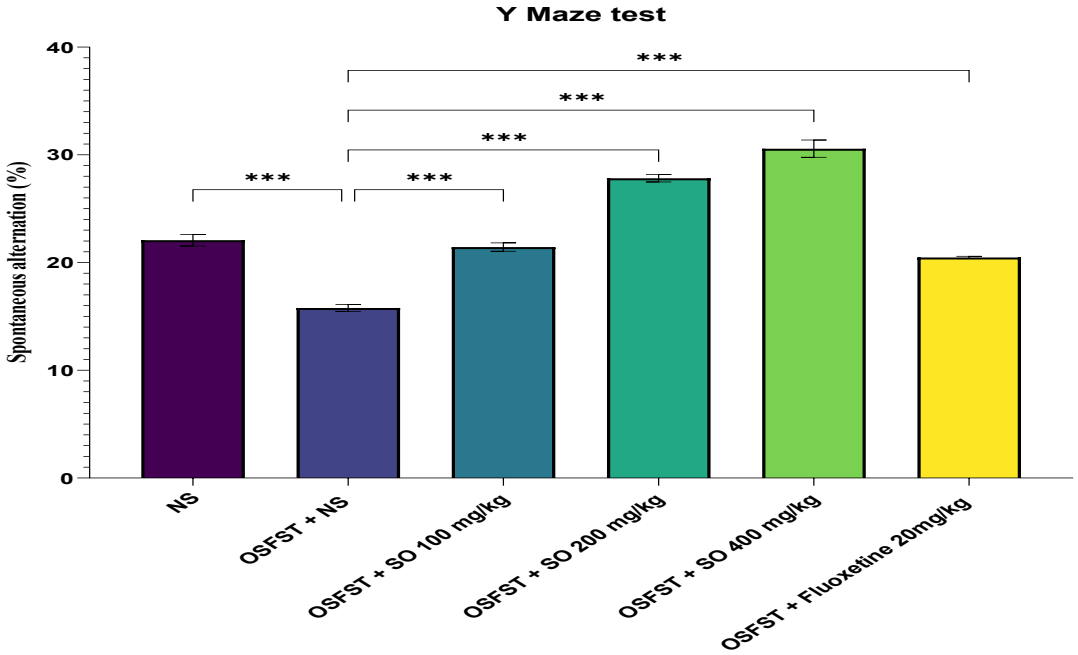

Figure 3: Effect of sesame oil on spatial short-term memory using Y-maze test in mice subjected to open-space forced swim test

Results expressed as mean ± SEM, *** Mean difference is statistically significant at p<0.05. GraphPad Prism. NS: normal saline, SO: sesame oil, OSFST: Open-Space Forced Swim Test

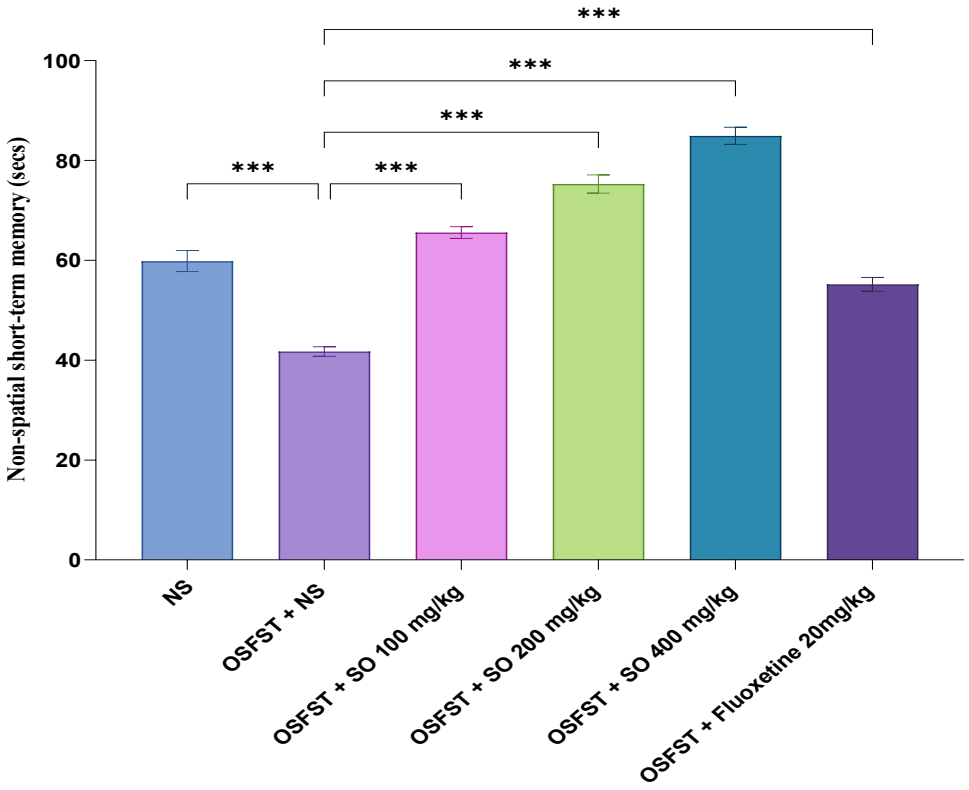

Figure 4: Effect of Sesame oil on non-spatial short-term memory using novel object recognition test in mice subjected to open-space forced swim test

Results expressed as mean ± SEM, *** Mean difference is statistically significant at p<0.05. GraphPad Prism. NS: normal saline, SO: sesame oil, OSFST: Open-Space Forced Swim Test

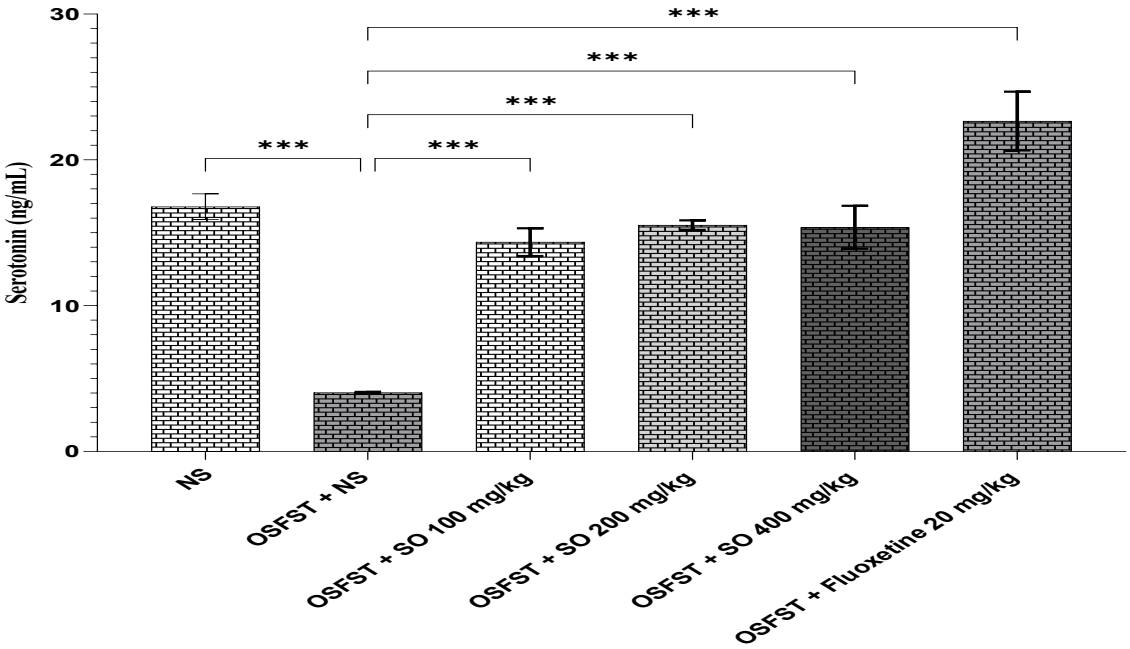

Figure 5: Effects of sesame oil on brain serotonin level in mice subjected to open-space forced swim test in mice.

Results expressed as mean ± SEM, *** Mean difference is statistically significant at p<0.05. GraphPad Prism. NS: normal saline, SO: sesame oil, OSFST: Open-Space Forced Swim Test

DISCUSSION

The study investigated the neuroprotective potentials of sesame oil on mice subjected to open space forced swim test. Our results demonstrated that Sesame oil reduced behavioural despair in mice subjected to OSFST. These findings agree with Liu *et al*. (2018), who reported that oral administration of sesame leaf extract and sesamol significantly reversed CUMS-induced mice antidepressant like behaviours, anhedonia, and anxiety. This results also suggest that SO can be a promising agent for the treatment of depression and reversal of cognitive impairment observed in this disorder by reversing CORT-induced memory and social deficits. Similarly, oral treatment of sesamin significantly alleviated chronic unpredictable mild stress induced depression and anxiety-like behaviours, improved NE and BDNF levels in mice corpus striatum and hippocampus, and suppressed the over activation of microglia (Wang *et al.,* 2012; Wang *et al.,* 2019).

The possible mechanism via which SO exerts its antidepressant-like effect from the present study might be to reduce behavioural despair as evidenced by decreased immobility time and promote cognitive behaviours. Sesame leaf extract and sesamol improved serum monoamine level (NE and 5-HT) in CUMS treated mice, Sesame leaf extract and sesamol treatment also normalized the length of postsynaptic densities (PSDs) and expression of BDNF and PSD-95 in CUMS-treated mice hippocampus (Liu *et al*., 2018). Sucrose preference is used as an indicator of a key symptom of depression, i.e., anhedonia, which indicates loss of interest or pleasure in activities that were previously enjoyable (Primo *et al*., 2023). In our study, Sesame oil reduced anhedonia in mice subjected to OSFST as indicated in the increase in the sucrose preference score after administration of Sesame oil. Previous studies suggest that chronic unpredictable stress damages nerve cells in the neural reward system, this damage is thought to be related to the serotonergic (5-HT) and dopaminergic (DA) systems, thus inducing a loss of the ability to experience happiness or pleasure (Bekris *et al*. 2005; Kalueff *et al*. 2006). The results indicate that sesame oil is effective in improving performance and mitigating depressive-like behaviours in the animals subjected to stress, suggesting a potential therapeutic use of sesame oil.

Our study also demonstrated that SO possessed a beneficial effect on spatial short-term memory by increasing the spontaneous alternation ratio of the Y-maze test in mice subjected to the OSFST. Our findings agree with Tabari *et al.* (2016), who found that pretreatment of rats with sesame oil prevented spatial memory deficit in streptoztocin-induced alzheimer model in rats. Sesame oil has also been reported to increase learning in both castrated and intact animals (Hovayda *et al.,* 2004). Similarly, fluoxetine also showed a beneficial effect on memory is in line with the study of Bortolato *et al*. (2016), who reported that SSRI treatment led to a significant improvement in memory performance in patients with depression. This improvement was observed in intermediate & delayed verbal, immediate visual and declarative memory.

Novel Object Recognition Testing (NORT) revealed that SO produced an improvement of recognition memory than fluoxetine, consistent with prior reports of the neuroprotective effects of Sesame oil on non-spatial short-term memory (Wang *et al*., 2012). Several possible mechanisms may underlie these cognitive benefits, they include; the potent antioxidant constituents in sesame's oil, which may help in attenuating oxidative stress induced neuronal dysfunction (Liu *et al*., 2019). While its anti-inflammatory constituents may suppress neuroinflammation to enhance cognitive performance (Wu *et al*., 2019). Additionally, restoration of central cholinergic signalling may also contribute to the positive cognitive effects (Liu *et al*., 2018). Collectively, these results suggest that SO exerts multifaceted neuroprotective effects associated with stress-induce cognitive deficit, thus warrants further mechanistic investigation.

Both sesame oil and fluoxetine significantly increased the brain serotonin level of mice subjected to OSFST. This result aligns with reports from a related botanical oil, Perveen *et al*. (2013). Demonstrated that *Nigella sativa* L. oil increases the availability of 5-HT at synaptic sites by increasing plasma and brain tryptophan concentrations, thus increasing 5-HT synthesis, a mechanism that is potentially share by sesame oil.

Sesame oil may also have caused direct activation of 5-HT1A and 5-HT2A receptors, which are known to facilitate serotonin release and synthesis (Herr *et al*., 2017). Furthermore, the hypothesis of Liu *et al.,* (2018) that Sesame oil high tyrosine content, may provide an explanation for enhance serotonergic activity, given that tyrosine is a precursor in monoamine biosynthetic pathways. Considering that

dysregulation of serotonin signaling is at the core of the pathophysiology of depressing and stress related disorders (Moncrieff *et al*., 2022). Restoration of serotonin homeostatic may be possible mechanism that accounts for its antidepressant effects. (Moncrieff *et al*., 2022).

In conclusion, sesame oil at administered at doses of 200 mg/kg and 400 mg/kg produced a significant reduction in immobility time and increased sucrose preference index, collectively indicating the potential antidepressant effects in the OSFST model. Additionally, Sesame oil at 100 mg/kg and 200 mg/kg also improved cognitive performance in in both spatial and recognition memory tasks. Furthermore, sesame oil significantly elevated brain serotonin concentration supporting a plausible serotonergic mechanism of action. These findings suggest that sesame oil possesses possible antidepressant and cognitive potentials.

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