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Quercetin reverses chronic unpredictable mild stress-induced depression and behavioural abnormalities in Swiss mice

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Abstract

Context: Chronic stress is a known trigger of inflammatory responses and oxidative stress that underpin the pathogenesis of depression. Although quercetin is a flavonoid widely known for its anti-inflammatory, antioxidant and adaptogenic effects, its potential against stress-related depression has not been fully studied.
Objective: This study aimed to investigate the effect of quercetin on chronic unpredictable mild stress (CUMS)-induced depression in mice.
Materials and Methods: Swiss mice were divided into four groups of seven animals each. Group 1 received vehicle, group 2 received vehicle, and groups 3 and 4 received quercetin (12.5 mg/kg and 25 mg/kg, respectively). All animals except those in group 1 were exposed daily to unpredictable stressors for twenty-one days. Behavioural studies were carried out twenty-four hours after the last treatment (day 22). The mice were anaesthetized and sacrificed, and their brain samples were removed for histology and biochemical assays of proinflammatory cytokines. The data was analysed using one way analysis of variance (ANOVA) and a post hoc test. The level of significance was set at $p<0.05$.
Results: Compared with vehicle treatment, CUMS induced behavioural dysfunction by significantly decreasing grooming activity in the sucrose splash test and increasing immobility time in the forced swim test (FST) and tail suspension test (TST). CUMS also increased proinflammatory cytokine levels in the brain and reduced the arborization of dendritic cells. All these parameters were significantly reversed ($p<0.05$) by quercetin (12.5 mg/kg and 25 mg/kg).
Conclusion: Our results showed that quercetin significantly attenuated depressive symptoms in CUMS-exposed mice and exerted neuroprotective effects by markedly inhibiting the reduction in the arborization of dendritic cells in the brain. This neuroprotective effect may be due to the inhibition of neuroinflammatory cytokines.

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Introduction

Major depression is one of the most common mood disorders among psychiatric patients, with an estimated 280 million patients worldwide. It is characterized by low mood, sadness, disrupted sleep, loss of interest, suicidal thoughts, anhedonia, and a reduced sense of satisfaction/gratification.[1] The exact cause of this disorder is still unclear and has been a subject of debate for many years. However, efforts to understand the aetiology of depression for proper approach to management have led to hypotheses of stressful life events, personality, gender identity, sexuality, illnesses, and medical treatment.[2-4]

Stress is a major factor among others and has been reported to play a key role in the pathogenesis of depression.[5-9] Chronic stress has been identified as a powerful predictor of the development of depression and can be associated with structural and functional changes in the brain.[10, 11] Chronic stress may result in anxiety, depression and other related disorders.[12,13] Preclinically, exposure of rodents to long-term stressors results in anxiety-like and depression-like symptoms,[14] while in humans, psychosocial stress reportedly triggers depression in susceptible individuals.[15,16] Duman et al demonstrated the link between molecular changes and the display of depressive-like symptoms in stress-exposed rodents.[17]

Various animal models of stress used to induce depressive-like behaviours have been shown to trigger inflammatory and oxidative stress responses.[14] For instance, chronic psychosocial stress has been associated with the induction of neuroinflammation and apoptosis and reduced neurogenesis in rodents.[18] Furthermore, chronic mild stress, learned helplessness, and repeated social defeat stress increase proinflammatory cytokines and increase insulin insensitivity. Consistently, stressful life events, which are a form of chronic stress in humans, have disrupted the immune system and caused an increase in proinflammatory cytokines, and according to several reports, these events have caused neuronal atrophy and the pathogenesis of depression.[19,20] Given that inflammation plays a significant role in stress-induced depression, it can therefore be hypothesized that anti-inflammatory compounds can ameliorate depressive symptoms in animals.

Quercetin is a flavonoid known for its memory-enhancing effect, antistress potential and stress-induced cortisol-reducing effect in humans.[21] Its effects on anxiety and depression have been documented.[21,22] It has demonstrated antioxidant effects[23] and anti-inflammatory effects in animal models[22] Quercetin downregulates vascular cell adhesion molecule 1 and protects against inflammation in human umbilical vein endothelial cells in a peroxide-induced inflammation model.[22] In addition, its beneficial effects against cancer and cardiovascular disorders have been reported.[21] Given the wide range of health benefits that quercetin offers, this study was designed to investigate its effect on chronic unpredictable mild stress-induced behavioural phenotypes in mice. This study further investigated the beneficial effects of quercetin on neuroinflammation, neuronal cell degeneration and stress-induced reductions in the arborization of dendrites and oligodendrocytes in the brains of mice.

Materials and Methods

Animals: Male Swiss mice (20–25 g) were obtained from the Laboratory Animal Centre of the College of Medicine, University of Ibadan, Nigeria. The animals were kept in a room maintained at 23°C with a 12:12 h light/dark cycle and 40–70% relative humidity, food, and water ad libitum. The experimental procedures were approved by the Afe Babalola University Animal Care and Use Research Ethics Committee (AB/EC/20/22/08) and performed in accordance with the National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals.[24]

Drugs and Chemicals: Quercetin (3,3',4',5,7-pentahydroxyflavone dihydrate), potassium dichromate, and silver nitrate were obtained from Sigma Aldrich St. Louis, Missouri, and fluoxetine (N-methyl-3-phenyl-3-[4-(trifluoromethyl)phenoxy]propan-1-amine) was obtained from Dalkeith Laboratories Limited, Woburn, MK17, UK.

Treatment Groups: Following a seven-day acclimatization period, the mice were randomly divided into four (4) groups of seven (7) animals each (n=7).

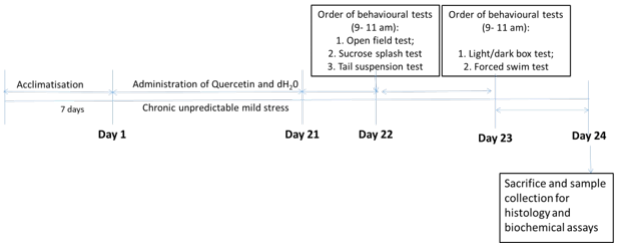
- Group 1 received vehicle (10 mL/kg distilled water, p.o.) only.
- Group 2 received vehicle and was subjected to the stress protocol.
- Groups 3 and 4 were given quercetin (12.5 mg/kg and 25 mg/kg, p.o. respectively) and were subjected to the stress protocol. The doses of quercetin used were selected based on a previous study by Adeoluwa et al.[25]

Experimental Protocol: The chronic unpredictable mild stress (CUMS) protocol was used in the present study as previously described by Yalcin et al.[26] and Yin et al.[10] with modifications. It comprises a good number of physical stressors, to which each mouse in groups 2-4 was randomly and individually exposed for twenty-one (21) consecutive days. The stressors included 12 hours of water deprivation, 7 hours of cage tilt at 45°, 12 hours of damp bedding, 12 hours of overnight illumination, 30 minutes of background noise, 12 hours of food deprivation, and 1 minute of tail pinch (Table 1).

All animals were housed singly, and mice were exposed to each of these stressors one after the other in an unpredictable manner for 21 days. The order of the stressors was randomized to avoid any habituation effect. The Table 1 below shows the schedule of the CUMS protocol. In addition, the experimental timeline is presented in Scheme 1.

Table 1: Schedule of the CUMS protocol

Week 1		
Days	**Stressors**	**Duration**
1	Water deprivation	12 hours
2	Cage tilt at 45°	7 hours (8 am - 3 pm)
3	Damp bedding	12 hours
4	Overnight illumination	12 hours (7pm – 7am)
5	Background noise	30 minutes (any time of day)
6	Tail pinch	1 minute
7	Food deprivation	12 hours
Week 2		
Days	**Stressors**	**Duration**
1	Background noise	30 minutes (any time of day)
2	Cage tilt at 45°	7 hours (12 pm – 7 pm)
3	Overnight illumination	12 hours (7pm – 7am)
4	Water deprivation	12 hours
5	Tail pinch	1 minute
6	Food deprivation	12 hours
7	Damp bedding	12 hours
Week 3		
Days	**Stressors**	**Duration**
1	Tail pinch	1 minute
2	Food deprivation	12 hours
3	Background noise	30 minutes (any time of day)
4	Damp bedding	12 hours
5	Water deprivation	12 hours
6	Cage tilt at 45°	7 hours (10 am – 5 pm)
7	Overnight illumination	12 hours (7pm – 7am)



Scheme 1 Experimental timeline

Behavioural tests: On days 22-23, all animals were subjected to behavioural tests. Depressive-like symptoms were assessed using the open field test, tail suspension test, and sucrose splash test on day 22, while the light/dark box and forced swim tests were conducted on day 23. The individuals involved in these behavioural tests were blinded to the treatment of the animals. All the data were manually recoded.

Open Field Test (OFT): The spontaneous motor activity of the animals was assessed using the open field box. For the test, each mouse was first placed at the centre of the box and allowed to explore freely for five minutes. The number of lines crossed by all four paws of a mouse was measured for five (5) minutes as an index of spontaneous motor activity.

Sucrose Splash Test (SST): A 10% sucrose solution was prepared for this test and administered using a spray bottle. Each mouse was removed from its home cage and sprayed with sucrose solution on its dorsal coat. The mouse was then placed in a clean transparent cage for observation. The duration of grooming within a five (5)-minute period was measured.

Tail Suspension Test (TST): This test was carried out according to the method described by Steru et al.[27] Each mouse was hung by the tail on an elevated wire using adhesive tape and allowed to hang freely for six (6) minutes. The duration of immobility within the final four (4) minutes was measured in this test. Immobility was defined when the mouse simply hung passively without showing signs of struggle.

Forced Swim Test (FST): The apparatus used for the FST was a cylindrical container 10 cm in

diameter and 25 cm in height. The container was filled with room temperature water to a height of 19 cm. Each mouse was dropped into the water and allowed to swim for 6 min. The duration of immobility was measured within the final 4 min. Immobility was defined as the mouse making subtle movements that ensured that only its head was kept above the water.

Light and dark box test: This test uses the light-dark box (LDB) which comprises a dark and light compartment. It is a popular animal model used to assess unconditioned anxiety responses in rodents.[28,29] Each mouse was placed in the light compartment of the apparatus and was allowed to move around for 5 minutes. The time spent exploring each compartment was recorded.

Collection and preservation of brain tissues: To prevent the mice from being subjected to further stress, the mice were euthanised 24 hours after the behavioural tests. This was performed by anaesthetizing each mouse with 200 mg/kg pentobarbital, and the whole brains were removed quickly. The tissues were preserved in phosphate-buffered saline (PBS) at 4°C in preparation for biochemical analysis.

Biochemical assays

Measurement of proinflammatory cytokines using ELISA techniques

The ELISA technique was used to quantify two crucial proinflammatory cytokines: interleukin-12 (IL-12) and interferon gamma (IFN-γ). For this assay, the frozen brain tissues were homogenized and cold centrifuged at 10,000 rpm for 10 min to obtain supernatants, which were then stored at -20°C. The manufacturer's instructions (BioLegend ELISA MAX™ Deluxe, USA) were followed for both assays, and the concentrations of the cytokines were measured and expressed in pg/mL.

Golgi staining

Selected brain tissues were stained using Golgi staining techniques[30] by fixation in 4% paraformaldehyde for 24 hours, followed by immersion in 3% potassium dichromate for 7 days in a dark chamber (potassium dichromate solution was changed daily). The tissues were subsequently immersed in 2% silver nitrate solution for 72 hours at room temperature in a dark chamber (after the tissues were dabbed with absorbent paper to remove excess potassium dichromate). The silver nitrate solution was changed several times until there were no brown precipitates. The various brain sections were serially cut into 60 μm thick sections in distilled water using a vibratome, mounted on foist plus slides and dried at room temperature for 10 minutes. The cut sections were then dehydrated through 95% and 100% alcohol and finally cleared in xylene before being covered with coverslips. Afterwards, photomicrographs were captured using a digital camera attached to the microscope and the images were analyzed using ImageJ software.

Statistical analysis

The values are expressed as the means ± standard deviation (SD). All the data were analysed using one-way analysis of variance (ANOVA). Correlation analysis was performed using Pearson's test. Tukey's post hoc test was carried out for multiple comparisons among the groups. Differences were considered significant at $p<0.05$.

Results

Quercetin attenuates CUMS-induced depressive-like behaviours in mice

TST and FST are usually employed as paradigms to assess depressive behaviours in animals and to screen for the antidepressant potential of compounds. The immobility of the animals in these behavioural tests was measured (Fig. 1). According to one-way ANOVA and post hoc tests, there were significant differences among the treatment groups, and animals exposed to CUMS alone exhibited significantly greater immobility in the TST [$F(4, 30) = 13.54$; $p<0.0001$] (Fig 1A) and FST [$F(4, 30) = 16.87$; $p<0.0001$] (Fig 1B) than did the control animals. However, CUMS-induced immobility was significantly lower in the groups treated with graded doses of quercetin than in the CUMS-exposed group. Furthermore, Figure 2A shows that compared with control animals, CUMS-exposed animals exhibited significantly less grooming in the sucrose splash test [$F(4, 30) = 31.07$; $p<0.0001$], suggesting anhedonia. However, post hoc tests showed that treatment with quercetin significantly increased grooming and reversed the anhedonic effect on the animals. CUMS significantly ($p<0.05$) reduced locomotor activity in the open field test compared to control (Fig 2B).

However, there was a nonsignificant (p>0.05) effect of quercetin on locomotor activity compared to the CUMS alone group.

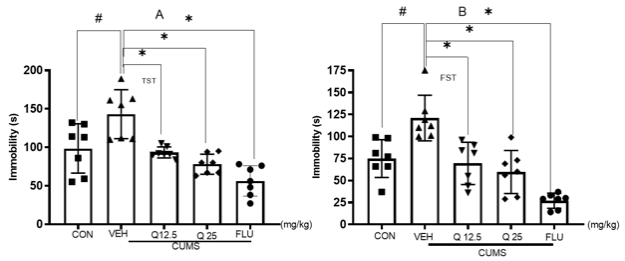


Fig. 1 Effect of quercetin on CUMS-induced depressive-like behaviours of mice in the despair tests of the TST (A) and FST (B)
The results are presented as the means ± SDs (*n*= 7).
# *p*< 0.05 versus control, **p*< 0.05 versus CUMS.
CON: Control, VEH: Vehicle, CUMS: Chronic unpredictable mild stress, TST: Tail suspension test, FST: Forced swim test.

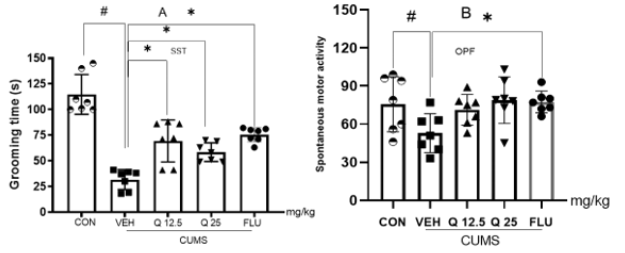


Fig. 2 Effect of quercetin on the sucrose splash test (A) and spontaneous motor activity (B)
The results are presented as the means ± SDs (*n*= 7).
# *p*< 0.05 versus control, **p*< 0.05 versus CUMS.
CON: Control, VEH: Vehicle, CUMS: Chronic unpredictable mild stress, SST: Sucrose splash test, OPF: Open field.

Quercetin attenuates CUMS-induced anxiety-like behaviours in mice

According to the one-way ANOVA and post hoc tests, there were significant differences among the treatment groups: animals exposed to CUMS alone spent significantly less time in the light phase of the experiment [F (4, 30) = 4.312; p=0.0071] (Fig. 3A) and more time in the dark phase [F (4, 30) = 9.018; p<0.0001] (Fig. 3B) compared to the control. Conversely, we observed that the groups treated with graded doses of quercetin had significantly increased activity in the light phase (Fig. 3A) and decreased activity in the dark phase (Fig. 3B) of the test compared with the CUMS-exposed group.

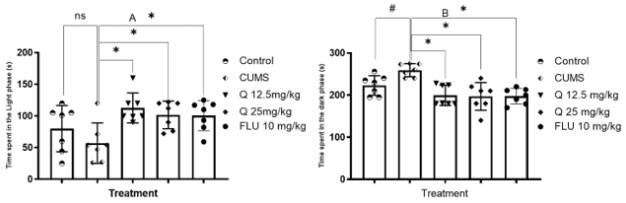


Fig. 3 Effect of quercetin on the CUMS-induced anxiety-like behaviour of mice
The results are presented as the means ± SDs (*n* = 7).
# *p*< 0.05 versus control, **p*< 0.05 versus CUMS.
CON: Control, VEH: Vehicle, CUMS: Chronic unpredictable mild stress, ns: not significant.

Quercetin attenuates CUMS-induced proinflammatory cytokines (IL-12 and IFN-gamma) in the brains of mice

To evaluate the anti-inflammatory effect of quercetin on stress-induced neuroinflammatory responses in a rodent model of depression, the levels of IL-12 and IFN-ɣ in the brain were assayed, as shown in Figure 4 below. One-way ANOVA revealed that there were significant differences in the levels of IL-12 [F (4, 20) = 11.15; p=0.000] (Fig. 4A) and IFN- ɣ [F (4, 20) = 5.519; p=0.0037] (Fig. 4B) among the treatment groups. Compared with those in the control group, the IL-12 and IFN-ɣ in the CUMS-exposed group were significantly greater. However, treatment with quercetin (Q 12.5 mg/kg and Q 25 mg/kg) significantly reduced the CUMS-induced increase in IL-12 (Fig. 4A) and IFN-ɣ (Fig. 4B) levels.

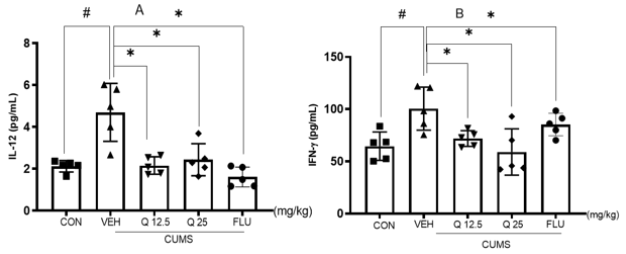


Fig. 4 Effect of quercetin on CUMS-induced inflammatory cytokines in mice
The results are presented as the means ± SDs (*n*= 5).
# *p*< 0.05 versus control, **p*< 0.05 versus CUMS.
CON: Control, VEH: Vehicle, CUMS: Chronic unpredictable mild stress.

Pearson's correlation analysis of the antidepressant-like effect of quercetin and proinflammatory cytokines

The Table 2 below shows the Pearson's correlation analysis between the effect of quercetin on grooming in the SST (an indicator of anhedonia) and the concentration of proinflammatory cytokines. The table shows that the grooming time in the SST was negatively correlated with IL-12 (r = -0.628, p= 0.003) and IFN-ɣ (r = -0.549, p = 0.012), suggesting that a reduced concentration of proinflammatory cytokines is correlated with increased grooming behaviour (i.e., disappearance of anhedonia) in mice pretreated with quercetin.

Table 2 Correlation analysis between depressive-like behaviour and proinflammatory cytokines

Grooming time in SST as correlate with cytokines	*Correlation coefficient and p value*	
	r	*p*
IL-12	-0.628	0.003
IFN-ɣ	-0.549	0.012

Quercetin protects pyramidal dendrites in the hippocampus of mice

In the CA1 region of the hippocampus of the controls, there were well-defined pyramidal neurons and well-arborized basal dendrites. However, in the CUMS-exposed group, shrunken neuronal cells and severe loss of dendritic processes were observed (Fig 5). The neurons in the CUMS groups exhibited no distinct basal dendritic arborization. Furthermore, no difference in the morphology of the apical and basal dendrites of the pyramidal neurons in the hippocampus was observed between the quercetin-treated groups and the control group.

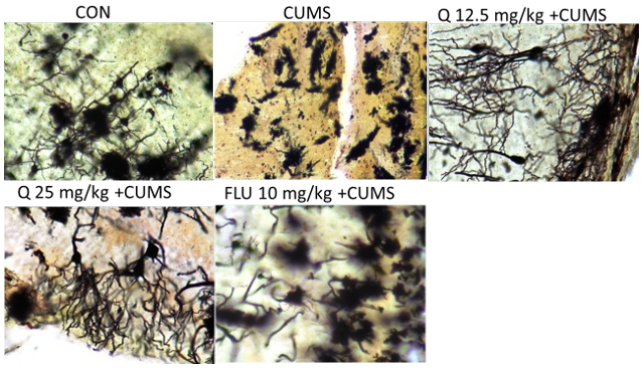


Fig. 5 Representative Golgi-stained sections of the hippocampus of stressed exposed animals

×400 magnification

Compared with those in the control group, the CA1 region exhibited fewer neuronal cells and severe loss of dendritic processes, and these effects were attenuated in the quercetin groups.

Discussion

The findings emerging from this study provide insight into the therapeutic potential of quercetin in the management of depression, as it ameliorates behavioural deficits and neuroinflammation associated with chronic stress in mice. In addition, quercetin protected susceptible portions of the brain and reversed chronic stress-induced behavioural abnormalities, biochemical changes, and morphological alterations.

The interplay between chronic stress and affective disorders has been reported in several studies, and this has formed the basis of the chronic unpredictable stress protocol in rodents as a means of modelling depressive phenotypes that mimic human clinical symptoms.[31-33] Animals exposed to CUMS exhibit dysfunctional serotonergic neurotransmission in the hippocampus, prefrontal cortex, and amygdala and later display depressive-like symptoms.[34] Preclinically, studies have consistently shown that animals exposed to chronic unpredictable stress exhibit prolonged immobility in the forced swim test and tail suspension test.[35] The phenotypes displayed by the animals have been interpreted as despair symptoms that closely resemble or mimic clinical depressive behaviour in humans.

Consistently, the chronic stress-exposed animals in our study displayed behavioural abnormalities in the FST, TST, LDB and sucrose splash test. There was markedly prolonged immobility in both despair tests and a marked decline in grooming behaviour during the sucrose splash test, all of which are indicative of depressive-like symptoms. In the FST and TST, increased immobility is interpreted as a sign of despair and hopelessness.[36,37] However, we observed that animals treated with graded doses of quercetin and exposed to chronic unpredictable stress in the same manner as those in the stress group showed a significant decrease in immobility in the FST and TST, suggesting that quercetin has antidepressant-like effects. Previous studies have shown that

quercetin has antidepressant-like effects on LPS-induced depression in rats and other animal models of depression.[22]

Anhedonia is a core symptom of depression, and it is described or defined as a decreased ability to experience pleasure. Preclinically, anhedonia can be measured in animals subjected to sucrose preference or sucrose splash tests. A decrease in sucrose preference signifies a reduced ability to experience pleasure, while in the sucrose splash test, a decrease in grooming behaviour signifies less self-care, which is indicative of depression. In this study, the sucrose splash test was employed to determine the anhedonic effect of CUMS on mice. We observed that chronic stress induced less grooming in animals exposed to chronic unpredictable stress than in control animals, indicating anhedonia. Evidence of reduced self-care in depressed individuals and reduced grooming behaviour in animals exposed to stressful conditions has been reported.[31,33] Conversely, treatment with quercetin significantly reversed CUMS-induced anhedonic symptoms by significantly increasing grooming behaviour and frequency in the sucrose splash test. Chronic treatment with antidepressants has reversed the anhedonic effect.[38,39]

Proinflammatory cytokines are immune molecules that regulate inflammatory responses. They have been largely implicated in the pathogenesis of affective disorders. Preclinically, there is compelling evidence of an increase in the amount of proinflammatory cytokines such as IL-1β, IL-6, TNF-α, and IL-12 in the brain, serum and plasma of rats exposed to chronic mild stress models of depression,[40-43] while elevated levels of peripheral cytokines have been detected in depressed patients.[44,45] A comparative study of the levels of proinflammatory cytokines in depressed and nondepressed patients revealed a higher concentration of proinflammatory cytokines in depressed patients than in their counterparts.[46] Therefore, an imbalance between pro- and anti-inflammatory cytokines may be implicated in depression.[42] In this study, we observed markedly elevated levels of IL-12 and IFN-Ɣ in the group exposed to chronic mild stress. There is evidence of an increase in the concentration of IL-12 in the basal plasma[43] and increased NF-kB and proinflammatory cytokine levels in the prefrontal cortex and hippocampus[47] of mice exposed to CUMS.

The correlational analysis of the behavioural and biochemical variables was performed with Pearson's correlation statistics. Earlier in this study, quercetin reversed the CUMS-induced decrease in grooming behaviour, an index of anhedonia, and the increase in proinflammatory cytokines, which are known to be associated with depressive disorder. Having subjected the variables to this statistic, the findings show that these two variables were negatively correlated with one another. The negative correlation indicates that, as quercetin increases grooming behaviour in the SST, which signifies the disappearance of anhedonia, there is a consistent decrease in the concentration of proinflammatory cytokines. This observation further reinforces the hypothesis that in depression, high concentrations of inflammatory mediators and agents with potent anti-inflammatory effects can ameliorate depressive symptoms. Studies have shown that antidepressants and quercetin possess anti-inflammatory properties and are able to ameliorate depressive-like symptoms in a lipopolysaccharide model of depression.[22]

The prefrontal cortex represents the brain region with the highest hierarchical level among the association cortices and is the most evolved cortex responsible for superior mental functions. The representation, planning and execution of actions; cognition, behaviour and emotional control; adaptation to the environment; and working memory are dependent on the integrity of the prefrontal cortex and its interconnections with cortical and subcortical areas. While the hippocampus is important in cognition, its role in helping to shape the stress response and emotion along the hypothalamus and the amygdala cannot be overemphasized.[48] Structural changes in these regions have been associated with depression. Evidence of reduced spine density in the neurons of the PFC and reduced dendritic complexity and loss of arborization of the hippocampus upon exposure to chronic stress has been reported.[49,50]

In this study, histological analysis of the hippocampus revealed clear degeneration of dendrites and loss of neuronal cells in the group of animals exposed to chronic stress compared to the control group. Gellner et al[51] reported a persistent reduction in the number of dendritic spines and disturbed spine dynamics in excitatory neurons during chronic social defeat stress. Conversely, the hippocampi of the animals pretreated with quercetin showed well-defined pyramidal neurons and well-arborized basal dendrites even after exposure to

chronic stress. This neuroprotective effect of this region may also contribute to the antidepressant-like effect of quercetin.

Conclusion

In conclusion, this study revealed the potential effect of quercetin on chronic stress-induced depression. Although the mechanisms of action of antidepressants may still be elusive, the effects of these agents on neuroinflammation and neuroprotection of dendritic cells in the brain may provide insight into the antidepressant mechanism of quercetin. Therefore, further studies are still required to investigate the molecular mechanisms involved in the antidepressant-like effect of quercetin.

Statements and Declarations

Ethics approval and consent to participate

The experimental procedures were approved by the Afe Babalola University Animal Care and Use Research Ethics Committee (AB/EC/20/22/08) and performed in accordance with international guidelines.

Conflicts of interest/Competing interests

The authors have no relevant financial or non-financial interests to disclose.

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The authors did not receive support from any organization for the submitted work.

Authors' contributions

This study was conceptualized and supervised by AOA, who also contributed to the methodology and manuscript writing. AOG was responsible for the investigation, data curation, and analysis. OLO and JIP contributed to the investigation, data analysis, and editing of the manuscript. OCB was involved in the investigation and took part in writing, review and editing. OLO and AOA prepared the original draft of the manuscript. MEJ and BAG contributed to the investigation and data analysis, while AFR was involved in the investigation and project administration. Finally, AAO, OMO, and FOM supported the review and editing of the manuscript. All authors read and approved the final manuscript.

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