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Methyl jasmonate attenuated lipopolysaccharide-induced depressive-like behaviour in mice

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ABSTRACT

Depression is a recurrent neuropsychiatric disorder that affects millions of individuals worldwide and impact negatively on the patients' social functions and quality of life. Studies have shown that i.p injection of lipopolysaccharide (LPS) induces depressive-like behavior in rodents via induction of oxidative stress and neuroinflammation. Methyl jasmonate (MJ), an isolated compound from jasmine plant has gained reputation in aromatherapy for treatment of depression, nervousness and memory deficits. This study was designed to evaluate the effects of MJ on LPS-induced depressive-like behavior in mice. Mice were given MJ (5–20 mg/kg), imipramine (10 mg/kg) or vehicle (10 mL/kg) intraperitoneally for 7 consecutive days. On day 7, treatment was carried out 30 min prior to i.p injection of LPS (830 μg/kg). Twenty four hours after LPS administration, tail suspension, forced swim and sucrose preference tests were carried out. Thereafter, serum corticosterone levels were determined using ELISA. The levels of malondialdehyde (MDA), glutathione (GSH) and tumor necrosis factor-alpha (TNF-α) were determined in brain tissue homogenates. LPS significantly increased immobility time in the tail suspension and forced swim tests when compared with vehicle ($p < 0.05$), which indicates depressive-like syndromes. However, the increased immobility time was significantly reduced by MJ (5–20 mg/kg) when compared with LPS-treated group. LPS administration also altered the levels of MDA, GSH, corticosterone and TNF alpha in mice, which was significantly reversed by MJ. These findings suggest that attenuation of LPS-induced depressive-like behavior by MJ may be related to suppression of oxidative stress and release of TNF alpha.

1. Introduction

Depression is a common psychiatric disorder, affecting the quality of life and overall productivity of the sufferers (Ferrari et al., 2013). Depression is an affective disorder characterized by change in mood, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep, appetite, low energy, psychomotor retardation and melancholia. Major depression is a severe health condition associated with high disability and it has a life time prevalence of about 10–15% (Kessing, 2012; Ferrari et al., 2013). The course of the disease is recurrent and most patients who recover from major depressive episodes still become depressed afterwards (Kessing, 2012; Gorwood et al., 2014). Moreover, repeated episodes of depression have been shown to cause atrophy of the hippocampus thereby increasing the risk of dementia and also contribute to treatment failures (Kessing, 2012; Gorwood et al., 2014). Major depression has been reported to be a major economic burden beyond the direct costs of its treatment. The indirect and intangible costs, which include decreased productivity, morbidity and increased mortality, are known to account for about 70–80% of the total cost (Khoo et al., 2015). Current available antidepressant drugs have certain drawbacks such as limited spectrum of activity, slow onset of action, serious adverse effects and poor compliance (Lépine and Briley, 2011; Gautam et al., 2013; Kumari et al., 2016). Thus, the need to search for new drugs as alternative treatments for severe depression still persist (Gautam et al., 2013; Kumari et al., 2016).

There are increasing evidences that support the notion that depression is closely connected with inflammation in the brain (Dantzer et al., 2008; Capuron and Dantzer, 2003). Moreover, prevalence of depression has been reported to be higher in patients with chronic infections, cancers and rheumatoid arthritis (all of which have a common identity of chronic inflammation as the

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underlying factor) than in the normal population (Evans et al., 2005; Capuron and Dantzer, 2003; O'Connor et al., 2009). Moreover, proinflammatory cytokines including IL-6 and IL-1β were elevated in the plasma or cerebrospinal fluid of depressed patients (O'Connor et al., 2009; Capuron and Dantzer, 2003) and these heightened levels of cytokines were associated with the severity of the disease (Yirmiya, 1996; O'Connor et al., 2009). Thus, the administration of the cytokine inducer lipopolysaccharide (LPS) is often used to produce depressive-like behavior, as measured by increased immobility in the forced-swim test (FST) and tail suspension test (TST), decreased consumption of a sweetened solution and a suppression of sexual behavior in laboratory animals, which can be attenuated by chronic antidepressant drugs (Yirmiya, 1996; O'Connor et al., 2009). Indeed, several studies have shown that systemic administration of LPS, a non-infectious component of a gram−ve bacterial cell produced behavioural changes that closely resemble depressive symptoms in humans (Yirmiya, 1996; De La Garza, 2005; Ge et al., 2015; Liu et al., 2016). Specially, LPS has been shown to cause behavioural and biochemical changes through induction of oxidative stress and neuroinflammation (De La Garza, 2005; Fan et al., 2014; Ge et al., 2015; Leonard and Maes, 2012; Miller et al., 2009; Qin et al., 2007). Thus, compounds with potent antioxidant and anti-inflammatory activities are being sought as alternatives for treatment of depression (Gautam et al., 2013).

Methyl Jasmonate (MJ) is a plant stress hormone that was first isolated from the essential oil of *Jasmonium grandiflorum* (Demole et al., 1962). It is secreted by plants in response to external stress and its level is known to increase when plants suffer wounds or infections (Cesari et al., 2014). The potential benefits of Jasmine flower for depression, nervousness, tension and memory deficits in aromatherapy have been reported in literature (Kuroda et al., 2005). Previous studies from our laboratory have shown that MJ possessed antinociceptive, anti-amnesic and adaptogenic properties in experimental models (Umukoro and Olugbemide, 2011; Eduviere et al., 2015; Umukoro et al., 2016). In addition, preliminary studies have also revealed that MJ exhibited antidepressant activity in naïve mice subjected to tail suspension and forced swim tests (Umukoro et al., 2011). However, this present study was designed to evaluate in details, its effects on LPS-induced depressive-like behaviors in mice and the likely mechanism(s) involved in its action.

2. Materials and methods

2.1. Experimental animals

Male Swiss mice (22–25 g) used in the study were obtained from the Central Animal House, University of Ibadan and were housed in plastic cages at room temperature with 12:12 h light–dark cycle. They were fed with rodent pellets and water *ad libitum*. The animals were allowed to acclimatize for few days before use in all experiments. The experimental procedures were approved by the University of Ibadan Animal Care and Use Research Ethics Committee (UIACUREC/App/2016/023).

2.2. Drugs and chemicals

Methyl jasmonate (5, 10, 20 mg/kg), imipramine (10 mg/kg) and lipopolysaccharide (830 μg/kg) used in the study were obtained from Sigma, Germany. MJ was dissolved in 95% ethanol and further diluted with distilled water as previously described (Umukoro et al., 2011). Imipramine and LPS were dissolved in distilled water immediately before use. The doses of 5, 10 and 20 mg/kg of MJ used in this study were selected based on the results obtained from previous studies (Umukoro et al., 2011). The dose of LPS (830 μg/kg) and the time point (24 h) for behavioural tests after LPS administration were chosen based on previous investigations (O'Connor et al., 2009).

2.3. Experimental procedures

Mice were randomly divided into 6 treatment groups (n = 6). Mice in group 1 were given vehicle (1% ethanol, 10 mL/kg), groups 2–4 received MJ (5, 10 and 20 mg/kg) whereas group 5 were pretreated with imipramine (10 mg/kg) daily for 7 days prior to i.p injection of LPS (830 μg/kg). Mice in group 6 were also given vehicle but were not injected with LPS. All treatments were administered intraperitoneally. The behavioural studies were carried out 24 h after LPS administration and blood samples were collected afterwards for estimation of serum corticosterone levels. The animals were then sacrificed for various biochemical studies.

2.4. Behavioural studies

2.4.1. Sucrose preference test

Sucrose preference test was carried out 24 h after LPS treatment as previously described (Gronli et al., 2005). Briefly, 72 h before the test, mice were trained to adapt to 1% sucrose solution (w/v). Two bottles of 1% sucrose solution were initially placed in each cage and 24 h later, 1% sucrose in one of the bottles was replaced with water for another 24 h. After adaptation, mice were deprived of water and food for 12 h, followed by the sucrose preference test, in which mice were allowed free access to the two bottles containing 100 mL of 1% sucrose and 100 mL of water, respectively.

Afterwards, the volumes of sucrose solution and water consumed were recorded. Sucrose preference was calculated using the following formula:

$$\frac{\text{Sucrose consumption} \times 100}{\text{Sucrose consumption} + \text{water consumption}}$$

2.4.2. Tail suspension test and forced swim test

The tail suspension test was carried out according to the procedure described by Cryan et al. (2005). The animals were suspended individually on a retort stand, placed 50 cm above the floor with the help of an adhesive tape placed approximately 1 cm from the tip of the tail. The total duration of immobility were recorded during the last 4 min of the 6 min test. An animal was considered to be immobile when it did not show any movement of the body and hangs passively. In the forced swim test, mice were forced to swim individually in a glass jar (height: 20 cm, diameter: 10 cm) filled with water (depth: 15 cm) at a temperature of 25 ± 2 °C for 6 min. The duration of immobility (s) was recorded during the last 4 min of a 6 min observation period. A mouse was judged to be immobile when it remained floating in an upright position with the head above the water level.

2.4.3. Assessment of locomotor activity (SMA)

The SMA was measured using activity cage (Ugo Basile, Italy). The animals were placed individually in the center of the cage and the SMA, which was measured for a period of 5 min, was expressed as activity counts per 5 min.

2.5. Biochemical assays

2.5.1. Estimation of serum costicosterone levels

After behavioural testing, 1 mL of blood sample was obtained

through cardiac puncture under ether anesthesia for the determination of serum corticosterone levels. The serum corticosterone (ng/mL) level was estimated using ELISA kit (Oxford Biomedical Research, USA) according to the manufacturer's instructions. Briefly, blood sample was centrifuged at 3000 rpm for 15 min and serum was collected for estimation of corticosterone levels. Samples, standards, controls and Cortisol-HRP conjugate were added to a micro-plate coated with mAb to cortisol and incubated at room temperature for 1 h. The bound cortisol-HRP was measured using tetramethylbenzidine (TMB) substrate. The TMB (150 μL) substrate was added to each well and incubated at room temperature for 30 min and the reading was taken at 650 nm using Spectramax M-5 (Molecular Devices, Sunnyvale, CA) multifunctional plate reader equipped with SoftmaxPro v5.4 (SMP 5.4), and a 5-parameter sigmoid minus curve fit determined unknown concentrations.

2.5.2. Determination of glutathione levels

Aliquots of brain homogenates of individual mouse in the respective treatment groups were taken and GSH concentration was determined using the method of Moron et al. (1979). Equal volume (0.4 mL) of brain supernatant and 20% trichloroacetic acid (TCA) (0.4 mL) was mixed and then centrifuged using a cold centrifuge at 10,000 rpm at 4 °C for 20 min. The supernatant (0.25 mL) was added to 2 mL of 0.6 mM DTNB and the final volume was made up to 3 mL with phosphate buffer (0.2 M, pH 8.0). The absorbance was read at 412 nm against blank reagent using a spectrophotometer. The concentrations of GSH in the brain tissues were expressed as micromoles per gram tissue (μmol/gtissue).

2.5.3. Determination of malondialdehyde levels

The levels of lipid peroxidation in the brain tissues were determined by estimating MDA formation using the thiobarbituric acid test. The MDA level was estimated according to the method of Adam-Vizi and Seregi (1982). An aliquot of 0.4 mL of the sample was mixed with 1.6 mL of Tris-KCl buffer to which 0.5 mL of 30% TCA was added. Then, 0.5 mL of 0.75% TBA was added and placed in a water bath for 45 min at 80 °C. This was then cooled in ice and centrifuged at 3000 rpm for 15 min. The clear supernatant was collected and absorbance measured against a reference blank at 532 nm using a spectrophotometer. The MDA concentration was calculated using a molar extinction coefficient of $1.56 \times 10^5\ M^{-1}\ cm^{-1}$ and values were expressed as μmoles of MDA per gram tissue.

2.5.4. Determination of super oxide dismutase levels

The level of SOD activity was determined by the method of Misra and Fridovich (1972). Briefly, 1 mL of brain homogenate was diluted in 9 mL of distilled water to make a 1 in 10 dilution. An aliquot of 0.2 mL of the diluted sample was added to 2.5 mL of 0.05M carbonate buffer (pH 10.2) to equilibrate in the spectrophotometer and the reaction was started by the addition of 0.3 mL of freshly prepared 0.3 mM adrenaline to the mixture, which was quickly mixed by inversion. The reference cuvette contained 2.5 mL buffer, 0.3 mL of adrenaline and 0.2 mL of water. The increase in absorbance at 480 nm was monitored every 30 s for 150 s.

2.5.5. Immunoassay for TNF alpha

Brain concentration of tumour necrosis factor-alpha (TNF-α) was estimated using ELISA kit (Assaypro, USA) according to the manufacturer's instructions. All reagents, standard solutions and samples were brought to room temperature before use. Samples, standards, controls and Streptavidin-peroxidase conjugate were added to a micro-plate coated with Biotinylated mouse TNF-α antibody and incubated at room temperature for 2 h. The Chromogen substrate (50 μL) was added to each well and incubated at room temperature for 20 min before the addition of Stop solution (50 μL) and reading was taken at 450 nm using Spectramax M-5 (Molecular Devices, Sunnyvale, CA) multifunctional plate reader equipped with Softmax Pro v 5.4 (SMP 5.4), and a log-log logistic curve-fit was used to determine the concentrations of the unknown sample in pg/mL.

2.6. Statistical analysis

The data were analyzed using Graph pad prism software version 4.00 and data were expressed as mean ± S.E.M. Statistical analysis of data was done using one-way ANOVA, followed by Newman-Keuls post-hoc test. P-values less than 0.05 were considered statistically significant.

3. Results

3.1. MJ reduces the duration of immobility in LPS-induced depressive-like behavior

The effects of MJ on the duration of immobility in mice treated with LPS in the TST and FST are shown in Figs. 1 and 2. One-way ANOVA revealed that there were significant difference between treatment groups: TST [$F(5, 30) = 111.30$, $p < 0.0001$] and FST [$F(5, 30) = 78.51$, $p < 0.0001$]. Post-hoc analysis by Newman Keuls test showed that injection of LPS (830 μg/kg, i.p.) ($p < 0.05$) significantly increased immobility time in the TST and FST when compared with vehicle, which suggests induction of depressive-like behavior in mice. However, pretreatment with MJ (5, 10 and 20 mg/kg, i.p.) produced significant ($p < 0.05$) decrease in the period of immobility in both TST and FST when compared with LPS (Figs. 1 and 2). As shown in Figs. 1 and 2, the reference drug, IMP (10 mg/kg, i.p.) also reduced the duration of immobility in a significant manner.

3.2. Effect on spontaneous motor activity (SMA)

Figure 3 showed the effect of MJ on the spontaneous motor activity of mice as measured by activity cage (Ugo Basile, Italy). One-way ANOVA showed that there were no significant difference between treatment groups: SMA [$F(5, 30) = 2.479$, $p = 0.540$. As shown in Fig. 3, neither LPS (830 μg/kg, i.p.) when given alone nor with MJ significantly changed the values of the SMA in mice. Our previous study had earlier shown that MJ, when given alone, did

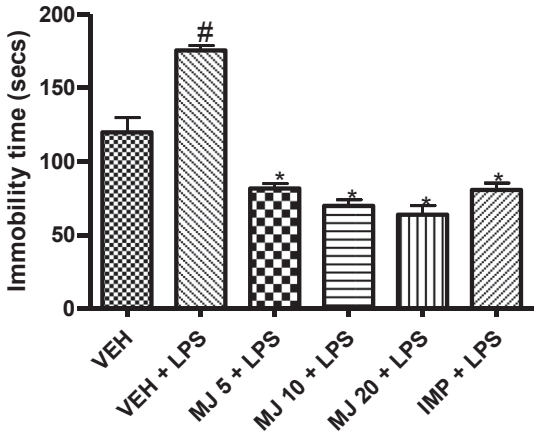

Fig. 1. Effect of methyl jasmonate (MJ) and imipramine on lipopolysaccharide (LPS)-induced depressive-like symptoms in the tail suspension test in mice. Each bar represents the mean ± S.E.M for 6 animals per group. #$p < 0.05$ compared to vehicle (VEH), *$p < 0.05$ compared to LPS (ANOVA followed by Newman Keuls test).

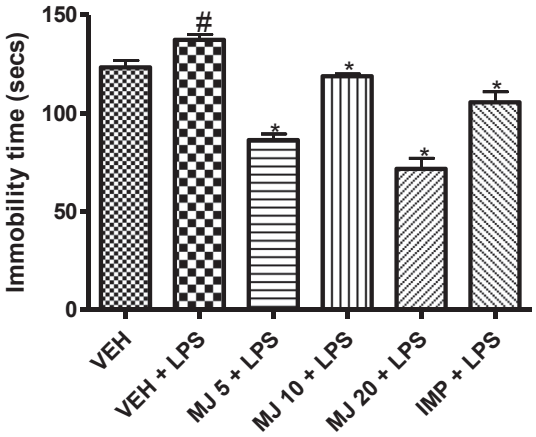

Fig. 2. Effect of methyl jasmonate (MJ) and imipramine on lipopolysaccharide (LPS)-induced depressive-like symptoms in the forced swim test in mice. Each bar represents the mean ± S.E.M for 6 animals per group. #p < 0.05 compared to vehicle (VEH), *p < 0.05 compared to LPS (ANOVA followed by Newman Keuls test).

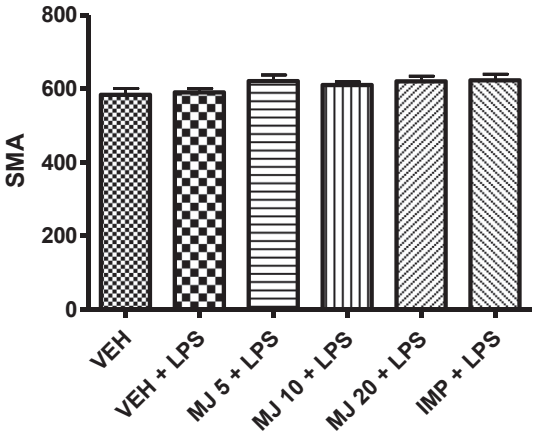

Fig. 3. Effect of methyl jasmonate (MJ) and imipramine on spontaneous motor activity (SMA) in lipopolysaccharide (LPS)-treated mice. Bars represent the mean ± S.E.M for 6 animals per group (ANOVA).

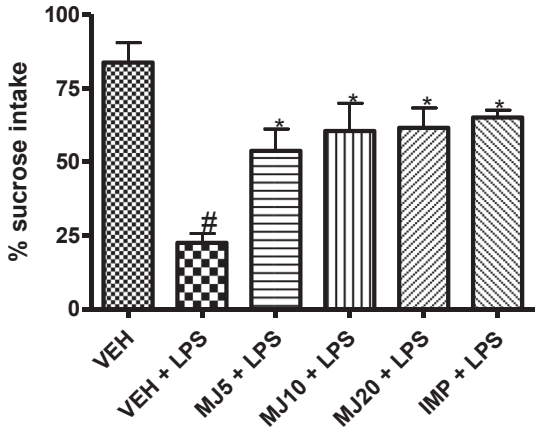

Fig. 4. Effect of methyl jasmonate (MJ) and imipramine on lipopolysaccharide (LPS)-induced decreased sucrose preference in mice. Each bar represents the mean ± S.E.M for 6 animals per group. #p < 0.05 compared to vehicle (VEH), *p < 0.05 compared to LPS (ANOVA followed by Newman Keuls test).

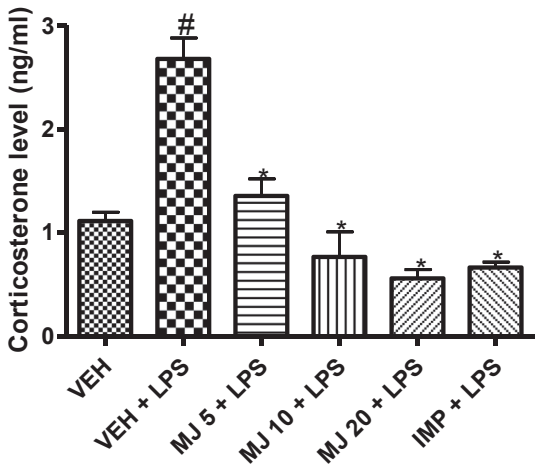

Fig. 5. Effect of methyl jasmonate (MJ) and imipramine on lipopolysaccharide (LPS)-induced serum corticosterone levels in mice. Each column represents the mean ± S.E.M for 6 animals per group. #p < 0.05 compared to vehicle (VEH), *p < 0.05 compared to LPS (ANOVA followed by Newman Keuls test).

not cause significant alteration in SMA of mice (Umukoro et al., 2011).

3.3. MJ reverses LPS-induced anhedonia in mice

The effect of LPS-induced anhedonia as measured by the preference for sucrose intake in mice is presented in Fig. 4. One-way ANOVA showed that there were significant difference between treatment groups: sucrose preference [$F(5, 30) = 17.28$, $p < 0.0001$]. Post-hoc analysis by Newman Keuls test showed that LPS (830 μg/kg, i.p.) significantly reduced the preference for sucrose intake ($p < 0.05$) in comparison with vehicle, which suggest depressive-like behaviour in mice. However, pretreatment with MJ (5, 10 and 20 mg/kg, i.p) or IMP (10 mg/kg, i.p.) produced significant ($p < 0.05$) increase in preference for the intake of sucrose, which further indicates antidepressant-like activity (Fig. 4).

3.4. MJ decreases LPS-induced elevated corticosterone and TNF alpha levels

As shown in Figs. 5 and 6, one-way ANOVA revealed that intraperitoneal injection of LPS (830 μg/kg) produced significant increases in the levels of corticosterone [$F(5, 30) = 43.23$, $p < 0.0001$] and TNF alpha [$F(5, 30) = 79.62$, $p < 0.0001$]. However, pretreatment with MJ (20 mg/kg, i.p) or IMP (10 mg/kg) reduced the increases in the levels of corticosterone and TNF alpha in LPS-treated mice in a significant manner ($p < 0.05$).

3.5. MJ reduces LPS-induced oxidative stress parameters in mice brains

The effects of MJ on LPS-induced increases in oxidative stress parameters in mice brains are shown in Table 1. One-way ANOVA revealed that there were significant difference between treatment groups: MDA [$F(5, 30) = 293.20$, $p < 0.0001$], GSH [$F(5, 30) = 153.40$, $p < 0.0001$] and SOD [$F(5, 30) = 19.10$, $p < 0.0001$]. Post-hoc analysis by Newman Keuls test show that LPS (830 μg/kg) produced a significant ($p < 0.05$) elevation of MDA level and decreased antioxidant defense system (GSH and SOD) in brains of mice suggesting increased oxidative stress. However, MJ (5–20 mg/kg) reduced MDA and elevated the concentrations of GSH in the brains of mice treated with LPS ($p < 0.05$) suggesting antioxidant

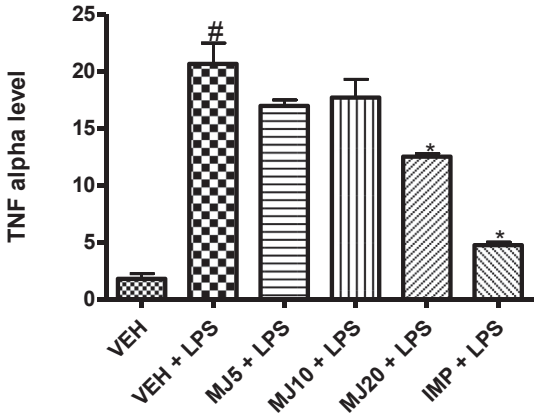

Fig. 6. Effect of methyl jasmonate (MJ) and imipramine on lipopolysaccharide (LPS)-induced brain levels of tumor necrotic factor (TNF) alpha in mice. Each column represents the mean ± S.E.M for 6 animals per group. #p < 0.05 compared to vehicle (VEH), *p < 0.05 compared to LPS (ANOVA followed by Newman Keuls test).

activity (Table 1). Similar effects were also produced in the group pretreated with IM (10 mg/kg). However, increased brain content of SOD in LPS-treated mice was not affected by MJ or IMP ($p > 0.05$).

4. Discussion

The results of this present study revealed that MJ decreased the period of immobility in LPS-treated mice subjected to TST and FST. The TST and FST are well known animal models used routinely for detection of compounds with antidepressant property (Cryan et al., 2005). The validity of these models in the discovery of antidepressant drugs is based on the observations that rodents exposed to TST and FST experienced behavioural despairs characterized by increased period of immobility (Cryan et al., 2005; Liu et al., 2016). Clinically useful antidepressant drugs are known to reduce the duration of immobility in these tests (Cryan and Slattery, 2007; Kang et al., 2010; Liu et al., 2016). Moreover, the effects of antidepressant drugs in these models have been reported to be specific since they do not increase spontaneous motor activity of the animals (Cryan and Slattery, 2007; Kang et al., 2010; Liu et al., 2016). In this study, the anti-immobility effect of MJ was not associated with central nervous system stimulation; as it did not produce any significant changes in the SMA of the animals. The ability of MJ to reduce the duration of immobility in LPS-treated mice therefore suggests the possession of an antidepressant-like activity in mice. These findings also corroborated our previous reports that MJ demonstrated anti-depressant-like effect in naïve mice subjected to TST and FST (Umukoro et al., 2011).

The effect of MJ on LPS-induced depressive-like behaviour was further investigated based on the preference for sucrose consumption in rodents (Willner et al., 1992). Anhedonia has been described as a loss of interest in pleasurable activities and the results of this study further confirm that LPS impair preference for sucrose intake suggesting precipitation of depressive-like behaviour. Indeed, preclinical studies have shown that rodents exposed to LPS display characteristic behaviours consistent with a loss of responsiveness to reward, such as sucrose consumption, which typify major depression (Moreau, 1997). However, antidepressant drugs are known to reversed LPS-induced impaired preference for sucrose consumption in rodents (Matthews et al., 1995). Thus, the finding that MJ produced increase in sucrose consumption in LPS-treated mice further indicates antidepressant-like activity.

Although altered brain levels of monoamines have been accepted for many years as the major pathological hallmark of major depression, current evidences have implicated increased levels of oxidative stress and neuroinflammation as the major factors for the genesis of the disease (Miller et al., 2009; Catena-Dell'Osso et al., 2011; Vaváková et al., 2015). Oxidative stress has been implicated in cell death, reduced neurogenesis, reduced neuronal plasticity and increased autoimmune responses, which in turn trigger and propagate neuroinflammation that further enhanced tissue destruction (Behr et al., 2012; Bakunina et al., 2015; Vaváková et al., 2015). The brain cells are known to be more susceptible to the deleterious effect of free radicals and the extent of tissue damage have been reported to be associated with increased level of MDA accompanied by decreased antioxidant defense mechanisms of the cells (Vaváková et al., 2015). High levels of MDA, a major biomarker of oxidative stress have been reported in patients with depressive illnesses (Bakunina et al., 2015; Vaváková et al., 2015). Moreover, preclinical studies have also shown that antidepressant treatments reduced oxidative stress, which was also shown to correlate with clinical outcome measures (Behr et al., 2012; Bakunina et al., 2015; Vaváková et al., 2015). Also, various biomarkers of neuroinflammation including TNF-α have been reported to be up-regulated in depressive illnesses suggesting that the disease has inflammation as the most important underlying factor (Miller et al., 2009; Catena-Dell'Osso et al., 2011; Leonard and Maes, 2012).

Although, previous studies have yielded conflicting results as to the validity of LPS in the induction of behavioural and neurochemical changes akin to clinical depression, the reports of Lopes (2016) have provided useful information on LPS-induced neurological derangement for future studies. The root of this conflict stem from the observations in some studies that LPS produce transient depressive behavior and that the changes in brain functions return to baseline after 24 h (Lopes, 2016). Meanwhile, there are also studies that show a single intraperitoneal injection of LPS that induce longlasting modifications in behavior and brain protein levels of inflammatory cytokines (Bossu et al., 2012; De La Garza, 2005; Qin et al., 2007; Fan et al., 2014). Indeed, Qin et al., 2007 reported that the systemic administration of LPS causes chronic neuroinflammation and progressive neurodegeneration in rats. The main reason for this conflicting observations can be clearly seen from the reports of Lopes (2016), which showed that LPS effects on brain functions depend largely on the dose administered. Studies

Table 1
Effects of methyl jasmonate (MJ) and imipramine (IMP) on lipopolysaccharide (LPS)-induced brain levels of biomarkers of oxidative stress in mice.

Treatment	GSH(μmol/gtissue)	MDA(μmole/g tissue)	SOD(units/mg protein)
Vehicle	5.61 ± 0.11	85.70 ± 1.08	4.14 ± 0.32
Vehicle + LPS 0.83 mg/kg	4.52 ± 0.07#	99.88 ± 1.80#	1.29 ± 0.36#
MJ 5 mg/kg + LPS	6.24 ± 0.37*	30.89 ± 2.47*	2.59 ± 0.42
MJ 10 mg/kg + LPS	9.34 ± 0.29*	68.15 ± 3.95*	2.02 ± 0.23
MJ 20 mg/kg + LPS	10.42 ± 0.30*	40.02 ± 1.38*	2.23 ± 0.44
IMP 10 mg/kg + LPS	5.38 ± 0.20*	90.75 ± 0.50*	3.15 ± 0.27*

Values represent the mean ± S.E.M for 6 animals per group. #p < 0.05 compared to vehicle; *p < 0.05 compared with LPS (ANOVA followed by Newman Keuls test).

that used low doses of LPS were shown to produce neuroinflammatory effects within a short period of time of post-injection (few hours), while studies that use high doses were found to cause neuroinflammatory effects in both the short- (few hours) and long-term that can even persist for months. In a similar study involving i.p injection of 830 μg/kg of LPS, an identical dose to the dose we used in this present study, LPS was shown to cause depressive-like behaviours after 24 h post-adminstration (O'Connor et al., 2009). According to O'Connor et al., 2009, a dose of 0.83 mg/kg was selected on the basis of its ability to induce the full spectrum of the acute sickness response and depressive-like behavior even though lower doses, for example 330 μg/kg have been shown to produce depression after 24 h post-LPS injection (Godbout et al., 2008). Thus, at this time point; 24 h post LPS injection, the depressive-like behavior is usually measured as the typical acute sickness behavior that characterize the early phase of LPS was no longer apparent or have been resolved (Godbout et al., 2008; O'Connor et al., 2009). Thus, the results of our studies are in accordance with existing literature (Godbout et al., 2008; O'Connor et al., 2009), which revealed that LPS can induce sustained behavioural and biochemical changes that epitomize major depression in experimental animals. In fact, several studies have shown that the behavioural sequelae due to systemic LPS are associated with increased oxidative stress and the release of pro-inflammatory cytokines like TNF-α, interleukin-1 beta (IL-1β), IL-6 and IL-18 (Bossu et al., 2012; De La Garza, 2005; Qin et al., 2007; Fan et al., 2014). However, TNF-α was reported as the one of the first cytokines release in response to peripheral administration of LPS, and was also shown to cause activation of microglia and subsequent release of other brain pro-inflammatory cytokines (Qin et al., 2007). Thus, TNF-α has been described as the prime mediator that convey inflammation from periphery to the brain, that ultimately leads to progressive neurodegeneration (Qin et al., 2007). Moreover, TNF-α has been implicated in the perpetuation of neuroinflammation by stimulating the activation of the transcription factor NF-κB, a potent stimulus for the production of several other pro-inflammatory mediators and concomitant impairment of behaviour (Capuron and Miller, 2011). Thus, increased TNF-α brain level in LPS-treated mice observed in this study may play a role in depressive-like behaviour due to intraperitoneal administration of LPS. However, MJ was found to reduce the brain levels of TNF-α in LPS-treated mice, which suggest that inhibition of this pro-inflammatory cytokine may contribute to its antidepressant-like effect. It is worthy to note that previous studies have shown that MJ and its congeners exhibited anti-inflammatory activity by decreasing the levels of proinflammatory cytokines in LPS-activated murine macrophage cells via inhibition of the NF-kB pathway (Lee et al., 2011). However, more studies are needful to confirm the relevance of these findings in the ability of MJ to attenuate depressive-like behaviour induced by LPS in mice.

5. Conclusion

The results of this study revealed that MJ exhibited antidepressant-like activity in LPS-treated mice and suggest its potential usefulness for the treatment of depression associated with neuropsychiatric disorders. The normalization of deregulated levels of oxidative stress parameters and inhibition of TNF-α as well as suppression of corticosterone may be playing significant roles in its antidepressant-like property observed in this study.

Conflict of interest

The authors declare that they have no conflict of interest.

Author contributions

All authors contributed to the design, conduct of behavioural and biochemical studies, data analysis and drafting as well revision of the manuscript. All authors approved the final version of the manuscript for publication and agreed to be accountable for the content of this paper.

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