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Original research article

Antidepressant-like activity of methyl jasmonate involves modulation of monoaminergic pathways in mice

Solomon Umukoro*, Adaeze Adebesin, Gladys Agu, Osarume Omorogbe, Stephen Babajide Asehinde

Neuropharmacology Unit, Department of Pharmacology and Therapeutics, College of Medicine, University of Ibadan, Ibadan, Nigeria

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ABSTRACT

Purpose: The efficacy of current antidepressant drugs has been compromised by adverse effects, low remission and delay onset of action necessitating the search for alternative agents. Methyl jasmonate (MJ), a bioactive compound isolated from *Jasminum grandiflorum* has been shown to demonstrate antidepressant activity but its mechanism of action remains unknown. Thus, the role of monoaminergic systems in the antidepression-like activity of MJ was investigated in this study.
Materials and methods: Mice were given i.p. injection of MJ (5, 10 and 20 mg/kg), imipramine (10 mg/kg) and vehicle (10 mL/kg) 30 min before the forced swim test (FST) and tail suspension test (TST) were carried out. The involvement of monoaminergic systems in the anti-depressant-like effect of MJ (20 mg/kg) was evaluated using *p*-chlorophenylalanine (pCPA), metergoline, yohimbine, prazosin, sulpiride and haloperidol in the TST.
Results: MJ significantly decrease the duration of immobility in the FST and TST relative to control suggesting antidepressant-like property. However, pretreatment with yohimbine (1 mg/kg, i.p., an α_2-adrenergic receptor antagonist) or prazosin (62.5 μg/kg, i.p., an α_1-adrenoceptor antagonist) attenuated the antidepressant-like activity of MJ. Also, pCPA; an inhibitor of serotonin biosynthesis (100 mg/kg, i.p) or metergoline (4 mg/kg, i.p., 5-HT_2 receptor antagonist) reversed the anti-immobility effect of MJ. Sulpiride (50 mg/kg, i.p., a D_2 receptor antagonist) or haloperidol (0.2 mg/kg, i.p., a dopamine receptor antagonist) reversed the anti-immobility effect of MJ.
Conclusion: The results of this study suggest that serotonergic, noradrenergic and dopaminergic systems may play a role in the antidepressant-like activity of MJ.

1. Introduction

The involvement of monoamines such as noradrenaline, serotonin and dopamine in the pathophysiology of depression and the mechanism of action of antidepressant treatments has been recognized many years ago [1,2]. The findings that pharmacological agents that increase synaptic concentrations of monoamines improved the symptoms of depression was one of the major reasons for the adoption of the monoamine hypothesis of depression for over 30 years ago [3]. Despite emerging theories challenging this popular belief, the role of central serotonergic and noradrenergic systems in the mediation of depressive symptoms and basis for the current approaches to treatment of the disease still remains very strong [3,4]. However, currently available antidepressant drugs whose action centered primarily on the enhancement of monoaminergic neurotransmission are known to be associated with several debilitating adverse effects, delayed therapeutic responses, limited efficacy and ineffectiveness in certain patients in the population [4]. In addition, relapse, and recurrence; psychosocial and physical impairment; and a high suicide rate still occur despite availability of these drugs [5]. Thus, the need to continue to search for new agents with better efficacy and tolerability still persists.

Methyl jasmonate, MJ is a well known bioactive compound that was first isolated from the essential oil of *Jasminum grandiflorum*, a jasmine plant, noted for its sweet smelling flowers. Moreover, MJ is also found virtually in all species of plant kingdom including fruits

* Corresponding author at: Neuropharmacology Unit, Department of Pharmacology and Therapeutics, College of Medicine, University of Ibadan, Ibadan, Nigeria.
E-mail addresses: umusolo@yahoo.com, solomon.umukoro@mail.ui.edu.ng (S. Umukoro).

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and vegetables, which forms significant proportion of our diets [6]. MJ is well recognized as a hormone released by plants in response to various external stressors and its stress-protective effect has been linked to activation of intracellular defense mechanisms of the plant cells [7,8]. However, the therapeutic potentials of MJ as a potent agent for the treatment of a wide range of cancer have gained global recognition [6,9]. MJ has been shown in various studies to selectively kill cancer cells without affecting normal cells and detailed toxicological investigations also confirmed that it is very safe for human consumptions [6].

However, the role of MJ in neuropsychiatric disorders was envisaged based on the studies of Hossain et al. [10], which revealed that MJ enhanced GABA currents and demonstrated sedative effect when given through inhalation in rodents. Also, we have reported in our previous studies that MJ has anti-nociceptive [11], anti-aggressive [12], anti-amnesic [13] and adaptogenic or anti-stress [14] activities in validated animal models. Furthermore, the use of jasmine in aromatherapy for depression and jasmine tea to calm nerves [15] prompted us to investigate MJ for the first time for antidepressant activity in behavioural models predictive of clinical depression [16]. The findings from this previous study revealed that MJ exhibited antidepressant-like activity in mice [16] but its mechanism of action was yet to be elucidated. Thus, this present study was designed to investigate the possible role of monoaminergic systems in the anti-depression-like activity of MJ in mice (Scheme 1).

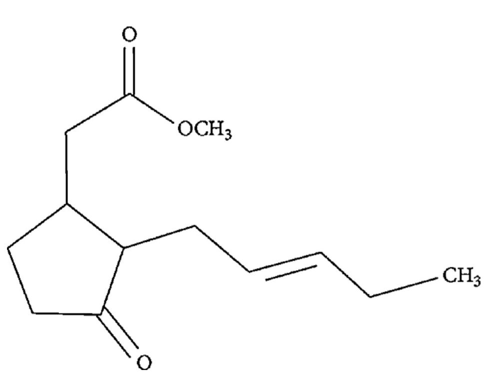
2. Materials and methods

2.1. Experimental animals

The male Swiss mice (20–25 g) used in the study were obtained from the Central Animal House of the University of Ibadan, Nigeria. The animals were kept at a temperature of about 26 °C with 12-h light:dark cycle and relative humidity of about 74%. They were fed with commercial rodent pellets and water ad libitum. The animals were allowed to acclimatize for at least one week before commencement of experiments. The experimental procedures were approved by the University of Ibadan Animal Care and Use Research Ethics Committee with approval number of UI-ACUREC/App/2015/030.

2.2. Drugs and chemicals

P-Chlorophenylalanine methyl ester (pCPA), sulpiride, prazosin, yohimbine, metergoline (all from Sigma Chemical Company, St. Louis, MO, USA) and methyl jasmonate (Sigma, Germany) were used in the study. Methyl jasmonate (MJ) was prepared according



Scheme 1. Chemical structure of methyl jasmonate [6].

to the procedure previously described [11]. Briefly, 0.5 mL of MJ was dissolved in 4.5 mL of ethanol (95%) to obtain a stock solution, which was further diluted with distilled water to attain the concentration used in the study. The final concentration of ethanol in the solution used as vehicle in this study was 1% [11]. The other drugs were dissolved in distilled water immediately before use. The doses of methyl jasmonate used in the study were selected based on the results obtained from preliminary investigations. However, in order to elucidate the possible mechanisms by which MJ causes antidepressant-like action in the TST, the animals were treated with intraperitoneal injection of pCPA (100 mg/kg), metergoline (4 mg/kg), prazosin (62.5 μg/kg), yohimbine (1 mg/kg), sulpiride (50 mg/kg) and haloperidol (0.2 mg/kg). The doses of the drugs and the route of administration used in this study were chosen based on existing data in literature [17–19].

2.3. Drug treatment

All the drugs were administered via intraperitoneal (i.p) route. The animals were divided into five treatment groups (n = 6). Mice in group I, which served as control received vehicle (10 mL/kg), group 2 received imipramine (10 mg/kg), which served as the reference drug while groups 3–5 were given MJ (5, 10, and 20 mg/kg) 30 min before FST, TST and SMA were carried out.

2.4. Experimental procedures

2.4.1. Forced swim test (FST)

This test was carried out according to the method of Porsolt et al. [20]. The animals were divided into various treatment groups and administered with the various drugs as described earlier. Then, 30 min after treatment, each mouse was placed into a Plexiglas cylinder (25 cm height, diameter 10 cm containing water to a height of 10 cm at 25 °C) and observed for the duration of immobility (s) for a period of 6 min. A mouse was judged immobile if it floats in the water in an upright position and made only slight movements to prevent sinking. The total duration of immobility was recorded during the last 4 min of the 6 min test.

2.4.2. Tail suspension test (TST)

This test was carried out according to the method of Steru et al. [21]. A new set of animals were treated with the various drugs as described earlier. Thirty minutes after treatment, mice 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 was 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.

2.4.3. Test for spontaneous motor activity (SMA)

In order to rule out any unspecific locomotor effect of MJ, new set of mice were administered with the same regimen as in the FST or TST. The SMA was measured using activity cage (Ugo Basile, Italy). The animals were placed individually in the center of the cage 30 min after drug treatment and the SMA, which was measured for a period of 5 min, was expressed as activity counts/5 min.

2.4.4. Role of serotonergic system in antidepressant activity of MJ

In order to investigate the possible contribution of the serotonergic system to the antidepressant-like activity of MJ in the TST, the animals were pretreated with metergoline (4 mg/kg, ip., a 5-HT_2 receptor antagonist) 30 min prior to administration of the most effective dose of MJ (20 mg/kg, i.p.) and were tested in the TST 30 min later [19,22]. The possible role of the serotonergic system in the antidepressant-like effect of MJ in the TST was also evaluated in a different group of animals (n = 6) pretreated with pCPA (100 mg/kg, ip., an inhibitor of serotonin biosynthesis) once daily for 4 consecutive days [22]. Then, 24 h after the last dose of pCPA, the animals were given MJ (20 mg/kg, i.p.) and were tested in the TST 30 min later.

2.4.5. Involvement of noradrenergic and dopaminergic systems

In order to investigate the possible involvement of the noradrenergic system in the antidepressant-like effect of MJ in the TST, the animals were pretreated with prazosin (62.5 μg/kg, i.p., an α_1-adrenoceptor antagonist) or yohimbine (1 mg/ kg, i.p., an α_2-adrenoceptor antagonist) 30 min before administration of MJ (20 mg/kg, i.p). Thirty minutes afterward, the animals were tested in the TST and the period of immobility was measured as earlier described. Moreover, in order to investigate the possible involvement of dopaminergic pathway in the antidepressant-like effect of MJ, mice were pretreated with sulpiride (50 mg/kg, i.p., a D_2 dopamine receptor antagonist) or haloperidol (0.2 mg/kg, i.p.; dopamine receptor antagonist) and after 30 min, they received MJ (20 mg/kg, i.p) before being tested in the TST 30 min later [17,23].

2.5. Statistical analysis

The data obtained were expressed as mean ± S.E.M (standard error of mean) and analyzed with Graph Pad Prism software version 4.00. Statistical analysis of data was done using One-way followed by Newman-Keuls post-hoc test or two-way ANOVA. P-values less than 0.05 ($p < 0.05$) were considered statistically significant.

3. Results

3.1. Methyl jasmonate decreases the duration of immobility in mice

The effects of MJ on the period of immobility in mice subjected to FST and TST are shown in Figs. 1 and 2. One-way ANOVA revealed there were significant differences between treatment groups: FST [$F(4,25) = 15.11$, $P < 0.0001$] and TST [$F(4,25) = 18.93$, $P < 0.0001$]. Post-hoc analysis by Newman-Keuls test showed that intraperitoneal injection of MJ (10 and 20 mg/kg; i.p) significantly ($p < 0.05$) reduced the immobility time in the FST and TST when compared with the control groups, which indicates antidepressant-like effect. However, the reference drug, imipramine (10 mg/kg; i.p) could only decrease the period of immobility in the TST ($P < 0.05$) (Figs. 1 and 2).

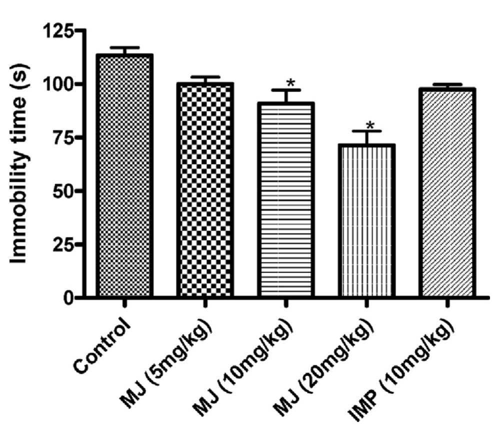


Fig. 1. Effect of methyl jasmonate (MJ) and imipramine (IMP) on the duration of immobility time in the forced swim test in mice. The control group was given vehicle (1% ethanol; 10 mL/kg, i.p.) and experimental groups received MJ (5, 10 and 20 mg/kg, i.p.) or IMP (10 mg/kg, i.p.) 30 min before the FST. Vertical bars represent the mean ± S.E.M for 6 animals per group. $^*p < 0.05$ compared to control (One-way ANOVA, followed by Newman Keuls test).

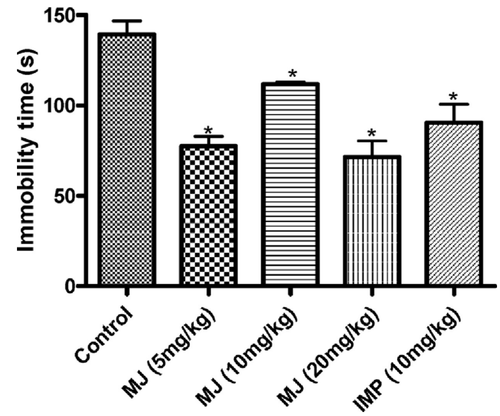


Fig. 2. Effect of methyl jasmonate (MJ) and imipramine (IMP) on the duration of immobility time in the tail suspension test in mice. The control group was given vehicle (1% ethanol; 10 mL/kg, i.p.) and experimental groups received MJ (5, 10 and 20 mg/kg, i.p.) or IMP (10 mg/kg, i.p.) 30 min before the TST. The immobility times were analyzed using one-way ANOVA, followed by post-hoc Newman Keuls' tests. Vertical bars represent the mean ± S.E.M for 6 animals per group. $^*p < 0.05$ relative to control.

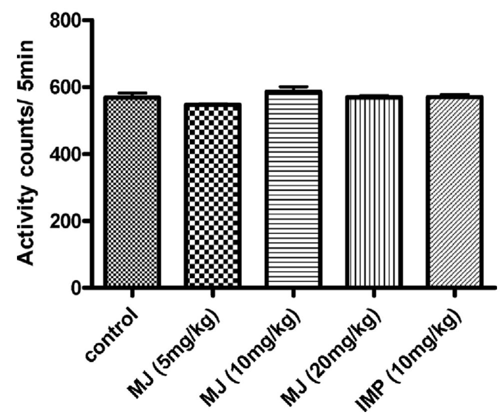


Fig. 3. Effect of Methyl jasmonate (MJ) and imipramine (IM) on spontaneous motor activity in mice. The control group was given vehicle (1% ethanol; 10 mL/kg, i.p.) and experimental groups received MJ (5, 10 and 20 mg/kg, i.p.) or IMP (10 mg/kg, i.p.) 30 min before the SMA test. The activity counts were analyzed using one-way ANOVA and each column represents the mean ± S.E.M for 6 animals per group.

3.2. Methyl jasmonate did not alter spontaneous motor activity

Fig. 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 are no significant differences between treatment groups: SMA [$F(4,25) = 1.67$, $P = 0.1882$. As shown in Fig. 3, MJ or IMP did not produce significant ($p > 0.05$) increase in the value of SMA when compared with control suggesting the absence of central nervous system stimulant effect (Fig. 3).

3.3. Involvement of serotonergic pathway

The effect of pretreatment of mice with pCPA (100 mg/kg; i.p) or with metergoline (4 mg/kg, i.p) on MJ (20 mg/kg, i.p)-induced

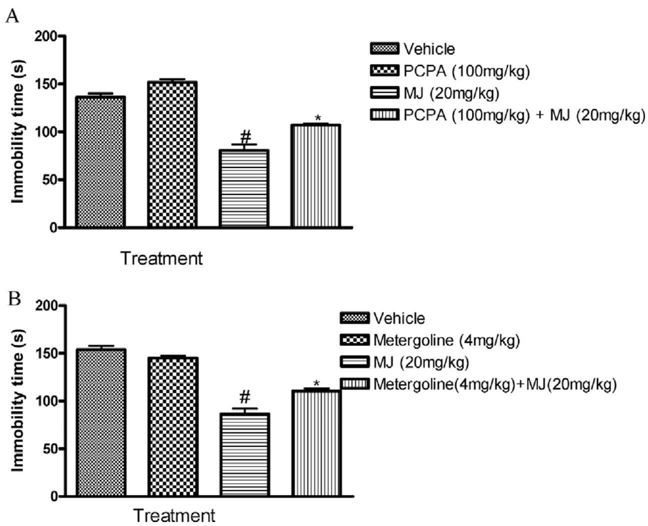


Fig. 4. Effect of pretreatment of mice with *p*-chlorophenylalanine (pCPA), panel A and metergoline (10 mg/kg, i.p., panel B) on methyl jasmonate (MJ)-induced decrease in immobility time in the tail suspension test. Each group was pre-treated with pCPA (an inhibitor of serotonin synthesis, 100 mg/kg, i.p.) once daily for 4 consecutive days, then administrated MJ (20 mg/kg, i.p.) 30 min before the TST. However, each group was pretreated with metergoline (4 mg/kg, i.p.) for 30 min before MJ (20 mg/kg, i.p.) was administered and the TST was done 30 min later. The immobility times were analyzed using two-way ANOVA. Vertical bars indicate the mean ± S.E.M for 6 animals per group. #$p < 0.05$ when compared with vehicle and *$p < 0.05$ when compared with MJ.

reduction in immobility time in the TST is shown in Fig. 4. Two-way ANOVA revealed a significant effect of MJ treatment:

[$F(2,10) = 32.69$, $P < 0.0001$], pCPA pretreatment × MJ treatment interaction; [$F(3,15) = 51.16$, $P < 0.0001$], pCPA pretreatment: [$F(2,10) = 45.04$, $P < 0.0001$]. As shown in Fig. 4A, pretreatment of mice with pCPA (100 mg/kg; i.p) once daily for 4 consecutive days before MJ (20 mg/kg; i.p) administration significantly ($p < 0.05$) attenuated its anti-immobility effect in the TST. The results in Fig. 4B revealed that pretreatment with metergoline (4 mg/kg, i.p) for 30 min before MJ (20 mg, i.p) administration also attenuated its anti-immobility effect in the TST (metergoline pretreatment: [$F(3,10) = 36.68$, $P < 0.0001$], MJ treatment: $F[3,10] = 84.44$, $P < 0.0001$], metergoline pretreatment x MJ treatment interaction: [$F(3,15) = 59.86$, $P < 0.0001$]).

3.4. Role of the noradrenergic system

Fig. 5 shows the effect of pretreatment of mice with prazosin (1 mg/kg; i.p) or with yohimbine (1 mg/kg, i.p) on MJ (20 mg/kg, i.p)-induced decrease in immobility time in the TST. Two-way ANOVA showed a significant effect of MJ treatment: [$F(3,10) = 34.66$, $P < 0.0001$], prazosin pretreatment × MJ treatment interaction: [$F(3,15) = 30.59$, $P < 0.0001$], prazosin pretreatment: [$F(2,10) = 6.21$, $P = 0.0176$]. The results presented in Fig. 5A showed that pretreatment of mice with prazosin (1 mg/kg, i.p) 30 min before administration of MJ (20 mg/kg, i.p.) reversed its antidepressant-like effect in the TST. As depicted in Fig. 5B, pretreatment of mice with yohimbine (1 mg/kg, i.p) 30 min prior to administration of MJ (20 mg/kg, i.p.) blocked its anti-immobility effect in the TST (yohimbine pretreatment: [$F(2,10) = 5.96$, $P = 0.0197$], MJ treatment: [$F(2,10) = 29.84$; $P < 0.0001$], yohimbine pretreatment x MJ treatment interaction: [$F(3,15) = 30.32$, $P < 0.0001$]).

3.5. Involvement of the dopaminergic pathway

The effect of pretreatment of mice with sulpiride (50 mg/kg; i.p) or with haloperidol (0.2 mg/kg, i.p) on MJ (20 mg/kg, i.p)-induced antidepressant-like activity in the TST is shown in Fig. 6. Two-way ANOVA revealed a significant effect of MJ treatment: [$F(2,10) = 28.66$, $P < 0.0001$], sulpiride pretreatment × MJ treatment interaction: [$F(3,15) = 31.57$; $P < 0.0001$], sulpiride pretreatment: [F

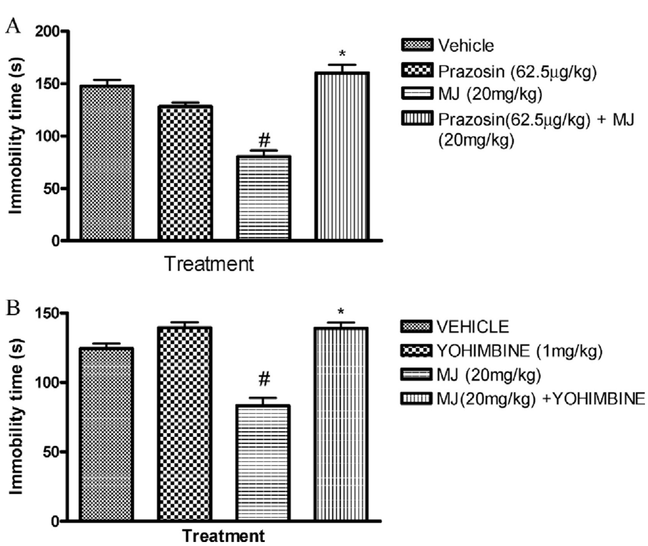


Fig. 5. Effect of pretreatment of mice with prazosin (Panel A) and yohimbine (Panel B) on methyl jasmonate (MJ)-induced decrease in immobility time in the tail suspension test. Each group was pre-treated with prazosin (an α_1-adrenoceptor antagonist, 62.5 µg/kg, i.p) or yohimbine (an α_2-adrenoceptor antagonist, 1 mg/kg, i.p) 30 min prior to i.p. injection of MJ (20 mg/kg). Thirty minutes later, the duration of immobility was measured using the TST. The immobility times were analyzed using two-way ANOVA. Each column represents the mean ± S.E.M for 6 animals per group. #$p < 0.05$ relative to vehicle and *$p < 0.05$ when compared to MJ.

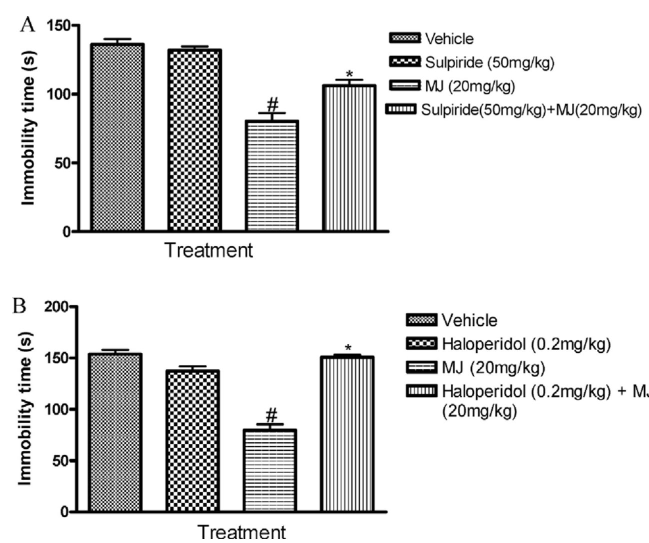


Fig. 6. Effect of pretreatment of mice with sulpride (Panel A) and haloperidol (Panel B) on methyl jasmonate (MJ)-induced decrease in immobility time in the tail suspension test. Each group was pre-treated with prazosin (an α_1-adrenoceptor antagonist, 62.5 µg/kg, i.p) or yohimbine (an α_2-adrenoceptor antagonist, 1 mg/kg, i.p) 30 min prior to i.p. injection of MJ (20 mg/kg). Thirty minutes later, the duration of immobility was measured using the TST. The immobility times were analyzed using two-way ANOVA. Each column represents the mean ± S.E.M for 6 animals per group. #$p < 0.05$ relative to vehicle and *$p < 0.05$ when compared to MJ.

(3,20) = 34.64, P < 0.0001]. Also, two-way ANOVA showed a significant effect of MJ treatment: [F(2,10) = 88.83; P < 0.0001], haloperidol pretreatment x MJ treatment interaction: [F (3,15) = 74.19; P < 0.0001], haloperidol pretreatment [F (2,10) = 5.47, P < 0.0248]. As shown in Fig. 6, anti-immobility effect of MJ (20 mg/kg, i.p.) was significantly (p < 0.05) attenuated by sulpiride (50 mg/kg, i.p) and was blocked by haloperidol (0.2 mg/kg, i.p) in the TST in mice.

4. Discussion

The results of this study showed that MJ produced a significant decrease in the period of immobility in the forced swim and tail suspension tests in mice, which suggest antidepressant-like activity. The FST and TST are well recognized validated experimental tests for the detection of compounds with antidepressant property in rodents [20,21]. In both tests, rodents are subjected to an aversive condition, from which there is no escape and after periods of agitation becomes immobile. Thus, the state of immobility is akin to a state of despairs or hopelessness that often characterized depressive illnesses and antidepressant drugs are known to decrease the period of immobility in rodents. However, antidepressant drugs have been found to cause little or no significant effect on the SMA in rodents unlike psychomotor stimulants such as amphetamine and cocaine [22,23]. The finding that the anti-immobility effect of MJ was not accompanied by increase in SMA shows that it has antidepressant-like activity in mice.

This study focused majorly on characterization of the possible mechanisms of action involved in the antidepressant-like effect of MJ that was reported in our previous study [16]. Since, monoaminergic system has been recognized as the neurochemical pathway implicated in the pathophysiology and treatment of depression [24,25], we decided firstly to investigate the involvement of the serotonergic, noradrenergic and dopaminergic systems in its anti-immobility effect in the TST. The TST is widely used for screening new antidepressant drugs and for elucidation of their mechanism (s) of action [26]. The TST is also known to be highly sensitive to the major classes of antidepressants, including the selective serotonin reuptake inhibitors (SSRIs), the tricyclic antidepressants (TCAs), and the monoamine oxidase inhibitors (MAOIs) [26,27]. Thus, the more sensitive method than the FST was used to investigate the likely mechanism(s) of action involved in the antidepressant-like effect of MJ.

To this end, the effects of some of the pharmacological agents that affect monoaminergic systems on the anti-immobility activity of MJ were investigated in this study using TST. The involvement of the serotonergic system in the antidepressant-like effect of MJ was studied using pCPA and metergoline in TST paradigm. pCPA is an inhibitor of tryptophan hydroxylase and its administration, for four consecutive days, depletes the endogenous stores of 5-HT [17–19]. Thus, pCPA has served as a pharmacological probe for elucidating the mechanism of action of novel agents that interact with serotonergic pathway. Previous studies have shown that pCPA specifically block the antidepressant action of serotonin reuptake inhibitors like fluoxetine [18,28]. The findings that pCPA attenuated the anti-mobility effect of MJ in the TST suggest that its antidepressant property may be mediated via enhancement of serotonergic neurotransmission. Moreover, the role of 5-HT_2 receptors in the pathophysiology and treatment of depressive illnesses has been recognized over the years [28–30]. Several preclinical studies have established that the pretreatment of animals with 5-HT_2 receptor antagonists like ketanserin reversed antidepressant-like effect of some compounds [28–32]. Conversely, the preferential 5-HT_{2A} receptor agonist was reported to enhance the antidepressant-like effect of some compounds [29–33]. Thus, the reduction in anti-mobility effect of MJ caused by pretreatment with metergoline, a 5-HT_{2A} receptor antagonist suggests the participation of 5-HT_2 receptors in its antidepressant-like effect in the TST.

The role of noradrenaline in the pathophysiology of endogenous depression has been well documented over many decades ago and enhancement of noradrenergic transmission is also the basis of action of some antidepressant drugs [2,24,25,34]. The tricyclic antidepressants like imipramine or desipramine with marked noradrenaline selectivity have enjoyed long patronage for the treatment of depressive illnesses but are known to have high affinity for cholinergic and histaminergic receptors, resulting in a wide range of adverse effects [2,24,32]. However, imipramine at the dose used in this study did not show significant anti-mobility effect in the FST but demonstrated antidepressant activity in the TST. The reason for this disparity is not obvious from this study but according to Cryan et al. [26] and Redrobe et al. [28], tricyclic antidepressants, which imipramine belongs are more sensitive to the TST than FST. Thus, the low sensitivity of imipramine to FST may perhaps accounts for its ineffectiveness in this antidepressant screening model. The well-known hypothermic stressful conditions associated with the FST have been implicated in its less sensitivity to response to most antidepressant drugs than the TST [26,28]. However, in this study, we use prazosin (an α_1-adrenoceptor antagonist) and yohimbine (an α_2-adrenoceptor antagonist) to evaluate the involvement of noradrenergic pathway in the antidepressant-like effect of MJ. Previous studies have shown that these adrenergic receptors are involved in some of the antidepressant-like effects of drugs in behavioral models of depression [35,36]. Moreover, the blockade of α_1-adrenergic receptors have been shown to produced depressive-like behaviours and also desensitized α_1-adrenoceptors [37] whereas antidepressant therapy enhanced the density and functional activity of these receptors in the frontal cortex and hippocampus [37]. However, upregulation of α_2-adrenoceptor autoreceptors has been reported in patients with depression while downregulation was observed with antidepressant treatments [38,39]. In the present study, we observed that pretreatment with prazosin or yohimbine significantly inhibited the antidepressant-like effect of MJ in a manner similar to previous results with other antidepressant agents [17–19,26], which suggests its possible interaction with both α_1 and α_2-adrenergic receptors. The decrease in adrenergic activity due to antagonism of central α_1-adrenergic receptors may perhaps accounts for the reduced anti-immobility effect of MJ caused by prazosin in this study. Meanwhile, antagonism of α_2-adrenoceptors has been reported to produce a complex, variable and opposing effects depending on the receptor subtypes involved [40]. However, the role of these receptor subtypes in yohimbine-induced attenuation of antidepressant effect of MJ and other substances reported in literature required further investigations. Although, the anti-immobility effect of MJ was reversed by yohimbine, the finding that MJ potentiated the lethal effect of yohimbine in our previous study [16] suggest that the involvement of noradrenergic system in its antidepressant-like effect needs further investigations.

The dopaminergic pathway is also involved in the regulation of mood and behaviours and plays a role in the pathophysiology of depression [41]. Biochemical evidence obtained from clinical studies have also shown that the plasma levels of dopamine metabolites (homovanillic acid and 3,4-dihydroxyphenylacetic acid) were significantly lower in the depressed patients indicating a diminished dopamine turnover in depressive illnesses [42]. Moreover, it has been reported that the potentiation of dopaminergic neurotransmission contribute to the therapeutic effect of antidepressant treatments [43,44]. Indeed, the anti-immobility effects of the tricyclic antidepressant imipramine were reported to be reduced by antisense dopamine D_2 receptor [44], which further implicates dopaminergic system as an important target for antidepressant action [45,46]. Moreover, clinical studies have also reported that dopamine D_2 receptor agonists are efficacious for treating patients with depressive illnesses [47]. As shown in our results, the selective dopamine D_2 receptor antagonist sulpiride attenuated the anti-immobility effect of MJ whereas haloperidol, a non-selective dopamine D_2 receptor antagonist, blocked the anti-depressant-like effect of MJ in the TST. These findings suggest that dopaminergic pathway might also play a role in the antidepression-like activity demonstrated by MJ in mice. However, in the interaction studies, the SMA of all drug combinations was not assessed, which is a limitation of this current investigation.

5. Conclusions

The results of this study suggest that methyl jasmonate produced antidepressant-like activity in mice, which may be related to activation of serotonergic, noradrenergic and dopaminergic pathways.

Conflict of interest and financial disclosure

The authors have no conflict of interest and financial disclosure to declare

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