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Involvement of Monoaminergic Systems / pathways in the mechanism of action of the Antidepressant effect of *Leptadenia hastata* (*Pers.*) Decne Methanol Leaf Extract

[1]*Ibrahim Haruna Sani, [2]Abdullahi Rabiu Abubakar, [2]Mustapha Abdullahi Huguma, [3]Aishatu Shehu, [2]Abdullahi Hamza Yaro and [2] Sani Malami

[1]Department of Clinical Pharmacology and Therapeutics,
College of Health Sciences,
Yusuf Maitama Sule University,
Kano, Nigeria.

[2]Department of Pharmacology and Therapeutics,
Faculty of Pharmaceutical Sciences,
Bayero University Kano,
Nigeria.

[3]Department of Pharmacology and Therapeutics,
Faculty of Pharmaceutical Sciences,
Ahmadu Bello University,
Zaria, Nigeria.
Email: ihsani@yumsuk.edu.ng

Abstract

Depression is a mental disorder that is highly prevalent in many parts of the globe and a source of burden to patients and their families. Existing treatments for depression are far from satisfactory because many patients with depression do not respond effectively and have significant adverse effects on standard antidepressant drugs. It is vital to develop novel antidepressant from medicinal plants, which are considered a good source of drugs with fewer adverse effects. An earlier study has established the in-vivo antidepressant effect of methanol leaf extract of Leptadenia hastata. However, no scientific data on its involvement in the monoaminergic mechanism of action. This study aimed to evaluate the involvement of monoaminergic systems in the antidepressant potential of methanol leaf extract of Leptadenia hastata. The acute toxicity studies of methanol leaf extract of Leptadenia hastata (MELH) was determined using Lorke's Method. The antidepressant effect of the MELH was evaluated using the Tail Suspension Test (TST) and Open Field Test (OFT) for psychostimulant effect. The possible mechanism of antidepressant actions of the MELH was also investigated by intraperitoneal pre-treatment with adrenergic, serotonergic, dopaminergic, opioidergic and muscarinic cholinergic receptor antagonists. The intraperitonial (i.p.) median lethal dose (LD_{50}) values were estimated to be >5000 mg/kg. Administration of standard drug, Imipramine (10 mg/kg) and MELH (250, 500, and1000 mg/kg) significantly ($p<0.01$) and dose-dependently decreased the duration of immobility time. However, the anti-immobility effect of the MELH was significantly ($p<0.05$) reversed by prazosin, cyproheptadine and naloxone, suggesting the involvement of adrenergic, serotonergic and opioidergic pathways. However, no significant interactions with dopaminergic and muscarinic cholinergic receptor

**Author for Correspondence*

antagonists were observed. This study concluded that the observed antidepressant effect in MELH is likely mediated through their interactions with adrenergic, serotonergic and opioidergic systems.

Keywords: *Leptadenia hastata*, Antidepressant effect, Anti-immobility, adrenergic and serotonergic systems

INTRODUCTION

Depression is a mental illness that has symptoms of depressed mood, loss of interest or pleasure (anhedonia), feelings of guilt or worthlessness, disturbed sleep, and anxiety (APA, 2013). The estimated number of people living with depression globally is 350 million, accounting for about 4.4% of the global population (WHO, 2017). The suicide due to depression is about 1 million lives yearly, translating to 3000 suicide deaths every day (WHO, 2017). It was predicted to be the leading cause of disease burden globally by 2030 (WHO, 2016). The Centre for Disease Control and Prevention established that depression in patients with chronic medical illness seriously affects the management and outcome of patient treatment (Shittu *et al*., 2013). There is growing evidence that patients with depression die prematurely due to medical illnesses such as cardiovascular disease, diabetes and cancer (Katon, 2011). Almost 30 million individuals suffer from depression in the African region, with Nigeria having the highest prevalence at 4.0 % of its total population (WHO, 2017). The study conducted by Salihu and Udofia (2016) in North-Western Nigeria reported a high prevalence of depression among general outpatients in Kano, with the prevalence of subtypes of depression as mild at 26.9%, moderate at 20.4% and severe at 2.5%.

Furthermore, the antidepressants therapies require several weeks (3-6) for treatment before some improvement in the symptoms and signs are observed, while a significant number of patients do not respond to the antidepressants (Goncalves *et al.,* 2012; Müller *et al.,* 2012; Adeoluwa *et al.,* 2015). Also, many synthetic drugs used as standard treatment for depression have adverse effects that can compromise their therapeutic benefit. These common adverse effects include sexual dysfunction associated with Tricyclic antidepressants/Selective serotonin reuptake inhibitors (TCAs/SSRIs), gastrointestinal or respiratory disturbances associated with monoamine oxidase inhibitors (MAOIs), anxiety (SSRIs), agitation (SSRIs), insomnia (SSRIs), drowsiness, hypertensive crisis (SSRIs/TCAs), cardiac arrhythmias (TCAs) and physical dependence (SSRIs) (Dhamija *et al.,* 2011; Adeoluwa *et al.,* 2015; Eloziia *et al.,* 2017). However, depressive illnesses are devastating and on the increase. Thus, with the high cost of acquiring synthetic drugs, side effects, toxicities, and limitations in use warrant the screening of potential alternative therapies.

Medicinal plant extracts have been shown to possess active principles that make them beneficial in managing depression. Some of the plants reported include *Hypericum perforatum L***.** (St. John's Wort) (Sarris *et al.,* 2011) and *Crocus sativus* L. (Saffron). (Talaei *et al*., 2015) and *Adansonia digitata* (*Malvaceae*) (Shehu *et al.,* 2018). *Leptadenia hastata* is a medicinal plant widely used as food in Tropical Africa, it belongs to the family *Asclepiadaceae,* locally called Yadiya in Hausa, Iran-aji in Yaruba and Isanaje in Igbo (Burkill, 1985). The plant is medicinally important in treating many ailments, including ease labour, back pain and scorpion bite (Hussain and Karatela, 1989), scabies, sexual potency, hypertension and skin diseases (Dambatta and Aliyu, 2011). This plant appears to be benign with a lack of toxicity and is used to treat evil spirits, psychiatric disorders, loss of consciousness, hallucination and urinary ailments (Burkill, 1985; Hussain and Karatela, 1989; Kinda *et al.,* 2017). An earlier study by Sani *et al.* (2019), has demonstrated the in-vivo antidepressant-like effects of methanol leaves

extract of *Leptadenia hastata*, but there is a lack of scientific data on its involvement of monoaminergic systems / pathways in the mechanism of actions. Hence, this study aimed to evaluate the involvement of monoaminergic systems in the antidepressant effect of methanol leaf extract of *Leptadenia hastata.*

MATERIALS AND METHODS

Drugs and Chemicals

The standard drugs used for the experiment were Imipramine (Tofranil® GSK, Britain), Prazosin, Cyproheptadine (Merck-Schuchardt, Germany), Amisulpride, Atropine and Naloxone (Sigma Chemical Co. St Louis USA). Solvents used include methanol (Sigma Chemical Co. St Louis USA) and distilled water.

Experimental Animals

Swiss albino mice (18 - 22 g) were obtained from the Animal House Facility of the Department of Pharmacology, Bayero University, Kano. Mice were housed and allowed to acclimatize with free access to food and water *ad libitum*, and maintained under standard laboratory conditions under the guidelines for the care and use of laboratory animals. All experimental protocols were approved by the College of Health Sciences, Animal Ethics Committee BUK (BUK/CHS/REC/VII/53).

Preparation of Plant Extracts

The leaf of *Leptadenia hastata* was collected in Kumbotso Local Government Area in Kano State. The *L. hastata* plant was identified and authenticated by a Taxonomist of the Department of Plant Biology, BUK, comparing it with an existing specimen voucher number (BUKHAN 0248). The plant was taken to the Department of Pharmacology and Therapeutics, where it was air-dried and crushed using a mortar and pestle. About 1000 *g* of the pounded leaf was extracted with 3.5 L of methanol via Soxhlet extraction. The resultant extract was dried in a water bath at 45 °C.

Acute Toxicity Studies: The extract LD_{50} determination was conducted using Lorke's (1983) method.

Antidepressant Studies

Tail Suspension Test (TST)

The TST was performed according to the method described by Steru *et al.* (1985). Animals were randomly divided into five groups of six mice each. Group I was treated (*i.p.*) with 10 ml/kg distilled water, group II with 10 mg/kg imipramine, while groups III, IV and V were treated (*i.p.*) with MELH at doses of 250 mg/kg, 500 mg/kg and 1000 mg/kg. Thirty minutes later, mice were suspended on the edge of the shelf 58 cm above a table top by an adhesive tape placed approximately 1 cm from the tip of the tail. The duration of immobility was then recorded for a 6 minutes period.

Open Field Test (OFT)

The OFT was performed according to the method described by Prut and Belzung (2003). The animals were divided randomly into groups of six each as in the TST protocol. After thirty minutes of administration, each mouse was placed in a white wooden open field apparatus (70×70×35 cm, length × breadth × height). The exploratory behaviour of the animal in the apparatus was recorded for 5 minutes. The apparatus was cleaned with 10% ethanol before

and after subjecting each mouse to the test.

Mechanistic Studies

Mechanisms of Antidepressant effect of MELH

To address the mechanisms through which MELH induced antidepressant effects in the tail suspension test, Adongo *et al.* (2015) method was adopted. Animals were divided randomly into groups of six each. Group I received distilled water as control, Group II received antagonist alone, Group III treated with MELH only, and Group IV received Imipramine. Group V and VI were treated with MELH and Imipramine, respectively, and they were pre-treated with antagonists. Mice were pre-treated with different pharmacological agents (adrenergic, serotonergic, dopaminergic, opioidergic and muscarinic cholinergic receptor antagonists) (Adongo *et al.,* 2015; Onasanwo *et al.,* 2016).

The involvement of adrenergic systems

This experiment was carried out to investigate the involvement of the adrenergic pathway in the anti-immobility effect of the MELH in the TST. Mice were pre-treated with prazosin (3 mg/kg, *i.p.*, an α_1-adrenoceptor antagonist) 15 min before administration of MELH (1000 mg/kg) or Imipramine (10 mg/kg, *i.p.*). The control group was given distilled water (10 ml/kg). Mice were tested in the Tail Suspension Test 30 min after administration of extract.

The involvement of the serotonergic system

This experiment was carried out to investigate the involvement of the serotonergic pathway in the anti-immobility effect of the MELH in the TST. Mice were pre-treated with cyproheptadine (8 mg/kg, *i.p.*, a $5HT_2$ receptor antagonist) 15 min before administration of MELH (1000 mg/kg, *i.p.*) or imipramine (10 mg/kg, *i.p.*). The control group was given distilled water (10 ml/kg). Mice were tested in the TST 30 min after administration of the extract.

The involvement of the dopaminergic system

This experiment was carried out to explore the involvement of the dopaminergic pathways on the anti-immobility effect of the MELH in the TST. Mice were pre-treated with amisulpride (80 mg/kg, *i.p.*, a D_2/D_3 dopaminergic receptor antagonist), 15 min before administration of MELH (1000 mg/kg, *i.p.*) or imipramine (10 mg/kg, *i.p.*). The control group was given distilled water (10 ml/kg, *i.p.*) and then tested in the TST 45 min after administration of an antagonist

The involvement of the cholinergic system

This experiment was carried out to investigate the involvement of the cholinergic pathway in the anti-immobility effect of MELH in the TST. Mice were pre-treated with atropine (2 mg/kg, *i.p.*, a muscarinic receptor antagonist) 15 min before administration of MELH (1000 mg/kg, *i.p.*) or imipramine (10 mg/kg, *i.p.*). The control group was given distilled water (10 ml/kg, *i.p.*); and then tested in the TST 45 min after administration of an antagonist.

The involvement of the opioidergic system

This experiment was carried out to investigate the involvement of the opioid system in the anti-immobility effect of the MELH in the TST. Mice were pre-treated with naloxone (1 mg/kg, *i.p.*, a non-selective opioid receptor antagonist) 15 min before administration of MELH (1000 mg/kg, *i.p.*) or imipramine (10 mg/kg, *i.p.*). The control group was given distilled water (10 ml/kg, *i.p.*) and then tested in the TST, 45 min after administration of an antagonist.

Statistical Analysis

All values were expressed as Mean ± SEM. Data were analysed by one-way ANOVA followed by Bonferroni as *post-hoc* tests using version 23 (IBM SPSS, Chicago, IL, USA). Values of $p < 0.05$ considered statistically significant. Results were presented in tables and figures.

RESULTS

Acute toxicity (LD_{50}) of methanol leaf extract of *L. hastata*

Result obtained from the study showed that the LD_{50} of methanol leaf extract of *L. hastata* was > 5000 mg/kg *i.p.* in mice.

Effects of MELH on tail suspension test (TST)

The MELH (250 mg/kg, 500 mg/kg, and 1000 mg/kg) decreased the duration of immobility in treated mice. A significant ($p<0.05$) decrease in immobility time was observed at all the tested doses and dose-dependent when compared to the distilled water (10 ml/kg) group. Similarly, the standard drug, Imipramine (10 mg/kg) also decreased significantly ($p<0.01$) the duration of immobility time (Table 1).

Table 1: The Effect of MELH on Immobility Time in Tail Suspension Test in Mice

Treatment (mg/kg)	Immobility Time (sec)
Control (10 ml/kg)	207.14±9.01
IMP (10)	89.11±5.68**
MELH (250)	149.14±5.88*
MELH (500)	123.25±5.67*
MELH (1000)	109.52±6.24**

The results expressed as Means ± SEM. With significance, * = $P<0.05$, ** = $P<0.01$, compared to control group using one-way ANOVA followed by Bonferroni test as the *post hoc:* n = 6, Control = Distilled water 10 ml/kg, MELH= *Leptadenia hastata* methanol extract and IMP = Imipramine

Effect of MELH on Locomotor Effect in Open Field Test

The control group in the open field arena exhibited locomotor activities marked by the number of squares crossing 54.21±4.51 (Table 2). MELH (250 mg/kg, 500 mg/kg, and 1000 mg/kg) and Imipramine (10 mg/kg) showed no significant difference in the number of squares crossed compared with the control group.

Table 2: Effect of MELH on Locomotor Effect in Open Field Test in Mice

Treatment (mg/kg)	The mean number of squares crossed
Control (10 ml/kg)	54.21±4.51
IMP (10)	51.20±4.72
MELH (250)	50.14±3.01
MELH (500)	56.34 ±4.18
MELH (1000)	61.77±5.71

The results are expressed as Means ± SEM. No significant difference ($P>0.05$) compared to the control group using one-way ANOVA followed by the Bonferroni test as the *post hoc*: n = 6, control = Distilled water 10 ml/kg, with the test duration of 5 min. MELH= *Leptadenia hastata* methanol extract

The involvement of the adrenergic system in the antidepressant effects of the MELH

Prazosin (3 mg/kg) produced a significant (p<0.01) increase in the immobility time in mice, whereas the MELH (1000 mg/kg) and imipramine (10 mg/kg) significantly (p<0.01) decreased the duration of immobility time as compared to control group treated with 10 ml/kg distilled water. However, prazosin pre-treatment significantly reversed the effect of the MELH treated group (Fig. 1).

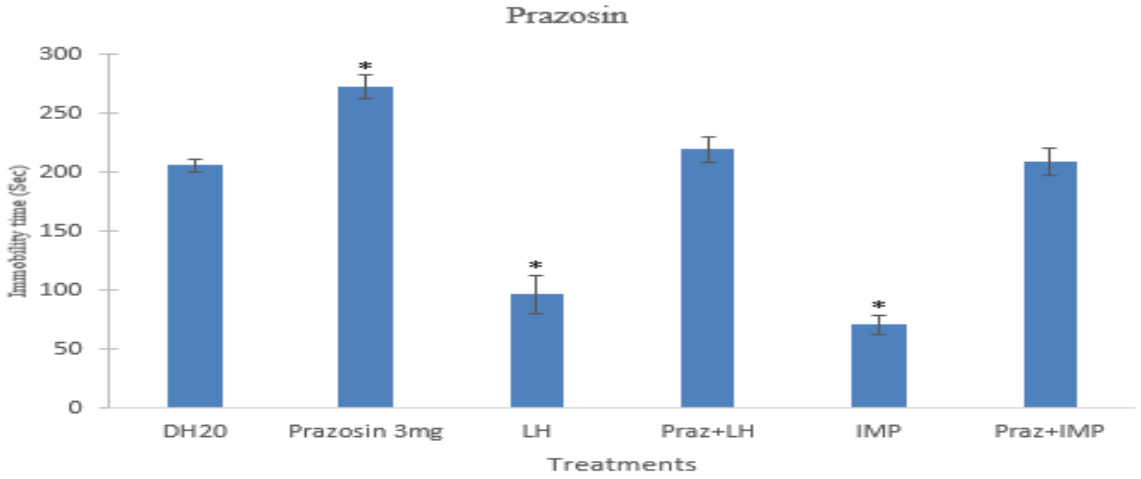

Figure 1: MELH, Imipramine and prazosin on immobility time in Tail Suspension Test. The results of this study presented as mean ± SEM (n = 6). All data were analysed using one-way ANOVA followed by Bonferroni posthoc test, *p<0.01 significant difference compared to the distilled water control group. LH=*Leptadenia hastata* methanol extract, IMP= Imipramine and DW=Distilled water.

The involvement of the serotonin receptor system in the antidepressant effects of the MELH

Cyproheptadine produced a significant (p<0.01) increase in the immobility time in mice, whereas the MELH (1000 mg/kg) and imipramine (10 mg/kg) significantly (p<0.01) decreased the duration of immobility time as compared to control group treated with 10 ml/kg distilled water. However, cyproheptadine pre-treatment significantly reversed the duration of immobility observed in MELH. On the other hand, cyproheptadine pre-treatment did not significantly change the duration of immobility of mice treated with Imipramine **(**Fig. 2).

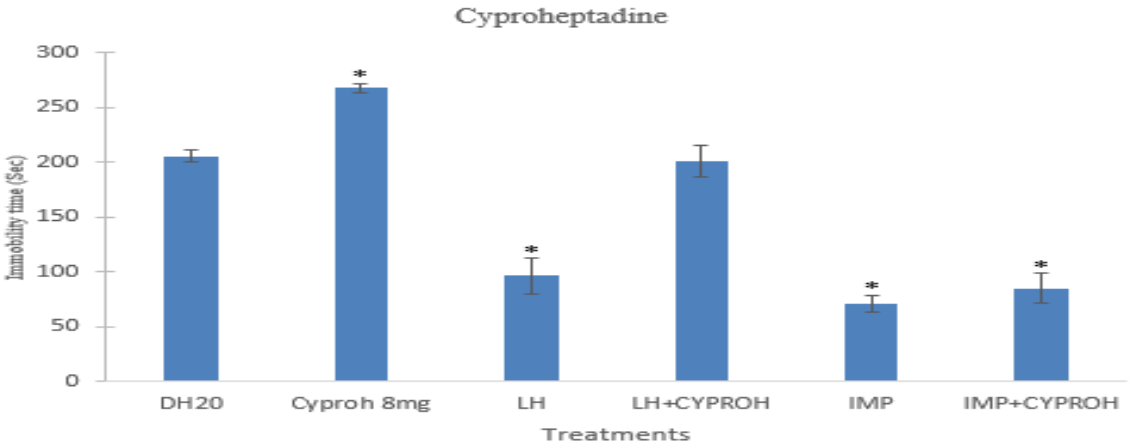

Figure 2: MELH, Imipramine and Cyproheptadine on immobility time in Tail Suspension Test. These results are presented as mean ± SEM (n = 6). All data were analysed using one-way ANOVA followed by Bonferroni *post-hoc* test, *p<0.01 significant difference compared to the distilled water control group. LH=*Leptadenia hastata*, IMP=Imipramine, Cyproh=Cyproheptadine and DW=Distilled water.

The involvement of the dopamine receptor system in the antidepressant effects of the MELH

Amisulpride produced a significant (p<0.01) increase in the immobility time in mice, whereas the MELH (1000 mg/kg) and imipramine (10 mg/kg) significantly (p<0.01) decreased the duration of immobility time when compared to control group treated with 10 ml/kg distilled water. However, amisulpride pre-treatment did not significantly change the duration of immobility of mice treated with MELH (Fig. 3).

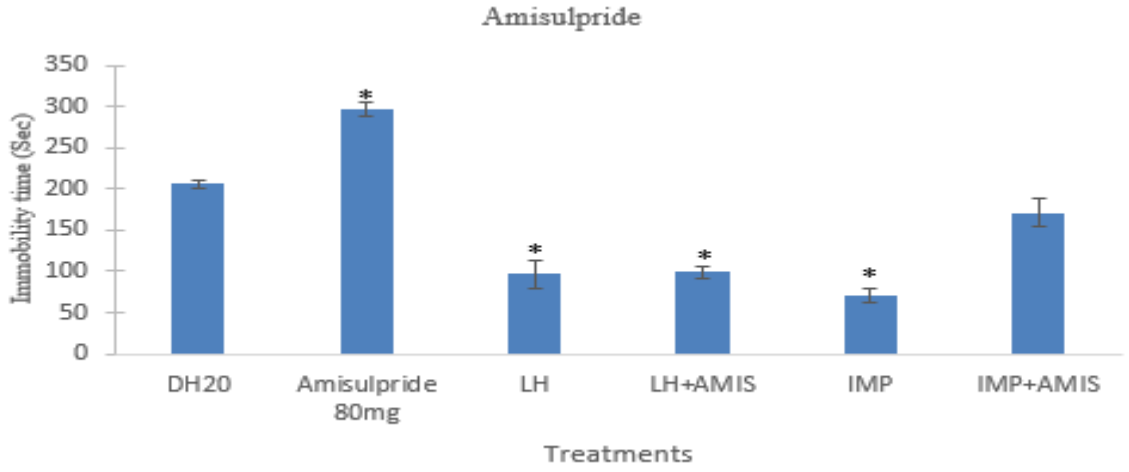

Figure 3: MELH, Imipramine and amisulpride on immobility time in Tail Suspension Test. The results of this study are presented as mean ± SEM (n = 6). All data were analysed using one-way ANOVA followed by Bonferroni *post-hoc* test, *p<0.01 significant difference compared to the distilled water control group, LH=*Leptadenia hastata* methanol, and IMP=Imipramine and DW=Distilled water.

The involvement of the opioid system in the antidepressant effects of the MELH

Naloxone produced a significant (p<0.01) increase in the immobility time in mice, whereas the MELH (1000 mg/kg) and imipramine (10 mg/kg) significantly (p<0.01) decreased the duration of immobility time as compared to control group treated with 10 ml/kg distilled water. However, naloxone pre-treatment significantly reversed the duration of immobility observed in MELH. On the other hand, naloxone pre-treatment did not significantly change the duration of immobility of mice treated with Imipramine (Fig. 4)

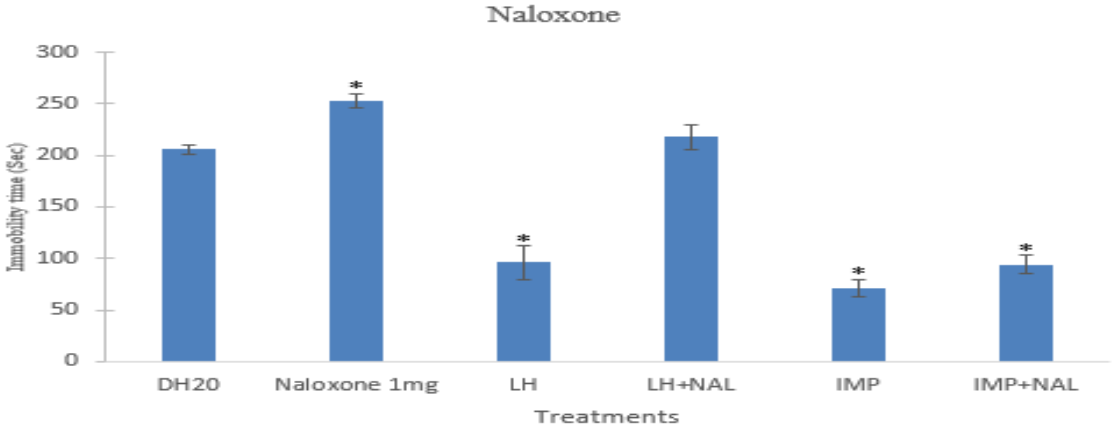

Figure 4: MELH, Imipramine and naloxone on immobility time in Tail Suspension Test. The study results are presented as mean ± SEM (n = 6). All data analysed using one-way ANOVA followed by Bonferroni *post-hoc* test, *p<0.01 significant difference compared to the distilled water control group, LH=*Leptadenia hastata*, and IMP= Imipramine and DW=Distilled water.

The involvement of the cholinergic system in the antidepressant effects of the MELH

Atropine produced a significant (p<0.01) decrease in the immobility time in mice, whereas the MELH (1000 mg/kg) and imipramine (10 mg/kg) significantly (p<0.01) decreased the duration of immobility time as compared to control group treated with 10 ml/kg distilled water. However, atropine pre-treatment did not significantly change the duration of immobility of mice treated with MELH (Fig. 5).

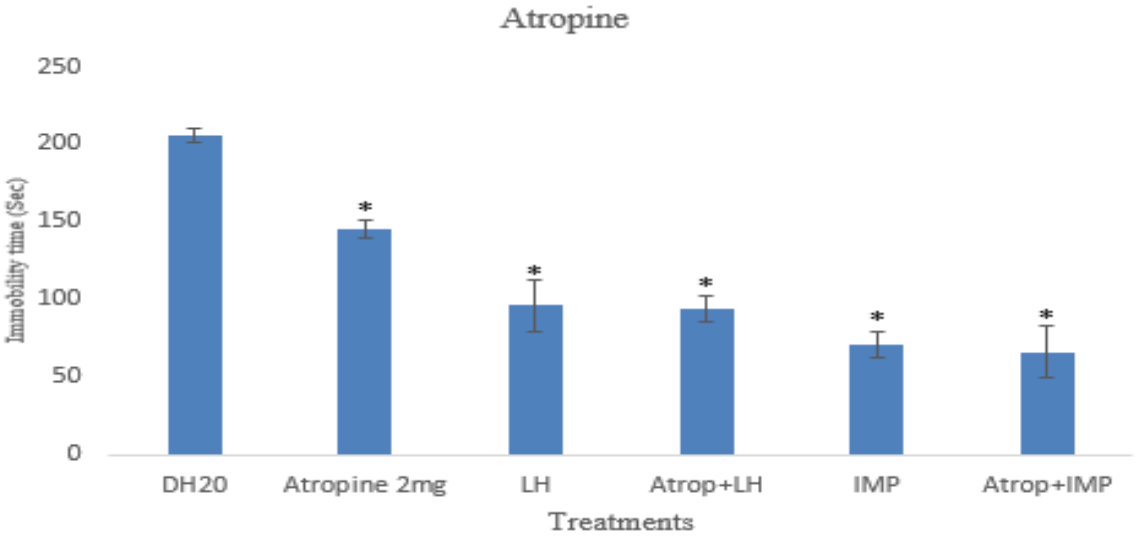

Figure 5: Effect of MELH, Imipramine and atropine on immobility time in Tail Suspension Test. The study results are presented as mean ± SEM (n = 6). Data analysed using one-way ANOVA followed by Bonferroni posthoc test, *p<0.01 significant difference compared to the distilled water control group, LH=*Leptadenia hastata,* IMP= Imipramine and DW=Distilled water.

DISCUSSION

The plant *Leptadenia hastata* is traditionally used to manage depression and validated scientifically (Sani *et al*., 2019). The tail suspension test gives some advantages over the forced swim test by allowing an objective measure of immobility in that it avoids hypothermia induced by immersion in water (Cryan *et al*., 2005). Hence, it is strongly linked with antidepressant effects in humans (Cryan *et al*., 2005). Thus, in this study, TST was chosen for the interactive study of the extract with adrenergic, serotonergic, dopaminergic, cholinergic and opioidergic systems. The TST is quite sensitive to major antidepressant drugs, such as selective serotonin reuptake inhibitors (SSRIs), tricyclics and monoamine oxidase inhibitors (MAOIs), which can effectively reduce the immobility time and increase activity (Porsolt *et al*., 1977; Steru *et al*., 1985). Therefore, in this study, the ability of MELH at the tested doses to significantly reduce the duration of immobility is an indication of their antidepressant properties. However, result from the open-field arena showed that MELH did not produce any significant changes in the number of squares crossed, which suggest that the decreased immobility time of mice in the depression model is relatively specific since they do not increase spontaneous locomotor activity. Hence, MELH decreases behavioural despair and, thus, antidepressant effect. Antidepressant drugs in clinical use cause the reduction of immobility period in these models (Steru *et al*., 1985; Fred-Jaiyesimi and Oredipe, 2013; Shehu *et al*., 2018).

Administration of prazosin (an α_1-adrenergic receptor antagonist) inhibited the antidepressant effect of Imipramine (an antidepressant drug that acts via α_1 - adrenergic receptor) (Onasanwo *et al*., 2016). In this study, pre-treatment with prazosin resulted in the reversal of the antidepressant effect of MELH, suggesting the interaction of MELH with α_1 -

adrenoceptor pathways. Hence, showed the involvement of α_1 adrenergic receptors in the antidepressant action of MELH. Our finding conforms with previous studies on extracts of *Hedyosmum brasiliense* and *Adansonia digitata* acting via these mechanisms (Goncalves *et al.,* 2012; Shehu *et al.,* 2021).

The serotonin system plays a vital role in the antidepressant effect of antidepressant drugs (Adongo *et al.,* 2015). Cyproheptadine is also a serotonin (5-HT_2 receptor) antagonist that causes sedation and reverses the antidepressant effect of the SSRIs but not tricyclic antidepressants (Hargrove and Molina, 2009). Furthermore, an antihistamine is used for allergic rhinitis and allergic skin conditions apart from its benefits in serotonin syndrome therapy (Chakraborty, 2019). In this study, pre-treatment with cyproheptadine reversed the antidepressant effect of MELH. The finding is in line with the hypothesis that activation of the 5-HT_2 receptors can produce an antidepressant effect (Goncalves *et al.,* 2012). This finding conforms to reports by Adongo *et al.* (2015) and Shehu *et al.* (2021) that cyproheptadine, a 5-HT_2 antagonist, reversed the antidepressant effect of leaves extract of *Pseudospondias microcarpa* and stem bark extract of *Adansonia digitata* respectively.

A Selegiline (dopaminergic agonist) on a dopaminergic neuronal pathway exerted an antidepressant effect, and it has been well established that dopamine agonists improve depressive symptoms (Amiri *et al.,* 2016). However, antagonism of the dopaminergic receptor pathway has been demonstrated to reverse the antidepressant effect of medicinal agents acting via dopaminergic neurotransmission (Rodrigues *et al*., 2002; Goncalves *et al*., 2012). Amisulpride is a newer agent of sulpiride, a class of benzamides highly selective for mesolimbic D_2/D_3 dopamine receptors with an antipsychotic property (Racagni *et al.,* 2004). Amisulpride affects postsynaptic D_2/D_3 receptors in the limbic and prefrontal areas, producing selective dopaminergic inhibition and eliciting an antipsychotic effect though, amisulpride effects did not significantly change the antidepressant actions of MELH. Hence, MELH was not shown to be acting via a dopaminergic neuronal pathway. This experimental finding is in line with earlier reports of the medicinal agents whose antidepressant effects were altered by administering D_2/D_3 dopaminergic receptor antagonists (Goncalves *et al.,* 2012; Shehu *et al.,* 2021).

The role of opioids as antidepressants is supported by the clinical effectiveness of μ-opioid receptor agonists such as oxycodone and oxymorphone in the treatment of refractory depression (Hegadoren *et al.,* 2009; Berrocoso *et al.,* 2013). Previous studies have also shown that the administration of mu- and delta-opioid receptor antagonists abolished the antidepressant effect produced by mu (μ) and delta (δ) opioid receptor agonists (Jutkiewicz, 2006; Carlezon *et al.,* 2006; Villard *et al*., 2011). However, the kaffa (κ) opioid receptor, on the other hand, is reported to be involved in the stress system and implicated in the pathophysiology of depression and other psychiatric disorders hence, an agonist to kaffa (κ) opioid receptor produced depressive symptoms (Berrocoso *et al.,* 2009; Crowley and Kash, 2015). Pre-treatment with naloxone (non-selective opioid receptor antagonist) reversed the antidepressant effect of MELH, suggesting that its antidepressant effect may be mediated via opioidergic neurotransmissions.

Atropine is an anticholinergic agent which antagonises acetylcholine muscarinic actions (Shehu *et al.,* 2021). In this study, pre-treatment of mice with atropine (a muscarinic receptor antagonist) did not reverse the antidepressant effect of MELH, indicating that the observed antidepressant effect of MELH may not be mediated via muscarinic cholinergic receptor

pathways. Moreover, the antidepressant potential of MELH was mediated via interactions with adrenergic, serotonergic, and opioidergic systems.

CONCLUSION

The methanol leaf extract of *Leptadenia hastata* may possess an antidepressant effect, and its likely neural mechanism of action may involve multiple receptor pathways.

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