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Anti-Depressant Potentials of Methanol Extract of *Artocarpus altilis* (Breadfruit) on Lipopolysaccharide-Induced Depression in Mice

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Abstract **Original Research Article**

This study evaluates the Anti-depressant potentials of *Artocarpus altilis* (Breadfruit) in lipopolysaccharide (LPS) induced depression in mice. A total of 36 Wistar albino mice weighing 25-30g, randomly categorized into six groups of six mice each were used for the study. Group 1 (control) received vehicle only (Normal Saline). Groups 2-4 were treated with MEAA (50, 100 and 200 mg/kg b.w. p.o, respectively) while Group 5 received imipramine (10mg/kg b.w.i.p) as the reference drug. The test groups and group 6 received LPS (0.5mg/kg i.p) 30 minutes after treatment with MEAA and IMP respectively. Test was carried out 24 hours after respective treatment of mice. The anti-depressant potentials of bread fruit on LPS-induces depression was studied using Open Field Test (OFT) and Forced Swimming Test (FST)experimental procedures and by means of brain neurochemicals evaluation. Depression-like behaviors such as line crossing (OFT)and duration of time spent immobile (FST) were observed. The test groups were compared with the control and LPS groups in both studies. The amount of protein, nitrite, reduced glutathione (GSH), Thiobarbituric acid reactive species (TBARS) and superoxide dismutase (SOD) were also evaluated. The result showed that oral administration of MEAA and imipramine (10mg/kg b.w.i.p) caused significant ($p< 0.05$) increased line crossing and reduces immobility time in mice. It also increased the level of GSH, SOD, and NO while it decreased TBARS when compared to the groups 6 animals treated with LPS (0.5mg/kgb.w.i.p) alone. In conclusion, MEAA, similarly to imipramine, has antidepressant effects in LPS-induced animal model of depression. This further implies that fruits of *Artocarpus altilis* can induce an Anti-depression like effects.

Keywords: Artocarpus altilis, Anti-depressant effect, MEAA (Methanol Extract of Artocarpus altilis, FST (Forced Swim Test), OFT (Open Field Test), LPS (lipopolysaccharide).

INTRODUCTION

Depression is a potentially life-threatening disorder that affects hundreds of millions of people all over the world. It is a state of low mood and aversion to activity that can affect a person's thoughts, behavior, feelings and sense of well-being (World Health Organization, 2023). It can occur at any age from childhood to late life and is a tremendous cost to society as this disorder causes severe distress and disruption of life and, if left untreated, can be fatal (National Institute of Mental Health, 2024).

The psychopathological state involves a triad of symptoms with low or depressed mood, anhedonia, and low energy or fatigue. Other symptoms, such as sleep and psychomotor disturbances, feelings of guilt, low self-esteem, suicidal tendencies, as well as autonomic and gastrointestinal disturbances, are also often present. They may lose interest in activities that were once pleasurable, experience loss of appetite or overeating, have problems concentrating, remembering details or making decisions and experience relationship difficulties (Villines, 2023). Insomnia, excessive sleeping, fatigue, aches, pains, or reduced energy may also be present (Sawchuk, 2022; National Institute of Mental Health, 2024).

Depression is not a homogeneous disorder, but a complex phenomenon, which has many subtypes and

probably more than one etiology (England & Sim, 2009). It includes a predisposition to episodic and often progressive mood disturbances, differences in symptomatology ranging from mild to severe symptoms with or without psychotic features, and interactions with other psychiatric and somatic disorders (Anderson & Williams-Markey, 2024)

Depression is a common mental disorder with apparent low mood as its main clinical symptom which is associated with somatic symptoms such as decreased appetite, sexual dysfunction, sleep disorders and recurrent thoughts of death (Sawchuk, 2022). It differs from sadness which is a transient emotional state and not a disorder (CDC, 2023; Whelan, 2027). Moreover, depression often comes with symptoms of anxiety (Watson, 2021). These problems can become chronic or recurrent and lead to substantial impairments in an individual's ability to take care of his or her everyday responsibilities (National Institute of Mental Health, 2024). At its worst, depression can lead to suicide. Almost 1 million lives are lost yearly due to suicide, which translates to 3000 suicide deaths every day (World Health Organization, 2025).

Breadfruit is a common name for fruits belonging to the genera *Artocarpus* (Morton, 1987). although it usually refers to Artocarpusaltilis (Ragone, 2007; Bailey, 1942). Breadfruit (*Artocarpusaltilis*) originated from A. camansi Blanco and A. marianmensistrecul (Zerega, & Mortley, 2001). The breadnut (A. camansi Blanco) is native to New Guinea, Moluccas (Indonesia) and the Philippines. Around 3000 years ago, breadfruit was first domesticated in the western pacific and spread throughout the tropics by migrating to Polynesia where it begun to be cultivated widely by pacific islanders (Morton, 1987; Ragone, 2007). Research on the efficacy of breadfruit extracts from various parts of the plants has shown promising results. Artocarpus extracts and metabolites from leaves, stem, fruit and bark contain numerous beneficial biologically active compounds and these compounds are used in the various biological activities including antibacterial, antitubercular, antiviral, antifungal, antiplatelet, antiarthritic, tyrosinase inhibitory and cytotoxicity (Jagtap & Bapat, 2004).

Previous research on the chemical constituents of *Artocarpusaltilis* has resulted in the isolation of several classes of compounds such as flavonoids (Lin et al., 1992) and triterpenoids (Altman & Zito, 1976). A previous study indicated that some flavonoids from *Artocarpusaltilis* could inhibit 5-lipoxygenas of cultured mastocytoma cells (Koshihara, 1988). The aqueous leaf extract *Artocarpusaltilis* proved has an antihypertensive as it produces negative chronotropic and hypotensive effects through α-adrenoceptor and Ca^{2+} channel antagonism (Nwokocha, 2012). In our area, due to the availability and accessibility to plant products and herbs, the alternative therapies to orthodox treatments are always these plant products and herbs (Morton, 1987; Igwe, 2008). The present study tends to investigate the ani-depressant potentials of methanol extract of *Artocarpusaltilis* (breadfruit) in LPS induced depression.

MATERIALS AND METHODS

This study was carried out in the University of Ibadan, Nigeria. Reagents used for this research were of analytical grade and purchased from Sigma Chemical Co. (St. Louis, MO, USA). Drugs were freshly prepared before use and administered in a volume of 10 ml/kg. Drug doses were also calculated as the base weight and expressed as milligram per kilogram (mg/kg). The following drugs were used: Imipramine hydrochloride (10 mg/kg, *i.p.*)(Sigma Aldrich, St. Louis, MO, USA and Dalkeith Laboratories Limited, Wosburn, MK 17, UK), Lipopolysaccharide (LPS) from Escherichia coli, strain 055: B5 (Sigma Aldrich Corp., St Louis, USA).

Experimental Animals:

36 Adult male Swiss mice (20-25g) were obtained from the animal house, College of Medicine, University of Ibadan, Nigeria. They were housed in cages at room temperature, with free access to mice cubes (Ladokun Feeds Nig. Limited, Ibadan, Nigeria) and water ad Libitum. Animals were acclimatized for two weeks. The experiments were carried out at the end of the acclimatization period.

Plant Materials:

Fresh fruit seeds (10kg) of *Artocarpusaltilis* (breadfruit) were collected, identified and authenticated at Forestry Research Institute, Nigeria (FRIN) Ibadan, Nigeria, where the voucher specimen number FHI 110483 was given and after which, fresh fruit seed of *Artocarpusaltilis* (breadfruit) were air dried at Room Temperature, grinded and was ready for extraction.

Methanol Extract:

Powdered dried *Artocarpusaltilis* extracted by cold extraction for 72 hours using methanol. The methanol extract provided a semi-solid residue (AA; 7.2kg) and the percentage yield is 96%.

DEPRESSION MODELS

The anti-depressant potentials of bread fruit on LPS-induced depression were studied using two experimental procedures. These include the Open Field Test and Forced Swimming Test. The test procedures were made up of 5 groups of 6 mice each. Group 1 (control) received vehicle only (Normal Saline). Groups 2-4 were treated with MEAA (50, 100 and 200 mg/kg b.w. p.o, respectively) while Group 5 received imipramine (10mg/kg b.w.i.p) as the reference drug. The test groups and group 6 received LPS (0.5mg/kg i.p) 30 minutes after treatment with MEAA and IMP respectively. Tests were carried out 24 hours after respective treatment of mice.

Open Field Test (OFT):

The ambulatory behaviour was assessed in an open-field test. The large open field is used for measuring anxiety, depression and exploration as well as locomotion as it has a large center arena (Rodrigues *et al.*, 2002).

***Forced Swimming Test (FST)*:**

This was performed as originally described by Porsolt and co-workers (Porsolt *et al.*, 1978).

Lipopolysaccharide-induced depression

LPS-induced depression test was carried out using 24 mice. Graded doses of MEAA (50-200mg/kg) and Imipramine (60mg/kg) were given to the four groups of animals 30 minutes before the administration of LPS (0.5mg/kg i.p) across the groups. Twenty-four hours later, the mice were screened for-like effects using the forced swimming test and open field test as described. The animals were sacrificed immediately after the behavioural studies and their brain were used for biochemical assay.

DETERMINATION NEUROCHEMICALS

Protein Analysis:

Immediately after the behavioural experiments, mice were sacrificed by cervical dislocation. Brains were quickly dissected, snap-frozen in liquid nitrogen and stored at 80°C until homogenization and Western blotting (Ahmed & Gardiner, 2011). Antibodies (Santa Cruz Biotechnology, Inc., Santa Cruz, CA, USA) were used for IDO (rat monoclonal antibody), and HPRT (hypoxanthine-guanine phosphoribosyltransferase) as an internal standard to correct for variations in protein content (rabbit polyclonal antibody), and stained with horseradish peroxidase-conjugated secondary antibodies (goat-anti-mouse, donkey-anti-rabbit, respectively). The proteins were detected using Enhanced Chemiluminescence (Pierce ECL Western Blotting Substrate, Rockford, IL, USA) and the Molecular Image Chemidoc XRS+ System (Biorad). The results were analyzed using Image Lab software (BioRad) (Fecková *et al.*, 2016).

Nitrite Assay:

This determination was based on the method described by Green *et al.*, (1982). The assay was based on Griess reaction to determine the production of NO. Briefly, 100 ml of the supernatant was incubated with 100 ml of the Griess reagent, which consisted of equal parts (1:1:1:1) of 1% sulfanilamide dissolved in 1% H_3PO_4, 0.1% N-(1-naphthyl) thylenediamine dihydrochloride and distilled water at room temperature for 10 min. The absorbance was measured at 560 nm in a microplate reader. Nitrite content was determined from a standard nitrite curve generated by using $NaNO_2$ (ranging from 0.75 to 100 mM) as standard and was expressed as mM/mg tissue.

Determination of Reduced Glutathione (GSH) Levels:

Reduced glutathione levels were evaluated to estimate endogenous defences against oxidative stress. The method was based on Elman's reagent (DTNB) reaction with free thiol groups (Ellman, 1959). The brain areas were diluted in EDTA 0.02 M buffer (10% w/v) and added to a 50% trichloroacetic acid solution. After centrifugation (3000 rpm/15 min), the supernatant of the homogenate was collected and mixed with 0.4 M trise HCl buffer, pH 8.9 and 0.01 M 5, 5-dithiobis (2-nitrobenzoic acid (DTNB)). The resultant yellow colour was immediately read at 412 nm using a spectrophotometer (Beckman coulter UV/Visible). Results were calculated based on a standard glutathione curve and expressed as ng of GSH/g wet tissue.

Thiobarbituric Acid Reactive Species (TBARS) Levels:

Lipid peroxides formation was analysed by measuring the thiobarbituric-acid reactive species (TBARS) in the homogenates (Draper et al., 1993) as an index of ROS production. The samples were mixed with 1 ml of trichloroacetic acid 10% (TCA) and 1 ml of thiobarbituric acid 0.67% (TBA), then heated in a boiling water bath for 15 min and immediately kept cold in a bath of ice. Lipid peroxidation was assessed by the absorbance at 532 nm and expressed as mmol of malonaldehyde (MDA)/g tissue.

Superoxide Dismutase:

Determination of SOD activity SOD activity was determined using a RANSODkit (Randox Labs, Crumlin, UK) (Delmas-Beauvieux & Clerc, 1995). Xanthine and xanthine oxidase were used to generate superoxide radicals that react with 2-4-iodophenyl-3-4-nitrophenol-5 phenyl tetrazolium chloride (INT) to form a red formazan dye. Substrate concentrations were 0.075 µmol/l for xanthine and 0.037µmol/l for INT. SOD inhibits this reaction by converting the superoxide radical to oxygen. An SOD unit inhibits the rate of reduction of INT by 50 % in a complex system with xanthine/xanthine oxidase. Due to the small linearity range of the test, the sample must be diluted so that the percentage of inhibition falls between 30 % and 60 %. A standard curve was prepared using the standard provided in the kit, and the value for the supernatant was read from this curve. SOD activity in the supernatant was measured at 505 nm on a Shimadzu UV-1201V spectrometer. Results were expressed as SOD U/mg protein.

Statistical Analysis

Data were analyzed using the Graph Pad prism 7 software, and Results were expressed as mean ± SEM. Comparisons was done by using One-way Analysis of Variance (One-way ANOVA) followed by Newman-Keuls' post hoc multiple comparison test.

RESULTS AND DISCUSSIONS

This result shows anti-depressant effect of ethanol extract of *Artocarpus altilis* in LPS induced depression in mice.

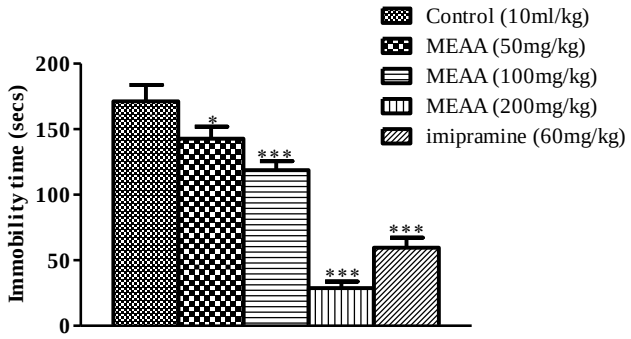

Fig 1: Behavioural potentials of methanol extract of *Artocarpusaltilis* and Imipramine on depression status of mice in Forced Swimming Test Model (FST).

The results are expressed as means ± SEM (n=6). Data were analyzed using One-way ANOVA followed by Newman-Keuls' post hoc test. *p<0.05, ***p<0.001 compared with control

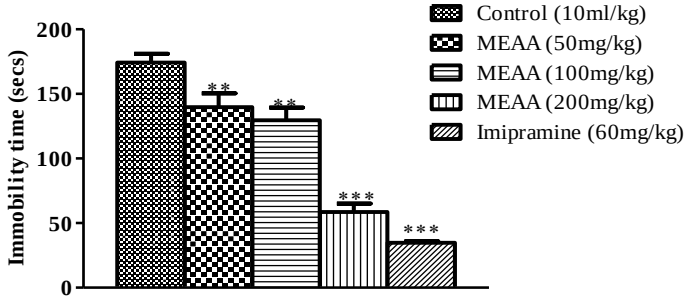

Fig 2: Behavioural potentials of methanol extract of *Artocarpusaltilis* and Imipramine on depression status of mice in Tail Suspension Test Model.

Statistical significance at **p≤0.01, ***p≤0.001 compared to control.

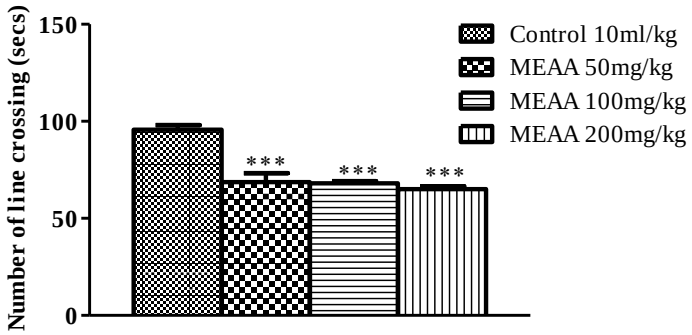

Fig 3. Behavioural potentials of methanol extract of *Artocarpusaltilis on*Locomotory status of mice in Open Field Test Model (OFT).

Statistical significance at ***p≤0.001 compared to control.

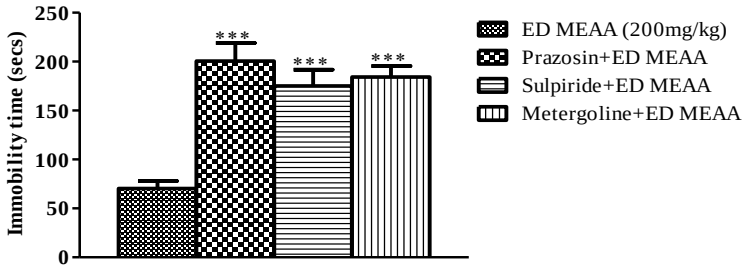

Fig 4: Test on the Mechanism of Action of MEAA using prazosin, sulpiride, as well as metergoline on depression status of mice.

Results presented as mean ± SEM (n=6). Data analyzed by Oneway ANOVA, before subjection to Newman Keuls' post hoc test. ***p<0.001 compare to MEAA (200mg/kg)

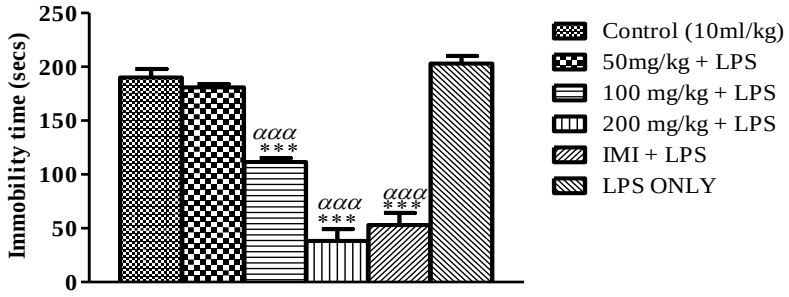

Fig 5: Behavioural potentials of MEAA *on* LPS Induced Depression-like Immobility status of mice in FST Model.
Results presented as mean ± SEM (n=6). Data analyzed by One way ANOVA, followed by Newman Keuls' post hoc test. ***p<0.001 compared with Control; ^{aaa}p<0.001 compared LPS only.

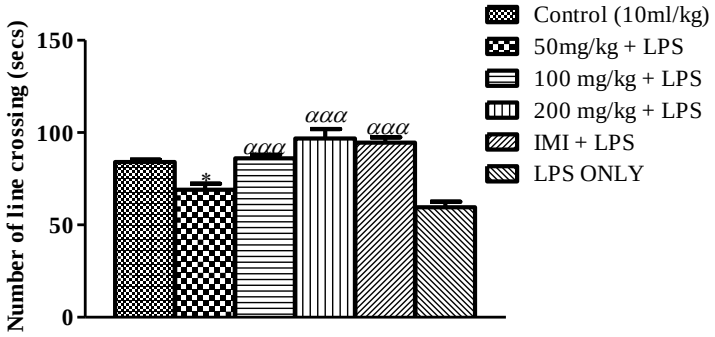

Fig 6: Behavioural potentials of MEAA *on* LPS Induced Depression-like Locomotory status of mice in OFT.
Results presented as mean ± SEM (n=6). Data analyzed by One way ANOVA, followed by Newman Keuls' post hoc test. *p<0.05; when compared with Control, ^{aaa}p<0.001 compared with LPS Only.

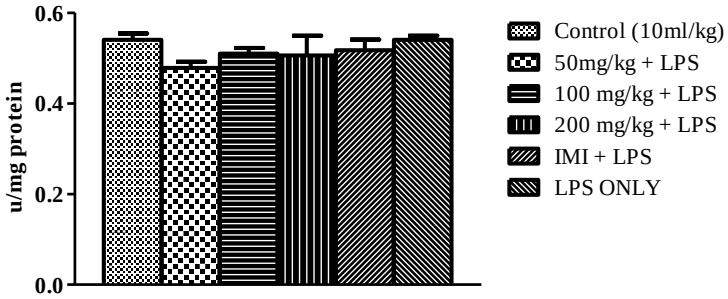

Fig 7: Determination of Protein Levels in the Brain of Animals Pre-treated with MEAA as well as Imipramine before LPS. Results presented as mean ± SEM (n=6).
Data analyzed by One way ANOVA, followed by Newman Keuls' post hoc test. Not significant when compared with both Control and LPS Only.

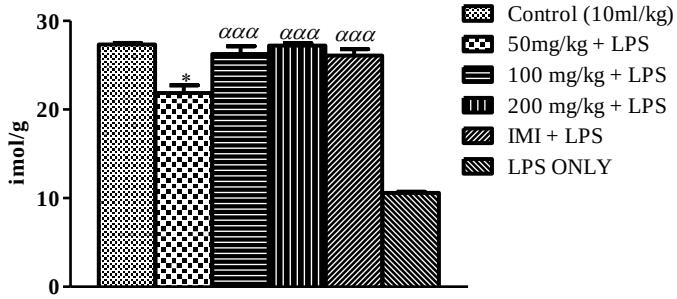

Fig 8: Effect of MEAA as well as Imipramine on the brain tissue level of Reduced Glutathione (GSH) (µmol/g tissue) content in the Brain of Mice in lipopolysaccharide- Pre-treated mice.
Results presented as mean ± SEM (n=6). Data analyzed by Oneway ANOVA, followed by Newman Keuls' post hoc test. *p<0.05 compared with Control; αααp<0.001 compared with LPS only.

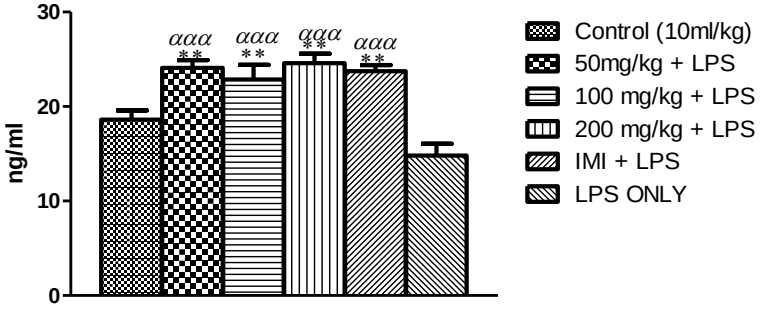

Fig 9: Determination of SOD Levels in the Brain of Mice Pre-treated with MEAA as well as Imipramine before LPS. Results presented as mean ± SEM (n=6).

Data analyzed by One way ANOVA, followed by Newman Keuls' post hoc test. **p<0.01 compared with Control; $^{\alpha}$p<0.05, ^{aaa}p<0.01 compared with LPS only.

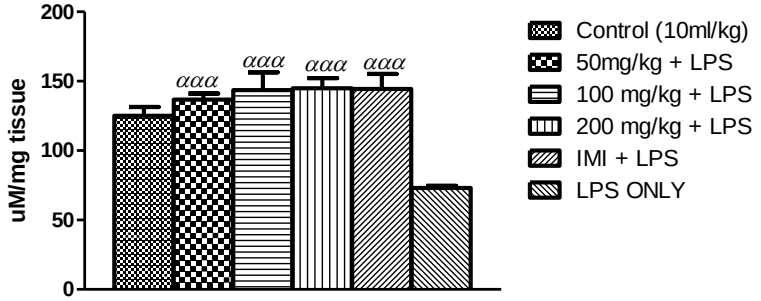

Fig 10: Determination of Nitrite Levels in the Brain of Animals Pre-treated with MEAA as well as Imipramine before LPS.

Results presented as mean ± SEM (n=6).

Data analyzed by One way ANOVA, followed by Newman Keuls' post hoc test. ^{aaa}p<0.001 compared with LPS only.

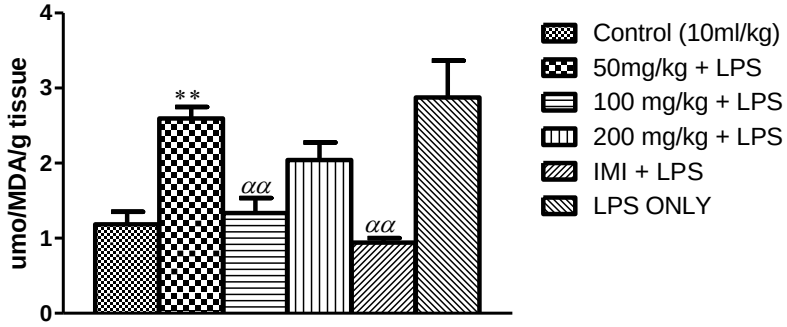

Figure 11: Determination of Thiobarbituric acid reactive species (TBARS) level in the Brain of Animals Pre-treated with MEAA as well as Imipramine before LPS.

Results presented as mean ± SEM (n=6). Data analyzed by One way ANOVA, followed by Newman Keuls' post hoc test. **p<0.01 compared with Control, ^{aa}p<0.01 compared with LPS only.

DISCUSSIONS

The social interaction test done in this study can be likened to an open field test in which the general locomotory activity of an experimental animal is tested. Open field tests carried out on rodents postulated that decreased general locomotion is a sign of depression (Andrade *et al.*, 2023)

The result of the experiment in Fig 1 revealed that oral administration of MEAA caused significant ($p<0.05$) increase in the behavioural scores of lines crossing when compared to the LPS group. The number of line crossing is usually used as a measure of locomotor activity. Therefore, anti-depressant effects of methanol extract of *Artocarpus altilis* on lipopolysaccharide induced depressive-like behaviour in mice. The results showed that 24 h pre-MEAA administration unaltered the locomotor activity. The same pattern of activity was observed in animals in pre-imipramine. Only pre-treatment with LPS decreased locomotor activity when compared to control. This might be as a result of the presence of sickness.

In Fig. 2, it was observed that the LPS administration (0.5 mg/kg, i.p.) significantly increased immobility time in the FST when compared to control animals, while MEAA (100 and 200mg/kg) and imipramine (10mg/kg) reduced immobility. LPS-

induced immobility, MEAA, similarly to imipramine, when administered pre- LPS treatment significantly decreased immobility time when compared to control animals, thereby indicating an antidepressant-like effect.

The vast majority of available antidepressant medications enhance or otherwise modulate monoaminergic neurotransmission (Jiang *et al.,* 2022). The identification of novel neurobiological targets for MDD is a research priority with the hope that these efforts would lead to the discovery of more effective and/or faster acting antidepressants (Machado-Vieira, 2009; Rizvi & Kennedy, 2011). In this regard, converging evidence indicate that disrupted neuroplasticity plays a critical role in MDD pathophysiology (Ota & Duman, 2012). For example, lower levels of neurotrophins (for example, brain-derived neurotrophic factor (BDNF) have been observed in the brain and serum of individuals with MDD when compared to healthy controls (Meshkat *et al.,* 2022).

Furthermore, the up-regulation of hippocampal BDNF signaling mediates the action of standard antidepressants (Zheng *et al.,* 2010)**.** Several lines of evidence indicate that an increase in oxidative and nitrosative stress (O&NS) is implicated in MDD pathophysiology (Maes *et al.,* 2012). Increased levels of reactive oxygen species (ROS) and reactive nitrogen species in MDD, including peroxide and NO have been reported (Liu *et al.,* 2015; Bandyopadhyay, 2025; Wigner *et al.,* 2018). Furthermore, altered levels of antioxidant defenses, such as glutathione (GSH) in the postmortem MDD brain has been demonstrated (Gawryluk *et al.,* 2011).

In this study, pre-treatment with MEAA and IMI restored LPS-induced decrease in nitrite content, an indirect measure of NO. Accordingly, a previous report indicates that the non-selective NO synthase inhibitor NG-nitro-L-arginine (L-NAME) increased LPS-induced sickness behaviour in rats, thereby suggesting that endogenous NO does not act as a mediator of LPS-induced sickness behaviour, but may rather have a protective role (Ribeiro *et al.,* 2013). One possible explanation for the decreased nitrite levels observed in this result is the possible role of endogenous NO in restraining the activation of the hypothalamic-pituitary-adrenal (HPA) axis during periods of increased cytokine and/or neuropeptide secretion, such as during immune stimulation (Uribe & Rivier, 1999; Jankord *et al.,* 2008). Of note, a recent study showed that patients with mood disorders exhibit decreased levels of nitrite/ nitrate in the cerebrospinal fluid indicating a more general decrease of NO production in this disorder (Gao *et al.,* 2012).

In addition, it was previously demonstrated that both an excess and shortage of NO may result in depressive-like behaviours and these effects are mediated by cAMP response element binding protein (CREB) activation (Hu *et al.,*2012). Accordingly, it was observed that LPS treatment promoted a decrease in GSH. Importantly, both MEAA (except 50mg/kg) and IMI to a large extent prevented and reversed these alterations.

Interestingly, standard antidepressants stabilize microglia cells following LPS stimulation (Mariani *et al.,* 2022). These observations may explain why MEAA and IMI had similar behavioural and neurochemical effects in our experimental conditions, providing support that microglia activation may be the pivotal pathophysiological event underlying LPS-induced depressive-like effects. A major limitation is the validity (e.g., pathological) of animal models of depression. However, the recent observation that a bolus LPS injection (0.4 ng/ml) to human subjects induced a pronounced transient increase in the plasma levels of TNF-a, IL-1ra, IL-6, IL-10 and cortisol, followed by a decrease in positive mood and an increase in state anxiety may provide support for the LPS-induced depressive-like behaviour (Grigoleit *et al.,* 2011; Dunjic-Kostic *et al.,* 2012). These and other series of observations including recent evidence that antidepressant treatment for mood disorders may facilitate recovery of a compromised immune response to varicella-zoster vaccination underscores the salience of the immune-inflammatory system in the pathophysiology and treatment of mood disorders (Irwin *et al.,* 2013).

In the present study, the induction of depression-like behaviour in mice by intraperitoneal administration of 0.5 mg/kg dose of LPS endotoxin increased oxidative stress in the brain. Malondialdehyde, expressed as Thiobarbituric acid reactive species (TBARS), a marker of lipid peroxidation activity (Leon & Borges, 2020) is increased in the brain tissue. This was associated with marked and significant decrease in the level of reduced glutathione, an important antioxidant defense mechanism.

CONCLUSION AND RECOMMENDATION

In conclusion, the data/results presented here indicate that MEAA, similarly to imipramine, has antidepressant effects in LPS-induced animal model of depression. This further implies that fruits of *Artocarpus altilis* can induce an Anti-depression like effects.

It is therefore recommended that, these findings be replicated in other animal models of depression. Since MEAA is widely used and inexpensive, the favourable safety profile should be ascertained, and be put to test in Major Depressive Disorder (MDD) in clinical trials, which may repurpose the therapeutic use of Bread fruit either as a sole antidepressant or as an add-on (i.e., augmentation) treatment.

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