Synthesis, molecular docking and anti-depressant activity of 2-((4-nitrobenzyl) thio)-5-(4-nitrophenyl)-1,3,4-oxadiazole (JC-41) and 3-(3-acetyl-5-(2,4-dichlorophenyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)-6-methylquinolin-2(1H)-one (JC-42) in mice model

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Abstract

The present study was designed to test the anti-depressant effects of two synthesized compounds, JC-41 and JC-42 in a chronic unpredictable mild stress (CUMS)-induced depression in the mice. Initially, the compounds were synthesized and they were docked with MAO-A inhibitor Protein (2BXR). The docking results revealed the probability of good antidepressant activity of both the compounds. Further, in-vivo anti-depressant activity was carried out in Swiss albino mice. Thirty animals were assigned to five groups (n = 6); group I received corn oil (p.o, unstressed control), group II (stressed control) administered corn oil, groups III received standard drug (Moclobemide), groups IV–V received JC-41 & JC-42. Open-field, tail suspension (TST), and forced swimming (FST) tests were used to evaluate the behavioural activity in addition to the biochemical parameters (reduced glutathione, monoamine oxidase, corticosterone, malondialdehyde and nitric oxide). The result showed that the administration of JC-41 and JC-42 during CUMS significantly ameliorated these behavioural activities and some biochemical parameters in mice. Both compounds exhibited significant antidepressant-like effects in a mice model of CUMS. The JC-42 was more effective than JC-41 in ameliorating depression in stressed mice. In conclusion, the study revealed that both the compounds relieved depression-like states through the mitigation of oxidative stress with a reduction in serum Corticosterone (CORT) and brain Monoamine Oxidase-A (MAO-A) levels.

Keywords: Depression, anti-depressant activity, MAO-A, Behavioural study, CUMS, biochemical parameters

1. Introduction

The most prevalent psychiatric disorder worldwide is depression. It is a common debilitating condition. The Diagnostic and Statistical Manual of Mental Disorders states that depression is characterized by a depressed mood and anhedonia (a diminished interest in and capacity for pleasure), along with symptoms that may include significant weight gain or loss, insomnia, psychomotor agitation or retardation, fatigue or loss of energy, a weakened capacity for thought or concentration and recurrent thoughts of death or suicide [1-2]. Additionally, depression has been linked to significant CNS disorders like Alzheimer's and Parkinson's disease, stroke, and chronic pain. It may also be a risk factor for cancer, diabetes, and cardiovascular diseases [3-9]. Different groups of antidepressants have been created over time. The existing approaches of treating depressed people are, however, insufficient. The fact that many patients only partially react and that some continue to be refractory is particularly concerning. Additionally, often prescribed drugs are linked to other side effects that are difficult to tolerate, such as cardiovascular, anticholinergic, neurologic, gastrointestinal, and other side effects. The fact that antidepressant therapy's full effectiveness doesn't manifest until 4-6 weeks or even longer into treatment is another major disadvantage [10-12].

The majority of synthetic medications used to treat depression work by affecting the brain's biogenic amines. Increasing their focus in the appropriate area of the brain as a result. Biogenic amines are rendered inactive by the MAO enzyme. Thus, by inhibiting MAO, endogenous amines' intracellular concentration may be raised, which seems to be the main contributor to the antidepressant effect. Market-available MAO medications can cause seizures, hypertension, tremors, and muscular rigidity, among other dangerous adverse effects [13]. Hence, there is a need of potent antidepressant with less or no side effects. Thus, the search for novel therapeutic strategies for the treatment of depression disorders represents an important research priority.

2. Material and Method:

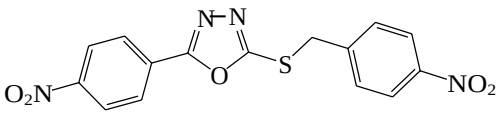
2.1 Material

All chemicals used for the study were of analytical grade and procured from various companies of repute. All assay kits were purchased from Sigma Aldrich, Japan.

2.2 Method:

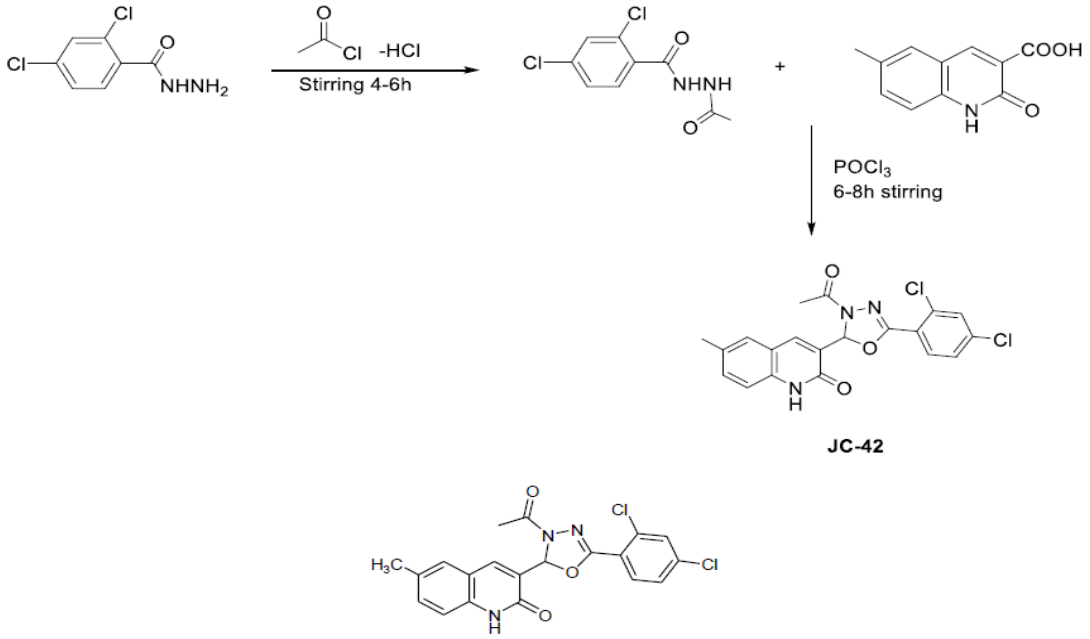
2.2.1 General Method for the Synthesis of Novel Hydrazide Derivatives

Acids are changed into their corresponding ester, which were then combined with the methanol and heated at 60°C before the addition of hydrazine hydrate (6 eq. mol.). The mixture for the reaction was refluxed for 6 hours, and the TLC analysis was done with chloroform/methanol (9:1) as the mobile phase. As soon as the reaction was finished, the reaction mixture was dumped onto crushed ice and allowed to cool to room temperature. Hydrazides precipitated out and were filtered out before being re-crystallized with ethanol. Equimolar amounts of the chemical produced hydrazide and several substituted aryl acids were added to a flask with a flat bottom, and the mixture was then chilled in an ice bath. Drop by drop, with constant stirring, 10-15 ml of $POCl_3$ were added to the reaction mixture. After adding $POCl_3$, the mixture was refluxed on a water bath for 6–8 hours while the reaction was observed using TLC and chloroform/methanol (9:1), after which the mixture was allowed to cool and crushed ice or cold water was gradually added.



2-((4-nitrobenzyl) thio)-5-(4-nitrophenyl)-1,3,4-oxadiazole (JC-41)

Same steps were followed as discussed above for the synthesis of JC-42, except the starting materials.



3-(3-acetyl-5-(2,4-dichlorophenyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)-6-methylquinolin-2(1H)-one (42)

2.2.2 Molecular Docking Study

For molecular docking investigations, the monoamine oxidase-A (MAO-A) enzyme has been employed. Molecular docking research was carried out utilizing AutoDock Tools 1.5.6. From Protein Data Bank (PDB ID: 2BXR), the crystal structure of monoamine oxidase-A co-crystallized with clorgyline inhibitor was downloaded. To fully comprehend the numerous interactions between the produced compound/ligand and enzyme active site, a molecular docking analysis of the ligand was conducted. Using AutoDock Tools 1.5.6, a molecular docking investigation for the target molecule was carried out. For AutoDock calculations, the structures were saved in a PDBQT format. Both the Lamarckian Genetic Algorithm and the Genetic Algorithm were used to do the docking calculations.

Chemdraw 11.0 was used to construct the synthesized substance. Monoamine oxidase-A's coordinate file and crystal structure were obtained from the RCSB PDB website (PDB ID: 2BXR). By removing water molecules, adding polar hydrogens, and removing further attached ligands, the protein file was created. The binding site used in the current study was chosen based on the amino acid residues involved in binding with the clorgyline inhibitor of MAO-A as found in the protein data bank. This region is thought to be the most likely to be the best accurate because it has been solved by experimental crystallographic data.

2.2.2.1 Docking Studies and Drug Likeness

Using AutoDock 4.2, docking calculations were done to determine the compounds' affinity for the protein 2BXR. Each atom type in the ligand being docked needs its own precalculated grid map, which is required by AutoDock. The helper application AutoGrid was used to calculate these maps. The six spatial degrees of freedom for orientation and torsional degrees of freedom within the grid box were made available to the compounds regarded as flexible molecules. When simulating docking operations, AutoDock evaluates conformations using a semi-empirical free energy force field. In order to determine the energy of the molecule for any given conformation, the energy functions define what factors, such as bond stretching, bending, etc., contribute to the energy of the molecule. The force field performs a two-step evaluation of binding. The transition from unbound states to the conformation of the ligand and protein in the bound state is estimated for the first step's intramolecular energetics. The intermolecular energetics of joining the ligand and protein in their bound configuration are then assessed in the second stage.

$$\Delta G = \Delta Gvdw + \Delta Ghbond + \Delta Gelec + \Delta Gtor + \Delta Gdesolv$$

The first three phrases, in that order, refer to van der Waal's, hydrogen bonds, and electrostatics. The terms "Gtor" and "Gdesolv" stand for "rotation and translation" and "desolvation upon binding" and "hydrophobicity," respectively. Molsoft performed drug-likeness and molecular property prediction for the molecule [14].

2.3 Pharmacological evaluation- In-vivo anti-depressant activity

Animal models were used to test the synthetic chemicals, JC-41 and JC-42, for antidepressant efficacy. Synthesized compounds' antidepressant effect was assessed using behavioral and biochemical metrics and compared to the reference standard medication moclobemide. In all, 30 animals were employed in the investigation.

The swiss albino mice (weight-15-20 g) were maintained in a well-ventilated room with a 12-hour light/dark cycle in standard poly propylene cages [43 × 27 × 15 (l × b × h) cms] under controlled temperature (26 ± 1ºC) and humidity (30%–40%). Throughout the experiment, they were given access to a normal pellet diet from Hyderabad-based Gold Moher and Lipton India Ltd. The CPCSEA's (Committee for the Purpose of Control and Supervision of studies on Animals) criteria were followed in all animal studies, and the IAEC's (Institutional Animal Ethics Committee) approval was obtained for the study.

2.3.1 Drug and Synthesized Compounds Administration

After the mice had had seven (7) days to adjust to their new habitat, they were randomly separated into five (5) equal groups according to their body weight. The mice in group I were vehicle controls and were not subjected to stressful situations. Mice in groups III to V were given normal medication (Moclobemide, 50 mg/kg) and synthetic substances, diluted in 2 ml of corn oil, respectively, whereas group II mice received oral treatment with 2 ml of corn oil. The levels were chosen in accordance with earlier research on the acute and sub-acute toxicity of synthetic substances. The chosen doses were less than the hazardous dose. Starting on the second day of the CUMS procedure, daily administration of CUMS, antidepressants, and the produced compounds was carried out for 5 weeks.

2.3.2 Chronic Unpredictable Mild Stress (CUMS) Procedure

To evaluate the antidepressant effects of synthetic substances in mice, an animal model of depression was adopted. Chronic unpredictable mild stress (CUMS) was used to create the chronic depression disorder model in accordance with the procedures outlined by Ekeanyanwu et al., 2021 with few protocol adjustments [15]. In a nutshell, all stressors were given once daily between 8:00 a.m. and 10:30 a.m., with the exception of the 24-hour length stressors. Mild stressors like 5 minutes of forced swimming in warm water (at 37°C) on day one and 24 hours of wet litter (100 ml of water and 50 G of mixed litter) on day 2 made up the stressors. Day 3 saw a 24 hour feed restriction, while Day 4 saw a 90-second tail pinch. Once more, a 24-hour water ban was implemented on day 5. On the 6^{th} day, they were forced to swim for 5 minutes in 40°C water before being towelled dry. On day 7, cages were tilted for approximately 24 hours (tilted cages to 450 from the plane).

The stressors were dispersed at random, spaced at least 7 days apart, and then administered three times over the course of 6 weeks, precisely on weeks 2, 4, and 6. The animals underwent behavioral tests at the conclusion of the administration period (the forced swim test and tail suspension test on day 1 and the open field test on day 2, respectively). The mice were briefly exposed to stress by being denied food for 24 hours following the forced swim test and the tail suspension test, before being put through the open field test. After an overnight fast, approximately 5 ml of blood was drawn from the retro-orbital plexus without the use of topical anesthesia, and the sera were then processed by centrifuging at 640 g and 4 °C for 10 min. They were then stored at 20 °C for various biochemical analyses. The mice were killed by decapitation with a rodent guillotine (Harvard Apparatus, USA), and their brains were swiftly and carefully removed, then rinsed in ice-cold saline (0.9% NaCl). This was done right after

blood was collected from the animals. According to Ekeanyanwu et al. (2021), the hippocampus from both sides of the brain was meticulously removed using the standard procedure. After homogenization, we collected and preserved the supernatant in dry ice [15]. The experimental protocol is shown in Figure 1.

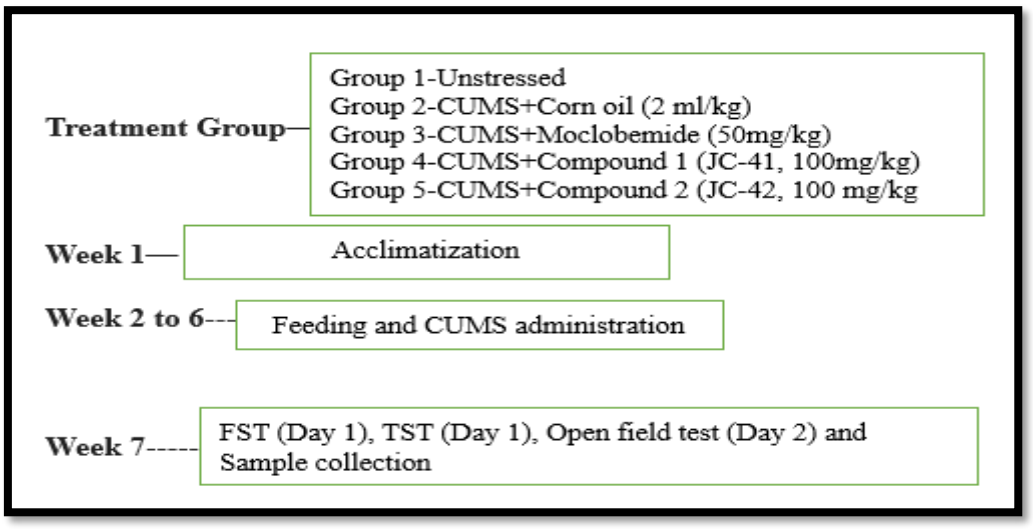


Fig. 1. Experimental Design

2.4 Behavioural Evaluation

About two hours before to behavioral evaluation, animals were brought to the testing area in a clean cage. All behavioral tests were conducted using a double-blinded method. The forced swim test, open field test, and tail suspension test were used to determine the behavioral changes.

2.4.1 Forced Swim Test and Measurement of Immobility

On week seven of the trial, the forced swim test was performed, and immobility was measured. The test setup for this study consisted of a vertical, cylindrical glass container that was 21 cm in diameter and 46 cm high, filled to a depth of 30 cm with tap water that was 25 0.5 °C. This depth was sufficient to prevent animals from touching the bottom of the container with their tails or hind paws. After a 15-minute swimming test, the mice were taken out, washed, and towelled before being put back in their cage. Each mice's water was changed individually. The following day, all the animals were forced to swim for four minutes. We observed three behaviors: (1) climbing behavior, defined as upward-directed forepaw movements along the swim chamber's side; (2) swimming behavior, defined as the (typically horizontal) movement in the swim chamber that also involves crossing into another quadrant; and (3) immobility,

defined as the absence of any other activity other than that required to keep the mice's head above the water [16].

2.4.2 Tail Suspension Test

The tail suspension test model, as defined by Can et al. (2012) of depressive-like behavior, was utilized to assess the behavior despair, a hallmark of depression. In this technique, mice were suspended upside-down on a metal rod in a tail suspension box at a height of 23.5 cm above the ground using an adhesive tape placed roughly 1 cm from the tip of the tail. Through direct observation and video capture, the total amount of immobilization time during the 6-minute test was documented. The mice were regarded as motionless if they didn't make any attempts to catch the sticky tape or body torsion or jerks for at least five seconds [17].

2.4.3 Open Field Test

The open field test, a widely used model of anxiety-like behavior created to gauge animal emotionality, involves exposing an animal to a strange environment on week 7 of the experiment while preventing its escape with surrounding walls. The open-field box was employed; it is a rectangular space with a firm floor that is made of white-painted wood and measures 60 cm × 60 cm × 40 cm. Each mouse was placed separately in a corner of the field, which had been divided into 16 identical squares at the bottom using permanent read markers. For each 10-minute cycle, the total locomotion and rearing frequency were then recorded. After each of these assays, to remove olfactory bias, the area was cleared with 70 per cent alcohol and the area allowed drying out before adding a fresh animal [18].

2.5 Biochemical Analysis

According to the instructions provided by their various manufacturers, conventional laboratory kits were used to analyze the various biochemical characteristics. Monoamine oxidase A test kit (Sigma Aldrich) and serum Corticosterone ELISA kit (DRG Diagnostics, Marburg, Germany) for mice were utilized for the assay of Brain Monoamine Oxidase (Mono-A) Activity and determination of serum Corticosterone Levels. Using the reduced glutathione assay kit (Cepharm Life Sciences, Baltimore, USA), the level of reduced glutathione (GSH) was measured. The Bradford protein assay kit (Cepharm Life Sciences, Baltimore, USA) was used to quantify the amount of protein in the supernatant taken from the mouse Hippocampi. Malondialdehyde (MDA), a sign of lipid peroxidation in animal tissues, was measured for oxidative stress using a thiobarbituric acid reacting substance (TBARS) assay kit (Bioassay

Systems, Hayward, USA). The Nitric Oxide test kit (Bioassay Systems, Hayward, USA) was used to measure the quantity of nitric oxide (NO) after converting nitrate to nitrite.

2.6. Statistical Analysis

Changes in all behavioural and biochemical parameters for all mice were determined using one way ANOVA followed by Bonferroni post hoc comparison test. A p-value of less than 0.05 was taken as significant. All data obtained were expressed as Mean ± Standard Error Mean (Mean ± SEM). SPSS 19.0 was used to analyze the data.

3.0 Results and Discussion

3.1 Synthesis of Novel compounds JC-41 & JC-42

Two substances, 2-((4-nitrobenzyl)thio)-5-(4-nitrophenyl)-1,3,4-oxadiazole (JC-41) and 3-(3-acetyl-5-(2,4-dichlorophenyl). As described in the methods section, -2,3-dihydro-1,3,4-oxadiazol-2-yl)-6-methylquinolin-2(1H)-one (JC-42) was synthesized. Equimolar amounts of the chemical produced hydrazide and several substituted aryl acids were added to a flask with a flat bottom, and the mixture was then chilled in an ice bath. Drop by drop, with constant stirring, 10-15 ml of $POCl_3$ were added to the reaction mixture. After adding $POCl_3$, the mixture was refluxed on a water bath for 6–8 hours while the reaction was observed using TLC and chloroform/methanol (9:1), after which the mixture was allowed to cool and crushed ice or cold water was gradually added. The physical characterisation data of the compounds are given in Table 1.

Table 1: Physical characterization data of synthesized compounds

Compound	IUPAC Name	Appearance	Yield	Melting Point
JC-41	2-((4-nitrobenzyl)thio)-5-(4-nitrophenyl)-1,3,4-oxadiazole	White solid	81%	190-192 ºC
JC-42	3-(3-acetyl-5-(2,4-dichlorophenyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)-6-methylquinolin-2(1H)-one	Buff white colour	85%	205-207 ºC

3.2 *In-Silico* Study

A molecular docking research and MMGBSA binding free energy calculation were carried out to better understand the molecular interactions of the produced compounds (JC-41 & JC-42) with the MAO-A (2BXR) inhibitor. Table 2 contains all of the ligands' docking scores and binding free energies, and Figure 2 shows the 2D ligand interaction diagram for the compounds JC-41 and JC-42.

Table 2: Molecular docking score and MMGBSA free-energy of binding of JC-41 & JC-42 docked against MAO-A (2BXR)

Compound	Glide docking score (kcal/mol)	MMGBSA ΔG binding (kcal/mol)
JC-41	-10.8	-30.15
JC-42	-11.5	-33.74

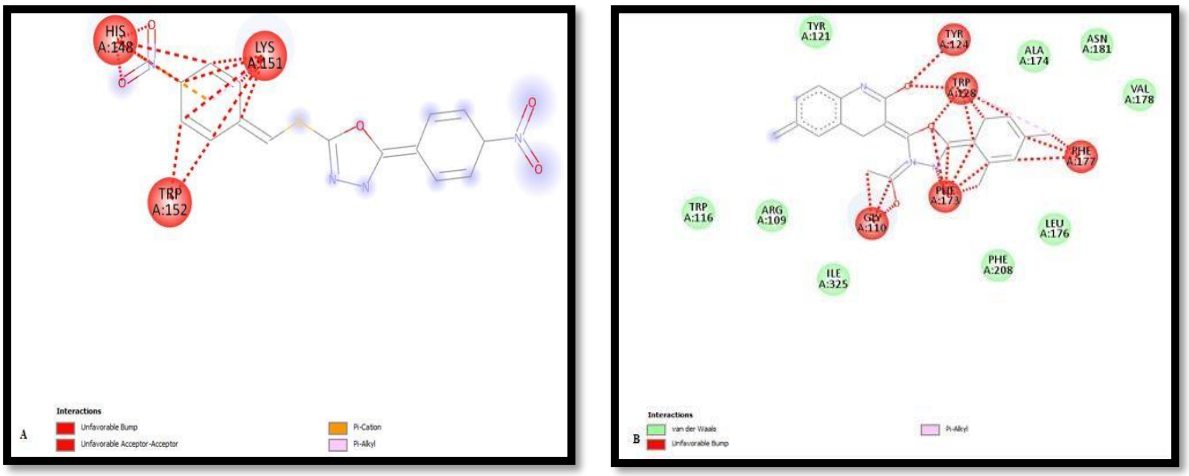


Fig. 2. Two-dimensional receptor-ligand interaction diagram for JC-41 (A) and JC-42 (B)

The compound JC-41 exhibited a good inhibitory effect on the MAO-A enzyme with a docking score of 10.80 kcal/mol and G binding of -30.15 kcal/mol with MAO-A (2BXR). The 2D ligand interaction diagram demonstrated that this substance forms a strong - stacking bond with the MAO-A enzyme (2BXR). The chemical JC-42 outperformed JC-41 in terms of docking score (-11.5 kcal/mol) and G binding (-33.74 kcal/mol).

3.3 Behaviour Assessment:

3.3.1 Forced Swim Test

The forced swim test was conducted and measurement of immobility was measured on week seven of the experiment. Generally, there was a significant increase ($p < 0.05$) in immobility duration and immobility time in the Forced swim test and Tail suspension test in mice exposed to CUMS when compared to the unstressed mice. The results were presented in figure 3 & 4.

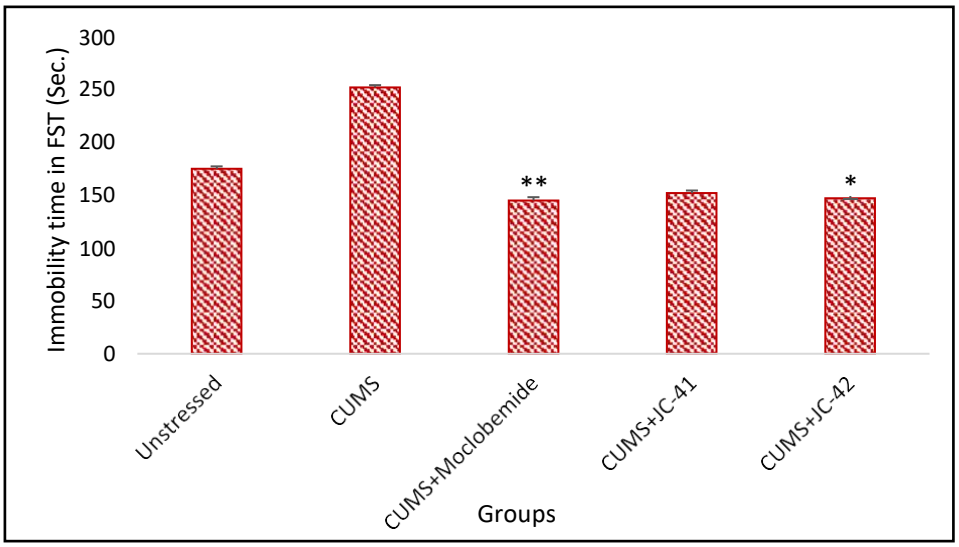


Fig. 3. Effect of JC-41 & JC-42 treatment on motor functions assessed using Forced swim test in mice model of depression. Values are expressed as mean ± SEM; n = 6/ group; A significant activity was shown by Moclobemide (**p<0.001) and JC-41 group (*p < 0.05) in comparison to CUMS group.

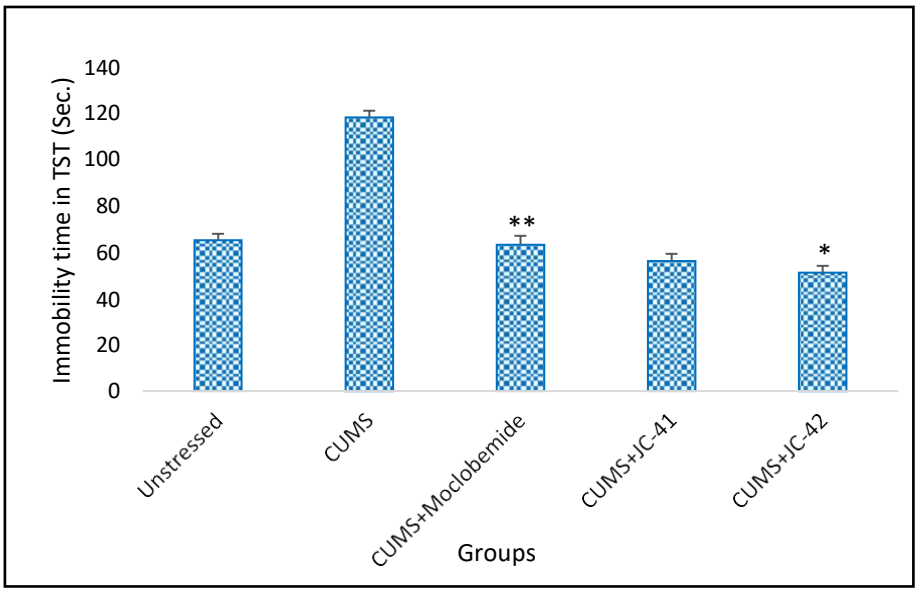


Fig. 4. Effect of JC-41 & JC-42 treatment on motor functions assessed using Tail suspension test in mice model of depression. Values are expressed as mean ± SEM; n = 6/ group; A significant activity was shown by Moclobemide (**p<0.001) and JC-41 group (*p < 0.05) in comparison to CUMS group.

Analysis of data showed differences between JC-41 and JC-42 and Moclobemide in forced swim test (FST) and tail suspension test (TST) parameters. Particularly, a trend towards a statistically significant decrease ($p < 0.05$) in immobility duration (in FST) is observed after oral administration of the compounds JC-41 & JC-42 when compared to the stressed group and corn oil (vehicle) group. However, statistical analysis indicates a significant increase ($p < 0.05$) in immobility duration in mice treated with JC-41 and JC-42 versus Moclobemide.

Similarly, there was a significant reduction ($p < 0.001$, Moclobemide & $p<0.05$, JC-42) in the number of squares crossed and the number of rearing instances in the open field test in the mice exposed to CUMS when compared to the unstressed mice (Figure 5A & 5B).

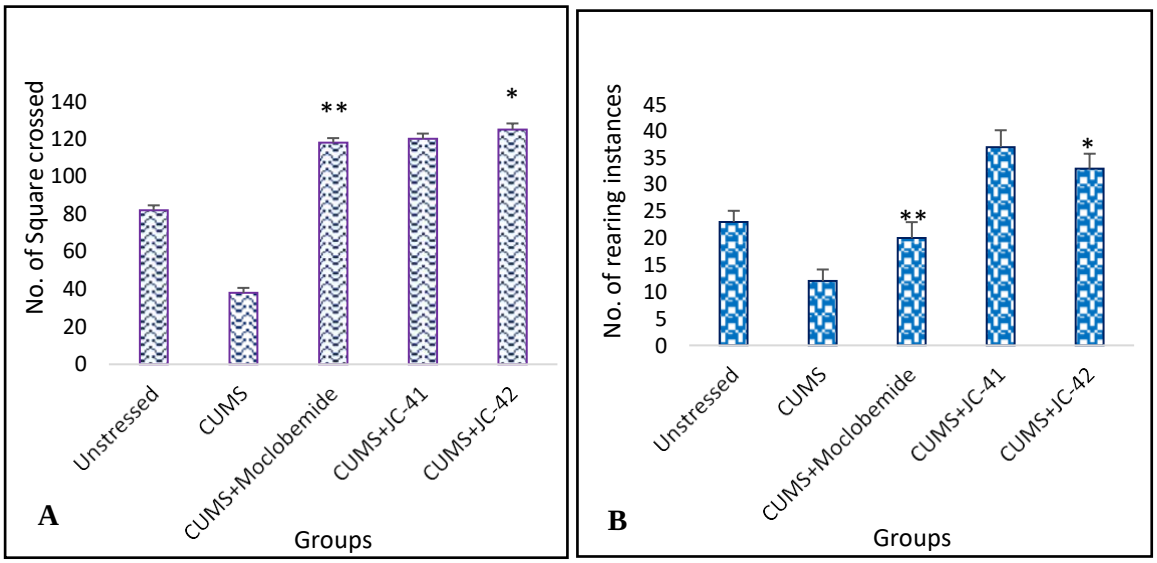


Fig. 5. Effect of JC-41 & JC-42 treatment on motor functions assessed using open field test in CUMS mice model of depression. Number of Square crossed (A) and Number of rearing instances (B). Values are expressed as mean ± SEM; n = 6/ group; A significant difference was seen in JC-42 group when compared with CUMS group ($p < 0.05$).

Analysis of data indicates that oral administration of JC-41 and JC-42 induced significant differences in the frequencies of crossing indicated in the number of squares crossed (Figure 5A) and rearing indicated in the number of rearing instances (Figure 5B) when compared to the corn oil (vehicle) group. Conversely, Moclobemide administration to stressed mice significantly ($p < 0.001$) increased the frequency of crossing and rearing when compared to the vehicle group.

3.4 Biochemical Analysis

A significant increase ($p < 0.05$) in the reduced GSH level was observed in mice administered CUMS. It was also observed that JC-41 and JC-42 significantly ($p < 0.05$) lowered the GSH level in stressed mice (Figure 6). As expected, Moclobemide significantly ($p < 0.001$) increased reduced GSH level while significantly ($p < 0.001$) lowering the various doses of the markers of oxidative stress in stressed mice. The result of the effect of treatment of JC-41, JC-42 and Moclobemide on some markers of oxidative stress such as malondialdehyde and nitric oxide was presented in figure 7A & 7B. Oral administration of JC-41 and JC-42 significantly ($p < 0.05$) increased MDA and NO levels in the stressed mice. Moclobemide administration to stressed mice expectedly decreased significantly ($p < 0.001$) the levels of MDA and NO in stressed mice.

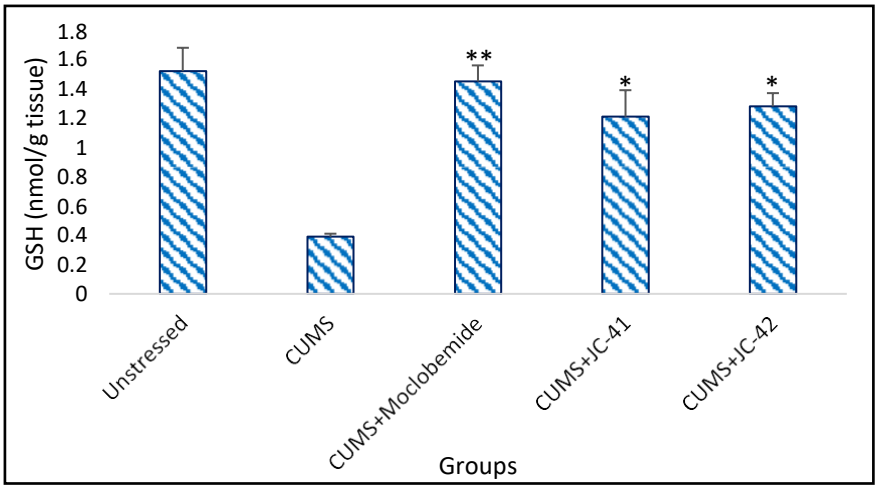


Fig. 6. Effect of JC-41 & JC-42 treatment on reduced GSH level in CUMS mice model of depression. Values are expressed as mean ± SEM; n = 6/ group; A significant difference was seen in Moclobemide group when compared with CUMS group (**p < 0.001).

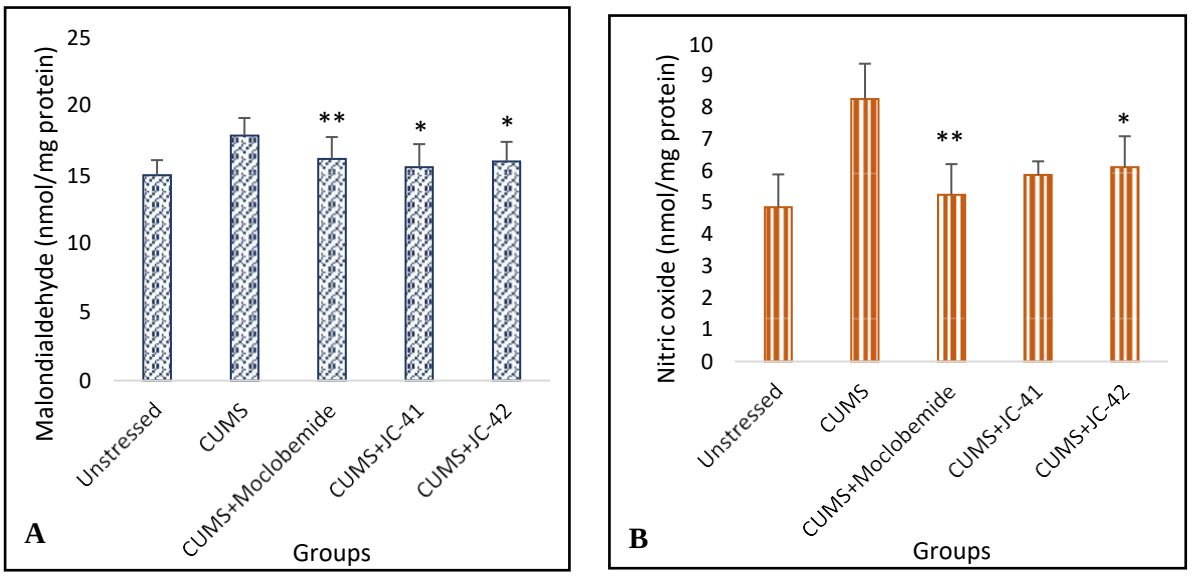


Fig. 7. Effect of JC-41 & JC-42 treatment on Malondialdehyde level (7A) and NO (7B) in CUMS mice model of depression. Values are expressed as mean ± SEM; n = 6/ group; A significant difference was seen in Moclobemide (**p<0.001) and JC-42 group (*p < 0.05) when compared with CUMS group.

Similarly, a significant increase (p < 0.05) in brain MAO-A activity was observed in the Hippocampi after administration of CUMS. Interestingly, oral administration of JC-41 and JC-42 significantly reduced brain monoamine oxidase activity in the stressed mice. As expected, administration of Moclobemide significantly decreased (p < 0.001) the brain monoamine oxidase activity in stressed mice (Figure 8A). A significant increase (p < 0.05) in the serum Corticosterone level was observed after administration of CUMS. As evident from figure 8B,

there was a significant decrease ($p < 0.05$) in the Corticosterone level in mice administered with JC-41 and JC-42 as well as Moclobemide ($p<0.001$).

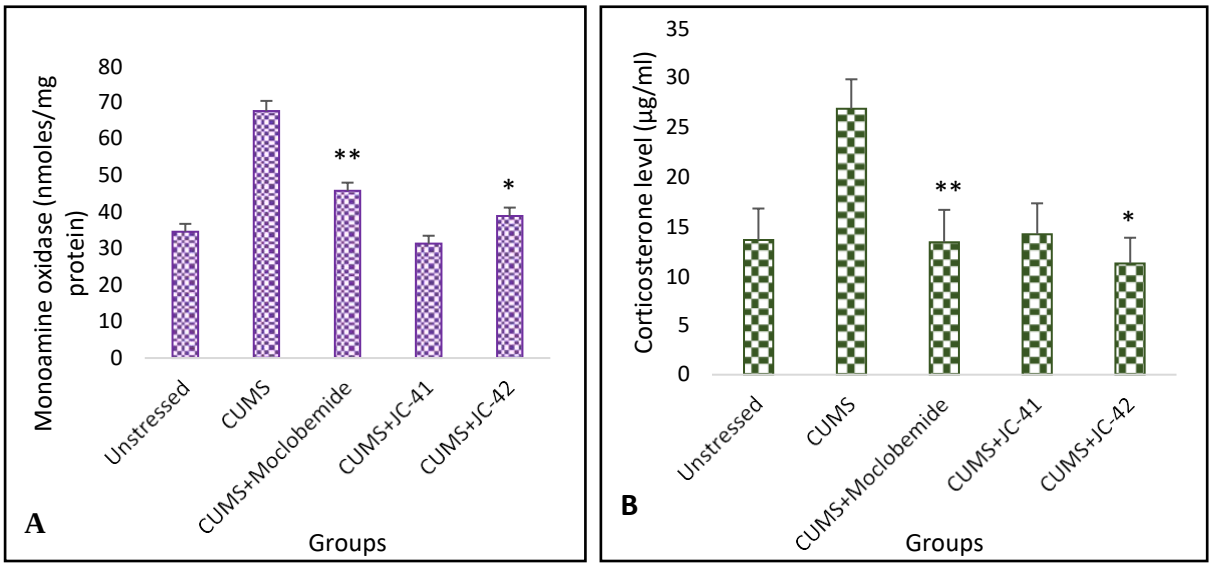


Fig. 8. Effect of JC-41 & JC-42 treatment on Monoamine oxidase level (8A) and Corticosterone level (8B) in CUMS mice model of depression. Values are expressed as mean ± SEM; n = 6/ group; A significant difference was seen in Moclobemide (**$p<0.001$) and JC-42 group (*$p < 0.05$) when compared with CUMS group.

4.0 Discussion

In the present work, novel synthetic compounds i.e., JC-41 & JC-42 were synthesized and their anti-depressant activity was accessed by molecular docking study which was further evaluated in animal model. Administration of JC-41, JC-42 and CUMS to mice significantly suppressed any changes in behavioural parameters in the stressed mice. Significant alteration in the non-enzymatic defence system parameters (Red. GSH) and markers of oxidative stress (MDA and NO) were suppressed in the stressed mice after administration of JC-41, JC-42 and the antidepressant drug Moclobemide was found. Significant decrease in the serum levels of the stress hormone CORT and a reduction in the activity of MAO-A which mediates the production of reactive oxygen species in the stressed mice after administration of JC-41, JC-42 and the antidepressant drug Moclobemide was observed. In general, it was shown that the JC-42 was superior to the JC-41 in reducing depression in anxious mice. According to the aforementioned research, moclobemide medication (50 mg/kg) temporarily corrected the decreased exploratory activity brought on by the CUMS procedure in an open field investigation for a period of four weeks. It is possible that the reduced FST immobility is not the result of any psychomotor stimulant activity, as suggested by the lack of enhanced exploratory activity in the open field

test in mice treated with JC-41 and JC-42. This confirms the antidepressant-like effect seen in the FST.

The results of the hippocampal antioxidant defence state demonstrated that stress-induced by CUMS in mice was associated with a significant depletion in levels of GSH as compared with unstressed mice. Also, the markers of lipid peroxidation (MDA) as well as NO, were significantly elevated in the stressed group, which confirmed the susceptibility of brain tissues to oxidative stress. These results suggested that decreased antioxidant enzyme activities result in the accumulation of ROS and negatively correlated with the severity of depression. On the contrary, oral administration of both JC-41 and JC-42 for 5 weeks to mice with stress-induced by CUMS significantly restored the hippocampal redox balance state and attenuated CUMS-induced oxidative damage and best effect was seen with Moclobemide. Several studies have shown that elevated CORT serum levels induced hippocampal ROS development, leading to memory function deficits and hippocampal dysfunction [19]. In this study, compared to unstressed mice, mice treated with CUMS showed a significant increase in serum CORT level and MAO-A brain activity. This effect was almost restored, reflecting the antidepressant-like capacity, by oral administration of both JC-41 and JC-42 and by Moclobemide relative to mice administered by CUMS. A growing body of proof has shown that MAO inhibition is effective in treating mice with depressive-like behaviour [20]. According to the monoamine hypothesis, the concentrations of monoamines, such as serotonin, noradrenaline, and dopamine, in synaptic gaps are decreased in the depressive state. The present work has shown that JC-41 and JC-42 can potentially lower the concentration of the stress hormone Corticosterone and stop reactive oxygen species formation by inhibiting MAO-A formation. MAOs are enzymes that metabolize monoamines and MAO-A levels are significantly increased throughout the brain in patients with depression [21]. The present study revealed that both the compounds were good antidepressant, and JC-42 was found more effective than JC-41. The result also suggests that JC-41 and JC-42 may have regulated the antidepressant pathways by restoring changes in oxidative stress and decreasing serum Corticosterone and MAO-A levels in the brain.

5.0 Conclusion

In conclusion, the study found that depression-like states are relieved by both JC-41 and JC-42 by reducing oxidative stress with a decrease in serum CORT and brain MAO-A levels. Nonetheless, more research is needed to explain these findings in humans, which may help a novel therapeutic approach to slow down depression symptoms.

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