Synthesis and anti-depressant activity of JC-41 and JC-42 in Interferon-alpha (IFN-α) induced depressant-like behaviour in mice

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Abstract

Interferon-alpha (IFN-α) is a useful therapy for some types of cancers and viral infections. Chronic use of IFN-α is related to psychological symptoms such as depression. The present study was designed to test the anti-depressant effects of two synthesized hydrazide derivatives, JC-41 and JC-42 in an IFN-α induced depression in the mice model. Female Swiss mice (25–30g) were used. Depression was induced by IFN-α 1600000 IU/kg, SC for six days. Various behavioural parameters viz., forced swim, tail suspension, locomotor, splash, sucrose preference and open field tests were carried out. The biochemical parameters in plasma and brain homogenate were also assessed. The selected treatments caused significant changes in the locomotor activity. IFN-α significantly increased the immobility time during FST indicating depressive-like effect, and JC-41 & JC-42 pretreatment reversed the condition. The sucrose preference was also improved with the treatment of selected compounds. The treatment with JC-41 & JC-42 both reduced the hyperactivity of the HPA axis brought on by IFN-α in mice, as seen by a significant decrease in plasma corticosterone levels in stressed mice. From the results, it can be concluded that compound JC-41 and JC-42 could be used as alternative drugs of depression. However, further exploration in this context is needed in other animal models in order to confirm the observed results in this study.

Keywords: Depression, interferon alpha (IFN-α), behavioural parameters, biochemical study

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Introduction

Depression is a psychiatric disease marked by poor mood, loss of interest in regular activities, anhedonia, feelings of worthlessness, sleep difficulty, and suicidal impulses [1]. Monoamine neurotransmitter abnormalities [2], as well as enhanced oxidative and nitrosative damage [3],

are the main mechanisms. The monoamine hypothesis states that depression is caused by a depletion of monoamines such as serotonin, norepinephrine, and dopamine in thehippocampus, limbic system, and frontal cortex [4]. The major enzyme involved in themetabolism of these monoamines is monoamine oxidase (MAO). Patients with significant depression had lower antioxidant levels, as well as increased oxidative and nitrosative stress [5]. Corticotrophin-releasing hormone hypersecretion and glucocorticoid response are impaired in depression [6]. Around 50% of depressive people (80% if seriously depressed) have hyperactivity in the hypothalamic–pituitary–adrenal axis. The hypothalamic–pituitary– adrenal axis hyperactivity changes when animals are exposed to chronic stress [7]. Stress playsa significant influence in the development of depression in humans [8].

Interferon-alpha (IFN-α) is broadly used for treatment of some types of malignancies as well as chronic hepatitis C [9]. Chronic use of IFN-α has been associated with psychological side effects such as depression and sometimes is followed by suicidal ideation and suicidal attempts [10]. According to studies, depression caused by IFN-α injection is reversible with antidepressants [11]. It has been reported that IFN-α stimulates nitric oxide synthase expression and influences the mechanistic target of rapamycin (mTOR) pathway [12].

Bielecka et al., (2010) investigated that the antidepressant, moclobemide (a reversible selective inhibitor of monoamine oxidase-A) has an influence on pro-inflammatory cytokines [interleukin (IL)-1β and tumor necrosis factor (TNF)-α] and anti-inflammatory cytokine (IL-10) in primary rat mixed glial cell cultures stimulated by lipopolysaccharide (LPS) [13]. The results suggested that moclobemide exerts anti-inflammatory effect in the central nervous system because it affects the balance between pro- and anti-inflammatory cytokines (IL-1β, TNF-α/IL-10) in primary mixed glial cell cultures. Thus, in the present study, the two novel synthesized compounds, 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) were investigated for their anti-depressant potential in an animal model using Moclobemide as standard drug.

Material and Method:

Material

All chemicals and study kits were acquired from standard sources. Moclobemide as supplied by Sigma-Aldrich.

Method

General Method for the Synthesis of Novel Hydrazide Derivatives (JC-41 and JC-42)

Acids were converted to respective ester which were then mixed with the methanol and heated at 60^0C then hydrazine hydrate (6 eq. mol.) was added drop wise. The reaction mixture was refluxed for 6 h and the progress of reaction was observed by TLC using chloroform/methanol (9:1) as the mobile phase. When the reaction was completed, the reaction mixture was kept cooling down at room temperature and poured onto crushed ice and hydrazides were precipitated out that were filtered out as well as re-crystalized with ethanol.

Equimolar quantities of compound formed hydrazide and different substituted aryl acid were added in a round–bottom flask and cooled in an ice bath. 10–15 ml of $POCl_3$ was added drop wise with continuous stirring into reaction mixture. After addition of $POCl_3$, the contents were refluxed on water bath for 6–8h and the reaction was monitored by TLC using chloroform/methanol (9:1), the content was allowed to cool and added crushed ice slowly or chilled water. In this way, compound JC-41 was produced. Same steps were followed as discussed above for the synthesis of JC-42 also. The synthesized compounds were evaluated for behavioural and biochemical parameters.

Animals

Swiss albino mice (25–30 g, 6–8 weeks old) were kept in standard conditions of humidity, temperature, and light/dark cycle and had free access to pellet chow and water. Six mice were housed in each cage. All the animal experiments were performed according to guidelines for the care and use of laboratory animals. All the efforts in the experiments were made to minimize animal suffering and to reduce the number of animals used in the experiments.

Experimental Design

All the mice utilized in the study were split into five groups with six mice in each group. The state of depression was induced in the selected animals by using IFN alpha (IFN-α) cytokines as they are associated with a high burden of central nervous system adverse effects. These include mood symptoms, neurovegetative symptoms, and cognitive symptoms. INFα (16×10^5 IU/kg body weight) was injected subcutaneously (SC) for six consecutive days.

Normal saline was given to Group-I as a vehicle, Group-II was IFN-α group, while Group-III, IV and V were received standard group, Moclobemide and synthesized groups, JC-41 & JC-42, respectively. Control group, received normal saline once daily for 6 days (i.p.); IFN-α group

animals received IFN-α (1600000 IU/kg) once daily for 6 days subcutaneously (SC). Moclobemide + IFN-α group animal received MO (50 mg/kg, i.p.) and IFN-α once daily for 6 days. Test groups received the synthesized compounds i.e., JC-41 & JC-42 (100 mg/kg, i.p.) and IFN-α once daily for 6 days. Study plan is depicted in table 1.

Table 1: Study Plan

Group	**Treatment**
Group 1 (Vehicle Control)	Normal Saline (1-1.5 ml)
Group 2 (IFN-α Control)	IFN-α (16×10^5 IU/kg, SC)
Group 3 (Standard Drug)	IFN-α + Moclobemide (50 mg/kg, i.p)
Group 4 (Test Group 1)	IFN-α + Compound 1 (JC-41, 100 mg/kg, i.p)
Group 5 (Test Group 2)	IFN-α + Compound 2 (JC-42, 100 mg/kg, i.p)

The behavioural tests were performed the day after the last injection (i.e., on day 7). After the completion of behavioural studies, biochemical estimation was done.

Behavioural Assessment

The animals were studied for behavioural parameters i.e., locomotor activity, forced swim activity, tail suspension activity and sucrose preference activity.

Forced Swimming Test (FST)

This test was performed as an animal model of despair behaviour. Mice were forced to swim in 25 °C water in a glass beaker (diameter 12.5 cm, depth 12 cm) for 6 min. The immobility time was measured during the last 4 min of the trial. Swimming behaviour, defined as horizontal movement throughout the beaker which involved at least two limbs; and, immobility behaviour measured when no additional activity was observed other than that required to keep the animals' head above the water. The whole experiment was recorded by a camera and analyzed later. After 6 min, the mice were dried carefully and returned to their home cage [14].

Tail Suspension Test (TST)

The established TST was conducted according to a methodology given by Can et al. (2012) [15], and immobility time was recorded. Using adhesive tape in a dimly lit environment, mice were briefly hung by their tails 60 cm above the floor. For the latter four minutes of a six-minute session, immobility was noted. When mice hung passively and motionlessly, they were perceived as immobile. Both control and test group animals were subjected to this test to determine the influence of intervention on immobility time.

Locomotor Activity

Using a photoactometer, the horizontal locomotor activity ratings of control and test animals were recorded for 5 min. Each mice was maintained in the device for five minutes. If the mice engaged in any exploratory behaviour, the light's beam would interrupt, and the instrument would automatically record the activity's duration on its digital recorder. Digital recordings ceased recording as soon as the animal paused its activities.

Splash Test

This test was conducted with minor modifications from previous study by Isingrini et al [16]. It was performed under a red light (230 V, 15 W), consists of squirting a 10% sucrose solution on the dorsal coat of a mouse in its home cage. Because of its viscosity, the sucrose solution dirties the mice fur and animals initiate grooming behaviour. After applying sucrose solution, the time spent grooming was recorded for a period of 5 minutes as an index of self-care and motivational behaviour. Grooming in rodents is an index of self-care and inspirational behaviour that is alike some symptoms of depression such as passive behaviour.

Sucrose Preference Test

Animals were trained to consume sucrose solution while fasted for two days prior to exposing them to stress. Three days later, after a 23-h fast, the animals were introduced to two bottles, one containing regular water and the other containing sucrose solution. The baseline percentage of sucrose solution preference was computed. The test was repeated after 21 days of therapy to ascertain the impact of therapy on the subjects' preference for sucrose solution as a percentage, which will serve as an indicator for depression brought on by stress [17].

Open Field Test

Open field test is a commonly used model of anxiety-like behaviour developed to measure animal emotionality and is focused on subjecting an animal to an unfamiliar area whose escape is prevented by surrounding walls on 21st day of the experiment. The open-field box is used in this, which is a rectangular area consisting of a hard floor measuring 60 cm × 60 cm × 40 cm and made of white painted wood. The floor was split into 16 equal squares at the bottom using permanent read markings, placed each mice individually in one corner of the field, and recorded the total locomotion and rearing frequency for each 10-minute cycle. 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].

Biochemical Parameters

The effect of synthesized compounds on biochemical parameters was also studied. Blood was collected on day 23 and centrifuged to separate plasma for nitrite and corticosterone measurement. This was performed 60 min after the treatment was provided.

Brain Homogenate

On the 23rd day, the mice were decapitated, and their brains were isolated after blood samples were taken. The obtained brain samples were washed with cold buffer (pH 7.4) consisting of 0.25 M sucrose, 0.1 M Tris, and 0.02 M ethylenediamine tetraacetic acid. The brain samples were centrifuged. The concentrations of catalase, reduced glutathione, and lipid peroxidation were measured in the centrifuged supernatant. The MDA level, reduced glutathione, and catalase activity were determined following the procedures reported by Alsanie et al., using UV–visible spectrophotometer [19].

Statistical Evaluation

Each group contained six animals, which were utilised to gather the data for the analysis. A one-way analysis of variance (ANOVA) and the Tukey test were used to assess the data (Graphpad Prism, San Diego, CA, USA). The data in the tables were expressed as mean ± SEM, and differences were deemed significant when the p-value difference between groups was less than 0.05.

3.0 Results and Discussion

3.1 Synthesis of JC-41 & JC-42

In the present study, two hydrazide compounds i.e., 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) were synthesised as presented in methodology section. The synthesized compounds were evaluated for behavioural and biochemical parameters and results were summarized in following sections.

3.2 Behaviour Assessment

The behavioural pattern was assessed in Swiss albino mice after treatment with the standard drug, Moclobemide and test compounds i.e., JC-41 & JC-42 in IFN-α induced depression.

3.2.1 Forced Swimming Test (FST)

The possible antidepressant effect of synthesized compounds i.e., JC-41 & JC-42 after administration was examined in the FST. Results of FST revealed that both the compounds exhibited significant antidepressant activity as becomes evident from their decrease in duration of immobility values compared to the control group, however, JC-42 produced more significant results than JC-41. Further, the antidepressant effect of synthesized compounds was compared with that of the standard drug and the results were presented in Figure 1.

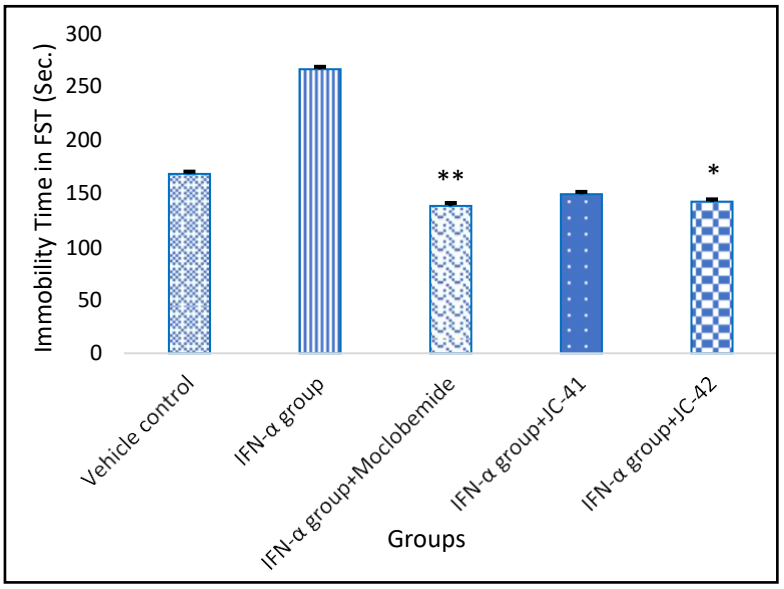

Figure 1: Effect of JC-41 & JC-42 treatment on motor functions assessed using Forced Swim Test in mice model of depression. Values are expressed as mean ± SEM; n = 6/group; A significant activity was shown by Moclobemide (**p<0.001) and JC-42 group (*p < 0.05) in comparison to IFN-α group

Tail Suspension Test

The amount of time spent immobile was slightly reduced by the synthesized compounds. Moclobemide also demonstrated a notable (**p<0.001) reduction in the time spent immobile. Moreover, both the test compounds i.e., JC-41 and JC-42 showed decrease in immobility time, while significant decrease (*p<0.05) in a time of immobility was obtained with JC-42 closed to Moclobemide. The results depicted in figure 2.

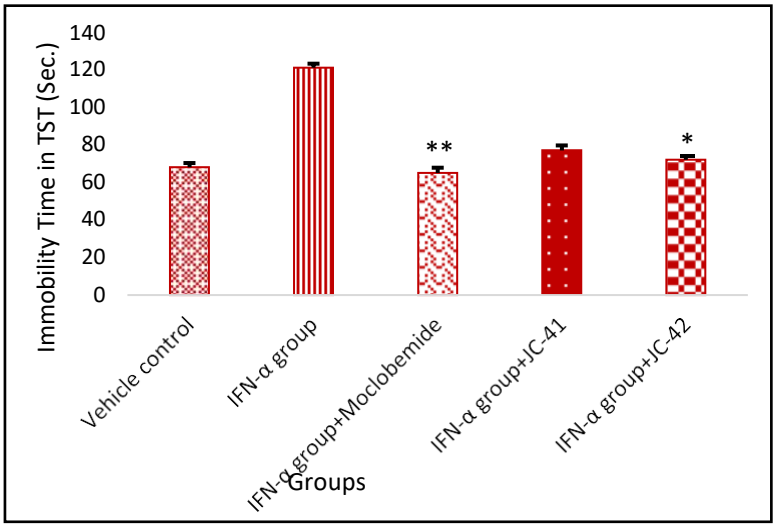

Figure 2: Effect of JC-41 & JC-42 treatment on motor functions assessed using Tail suspension test in mice model of depression. Values are expressed as mean ± SEM; n = 6/group; A significant activity was shown by Moclobemide (**p<0.001) and JC-42 group (*p < 0.05) in comparison to IFN-α group

Locomotor Activity

The effect of standard anti-depressant (Moclobemide) drug and selected test drugs i.e., JC-41 & JC-42 on locomotion was observed. In terms of locomotor function, Moclobemide showed a significant increase (*p<0.001) in locomotor activity, whereas test compounds, also demonstrated a considerable rise in locomotor activity, however, more significant effect in locomotion was observed with JC-42 (*p<0.05) against IFNα induced depression (Figure 3).

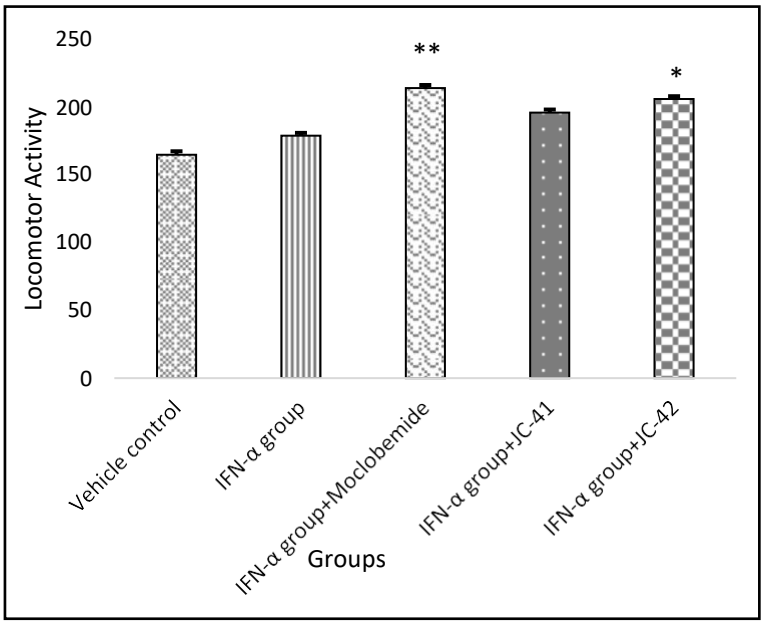

Figure 3: Effect of JC-41 & JC-42 treatment on motor functions assessed using Locomotor activity in mice model of depression. Values are expressed as mean ± SEM; n = 6/group; A significant activity was shown by Moclobemide (**p<0.001) and JC-42 group (*p<0.05) in comparison to IFN-α group

Splash Test

As per the results obtained from Splash test, after receiving IFN for six days, grooming time significantly decreased, whereas grooming latency was higher than the control. The animal's latency time is the amount of time it takes for it to become motionless. Significant results were obtained with standard drug, Moclobemide (**p<0.001) and JC-42 group (*p<0.05) in comparison to IFN-α group (figure 4).

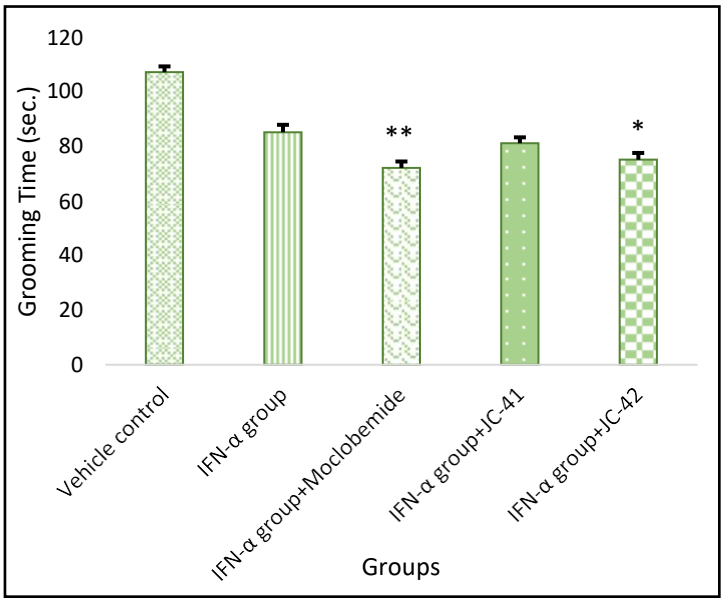

Figure 4: Effect of JC-41 & JC-42 treatment on motor functions assessed using Grooming time in mice model of depression. Values are expressed as mean ± SEM; n = 6/group; A significant activity was shown by Moclobemide (**p<0.001) and JC-42 group (*p<0.05) in comparison to IFN-α group

Sucrose Preference Test

The results of the sucrose preference test supported those of the IFN-α induced anhedonia in mice, selected drugs improved the preference. The results obtained with JC-41 and JC-42 supported the antidepressant results. Results of Sucrose preference test were presented in figure 5 and more preference was observed in the groups treated with standard drug, Moclobemide (**p<0.001) and JC-42 (*p<0.05). The observation was done at the beginning (Day 0) and on Day 21.

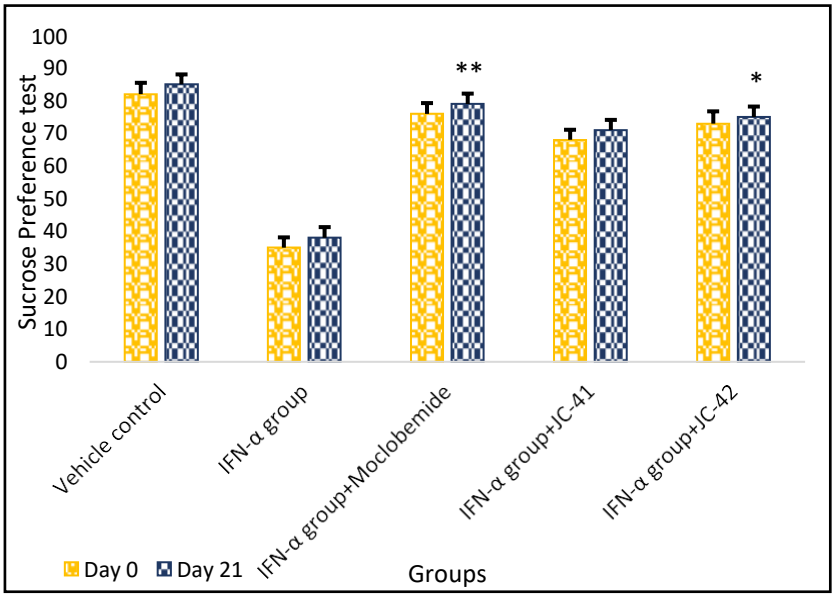

Figure 5 Effect of JC-41 & JC-42 treatment on motor functions assessed using Sucrose preference test in mice model of depression. Values are expressed as mean ± SEM; n = 6/group; A significant activity was shown by Moclobemide (**p<0.001) and JC-42 group (*p<0.05) in comparison to IFN-α group

Open field test

Data analysis showed that, when compared to the IFN-α groups, the administration of test compounds, caused significant differences in the frequencies of crossing indicated by the number of squares crossed and rearing indicated by the number of rearing instances. After administration of Moclobemide to anxious mice, when compared to the IFN-α group, there was an increase in the frequency of crossing and rearing (**p<0.001). The compound JC-42 showed promising results (*p<0.05) comparable to standard drug. Results were represented in figure 6.

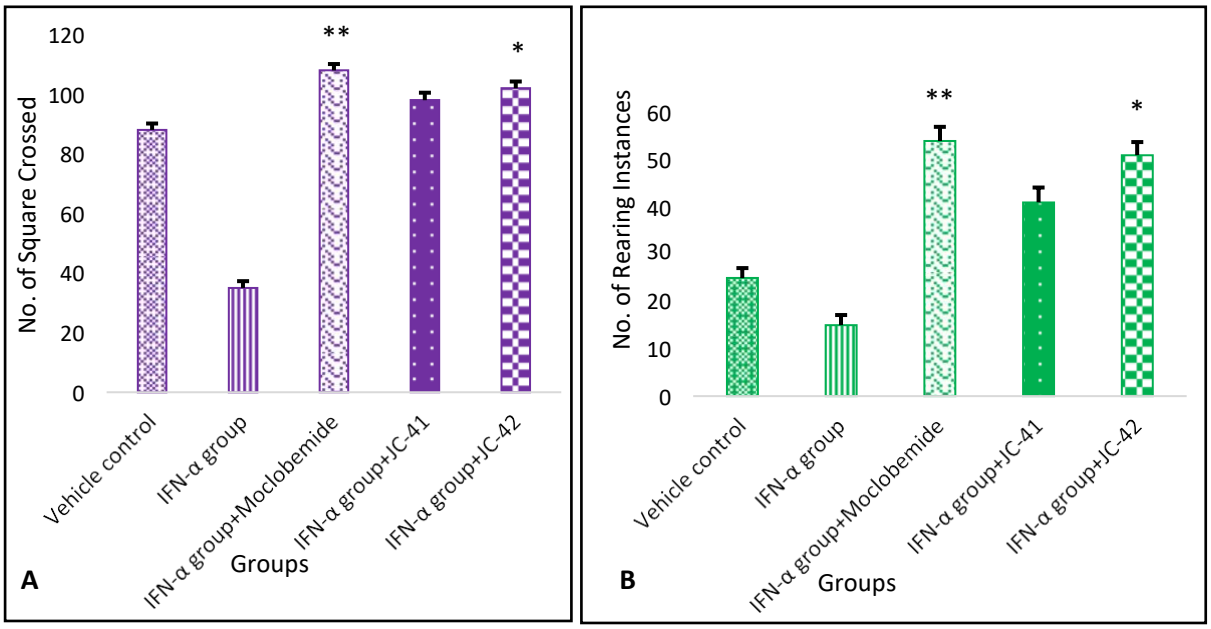

Figure 6. Effect of JC-41 & JC-42 treatment on motor functions assessed using open field test in mice model of depression, Number of Square crossed (A) and Number of rearing instances (B). Values are expressed as mean ± SEM; n = 6/group; A significant difference was seen in Moclobemide (**p<0.001) and JC-42 group (*p<0.05) when compared with IFN-α group

Biochemical Parameters

The stress produced by IFN-α causes the body to produce oxygen free radicals, which are shown to rise in blood nitrite levels. The selected standard drug i.e., Moclobemide produced significant reduction in plasma nitrite level compared to vehicle treated group, indicated a decrease in nitrosative stress. The administration of synthesized compounds i.e., JC-41 & JC-42 also caused a significant decrease in plasma nitrite level. More significant results were obtained with JC-42 (*p<0.05) in comparison to JC-41.

Moreover, plasma corticosterone level was significantly (**p<0.001) declined in animals that received Moclobemide. Significant decline of corticosterone was also demonstrated by compound JC-42 (*p<0.05). Results were depicted in figure 7.

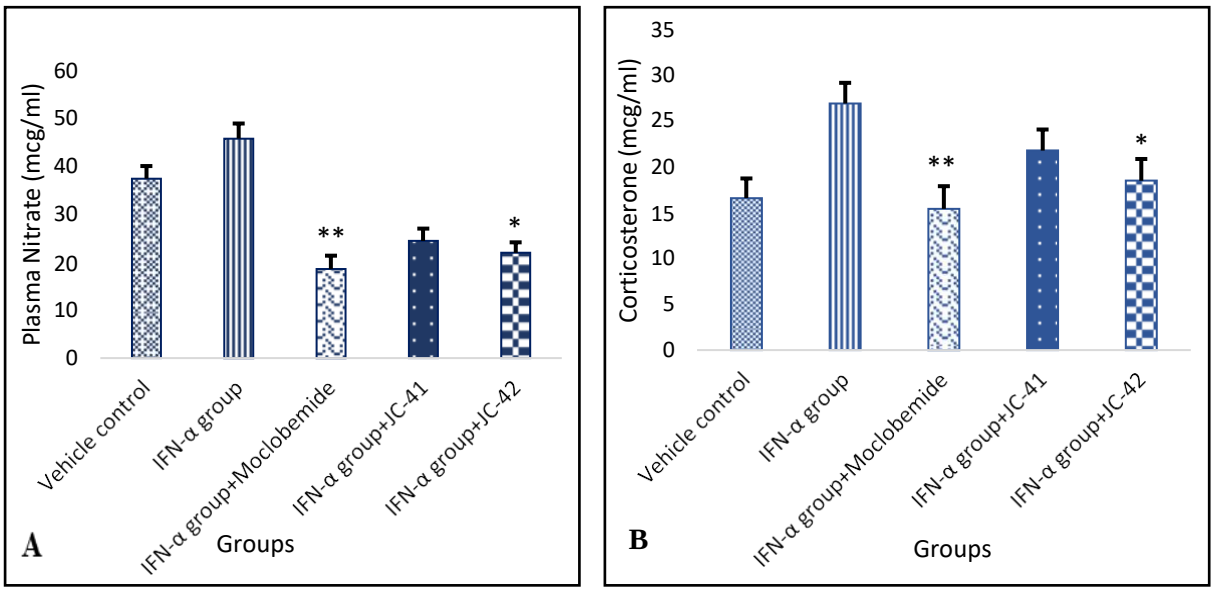

Figure 7 Effect of JC-41 & JC-42 treatment on Plasma nitrate (7A) and Corticosterone (7B) level in IFN-α mice model of depression. Values are expressed as mean ± SEM; n = 6/group; A significant difference was seen in Moclobemide group (**p<0.001) and JC-42 group (*p<0.05) when compared with IFN-α group

Moreover, it was also noticed that mice given the standard anti-depressant drug and compound JC-42 had considerably lower brain MDA level when compared to the IFN-α group. Both the chosen compounds and Moclobemide reduced the level of MDA in the brain in a nearly identical manner (Figure 8).

A significant increase (*p<0.05) in the reduced GSH level was observed in mice administered IFN-α. It was also observed that JC-41 and JC-42 significantly (*p<0.05) lowered the GSH level in stressed mice (Figure 8A). As expected, Moclobemide significantly (**p<0.001) increased reduced GSH level. The result of the effect of treatment of JC-41, JC-42 and Moclobemide on some markers of oxidative stress such as malondialdehyde was presented in figure 8B. Moclobemide administration to stressed mice expectedly decreased significantly (**p< 0.001) the levels of MDA in stressed mice. Similarly, oral administration of JC-41 and JC-42 significantly (*p<0.05) increased MDA level in the stressed mice. The standard drug, Moclobemide significantly reduced (**p< 0.001) the brain catalase level when compared to IFN-α group (Figure 8C). Although there was reduction in catalase activity with JC-41 & JC-42 also, however, this was less significant (*p<0.05).

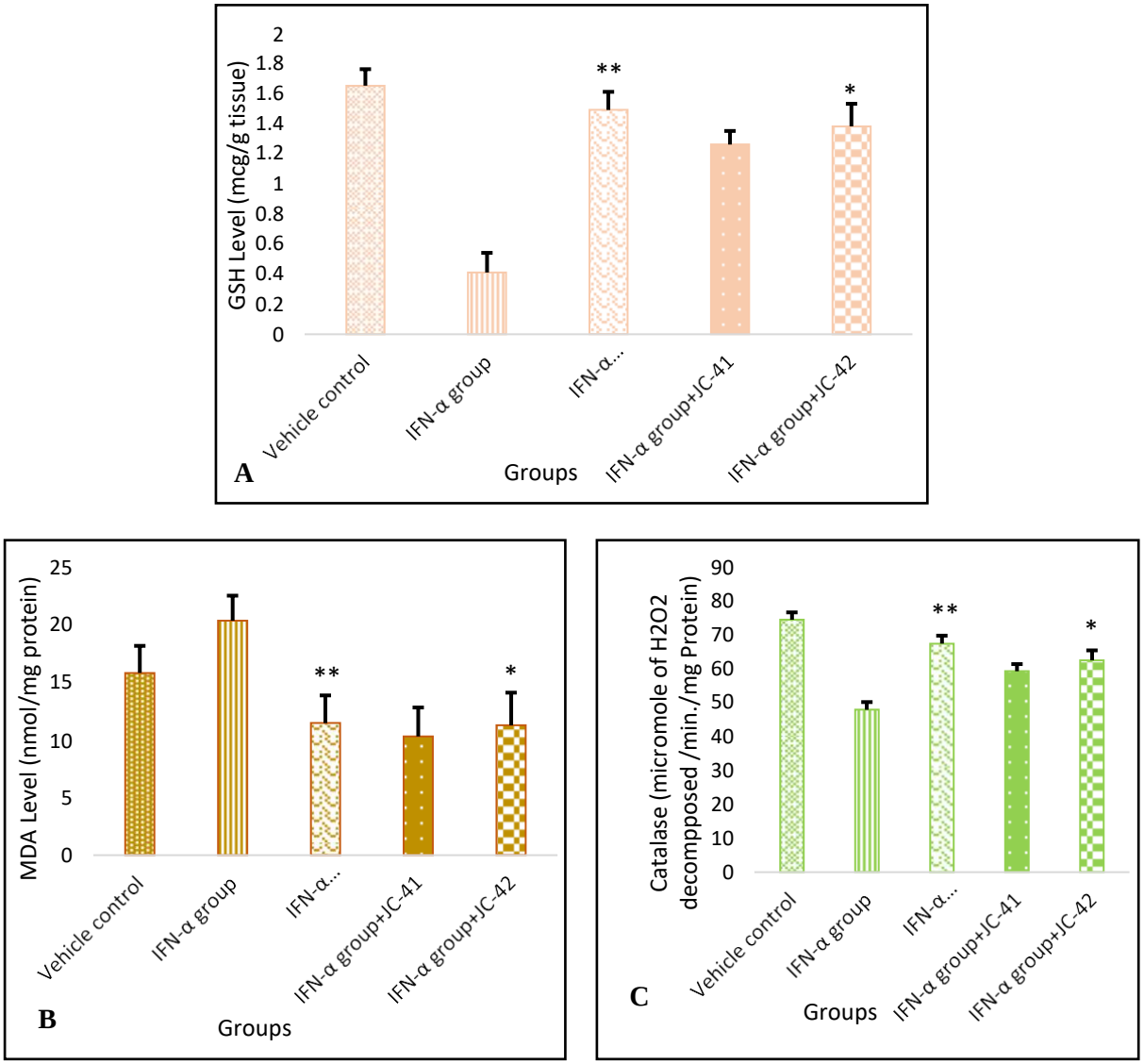

Figure 8. Effect of JC-41 & JC-42 treatment on GSH level (8A), Malondialdehyde level (8B) and Catalase level (8C) in IFN-α mice model of depression. Values are expressed as mean ± SEM;

n = 6/group; A significant difference was seen in Moclobemide (**p<0.001) and JC-42 group (*p<0.05) when compared with IFN-α group.

Discussion

In this study, the effect of two novel synthesized hydrazide compounds on IFN-α-induced depression was evaluated and the findings showed promising antidepressant activity. The FST has been used worldwide as a reliable and sensitive test for evaluation of different classes of antidepressants and also for screening of new compounds in industry [20]. Our results showed that the selected compounds reduced immobility time comparable to Moclobemide. Locomotor activity test is also a complementary and helpful test for FST as alteration of locomotor activity can deviate the results of FST [21]. In our study, the administration of Moclobemide increased locomotor activity on IFN-α induced depression. IFN-α showed depressive-like behaviour in FST which was in favour of previous reports. Clinical reports also indicated that despite the effectiveness of IFN-α in the treatment of chronic hepatitis C virus (HCV), many patients (up to 35%) receiving the drug show depression [22]. IFN-α-induced depression is so common that some researchers emphasized on prophylactic treatment with antidepressant drugs.

In a recent clinical study, Citalopram and Escitalopram were compared for their antidepressant effect following IFN-α induced depression and they emphasized on better tolerability of Escitalopram [23]. IFN-α increases production and release of several cytokines that arebelieved to promote depression and the association between up-regulation of interleukin-1beta(IL-1β), IL-6, and tumor necrosis factor-alpha (TNF-α) and depression have been reported in previous studies [24]. In our study, the synthesized compounds inhibited the depressant effectof IFN-α in mice.

Another technique utilised to evaluate the antidepressant potential of the synthesized compounds in IFN-α stressed mice was the sucrose preference test. This test is designed to identify anhedonia-like behaviour, which is characterised by a subject's loss of interest in or satisfaction in ordinarily pleasurable or happy activities. It is one of the most prevalent signs of depression in people [25]. In the present study, it was found that mice demonstrated a high preference for sucrose before the onset of stress. The percentage of sucrose preference had, however, diminished significantly three weeks following IFN-α stress. A restoration of sucrose preference percentage occurred after administration of synthesized compounds (JC-41 & JC-42) comparable to standard anti-depressant drug, Moclobemide. When compared to the control group, the recovery brought about by JC-42 was more than JC-41 in terms of sucrose preference.

Plasma glucocorticoid levels will change when the hypothalamic–pituitary–adrenal (HPA) axis is active, which may cause depression [26]. According to Sousa et al. [27], elevated cortisol level may influence the development of depressive symptoms by affecting various mental processes. Chronic antidepressant use is known to lower HPA activity, which returns the HPA axis to its natural state [27]. According to findings from another study, mild chronic stress increases plasma corticosterone levels via hyperactivating the HPA axis [28]. In the present study, the treatment with the synthesized compounds both reduced the hyperactivity of the HPA axis brought on by IFN-α in mice, as seen by a significant decrease in plasma corticosterone levels in stressed mice. Free radicals from oxygen contribute to serious depression. Reactive oxygen species formation, lipid peroxidation, and reduced antioxidant enzyme activities may be caused by immune-inflammatory process activation, anomalies in lipids, and these processes may be linked to depression [29]. It has been shown that 4-tert-butylphenol-induced stress increased MDA level, decreased GSH activity, and caused a decline in antioxidant capability [30]. It was found that IFN-α increased lipid peroxidation and catalase activity while decreasing reduced glutathione levels. These characteristics were markedly reversed after receiving the selected compounds for three consecutive weeks. Therefore, we contemplated that the synthesized compounds had the potential to be antidepressant in animal models via a variety of mechanisms, most likely through boosting antioxidant potential, re-establishing the HPA axis, and removing free radicals.

Conclusion

According to the results of the present investigation, the synthesized compounds, JC-41 & JC-42 may have antidepressant characteristics that are comparable to those of the widely used antidepressant, Moclobemide. JC-42 had antioxidant and corticosterone-restorative properties, and it may also have an antidepressant effect due to an increase in brain glutathione level. However, additional study is required to determine how neurotransmitters, among other pathways, contribute to the antidepressant effect of these novel compounds.

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