Original Article

Antidepressant Effect Of Indomethacin In Mice With Ifn Alpha-Induced Depression

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Abstract

The present study aimed to investigate the antidepressant property of Indomethacin using an IFN-α-induced depression model in albino mice. The locomotor activity, splash test, forced swimming test, tail suspension, sucrose preference and open field tests were used to evaluate the antidepressant effect of selected drug on albino female mice after induction of stress. The period of immobility in the TST and percentage preference for sucrose solution were recorded. By monitoring brain malondialdehyde (MDA) level, catalase (CAT) activity, and reduced glutathione (GSH) level, the antioxidant potential was assessed. When compared to stressed group, animals that received Indomethacin had considerably shorter immobility times during the TST. Indomethacin treatment also raised the percentage preference for sucrose solution, nearer to the conventional antidepressant, Amitriptyline. Furthermore, Indomethacin remarkably lowered plasma corticosterone and nitrite levels, reduced glutathione levels while considerably reducing the brain's MDA and catalase activities. However, further studies should be carried out to explore the antidepressant property of Indomethacin clinically.

Keywords: Depression, Indomethacin, anti-depressant activity, behavioral study, biochemical estimation

Introduction

Depression is the most common affective disorders (defined as disorders of mood rather than disturbances of thought or cognition); it may range from very mild conditions, bordering on normality, to severe (psychotic) depression accompanied by hallucinations and delusions (Gupta et al., 2015). The emotional symptoms of depression described by Diagnostic and Statistical Manual of Mental Disorders are lack of interest, sadness, guiltiness, and suicidal thoughts while lack of sleep, headaches, pain, sleep disorders, changes in appetite, gastrointestinal disorders, and changes in psychomotor function are the physical symptoms of depression. Around 6.3 to 15.7% of the world's population is estimated to suffer depression once in life according to World Health Organization International Consortium of Psychiatric Epidemiology (WHO ICPE). Additionally, 7 to 12% in men and 20 to 25% in woman are the estimation of lifetime prevalence of major depression in adults (GUZE, 2006; Saleh et al., 2014). Major depressive disorder is a debilitating disease with a prevalence estimated to be as high as 16.2% according to the National Comorbidity Survey (Isingrini, Camus, le Guisquet, et al., 2010). Depression is the most common and serious side effect, affecting approximately 30%–45% of patients receiving IFN-α treatment, resulting in occasional discontinuation of the therapy (Zheng et al., 2014). IFN-α induces neuropsychiatric and neurotoxic side effects, including depression, anxiety,

insomnia, lethargy, confusion, and psychosis. Of particular interest, a number of patients develop full psychiatric syndromes, particularly depressive disorders (De & Garza, 2003). Clinical and preclinical studies have reported that co-administration of nonsteroidal anti-inflammatory drugs (NSAIDs) and antidepressant drugs are effective in patients with depression and in animal models of depression (Seo et al., 2019). Non-steroidal anti-inflammatory drugs (NSAIDs) are known to counteract a number of IFN-α induced side effects, including pro-inflammatory cytokine activation and stress hormone release. NSAIDs in modulating IFN-a-induced neurochemical alterations, and raise the possibility of the use of NSAIDs for the prevention of IFN-α-induced depression (de La Garza & Asnis, 2003).

Indomethacin (IND) is in a class of medications called NSAIDs. The effects of indomethacin occur because it inhibits the synthesis of prostaglandins. Prostaglandins are produced primarily by cyclooxygenase (COX) enzymes, and prostaglandins are critical mediators of inflammation, fever, and pain (Munjal & Allam, 2022). Indomethacin (IND) is used to relieve moderate to severe pain, tenderness, swelling, and stiffness caused by osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis. Indomethacin is also used to treat pain in the shoulder caused by bursitis. Indomethacin immediate-release capsules and suspension (liquid) are also used to treat acute gouty arthritis. It works by stopping the body's production of a substance that causes pain, fever, and inflammation (Indomethacin: MedlinePlus Drug Information, 2021). It is reported that a single dose of IND was able to reverse IFNα induced depression. Thus, in the present work, the anti-depressant activity of Indomethacin was explored in the animal model.

Material and Methods

The outbred adult Swiss Albino female mice, weighing between 25-30 gm were obtained from the animal house in Shri Guru Ram Rai Institute of Medical & Health Sciences, Dehradun, Uttarakhand India. The animals were housed in well ventilated polypropylene cages and kept under standard environmental conditions of 12/12 light/dark rhythm, maintained under controlled (23 $\pm 2^0$C) room temperature. They were fed with standard pellet diet (Pranav Agro Industries Ltd., Sangali) and water ad libitum. The immature animals were acclimatized to laboratory condition three days prior to initiation of experiment. The cages were cleaned daily by changing the sawdust bedding.

The Experimental protocol was approved by the Institutional Animal Ethical Committee (IAEC) IAEC no. 1435/PO/Re/S/11/CPCSEA of SGRRI- Uttarakhand, India; Care and use of laboratory animals were confirmed to CPCSEA guidelines. The whole experimental protocol was designed as per OECD guidelines no. 425 (OECD/OCDE, 2001).

Acute toxicity study of Indomethacin

The acute toxicity of Indomethacin was determined by method given by Majeed R.K et al., with some modifications. In-vivo acute toxicity was carried out in albino mice. Doses of Indomethacin (5, 10, 20, 50, 100 and 200 mg/kg body weight) were given to mice through i.p. injection and were observed for 24 h after each dose. The purpose of this activity was to measure the maximum safe amount of Indomethacin (IND) for organisms (Al., 2018).

Induction of Depression

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 (Capuron & Miller, 2004). INFα (16 × 105 IU/kg) body weight was injected subcutaneously (SC) for six consecutive days (Mesripour et al., 2018).

Drug Administration

Drugs, Indomethacin (25 mg/kg) and Amitriptyline (10 mg/kg) were suspended in 0.1% (v/v) tween 80 and diluted in normal saline (vehicle). The vehicle of each drug was administered in the respective control mice. Both drugs were administered orally by gavage in a constant volume of 1 ml/kg. The control groups received vehicle (0.1% (v/v) tween 80 in normal saline).

The tests were performed on the seventh day following IFNα therapy. Each animal was first subject to the Locomotor test, Splash test, Forced Swim Test, Tail suspension test, Sucrose preference test and open field test. The NSAIDs were co-administered with IFNα for 6 days. Further, the effect of NSAIDs on biochemical parameters was also studied (Mesripour et al., 2020).

Study Plan

In this experiment, the Swiss albino mice were randomly distributed into four groups including six mice in each of the test as presented below

Group 1 (Control) : Vehicle (Normal Saline) (1-1.5 ml-Oral)

Group 2 (Depression control) : IFN-α (16 × 105 IU/kg-IP)

Group 3 (Standard drug) : IFN-α + Amitriptyline (10 mg/kg-IP)

Group 4 (Test drug) : IFN-α + Indomethacin (25 mg/kg-IP)

Effect of NSAIDs in behavioral paradigms

The treated animals were subjected to locomotor activity, Splash activity, Forced Swim Test, Tail suspension test, Sucrose preference and open field test to study the effect of NSAIDs on behavioral pattern in the treated animals.

Locomotor activity

Using a photo actometer, the horizontal locomotor activity ratings of control and test animals were recorded for 5 min. Each mouse was maintained in the device for five minutes. If the mouse engaged in any exploratory behaviors, the light's beam is interrupt, and the instrument automatically record the activity's duration on its digital recorder. Digital recordings ceased recording as soon as the animal paused its activities (Dinesh Dhingra, 2012).

Splash test

This test was conducted with minor modifications from previous study by Isingrini et al. 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 mouse 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 (Isingrini, Camus, Le Guisquet, et al., 2010).

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 (Cryan et al., 2002a).

Tail suspension test

Tail suspension test (TST) is another important behaviour test to measure the response on the stress situation. The rodent tails were suspended with adhesive tape to a horizontal bar for 6 minutes and the time of immobility was observed. If the subject shows more depressive-like behaviour, it will exhibit an increase in the amount of immobility time. To be noted, the TST is used only in mice, but not in rats due to the larger size and weight; in a majority of cases. TSTs are used to detect the antidepressant response (Wang et al., 2017) (Zaminelli et al., 2014)

Sucrose preference test

Animals were trained to consume sucrose solution while fasted for two days prior to exposing them to persistent mild 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 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 (Alsanie et al., 2022). The percentage of sucrose intake was calculated using the following equation:

$$\% \text{ Sucrose preference} = \frac{\text{Sucrose intake}}{\text{Total intake}} \times 100$$

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 rat 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 rat (Ekeanyanwu et al., 2021).

Effect of NSAIDs in Biochemical Parameters

The effect of NSAIDs on biochemical parameters was also studied and following parameters were assessed.

Determination of SOD enzyme activity

The level of SOD enzyme activity in PC12 cells was measured using the SOD Assay Kit-WST. After incubation of the PC12 cells with the experimental reagents for the indicated time periods, the original medium was removed from the 96-well plates, and the PC12 cells were lysed with Nonidet P-40 lysis buffer (1% NP-40, 50 mmol/L Tris-HCl [pH 7.5], 0.05 mmol/L ethylenediamine tetra-acetate) for 20 minutes at 4°C. The lysates were centrifuged at 300g for 10 minutes, and 20 µL of this sample solution was used for determination of SOD enzyme activity. The value for each treatment group was converted to the percentage of control (Kolla et al., 2005).

Biochemical parameters estimation in Plasma

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 (Alsanie et al., 2022).

Biochemical Estimations in 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 tetra acetic acid. The brain samples were centrifuged. The concentrations of catalase, reduced glutathione, and oxidative stress markers, malondialdehyde (MDA), an indication of lipid peroxidation in animal tissues were measured in the centrifuged supernatant. The MDA (Malondialdehyde) level, reduced glutathione, and catalase activity were determined by reported procedures (Greenwald, 2018; Jollow D.J., 1974; Wills, 1965) respectively, using UV–visible spectrophotometers (Alsanie et al., 2022). For the assay of Brain Monoamine oxidase (Mono-A) activity, Monoamine oxidase A assay kit (Sigma Aldrich) was used.

Statistical Analysis

Each group contained six animals, which were utilised to gather the data for the analysis. A one-way analysis of variance (ANOVA) and the Dunnett's test were used to assess the data (Graphpad Prism 9.0, 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.

Result & Discussion

In-vivo acute toxicity activity of Indomethacin

Acute toxicity study of Indomethacin was carried out in albino mice and it was observed that doses up to 100 mg/kg were well tolerated to the animals, however, when dose was increased up to 200 mg/kg, the animal started dying.

Effect of NSAIDs in behavioral paradigms

The treated animals were subjected to locomotor activity, Splash activity, Forced Swim Test, Tail suspension test and Sucrose preference test to study the effect of NSAIDs on behavioral pattern in the treated animals. The results of various activities were presented in following sections.

Locomotor activity

The effect of standard anti-depressant (Amitriptyline) drug and selected test drug i.e., Indomethacin was observed. In locomotor activity, as per figure 1, Amitriptyline (10 mg/kg) showed a significant increase (***$p<0.001$) in locomotor activity. Moreover, Indomethacin also showed improved (*$p<0.05$) locomotor activity against IFNα induced depression. Our findings were parallel with previous results regarding the acute treatment with piroxicam promoted an antidepressant-like effect (Santiago et al., 2015).

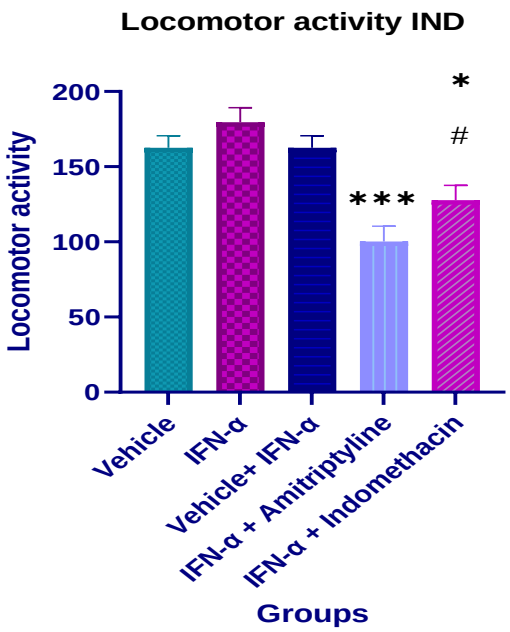

Figure 1: The changes in number of locomotor activity due to Indomethacin and Amitriptyline. Data were given as mean and standard error of mean. Each group had six animals. Statistical analysis was performed by one-way analysis of variance (ANOVA) and post-ANOVA Dunnett's test; #p < 0.01 when compared with control; *p<0.05 and ***p<0.0001when compared to Vehicle+ IFN-α

Splash test

As per the results obtained from Splash test (figure 2), the grooming time significantly reduced after exposure to IFNα for 6 days, while grooming latency was higher than control. The latency time is the time spent until the animal becomes immobile. Amitriptyline (10 mg/kg) showed a significant increase (***p<0.0001), whereas Indomethacin (*p<0.05), also increased splash activity against IFNα induced depression, respectively. Our findings were parallel with previous results regarding behavioural tests, a high fat diet regimen abolished the ability of the AD fluoxetine to reverse UCMS-induced depressive-like state at the end of the second period of the UCMS procedure (Isingrini, Camus Mandal S et al., 2021, le Guisquet, et al., 2010).

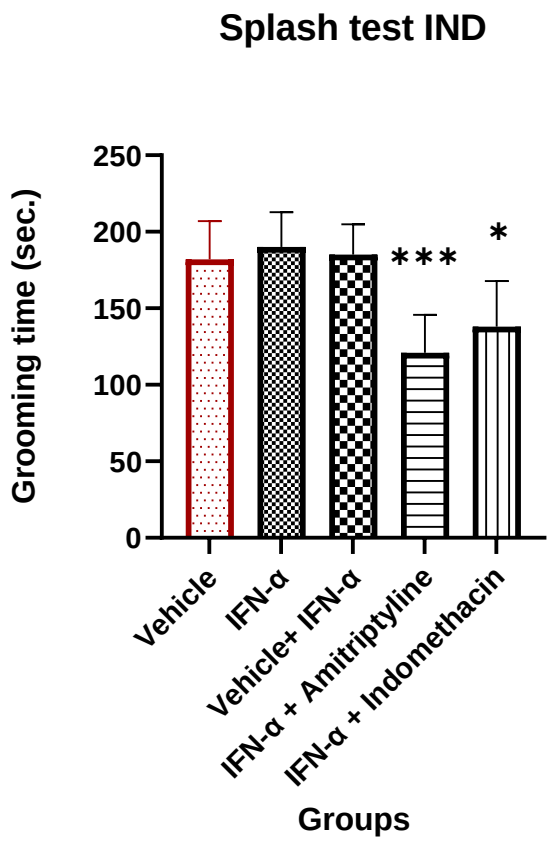

Figure 2 Grooming time (sec.) was presented for Indomethacin and Amitriptyline. Data were given as mean and standard error of mean. Each group had six animals. Statistical analysis was performed by one-way analysis of variance (ANOVA) and post-ANOVA Dunnett's test; *p<0.05, ***p<0.0001 compared with vehicle+ IFN-α group

Forced swimming test (FST)

The effect of NSAIDs and IFNα on the immobility time during the forced swimming test (FST) was measured (figure 3). The immobility time is the total time animals were immobile during the last 4 min of the total 6 min FST. IFNα was injected for 6 days and the NSAIDs were administered simultaneously for 6 days with IFNα. The control groups received normal saline the vehicle was 0.1% (v/v) tween 80 in normal saline Animal immobility time during the FST reduced by the NSAIDs that clearly indicated the antidepressant effects by 25 mg/kg IND (* p<0.05). Our findings were parallel with previous results regarding IFN-α increased the immobility time in the FST, that denotes depression in mice (Fashi et al., 2017) (O'Connor et al., 2009).

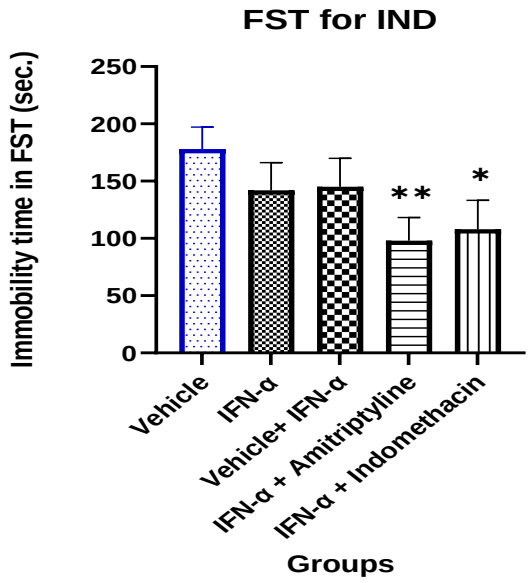

Figure 3: The effect of Indomethacin (IND) and Amitriptyline (AMI) on Immobility time in FST. Data were given as mean and standard error of mean. Each group had six animals. Statistical analysis was performed by one-way analysis of variance (ANOVA) and post-ANOVA Dunnett's test; *p<0.05, **p<0.001 compared with vehicle+ IFN-α group

Tail suspension test

Indomethacin caused a slight decrease (*p<0.05) in the period of immobility (Figure 4). Further, a standard tricyclic antidepressant (Amitriptyline) also exhibited a significant (**p<0.001) reduction in the immobility period. The majority of studies use simple tests such as the forced swim test (FST) or tail suspension test (TST) to elucidate their behavioral changes (Cryan et al., 2002b; Zaminelli et al., 2014)

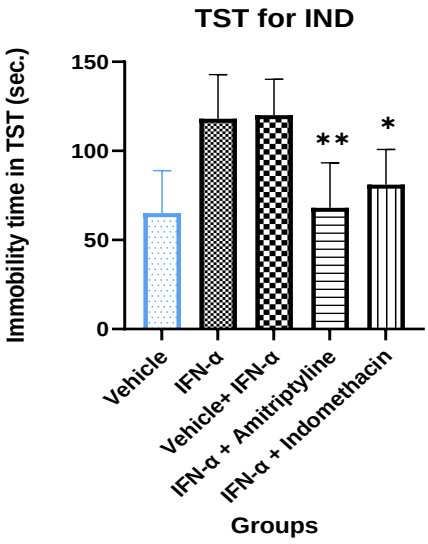

Figure 4: The effect of Indomethacin and Amitriptyline on Immobility time in TST. Data were given as mean and standard error of mean. Each group had six animals. Statistical analysis was performed by one-way

analysis of variance (ANOVA) and post-ANOVA Dunnett's test; *p<0.05, **p<0.001 compared with vehicle+ IFN-α group

Sucrose preference test

The sucrose preference test also supported the results, while IFNα caused anhedonia in mice, selected drug improved the preference. Results of Sucrose preference test were presented in Figure 5. IFN-α has also been used as a model to study the role of inflammation in depression. The standard antidepressant drug, Amitriptyline has shown significant (**p<0.001) improvement in sucrose preference in stressed animals. Selected anti-inflammatory drug, Indomethacin also showed comparable results (**p<0.001) to Amitriptyline. Similar results were shown by Non-steroid anti-inflammatory drugs (Ibuprofen, and Celecoxib) in IFN-α induced depression in mice (Mesripour & Almasi, 2021).

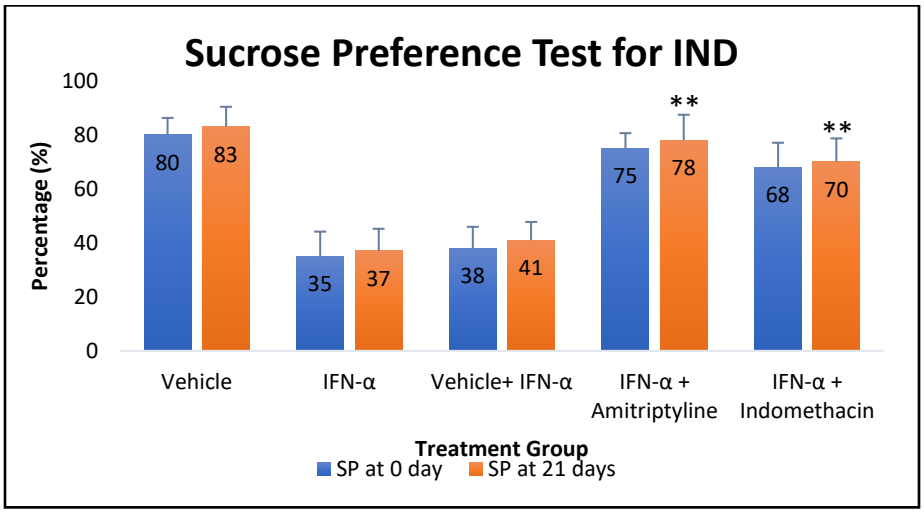

Figure 5: The changes in percentage sucrose preference test due to Indomethacin and Amitriptyline. Data were given as mean and standard error of mean. Each group had six animals. Statistical analysis was performed by one-way analysis of variance (ANOVA) and post-ANOVA Dunnett's comparison tests. * p<0.05 compared with vehicle+ IFN-α group

Open field test

Analysis of data indicated that administration of Indomethacin induced significant differences (*** p=0.0001) in the frequencies of crossing indicated in the number of squares crossed and rearing indicated in the number of rearing instances when compared to the vehicle+ IFN-α group. Conversely, Amitriptyline administration to stressed mice significantly (****p<0.0001) increased the frequency of crossing and rearing when compared to the vehicle+ IFN-α group (figure 6A-6B). Our findings were parallel with previous results regarding open field test was used to measure the behavioral and locomotor activity of mice (Santiago et al., 2015) (Rakib et al., 2020).

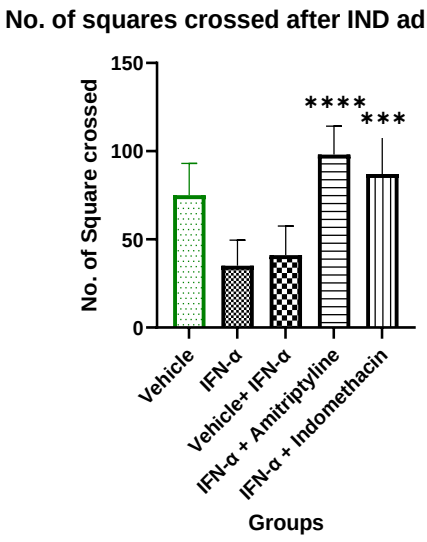

Figure 6A: Number of squares crossed in mice after administration of Indomethacin and Amitriptyline. *** p<0.001, ****p<0.0001 compared with vehicle+ IFN-α group

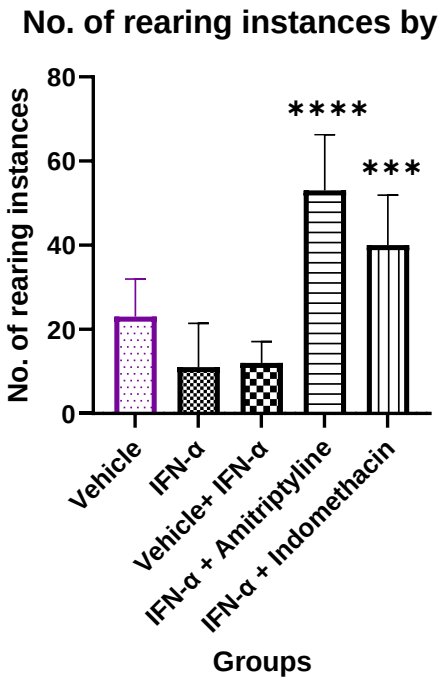

Figure 6B: Number of rearing instances in mice after administration of Indomethacin and Amitriptyline. *** p<0.001, ****p<0.0001 compared with vehicle+ IFN-α group

Effect of NSAIDs on biochemical parameters

The effect of NSAIDs on biochemical parameters was also studied and following parameters were assessed.

Effects of Indomethacin (IND) and Amitriptyline (AMI) on SOD activity of PC12 cells

From the results, it was observed that SOD activity increased with increasing concentrations of Indomethacin (IND) and Amitriptyline (AMI), reaching its highest level with incubation at 100 µmol/L for 24 hours (Figure 7).

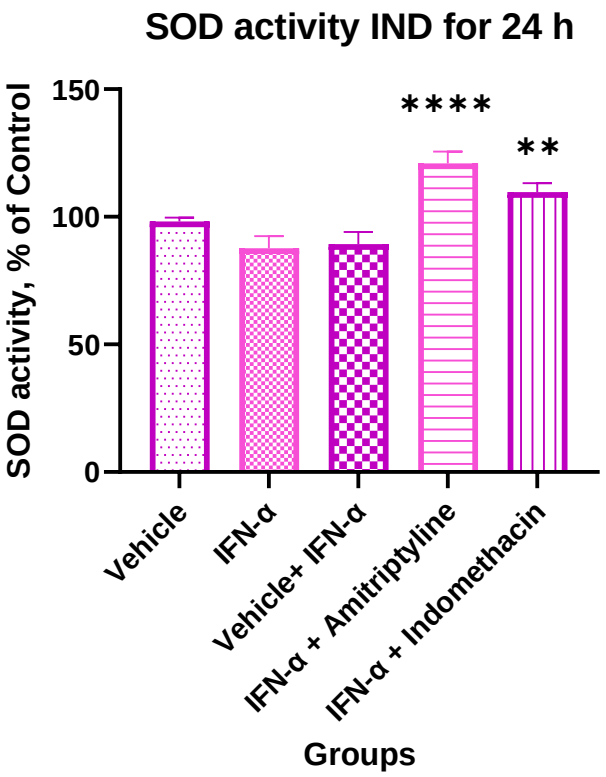

Fig. 7: Effects of Indomethacin (IND) and Amitriptyline (AMI) on superoxide dismutase (SOD) activity of PC12 cells. PC12 cells were treated with (A) vehicle, 200 µmol/L hydrogen peroxide for 4 hours, 100 µmol/L Indomethacin (IND) and Amitriptyline (AMI) for 24 hours; Data are presented as mean (and standard error of the mean). **p<0.001, ****p<0.0001 compared with vehicle+ IFN-α group

Effect of Indomethacin (IND) and Amitriptyline (AMI) on Plasma Nitrite and Corticosterone

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 drug i.e., Indomethacin (IND) produced significant reduction (**p<0.001) in plasma nitrite level compared to vehicle treated group, indicated a decrease in nitrosative stress. The administration of Amitriptyline (AMI) also caused a significant (***p<0.0001) decrease in plasma nitrite level (Figure 8).

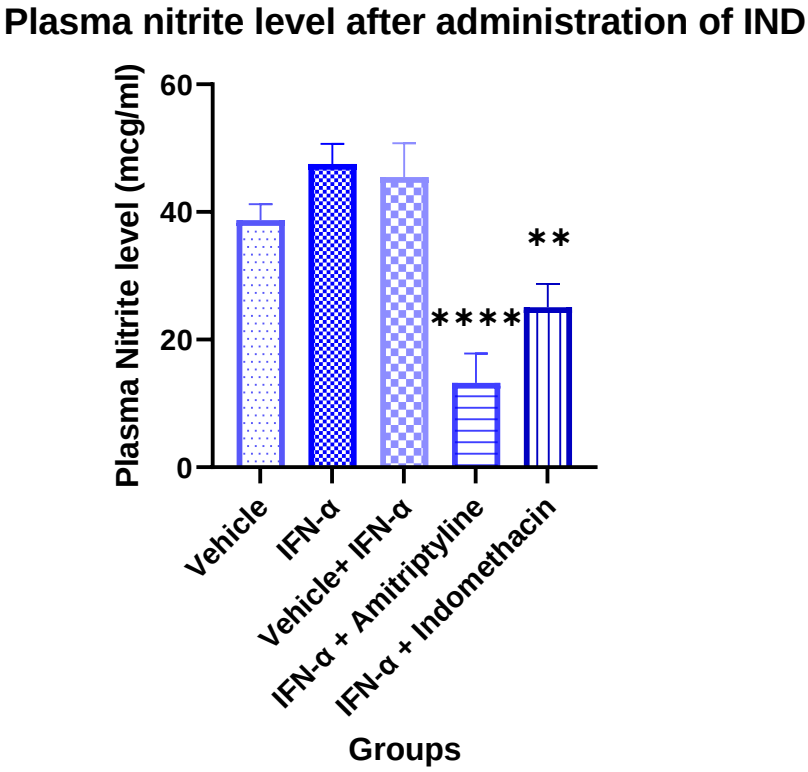

Figure 8. The changes on plasma nitrite levels due to Indomethacin (IND) and Amitriptyline (AMI). Data were given as mean and standard error of mean. Each group had six animals. Statistical analysis was performed by one-way analysis of variance (ANOVA) and post-ANOVA Dunnett's test; **p<0.001, ****p<0.0001 compared with vehicle+ IFN-α group

Moreover, plasma corticosterone level was significantly ($p<0.001$) declined in animals that received Indomethacin (IND) and Amitriptyline (AMI). However, more promising results were obtained with standard anti-depressant drug Amitriptyline (AMI) ($p<0.001$). According to findings from a study, IFN-α increases plasma corticosterone levels via hyperactivating the HPA axis (Franscina Pinto & Andrade, 2016). In our experiment, Indomethacin (IND) and Amitriptyline (AMI) treatment 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. However, the standard tricyclic antidepressant, Amitriptyline (AMI), produced a stronger significant ($p<0.001$) reduction in plasma corticosterone (Figure 9).

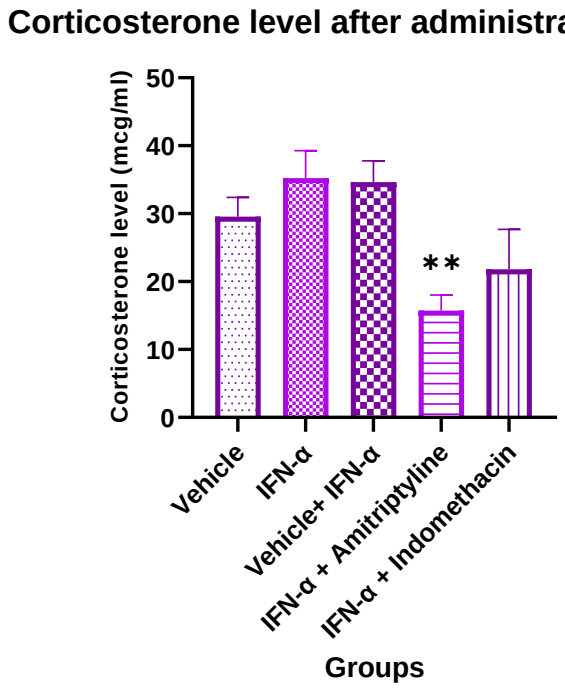

Figure 9. The changes on plasma corticosterone levels due to Indomethacin (IND) and Amitriptyline (AMI). Data were given as mean and standard error of mean. Each group had six animals. Statistical analysis was performed by one-way analysis of variance (ANOVA) and post-ANOVA Dunnett's test; **p<0.001 compared with vehicle+ IFN-α group (shown by Amitriptyline only)

Effect of Indomethacin (IND) and Amitriptyline (AMI) on Brain Malondialdehyde (MDA) Level

From the results, it was observed that brain MDA level was significantly reduced in animals that received the dose of Indomethacin ($p < 0.05$) and Amitriptyline (AMI) ($p < 0.001$) when compared to the vehicle+IFN-α group. The selected drug and Amitriptyline (AMI) showed almost similar reduction in brain MDA level (Figure 10)

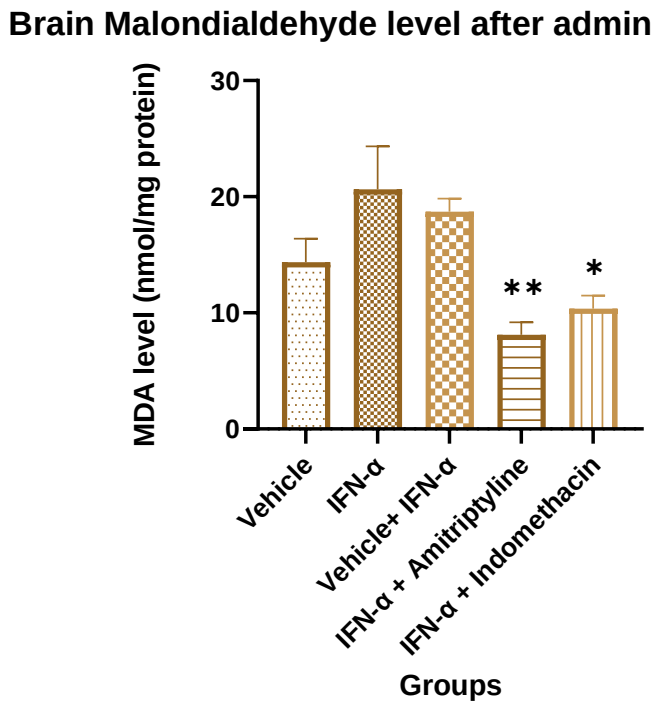

Figure 10. The changes on brain MDA level due to Indomethacin (IND) and Amitriptyline (AMI). Data were given as mean and standard error of mean. Each group had six animals. Statistical analysis was performed by one-way analysis of variance (ANOVA) and post-ANOVA Dunnett's test; * p< 0.05, and **p< 0.001 when compared to vehicle & vehicle+ IFN-α group

Effect of Indomethacin (IND) and Amitriptyline (AMI) on Brain Catalase Activity

From the results, it was seen that selected drug i.e., Indomethacin (IND) and Amitriptyline (AMI) were able to significantly ($p<0.01$) reduce the brain catalase activity when compared to the vehicle treated group (Figure 11).

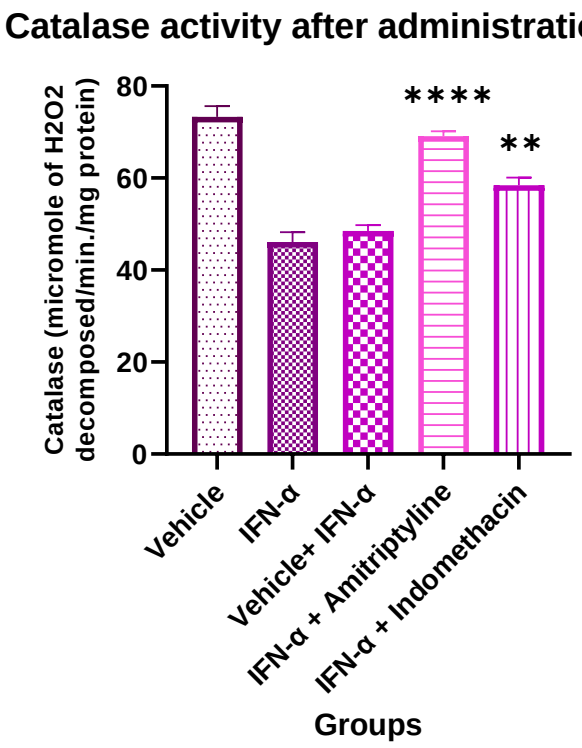

Figure 11. The changes on brain catalase activity due to Indomethacin (IND) and Amitriptyline (AMI). Data were given as mean and standard error of mean. Each group had six animals. Statistical analysis was performed by one-way analysis of variance (ANOVA) and post-ANOVA Dunnett's test; **p<0.001, ****p<0.0001 when compared to vehicle+ IFN-α group

The results demonstrated that, a significant decrease ($p<0.01$) in the enzymatic defense system parameter (CAT) in mice administered with IFN-α was seen, while, administration of Indomethacin (IND) increased ($p<0.001$) the CAT activities in the stressed mice. However, the administration of Amitriptyline (AMI) showed more profound results ($p<0.0001$), pertaining to standard anti-depressant drug.

Effect of Indomethacin (IND) and Amitriptyline (AMI) on Brain Glutathione (GSH) Level

Administration of animals with Indomethacin ($p<0.001$) and standard antidepressant, Amitriptyline ($p<0.001$) produced significantly elevated brain GSH levels compared to vehicle+ IFN-α group (Figure 12).

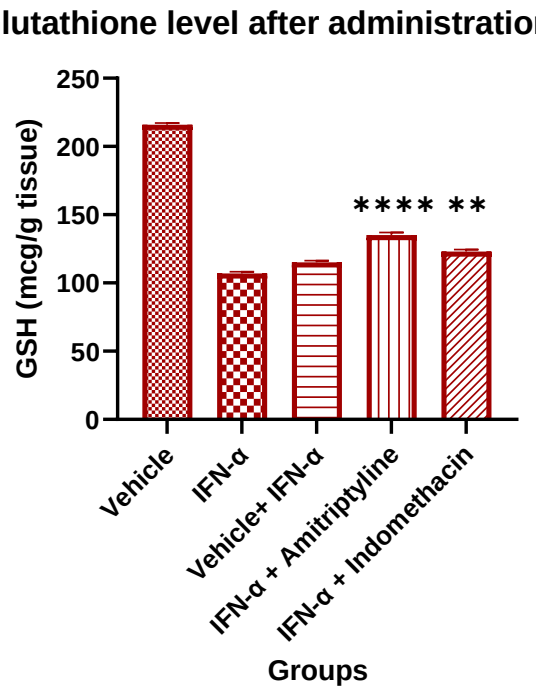

Figure 12. The changes in brain Hippocampal glutathione levels after administration of Indomethacin (IND) and Amitriptyline (AMI). Data were given as mean and standard error of mean. Each group had six animals. Statistical analysis was performed by one-way analysis of variance (ANOVA) and post-ANOVA Dunnett's test; **p<0.001, ****p<0.0001 when compared to vehicle+ IFN-α group

Monoamine oxidase activity

A significant increase ($p<0.01$) in brain MAO-A activity was observed in the Hippocampi after administration of IFN-α. Interestingly, administration of Indomethacin (IND) significantly reduced brain monoamine oxidase activity in the stressed mice. As expected, administration of Amitriptyline significantly decreased ($p<0.01$) the brain monoamine oxidase activity in stressed mice (Figure 13).

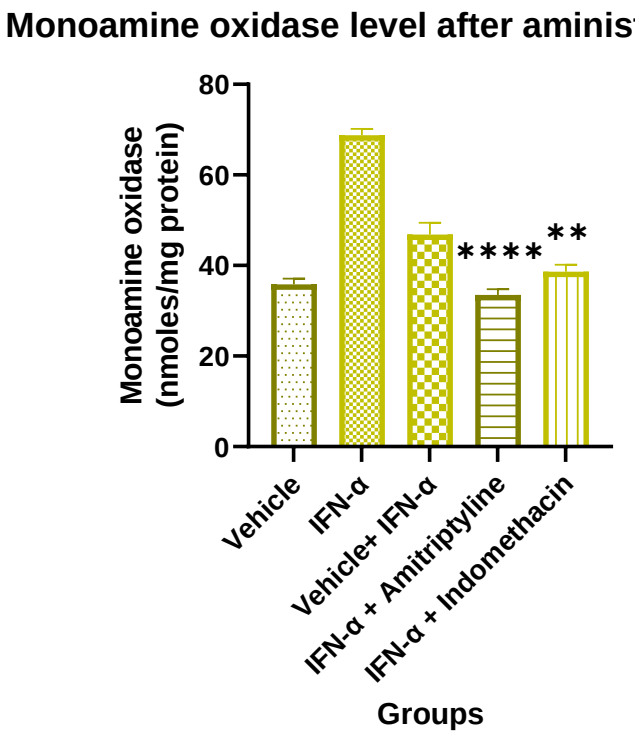

Figure 13. Effect of Indomethacin (IND) and Amitriptyline (AMI) on Monoamine oxidase level in mice (one way ANOVA followed by Dunnett's comparison tests). **p< 0.001, ****p < 0.0001 with vehicle+IFN-α group

From the above results, it was observed that the selected NSAIDs were able to decrease the despair behavior induced by IFNα.

Conclusion

Depression is a common psychiatric disease with high personal and socio-economical costs. It is suggested from our study that Indomethacin (IND) are effective in reducing the symptoms of depression based on behavioral and biochemical tests. This research showed that selected NSAIDs (IND) was able to decrease the despair behavior induced by IFNα in mice model. FST was the main test, splash test and sucrose preference test virtually supported the results. The SOD activity in PC12 cells was also assessed. The anti-depressant action of the drug can be attributed to improvement of brain neurotransmitter levels, decrease hyperactivity of the HPA axis reduction in the plasma corticosterone level. This may have clinical implications as it could be speculated that patients with stress-related depression are more likely to benefit from NSAID treatment than other types of depression and that the most efficient treatment.

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