Antidepressant effects of indomethacin and diclofenac (IND) in interferon-alpha-induced depression in rats

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Abstract

The present study aimed to investigate the antidepressant property of indomethacin using an interferon-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, Diclofenac, anti-depressant activity, behavioral study, biochemical estimation

Introduction

Depression, which is defined as irregularities of mood as opposed to disturbances of mind or cognition, is the most common affective disease (Gupta et al., 2015). Extremely mild conditions that are almost normal to severe (psychotic) depression accompanied by hallucinations and delusions are all possible. The Diagnostic and Statistical Manual of Mental Disorders lists a number of emotional symptoms of depression, including lack of interest, sadness, guilt, and suicidal thoughts, while listing a number of physical symptoms, including

lack of sleep, pain, headaches, sleep disorders, changes in appetite, gastrointestinal disorders, and changes in psychomotor function. The International Consortium of Psychiatric Epidemiology (WHO ICPE) of the World Health Organisation has estimated that between 6.3 and 15.7% of persons worldwide would suffer depression at some time in their life. According to estimates from GUZE (2006) and Saleh et al. (2014), serious depression affects 7 to 12% of men and 20 to 25% of women during the course of their lifetimes. Major depressive illness is thought to be prevalent in as many as 16.2% of people, according to the National Comorbidity Survey (Isingrini, Camus, le Guisquet, et al., 2010). Depression, which affects 30% to 45% of patients and may sometimes result in the cessation of therapy, is the most common and hazardous side effect of interferon medication (Zheng et al., 2014). In addition to psychosis, interferon's neuropsychiatric and neurotoxic side effects also include sorrow, anxiety, insomnia, sleepiness, and disorientation. It's particularly intriguing because a fraction of people have full mental disorders, notably depressive diseases (De & Garza, 2003). According to clinical and preclinical studies, nonsteroidal anti-inflammatory drugs (NSAIDs) and antidepressants may be provided combined with favourable results in both human and animal models of depression (Seo et al., 2019). Non-steroidal anti-inflammatory drugs (NSAIDs) are known to counteract some of the detrimental effects of interferon, including the activation of pro-inflammatory cytokines and the release of stress hormones. NSAIDs are effective in reducing the neurochemical abnormalities generated by interferon-alpha, and this suggests that they could be used to stop depression brought on by interferon-alpha (de La Garza & Asnis, 2003).

A NSAID medication, indomethacin belongs to this group of medicines. Indomethacin 's effects stem from its capacity to inhibit prostaglandin synthesis. Cyclooxygenase (COX) enzymes are primarily responsible for producing prostaglandins, which are significant mediators of inflammation, fever, and discomfort (Munjal & Allam, 2022). IND is used to treat moderate to severe pain, soreness, edoema, and stiffness associated with osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis. Indomethacin is also used to relieve shoulder pain brought on by bursitis. Indomethacin suspension (liquid) and quick-release tablets are also used to treat acute gouty arthritis. MedlinePlus Drug Information, Indomethacin, 2021. It works by halting the body's production of a chemical responsible for inflammation, fever, and discomfort. According to reports, indomethacin has the ability to reverse the depression brought on by interferon with only one dose. As a consequence, the present study used an animal model to examine the anti-depressant effects of indomethacin.

Material and Methods

The outbred adult Swiss Albino female mice, weighing between 25-30 gm were obtained from the animal house in Nagpur College of Pharmacy. Wanadongri, Nagpur, Maharashtra, 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.

The Experimental protocol was approved by the Institutional Animal Ethical Committee (IAEC) IAEC no. 14389/PO/Re/S/11/CPCSEA of Nagpur College of Pharmacy, Wanadongri; 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

With slight changes, the approach described by Majeed R.K. et al. was used to evaluate the acute toxicity of indomethacin. Acute toxicity tests in vivo were performed on albino mice. Mice were given doses of indomethacin (5, 10, 20, 50, 100, and 200 mg/kg body weight) intravenously, and they were monitored for 24 hours following each treatment. This activity's goal was to determine the maximum safe dosage of IND for organisms (Al., 2018).

Induction of Depression

The state of depression was induced in the selected animals by using interferon alpha (interferon-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, IND (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 interferon-α 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 interferon-α 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)	:	interferon-α (16 × 105 IU/kg-IP)
Group 3 (Standard drug)	:	interferon-α + Amitriptyline (10 mg/kg-IP)
Group 4 (Test drug)	:	interferon--α + IND (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

The mice were killed on the 23rd day, their brains were removed, and blood samples were obtained. Cold buffer (pH 7.4) made up of 0.25 M sucrose, 0.1 M Tris, and 0.02 M ethylenediamine tetraacetic acid was used to wash the acquired brain samples. Centrifuging was done on the brain samples. The centrifuged supernatant was tested for the presence of catalase, reduced glutathione, and the oxidative stress marker malondialdehyde (MDA), which is a sign of lipid peroxidation in animal tissues. Malondialdehyde (MDA) levels,

reduced glutathione, and catalase activity were assessed using UV-visible spectrophotometers in accordance with previously described methods (Greenwald, 2018; Jollow D.J., 1974; Wills, 1965), respectively (Alsanie et al., 2022). The Monoamine oxidase A assay kit (Sigma Aldrich) was used to measure the brain enzyme's (Mono-A) activity.

Statistical Analysis

Six animals from each group were used to collect the data needed for the study. The data were evaluated using a one-way analysis of variance (ANOVA) and the Dunnett's test (Graphpad Prism 9.0, San Diego, CA, USA). Differences were considered significant when the p-value difference between groups was less than 0.05. The data in the tables were reported as mean SEM.

Result & Discussion

In-vivo acute toxicity activity of Indomethacin

When IND was tested for acute toxicity in albino mice, it was found that dosages up to 100 mg/kg were well tolerated by the animals, but that when the dose was raised to 200 mg/kg, the animals began to perish.

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., IND 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 INTERFERONα induced depression. Our findings were parallel with previous results regarding the acute treatment with piroxicam promoted an antidepressant-like effect (Santiago et al., 2015).

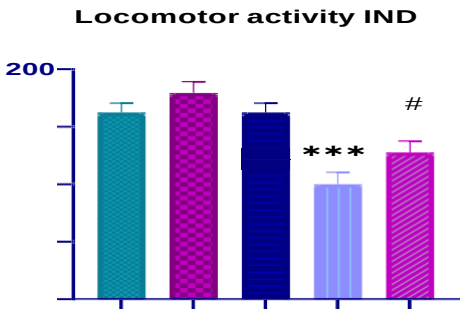


Figure 1: The changes in number of locomotor activity due to IND and Amitriptyline. Data were given as mean and standard error of mean. Each group had six animals. Statistical analysis was performed by one-way analysis of variance (ANOVA) and post-ANOVA Dunnett's test; #p < 0.01 when compared with control;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

Splash test

As per the results obtained from Splash test (figure 2), the grooming time significantly reduced after exposure to INTERFERONα 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 interferon-α 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).

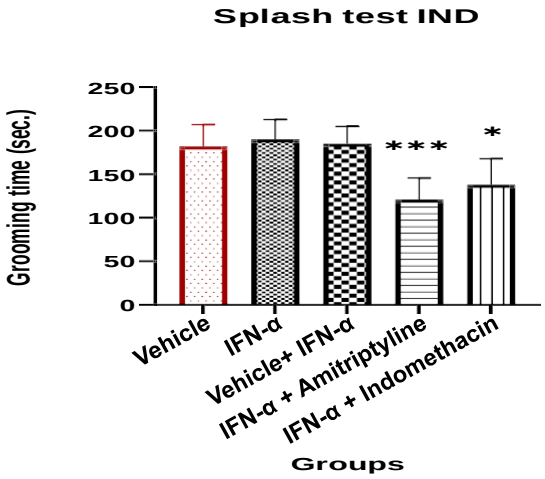
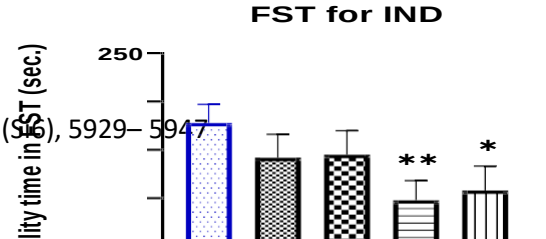


Figure 2 Grooming time (sec.) was presented for IND and Amitriptyline. Data were given as mean and standard error of mean. Each group had six animals. Statistical analysis was performed by one-way analysis of variance (ANOVA) and post-ANOVA Dunnett's test; *p<0.05, ***p<0.0001 compared with vehicle+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

Forced swimming test (FST)

The effect of NSAIDs and interferon-α 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. Interferon-α was injected for 6 days and the NSAIDs were administered simultaneously for 6 days with interferon-α. 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 interferon-α increased the immobility time in the FST, that denotes depression in mice (Fashi et al., 2017) (O'Connor et al., 2009).



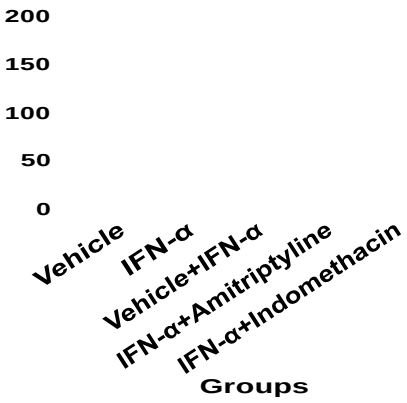


Figure 3: The effect of IND and Amitriptyline (AMI) on Immobility time in FST. Data were given as mean and standard error of mean. Each group had six animals. Statistical analysis was performed by one-way analysis of variance (ANOVA) and post-ANOVA Dunnett's test; *p<0.05, **p<0.001 compared with vehicle+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

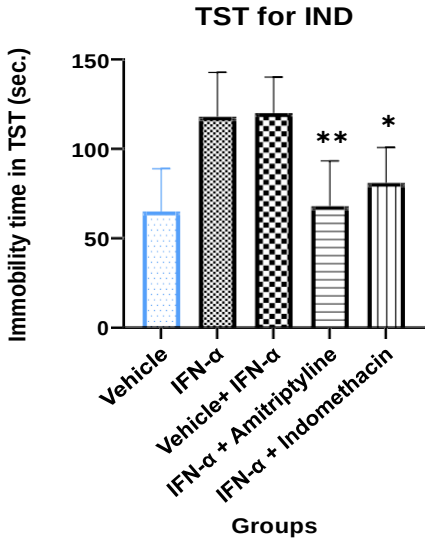


Figure 4: The effect of IND and Amitriptyline on Immobility time in TST. Data were given as mean and standard error of mean. Each group had six animals. Statistical analysis was performed by one-way analysis of variance (ANOVA) and post-ANOVA Dunnett's test; *p<0.05, **p<0.001 compared with vehicle+ INTERFERON-α group

Sucrose preference test

The sucrose preference test also supported the results, while INTERFERONα caused anhedonia in mice, selected drug improved the preference. Results of Sucrose preference test were presented in Figure 5. INTERFERON-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 INTERFERON-α induced depression in mice (Mesripour & Almasi, 2021).

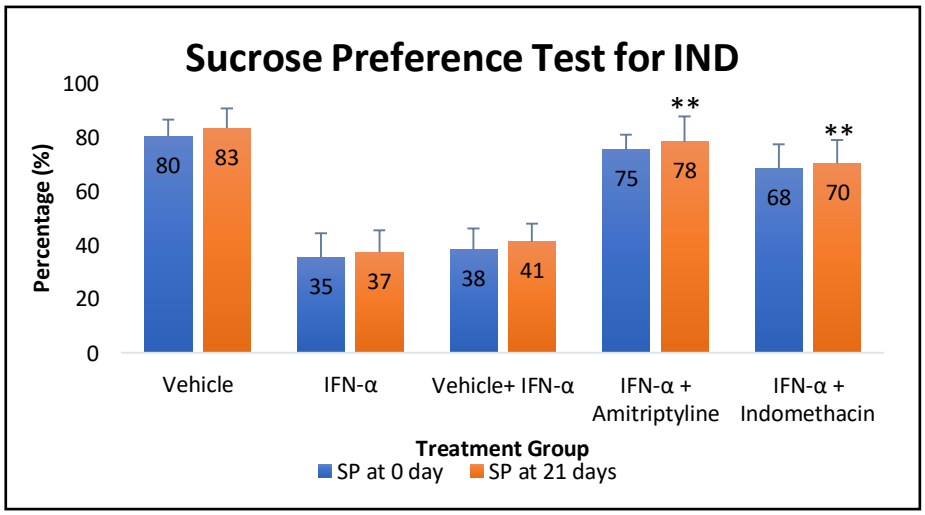
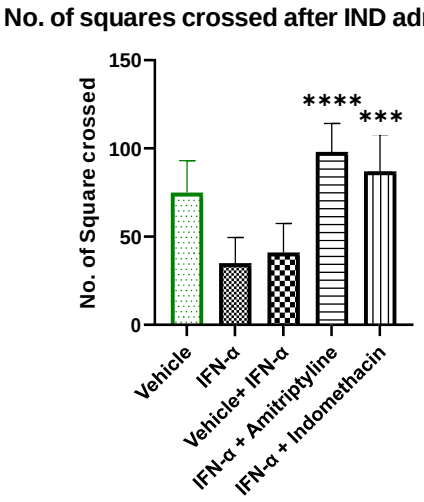


Figure 5: The changes in percentage sucrose preference test due to IND and Amitriptyline. Data were given as mean and standard error of mean. Each group had six animals. Statistical analysis was performed by one-way analysis of variance (ANOVA) and post-ANOVA Dunnett's comparison tests. * p<0.05 compared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

Open field test

Analysis of data indicated that administration of IND 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+ interferon-α group. Conversely, Amitriptyline administration to stressed mice significantly (****p<0.0001) increased the frequency of crossing and rearing when compared to the vehicle+ INTERFERON-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).



Groups

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

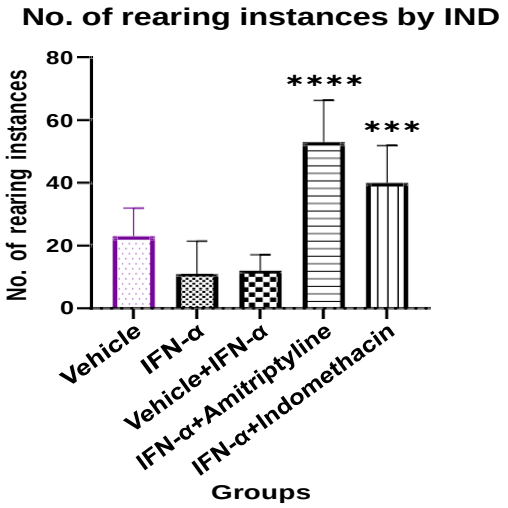


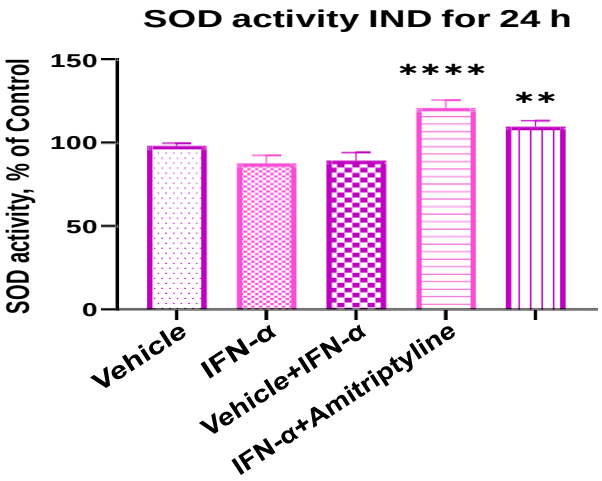
Figure 6B: Number of rearing instances in mice after administration of IND and Amitriptyline. *** p<0.001, ****p<0.0001 compared with vehicle+ INTERFERON-α group

Effect of NSAIDs on biochemical parameters

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

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

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



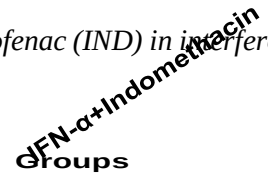


Fig. 7: Effects of IND and Amitriptyline (AMI) on superoxide dismutase (SOD) activity of PC12 cells. PC12 cells were treated with (A) vehicle, 200 µmol/L hydrogen peroxide for 4 hours, 100 µmol/L IND and Amitriptyline (AMI) for 24 hours; Data are presented as mean (and standard error of the mean). **p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

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

The stress produced by INTERFERON-α causes the body to produce oxygen free radicals, which are shown to rise in blood nitrite levels. The selected drug i.e., 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).

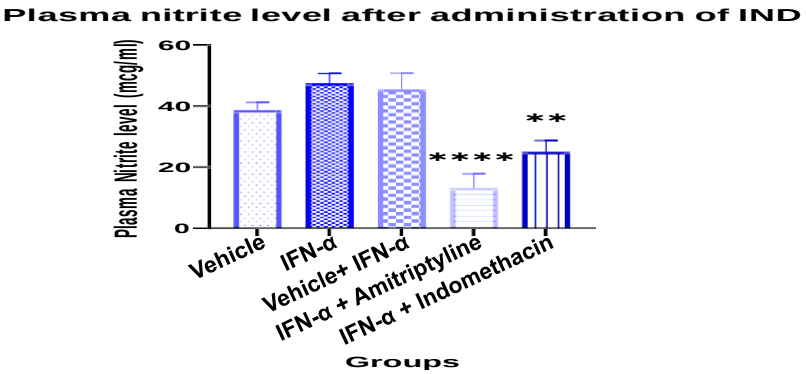


Figure 8. The changes on plasma nitrite levels due to IND and Amitriptyline (AMI). Data were given as mean and standard error of mean. Each group had six animals. Statistical analysis was performed by one-way analysis of variance (ANOVA) and post-ANOVA Dunnett's test; **p<0.001, ****p<0.0001 compared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

Additionally, plasma corticosterone levels in the animals given amitriptyline (AMI) and IND considerably decreased (p 0.001). Amitriptyline (AMI), a common antidepressant, had more encouraging outcomes (p 0.001). In research, Franscina Pinto and Andrade (2016) found that interferon-alpha hyperactivates the HPA axis, which raises plasma corticosterone levels. In our study, amitriptyline (AMI) and IND therapy significantly decreased plasma corticosterone levels in stressed mice and inhibited the hyperactivity of the HPA axis induced by interferon-alpha in mice. Amitriptyline (AMI), a common tricyclic antidepressant, had a greater significant (p0.001) impact on plasma corticosterone levels, albeit (Figure 9).

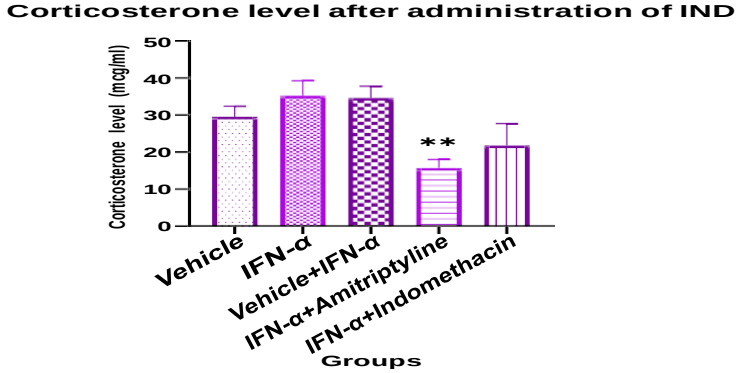


Figure 9. The changes on plasma corticosterone levels due to IND and Amitriptyline (AMI). Data were given as mean and standard error of mean. Each group had six animals. Statistical analysis was performed by one-way analysis of variance (ANOVA) and post-ANOVA Dunnett's test; **p<0.001 compared with vehicle+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

Effect of 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 IND ($p < 0.05$) and Amitriptyline (AMI) ($p < 0.001$) when compared to the vehicle+interferon-α group. The selected drug and Amitriptyline (AMI) showed almost similar reduction in brain MDA level (Figure 10)

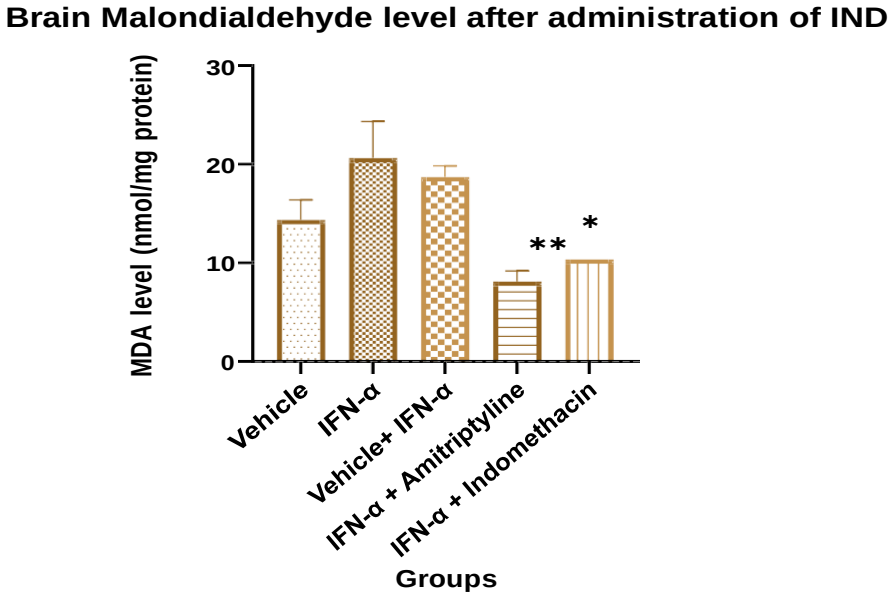


Figure 10. The changes on brain MDA level due to IND and Amitriptyline (AMI). Data were given as mean and standard error of mean. Each group had six animals. Statistical analysis was performed by one-way analysis of variance (ANOVA) and post-ANOVA Dunnett's test; * p< 0.05, and **p< 0.001 when compared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

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

From the results, it was seen that selected drug i.e., 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).

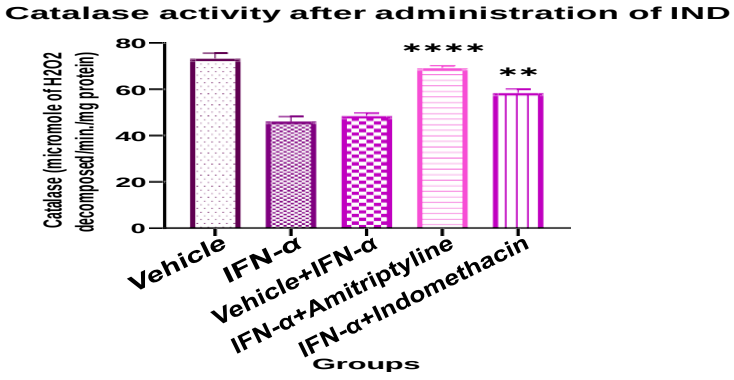


Figure 11. The changes on brain catalase activity due to IND and Amitriptyline (AMI). Data were given as mean and standard error of mean. Each group had six animals. Statistical analysis was performed by one-way analysis of variance (ANOVA) and post-ANOVA Dunnett's test; **p<0.001, ****p<0.0001 when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

The results demonstrated that, a significant decrease (p<0.01) in the enzymatic defense system parameter (CAT) in mice administered with INTERFERON-α was seen, while, administration of 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 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+ interferon-α group (Figure 12).

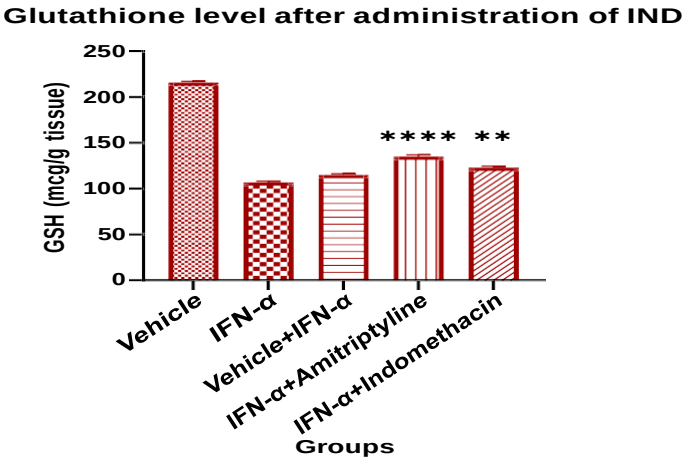


Figure 12. The changes in brain Hippocampal glutathione levels after administration of IND and Amitriptyline (AMI). Data were given as mean and standard error of mean. Each group had six animals. Statistical analysis was performed by one-way analysis of variance (ANOVA) and post-ANOVA Dunnett's test;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

Monoamine oxidase activity

A significant increase (p<0.01) in brain MAO-A activity was observed in the Hippocampi after administration of interferon-α. Interestingly, administration of 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).

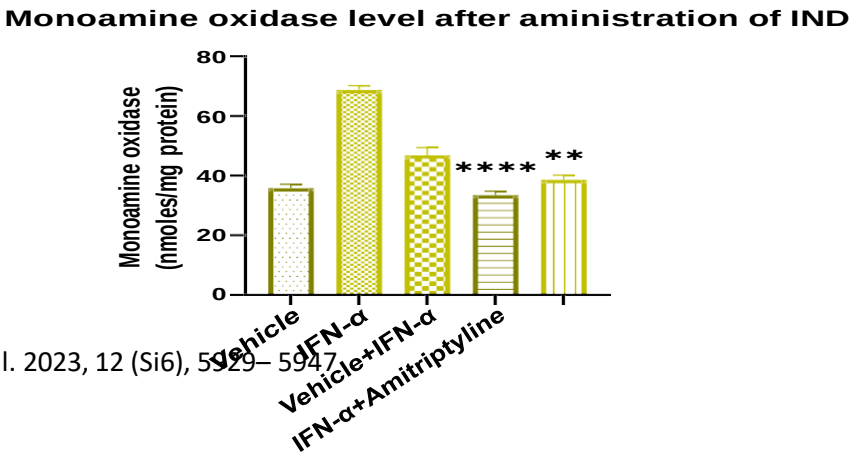


Figure 13. Effect of IND and Amitriptyline (AMI) on Monoamine oxidase level in mice (one way ANOVA followed by Dunnett's comparison tests). **p< 0.001, ****p < 0.0001 with vehicle+INTERFERON-α group

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

Conclusion

Depression is a common mental illness with serious personal and societal repercussions. Our study reveals that IND are helpful in reducing the symptoms of depression based on behavioural and physiological tests. This research shown that certain NSAIDs (IND) may reduce the interferon-induced despondency behaviour in mice. The FST was the main test, and the splash test and sucrose preference test mainly confirmed the results. The SOD activity in PC12 cells was also assessed. Increased brain neurotransmitter levels, reduced HPA axis hyperactivity, and lower plasma corticosterone levels may all contribute to the drug's antidepressant effects. Since it may be concluded that NSAID treatment is the most successful and advantageous for patients with stress-related depression, this may have therapeutic ramifications.

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