Section : Research Paper

Antidepressant effects of diclofenac in interferon alpha-induced depression in rats

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Abstract

The present study tested diclofenac's antidepressant properties in albino mice using an IFN-induced depression paradigm. After inflicting stress on albino female mice, the antidepressant effects of a selected medication were evaluated using the locomotor activity, splash test, forced swimming test, tail suspension, sucrose preference, and open field tests. It was noticed how long patients remained still throughout the TST and what percentage of them preferred the sucrose solution. Monitoring brain malondialdehyde (MDA) levels, catalase (CAT) activity, and reduced glutathione (GSH) levels allowed researchers to assess the antioxidant capacity. When compared to the stressed group, animals administered Diclofenac had substantially shorter durations of immobility during the TST. Sucrose solution became more popular after diclofenac treatment, putting it closer to the common antidepressant Amitriptyline. Additionally, diclofenac dramatically lowered brain MDA and catalase activity as well as plasma corticosterone, nitrite, and glutathione levels. However, further investigation is needed to determine if the antidepressant effects of diclofenac are therapeutically useful.

Keywords: Depression, Diclofenac, anti-depressant activity, behavioral and 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 Organization 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 sometimes results in therapy discontinuation, is the most common and serious side effect of IFN treatment (Zheng et al., 2014). IFN- has neuropsychiatric side effects and is neurotoxic, resulting in psychosis, lethargy, disorientation, anxiety, and insomnia. 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). The activation of pro-inflammatory cytokines and the creation of stress hormones are two effects of IFN- that are known to be blocked by non-steroidal anti-inflammatory drugs (NSAIDs). Due to their capacity to control IFN-a's effects on neurochemical alterations, NSAIDs may be utilised to prevent IFN-a-induced depression (de La Garza & Asnis, 2003).

A NSAID medication, diclofenac belongs to this group of medicines. Diclofenac'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). Diclofenac is used to treat moderate to severe pain, soreness, edoema, and stiffness associated with osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis. Diclofenac is also used to relieve shoulder pain brought on by bursitis. Diclofenac suspension (liquid) and quick-release tablets are also used to treat acute gouty arthritis. MedlinePlus Drug Information, Diclofenac, 2021. It works by halting the body's production of a chemical responsible for inflammation, fever, and discomfort. A single dose of IND may be able to reverse IFN-induced depression, according to studies. As a consequence, the present study used an animal model to examine the anti-depressant effects of diclofenac.

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. Pin 441110. 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 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. 14389/PO/Re/S/11/CPCSEA; Care and use of laboratory animals were confirmed to CPCSEA guidelines.

Acute toxicity study of Diclofenac

The approach described by Majeed R.K. et al. was modified to measure the acute toxicity of diclofenac. Acute toxicity tests were conducted in vivo on albino mice. Mice received i.p. injections of doses of diclofenac (5, 10, 20, 50, 100, and 200 mg/kg body weight) and were monitored for 24 hours after each treatment. In this experiment, the maximum safe dosage of Diclofenac for organisms was determined (Al., 2018).

Induction of Depression

IFN alpha (IFN-) cytokines were used to produce depression in the chosen animals because they have a high load of negative effects on the central nervous system. Cognitive symptoms, neurovegetative symptoms, and mood symptoms are some of them (Capuron & Miller, 2004). For six days in a row, subcutaneous (SC) injections of INF (16 105 IU/kg) body weight were given (Mesripour et al., 2018).

Drug Administration

Diclofenac (25 mg/kg) and Amitriptyline (10 mg/kg) were two medications that were diluted in normal saline and suspended in 0.1% (v/v) tween 80. Each drug's vehicle was given to the corresponding control mice. Both medications were given orally by gavage at a fixed rate of 1 ml/kg. The vehicle (0.1 % (v/v) Tween 80 in normal saline) was given to the control groups.

The tests were conducted seven days after starting IFN treatment. First, each animal underwent the open field test, sucrose preference test, forced swim test, tail suspension test, locomotor test, splash test, and forced swim test. For 6 days, IFN and NSAIDs were given together. Also investigated was how NSAIDs affected biochemical parameters (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 + Diclofenac (25 mg/kg-IP)

Effect of NSAIDs in behavioral paradigms

To investigate the impact of NSAIDs on the treated animals' behavioural patterns, tests on the treated animals' locomotor activity, splash activity, forced swim test, tail suspension test, preference for sucrose, and open field test were performed on 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

Another crucial behavioural test to gauge a person's reaction to a stressful circumstance is the tail suspension test (TST). The rodent tails were taped to a horizontal bar and left there for six minutes to record the duration of immobility. The length of time the person spends stationary will rise as depressive-like conduct worsens. It should be mentioned that the TST is often exclusively utilised on mice because of their smaller size and weight. According to Wang et al. (2017), TSTs are utilised to measure the antidepressant response. 2014's (Zaminelli et al.)

Sucrose preference test

Prior to subjecting animals to prolonged moderate stress, they were taught to ingest sucrose solution while fasting for two days. Following a 23-hour fast, the animals were given two bottles: one contained ordinary water, the other a sucrose solution, three days later. To determine the effect of treatment on the patients' preference for sucrose solution as a percentage—which will serve as an indication for depression brought on by stress—the test was repeated after 21 days of therapy (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

On the 21st day of the experiment, an animal is placed in an unknown environment where escape is impeded by surrounding walls, using a model of anxiety-like behaviour known as the "open field test" to quantify animal emotionality. The open-field box is used in this, and it is a rectangular space with a firm floor that is built of white painted wood and measures 60 cm 60 cm 40 cm. Each rat was put separately in one corner of the field, which had been divided into 16 equal squares at the bottom using permanent read marks. For each 10-minute cycle, the total locomotion and rearing frequency were then recorded. To eliminate olfactory bias after each of these tests, the surface was cleaned with 70% alcohol and allowed to dry before a new rat was added (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

Using the SOD Assay Kit-WST, the amount of SOD enzyme activity in PC12 cells was assessed. The original medium from the 96-well plates was removed after the PC12 cells had been incubated with the experimental substances for the specified amounts of time. The PC12 cells were then 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 SOD enzyme activity was assessed using 20 L of the sample solution obtained after centrifuging the lysates at 300g for 10 minutes. Each treatment group's value was translated to a percentage of the control. (Kolla et al., 2005).

Biochemical parameters estimation in Plasma

On day 23, blood was drawn, and plasma was separated using a centrifuge in order to evaluate the levels of nitrite and corticosterone. This was carried out 60 minutes following the therapy. (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

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 Diclofenac

Acute toxicity study of Diclofenac 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., Diclofenac was observed. In locomotor activity, as per figure 1, Amitriptyline (10 mg/kg) showed a significant increase (***$p<0.001$) in locomotor activity. Moreover, Diclofenac 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).

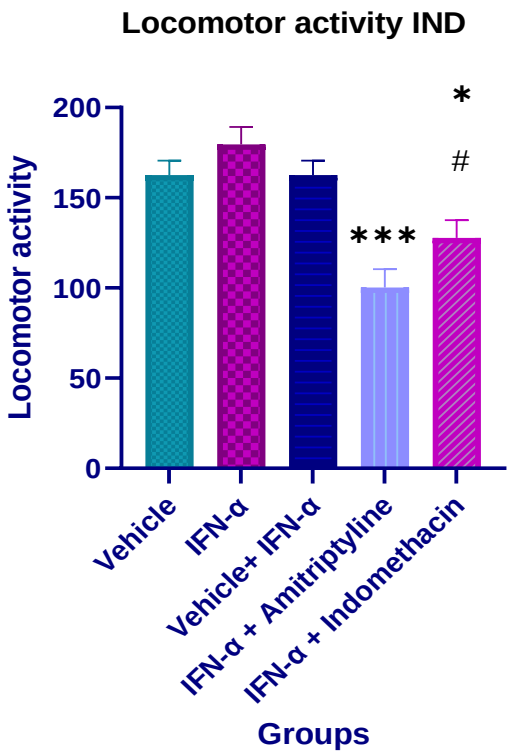

Figure 1: The changes in number of locomotor activity due to Diclofenac and Amitriptyline. Data were given as mean and standard error of mean. Each group had six animals. Statistical analysis was performed by one-way analysis of variance (ANOVA) and post-ANOVA Dunnett's test; #p < 0.01 when compared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

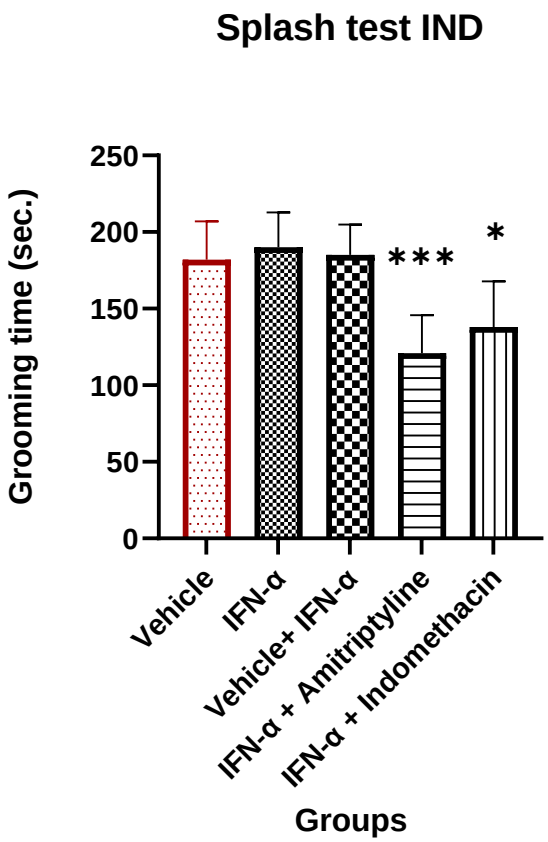

Figure 2 Grooming time (sec.) was presented for Diclofenac and Amitriptyline. Data were given as mean and standard error of mean. Each group had six animals. Statistical analysis was performed by one-way analysis of variance (ANOVA) and post-ANOVA Dunnett's test; *p<0.05, ***p<0.0001 compared with vehicle+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

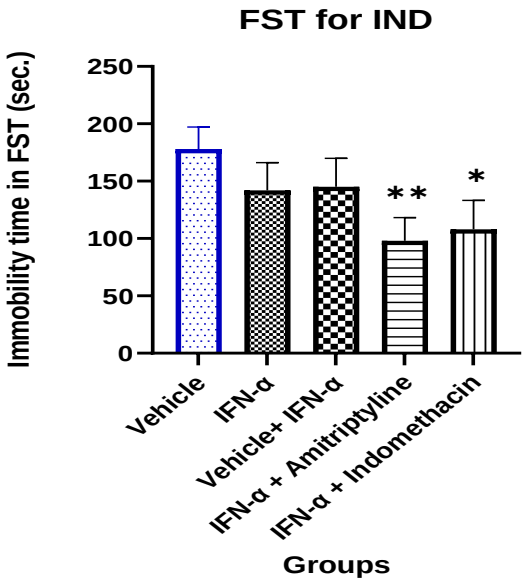

Figure 3: The effect of Diclofenac and Amitriptyline (AMI) on Immobility time in FST. Data were given as mean and standard error of mean. Each group had six animals. Statistical analysis was performed by one-way analysis of variance (ANOVA) and post-ANOVA Dunnett's test; *p<0.05, **p<0.001 compared with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

Tail suspension test

Diclofenac 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)

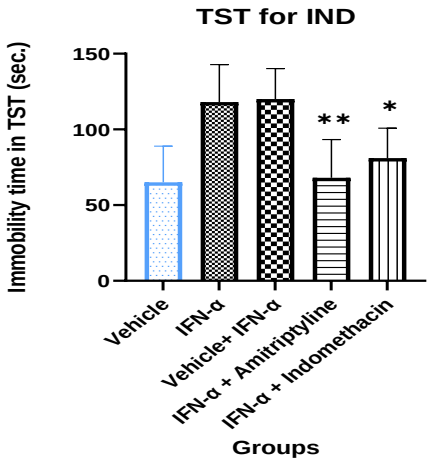

Figure 4: The effect of Diclofenac and Amitriptyline on Immobility time in TST. Data were given as mean and standard error of mean. Each group had six animals. Statistical analysis was performed by one-way analysis of variance (ANOVA) and post-ANOVA Dunnett's test; *p<0.05, **p<0.001 compared with vehicle+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

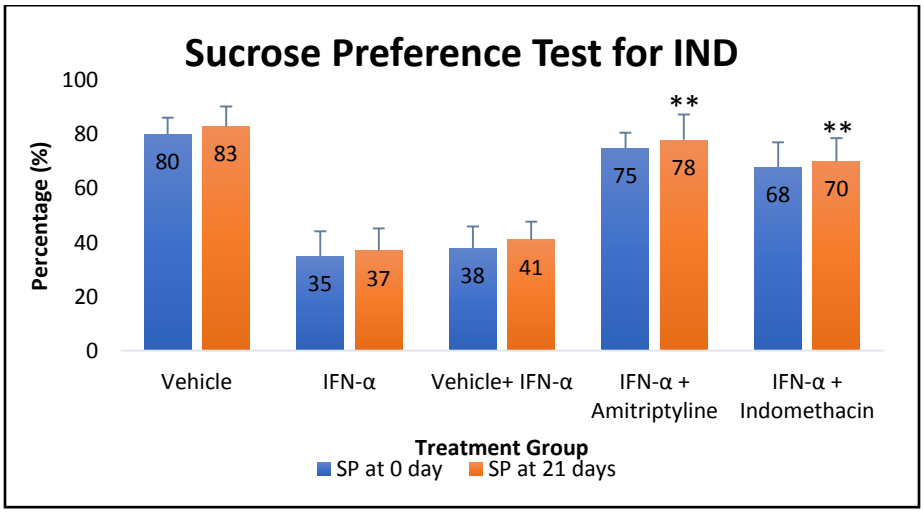

Figure 5: The changes in percentage sucrose preference test due to Diclofenac and Amitriptyline. Data were given as mean and standard error of mean. Each group had six animals. Statistical analysis was performed by one-way analysis of variance (ANOVA) and post-ANOVA Dunnett's comparison tests. * p<0.05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

Open field test

Analysis of data indicated that administration of Diclofenac 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).

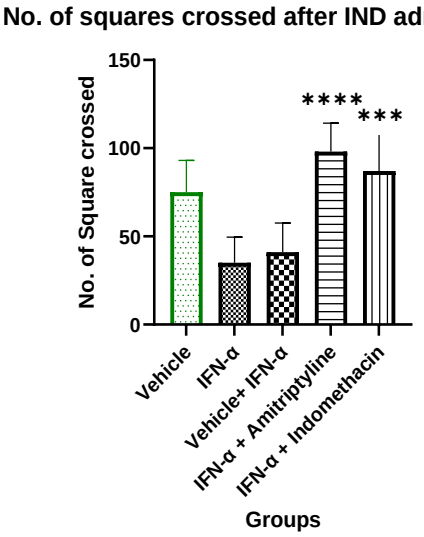

Figure 6A: Number of squares crossed in mice after administration of Diclofenac and Amitriptyline. *** p<0.001, ****p<0.0001 compared with vehicle+ IFN-α group

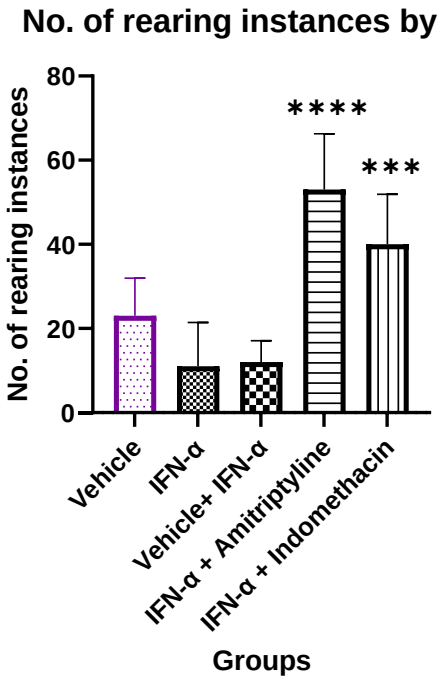

Figure 6B: Number of rearing instances in mice after administration of Diclofenac and Amitriptyline. *** p<0.001, ****p<0.0001 compared with vehicle+ IFN-α group

Effect of NSAIDs on biochemical parameters

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

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

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

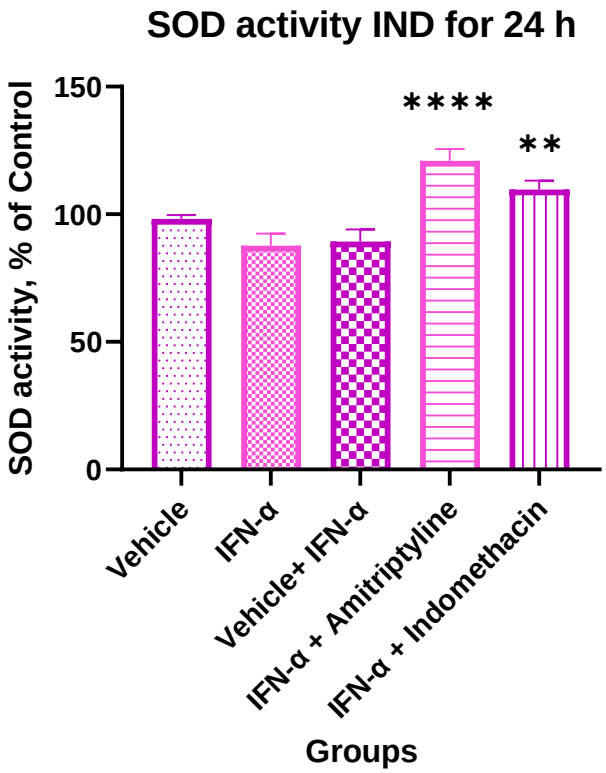

Fig. 7: Effects of Diclofenac and Amitriptyline (AMI) on superoxide dismutase (SOD) activity of PC12 cells. PC12 cells were treated with (A) vehicle, 200 µmol/L hydrogen peroxide for 4 hours, 100 µmol/L Diclofenac and Amitriptyline (AMI) for 24 hours; Data are presented as mean (and standard error of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

Effect of Diclofenac 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., Diclofenac 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).

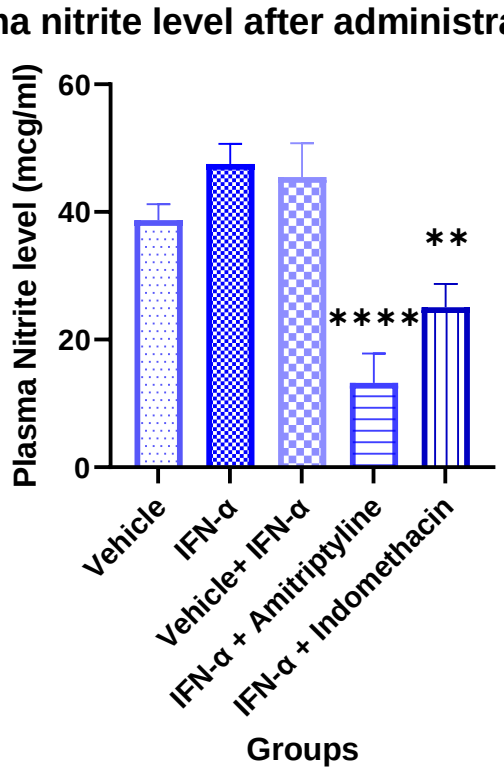

Figure 8. The changes on plasma nitrite levels due to Diclofenac and Amitriptyline (AMI). Data were given as mean and standard error of mean. Each group had six animals. Statistical analysis was performed by one-way analysis of variance (ANOVA) and post-ANOVA Dunnett's test; **p<0.001, ****p<0.0001 compared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

Moreover, plasma corticosterone level was significantly ($p<0.001$) declined in animals that received Diclofenac 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, Diclofenac 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).

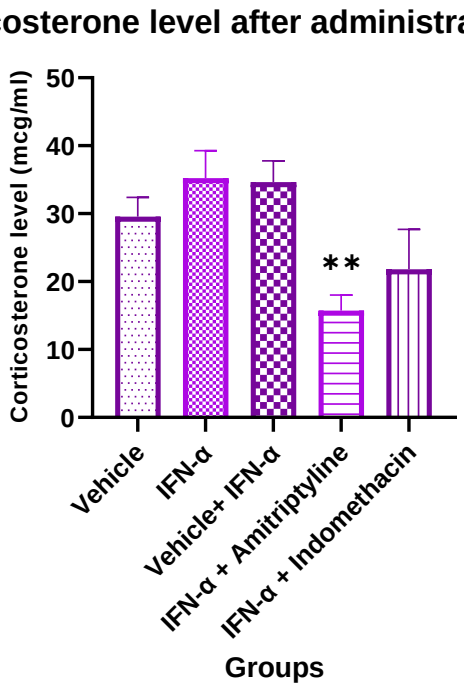

Figure 9. The changes on plasma corticosterone levels due to Diclofenac and Amitriptyline (AMI). Data were given as mean and standard error of mean. Each group had six animals. Statistical analysis was performed by one-way analysis of variance (ANOVA) and post-ANOVA Dunnett's test; **p<0.001 compared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

Effect of Diclofenac 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 Diclofenac ($p < 0.05$) 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)

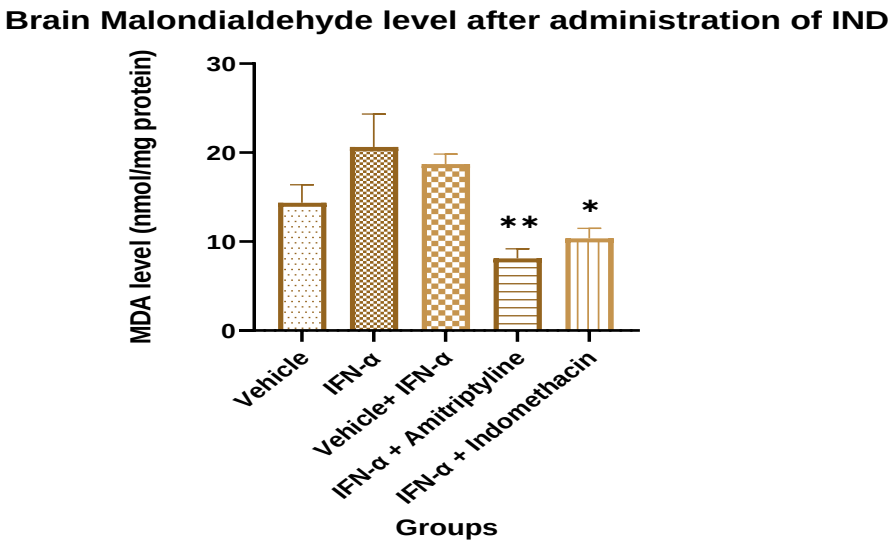

Figure 10. The changes on brain MDA level due to Diclofenac and Amitriptyline (AMI). Data were given as mean and standard error of mean. Each group had six animals. Statistical analysis was performed by one-way analysis of variance (ANOVA) and post-ANOVA Dunnett's test; * p< 0.05, and **p< 0.001 when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

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

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

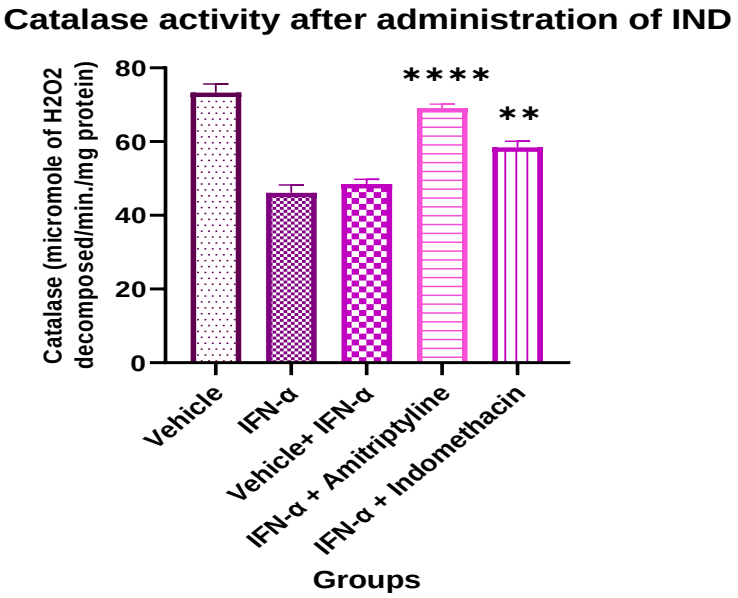

Figure 11. The changes on brain catalase activity due to Diclofenac and Amitriptyline (AMI). Data were given as mean and standard error of mean. Each group had six animals. Statistical analysis was performed by one-way analysis of variance (ANOVA) and post-ANOVA Dunnett's test; **p<0.001, ****p<0.0001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

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

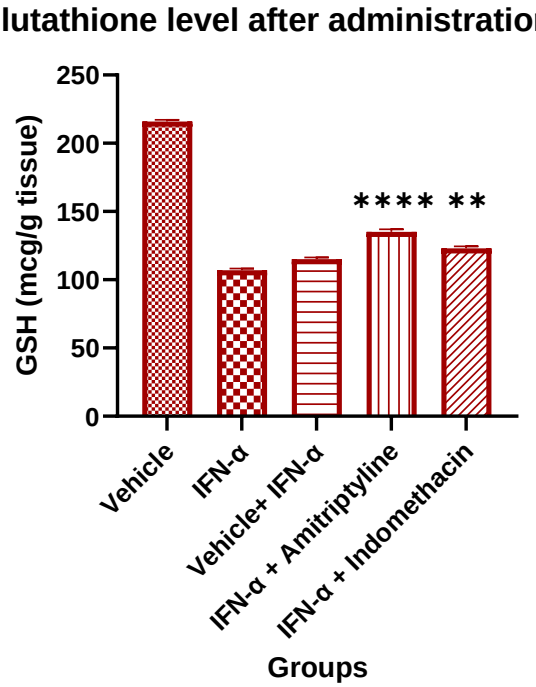

Figure 12. The changes in brain Hippocampal glutathione levels after administration of Diclofenac and Amitriptyline (AMI). Data were given as mean and standard error of mean. Each group had six animals. Statistical analysis was performed by one-way analysis of variance (ANOVA) and post-ANOVA Dunnett's 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 Diclofenac 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).

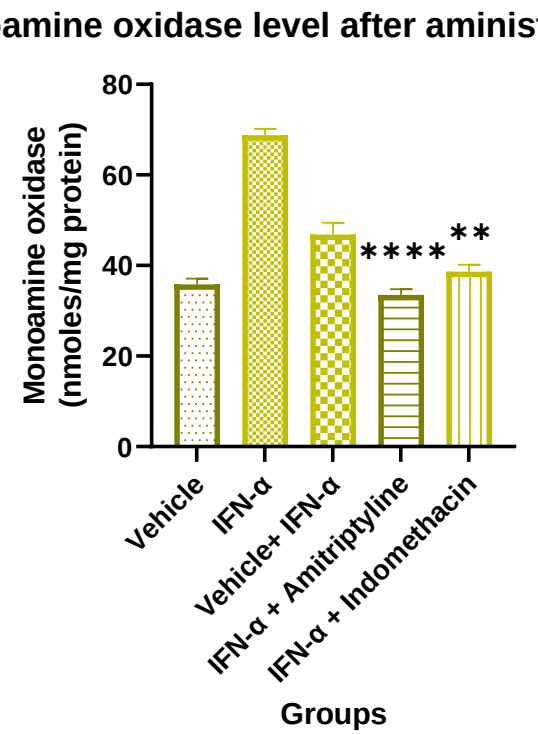

Figure 13. Effect of Diclofenac and Amitriptyline (AMI) on Monoamine oxidase level in mice (one way ANOVA followed by Dunnett's comparison tests). **p< 0.001, ****p < 0.0001 with vehicle+IFN-α group

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 prevalent mental condition that has significant personal and social implications. Based on behavioral and biochemical testing, our research suggests that Diclofenac is beneficial in lowering the symptoms of depression. This study shown that certain NSAIDs may lessen the desperation behavior in mouse models generated by IFN. The FST was the primary test, and the findings were mostly corroborated by the splash test and sucrose preference test. Also evaluated was the SOD activity in PC12 cells. The drug's antidepressant effects may be ascribed to increased levels of brain neurotransmitters, decreased HPA axis hyperactivity, and decreased plasma corticosterone levels. This may have therapeutic repercussions since it is possible to infer that NSAID therapy is the most effective and beneficial for people with stress-related depression.

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