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Etoricoxib Alleviate Depression Like Behavior Induced By Interferon-A In Mice: Behavioral And Biochemical Indications

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ABSTRACT

Interferon-α (IFN-α) administration induces major depression in a significant number of patients undergoing treatment for viral illnesses and other chronic diseases. 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. To investigate this possibility further, we sought to determine the effect of the Etoricoxib on behavioral and biochemical parameters in brain induced by acute IFN-α exposure. Depression was induced by INFα (16×10^5 IU/kg, body weight) for six consecutive days in outbred adult Swiss Albino female mice. The standard anti-depressant drug Amitriptyline (10 mg/kg, orally) and chosen NSAID, Etoricoxib (10 mg/kg, orally) were administered simultaneously and behavioral & biochemical responses were recorded. The study's findings demonstrated that the selected drug had antidepressant properties comparable to Amitriptyline. Analysis of Open field test data indicated that administration of Etoricoxib induced significant differences 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 control and vehicle+ IFN-α group. Etoricoxib (ET), produced significant reduction ($p<0.001$) in plasma nitrite level compared to vehicle treated group, indicated a decrease in nitrosative stress. Moreover, plasma corticosterone level was significantly ($p<0.001$) declined in animals that received Etoricoxib (ET) and Amitriptyline (AMI). Brain MDA level was also significantly reduced with ET ($p<0.05$) and Amitriptyline (AMI) ($p<0.001$) when compared to the vehicle+IFN-α group. Conclusively, the selected drug significantly reduced the brain catalase activity also. These data offer support for a novel role of NSAIDs in modulating IFN-a-induced neurochemical alterations, and raise the possibility of the use of NSAIDs for the prevention of IFN-a-induced depression.

Keywords: Etoricoxib, Interferon-α, Amitriptyline, behavioral paradigm, biochemical indications

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Introduction

Interferon-alpha (IFN-α) is a cytokine with various clinical applications, but it may induce depression by decreasing tryptophan level and producing neuroactive metabolites (Mesripour & Almasi, 2021). There has been increasing interest in the role of innate immune cytokines in behavioral disorders including depression in medically ill and medically healthy individuals. For example, elevations in the innate immune cytokines, interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-α as well as their soluble receptors, have been found in peripheral blood and cerebrospinal fluid (CSF) of patients with major depression (Raison et al., 2009). IFN-α exposure induces a variety of neuropsychiatric side effects, including cognitive impairments, anxiety and depression (de La Garza & Asnis, 2003). Inflammation is increasingly recognized as contributing to the pathogenesis of depression, and the most strikingly supportive evidence for this inflammation theory is major depressive episode (MDE) induced by interferon (IFN)-alpha in patients with cancers or chronic viral infection (Su et al., 2019). Some common NSAIDs are Ibuprofen, Naproxen, Diclofenac, Celecoxib, Mefenamic acid, Etoricoxib, Indomethacin, and Aspirin are reported to be used for the treatment of depression (Dr. Bryan Bruno, 2021). The use of anti-inflammatory agents could improve the antidepressant response (Köhler et al., 2014). 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; De & Garza, 2003). Etoricoxib (ET), 5-chloro-2-(6-methylpyridin-3-yl)-3-(4-methylsulfonylphenyl) pyridine, is a highly selective COX-2 inhibitor. Etoricoxib (ET) has been approved in Europe as a once-daily treatment for symptomatic relief of OA, RA and acute gouty arthritis (Capone et al., 2005). Etoricoxib (ET) are effective in reducing the symptoms of depression based on behavioral tests. The anti-depressant action of this drug can be attributed to improvement of brain neurotransmitter levels, reduction in the corticosterone and quinolinic acid leading to neuroprotection in the CNS

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(Patel & Goswam, 2022). Thus, in the present study, an attempt was made to investigate the anti-depressant activity of Etoricoxib in IFN-α induced depression.

Material and Methods

Selection of Animals

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 (Dayan, 1998; OECD guidelines, 2022).

Acute toxicity study of Etoricoxib

The acute toxicity study was carried out in albino mice through the median lethal dose (LD50) method (N Pohocha, 2001; Sulaiman et al., 2022; Zhang et al., 2022). Doses of Etoricoxib (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 Etoricoxib (ET) for organisms.

Induction of Depression

The state of depression was induced in the selected animals by using IFN alpha (IFN-α) as it is associated with a high burden of central nervous system adverse effects. These include mood symptoms, neurovegetative symptoms, and cognitive symptoms (Capuron & Miller, 2004). INFα

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(16×10^5 IU/kg) body weight was injected subcutaneously (SC) for six consecutive days (Mesripour et al., 2018).

Drug Administration

Drugs Etoricoxib (10 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 the 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. The animals were first subject to the Locomotor test, Splash test, Forced Swim Test, Tail suspension test and 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 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. Group 1 (Control)-Vehicle (Normal Saline) (1-1.5 ml-Oral); Group 2 (Depression control)-IFN-α (16×10^5 IU/kg-IP) Group 3 (Standard drug)-IFN-α+ Amitriptyline (10 mg/kg-IP) and Group 4 (Test)-IFN-α + Etoricoxib (10 mg/kg-IP).

Effect of NSAIDs in behavioral paradigms

The animals were subjected to locomotor activity, Splash activity, Forced Swim Test, Tail suspension test, Sucrose preference test 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 behaviours, the light's beam is interrupt, and the instrument

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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 behaviours, 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., 2002).

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).

Sucrose preference test

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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 Parameter

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

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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. 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 utilized 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

Acute toxicity study of Etoricoxib

This activity was carried out in albino mice through median lethal dose (LD50) method. Different doses of Etoricoxib were given to mice and were keenly monitored for a period of 24 h. The mice

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were natural up to a dose of 100 mg/kg body weight. But died when the dose was increased to 200 mg/kg body weight. It was confirmed that the drug doses were acute toxic at or above 200 mg/kg body weight (Parra et al., 2001).

Effect of NSAIDs in behavioral paradigms

The treated animals were subjected to locomotor activity, Splash activity, Forced Swim Test, Tail suspension, Sucrose preference and open field 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., Etoricoxib was observed. In locomotor activity, Amitriptyline (10 mg/kg) showed a significant increase (***$p<0.001$), whereas Etoricoxib (*$p<0.05$), also increased locomotor activity against IFNα, induced depression, respectively (Figure 1). Our findings were parallel with previous results regarding the acute treatment with piroxicam promoted an antidepressant-like effect (Santiago et al., 2015).

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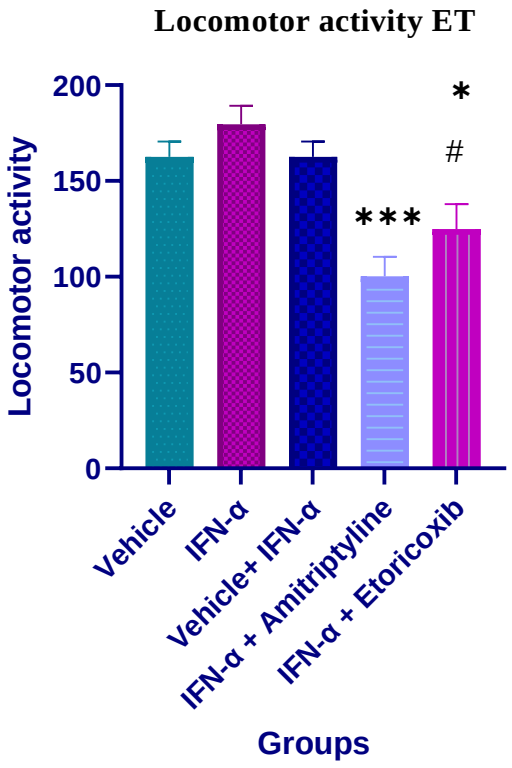

Figure 1. The changes in number of locomotor activity due to Etoricoxib (ET) and Amitriptyline (AMI). Data were given as mean and standard error of mean. Each group had six animals. Statistical analysis was performed by one-way analysis of variance (ANOVA) and post-ANOVA Dunnett's test; #p < 0.01 when compared with control; *p<0.05 and ***p<0.001when compared to Vehicle+ IFN-α

Splash test

As per the results obtained from Splash test, 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). Etoricoxib also exhibited improved splash activity (**p<0.001) against IFNα induced depression. Our findings were parallel with previous results regarding behavioral 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. The results were presented in figure 2 (Isingrini, Camus, le Guisquet, et al., 2010; Zheng et al., 2014).

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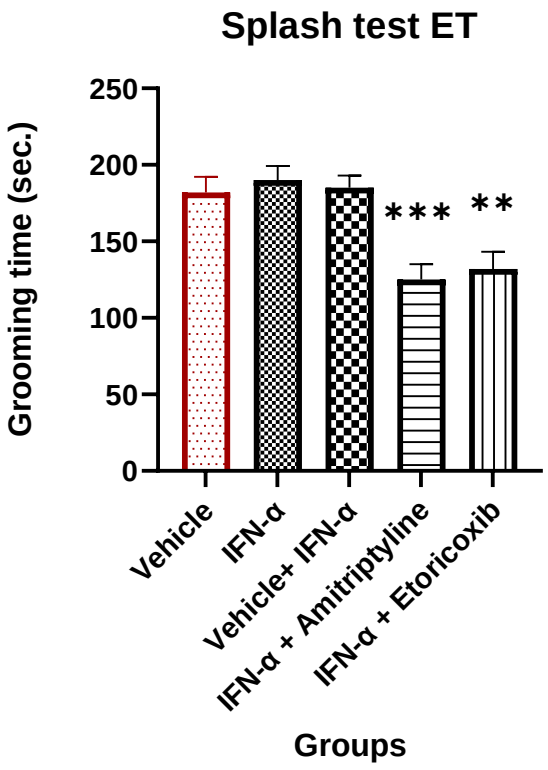

Figure 2. Grooming time (sec.) was presented for Etoricoxib (ET) and Amitriptyline (AMI). Data were given as mean and standard error of mean. Each group had six animals. Statistical analysis was performed by one-way analysis of variance (ANOVA) and post-ANOVA Dunnett's test; **p<0.001 and ***p<0.0001when compared to Vehicle+ IFN-α

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. The control groups received normal saline the vehicle was 0.1% (v/v) tween 80 in normal saline. The results of FST shown that immobility time was reduced by Etoricoxib (*p<0.01) administration, whereas significant effect (**p<0.001) was shown by Amitriptyline. 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).

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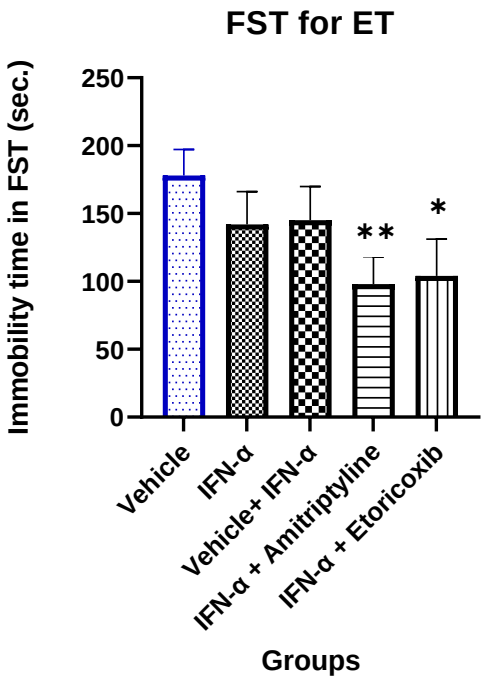

Figure 3. The effect of Etoricoxib and Amitriptyline on Immobility time in FST. Data were given as mean and standard error of mean. Each group had six animals. Statistical analysis was performed by one-way analysis of variance (ANOVA) and post-ANOVA Dunnett's test; *p<0.01, **p<0.001 compared with vehicle+ IFN-α group

Tail suspension test

Etoricoxib 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 (Mandal S., Zaminelli et al., 2014).

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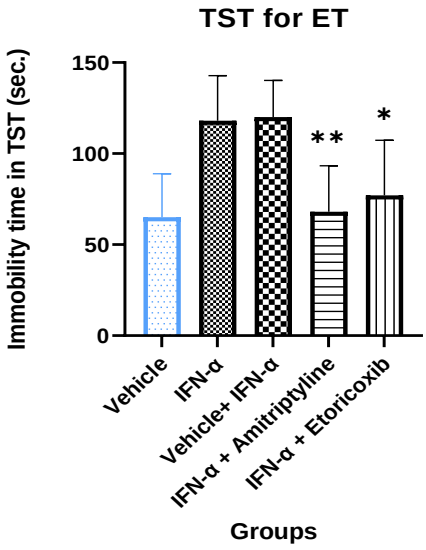

Figure 4. The effect of Etoricoxib (ET) and Amitriptyline (AMI) on Immobility time in TST. Data were given as mean and standard error of mean. Each group had six animals. Statistical analysis was performed by one-way analysis of variance (ANOVA) and post-ANOVA Dunnett's test; *p<0.05, **p<0.001 compared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

Sucrose preference test

INF-α induced anhedonia in animals. The vehicle group had shown good sucrose preference pertaining to lack of stress induction. The percentage of sucrose preference had, however, diminished significantly following stress. When compared to the control, the recovery brought about by Etoricoxib was remarkable (**p<0.001) comparable to Amitriptyline (**p<0.001). Non-steroidal anti-inflammatory drugs (Ibuprofen, and Celecoxib) were able to prevent IFN-α induced depression in mice and presented improvement in behaviour parameters (Mesripour & Almasi, 2021; Santiago et al., 2014).

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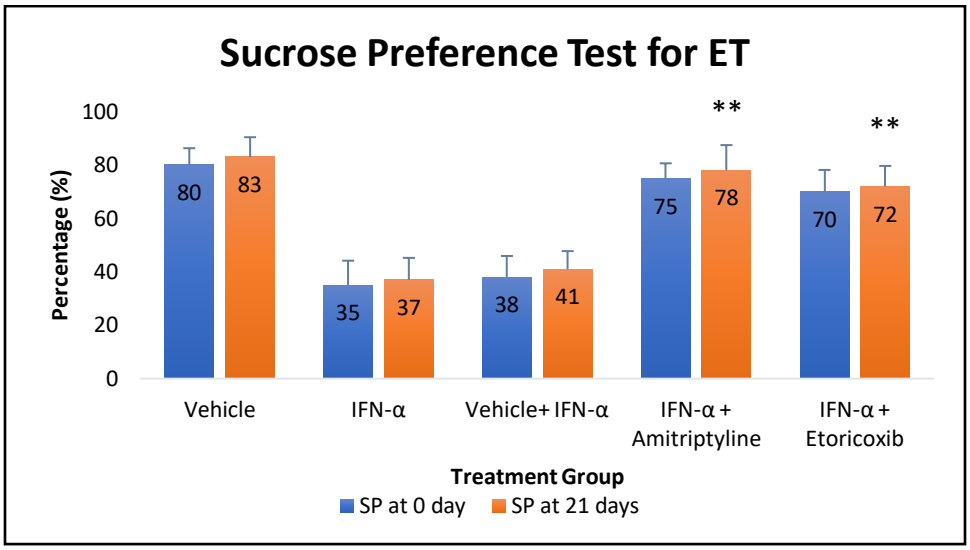

Figure 5. The changes in percentage sucrose preference test due to Etoricoxib and Amitriptyline. Data were given as mean and standard error of mean. Each group had six animals. Statistical analysis was performed by one-way analysis of variance (ANOVA) and post-ANOVA Dunnett's comparison tests. ** p<0.001 compared with vehicle+ IFN-α group

Open field test

Analysis of data indicated that administration of Etoricoxib induced significant differences 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 control and vehicle+ IFN-α group (Figure 6A-6B). 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. Similar results were presented by Santiago et al. (Santiago et al., 2015).

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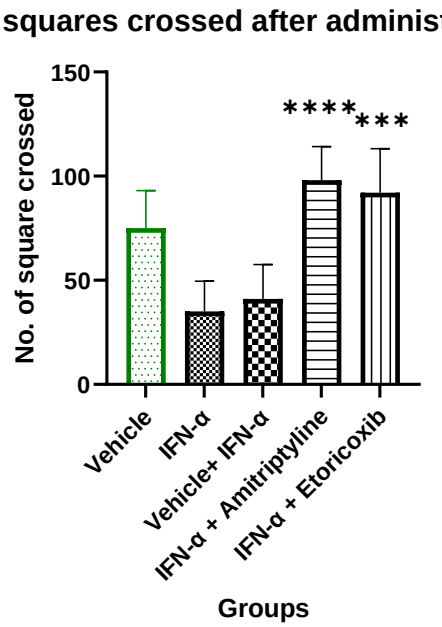

Figure 6A. Number of squares crossed in mice after administration of Etoricoxib and Amitriptyline. *** p=0.0001, ****p<0.0001 compared with vehicle+ IFN-α group

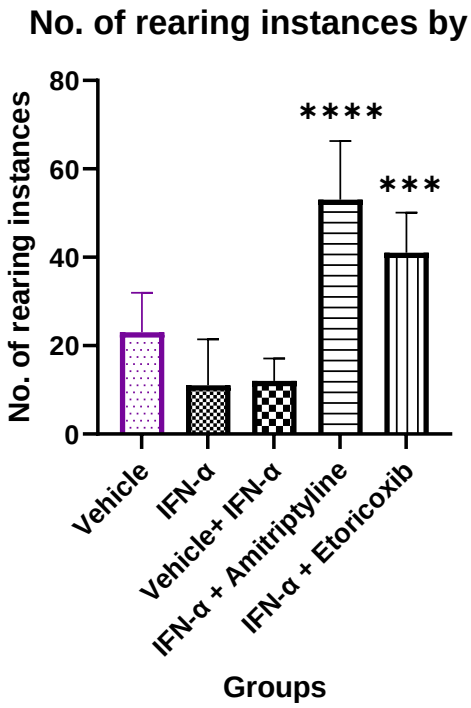

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Figure 6B. Number of rearing instances in mice after administration of Etoricoxib and Amitriptyline. *** p=0.0001, ****p<0.0001 compared with vehicle+ IFN-α group

Effect of NSAIDs on biochemical parameters

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

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

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

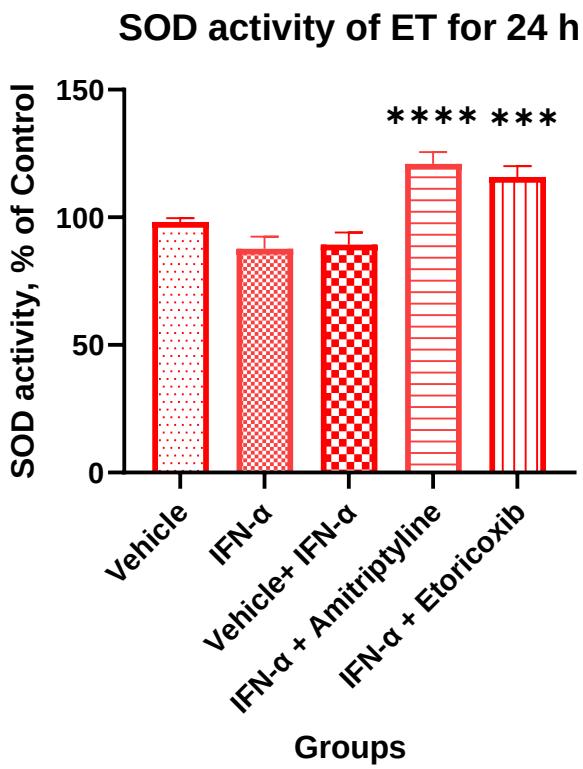

Figure 7. Effects of Etoricoxib (ET) and Amitriptyline (AMI) on superoxide dismutase (SOD) activity of PC12 cells. PC12 cells were treated with (A) vehicle, 200 µmol/L hydrogen peroxide for 4 hours, 100 µmol/L Etoricoxib (ET) and Amitriptyline (AMI) for 24 hours; Data are presented as mean (and standard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

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One-way ANOVA revealed that the SOD activity of PC12 cells treated with 100 µmol/L of Etoricoxib (ET) and Amitriptyline (AMI) for 24 hours was significantly greater than SOD activity (***p=0.0001) in control cells.

Biochemical Estimations in Plasma

The Effect of Etoricoxib (ET) 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., Etoricoxib (ET), 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).

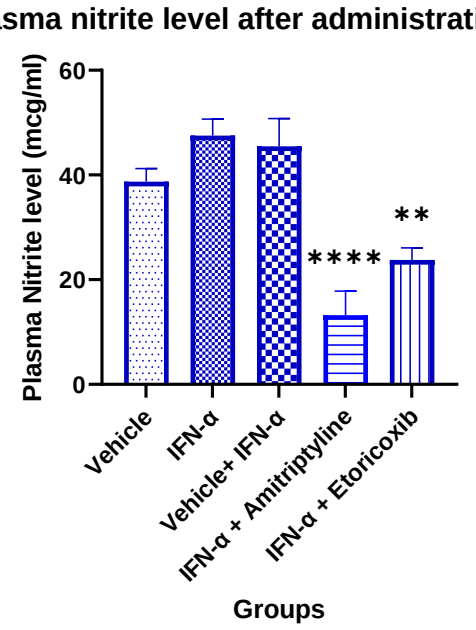

Figure 8. The changes on plasma nitrite levels due to Etoricoxib (ET) and Amitriptyline (AMI). Data were given as mean and standard error of mean. Each group had six animals. Statistical analysis was performed by one-way analysis of variance (ANOVA) and post-ANOVA Dunnett's test; **p<0.001, ****p<0.0001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

Moreover, plasma corticosterone level was significantly (*p<0.05) declined in animals that received Etoricoxib (ET) 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

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axis (Franscina Pinto & Andrade, 2016). In our experiment, Etoricoxib (ET) 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 than Etoricoxib (ET) (Figure 9).

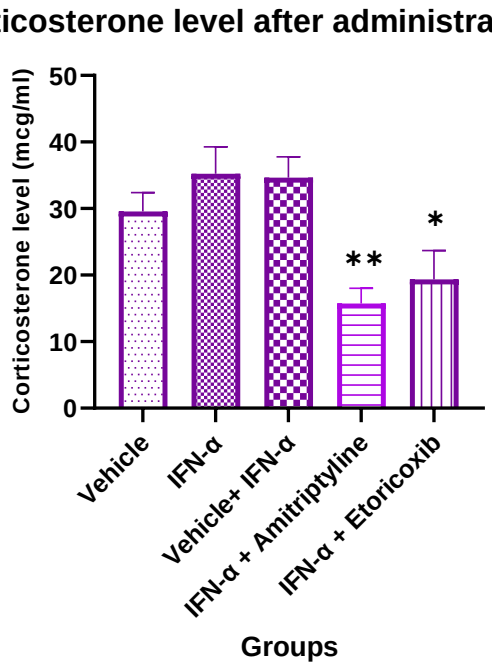

Figure 9. The changes on plasma corticosterone levels due to Etoricoxib (ET) and Amitriptyline (AMI). Data were given as mean and standard error of mean. Each group had six animals. Statistical analysis was performed by one-way analysis of variance (ANOVA) and post-ANOVA Dunnett's test; *p<0.05, **p<0.001 compared with vehicle+ IFN-α group

Effect of Etoricoxib (ET) 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 Etoricoxib (ET) (*$p<0.05$) 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).

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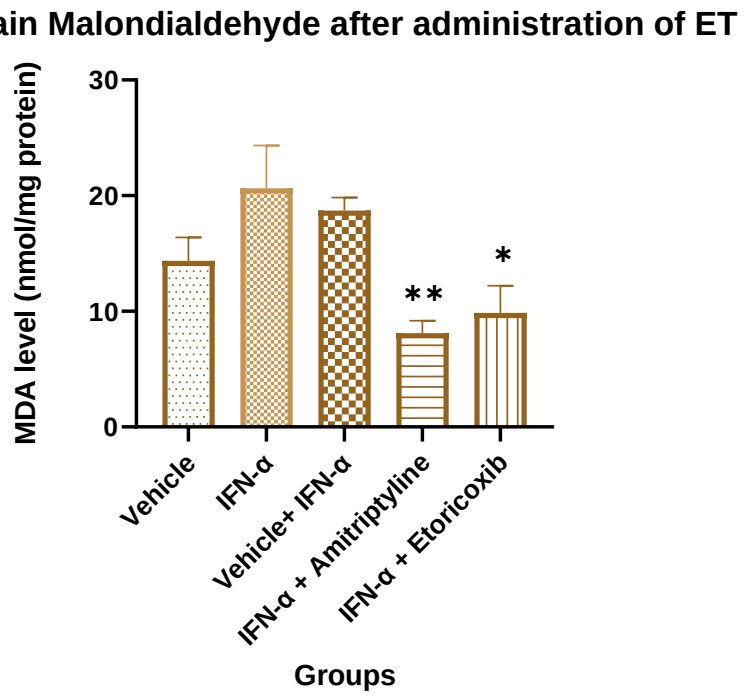

Figure 10. The changes on brain MDA level due to Etoricoxib (ET) and Amitriptyline (AMI). Data were given as mean and standard error of mean. Each group had six animals. Statistical analysis was performed by one-way analysis of variance (ANOVA) and post-ANOVA Dunnett's test; * p<0.05, and **p<0.001 when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

Effect of Etoricoxib (ET) and Amitriptyline (AMI) on Brain Catalase Activity

From the results, it was seen that selected drug i.e., Etoricoxib (ET) showed significant reduction (***p=0.0001) in the brain catalase activity when compared to the vehicle treated group (Figure 11). However, the administration of Amitriptyline (AMI) showed more profound results (****p<0.0001), pertaining to standard anti-depressant drug.

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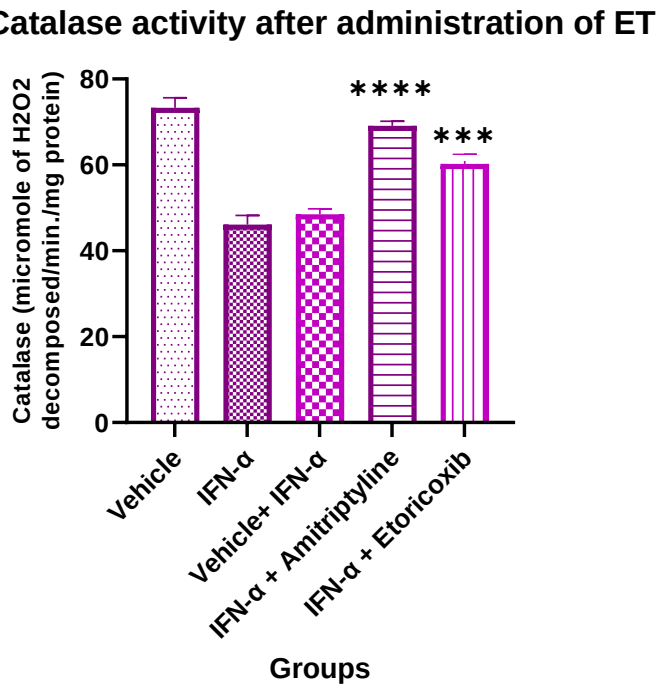

Figure 11. The changes on brain catalase activity due to Etoricoxib (ET) and Amitriptyline (AMI). Data were given as mean and standard error of mean. Each group had six animals. Statistical analysis was performed by one-way analysis of variance (ANOVA) and post-ANOVA Dunnett's test; ***p=0.0001, ****p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

Effect of Etoricoxib (ET) and Amitriptyline (AMI) on Brain Glutathione (GSH) Level

Administration of animals with Etoricoxib (***p=0.0001) and standard antidepressant, Amitriptyline (****p<0.0001) produced significantly elevated brain GSH levels compared to vehicle+ IFN-α group (Figure 12).

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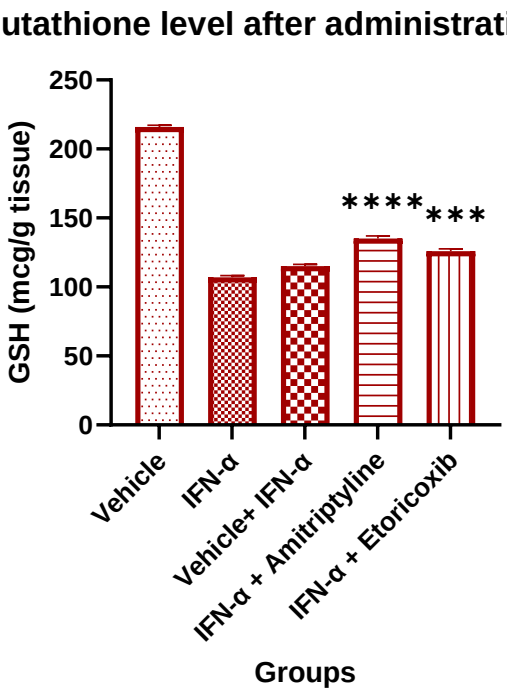

Figure 12. The changes in brain Hippocampal glutathione levels after administration of Etoricoxib (ET) and Amitriptyline (AMI). Data were given as mean and standard error of mean. Each group had six animals. Statistical analysis was performed by one-way analysis of variance (ANOVA) and post-ANOVA Dunnett's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

Monoamine oxidase activity

A significant increase in brain MAO-A activity was observed in the Hippocampi after administration of IFN-α. Interestingly, administration of Etoricoxib (ET) significantly reduced (**p<0.001) brain monoamine oxidase activity in the stressed mice. As expected, administration of Amitriptyline significantly decreased (****p<0.0001) the brain monoamine oxidase activity in stressed mice.

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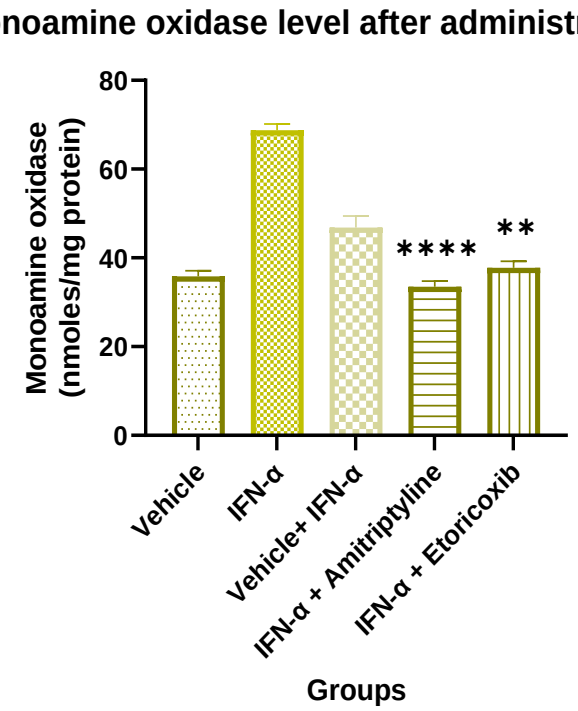

Figure 13. Effect of Etoricoxib (ET) and Amitriptyline (AMI) treatment on Monoamine oxidase level in mice (one way ANOVA followed by Dunnett's comparison tests). **p< 0.001, ****p < 0.0001 with vehicle+IFN-α group

Conclusion

In conclusion, Depression is different from usual mood fluctuations and short-lived emotional responses to challenges in everyday life. Especially when recurrent and with moderate or severe intensity, depression may become a serious health condition. The present data provide evidence that the anti-inflammatory drugs also exert antidepressant effects. In this research we considered Swiss Albino female mice model for the evaluation of antidepressant activity of NSAIDs Etoricoxib (ET) and effectiveness in preventing IFN-α induced depression. Our findings were parallel with previous results regarding the benefit effects of Etoricoxib (ET) on IFNα-induced neurochemical changes and depression. The results showed that stress models using selective COX-2 inhibitors provided the most robust antidepressant response. This may have clinical implications as it could be speculated that patients with stress-related depression are more likely

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to benefit from NSAID treatment than other types of depression and that the most efficient treatment would be selective COX-2 inhibitors such as Etoricoxib.

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