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To Examine The Anti-Depressant Activity Of Nefopam In Wistar Rats

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ABSTRACT
Depression, a mood illness, is characterised by a lingering sense of melancholy and indifference. Defines distinct forms of depressive illnesses in order to categorize them: Disorder of Disruptive Mood Dysregulation severe depression Dysthymia is a chronic depressive illness characterised by premenstrual dysphoria. This study evaluates the therapeutic potential of Nefopam a non-steroidal anti-inflammatory drug in Depression. The experimental technique involves generating Depression via Tail Suspension Method and Forced Swim Test, followed by therapy with Nefopam. The research focused on analysing the physical parameters, clinical parameters and cortisol level in blood. Results demonstrated that Nefopam dramatically restored memory, improved cortisol level, regulated behavioural parameters disturbed by depression. The findings showed the potential effect of Nefopam in the treatment of depression, giving a possible alternative to current pharmaceutical treatments.
Keywords: *Depression, Forced Swim Test, Tail Suspension Test, Wistar rats, cortisol level, behavioural parameters.*

INTRODUCTION

Depression, a mood illness, is characterised by a lingering sense of melancholy and indifference. **[1]** Defines distinct forms of depressive illnesses in order to categorize them: Disorder of Disruptive Mood Dysregulation severe depression Dysthymia is a chronic depressive illness characterised by premenstrual dysphoria. **[2] [3]** Melancholy, emptiness, or irritation are traits shared by all depressive disorders, as are physical and mental abnormalities that hinder functioning. **[4] [5]** Misconceptions prevent about 60% of depressed people from seeking medical help. Many people believe that the stigma attached to mental health illnesses is intolerable in society and that it interferes with both one's personal and professional life. **[6] [7]**

The symptoms listed below could be present:

Depression, Significant changes in appetite or weight, loss of interest or pleasure, Sleeplessness or hyposomnia, Retardation, Fatigue, Worthlessness feeling, Diminished concentration or ability to think, Suicidal thoughts. **[8] [9] [10]**

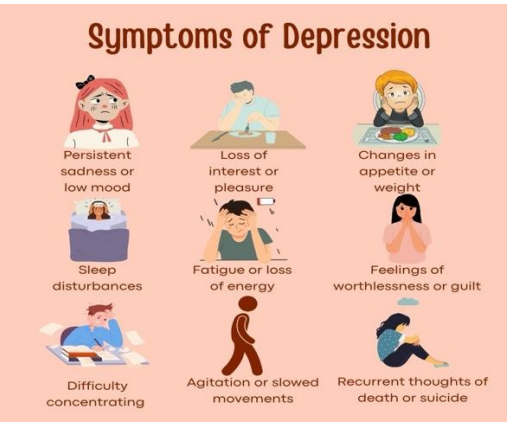


Fig no. 1 Sign and symptoms of depression

In subgroups of depressed people, an inflammatory state is linked to the etiology and a higher chance of developing depression. Because of their similar anti-inflammatory mechanisms, which are most

likely caused by inhibition of Cyclooxygenase-2 (COX-2), nonsteroidal anti-inflammatory medications (NSAIDs) may be used as an adjuvant treatment option for depression in conjunction with antidepressants. In addition to inhibiting COX-2, NSAIDs may also have antidepressant effects by lowering oxidative and nitrosative stress, preventing the rise of proinflammatory cytokines, and raising central serotonin levels. **[11]**

The pain relieving nefopam (NFP) is one drug whose action target is predictable yet unknown. A common non-steroidal, non-opioid, centrally acting pain reliever drug in European countries, fenazocine was developed in the 1960s and belongs to the class of chemicals called benzoxazocine**.[12] [13]** The majority of Research on NFP has concentrated on how well it relieves pain Compared to non-steroidal anti-inflammatory medications (NSAIDs) or opioids, since managing severe pain following surgery has been its most popular usage. **[14] [15]** However, we are aware that its pain-relieving results are comparable to anticonvulsants and triple receptor (dopamine, serotonin, and norepinephrine) reuptake inhibitors. Thus, NFP may be helpful in treating neuropathic pain in addition to its impact on nociceptive pain and other illnesses. **[16] [17]**

Nefopam also interferes with serotonergic transmission so nefopam can also be used as antidepressant drug. **[18]**

Nefopam's precise mechanism of action is unknown, however it is thought to be connected to the suppression of serotonin, dopamine, and noradrenaline reuptake. Other mechanisms may also be involved, such as through glutamate and histamine H3 receptors. Like its analgesic analogue orphenadrine, nefopam has recently been found to behave being a voltage-gated sodium channel blocker, that could fully or partially mediate its antinociceptive effects. **[19]**

MATERIALS AND METHODOLOGY

The animals were bought at the Shri Guru Ram Rai Institute in Dehradun, Uttarakhand. All five of them propylene cages that house the rats has a light/dark cycle of 12:12 and is kept at ambient temperature (25 ± 2 °C). The animals are provided water and a nutritious pellet meal. The Siddhartha Institute of Pharmacy's institutional animal ethics committee passed the application (application No. SIP/IAEC/PCOL/07/2025) to carry out the animal experimental research after Form B was completed.

Every day, fresh nefopam and escitalopram stock solutions were made. The standard medication used to treat depression was escitalopram (10 mg/kg). 10 mg/kg/day of escitalopram is the recommended dosage orally. 6 mg of escitalopram were dissolved in 6ml of water per day for a week in order to create the stock solution **[55]**

The first medication used to treat depression was nefopam (10 mg/kg). dose of 10 mg/kg of nefopam is the recommended dosage per oral. Every day for a week, 6 mg of nefopam was dissolved in 6 ml of distilled water to create the stock solution.

The treatment 2 drug used to treat depression was nefopam (20 mg/kg). 20 mg/kg/day of nefopam is the recommended dosage orally. The stock solution was made by dissolving 18 mg of nefopam in 9 ml of water each day for a week.

INDUCTION OF DEPRESSION

Force Swim test

Both male and female rats were allowed to swim alone in an open container that measured 10 cm in diameter. According to the study design, the treatment was administered 60 minutes before the study began. Every animal was made to swim for six minutes, and during the test's last four minutes, the length of time each animal stayed immobile was noted and recorded. hen a rat in the water ceased to struggle and remained motionless, just moving to keep its head up. The water, it was regarded as immobile. There was evidence of an antidepressant-like effect by a reduction in the length of immobility. **[56]**

Tail suspension test

This investigation employed the tail suspension method. According to the study design, the treatment was administered 60 minutes before the study began. With the aid of sticky tape positioned about 1

centimetre from the tip of the tail, Rats were hung 50 cm above the ground on the table's edge. Six minutes of the ten-minute interval were used to record the overall amount of time that tail suspension caused immobility. An animal was deemed immobile if the animal was still move and it was suspended passively and without any movement **[56].**

All groups, with the exception of the control group, experienced depression. There were five groups of rats (n=6). For 21 consecutive days, the animals received drugs or a vehicle 60 minutes before the trial began

Table no. 1: Treatment Protocol [57]

Group Name	**Treatment**	**Dose**	**Route**	**frequency**
Normal control	Normal saline	-	Oral	OD
Diseased control	No treatment	-	-	-
Standard group	Escitalopram	10 mg/kg	Oral	OD
Treatment group I	Nefopam	10mg/kg	Oral	OD
Treatment group I	Nefopam	20mg/kg	Oral	OD

At the end of the treatment biochemical parameters were performed to check level cortisol in blood. Physical parameters were also evaluated.

RESULT

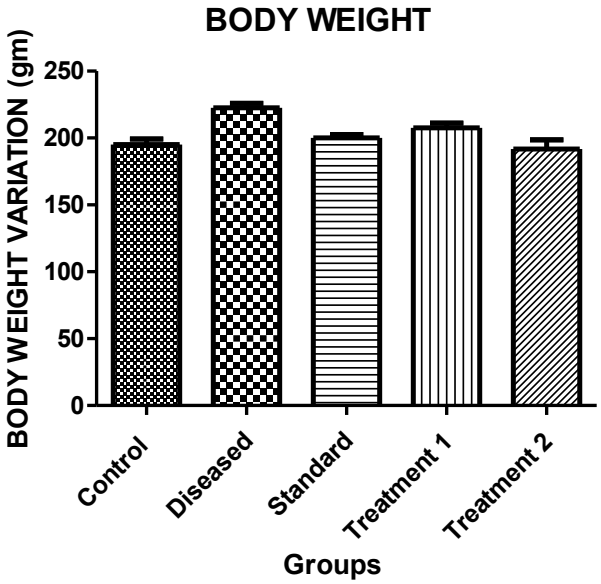
The antidepressant effects of nefopam (10 and 20 mg/kg) and Escitalopram were studied by observing the changes in the duration of immobility in the two models: Forced swim test (FST) and Tail suspension test (TST). In both TST and FST, nefopam 10 and 20 mg/kg, p.o. produced significant reduction in the immobility period when compared with that of control group animals that received only the vehicle.

Physical parameter

Bodyweight

Table no. 2: Showing the body weight of rats

Groups	**Body weight (gm)**
Normal Control Group	195 ±10.5
Disease Control Group	222 ± 8.2
Standard	200 ± 6.3
Treatment 1	207 ± 8.8
Treatment 2	191 ± 17.22

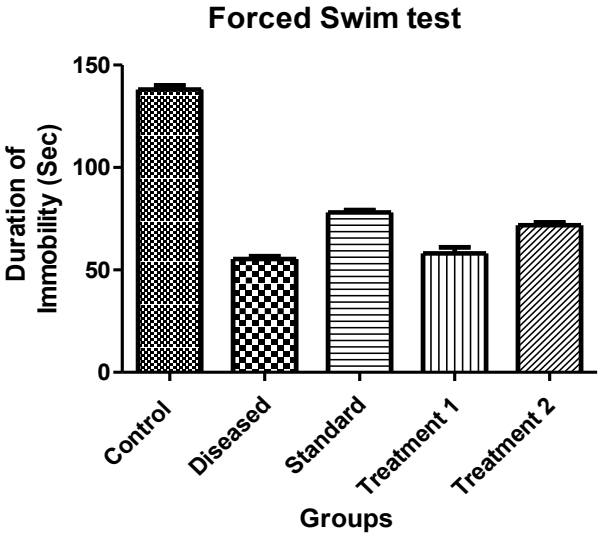


Graph no.1: Depicting the difference in body weight

FORCE SWIM TEST (FST)

Table no. 3: Showing the immobility time of rats

Groups	Immobility (in sec)
Normal Control Group	138 ±5
Disease Control Group	55± 3.3
Standard	78±2.8
Treatment 1	58 ± 7.4
Treatment 2	71 ± 3.1

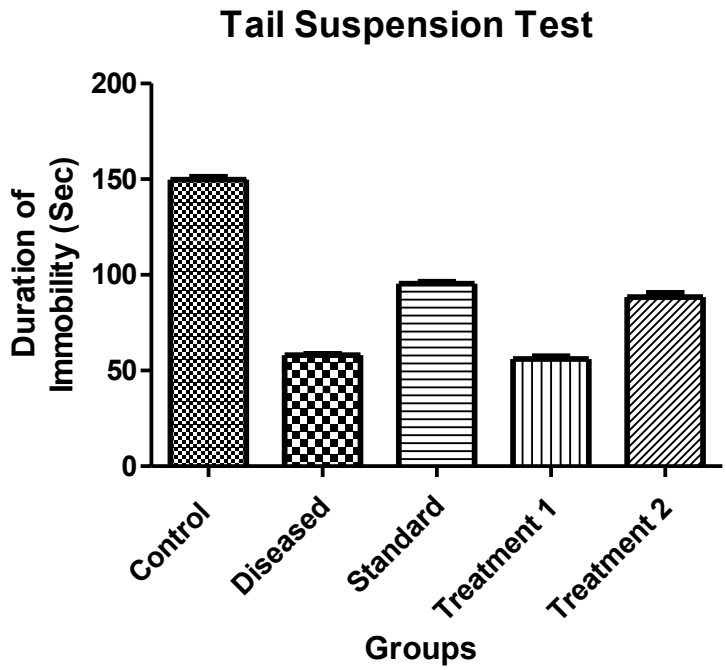


Graph no.2: Depicting the immobility in Force Swim Test

TAIL SUSPENSION TEST (TST)

Table no. 4: Showing the immobility time of rats

Groups	Immobility (in sec)
Normal Control Group	149±3.5
Disease Control Group	58± 1.7
Standard	95±2.8
Treatment 1	56 ± 3.4
Treatment 2	88 ±5.5



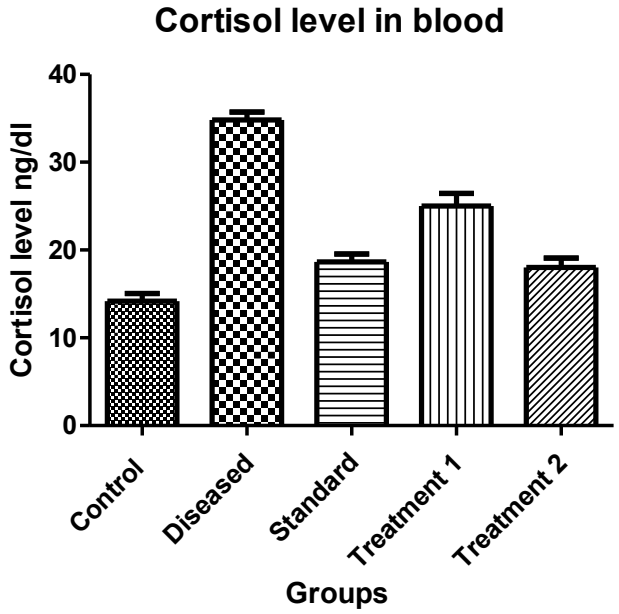
Graph no.3: Depicting the immobility of rats

6.4 CORTISOL LEVEL IN BLOOD

Table no. 5: Showing the cortisol level in rats

Groups	Cortisol level(ng/dl)
Normal Control Group	14±2.1
Disease Control Group	34± 2.1

Standard	18±2.1
Treatment 1	25 ± 3.5
Treatment 2	18 ±2.6



Graph no.4: Depicting the Cortisol level

DISCUSSION

Depression is a condition and an immense public health issue. Even though a range of variables probably influence to the process of depression, improving the wellbeing of those who are impacted by the condition demands an awareness of its consequences, potential causes, and treatments. To determine the necessity and length of ongoing treatment, it is necessary to research the development of depressive illnesses worldwide. for the purpose of effectively treating depression, studies should also evaluate the treatment's cost-effectiveness models that are simple to implement in primary care settings. Clinical drug therapy uses medications such as particular serotonin–noradrenaline reuptake inhibitors (SNRIs), selective reversible inhibitors of monoamine oxidase A (RIMAs), tricyclic antidepressants (TCAs), and selective serotonin reuptake inhibitors (SSRIs).

These medications may cause adverse effects, including as Fat gain, sexual dysfunction, hypopiesia, heart toxicity, and sleep disorders. FST and TST, two animal models, were employed in the study.

Both paradigms are frequently employed behavioural models to evaluate the effectiveness of pharmaceutical antidepressants. Immobility, which reflects behavioural despair as observed in human depression, is the word used to describe characteristic behaviour scored on these tests. Furthermore, it is usually known that a many of antidepressant medications can shorten rodent immobility times. In rats FST and TST, nefopam significantly shortened immobility times at doses 10 and 20 mg/kg, with a profile similar to that seen with the traditional antidepressant medication escitalopram.

Numerous investigations have demonstrated a connection between central neurotransmitters and inflammatory mediators. Based on these earlier findings, The study employed the Tests for forced swimming and tail suspension to check for antidepressant activity. When comparing the nefopam

10mg/kg and nefopam 20mg/kg treated animals to the disease control group, the immobility was greatly reduced, and the results were statistically remarkable when compared to the diseased animals. Compared to animals without depression, cortisol levels—a crucial stress hormone—are frequently found to be higher. Depression frequently results in this disruption of the cortisol-regulating (HPA) axis. In the current investigation, the standard treatment 1 and treatment 2 groups' cortisol levels were reduced than those of the diseased group.

CONCLUSION

Depression is a mood illness characterised by persistent sadness, indifference, and challenges with day-to-day functioning; it is considerably more than a fleeting low mood. Increased cortisol levels, those are particularly apparent in the evening or in reaction to stress, are a contributing factor to depressive symptoms, and the HPA axis is commonly dysregulated. Clinically, this could manifest as psychomotor slowness, decreased physical activity, or even catatonic symptoms like immobility or stupor. Weight fluctuations are also related with depression. Few people shed weight while others gain it due to emotional eating, a sedentary lifestyle, and hormonal imbalances, especially persistently high cortisol, which promotes fat storage.

In our investigation, the animals in the disease group put on a significant amount of weight. Treatment 2 (nefopam at 20 mg/kg) was considerably effective than Treatment 1 (nefopam at 10 mg/kg) in lowering weight gain, immobility time, and cortisol levels when compared to untreated disease controls. These results showed that nefopam at the higher dosage was more successful in lowering both depressive-like symptoms and metabolic abnormalities. These results showed that nefopam at the higher dosage was more successful in lowering both depressive-like symptoms and metabolic abnormalities.

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