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RESEARCH ARTICLE

EVALUATION OF ANTIDEPRESSANT AND ANXIOLYTIC ACTIVITY OF OXAPROZIN IN SWISS ALBINO MICE

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Abstract

Depression is a prevalent mental illness. According to estimates, 5 percent of adults worldwide experience depression. Depression affects more women than males. Oxaprozin is a non-narcotic, non-steroidal anti-inflammatory medication (NSAID) used to treat osteoarthritis and rheumatoid arthritis-related inflammation, edoema, stiffness, and joint discomfort. The present study is based on the evaluation of antidepressant and anxiolytic activity of oxaprozin in Swiss albino (either sex) weight 20-25 gm were procured from ICAR-Indian Veterinary Research Institute (ICAR-IVRI**),** Izzat nagar, Bareilly, Uttar Pradesh. All the mice were divided into 4 groups (n=6) i.e., normal control which was given normal saline, positive control given Imipramine (10mg/kg, i.p.) and diazepam (10mg/kg, subcutaneously), test 1given oxaprozin(10mg/kg, p.o.) and test 2 given Oxaprozin (20mg/kg, p.o.) up to 7 days. The anxiolytic and antidepressant activity were evaluated by parameters i.e., elevated plus maze, FST, rota-rod test and biochemical parameters. It resulted that oxaprozin demonstrates anxiolytic and antidepressant activity. It exhibits antidepressant action probably by facilitating the release of neurotransmitters i. e., serotonin, dopamine. It also increases the release of GABA (Gamma Amino Butyric Acid) and chloride ions influx that leads to hyperpolarization .In conclusion, Oxaprozin is a predominant anxiolytic & anti-depressant drug. It can be effectively used in the treatment of depression, mental agitation and other neurological disorders after successfully evaluating mechanism of action against the same.This study refers, that it might be used in the treatment of depression among human beings after clinical trials.

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Introduction:-

Depression is a prevalent mental illness. According to estimates, 5 percent of adults worldwide experience depression. The largest cause of disability in the world today is depression, which also significantly contributes to the overall burden of sickness on the planet.Depression affects more women than males. Suicide can result from depression (WHO, 2022).Major depression is influenced by several important elements, including genetic, neurological, hormonal, immunological, and neuroendocrinological mechanisms. Chronic stress, traumatic childhood experiences, and recent life events are examples of environmental factors linked to depression(National Academies Press, 2009; Saveanu&Nemeroff, 2012).Anxiety disorders are characterised by a high level of stress. According to several research, a traumatic experience or a long-term illness might trigger secondary biological changes in specific brain areas (Bremner, 2003).

According to a study looking at cortisol levels in 4.5-year-olds, children who had been exposed to maternal stress in infancy and simultaneously had significantly higher cortisol levels than non-stressed children or those exposed to either but not both periods of parental stress(Heim et al., 2000).Anxiety refers psychiatric disorder observed by frequent uneasiness or feeling of disgusting & uneasiness in nature. Sometimes, compulsive behavior is precipitated(Runcan, 2021; Thibaut, 2017).Anxiety diseases resembles most prevalent type of mental disorder in children with 24.9% prevalence over a 12-month period(Kessler et al. 2012).According to World Health Organization, depression is highly occurring mental illness. It is determined that 5% adults suffer from depression, around the globe (Depression, WHO, 2021).

Oxaprozin is a non-narcotic, non-steroidal anti-inflammatory medication (NSAID) used to treat osteoarthritis and rheumatoid arthritis-related inflammation, edoema, stiffness, and joint discomfort.

Formula: $C_{18}H_{15}NO_3$

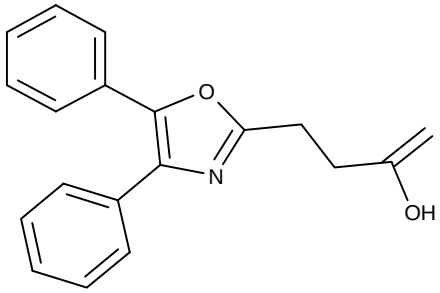


Fig. 1:- Structure of oxaprozin.

It is thought that Oxaprozin's anti-inflammatory actions result from the suppression of platelet cylooxygenase, which prevents prostaglandin formation. The hypothalamus may be affected by antipyretic actions, which enhance peripheral blood flow, vasodilation, and ultimately heat dissipation. The present study was based on the evaluation of the antidepressant activity of oxaprozin in Swiss albino mice.

Materials and Methods:-

Experimental requirements

Oxaprozin (API), Imipramine (API), Diazepam, Water bath, distilled water, Swiss albino mice (either sex), rotatory evaporator, forced swim test apparatus, elevated plus maize test apparatus, percolator, beaker, capillary tube, china dish, conical flask, digital balance, eppendorf tube, glass rod, inhalation chamber, measuring cylinder, weighing machine ,feeding bottles, spatula, surgical cotton, syringe (1ml,2.5ml) weighing machine and ethanol .

Experimental animal

Swiss albino mice (either sex) weight 20-25 gm were procured from ICAR-Indian Veterinary Research Institute (ICAR-IVRI), Izzat nagar, Bareilly, Uttar Pradesh. They were kept in department animal house, Aryakul College of Pharmacy & Research. The animals were housed separately in polypropylene cage for acclimatization at a temp of 21ºC-25ºC and relative humidity 45-55% with a 12hours light- dark cycle before and duringthe commencement of the experiment. Animals will be kept on standard pallet diet with drinking water ad libitum through the study period. The study period was approved by institutional animal ethics committee (IAEC), Faculty of pharmacy, Aryakul

College of Pharmacy & Research, Lucknow. At the end of experiment animals were sacrificed under high dose of anesthesia (Isoflurane).

Institutional Ethical Committee Approval

The Institutional Animal Committee (IAEC) has approved the experimental protocols for the anxiolytic and anti-depressant activity and approval number is1896/PO/Re/S/16/CPCSEA/2022/6.

Anxiolytic activity

Animal:

Swiss albino mice

Age & weight:

8-11weeks, 20-25g

Gender:

Either sex

Table 1:- Experimental design for anxiolytic activity.

Group (n=6)	Treatment & route of administration	Dose and duration
Normal control	Normal saline	10ml/kg
Positive control/std. (subcutaneously)	Diazepam	10 mg/kg (1 day)
Treatment group I Low dose (p. o.)	Oxaprozin	10mg/kg (7 days)
Treatment group II High dose (p. o.)	Oxaprozin	20mg/kg (7 days)

Elevated Plus Maze (EPM)

In mouse models of CNS diseases, the Elevated Plus Maze (EPM) test is used to measure anxiety-related behaviour. The EPM device is made up of a core region, two oppositely positioned open arms, two oppositely positioned closed arms, and an elevated "+"-shaped maze. The no. of entries and time spent in open arm were recorded in 5 min. (Kulkarni, 1999).

Rota rod apparatus test

Animals from the same cage are placed in different lanes on a rod that is initially moving at 4 rpm, and the apparatus is designed to accelerate from 20 to 25 rpm.Trial starts when acceleration is initiated, and it is completed when the animal leaves the rod. If the animal clings to the rod and completes the entire passive revolution or when the mice falls from the rotating rod the timer is stopped for the animal, the passive rotation is documented, and the animal is then brought back to its home cage while being careful not to startle other animals in nearby lanes. (Kulkarni, 1999).

Antidepressant activity

Animal:

Swiss albino mice

Age & weight:

8-11weeks, 20-25g

Gender:

Either sex

Table 2:- Experimental design for antidepressant activity.

Group (n=6)	Treatment & route of administration	Dose and duration
Normal control	Normal saline	10ml/kg
Positive control/std. (i.p)	Imipramine	10 mg/kg (7 day)
Treatment group I Low dose (p. o.)	Oxaprozin	10mg/kg (7 days)

Treatment group II High dose (p. o.)	Oxaprozin	20mg/kg (7 days)

Forced Swimming Test

Mice are dropped into a glass (30 x 20 cm) that is 15 cm deep and kept at a temperature of about 30ºC. Micewere let to swim against their will for five minutes. Using a stopwatch, the total mobility time is recorded once every five minutes in seconds (Kishore, 2015) .

Biochemical evaluation

To produce anaesthesia, ketamine (60 mg/kg) and xylazine (5 mg/kg) were administered intraperitoneally 24 hours after the last treatment. Blood samples were collected from animals during experiments using the retro orbital sinus puncture technique. Once the blood was gathered, it was transferred to a clean container. The blood sample receptacles were kept at 37 °C for 40 minutes to allow for blood coagulation. After the clot was taken from the container, the leftover serum from the test animals was added to the centrifuge tube. Centrifuge containers containing serum were spun at 3000RPM for 10 minutes. The resulting transparent serum was poured into a clean receptacle and refrigerated. These calculations are made using an Erba diagnostic kit and a semi-automatic analyzer.

The serum was then separated to examine the levels of TG, HDL, LDL, VLDL, and antioxidants.

Statistical analysis

Results from the data were expressed as Mean ± standard error of the mean (SEM). Differences between the control and treatment groups in the experiments were tested for significance using unpaired student's 't' test. $P < 0.05$ were considered significant. the difference between all four group groups were analysed using ANOVA. All statistical analysis was done using SPSS version 20.

Results and Discussion:-

Elevated Plus Maze test

In EPM test, control group showed no. of entries and time spent in open arm as 2.82±0.31 and 17.32±0.30, respectively. Whereas, Oxaprozin treated group (20mg/kg) showed no. of entries and time spent as 7.29±0.43 and 59.10±0.21, respectively. In contrast, Oxaprozin (10mg/kg) administered group exhibited no. of entries and time spent as 5.20±0.21 and 53.29±0.42, respectively. It successfully decreased the no. of entries and time spent in close arm. It can easily be seen difference between test and control group. This model clearly confirms that the Oxaprozin is effective in treatment of anxiety and depression in animal model.

Table 3:- Effect of oxaprozin in Elevated Plus Maize Test on mice.

Treatment	Dose	No. of entries (N)		Time spent (sec)	
		Enclosed	Open arm	Enclosed	Open arm
Vehicle	_	22.29±0.22*	2.82±0.31	218.10±0.17**	17.32±0.30
Diazepam	10 mg/kg	7.20±0.17**	9.11±0.28	155.45±0.28*	69.20±0.29
Oxaprozin	10mg/kg	13.43±0.10**	5.20±0.21	183.76±0.22**	53.29±0.42
Oxaprozin	20mg/kg	15.78±0.30**	7.29±0.43	178.35±0.34**	59.10±0.21

Significance level was represented by *; P<0.05,** P< 0.01, *** P < 0.001
n=6; readings were given in Mean± SEM

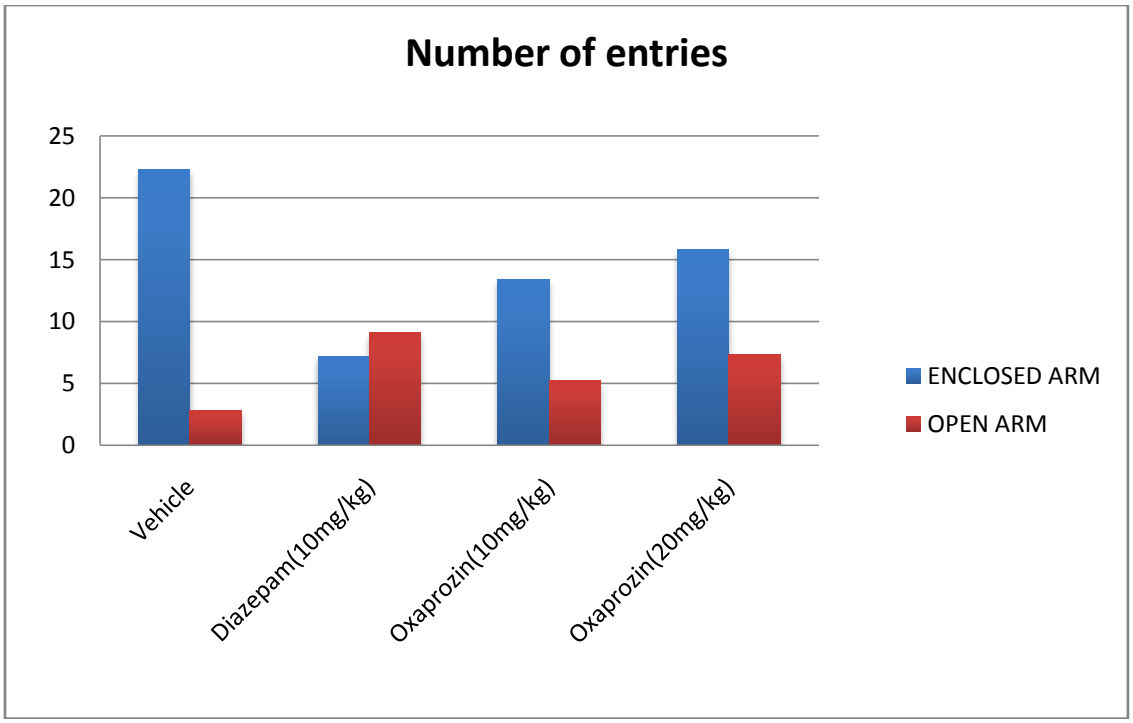


Fig 2:- Depiction of no. of entries (N) in open arm of EPM.

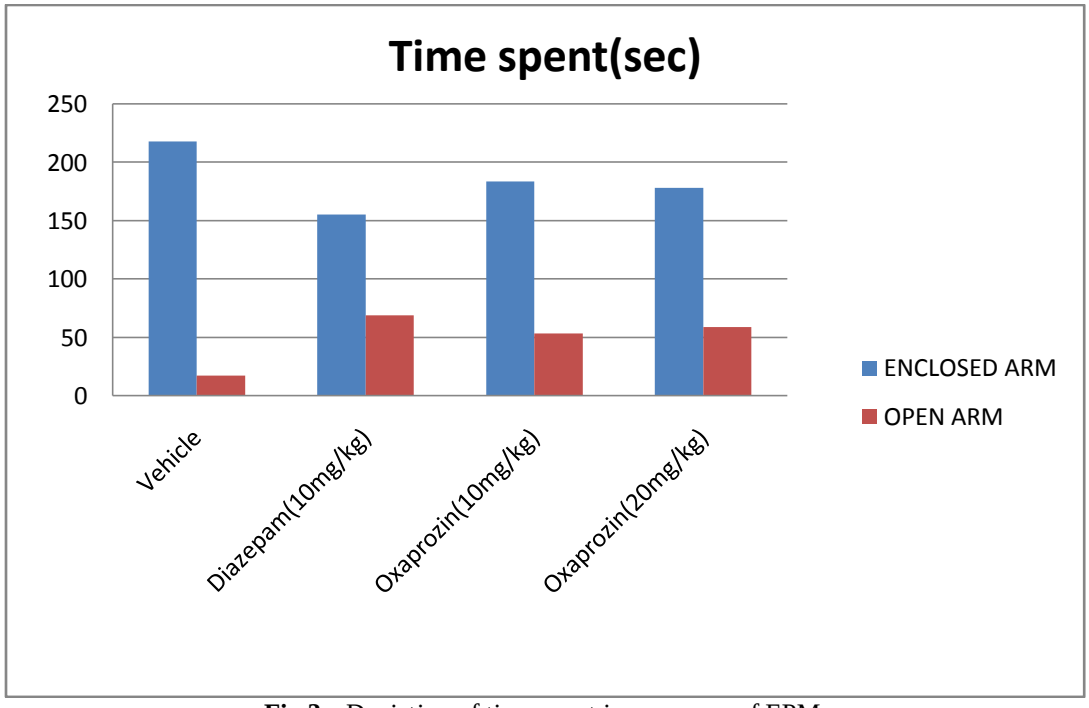


Fig 3:- Depiction of time spent in open arm of EPM.

Rota rod apparatus test

In context to determine the anti-depressant and anxiolytic potential of Oxaprozinmice were taken into 4 different groups. Group 1 was served as control that was fed with normal saline. Group 2 was given Diazepam (10mg/kg) and served as standard. Whereas, group 3 was administered Oxaprozinat the dose of 10mg/kg and group administered Oxaprozinat the dose of 20mg/kg. All the treatments were proceeded once a day for 15 days.

In locomotor activity score test, highest time of fall was achieved in control as 117.19±0.24* whereas lowest activity score as found in Diazepam treated group as 28.31±0.24** in 10 min. Fall time was exhibited as 87.40±0.65** and 57.29±0.75** at the dose of 10mg/kg and 20mg/kg respectively, of Oxaprozin. It significantly decreased locomotion activity score at both the doses- proving itself a better anti-depressant and anxiolytic moiety.

Table 4:- Effect of Oxaprozin on mice in rotarod test.

Treatment	Dose(mg/kg)	Falling time (sec)
Vehicle	_	117.19±0.24*
Diazepam	10 mg/kg	28.31±0.24**
Oxaprozin	10mg/kg	87.40±0.65**
Oxaprozin	20mg/kg	57.29±0.75**

Significance level was represented by *; P<0.05 ,** P< 0.01, *** P < 0.001
n=6; readings were given in Mean± SEM

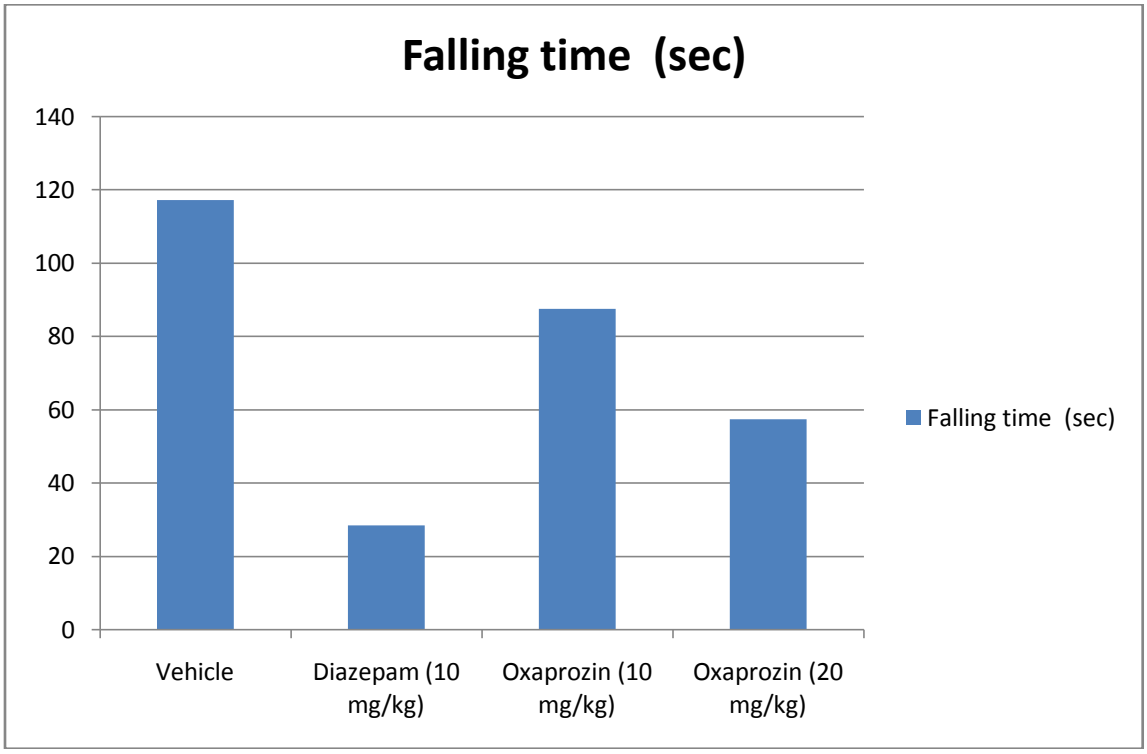


Fig 4:- Depiction of Time of fall (sec) of Rota rod test.

Forced swimming test

To determine the anti-depressant and anxiolytic potential of Oxaprozinmice were taken into 4 different groups. Group 1 was served as control that was fed with normal saline. Group 2 was given Imipramine (10mg/kg) and served as standard. Whereas, group 3 was administered Oxaprozinat the dose of 10mg/kg and group administered Oxaprozinat the dose of 20mg/kg. All the treatments were proceeded once a day for 15 days.

In FST, mobility time was observed lowest in the case of control and highest in control which indicates for their anti-depressant accordingly. Oxaprozinexhibited increase in mobility time as 178.25±0.73** at dose 10mg/kg and 170.13±0.84** at 20mg/kg. In both the doses, it significantly proved for its anxiolytic and anti-depressant potential by facilitating the mood of animals. At higher dose, its effect was similar about same to standard group. It might be effective in relieving the depression, anxiety and low mood in human too.

Table 5:- Effect of Oxaprozin on immobility time in FST.

Treatment	Dose(mg/kg)	Immobility time (sec)
Vehicle	_	181.19±0.74***
Imipramine	10 mg/kg	113.36±0.87***
Oxaprozin	10mg/kg	178.25±0.73**
Oxaprozin	20mg/kg	170.13±0.84**

Significance level was represented by *; P<0.05 ,** P< 0.01, *** P < 0.001
n=6; readings were given in Mean± SEM

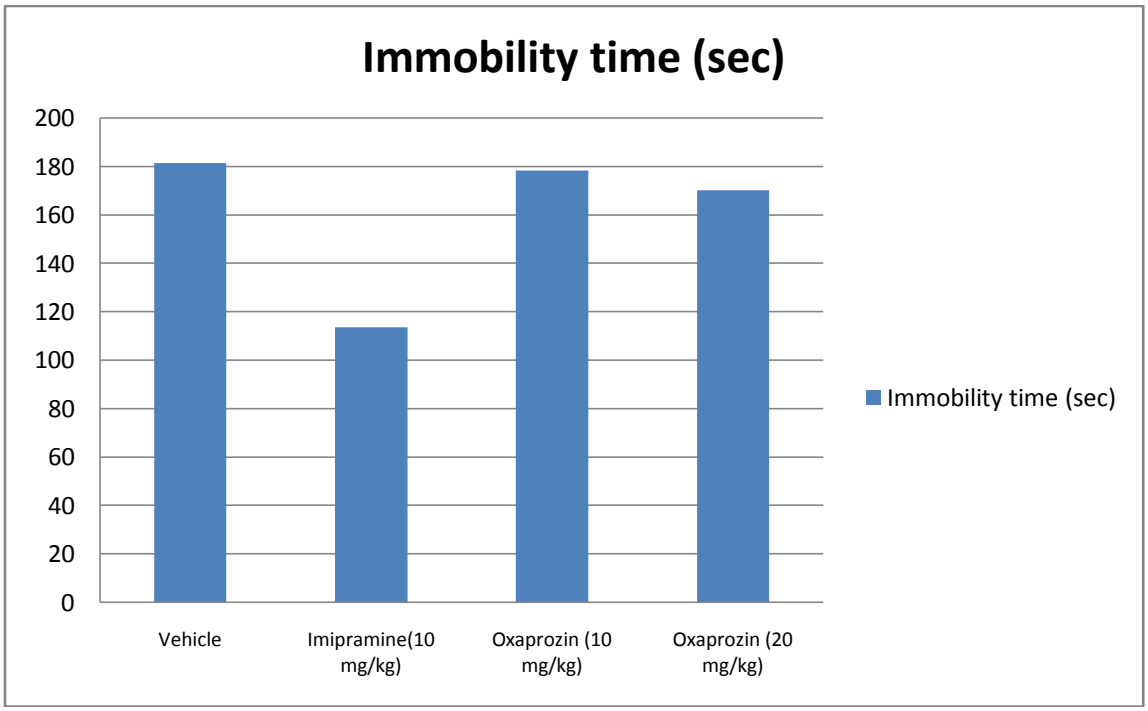


Fig 5:- Depiction of immobility time (sec) of FST.

Estimation of anti-oxidant parameter

Anti-oxidant activity of mice was estimated in terms of SOD, CAT, PC etc. T1 & T2 showed SOD level as 0.21±0.03*** U/µg & 0.24±0.01*** U/µg, CAT level as 10.24±1.72*** nm & 12.92±0.88*** nm, PC level as 1.99±0.68*** µm/µg& 1.51±0.86***µm/µg, TBARS as 0.85±0.02*** nM of MDA/mg & 0.62±0.01*** nM of MDA/mg and GSH as 4.53±1.62** µm/µg of protein & 5.87±1.98*** µm/µg of protein. When these parameters were compared with control, they showed a remarkable change/ modulation behaviour on the anti-oxidant parameters.

Table 6:- Estimation of anti-oxidative parameters.

Parameters	NC	PC	T1	T2
SOD (U/µg of protein)	0.29±0.07	0.12±0.02	0.21±0.03***	0.24±0.01***
CAT (nM of H_2O_2/min/µg of protein)	14.15±1.08	7.13±0.87	10.24±1.72***	12.92±0.88***
PC (µM/µg of protein)	1.45±0.13	3.45±0.95	1.99±0.68***	1.51±0.86***
TBARS (nM of MDA/mg of protein)	0.51±0.02	1.55 ±0.02	0.85±0.02***	0.62±0.01***
GSH (µM/µg of protein)	7.82±1.82	3.02±1.16	4.53±1.62**	5.87±1.98***

Significance level was represented by *; P<0.05
n=6; readings were given in Mean± SEM

Lipid profile in serum

T1 & T2 demonstrated PC as 135.62±3.02*** mg/dl & 120.03±3.55*** mg/dl, TG as 78.22±2.81*** mg/dl & 71.37±2.01*** mg/dl, HDL as 38.17±2.14*** mg/dl & 44.67±1.68*** mg/dl, LDL as 42.66±2.66*** mg/dl & 36.51±2.03*** mg/dl and VLDL as 22.11±1.21*** mg/dl & 18.27±1.33*** mg/dl, respectively.

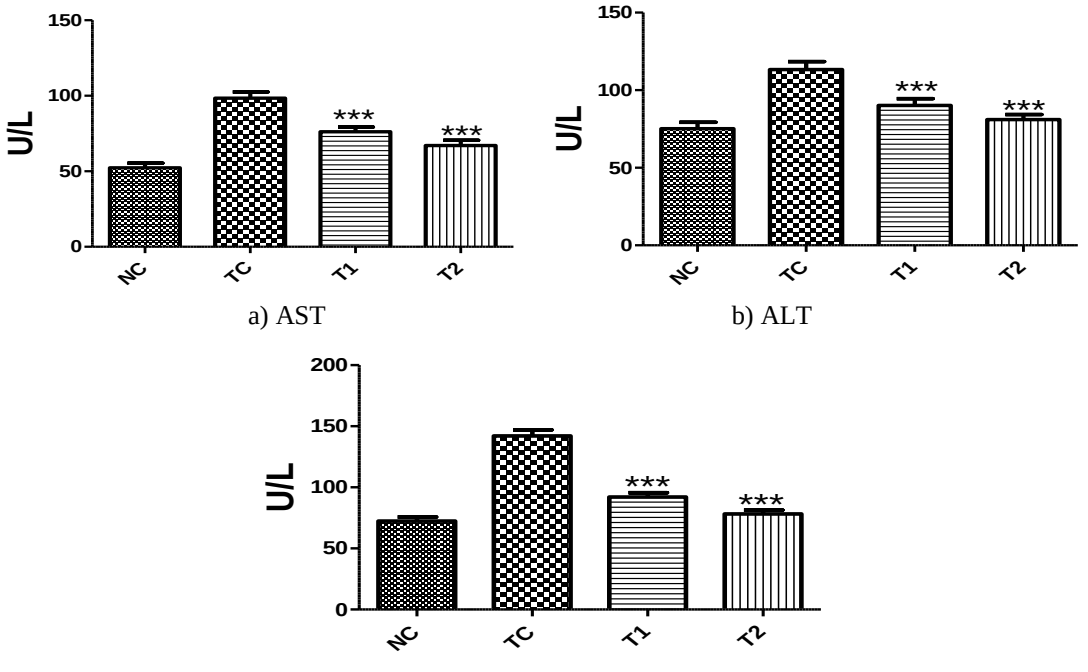
Table 7:- Lipid profiles in serum.

Parameter	NC	PC	T1	T2
PC (mg/dL)	118.17±3.76	167.14±6.82	135.62±3.02***	120.03±3.55***
TG (mg/dL)	68.51±2.61	132.21±3.16	78.22±2.81***	71.37±2.01***
HDL (mg/dL)	52.44±2.25	26.37±2.16	38.17±2.14***	44.67±1.68***
LDL (mg/dL)	35.17±2.04	79.52±2.23	42.66±2.66***	36.51±2.03***
VLDL (mg/dL)	16.73±1.86	32.16±1.84	22.11±1.21***	18.27±1.33***

Significance level was represented by *; P<0.05
n=6; readings were given in Mean± SEM

Enzyme levels of AST, ALT and LDH in serum

When observed T1 & T2 significantly decreased the levels of AST, ALT & LDH when compared with the control group.



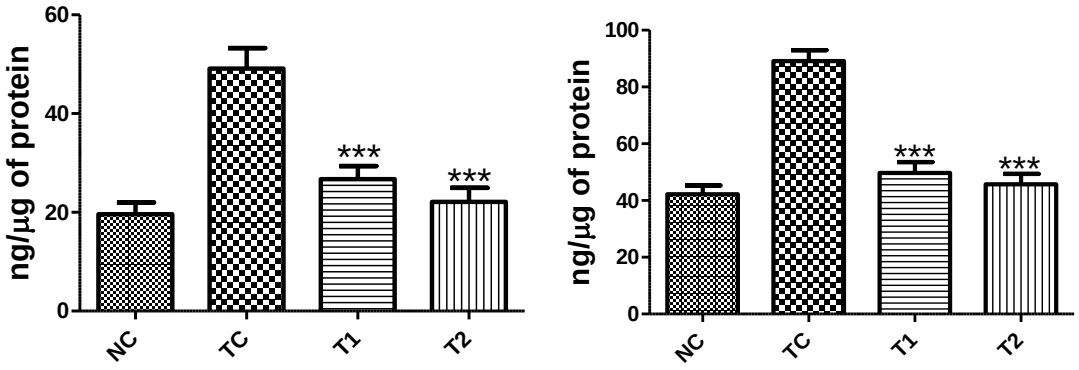
a) AST b) ALT

d) LDH

Fig. 6:- Depiction of enzymes level in Oxaprozin treated mice (Significance level was represented by *; P<0.05 n=6; readings were given in Mean± SEM).

Catabolic by-products (bilirubin and biliverdin)

Bi-products were estimated in different groups of animals. Group 1 was served as control that was fed with normal saline. Group 2 was given Imipramine (10mg/kg) and served as standard. Whereas, group 3 was administered Oxaprozinat the dose of 10mg/kg and group administered Oxaprozinat the dose of 20mg/kg. All the treatments were proceeded once a day for 15 days. In this aspect, T1 & T2 lowered the production and release of bi-products-bilirubin & biliverdin when compared with control mice.



a) Bilirubin b) Biliverdin

Fig. 7:- Depiction of enzymes level in Oxaprozin treated mice (Significance level was represented by *; P<0.05 n=6; readings were given in Mean± SEM).

It exhibits antidepressant action probably by facilitating the release of neurotransmitters i. e., serotonin, dopamine. It also increases the release of GABA (Gamma Amino Butyric Acid) and chloride ions influx that leads to hyperpolarization. The effect was determined in dose-dependent manner.

Conclusion:-

People have been employing a variety of plants as a source of medicine in various forms since ancient times. We can conclude from the foregoing preclinical study that Oxaprozin have antidepressant and anxiolytic activity in EPM, Rota rod apparatus & FST modelsOxaprozin has the ability to be employed as an adjunct in the therapy of depression and other mood disorders, according to the researchers. More research is needed to acquire a better understanding of the specific mechanism of its activity.

It can be assumed that Oxaprozin dominates the inhibitory action of central nervous system. Its mode of action is required to confirm by screening in clinical trials to confirm for safety and efficacy.

In conclusion, Oxaprozin is a predominant anxiolytic &anti-depressant drug. It can be effectively used in the treatment of depression, mental agitation and other neurological disorders after successfully evaluating mechanism of action against the same.

As anxiety and depression has become commonest form of mental disability, so it may demonstrate an economic and pharmacological impact in modulating behavioral of humans. This study refers, that it might be used in the treatment of depression among human beings after clinical trials.

Funding
Nil.

Conflict Of Interest
None.

References:-

1. Bremner JD. Functional neuroanatomical correlates of traumatic stress revisited 7 years later, this time with data. Psychopharmacol Bull. 2003;37(2):6–25.
2. Depression- Overview. World Health Organization. 2021; www.who.int
3. Heim, C., Newport, D.J., Heit, S., Graham, Y.P., Wilcox, M., Bonsall, R., Miller, A.H., and Nemeroff, C.B. (2000). Pituitary-adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. Journal of the American Medical Association**,** 284, 592–597.
4. Kessler RC., Petukhova M., Sampson NA., Zaslavsky AM., Wittchen HU. Twelve-month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorders in the United States. Int J Methods Psychiatr Res**.** 2012;21(3):169–184.

5. Runcan R. Anxiety in Adolescence: A Literature Review. Innovative Instruments for Community Development in Communication and Education, 2021; 113-128.
6. Saveanu R V &Nemeroff C B. Etiology of Depression: Genetic and Environmental Factors, Psychiatric Clinics, 2012; 35(1): 51-71.
7. The Etiology of Depression. Depression in Parents, Parenting, and Children: Opportunities to Improve Identification, Treatment, and Prevention. National Academies Press, 2009.
8. Thibaut Florence. Anxiety disorders: a review of current literature. Dialogues in Clinical Neuroscience, 2017; 19(2): 87–88.
9. Attia Eman Zekry, Marwa Fathy Khalifa John Refaat Fahim Mohamed Salah Kamel. Anti-diabetic potential of mucilage from Hippeastrum vittatum bulbs in streptozotocin-induced diabetic rats. South African Journal of Botany, 2021; 136:100-104.
10. Bevilacqua M. Effect of oxaprozin and of other 2-arylpropionic acid derivatives on nuclear factor kB (NFkB) activation. Inflammopharmacology (2002) 10:173-183.
11. Bremner JD. Functional neuroanatomical correlates of traumatic stress revisited 7 years later, this time with data. Psychopharmacol Bull. 2003;37(2):6–25.
12. Burris KD, Sanders-Bush E. Unsurmountable antagonism of brain 5- hydroxytryptamine-2 receptors by (+)-lysergic acid diethylamide and bromo- lysergic acid diethylamide. Mol Pharmacol. 1992;42(5):826–830.
13. Bystritsky A, Kerwin L, Feusner JD, Vapnik T. A pilot-controlled trial of bupropion XL versus escitalopram in generalized anxiety disorder. Psychopharmacol Bull. 2008;41(1):46–51.
14. Charney DS, Heninger GR. Noradrenergic function and the mechanism of actionof antianxiety treatment: I. The effect of long-term alprazolam treatment. Arch Gen Psychiatry. 1985;42(5):458–467.
15. Charney DS. Neuroanatomical circuits modulating fear and anxiety behaviors. Acta Psychiatr Scand Suppl. 2003;(417):38–50.