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Evaluation of Antidepressant Activity of Curcuma Longa in Albino Rats - An Experimental Study

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KEYWORDS: Curcumin, Antidepressant, Tail suspension test (TST), Forced swimming test (FST), Open field behaviour

ABSTRACT:

Introduction- Depression is a mental health condition with various symptoms including low energy, disrupted sleep, and suicidal ideation. Antidepressants have negative side effects and can cause drug interactions. *Curcuma longa*, a herbal extract, has shown potential in treating depression due to its antioxidant and anti-inflammatory properties. A study is planned to evaluate its antidepressant activity

Objectives: To study the anti-depressant activity of *Curcuma longa* rhizome using animal models and to find out its mechanism of action

Methods. Ethanolic extraction using soxhlet apparatus, tail suspension test and forced swimming test for evaluating antidepressant activity

Results: *Curcuma longa* rhizome possess antidepressant *property*

Conclusions: The study investigated the effectiveness of *Curcuma longa* rhizome in treating depression. Two doses of the ethanol extract were tested in mice, and their behaviour was assessed in various tests. The extract showed antidepressant action by increasing serotonin, norepinephrine, and dopamine levels in the brain and antagonizing the GABA receptor. No sleep-promoting compounds were found in the extract.

1. Introduction

Depression is a mental or emotional condition characterised by feelings of guilt or poor self-worth. Several of the following signs and symptoms are frequently present in someone who is depressed. Reduced energy and vigour, slowness of thought or activity, lack of appetite, diminished or lost capacity to enjoy routine activities, disrupted sleep, or insomnia. Suicide is a prominent cause of death in young people in India, with the risk being the highest for those between the ages of 15 and 19. Suicidal ideation and attempts in adolescents are significantly predicted by depression. Depression patients have a 25 times higher risk of suicide than non-depressed people. Antidepressant medications have a variety of adverse side effects and frequently cause drug interactions. The extract of rhizomes from *Curcuma longa* has been shown to have powerful antioxidant, anti-inflammatory, lipid-reducing, immunomodulatory and sedative properties (Kumar A et al., 2015). In the last few years, there has been increased growth in the field of herbal medicine research because of their lesser side effects, natural origin and promising results. This study is planned to evaluate the antidepressant activity of *Curcuma longa*.

2. Objectives

To study the anti-depressant activity of *Curcuma longa* rhizome using animal models and to find out its mechanism of action

3. Methods

The study was carried out from December 2020 to October 2022 at the Department of Pharmacology, Jawaharlal Nehru Medical College, Aligarh Muslim University, Aligarh.

Plant material

Curcuma longa rhizome was purchased from the local market in Aligarh. The specimen was submitted and

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authenticated by Prof. M. Badruzzaman Siddiqui, Department of Botany, Aligarh Muslim University, Aligarh. Vide Voucher number -31006. *Curcuma longa* was shade dried and pulverised in an electric grinder. The powder obtained was extracted in ethanol.

Preparation of plant extract (Pawar et al., 2015)

Ethanolic extract of *Curcuma longa* rhizome 100 grams of finely powdered *Curcuma longa* rhizome was extracted in 400 ml absolute alcohol for 72 hours with the help of the Soxhlet apparatus. The extract obtained was collected in Petri dishes and air-dried for a week. The dried mass thus obtained was weighed and its yield was calculated, sealed with aluminium foils and then stored in a refrigerator for further experimental work

Experimental animals

1. Albino Wistar rats of either sex (150-250gm)
2. Swiss albino mice of either sex (25-50gms)

These animals were obtained from Central Animal House, JNMC, Aligarh Muslim University, Aligarh. The animals were housed in polypropylene cages bedded with paper strips in the Pharmacology section of Central Animal House. Cages were held tilted, covered with cloth, under a dark environment and rats were also deprived of food overnight for at least 8 hours before the experiment to induce depression which is based on well-documented Time-dependent sensitisation (Antelman SM et al., 1997). The animal room was well-ventilated and maintained under standard conditions (Temperature 27±3°C and 12-hour light/dark cycle) throughout the experimental period. All animals were fed with a standard pellet diet and water ad libitum. They were acclimatised to the laboratory conditions for one week prior to the Experiments.

Approval for study

The Institutional Animal Ethics Committee approved the study protocol (IAEC) on 03.12.2020 (Registration No. 401/GO/Re/S/2001/CPCSEA dated 28-11-2020). All animal experiments were carried out as per the rules and regulations of CPCSEA (Committee for the Purpose of Control and Supervision of Experiments on Animals) under the “Guidelines for Care and Use of Animals in Scientific Research”.

Chemicals used

1. Imipramine (Torrent)
2. Distilled water
3. Ethanol
4. Normal saline

The solvent and other chemicals used were of analytical grades manufactured by Merck Laboratories (Mumbai, India), BDH Laboratories (Mumbai, India), and CDH Laboratories (New Delhi, India).

Instruments used

1. Soxhlet extraction apparatus
2. Electronic balance
3. Weighing balance
4. Test tubes and test tube stand

Experimental design

Acute toxicity testing (Yu ZF et al., 2002; Sahebrao KR et al., 2014)

Doses of 140 mg/kg and 560 mg/kg were determined according to previous studies

Grouping of Animals

Animals were divided into 20 groups of 5 animals each (n=5), consisting of a normal control group, a positive control group and 2 test groups in each study model. Fresh animals were taken for each group in each screening method.

Screening of antidepressant activity

Tail suspension test (Stera L, et al., 1985).

Mice were treated with Standard drug /Vehicle/ CL extracts for 7 days. The test was carried out on the 7th day, 1 hour after drug/vehicle/CL extracts were administered. Mice were suspended by woollen thread secured with adhesive tape placed approximately 1 cm from the tip of the tail. The duration of immobility was recorded for a period of 6 mins. Mice were considered immobile when they hung passively and completely motionless. Intermittent periods of immobility during 5 mins time period were recorded and their sum showed the total period of immobility

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Forced swimming test (Vogel, H et al., 2002).

Rats were brought to the laboratory at least one day before the experiment and were housed separately in cages with free access to food and water. Naive rats were individually forced to swim inside a vertical Plexiglas cylinder (height: 40 cm; diameter: 18 cm, containing 15 cm of water maintained at 25°C). Rats placed in the cylinders for the first time were initially highly active, vigorously swimming in circles, trying to climb the wall or diving to the bottom. After 2–3 min activity began to subside and to be interspersed with phases of immobility or floating of increasing length. After 5–6 min immobility reached a plateau where the rats remained immobile for approximately 80%. After 15 min in the water, the rats were removed and allowed to dry in a heated enclosure (32 °C) before being returned to their home cages. They were again placed in the cylinder 24 h later and the total duration of immobility was measured during a 5 min test. Floating behaviour during this 5 min period was reproducible in different groups of rats. An animal was judged to be immobile whenever it remained floating passively in the water in a slightly hunched but upright position, its nose just above the surface. Test drugs or standards were administered one hour prior to testing.

Open Field Behaviour (Santosh P et al., 2014)

This test utilises behavioural changes in rodents exposed to novel environments and was used to confirm that the observed antidepressant effect is not due to stimulation of general motor activity such as sound and light. The open field test was carried out on the dark grey floor subdivided into 16 equal parts in a wooden box. Each square and the central square were 18cm×18cm in dimension. Respective treatment was given to the animals and 30 min later, the animals were individually placed in the corner square of the open field.

The following parameters were observed for 5 min.

- Activity in the centre (number of times central square crossed)
- Spontaneous Ambulation
- Number of Rearings

Statistical Analysis

Values were expressed as Mean ± SEM. Statistical significance was calculated by paired Student's t-test; one-way ANOVA followed by post hoc Tukey HSD comparison test using SPSS-23 software. P<0.05 was considered to be statistically significant.

4. Results

Plant extracts

The ethanolic extract of *Curcuma longa* rhizome was prepared by soxhlet extraction using ethanol

TABLE 1.1: Yield and Characteristics of Ethanolic and Aqueous extract of *Curcuma longa* rhizome extract

Extract	% yield	Characteristics
Ethanolic	7.69%	Yellowish brown semi-solid mass

Table 1.1

Acute toxicity studies

Dose of 140 mg/kg and 560 mg/kg were determined according to previous studies (Yu ZF et al., 2002; Sahebrao KR et al., 2014).

Effect of *Curcuma longa* rhizome ethanolic extracts in tail suspension test

Tail suspension test was used to assess the antidepressant activity of *Curcuma longa* rhizome in mice. Values are expressed as mean±SEM

TABLE 1.2: Effect of ethanolic extract of *Curcuma longa* on immobility time in tail suspension test

GROUPS	IMMOBILITY TIME (seconds) Mean±SEM
Normal control 10 ml/kg	192.125 ± 2.65
Positive control 15mg/kg	87.875 ± 3.26***
EECL 140 mg/kg	153.125 ± 2.85***
EECL 560 mg/kg	114.875 ± 3.95***

Table 1.2

EECL: Ethanolic extract of *Curcuma longa* rhizome, n = 5 mice in each group. *p<0.05, ** - p <0.01, *** - p <0.001, Level of significance compared to the normal control group. Immobility time was significantly decreased (p <0.001) in the positive control group compared to normal control group. A significant decrease in Immobility time was noted in EECL 140

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mg/kg (p<0.001) and EECL 560 mg/kg (p<0.001) received groups.

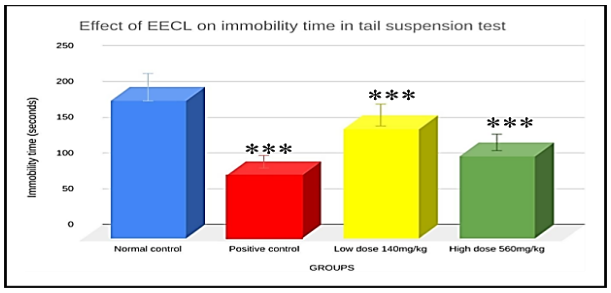


Fig 1.1

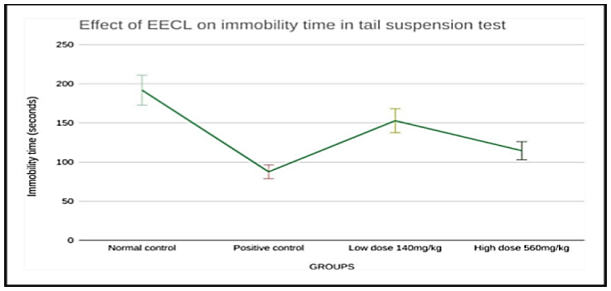
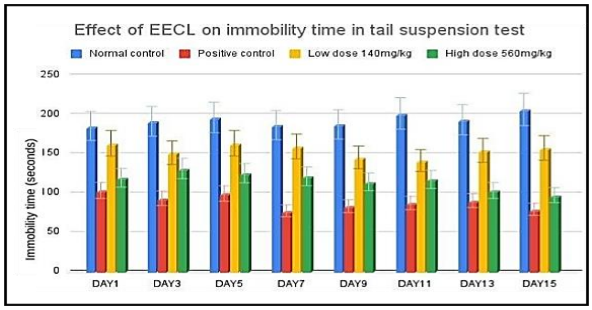


Fig 1.2

Fig 1.1 and Fig 1.2: Showing the Immobility time in Normal Control, Positive Control and EECL treated groups (n = 5 mice in each group. *p<0.05, ** - p <0.01, *** - p <0,001, Level of significance compared to normal control group)



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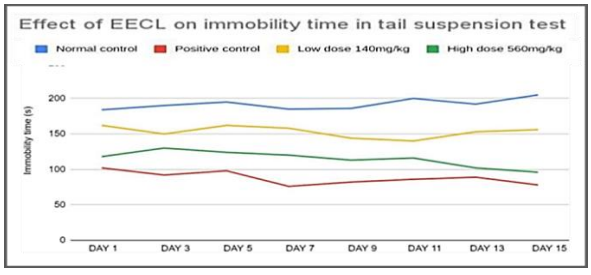


Fig 1.4

Fig 1.3 and Fig 1.4: Showing Comparison of Immobility time in Normal Control, Positive Control and EECL treated groups from Day 1 to Day 15.

Effect of *Curcuma longa* rhizome ethanolic extracts in forced swimming test

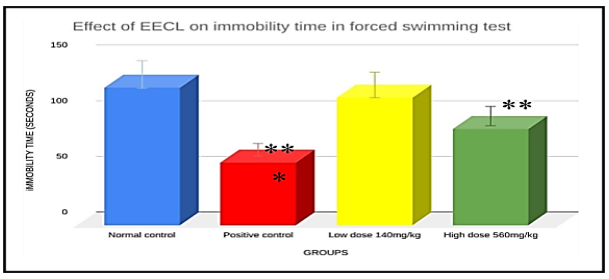
Forced swimming test was used to assess the antidepressant activity of *Curcuma longa* rhizome in rats. Values are expressed as Mean±SEM

TABLE 1.3: Effect Of Ethanolic Extract of *Curcuma longa* on Immobility Time in Forced Swimming Test

GROUPS	IMMOBILITY TIME(seconds) Mean±SEM
Normal control 10 ml/kg	123.625 ± 6.90
Positive control 15mg/kg	56.125 ± 5.27***
EECL 140 mg/kg	114.25 ± 5.80
EECL 560 mg/kg	86.32 ± 5.57**

Table 1.3

EECL: Ethanolic extract of *Curcuma longa* rhizome, n = 5 rats in each group. *p<0.05, **- p <0.01, *** - p <0,001, Level of significance compared to the normal control group. Immobility time was significantly decreased (p <0.001) in the positive control group compared to normal control group. A significant decrease in Immobility time was noted in EECL 560 mg/kg (p<0.01) received group. No significant decrease in Immobility time was noted in EECL 140 mg/kg received group.



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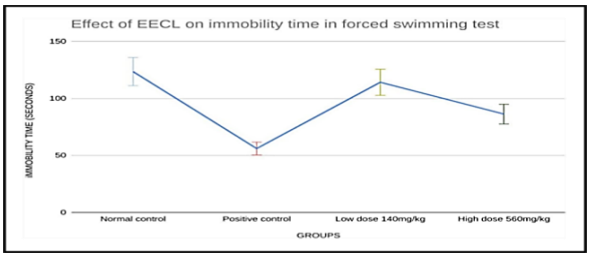

Fig 1.6

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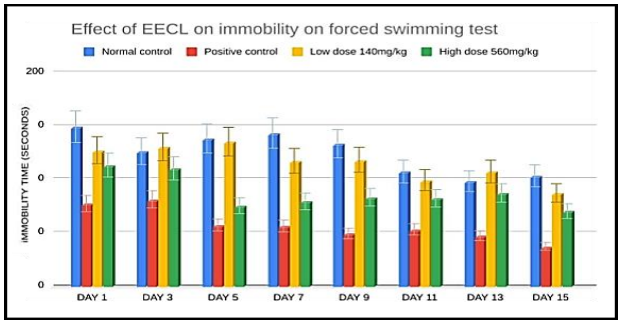
Fig 1.5 and Fig 1.6: Showing the Immobility time in Normal Control, Positive Control and EECL treated groups (n = 5 rats in each group. *p<0.05, ** - p <0.01, *** - p <0,001, Level of significance compared to normal control group)



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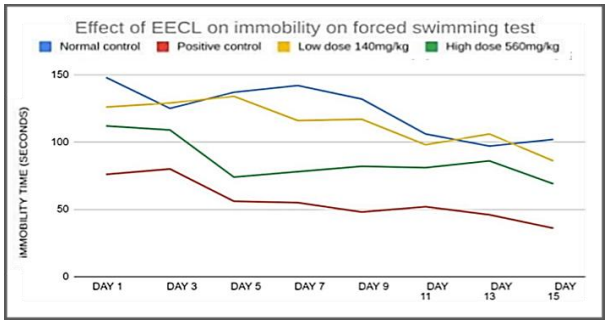

Fig 1.8

Fig 1.7 and Fig 1.8: Showing Comparison of Immobility time in Normal Control, Positive Control and EECL treated groups from Day 1 to Day 15

Effect of *Curcuma longa* rhizome ethanolic extracts in Open field test

Open field behaviour test was used to assess the antidepressant activity of *Curcuma longa* rhizome in rats. Values are expressed as mean±SEM

TABLE 1.4: Effect of Ethanolic Extract of *Curcuma longa* on Open Field Behaviour Test

GROUPS	ACTIVITY IN CENTRE (Central squares crossed)	SPONTANEOUS AMBULATION (Peripheral squares crossed)	NUMBER OF REARINGS
Normal control 10 ml/kg	22	42	3
Positive control 15mg/kg	106***	17***	30***
EECL 140 mg/kg	50***	35	10
EECL 560 mg/kg	96***	26**	18***

Table 1.4

EECL: Ethanolic extract of *Curcuma longa* rhizome, n = 5 rats in each group. *p<0.05, **- p <0.01, *** - p <0,001, Level of significance compared to the normal control group. Activity in the centre was significantly increased (p <0.001) in the positive control group compared to the normal control group. A significant increase in Activity in the centre was noted in EECL 140 mg/kg (p<0.001) and EECL 560 mg/kg (p<0.001) received groups.

Spontaneous Ambulation was significantly decreased (p <0.001) in the positive control group compared to normal control group. A significant decrease in Spontaneous Ambulation was noted in EECL 560 mg/kg (p<0.01) received groups. No significant decrease in Spontaneous Ambulation was noted in EECL 140 mg/kg received groups.

The number of rearing was significantly increased (p <0.001) in the positive control group compared to the normal control group. A significant increase in Number of rearing was noted in EECL 560 mg/kg (p<0.001) received groups. No significant increase in the Number of rearing was noted in EECL 140 mg/kg received groups.

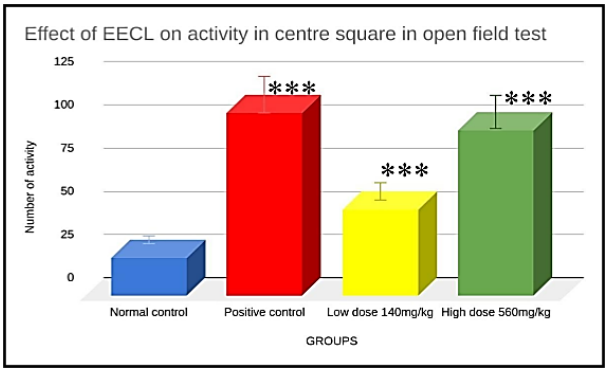

Fig 1.9

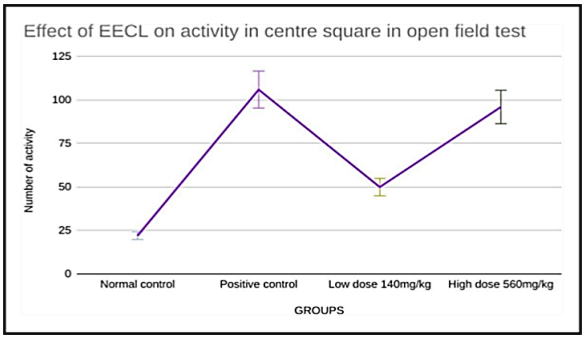

Fig 1.10

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Fig 1.9 and Fig 1.10: Showing the Number of Activity in the Centre square in Normal Control, Positive Control and EECL treated groups (n = 5 rats in each group. *p<0.05, ** - p <0.01, *** - p <0,001, Level of significance compared to normal control group)

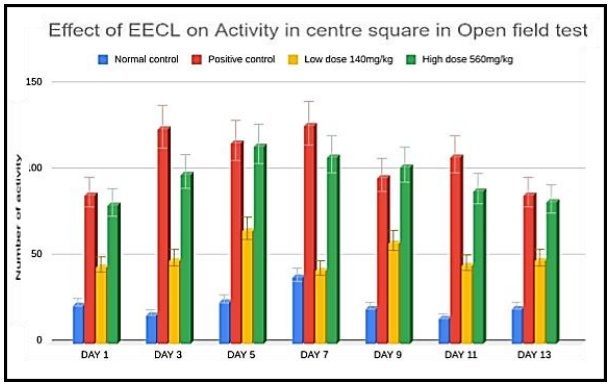


Fig 1.11

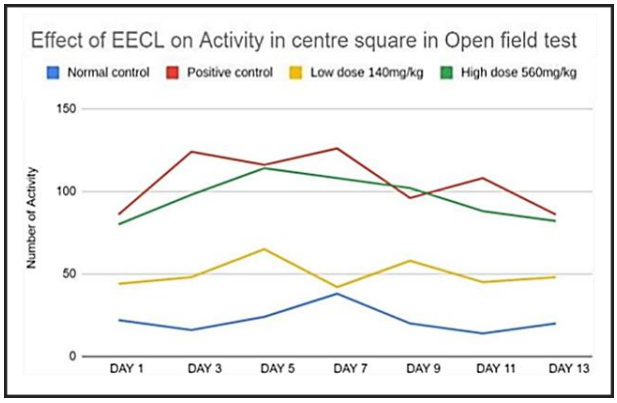
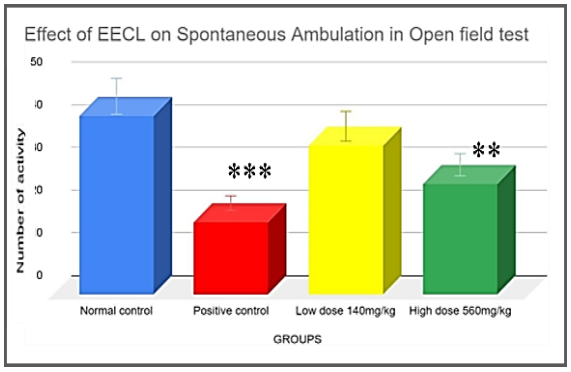


Fig 1.12

Fig 1.11 and Fig 1.12: Showing Comparison of Number of Activity in Centre square in Normal Control, Positive Control and EECL treated groups from Day 1 to Day 13



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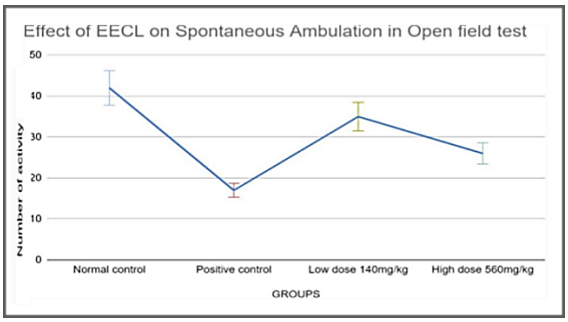
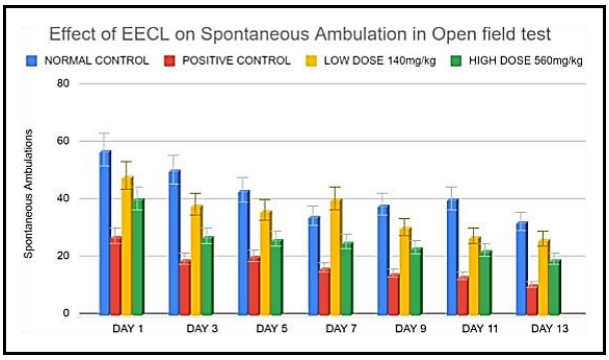


Fig 1.14

Fig 1.13 and Fig1.14: Showing the Spontaneous Ambulation in Normal Control, Positive Control and EECL treated groups (n = 5 rats in each group. *p<0.05, ** - p <0.01, *** - p <0,001, Level of significance compared to normal control group)



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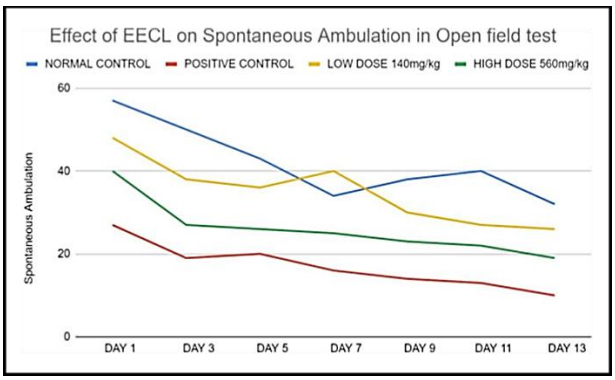

Fig 1.16

Fig 1.15 and Fig 1.16: Showing Comparison of Spontaneous Ambulation in Normal Control, Positive Control and EECL treated groups from Day 1 to Day 13

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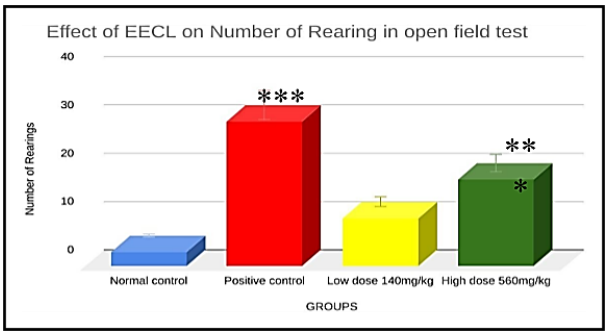

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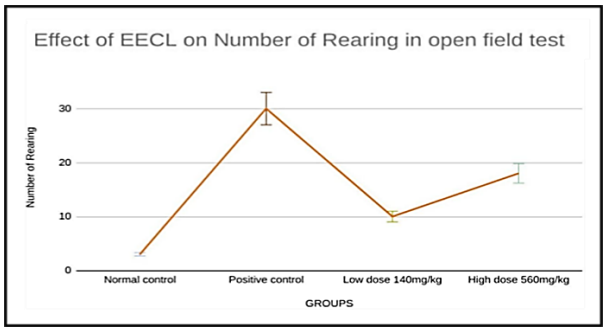
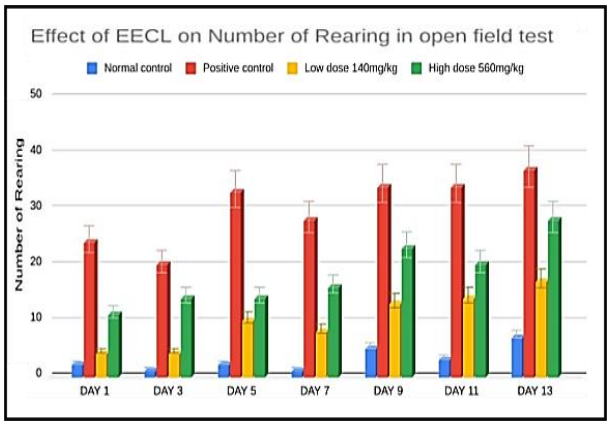


Fig 1.18

Fig 1.17 and Fig 1.18: Showing the Number of Rearings in Normal Control, Positive Control and EECL treated groups (n = 5 rats in each group. *p<0.05, ** - p <0.01, *** - p <0,001, Level of significance compared to normal control group)



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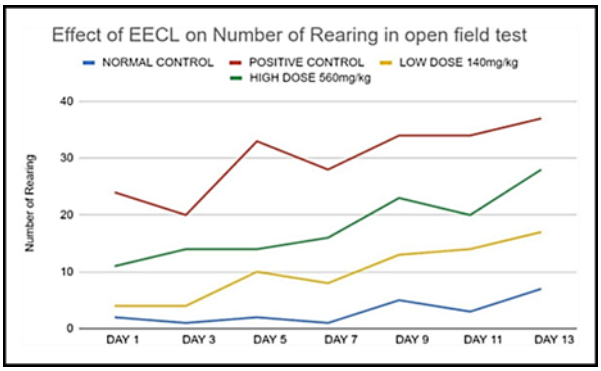

Fig 1.20

Fig 1.19 and Fig 1.20: Showing Comparison of Number of Rearing in Normal Control, Positive Control and EECL treated groups from Day 1 to Day 13

5. Discussion

Depression is a highly prevalent psychiatric illness worldwide, and according to recent studies, its prevalence is expected to rise. The severity of depressive symptoms varies from person to person and is subjective. It affects all age groups, including teenagers, adults, and the elderly of both sexes. As a result, the disease must be treated effectively and quickly. Some signs of depression, such as guilt and suicidality, are challenging to replicate in animals (Krishnan V et al., 2008). Since there are many different etiologies for human depression, animal models of depression do not pathologically mirror human depression. In contrast, animals develop the human symptom profile and have a more complete understanding of the human condition. SSRIs and MAO inhibitors are the most commonly prescribed antidepressants. Imipramine is one of the widely used antidepressant agents used in this study as a positive control group. The tail suspension test is an extensively used behaviour model. It has higher sensitivity and predictability. It is also a well-established model for drugs acting through SERT. The Tail Suspension Test (TST) is a behavioural despair test used to assess the antidepressant activity of drugs in rodents. The test involves suspending mice by their tails, leading to immobility, and recording the duration of immobility. In this study, the ethanolic extract of *Curcuma longa* showed significant antidepressant activity at doses of 140 mg/kg and 560 mg/kg, as evidenced by a decrease in the duration of immobility. The positive control group treated with Imipramine showed the maximum decrease

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in immobility duration. The forced swimming test (FST) is a widely used screening test to evaluate the antidepressant effects of agents. The test is based on the observation that animals become immobile when placed in a confined water-filled space. The immobility reflects either a failure of persistence in escape-directed behaviour or a compromised ability to cope with stressful stimuli. In a study on the ethanolic extract of Curcuma longa, it was found that a dose-dependent effect was seen in the duration of immobility in rats. Imipramine (15mg/kg) treated rats showed a decrease in immobility duration ($p<0.001$). The ethanolic extract at a dose of 560 mg/kg also decreased immobility duration significantly ($p<0.01$), while the 140 mg/kg dose did not show a significant effect. The extract decreased depression by decreasing serum corticosterone levels and increasing serotonin (5-HT), norepinephrine (NE), and dopamine (DA) levels in the brain. Within depressive animals, several interacting molecular changes mimic those in humans (Hill et al., 2012). Overuse of reserpine can deplete monoamines and induce depression in patients and animals (Belmaker, R.H. et al., 2008). Gamma amino butyric acid (GABA) is an inhibitory amino acid neurotransmitter whose reduction has been observed in the ventral hippocampus and frontal cortex of animals with depression. Glutamate is an excitatory amino acid neurotransmitter (the glutamate level in the brains of animals with depression was found to have increased within 24 h and decreased over the next four weeks). A reduced concentration of synaptic vesicle protein vesicular glutamate transporter-1 (VGLUT-1) in the CA1 region of the hippocampus was detected. Corticotropin-releasing hormone (CRH) and (a low level of BDNF are crucial parameters in the animal depression modelling process (Hashimoto K et al., 2004). Furthermore, oxidative stress and inflammatory pathway abnormalities are two important components of depression (Maes, M. et al., 2011). The open field test is a commonly used measure of exploratory behaviour and general activity in mice and rats, which can assess locomotion, exploration, anxiety, depression, and emotionality. The test is also used to evaluate the effects of compounds, including their sedative, toxic, or stimulant properties. In a study comparing the antidepressant effects of Ethanolic extract of Curcuma longa (EECL) and Imipramine in rats, the EECL-treated groups demonstrated a significant increase in the number of activities in the center squares, but no significant decrease in spontaneous ambulation or increase in the number of rearings compared to the Imipramine-treated group. However, the EECL-treated group at a dose of 560 mg/kg demonstrated a better antidepressant effect than the EECL 140 mg/kg and Normal control treated groups, as it significantly increased the activity in the center squares, increased the number of rearings, and significantly reduced spontaneous ambulation. The Positive control and EECL 560 mg/kg treated groups also demonstrated an overall increase in the number of rearings throughout the study duration. These observations suggest that EECL at a dose of 560 mg/kg has more potential than the lower dose and Normal control to modulate Dopaminergic transmission in the striatum by Nicotinic Acetylcholine Receptors (nAChR) and exhibit antidepressant effects**.**

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