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Screening of Anxiolytic Potential of Ethanolic Extract of *Cucumis sativus* L. Fruit in Rats

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Keywords: Anxiolytic, *Cucumis sativus*, Diazepam, Elevated plus maze, Rota rod model, Hole board model, Open field model.

ABSTRACT

Background: Stress and anxiety are common psychiatric manifestations of the modern world and lifestyles. Over stress contribute to anxiety, a state of constant worry leads to worsening physical and mental conditions. Herbal psychopharmacology has revealed a variety of promising medicines that may provide benefits in the treatment of many psychiatric disorders. So, *Cucumis sativus* which comprise both wild and cultivated species and is consumed in different ways like vegetables and salads, but less is known about its medicinal importance. The various phytoconstituents and pharmacological properties initiated to explore the anxiolytic potential of ethanolic extract of *Cucumis sativus* L. (EECS) fruit in rats. **Methods:** EECS prepared by the Soxhlet extraction process, phytochemical screening was performed, and screened for anxiolytic potential in Wistar albino rats. EECS low dose (200mg/kg) and high dose (400mg/kg) were used as test doses. Anxiolytic activity was screened by using different models such as Elevated Plus Maze, Rota rod model, Open Field Model, and Hole Board model in Wistar albino rats. Diazepam (1mg/kg) was used as a standard drug. **Results:** Phytochemical investigation resulted in the presence of flavonoids, steroids, triterpenes, alkaloids, phenols, and tannins. Standard drug (Diazepam 1mg/kg) treated group showed high significance (***P<0.001) followed by low dose (200mg/kg) (**P<0.01) and high dose of EECS (400mg/kg) (*P<0.05) in Elevated Plus Maze, Rota rod model, Open Field Model, and Hole Board model compared to control group respectively. **Conclusion:** Based on the result obtained the study concludes that the test EECS possess significant anxiolytic activity.

INTRODUCTION

Humans frequently experience anxiety. It becomes a disorder when it disturbs behavior and finally leads to suffering.[1] The word anxiety is derived from the Latin word 'anxietas' (to choke, throttle, trouble, and upset). It compresses behavioral, affective, and cognitive responses to the perception of danger.[2] Anxiety is a future-oriented mood state associated with preparation for possible upcoming negative events.[3] Mental disorders are estimated to account for 12% of the global burden of disease. The most common psychiatric condition is anxiety. According to epidemiological surveys, 1/3 population is affected by an anxiety disorder in their lifetime. According to the Diagnostic and Statistical Manual of Mental Disorders (**DSM)** – V anxiety disorder is classified as Social Anxiety Disorder (SAD), Generalized Anxiety Disorder (GAD), Specific Phobia, Panic Disorder (PD), Separation Anxiety Disorder (SeAD), Selective Mutism.[4,5]

The etiopathogenesis of anxiety is still not fully known. It is supposed that both genetic variants and environmental factors contribute to the onset of anxiety disorders. It is thought that an under-activation of serotonergic and over-activation of noradrenergic causes anxiety disorder. Therefore, selective serotonin reuptake inhibitors (SSRI) and serotonin noradrenergic reuptake inhibitors (SNRI) are first-line agents for anxiety treatment.[6] Based on the patient's preference anxiety treatment includes combination of psychotherapy, behavioral therapy, and medication.[7]

Use of plants, parts of plants, and isolated phytochemical constituents for the prevention and curing of various health disorders has been in practice from ancient time Studies have demonstrated that many phytochemicals such as saponins, alkaloids, polyphenols, flavonoids, triterpenoids, essential oils, and fatty acids possess an anxiolytic effect.[8]

Cucumbers (*Cucumis sativus* L.) are the members of Cucurbitaceae family, these are rich in water content and very low in calories.[8] Among 30 species of Cucumis, *Cucumis sativus* L. has the highest economical value. All parts of plants such as roots, leaves, fruit, and seeds are useful in treating diseases.[9] Cucurbits are primarily comprised of species consumed as food worldwide. These are having a composition of all the essential constituents required for a healthy diet in humans. The vast study on this plant proves that phytoconstituents like glycosides, flavones, terpenoids, phytosterols, saponins, tannins, etc. This plant has been reported to have antibacterial, antifungal, antidiabetic, cytotoxic, antacid, carminative,

hepatoprotective, ulcer, wound healing, antiwrinkle properties, etc. Hence, this plant possesses a significant role in the prevention and treatment of disease.[10]

Current allopathic treatment for anxiety is associated with side effects and adverse effects. Based on the above considerations the present study aimed to evaluate the anxiolytic potential of ethanolic extract of *Cucumis sativus* L. fruit by using experimental animals.

MATERIALS AND METHODS

Plant materials

Fruits of *Cucumis sativus* L. were purchased from local market Chitradurga, Karnataka and they were washed, cut into slices and dried under shade. The fruit material was identified and authenticated by botanist, Chitradurga, Karnataka.

Preparation of plant extracts[11]

Fruits were cleaned, cut into slices and shade dried (25ºC) and pulverised. Powder of fruit was packed in Soxhlet extractor and extracted using ethanol as solvent, temperature maintained at 40ºC. Extract was filtered through Whatman No.1 filter paper, concentrated under reduced pressure and stored in airtight container, and used for further studies. The yield was about 20.88%.

Extract was dissolved in alcohol and performed preliminary phytochemical screening.

Preliminary phytochemical screening:[12,13]

Preliminary phytochemical investigations were carried out on the ethanolic extract of *Cucumis sativus* L. fruit for the detection of various phytochemicals by using standard methods prescribed in practical pharmacognosy by C K Kokate and R K Khandelwal.

Experimental animals:

Animal ethical clearance is obtained from Institution Animal Ethics Committee (IAEC) for the experimental purpose **(Ref no:02/SJMCP/IAEC/2021-22)**. Healthy Adult Wistar Albino rats weighing about 150-200g of either sex was used for this study. The animals were obtained from Biogen Laboratory Animal Facility, Bangalore – 562107. Before the initiation of the experiment, the animals were randomized and acclimatized for 10 days under standard environmental conditions such as temperature (26±2ºC), relative humidity (45-55%), and 12hrs light/dark cycle maintained as per Committee for the Purpose of Control and

Supervision of Experiments on Animal (CPCSEA) guidelines. All the animals were allowed free access to standard laboratory pellets and drinking water *ad libitum* under strict hygiene conditions.

Selection of screening dose:[14]

Screening of anxiolytic activity dose was considered based on the literature of acute toxicity studies (OECD 420) of ethanolic extract of *Cucumis sativus* L. fruit given by, Low dose: - 200mg/kg. High dose: - 400mg/kg.

SCREENING OF ANXIOLYTIC ACTIVITY

Experimental Design:[15]

The obtained Wistar rats weighing 150-250g were randomly divided into 4 groups each containing 6 animals. (n=6).

Group I: - Treated with saline (10ml/kg p.o).

Group II: - Treated with Diazepam (standard drug) (1mg/kg, i.p).

Group III: -Treated with a low dose of *Cucumis sativus* L. extract (200mg/kg p.o).

Group IV: -Treated with a high dose of *Cucumis sativus* L. extract (400mg/kg p.o).

Doses of the extract were calculated according to body weight of animal. All drugs were freshly prepared before each experiment. The anxiolytic activity was examined using elevated plus maze model, rota rod model, hole board model and open field model.

1. Elevated plus maze:[15]

Elevated plus maze is a commonly used behavioral assay to determine anxiolytic activity. Elevated plus maze test was performed according to Handley and Mithani. Elevated plus maze consists of 4 arms (2 open arms and 2 closed arms) attached at a junction (central platform). The plus maze was elevated to a height of 50cm above ground level. Animals of each group control, standard, and test were given with a single dose of normal saline, standard drug (Diazepam), and test extracts of EECS at 200mg/kg and 400mg/kg respectively one hour before the experiment. Rats were placed at the junction of four arms, facing toward an open arm. The number of entries, time spent in each arm and center was recorded for 5mins. Increase in open-arm activity reflects anti-anxiety behavior. The apparatus was

cleaned with alcohol in between the trials. Precautions taken to maintain noise free environment.

2. Rota rod model:[16]

Effect of motor coordination was assessed using rota rod model. Rota rod consists of a base platform and anon-slippery surface rotating rod of 3cm diameter and divided into five equal sections. The animals were pre-selected in a training session based on ability to remain on rod (at 20 rpm) for 2mins. Animals of each group control, standard and test were given with single oral of normal saline, standard drug (Diazepam) and test extracts of EECS at 200mg/kg and 400mg/kg respectively. Animals were placed on rod at a speed of 20 rpm over a period of 30, 60, and 90mins. Falling off time was automatically recorded. Time spent in the apparatus was observed for 5min duration (300s). The apparatus was cleaned thoroughly with alcohol in between trials.

3. Hole board model:[16,17]

Hole board model was performed according to Boissier and Simon. The apparatus consists of square open field (50×50×50 cm) divided into 9 equal squares and consisting for four equidistant holes 4cm in diameter. Hole board was positioned 15cm above the ground. Animals of each group control, standard and test were given with single oral dose of normal saline, standard drug (Diazepam) and test extracts of EECS at 200mg/kg and 400mg/kg respectively. After one hour animal was placed in center of hole-board and allowed to explore freely in the apparatus for 5mins. Total number of head dipping into hole by animal was recorded. A head dip was scored if both eyes disappeared into the hole.

4. Open field model:[18]

Open field model/ test was performed according to Hall. The apparatus consisted of wooden box (60 × 60 × 60 cm). Floor of the box was divided into 16 squares (15 × 15 cm). As per the experimental design, animals were treated respectfully. After 30mins, animals were placed individually in one corner square. The number of rearings assisted, rearings (forepaws touching the walls of the apparatus) and number of squares crossed were counted for 5mins. Increasing in square crossing indicates locomotory activity.

STATISTICAL ANALYSIS:

The data obtained from the above findings was subjected to statistical analysis using one-way ANOVA followed by Tukey's Kramer Multiple Comparison Test to assess the statistical significance of the result.

RESULTS

Percentage yield of ethanolic extract: 20.88%.

Colour and consistency: Dark green-brown, sticky and slurry consistency.

Preliminary phytochemical screening:

Preliminary phytochemical screening of EECS fruit confirms the presence of carbohydrates, alkaloids, glycosides, flavonoids, tannins, steroids, triterpenes and phenolic compounds.

Anxiolytic activity: -

A test sample of *Cucumis sativus* L. fruit was screened for anxiolytic potential by employing the Elevated Plus Maze Model, Rota Rod Test, Hole Board Test, and Open Field Test in Wistar albino rats of either sex weighing 150-200g.

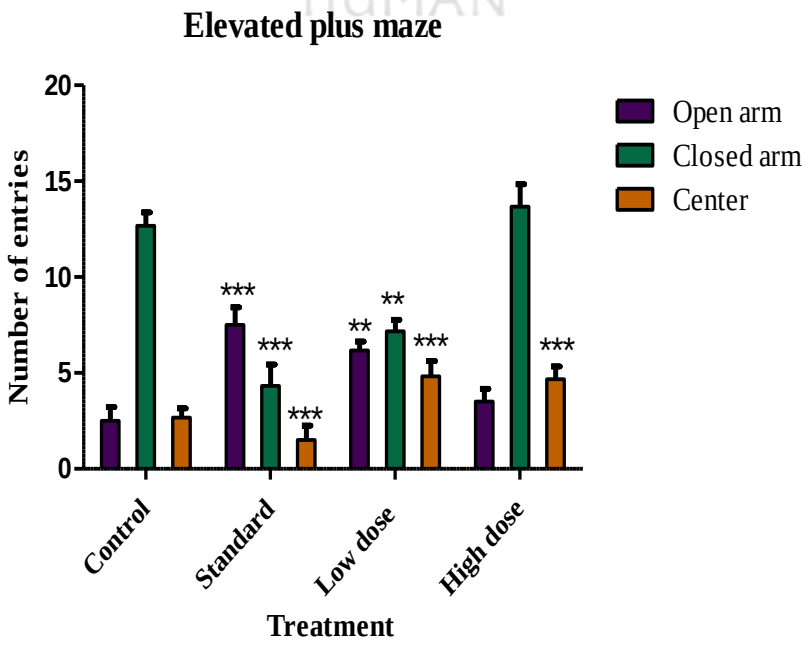
1. Elevated plus maze model:

The ethanolic extract of *Cucumis sativus* L. fruit was screened for anxiolytic activity in an elevated plus maze model using Wistar albino rats of either sex weighing 150-200g, parameters studied in this model were a number of entries and time spent by the rat in open arm and center. Assessment of cognitive behaviour. Standard group (Diazepam 1mg/kg) produced high significance (***P<0.001) increase in the permeance to the open arm and center compared to other groups suggesting the anxiolytic bahavior. Test extarct of EECS at low dose (200mg/kg) had shown moderately significant (**P <0.01) increase in number of entries and time spent in open arm and control compared to control group. EECS at high dose (400mg/kg) had shown less significance (*P<0.05, and ^{ns}P>0.05) compared to control group. (Results are shown in Table No.1, Fig. No. 1)

Table No 1: Effect of EECS fruit in Elevated Plus Maze model

Sl no	Treatment	Number of entries (counts/5min)			Time spent (sec) in 5mins		
		Open arm	Closed arm	Center	Open arm	Closed arm	Center
I	Control (Saline) 10ml/kg	2.50 ± 0.72	12.67 ± 0.71	2.67 ± 0.49	20 ± 7.6	265.5 ± 10.74	14.50 ± 4.121
II	Standard (Diazepam) 1mg/kg	7.50 ± 0.92***	4.33 ± 1.11***	10.50 ± 0.76***	154.8 ± 8.53***	95.20 ± 6.779***	50 ± 9.135*
III	Low dose (EECS) 200mg/kg	6.167 ± 0.47**	7.17 ± 0.60**	4.83 ± 0.79***	139.5 ± 6.31*	126.5 ± 3.894***	40 ± 6.170ns
IV	High dose (EECS) 400mg/kg	3.5 ± 0.67 ns	10.67 ± 1.17 ns	4.67 ± 0.67***	127.8 ± 12.33ns	145.7 ± 13.33**	26.50 ± 1.892 ns

Values were expressed as Mean ± SEM (n=6); Significance values are: ***P < 0.001, **P < 0.01 and *P < 0.05 and nsP> 0.05. Control group vs all groups. (By one-way ANOVA followed by Tukey-Kramer Multiple comparison tests).



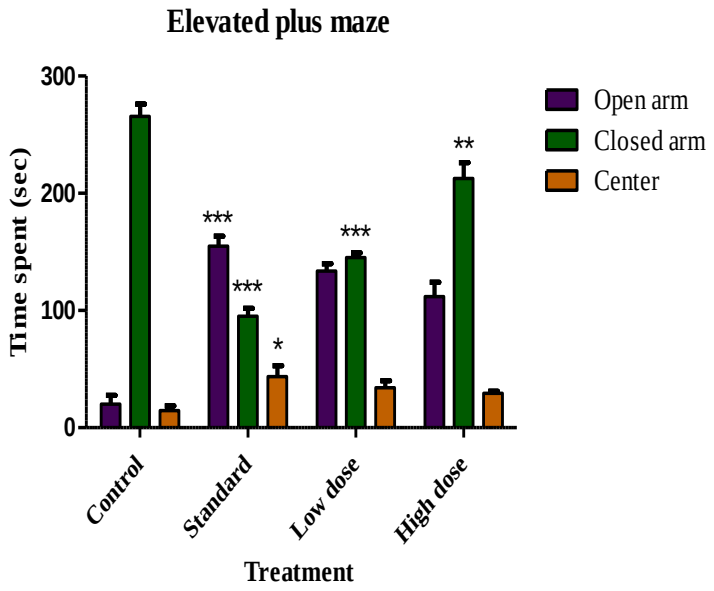


Fig. No. 1: Effect of EECS fruit in Elevated Plus Maze model

2. Rota rod model:

The ethanolic extract of *Cucumis sativus* L. fruit was screened for anxiolytic activity in a Rota-rod model using Wistar albino rats of either sex weighing 150-200g, assessment of spontaneous activity and muscle coordination. Control group animal motor coordination (locomotion and maintenance of equilibrium on rod) was compared to other groups. Standard group (Diazepam 1mg/kg) produced a highly significant (***P<0.001) decrease in the locomotor score when compared to the other three groups in all time intervals (30mins, 60mins, 90 mins). Test drug EECS at low dose (200mg/kg) had shown high significance (***P<0.001) at 30 and 60 mins, and moderately significant (**P<0.01) at 90 mins. EECS at high dose (400mg/kg) had shown a high significance (***P<0.001) at 30mins and moderately significance at 60mins, at 90 mins it had shown increase in locomotion and animals-maintained equilibrium and stayed on rotating rod for long period without falling compared to control group. (Results shown in Table No: 2, Fig No.: 2)

Table No. 2: Effect of EECS fruit in Rota-rod model

Sl no.	Treatment	Falling time (Sec)		
		30 mins	**60 mins**	**90 mins**
I	Control (Saline) 10ml/kg	293 ± 3.493	288.3 ± 3.393	270 ± 7.97
II	Standard (Diazepam) 1mg/kg	81.67 ± 3.547***	51.33 ± 3.373***	45.83 ± 2.535***
III	Low dose (EECS) 200mg/kg	193.7 ± 9.355***	164 ± 6.962***	232.3 ± 9.33**
IV	High dose (EECS) 400mg/kg	187.8 ± 9.707***	258.2 ± 4.708**	274.5 ± 6.464ns

Values were expressed as Mean ± SEM (n=6); Significance values are: ***P < 0.001, **P < 0.01 and nsP> 0.05. Control group vs all groups. (By one-way ANOVA followed by Tukey-Kramer Multiple comparison tests)

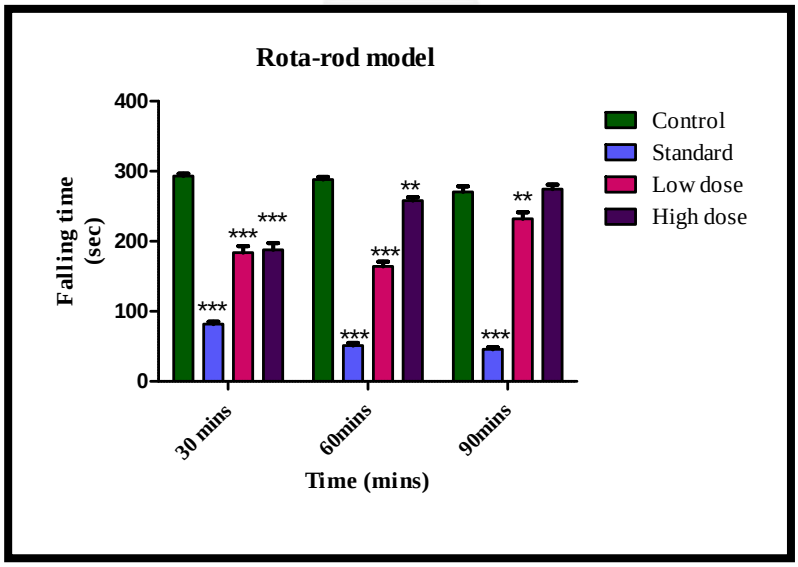


Fig. No. 2: Effect of EECS fruit in Rota-rod model

3. Hole board model:

The ethanolic extract of *Cucumis sativus* L. fruit was screened for anxiolytic activity in a Hole board model using Wistar albino rats of either sex weighing 150-200g, assessment of exploratory activity (head dipping behavior) was done. Control group animal head dipping

behavior was compared to other groups. Standard group (Diazepam 1mg/kg) showed a highly significant (***P < 0.001) increase in the number of head dips compared to other three groups, indicating the anxiolytic state. Low dose of EECS (200mg/kg), had shown a moderately significant (**P <0.01) increase in head dips. At high dose of EECS (400mg/kg), the treated group had shown less significant (*P<0.05) increase in head dips as compared to control group. (Results shown in Table No: 3 Fig No: 3)

Table No. 3: Effect of EECS fruit in Hole Board model

Sl no.	Treatment	Number of Head Dipping (5mins)
I	Control (Saline) 10ml/kg	11.17±1.167
II	Standard (Diazepam) 1mg/kg	28.83±1.641***
III	Low dose (EECS) 200mg/kg	18.83±1.302**
IV	High dose (EECS) 400mg/kg	17.33±0.955*

Values were expressed as Mean ± SEM (n=6); Significance values are: ***P < 0.001, **P < 0.01, *P < 0.05 and ^{ns}P> 0.05. Control group vs all groups. (By one-way ANOVA followed by Tukey-Kramer Multiple comparison test.

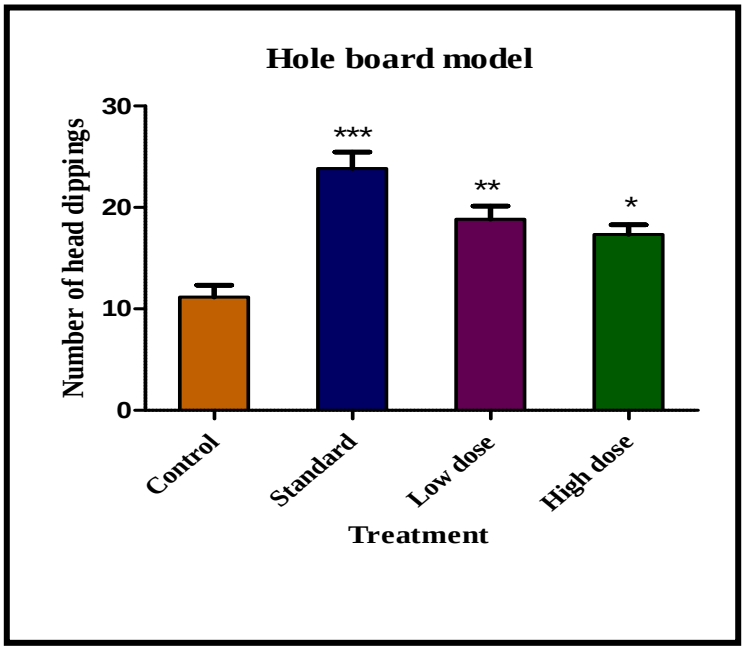


Fig. No. 3: Effect of EECS fruit in Hole Board model

4. Open field model

The ethanolic extract of *Cucumis sativus* L. was screened for anxiolytic activity in an Open field model using Wistar albino rats of either sex weighing 150-200g, assessment of locomotor and exploratory activity in an open space was done. Control group animal locomotion (rearing, line crossed) and exploration (center square crossed) activity was compared to other groups. Diazepam-treated group have shown a highly significant (***P<0.001) increase in locomotor and exploratory activity compared to the other three groups indicating anxiolytic activity. In a low dose of EECS (200mg/kg), the treated group had shown a moderately significant (**P <0.01) increase in locomotor and exploratory activity. In a high dose of EECS (400mg/kg), the treated group had shown less activity as compared to control group. (Results shown in Table No: 4, Fig No: 4)

Table No. 4: Effect of EECS fruit in Open field model

Sl no.	Treatment	Rearings	Assisted rearings	Number of squares traversed in 5mins		
				Central	Peripheral	Total
I	Control (Saline) 10ml/kg	3.833 ± 0.945	7 ± 1.461	1.66 ± 0.49	68.33 ± 7.159	69.50 ± 7.361
II	Standard (Diazepam) 1mg/kg	8.667 ± 0.881***	14.52 ± 0.96**	8.0 ± 0.82***	109.8 ± 5.799***	117.7 ± 5.408***
III	Low dose (EECS) 200mg/kg	7.833 ± 0.48**	12.67 ± 1.45*	5.0 ± 0.58*	99.17 ± 3.58**	102.7 ± 3.353**
IV	High dose (EECS) 400mg/kg	4.833 ± 0.946ns	8 ± 1.461ns	2.83 ± 0.87 ns	80.67 ± 6.912ns	80.50 ± 7.361ns

Values were expressed as Mean ± SEM (n=6); Significance values are: ***P < 0.001, **P < 0.01, *P < 0.05 and nsP> 0.05. Control group vs all groups. (By one-way ANOVA followed by Tukey-Kramer Multiple comparison tests).

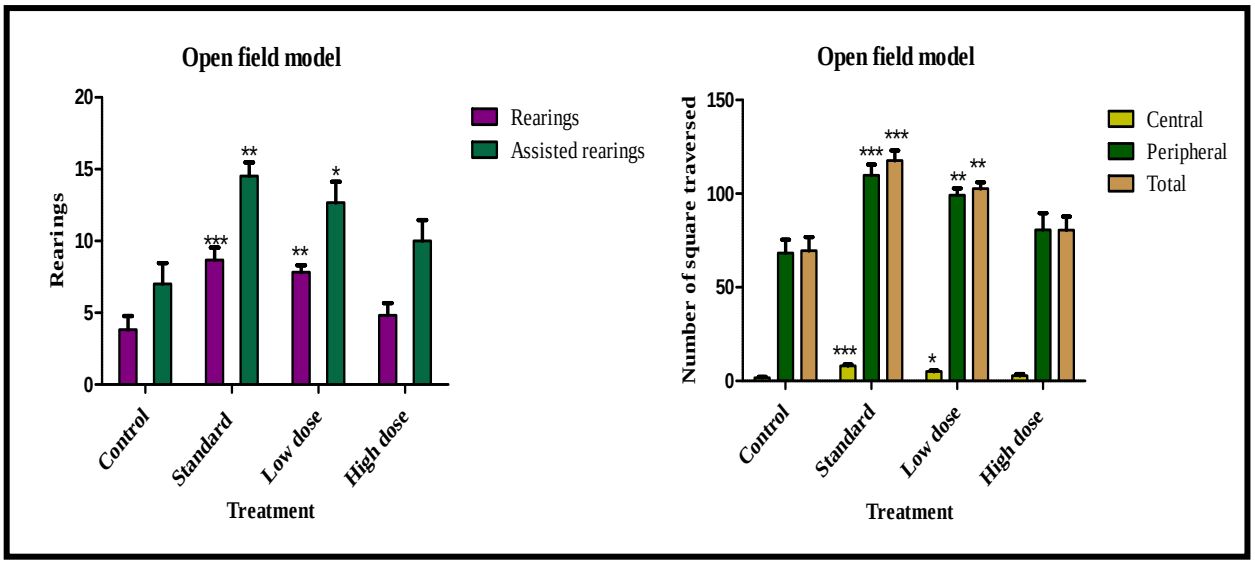


Fig. No. 4: Effect of EECS fruit in Open field model

DISCUSSION

Anxiety is a negative emotion that arises in response to perceived threats that are either genuine or imagined and can come from either internal or external. The etiology of most anxiety disorders is not yet fully understood, but the picture has become a little clear in the recent past.[16] Dysregulation of the GABAergic, serotoninergic, dopaminergic, and adrenergic neuro systems have all been implicated in the pathophysiology of anxiety. Anxiolytics are used in the treatment of anxiety in addition to psychotherapy.[19] Animal models are considered as most widely validated test for assaying anxiety and antidepressant substances.[20] Self-administration of herbal medicines was among the most popular alternative therapies, and there is considerable interest in the development of new anxiolytics, new therapies for the treatment of anxiety disorders are necessary, and the study of medicinal plants could provide new therapeutic options.[16]

Elevated plus maze:

Elevated plus maze model used to study neuroprotective effect and anxiolytic reaction produced. Test is based on the principle that when animal exposed to novel maze alley experiences atactic conflict that is more intense in open arm compared to closed arm. Rodents (rats and mice) spend more time in the enclosed arm due to aversion to heights and open spaces. When they enter open arm they stiffen, become immobile, urinate and exhibits fear-like response. Upon previous exposure, animal occupies a safe position to avoid feeling fear.

An animal's ability to learn is indicated by how long it takes to reach the EPM's central platform. When animal is placed in apparatus, they prefer to stay in enclosed arm due to development of fear due to anxiety but when they were treated with anxiolytics, they overcome fear and spend more time in open area.[21,22] In our study standard drug had shown highly significant increase in permeance to open arm and center. Whereas test drug shown significant increase in permeance to open arm and center. Decrease aversion to open arm indicates anxiolytic activity.

Rota rod model:

Rota rod model is used to evaluate motor coordination and spontaneous activity in rodents. When animal is repeatedly placed on rotating rod which is rotating at a constant speed, animal gradually learns to walk on it, adopts itself to rotating speed. Drugs known to alter neuromuscular coordination, such as benzodiazepines shorten the amount of time that animals can retain on the rod.[23] In present study diazepam treated group had shown high significant decrease in falling time. Test drug EECS had shown significant decrease in falling time compared to control group. Decrease in falling time from rotating rod indicates muscle relaxing property.

Hole board model:

Hole board model is commonly used to determine the exploratory behaviour such as head dipping and rearings. Treatment with anxiolytic agents and anxiogenic affects head- dipping behavior. Anxiolytics would be expected to increase these behaviours such as locomotory, head dipping, and rearing. The head dipping of animals is inversely proportional to their anxiety state in the moderately aversive environment.[24] In the present study diazepam treated group had shown high significant increase in head dipping behavior and test doses showed increase in number of head dipping compared to control group. An increase in number of head dipping into hole by animal indicates the exploratory activity and decreased anxiety state.

Open field model:

Open field model is a classical method used to evaluate motor activity and exploratory behavior. Mainly examines anxiety related behavior characterized by normal aversion of animals to open, brightly lit areas. Animals were placed in an open arena to express fear and anxiety by showing changes in parameters such as locomotion (number of line crosses and

frequency of rearing) and exploratory (number of central square entries and duration of time spent). A high frequency/duration of these behaviors indicates high exploratory behavior and low anxiety levels.[22] In present study diazepam treated group had shown increase in locomotor and exploratory activity and test dose has shown significant increase locomotor and exploratory activity compared to control group which indicates the anxiolytic behaviour.

CONCLUSION

From the above findings EECS had shown significant anxiolytic activity it may be due to presence of phytoconstituents such as flavonoids, steroids, triterpenes and other phytochemicals acting though different receptors (GABA, 5HT etc.). Further studies are necessary to find the exact mechanism of anxiolytic activity and isolate active components responsible for the activity.

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