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PHARMACOLOGICAL EVALUATION OF ANTIDEPRESSANT ACTIVITY OF *ALLIUM CEPA* IN ANIMAL MODEL

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Abstract:

People in modern society suffer from different psychiatric disorders, particularly the depression. The exact cause of depression is unknown, but researchers suggest that depression is due to imbalancing of neurotransmitters like serotonin, norepinephrine, and dopamine in the brain. Factors that may contribute to depression include heredity, stress, chronic illnesses, certain personality traits and hormonal changes. However, several syntetic drugs are available in market, but all are associated with some limitations and there is an urgent need for alternative medications for these disorders.

Depression is a widely prevalent form of mental illnesses worldwide. It is commonly associated with sad mood, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, and low energy. Allium cepa has many medicinal properties, and are used in traditional medicine in the treatment of various medical conditions. This study was conducted to better understand the antidepressant activity of Allium cepa.

To evaluate the in vivo antidepressant activity of Methanolic extract of Allium cepa leave in Swiss albino mice. Methanolic extract of Allium cepa (EEAC) leaves was prepared by a continuous method using Soxhlet apparatus. The extract was subjected to phytochemical screening followed by acute oral toxicity studies in mice. EEAC in the doses of 100mg/Kg, 200mg/Kg and 400mg/Kg mg/kg body weight was administered to test groups Group 3, 4 and 5 respectively. Imipramine hydrochloride 15mg/kg body weight was administered to Standard group by oral route. Test group 3 received 100mg/kg (p.o). Control group received Normal saline 10ml/kg body weight. Antidepressant activity was identified by using modified Forced Swimming Test (FST) and Tail Suspension Test (TST). Period of immobility was observed in both the models which was indicative of anti-depressant activity. Standard statistical methods were used to evaluate the results. The results showed significant dose dependent antidepressant effect of EASL in Swiss albino mice for both the models in all the test groups (Test group I, II and III). EEAC possess significant antidepressant activity. However, further investigations are required to determine its active constituents and molecular level of target mechanism of the extract for further use in humans.

Keywords: *Allium cepa, Antidepressant activity, forced swim test, Open Field Test.*

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INTRODUCTION:

Depression: It is basically acknowledged as illness with symptoms such as anxiety and sleep disturbances. It can be a persistent, recurring illness that can cause many personal suffering for individuals and their families. At present, disability caused by depression is estimated to be the fourth most important cause of worldwide loss of life years. This has resulted into a requirement of search for effective treatments, including antidepressant drugs, herbal remedies, psychotherapy and electroconvulsive shock therapy.

The Neurobiology And Pharmacology Of Depression:

I. Neurotransmitter Systems:

Within the central nervous system (CNS), the catecholamines, adrenaline, noradrenaline and dopamine forms the adrenergic systems. Out of these, few of the adrenergic neurons are radiating from the ancient limbic system and plays to role of discharging the catecholamines within the frontal cortex. Thus, the catecholaminergic pathways are claimed to be responsible for mood, alertness and stress responses. The primary neurotransmitter, which modulates the excitatory catecholamine systems of the CNS is Serotonin. The Serotonin neurons are responsible for the control of memory, mood, sex drive and appetite. [1]

The systems of serotonin and noradrenaline are the important their main cell small bodies in brainstem areas that serve as headquarters for shipping axonal projections by the brains in specific pathways that mediate specific functions (See Figure No. 1 for an illustration of the serotonin projections and Figure No. 2 for an illustration of the noradrenergic projections).

Multiple serotonergic and noradrenergic pathways may be dysfunctional in depression, generating many different symptoms.

The nucleus of the dorsal raphe projects the serotonin system and the raphemagnus. The serotonin receptors (5-HT) have been identified into various sub-types with the 5-HT1 and 5- HT2 sub-types being of greater interest in psychiatry. The most important of the 5-HT1 subclass is 5- HT1A which is concentrated in the hippocampus and raphe. The release of this 5 – HT from presynaptic neurons is modulated by this autoreceptor. The 5 - HT2 rceptors occur in high concentrations in the frontal cortex and nucleus accumbens.

II. Hypotheses of Depression:

Several hypotheses of the biological determinants of depression have emerged over the past century. The most important of these and the implications thereof are reviewed below. Today it is generally accepted that depression is not necessarily due to a shortage of one vital brain neurotransmitter, but rather to a disruption in the equilibrium between different regulatory systems.

A. The Biogenic Hypothesis of depression

The most common characteristic of depresion as claimed by monoaminergic hypothesis are a result of inadequate concentration of serotonin and noradrenaline in the synaptic clefts of the neurons in the brain.

B. The dopamine hypothesis of depression

The original hypothesis was formulated in the late nineteen seventies by Solomon Snyder and linked schizophrenia with dopamine (DA) activity. Later, this hypothesis was extended to include depression following the observation that many antidepressants influence the metabolism of dopamine.

C. The permissive hypothesis of depression

This hypothesis emphasizes 5-HT as a neuro-modulator and its importance as a focus for antidepresant action. According to this theory, a lowered concentration in the central nervous system (CNS) of 5-HT results in an affective state regulated by NA. Decreased 5-HT and NA levels will give rise to depression. This Averages that 5-HT may act as a ‘permissive’ modulator of neurotransmitter function through connections between serotonergic pathways and make connections with noradrenergic and dopaminergic pathways via the associated receptors.

III. Treatments for Depression:

MAOIs & tricyclic antidepresants (TCAs) were launched as the drug products approximately 60 years ago. These were found to have many side effects and to be highly toxic in the treatment of depression. This resulted into introduction of the selective noradrenaline reuptake inhibitors (SNRIs) and selective serotonin reuptake inhibitors (SSRIs), which are better tolerated and safer. However, these have not been shown to be conclusively superior to the TCAs and MAOIs. [4]

The chemical structures of antidepressant drugs vary significantly and therefore cannot be considered to be the most important factor in the search for new drugs with antidepressant activity. However, the mechanism of action of these drugs has provided insights into the pathology of depression. The basic biochemistry and possible Mode of action of major categories of antidepressant drugs are discussed below.

A. Tricyclic Antidepressants (TCA)

These drugs all have a characteristic three ring structure and are chemically similar to the phenothiazines. The discovery of their antidepressant action was fortuitous when imipramine, originally considered as a neuroleptic was found to have antidepressant activity.

Thereafter, first generation antidepressants emerged which display activity as mixed noradrenaline and serotonin reuptake inhibitors. The reuptake of monoamine neurotransmitters into the presynaptic neuron is inhibited by many of the TCAs by competitive inhibition of the ATPase in the membrane pump. Some TCAs are more selective than others but this has not been shown to influence the efficacy of the drug. The different monoamine reuptake properties can also include an increase in dopaminergic activity via a presynaptic mechanism for amitriptyline and a post synaptic mechanism for desipramine and imipramine.

The major drawback of the TCA drugs is the side effects which result from their antimuscarinic, antihistaminic and alpha adrenoceptor-blocking activity.

B. Selective Serotonin Reup take Inhibitors (SSRI)

Unlike the tricyclic antidepressants, the SSRIs reduce the neuronal uptake of serotonin but have no effect on noradrenaline. Therefore, the SSRIs have a better side effect profile in comparison with TCAs because these drugs have a low affinity for muscarinic, histaminergic and adrenergic receptors.

Fluoxetine was the first SSRI to be used clinically followed by paroxetine and sertraline. The latter two have shorter half-lives and different potencies as inhibitors of specific P450 isoenzymes.

MATERIALS AND METHODS:

The designing of methodology involves a series of steps taken in a systematic way in order to achieve the set goal (s) under the prescribed guidelines and recommendations. It includes in it all the steps from field trip to the observation including selection and collection of the medicinal plant, selection of dose value, standardization of protocol, usage of instruments, preparation of reagents, selection of specific solvents for extraction, formation of protocols and final execution of the standardized protocol. All this requires good build of mind and a good and soft technical hand to handle the materials and procedure in a true scientific manner.

Drugs and Chemicals

Drugs and Chemicals used in this study were of analytical grade and of highest purity procured from standard commercial sources in India.

Table No: Drugs and Chemicals

S.No	***Materials***	***Company Name***
1.	Imipramine	Nicholos Piramal Ltd

Instruments:

Following instruments were required for the study:

Table No: List of Instruments used for study

Name of the instrument	***Source***
Centrifuge	Dolphin
Digital weighing balance	Horizon
Glucometer	Horizon
Heating mantle	ASGI®
Refrigerator	Videocon
Actophotometer	Dolphin
Elevated Plus maze apparatus	Dolphin
Glass cylinder	ASGI®
Adhesive tape	YVR medivision Pvt Ltd
Thread	YVR medivision Pvt Ltd
Stop watch	ASGI®
Syringes	YVR medivision Pvt Ltd

Needles	YVR medivision Pvt Ltd
Soxhlet extractor	ASGI®
Condenser	ASGI®
Burette stand	Dolphin
Round bottom flask	ASGI® , Amar
Mixer	Videocon
Oven	ASGI®
Water bath	ASGI®
Stirrer/glass rod	ASGI®
Watch glass	ASGI®
Whatmann filter paper	Manipore microproducts, Ghaizabad.
Butter paper	ASGI®
Spatula	ASGI®
Rubber pipes	ASGI®

EXPERIMENTAL ANIMALS:

Swiss albino rats, 60 in number, weighing 20-30 g, of either sex, maintained under standard conditions in the Institutional animal house were used. They were housed in clean, transparent polypropylene cages in groups of six and maintained at standard laboratory temperature and humidity (40-60%) with light/dark cycle of 12:12 hours. Animals were fed commercial pelleted chow and water. The rats were allowed to acclimatize to these conditions for a week before starting the experiments. The standard drug, Imipramine hydrochloride, was obtained from Abbot Healthcare Pvt Ltd (Depsonil 25).

Wistar rats (150-200 g) and Swiss albino mice (18-22g) of either sex selected for the study. Animals were housed in appropriate cages in uniform hygienic conditions and fed with standard pellet diet (Amrul Laboratory Animal Diet) and water ad libitum. All the animals were maintained under standard conditions, that is room temperature 26 ± 1°C, relative humidity 45 - 55% and12:12 h light – dark cycle. Animal studies had approval of IAEC.

Plant Material Collection:

The fresh leaves of *Allium cepa* was collected from local market. The plant material was cleaned, reduced to small fragments, air dried under shade at room temperature and coarsely powdered in a mixer. The powdered material was stored or taken up for extraction process.

Preparation of plant extracts:

Preparation of Methanolic Extract:

The *Allium cepa* plants were washed, the leaves were shade dried and powdered. About 200 g of the dried leaf powder of *Allium cepa* was extracted with 99.9% Methanol in Soxhlet extractor for about 36 hours. The Methanol was then evaporated from the mixture by placing it in a beaker and heating it over a water bath. The extract gave a yield of brownish paste like mass weighing 6g. The yield obtained was 3% w/w with respect to dried powder.

Preliminary phytochemical screening:

Preliminary phytochemical screening of the plant extract was carried out for the analysis of Alkaloids, Carbohydrates, Tannins, Saponins, Steroids, Phenols, Flavonoids .as per the standard methods.

1. Detection of Alkaloids: Extracts were dissolved individually in dilute Hydrochloric acid and filtered.

a) Mayer's Test: Filtrates were treated with Mayer's reagent (Potassium Mercuric Iodide).Formation of a yellow colored precipitate indicates the presence of alkaloids.

b).Wagner's Test: Filtrates were treated with Wagner's reagent (Iodine in Potassium Iodide). Formation of brown/reddish precipitate indicates the presence of alkaloids.

c).Dragendroff's Test: Filtrates were treated with Dragendroff's reagent (solution of Potassium Bismuth Iodide). Formation of red precipitate indicates the presence of alkaloids.

d).Hager's Test: Filtrates were treated with Hager's reagent (saturated picric acid solution).Presence of alkaloids confirmed by the formation of yellow colored precipitate.

2. Detection of Carbohydrates: Extracts were dissolved individually in 5ml distilled water and filtered. The filtrates were used to test for the presence of carbohydrates.

a).Molisch's Test: Filtrates were treated with 2 drops of alcoholic α-naphthol solution in a test tube. Formation of the violet ring at the junction indicates the presence of Carbohydrates.

b).Benedict's Test: Filtrates were treated with Benedict's reagent and heated gently. Orange red precipitate indicates the presence of reducing sugars.
c).Fehling's Test: Filtrates were hydrolysed with dil. HCl, neutralized with alkali and heated with Fehling's A&B solutions. Formation of red precipitate indicates the presence of reducing sugars.
3. Detection of saponins
a). FrothTest: Extracts were diluted with distilled water to 20ml and this was shaken in a graduated cylinder for15 minutes. Formation of 1cm layer off a am indicates the presence of saponins.
b).FoamTest:0.5gm of extract was shaken with 2ml of water. If foam produced persists forten minutes it indicates the presence of saponins.
4.Detection of steroids.
a).Salkowski's Test: Extracts were treated with chloroform and filtered. The filtrates were treated with few drops of Conc. Sulphuric acid, shaken and allowed to stand. Appearance of golden yellow colour indicates the presence of triterpenes.
b).Libermann Burchard's test: Extracts were treated with chloroform and filtered. The filtrates were treated with few drops of acetic anhydride, boiled and cooled. Conc. Sulphuric acid was added. Formation of brown ring at the junction indicates the presence of phytosterols.
5. Detection of Phenols
Ferric Chloride Test: Extracts were treated with 3-4 drops of ferric chloride solution. Formation of bluish black colour indicates the presence of phenols.
6. Detection of Tannins
Gelatin Test: To the extract,1 %gelatin solution containing sodium chloride was added. Formation of white precipitate indicates the presence of tannins.
7. Detection of Flavonoids
Alkaline Reagent Test: Extracts were treated with few drops of sodium hydroxide solution. Formation of intense yellow colour, which becomes colourless on addition of dilute acid, indicates the presence of flavonoids.
Leadacetate Test: Extracts were treated with few drops of lead acetate solution. Formation of yellow colour precipitate indicates the presence of flavonoids.
Selection of dose for animal study
The dose considered for the experiment on rats was obtained from conversion of human dose of *Allium cepa* (3-5 g/kg). The conversion factor of human dose (per 200 g body weight) is 0.018 for rats and 0.002 for mice (Ghosh 1984). Hence the calculated dose for the rats (considering human dose 3 and 5 g/kg) is 200 mg/kg and for mice is 20 mg/kg. Acute toxicity was done at dose of 2000mg/kg body weight.

Pharmacological evaluation:

Acute oral toxicity:
The acute oral toxicity of aqueous and alcoholic extracts of *Allium cepa* was determined by using rats and mice which were maintained under standard conditions. The animals were fasted 12 hour prior to the experiment, up and down procedure OECD guideline no. 425 were adopted for toxicity studies. Animals were administered with single dose of individual extract up to 2000mg/kg and observed for its mortality during 2days and 7days study period (short term) toxicity and observed up to 7days for their mortality, behavioral and neurological profiles.

Screening for antidepressant activity:
The Methanolic extracts of *Allium cepa* leaves were tested for antidepressant activity using despair swim test and tail suspension test.
Treatment
The Wistar albino rats (n=60) were divided into two arms which was further divided into five groups, each group having six Wistar albino rats. Drugs were given orally after 12 hours of fasting every day, for ten days. The drugs were prepared and administered per oral (0.1ml/10g).
Group 1 was administered normal saline (10ml/kg).
Group 2 was given standard drug Imipramine (15mg/kg). 12
Group 3, 4 and 5 received 100mg/kg, 200mg/kg, and 400mg/kg doses of the test compound Methanolic Extract of *Allium cepa* respectively.

For the Acute study, on day 1, one arm of 30 Wistar albino rats were subjected to Tail Suspension Test (TST), while 30 mice in the other arm were subjected to Forced Swim Test (FST), one hour after feeding the respective drugs. For Sub acute study, on day 10, the Wistar albino rats were again subjected to TST and FST, one hour after feeding respective drugs.

Procedure for antidepressant activity:
Forced swim test (fst):
The method used was as described by Porsolt et al. The rats were individually forced to swim in a vertical plexiglass cylinder (capacity: 5L, height: 50cm diameter: 18cm) containing l5cm of water maintained at temperature: 25◦C. Rats were subjected to pre-screening, which lasted for 15 minutes. 24 hours after pre-screening, the trial was performed for 6 minutes of which the first two minutes were not recorded, and the periods of immobility for the latter four minutes was measured (in seconds) with a stopwatch. Rats were considered to be immobile when they made only the bare necessary movements to stay afloat, or when they were motionless. The Rats were taken out of the plexiglass cylinder after 6 minutes. They were dried

with a dry towel, and kept under a dim lamp for drying. The water was discarded after every test, and fresh water was used for the next rats.

Tail Suspension Test (Tst):
The method used was as described by Steru et al. Antidepressants that are used in practice are able to reduce the period of immobility of rats when they try to escape when suspended by their tail. This test was a reliable screening method for antidepressants, including those involving serotonergic system. Mice ware hung on a wooden rod, 50 cm above the table, by attaching them from their tail end with the use of an adhesive tape. The first two minutes were not recorded, and the periods of immobility for the latter six minutes was recorded (in seconds) with a stopwatch. Rats were considered to be immobile only when they were motionless and not attempting to escape.

Open-field test:
For open-field test, animals were divided into four groups (n = 10 /group): control (0.9% saline), the three doses of *Allium cepa* (100, 200, 300 mg/kg) for one-week treatment. To assess the effect of *Allium cepa* on locomotor activity, mice were evaluated in the open-field paradigm (TRU SCAN Activity Monitoring Systems, Coul bourn Instruments) previously described. Animals were individually placed in a box (40 × 60 × 50 cm). The rats were not habituated to the box before the test. The mice were placed in the center and their behavior was noted immediately and continued for 4 min. The parameters such as total movements, total distance, total ambulatory move time were recorded by video camera and registered in the computer. During the interval of the test the apparatus was cleaned.

Statistical analysis:
Statistics The recorded data was entered in Microsoft Excel. The variables recorded followed normal distribution, hence, results have been expressed as mean (in seconds) ± standard error of mean (SEM). The data was analysed using one way ANOVA followed by post-hoc Dunnet's test. Probability 'p' value less than 0.05 was considered as statistically significant.

RESULTS:

Phytochemical screening test:
The freshly prepared extract of the leaves of *Allium cepa* was subjected to phytochemical screening tests for the detection of various active constituents. The extract showed the presence of alkaloids, tannins, steroids, phenolic and flavonoids, carbohydrates, and glycosides in crude extract of *Allium cepa* leaves as depicted in Table 1.

Table 1: Result of chemical group tests of the Ethanolic extract of *Allium cepa* leaves.

Test	Ethanolic extract
Carbohydrates	+
Tannins	++
Flavonoid	+++
Saponin	++
Phenols	+
Steroids	+
Alkaloids	+++
Glycosides	+

Antidepressant activity of *allium cepa:*
In the Acute study, on Day 1, standard drug Imipramine (15mg/kg) and test drug EEAC (100mg/kg, 200mg/kg, 400mg/kg) showed significant reduction in immobility times when compared to control in both FST and TST (Table 1, Figure 1). In the Sub acute study, on Day 10, both Imipramine (15mg/kg) and EEAC (100mg/kg, 400mg/kg) showed significant reduction in immobility times when compared to control in both FST and TST.

Table 1

Day 1	Tail Suspension Test	Forced Swim Test
Normal Saline	223.4(±20.01)	138.9(±1.23)
Imipramine 15mg/kg	176.5(±2.30)*	103.19(±0.54)*
EEAC 100mg/Kg	163.0(±15.1)*	98.06(±1.09)*
EEAC 200mg/kg	183.6(±1.12)*	109.05(±1.06)*
EEAC 400mg/kg	118.3(±1.20)*	108.21(±2.25)*

Immobility time shown in seconds as mean (± SEM),*denotes statistically significant value, # denotes statistically not significant value.

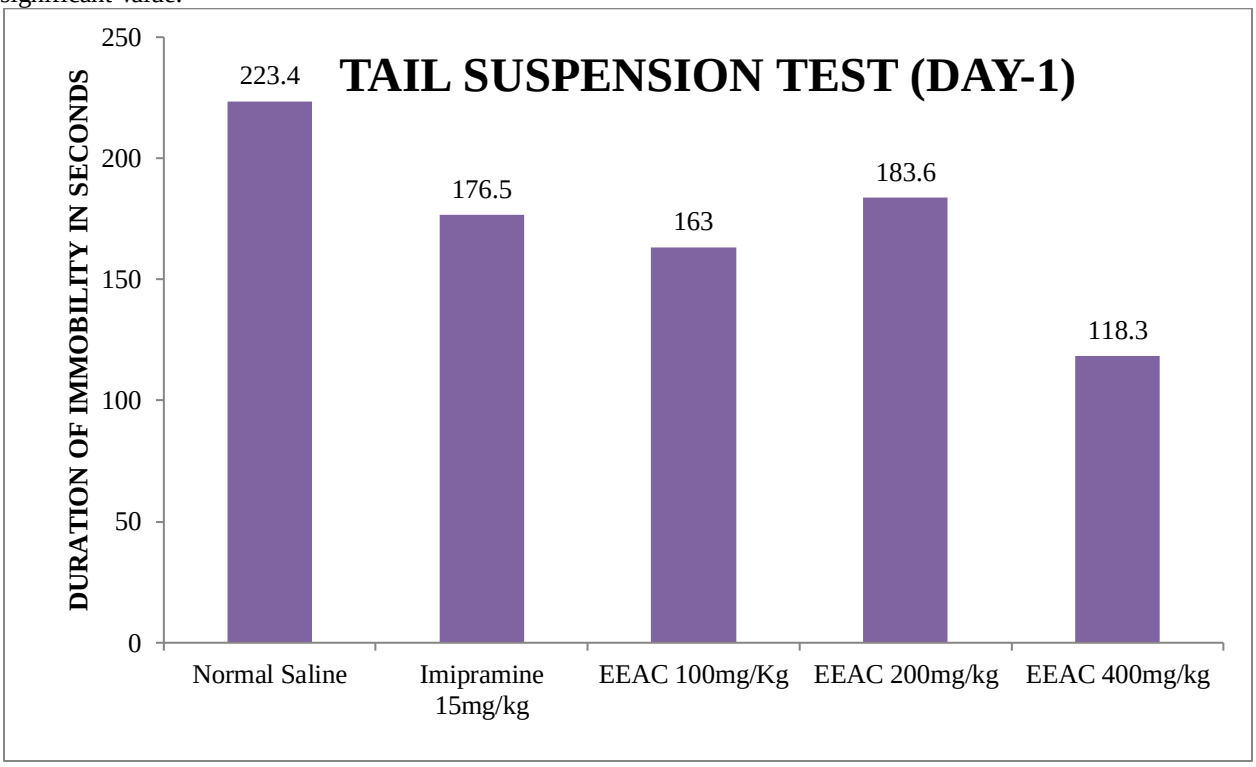

Fig: Tail Suspension Test Day-1

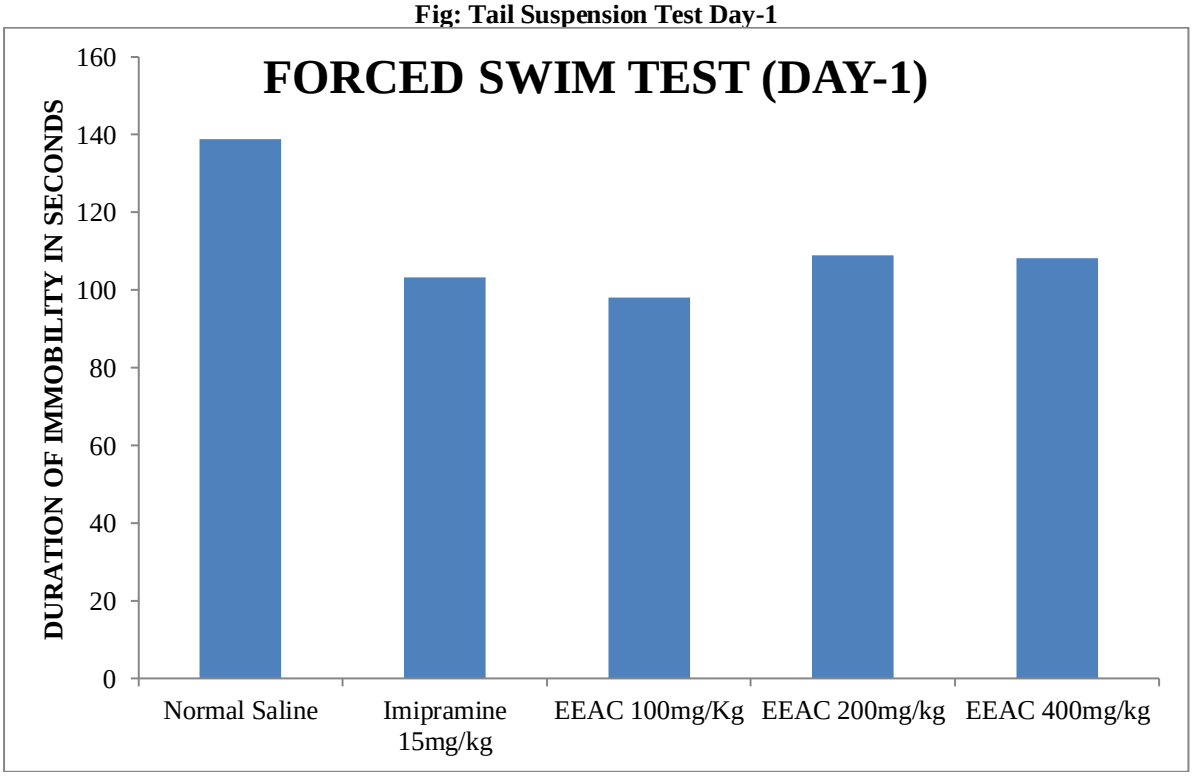

Fig: Forced Swim Test Day-1

Table 2

Day 10	Tail Suspension Test	Forced Swim Test
Normal Saline	222.24(±05.36)	147(±2.14)
Imipramine 15mg/kg	148.31(±15.39)*	94.26(±0.16)*
EEAC 100mg/Kg	93.05(±3.142)*	69.816(±4.10)*
EEAC 200mg/kg	206.24(±10.12)#	93.415(±5.10)*
EEAC 400mg/kg	101(±10.14)*	88.21(±03.34)*

Immobility time shown in seconds as mean (±SEM), *denotes statistically significant value, #denotes statistically not significant value.

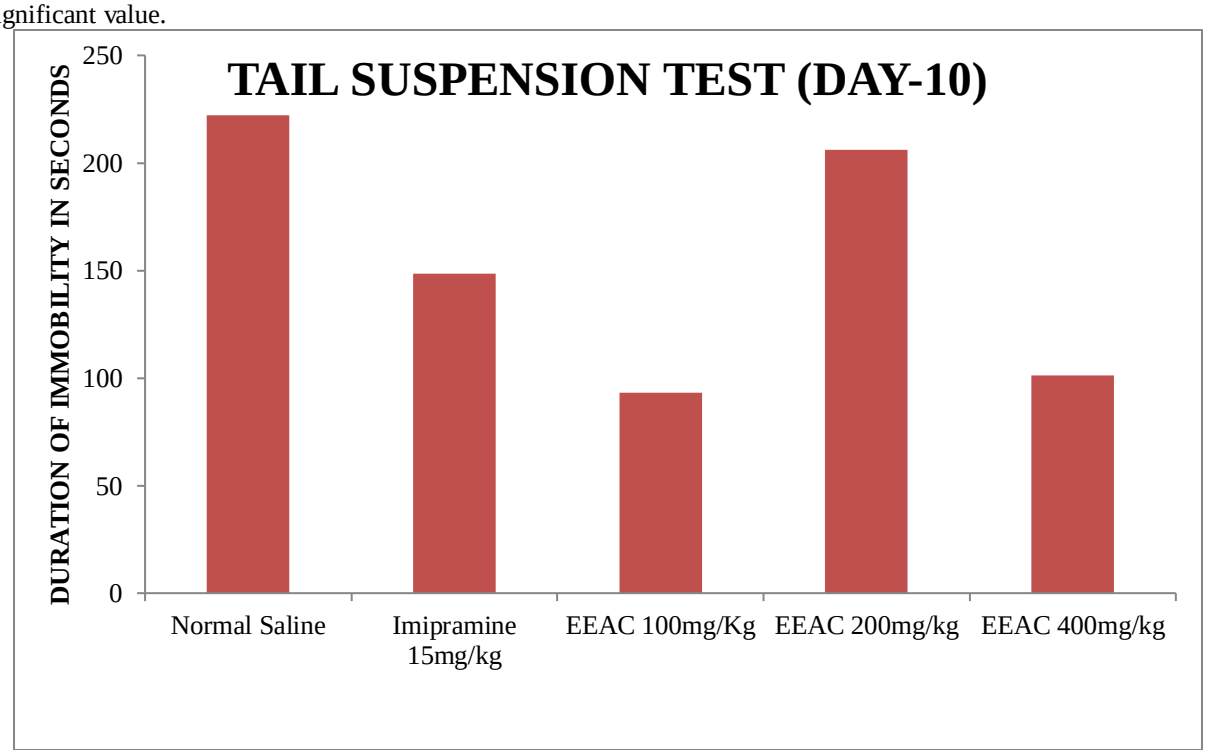

Fig: Tail Suspension Test Day-10

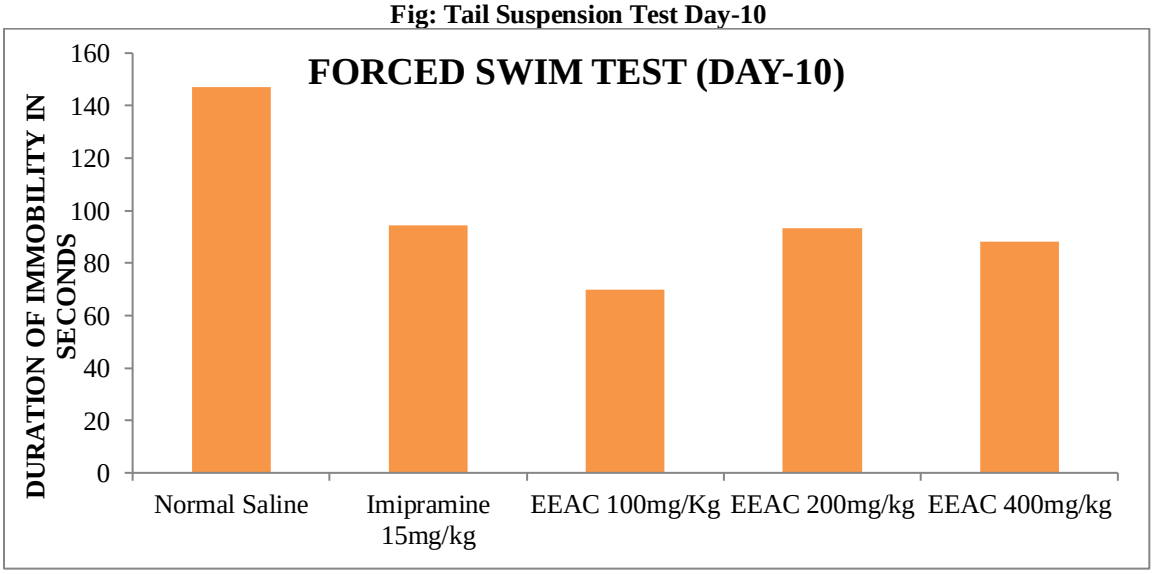

Fig: Forced Swim Test Day-10

CONCLUSION:

In the present study plant parts of *Allium cepa* have been be evaluated for antidepressant activity. As literature shows that traditionally this plant is being use in the treatment of depression. The plants materials *Allium cepa* used for the present studies were commercially procured from local market. Albino rats were used for the antidepressant activity.

The present study provides the evidence indicating that ethanolic extract of *Allium cepa* showed significant antidepressant activity in TST and FST models of depression.

Phytochemical analysis showed the presence of Flavonoids and phenolic compounds have been reported to have multiple biological effects such as Central nervous system disorders.

Similarly, the results of this study suggest that the leaf extract exhibited significant antidepressant activity with a strong psychomotor stimulation. The leaf extract was reported to contain chemical constituents such as Carbohydrates, Tannins, Flavonoid, Saponins, Phenols, Steroids, Alkaloids and Glycosides.

The results obtained in this study suggest that ethanolic Extract of *Allium cepa* has anti-depressant activity and can be considered for use in therapy of depression after further testing.

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