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Pharmacological Evaluation of Plant Derived Compound for Antidepressant Activity

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ABSTRACT

The present study was undertaken with the aim & objectives of exploring the antidepressant effect of ethanolic *Semecarpus anacardium Linn* extract (ESAE) of fruits. The phytochemical analysis and confirmatory test of ESAE showing presence of biflavonoids in extract. Using *in-vitro* models such as DPPH assay, extracted compound showed significant dose dependent reduction in oxidant level indicates the compound posses anti-oxidant activity. The anti-depressant activity of *Semecarpus anacardium Linn (SA)* was studied using 3 models, Behavioral despair test (FST), Haloperidol induced model and Reserpine induced model. The ESAE was administered orally to mice at dose 200mg/kg and 400mg/kg. At that dose extract significantly reduced the immobility times of mice in both FST and reserpine induced TST model, and significantly increase the locomotor activity of mice in a haloperidol induced model. It is compared with imipramine (15mg/kg) and fluoxetine (5mg/kg) which was used as standard drug. Reserpine -mediated depletion of monoamine neurotransmitters in the synapses and haloperidol produces blockade of dopamine receptors which leads to decrease dopamine level; reproduce a condition similar to depression in human. The result of *in-vivo* model suggested that ESAE reverse the action of reserpine & haloperidol; may exert its antidepressant effect through a mechanism related to the neurotransmitter system.

INTRODUCTION

Depression is very complex neuropsychiatric disorder, affects the lifestyle and daily life of a person and it has been classified and treated in a variety of ways. This complex mood disorder has many subtypes, multiple causes, multiple symptoms ranging from mild to severe with or without psychotic features and interactions with other psychiatric disorders.[1] Globally, depression is the top cause of illness or disorder among young and middle-aged populations. It was estimated 322 million people are affected by depression. As per NMHS (2015-16) in India, one in 20 (5.25%) people over 18 years of age have ever suffered (at least once in their lifetime) from depression amounting to a total of over 45 million persons with depression.[2] In depression some studies have showed that females are at greater risk than males.[3] Various evidence have said that depression is caused by a genetic, biochemical, environmental and psychological factors rather than a single cause.[4] From the research several theories have been investigated behind the pathophysiology of depression, including imbalanced of neurotransmitter, dysregulated GABA and glutamate signaling, neurogenesis, neuroplasticity, altered HPA axis activity. Whereas the latter, frequently referred to as the 'Monoamine Hypothesis', has been the most extensively investigated from 1960, it is most common hypothesis.[5] Although this hypothesis in its simple form is insufficient as an explanation of depression, pharmacological manipulation of monoamine transmission remains the most successful therapeutic approach. treatment with clinically available antidepressants drug such as norepinephrine reuptake inhibitors like amitriptyline, selective serotonin reuptake inhibitors like fluoxetine, atypical antidepressants like trazodone, monoamine oxidase inhibitors like selegiline etc., are effective only in a certain portion of the patients. They often associated with more side effects or adverse effects such as nausea, vomiting, gastrointestinal discomfort, sexual dysfunction and weight loss, etc. Occasionally, some patients may experience excitement, anxiety, insomnia, restlessness or seizure, blurred vision, difficulty passing urine, and orthostatic hypotension, hypertensive crisis, insomnia, restlessness and these are collectively affected cognition and behavior.[6] To obtain better therapeutic benefits and minor adverse reactions, search for alternative antidepressant from natural source i.e., herbal remedies, used traditionally, now consider as safe profile.

Medicinal plants play an important role in the development of potent therapeutic agents. Today estimate that about 80 % of people in developing countries still relays on traditional medicine based largely on species of plants and animals for their primary health care. Herbal

medicines are currently in demand and their popularity is increasing day by day. Plants are highly enriched with various bioactive components which are highly beneficial for maintaining good health.[7] One such plant which having various medicinal properties is *Semecarpus anacardium Linn*, a popular medicinal plant extensively used in ayurveda system of medicine belong to family anacadiaceae; commonly known as marking nut, *Bhallataka bhilawa*, biba. In standard reference book of Ayurveda (Materia Medica) it has been mentioned that *Semecarpus anacardium Linn*. possess stimulant and nervine activity.[8] Preliminary phytochemical analysis of whole fruit reveals the presence of tannins, steroids, phenolic compounds, flavonoids, oils and fat. It also contains vitamins such as: nicotinic acid, thiamine and riboflavin, amino acids like histidine, isoleucine, leucine, lysine, methionene, phenylalanine, arginine, threonine, tryptophan and valine. Also contain tetrahydro amentoflavone, biflavonoids like: biflavone-A, C, A1, A2, jeediflavanone, semecarpuflavanone, galluflavanone and anacardoflavanone; Phenolic compounds such as: bhilawanols, semecarpol & anacardol. [9] Bhallataka has potent efficacy to cure haemorrhoid. It is also cures all types of skin diseases, -Bhallataka should given with Guda (jaggery) to prevent fever. It cures cystic growth, anaemia, asthama, irritable bowel syndrome, cough. SA also possess anti-inflammatory, anti-arthritic effect, anticarcinogenic activity, hypoglycaemic activity cardioprotective activity, anthelmintic & antimicrobial activity.[10]

From the literature, it was found that, So far its antidepressant activity has not been explored pre-clinically. As aim of this study is to evaluate potential of antidepressant activity of plant *Semecarpus anacardium Linn.* The present study was designed in order to explore the fruits of *Semecarpus anacardium Linn.* with potential antidepressant activity using *in-vitro* and *in-vivo* model of depression. The main objective of present study is -a) To identify the compound (biflavonoids) from *Semecarpus anacardium Linn* fruit (nuts) and to obtain the extract of plant containing biflavonoids. b) To perform phytochemical analysis of extract. c) To perform evaluation of antioxidant activity of ESA extract. d) To perform the acute toxicity study for ESA extract. e) To evaluate the biflavonoid rich extract of *Semecarpus anacardium Linn* for antidepressant activity using various *in-vivo* models.

MATERIALS AND METHODS:

Drugs and Chemicals:

Semecarpus anacardium Linn friut (nuts) powder (Ekvira Ayurvedic shop, kalwa). Ethanol, Methanol & DPPH were purchased from Molychem. n- Hexane (Merk). Haloperidol injection IP (5mg/1ml) (Mfg by RPG Life Science ltd), Reserpine Puriss API (LOBA CHEME PVT.LTD, Imipramine hydrochloride API (SD Fine chem ltd), Fluoxetine Capsule IP (20mg) (Mfg by CADILA pharmaceuticals).

Animals:

The swiss albino mice (female) 18-22gm were purchased from Bombay veterinary college, Parel, Mumbai- 400012 and from National Institute of Bioscience, Pune. The animals were brought to animal house of Dr. L. H. Hiranandani College of Pharmacy, Ulhasnagar-03. These animals were acclimatized in animal house under standard husbandry conditions, i.e. room temperature of 24 ± 100C, relative humidity 45-55% and 12:12 hr. light/dark cycle. The animals had free access for food and water supplied *libitum* under strict hygienic condition. Animals were acclimatized for at least two weeks before behavioral experiments. The study protocol was approved by Institutional Animal Ethics Committee (IAEC) of the college and the experiments were carried out as per CPCSEA guidelines.

Collection, Authentication and extraction of plant:

The fruit (nuts) powder of *Semecarpus anacardium Linn* were collected from Ekvira Ayurvedic shop, kalwa (W), and powder were authenticated from former HOD botany of Khalsa College, Matunga, Dr. Harshad M. Pandit, PhD (Botany), Andheri west, Mumbai 400058. The fruit (nuts) powder was kept in petroleum ether for 30hrs. (for defatation of nuts powder). Next day, it was washed with fresh petroluem ether, washed powder (100gm) were dried and extracted with ethanol (400ml) in soxhlet apparatus. Then extract was concentrated in rotary evaporator & then liquid mass was washed with hexane to obtain semisolid mass and extract was stored in refrigerator for further use. [11, 12]

Physico-chemical & Preliminary Phytochemical analyasis: Physicochemical analysis of crude drug was performed, parameters such as total ash value, water soluble & acid insoluble ash value, loss on drying etc was performed.[13] Preliminary phytochemical test was carried out

to identify flavonoids and other compound present in extract.[14] The presence of biflavonoids was confirm by confirmatory test of bioflavonoids.[12]

***In-vitro* studies**

DPPH Assay: The free radical scavenging activity of the extract (Test drug) and ascorbic acid as standard were measured in terms of hydrogen donating or radical scavenging ability using the stable radical DPPH. Different concentrations were prepared for test (2µg/ml, 4µg/ml, 6µg/ml, 8µg/ml, 10µg/ml) and Standard (2µg/ml, 4µg/ml, 6µg/ml, 8µg/ml, 10µg/ml). Freshly DPPH solution was prepared in methanol. Reaction mixture was allowed to stand for 10 min. and absorbance was taken at 517nm. The percentage inhibition of DPPH free radical scavenging activity and IC50 was calculated.[15, 16]

Acute toxicity study:[17]

According to OECD guideline 423, acute toxicity study of test drug was performed on swiss albino mice (female) weighing around 25-30gm. Animals were fasted overnight and then test drug (ESA extract) was suspended in calculated volume of 0.5% CMC solution, administered orally with single dose of 2000mg/kg. Mice were observed individually after dosing at least once during the first 30minutes, periodically during the first 24hours, with special attention given the first 4 hours and daily there after upto 14 days. Parameter to be observed: Alertness, Grooming, Hyperactivity, Convulsion, Hypoactivity, Ataxia, body weight, other behavioral changes.

***In-Vivo* studies:**

To study the anti-depressant effect of the test drugs, three models namely, Behavioral despair test [Forced swim test (FST), Haloperidol induced model and Reserpine induced model were utilized.

Behavioral despair test (FST):

The behavioral despair test was developed in 1977 by Porsolt and was proposed as model to test the antidepressant activity. [18] Swiss albino mice (female) weighing around 25-30gm were used. The animals were selected randomly and divided into four groups as, Control (0.5% CMC solution), Standard (Imipramine–15mg/kg i.p.), Test 1 compound (200mg/kg p.o.) & Test 2 compound (400mg.kg p.o.) containing 6 animals each. All doses were administered to

animals for 7 days. In this test mice were forced to swim inside the vertical cylinder, first they were showed vigorous movement during initial 2 min. Then after that mice were remain immobile, duration of immobility was measured one hr after administration of test compound and standard compound Imipramine on 7th day. [19]

Haloperidol induced model:

The antidepressant effect of extract was assessed by using actophotometer. Swiss albino mice (weight 25-30g) used. The animals were randomly divided into five groups, Control (Normal saline), Disease control (Haloperidol-1mg/kg i.p), Standard (Fluoxetine-5mg/kg i.p), Test 1 compound (200mg/kg p.o) and Test 2 compound (400mg/kg p.o.) containing 6 animal each. Catalepsy was induced with haloperidol after 30 min. of respective drug administration, then after 60min. mice were observed in chamber for their locomotor activity by using actophotometer on every 4th, 8th & 14th day of drug treatment. [20, 21]

Reserpine induced model:

In this model reserpine induced immobility behavior of animals was measured by using tail suspension test and locomotor activity of mice by actophotometer. The tail suspension test (TST) was introduced by Steru (1985) to research the potential antidepressant activity of new drugs.[22] For this test the mice were suspended on the edge of a shelf 58 cm above a table top by adhesive tape placed approximately 1 cm from the tip of the tail. Mice were considered to be immobile when they hung passively and completely motionless. The duration of immobility was recorded for a period of 6 minutes. Overnight fasted swiss albino mice were randomly divided into four groups Control (distilled water), Disease control (Reserpine-2mg/kg i.p), Standard (Imipramine-15mg/kg i.p), Test 1 compound (200mg/kg p.o) and Test 2 compound (400mg/kg p.o.) containing 6 animal each. Vehicle, Standard & Test group was received their respective dose for 7 days, on 7th day animal were received reserpine. After 2.5h of reserpine injection test group & standard group were received their respective dose, then after 90min of test & after 60min of standard animal were subjected to tail suspension test for 6 min. and for locomotor activity test by using actophotometer.[23]

Statistical analysis

The results of antidepressant activity are expressed as MEAN± SEM from 6 animals in each group. Results were statistically analyzed using one–way ANOVA followed by Dunnett's

multiple comparison tests; all groups were compared with disease control group and $P<0.05$, $P<0.01$ was considered significant. GraphPad Prism was the software used for statistical analysis.

RESULTS

Physico-chemical & Preliminary Phytochemical analysis: As per phytochemical test ESA extract showed presence of alkaloids, carbohydrates, flavonoids, glycoside, phenol and proteins. Result obtained for physicochemical parameter and confirmatory test mentioned in table no. 1 and table no. 2.

Table No. 1 Physico-chemical parameter evaluation of crude drug SA

Total ash value	Acid insoluble ash value	Water soluble ash value	Loss on drying
14%	6%	1.5%	1%

Table No. 2 Confirmatory test for Bioflavonoids

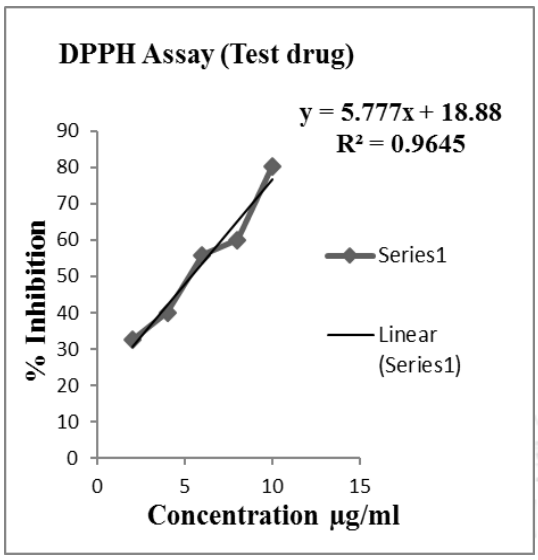
Test	Observation	Inference
Aq. NaOH + (Extract+ water) Filter	Readily soluble & formation of yellowish orange color	Bioflavonoids Present

***In-vitro* antioxidant activity DPPH Assay**

ESA extract showed free radical scavenging effect on DPPH radical in concentration dependent manner. Antioxidant activity of ESA extract (test drug) and standard drug ascorbic acid is shown by graph. The IC50 value of ESA extract was found to be 5.38µ/ml. The correlation coefficient (R^2) was calculated from graph and was found to be 0.9645. This was compared with ascorbic acid which was used as standard antioxidant having IC50 value 2.29µ/ml and the correlation coefficient (R^2) was calculated from graph and was found to be 0.9856.

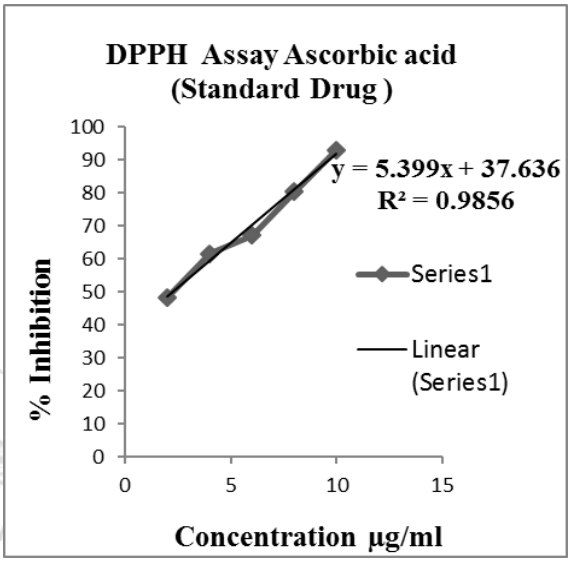
Acute toxicity study:

The test drug was found safe at 2000mg/kg bodyweight. There was no death of animals during or after 14 days. The parameter such as alertness was found to be normal in mice. Parameter such as grooming, hyperactivity, convulsion, hypoactivity and ataxia were found to be absent in mice. Autonomic (eye, salivation) parameter and body weight of mice were found to be normal in mice. $1/10^{th}$ as minimum dose and $1/5^{th}$ as maximum dose of test drug (ESA extract) used in acute toxicity testing was considered as therapeutic dose for experiment.



Graph 1

DPPH free radical scavenging activity of ESA extract (Test drug)



Graph 2

DPPH free radical scavenging activity of Ascorbic acid (Test drug)

Behavior despair test (forced swim test)

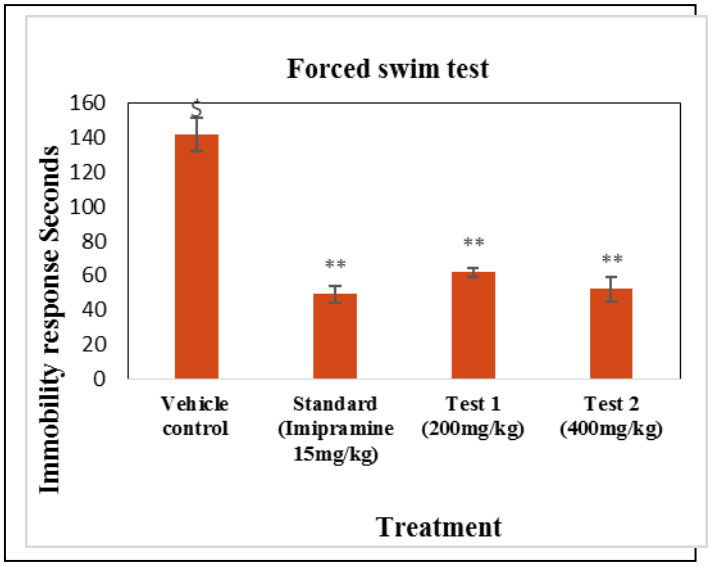
The change in duration of immobility is summarized as shown in table no. 4. Effect of ESA extract, standard drug and vehicle is shown by graph 3 in which duration of immobility presented against groups of animal. The ESA extract (Test drug) at the dose of 200mg/kg and 400mg/kg showed significant decrease in immobility period when compared with stress control group. Hence, in other words, the result suggested that the antidepressant effect of ESA extract (test drug).

Haloperidol induced model:

The change in count of locomotor activity of animals is summarized as shown in table no. 5. Effect of ESA extract, standard drug, disease control group and vehicle group is shown by graph 4 in which locomotor activity count presented against groups of animal. The disease control group showed significant decreasing locomotor activity; as compared with vehicle control group indicating cataleptic behavior. On other hand, standard drug group, test 1(200mg/kg) & test 2 400mg/kg) group significantly increase the locomotor activity of animals; as compared with disease control group. The reduction in locomotion by haloperidol significantly reversed by test drug (ESA extract) treated groups compared with the disease control group indicating antidepressant effect.

Table No. 3 Observation table for immobility period second (FST) in seconds

Groups	Treatment	Duration of immobility (sec)
Stress control	Vehicle (p.o.)	141.66 ± 9.61$
Standard (Imipramine)	15mg/kg (i.p.)	49.16 ± 5.08**
Test 1	200mg/kg (p.o)	62 ± 2.64 **
Test 2	400mg/kg (p.o)	52.16 ± 6.95**



Graph 3 Effect of ESA extract on Immobile In response in FST

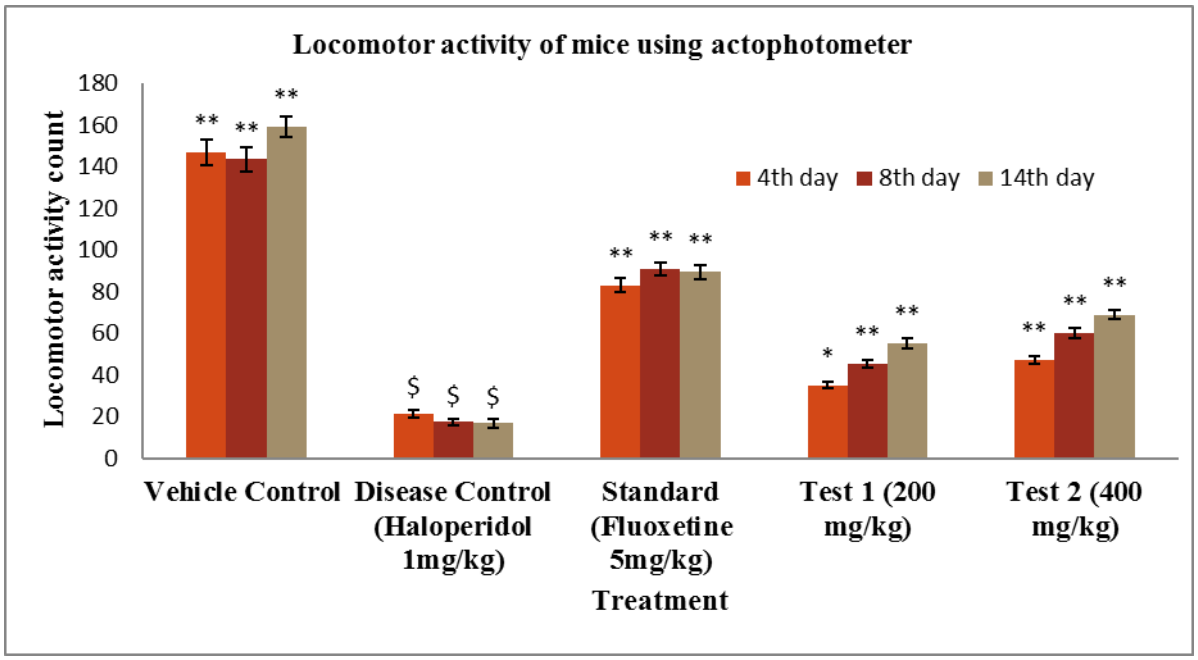
All value are expressed in Mean ± SEM for 6 animal in each group.(**P<0.01)

Table No. 4: Observation table for locomotor activity of animals

Groups (Treatment)	Locomotor activity count (Mean± SEM)		
	4th day	8th day	14th day
Vehicle control (Normal saline p.o)	146.65±6.31	143.33±6.00	159±4.69
Disease control (Reserpine 2mg/kg i.p)	21.33±1.87$	17.33±1.74$	16.66±1.94$
Standard (Imipramine 15mg/kg i.p)	83±3.24**	91±3.08**	89.33±3.25**
Test group 1 (200mg/kg p.o)	35±1.50*	45.16±1.92**	55.16±2.50**
Test group 2 (400mg/kg p.o)	47±1.71**	59.83±2.3**	68.83±2.08**

All values are expressed in Mean ± SEM for 6 animals in each group. (*p≤0.05, **P<0.01)

Effect of ESA extract on Locomotor activity of mice using actophotometer



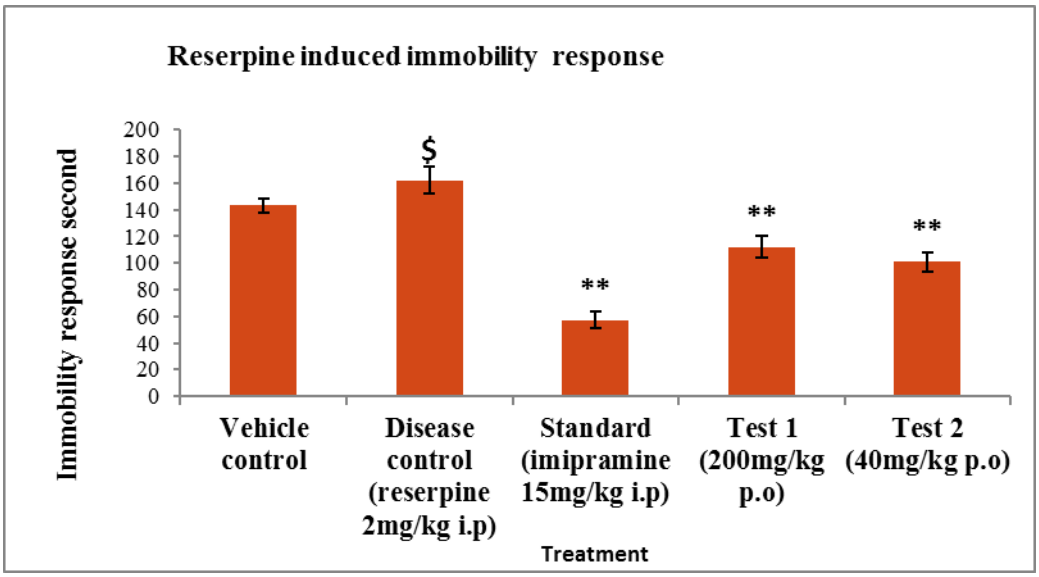
Graph 4

All values are expressed in Mean ± SEM for 6 animals in each group. (*p≤0.05, **P<0.01)

Table No. 5: Observation table for reserpine induced Immobility period (Sec) & locomotor activity count

Groups (Treatment)	Immobility response in sec.(7th day) Mean ±SEM	Locomotor activity count (7th day) Mean ± SEM
Vehicle control (Distilled water)	143.83±5.016	168.33±4.66
(Disease control) Reserpine (2mg/kg i.p)	162±9.856$	28.16±2.35$
Standard (Imipramine15mg/kg i.p)	57.16±6.400**	95.33±2.51**
Test group 1 (200mg/kg p.o)	112.16±8.432**	50.16±4.25**
Test group 2 (400mg/kg p.o)	100.83±7.134**	76.66±4.99**

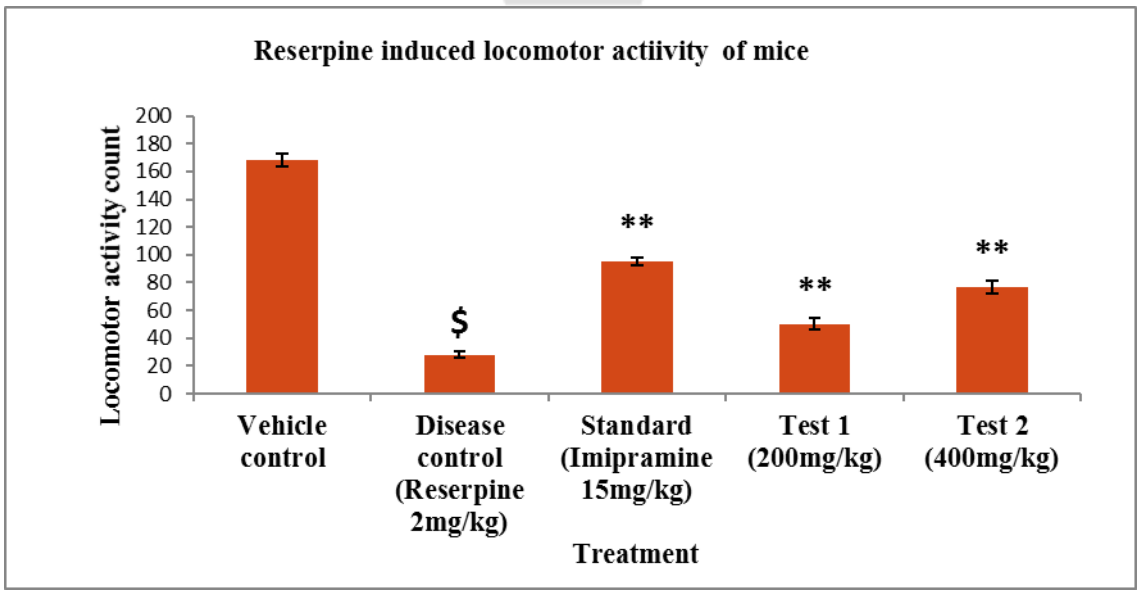
Effect of ESA extract on reserpine induced immobility time



Graph 5

Values are expressed in Mean ± SEM for 6 animals in each group. (*p≤0.05, **P<0.01)

Effect of ESA extract on reserpine induced locomotor activity of mice



Graph 6

Values are expressed in Mean ± SEM for 6 animals in each group. (*p≤0.05, **P<0.01)

Animals treated with reserpine were found to be showed increase in immobility time and decrease in locomotor activity. In this test, ESAE treated group significantly decrease duration of immobility and significantly increase locomotor activity of animals at dose of 200mg/kg and 400mg/kg; compared with reserpine treated animals.

DISCUSSION

Depression is one of the most common diseases, which can affect person's behavior, feeling & sense of well-being. Hence it is important to manage these problems and find out some alternative antidepressant. Though several synthetic antidepressants are available, all are associated with side effects and the drug interactions in their clinical applications. Because of these, there is need to find out alternative curative approaches that improve depression.

The present study was undertaken with the aim & objectives of exploring the antidepressant effect of fruits of *Semecarpus anacardium Linn* extract by using *in-vitro* and *in-vivo* models. The fruit powder of SA was subjected to ethanolic extraction by soxhlet extraction apparatus. Fruit extract showed presence of flavonoid in preliminary phytochemical study. Further presence of biflavonoids was confirmed by performing confirmatory tests. Biflavonoids are dimer of flavones and flavanone. Several experimental and clinical studies have shown that biflavonoids has been proved to be antidepressant. [25, 26]

The acute toxicity study indicate that no toxic reaction were observed & ESAE (Test drug) did not showed any toxic effects on administration of 2000 mg/kg(OECD 423) oral dose. The *in-vitro* antioxidant potential of ESAE was evaluated using DPPH free radical scavenging activity. DPPH radical scavenging test is based on the exchange of hydrogen atoms between the antioxidant and the stable DPPH free radical. DPPH is a stable free radical at room temperature which accepts an electron or hydrogen radical to form a stable diamagnetic molecule. DPPH radical is reduced to the corresponding hydrazine, a colour change of the solution from violet to yellow is observed and that is monitored spectrophotometrically. More reduction of DPPH radical is related to the high scavenging activity of the particular extract.[27] The reduction capability of DPPH radicals was determined by the decrease in its absorbance at 517 nm, which is induced by antioxidants. The results indicate that ESA extract showed significant free radical scavenging action against DPPH free radical by binding with it and there by showing reduction in absorbance in concentration dependent manner.

The FST concluded that the immobility time observed in the test is indicate a state of lowered mood or helplessness in animals; reproduce a condition similar to depression in humans.[28] Thus, this animal model widely used tool for preclinical screening of antidepressant agent. In this test, test drug (ESA extract) treated group at the dose 200mg/kg & 400mg/kg significantly decrease (**P<0.01) duration of immobility behavior of animals. These tests are quite sensitive and relatively specific to all major classes of antidepressant drugs including tricyclics, selective serotonin reuptake inhibitors. The imipramine belongs to the category of tricyclic antidepressant drugs was used as standard and inhibit the reuptake of NE and 5-HT into their respective neurons. Administration of imipramine at dose 15mg/kg also showed decrease in duration of immobility. Based on these findings it can be suggested that the ESA extract which was able to reduce immobility time in mice may exert its effect through a mechanism related to the neurotransmitter system and may also mediate its activity through the same mechanism as that of imipramine.

The locomotor activity of animals was evaluated in Haloperidol induced model. Haloperidol is neuroleptic drug, produces blockade of dopamine receptors which leads to decrease dopamine level and also produces oxidative stress which causes necrosis in brain cells. Oxidative stress further produces depression like behavior (Catalepsy) in mice.[29] Administration of haloperidol (1mg/kg) was found to be decrease locomotor activity of mice. ESAE at dose of 200mg/kg and 400mg/kg p.o. significantly increase (**P<0.01,*P<0.05) locomotor activity of mice as compared with haloperidol treated mice. Fluoxetine belongs to category of SSRI was used as standard antidepressant at dose 5mg/kg also showed significant increase in locomotor activity. This finding suggested that ESAE show antidepressant effect may be by modulating dopaminergic or serotonergic pathway and antagonizing effects of haloperidol.

Reserpine-mediated depletion of monoamine neurotransmitters in the synapses is often cited as evidence to the theory that depletion of the monoamine neurotransmitters in brain to produced depression like syndrome in humans & animals.[29, 30] Animals treated with reserpine was found to be showed increase in immobility time and decrease in locomotor activity. ESAE treated group significantly decrease (**P<0.01) duration of immobility and significantly increase locomotor activity of animals at dose of 200mg/kg and 400mg/kg; compared with reserpine treated animals. Administration of imipramine at dose 15mg/kg also showed significantly decrease in duration of immobility and increase in locomotor activity of

animals. As, imipramine belongs to the category of tricyclic antidepressant drugs was used as standard and inhibit the reuptake of NE and 5-HT into their respective neurons. This result suggested that the ESA extract which was able to reduce immobility time and increase locomotor activity in mice may exert its effect through a mechanism related to the neurotransmitter system and may have same mechanism as that of imipramine and reversed the action of reserpine.

CONCLUSION

Depression is a medical condition with a complex biological pattern of etiology. The present study undertaken gave us a very good potential to explore the antioxidant and antidepressant activity of compound extracted from *Semecarpus anacardium Linn*. After extraction of the bioflavonoid compound were assessed for their potential antioxidant and antidepressant activity. It is concluded from the results & discussion that, using *in-vitro* models such as DPPH assay, extracted compound showed significant dose dependent reduction in oxidant level indicates the compound posses anti-oxidant activity. Further the *in-vivo* studies performed to confirm the antidepressant activity of extracted compound. The results of *in-vivo* studies, suggested that the action of ESAE as an antidepressant may be due to mechanisms such as inhibition of reuptake of monoamine, reducing oxidative stress due to presence of biflavonoids in extract.

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