



Evaluation of Antidepressant and Anxiolytic Activity of *Solanum melongena* L. Fruits Aqueous Extract via Monoaminergic and GABAergic Pathway

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Authors' contributions

This work was carried out in collaboration among all authors. Authors TJ, NT and MK participated in the conception of the study and the research question. Authors NT and TJ performs review work and experimental designing. Authors OAA, AMA, WMAS and SMA defined and discussed the outcomes of interest. Authors TJ and NT performed the extraction and preliminary drafting of the results. Authors OAA, AMA and MK carried out the cost estimates. Authors TJ, NT, MK, OAA, AMA, WMAS and SMA reviewed the results and delineated. All authors read and approved the final manuscript.

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ABSTRACT

The current study proposed the in vivo antidepressant and anxiolytic activities of the aqueous extract from *Solanum melongena* fruits (AESM) in mice. The mice were administered with AESM 100 and 200 mg/kg, p.o. for anxiolytic (elevated plus maze test (EPMT) and locomotor action), and antidepressant (forced swimming test (FST) and tail suspension test (TST) activities. The possible

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mechanism of action of *Solanum melongena* fruits was also analyzed by measuring the level of serotonin (5HT), monoamine oxidase enzyme (MAO-A) and GABA activity in the blood of experimental animals. When mice were treated for seven days with 100 (**P < 0.01) and 200 mg / kg, AESM p.o. and 2 mg / kg, diazepam p.o. (**P < 0.001) showed significant increases in the average time expended and the number of entries into the open arms of the EPMT, as compared to control group in dose dependent fashion. However, when mice were treated with standard Imipramine (10 mg/kg) (**P < 0.001), AESM 100 mg/kg (**P < 0.01) and 200 mg/kg (*P < 0.05) after day 7, there was significant reduction in locomotor activity in both TST and FST in dose dependent fashion. Monoamine oxidase - A level in the entire brain of mice were significantly reduced when pretreated with AESM 100 and 200 mg/kg, p.o. for 7 days as compared to control group in dose dependent fashion. The mechanisms of action of antidepressant effect of *Solanum melongena* fruits extract act by increasing serotonin and also GABA. Moreover, the extract also decreased the MAO-A enzyme in the experimental animals. These results demonstrated that both of these doses. Of aqueous extract from *Solanum melongena* fruits possess potential antidepressant activities in dose dependent fashion.

Keywords: *Solanum melongena*; EPMT; locomotor activity; TST; FST; diazepam.

ABBREVIATIONS

AESM: aqueous extract from *Solanum melongena* fruits; **EPMT:** elevated plus maze test; **FST:** forced swimming test; **TST:** tail suspension test; **MAO-A:** monoamine oxidase A; **GABA:** gamma amino butyric acid; **5-HT:** serotonin; **p.o.:** per oral; **i.p.:** intraperitoneally; **C:** degree celsius; **g:** gram; **%:** percentage; **L:** litre; **n:** number; **P:** probability; **b.w.:** body weight; **M:** molarity.

1. INTRODUCTION

Monoamine oxidase enzyme (MAO) plays a vital role in the catabolism of monoamines in the central nervous system. Many MAOI is available now a days to treat various types of ailments like depression and anxiety. Worldwide approximately 450 million people are affected from behavioral or mental disorders, which contribute 12.3% of the burden of disease globally [1]. It is expected that this percentage will reach 15% by 2020 [2]. Among the many mental illnesses and behavioral disorders, anxiety and depression are the two major psychological disorders [3]. Depression is a mood disorder occur due to deficiency of amines in brain. When a person suffered from depression, it needs emergency treatment because the major drawback of depression is suicidal tendency. Because of this it increases mortality rate in patients suffering from depression. Anxiety is also a serious condition that involves extreme fear or worry. Anxiety does not go away and can become worse with time. Several conventional anxiolytic and antidepressant drugs such as selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), benzodiazepines (BZDs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and noradrenergic and specific

serotonergic drugs are used extensively in clinical practice to cure these disorders. Though, treatment by the above-mentioned drugs can also bring detrimental adverse effects viz. cardiac toxicity, weight gain, sexual dysfunction and drug-drug interactions [4-6]. Therefore, it is urgently required to develop some novel advantageous anxiolytic and antidepressant therapies with fewer harmful effects.

In addition, we found the changes in biogenic amine levels such as serotonin, monoamine oxidase A (MAO-A), gamma aminobutyric acid (GABA) and may anticipate the antidepressant properties of *Solanum melongena* L. fruits aqueous extract in rat blood.

During last few years, many traditional medicinal plants such as *Camellia euphlebica* [7], *Valeriana officinalis* L. [8], *Kaempferia parviflora* [9], *Salvia elegans* [10], *Aloysia polystachya* [11], *Melissa officinalis* [12] and *Palisota hirsuta* [13] have been practiced successfully, to prevent or treat anxiety and depression.

Solanum melongena L. (Egg plant) is extensively cultured and consumed globally. It is categorized as one of the top 10 vegetables having capacity of scavenging oxygen free radicals (RO⁻) [14]. The purple variety (either dark or light) is the most common and easily available. However, a

green variety of this plant is commonly cultivated and eaten in the peninsular India. The peel of the purple variety is rich in antimicrobial substances like nasunin, delphinidin [15] along with chlorogenic acids [16]. These antimicrobial substances are also found in the pulp of the fruit in variable quantities. However, all these substances are beneficial against minor infections of gastro-intestinal tract. It is suspected that the green variety contains high amount of chlorogenic acids rather than the anthocyanins. Solanine is another potent glycoalkaloid present in the fruits of *Solanum melongena*, which has antimicrobial properties against many fungi and bacteria [17-18].

The *In vivo* influence of *Solanum melongena* L. fruits has not been discussed in previous studies. This research was therefore aimed to identifying out the antidepressant and anxiolytic activity of AESM (100 and 200 mg/kg, orally) in animal.

2. MATERIALS AND METHODS

2.1 Plant Materials

Fresh fruits of *Solanum melongena* L. were procured from a street market of the Lucknow and authenticated by NBRI, Lucknow (Authentication Reference Number: NBRI/CIF/262/2011).

2.2 Preparation of Extract

Solanum melongena L. fruits were shade-dried for 10 days and ground into a coarse powder. 1 kg of coarse powder were extracted by boiling in distilled water (3L) for 15 minutes. The heated extract was subjected for cooling at room temperature, then filtered and evaporated to dryness using rotatory evaporator. A brownish residue weighing 60.5 g was obtained and kept in air tight containers in a refrigerator for further investigations [19].

2.3 Drugs and Chemicals

Diazepam (Ranbaxy Laboratories Ltd. (Mumbai) and Imipramine (Pfizer Ltd., Mumbai) were used as the standard anxiolytic and anti depressant drugs respectively. Normal saline (0.9%) was used as vehicle.

2.4 Preliminary Phytochemical Screening

Solanum melongena L. fruits extract was subjected to various chemical tests for

determination of its phytochemical constituents according to standard publish protocols [20].

2.5 Animals

In current study male albino mice (25-30 g) were used and was obtained from the CDRI, Lucknow, India. All the animals were maintained in polypropylene cages (22.5 × 37.5 cm²) at room temperature (RT) (25 ± 3°C) and provided with natural day and night cycle with 50 ± 10% relative humidity (RH). All the animals had free access to standard pellets and water, *ad libitum*. This procedure was approved by CPCSEA and ethical norms were strictly followed [Hygia/M.Pharm/1087/07/CPCSEA].

2.6 Experimental Protocols

2.6.1 Acute toxicity study

The study for acute toxicity was carried out as per the guidelines of OECD 423. The animals were administered with AESM (2000 mg/kg b.w., *p.o.*) to various groups of albino mice. All the animals were kept under observation to record the signs of neurological toxicity, behavioral toxicity and mortality for fourteen days [21].

2.6.2 Antianxiety tests in mice

In the present study, animals were divided into four different groups (*n* = 6). Group I served as control and administered with the vehicle (normal saline 1 ml/100 g/b.w.) orally. Group II was administered intraperitoneally standard Diazepam (2 mg/kg/b.w.) whereas Group III and IV were administered with the aqueous extract of the plant under investigation at two doses (100 & 200 mg/kg/b.w. respectively) orally.

2.6.3 Elevated Plus Maze Test (EPMT)

The EPMT was carried out according to the method described by Kulkarni et al. [22]. The elevated plus maze apparatus consist of two open arms (16 × 5 cm) and two enclosed arms (16 × 5 × 12 cm) and placed at a height of 25 cm for mice. The animals are placed separately at the center of the EPM with their head facing toward one of the open arm. The number of open arms entries and the average time expended in the enclosed and open arms were observed for 5 minutes with a video camera. Increased activity in the open arms indicates less anxiety. Entrance into an arm was defined when mice placed all four feet into the arm. Cleaning of the maze was

done with 10% ethanol solution after each experiment.

2.6.4 Locomotor activity

Actophotometer was used to evaluate the locomotor activity in animals. Animal's movement interjects a beam of light dropping on a photocell, on which a count has been noted and shown digitally. Each animal was individually positioned in the actophotometer for a time period of 10 minutes and the basal activity score was recorded. Afterwards, the animals were divided into different groups ($n = 6$). AESM (100 and 200 mg/kg, *p.o.*), diazepam (2 mg/kg, *i.p.*) or normal saline was administered and after 30 minutes the mice were positioned again in the actophotometer for recording the activity score. A decreased locomotor activity represents a sedative effect whereas increased motility represents stimulant effect [23].

2.6.5 Antidepressant tests in mice

The animals were divided into four different groups ($n = 6$). Group I served as control group and administered with the vehicle (normal saline 1 ml/100 g/b.w.) orally. Group II was administered standard Imipramine (10 mg/kg/b.w.) orally whereas Group III and IV were administered with the aqueous extract of the plant under investigation at two doses (100 & 200 mg/kg/b.w. respectively) orally.

2.6.6 Forced Swimming Test (FST)

The forced swimming test was based on the method published by Porsolt et al. [24]. Animals were allowed to swim separately in a glass cylinder (22 cm height × 15 cm diameter) holding water up to a height of 11 cm at $24 \pm 1^\circ\text{C}$. All animals were allowed to swim for 6 mins. period and the entire period of immobility was documented during the last 4 minutes with a video camera on day 1 and 7. When the animals start floating in the water devoid of struggling and moving only to keep their heads above the water *i.e.* considered as immobile [24-25].

2.6.7 Tail Suspension Test (TST)

The TST was done by following method published by Steru et al. Animals were hung individually 5-6 cm from base of the floor by keeping an adhesive tape approx. 1.5 cm from the tip of the tail. The experiment was carried out in a dark place with nominal noise on first and

seventh day. When the animals were without any motion or motionless *i.e.* considered as immobile. The overall period of immobility was documented during the period of last 4 minutes of the 6 minutes. test and observed the score [26-27].

2.6.8 Blood collection

The animals were sacrificed and 10 ml of blood was withdrawal through orbital puncher from all the groups. The blood was kept in ethylene diamine tetra acetic acid (EDTA) coated tubes. The tubes were centrifuged for 25 minutes at 4°C (2000 rpm) and the plasma was separated. It was collected and dispensed into 1.5 ml of Eppendorf tubes and stored at -75°C until estimation. Quantification of Serotonin, MAO-A and GABA by kit enzyme-linked immunosorbent assay. The ELISA Kit has been bought from Sigma-Aldrich.

2.7 Statistical Analysis

Statistical analysis of the results was done with one-way ANOVA followed by Dunnett's test using GraphPad Prism 7 Software (GraphPad Software Inc., San Diego, USA). The data were expressed as the mean \pm standard error (S.E.M.). Differences among groups were found to be statistically significant at $*P < 0.05$.

3. RESULTS

3.1 Phytochemical Screening

Phytochemical screening of *Solanum melongena* L. fruits has indicated the occurrence of saponins, flavonoids, proteins and/or amino acids, alkaloids, tannins, unsaturated sterols and/or triterpenoids, glycosides or carbohydrates.

3.2 Acute Toxicity Study

Solanum melongena L. fruits extract was taken for acute toxicity study at doses of 2000 mg/kg, orally. There was no mortality found in any animals. Henceforth, 100 and 200 mg/kg, orally doses were selected for the antidepressant and anxiolytic activities.

3.3 Effects of AESM on Mice Behavior in the EPMT

The results indicated that mice treated with *Solanum melongena* L. fruits extract at doses of 100 (** $P < 0.01$) or 200 mg/kg, *p.o.* for 7 days

showed significant increase in the number of entries in open arms of the EPMT, as compared to control group in dose dependent fashion.

Treatment with *Solanum melongena* L. fruits extract at a dose of 100 mg/kg (Table 1) resulted in statistically significant changes in the time expended in the open arm, when compared to control group (***P* < 0.01), while the dose of 200 was not statistically significant. In addition, standard drug diazepam (2 mg/kg) significantly increased the entries into open arm and the average time expended in the open arms in the EPMT (****P* < 0.001).

3.4 Effects of AESM on Locomotor Activity

On the 1st day of treatment with *Solanum melongena* L. fruits extract at doses of 100 (***P* < 0.01) and 200 mg/kg (**P* < 0.05) and diazepam 2

mg/kg (****P* < 0.001) did not exhibit significant change (Table 2) in the integer of crossings and rearing as compared to the control group whereas on the 5th day of treatment with AESM at doses of 100 (***P* < 0.01) and 200 mg/kg (**P* < 0.05) and diazepam 2 mg/kg (****P* < 0.001) exhibited significant decrease in the number of crossings and rearing as compared to the control group.

3.5 Effects of AESM on the Duration of Immobility in the FST

Animals treated with two different doses of *Solanum melongena* L. fruits extract (100 and 200 mg/kg, orally) indicated reduced immobility times (Table 3), which was significant (***P* < 0.01 and **P* < 0.05 respectively) as compared to control. Likewise, animals administered with imipramine (10 mg/kg, orally), indicated a significant reduction in the time of immobility (****P* < 0.001).

Table 1. Effects of AESM and diazepam (2 mg/kg) on the behaviors in the elevated plus maze test in mice

Group	Treatment	Time spent in the open arm (s)	Time spent in the enclosed arm (s)	Entries into open arm(s)	Entries into enclosed arm (s)
I	Control	29.8 ± 6.5	242.5 ± 8.9	7.3 ± 2.26	13.7 ± 2
II	Diazepam (2 mg/kg)	106 ± 13***	16.8 ± 13.2***	19.5 ± 1.3***	8.7 ± 0.9***
III	AESM (100 mg/kg)	35.5 ± 9.1**	217.7 ± 8.5**	8.3 ± 1.9**	10.5 ± 1.3**
IV	AESM (200 mg/kg)	88.8 ± 8.97***	215.8 ± 9.6**	10.2 ± 1.3	9.7 ± 1.4

Values are expressed as mean ± S.E.M. (n = 6), compared with control. Data were analyzed by using One-way ANOVA followed by Dunnett's test. **P* < 0.05, ***P* < 0.01, ****P* < 0.001

Table 2. Effects of AESM and diazepam (2 mg/kg) on the spontaneous locomotor activity in the actophotometer in mice

Group	Treatment	Day 1	Day 5
I	Control	270.7800 ± 12.360	265.56 ± 12.390
II	Diazepam (2 mg/kg)	260.5600 ± 2.8000***	106.43 ± 2.9400***
III	AESM (100 mg/kg)	258.0800 ± 9.7800**	226.98 ± 7.4500**
IV	AESM (200 mg/kg)	250.9800 ± 8.8900***	240.12 ± 6.5200*

Values are expressed as mean ± S.E.M (n = 6), compared with control. Data were analyzed by using One-way ANOVA followed by Dunnett's test. **P* < 0.05, ***P* < 0.01, ****P* < 0.001

Table 3. Effects of AESM and Imipramine (10 mg/kg) on the period of immobility in the forced swimming test in mice

Group	Treatment	Day 1 (Immobility time in sec.)	Day 7 (Immobility time in sec.)
I	Control	169.00 ± 3.8100	172.00 ± 5.6100
II	Imipramine (10mg/kg)	146.00 ± 2.1700***	117.00 ± 3.5900***
III	AESM (100 mg/kg)	153.00 ± 4.9900**	147.00 ± 3.2600**
IV	AESM (200 mg/kg)	110.00 ± 3.5700**	108.00 ± 3.3100*

Values are expressed as mean ± S.E.M (n = 6), compared with control. Data were analyzed by using One-way ANOVA followed by Dunnett's test. **P* < 0.05, ***P* < 0.01, ****P* < 0.001

Table 4. Effects of AESM and Imipramine (10 mg/kg) on the period of immobility in the tail suspension test in mice

Group	Treatment	Day 1 (Immobility time in sec.)	Day 7 (Immobility time in sec.)
I	Control	269.00 ± 4.8100	272.00 ± 6.6100
II	Imipramine (10 mg/kg)	246.00 ± 3.1700**	217.00 ± 4.5900**
III	AESM (100 mg/kg)	253.00 ± 5.9900*	247.00 ± 4.2600*
IV	AESM (200 mg/kg)	210.00 ± 4.5700	208.00 ± 4.3100

Values are expressed as mean ± S.E.M (n = 6), compared with control. Data were analyzed by using One-way ANOVA followed by Dunnett's test. *P < 0.05, **P < 0.01, ***P < 0.001

Table 5. Effects of AESM on monoamine neurotransmitter level (g/ml) in FST

Group	Treatment	MAO-A	5-HT	GABA
I	Control	7.7 ± 0.31	575.1 ± 6.2	0.2 ± 0.01
II	Imipramine (10mg/kg)	4.0 ± 0.19***	862.9 ± 50.7***	0.5 ± 0.04
III	AESM (100 mg/kg)	5.9 ± 0.20*	850.8 ± 17.0*	0.4 ± 0.01
IV	AESM (200 mg/kg)	4.6 ± 0.38***	742.2 ± 22.49***	0.4 ± 0.04

Values are expressed as mean ± S.E.M. (n = 6), compared with control. Data were analyzed by using One-way ANOVA followed by Dunnett's test. *P < 0.05, **P < 0.01, ***P < 0.001

Table 6. Effects of AESM on monoamine neurotransmitter level (pg/ml) in TST

Group	Treatment	MAO-A	5-HT	GABA
I	Control	8.1 ± 0.31	5731 ± 6.2	0.2 ± 0.01
II	Imipramine (10mg/kg)	4.8 ± 0.19***	868.9 ± 50.7***	0.6 ± 0.04
III	AESM (100 mg/kg)	5.3 ± 0.19*	859.8 ± 17.0*	0.4 ± 0.02
IV	AESM (200 mg/kg)	4.2 ± 0.38***	746. ± 22.49***	0.3 ± 0.03

Values are expressed as mean ± S.E.M (n = 6), compared with control. Data were analyzed by using One-way ANOVA followed by Dunnett's test. *P < 0.05, **P < 0.01, ***P < 0.001

3.6 Effects of AESM on the Duration of Immobility in the TST

Animals treated with two different doses of *Solanum melongena* L. fruits extract 100 mg/kg, orally (*P < 0.05) and 200 mg/kg, orally indicated reduced immobility times (Table 4), which was significant as compared to control. Likewise, animals administered with imipramine (10 mg/kg, orally.), indicated a significant reduction in the time of immobility (**P < 0.01).

3.7 The Effect of *Solanum melongena* L. and Imipramine Mono Amino Oxidase A (MAO-A), Gamma Amino Butyric Acid (GABA) and Serotonin (5-HT)

The effect of *Solanum melongena* L. fruits extract (100 and 200 mg/kg, orally) and imipramine (10 mg/kg, orally) after treatments in the monoamine neurotransmitter levels in the rat in both TST and FST in Tables 4 and 5. Significant decrease in serotonin (5-HT), gamma amino butyric (GABA) levels in rats were observed after tail suspension

and Forced Swim test (5-HT; F = 34.56, P < 0.01). There is increase in monoamine oxidase A (MAO-A) (F = 14.55, P < 0.001) level in disease group as compared to treatment group.

The effect of *Solanum melongena* L. fruits extract (100 and 200 mg/kg, orally) produced a significant increase in 5-HT levels as compared to control. Imipramine significantly increase the 5-HT level in rat. Treatment with different doses of *Solanum melongena* L. (100 and 200 mg/kg, orally) decreases MAO-A levels as compared to control groups.

The maximum effect was observed with rats was treated 200mg /kg dose of *Solanum melongena* L extract.

As we know the forced swim stress increased MAO-A levels in the plasma whereas administration of the *Solanum melongena* L. (100 and 200 mg/kg, orally) significantly decreases the MAO-A level as compared to control. However, pretreatment with *Solanum melongena* L (200 mg/kg) showed more decrease in MAO-A

level as compared to 100 mg/kg dose (Tables 5 and 6).

4. DISCUSSION

The current study evaluated the pharmacological profile *i.e.* anxiolytic and antidepressant properties of aqueous extract from *Solanum melongena* L. fruits in mice. It was proven that the animals treated with different doses of the aqueous extract of *Solanum melongena* L. fruits was able to exhibit anxiolytic and antidepressant properties. Standard diazepam (2 mg/kg) and *Solanum melongena* L. fruits extract (100 mg/kg and 200 mg/kg) displayed significant reduction in locomotor action in mice treated after day 5. When the mice were subjected to the EPMT, total mice were found to be sensitive to the AESM in dose dependent fashion and displayed similar activities to that of mice treated with Diazepam. The plant extract showed anxiolytic effect in dose dependent fashion. Most important variables of the EPMT *i.e.* the time expended in the open arms and the number of open arm entries was found increased.

Concerning the remedial management of mental illnesses, the outcomes achieved in the current study was found to be significant because not only anxiolytic activity was witnessed; antidepressant activity was also revealed. Our study outcomes revealed that the administration of AESM showed decreased immobility time in mice subjected to FST and TST in dose dependent fashion. Behavioral effects were found to be similar as that of other conventionally used antidepressant drugs like imipramine [28-29].

MAO-A level significantly reduced after treatment with *Solanum melongena* L. fruits extract in dose dependent manner. Serotonin level significantly increase in treatment group as compared to control.

The mechanism of action through which *Solanum melongena* exerts both the activities was not clear by performing this experimental test. However, decreased MAO-A and increase in serotonin (5-HT) level could be a possible reason of reported antidepressant effect. The effects here reported may be a result of one chemical substance, or different secondary metabolites of the plant.

5. CONCLUSION

All mice were found to be sensitive to the AESM in dose dependent fashion in EPMT for anxiolytic

activity. AESM displayed significant reduction in locomotor action in mice. AESM showed decreased immobility time in mice subjected to FST and TST in dose dependent fashion for antidepressant activity. MAO-A level significantly reduced after treatment with *Solanum melongena* L. fruits extract in dose dependent manner. The level of 5HT and GABA were significantly increased when its treated with *Solanum melongena* L. fruits extract. As a conclusion the data showed the efficacy of aqueous extract of fruits of *Solanum melongena* against anxiety and depression in mice. Overall, results justify and support the use of *Solanum melongena* as anxiolytic and antidepressant medicine.

CONSENT

It is not applicable.

ETHICAL APPROVAL

All the animals had free access to standard pellets and water, *ad libitum*. This procedure was approved by CPCSEA and ethical norms were strictly followed [Hygia/M.Pharm/1087/07/ CPCSEA].

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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