



## ANTIDEPRESSANT EFFECT OF SESAMOL IN CORTICOSTERONE INDUCED MAJOR DEPRESSION PARADIGM IN MICE: BEHAVIOURAL EVIDENCE.

### Pharmacology

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### ABSTRACT

**Rationale** Neuropsychiatric diseases are main cause of morbidity and mortality among human. Depression is one of the main cause of neuropsychiatric diseases. Existing pharmacological treatments has lots of sides effects and currently phytochemicals are vigorously explored, so in this context we explored sesamol for antidepressant effect in corticosterone induced major depression model in mice. **Method** In Our study, we assessed antidepressant activity of sesamol in C57BL/6 mice. Depression was induced in mice by subcutaneous administration of 40 mg/kg corticosterone for 21 days. Exploration of antidepressant activity was done by two behavioural tests namely forced swim test and tail suspension test. **Objective** To evaluate behavioural effect of sesamol on corticosterone induced major depression model with forced swim test and tail suspension test. **Method** In our study, sesamol was evaluated in C57BL/6 mice for antidepressant activity. Depression was induced by subcutaneous corticosterone administration for 21 days, the animals were subjected two behavioural tests, as forced swim test and tail suspension test. In both forced swim test and tail suspension test parameter assessed was time of immobility, that was considered as a measure of antidepressant activity. In both behavioural tests, decrease in time of immobility was indicative of antidepressant activity. **Result** In both behavioural test, forced swim test and tail suspension test, sesamol 20 mg/kg group, decrease in time of immobility was statistically significant ( $p < 0.05$ ) in post hoc comparison suggesting that sesamol exhibited antidepressant activity in corticosterone induced major depression model. **Conclusion** So to conclude, sesamol exhibited significant antidepressant activity in forced swim test as well as tail suspension test.

### KEYWORDS

Sesamol, C57BL/6, Corticosterone, antidepressant activity, time of immobility

### INTRODUCTION

Depression is a common mental disorder that affects people of all ages, genders, and socioeconomic backgrounds in India and around the world. Global prevalence of major depressive disorder. In World Mental Health Survey is range from 0.8% to 9.6%. By 2030, unipolar depression is expected to be the second leading contributor to the global disease burden. The burden of depression is exacerbated by its 'cause and effect' relationship with many noncommunicable diseases. Individuals, families, and society are affected significantly.<sup>1</sup>

In depressive disorders, the available strategies include tricyclic antidepressants (TCAs) like amitriptyline, amoxapine, desipramine; selective serotonin reuptake inhibitors (SSRIs) like fluoxetine, paroxetine, sertraline and are mainly used to treat depression. TCAs inhibit reuptake of serotonin (5-HT) and noradrenaline (NA) in neurons, also have direct effects on adrenergic, cholinergic and histaminergic receptors. These drugs on long term use cause adverse effects as dry mouth, weight gain, dizziness, blurring of vision while SSRIs that inhibit reuptake of 5-HT selectively are well tolerated drugs and have fewer side effects. Through the single class of drug, TCA is effective in most of the cases, it has been noted that complete resolution of symptoms occur only in 30% cases, so if addition of different class of drug is required, the adverse effects are increased. Selective serotonin noradrenaline reuptake inhibitors (SNRIs) is a class of antidepressant which selectively inhibit NA and 5-HT that do not produce the usual side effects of TCAs.<sup>2</sup>

An essential component of managing psychiatric illnesses is non-pharmacological therapy, which includes cognitive behavioural therapy, deep brain stimulation, electroconvulsive therapy, transcranial magnetic stimulation, vagal nerve stimulation, magnetic seizure therapy, physical activity, and dietary changes.<sup>3</sup>

According to our literature search, plant products are increasingly being investigated as extracts—ethanolic, methanolic, or hydroalcoholic—or developed as alternative herbal formulations. Therefore, the current situation sees a rise in natural goods or herbal medicines that have attracted significant attention and have resulted in many innovative approaches for treating various illnesses as well as newer drug discoveries and development<sup>4</sup>. So in this context we explored sesamol for its antidepressant activity.

### METHODS

The animal were used from Central Animal Facility of AIIMS Bhopal

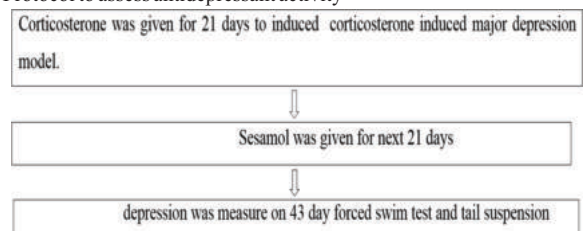
and all the procedure were conducted inside the same facility. The study was conducted after obtaining approval (IAEC-034) from the Institutional Animal Ethics Committee (IAEC), AIIMS Bhopal. In this study total 60 mice (C57BL/6 strain, 25-30 gm) were used. The animals were maintained under standard laboratory conditions with natural dark and light cycle. Animals were allowed free access to dry rodent diet and tap water ad libitum. All efforts were made to minimize animal suffering and to use only the number of animals to produce reliable scientific data. Drugs sesamol and corticosterone were purchased from authorized commercial supplier (Sigma Aldrich Pvt Ltd India). Drugs were freshly prepared before administration, and dosing done as per protocol. Normal saline or DMSO was used as vehicle. Doses of drugs were used according to previously done studies.

Mice were injected with corticosterone (40 mg/kg s.c.) for 21 days to induce model for major depression<sup>5</sup>. After that sesamol was given for 21 days<sup>6</sup>. after dissolving in appropriate vehicle. Groups are as following-

**Table.1**

Groups	Interventions	Number of mice
1.	Vehicle	6
2.	Corticosterone(40 mg/kg s.c)	6
3.	Sesamol (10mg/kg p.o)+corticosterone (40 mg/kg s.c)	6
4.	Sesamol (20 mg/kg p.o)+ corticosterone (40mg/kg s.c)	6
5.	Fluoxetine (20 mg/kg p.o)+corticosterone(40mg/kg s.c)	6

Protocol to assess antidepressant activity



We used two validate tests for measure of depression. Forced swim test and tail suspension test both are done in single setting.

**Forced Swim Test**

In forced swim test performed by previously described method by Porsolt et al (1978). Each mouse forced to swim in a transparent cylindrical tank (24 cm high X 13 cm in diameter) with water at 25±3 °C, and water depth adjusted according to mouse size, so that it cannot touch the bottom of the container with hind legs. Each mouse kept in water filled cylindrical tank and video recording done for 6 minutes. Each mouse behaviour was observed for last 4 minutes. Time of immobility was calculated in seconds. Mice considered as immobile when it was floating in an upright position, those movement necessary to maintain mice head above water was not score as immobile. The changes in the duration of immobility of separate groups of mice is recorded. Fresh water was used for each mouse. Following each swimming test session, the mice was towel-dried, then returned to their home cages and was able to access food and water for the remainder of the day<sup>7</sup>. Parameter assessed was time of immobility (in secs).

**Tail Suspension Test**

Tail suspension test was performed according the method described by Belozertseva et al (2007). Mice was individually suspended on by a paper adhesive tape, 65 cm above the tabletop. The tape was placed approximately 1 cm from the tip of the tail. Mice was allowed to hang for 6 minutes and the duration of immobility was recorded. Mice was considered immobile only when hanging passively and completely motionless<sup>8</sup>. Parameter assessed was time of immobility (in secs).

**RESULTS**

The quantitative and continuous data obtained from the all study groups was analysed using statistical package, SPSS. Data was presented as mean ± SD. Analysis of variance (ANOVA) was used to compare outcomes in intergroup data and control groups. Post-hoc analysis of study was done by using 2 tailed Dunnet test. Probability value less than 0.05 (p<0.05) taking 95% Confidence Interval (CI) was considered for testing statistically significance.

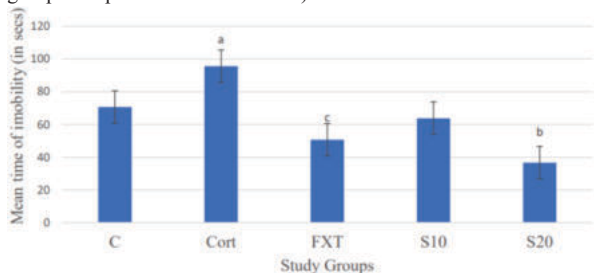
Depression was explored in forced swim test and tail suspension test. All group was compare with control group. Time of immobility was tested for different groups.

In forced swim test mean time of immobility were compared with control group. There was significant decrease in mean time of immobility in sesamol 20mg/kg group and fluoxetine group as compare to control group and there was significant increase in time of immobility in corticosterone group.

**Table.2 Mean difference in time of immobility ( in secs) among different study group in Forced swim test**

Study groups	Treatment	Mean±SD( time of immobility)	p-value*
Control	DMSO	70.67±3.8	
Corticosterone	Corticosterone(40mg/kg,s.c.)	95.67±8.23	0.001*
Sesamol 10 mg/kg	Sesamol(10mg/kg, p.o.)+ corticosterone(40mg/kg,s.c)	63.83±13.33	0.603
Sesamol 20 mg/kg	Sesamol(20mg/kg,p.o.)+ corticosterone (40mg/kg,s.c)	36.67±8.09	0.001**
Fluoxetine 20mg/kg	Fluoxetine (20mg/kg,p.o) +corticosterone (40mg/kg,s.c)	50.67±13.85	0.008**

p\* value-one way ANOVA followed by 2 tailed Dunnet's test (all groups compared to control vehicle).



**Figure.1** Bar diagram showing time of immobility (in secs) among different study groups in forced swim test

\*Mean time of immobility significantly increased in corticosterone group.  
 \*\* Mean time of immobility significantly decreased in sesamol 20mg/kg group.

\*\*\*Mean time of immobility significantly decreased in fluoxetine group.

All value are mean (N=6) <sup>a</sup>p<0.05, <sup>b</sup>p<0.05, <sup>c</sup>p <0.05 (one way ANOVA followed by Dunnet's 2 tailed test) C= control, FXT= fluoxetine, S10=sesamol 10mg/kg, S=sesamol 20 mg/kg, Cort=corticosterone group.

In tail suspension test mean time of immobility were compared with control group. There was significant decrease in time of immobility in sesamol 20 mg/kg group as compare to control group and there was significant increase in time of immobility in corticosterone group.

**Table.3 Mean difference in time of immobility (in secs) among different study groups in tail suspension test**

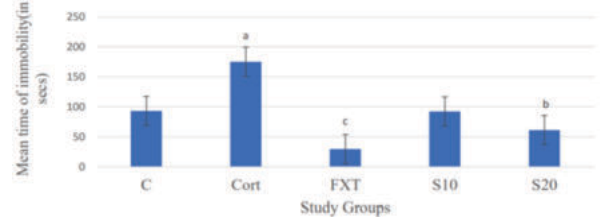
Study groups	Treatment	Mean ± SD (time of immobility )	p*-value
Control	DMSO	93.17 ± 26.50	-
Corticosterone	Corticosterone (40mg/kg,s.c)	175.00±32.56	0.001*
Sesamol 10 mg/kg	Sesamol(10mg/kg, p.o)+ corticosterone(40mg/kg, s.c)	92.33±9.3	1.00
Sesamol 20mg/kg	Sesamol(20mg/kg,p.o)+ corticosterone(40mg/kg,s.c)	61.33±8.9	0.045**
Fluoxetine	Fluoxetine(20mg/kg,p.o)+corticosterone (40mg/kg,s.c)	29.67±15.01	0.001***

p\* p-value-one way ANOVA followed by 2 tailed Dunnet's test (all groups compared to control vehicle).

\*Mean time of immobility significantly increased in corticosterone group.

\*\*Mean time of immobility significantly decreased in sesamol 20mg/kg group.

\*\*\*Mean time of immobility significantly decreased in fluoxetine group.



**Figure. 2** Bar diagram showing time of immobility ( in secs) among different study groups

All value are mean (N=6) <sup>a</sup>p<0.05, <sup>b</sup>p<0.05, <sup>c</sup>p <0.05 (one way ANOVA followed by Dunnet's 2 tailed test) C= control, FXT= fluoxetine, S10=sesamol 10mg/kg, S=sesamol 20 mg/kg, Cort=corticosterone group.

**DISCUSSION**

In our study we also explored antidepressant activity of sesamol in doses of 10 mg/kg and 20 mg/kg in corticosterone induced major depression model, and then animals were subjected to forced swim test and tail suspension behavioural tests. Decreased in time of immobility is indicative of antidepressant activity in forced swim test and tail suspension test. Results of our study suggested that there was significant decrease in time of immobility in between groups. In post hoc comparison sesamol 20 mg/kg group showed to significant reduction in time of immobility in comparison to control group in forced swim test and this reduction in time of immobility was comparable with fluoxetine group. Finding from Tail suspension test also supports these findings. In Unpredictable chronic mild stress(UCMS) model induced in my in study by Kumar et al.(2011), animals were subjected to several stress paradigms in order to generate depressive-like behaviour for 21 days. Results from this study also showed that chronic sesamol therapy considerably reduced the unpredictable behavioural (increased immobility period, lower sucrose preference) and biochemical (increased lipid peroxidation and nitrite levels) effects of chronic stress, indicative of antidepressant-like effects, specifically by regulating dopamine levels, oxidative-nitrosative stress and inflammation in the central nervous system. Finding from this previously done study also supports our finding for antidepressant activity of sesamol, but we have explored with different model<sup>9</sup>.

**CONCLUSION**

We found significant antidepressant activity of sesamol in a dose of 20mg/kg in forced swim test and tail suspension test, assessed by decreased in time of immobility.

**Future Scope**

Due to the negative side effects of current conventional medications on a variety of diseases, there is a constant rise in demand for nutraceutical compounds. In our investigation, sesamol was proven to have an antidepressant effect. Different formulations could be used to further investigate the antidepressant effects of sesamol.

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**Declaration**

- Funding source -none
- All rights reserve for the study, there is no conflict of interest.



**Figure.1** Mouse in forced swim test



**Figure.2** Mouse in tail suspension test

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