Potentiating Antidepressant Action of *Boswellia Serrata* in Acute Models of Depression: A Preclinical Study.

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**ABSTRACT**

**Objective:** To evaluate potentiating antidepressant activity of *Boswellia serrata* in Swiss albino mice by using experimental models of depression.

**Methodology:** In the present study, a total of 36 (n=36) Swiss albino male mice were used. They were divided into six groups containing six mice in each group. Control group received normal saline 10mg/kg, for standard group imipramine 10mg/kg and the test groups III, IV and V received *Boswellia serrata* in three different doses 50mg/kg, 100mg/kg, and 200mg/kg, whereas sixth group received *Boswellia serrata* 100mg/kg along with imipramine 10mg/kg per orally. After sixty minutes of drug administration, mice were evaluated for antidepressant activity using two behavioral animal models, Forced Swim Test (FST) and Tail Suspension Test (TST). Each mouse was observed for its immobility period in both the behavioral tests for six minutes.

**Results:** Results are presented as Mean ± SEM. ANOVA followed by Dunnet’s multiple comparison test were used to analyze the results. In FST, *Boswellia serrata* (100 mg/kg) when given with imipramine (10mg/kg) significantly reduced immobility period to 54±20.26 seconds (p<0.001) compared to control group (139.33±11.04 seconds). Similarly in TST, immobility period reduced to 160.33±13.93 seconds when compared to control group (245 ± 11.26 seconds) with p <0.05.

**Conclusion:** Present study has shown potentiating antidepressant activity of *Boswellia serrata* at the dose of 100mg/kg when combined with imipramine in acute models of depression. This drug combination can be considered for future studies in drug resistant depression.

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INTRODUCTION

Depression is a psychiatric disorder characterized by low mood, feelings of worthlessness, difficulty in concentrating and changes in sleep pattern. Normally most of us feel these symptoms at one or another time for short periods. Clinical depression is a mood disorder in which symptoms interfere with life style of an individual for a longer period of time. [1] Major Depressive Disorder (MDD) is one of the major cause of morbidity in worldwide. MDD is usually relapsing and remitting illness with 40% recurrence rate over a period of two years.[2,3] Childbirth, menopause, financial difficulties, job problems, relationship troubles, separation, bereavement and catastrophic injury can also precipitate depressed mood in normal individuals. [4,5] Recent data has shown that young adults are at higher risk of depression.[6] MDD is often undiagnosed and frequently undertreated. [7]

Monoamine hypothesis of depression is the most accepted theory for depression. Functional deficiency of nor-epinephrine, dopamine and serotonin in the brain is the important biochemical finding in depressive patients. [8-10] Most of the conventional antidepressants increase the levels of one or more of these neurotransmitters in the synaptic cleft between neurons in the brain. Some medications affect the monoamine receptors directly. Around two-thirds of the depressed patients respond to the currently available treatments but the magnitude of improvement is still disappointing. [11] Moreover, these drugs have unusual side effects by interacting with other receptors. Approximately 15% MDD patients are resistant to all known types of therapy.[12] It has been found that combining antidepressants with different mechanisms of action add independent additional benefits and provide synergistic actions to the patients.[13-16] Hence there is a need for better-tolerated, more efficacious antidepressant drug combinations.

*Boswellia serrata* is an Indian herb with a rich therapeutic health values mentioned in the ancient health system of Ayurveda. [17] Boswellia is mainly found in Western and Central part of India. It is tree of moderate height, which grows mainly in hilly areas. The therapeutic value of dried resinous gum (guggulu) from *Boswellia serrata*, has been known since long time. Gum resin possesses good anti-inflammatory, anti-arthritic and analgesic activity. [18] So the objective of the present study was to elucidate the possible potentiating antidepressant activity of *Boswellia serrata* in Swiss albino mice.

MATERIALS AND METHODS

Animals: Experiment was started after obtaining approval from Institutional Animal Ethical Committee (IAEC), Yenepoya University, Mangalore, Karnataka, India. Male Swiss albino mice of 3-4 months age, weighing 25-35 g. were procured for the study from the central animal house of the Department of Pharmacology, Yenepoya Medical College, Yenepoya University, Mangalore, Karnataka, India. The study was conducted according to standard CPCSEA guidelines.

Drugs: *Boswellia serrata* was obtained from Natural Remedies, Bangalore, Karnataka, India, whereas pure form of imipramine from Torrent Pharmaceutical Company, Ahmadabad, India. Normal saline (NS) was purchased from Yenepoya Medical College Pharmacy, Yenepoya University, Mangalore, Karnataka, India. On the basis of previous studies, the doses of *Boswellia serrata* were selected in the present study. [19]

EXPERIMENTAL METHODOLOGY

In the present study, a total of 36 (n=36) Swiss albino male mice were used. They were divided into six groups containing six mice in each group. Control group received normal saline 10mg/kg, for standard group imipramine 10mg/kg and the test groups III, IV and V received *Boswellia serrata* in three different doses 50/kg, 100mg/kg, and 200/kg, whereas sixth group received *Boswellia serrata* 100mg/kg along with imipramine 10mg/kg per orally. After sixty minutes of drug administration, mice were evaluated for antidepressant activity using Forced Swim Test (FST) and Tail Suspension Test (TST). Each mouse was observed for its immobility period in both the behavioral tests for six minutes. The experiment was conducted in the morning hours preferably between 8:00 A.M. to 2:00 P.M. in Post Graduate Experimental Laboratory, Department of Pharmacology, Yenepoya Medical College, Yenepoya University, Mangalore, Karnataka, India.
Forced Swim Test (FST): Forced Swim Test model for antidepressant evaluation was first developed by Porsolt et al. [20] The procedure followed in the present experiment was similar to the original method. The mice were placed in a plastic cylinder measuring 30 X 30 cm containing water to a depth of 20 cm at room temperature. Initially mice exhibit vigorous activity for two minutes, followed by typical immobile posture. The mouse was considered immobile when it remained floating in the water making minimal movements of its limbs necessary to keep its head just above the water level. Total duration of immobility was noted during next four minutes of total six minutes duration. The differences in the immobility period were recorded in all the group of animals after administering drugs. Each mouse was tested only once.

Tail Suspension Test (TST): Tail Suspension Test is an another behavioral model to evaluate antidepressant activity, which was first described by Steru et al. [21] In this model, mice were suspended upside down on a metal rod at a height of 55 cm from the ground level with the help of an adhesive tape placed approximately 1 cm from the tip of the tail. Initially, the mice tried to escape the condition by making vigorous movements of all limbs but became immobile when unable to escape. The mouse was considered immobile when it did not show any movement of the limbs and hanged passively. This kind of unavoidable and inescapable stress in rodents has been hypothesized to reflect depressive disorders in humans. The total duration of immobility was observed for six minutes. Each mouse was tested only once.

Statistical analysis: Results are presented as Mean ± SEM. One way ANOVA followed by Dunnet’s multiple comparison test was used for comparison between groups. For all the tests a ‘P’ value of 0.05 or less was considered for statistical significance.

RESULTS

Table 1: Effect of *Boswellia Serrata* on immobility period in Forced Swim Test.

<table>
<thead>
<tr>
<th>Group No.</th>
<th>Drug/Treatment</th>
<th>No of Animals</th>
<th>Dose (Kg⁻¹)</th>
<th>Immobility Time in Sec. (Mean±SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Control (NS)</td>
<td>6</td>
<td>10ml</td>
<td>139.33±11.04</td>
</tr>
<tr>
<td>2.</td>
<td>Standard (Imipramine)</td>
<td>6</td>
<td>10mg</td>
<td>71.66±3.24**</td>
</tr>
<tr>
<td>3.</td>
<td><em>Boswellia serrata</em></td>
<td>6</td>
<td>50mg</td>
<td>88.16±24.79*</td>
</tr>
<tr>
<td>4.</td>
<td><em>Boswellia serrata</em></td>
<td>6</td>
<td>100mg</td>
<td>75.83±6.93**</td>
</tr>
<tr>
<td>5.</td>
<td><em>Boswellia serrata</em> + Imipramine</td>
<td>6</td>
<td>200mg</td>
<td>110.16±22.14</td>
</tr>
<tr>
<td>6.</td>
<td><em>Boswellia serrata</em> + Imipramine</td>
<td>6</td>
<td>100mg+10mg</td>
<td>54±20.26***</td>
</tr>
</tbody>
</table>

Observations are Mean±S.E.M. ANOVA followed by Dunnet’s Multiple comparison test.

*p>0.05, **p<0.05, ***p<0.01.

Figure 1: Bar diagram showing effect of *Boswellia Serrata* on immobility period in Forced Swim Test.

Observations are in Mean±S.E.M. ANOVA followed by Dunnet’s Multiple comparison BS-*Boswellia serrata*, BS+IMI-*Boswellia serrata* + Imipramine
Table 2: Effect of *Boswellia Serrata* on immobility period in Tail Suspension Test.

<table>
<thead>
<tr>
<th>Group No.</th>
<th>Drug/Treatment</th>
<th>No of Animals</th>
<th>Dose (Kg⁻¹)</th>
<th>Immobility Time in Sec. (Mean±SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Control (NS)</td>
<td>6</td>
<td>10ml</td>
<td>245 ± 11.26</td>
</tr>
<tr>
<td>2.</td>
<td>Standard (Imipramine)</td>
<td>6</td>
<td>10mg</td>
<td>80.66±13.22***</td>
</tr>
<tr>
<td>3.</td>
<td><em>Boswellia serrata</em></td>
<td>6</td>
<td>50mg</td>
<td>177.83±25.62*</td>
</tr>
<tr>
<td>4.</td>
<td><em>Boswellia serrata</em></td>
<td>6</td>
<td>100mg</td>
<td>126±25.16**</td>
</tr>
<tr>
<td>5.</td>
<td><em>Boswellia serrata</em></td>
<td>6</td>
<td>200mg</td>
<td>201.16±17.19*</td>
</tr>
<tr>
<td>6.</td>
<td><em>Boswellia serrata</em> + Imipramine</td>
<td>6</td>
<td>100mg+10mg</td>
<td>160.33±13.93**</td>
</tr>
</tbody>
</table>

Observations are Mean±S.E.M. ANOVA followed by Dunnet’s Multiple comparison test.

*p>0.05, **p<0.05, ***p<0.01.

Figure 2: Bar diagram showing effect of *Boswellia Serrata* on immobility period in Tail Suspension Test.

**DISCUSSION**

It is a general principle of Pharmacology that mechanism of one drug can add independently to the actions of others. Moreover, combination of drugs with different mechanism of actions can even provide “supra-additive” or synergistic actions. This principle is applied for the management of many diseases like tuberculosis, cancer, hypertension and HIV. [22] Even for depression, it is an active theory that multiple simultaneous pharmacotherapies may be superior in terms of efficacy compared to monotherapy[23-25].

A novel strategy to enhance therapeutic efficacy of antidepressants is by combining multiple simultaneous pharmacological agents from the initiation of antidepressant treatment rather than waiting until several treatments fail.[26] Recently, most experienced clinicians who treat severe depression and treatment resistant cases of depression with inadequate responses to single agents have seen patients responding better to combinations of drugs with more than one mechanisms.[23,27,28] However, whether the depression will be amenable to a combination approach still remains to be determined, but anecdotal clinical observations and preliminary evidence shown promising results.

Apart from deficiency of biochemical neurotransmitter in central nervous system, increased pro-inflammatory cytokines (IL-6, TNF-α, NF-κB), increased Nitric Oxide (L-arginine-NO-cGMP pathway), and increased oxidative stress are implicated in the pathogenesis of depression recently.[29-31] Extracts of *Boswellia serrata* which have been traditionally used in the Ayurvedic system of medicine for variety of disease ailments also shown significant antidepressant activity in animal models recently, possibly due to its potent antioxidant action.[32] Many studies on natural herbal products have shown favorable results as adjunctive treatments for depression.[33]
As *Boswellia serrata* is proven antidepressant, the present study was carried out to evaluate its possible potentiating antidepressant activity in acute models of depression. Three different doses of *Boswellia serrata* (50mg/kg, 100mg/kg and 200mg/kg) evaluated for its antidepressant activity using Forced Swim Test (FST) and Tail Suspension Test (TST) models. Immobility period for all the six different groups of mice are explained in the Table 1, Table 2, Figure 1 and Figure 2. *Boswellia serrata* in a dose of 100mg/kg significantly reduced immobility period in FST and TST compared to control group (P<0.05). To evaluate potentiating action of *Boswellia serrata*, sixth group was administered with *Boswellia serrata* 100mg/kg (antidepressant dose) with imipramine 10mg/kg orally. Immobility period in FST significantly reduced to 54±20.26 seconds (p<0.001) compared to control group (139.33±11.04 seconds) for sixth group. Similarly in TST, immobility period reduced to 160.33±13.93 seconds when compared to control group (245 ± 11.26 seconds) with p <0.05. This shows that *Boswellia serrata* has significant potentiating antidepressant activity in a dose of 100mg/kg when combined with imipramine. However, the extensive research is needed to reveal the exact mechanism of potentiating action of *Boswellia serrata*.

CONCLUSION
Present study has shown significant potentiating antidepressant activity of *Boswellia serrata* in experimental animal models when combined with imipramine. Hence, this drug combination can be recommended for future research especially in drug resistant depression.

AUTHORS’ STATEMENTS

Competing Interests
The authors declare no conflict of interest.

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