Pharmacological Evaluation of *Cordia dichotoma* as Antidepressant in Experimental Animal Model

Ruchika Srivastava¹*, Dharamveer Panjwani², Sandeep Kumar Singh³, Babita Kumar¹, Ajeet¹*

¹Sanskar College of Pharmacy and Research, Ghaziabad, U.P., India  
²Department of Pharmacology, Hygia Institute of Pharmaceutical Education and Research, Lucknow, U.P., India  
³Department of Pharmacology, School of Pharmacy, Babu Banarasi Das University, Lucknow, U.P., India  
*Corresponding author: ruchikasrivastava86@yahoo.co.in, ajeet_pharma111@rediffmail.com

Received October 22, 2022; Revised November 27, 2022; Accepted December 12, 2022

Abstract Depression is a most serious stress related mental disorder affecting 450 million people worldwide. Due to clinical limitation and adverse effects researchers have focused on novel pharmacotherapy for safe and efficient treatment of depression. The aim of present study is to investigate the antidepressant activity of *Cordia dichotoma* (Family-Boraginaceae). The plant was authenticated by NISCAIR Delhi (Reference letter no. NISCAIR/RHMD/ Consult/2013/2307/87). Swiss albino mice were selected & assigned to four group of six mice each, in which standard group was treated with imipramine (15 mg/kg) and control group was treated with CMC (0.25ml), test groups were treated with lower and higher dose of Ethanolic extract of *Cordia dichotoma* (EECD). All groups of animals were separately submitted to forced swim test (FST), Tail suspension test (TST) and open field test (OFT) for the bio-screening of fruit extract with antidepressant profile. Administration of higher and lower dose of *Cordia dichotoma* revealed a significant reduction in immobility time in forced swim and tail suspension test. The effect of extract was similar to imipramine and they may affect neurotransmitters norepinephrine and serotonin. This herb might be considered as useful drug in the management of depression.

Keywords: *cordia dichotoma*, forced swim test, tail suspension test, imipramine, CMC, open field test


1. Introduction

Depression is a heterogeneous disorder that affects a person’s mood, physical health and behavior. It can also be described as a mood, a state of being or energy level that includes lack of motivation, a sense of hopelessness and a lack physical energy, it is an emotional status that can result from many aspects of our life [1]. Depression also poses a significant economic burden to society as it leads to reduced productivity, treatment costs and loss of human life by suicide. More than half of the economic burden will be accounted for by reduced productivity. According to the 2008 world health organization (WHO) report, major depressive disorder (MDD) had overtake required immune deficiency syndrome (AIDS) cardiovascular disease, and cancer and ranked in the top three of high burden and disability disease in the world, first in middle and high income countries, and predicted to be the world’s top first by the year 2030 [2]. The magnitude of improvement of depression is still disappointing. Although there are many synthetic antidepressant drugs are available like (tricyclic antidepressants such as imipramine, amitryptaline etc.), selective reversible inhibitors of monoamine oxidase-A (MAO-A), selective serotonin reuptake inhibitors (SSRIs) and selective noradrenaline reuptake inhibitors (SNRIs) are used frequently. However, these drugs can impose variety of side-effects including sedation, apathy, fatigue, sleep disturbance, cognitive impairment & sexual dysfunction. So, people are preferring herbal medicine as compare to chemical medicine.

*Cordia dichotoma* L.(Boraginaceae) known as lasura, lisora, is a medium sized tree with short usually crooked trunk (90-120 cm in girth) and bearing globose yellowish brown pink or black and pulpy fruit grows in India, srilanka and other warmer countries. The seeds of this plant reported to contain α amyrin & taxifolin 3,5dirhmnoside, fatty acids & four flavanoid glycosides (robin, rutin (rutoside, datiscoside & hesperidin)). Its fruit are used as cooling, astringent, emollient, analgesic, anti-inflammatory and hepatoprotective activity. It’s antioxidant activity have been reported recently the present study was undertaken in an effort to develop a novel medicinal material with potential antidepressant profile. In continuation of our research on the plant, the aim of this investigation was to evaluate the probable mechanisms of antidepressant-like activity of *Cordia dichotoma* in behavioral models of depression.
2. Materials and Methods

2.1. Plant Material

The *Cordia dichotoma* fruits were collected from Lucknow, India, during the month of June 2013. The plant material was authenticated from NISCAIR New Delhi and voucher specimens no. NISCAIR/RHMD/Consult/2013/2307/87 was deposited for future reference.

2.2. Extraction of *Cordia dichotoma* Fruit

The dried fruits of the plant (200 g) were washed, dried, and comminuted to powder and sieved. The powder was extracted with 95% ethanol and petroleum ether using a Soxhlet’s apparatus. The extract was dried in vacuum on a rotary evaporator (Buchi type). Complete dryness was achieved in a calcium chloride desiccators and the dry extract was used for all experimental studies.

2.3. Animals

Male Swiss albino mice weighing 20-25 g were used for the present study. The animals were housed in clean cage and the bedding material of cage was changed every day. They had free access to food and water *ad libitum*. The animals were acclimatized for a period of 7 days before the study and the experimental protocol was approved by the animal ethic committee (IEAC) of college of pharmacy BBDU Lucknow.

2.4. Drugs & Chemicals

Imipramine (sample from Zenith health care limited, Mehsana, Gujarat), Carboxy methyl cellulose (SD Fine-came limited Mumbai), Distilled water.

2.5. Experimental Protocol

Swiss albino mice were randomly selected & assigned to four groups of six mice each. All the drugs were administered one hour before the test procedure for acute study & daily for 14 days.

Standard group was treated with imipramine (15 mg/kg P.O) and control group was treated with CMC (0.25ml P.O), test groups were treated with lower (200 mg/kg P.O) and higher dose (400 mg/kg P.O) of Ethanolic extract of *Cordia dichotoma* (EECD). All behavioral procedures were carried out in animal models of depression (FST, TST and OFT) for the evaluation of antidepressant-like effects of EECD.

2.5.1. Forced Swim Test

Forced swim test, the most frequently used behavioral model for screening antidepressant-like activity. Mice were individually forced to swim into glass cylinder (20 cm height and 12 cm in diameter containing 8 cm deep water at 22-23°C and left there for 6 min. at this height of water, animals were not able to support themselves by touching the bottom or side walls of the chamber with their hind paws or tail. Water in the chamber must be changed after subjecting animals to FST used water has been shown to alter the behavior. The duration of immobility during the final 4 min interval of the swimming test was measured. Mice considered immobile when floating motionless or making only those movements necessary to keep its head above water [3-8].

2.5.2. Tail Suspension Test

Tail suspension test commonly employed behavioral model for screening antidepressant like activity in mice. Animals were allowed to adopt to the laboratory condition for 1-2 hr. Each mice were individually hung by the tail using an adhesive tape placed approximately 1 cm from the tip of the tail and attached to a hook and suspended 50 cm above the floor. The immobility duration was recorded for 6-min. Mice considered immobile when it did not show any movement of body and hanged passively [9-13]

2.5.3. Open Field Test

After this test utilizes behavioral changes in mice exposed to novel environment and is used to confirm that observed antidepressant effect is not due to stimulation of general motor activity. The open field test was carried out in apparatus made up of Perspex plastic with dimensions (40×60×50 cm) and the floor was divided into 25 equal squares by lines. The latency to move from the centre square (in seconds) and numbers of squares crossed with all paws (crossing), Occupancy of peripheral areas were counted in a 5 min session [14-19].

2.5.4. Statistical Analysis

Experimental results were expressed as means ± SEM. The data were analyzed by analysis of variance, one way ANOVA with Turkey post test [20-24].

3. Results and Discussion

3.1. Acute Toxicity Study

Acute toxicity studies revealed the non-toxic nature of plant extract *C. dichotoma*. there were no toxic reaction or lethality found at any dose selected until the end of the study period. All The animals were alive, healthy, and active the observation period.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Treatment</th>
<th>Dose (kg)</th>
<th>Immobility time (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>CMC</td>
<td>1 ml</td>
<td>272±5.32</td>
</tr>
<tr>
<td>Standard</td>
<td>Imipramine</td>
<td>15 mg</td>
<td>120±2.12***</td>
</tr>
<tr>
<td>Test1</td>
<td><em>Cordia</em> dichotoma</td>
<td>200 mg</td>
<td>116±3.22***</td>
</tr>
<tr>
<td>Test 2</td>
<td><em>Cordia</em> dichotoma</td>
<td>400 mg</td>
<td>95.83±4.45***</td>
</tr>
</tbody>
</table>

Value are Mean±SEM (n=6), one way ANOVA followed by Tukey test. Where *p<0.05, ** p<0.01, ***p<0.001 when compared to control.
3.2. Forced Swim Test

As shown in Table 1, the results indicated that animals pre-treated with EECD fruit reduced total immobility time as compared to control group in FST. The obtained results were found to be statistically significant (p< 0.001) for both the doses i.e. 200mg/kg & 400mg/kg (Table 1 and Figure 1).

3.3. Tail Suspension Test

As shown in Table 2 and Figure 2, a significant (p<0.001) decrease in the duration of immobility was seen with the standard drug as compared to the control. In study of EECD at both the doses i.e. 200 and 400mg/kg significantly decreased the duration of immobility.

3.4. Open Field Test

The latency to move from the centre square, numbers of squares crossed with all paws (crossing), and time spent in periphery were counted in a 5 min session.

3.4.1. Effect of Cordia dichotoma Fruit Extract on Total no. of Crossing in Open Field Test

As shown in Table 3 and Figure 3, the results indicated that animals pre-treated with CdEe fruit in Total no. of crossing was significantly (p<0.05) decreased in test 2 and standard groups as compared to control group.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Treatment</th>
<th>Doses (kg(^{-1}))</th>
<th>Immobility time (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>CMC</td>
<td>1ml</td>
<td>197.33±2.16</td>
</tr>
<tr>
<td>Standard</td>
<td>Imipramine</td>
<td>15mg</td>
<td>127.8±2.283***</td>
</tr>
<tr>
<td>Test 1</td>
<td>Cordia dichotoma</td>
<td>200mg</td>
<td>154.833±3.09**</td>
</tr>
<tr>
<td>Test 2</td>
<td>Cordia dichotoma</td>
<td>400mg</td>
<td>138.33±1.948***</td>
</tr>
</tbody>
</table>

Values are Mean±SEM (n=6) ** p<0.01; *** p< 0.001 as compared with control group by One way ANOVA followed by Tukey test.
Table 3. Effect of ethanolic extract of *Cordia dichotoma* on Total no. of crossing

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Groups</th>
<th>Treatment</th>
<th>Doses (kg⁻¹)</th>
<th>Total no. of crossing (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Control</td>
<td>CMC</td>
<td>1ml</td>
<td>55.67±1.64</td>
</tr>
<tr>
<td>2</td>
<td>Standard</td>
<td>Imipramine</td>
<td>15mg</td>
<td>92.67±3.86*</td>
</tr>
<tr>
<td>3</td>
<td>Test 1</td>
<td><em>Cordia dichotoma</em></td>
<td>200mg</td>
<td>86.00±5.34</td>
</tr>
<tr>
<td>4</td>
<td>Test 2</td>
<td><em>Cordia dichotoma</em></td>
<td>400mg</td>
<td>91.83±1.64*</td>
</tr>
</tbody>
</table>

Value are Mean±SEM (n=6) * p<0.05 as compared with control group by One way ANOVA followed by Tukey test.

Figure 3. Effect of *Cordia dichotoma* on Total no. of crossing in Open field test

Table 4. Effect of *Cordia dichotoma* Fruit extract on time spent in centre in Open field test

<table>
<thead>
<tr>
<th>S.No</th>
<th>Groups</th>
<th>Treatment</th>
<th>Doses (kg⁻¹)</th>
<th>Time spent in centre (sec.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Control</td>
<td>CMC</td>
<td>1ml</td>
<td>1.66±0.27</td>
</tr>
<tr>
<td>2</td>
<td>Standard</td>
<td>Imipramine</td>
<td>15mg</td>
<td>1.83±0.24</td>
</tr>
<tr>
<td>3</td>
<td>Test 1</td>
<td><em>Cordia dichotoma</em></td>
<td>200mg</td>
<td>1.83±0.19</td>
</tr>
<tr>
<td>4</td>
<td>Test 2</td>
<td><em>Cordia dichotoma</em></td>
<td>400mg</td>
<td>1.83±0.12</td>
</tr>
</tbody>
</table>

Figure 4. The effect of *Cordia dichotoma* on Time spent in centre in Open field test

3.4.2. Effect of *Cordia dichotoma* Fruit Extract on Time Spent in Centre in Open Field Test

As shown in Table 4 and Figure 4, the results indicated that CdEE did not show any significant change (p>0.05) in time spent in centre in open field test as compared to control group.

3.4.3. Effect of *Cordia dichotoma* Fruit Extract on Time Spent in Periphery in Open Field Test

As shown in Table 5 and Figure 5, the results indicated CdEe did not show any significant change (p>0.05) on time spent in periphery in open field test as compared to control group.

Table 5. Effect of *Cordia dichotoma* Fruit extract on time spent in periphery in Open field test

<table>
<thead>
<tr>
<th>S.No</th>
<th>Groups</th>
<th>Treatment</th>
<th>Doses (kg⁻¹)</th>
<th>Time spent in Periphery (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Control</td>
<td>CMC</td>
<td>1ml</td>
<td>58.5±5.189333</td>
</tr>
<tr>
<td>2</td>
<td>Standard</td>
<td>Imipramine</td>
<td>15mg</td>
<td>88.666±11.3899</td>
</tr>
<tr>
<td>3</td>
<td>Test 1</td>
<td><em>Cordia dichotoma</em></td>
<td>200mg</td>
<td>59.5±5.9055</td>
</tr>
<tr>
<td>4</td>
<td>Test 2</td>
<td><em>Cordia dichotoma</em></td>
<td>400mg</td>
<td>58.6667±5.922333</td>
</tr>
</tbody>
</table>
Depression constitutes the second most common chronic condition in clinical practice and will become the second leading cause of premature death or disability worldwide by the year 2020 [25]. It is a heterogeneous disorder that affects a person’s mood physical health and behavior patient with major depression have symptoms that reflect changes in brain monoamine neurotransmitters especially Norepinephrine, Serotonin, Dopamine. Depression is considered as an affective disorder with a prevalence of approximately 5% in the general population. It is characterized by change in mood, lack of interest in the surroundings, psychomotor retardation, and melancholia.

Both FST & TST are the established behavioral stress model of depression. Rodents under stress from which they cannot escape, becomes immobile after an initial period of struggling. This immobility signifies behavioral despair, resembling the state of mental depression and it is believed that when animals are exposed to such type of conditions it leads to the depletion of biogenic amines such as Norepinephrine and Serotonin, which are considered as one of the causes of depression [26].

The forced swim test (FST) developed by Porsolt and colleagues in rat and subsequently in the mice [27]. This test is the most widely used tool for assessing antidepressant activity preclinically. The swimming test has been extensively employed to evaluate the effect of various agents on the central nervous system such as antidepressant, sedative –hypnotics, adaptogenic etc. in this test mice or rats forced to swim in a restricted space from which they cannot escape are characteristic behavior of immobility. The swimming test has been extensively employed to evaluate the effect of various agents on the central nervous system such as antidepressant, sedative –hypnotic psycho stimulants. It was suggested that mice or rats forced to swim in a restricted space from which they cannot escape are characteristic behavior of immobility euphoric, no tropics, adaptogens, etc. This behavior reflects a state of despair by several agents which are therapeutically effective in human depression [26]. Table 1 showed the result of effect of extract on the duration of immobility during forced swimming test. The extract shortened the immobility period during the forced swimming test. Obtained results were found to be statistically significant (p>0.001) for both the doses i.e. 200mg/kg & 400mg/kg as compare to control group.

The tail suspension test has been described by researchers in the field as a facile mean of evaluating potential antidepressants. The immobility displayed by rodents when subjected to an unavoidable and inescapable stress has been hypothesized to reflect behavioral despair which in turn may reflect depressive disorders in humans. The tail suspension test is a facile method evaluating potential antidepressants [25]. The immobility displayed by rodents when subjected to an unavoidable and inescapable stress has been hypothesized to reflect behavioral despair which in turn may reflect depressive disorders in humans. Clinically effective antidepressants reduce the immobility that mice display after active and unsuccessful attempts to escape when suspended by the tail. Tail suspension test represents the behavioral despair model, claimed to reproduce a condition similar to human depression. The test is based on the observation that animals, following initial escape oriented movements, develop an immobile posture when placed in an inescapable chamber. The immobility is thought to reflect either a failure of persistence in escape-directed behavior (i.e. behavioral despair) or the development of passive behavior that disengages the animal from active forms of coping with stressful stimuli. TST detects the anti-immobility effects of a wide array of antidepressants, including tricyclic antidepressants (TCA), selective serotonin reuptake inhibitors (SSRI), monoamine oxidase inhibitors (MAOI), electro-convulsive shock (ECS), and even atypical antidepressants [3]. Table 2 showed the result of effect of extract on duration of immobility during TST. The obtained results were found to be statistically significant p>0.01 and p>0.001 for the doses of 200mg/kg & 400mg/kg respectively.

Open field behavioral model was used to study exploratory and locomotory activity. In this investigation this test is thought to provide indices of motor activity, and exploration. Three factors were measured i.e. Total locomotion and Central locomotion, and Occupancy of the peripheral area. The number of central square entries and the duration of time spent in the central square and the number of line crosses are measures of exploratory behavior, anxiety and locomotory activity. A high
frequency duration of these behaviors indicates high exploratory behavior and low anxiety levels. [28]

The antidepressant activity observed in extract due to chemical constituent present in the compound and According to results of phytochemical screening and the literature, the antidepressant like potential might be due to the presence of Flavonoids, Glycosides and Alkaloids. Flavonoids and glycosides are mostly hydrolysed into their aglycon by mucosal and bacterial enzymes in the intestine and then converted to conjugated metabolites. During the absorption process transportation of these metabolites into the brain through BBB and protect brain function from CNS disturbance consequently and exerting antidepressant activity [1].

Oxidative stress represents a loss of balance in oxidation reduction reactions. It is characterized by the reduced ability of the antioxidant defense system to efficiently eliminate the excess of the oxygen-derived species production, eliciting the toxicity of oxygen and its detrimental effect. Increased oxidative stress is seen in patient suffering from depression more over the plant also possessed antioxidant property.

4. Conclusions

From the above valuable animal study, it was concluded that the plant extract of fruits of Cordia dichotoma shows a significant antidepressant activity in TST, FST and OFT model of depression. Thus Cordia dichotoma reduces the immobility period in TST, FST and total locomotion in OFT.

Funding

None.

Conflicts of Interest

None.

References


© The Author(s) 2022. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).