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## **Analysis of possible antidepressant effects of Cordia Myxa extract in male rats: Behavioral study**

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**Abstract**---Depression is one of the most frequent psychiatric illnesses, and it is treated with a number of drugs that have serious side effects on human health and lead to a rise in suicide rates. Due to their safety, efficacy, and cost-effectiveness, herbal drugs have lately sparked a lot of interest in the treatment of depression. As a result, the goal of this study was to see how C.Myxa fruit extract affected a model of chronic unexpected stress (CUS). Six groups of sixty male rats were formed as a result. Group 1 (control) was not exposed to CUMS and did not receive any treatment, whereas group 2 was exposed to CUMS for 24 days and received normal saline treatment for 14 days, group 3 was exposed to CUMS for 24 days and received 10 mg/kg fluoxetine daily on day 10 for 14 days, and groups 4,5 and 6 were exposed to CUMS for 24 days and received C.Myxa extract (125, 250, and 500 mg/kg respectively) on day 10 for 14 days. Open field test groomings and line crossing frequency were used to assess the antidepressant impact of fluoxetine and C.Myxa extract. On day 10, the means of groomings and line crossings in groups 3, 4, 5 and 6 considerably reduced (P-value 0.05) when compared to day 0, but the means of groomings and line crossings in groups 3,4,5 and 6 significantly increased (P-value 0.05) when compared to day 10. On day 25, the mean of groomings and line crossings in group 2

considerably reduced (P-value 0.05) when compared to group 1, whereas the mean of groomings and line crossings in groups 3, 4, 5, and 6 significantly increased (P-value 0.05) when compared to group 2. *C. Myxa* shows antidepressant-like effects, according to these behavioral tests.

**Keywords**---chronic mild stress, depression, *Cordia myxa*, groomings, line crossings.

## Introduction

Depression is a chronic mental illness that affects one's emotions, thoughts, behavior, and physical well-being. It is a common but dangerous illness that may rob a person of their ability to enjoy life and cause a deterioration in their ability to do even the most basic daily chores. Depression is characterized by a variety of emotional symptoms, such as bouts of persistently low mood, a lack of interest in any activity, anhedonia, poor self-esteem, and cognitive impairment. In addition, several physical symptoms such as sleeplessness, restlessness, anorexia, and libido loss are common in patients. Recurrence of symptoms is also a typical sign of major depressive illness. [1]

Depression affects 12% of the world's population at some point in their lives. It is considered as one of the most prominent variables among neuropsychiatric disorders, which account for 11% of Disability Adjusted Life Years [2]. Suicides linked to depression account for up to 16 per 100,000 deaths. When depressed individuals are given current conventional medication therapy, which primarily targets 5-HT receptors, only around two-thirds of them achieve remission. [3]

Herbal medications have received a lot of attention because of their potential to treat mental illnesses. There has been an increase in their usage in depression therapies because their high effectiveness, safety, and inexpensive cost [4]. So this study was aimed to evaluate the antidepressant effects of the ethanolic extract of the *Cordia Myxa* fruit in male rats using behavioral test parameters line crossings and groomings.

## Materials and Methods

### Animals

In this study, there were sixty mature male albino rats. They were 185–245 grams in weight. The rats were housed in the Animal House at the Medical College/University of Babylon at a temperature of roughly 25°C, with a 14-hour light/ten-hour dark cycle and unlimited access to water and food. They were kept in cages with five rats in each. The animals were assigned into six groups at random for the experiment planned after a three-week acclimation period.

### **Plant preparation**

*Cordia Myxa* dried fruits were processed into powder and kept at 4 degrees Celsius using a mechanical grinder. Ethanol maceration was used to extract fruit powder. In 70 percent (v/v) ethanol (5:10 w/v), the powdered fruits were macerated at room temperature for 72 hours. For the next four hours, it was shaken[5]. The mixture was filtered using a Buchner funnel and Whatman filter paper No. 1. The resulting extract was condensed under pressure in a rotary evaporator at 40°C. The extract was kept refrigerated.[6]

### **General Experimental Procedure**

1. Each animal was tested for OFT on days 0, 10, and 25.
2. The animals in group 1 (control) were not given any medications and were not under any stress.
3. Each animal in groups two, three, four, five, and six was subjected to a 24-day period of mild stress that was unexpected (CUS).
4. Starting on the tenth day of CUS, each rat in group two received 0.2 milliliters of normal saline through oral gavage for 14 days.
5. Each animal in group 3 received fluoxetine therapy at a dose of 10 mg/kg orally for 14 days.
6. Each rat in groups 4, 5, and 6 received a daily dosage of *C.myxa* fruit extract of 125 mg/kg, 250 mg/kg, and 500 mg/kg, respectively, for fourteen days.[7]

### **Chronic unpredictable mild stress (CUMS)**

The Katz method[8], It was used to generate chronic stress with modest adjustments. Because it has previously been used to induce anxiety in animals, this procedure was chosen. CUMS is used to treat stressed animals. The CUS protocol consisted of the following stressors: (A) Wet bedding: 300 mL of water was poured on and mixed with 1 L of sawdust bedding. (B) Cage tilting: the cage was tilted up to 45 degrees with food and water located at the higher top. (C) Crowded cage : 10 rats per cage (D) Restraint : five rats per small cage render them on immobile position. Animals were exposed to every stressor 3 to 4 times throughout the protocol. [9]

### **Open arena analysis**

wooden box (100 x 100cm) was built by a researcher and consists of a square floor divided into 100 equal squares by thin white lines[10]. To prevent escape, the equipment consists of an arena surrounded by high walls. The number of square crossings utilized to evaluate the rat's activity throughout the test period. Crossings behaviors are used to assess hyperactivity in the open-field apparatus. The total number of square crossings throughout the test time is referred to as crossings, and it is used to determine the animals' locomotor activity. Grooming and sniffing habits might be used to assess it. Grooming refers to the total time spent grooming during the test period. [11]

## Analysis of Statistics

The information was provided as a mean with standard deviation (SEM). In the statistical analysis, the post hoc test and one-way analysis of variance (ANOVA) were performed (sidak). The differences were considered statistically significant if the probability *p* value was less than 0.05. For statistical analysis, the 23rd edition of (SPSS v24) statistics for Windows ® 10 was employed.

## Results

### Frequency of line crossing within the group

There were no significant differences in means of line crossings on days 10 and 25 as compared to day 0 in group 1 (control group, untreated and unexposed to CUS), whereas in group 2 (untreated and exposed to CUS), the mean of line crossing frequency on day 25 significantly increased (*P-value* <0.05) as compared to 10 (Table 3.1 and Figure 3.1). (Table 1 and Figure 1). In groups 2, 3, 4, 5 and 6, the means of rearing frequency on day10 significantly decreased (*P-value* <0.05) as compared with day 0, while the means of line crossing frequency on day 25 of groups 3,4,5 and 6 significantly increased (*P-value* <0.05) as compared with day 10. (Table 1 and Figure 1)

Table 1 Comparison in the means of Line-crossing frequency  $\pm$  SEM between groups on days 0, 10, 25

| Line-Crossings | Group 1                     | Group 2                      | Group 3                              | Group 4                                | Group 5                                | Group 6                               |
|----------------|-----------------------------|------------------------------|--------------------------------------|----------------------------------------|----------------------------------------|---------------------------------------|
| Day 0          | 314.6000 $\pm$ 2<br>1.58250 | 353.000 $\pm$ 8.<br>78888    | 312.5000 $\pm$ 16<br>.17972          | 311.1000 $\pm$ 16<br>.55056            | 320.3000 $\pm$ 1<br>2.29458            | 301.4000 $\pm$ 18<br>.61135           |
| Day10          | 316.6000 $\pm$ 8<br>.58966  | 121.9000 $\pm$ 1<br>4.83723* | 121.5000 $\pm$ 12<br>.41348*         | 104.000 $\pm$ 11.<br>31371*            | 128.6000 $\pm$ 1<br>1.88108*           | 122.8000 $\pm$ 11<br>.69026*          |
| Day25          | 307.7000 $\pm$ 1<br>4.09653 | 116.5000 $\pm$ 1<br>4.78682* | 278.4000 $\pm$ 20<br>.55032 $\alpha$ | 253.1000 $\pm$ 13<br>.02856 $\alpha^*$ | 246.1000 $\pm$ 1<br>0.69314 $\alpha^*$ | 218.6000 $\pm$ 8.<br>08043 $\alpha^*$ |

\* = significantly decreased (*P* <0.05) as compared with day 0,

$\alpha$  = significantly increased (*P* <0.05) as compared with day 10,

Group 1 (control group, untreated and unexposed to CUS), group 2 (untreated and exposed to CUS), group 3 (treated with 10mg/kg fluoxetine for 14 days), group 4 (treated with 125mg/kg C.Myxa extract for 14 days), group 5 (treated with 250mg/kg C.Myxa extract for 14 days), group 6 (treated with 500mg/kg C.Myxa extract for 14 days), no.of rats=10 for each group.

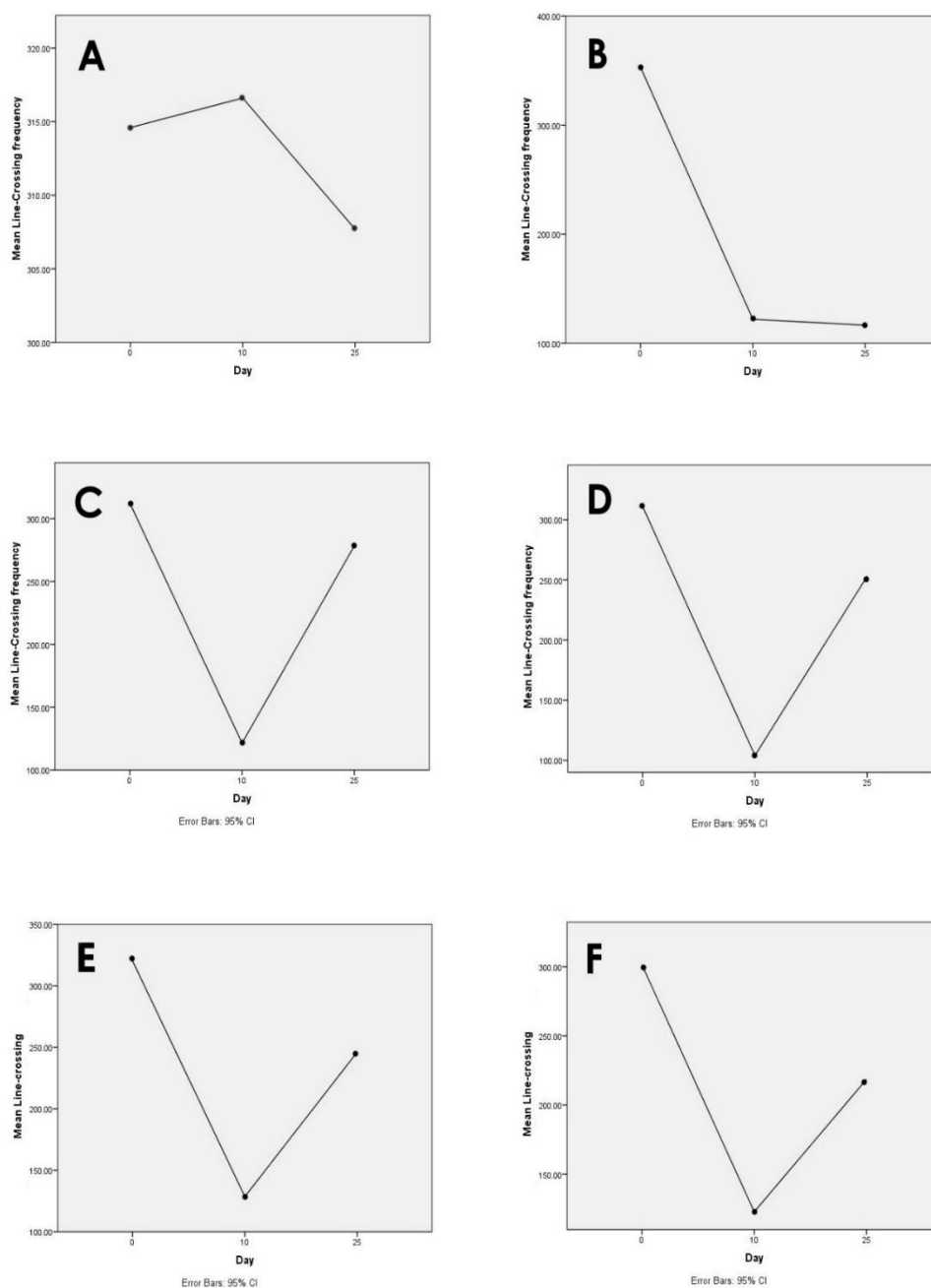


Figure 1: the means of Line-crossing frequencies on days 0, 10, and 25 for all groups.

A: group 1 (control group, untreated and unexposed to CUS), B: group 2 (untreated and exposed to CUS), C: group 3 (treated with 10 mg/kg fluoxetine for 14 days), D: group 4 (treated with 125 mg/kg *C. Myxa* extract for 14 days), E: group 5 (treated with 250 mg/kg *C. Myxa* extract for 14 days), F: group 6 (treated with 500 mg/kg *C. Myxa* extract for 14 days). no. of rats =10 for each group.

## Open Field Test (OFT) results

### frequency of groomings within the group

There were no significant differences in number of groomings on days 10 and 25 as compared to day 0 in group 1 (control group, untreated and unexposed to CUS), whereas in group 2 (untreated and exposed to CUS), the mean of grooming frequency on day 25 significantly increased ( $P$ -value  $<0.05$ ) as compared to 10 (Table 2 and Figure 2).

In groups 2, 3, 4, 5 and 6, the means of grooming frequency on day10 significantly decreased ( $P$ -value  $<0.05$ ) as compared with day 0, while the means of groomingfrequency on day 25 of groups 3,4,5 and 6 significantly increased ( $P$ -value  $<0.05$ ) as compared with day 10. (Table 2 and Figure 2)

Table 2 Comparison in the means of Grooming frequency  $\pm$  SEM between groups on days 0, 10, 25

| Groomings | Group 1                  | Group 2                   | Group 3                           | Group 4                           | Group 5                           | Group 6                           |
|-----------|--------------------------|---------------------------|-----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|
| Day 0     | 7.8000 $\pm$ 0.9<br>0431 | 6.6000 $\pm$ 0.9<br>4516  | 6.8000 $\pm$ 0.44<br>222          | 5.5000 $\pm$ 0.40<br>000          | 8.1000 $\pm$ 0.99<br>387          | 5.6000 $\pm$ 0.70<br>238          |
| Day10     | 7.3000 $\pm$ 0.6<br>3333 | 0.6000 $\pm$ 0.2<br>2111* | 0.9000 $\pm$ 0.17<br>951*         | 1.1000 $\pm$ 0.31<br>447*         | 1.3000 $\pm$ 0.36<br>667*         | 1.3000 $\pm$ 0.30<br>0000*        |
| Day25     | 7.7000 $\pm$ 0.7<br>8951 | 1.1000 $\pm$ 0.3<br>1447* | 4.8000 $\pm$ 0.35<br>901 $\alpha$ | 4.7000 $\pm$ 0.59<br>722 $\alpha$ | 5.5000 $\pm$ 0.68<br>718 $\alpha$ | 5.3000 $\pm$ 0.55<br>877 $\alpha$ |

\* = significantly decreased ( $P <0.05$ ) as compared with day 0,

$\alpha$  = significantly increased ( $P <0.05$ ) as compared with day 10,

$\pi$  = significantly increased ( $P <0.05$ ) as compared with day 0.

Group 1 (control group, untreated and unexposed to CUS), group 2 (untreated and exposed to CUS), group 3 (treated with 10mg/kg fluoxetine for 14 days), group 4 (treated with 125mg/kg C.Myxa extract for 14 days), group 5 (treated with 250mg/kg C.Myxa extract for 14 days), group 6 (treated with 500mg/kg C.Myxa extract for 14 days), no.of rats=10 for each group.

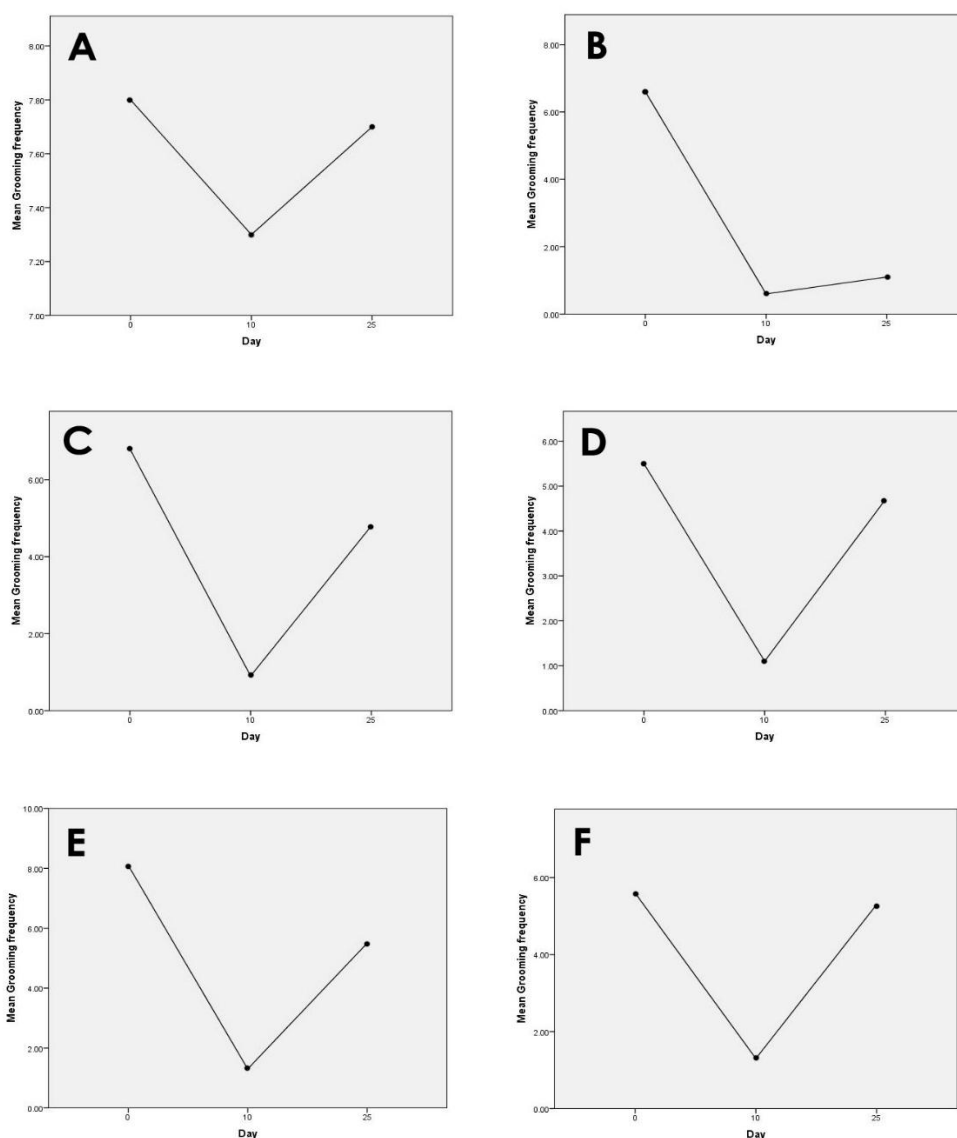


Figure 2: the means of Groomings frequencies on days 0, 10, and 25 for all groups.

A: group 1 (control group, untreated and unexposed to CUS), B: group 2 (untreated and exposed to CUS), C: group 3 (treated with 10 mg/kg fluoxetine for 14 days), D: group 4 (treated with 125 mg/kg *C. Myxa* extract for 14 days), E: group 5 (treated with 250 mg/kg *C. Myxa* extract for 14 days), F: group 6 (treated with 500 mg/kg *C. Myxa* extract for 14 days). no. of rats =10 for each group.

### Line-crossing frequency in open field test on day 25

In group 2, the mean of Line-crossing frequency significantly decreased ( $P$ -value <0.05) as compared with group1, while in groups 3, 4, 5, and 6 the means of Line-crossing frequency significantly increased ( $P$ -value <0.05) as compared with

group 2 (Table 3.6 and Figure 3.9) and in groups 4,5, and 6 the mean of Line-crossing frequency significantly decrease ( $P$ -value  $<0.05$ ) as compared with group 1 (Table 3.6 and Figure 3.9). In group 5, the mean of line crossing frequency significantly decreased ( $P$ -value  $<0.05$ ) as compared with group 3 (Figure 3).

### Grooming frequency in open field test on day 25

In group 2, the mean of Grooming frequency significantly decreased ( $P$ -value  $<0.05$ ) as compared with group 1, while in groups 3, 4, 5, and 6 the means of Grooming frequency significantly increased ( $P$ -value  $<0.05$ ) as compared with group 2 (Figure 4).

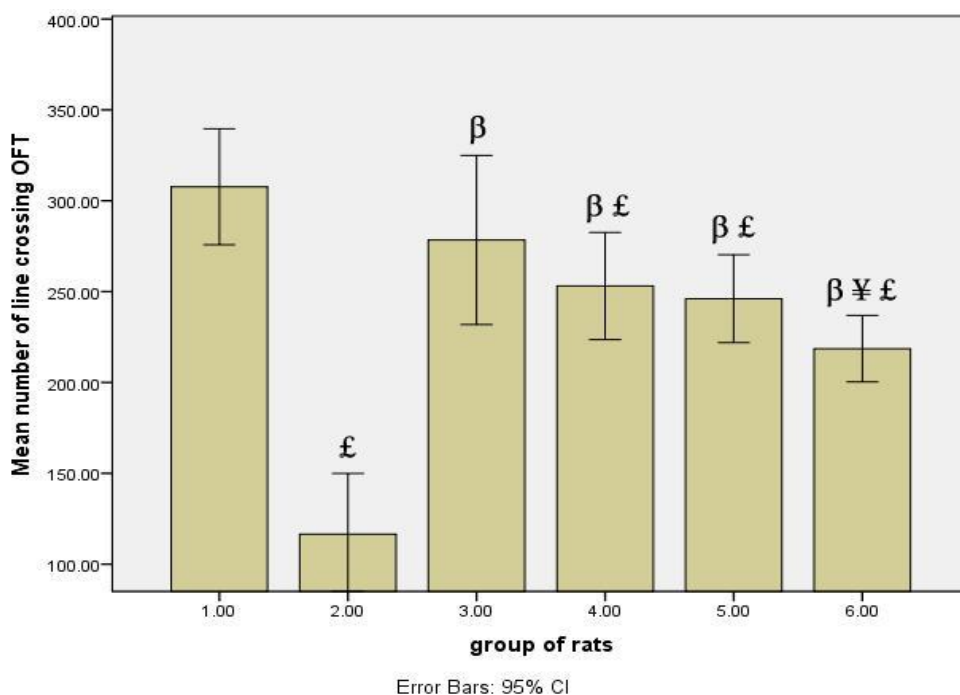


Figure 3: Means  $\pm$  SEM of line-crossings frequencies in open field test on day 25 for all groups

β = significantly increase ( $P$  value  $<0.05$ ) as compared with group 2,  
 £ = significantly decrease ( $P$  value  $<0.05$ ) as compared with group 1,  
 ¥ = significantly decrease ( $P$  value  $<0.05$ ) as compared with group 3.

Group 1 (control group, untreated and unexposed to CUS), group 2 (untreated and exposed to CUS), group 3 (treated with 10mg/kg fluoxetine for 14 days), group 4 (treated with 125mg/kg C.Myxa extract for 14 days), group 5 (treated with 250mg/kg C.Myxa extract for 14 days), group 6 (treated with 500mg/kg C.Myxa extract for 14 days), no.of rats=10 for each group.

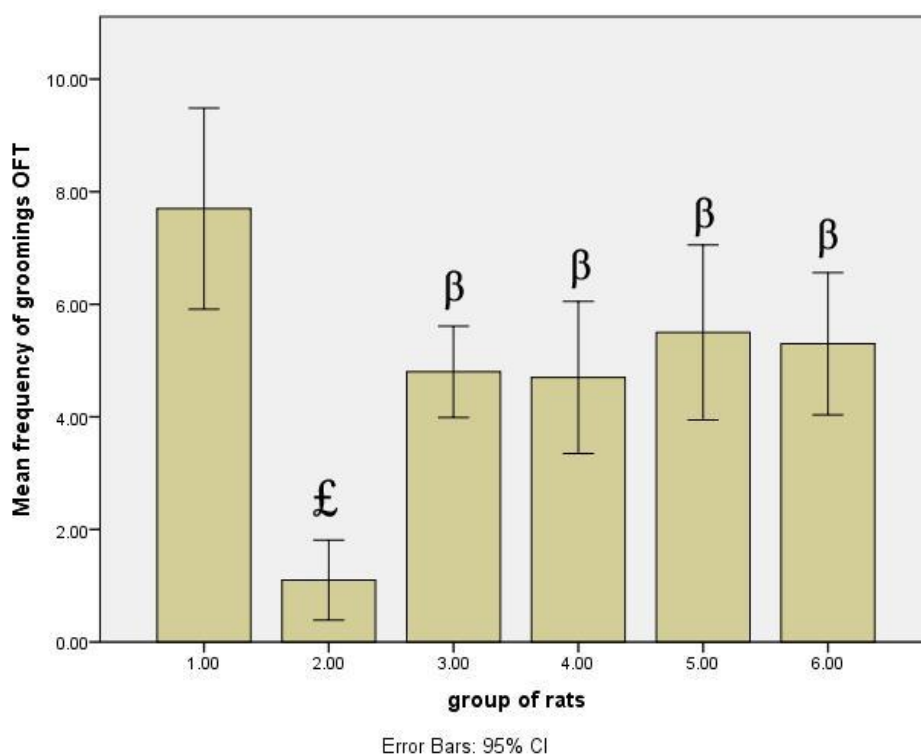


Figure 4: Means  $\pm$  SEM of the Groomings frequencies in open field test on day 25 for all groups

β = significantly increase ( $P$  value  $<0.05$ ) as compared with group 2.

£ = significantly decrease ( $P$  value  $<0.05$ ) as compared with group 1

Group 1 (control group, untreated and unexposed to CUS), group 2 (untreated and exposed to CUS), group 3 (treated with 10mg/kg fluoxetine for 14 days), group 4 (treated with 125mg/kg C.Myxa extract for 14 days), group 5 (treated with 250mg/kg C.Myxa extract for 14 days), group 6 (treated with 500mg/kg C.Myxa extract for 14 days), no.of rats=10 for each group.

## Discussion

Depression is a debilitating disorder that affects a significant portion of the population. It is an illness that is very heterogeneous and can be caused by a variety of causes. This necessitates the use of animal models to verify the relationship between stress and depression, which should exclude animals that are tolerant to stress in order to simulate the real-life scenario in humans. Animal models created with maternal separation and chronic unpredictable stress-exposure, for example, are commonly used models that simulate stress experienced by humans during childhood and maturity. [12]

Several studies have found that CUS can cause long-term behavioral changes that are similar to clinical depressive symptoms. As a matter of fact, this study looked into the anti-depressant effect of Cordia Myxa fruit extract against CUS-

induced depression using behavioral tests line crossings and groomings in open field test OFT. The groomings and line crossings in OFT were not significantly different between animals from all groups on day 0 (baseline) in this study. When compared to baseline (day 0), there was a decline in groomings and line-crossings in OFT for all groups of rats exposed to CUS after 10 days of unpredictable stress. This indicates that these animals have evolved a depression model. These results agree with previous studies had found that rats acquired a behavioral model of depression after being exposed to unpredictable stress procedures utilizing various stressors.

The OFT was used as behavioral index of locomotor activity, and self care behavior. The decreased activity in open field arena contrast with group 1 (rats not exposed to CUS ) that increased line crossing and grooming, which is driving by the interests of rats to explore a new environment. However, rats show reduced line crossing and grooming in an unfamiliar open field after CUS , which might imply a "refractory loss of interest", which is another fundamental characteristic of human severe depression [13].

Several pathways have been postulated for CUS to produce depressive-like behavior[14]. The first is BDNF, which affects neural plasticity, suppresses cell death cascades, and promotes cell survival proteins necessary for the proliferation and maintenance of central nervous system neurons, suggesting that it might have a role in the development and treatment of depression. It was discovered in experimental studies that a decrease in BDNF expression in the hippocampus and frontal cortex among animals exposed to chronic stress can be reversed by antidepressant treatment showed that conditional BDNF knockout mice displayed an increase in depression-like behavior, as measured by the forced swim test and sucrose preference tests, demonstrating that BDNF deficit can be reversed by antidepressant treatment. These findings support the function of BDNF in depression and suggest that upregulating BDNF expression may help antidepressants work more effectively. [15]

Histone acetylation, which has been related to depression, is another mechanism (histones are composed of mostly positive charged amino acid residues such as lysine and arginine that provide structural support to a chromosome)[16]. Histone acetylation, particularly targeting the N-terminal lysine residues in histone 3 (H3) and histone 4 (H4), has raised concerns in depression because it affects the transcription of certain genes, including brain-derived neurotrophic factor (BDNF) and serotonin transporter. The rate-limiting enzymes for the production of monoaminergic transmitters are tyrosine hydroxylase (TH) and tryptophan hydroxylase (TPH) (such as norepinephrine, dopamine, and serotonin). Histone acetylation and regulation of these enzymes' production, TH, and TPH, in the hippocampus, are linked in the CUS-induced depressed model of rats, suggesting that they may play a role in the genesis of depression. [17]

this study has revealed that after the treatment of rats with either fluoxetine or three concentrations of Cordia Myxa fruit extract; antidepressant effect has been shown. That increased line crossing and grooming in open field on day 25 as compared with day 10 for group 3 rats (treated with 10 mg/kg fluoxetine for 14 days).

According to behavioral tests cordia myxa have antidepressant activity may be related to antioxidant properties of plant constituents such as flavonoids and this run with macrophage hypothesis of depression pathology[18].

## Conclusions

This study reveals that prolonged unpredictable stress causes depressive-like behavior in rats. Increased formation of cytokines and development of oxidative stress plays an important role in the pathogenesis of depression. Stress-induced low rates of groomings and line crossings are reversed by C. Myxa treatments in treated groups and this may be related to possible antidepressant effects of cordia myxa extract.

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