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Evaluation of the Antidepressant Potential of Curcumin Extract in Mice

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ABSTRACT

Depression is a disorder often manifested with symptoms at the psychological, behavioral and physiological levels. Herbal medicine holds a valuable place in the treatment of depression. It is also a reasonable alternative for developing novel drugs. The present study was to investigate the effect of curcumin extract on depression in mice using force swim test (FST) and tail suspension test (TST). In the present study, mice of either sex were divided into 7 groups of 5 animals in each group as mentioned below. All the test solutions were freshly prepared daily and administered in animals for 14 days by intraperitoneal (i.p.) route. Group I- Dimethyl sulfoxide (DMSO, 0.5 M, 10 ml/kg, i.p), Group II- Saline water (10 ml/kg, i.p.), Group III- Imipramine (15 mg/kg, i.p.), Group IV- Curcumin extract (25 mg/kg, i.p.), Group V- Curcumin extract (50 mg/kg, i.p.), Group VI- Curcumin extract (25 mg/kg, i.p.) + Imipramine (15 mg/kg, i.p.), Group VII- extract (50 mg/kg, i.p.) + Imipramine (15 mg/kg, i.p.). Curcumin (50 mg/kg) exert antidepressant effect in mice by using FST and TST method. The antidepressant effect of curcumin (50 mg/kg) may be inhibiting the MAO enzymes and increases the level of serotonin and dopamine neurotransmitters in the brain. Curcumin is less potent than imipramine, and Curcumin (50 mg/kg) with imipramine did not synergetic antidepressant action in mice.

INTRODUCTION

Depression is a mental disorder characterized by a feeling of sadness or despair and or loss of interest in things that were once pleasurable. Depression is a major disease affecting nearly 13-20% of the world population. The lifetime risk of depression varies from 10-20% in women and 5-12% in men[1]. Patients with depression have reduced interest in social, educational and occupational life. It is reported that at least 15% of the patients with severe depression follow sucide[2]. Depression is a chronic mental disorder that causes changes in mood, thoughts, behavior and physical health. It's a common but serious disease that can take away a person's ability to enjoy life and cause decline in capacity to undertake even the simplest daily tasks. Other than its chronic nature, symptoms associated with this mental disorder are often recurring and life threatening. According to the World Health Organization (WHO) unipolar depression is one of the leading causes of disability-adjusted life year (DALY) and approximately 350 people worldwide are said to suffer from this mental disorder.

Types of depression: Depression is a heterogeneous disorder often mistaken for a single clinical mental illness. Diagnosis of this disorder is complicated because of the co-occurrence of many other mental conditions such as anxiety disorders, including panic agoraphobia syndrome, severe phobias, generalized anxiety disorder, social anxiety disorder, post-traumatic stress disorder (PTSD) and obsessive-compulsive disorder (OCD).

Extract of rhizomes of *Curcuma longa* Linn. has been used to treat mental disorders in the past. Curcumin is the active principle of the extract of rhizomes of turmeric. Curcumin shows a wide spectrum of pharmacological activities such as wound healing[3-4], anti-inflammatory[5], anti-arthritic[6], analgesic[7], anti-pyretic[8], anti-bacterial[9], anti-viral[10], anti-fungal[11], anti-allergic, anti-spasmodic[12], anti-oxidant[12], neuroprotective[13], anti-depressant[14], cardio disorder protective[15], hypolipidaemic activity[15], anti-coagulant[16], anti-ulcer[17], anti-diabetic[18], hepatoprotective[19], anti-cancer[20], anti-fertility[21] and anti-venom[22] activities. It has been also reported that the volatile oil of *Curcuma longa* possesses anti-inflammatory[23], anti-bacterial and anti-fungal activities[24]. Turmeric volatile oil is effective against disorder of respiratory tract[25].

On the basis of literature survey, major researches are not found on antidepressant properties of curumin and none of the Study of curcumin is found to be carry out on Forced swim test (FST) and Tail suspension test (TST), so the aim of our study to assess the antidepressant

potential of curcumin extract in mice using Forced swim test (FST) and Tail suspension test (TST).

PREPARATION OF CURCUMIN EXTRACT

The rhizomes of plant was collected, cleaned and dried under shade. The dried material powdered using a laboratory blender. About 200 gm of turmeric powder is extracted with 95% alcohol in a Soxhlet assembly until all the colouring matter was extracted. Alcoholic extract distilled off to a semi-solid brown coloured mass (about 75%). Then the crude extract was dissolved in 200 ml of benzene and extracted twice with equal volume of 0.1% Sodium hydroxide solution. The alkaline extracts combined and acidified with dilute hydrochloric acid. Obtained precipitate was allowed to settle for 15 minutes. After setting of precipitate, the extract concentrates by boiling on water bath and at the same time dissolving precipitate in boiling water. During this process of boiling, the resinous material was agglomerate and form lumpy mass. Then the solution filtered in hot condition and filtrate was concentrated to very small volume and finally cooled to get curcumin (1.5%)[26].

MATERIALS AND METHODS:

Animals: Animals used for this study are mice (6-8 weeks, 20–30 g). A total of 35 animals were used for this study. Rodent models were used for acute toxicity test and male rats were used for activity testing. The animals were housed in groups of 7 (each group contain 5 animals) and will allow acclimatizing to laboratory conditions for a minimum of 7 days before the time of experimentation. The experimental protocol were approved by the Institutional Animal Ethical Committee and conducted according to the CPCSEA guideline on the use and Care of experimental animals.

Drugs and Chemicals: All drug solution was freshly prepared before use. Carboxymethylcellulose (Hi-Media, Mumbai, India), Curcumin extract dissolved and diluted with dimethyl sulfoxide (DMSO) and imipramine hydrochloride (Sigma-Aldrich, St. Louis, USA) dissolved in distilled water.

Apparatus: **(a) Forced swim test (FST):** Forced swim test model was used to test for antidepressant activity by Porsolt *et al*[27]. The procedures will same as followed earlier. Mice will force to swim individually in a glass jar (25 × 12 × 25 cm^3) containing freshwater of 15 cm height and maintained at 25°C (± 3°C). After an initial 2 min period of vigorous activity,

each animal assumed a typical immobile posture. A mouse will considered to be immobile when it remained floating in the water without struggling, making only minimum movements of its limbs necessary to keep its head above water. The total duration of immobility will recorded during the next 4 min of a total 6 min test. The changes in immobility periods will study after administering drugs in separate groups of animals. Each animal was used only once.

(b) Tail suspension test (TST): The mouse was suspended from the edge of a lever above the tabletop (58 cm) by using adhesive tape placed approximately 1 cm from the tip of the tail. The other side of the lever should contain the writing pen tip to record the animal activity on the moving drum. The duration of immobility period was recorded on the moving drum rotating at a speed of 15 cm/min. A mouse is considered to be immobile when it is suspended passively and completely motionless. The recordings were done for a total period of 6 min and the percent immobility period was calculated from the tracings on the rotating drum.

Experimental protocol:

Treatment: Mice of either sex were divided into 7 groups of 5 animals in each group as mentioned below. All the test solutions were freshly prepared daily and administered in animals for 14 days by intraperitoneal (i.p.) route. Group I- Dimethyl sulfoxide (DMSO, 0.5 M, 10 ml/kg, i.p), Group II- Saline water (10 ml/kg, i.p.), Group III- Imipramine (15 mg/kg, i.p.), Group IV- Curcumin extract (25 mg/kg, i.p.), Group V- Curcumin extract (50 mg/kg, i.p.), Group VI- Curcumin extract (25 mg/kg, i.p.) + Imipramine (15 mg/kg, i.p.), Group VII- extract (50 mg/kg, i.p.) + Imipramine (15 mg/kg, i.p.).

Forced swimming test (FST): The animal was placed individually to swim inside the jar (25 × 12 × 25 cm^3) containing water up to 15 cm height and maintained at 25^0C. Allow the mouse to swim for 6 minutes. Note that after initial struggle to escape for 1-2 minutes, the animal become immobile or has little movements to keep floating in the water. Measure total immobility period during the 6 minutes of the test. Consider the animal immobile when it ceases to struggle and remain floating motionless in water making only those movements necessary to keep its head above water.

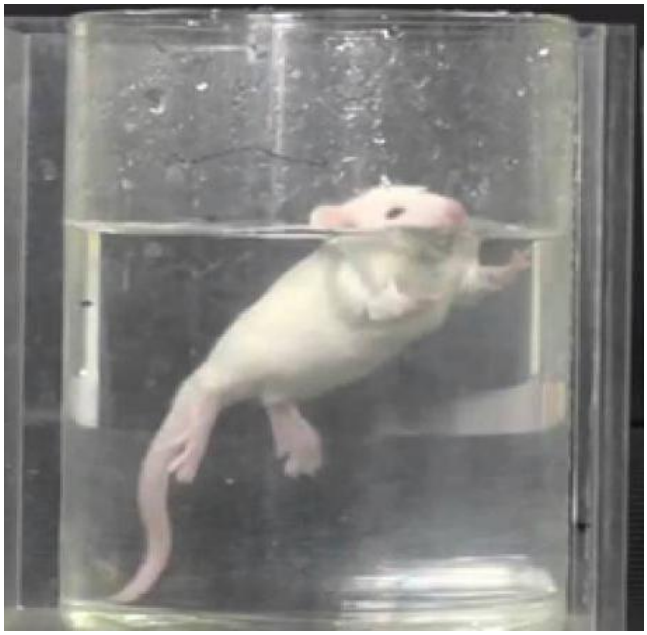

Figure No. 01: Forced swim test model

Tail-suspension Test (TST): The animal was suspended individually from the edge of lever above the tabletop (58 cm) by using adhesive tape placed approximately 1 cm from tip of the tail. The other side of the lever should contain the writing pen to record the animal activity on the moving drum. The duration of immobility period was recorded on the moving drum rotating at a speed of 15 cm/minutes. A mouse is considered to be immobile when it is suspended passively and completely motionless. The recording was done for a total period of 6 min and the immobility period was calculated from tracings on the rotating drum.

Figure No. 02: Tail suspension test model

Statistical Analysis: All results were expressed as mean ± SEM. Data was analyzed using one-way ANOVA followed by Dennett's test and Student t-test using Graph pad prism. $P < 0.05$ was considered to be statistically significant.

RESULTS

Saline water and DMSO administered mice groups were found no significant difference on the Immobility period of mice, during trail conducted on day 1, day 7 and day 14 by using FST and TST method. Imipramine (15 mg/Kg) administered mice groups were found large significant difference on the Immobility period of mice as compared to Saline water administered mice group, during trail conducted on day 1, day 7 and day 14 by using FST and TST method. Curcumin extract 25 mg/Kg administered mice groups were found some significant difference on the Immobility period of mice as compared to DMSO administered mice group, during trail conducted on day 1, day 7 and day 14 by using FST and TST method. Curcumin extract 50 mg/Kg administered mice groups were found large significant difference on the Immobility period of mice as compared to DMSO administered mice group, during trail conducted on day 1, day 7 and day 14 by FST and TST method. Curcumin extract 25 mg/Kg + Imipramine 15 mg/kg administered mice groups were found no significant difference on the Immobility period of mice as compared to Imipramine 15 mg/kg administered mice group, during trail conducted on day 1, day 7 and day 14 by FST and TST method. Curcumin extract 50 mg/Kg + Imipramine 15 mg/kg administered mice groups were found no significant difference on the Immobility period of mice as compared to Imipramine 15 mg/kg administered mice group, during trail conducted on day 1, day 7 and day 14 by using FST and TST method.

Table No. 1: Effect of various treatment group on immobility period of mice using forced swim test (FST) [Values are mean ± SE]

Group Number	Treatment Group of Mice (i.p.)	Immobility Period (sec) on Day 1	Immobility Period (sec) on Day 7	Immobility Period (sec) on Day 14
I	DMSO (Vehicle)	226 ± 2.10	230 ± 2.20	232 ± 2.24
II	Saline water	228 ± 2.25	233 ± 2.30	230 ± 2.42
III	Imipramine 15 mg/kg	157 ± 3.2$^{\#}$	140 ± 4.6$^{\#}$	128 ± 3.4$^{\#}$
IV	Curcumin extract 25 mg/kg	210 ± 4.2*	188 ± 5.3*	174 ± 3.4*
V	Curcumin extract 50 mg/kg)	198 ± 5.2*	172 ± 8.3*	148 ± 7.4*
VI	Curcumin extract 25 mg/kg + Imipramine 15 mg/kg	152 ± 4.2$^{\$}$	144 ± 6.2$^{\$}$	125 ± 5.4$^{\$}$
VII	Curcumin extract 50 mg/kg + Imipramine 15 mg/kg	154 ± 5.2$^{\$}$	141 ± 4.7$^{\$}$	122 ± 6.2$^{\$}$

[Values are expressed as mean ± SEM. *$P \leq 0.05$ as compared to DMSO group, #$P \leq 0.05$ as compared to saline water group and $ $P \leq 0.05$ as compared to Imipramine (15mg/kg) group].

Table No. 2: Effect of various treatment group on immobility period of mice using for Tail Suspension test (TST) [Values are mean ± SE]

Group Number	Treatment Group of Mice (i.p.)	Immobility Period (sec) on Day 1	Immobility Period (sec) on Day 7	Immobility Period (sec) on Day 14
I	DMSO (Vehicle)	227 ± 2.10	230 ± 2.20	231 ± 2.24
II	Saline water	229 ± 2.25	228 ± 2.30	230 ± 2.42
III	Imipramine 15 mg/kg	151± 4.2$^{\#}$	138± 5.6$^{\#}$	124 ± 4.4$^{\#}$
IV	Curcumin extract 25 mg/kg	204± 4.5*	178± 5.6*	168 ± 3.7*
V	Curcumin extract 50 mg/kg)	188± 6.2*	162± 7.4*	138 ± 5.4*
VI	Curcumin extract 25 mg/kg + Imipramine 15 mg/kg	152± 4.4$^{\$}$	145± 5.2$^{\$}$	124 ± 6.4$^{\$}$
VII	Curcumin extract 50 mg/kg + Imipramine 15 mg/kg	150± 5.2$^{\$}$	141± 5.7$^{\$}$	119 ± 5.2$^{\$}$

[Values are expressed as mean ± SEM. *$P \leq 0.05$ as compared to DMSO group, #$P \leq 0.05$ as compared to saline water group and $ $P \leq 0.05$ as compared to Imipramine (15mg/kg) group].

DISCUSSION

In the present study, the antidepressant activity of curcumin in mice was studied by using Forced swimming test (FST) and Tail suspension test (TST). Forced swim test model was used to test for antidepressant activity by Porsolt et al[27]. In this procedure, mouse was force to swim individually in a glass jar (25 × 12 × 25 cm^3) containing freshwater of 15 cm height and maintained at 25°C (± 3°C). After an initial 2 min period of vigorous activity, each animal assumed a typical immobile posture. A mouse was considered to be immobile when it remained floating in the water without struggling, making only minimum movements of its limbs necessary to keep its head above water. The total duration of immobility was recorded during the next 4 min of a total 6 min test. The change in immobility periods was study after administering drugs in separate groups of animals. Each animal was used only once. In TST, mouse was suspended from the edge of a lever above the tabletop (58 cm) by using adhesive tape placed approximately 1 cm from the tip of the tail. The other side of the lever should contain the writing pen tip to record the animal activity on the moving drum. The duration of immobility period was recorded on the moving drum rotating at a speed of 15 cm/min. A mouse is considered to be immobile when it is suspended passively and completely motionless. The recordings were done for a total period of 6 min and the percent immobility period was calculated from the tracings on the rotating drum.

Control group (Saline water and DMSO administrated group) showed no significant difference in their immobility period during FST and TST. These results show that saline water and DMSO not affect the behavior of rats. Imipramine (15 mg/kg) (reference drug) treated group was significantly decrease the immobility time as compared to control group (saline water). This result showed that Imipramine decreases depression in animal. All synthetic antidepressant drugs include imipramine inhibit the reuptake of serotonin and norepinephrine neurotransmitters into their respective neurons the brain. This result increases the availability of serotonin and norepinephrine on their receptors and produces antidepressant effect. Curcumin (25 mg/kg) treated group was significantly some decrease the immobility time of mice during FST and TST as compared to control (DMSO) treated group. This result showed that curcumin 25 mg/kg is not a sufficient dose to produce antidepressant effect in mice. Curcumin (50 mg/kg) treated group was significantly large decrease the immobility time of

mice during FST and TST as compared to control (DMSO) treated group. This result showed that curcumin 50 mg/kg is a sufficient dose to produce antidepressant effect in mice. This result supported by previous study which declared that curcumin inhibits the MAO enzymes and increases the level of serotonin and dopamine neurotransmitters, which induce antidepressant activities[28]. Curcumin (25 mg/kg) + Imipramine (15 mg/kg) treated group was showed no significant difference in their immobility period during FST and TST, as compared to Imipramine (15 mg/kg) treated group. This result indicate that curcumin 25 mg/kg does not enhance the activity of imipramine when it given in combination. Curcumin (50 mg/kg) + Imipramine (15 mg/kg) treated group was showed no significant difference in their immobility period during FST and TST, as compared to Imipramine (15 mg/kg) treated group. This result indicate that curcumin 50 mg/kg does not enhance the activity of imipramine when it given in combination, because the mechanism of antidepressant action is different in Imipramine as well as curcumin.

CONCLUSION

Finally, it may be concluded that Curcumin (50 mg/kg) exert antidepressant effect in mice by using FST and TST method. The antidepressant effect of curcumin (50 mg/kg) may be inhibiting the MAO enzymes and increases the level of serotonin and dopamine neurotransmitters in the brain. Curcumin is less potent than imipramine, and Curcumin (50 mg/kg) with imipramine give not synergetic antidepressant action in mice. Thus, inclusion of curcumin in our normal diet and its use as a nutritional supplement may have tremendous potential for health improvement and protection from depression.

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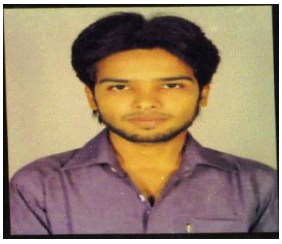	**Akhalesh K. Dubey** Shri Ramnath Singh Institute of Pharmaceutical Science and Technology, Gwalior
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