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Evaluation of antidepressant like activity of *curcumin* and its combination with sertraline and imipramine on mice

P. Sailaja*, SK. Karishma, G. Vijayamma, P.V. Durga Seshu Priya

Swathi College of Pharmacy, NH-5, Venkatachalam, SPSR Nellore-524320, Andhra Pradesh, India

ABSTRACT

Curcumin (Zingiberace) popularly known as Turmeric (beauty aid, cooking spice and a dye.), is an herbaceous climber that has been widely used in Mexican traditional medicine for the treatment of different central nervous system (CNS) disorders. Nevertheless, the available scientific information about this species is scarce and there are no reports related to its possible effect on the CNS. In this work, the effects of *curcumin* were evaluated in mice using behavioral tests sensitive to clinically effective antidepressant compounds. The extract (50mg/kg), administered (p.o), was able to decrease the immobility time of mice dose-dependently when subjected to both tail suspension and forced swim tests and the effects are comparable to that of standard drugs i.e., sertraline (5mg/kg) and imipramine (15mg/kg). Neither the extracts of *curcumin* and sertraline, at the doses tested, produced significant effects on locomotor activity when subjected to open field behavioral test. These results demonstrated that *curcumin* had specifically antidepressant effects in vivo. In conclusion, the present study suggested that *curcumin* extracts possessed potential antidepressant effects which could be of therapeutic interest for using in the treatment of patients with depressive disorders.

Keywords: *Curcumin*, antidepressant activity, tail suspension test, forced swim test

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*Corresponding Author

P. Sailaja
Swathi College of Pharmacy,
NH-5, Venkatachalam, SPSR Nellore,
Andhra Pradesh, India-524320
Manuscript ID: IJPNM3086



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1. Introduction

According to World Health Organization, depression is a serious emotional disorder causing a huge burden on health. Depression is a state of low mood and aversion to activity that affects person's thoughts, behaviour, feelings and physical well-being. Depressed mood is also a main or common feature of certain psychiatric syndromes such as clinical depression.[1] Major depressive disorder (MDD) is the most common form of psychiatric illness, affecting around 16-17% of the adult population in their lifetime.[2] The World Health Organization (WHO, 2002) noted that MDD is one of the disorders with the highest disease burden in the world, projected to be the second leading cause of disability worldwide. In spite of the availability of antidepressant drugs like tricyclic antidepressants, selective reversible inhibitors of monoamine oxidase-A (MAO-A), [3] selective serotonin reuptake inhibitors (SSRIs) and selective noradrenaline reuptake inhibitors (SNRIs), depression continue to be a major medical problem.

Basic neuroscience offers the promise of improving our understanding of disease pathophysiology, identifying novel mechanisms that can be targeted by more effective pharmacotherapies and screening of herbal sources of drugs.[4] These considerations implicate the search for new antidepressant agents that have a fast onset of action, with less side effects and a wider safety margin.[5] On the basis of the above information, the *curcumin* was selected for evaluating its anxiolytic and antidepressant activity due to its traditional use in the management of anxiety, stress, insomnia, hysteria, skin inflammation, cough and fever.[7]

Chemical constituents in curcumin include hydrocyanic acid, groups of flavonoids and Harman alkaloids.[8] Some reports have pointed out the harman alkaloids as the bioactive constituents of *curcumin Longa*, one of the species of *curcumin* that have been extensively studied chemically and biologically.[9] Harman alkaloids were also found to be present in *curcumin*. So far there has been no scientific report in literature about the antidepressant activity (in experimental animal models) of this species.[10] Therefore, the present study has been undertaken to investigate the effect of *curcumin*. on depression in mice.

2. Materials and method

Experimental methods:

Plant material: The powdered were purchased from the Ayurvedic pharmacy, Nellore. Andhra Pradesh. The plant material was identified and authenticated by the botanist, Botanical garden, Tirupathi. The botanical nomenclature of the plants was duly identified by using standard floras and also cross-checked with Herbarium records. [12, 13]

Drugs and chemicals:

Normal saline, rectified spirit, imipramine, sertraline tablets (Apollo pharmacy, Nellore) and powder of curcuma longa (Turmeric). [14]

Preparation of extract:

Curcumin was suspended in 0.9% normal saline and was administered orally to mice for a period of 7 days. [15]

Experimental Animals

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Healthy adult albino mice of Wistar strain (25-30g) were used in the present study. The animals were caged in clean polypropylene cages under controlled temperature 20-24 and 12 h light/ dark and were fed with standard mice pellet (Hindustan lever limited, Mumbai, India) diet and clean drinking water was made available ad libitum. All the animals were carefully monitored and all the experimental protocols were approved by Institutional Animal Ethical Committee (01/NIPER/CPCSEA/351). [16]

Acute toxicity study

The acute toxicity study was conducted as per the OECD guidelines 423 (OECD, 2001) ANNEX-423.⁽¹⁸⁾

Experimental protocol for antidepressant activity

The animals were divided in to five groups consisting of six mice in each group.

Group I: Received only distilled water, daily and served as normal control.

Group II: Received imipramine (15mg/kg i.p, daily) for 7 days.

Group III: Received curcumin (50mg/kg i.p, daily) for 7 days.

Group IV:

Received sertraline+ curcumin (5mg/kg/i.p+50mg/kg i.p, daily) for 7 days.

Group V:

Received imipramine + Curcumin (15mg/kg i.p+50mg/kg i.p,daily)for 7 days.

Behavioral Parameters

Behavioral assessments were carried out on day 0, 1, 3 and day 7.

Test for locomotor activity

The locomotor activity was measured using Actophotometer. It consists of cage which has 30 X 30 X 30 cm, and at the bottom six lights and photocells were placed in the outer periphery of the bottom in such a way that a single mouse blocks only one beam.⁽¹⁹⁾ Photocell is activated when the rays of light falls in photocells, the beam of light is interrupted as and when animal crosses the light beam, the number of interruptions were recorded for a period of 10 minutes.⁽²⁰⁾

Tail suspension test

The total duration of immobility by tail suspension was measured according to the method of Steru et al., 1985.

⁽²¹⁾Mice both acoustically and visually isolated and suspended 50cm above the floor by adhesive tape placed approximately 1cm from the tip of the tail, immobility time was recorded during a 4 minutes test for animals of all groups.⁽²²⁾

Forced swim test

FST is the most widely used pharmacological in vivo model for assessment of antidepressant activity. In this model, mice were forced to swim in condition from which they cannot escape and rapidly become immobile, floating in an upright position and making only small movements to keep their heads above water.⁽²³⁾ The development of immobility reflects the cessation of persistent escape directed behavior or learned helplessness, and a decrease in the duration of immobility, is interpreted as an antidepressant like effect. Mice were placed individually in a glass cylinders (height: 21 cm, diameter: 14.5 cm) containing 15 cm of water at 23

± 1°C. First 2 min were allowed for acclimatization and the duration of climbing, swimming and immobility during 4 min were recorded. [24]

Statistical Analysis: All the values are expressed as mean ± S.E.M for groups of six animals each. Analyzed by one way ANOVA and compared by using Tukey- Kramer multiple comparison test. The values are statistically significant at three levels, ***p<0.001, **p<0.01, *p<0.05. But no significant if p > 0.05.

3. Results and Discussion

Behavioural Parameters

Spontaneous motor activity in mice

The results of the effect of Curcumin and its combination with sertraline and imipramine on spontaneous motor activity were summarized in Figure 8 and showed that there is no significant change in the spontaneous motor activity of Curcumin and its combination with sertraline and imipramine at lower and higher doses when compared to disease control group and normal control group. [25]

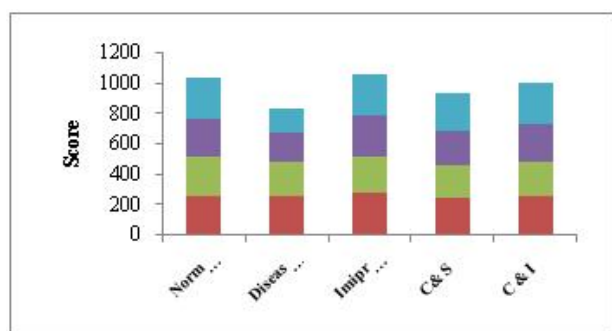


Figure 1: Effect of curcumin and its combination with sertraline and imipramine on spontaneous motor activity

Values are expressed as Mean ± SEM [n = 6] *P<0.05, **P<0.01,***p<0.001 as compared to respective control group.

Mobility time in TST

The results of the effect of Curcumin and its combination with sertraline and imipramine on immobility time in TST were summarized in figure 9 and showed that Curcumin and its combination with sertraline and imipramine lower and higher doses and imipramine at a dose of 25 mg/kg showed significant decrease in immobility time (P<0.01; P<0.001) as compared to disease control group.⁽²⁶⁾

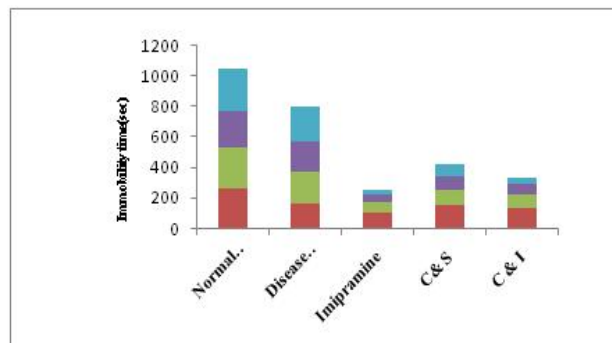


Figure 2: Effect of Curcumin and its combination with sertraline and imipramine on immobility time in TST

Values are expressed as Mean ± SEM [n = 6] *P<0.05, **P<0.01,***p<0.001 as compared to respective control group.

Immobility time in FST

The results of the effect of Curcumin and its combination with sertraline and imipramine on immobility time in FST were summarized in Figure 10 and imipramine at a dose of 15 mg/kg showed significant decrease in immobility time (P<0.01) as compared to disease control group. Curcumin and its combination with sertraline and imipramine showed significant decrease in immobility time and increase in swimming and climbing time (P<0.05, P<0.01) in a dose dependent manner as compared to disease control group.⁽²⁷⁾

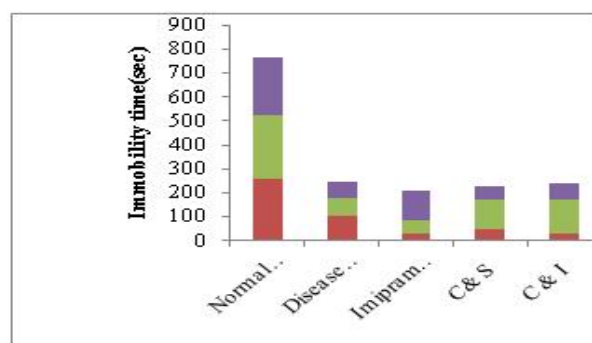


Figure 3: Effect of Curcumin and its combination with sertraline and imipramine on FST

Values are expressed as Mean ± SEM [n = 6] *P<0.05, **P<0.01,***p<0.001 as compared to respective control group.

Table 1: Table 1: Effect of Curcumin and its combination with sertraline and imipramine on Spontaneous motor activity

Groups	Score			
	0 th Day	1 st Day	3 rd Day	7 th Day
Normal Control	259.2±9.26	262.0±6.96	246.21±10.20	2692.4±8.120
Disease Control	260.0±13.08	230.8±12.90	184.7±7.42	1627.8±9.981
Imipramine (15mg/kg)	279.0±9.24	244.5±10.29*	263.3±9.182**	274.2±9.529**
Curcumin(50mg/kg)+Sertraline (5mg/kg)	251.2±7.463	210.1±4.940**	234.2±6.570**	245.8±8.085**
Curcumin (50mg/kg)+Imipramine (15mg/kg)	260.2±9.453	223.8±8.080**	256.0±8.065**	264.2±9.343**

Values are expressed as Mean ± SEM [n = 6] *P<0.05, **P<0.01,***p<0.001 as compared to respective control group.

Table 2: Effect of Curcumin and its combination with sertraline and imipramine on immobility time in TST

Groups	Immobility time in sec			
	0 day	1 st day	3 rd day	7 th day
Disease control	162.80±8.1	199.70±7.2	204.0±9.9	224.4±6.7
Imipramine (15mg/kg)	101.12±5.2	72.30±6.1***	49.6±3.8***	26.00±5.1***
Curcumin (50mg/kg)+Sertraline (5mg/kg)	146.1±6.3	104.42±4.1**	91.26±5.01**	70.69±5.33**
Curcumin (50mg/kg)+Imipramine (15mg/kg)	128.80±8.21	91.90±6.92***	67.13±4.14***	40.89±3.81***

Table 3: Effect of Curcumin and its combination with sertraline and imipramine on Forced Swim Test.

Groups	Immobility time (sec)	Swimming time (sec)	Climbing time (sec)
Disease control	105.0±7.18	71.15±10.30	68.15±6.01
Imipramine (15mg/kg)	28.4±2.7**	58.3±9.7	125.25±6.01*
Curcumin (50mg/kg)+Sertraline (5mg/kg)	49.0±1.58*	124.6±5.0**	57.2±5.02
Curcumin (50mg/kg)+Sertraline (15mg/kg)	28.9±2.557**	142.9±5.74**	68.1±3.542

4. Conclusion

In the present study, curcumin and its combination with sertraline and imipramine was evaluated for antidepressant activity in mice for a period of 7 days. Antidepressant activity was evaluated by Forced Swim Test and Tail Suspension Test, spontaneous locomotor activity.[28] Reduced immobility time in both FST and TST, spontaneous locomotor activity in mice by curcumin and its combination with sertraline and imipramine treatment indicating antidepressant activity. Results obtained in this study prove the efficacy of curcumin and its combination with sertraline as anti-depressant agent, which is comparable to the standard drug Imipramine by its behavioural effects. Further studies are required to prove the possible mechanism of action of curcumin and its combination with sertraline and imipramine and also clinical studies for evaluating its efficacy in patients' [29]

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