EVALUATION OF ANTIDEPRESSANT LIKE ACTIVITY OF CURCUMIN AND ITS COMBINATION WITH FLUOXETINE AND IMIPRAMINE: AN ACUTE AND CHRONIC STUDY

JAYESH SANMUKHANI, ASHISH ANOVADIYA and CHANDRABHANU B. TRIPATHI*

Department of Pharmacology, Government Medical College, Bhavnagar – 364001, Gujarat, India

Abstract: Curcumin is the active ingredient of commonly used spice *Curcuma longa* Linn. In the present study, the antidepressant like activity of curcumin and its combination with fluoxetine and imipramine was studied in acute model (three doses 24, 5 and 1 h before test) of forced swimming test (FST) in glass jar and tail suspension test (TST) in mice and in chronic model (14 day study) of FST with water wheel in rats. All the tests were carried out in the following seven groups (n = 6 in each group), drugs being given orally (doses for mice): Group 1 (vehicle), group 2 (curcumin 50 mg/kg), group 3 (curcumin 100 mg/kg), group 4 (fluoxetine 20 mg/kg), group 5 (imipramine 15 mg/kg), group 6 (curcumin 100 mg/kg plus fluoxetine 20 mg/kg) and group 7 (curcumin 100 mg/kg plus imipramine 15 mg/kg). Equivalent doses for rats were used. Both the acute model of FST and TST, and the chronic model of FST with water wheel showed significant antidepressant like activity of curcumin in 100 mg/kg dose as compared to vehicle control (p < 0.05). The effect of curcumin (100 mg/kg) was similar to that of fluoxetine and imipramine (p > 0.05) but its addition to fluoxetine and imipramine did not improve their antidepressant activity (p > 0.05). Curcumin increased both the swimming and climbing behavior in FST, thus its antidepressant like activity could be due to an increase in serotonin, norepinephrine and dopamine levels in the brain. Curcumin can be a useful antidepressant especially in cases which respond to drugs having mixed effects on serotonin and catecholamines levels in the brain.

Keywords: curcumin, antidepressant, forced swimming test (FST), tail suspension test (TST)

Depression is a mental illness characterized by profound and persistent feeling of sadness or despair and/or loss of interest in things that were once pleasurable. The life time risk of depression varies from 5% to 12% in men and 10% to 25% in women (1). It is responsible for the largest proportion of disease burden attributable to non-fatal health outcomes, accounting for almost 12% of total years lived with disability worldwide (2). Patients with depression have decreased social, occupational, and educational functioning. Moreover, they have high medical morbidity and are often plagued with more pain and physical illness than the general population. It has been estimated that 15% of patients with severe depressive episodes commit suicide. An accurate diagnosis followed by effective treatment can improve this outcome (3).

Depression shows a good response to pharmacological and behavioral treatments, individually or in combination. Among the various pharmacological agents selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) are most commonly used but have a lot of distressing adverse effects as they are often used for very long period of time. Moreover, most of the patients respond to a single drug (most commonly a SSRI or a TCA) but only about 30% achieve remission (complete normalization of symptoms), thus, combination therapy of antidepressants with different mechanism of action or those having mixed effects on serotonin (5HT) and catecholamines i.e., norepinephrine (NE) and dopamine (DA) levels in brain are often required (4). This also adds up to the adverse effects of individual drugs. Therefore, search for antidepressants with broader spectrum of action and a benign profile of adverse effects continues.

Extract of rhizomes of *Curcuma longa* Linn. has been used to treat mental disorders in the past. It is a major constituent of Xiaoyao-san and Jieyu-wan, the traditional Chinese herbal medicines, which have been effectively used to manage stress and depression related disorders in China (5). Curcumin is the active principle in this extract of

* Corresponding author: e-mail: cbrtripathi@yahoo.co.in; mobile: +919825951678

rhizomes of *Curcuma longa* Linn. It is known to have antioxidant, anti-inflammatory, immunodulatory, anticancer and neuroprotective properties (6–9). Though there have been some reports of anti-depressant like action of curcumin, its effect as add on to commonly prescribed antidepressants *via* oral route has not been studied. The route of administration of curcumin holds special importance as bioavailability of curcumin *via* oral route is quite low.

This work was planned to assess the antidepressant like activity of curcumin in two different doses and to see its effect as an add on therapy to the two most commonly prescribed antidepressants in our setting, fluoxetine and imipramine, *via* oral route in acute and chronic models in two different animal species.

MATERIALS AND METHODS

Drugs

Curcumin not less than (NLT) 95% (Bio-cur-cumin®, Arjuna Natural Extracts Ltd., Alwaye, Kerala, India); fluoxetine hydrochloride (Cadila Pharmaceuticals Ltd., Gujarat, India) and imipramine hydrochloride (Sun Pharmaceutical Industries Ltd., Mumbai, India); gum acacia (Fischer Scientific, Mumbai, India) were used in the study (Fig. 1). Curcumin suspension was made in 5% gum acacia, which was used as vehicle control. Fluoxetine hydrochloride and imipramine hydrochloride were dissolved in distilled water.

Dose of curcumin was calculated by using data from ancient Chinese medicine. They used dry rhizome of *Curcuma longa* Linn. in a dose of 3–9 g/70 kg adult for treating depressive disorders (5). Considering a median dose of 6 g/70 kg and curcumin content of dry rhizomes to be about 5–6% (10), dose of curcumin NLT 95% comes out to be 50 mg/kg in mice using surface area ratios (11). Therefore, curcumin was tested in a dose of 50 mg/kg and 100 mg/kg in mice and equivalent doses used for rats were 35 mg/kg and 70 mg/kg.

Fluoxetine hydrochloride was used in a dose of 20 mg/kg in mice; equivalent dose for rats was calculated (14 mg/kg) using surface area ratios (11). Imipramine hydrochloride was used in dose of 15 mg/kg in mice and 10.5 mg/kg in rats (12).

Animals

Swiss albino mice three–four months of age (26 to 34 g) and albino rats of Wistar strain (160 to 220 g) of either sex were procured from the central animal house of the institute. They were housed in
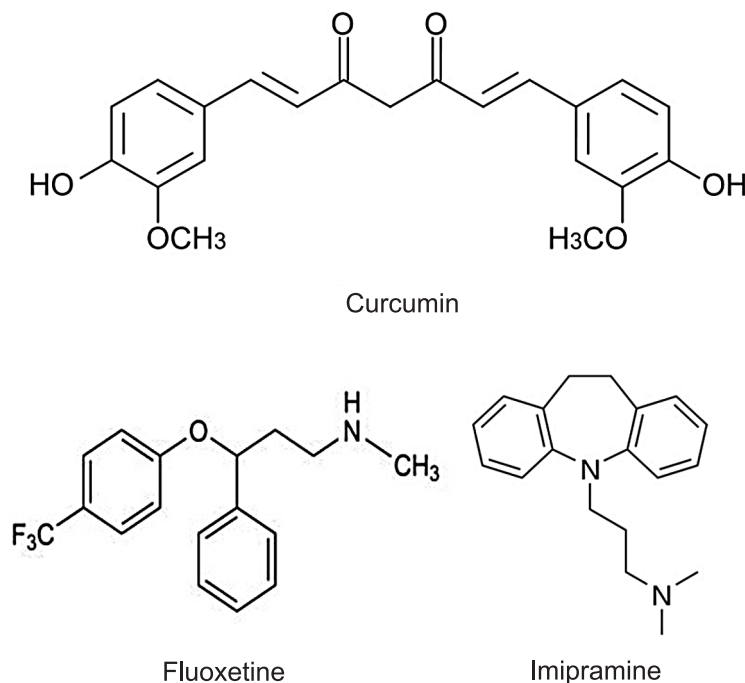

Figure 1. Chemical structure of curcumin, fluoxetine and imipramine

standard polypropylene cages and kept under controlled room temperature (24 ± 2°C) in a 12 h light-dark cycle. The animals were given standard laboratory diet and water *ad libitum*. The animals were acclimatized to the laboratory conditions at least one day prior to the behavioral experiments. All the experiments were carried out between 12:00 to 16:00 h. Food was withdrawn 12 h before the experiments. Each animal was used only once. The animal handling was performed according to the Good Laboratory Practice (GLP) guidelines. All the experiments were performed after the prior permission from the Institutional Animal Ethics Committee (IAEC), Government Medical College, Bhavnagar (Gujarat, India).

Study design

The antidepressant like activity of curcumin and its combination with fluoxetine and imipramine was evaluated by forced swimming test (FST) in glass jar and tail suspension test (TST) after acute (three doses) dosing in mice; and forced swimming test with activity wheel after chronic (14 days) dosing in rats. Locomotor activity was also tested after acute dosing in mice. All the tests were done in seven groups of animals with at least six animals in each group.

Acute study

The groups for acute dose study in mice were as follows: Group 1 (vehicle control group): 5% gum acacia (2.5 mL/kg) 24, 5 and 1 h orally before the test. Group 2 (curcumin 50 mg/kg): curcumin suspension in a dose of 50 mg/kg orally 24, 5 and 1 h orally before the test. Group 3 (curcumin 100 mg/kg): curcumin suspension in a dose of 100 mg/kg orally 24, 5 and 1 h orally before the test. Group 4 (fluoxetine): fluoxetine hydrochloride in a dose of 20 mg/kg orally 24, 5 and 1 h orally before the test. Group 5 (imipramine): imipramine hydrochloride in a dose of 15 mg/kg orally 24, 5 and 1 h orally before the test. Group 6 (curcumin plus fluoxetine): fluoxetine hydrochloride in a dose of 20 mg/kg and curcumin suspension in a dose of 100 mg/kg orally 24, 5 and 1 h orally before the test. Group 7 (curcumin plus imipramine): imipramine hydrochloride in a dose of 15 mg/kg and curcumin suspension in a dose of 100 mg/kg orally 24, 5 and 1 h orally before the test.

Chronic study

The protocol for drug administration in chronic study in rats was the same as that in acute study except that the drugs were given for fourteen days,

last dose being given 1 h before the test and equivalent doses for rats as calculated by surface area ratios were used.

Forced swimming test in glass jar

FST in glass jar was performed as described by Porsolt et al. with few modifications (13). This test consists of two parts, an initial training period of 15 min followed by actual test for 5 min duration 24 h later. Mice were individually forced to swim inside a vertical borosilicate glass cylinder (height: 40 cm; diameter: 15 cm; containing 15 cm hight of water maintained at 25 ± 1°C). Mice placed in the cylinder for the first time were initially highly active, vigorously swimming in circles, trying to climb the wall or diving to the bottom. After 2–3 min, activity began to subside and was interspersed with phases of immobility or floating of increasing length. After 5–6 min, immobility reached a plateau where the mice remained immobile for approximately 80% of the time. After 15 min in the water, the mice were removed, wiped with dry cloth and allowed to dry before being returned to their home cages. The cylinders were emptied and washed thoroughly after testing for each mouse. The mice were again placed in the cylinder 24 h later after three doses of drug and their activity was recorded from above for 5 min using a digital camera The recordings were later analyzed by a rater who was blinded to the treatment condition, to find the duration of immobility, swimming behavior and climbing behavior in the 5 min test period using stopwatch. An animal was judged to be immobile whenever it remained floating passively in the water in a slightly hunched but upright position, its nose just above the surface, with no additional activity other than that necessary to keep its head above water. Swimming was defined as active movement throughout the swim chamber, which included crossing into another quadrant. Climbing activity (also termed thrashing) consisted of upward directed movements of the forepaws along the side of the swim chamber.

Tail suspension test

TST was done as described by Steru et al. (14). After three doses of drugs, mice were suspended on a string held by a metal stand, by an adhesive tape placed 1 cm from the tip of the tail. This string was 58 cm above the table top. The activity of the mice was recorded using a digital camera for a period of 5 min. During the experiment, each animal under test was both acoustically and visually isolated from other animals. The videos were analyzed by a rater blinded for treatment condition to find the duration

Table 1. Effect of drugs on immobility, swimming and climbing time in forced swimming test in mice in acute study.

Treatment group	Dose (mg/kg) *per os*	Immobility time (s) (mean ± SEM)	Swimming time (s) (mean ± SEM)	Climbing time (s) (mean ± SEM)
Vehicle control	2.5 mL/kg	224.7 ± 13.8	40.0 ± 5.5	35.3 ± 11.8
Fluoxetine	20	110.7 ± 16.5*	144.5 ± 11.1*	41.8 ± 5.3
Imipramine	15	127.3 ± 15.9*	126.8 ± 10.8*	45.8 ± 9.4
Curcumin 50 mg/kg	50	173.5 ± 18.4	67.7 ± 10.7[#^]	56.2 ± 9.7
Curcumin 100 mg/kg	100	111.7 ± 8.6*	90.0 ± 13.7[#]	98.3 ± 16.0*[#]
Fluoxetine plus curcumin	20 + 100	76.5 ± 22.0*	143.8 ± 10.5*	79.7 ± 16.6
mipramine plus curcumin	15 + 100	113.5 ± 15.1*	123.0 ± 19.2*	63.5 ± 10.9
One way ANOVA	F	9.27	10.77	3.55
	dF	6,35	6,35	6,35
	p	< 0.0001	< 0.0001	0.007

Statistical analysis of data was carried by one-way ANOVA followed by Tuckey-Kramer multiple comparisons test. *p < 0.05 as compared to vehicle control; [#]p < 0.05 as compared to fluoxetine; [^]p < 0.05 as compared to imipramine; n = 6 in each group.

Table 2. Effect of drugs on immobility time in tail suspension test and total counts of locomotor activity in photoactometer in mice in acute study.

Treatment group	Dose (mg/kg) *per os*	Immobility time (s) (mean ± SEM)	Total counts (mean ± SEM)
Vehicle control	2.5 mL/kg	157.8 ± 17.9	115.7 ± 11.1
Fluoxetine	20	40.7 ± 13.0*	116.8 ± 22.1
Imipramine	15	64.5 ± 23.4*	105.8 ± 13.5
Curcumin 50 mg/kg	50	72.8 ± 14.5*	119.3 ± 16.4
Curcumin 100 mg/kg	100	69.7 ± 21.7*	114.5 ± 14.2
Fluoxetine plus curcumin	20 + 100	42.5 ± 14.1*	120.5 ± 11.0
Imipramine plus curcumin	15 + 100	84.7 ± 5.2	140.3 ± 25.5
One way ANOVA	F	5.6	0.381
	dF	6,35	6,36
	p	< 0.001	0.886

Statistical analysis of data was carried by one-way ANOVA followed by Tuckey-Kramer multiple comparisons test. * p < 0.05 as compared to control; n = 6 in each group.

Table 3. Effect of drugs on number of counts in forced swimming test with activity wheel in rats in chronic study

Treatment group	Dose (mg/kg) *per os*	No. of rotations (mean ± SEM)
Vehicle control	5 mL/kg	17.7 ± 1.1
Fluoxetine	14	42.5 ± 1.3*
Imipramine	10.5	49.5 ± 2.6*
Curcumin 35 mg/kg	35	37.2 ± 2.7*
Curcumin 70 mg/kg	70	46.7 ± 1.7*
Fluoxetine plus curcumin	14 + 70	42.0 ± 5.4*
Imipramine plus curcumin	10.5 + 70	46.6 ± 2.0*

Statistical analysis of data was carried by one-way ANOVA followed by Tuckey-Kramer multiple comparisons test. F (6,35) = 15.1 (p < 0.0001). * p < 0.05 as compared to control; n = 6 in each group.

of immobility in seconds. Mice were considered immobile when they hang passively and completely motionless.

Forced swimming test (FST) with activity wheel

The FST with activity wheel was first described by Nomura et al. (15) and is based on despair swim paradigm described by Porsolt et al. One hour after the last dose of fourteen day treatment of rats, they were forced to swim in an apparatus consisting of a water tank (30 × 20 × 15 cm) with a water wheel (25 cm diameter) in its centre. The tank was filled with water up to a height of 13 cm maintained at 25 ± 1°C. When placed in the tank, rats tried to escape from the tank but ended up in rotating the wheel. The number of times the wheel was rotated by rats in a 5 min test period, as recorded in the digital counter of the instrument, was noted. The tank was cleaned after experiment with each rat.

Measurement of locomotor activity

The locomotor activity of animals was measured to differentiate between sedative and central nervous system stimulant activity of drugs. It was measured by using a digital photo actometer (Teknik, India). After three doses of drugs 24, 5 and 1 h before the test, mice were placed in the photo actometer covered with the fibre lid. Mice tried to explore the area and during their movement they intercepted the photobeams. The number of interceptions was counted by the photoactive cells. Locomotion of the animal was expressed in terms of total number of ambulations (total photobeam counts) during a 5-min test for each mouse.

Statistical analysis

All the results are expressed as the mean ± standard error (SEM). Data were analyzed using one-way analysis of variance (ANOVA), followed by Tukey-Kramer multiple comparisons test to determine statistical significance of various groups as compared to vehicle, fluoxetine and imipramine groups. Statistical significance was set at $p < 0.05$. All the analyses were done using SPSS Statistics (17.0).

RESULTS

In the acute model of FST in glass jar with mice (Table 1) all the test groups, except curcumin in a dose of 50 mg/kg, showed a significant decrease in immobility time as compared to the vehicle control group ($p < 0.05$). There was a trend towards decreasing the immobility time with increasing dose of curcumin. The effect of 100 mg/kg curcumin was similar to that of fluoxetine and imipramine. Combination of curcumin in a dose of 100 mg/kg further decreased the immobility time of fluoxetine and imipramine, but the decrease was not statistically significant. The swimming time in fluoxetine, imipramine, fluoxetine plus curcumin and imipramine plus curcumin groups was significantly higher as compared to the vehicle control ($p < 0.05$), while that in curcumin (100 mg/kg) group, though not statistically significant, was more than twice than that in the vehicle control. The climbing time significantly increased only in curcumin 100 mg/kg group as compared to vehicle control ($p < 0.05$).

In the TST model in mice (Table 2) there was a significant decrease in immobility time in all the groups as compared to vehicle control ($p < 0.05$) except in imipramine plus curcumin group. The antiimmobility effect of curcumin was comparable to that of fluoxetine and imipramine ($p > 0.05$). Combination of curcumin and imipramine nonsignificantly increased the immobility time of mice as compared to imipramine alone ($p > 0.05$).

In the chronic study model of FST in rats (Table 3), the study groups affected the number of rotations significantly [F (6,35) = 15.1 ($p < 0.0001$)]. All the drugs showed a significant increase in the number of rotations as compared to vehicle ($p < 0.05$) but neither curcumin, nor its combination with fluoxetine or imipramine showed statistically significant difference as compared to fluoxetine or imipramine alone ($p > 0.05$).

Locomotor activity of mice (Table 2), as measured using digital photo actometer, was found to be similar in all the groups [F (6,35) = 0.381 ($p = 0.886$)].

DISCUSSION

The present study showed that curcumin has antidepressant like activity similar to that of fluoxetine and imipramine in both acute and chronic models but fails to significantly improve the activity of fluoxetine and imipramine when added to them.

The findings that curcumin (active ingredient of *Curcuma longa* Linn.) significantly decreases the time of immobility in FST and TST and increases the number of rotations in FST with water wheel as compared to vehicle control are in accordance with previous reports with crude aqueous extract of *Curcuma longa* Linn. (16). The study showed that curcumin does not improve the antiimmobility effect of fluoxetine and imipramine when given *per*

os whereas in an earlier study Kulkarni SK et al. (17) it was shown that curcumin, when given by intraperitoneal route, significantly increased the antiimmobility effect of subthreshold dose of fluoxetine (5 mg/kg) but not of imipramine (5 mg/kg). The difference in findings could be due to use of subtherapeutic dose in the previous study, while full recommended dose of fluoxetine was used in the present study. Another reason for the different observation could be a pharmacokinetic interaction of curcumin with fluoxetine and imipramine. In the present study both the drugs were administered together *via* oral route, while the previous study used the drugs *via* intraperitoneal route.

The distinction in the swimming and the climbing behaviors helped in prediction of the possible neurotransmitters involved in the antidepressant like action of curcumin. Curcumin in a dose of 100 mg/kg increased both the swimming and the climbing behaviors in mice. It has been previously suggested by Rénéric and Lucki (18) that an increase in both swimming and climbing behaviors in the FST occurs when the animal is treated by a drug which increases serotonin, norepinephrine and dopamine levels in the nerve terminals. An increase in all the three neurotransmitters could be by inhibition of monoamine oxidase (MAO) activity in the brain. These findings are supported by other studies showing inhibition of MAO activity by curcumin and involvement of serotonergic and dopaminergic system in its antidepressant like activity (17, 19, 20).

A growing body of research indicates that besides depletion of serotonin and catechoamine neurotransmitters, depression could result from various other pathophysiological mechanisms as well. Researchers suggest that depression may inhibit neurogenesis in the hippocampus (21). This idea is supported by the finding that antidepressants can promote neurogenesis (22). Curcumin administration has also shown to increase hippocampal neurogenesis in chronically stressed rats; this could be *via* modulation of hypothalamic-pituitary-adrenal (HPA) axis and up regulation of 5-HT_{1A} receptors and the brain derived neurotrophic factor (BDNF) in the hippocampus (9). This mechanism may also underlie the therapeutic actions of curcumin during chronic treatment. Activation of innate immunity *via* nuclear factor-κB (NF-κB) and mitogen activated protein kinases has also been implicated in the pathophysiology of depression. NF-κB leads to increased release of interferon-α and other cytokines, which eventually lead to dysregulation of HPA axis, metabolism of monoamine neurotrans-

mitters and neuronal plasticity (23). Curcumin inhibits the NF-κB activation pathways and thus can help in treatment of depression by interfering at an early stage in its pathogenesis (24).

The battery of tests applied in two different species of animals has minimized the false positive and false negative results in this study. Rats are more selective (fewer false positives) while mice are more sensitive (fewer false negatives) for screening new antidepressants (25). The modified FST with water wheel gives an objective approach and helps to remove observational errors. As increasing of diameter of glass jar in FST decreases, the more false are positive results (26); using a diameter of 15 cm, larger than one used by Porsolt et al. (10 cm), reduces the false positive results. The results of photoactometer showed that curcumin did not increase the locomotor activity as compared to vehicle control, fluoxetine and imipramine, thus showing that the antidepressant like effect was not due to central nervous stimulation.

The most important hindrance in the use of curcumin is its low bioavailability *via* oral route. The curcumin formulation (Bio-curcumin®) used in this study had other curcuminoids and volatile oils added to it, increasing its retention and bioavailability by seven times (27).

Curcumin can be an antidepressant of choice especially in cases which respond to drugs having mixed effects on serotonin and catecholamines levels in the brain (28). Previously, reversible inhibitors of monoamine oxidase were used in such cases but their use has declined due to their adverse effects and life threatening interactions. Curcumin might be useful in such cases, as it increases the serotonin, norepinephrine and dopamine levels in the brain. Moreover, it has been proved to be safe and devoid of adverse effects even in high doses of up to 8 g/day taken for several weeks in human studies (29).

CONCLUSION

This study shows that curcumin in the doses of 50 mg/kg and 100 mg/kg in mice; and 35 mg/kg and 70 mg/kg in rats has antidepressant like action, similar to that of fluoxetine and imipramine; however, it does not increase the antidepressant action of fluoxetine and imipramine when administered by oral route. Curcumin may be developed as an antidepressant but might not be useful in combination with fluoxetine and imipramine. Further research is required to gain closer insights into the exact mechanism of its action.

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