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Efficacy and Safety of Curcumin in Major Depressive Disorder: A Randomized Controlled Trial

Jayesh Sanmukhani,[1]* Vimal Satodia,[2] Jaladhi Trivedi,[2] Tejas Patel,[1] Deepak Tiwari,[2] Bharat Panchal,[2] Ajay Goel[3,4] and Chandra Bhanu Tripathi[1]

[1]Department of Pharmacology, Government Medical College, Bhavnagar, Gujarat, India
[2]Department of Psychiatry, Sir T General Hospital, and Government Medical College Bhavnagar, Gujarat, India
[3]Baylor Research Institute and Charles A Sammons Cancer Center, Baylor University Medical Center, Dallas, TX, USA
[4]Gastrointestinal Cancer Research Laboratory, Baylor University Medical Center, Dallas, TX, USA

Curcumin, an active ingredient of *Curcuma longa* Linn (Zingiberaceae), has shown potential antidepressant-like activity in animal studies. The objectives of this trial were to compare the efficacy and safety of curcumin with fluoxetine in patients with major depressive disorder (MDD). Herein, 60 patients diagnosed with MDD were randomized in a 1:1:1 ratio for six weeks observer-masked treatment with fluoxetine (20 mg) and curcumin (1000 mg) individually or their combination. The primary efficacy variable was response rates according to Hamilton Depression Rating Scale, 17-item version (HAM-D_{17}). The secondary efficacy variable was the mean change in HAM-D_{17} score after six weeks. We observed that curcumin was well tolerated by all the patients. The proportion of responders as measured by the HAM-D_{17} scale was higher in the combination group (77.8%) than in the fluoxetine (64.7%) and the curcumin (62.5%) groups; however, these data were not statistically significant ($P = 0.58$). Interestingly, the mean change in HAM-D_{17} score at the end of six weeks was comparable in all three groups ($P = 0.77$). This study provides first clinical evidence that curcumin may be used as an effective and safe modality for treatment in patients with MDD without concurrent suicidal ideation or other psychotic disorders. Copyright © 2013 John Wiley & Sons, Ltd.

Keywords: curcumin; antidepressant; clinical trial simulations; major depressive disorder; CNS.

INTRODUCTION

Depression is a major global public-health issue leading to substantial disability. 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 (Ustun *et al*., 2004). It causes subjective distress, impaired functional capacity, secondary mental and somatic complications and can even lead to suicides. An accurate diagnosis followed by effective treatment can improve the outcome (Cizza, 2011; Nutt, 2011). Some proportion of patients with depression respond very well to various pharmacologic and behavioral treatments, when given individually or in combination. Pharmacologically, reversible inhibitors of monoamine oxidase A, tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin noradrenaline reuptake inhibitors and atypical antidepressants like mianserin, tianeptin, agomelatine, bupropion, trazondone, nefazodone, maprotiline etc. are currently being used for its treatment. Being a chronic and recurrent disorder, the treatment has to be taken continuously for a long time, which results in significant and distressing side effects. Even though a wide range of clinically effective antidepressants are available, search for safer antidepressants with a benign profile of adverse effects continues. Curcumin is one such compound which has antidepressant potential without significant side effects.

Curcumin is an active ingredient in *Curcuma longa* Linn (Zingiberaceae), more commonly known as the Asian yellow spice, Turmeric (Goel *et al*., 2008a; Goel *et al*., 2008b), which has been shown to have anti-oxidant (Motterlini *et al*., 2000), anti-inflammatory (Motterlini *et al*., 2000), immunomodulatory (Varalakshmi *et al*., 2008), anti-cancer (Sharma *et al*., 2004) and neuroprotective (Xu *et al*., 2007) activities. Turmeric is a well-known ancient remedy used in Indian Ayurvedic medicine. It is also a major constituent of Xiaoyao-san and Jieyu-wan, the traditional Chinese herbal medicines, which have been used to effectively manage stress and depression-related disorders in China (Xia *et al*., 2007). They have been used to treat the symptoms of mental stress, hypochondriac pain and mania. Antidepressant activity of curcumin has been explored in various animal models of depression such as the forced swimming test, tail suspension test and chronic stress model (Yu *et al*., 2002; Xu *et al*., 2005; Xia *et al*., 2007; Xu *et al*., 2007; Kulkarni *et al*., 2008; Wang *et al*., 2008). It has been attributed to two primary effects: neurogenesis in the hippocampus (Xu *et al*., 2007) and rise in the serotonin, dopamine and noradrenaline brain levels by inhibiting monoamine oxidase enzyme (Xia *et al*., 2007; Kulkarni *et al*., 2008). It has also shown to enhance the activity

* Correspondence to: Jayesh Sanmukhani, Department of Pharmacology, Government Medical College, Bhavnagar, Gujarat, India; Ajay Goel, Gastrointestinal Cancer Research Laboratory, Baylor University Medical Center, Dallas, TX, USA.
E-mail: jayesh_sanmukhani@yahoo.co.in; ajay.goel@baylorhealth.edu

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of other antidepressant drugs like fluoxetine, venlafaxine and bupropion (Kulkarni *et al*., 2008). Moreover, toxicity studies of curcumin have shown it to be safe even in very high doses. The LD_{50} in mice has been reported to be 1500 mg/kg by intraperitoneal route and more than 2000 mg/kg by oral route. The LD_{50} in rats is also more than 2000 mg/kg (Srimal and Dhawan, 1973). Based on the results of these animal studies, curcumin is being marketed as an antidepressant in the United States under brand name Avea Mood by Nutramedix (Kulkarni and Dhir, 2009; Kulkarni *et al*., 2009). However, to the best of our knowledge, since no evidence exists on the clinical effectiveness of curcumin, we undertook this first, randomized controlled clinical trial to compare the efficacy and safety of curcumin with fluoxetine, and to study the effect of curcumin as a supplement to fluoxetine in patients with major depressive disorder (MDD). Herein, we provide data of this comparative study of curcumin with fluoxetine and their combination in patients suffering from MDD.

MATERIALS AND METHODS

Ethics statement. The study was conducted according to Declaration of Helsinki and International Conference on Harmonization-Good Clinical Practice Guidelines. The protocol was approved by the Institutional Review Board, Government Medical College, Bhavnagar, Gujarat (India). The study was registered on clinicaltrials.gov (NCT01022632).

Study subjects. Patients attending the psychiatry outpatient department of Sir Takhatsinhji General Hospital, a tertiary care hospital in Bhavnagar, Gujarat (India) were enrolled in the study. A written informed consent was taken from all the patients prior to screening. To qualify for randomization, the patients were required to be aged greater than 18 years, diagnosed MDD according to criteria of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (American Psychiatric Association, 1994) and score more than seven on Hamilton Depression Rating Scale, 17-item version ($HAM\text{-}D_{17}$) (Hamilton, 1960). Patients were also required to have caregivers for enrolment in the study.

Patients with suicidal ideation, schizophrenia, schizoaffective or other psychotic disorders, mental retardation or cognitive impairment, bipolar disorder, current panic disorder or obsessive compulsive disorder, other uncontrolled organic disease, abnormal laboratory tests, history of seizure disorder (other than febrile), unstable thyroid disorder or known allergy or hypersensitivity to the study medications were excluded. Patients who had failed to respond to at least two adequate antidepressant therapies in the past or had taken any antidepressant or investigational new drug in last 30 days or currently receiving psychotherapy specifically designed to treat depression were also excluded. Females randomized in the study were required to use effective method of contraception throughout the study period with negative urine pregnancy test prior to randomization.

Study drugs and doses. Curcumin was provided as 500 mg capsule (BCM-95 from Arjuna Natural Extracts, Kochi, Kerala, India). Each capsule contained total curcuminoids 88% (curcumin, bisdemethoxycurcumin, demethoxycurcumin) and volatile oils 7% from rhizomes of *Curcuma longa* Linn. Fluoxetine was used as 20 mg capsule (Flunil-20®, Intas Pharmaceuticals, India). Curcumin was used in a dose of 1000 mg/day. It was calculated using data from Chinese medicine using dry rhizome of *Curcuma longa* at 3–9 g/70 kg adult for treatment of depression like disorders. Fluoxetine was used in a fixed dose of 20 mg/day as its dose escalation is not recommended before four–six weeks of treatment (Ruhe *et al*., 2006).

Study design. This study was randomized, observer masked, with three parallel treatment arms as illustrated in Fig. 1. The screening visit included complete psychiatric and physical examination, $HAM\text{-}D_{17}$ evaluation, vital signs, laboratory tests (haemogram, liver function test, renal function test, blood sugar level and urine analysis for sugar, ketones and proteins) and electrocardiogram. Patients who met the eligibility criteria were randomized using random allocation software (RANDO, version 1.0) to either of the three groups: group I received fluoxetine 20 mg/day in the morning, group II received curcumin 1000 mg/day (500 mg BD) while group III received fluoxetine 20 mg/day and curcumin 1000 mg/day (500 mg BD). Patients were asked to take curcumin 500 mg capsules after breakfast and after dinner at 12 h intervals. No other drug, except paracetamol 500 mg/day for headache and benzodiazepines in dose equivalent to diazepam 5 mg/day for management of insomnia, was allowed in first two weeks of study. The study was observer masked, i.e. the raters were not told about the treatment allotted to the patients, and the patients were instructed not to discuss their treatment regimens with the raters. Physical examination and history regarding adverse events were taken by other investigators who were not involved in rating.

Efficacy and safety were evaluated after two, four and six weeks in outpatient department. The primary efficacy measure was response rate according to $HAM\text{-}D_{17}$ scale. The secondary efficacy measures were: mean change in $HAM\text{-}D_{17}$ score at two, four and six weeks; remission rate according to $HAM\text{-}D_{17}$ scale; response rate on clinical global impression-improvement (CGI-I) (Mortimer, 2007) assessment scale; score on clinical global impression-severity of illness (CGI-S) (Mortimer, 2007) scale and global efficacy at the end of study. Data for evaluation of safety comprised of treatment emergent adverse events (TEAEs), measurement of vital signs and physical examination at each visit. Laboratory tests, electrocardiogram and investigators' opinion on global tolerability were noted at the end of study. All the investigators were trained in the use of assessment scales by the principal investigator to improve reliability of rating. No major protocol deviation or violation was recorded during the conduct of the study. Remission was defined as total $HAM\text{-}D_{17}$ score ≤ 7, while response was defined as 50% decrease in $HAM\text{-}D_{17}$ score as compared to baseline. Response on CGI-I assessment was defined as score of 1 or 2 on seven point rating scale (1 for 'very much improved' and 7 for 'very much worse'. Investigators' opinion for global efficacy was taken

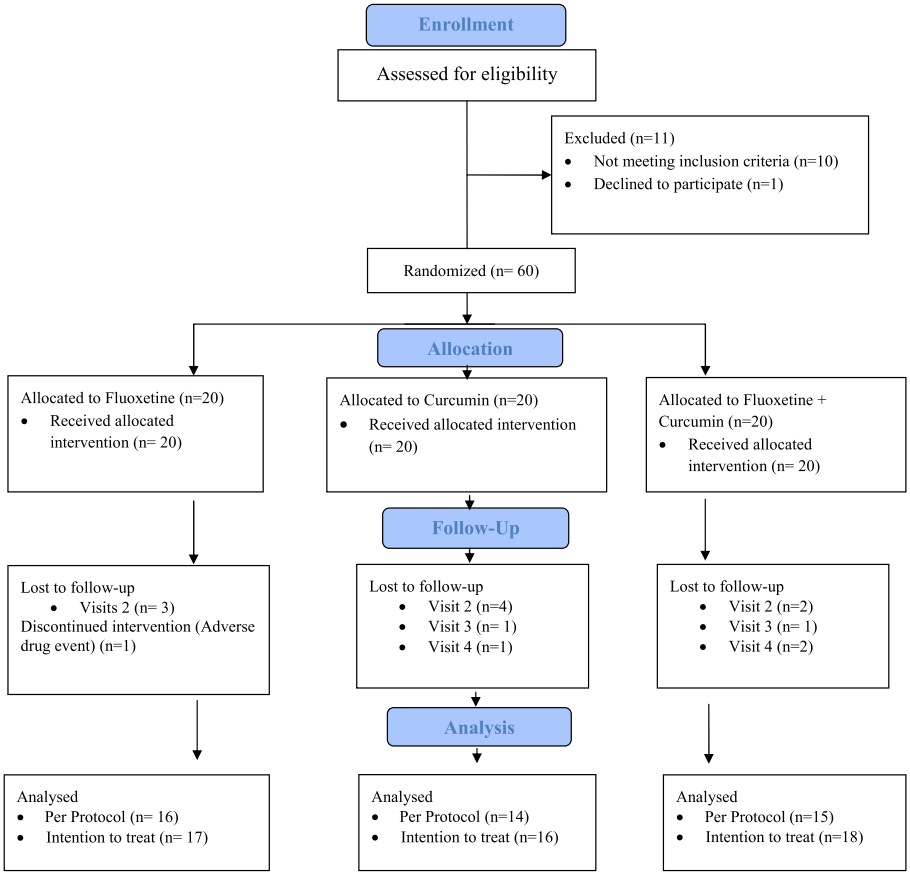

Figure 1. A systematic illustration of the study design including criteria used for patient enrolment, randomization, treatment allocation, follow-up and data analysis.

as either: excellent (total or near total resolution of symptoms); good (significant resolution); fair (some resolution) or poor (no resolution or worsening). For global tolerability, investigators' opinion was taken as either excellent (no TEAEs reported); good (TEAE not requiring additional medication for its treatment); fair (TEAE requiring concomitant medication but did not necessitate stoppage of the study medication) or poor (TEAE which necessitated stoppage of the study medication). Compliance of the patient was checked by pill count method and was judged noncompliant if he missed more than two doses of medication during the fourteen day inter-visit period.

Statistical analysis. Descriptive analysis was used for demographic data. Intention-to-treat (ITT) analysis using last observation carried forward was used to compare efficacy variables of all randomized patients who attended at least one follow-up visit. Baseline characteristics of the three study groups were compared using chi-square test for categorical variables and analysis of variance (ANOVA) for numerical variables. Among the efficacy variables, response rate and remission rate on HAM-D_{17} scale and response rate on CGI-I scale were compared using chi-square test. One-way analysis of covariance was used to compare the change in HAM-D_{17} score at the end of second, fourth and sixth week. Baseline HAM-D_{17} score served as the covariate. The CGI-S score at the end of study was also compared using ANOVA with baseline CGI-S score as a covariate. Safety data were compared using chi-square test. Data are expressed as means for continuous variables and proportions for categorical variables and are accompanied by 95% confidence intervals. For all the tests, statistical significance was set at $P < 0.05$. All the statistical tests were done using SPSS Statistics 17.0.

RESULTS

Sixty patients met the eligibility criteria and were randomized in the study with 20 patients in each group. The three treatment groups were comparable for baseline demographics and clinical characteristics (Table 1). Overall, 45 patients completed the six weeks study per protocol, with no significant difference in the dropout rate in each group (fluoxetine, 25% [11.2 – 46.8]; curcumin, 20% [8.1 – 41.6]; fluoxetine and curcumin, 30% [14.5 – 51.9]; P value = 0.77). Nine patients abandoned treatment and were lost to follow-up before the first follow-up visit, and thus 51 patients were included in our ITT analysis (n = 17, fluoxetine; n = 16, curcumin; n = 18, fluoxetine and curcumin). Three patients were judged noncompliant only once during their study period, so the overall compliance of the patients was excellent.

Efficacy outcomes

The proportion of responders in ITT population as measured by the HAM-D_{17} scale was higher in the combination of fluoxetine and curcumin group (77.8%) than in the fluoxetine (64.7%) group and the curcumin

Table 1. Baseline characteristics of patients randomized in the study

	Group 1: Fluoxetine (n = 20)	Group 2: Curcumin (n = 20)	Group 3: Fluoxetine and curcumin (n = 20)	*P* value
Age (years), mean	33.6	37.8	40.4	0.21‡
(95% CI)	(28.9 – 38.3)	(31.9 – 43.8)	(34.1 – 46.7)	
Sex, n (%)				
Male	10 (50)	5 (25)	6 (30)	0.22§
(95% CI)	(29.9 – 70.0)	(11.3 – 46.8)	(14.6 – 51.9)	
Females	10 (50)	15 (75)	14 (70)	
(95% CI)	(29.9 – 70.0)	(53.1–88.8)	(48.1 – 45.5)	
Previous episode of depressive illness, n (%)				0.62§
Yes	4 (20)	4 (20)	2 (10)	
(95% CI)	(8.0 – 41.6)	(8.0 – 41.6)	(2.8 – 30.1)	
No	16 (80)	16 (80)	18 (90)	
(95% CI)	(58.4 – 91.9)	(58.4 – 91.9)	(69.9 – 97.2)	
Duration of current episode				0.61‡
(months), mean	5.1	8.0	5.0	
(95% CI)	(0.05 – 10.1)	(2.3 – 13.6)	(1.4 – 8.6)	
Baseline HAM-D_{17}* total score,				0.43‡
Mean	21.0	19.3	21.9	
(95% CI)	(17.6 – 24.4)	(16.4 – 22.1)	(18.9 – 24.8)	
Baseline CGI-S† score,				0.96‡
Mean	4.2	4.1	4.2	
(95% CI)	(3.8 – 4.6)	(3.8 – 4.4)	(3.9 – 4.5)	

*Hamilton Depression Rating Scale, 17-item version

†Clinical Global Impression-Severity of Illness

‡Analysis of variance

§Chi-square test

(62.5%) group, but was not statistically significant ($P = 0.58$; Table 2). Analysis of the secondary outcome measures also showed similarity among the three groups (Table 2). The mean change in HAM-D_{17} scores at the end of sixth week from baseline was −14.0 (−18.2 – −9.8) for fluoxetine group, −12.6 (−15.8 – −9.5) for curcumin group and −14.8 (−17.6 – −12.0) for fluoxetine and curcumin combination group ($P = 0.77$). The remission rate on HAM-D_{17} scale was also similar in the three groups (fluoxetine, 52.9% [30.9 – 73.8]; curcumin, 37.5% [18.5 – 61.3]; fluoxetine and curcumin, 55.5% [33.7 – 75.4]; $P = 0.53$). These findings were unchanged even when per protocol analysis was done. As per the investigators opinion on global efficacy, there was no statistical difference in the three treatment groups, ($P = 0.66$). 70.5% [46.8 – 86.7] patients in fluoxetine group, 75% [50.5 – 89.8] in curcumin group and 83.3% [60.7– 94.1] in fluoxetine and curcumin group showed 'excellent' or 'good' efficacy of the study medication, while the proportions were 41.1% (21.6 – 63.9), 25% (10.1 – 49.5) and 38.8% (20.3 – 61.4), respectively, when only 'excellent' efficacy was considered.

Safety outcomes

Five (27.8%; 12.5 – 50.8) patients in the fluoxetine and curcumin combination group, two (11.7%; 3.3 – 34.3) in fluoxetine group and two (12.5%; 3.5 – 36.0) in curcumin group reported TEAEs. Patients in fluoxetine and curcumin combination group reported gastritis (16.6%; 5.8 – 39.2), giddiness (5.5%; 0.9 – 25.9), hot flushes (5.5%; 0.9 – 25.9), nausea (5.5%; 0.9 – 25.9) and photosensitivity (5.5%; 0.9 – 25.9). TEAEs reported by patients in the fluoxetine group were gastritis (5.8%; 1.0 – 26.9) and mouth ulcers (5.8%; 1.0 – 26.9), while that in curcumin group were gastritis (6.25%; 1.1 – 28.3) and nausea (6.25%; 1.1 – 28.3). All the patients had mild TEAEs, and the medications were well tolerated (Hartwig *et al.*, 1992). There was no significant difference in vital signs, physical examination, laboratory tests and electrocardiogram from baseline. Fluoxetine (82.3%; 58.9 – 93.8) and curcumin (87.5%; 63.9 – 96.5) had higher proportion with 'excellent' tolerability than fluoxetine and curcumin combination group (66.6%; 43.7 – 83.7) on global tolerability scale, but the difference was not statistically significant ($P = 0.30$).

DISCUSSION

These results represent the findings of a first randomized controlled trial of curcumin for the treatment of MDD. The response rate of fluoxetine (64.7%) and curcumin (62.5%) on Hamilton depression scale observed in our study is within the known range of studies with currently prescribed antidepressants (31.6%–70.4%) (Walsh *et al.*, 2002) and was higher than the maximum response rate expected with placebo (12.5%–51.8%) (Walsh *et al.*, 2002). The remissions rates of fluoxetine and curcumin were also in accordance with the previous reports (Thase *et al.*, 2007). Curcumin was found to be equivalent to fluoxetine in terms of change in HAM-D_{17} score from baseline after six weeks of treatment. Though the combination group showed better response than fluoxetine and curcumin alone, it was not statistically significant.

Even though curcumin has shown similarity to fluoxetine, the maximal response of curcumin was lesser than that of fluoxetine, as can be seen by lesser proportion of patients achieving remission after responding to treatment on HAM-D_{17} scale. 62.7% of patients in curcumin group responded to the treatment and 37.5% patients achieved remission, while in the fluoxetine group 64.7% responded to treatment and 52.9% achieved remission. Results of the global efficacy scale show that proportion of the patients in curcumin group having 'excellent' response was lesser than in fluoxetine group (25% curcumin; 43% fluoxetine), while, when both 'good' and 'excellent' responses were taken together, the proportion of patients was similar in both the groups (75% curcumin; 70.5% fluoxetine).

The antidepressant action of curcumin has been extensively studied in animal models and is found to be comparable to fluoxetine, imipramine, amitriptyline and bupropion (Yu *et al.*, 2002; Xu *et al.*, 2005; Xia *et al.*, 2007; Kulkarni *et al.*, 2008; Wang *et al.*, 2008). Curcumin increases the brain levels of serotonin, noradrenaline and dopamine by inhibiting the MAO enzyme (Yu *et al.*, 2002; Xu *et al.*, 2005; Xia *et al.*, 2007; Kulkarni *et al.*, 2008; Wang *et al.*, 2008). Various meta-analyses have shown that MAO inhibitors like moclebemide have response rate of ~58% (Lotufo-Neto *et al.*, 1999). Curcumin has also shown similar response rate like MAO inhibitors in this study, but as compared to others, it has proved to be safe even at supra-therapeutic doses. Furthermore, a combination of curcumin with other antidepressants has shown to synergistically increase the serotonin levels and enhance antidepressant like activity in various animal models (Kulkarni *et al.*, 2008). Curcumin also increases hippocampal neurogenesis in chronically stressed rats via modulation of HPA axis and up regulation of 5-HT_{1A} receptors and BDNF in the hippocampus (Xu *et al.*, 2007). It inhibits the NF-κB activation pathways of innate immunity and thus prevents release of IFN-α and other cytokines. These cytokines lead to dysregulation of HPA axis, metabolism of monoamine neurotransmitters and neuronal plasticity. Thus, curcumin might be helpful in depression by interfering at an early stage in its pathogenesis (Lao *et al.*, 2006; Raison and Miller, 2011). The advantage of curcumin as an antidepressant is its benign profile of adverse events as compared to other antidepressants. Curcumin is known to be safe even up to dose of 8 g/day (Singh and Aggarwal, 1995). It was well tolerated in our study as well. The combination group had more TEAEs, but it was not statistically significant. The increase in adverse events could be due to pharmacodynamic interaction between fluoxetine and curcumin resulting in excessive serotonin and noradrenaline at nerve terminals. Although a possible risk of development of serotonin syndrome does exist with this combination of curcumin and fluoxetine, no such symptoms were observed in any of the patients in the combination group during our study.

The concern with the use of curcumin is its low bioavailability. The product we have used in our study had curcuminoids and volatile oils added to it, increasing its retention time and bioavailability by seven times (Antony *et al.*, 2008). Though the study was not blinded, it was observer masked, i.e. the raters were not told about the treatment allotted to the patients. The sample

Table 2. Results summary of primary and secondary efficacy outcome variables in ITT patients

Efficacy variable	Group 1: Fluoxetine (n = 17)	Group 2: Curcumin (n = 16)	Group 3: Fluoxetine and curcumin(n = 18)	*P* value
Response rate, HAM-D_{17}*scale, n (%)	11 (64.7)	10 (62.5)	14 (77.8)	0.58[||]
(95% CI)	(41.3 – 82.7)	(38.6 – 81.5)	(54.7 – 91)	
Change in HAM-D_{17}* score from baseline, mean (95% CI)				
End of second week	−9.7	−7.5	−9.5	
	(−13.3 to −6.0)	(−10.4 to −4.6)	(−12.6 to −6.4)	0.76[¶]
Adjusted mean[†]	−9.3	−8.1	−9.3	
	(−12.0 to −6.6)	(−10.9 to −5.3)	(−11.9 to −6.7)	
End of fourth week	−12.7	−9.2	−12.6	
	(−16.7 to −8.7)	(−12.6 to −5.8)	(−15.4 to −9.8)	0.33[¶]
Adjusted mean[†]	−12.2	−10.0	−12.3	
	(−14.7 to −9.7)	(−12.5 to −7.4)	(−14.7 to −9.9)	
End of sixth week	−14.0	−12.6	−14.8	
	(−18.2 to −9.8)	(−15.8 to −9.5)	(−17.6 to −12.0)	
Adjusted mean[†]	−13.6	−13.3	−14.6	0.77[¶]
	(−16.3 to −10.9)	(−16.1 to −10.5)	(−17.2 to −11.9)	
Remission rate, HAM-D* scale, n (%)	9 (52.9)	6 (37.5)	10(55.5)	0.53[||]
(95% CI)	(30.9–73.8)	(18.5 – 61.3)	(33.7 – 75.4)	
Response rate on CGI-I[‡], n (%)	10 (58.8)	8 (50.0)	13 (72.2)	0.41[||]
(95% CI)	(36.0 – 78.4)	(28.0 – 72.0)	(49.1 – 87.5)	
CGI-S[§] score, mean (95% CI)	2.2(1.5 – 2.8)	2.4 (1.9 – 2.8)	2.2 (1.6 – 2.7)	
Adjusted mean[†]	2.1 (1.6 – 2.6)	2.4 (1.9 – 2.9)	2.2 (1.7 – 2.9)	0.74[¶]

*Hamilton Depression Rating Scale, 17-item version
[†]Values represent means adjusted for baseline values
[‡]Clinical Global Impression-Improvement
[§]Clinical Global Impression-Severity of Illness
[||]Chi-square test
[¶]Analysis of Covariance

size of this study was kept low as it was designed as a preliminary study to know the efficacy and safety of curcumin in patients of depression. As curcumin was found to have good efficacy and benign safety profile in patients of depression, it should be further studied as monotherapy and in combination with fluoxetine and other antidepressants in trials with larger sample sizes, longer duration and higher doses to detect smaller, clinically meaningful differences in the outcome measures.

The present study has several limitations which may affect the conclusion drawn from this study. One of the limitations is that a placebo group was not included in the study. This was due to ethical considerations as this was the first, pilot feasibility study to study the efficacy of curcumin in patients with MDD. Second, the number of study participants was low. The number was purposely kept low as it was designed as a preliminary pilot study, and because curcumin has not been studied for such a clinical indication previously, and we wanted to avoid any harm to participants. Our main emphasis was to obtain a proof of principle evidence to show that curcumin was at least not inferior to standard treatment and can be substituted at least partially to the standard treatment.

In conclusion, ours is the first randomized clinical trial that clearly highlights that curcumin may be an effective and safe agent when used as a modality of treatment in patients of MDD without concurrent suicidal ideation or other psychotic disorders. In addition, given the efficacy of curcumin treatment by itself, this study highlights the need for future large-scale clinical trials evaluating the use of this safe and natural dietary botanical as a possible mono-therapy in patients with depressive disorders.

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Conflict of Interest

The Authors state no conflict of interest.

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