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Curcumin as an add-on to antidepressive treatment: A randomized, double-blind, placebo-controlled, pilot clinical study

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	Conclusions: Although there is no definitive proof that curcumin can induce an earlier beneficial effect of antidepressive agents, it seems like an extended study is needed to prove it, using higher therapeutic doses of curcumin.

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Curcumin as an add-on to antidepressive treatment: A randomized, double-blind, placebo-controlled, pilot clinical study

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Abstract

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Conclusions: Although there is no definitive proof that curcumin can induce an earlier beneficial effect of antidepressive agents, it seems like an extended study is needed to prove it, using higher therapeutic doses of curcumin.

Key words: Depression, curcumin, augmentation, antidepressants, antioxidants, neuroprotection, clinical trial

Clinical depression is characterized mainly by the combination of decreased mood, markedly diminished interest and impairment of physical, social and occupational functioning. Depression may affect up to 10% of the general population. About half of the affected people have recurrent symptoms. In mild to moderate depression, there is no reliable evidence that any treatment is superior in improving symptoms of depression, but the strength of evidence supporting different treatments varies.[1] There are a number of effective interventions for treating depression, however approximately 30% of patients failed to respond to any of these pharmacological therapies.[2] Antidepressants are associated with different side-effects and drug-drug/drug-food interactions. Therefore, it is important to find alternative drug therapies to be effective and safe for treating patients with major depression. Despite a striking increase in the number of antidepressants options over the last 50 years, their effectiveness remains largely unchanged.[3]

Unfortunately, antidepressive agents generally do not produce an immediate relief of symptoms. Most people will not see a significant improvement for at least 3-4 weeks. However, this timeline is variable among individuals. [4]

There are many ways to potentiate the efficacy of antidepressants, including lithium, antipsychotics and antidepressant combinations. However, drug combinations may produce cumulative side effects especially in elderly and physically ill patients.[5]

Curcuma longa Linn is a plant, which belongs to the Zingiberaceae family, and is distributed throughout the tropical and subtropical regions of the world. It is widely cultivated in Asiatic countries, mainly in India and China. As a gold-colored powder, called turmeric, derived from the rhizome of the plant, it has been used for its flavoring, as a yellow dye for textiles, as a spice in both vegetarian and non-vegetarian food preparations, for the preservation of food and it also has digestive

properties. [6, 7] Traditionally, it is used as a condiment to give distinctive flavor to the curry.

Curcumin was first isolated almost two centuries ago, and its structure - diferuloylmethane was determined in 1910.[7] It has been used for thousands of years in India, China, and Indonesia as a traditional medicine for a wide variety of diseases and conditions, including pulmonary and gastrointestinal systems, pain, wound and sprains treatment, as well as skin and liver disorders. In contrast, in Western cultures it was unknown for hundreds of years. [8]

The first article referring to the use of curcumin for treatment of humans was published in The Lancet in 1937. Since more than 4,000 scientific publications were reported, and only during the first half of 2011 more than 300 articles were published. Today, curcumin is an exciting new research topic for scientists all over the world for its powerful abilities to fight against some maladies and its low cost.

The significance of turmeric in health and nutrition has changed considerably since the discovery of the antioxidant and neuroprotective properties of naturally occurring phenolic compounds, curcuminoids. Curcumin is one of the main curcuminoids isolated from this perennial herb.[9] It possesses a variety of pharmacological activities, including anti-inflammatory, antiproliferative, antioxidant, and neuroprotective effects.[10-13] Fluorescent imaging in a mouse model of Alzheimer's disease showed that curcumin crosses the blood-brain barrier. [14]

To present day, there are a few clinical studies mainly concerning the use of curcumin in the therapy of malignant and inflammatory diseases and its potential application in the treatment of degenerative neurological diseases. [15-17]

Curcumin has been found to possess antidepressive activity in various animal models of depression. [18-21] Chronic administration of curcumin has been reported to

exert antidepressant-like action in olfactory bulbectomy model of depression in rats.[21] Although the mechanism of the antidepressive effect of curcumin is not fully understood, it is hypothesized that it acts through inhibiting the monoamine oxidase enzyme and modulating the release of serotonin and dopamine.[20, 22] Moreover, there are evidences that curcumin enhances neurogenesis, notably in the frontal cortex and hippocampal regions of the brain.[19]

Since all researches concerning this issue examined it on animals only, we decided to perform the study in a 5-week clinical trial. To the best of our knowledge, this is the first scientific report concerning adjunctive use of curcumin in patients with depression.

Methods

Subjects

From August 2010 through June 2011 in Tirat Carmel Mental Health Center, 53 inpatients suffered from depression were screened for enrollment into the study. Inclusion criteria for participation in this study were: a) males and females in age 20-60 years old suffering from major depressive episode according to the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* [23] criteria, (first episode or at least a year to be in remission without any medication after a previous episode); b) score of 4 or higher on the Clinical Global Impression Severity Scale (CGI-S) [24]; c) Hamilton Depression Rating Scale[25] ($HDRS_{17}$), score more than 21; d) Montgomery and Asberg Depression Rating Scale[26] (MADRS), score more than 22; and e) ability and willingness to sign informed consent.

The following conditions were exclusion criteria for taking a part in this study: a) any of the following DSM-IV diagnoses: schizophrenia, schizoaffective, or other psychotic disorder, and bipolar disorder; b) evidence of organic brain damage; c)

mental retardation; d) alcohol or drug abuse; e) an unstable medical condition; f) any significant medical or neurological illness; g) patients with a known hypersensitivity to curcumin or other components of the product; h) pregnant women or women who intend to become pregnant; i) receiving any antidepressant and mood-stabilizers; j) receiving psychotherapies which are specifically designed to treat depression.

The absence of medical or neurological illnesses was verified by means of a routine laboratory investigation, physical and neurological examination, reports of the treating physician, and medical records. It was forbidden to add any other psychoactive medication before entry and along the entire study period. After the screening procedure, participants who met all inclusion criteria and no exclusion criteria were enrolled into this 5-week study.

Of all screened subjects, 13 patients did not enter the study: 6 subjects were excluded due to comorbidity with substance abuse, and 7 patients disagreed to participate. Thus 40 subjects were enrolled into the study. Prior to starting the study, all subjects provided written informed consent after receiving a full explanation regarding the nature of the study, its potential risk and benefits. The study was approved by the Institutional Review Board.

Study design

It was a randomized, double-blind, placebo-controlled, five weeks study, initiated by the investigators and conducted independently of any commercial entities. After screening and baseline assessments, patients were randomized (by random number generation) to receive either 500 mg/day of curcumin (CurcuminForte Balance®,–from Extracts H.Plant) or placebo in identical capsules as an addition to antidepressants. Each capsule of CurcuminForte® contains: 330 mg of curcumin (97% concentrate); 120 mg of ellagic acid (70% concentrate), extracted from

pomegranate's peel and 50 mg of piperine (the active ingredient in black pepper). This combination enhances curcumin's absorption in the intestine and generates a very effective formula.[27]

The pharmacist conducted a randomization of participants and was responsible for keeping the blindness of the trial. Allocated patient's details were coded and kept confidentially until the trial was completed. Neither the clinicians, nor the patients were able to identify the impending treatment allocation. None of the codes were broken during the trial period.

Outcome measures

The primary rating tools were the HDRS, MADRS and CGI-S. The outcome measures were collected over 6 visits: a baseline visit before starting the therapy, and then every week through the trial. Moreover, laboratory tests including complete blood count and basic blood chemistry were performed before the trial and at the end of the study. All observed or self-reported adverse events, during the study, had to be recorded and evaluated for severity, duration, and possible connection to the received treatment.

Statistical analysis

All randomly assigned patients, who participated in the study for at least one week and had at least one primary efficacy rating, were included for efficacy analyses (based on total MADRS, HDRS and CGI-S). The final analysis of all efficacy variables was performed by using last observation carried forward (LOCF) data (one patient from the placebo group).

All statistical analyses were performed by using “Statistica 11” for Windows (StatSoft 2011). Two way ANOVA, with time as within subject factor, were performed. In case significant effects were detected, LSD post hoc test was

performed. The baseline characteristics were compared between the 2 groups by t-test analysis or the chi-square test (χ^2), as appropriate.

Results

Forty subjects (17 men and 23 women) were enrolled into the study. Their ages ranged from 21 to 81 years old (mean 63.6 years, SD = 13.2). The clinical and demographic characteristics of the patients are presented in Table 1. All patients were treated with antidepressive agents (escitalopram or venlafaxine XR): twenty of them with add-on curcumin, while the other 20 patients received placebo. At baseline assessment, there were no significant differences between the curcumin and placebo groups in any of the variables (Table 1). Thirty-nine subjects completed the whole study: 1 patient from the curcumin group dropped out during the 1st week. There were no differences between the treatment groups regarding the distribution of antidepressants and their doses.

Analysis of variance showed significant positive changes in both groups from the baseline to the end of the study in all scales of measurement (Table 2). These changes became significant after 7 days of treatment (1st visit). In the placebo group, the MADRS scores decreased in average by 5.3 points (confidence interval (CI) 95% 2.1-8.5), $p<0.01$, while in the curcumin group, the scores decreased in average by 10.4 points (CI 95% 7.2-13.7), $p<0.001$. The HDRS scores in the placebo group diminished in average by 5.1 points (CI 95% 2.0-8.1), $p<0.01$, and in the curcumin group in average by 8.0 points (CI 95% 4.8-11.1), $p<0.001$. The CGI-S scores in the placebo group diminished in average by 0.6 points (CI 95% 0.2-0.9), $p<0.01$, and in the curcumin group diminished in average by 0.7 points (CI 95% 0.4-1.1), $p<0.001$. There was no treatment effect or treatment-time interaction. None of patients complained of any side effects during the study.

Discussion

According to our knowledge, this is the first randomized, double-blind, placebo-controlled trial of curcumin as an add-on agent to treatment of patients suffering from depression. Although we did not find a significant difference between the effect of curcumin or placebo on shortening the time up to improvement of depressive symptoms, a trend of a small preference of curcumin add-on could be seen on the MADRS and HDRS scores during the 1st week of the trial. All patients treated with curcumin tolerated the dose of 500 mg/day without side effects.

According to recent researches, curcumin has multiple biological activities, including an antidepressive effect. [20, 28-30] Several mechanisms may explain this activity. The potentiation effect on antidepressive agents, such as venlafaxine, fluoxetine and bupropion, was demonstrated in animal models experiments. [20] When mice's brain was checked for neurotransmitter levels following curcumin administration, increased levels of serotonin and dopamine but not norepinephrine were found. It was discovered that curcumin enhanced the anti-immobility effect of sub-effective doses of some antidepressants (not including desipramine and imipramine). [20] Moreover, curcumin potentiated the brain levels of serotonin when combined with various antidepressant agents.[20] In vitro studies have shown that curcumin exhibits monoamine oxidase inhibiting activity. [21, 31] Antidepressive action of curcumin may also appear via its neuroprotective and antioxidant activities. [10, 12, 13] It is a free radical scavenger inhibiting lipid peroxidation [11] and oxidative DNA damage.[30] Curcumin increases the levels of neurotrophic factors, particularly brain derived neurotrophic factor (BDNF).[13, 32]

Pharmacokinetic studies of curcumin revealed in general a low bioavailability of curcumin following oral application. Efforts to make curcumin more bioavailable

have included combinations with lecithin, a lipid generally sourced from soy, and/or piperine, a compound from black pepper. In a clinical study, Shoba and colleagues demonstrated that co-ingestion of curcumin with 20 mg of the pepper constituent l-piperoylpiperidine significantly enhances the plasma curcumin concentration in animals and in humans by 2000%. [33] Therefore, with a new curcumin-pepper formulation there is no need to use high doses in order to raise its level in the bloodstream.

Although we used a combination of curcumin with piperine in order to enhance its bioavailability, the absence of significant differences between both patient groups concerning the rapid influence on depressive symptoms may be explained by a low dose of curcumin (500 mg/day) used in this trial. Experimental studies on mice found that curcumin, in a starting dose from 20 mg/kg and up to 80 mg/kg, increased the brain monoamine levels. [20] Such doses are the equivalent of approximately 1500 mg/day or even higher in humans. In a clinical study in patients suffering from Alzheimer's disease, the researchers used curcumin from 1 to 4 g/day without any considerable side effects. [34]

Clinical studies in humans with high doses (2–12 grams) of curcumin have shown few side effects, with some subjects reporting mild nausea or diarrhea.[15,35, 36] This data suggest that curcumin is a safe substance.

Our trial has some limitations. The duration of the study was relatively short and sample size was relatively small. In this trial we used only a single and low curcumin dose. In future researches, more variants of curcumin doses should be used on a larger sample.

Despite of negative results demonstrated in our study, we suggest that further researches are necessary to establish the effective dose and the benefit profile of

curcumin as an additional medicine in the race for shortening the response period of antidepessive effect.

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Table

Table 1. Demographic Data and Clinic Characteristic of Patients at Baseline

	Randomization		P
	Curcumin **(N=20)**	Placebo **(N=20)**	
Gender: *			
Female	9	14	NS*
Male	11	6	
Age (years)			
Mean ± SD:	65.8±10.7	61.3±15.2	NS**
Range:	36-81	21-81	
DSM-IV diagnosis:			
Depressive episode	10	7	NS*
Recurrent depression	10	13	
Treatment			
Escitalopram (mg/d)	9 (11.4±3.3)	10 (10.9±3.8)	NS**
Venlafaxine XR (mg/d)	11 (107.3±24.8)	10 (115.1±27.3)	
MADRS	34.1±6.6	32.8±6.8	
HDRS	32.7±4.9	32.7±5.9	NS**
CGI-S	4.6±0.6	4.7±0.8	

MADRS – Montgomery and Asberg Depression Rating Scale; **HDRS –** Hamilton Depression Rating Scale;

CGI-S - Clinical Global Impression Severity Scale

* χ^2; **** t-test; NS –** non significant p>0.05

Table 2. The Changes in Measurement Scales during the Trial (X ±SD)

	Treatment	Baseline	Week 1*	Week 2	Week 3	Week 4	Week 5	Treatment effect (df =1,37)	Time (df=5.185)	Treatment x Time (df =5.185)
MADRS Mean (SD)	**Placebo (n=20)**	32.8 (6.8)	27.5 (5.5)	21.3 (6.3)	17.7 (6.7)	14.7 (7.4)	15.4 (7.7)	F= 1.0 p=0.3	F= 34.7 p<0.001	F= 1.1 p=0.4
	Curcumin n=19)	34.4 (6.6)	23.9 (7.4)	19.1 (7.2)	15.7 (6.3)	13.7 (6.8)	14.0 (6.9)			
HDRS Mean (SD)	**Placebo (n=20)**	32.7 (5.9)	27.6 (5.5)	22.1 (6.6)	19.0 (8.1)	15.8 (8.0)	16.5 (8.5)	F= 1.4 p=0.3	F= 76.7 p<0.001	F= 0.4 p=0.8
	Curcumin n=19)	32.6 (5.0)	24.7 (6.2)	19.4 (6.6)	17.0(7.5)	13.9 (7.6)	14.7 (7.2)			
CGI-S Mean (SD)	**Placebo (n=20)**	4.6 (0.8)	4.1 (0.6)	3.7 (0.7)	3.4 (0.8)	3.1 (0.9)	3.1 (0.9)	F= 3.2 p=0.08	F= 55.9 p<0.001	F= 1.1 p=0.4
	Curcumin n=19)	4.6 (0.6)	3.9 (0.7)	3.4 (0.8)	2.9 (0.8)	2.7 (0.9)	2.6(0.9)			

Two way ANOVA with time as within subject factor .

*All data in week 1 were statistically differenced from baseline (LSD post hoc test; $p < .01$).

CGI-S – Clinical Global Impression Severity of Illness

HDRS – Hamilton Depression Rating Scale

MADRS – Montgomery-Asberg Depressive Rating Scale

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