ORIGINAL ARTICLE

An Investigation of the Effects of Curcumin on Anxiety and Depression in Obese Individuals: A Randomized Controlled Trial*

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ABSTRACT **Objective**: To investigate the effectiveness of curcumin, a natural polyphenolic compound with antioxidant and anti-inflammatory activities, on the frequency of symptoms of anxiety and depression in obese individuals. **Methods**: In this double blind, cross-over trial, 30 obese subjects were randomized to receive either curcumin (1 g/day) or placebo for a period of 30 days. Following a wash-out interval of 2 weeks, each subject was crossed over to the alternative regimen for a further 30 days. Severity of anxiety and depression was assessed at baseline and at weeks 4, 6 and 10 of the trial using the Beck Anxiety Inventory (BAI) and Beck Depression Inventory (BDI) scales, respectively. **Results**: Mean BAI score was found to be significantly reduced following curcumin therapy (P=0.03). However, curcumin supplementation did not exert any significant impact on BDI scores (P=0.7). **Conclusion**: Curcumin has a potential anti-anxiety effect in individuals with obesity.

KEYWORDS *Curcuma longa*, curcumin, phenolic, psychological disorders, Beck Anxiety Inventory scale, Beck Depression Inventory scale

Anxiety is a common and potentially serious condition that may significantly affect the quality of life of individuals and may also predispose to psychiatric comorbidities.[1] Depression is a common consequence of anxiety that affects 21% of the world's population.[2] Epidemiologic findings have revealed that obesity is more prevalent in patients suffering from anxiety and/or depression. Another noticeable finding has been the high frequency of obesity in more severe cases of anxiety and depression, which poses a plausible relationship with the pathophysiology of these mental disorders.[3]

Heretofore, several underlying pathophysiological mechanisms have been identified for anxiety and depression. Disruption of the hypothalamic–pituitary–adrenal (HPA) axis and autonomic nervous system (ANS) are distinct features of anxiety and depression. These dysregulations are usually manifested in the form of sympathetic activation and parasympathetic deactivation. A heightened state of inflammation, detected as elevated levels of markers such as C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), has been detected in patients with depressive disorders. These imbalances in HPA axis, ANS and inflammatory status along with lifestyle alterations are thought to jointly induce obesity.[4]

Research has shown that inflammation plays a pivotal role in the pathogenesis of chronic diseases, including neurologic and psychological disorders such as major depressive syndrome and anxiety.[5,6] The role of T-cell dysfunction in the pathophysiology of depression has been reported previously.[7] There is a predominance of cytokine-producing helper T cells in major depression.[7] Also, nitric oxide synthase (NOS), a key enzyme in the generation of nitric oxide (NO), has been localized to brain regions involved in anxiety, such as the hypothalamus, amygdala and hippocampus.[8]

Curcumin is a yellow pigment that may be

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extracted from the rhizomes of the plant *Curcuma longa* (turmeric) and is responsible for several of the biological and pharmacological properties of turmeric.[9-18] This molecule has been shown to regulate multiple transcription factors, cytokines, protein kinases, adhesion molecules, redox state enzymes and inflammatory mediators.[19-21] Interestingly, there is evidence indicating that curcumin has beneficial effects in the treatment of psychiatric disorders including anxiety[22] and depression.[23]

Inflammation and oxidative stress are regarded as key factors in the pathogenesis of psychiatric disorders. Curcumin mitigates inflammation and oxidative stress by down-regulating the activity of cyclooxygenase-2 (COX-2), lipoxygenase and inducible NOS (iNOS) enzymes, lowering CRP, and inhibiting the production of inflammatory cytokines such as TNF-α, monocyte chemoattractant protein (MCP) and interleukins 1, 2, 6, 8 and 12.[24,25] With respect to the above properties, curcumin could serve as a potential therapeutic agent for anxiety and depression.

Inspite of the preclinical evidence that exists on the anti-depressant and anti-anxiety activities of curcumin,[26-28] there is a lack of scientific evidence on its clinical efficacy. Furthermore, curcumin is reported to possess anti-obesity effects which due to the close relationship between obesity and psychiatric disorders, could lead to the improvement of psychiatric disorders. Hence, the present study set out to evaluate the impact of curcumin supplementation on measures of depression and anxiety in a cross-over randomized double-blind placebo-controlled trial among obese individuals. The cross-over design could be regarded as the most reliable design for clinical trials due to the elimination of the interference of several potential sources of bias and confounding covariates. Such an advantage for cross-over trials lies in the fact that each patient would serve as his/her own control thereby obviating the problems of between-subject variability and increasing the precision of findings.

METHODS

Subjects

This study was conducted between August 2012 and August 2013. Study participants were selected from among those obese patients who were referred to the Nutrition Clinic at the Ghaem Hospital, Mashhad, Iran. Inclusion criteria were subjects with a body mass index (BMI) ⩾30, who had either <2 risk factors (except for diabetes mellitus) for coronary heart disease (CHD) plus low-density lipoprotein cholesterol (LDL-C) between 160–190 mg/dL, or ⩾2 CHD risk factors (except for diabetes mellitus) and LDL-C between 130-160 mg/dL. Exclusion criteria were a history of systemic diseases (such as systemic lupus erythematosis, kidney diseaseand cardiovascular disease), consumption of drug supplements within the preceding 6 months and history of taking any lipid-lowering drugs.[29] Thirty-five subjects (mean age: 38.37±11.51; 83% females) fulfilled the inclusion criteria and were entered into the trial. The study protocol was approved by the Ethics Committee of the Mashhad University of Medical Sciences (Approval No. 88313) and all participants provided a written informed consent. The trial has been registered in the Iranian Registry of Clinical Trials (No. IRCT2013082914521N1).

Drugs

C3 Complex® formula (obtained from Sami Labs Ltd., Bangalore, India) was used as the source of curcuminoids (comprising curcumin, demethoxycurcumin and bisdemethoxycurcumin) for the present study. Co-administration with bioperine® (Sami Labs Ltd., Bangalore, India) was used in order to enhance the bioavailability of curcuminoids. Hence, the participants were administered this curcumin preparation in the form of hard gelatin capsules containing 500 mg C3 Complex® plus 5 mg bioperine®. Placebo capsules matched with respect to size and shape and contained bioperine® (5 mg) alone.

Study Design

Patients underwent a standard clinical assessment comprising a psychiatric evaluation, a structured diagnostic interview and a medical history, at baseline. This was a randomized, double blind, cross-over trial in which each patient received curcuminoids (1 g/day) or placebo and then crossed over to the alternate regimen. Randomization was carried out by alternative allocation of participants to matched drug and placebo capsules. Each treatment period was 30 days and there was a 2-week wash-out interval between the regimens. Beck Anxiety Inventory (BAI) and Beck Depression Inventory (BDI) scales were filled out for each participant at baseline and after 4, 6 and 10 weeks of trial initiation (Figure 1).

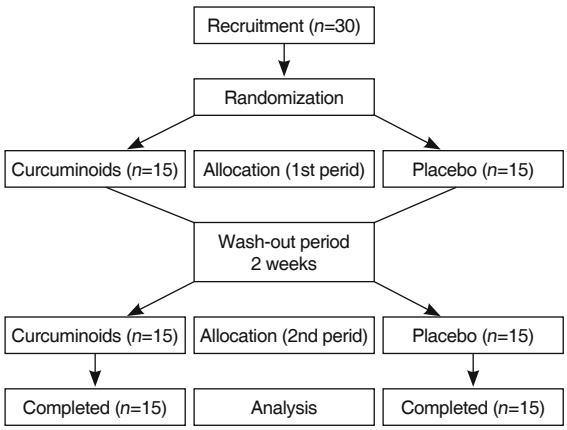

Figure 1. Flow Chart of Trial in Obese Individuals

Evaluation of Anxiety and Depression

Anxiety and depression were assessed using the BDI and BAI scales, respectively. The BAI consists of 21 item questionnaire which deals with the subject's feeling during the preceding week. The BAI scale evaluates common symptoms of anxiety such as numbness and tingling, sweating not due to heat, and fear of the worst happening. BAI is a 21-item self-report scale that could be used for the age range of 17–80 years.[30] The BDI is also a 21-item scale self-report that asks about symptoms such as sadness, pessimism about the future, feelings of failure, lack of satisfaction/pleasure, feeling of guilt, grief, hatred of oneself, to reproach against oneself, suicidal ideation, bursting into tears, irritability, social interest, indecision, sleep disorders, fatigue, appetite, weight loss; attention towards health and libido.[31] The participants were asked to complete each the questionnaires at baseline as well as at the end of each study period. Classification of scores for the assessment of anxiety and depression severity was performed according to Table 1. Adverse reactions were systematically recorded during the treatment course.

Table 1. BDI and BAI Scoring in Obese Individuals

Item	Degree	Score
Depression	Minimal	0–9
	Mild	10–18
	Moderate	19–29
	Severe	30–63
Anxiety	Minimal	0–7
	Mild	8–15
	Moderate	16–25
	Severe	26–63

Statistical Analysis

All statistical analyses were performed using the Statistical Analysis Software (SAS; version 9.1). A mixed model analysis of variance for 2×2 cross-over studies was fitted when assumption for normality was met. A two-sided *P*-value of less than 0.05 was considered as statistically significant. In addition, a one-way repeated measures analysis of variance (ANOVA) with a two tailed post-hoc Tukey mean comparison test was performed to detect changes from baseline for BDI and BAI scores in each group.

RESULTS

Demographic characteristics of study subjects are summarized in Table 2. The two arms were well matched for the aforementioned parameters.

Table 2. Demographic Characteristics of Study Population ($\bar{x} \pm s$)

Parameter	Curcumin-placebo	Placebo-curcumin
Case	15	15
Female (%)	13	11
Age (year)	38.84 ± 11.12	37.81 ± 12.31
Height (cm)	158.50 ± 6.36	159.94 ± 9.64
Weight (kg)	85.57 ± 12.95	83.83 ± 17.43
BMI (kg/m^2)	33.95 ± 3.81	32.66 ± 4.69
TC (mg/dL)	193.11 ± 29.16	188.94 ± 27.63
LDL-C (mg/dL)	119.79 ± 23.15	118.75 ± 27.73
HDL-C (mg/dL)	46.89 ± 9.55	46.12 ± 7.77
Triglycerides (mg/dL)	105.05 ± 30.22	124.94 ± 55.44
Waist circumstance (cm)	110.34 ± 10.41	106.53 ± 10.43
Hip circumstance (cm)	117.97 ± 9.85	115.07 ± 9.31
Arm circumstance (cm)	34.46 ± 2.64	33.47 ± 3.15
Fat percentage (%)	41.25 ± 5.49	36.48 ± 5.83
hs-CRP (mg/L)	8.44 ± 3.20	8.35 ± 2.62
SBP (mm Hg)	118.84 ± 13.29	117.62 ± 10.99
DBP (mm Hg)	79.63 ± 10.21	80.44 ± 8.41

Notes: BMI: body mass index; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; hs-CRP: high-sensitivity C-reactive protein; SBP: systolic blood pressure; DBP: diastolic blood pressure

Supplementation with curcuminoids (1 g/day) did not cause any significant change in weigh or BMI by the end of trial (*P*>0.05; Figure 2). There was no significant carry-over effect from the first period to the second period of study for all of the evaluated parameters including weight, BMI, BDI and BAI score (*P*>0.05). The mean decrease in BDI and BAI scores were used as outcome measures for the assessment of depression and anxiety responses to treatment, respectively. At

baseline the overall study population was found to have mild depression (BDI score: 9.89 ± 6.50), whilst being categorized as having severe anxiety based on the BAI score (28.66 ± 5.80). The same results were also found in the stratified analysis for curcumin-placebo (BDI: 9.47 ± 6.02; BAI: 29.53 ± 6.76) and placebo-curcumin (BDI: 10.37 ± 7.20; BAI: 27.62 ± 4.38) groups. Curcumin had no significant effect on the index of depression, but the average BAI score was found to be significantly different between the treatment conditions. The curcumin treatment was associated with a significant reduction in mean BAI score compared with the placebo group (P<0.05). The mean BDI and BAI scores of the two groups of participants are shown in Figures 3 and 4.

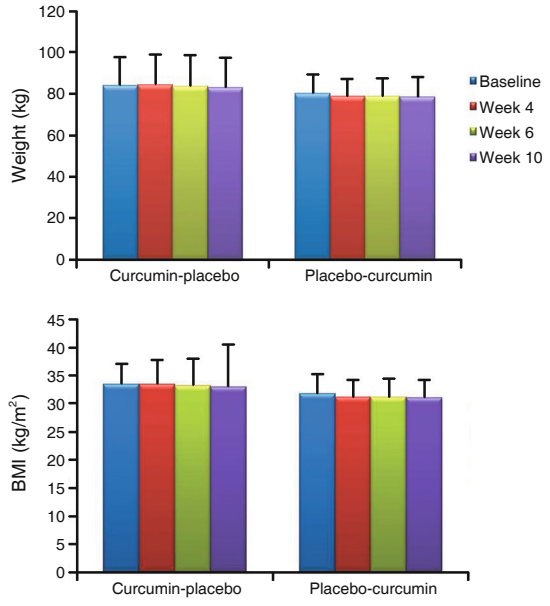

Figure 2. Effect of Curcuminoids *vs*. Placebo on Mean Weight and BMI ($\bar{x} \pm s$)

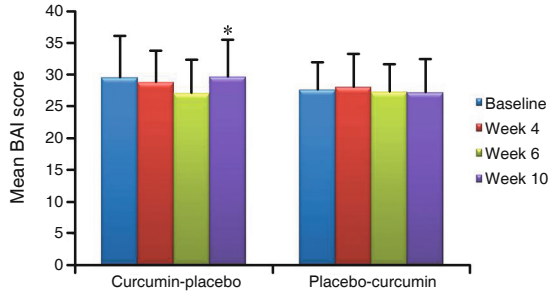

Figure 3. Effect of Curcuminoids *vs*. Placebo on Mean BAI Score ($\bar{x} \pm s$)

Note: Mixed-model analysis revealed a significant effect for curcumin compared with the placebo group (*P<0.05)

DISCUSSION

The current study suggests that there was a significant anti-anxiety effect of curcuminoids in

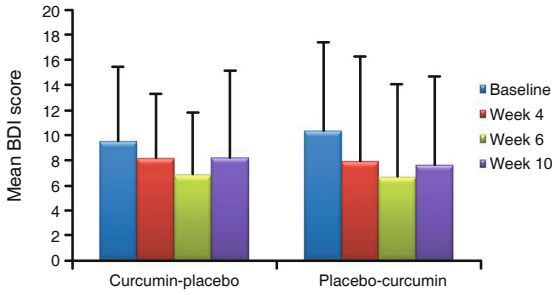

Figure 4. Effect of Curcuminoids *vs*. Placebo on Mean BDI Score ($\bar{x} \pm s$)

obese individuals following a 4-week supplementation period. Due to its high demand for oxygen, the brain is a very sensitive to oxidant species.[32] High oxygen metabolism can lead to the overproduction of reactive oxygen species (ROS) such as superoxide and hydroxyl radicals, as well as reactive nitrogen species (RNS) e.g. peroxynitrite. Numerous studies have shown that the generated ROS and RNS could damage several important biomolecules (e.g. proteins, DNA and membrane lipids) that are vital for normal functioning of neural cells.[33] Oxidative damage has been identified as a common feature of psychiatric disorders including anxiety[34] and could trigger the overexpression of pro-inflammatory cytokines causing neuroinflammation and neurodegeneration.[35] Several studies have indicated the elevated levels of cytokines such as interleukin IL-1, IL-6, interferon γ and TNF-α in individuals with anxiety and/or depression.[36] On the other hand, inflammation can also exacerbate oxidative stress through the recruitment of leukocytes and subsequent ROS generation. Hence, any agent that could disrupt such a vicious cycle between inflammation and oxidative stress would be of therapeutic efficacy for anxiety and depressive disorders.

The mechanisms accounting for the anxiolytic properties of curcumin are yet to be determined. Previous findings in mice implied that curcumin could reverse behavioural impairments and anxiety-like symptoms in stressed mice. Further tests indicated that the observed anxiolytic effects could be due to the inhibition of inducible but not neuronal nitric oxide synthase. Furthermore, curcumin has been reported to be ineffective on brain γ-aminobutyric acid (GABA) content.[26,27] Curcumin was shown to exert anxiolytic and memory-retentive effects in the elevated plus maze mouse model; these effects of curcumin were accompanied by increases in the brain levels of monoamines serotonin, norepinephrine, and

dopamine.[28] This latter finding on the enhancement of serotonin and norepinephrine by curcumin is of particular importance due to the important role of these neurotrransmitters in mood regulation.[37] The serotonergic system plays a crucial role in the pathogenesis of neuropsychiatric disorders. In this context, behavioral, genetic and pathological findings have consistently shown that altered expression and/or activity of 5 hydroxyl tryptamine (5HT) 1A type serotonergic receptors have a prominent role in the development of anxiety and depression.[38] 5HT1A agonists have been found to exert anti-anxiety effects.[39-41] Interestingly, curcumin can up-regulate the 5HT1A mRNA expression in rats under chronic stress, thereby promoting anxiolytic effects.[42] The stimulatory effects on serotonin and other neurotransmitters could be secondary to the inhibition of monoamine oxidases A and B, as reported by Yu, et al[43] for Curcuma longa extract. Several lines of evidence have confirmed the neuroprotective effects of curcumin and its therapeutic activity against a range of neurological and psychological disorders including Alzheimer's disease, Parkinson's disease, ischemic stroke, epilepsy, multiple sclerosis and depression.[44]

There are several new findings arising from the present study, First, it represents the randomized controlled trial conducted to assess the impact of curcumin on indices of anxiety and depression. Second, although simple measures were employed, the findings arising from the current trial are of considerable importance as there is a substantial gap between animal models of psychological and affective disorders and human. As these animal models may not represent the clinical case in a reliable manner, trials are warranted to verify if positive preclinical results could be successfully translated into clinical practice. Third, we used a bioavailable formulation of curcumin in the present trial that contained piperine as a widely known bioavailability enhancer. Hence, it is expected that the main obstacle for the biological activity, i.e. poor bioavailability, has been sufficiently addressed by using curcumin/piperine combination. Finally, the present trial had a unique cross-over design which is considered to provide the highest level of evidence.

However, the present study had a number of important limitations. The most important limitation was that present trial was a sub-study of an investigation of the effects of curcuminoids on cardiovascular risk markers.[45] Therefore, the study population was not representative of patients with anxiety and/or depression though these disorders could be regarded as comorbidities of obesity. It is interesting to note that participants of the present trial had severe anxiety at inclusion (based on the BAI score), whilst having only a slightly increased BDI score. Therefore, differential impact of curcumin supplementation on the evaluated measures of anxiety and depression could be due to the differences at baseline status. Second, no pharmacokinetic evaluation of curcuminoids was conducted on serum samples collected from patients. Awareness of the kinetic profile of curcuminoids may have been helpful to understand if the preparation of curcumin used did result in detectable changes in serum levels of curcuminoids, and also confirm the participants' adherence to the treatment. Third, females constituted the major fraction of participants in the present trial (83%). Therefore, the results may not be generalizable to male subjects. Finally, the relatively short duration of supplementation and small number of participants are other factors that could limit the effect size of curcumin and thus account for the lack of observed efficacy in terms of improving depressive symptoms.

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Conflict of Interest

The authors have no competing interests to declare.

Author Contribution

MG, AS and MI discussed core ideas and designed the study. AM and SG were involved in data collection. AS, HA, SG and GF prepared the manuscript draft. All authors approved the final version.

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