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Efficacy of curcumin in cognitive functions and inflammatory markers of major depressive disorder

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ABSTRACT

Objective: Major depressive disorder (MDD) is associated with cognitive deficits and inflammation which predict treatment resistance. This study aimed to investigate the efficacy of Curcumin in cognitive functions and inflammation in depression. *Methods:* The present study was a double-blind, randomized clinical trial design. One hundred twenty MDD outpatients, aged 18 to 55, were selected regarding the inclusion and exclusion criteria and randomly assigned to Curcumin (n = 60) and control groups (n = 60). Participants were assessed at baseline, sixth and twelfth week for depressive symptoms and cognitive functions. Inflammatory markers (IL-6, IL-1β) were measured at baseline and the twelfth week. Both groups received sertraline. Experimental group received Curcumin while the control group received placebo. Data were analyzed by repeated measures MANOVA. *Results:* Curcumin out performed control on trial making test-B (P= 0.011), backward digit span, verbal fluency task and Tower of London (P< 0.001) at the twelfth week of assessment and forward digit span (P<0.001) and trial making test-A (P=0.041) at the sixth and twelfth week of assessment. Moreover, inflammatory markers reduced in the curcumin group more than in the control group (P< 0.011). *Conclusion:* According to the results of this study, Curcumin could be considered as an antidepressant to bring more therapeutic benefits in improving clinical symptoms and cognitive deficits, especially the executive functions of MDD patients. Moreover, it could lead to reduction of inflammatory markers and would target cognitive function more than conventional treatments.

Keywords: Depression, Curcumin, Cognitive Function, Inflammation

1. INTRODUCTION

Depression is a common disorder that affected many people and is the most common cause of disability worldwide (World Health Organization, 2020). According to MDD diagnostic criteria of DSM-5, in addition to mood symptoms, reduced concentration, attention, and diminished thinking ability or decision making are also among the diagnostic criteria (American

Psychiatric Association, 2013). Approximately 20% of patients exhibited deficits of two standard deviations below the mean on two or more cognitive domains (Gualtieri et al., 2008). According to review articles, impairment in attention, memory, executive function and psychomotor (Cohen's effect sizes ranging from -0.32 to -0.97) are the most common cognitive impairments (Rock et al., 2014). Also, some studies reported that depressed patients demonstrate increased peripheral inflammation (Raison et al., 2011). These findings imply tothe underlying inflammatory process in MDD, even in medically healthy individuals.

Despite the existence of evidence-based medical guidelines, which rely on monoaminergic theory, these approaches are more effective in improving mood symptoms (Carvalho et al., 2014) and only 30-40% of patients return to pre-disease functional levels (Bortolato et al., 2016). Furthermore, Ji et al., (2020) in a study of 67 depressed patients treated with selective serotonin reuptake inhibitors (SSRI) for at least 6 months found that despite the reduction of patients' cognitive deficits, executive functions and attention still were significantly weaker than the healthy group. Moreover, Setiawan et al., (2015) pointed out the increased inflammatory activity of microglia in the anterior cingulate and prefrontal cortex of MDD patients, that indicates the underlying neuro-anatomical regions of executive function. Venneti et al., (2013), demonstrated that even in a healthy individual's macrophage activation could elicit depressive like syndrome and activate the hypothalamic, pituitary and adrenal (HPA) axis. Chronic activation of Microglia leads to considerable inflammation, which could affect cognitive functions. Although, some studies have shown that treatment with SSRIs would improve memory functions, psychomotor speed, and executive functions (Constant et al., 2005), other studies implied that SSRIs were not associated with improved cognitive function in MDD (Fava et al., 2006).

Apparently, medications that simultaneously affect multiple neurochemical targets show greater improvement in cognitive functions than single-target therapies such as SSRIs (Herrera-Guzmán et al., 2010). Therefore, the addition of a supplementary medication that, in addition to the serotonin pathway, could affect other neurochemical mechanisms of depression would be more effective in improving the cognitive functions of MDD patients. According to "Depression Inflammatory Theory", increased level of cytokines such as Interleukins (IL-6, IL-1β, IL-18) and tumor necrosis factor (TNF-α)is associated with acute depression (Gałecki et al., 2018; Kappelmann et al., 2018; Yuan et al., 2019). Central depletion of Serotonin occurs by these cytokines activating enzyme Indoleamine 2,3-dioxygenase (IDO) which increase production of Quinolinic acid (QA), a N-methyl-D-aspartate receptor (NMDA) agonist leading to synaptic loss (Gałecki et al., 2018). Leaky gut hypothesis (Ohlsson et al., 2019) also suggests an abnormal increase in intestinal permeability to bacterial toxins as an underlying cause of the immune dysfunction in depression (Hannestad et al., 2013).

This inflammatory process causes mood and cognitive changes (Gałecki et al., 2018) and psychomotor retardation, inattentiveness, and speed processing and executive function deficits are among the most prominent changes (Gałecki et al., 2015). As well, Inflammation is considered the underlying mechanism of HPA disruption, which ultimately leads to hippocampus volume decrement and is caused by decreased expression of neurotrophic factors in the brain (Milne et al., 2012). Although several studies have pointed out the role of inflammation in the incidence, exacerbation and persistence of MDD, current medications have been focused mainly on the monoaminergic system, but the effect of these agents may be somehow due to their intrinsic anti-inflammatory properties (Hannestad et al., 2013; Kappelmann et al., 2018; Obuchowicz et al., 2014). Hence, some studies have shown the efficacy of anti-inflammatory agents such as cyclooxygenase inhibitors in treatment of depression (Pasco et al., 2010) But, cyclooxygenase inhibitors could be associated with significant side effects such as gastrointestinal, renal and vascular complication (Harirforoosh et al., 2013). The other anti-inflammatory agent that could be effective in treatment of depression is Curcumin.

Curcumin is the active component of turmeric, which is safe at high doses and possess several anti-inflammatory, antioxidant and antidepressant properties by inhibiting the inflammatory pathways of cyclooxygenase-2 and nitrite oxide synthase, which both are active in depressive disorder (Daverey et al., 2016; Agarwal & Agarwal, 2016; Ishaque et al., 2018). These mechanisms could suggest curcumin as a putative agent in the treatment of the neurological deficits of depression. Some studies have shown that curcumin can reverse the decline in brain neurotrophic factor (BDNF) (Hurley et al., 2013). Cox et al., (2015) also showed that using 80 mg of oily curcumin for 12 weeks can improve working memory in healthy adults. Likewise, Raneiy-smith et al., (2016) showed that taking 1500 mg/day of biocurcomax for 52 weeks can prevent cognitive decline in older age groups (60 years and older).

Although a few studies have examined the effectiveness of curcumin on cognitive functions and inflammation in depression, but according to a systematic review by Seddon et al., (2019) published on clinical trials between 2011 and 2018, only three out of 5 studies reported the effectiveness of curcumin in improving cognition. Also, these studies have been performed on non-depressed populations and bear methodological problems such as insufficient duration and nonstandard dose of curcumin prescription, and lack of MDD specialization neuropsychological measurement tools. Therefore, the present study aimed to investigate and compare the efficacy of curcumin as add-on therapy with sertraline in improvement of clinical symptoms, cognitive functions and inflammatory biomarkers of MDD patients.

2. METHODS

The present study was a double-blind, randomized clinical trial design. Assessments performed at three phases (the baseline, sixth and twelfth week). The statistical population of the study consisted of all the referral outpatients from medical centers of Tehran's 2nd, 3rd and 16th district from October 2020 to September 2021 who met the criteria of MDD based on psychiatrists' clinical interview. One-hundred twenty patients were selected regarding the inclusion and exclusion criteria. All participants were randomly (according to a computer-generated randomization list) assigned to curcumin and control groups. Each group consisted of 60 participants (n = 60 Curcumin group and n = 60 Control group, β-1= 0.91, effect size = 0.3, α = 0.05) (Stevens, 2007).

Inclusion criteria were: 1- MDD diagnosis, 2- age between 18 to 55 years, 3- ability to read and write. The exclusion criteria included: 1- Substance use and smoking, 2- Regular use of cyclooxygenase inhibitors, 3- History of diseases affecting brain, 4- Autoimmune diseases, 5- Other psychiatric diseases, 6- History of Electro-convulsion, 7- Infection in the last month. The discontinue criteria included: 1- Suicidal ideation, 2- Altered hormonal conditions, 3- Need for hospitalization, 4- Any change of received medications, 5- Taking less than 80% of the received pills, 6- Systemic disease, 6- Reluctance to continue cooperation. The study was registered in IRCT.ir (IRCT20200607047672N1) and approved by the ethical committee of Iran University of Medical Science (IR.IUMS.REC.1397.1167).

Hamilton Depression Rating Scale (HDRS)

This scale is designed to measure the severity of depressive symptoms by clinical interview. The 17-factor form is commonly used in studies. The scoring is from 0 to 50. The validity of the Persian version of the questionnaire through correlation with Beck Depression Scale has been reported 0.55 and the reliability between evaluators was 0.95 (Ebrahimi et al., 2013).

Wechsler Forward/ Backward digit span

To assess verbal working memory of the participants, the digit span sub-tests of the Wechsler memory scale (WMS-III) were used. In this study, short-term memory was assessed by forward digit span and working memory was assessed by backward digit span. In the Persian population coefficient's reliability of the sub-tests have been reported by test-retest ranging from 0.28 to 0.98 (Orangi et al., 2002).

Trial Making Test A & B (TMT)

This test is a psychomotor speed measure. Participants are asked to quickly connect numbered dots from 1 to 25 (Form A) and 1 to 12 and the letters A to R (Form B) in the ascending order. The outcome measure is the taken time for completing the task; the lower score means better performance. The reliability of this test is reported 0.78 to 0.70 and the inter-test reliability is reported 0.98 to 0.96 (Reynolds, 2002).

Verbal Fluency task (VFT)

The Farsi verbal fluency test consists of letter fluency and category fluency. Each part consists of three one-minute trials, and the overall trials are six one-minute trials for each participant. In letter fluency, one of the three selected Farsi letters are given to the participant and he is asked to name as many words that start with the selected letter in a limited time (one minute). The sum of the scores in each section is between 0 to 90 (Ghasemian-Shirvan et al., 2018).

Tower of London (TOL)

In the present study, the Tower of London test was recruited to measure the executive planning ability of the participants. This test has appropriate construct validity in assessing the planning and organization ability of individuals. The validity of this test was also reported as 0.79 (Krikorian et al., 1994).

Serum Analysis

Commercially available ELISA kits were used to measure the serum concentrations of and human IL-1β (Cat. No: ZB-10143C-H9648 Zellbio GmbH) and humanIL-6 (Cat No: 950.30.096 Diaclone France) according to the manufacturer's recommended protocols.

Procedure

In the first stage, 120 patients with MDD were selected based on inclusion and exclusion criteria, entered the study after completing the informed consent form. Patients were randomly assigned to Curcumin and control groups. Both participants and assessors were

blind. Both groups received standard treatment with sertraline; thus, in the first four days, 25 mg of sertraline was prescribed, and then the dose increased to 50 mg/day. The Curcumin group received two Curcumin doses of 500 mg/day, in addition to the standard treatment. The control group received placebo similar to Curcumin (weight, color, prescription dose). Participants were evaluated for clinical symptoms, cognitive functions such as memory, verbal fluency, speed processing, and executive planning at the baseline, sixth-and twelfth-week phases. Inflammatory markers such as IL-6 and IL-1β were evaluated. Subsequent to overnight 8h fasting, blood samples were obtained at baseline and 12th week. The serum was separated by centrifugation of the blood samples at 1,500 × g for 10 min at 4°C. The serum samples were stored at −80°C until analytical measurements were performed. Commercially available ELISA kits were used to measure the serum concentrations of IL-6 and IL-1β according to the manufacturer's recommended protocols. Assessment for side effects and medication competence were done by phone every week. At the sixth week of the intervention in the control group, two subjects were excluded from the study due to suicidal ideation and pregnancy. In each group, there was a case of withdrawal due to unwillingness to continue cooperation (figure 1).

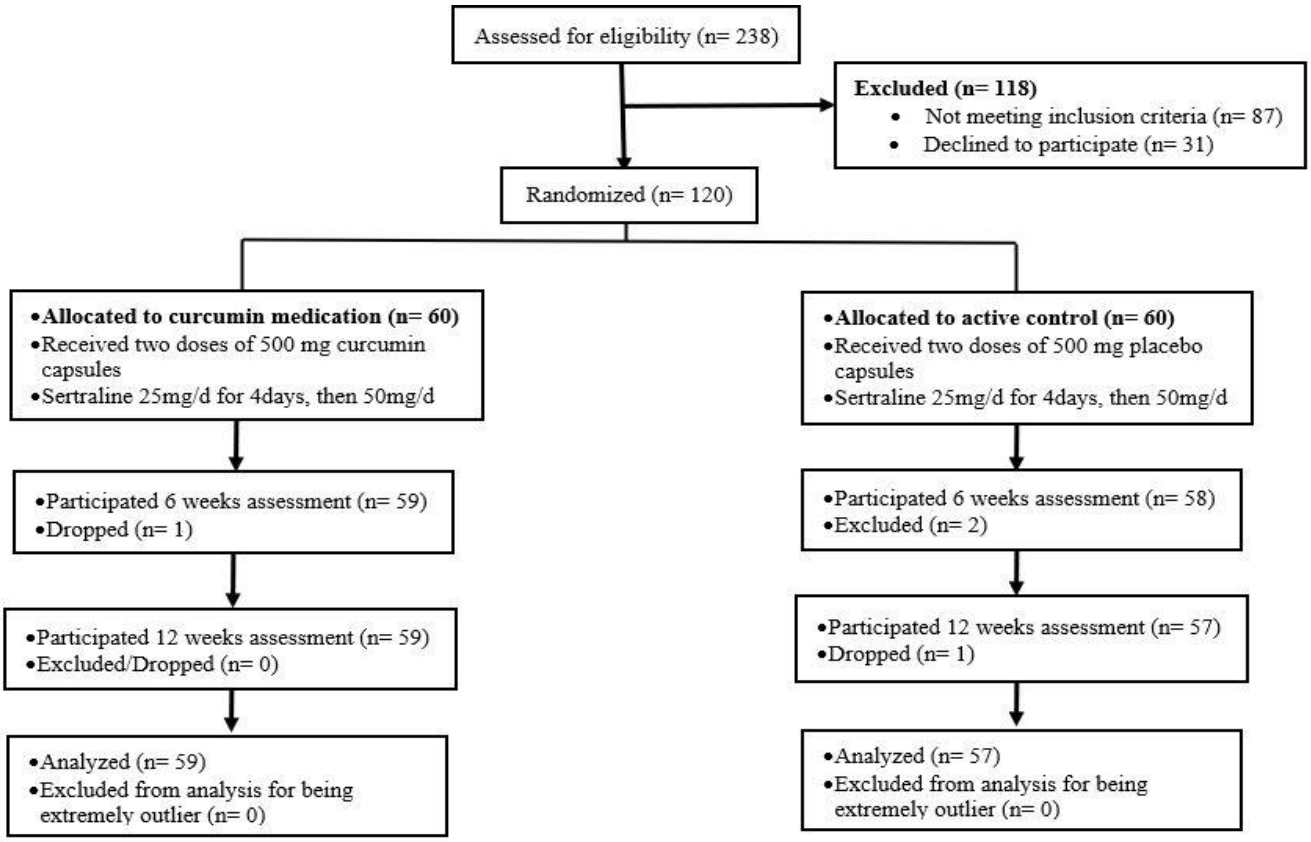

Figure 1 flow of the participants through the trial

Statistical Analysis

The repeated measures MANOVA test were applied for the determination and comparison the trend of changes between two groups in three assessment phases. The SPSS software, version 19, (SPSS, Chicago, IL, USA) was employed for the analyses. Independent t-tests and chi-square were utilized to compare the demographic characteristics of the two groups. A P value of less than 0.05 (2-tailed) was considered to be statistically significant.

3. RESULTS

As shown in Table 1, the final sample was composed of 59 MDD patients in Curcumin group and 57 MDD patients in the control group. Analysis of demographic characteristics of the sample showed that there was no significant difference between the mean age of the curcumin (32.54 ± 8.219) with the Control group (32.59 ± 8.843) (t= 0.034, P= 0.97). Also, in terms of illness duration, no significant difference was found between the two groups of curcumin (1.89 ± 0.715) and Control (1.66 ± 0.884) (t= 1.54, P= 0.12).

Table 1 demographic characteristic for all participants

		Curcumin (N=59)	Control (N= 57)
Sex Female (Percent)		71.2	68.4
Age (Mean± SD)		32.54 ± 8.219	32.59 ± 8.843
Illness Duration (Mean± SD)		1.89 ± 0.884	1.59 ± 0.703
BMI		24.35 ± 2.984	24.71 ± 2.827
Education (Percent)	Diploma	27.1	22.8
	Associate	5.1	1.8
	Bachelor	47.5	35.1
	Master	16.9	33.3
	Doctoral	3.4	7

Note: SD= Standard Deviation.

According to three times of assessment phases and multiple dependent variables, repeated measures MANOVA test was utilized. First, its assumption such as homogeneity of variances by Levene's test (P= 0.052) and Bartlett's test (P= 0.009) was checked. The results shown that the main effect of time (Pillai's Trace= 0.975, P< 0.001, F (16, 99) = 246.08, Partial Eta Squared= 0.975), main effect of group (Pillai's Trace= 0.293, P< 0.001, F (8, 107) = 5.539, Partial Eta Squared= 0.293) and interaction effects of time*group (Pillai's Trace= 0.736, P< 0.001, F (16, 99) = 17.217, Partial Eta Squared= 0.736) were statistically significant. In the next step, the results of within-subjects contrasts based on assessment phases (Baseline, Sixth & Twelfth week) and experimental groups (Curcumin & Active control) are presented. Since that the results of Mauchly's test indicated that the sphericity assumption was not met, so the Greenhouse-Geiser test used to correct the degrees of freedom.

Table 2 Results of within-subjects contrasts in cognitive functions and clinical symptoms based on grouping and assessment phases

Scales	Group	Baseline		6th week-intervention			12th week-intervention		
		Mean ± SD	P	Mean ± SD	P	η^2	Mean ± SD	P	η^2
Forward digit span	Curcumin	5.27±1.126	0.37	6.69±1.118	<0.001	0.106	8.32±1.382	<0.001	0.286
	Control	5.47±1.297		5.94±1.076			6.73±1.126		
Backward digit span	Curcumin	3.44±1.054	0.10	3.72±0.826	0.54	0.003	5.55±1.178	<0.001	0.390
	Control	3.77±1.149		3.82±0.868			3.91±0.871		
TMT.A	Curcumin	45.38±6.167	0.74	42.76±5.462	0.041	0.035	38.79±5.941	<0.001	0.161
	Control	45.75±5.654		44.91±5.883			43.52±4.881		
TMT.B	Curcumin	84.32±8.226	0.86	81.37±7.794	0.77	0.001	77.03±7.814	0.012	0.026
	Control	84.05±8.519		81.78±7.834			80.26±7.565		
VFT. Letter	Curcumin	15.77±4.119	0.88	16.08±3.944	0.95	0.001	20.0±5.854	<0.001	0.105
	Control	15.66±4.045		16.03±4.503			16.43±4.508		
VFT. Category	Curcumin	16.54±3.720	0.89	17.05±3.645	0.76	0.001	19.94±3.780	<0.001	0.128
	Control	16.43±4.659		16.84±3.872			17.12±3.664		
TOL Score	Curcumin	23.54±2.866	0.86	24.03±2.385	0.83	0.001	26.54±2.712	<0.001	0.211
	Control	23.63±2.553		23.94±2.124			24.10±1.961		
HDRS	Curcumin	26.00±3.969	0.69	13.15±3.666	0.02	0.04	5.98±2.757	<0.001	0.136
	Control	26.29±4.250		14.56±2.666			8.01±2.375		

Note: TMT.A= Trial Making Task, VFT= Verbal Fluency Test, TOL= Tower of London, HDRS= Hamilton Depression Rating Scale, SD= Standard Deviation, η^2= Partial Eta Square.

As shown in Table 2, there was a significant difference in the trend of changes in each group at Baseline-Sixth week assessment phase on HDRS ($F_{control}$= 34.69, P< 0.001; $F_{Curcumin}$= 139.30, P< 0.001), Forward digit span ($F_{control}$= 6.38, P= 0.014; $F_{Curcumin}$= 104.45, P< 0.001) and TMT.A ($F_{control}$= 4.82, P= 0.032; $F_{Curcumin}$= 41.16, P< 0.001) components (effect sizes ranging from 0.078 to 0.706) which indicates the ameliorating effect of interventions in both groups. Moreover, the trend of changes on Backward digit span ($F_{Curcumin}$= 4.89, P= 0.031) and TMT.B ($F_{Curcumin}$= 4.09, P= 0.048), was significant only in the Curcumin group at Baseline-Sixth-week assessment phase (see appendix figures).

Continue Table 2 Results of within-subjects contrasts in cognitive functions and clinical symptoms based on grouping and assessment phases

Scales	Group	Test of within subjects' contrasts					
		Level 1 Vs. Level 2		Level 2Vs. Level3		Level 1 Vs. Level3	
		P	η^2	P	η^2	P	η^2
Forward digit span	Curcumin	<0.001	0.643	<0.001	0.691	<0.001	0.830
	Control	0.014	0.102	<0.001	0.670	<0.001	0.433
Backward digit span	Curcumin	0.031	0.078	<0.001	0.668	<0.001	0.654
	Control	0.762	0.002	0.168	0.034	0.442	0.009
TMT.A	Curcumin	<0.001	0.415	0.001	0.773	<0.001	0.745
	Control	0.032	0.079	0.024	0.088	<0.001	0.195
TMT.B	Curcumin	0.048	0.066	<0.001	0.576	<0.001	0.298
	Control	0.156	0.036	<0.001	0.315	0.017	0.098
VFT. Letter	Curcumin	0.427	0.011	0.001	0.604	<0.001	0.487
	Control	0.409	0.012	0.523	0.007	0.217	0.033
VFT. Category	Curcumin	0.067	0.056	<0.001	0.601	0.001	0.589
	Control	0.161	0.035	0.349	0.016	0.053	0.062
TOL Score	Curcumin	0.059	0.060	<0.001	0.417	<0.001	0.414
	Control	0.270	0.022	0.631	0.004	0.291	0.019
HDRS	Curcumin	<0.001	0.706	<0.001	0.884	<0.001	0.932
	Control	<0.001	0.383	<0.001	0.857	<0.001	0.839

Note: TMT.A= Trial Making Task, VFT= Verbal Fluency Test, TOL= Tower of London, HDRS= Hamilton Depression Rating Scale, SD= Standard Deviation, η^2= Partial Eta Square, Level 1= Baseline, Level 2= Sixth week of assessment, level 3= Twelfth week of assessment. Also, at Baseline-Twelfth-week assessment phase the trend of changes on Backward digit span ($F_{Curcumin}$= 109.58, P= 0.0001), VFT-letter ($F_{Curcumin}$= 55.10, P< 0.001), VFT-category ($F_{Curcumin}$= 83.04, P< 0.001), TOL-Score ($F_{Curcumin}$= 40.95, P= 0.0001), was significant only in Curcumin group. On other components such as HDRS, Forward digit span, TMT-A and TMT-B, the pattern of changes in both groups was significance at the Sixth-Twelfth-week assessment phase (effect sizes ranging from 0.315 to 0.884) and Baseline-Twelfth-week assessment phase (effect sizes ranging from 0.195 to 0.932).

Moreover, according to table 2, Curcumin group outperformed Control group on Forward digit span (F= 13.44, P= 0.001) and TMT.A (F= 4.16, P= 0.04) at sixth week assessment phase. In addition, Curcumin group scored lower than Control on HDRS at both sixth (F= 5.57, P= 0.02) and twelfth (F= 17.91, P= 0.001) week assessment phase. At twelfth week of assessment, Curcumin group outperformed Control group on Forward digit span (F= 45.64, P= 0.001), Backward digit span (F= 71.83, P= 0.001), TMT-A (F= 21.86, P= 0.001), TMT-B (F= 5.10, P= 0.01), VFT-Letter (F= 13.41, P= 0.001), VFT-Category (F= 16.69, P= 0.001) and TOL-Score (F= 30.57, P= 0.001). Regarding the inflammatory markers, the results of time*group interaction effects (Pillai's Trace= 0.295, P< 0.001, $F_{(2, 113)}$= 23.684, Partial Eta Squared= 0.295)indicated that there was a significant interaction between experimental groups (Curcumin & Active control) and assessment phases (Baseline, Twelfth week).

Table 3 Results of within-subject's contrasts in inflammatory markers based on grouping and assessment phases

Scales	Group	Baseline			12^{th} week-intervention			Test of within subjects' contrasts	
		Mean ± SD	P	η^2	Mean ± SD	P	η^2	Level1 Vs. Level 2	
								P	η^2
IL-6(Pg./ml)	Curcumin	17.88±3.995	0.31	0.009	12.05±2.913	<0.001	0.121	<0.001	0.914
	Control	18.51±2.624			13.91±2.065			<0.001	0.926
IL-1β(Pg./ml	Curcumin	1.33±0.211	0.64	0.002	0.99±0.131	<0.001	0.097	<0.001	0.891
	Control	1.31±0.198			1.09±0.167			<0.001	0.876

Note: IL-6= interleukin- 6, IL=1β= interleukin- 1beta, SD= Standard Deviation, η^2= Partial Eta Square, Level 1= Baseline, level 2= Sixth week of assessment.

According to Table 3, there was a significant difference in trend of changes at Baseline-Sixth week assessment phase on IL-6 ($F_{control}$= 699.88, P< 0.001; $F_{Curcumin}$= 615.64, P< 0.001) and IL-1β ($F_{control}$= 396.66, P< 0.001; $F_{Curcumin}$= 476.55 P< 0.001) in both groups (appendix figures I & j), but the reduction in Curcumin group was significantly more than Control group on IL-6 (F= 15.66, P< 0.001) and IL-1β (F= 12.20, P< 0.001).

4. DISCUSSION

This study aimed to investigate the effects of Curcumin on cognitive functions and inflammatory markers of depression and compare these findings with a Control group.

Cognitive Functions

Regarding the cognitive functions, results showed that short-term memory (STM) which was measured by forward digit span, improved significantly at the Baseline-Sixth week assessment phase in both groups but, the performance of the Curcumin group was significantly better. At Baseline-Twelfth and Sixth-Twelfth week assessment phase, both groups showed a significant improvement in STM, but still, Curcumin group had significantly better performance (partial Eta squared effect size 0.286). These findings are consistent with Gorenstein et al., (2006). Also, Liu et al., (2014) showed that daily consumption of 10 mg/kg of Curcumin for 5 weeks increases the level of BDNF in the mice hippocampus and improves memory.

In the working memory domain, which was measured by backward digit span, the Control group showed no significant changes at week sixth, but the Curcumin group improved significantly. Moreover, at Baseline-Twelfth and Sixth-Twelfth week assessment phase, only the performance of the Curcumin group improved significantly. This is consistent with Cox et al., (2015) that have shown the effect of Curcumin on improving working memory in healthy individuals. Therefore, more improvement of memory functions of the Curcumin group could be due to its effects on NFkB-BDNF positive feedback loop. Some researchers suggest that activation of this loop would accelerate recovery from clinical symptoms especially cognitive dysfunctions in MDD (Hurley et al., 2013).

The processing speed was measured by TMT-A at Baseline-Sixth week assessment phase. Performance of both groups was significantly enhanced but the Curcumin group had more significant improvement. Similarly, at the Baseline-Twelfth and Sixth-Twelfth week assessment phase, both groups had significant improvement, but changes in the Curcumin group were more prominent (Partial Eta squared effect size 0.161). This finding is consistent with the results of Mowla et al., (2016). They reported the positive effect of 6 weeks of sertraline consumption on the psychomotor function of 19 MDD patients.

In the TMT-B, which requires higher-order levels of cognitive function, at the baseline-Sixth week assessment phase, only Curcumin group performance was significantly improved. In between group's comparison, no significant difference was observed. Furthermore, at Baseline-Twelfth and Sixth-Twelfth week assessment phase, both groups showed a significant improvement, but the Curcumin group held its superiority (partial Eta squared effect size 0.026). Since the main brain executive function pathways are dopaminergic and curcumin exerts a regulatory role on these pathways (Cox et al., 2015), the better performance of the curcumin group in higher-level cognitive tasks could be explained.

Verbal fluency also has two sub-components of letter and category. Verbal fluency measured by VFT showed no significant difference at Baseline-Sixth week in both groups. Also, no significant difference was observed between the groups. At Baseline-Twelfth and Sixth-Twelfth week assessment phase, only performance of the Curcumin group was significantly improved. This finding is consistent with Fava (2006) based on the ineffectiveness of antidepressants on improving executive function. Regarding the association of IL-1β gene expression and circulating levels of its mRNA with verbal fluency impairment and Broca's volume reduction in some psychiatric disorders and modulating effects of Curcumin on it, improvement of the verbal fluency in this group, could be expected (Fillman et al., 2016).

In executive planning which was measured by Tower of London, at Baseline-Sixth week, no significant difference was found in both and between groups. At Baseline-Twelfth and Sixth-Twelfth week assessment phase, only the performance of the Curcumin group improved significantly. Moreover, based on within-group comparison the Curcumin group performance was significantly better than the Control group (partial Eta squared effect size 0.211). This finding could indicate the effect of Curcumin on the glutamatergic system. Lin et al., (2011) found that Curcumin was more potent in inhibiting glutamate release in the PFC region than SSRIs in rat. Glutamate is a stimulatory neurotransmitter in the brain that plays a key role in neuroplasticity, problem-solving abilities, and memory (McEntee et al., 1993).

Clinical Symptoms

The results showed that at Baseline-Sixth week assessment phase, the mean score of depression decreased in both groups, but the Curcumin group showed more significant reduction than the Control group. It is consistent with the fact that sertraline as an SSRI is the first line treatment of MDD (Lydiard et al., 1999). At Baseline-Twelfth and Sixth-Twelfth week assessment phase, the mean score of depression in both groups decreased significantly, but the reduction in the Curcumin group was significantly more than the Control group (partial Eta squared effect size 0.382). This synergistic effect of Curcumin in reducing the clinical symptoms of depression could be through its effects on noradrenergic and dopaminergic pathways, beside of the serotonergic pathway (Patel Pankti, 2014). Moreover, Ramaholimihaso et al., (2020) showed that Curcumin changes the permeability of gastrointestinal barriers and thus can affect cerebral-intestinal signaling, so curcumin may indirectly alter the BBB permeability and thus increase the effectiveness of other medications while decreasing gut permeability to bacterial lipopolysaccharides.

Inflammatory Markers

In addition, inflammatory indices of IL-6 and IL-1β in both Curcumin and Control groups were significantly reduced; however the effect of intervention was more prominent in the Curcumin group. Recently, there was growing evidence that antidepressants such as Sertraline exert their effects at least to some extent by reducing inflammatory cytokines (Kappelmann et al., 2018). In addition, Obuchowicz et al., (2014), in their study on animal model of lipopolysaccharide induced depression, showed that Imipramine and Fluoxetine through regulation of microglia activation could reduce the production of inflammatory cytokines, especially IL-1β, in the central nervous system. Furthermore, Fan et al., (2019) showed the effect of consumption of 40 mg/kg curcumin for 5 weeks in reducing the expression and production of IL-1β and neuronal apoptosis in the ventromedial prefrontal cortex of rats. In addition, Ghandadi & Sahebkar (2017) in their review on the anti-inflammatory effects of Curcumin showed that Curcumin could reduce the level of IL-6 in a variety of inflammatory conditions. According to the innate anti-inflammatory effect of Sertraline itself, Curcumin and SSRIs would target inflammation through different mechanisms, especially specified that existing inflammation in MDD predicts resistance to treatment with SSRIs.

5. CONCLUSION

It seems that Curcumin as an antidepressant could accelerate the improvement of clinical symptoms, inflammatory markers and cognitive functions, especially the executive function, which may appear much later or not at all with conventional antidepressants. Furthermore, depression is an important risk factor for a variety of common neurodegenerative diseases, such as Alzheimer's disease. Curcumin not only could enhance the cognitive function of MDD patients but also may prevent the neuroprogression in this group of patients. Finally, although combination therapy has traditionally been discouraged in psychiatry because of the increased risk of drug interactions, at least in a subgroup of affected patients, it may be necessary to consider anti-inflammatory strategies in the management of depression, so further research is required.

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Author's contributions

Conceptualization, methodology, editing & review: All authors; Investigation, resources, original draft preparation, visualization: Zeynab Alimadadi; Supervision: Shima Jazayeri; Data analysis: Zeynab Alimadadi & Saeed Azami.

Ethical Approval

The study was approved by the ethical committee of Iran University of Medical Science. IR.IUMS.REC.1397.1167.

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Conflict of interests

The authors declare that there are no conflicts of interests.

Data and materials availability

All data associated with this study are present in the paper.

Appendix

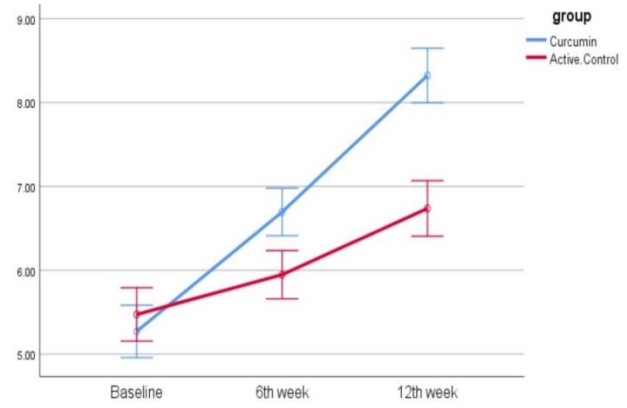

Figure a Forward digit span

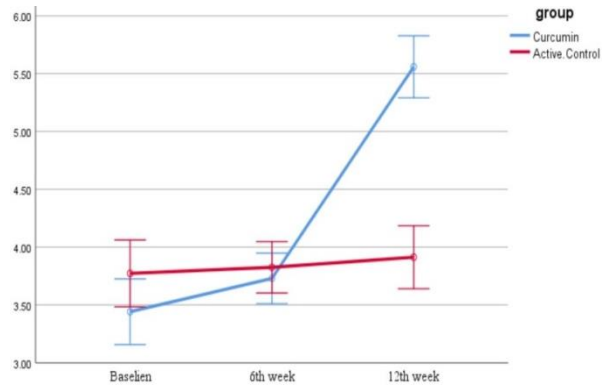

Figure b backward digit span

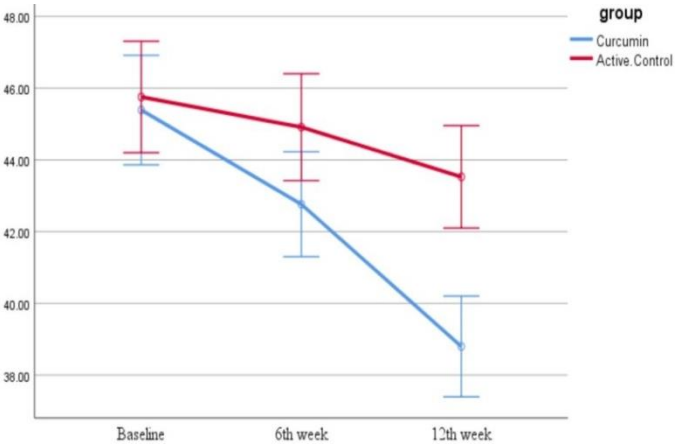

Figure c Trial Making Task A (TMT-A)

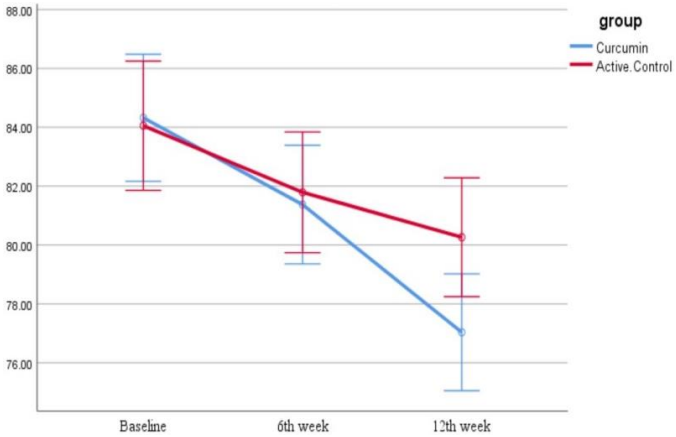

Figure d Trial Making Task B (TMT-B)

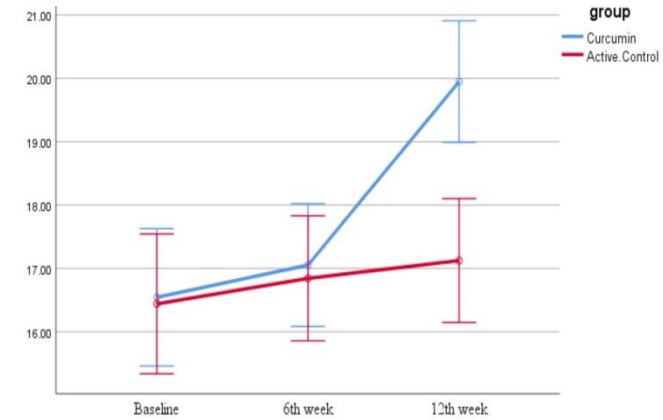

Figure e Verbal Fluency Test (VFT. Category)

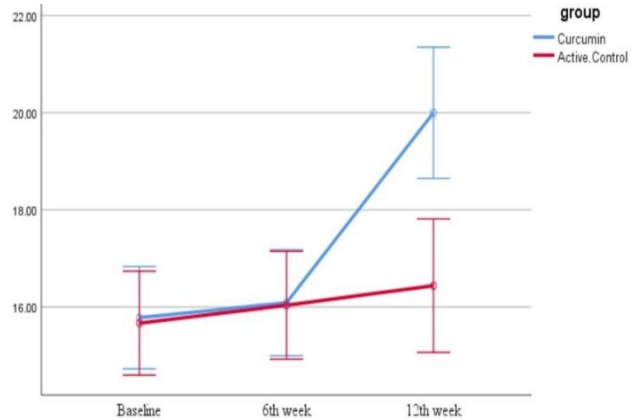

Figure f Verbal Fluency Test (VFT. Letter)

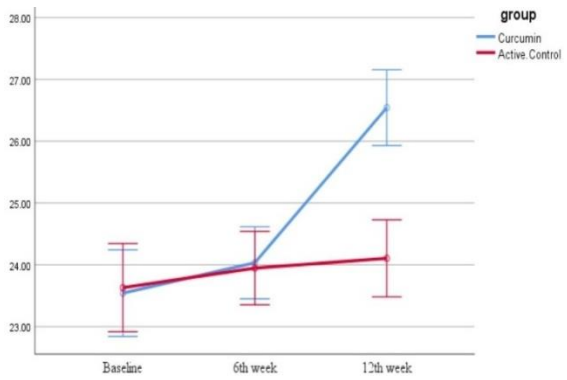

Figure g Tower of London, (TOL Score)

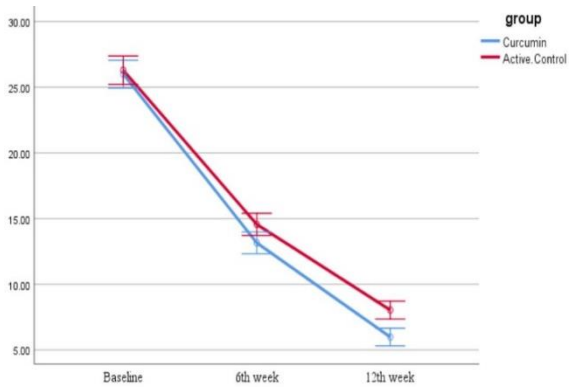

Figure h Hamilton Depression Rating Scale (HDRS)

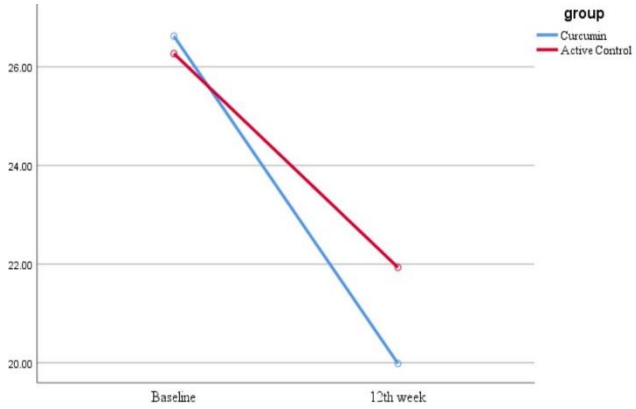

Figure i Interleukin- 1B (IL-1B)

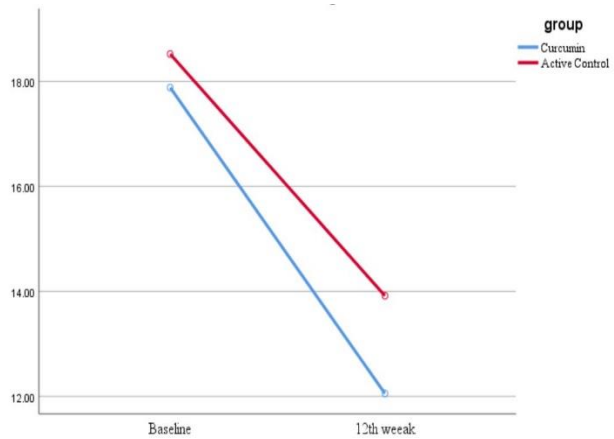

Figure j Interleukin-6 (IL-6)

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