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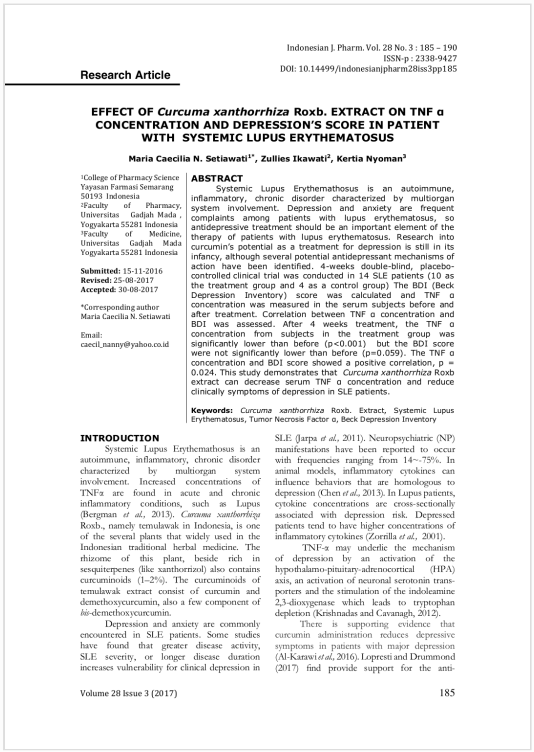

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Research Article

EFFECT OF *Curcuma xanthorrhiza* Roxb. EXTRACT ON TNF α CONCENTRATION AND DEPRESSION'S SCORE IN PATIENT WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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ABSTRACT

Systemic Lupus Erythemathosus is an autoimmune, inflammatory, chronic disorder characterized by multiorgan system involvement. Depression and anxiety are frequent complaints among patients with lupus erythematosus, so antidepressive treatment should be an important element of the therapy of patients with lupus erythematosus. Research into curcumin's potential as a treatment for depression is still in its infancy, although several potential antidepressant mechanisms of action have been identified. 4-weeks double-blind, placebo-controlled clinical trial was conducted in 14 SLE patients (10 as the treatment group and 4 as a control group) The BDI (Beck Depression Inventory) score was calculated and TNF α concentration was measured in the serum subjects before and after treatment. Correlation between TNF α concentration and BDI was assessed. After 4 weeks treatment, the TNF α concentration from subjects in the treatment group was significantly lower than before ($p<0.001$) but the BDI score were not significantly lower than before ($p=0.059$). The TNF α concentration and BDI score showed a positive correlation, $p = 0.024$. This study demonstrates that *Curcuma xanthorrhiza* Roxb extract can decrease serum TNF α concentration and reduce clinically symptoms of depression in SLE patients.

Keywords: *Curcuma xanthorrhiza* Roxb. Extract, Systemic Lupus Erythematosus, Tumor Necrosis Factor α, Beck Depression Inventory

INTRODUCTION

Systemic Lupus Erythemathosus is an autoimmune, inflammatory, chronic disorder characterized by multiorgan system involvement. Increased concentrations of TNFs are found in acute and chronic inflammatory conditions, such as Lupus (Bergman *et al.*, 2013). *Curcuma xanthorrhiza* Roxb., namely temulawak in Indonesia, is one of the several plants that widely used in the Indonesian traditional herbal medicine. The rhizome of this plant, beside rich in sesquiterpenes (like xanthorrizol) also contains curcuminoids (1–2%). The curcuminoids of temulawak extract consist of curcumin and demethoxycurcumin, also a few component of *bis*-demethoxycurcumin.

Depression and anxiety are commonly encountered in SLE patients. Some studies have found that greater disease activity, SLE severity, or longer disease duration increases vulnerability for clinical depression in SLE (Jarpa *et al.*, 2011). Neuropsychiatric (NP) manifestations have been reported to occur with frequencies ranging from 14~-75%. In animal models, inflammatory cytokines can influence behaviors that are homologous to depression (Chen *et al.*, 2013). In Lupus patients, cytokine concentrations are cross-sectionally associated with depression risk. Depressed patients tend to have higher concentrations of inflammatory cytokines (Zorrilla *et al.*, 2001).

TNF-α may underlie the mechanism of depression by an activation of the hypothalamo-pituitary-adrenocortical (HPA) axis, an activation of neuronal serotonin transporters and the stimulation of the indoleamine 2,3-dioxygenase which leads to tryptophan depletion (Krishnadas and Cavanagh, 2012).

There is supporting evidence that curcumin administration reduces depressive symptoms in patients with major depression (Al-Karawi *et al.*, 2016). Lopresti and Drummond (2017) find provide support for the anti-

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depressant and anxiolytic effects of curcumin in people with the major depressive disorder, although no significant differences in efficacy between high and low-doses.

Given its high safety and tolerability profile, together with its demonstrated effect, the role of curcumin administration as a new avenue in the treatment of major depression is worth exploring (Panahi, *et al.,* 2015). The aim of this study was to determine the effects of *Curcuma xanthorrhiza* Roxb. *e*xtract containing 50mg curcuminoids, as anti-inflammatory and antidepressive in SLE outpatients on the 4-weeks double-blind, placebo-controlled *clinical trial.*

MATERIALS AND METHODES

Design and subjects

The study was a 4-weeks, double-blind, randomized, placebo-controlled clinical trial. Patients were included in the study if they were (i) women, 20-59 years old, (ii) fulfilled at least four criteria of American College of Rheumatology (ACR) and (iii) agreed to sign the patient informed consent. Patients who (i) being flares and (ii) undergoing regular hemodialysis were excluded from the study.

Study drug

The drug was provided in no 0 hard gelatin capsule form, as a powder extract obtained from *Curcuma xanthorrhiza* Roxb. extract. It contains 50mg curcuminoids per capsule.

Patients

Fourteen SLE patients who fulfilled the inclusion criteria, were participated in this study, devided into 2 groups (treatment 10 and placebo 4 persons). The subjects were treated with either 3x/d capsule or placebo together with methylprednisolone and mycofenolate mofetyl (as the main therapy for SLE). The outcome measures were sera TNF α concentration and BDI Beck Depression Inventory score (before and after treatment).

Blood samples

The peripheral blood was drawn through venipuncture of the antecubital veins in all subjects. Serum was obtained by centrifugation (3000rpm for 15min), and separated sera wer e kept in aliquots at −80°C until the time of assay (in Parasitology lab Faculty of Medicine Universitas Gadjah Mada). Commercially available enzyme-linked immunosorbent assay kits (Quantikine HS, R&D Systems) were used for measurement of sera TNF-α concentrations by ELISA, carried out in accordance with the manufacturer's instructions.

Clinical data collection

To assess clinical symptoms of depression, the Beck Depression Inventory (BDI) is used. All the participants answered the inventories. These scales consist of 21 items, each describing a common symptom of depression. The respondent is asked to rate how much he or she has been bothered by each symptom over the past month on a 4-point scale ranging from 0 to 3. The items are summed to obtain a total score that can range from 0 to 63. The cutoffs used for the BDI are 0-13, no/minimal depression; 14-19, mild depression; 20-28, moderate depression; and 29-63, severe depression.

Ethics statement

This study was approved by the ethics committee at Faculty of Medicine, Universitas Gadjah Mada, and informed written consent was obtained from each participant and/or legal guardian.

Statistical analysis

Data were expressed as the mean value ±SD. Independent t- test was used to compare TNFα concentrations and BDI between groups. Paired sample t test was used to compare TNFα concentrations and BDI score before and after treatment in each group. The association of the TNF α concentration and BDI before and after treatment were evaluated by Pearson's correlation coefficient. The concentration of significance was set at $p < 0.05$. Statistical analysis was performed using SPSS® 16.0.

RESULT AND DISCUSSION

Patient group

Ten SLE patients fulfilled the study in the treatment group and the control group consists 4 SLE patients. The baseline characteristics of patients with SLE (Table I).

Table I. Characteristic of subjects

	Treatment n=10	Control n=4
Age (year)	29.7±7.2	42.25±15.65
Education (year)	13.2±2.09	13.25±2.5
Disease duration (year)	6.6±4.7	2.75±0.96
First diagnosed (year)	23.1±8.29	39.5±16.58
Menarche (year)	13.3±1.7	13±1.16

Table II. Sera level of TNF α and BDI score in treatment and control groups before and after administration of *Curcuma xantorrhiza* Roxb extract contains 50 mg curcuminoids and placebo

.

	Treatment group n=10			
	TNF α conc. (pg/mL)		BDI score	
	Before	After	before	after
1	4.75	3.75	23	13
2	15.625	11.25	13	7
3	7.625	1.25	32	8
4	12.375	5.875	25	6
5	8.125	7	15	6
6	10	0	10	9
7	34	28.625	29	39
8	10.25	0	19	18
9	7.25	1.625	3	3
10	7.75	1.75	24	20

	Control group n =4			
	TNF α conc. (pg/mL)		BDI score	
	before	After	before	after
1	10.125	8.25	6	14
2	12.75	11.875	7	20
3	4.75	0	16	15
4	22	14.38	1	20

There was no significant correlation between TNF α concentration, BDI scores with subject's age, education, disease duration, first diagnose, and menarche.

Concentration of TNF α

The mean ±SD interval of the concentration of TNF α on the treatment group before treatment was 11.77±8.37 pg/mL (range 4,.75–34pg/mL) and after treatment was 6.11±8.67pg/mL (range 0-28.62pg/mL), (Table II). The concentration of TNF α after treatment was significantly lower than before treatment p <0.001 (Figure 3) but not in the control group (Figure 4). The Pearson's correlation coefficient between TNF α concentration and BDI score before treatment was 0.690 (p=0.006). The Pearson's correlation coefficient between TNF α concentration and BDI score after treatment was 0.699 (p= 0.024).

Depressive symptoms

To assess clinically symptoms of depression, the Beck Depression Inventory (BDI) were used. At the beginning of the study, the BDI score from the control group 7.5±6.24 (range 1-16) was lower than the treatment group 19.3±9.03 (range 3-32). It was a significant differences (p=0.036), cause the subjects in the control group were older than in the treatment group. It was a fact that one's emotional respond was reduced concomitant with increasing age (Snowdon, 2001). After treatment, the BDI score from the control group 17.25±3.20 (range 14-20) was higher than the treatment group 12.9±10.67 (range 3-39).

People with SLE, who receive *Curcuma xanthorrhiza* Roxb. extract contains 50mg curcuminoids per capsule, 3 times each day for 4 weeks, showed decreasing measures of sera TNF α concentration, compared with those receiving placebo.

Table III. Test Result after administration of *Curcuma xantorrhiza* Roxb extract contains 50mg curcuminoids and placebo

	Result					
	Treatment (mean±SD)			Control (mean±SD)		
Parameter	Before	after	p	before	After	p
TNF α (pg/mL)	11.77±8.37	6.11±8.67	<0.001	12.41±7.21	8.63±6.28	0.089
BDI (score)	19.3±9.03	12.7±10.89	0.059	7.5±6.24	17.25±3.20	0.105

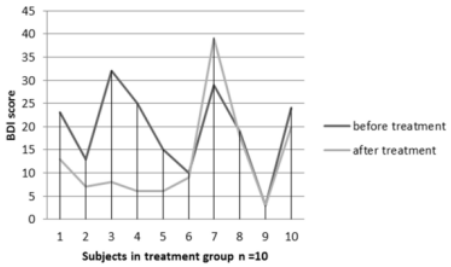

Figure 1. BDI score in treatment group who received *Curcuma xantorrhiza* Roxb extract capsules contains 50mg curcuminoids

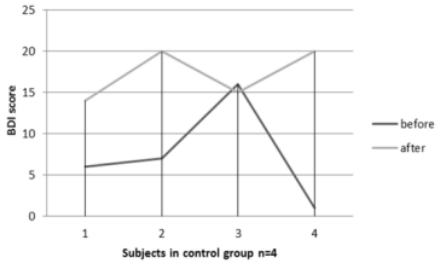

Figure 2. BDI score in control group who received placebo capsules

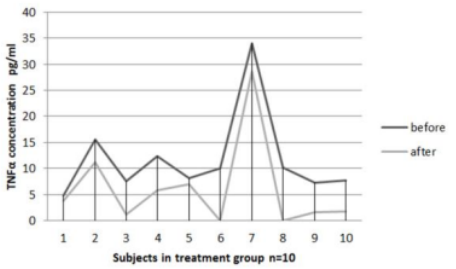

Figure 3. TNF α concentration in treatment group who received *Curcuma xantorrhiza* Roxb extract capsules contains 50mg curcuminoids

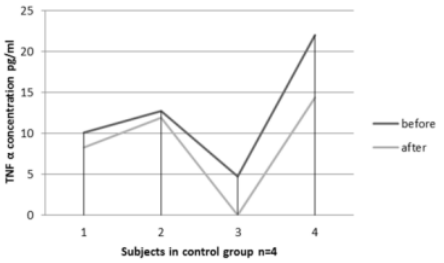

Figure 4. TNF α concentration in control group who received placebo capsules

Curcumin inhibits multiple proinflammatory pathways and is affordable, this phytochemical should be further explored for prevention and treatment of various chronic diseases. (Jurenka, 2009). Curcumin is a highly pleiotropic molecule capable of interacting with numerous molecular targets involved in inflammation. (Aggarwal, 2009). Only a few clinical studies have been reported on the effect of administration of curcumin on inflammatory diseases. However, curcumin has been known to possess anti-inflammatory activity in experimental animals. (Jagetia and Aggarwal, 2007). Curcumin also decreases the expression of Th-1 cytokines (e.g., IFN-γ, TNF- α) (Zhang *et al*., 2006).

Table IV. TNF α concentration and BDI score in treatment group after receiving *Curcuma xantorrhiza* Roxb extract capsules contains 50mg curcuminoids

Treatment group N=10			1	2	3	4	5	6	7	8	9	10
	TNF α conc. (pg/mL)	**After**	3.75	11.25	1.25	5.875	7	0	28.625	0	1.625	1.75
	BDI score	**After**	13	7	8	6	6	9	36	18	3	20

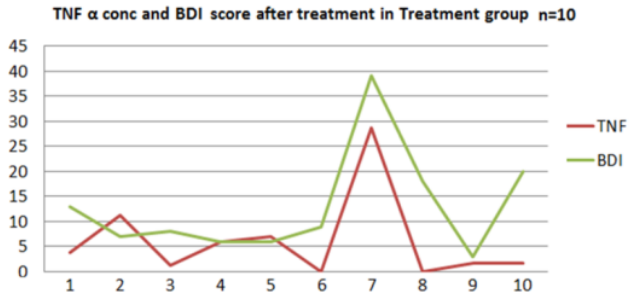

Figure 5. TNF α concentration and BDI score in treatment group after receiving *Curcuma xantorrhiza* Roxb extract capsules contains 50mg curcuminoids

The BDI scores were reduced by the end of the trial in treatment groups but increased in the control group. There were no significantly reductions in BDI score in the treatment group before and after treatment (p 0.059) (Table II). There was a correlation between TNF α concentration and BDI score before and after treatment (p=0.006 and 0.024), (Table IV or Figure 5). According sera TNF-α levels in SLE patients were positively correlated with the severity of depression, the relation between TNF-α and depression may be explained by the long-term use of corticosteroids. The hypothesis of depression as a stress-related disorder is that chronic stress derived from long-term use of corticosteroids impairs corticosteroid receptor signaling.

Curcumin has been shown through *in vitro* and *in vivo* studies to influence a range of neurotransmitters and hormones commonly observed to be disturbed in major depression. (Lopresti and Drummond 2012). Curcumin produces anti-depressant effects via activating MAPK/ERK-dependent brain-derived neurotrophic factor expression in the amygdala of mice.

Curcumin dose dependently inhibited the immobility period, increased serotonin (5-hydroxytryptamine, 5-HT) as well as dopamine levels (at higher doses), and inhibited the monoamine oxidase enzymes (both MAO-A and MAO-B, higher doses) in mice (Kulkarni, 2009).

CONCLUSIONS

The study drug (*Curcuma xanthorrhiza* Roxb. extract) contains 50mg curcuminoids per capsule could reduce TNF α concentration on SLE patients. But its effect on reducing BDI score is still needed proof. Although there is no definitive proof that curcuminoids can induce an earlier beneficial antidepressive effect, it seems like an extended study is needed to prove it, using higher therapeutic doses of curcuminoids.

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