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

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INTRODUCTION

Systemic Lupus Erythematosus is an autoimmune, inflammatory, chronic disorder characterized by multiorgan system involvement. Increased concentrations of TNF-α are found in acute and chronic inflammatory conditions, such as Lupus (Bergman et al., 2013). Curcuma xanthorrhiza Roxb., namely temulawak extract, 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 xanthorrhizol) 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 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-
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. extract containing 50mg curcuminoids, as anti-inflammatory and antidepressive in SLE outpatients on the 4-weeks double-blind, placebo-controlled clinical trial.

**MATERIALS AND METHODS**

**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 were 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).
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 4.75–34 pg/mL) and after treatment was 6.11±8.67 pg/mL (range 0-28.62 pg/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.
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 III. Test Result after administration of Curcuma xanthorrhiza Roxb extract contains 50mg curcuminoids and placebo

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment (mean±SD)</th>
<th>Control (mean±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before after p</td>
<td>before After p</td>
</tr>
<tr>
<td>TNF α (pg/mL)</td>
<td>11.77±8.37 6.11±8.67 &lt;0.001</td>
<td>12.41±7.21 8.63±6.28 0.089</td>
</tr>
<tr>
<td>BDI (score)</td>
<td>19.3±9.03 12.7±10.89 0.059</td>
<td>7.5±6.24 17.25±3.20 0.105</td>
</tr>
</tbody>
</table>

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

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

**ACKNOWLEDGMENT**

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

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