Original article:

Effect of *Moringa oleifera* Leaf Extract on High Sensitivity C-Reactive Protein, ESR And MEX SLEDAI Score in Lupus Patients

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Abstract:

Introduction: No definitive treatment is available for SLE. *Moringa oleifera* Leaf Extract is one of promising novel treatments in SLE because of anti inflammatory and immunomodulatory effect. Our study aimed to identify the effect of *Moringa oleifera* Leaf Extract on the level of hs-CRP, ESR and MEX SLEDAI score in lupus patients. HsCRP and ESR levels are related to the pathogenesis of SLE and they are positively correlated with the disease activity. The MEX SLEDAI score is a simple method that is quite valid for finding the degree of SLE activity, and MEX SLEDAI has the ability to evaluate clinical changes in SLE patients. ***Methods:*** Experimental study consisted of 29 samples of SLE patients, divided into 2 groups, namely 13 SLE patients who received *Moringa oleifera* leaf extract as much as 40.5 mg / kg per day and 16 SLE patients who received placebo. The study was conducted for 28 days. MEX SLEDAI scores, hsCRP and ESR levels were measured before and after administration of therapy. Statistical analysis was applied using SPSS 23, with different t-test, Mann Whitney, and Will Coxon tests. P is significant if $p < 0.05$. ***Result:*** Result of the study showed that before *Moringa oleifera* leaf extract was given, the average MEX SLEDAI score was (1.56 ± 2.16) for control, and (2.69 ± 3.01) for treatment, hsCRP (0.24 ± 0.22) for control and (0.76 ± 1.01) for treatment, ESR (25.56 ± 23.44) for control and (26.00 ± 25.27) for treatment. There was a significant decrease in MEX SLEDAI score in the treatment group. There was no significant reduction in hsCRP and ESR of SLE patients in both groups. ***Conclusion:*** This study showed that the effect of lowering the MEX SLEDAI score on the administration of Moringa leaf extract was significant and could not significantly reduce hsCRP and ESR levels.

Keywords: MEX SLEDAI, hsCRP, ESR, *Moringa oleifera*, Systemic Lupus Erythematosus.

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Background

Systemic Lupus erythematosus (SLE) is a complex autoimmune disease caused by forming of antibodies that can cause inflammation in many organs[1,2]. Clinical Manifestation of SLE is various depending on which organ is effected. There is no definitive therapy of SLE and this disease is various, therefore, SLE cannot be able to be predicted easily[3]. Because of this condition, study about diagnostic equipment and new therapy are needed to find better solution[3].

There are many index to measure the activity of SLE, such as: using ECLAM *(European Consensus Lupus Activity Measurement);* LAI *(Lupus Activity Index);* SLAM *(Systemic Lupus Activity Measure);* BILAG *(British Isles Lupus*

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Assessment Group); dan SLEDAI *(Systemic Lupus Erythematosus Disease Activity Index)*[4,5,6]. The last three measuring index are valid enough and have strong correlation toward disease activity[6,7].

There are some modifications from SLEDAI, namely SLEDAI-2K and MEX-SLEDAI *(Mexican SLE Disease Activity Index*)[6,7]. In this study, researchers used MEX-SLEDAI to investigate disease activity of SLE. Due to the study in 2011, this was showed that MEX-SLEDAI had a higher validity compared to BILAG and SLAM. Besides, MEX-SLEDAI was affordable and easily used to measure SLE activity[6,7].

SLE patients have high levels of Interleukin-6 (IL-6), Interleukin-10 (IL-10), Interleukin-12 (IL-12), and Interferon γ (IFN-γ)[8,9,10]. Serum levels of IL-6 increase significantly in active SLE patients and correlate to SLE activity index (SLEDAI), Erythrocyte Sedimentation Rate (ESR) and *C-reactive protein* (CRP) [9,10,11]. ESR describes the speed of erythrocyte that becomes sediment at the bottom of the tube and becomes measuring instrument of SLE disease which shows that the higher ESR in the body describes the higher degree of SLE disease[11,12,13].

CRP can activate complement system and has a role as a clearance of apoptotic particles. There is a correlation between hsCRP and SLE disease activity[14,15,16,17]. CRP increases upper the normal limit every 6 hour and the peak is about 48 hours. Patients with chronic inflammation, like SLE, CRP levels increase along with the increase of cardiovascular risk[18,19].

Some studies reported that CRP levels increased in SLE patients especially when they were examined using high sensitivity method[14,15].

***Moringa oleifera* (Kelor)**

Moringa oleifera is a native plant from India sub Himalaya that grows in tropical and subtropical area in the world. This plant has been used for thousand years as food and medicine because this plant is highly nutritious[21]. Morinanga is known with many kinds of name in the world. Morinanga belongs to *horse radish tree*, *drum stick tree*, and *tree of life*[22].

Nowadays, there are many studies to add our knowledge about its phytochemical composition and effect of MO in both animals and human's health. Taken from the effect of this plant, anti-inflammation, immunomodulation, and anti-bacteria are mostly learned by researchers[21,22,23].

Inflammation effect of *Moringa oleifera* was learned by conducting study using animal model[23,24,25]. This study showed that anti inflammation activity of *Moringa oleifera* was potential. However, the complete identification of compound or appropriate compound for this activity has not been clear enough. Now, glucosinolates and isothiocyanates with flavonoid is the most possible finding[26,27].

Besides, Moringa contains some compounds that are rarely found generally. Nevertheless, the specific role of these compounds has not been described clearly[23,25,27].

Glucosinulate is an organic compound containing sulfur and nitrogen coming from glucose and amino acid. These substances are known as having strong inhibitory effect to produce NO[23,25,28].

Concentration of *M. oleifera* isothiocyanate is also found to reduce insulin, leptin, resistin, cholesterol, interleukin-1ß (IL-1ß), tumor necrosis factor-alpha (TNFα), and glucose-6-phosphotase in diabetic mice[24,26,28]. Based on this research, this can be concluded that isothiocyanate compound may be as a main bioactive substance having effective activity of anti-diabetes and anti-inflammatory response in *M. oliefera*[26,29].

Flavonoid including quersetin, kaempferol, glucoside, and malphite flavonoid showed that there was an activity of anti –inflammation through NO product inhibition in LPS macrophage[22].

Previous studies decided the inhibitory effect of *M. Oleifera in* NO, VEGF, TNFα, IL-2, IL-1ß, IL-6, glucose-6-phosphotase, insulin, leptin, resistin dan cholesterol[22,28,29].

Study conducted in Universitas Brawijaya Malang had proved that aqueous extract of *M. Oleifera* in vitro had an activity as immunomodulator through its active compounds , such as: saponin and Flavonoid. Both of these compounds contribute as immunostimulant in CD4 + (T helper cell) , CD4 + (cytotoxic T cell), and B220 +, which low dose can increase the number of CD 4+ and CD 8+ cells[22].

In fact, methanol extract of M. oleifera is more necessary than the other extracts during the study of immunomodulation. Methanol extract stimulates cellular and humoral immunity. Methanol extract also describes the potential effect in haemotopoietic system. Moreover, Potency of immunomodulator from M. oliefera can be associated with flavonoid, polyphenol and terpenoid which can modulate one of immune mechanisms mentioned above[27,25].

Based on those data, researchers plan to investigate the effect of *M. oleifera*, mainly on its leaves to SLE patients related to levels of hsCRP , ESR and

MEX-SLEDAI as the marker of SLE activity.

Methods

This study was an experimental to human. Treatment conducted was by giving MO extract with *randomized control trial.* Population consisted of diagnosed SLE patients according to ACR 1997 taken from SLE patients having outward treatment in polyclinic RSUD. Dr. Moewardi Central Java Indonesia. Sample was taken randomly in those SLE patients and they had signed informed consent. This study was conducted from 1st to 8th August 2018 or until the sample had been fulfilled completely. Sample was based on study conducted by researchers. Minimal samples suggested for experimental study were 11 subjects every group. This study consisted of 2 groups, a group of control and treatment.

Inclusion creiteria were:

1. Age ≥ 18 years old and ≤ 60 years old
2. Fulfilled Lupus criteria based on ACR 1997
3. Female
4. SLE patients > 1 year

Exclusion criteria were:

1. Pregnant women
2. SLE patients with complications, such as: Tuberculosis, Diabetes mellitus, liver cirrhosis and CKD (Chronic Kidney Disease).

Moringa oleifera

Moringa oleifera can be found in Tawangmangu Karanganyar taken during rainy season in November 2018. Part of this plant used is leaf which is extracted using aqueous method conducted in Laboratory of B2P2TO FK UNS.

Leaves are washed in flowing water to clean contamination. Fresh leaves of MO are dried for 7 days in the temperature 30'C and grinded well. Then, dry materials are macerated in distilled water (100 g in 2 L). Extract is left for 24 hours, then it is evaporated in the oven for 4 days in the temperature 40'C until it becomes greenish brown with the result of 22%. Dry extract is weighed and dissolved in distilled water (pH = 6,8), then extract is given for sample based on a dose for previous mice model with 500mg/kgBB[22].

This dose is converted equivalently to human with the formula:

Human equivalent dose (mg/kg) = dose for animals (mg/kg) x Km ratio= 40.5 mg/kgbb, nominal scale.

Note:

Km ratio : animal Km / Human Km is 3/37 = 0.081

Km : correction factor for mice= 3, correction factor for human= 37

Data Analysis

Data was analyzed using these procedures, such as:

a. Descriptive analysis.

b. Normality Analysis of variable data using Shapiro-Wilk test.

c. 2 mean differences analysis using t-test for independent sample (if data distribution is normal) or using Mann-Whitney test (if data distribution is not normal). Besides, 2 mean differences analysis using t-test for paired sample (if data distribution is normal), or using Wilcoxon test (if data distribution is not normal) are applied[30].

Results

Result of homogeneity test for variables can be seen that all characteristics variables of this study are homogeneous between treatment group of MO and control group.

Variable of Mex-Sledai score, ESR and hs CRP before and after giving MO leaf extract for control group did not differ significantly, or they were still the same. This could be stated that score of Mex-Sledai, ESR and hsCRP in control group did not change automatically before and after giving MO leaf extract.

Variable scores of MEX SLEDAI before and after giving M.O leaf extract for treatment group differ significantly or they were not the same. This meant that Scores Mex Sledai in treatment group had a change before and after giving MO leaf extract, or they decreased insignificantly after giving MO leaf extract.

There was no a significant difference in hsCRP and ESR variables before and after giving MO leaf extract for treatment group , or they are still the same. This meant that hsCRP and ESR in treatment group did not change significantly before and after giving MO leaf extract, or they decreased insignificantly after treatment.

Variables of delta-mexSLEDAI in both control and treatment groups had the non-normal data distribution. Therefore, Mann Whitney test could be applied to test for mean differences (MD) of delta mexSLEDAI in both control and treatment groups.

Variables of delta-hscrp in control group had non-normal data distribution, meanwhile those in treatment group had normal data distribution. After normality test for variables data of delta-hscrp was conducted in both paired data of control and treatment groups, the non-normal data distribution in variables could be seen clearly. Therefore, test

for mean differences (MD) for variables of delta-hscrp in both control and treatment groups used Mann Whitney test

Variables of delta-ESR in control group had normal data distribution, whereas in treatment group, Variables of delta-ESR had non-normal data distribution. After normality test for variables data of delta-ESR was conducted in both paired data of control and treatment groups, the normal data distribution of variables was obviously found.

Table1. Homogeneity Test for Characteristic Variables in Treatment and Control Groups

Variables	Control		Treatment		Test of MD	
	Mean	Std	Mean	Std	t value	P value
Weight	53,00	10,25	55,00	10,42	0,519	0,608
Height	154,25	5,11	155,38	6,74	0,516	0,610
Age	36,56	10,09	30,92	10,04	1,501	0,145
HB	12,36	1,42	11,84	1,64	0,923	0,364
Hematocrit	38,06	4,14	36,92	3,97	0,751	0,459

Table 2. Description and Result of Homogeneity Test for Variables

Variable	Control		treatment		Test of MD	
	Rerata	Std	Rerata	Std	Nilai t	P value
Leukocytes	8,28	1,67	9,73	2,64	1,810	0,082
Thrombocytes	314,81	55,67	312,46	68,67	0,102	0,920
Erythrocytes	4,51	0,61	4,52	0,41	-0,057	0,955
MCV	84,01	5,86	81,92	5,01	-1,017	0,318
MCH	27,44	2,78	26,47	3,06	0,892	0,380
MCHC	32,60	1,47	32,22	2,26	0,543	0,592
RDW	14,11	1,99	14,14	1,63	-0,038	0,970
MPV	8,74	1,55	8,27	2,05	0,709	0,485
PDW	20,44	13,95	20,31	13,19	-0,243	0,808
Eosinophils	0,98	1,23	2,31	2,38	-1,756	0,083
Basophils	0,50	0,25	0,61	0,42	-0,872	0,391
Neutrophils	68,83	12,28	69,14	9,86	-0,122	0,904
Lymphocytes	22,73	9,81	21,29	7,91	0,428	0,672
Monocytes	6,44	2,11	5,93	1,79	0,697	0,492
SGPT	17,88	9,74	19,38	7,49	-0,459	0,650
Creatinine	0,86	0,24	0,72	0,34	-0,541	0,619
Protein-Urine	0,63	0,89	0,38	1,12	-1,453	0,249

Table 3. Comparison of Mex-Sledai scores, hsCRP, and ESR in control and treatment groups before treatment.

Variables	Control		Treatment		Test of MD	
	Mean	Std	Mean	Std	Mean (Z test)	Std
Mex-Sledai scores	1,56	2,16	2,69	3,01	-1,440	0,184
hsCRP	0,24	0,22	0,76	1,01	-1,207	0,232
ESR	25,56	23,44	26,00	25,27	-0,176	0,880

Table 4. Table 4. Comparison of Mex-Sledai score, hsCRP and ESR before and after giving MO leaf extract in Control Group

Variables	Control		Treatment		Test of MD	
	Mean	Std	Mean	Std	Mean (t test)	Std
Mex-Sledai scores	1,56	2,16	1,94	2,69	-0,071	0,948
hsCRP	0,24	0,22	0,29	0,20	-0,692	0,495
LED	25,56	23,44	24,19	15,08	0,720	0,478

Table 5. Comparison of Mex-Sledai score, hsCRP and ESR before and after giving MO leaf extract in Treatment Group

Variables	Control		Treatment		Test of MD	
	Mean	Std	Mean	Std	Mean (t test)	Std
Mex-Sledai scores	2,69	3,01	1,85	2,51	-2,232	0,026
hsCRP	0,76	1,01	0,38	0,44	-0,904	0,366
LED	26,00	25,27	19,00	23,55	-1,922	0,055

Table 6. Comparison of Delta-mexsledai, Delta-hscrp, and Delta-ESR in Control and Treatment Groups

Variables	Control		Treatment		Test of MD	
	Mean	Std	Mean	Std	Mean (t test)	Std
Delta-mexsledai	0,38	2,09	-0,85	1,07	-2,482	0,050*
Delta-hscrp	0,06	0,20	-0,38	1,06	-1,186	0,249
Delta-ESR	-1,38	20,56	-7,00	12,61	0,862	0,398

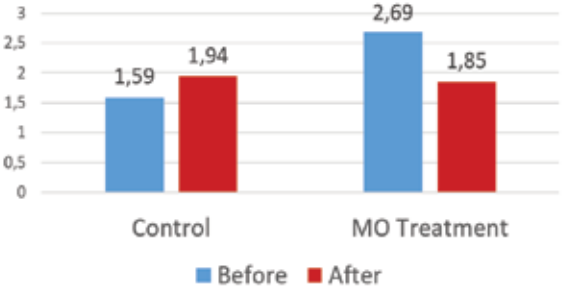
Table 7. The Formula use on kind of drugs except giving MO leaf extract for patients in Control and Treatment Groups

Variables	Control		Treatment	
	Total	%	Total	%
Multiprednisolone	5	31,20	5	38,50
Cellcept (*mycophenolic acid*)	0	0,00	2	15,40
Sandimmune (cyclosporine)	0	0,00	1	7,70
Multiprednisolone +Myfortic (*Mycphenolic sodium*)	8	50,00	2	15,40
Multiprednisolone +Cellcept	1	8,20	3	23,10
Multiprednisolone +Imuran (*Azathioprine*)	1	6,20	0	0,00
Multiprednisolone +Sandimmunn	1	6,20	0	0,00
Total	**16**	**100,00**	**13**	**100,00**

Hence, test of differences between 2 means for Variables of Delta –ESR in both control and treatment groups could use t-test for independent samples. The result of test of differences between 2 means using Mann Whitney test in variables of delta-mexsledai and delta-hscrp had shown that there was no significant difference in changing of both variables with p value 5%($p > 0,05$). This condition showed that although giving MO leaf extract could decrease variables of Mex Sledai score and hsCRP, the effect of variables of Mex Sledai score and hsCRP after giving MO leaf extract was no a significant difference in control group.

Thus, the result of test of differences between 2 means using t-test for independent samples in variables of delta ESR indicated that change of variables (delta ESR) did not differ significantly with p value 5%($p > 0,05$).

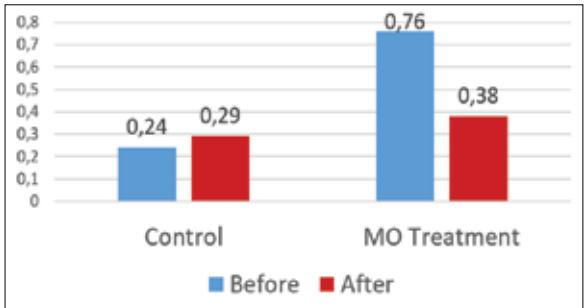
Analysis result of the effect in giving MO leaf extract toward Mex Sledai score, hsCRP, and ESR indicated that only variables of Mex SLEDAI score were influenced significantly after giving MO leaf extract. Besides, Variables of hsCRP and ESR did not significantly influenced after giving MO leaf extract. Besides, giving MO leaf extract, patients also received various drugs during the study. Proportion on how the use of drugs could be seen in table. Various drugs either types or dose were used by patients not only giving MO leaf extract but also having the effect on giving MO leaf extract toward variables of Mex Sledai score, hs CRP and ESR.



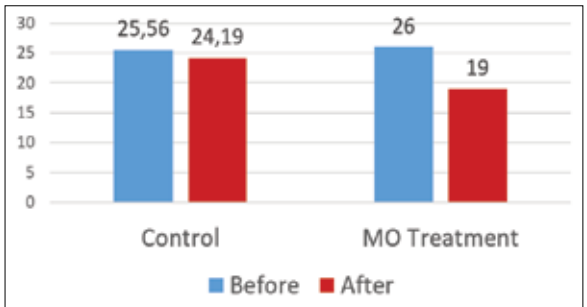
Picture 1. Mex-Sledai comparison before and after Moringa Oleifera (MO) leaf extract in control grup and MO treatmet grup

In general, the benefit of this study on giving 40,5mg/kgBB of *Moringa oleifera* leaf extract could improve or decrease Mex-Sledai Score. However, this did not decrease ESR and hsCRP levels. In this study, te results of ESR and hsCRP did not base on theory. Even though, this decreased the levels, but statistical analysis indicated insignificantly. Possible causes of this condition are patients having acute infection which was not reported, consuming low dose of *Moringa oleifera* leaf extract which was not instructed by the clinicians, and consuming steroid drugs or immunosuppressant differently as a part of ongoing treatment.

Study using animal models had shown clearly about anti-inflammation activity of potential *Moringa oleifera* leaf extract. However, the identification of complete compounds or proper compounds having responsibility to form an activity has not been clear yet. Nowadays, *Glucosinulate* and *isothiocyanates* with flavonoid are the most possible findings. Glucosinulate is a substance recognized having strong inhibitory effects to produce NO. Concentration of *Moringa oleifera* is also known to decrease insulin, leptin, resistin, cholesterol, interleukin-1ß (IL-1ß), tumor necrosis factor-alpha (TNFα), and glucosa-6-phosphotase in diabetic mice[26,28,29,31]. Based on these findings, this study concluded that isothiocyanate compounds was possible as a main bioactive substance having anti-diabetic responses and effective anti- inflammatory responses in *Moringa oleifera*.



Picture 2. hsCRP comparison before and after Moringa Oleifera (MO) leaf extract in control grup and MO treatmet grup



Picture 3. ESR comparison before and after Moringa Oleifera (MO) leaf extract in control grup and MO treatmet grup

There was a limitation in this study since this study did not observe and monitor strictly in giving *Moringa oleifera* leaf extract after the patients had gone home. This study measures patients' Mex Sledai score before and after having

treatment with different clinicians, having acute infection at home that could not be observed well, and consuming various drugs.

This strength of this study was by applying randomized controlled trial and double blind trial study. According to researchers, there have not been similar studies conducted previously.

Conclusion

Based on study results, this could be concluded as follows:

A) Giving *Moringa oleifera* leaf extract influenced MEX SLEDAI in SLE patients. In addition, the statistical analysis was significant.
B) Giving *Moringa oleifera* leaf extract influenced the level of hsCRP in SLE patients. However, the statistical analysis had shown insignificantly.
C) Giving *Moringa oleifera* leaf extract influenced the level of ESR in SLE patients. However, the statistical analysis indicated insignificant results.

Ethical clearance

Ethical clearance was sought from the Ethical Review Board from Medical Faculty of Sebelas Maret University

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Conflict of interest

The author declares that they have no conflicts of interest

Author's contribution

All authors equally contributed and approved the final manuscript.

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