

The Effectiveness of Lumbricus rubellus Extract Toward Interleukin-10 and Immunoglobulin E and Atopic Dermatitis Scoring Index (SCORAD)

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The Effectiveness of *Lumbricus rubellus* Extract Toward Interleukin-10 and Immunoglobulin E and Atopic Dermatitis Scoring Index (SCORAD)

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Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease that often occurs in children. It is characterized by symptoms of pruritus and dry skin. This disease is often associated with genetic factors, impaired skin barrier function, allergen sensitization, and recurrent skin infections, and is often associated with increased serum levels of immunoglobulin E (IgE) and a personal or family history of atopy [1]. According to the International Study of Asthma and Allergies in Childhood, AD has a prevalence that varies from 0.3% to 20.5% in 56 countries [2], [3]. Nutten (2016) explained that the incidence of AD is estimated to occur around 15–20% in children and 1–3% in adults worldwide, and has increased by 2–3 times over the past decade [4]. According to the Indonesian Child Dermatology Study Group (KSDAI) In Indonesia, AD, ranks in the top 10 of other skin diseases, which obtained 23.67% of cases [5]. AD is divided into two groups, intrinsic and extrinsic types. The intrinsic type of AD has normal IgE levels and is not associated with other atopic diseases compared to the extrinsic

Abstract

BACKGROUND: Atopic dermatitis (AD) is a chronic inflammatory skin condition characterized by severe pruritic symptoms and chronic AD related to clinical features in form of lichenification associated with a history of atopic disease both for himself and family.

AIM: This study aims to determine the effectiveness of using earthworm extract (*Lumbricus rubellus*) to increase interleukin (IL)-10 and decrease immunoglobulin E (IgE), and to describe the AD (SCORAD) scoring index of patients with AD.

METHODS: This research used quantitative with quasi experiment method. The data were analyzed using SPSS v19 program. To determine the basic characteristics of numerical variables, the mean standard deviation is functioned if the data distribution amount is even, if it is not, it used the median. Meanwhile, to observe the relationship between *L. rubellus* extract and IgE, Mann-Whitney test analysis (U-Test) was used.

RESULTS: The results of this study indicate that the administration of *L. rubellus* extract showed a changes and differences before and after being involved with the extract. IgE levels between ERL and no ERL groups had differences ($p < 0.05$), however on day 15 both groups did not show any differences. Meanwhile, the SCORAD index indicated that the influence of lumbricus rebellus extract has an effect on low number of AD patients.

CONCLUSION: It can be concluded that the administration of *L. rubellus* extract in patients with AD is quite effective.

type, which requires intermediate sensitization by IgE. IgE-mediated sensitization is usually associated with bronchial asthma or allergic rhinoconjunctivitis and has a positive response to both food and environmental allergens [6]. There are two involved hypotheses in the pathogenesis of AD [7]. The first hypothesis stated that there is a disruption of skin epithelial cells that causes disruption on the function of skin barrier function and has an effect on immune response. The second hypothesis suggests an abnormal immune response that causes in the predominance of T helper 2 (TH2) and IgE cells.

The pathophysiology of AD is multifactorial involving disruption of the skin barrier, changes in the immune response mediated by cellular and humoral immune systems, and the hypersensitivity reactions of type I that lead to increased IgE [8]. Human T cells are categorized into T helper 1 (Th1) cells and TH2 cells it depends on the produced cytokine profile. The exposure to antigen that happens in continuity will change the cytokine profile in skin lesions from Th1 to TH2 [9]. The pathophysiology of AD occurs due to several mechanisms, one of the dominant mechanisms is inflammation. This process occurs due to TH2 cells that are associated with cytokines such as IL-4 and IL-13,

and chemokines such as TARC (thymus and activation-regulated chemokine) and eotaxin. TH2 cytokines of IL-4 and IL-13 stimulate fibroblasts to produce periostin, a protein that causes keratinocytes to produce TSLP, it induces the production of TARC/CCL17 by dendritic cells [10]. High levels of IL-4 that produced by T cells during human birth can increase the risk of developing AD. The European Task Force on AD created an index which known as Scoring Atopic Dermatitis (SCORAD) to assess the degree of inflammation on AD [5].

One of the natural ingredients that can be used as additional medicine is an earthworm extract of *Lumbricus rubellus*. Earthworm (*Lumbricus* sp) extract contains antibacterial properties that can inhibit the growth of pathogenic bacteria, such as gram-positive and gram-negative bacteria [11]. Kiss et al. (2020) in their research stated that worms induce a stereotypical TH2 immune response, characterized by the existence of IL-4, IL-5, IL-3, and IL-10 cytokines, antibody isotopes IgG1, IgG4, and IgE [12]. It is supported by Taylor et al. (2012) who found that worm-infected patients can stimulate the formation of IL-10 and transforming growth factor-beta (TGF- β) through an increase of T regulatory cells [13]. The increased of IL-10 and TGF- β can reduce the increased TH2 cells in AD patients. IL-10 has the main function of preventing extensive tissue damage after the inflammation and infection [14].

However, until today no one has researched the use of earthworms in AD, even though earthworms have many available extract. Thus, this study aims to determine the effectiveness of using earthworm extract on increasing IL-10 and reducing IgE in AD patients, moreover, it has an aim to describe the SCORAD index.

Material and Methods

This study uses quasi-experimental research type with pretest and posttest within the control group design. Pretest and posttest are research designs. Quasi-experimental research is research similar to experimental research but not real experimental research. Although the independent variables are manipulated, participants will not be randomly assigned to conditions or order of conditions [15]. Pretest was done before being given treatment and posttest was done after being given treatment, therefore the obtained results will be more accurate. The study was conducted during February 2020 to September 2020 at Dermatology and Venereology Polyclinic of Pendidikan Hospital that affiliated with the Department of Dermatology and Venereology, Hasanuddin University. The population of this study was every patients who met the criteria of inclusion. The Samples were taken collectively since the patient came for treatment at Dermatology and Venereology Polyclinic that was

grouped with AD. There were 30 samples collected then divided into two groups, (a) the intervention group with *L. rubellus* extract and (b) the control group without *L. rubellus* extract.

For adult, the specimen was taken directly from patient's blood intravenously. As for the serum specimens of pediatric patients, it was taken after the parents signed the informed consent. A clinical examination was then performed to confirm the diagnosis by SCORAD index. Furthermore, to check the levels of IL-10 and IgE in patient, a blood specimen or blood sample of 5 cc was taken. The blood sample is then divided into three tubes of sample. Samples 1 and 2 were put into a tube containing EDTA to collect blood plasma, while sample 3 was put into a micro centrifuge tube without EDTA to collect serum. Furthermore, those three blood samples were centrifuged to separate blood plasma and blood serum from the cell. Total IgE examination was carried out using the Enzyme-Linked Immunosorbent Assay (ELISA) method (the ELISA kit for total Human IgE) to observe the total IgE concentration of the examined blood samples.

The collected data were then analyzed by SPSS v.19 program. To determine the basic characteristics of numerical variables, the mean standard deviation was used if the data distribution is even, otherwise, it used the median. It is used to observe the basic numerical data, mean standard deviation is used if the data distribution is evenly distributed. To observe the relationship between earthworm extract (*L. rubellus*) and IL-10, paired T-Test analysis was used, while to observe the effect on IgE, U-Test was used.

The observations on patients were carried out to determine the severity of AD and the occurred side effects. The patients are also obtained several advice as they consume *L. rubellus* extract within the following details;

- a. Dosage for children of 1–3-years-old (2 × 250 mg)
- b. Dosage for children of >3–12-years-old (2 × 500 mg)
- c. Dosage for adult within the amount of (2 × 1000 mg) for 7 days.

This research has been declared as ethically feasible by the ethics committee of biomedical research of humans at Hasanuddin University Medical Faculty and Hasanuddin University General Teaching Hospital Makassar within the ethical approval number of 125/UN4.6.4.5.31/PP36/2020.

Results

In order to determine the effect of *L. rubellus* extract on IgE and AD (SCORAD) scoring index, it is

necessary to conduct direct research on each research subjects, which consist of the patients with AD who are divided into two groups. The first group (X) was a control group consisting of the patients with AD and the second group (B) patients with AD who were given *L. rubellus* extract. Both groups were monitored for IgE and SCORAD levels on day 0, day 8 and day 15. Both of the groups were monitored for IgE and SCORAD levels on day 0, day 8, and day 15. The number of male subjects is more than the number of female samples, with a ratio of 3:2, and most of the age group is 25–44-years-old (50%) followed by the age group of 5–14 years (30%).

Before beginning the difference test, it is required to test the normality test and homogeneity test. Homogeneity test was carried out to find out the obtained data from the two groups that had homogeneous variants or not, and the obtained results from the data of both groups, the intervention group and the control group, were not homogeneous within the Asymp. Sig. (2-tailed) 0.05. Based on the two previous tests above, the obtained data from both groups, control group and intervention group, were not normally distributed and not homogeneous, therefore the hypothesis testing used non-parametric testing, the Mann-Whitney Test (U-Test) and the Wilcoxon test.

The difference of IL-10 levels in AD patients of the two groups at day 0, 8, and 15

To assess the effect of *L. rubellus* extract on IL-10 in AD patients, the Mann-Whitney test (U-Test) was conducted to determine whether there was a difference between two different treatments (treated with *L. rubellus* extract and not treated with *L. rubellus* extract) or not on day 0, 8, and 15. The results of the Mann-Whitney test can be seen in Table 1.

Based on Table 1 and Figure 1, it can be seen that in the Mann-Whitney test, there is a difference ($p < 0.05$) in IL-10 levels between ERL group and the group without ERL on day 0 and day 8, however it is different on day 15 there are no differences ($p > 0.05$) of IL-10 levels in ERL group and the group without ERL.

To assess the difference in IL-10 levels between pretest and posttest application of *L. rubellus* extract at H0 (before application), H8 (8th day after application), and H15 (15th day after application) it used

Wilcoxon test. The results of Wilcoxon test can be seen in Tables 2 and 3.

Based on Tables 2 and 3, it can be seen that in the Wilcoxon test of the ERL group, there is no difference ($p > 0.05$) in IL-10 levels before and after the application of *L. rubellus* extract at H0 (before application), day 8 (8 days after application), and day 15 (15 days after absorption). In a group without ERL, there was also no difference ($p > 0.05$) of IL-10 levels on days 0, 8, and 15.

Based on Table 4 and Figure 2, it can be seen in Mann-Whitney test that there is a difference ($p < 0.05$) in IgE levels between the ERL group and the group without ERL on day 0 and day 8, however on day 15 it shows different result, there are no difference ($p > 0.05$) IgE levels on a group with ERL and a group without ERL.

To assess the difference of IgE levels before and after the application of *L. rubellus* extract at day 0 (before application), day 8 (8th day after application), and day 15 (15th day after application) it used Wilcoxon test. The results of the test by Wilcoxon test can be shown in Tables 5 and 6.

Based on Tables 5 and 6, it can be seen that, based on Wilcoxon test in ERL group, there was no difference ($p > 0.05$) in IgE levels before and after the application of *L. rubellus* extract at day 0 (before application), day 8 (8th day after application), and day 15 (15th day after absorption). In a group without ERL, there was no difference ($p > 0.05$) in IgE levels on day 0, 8 and 15. The results of the Scored Patient sample who consume *L. rubellus* extract on day 0, day 8 and day 15 can be seen in the following Table 7.

Meanwhile, for patients who did not consume *L. rubellus* extract, the SCORAD value of each patient on each day describes a different situation. The results above illustrate that mild AD has SCORAD index under 15. It has a characteristic such as skin discoloration to redness, mild dry skin, mild itchy skin, and there is no secondary infection. Medium AD has SCORAD index between 15 until 40. It has several characteristics such as: skin redness, mild or medium skin infection, itching, sleep disturbances, and lichenification. The last is, severe AD has SCORAD index more than 40. It has several characteristic such as: skin redness, itching, lichenification, sleep disturbances, and severe skin infections. According to the Table 7, there are differences

Table 1: The differences in IL-10 levels patients with atopic dermatitis in two groups

Treatment	Mann-Whitney test		Mean	Standard deviation	Median	p	Description
	Min	Max					
IL-10 (H0)							
ELR	64.39	119.48	77.3157	15.45106	70.5219	0.010	Different
Without ELR	64.74	1802.47	219.7086	439.96753	102.1230		
IL-10 (H8)							
ELR	65.61	137.05	83.1810	20.33293	75.5281	0.006	Different
Without ELR	73.19	226.66	118.0581	47.20522	108.2801		
IL-10 (H15)							
ELR	63.70	224.84	103.2225	49.54104	85.2536	0.395	There is no difference
Without ELR	64.91	570.09	116.0181	131.49605	70.8765		
Without ELR	1.50	12.00	5.2933	3.09619	4.9000		

IL-10: Interleukin-10, ELR: *Lumbricus rubellus* extract

between patients who consume *L. rubellus* extract and patients who did not consume lumbricus extract.

SCORAD index before and after the application of *L. rubellus* extract

Based on the difference of the average of SCORAD index above, it can be seen that there is a difference in the average SCORAD index between the patients that obtain *L. rubellus* extract (ELR) and patients who did not obtain lumbricus extract (no ELR). It is explained that on day 0, patients given lumbricus extract obtained a slightly higher SCORAD index with 11.9. The SCORAD index for is slightly reduced on day 8th and day 15th for 11.4 and 10.8. Meanwhile, on the

day 8th of patients without *L. rubellus* extract obtained a higher score index for 11.46 but it is reduced on the day 15th for 11.2.

These results indicate that the involvement of lumbricus extract cause an effect on the SCORAD index level of AD patients. The lower the index value, the minor suffered disease. Obtaining lumbricus extract tends to affect the SCORAD index levels to be lower than patients without *L. rubellus* extract.

Discussion

AD is a residual chronic disease characterized by clinical symptoms of itching, usually affecting children. The pathogenesis of AD includes skin barrier disorders, such as the destruction of filaggrin gene expression, genetic, environmental, and immune system abnormalities. The destruction of the skin's protective structure will reduce the ability and function of the skin, causing immune and inflammatory reactions [16]. The function of the skin barrier can minimize the loss of moisture from the epidermis and protect it from external factors, such as; heat or cold, penetration of potentially harmful substances, and colonization of pathological bacteria [17]. Both the natural and innate immune system contribute to the pathogenesis of AD. TH2 cells play an important role in increasing the IgE patients with AD. Kay (2001) explained that in acute AD lesions, the release of

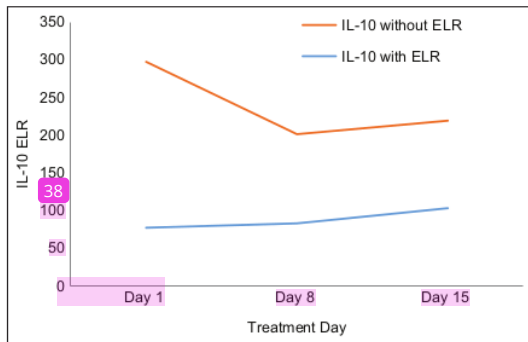


Figure 1: Interleukin-10 levels in two control and intervention groups on day 1, 8, and 15

Table 2: The differences in IL-10 levels between before and after the application of ELR on day 0, 8, and 15

	Mean	N	SD	SEM	Sig. Wilcoxon	Description
Pair 4						
IL-10 ELR (H8)	83.1810	15	20.33293	5.24994	0.156	There is no differences
IL-10 ELR (H1)	77.3157	15	15.45106	3.98945		
Pair 5						
IL-10 ELR (H15)	103.2225	15	49.54104	12.79144	0.140	There is no differences
IL-10 ELR (H1)	77.3157	15	15.45106	3.98945		
Pair 6						
IL-10 ELR (H15)	103.2225	15	49.54104	12.79144	0.281	There is no differences
IL-10 ELR (H8)	83.1810	15	20.33293	5.24994		

IL-10: Interleukin-10, ELR: Lumbricus rubellus extract.

Table 3: Differences in IL-10 levels for patient without application of ELR on day 0, 8, and 15

	Mean	N	Std. Deviation	Std. Error Mean	Sig. Wilcoxon	Description
Pair 4						
IL-10 Without ELR (H8)	118.0581	15	47.20522	12.18834	0.820	There is no differences
IL-10 Without ELR (H1)	219.7086	15	439.96753	113.59913		
Pair 5						
IL-10 Without ELR (H15)	116.0181	15	131.49605	33.95213	0.036	Different
IL-10 Without ELR (H1)	219.7086	15	439.96753	113.59913		
Pair 6						
IL-10 Without ELR (H15)	116.0181	15	131.49605	33.95213	0.078	There is no differences
IL-10 Without ELR (H8)	118.0581	15	47.20522	12.18834		

IL-10: Interleukin-10, ELR: Lumbricus rubellus extract.

Table 4: The differences in IgE levels of atopic dermatitis patients in a group with ERL and without ERL

Treatment	Mann-Whitney Test						Description
	Min	Max	Mean	Standard Deviation	Median	p	
IgE (H0)							
ELR	175.46	1057.21	576.1896	255.78367	513.9254	0.001	Different
Without ELR	58.99	521.13	230.1328	162.60585	199.9720		
IgE (H8)							
ELR	82.72	996.37	440.8090	315.38880	379.3188	0.059	Different
Without ELR	60.90	457.38	232.4674	142.84166	199.2657		
IgE (H15)							
ELR	37.33	816.47	370.3055	262.32755	294.3760	0.272	There is no differences
Without ELR	89.77	781.19	257.5831	192.89845	173.4884		

IgE: Immunoglobulin E, ELR: Lumbricus rubellus extract.

TH2 is characterized by the dermal infiltration of CD4+ T cells and eosinophils. It can increase the expression of cytokines IL-4, IL-5, and IL-13 by increasing eosinophil-derived products form, and IFN- γ is rarely expressed [18]. In chronic AD, there is a transition from TH2 to TH1, the expression of IFN- γ , IL-12, GM-CSF, and tissue remodeling increase, collagen deposition increases and skin thickens. Specific antigens that can penetrate the skin due to skin barrier barriers are captured by antigen-specific IgE on inflammatory dendritic epidermal cells and Langerhans cells (LC). Specific IgE mainly reacts in the environment and bacterial antigens. The LC of AD patients mainly secretes the TH2 cytokine IL-10, not the TH1 cytokine IL-12 [19].

The role of cytokines in AD begins with an adaptive immune response mediated by T cells and B cells associated with Antigen Presenting Cells (APC). The adaptive immune system consists of cellular and humoral immune system [19]. T cells are produced in the bone marrow and grow in the thymus. The T Cell Receptor will recognize a specific peptide that binds to the Major Histocompatibility Complex (MHC)/Human Leukocyte Antigen, which is the cell surface molecule of the infected APC. This combination

activates T cell proliferation. In AD, MHC class II within lymphoid tissues works by removing proteins that are present in lysosomes, endosomes, or extracellularly. T lymphocytes secrete cytokines to help T cells, B cells, and macrophages, thereby activating T helper cells (CD4). TH1 cells play a major role in the activation of macrophages. TH1 cells produce the cytokine profile IL-2 (T-cell proliferation) and IFN- γ stimulate and activate the NK cells, while dominant TH2 cells are associated with activation of B cells and production of antibody. TH2 cells produce cytokine profiles IL-4, IL-5 (synthesizing IgE and activating eosinophils), and IL-10 (inhibiting proliferation of TH1).

Allergens are captured by dendritic cells and presented to T cells. This cause an imbalance between TH1 and TH2 cells. TH2 cells induce B cells to produce IgE. Allergen-specific IgE binds to IgE (Fc ϵ R1) receptors on mast cells [18]. The production of IgE by B cells in atopic diseases depends on the support of TH2 cells, which produce IL-4, IL-5, IL-9, and IL-13. Mostly, TH1 cells promote cellular immune responses rather than humoral immune responses and play a greater role in chronic infections [20]. However, re-exposure to similar allergens in sensitive mucosal membranes will cause the IgE molecules on mast cells to bind to the allergens, and stimulate mucosal mast cells to have degranulation by releasing histamine, leukotriene, heparin, and other toxic products [18]. Yusriana (2008) stated that alkaloid compounds in *L. rubellus* contain nitrogen atoms and have alkaline characteristics with pH >7, which also have antibacterial and antipyretic effects. The mechanism in inhibiting the bacterial growth is by interfering the constituent components of peptidoglycan with the bacterial cells [21]. Therefore the cell wall cannot be formed completely.

In the results of the study, there was a difference between the ERL group and the non-ERL group on the 8th day of ERL administration ($p < 0.05$). Although there was no significant difference on the 15th day but there was an increase in IL levels 10 and reduction in IgE.

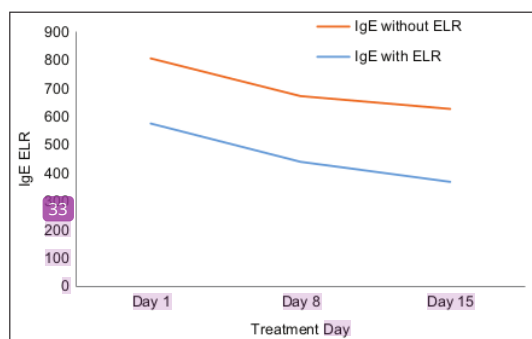


Figure 2: Immunoglobulin E levels in two control intervention groups on day 1, 8, and 15

Table 5: The Differences in IgE levels before and after the application of ELR on day 0, 8, and 15

	Mean	N	Std. Deviation	Std. Error Mean	Sig. Wilcoxon	Description
Pair 7						
IgE ELR (H8)	440.8090	15	315.38880	81.43304	0.191	There is no differences
IgE ELR (H1)	576.1896	15	255.78367	66.04306		
Pair 8						
IgE ELR (H15)	370.3055	15	262.32755	67.73268	0.100	There is no differences
IgE ELR (H1)	576.1896	15	255.78367	66.04306		
Pair 9						
IgE ELR (H15)	370.3055	15	262.32755	67.73268	0.460	There is no differences
IgE ELR (H8)	440.8090	15	315.38880	81.43304		

IgE: Immunoglobulin E, ELR: *Lumbricus rubellus* extract.

Table 6: The Differences in IgE levels on a group without the application of ELR day 0, 8, and 15

	Mean	N	Std. Deviation	Std. Error Mean	Sig. Wilcoxon	Description
Pair 7						
IgE Without ELR (H8)	232.4674	15	142.84166	36.88156	0.776	There is no differences
IgE Without ELR (H1)	230.1328	15	162.60585	41.98465		
Pair 8						
IgE Without ELR (H15)	257.5831	15	192.89845	49.80617	0.865	There is no differences
IgE Without ELR (H1)	230.1328	15	162.60585	41.98465		
Pair 9						
IgE Without ELR (H15)	257.5831	15	192.89845	49.80617	0.733	There is no differences
IgE Without ELR (H8)	232.4674	15	142.84166	36.88156		

IgE: Immunoglobulin E, ELR: *Lumbricus rubellus* extract.

Table 7: SCORAD index scores of patients who consumed and not consumed ELR on Day 0, day 8 and day 15

	Day 0	Day 8	Day 15	No ELR-1	Day 0	Day 8	Day 15
ELR-1	10	10	9	No ELR-1	12	12	12
ELR-2	13	12	12	No ELR-2	11	10	10
ELR-3	11	11	10	No ELR-3	10	9	9
ELR-4	12	12	10	No ELR-4	12	12	11
ELR-5	13	11	11	No ELR-5	12	11	11
ELR-6	14	14	12	No ELR-6	11	10	10
ELR-7	13	12	12	No ELR-7	10	11	10
ELR-8	10	10	10	No ELR-8	13	12	12
ELR-9	11	10	11	No ELR-9	14	14	14
ELR-10	14	13	12	No ELR-10	11	12	12
ELR-11	12	12	11	No ELR-11	14	14	12
ELR-12	12	11	11	No ELR-12	13	12	12
ELR-13	11	10	10	No ELR-13	10	10	10
ELR-14	10	11	10	No ELR-14	11	10	11
ELR-15	13	12	12	No ELR-15	14	13	12

SCORAD: Scoring atopic dermatitis, ELR: *Lumbricus rubellus* extract.

The side effects that occurred during the study were intestinal diseases, such as nausea and intestinal diseases. Deworming therapy (or the use of *L. rubellus* extract) can be used as an adjuvant treatment for allergic patients. It showed that the rural population is severely infected with helminths and the prevalence of allergic diseases is low. It has been proved through animal model studies that it inhibits IL by stimulating the formation of TGF β and IL-10.

Conclusion

Based on the analysis above, *L. rubellus* extract is quite effective to be given to AD patients. *L. rubellus* extract can stimulate the construction of IL-10 and suppress TH2 cells to reduce IgE in AD patients. It can be seen from the ability of lumbricus extract to increase IL-10 levels and decrease IgE on day 0, day 8, and day 15 although it is not really significant. Furthermore, the results of the SCORAD Index indicated that the distribution of *L. rubellus* extract has an effect on low levels of SCORAD index. *L. rubellus* extract can reduce the SCORAD index levels in AD patients which concluded that the lower patient's SCORAD index, the better patient's condition.

After conducting the research and concluding the results, for further research, the authors suggest to examine the side effects of the long-term distribution of *L. rubellus* extract in patients with AD disease.

What is known about this topic

- AD is a chronic inflammatory skin condition characterized by severe pruritic symptoms.
- Earthworm (*L. rubellus*) extract contains antibacterial properties that can inhibit the growth of pathogenic bacteria.

What this study adds

- L. rubellus* extract can stimulate the construction of IL-10 and suppress TH2 cells

to reduce IgE in AD patients.

- SCORAD Index used to indicate the effect of *L. rubellus* extract to atopic dermatitis patients.

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