

# The Effect of Nigella Sativa and zinc on IgE and IL-5 serum levels, the experimental study in ovalbumin induced BABLB/C mice

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# The effect of *Nigella sativa* and zinc on IgE and IL-5 serum levels, the experimental study in ovalbumin induced BALB/C mice

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### ABSTRACT

**Background:** Allergy is a hypersensitivity reaction due to induction of specific IgE binding to allergens on the surface of mast cells. Interleukin-5 is an important marker of hypersensitivity inflammation reactions. *Nigella sativa*, contain active substance thymoquinone, can reduce inflammatory mediators. Zinc as anti-inflammatory by inhibit releasing mediators from mast cells. Objective was to determine the effect of *Nigella sativa* (NS) and zinc on IgE and IL-5 serum levels on ovalbumin-induced BALB/C mice.

**Methods:** The study design was a true experiment with post-test only control group using BALB/C mice. The study was conducted at Sultan Agung Islamic University's laboratory on March-June 2020. Inclusion criteria were female BALB C mice, 6-8 weeks, 22-25 grams, and healthy. Thirty mice were divided randomly into 5 groups; negative control, positive control, NS group, zinc group, and NS + zinc group. All groups treated for 28 days. Allergic reactions tested by skin test with OVA, intervention response assessed by IgE and IL-5 serum levels.

**Results:** At the end of study completed, obtained 6 negative controls, 6 positive controls, 6 NS groups, 5 zinc groups, and 5 NS+zinc groups. Two mice s died before intervention completed. Serum IgE and IL5 levels were significantly difference between treatment groups (Kruskal Wallis test;  $p=0.007$  and One-way ANOVA test;  $p=0.020$ ). The result of logistic regression test, IgE levels was the most significant in the NS+zinc group ( $p=0.006$ ) and IL-5 levels was the most significant in the zinc group ( $p=0.002$ )

**Conclusions:** *Nigella sativa*, zinc, and its combination can reduce IgE and IL-5 serum levels of ovalbumin-induced BALB / C mice.

**Keywords:** *Nigella sativa*, IgE, IL-5, Zinc

### INTRODUCTION

Allergy is a hypersensitivity reaction that is initiated by the induction of specific IgE against certain allergens.<sup>1,3</sup> Continuous exposure to low-dose allergens in a patient with allergic tendencies (atopy) and presentation of the allergen to Th2 cells, which in turn produce IL4 cytokine that induces B cells to produce specific IgE. The specific IgE follows blood circulation to the tissues, binds to its receptors on the surface of mast cells forming IgE-Mast

cell bonds. This result to the patient becoming sensitized and gives positive results on skin tests.<sup>4</sup>

The nasal mucosa of an individual who has been sensitized when re-exposed to the same allergen which will bond with specific IgE on the surface of the mast cells resulting in degranulation of these cells.<sup>5</sup> Mast cell granules contain chemical mediators resulting immediate phase reaction which cause of allergic rhinitis symptoms such as nasal itching, sneezing, nasal congestion, and

rhinorrhea. In the slow phase allergic reaction there are cytokine release and endothelial activation that occurs 4-6 hours after allergen exposure and persists for 24-48 hours. The typical feature of late phase allergic reaction is the accumulation of various kinds of inflammatory cells, especially eosinophils, to the allergy site, which are major effector cells in chronic allergic reactions.<sup>5</sup> The IL-5 cytokines produced by Th2 cells are the main growth factors for eosinophils and also play a role in inducing eosinophil activation. Interleukin-5, can be a marker of inflammation in hypersensitivity reactions.<sup>5</sup>

*Nigella sativa* (NS) has an anti-inflammatory role because thymoquinone, the active content of *Nigella sativa* can increase the formation of antioxidants and decrease inflammatory mediators (IL-1 $\beta$ , IL-6, TNF- $\alpha$ , IFN- $\gamma$ , and PGE).<sup>6</sup> *Nigella sativa* has been studied for anti-inflammatory, analgesic, and antipyretic effects in experimental animals. Extract of *Nigella sativa* also showed inhibition of NO (Nitric Oxide) production, a pro-inflammatory mediator. Its anti-inflammatory action is mediated by the suppression mechanism of NO production by macrophages in experimental animals.<sup>6</sup>

Zinc has an important role in physiological processes such as growth, development, maintenance of immune system, as well as tissue repair.<sup>7</sup> Several mechanisms of zinc as an anti-inflammatory are inhibit polysaccharides and interleukin-1 $\beta$  which induce NO formation, inhibit the activation of Nuclear Factor-Kappa Beta (NF- $\kappa$ B), which is involved in pro-inflammatory gene expression, inhibits the release of chemical mediators from mast cells and basophils (eg histamine) and eosinophils, and 4) as a modulator of the immune system through the NF $\kappa$ B pathway, as a transcription factor that controls several immune response genes and decreases the inflammatory response.<sup>8</sup>

This study aimed to determine the effect of *Nigella sativa* and zinc for IgE and IL-5 serum levels in ovalbumin-induced BALB/C mice.

## METHODS

This study was a true experiment with post-test only control group design, using female BALB/C mice as research subjects. The inclusion criteria were 6-8 weeks, 22-25 grams, healthy and active. The exclusion criteria was weight loss more than 10% during adaptation period. The drop out criteria was mice that died during the study before taking the blood sample. Thirty mice were arranged by simple random assignment divided into 5 groups consists of negative control, positive control (ovalbumin), *Nigella sativa* group, zinc group, and combination NS + zinc group.

The study was conducted at the Sultan Agung Islamic University's laboratory, Semarang. The preliminary study conducted on 4 mice divided into two groups, consists of positive control and a negative control group. In the

positive control group, mice were sensitized using ovalbumin (OVA 10  $\mu$ g and 2 mg AL (OH)3 in 0.2 mL normal saline) by intraperitoneal injection on days 0, 3, 6, 9, 12 then all mice were examined for the Skin Prick Test with OVA.

The SPT result, in the positive control group showed induration and hyperemia and the negative control group it did not show any reaction. The study was continued with 30 female mice. The sensitization of ovalbumin (OVA 10  $\mu$ g and 2 mg AL (OH) 3 in 0.2 mL normal saline) did by intraperitoneal injection on days 0, 3, 6, 9, 12 in all groups of mice, except for the negative control group. The intervention using *Nigella sativa* oil (Amazing Herbs Black Seed of Amazing herbs) at 0.03 mg, and zinc (L-Zinc syrup from LAPI) at 0.12 mg was carried out on days 1 to 28 days. The interventions of this study were NS (0.03 mg), zinc (0.13 mg), and a combination of NS (0.03 mg) + zinc (0.13 mg) via feeding tube. The data collected by taking blood from the retrobulber vein with a hematocrit pipette on the 29th day, for an examination of serum IgE (ng / L) and IL-5 (ng / mL) levels were measured by the ELISA method.

The results obtained, the levels of IgE and IL5 were tested for the normality of data distribution by the Shapiro-Wilk test. For normal data distribution, statistical test of the data was carried out by one-way ANOVA test followed by the Post Hoc test, while for abnormal data distribution a test was carried out by Kruskal-Wallis test, followed by the Mann-Whitney test. This study has Ethical approval from the Research Ethic Committee Faculty of Medicine, Diponegoro University; (23 / EC / FK-UNDIP / III / 2020).

## RESULTS

During the study, 2 samples dropped out because mice died before intervention completed (one mouse died in zinc group and one in NS + zinc group). The data distribution and the mean IgE serum levels in 5 groups can be seen in Table 1 and Figure 1.

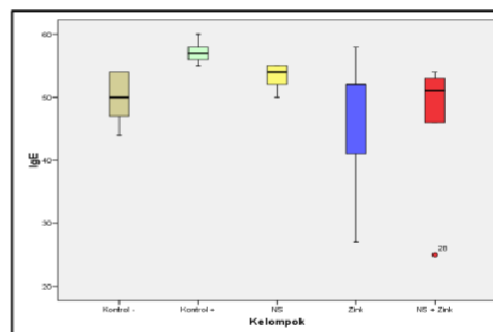


Figure 1: The box plot of IgE levels in ng/mL (p=0.007).

\*Kruskal Wallis test, p<0.05

Among the mean of IgE serum levels, the NS + zinc group has the lowest mean levels compared to the other groups (Table 1 and Figure 1).

The data of IgE serum levels distribution is abnormal, therefore comparison of IgE serum levels among groups were done by Kruskal Wallis test (Table 2) followed by the Mann Whitney test (Table 3).

**Table 1. Mean IgE serum levels distribution (ng/ml) after treatment.**

Sample code	Negative control	Positive control	NS group	Zinc group	NS+zinc group
1	54	55	54	52	54
2	47	56	55	58	46
3	51	58	55	27	51
4	49	60	54	41	25
5	54	56	52	52	53
6	44	58	50	-	-
<b>Mean</b>	49.83 (SD=3.97)	57.17 (SD=1.84)	53.33 (SD=1.97)	46.0 (SD=12.27)	45.0 (SD=12.03)

**Table 2: The comparison tests result of IgE serum levels between groups after intervention.**

Group	Mean	SD	P
<b>Negative control</b>	49.83	3.97	0.007*
<b>Positive control</b>	57.17	1.84	
<b>NS group</b>	53.33	1.97	
<b>Zinc group</b>	46.00	12.27	
<b>NS + zinc group</b>	45.80	12.03	

\* Kruskal Wallis test

The result of Kruskal Wallis test showed that the mean IgE serum levels between groups, was significantly different (p = 0.007, 95% CI= 27.52-31.28) (Table 2).

**Table 3: Comparison of serum IgE levels between groups.**

Group	Positive control	NS group	Zinc group	NS + zinc group
<b>Negative control</b>	0.004*	0.072	0.854	0.782
<b>Positive control</b>	-	0.006*	0.042*	0.006*
<b>NS group</b>	-	-	0.267	0.096
<b>Zinc group</b>	-	-	-	0.917

\*test Mann Whitney

**Table 4: Mean of IL-5 serum levels distribution after treatment.**

Code sample	Control negative	Control positive	Perlakuan 1 (NS)	Zinc group	NS + zinc group
1	28	29	27	28	30
2	26	32	26	29	27
3	29	31	34	29	31
4	29	33	31	26	29
5	32	33	28	27	30
6	28	39	30	-	-
<b>mean</b>	28.67 (SD = 1.97)	32.83 (SD = 3.37)	29.33 (SD = 2.94)	27.80 (SD = 1.30)	29.40 (SD = 1.52)

The mean IgE serum levels were significantly difference between all groups, then the statistical analysis followed by the Mann Whitney test to see the differences between each intervention and control groups.

The results of the Mann Whitney test showed that the IgE serum levels in negative control group was significantly lower than positive control group (p=0.004). While all of the intervention groups i.e. NS group, zinc group and NS+ zinc group, the IgE serum levels were significantly lower than positive control group (p=0.006, p=0.042, p=0.006) respectively. The other hand, there was not any difference of IgE serum level of all intervention group compare to negative control group (Table 3). The mean

of IgE serum levels showed that the NS + zinc group was the lowest compared to the other groups (Figure 1, Table 2).

**Table 5: One way ANOVA test result of IL-5 serum levels after treatment.**

Group	Mean	SD	P
<b>Negative control</b>	28.67	1.97	0.020
<b>Positive control</b>	32.83	3.37	95% CI=
<b>NS group</b>	29.33	2.94	30.77-61.23
<b>Zinc group</b>	27.80	1.30	
<b>NS + zinc group</b>	29.40	1.52	

\* One Way ANOVA

**Table 6: The differences of IL-5 levels on each groups.**

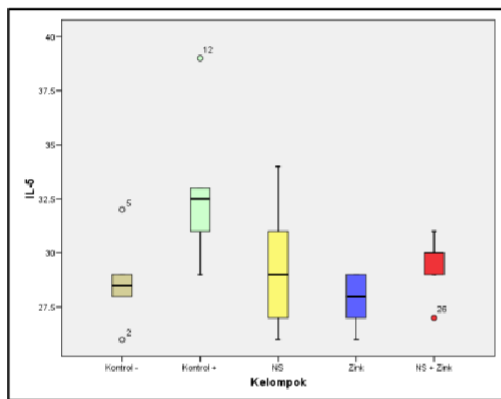
Group	Positive control	NS group	Zinc group	NS + zinc group
<b>Negative control</b>	0.007*	0.639	0.561	0.623
<b>Positive control</b>	-	0.020*	0.002*	0.029*
<b>NS group</b>	-	-	0.308	0.964
<b>Zinc group</b>	-	-	-	0.308

\* p value of Post Hoc test.

The data distribution and the mean IL-5 serum levels in 5 groups can be seen in (Table 4 and Figure 2). Among the mean of IL-5 serum levels, it appear that the zinc group has the lowest compared to the other groups (Table 4 and Figure 2). The data distribution of IL-5 serum levels was normal, therefore to compare IL-5 levels used One way ANOVA test (Table 5) followed by Post Hoc test (Table 6).

To see whether there were differences of mean IL-5 serum levels between the treatment groups, the One Way ANOVA test was performed and the results was significantly different (p=0.020, 95% CI=27.52-31.28) (Table 5).

To see the differences between groups of treatments, the statistic test was continued with Post Hoc test. The results showed that IL-5 serum levels in negative control group was significantly lower than positive control group (p=0.007). The result of the intervention groups showed that IL5 serum levels in NS group, the zinc group and in the NS + zinc group were significantly lower than positive control group (p=0.02, p=0.002, p=0.029 respectively) (Table 6 and Figure 2).



**Figure 2: Box Plot of IL-5 serum levels in ng/ml (p=0.020).**

\*test One Way ANOVA, p<0.05

The mean IL-5 serum levels shows that in the zinc group has the lowest serum level compared to the other groups (Figure 2, Table 5).

**DISCUSSION**

The formation of IgE in the positive control group was the result of ovalbumin sensitization through intraperitoneal OVA injection on days 0, 3, 6, 9, and 12. The success result of the allergen/OVA sensitization on the mice was evaluated by skin tests on mice with OVA, at the preliminary study. The SPT showed positive result which showing induration formation and hyperemia. Thus sensitization technique carried out in this study was successful so this study which requires the allergy mouse model was continued.

Continuous allergen exposure triggers B cell activation and produces IgE which is released into the blood circulation.<sup>9-11</sup> Chen's study reported that giving OVA five times increased IgE levels significantly compared to administering OVA twice.<sup>12</sup> In this study, 5 times OVA administration on days 0, 3, 6, 9, and 12.

*Nigella sativa* can reduce IgE levels and there is a significant difference in IgE serum levels between the positive control group compared to other groups receiving *Nigella sativa* as shown in the Table 3. These results are consistent with Nikakhlag's study of *Nigella sativa* for 15 days in patients with allergic rhinitis, which decreased IgE levels compared to the placebo group.<sup>13</sup>

Thymoquinone as the active substance of *Nigella sativa* has anti-inflammatory effects and reduces IL-5.<sup>14,15</sup> It was also reported by Balaha that intraperitoneal injection with the extract of *Nigella sativa* compared to positive control in OVA-induced BALB /C mice can reduce the level of airway hyperresponsivity, the total number of leukocytes, macrophages, eosinophils, levels of IL-4, IL-5, IgE, and significantly increase levels of IFN-γ and serum IgG.<sup>14</sup>

The IgE levels in the NS + zinc group was the lowest compared to other groups, including the positive control, the NS group, and the zinc group (Table 3). These results are consistent with the Balaha study which reported that administered *Nigella sativa* for 30 days in BALB /C mice decrease levels of IL-4, IL-5, and IgE compared to the OVA group.<sup>14</sup>

Zinc has an anti-inflammatory effect on the airways and zinc deficiency can increase IL-5 production, as shown in Table 5, there is a significant difference in IL-5 serum levels in the positive control group compared to the zinc group.

Zinc can also reduce serum IgE levels as shown in Table 3. In addition to reducing blood IgE levels, zinc has also been reported to reduce airway hyperresponsiveness.<sup>16,17</sup> Seo's study reported that zinc deficiency increases allergic and hypersensitivity reactions to the airway.<sup>18</sup>

Ghaffari's research also showed that increased zinc levels led to decreased IgE levels.<sup>19</sup>

Zinc has an important function in the immune system as an antioxidant, anti-inflammatory, in addition to the Zinc has an important component in the majority of antioxidant enzymes, namely Cu-Zn superoxide dismutase (Cu-Zn SOD) which was found in the cytoplasm of epithelial cells of the airways and alveoli. Cu-Zn SOD acts to remove superoxides anions in the airways so they are more resistant to allergens.<sup>16,18</sup>

Zinc inhibit the release of inflammatory mediators and affect the balance of Th1 and Th2.<sup>16,20</sup> Lu's research shows that zinc administration can reduce IL-4, IL-5, and IL-10. The IL-5 serum levels (in Table 6) in zinc group was the lowest compared to the positive control group, NS group and NS + zinc group. Morgan's study explained that giving intraperitoneal zinc injection to allergy-model mice for 3 days reduced Th2, IL-5, and IL-4 levels compared to the control group.<sup>8</sup> Lu's research also showed that by giving zinc for 30 days to mice induced by OVA reduced IL-4 and IL-5 levels compared to the OVA group.<sup>17</sup>

## CONCLUSION

*Nigella sativa*, zinc, and the combination of *Nigella sativa* + zinc can decrease IgE and IL-5 serum levels on ovalbumin-induced BALB / C mice.

## Recommendation

Further research is needed on the effect of *Nigella sativa* and zinc by using other inflammatory mediator parameters such as IFN- $\gamma$  and airway tissue histopathology as well as clinical trials in humans with IgE and IL-5 parameters with pre and post-test examinations.

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*Conflict of interest: None declared*

*Ethical approval: The study was approved by the Institutional Ethics Committee*

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