The Effect Of Giving Genistein In Various Doses In Level Receptor A Interleukin 8 (Cxcr1) In Peritoneal Lesions Of Mice-Model Endometriosis

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Abstract: Objective: To prove the effect of genistein in various doses on Interleukin 1 receptor A (CXCR1) level in peritoneal lesion of mice model endometriosis.

Method: This study used a true experimental design (true experimental) with a factorial design Post-Test Only With Control Group Design. Involves eight groups: negative control group, positive control group, mice model of endometriosis without genistein, and treatment group with the group that was given a variety of different doses of genistein: 50mg/day, 100mg/day, 200mg/day, 300mg/day, 400mg/day, and 500mg/day. This research was conducted at the Laboratory of Physiologof the Faculty of Medicine, University of Brawijaya and Reproductive Physiology Laboratory Embryology Faculty of Veterinary Medicine, Airlangga University Surabaya sample of mice used were 32 mice, with 2-3 months of age and body weight 20-30 grams. Homogeneity of peritoneal lesion done with micro paste continued with centrifugation and put in tube to be processed in order to measure levels of CXCR1 by ELISA.

Result: According to anova analysis, there is significant result in giving genistein in various doses in CXCR1 level that is continued in statistic analysis regression expression CXCR1. Regression coefficient is -0.0027 with p-value 0.000. Determination coefficient (R-square) is 69.49%, which means that a various expression CXCR1 is 69.49%, depend on effect of giving genistein in various doses. The residue, 30.51%, explained by another factors that is not included in experiment. R-square which is high means that linear model can explain the effect of genistein in the expression of CXCR1.

Conclusion: Giving genistein shows decrease Interleukin 8 receptor A (CXCR1) level in peritoneal lesion of mice model endometriosis.

Keywords: Interleukin 8 receptor A (CXCR1) genistein, endometriosis

Abstrak: Tujuan: Membuktikan pengaruh pemberian genistein berbagai dosis terhadap kadar Receptor A Interleukin 1 (CXCR1) pada leson peritoneum cacingan model endometriosis. 

Metode: Penelitian ini menggunakan desain eksperimen (true experimental) dengan desain faktorial post-test only with control group design. Involves eight groups: negative control group, positive control group, mice model of endometriosis without genistein, and treatment group with various doses of genistein: 50mg/day, 100mg/day, 200mg/day, 300mg/day, 400mg/day, dan 500mg/day. This research was conducted at the Laboratory of Physiology Faculty of Medicine, University of Brawijaya and Reproductive Physiology Laboratory Embryology Faculty of Veterinary Medicine, Airlangga University Surabaya sample of mice used were 32 mice, with 2-3 months of age and body weight 20-30 grams. Homogeneity of peritoneal lesion done with micro paste continued with centrifugation and put in tube to be processed in order to measure levels of CXCR1 by ELISA.

Hasil: Berdasarkan analisa Anova didapatkan hasil bermakna pemberian genistein berbagai dosis pada kadar CXCR1 yang kemudian dilanjutkan pada hasil analisis regresi ekspresi CXCR1, didapatkan koefisien regresi sebesar -0.0027 dengan p-value sebesar 0.000. Koefisien determinasi (R-square) sebesar 69.49% menunjukkan bahwa keragaman ekspresi CXCR1 sebesar 69.49% ditentukan oleh pengaruh pemberian genistein berbagai dosis. Sisanya sebesar 30.51% dijelaskan oleh faktor lain yang tidak terlibat dalam penelitian. Nilai R-square yang relatif tinggi menunjukkan bahwa model linier mampu menjelaskan pengaruh genistein terhadap ekspresi CXCR1.
The Effect Of Giving Genistein In Various Doses In Level Receptor A Interleukin... 

Kesimpulan: Pemberian genistein menunjukkan kecenderungan penurunan kadar Receptor A Interleukin 8 (CXCR1) pada Lesi peritoneal mencit model endometriosis. 

Kata Kunci: Receptor A Interleukin 8 (CXCR1), genistein, endometriosis.

1. Introduction

Endometriosis is a disease that affects many women at reproductive age. The incidence of this disease varies greatly. Endometriosis affects 15-40% of women at reproductive age, and 17 million women worldwide are infected with endometriosis. The incidence of endometriosis among all women is about 5-15%, and that interest was found in the younger age group. Universally, endometriosis is visible in the syncytium, dyspareunia, dysuria, chronic abdominal pain, pelvic pain, and endometrioma.

Progression of endometriosis in elderly women is influenced by the estrogen hormone (estrogen dependent). The presence and growth of endometriotic cells begin at the time of retrograde menstruation, and endometrial cells are shed along with menstrual blood and metabolites will reverse direction (reflux) through fallopian tubes then into the peritoneal cavity causes endometrial cells and tissue attached to the peritoneal surface.

In the development of peritoneal endometriosis, immune cells appear in the peritoneal cavity as a result of inflammation. Among immune cells, macrophages are the predominant cells that promote the peritoneal cavity. Macrophages are involved in phagocytosis mainly cleaning debris and endometrial cells. Supposedly, peritoneal macrophages capable of removing debris regain endometrial cells. But in the case of endometriosis, macrophages fail to perform the function of phagocytosis in retrograde endometrial tissue and thus allow the implantation and proliferation of endometriosis lesions.

Interleukin-8 (IL-8), alternatively known as CXCL8, is a pro-inflammatory CXC chemokine. Transcription of the IL-8 gene encodes for a protein of 99 amino acids that is subsequently processed to yield a signaling competent protein of either 77 amino acids in nonimmune cells or 72 amino acids in monocytes and macrophages. The biological effects of IL-8 are mediated through the binding of IL-8 to two cell-surface G protein-coupled receptors, termed CXCR1 and CXCR2. These receptors share considerable structural similarity suggesting that these genes arose through gene duplication. Signals are transmitted across the membrane through ligand-induced conformational changes, exposing epitopes on the intracellular loops and carboxy-terminal tail of the receptor that promote coupling to functional heterotrimetric G proteins.

The activation of these G protein subunits by agonist-bound receptors triggers a typical signal transduction pathway involving activation of phospholipase C b isozymes. This results in the generation of diacylglycerol and inositol 1,4,5-trisphosphate with a subsequent increase in protein kinase C (PKC) activity and intracellular Ca²⁺ mobilization. In addition, although chemoattractant receptors lack tyrosine kinase activity, they can stimulate the phosphorylation of cytoskeletal proteins, p130Cas and Paxillin, and the activation of the related adhesion focal complex kinase (also known as Pyk2 or CAKb, mitogenactivatedprotein kinases (Erk1/2, p38, and c-Jun kinase phosphatidylinositol 3-kinase, and Janus kinase 2, MAP kinases), also termed extracellular signal-regulated kinases (Erk1 and Erk2), are important mediators of cell growth and other signals from cell surface receptors to the nucleus. Because most of the G protein-coupled receptors (GPCR) can activate a variety of effector pathways via various G protein subunits, considerable heterogeneity exists in the signaling pathways leading to Erk1/2 phosphorylation and the subsequent activation of transcription factors.

Estrogen induces the production of pro-inflammatory cytokin (TNF-α, IL-β, TGF-β and COX2), which subsequently activates the transcription factor NF-κB. Estradiol binds to ER-α and ER-β, forming bonds of estrogen and estrogen-receptor complex then binds to a specific piece of DNA called a promoter ERE genes in the nucleus. 16,17,18,19,20

To activate the transcription process, binding of estrogen and estrogen-receptor complex to the ERE is necessary. The transcription factor that has been involved in the binding of DNA and the enhancement of the transcription activity of endometriosis is resulting in the synthesis of mRNA and proteins. The RNA and synthesis of target genes are regulated in the major increase in inflammatory cytokines (IL-6, IL-8) angiogenesis factor (HIF-1α, VEGF-A), matrix metalloproteinase (MMP-2 and MMP-9), anti-apoptotic genes (Bcl-2) and decrease in pro-apoptotic protein (Bax), increased apoptosis proteins (Caspase 3) and cell adhesion molecules. 14,17,19 The activation of estrogen has a role in the process of invasion and differentiation, cell adhesion and tissue remodeling (throughout ectopic ectometrial stromal cell endometriosis) survival (cell survival) and increase in cell proliferation and endometriosis. Genistein worked as SERMs, are antiestrogenic in higher doses. Genistein binding affinity to ER-α is 4%, and for the ER-β was 87%, compared with estradiol. 16,21 Pre treatment of cells with PTX (100 ng/ml) or tyrosine kinase specific inhibitors genistein (20 mM) and herbimycin A (1 mM) or down-regulation of PKC by prolonged exposure to phorbol 12-myristate 13-acetate (100 nM) each had a significant effect on reducing enzyme activity. This suggested the involvement of tyrosine kinases in CXCR-1.
and CXCR-2 mediated signaling in these cells. Khandaker et al 1998 found the effect of tyrosine and serine/threonine kinase inhibitors and PT on the LPS induced down-modulation of CXCR1 and CXCR2 and Sandra et al 2006 found that genistein (80_M), an inhibitor of tyrosine kinases, reduced phagocytosis of opsonized targets in controls and septic cells. 12,15

According research above we examine the effect of genisteinat peritoneal lesion mice endometriosis that resulting decreased expression levels of Interleukin 8 Receptor A (CXCR1) in the cell with ELISA.

II. Materials And Method

This experiment used ature experimental design weredonein the laboratory in vivo infemale mice (Mus musculus) with study design With Post-Test Only Control Group Design. Involverseightgroups: negative control (healthy mice without genistein), positive control group (model mice with genistein) and the treatment group. The group that was given variable different doses of genistein: 50mg/day, 100 mg/day, 200 mg/day, 300 mg/day, 400 mg/day and 500mg/day.

This research was conducted at the Laboratory of Physiology of the Faculty of Medicine, University of Brawijaya and Reproductive Physiology Laboratory Embryology Faculty of Veterinary Medicine, Airlangga University Surabaya. The implementation was conducted over three months from August to October 2014, with details for 1 week done adaptation, 2 weeks for treatment, then used for the manufacture of examination preparation Elissathen reading the results of research data (statistical test).

Samples of a study using female mice (Mus musculus) model of endometriosis as much as 32 head, with 2-3 monthsof age and weigh 20-30 grams. Mus musculus obtained from the Laboratory of Reproductive Physiology Embryology, Airlangga University Faculty of Veterinary Medicine (FKH Airlangga University), Surabaya. Mus musculus selected as the study sample because it is easily maintained and relatively healthy in a mild and suitable for use in various types of research experiments and immunology responses can be observed. Treatment dose into experimental animals (Mus Musculus) will be converted by the body surface area to the body surface of 70 kg to mice 20 grams, with acclimation at 0.0026. Micemodel of endometriosis based on the method performed on the preliminary research conducted by Sutrisno et al., 2014. The animals that used for experimental were female mice (Mus musculus) approximately 3 monthsold, weighing 20-30 grams were selected based on inclusion and exclusion criteria. After adaptation in the same cage and get the same food and drink for 1 week, do reselection if there are micemicethat qualify as breaking up the testornot. Then do the injection of cyclosporin A in mice in the positive control group and the treatment group. The drug which available in Indonesia is Sandimmun Novartis production. One ampoule contains 50mg/ml x 5ml. Thedose is 10mg/kg/day. In this case the weight of micemice are 20-30 mg, the dose is also adjusted. After conversion calculation at mice and getting dose 1,8 mg/mice. So the dose micemic after recombination with water for injection is 0.2cc sandimmunaderidiluted. Endometrial biopsy material taken from the uterus operation of benign tumoruterine and stored in PBS. Doverashing 2 times with cetrifugac3000 rpm in temperature 4°C for 10 minutes, and then take the supernatant (containing struma, gland, and epithelial cell). Each mouse will get 0.1ml and then injected blind to peritoneal cavity of mice slowly. Injection sat intraperitonealendometrial tissuein the positive control group and the treatment group. Performed intramuscular injection of estrogen per day 1 and 5. The preparation of ethynylestradiol a dose of 300μgr/kg. With the conversion into dose the micemic will get 5,4 Φgr. The equivalent of 1 μg equal with 10 μl. 1 vial contains 30cc containing 20000 μl, the equivalent of 0.1cc equal with 66μl. By adjusting the dose equivalent conversion mice of 5,4 Φgr equal with 54μl, the micemie will get around 0.095cc or 0.1cc. After injection the micemic will be evaluated whether the criteria for dropping the testor not. Furthermore, after adaptation, mice were divided into 8 groups, one group was the negative control group, one group was the positive control group, and 6 groups were the treatment group. Genistein that has been dissolved in sesame oil will be given orally by the sonde. The duration of genistein the treatment group prefers to astudy conducted by Yavuzetal (2007) on the Granting of Genisteinon Regression Implants Endometriosis in Rat Model. Genistinwas given for 14-daysand given once daily.

Taking material inspection is done after 14days of treatment with the following steps: Mice were terminated beforehand by inhalation of anesthesia by entering the mice into a covered container (glass jar), which contains cotton has been filled with ether. Then cover tightly and wait a few minutes until the mice cereally did not move again. Furthermore, mice were dissected and placed on the baseboard with the belly facing up. After plugging the feet of mice, the abdominal wall was opened using tweezers and scissors carefully, with amid line incision was continued to the left and right side of the top and bottom the diaphragm opened. After that, peritoneal lesions came to homogenize with micro paste and centrifugation than taken and put into the testor then be processed in order to measure levels of Interleukin 8 Receptor A (CXCR1) in the Laboratory of Physiology, Faculty of Medicine, University of Brawijaya, Malang.
Analysis of CXCR1 level
The level of CXCR1 in supernatant cells was measured using sandwich ELISA (Elisa kit, Elabscience Biootechnology, Hubei province, P.R. China). All procedures were performed according to kit instruction.

Ethics: This research has been approved by the Research Ethics Committee of the Faculty of Medicine, University of Brawijaya, Malang, Indonesia.

III. Results
In this study, the results of data analysis on the normality test performed using the Shapiro-Wilk test. The criteria for the decision, that is, when the Sig or value is greater than the significance level α=0.05 then normally distributed data and vice versa. The results of the multiple comparison test showing that the mean levels of CXCR1 are not normally distributed. In the Shapiro-Wilk test, the data was obtained and described in detail shown in the table below.

Table 1. Result of normality distribution test

<table>
<thead>
<tr>
<th>Variabel</th>
<th>Koefisien</th>
<th>Sig.</th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>CXCR1</td>
<td>0.960</td>
<td>0.444</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Table 1 based on the Shapiro-Wilk test result showed that the data content of IL-8 Receptor A (CXCR1) for each group of observations have demonstrated that values which are larger than the significance level α=0.05. So all the data met the prerequisites of parametric test, the data proved to be normally distributed.

Table 2. Result of Homogenitas test.

<table>
<thead>
<tr>
<th>Variabel</th>
<th>Koefisien</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CXCR1</td>
<td>1.565</td>
<td>0.216</td>
</tr>
</tbody>
</table>

Table 2 based on the Levene test result showed that the data content of IL-8 Receptor A (CXCR1) for each group of observations have demonstrated that values which are larger than the significance level α=0.05. So all the data met the prerequisites of parametric test, the data proved to be homogenous.

Table 3. Results of the comparison control group

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean Difference (I-J)</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative control</td>
<td>Positive control</td>
<td>-1.598</td>
</tr>
</tbody>
</table>

Table 3 based on the results of the independent sample test (independent sample t test) showed that there were significant differences (p<0.000<α) mean levels of CXCR1 between the negative control group (healthy mice without given genistein) with the positive control group (mice given the model of endometriosis without given genistein). This means that the mice model of endometriosis without given genistein as a positive control was able to reduce the mean levels of CXCR1 which are high when compared to healthy mice.

Based on the result of the one-way ANOVA test, the data content of CXCR1 obtained shows no significant difference in the mean levels of CXCR1 seven groups of samples observations, as shown by the value p<0.000<α. Furthermore, the multiple comparison test with Tukey HSD test is obtained and displayed are presented in the table below.

Table 4. Comparison of the Level of CXCR1

<table>
<thead>
<tr>
<th>Groups</th>
<th>Mean ± SD</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>K</td>
<td>0.92 ± 0.15</td>
<td>*</td>
</tr>
<tr>
<td>K+</td>
<td>2.52 ± 0.15</td>
<td>*</td>
</tr>
<tr>
<td>P1</td>
<td>1.74 ± 0.49</td>
<td>*</td>
</tr>
<tr>
<td>P2</td>
<td>2.19 ± 0.24</td>
<td>*</td>
</tr>
<tr>
<td>P3</td>
<td>1.37 ± 0.17</td>
<td>*</td>
</tr>
<tr>
<td>P4</td>
<td>1.34 ± 0.14</td>
<td>*</td>
</tr>
<tr>
<td>P5</td>
<td>1.15 ± 0.18</td>
<td>*</td>
</tr>
<tr>
<td>P6</td>
<td>1.01 ± 0.15</td>
<td>*</td>
</tr>
</tbody>
</table>

Table 4 based on the results of the multiple comparison test with Tukey HSD test, showed that there were significant differences in mean levels of IL-8 Receptor A (CXCR1) between the positive control group (2.52±0.15) with the administration of genistein treatment group 50mg (1.74±0.49) and 100mg of genistein (2.19±0.24), with 200mg of genistein (1.37±0.17) and 300mg of genistein (1.34±0.14), with 400mg of genistein (1.15±0.18) and 500mg of genistein (1.01±0.15). Based on the mean value, there is a decrease in the group treated with increased doses of genistein. This means that the treatment of genistein administration of 50mg, 100mg, 200mg, 300mg, 400mg, and 500mg in the mice model of endometriosis will affect the levels of IL-8 Receptor A (CXCR1), which is able to reduce the levels of IL-8 Receptor A (CXCR1) when...
compared the micromodel of endometriosis without giving genistein. The differences between the mean levels of Interleukin 8 receptor A (CXCR1) in the eighth group of the sample are presented in full appearance on the image histogram below.

![Image](image_url)

**Figure 1. Histogram mean level of CXCR1.**

In Figure 1, the histogram shows the mean levels of Interleukin 8 receptor A (CXCR1) in the mice model of endometriosis at all eighth sample group observations with the administration of genistein treatment dose of 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, and 500 mg. There was an increase in mean levels of Interleukin 8 receptor A (CXCR1) to the negative control group and positive control group there was a mean decrease in the levels of Interleukin 8 receptor A (CXCR1) from the positive control group to the treatment group administration of genistein. Looks mean levels of Interleukin 8 receptor A (CXCR1) decreased with increasing doses of genistein. The average value of the levels of Interleukin 8 receptor A (CXCR1) is the lowest in the group treated with genistein administration of 500 mg. It can be said that in this study, a dose of 500 mg of genistein were considered the most rapidly reduce levels of Interleukin 8 receptor A (CXCR1) in the micromodel of endometriosis. The trend of change between group observations are presented in Figure 2.

![Image](image_url)

**Figure 2. Trends change in mean levels of CXCR1.**

Shown in Figure 2 shows the trend of increase in the mean levels of Interleukin 8 receptor A (CXCR1) from the negative control group to the positive control group. Furthermore, there is a decrease in the average levels of Interleukin 8 receptor A (CXCR1) from the positive control group to the treatment group administration with increased doses of genistein. Therefore, the average value of the levels of Interleukin 8 receptor A (CXCR1) is the lowest in the group of genistein administration of 500 mg. So genistein dose of 500 mg is a dose of the most rapidly reduce levels of Interleukin 8 receptor A (CXCR1) dosage-dose compared to others.

![Image](image_url)

**Figure 3. Scatter plot effect of genistein to CXCR1.**
Figure 3 shown that analysis regression expression CXCR1, regression coefficient is -0.0027 with p-value 0.000. Determination coefficient (R-square) is 69.49%, that means a various expression CXCR1 is 69.49%, depend on effect of giving genistein in various doses. The residue, 30.51%, explained by another factors that is not included in experiment. R-square which is high means that linear model can explain the effect of genistein in the expression of CXCR1.

IV. Discussion

IL-8 binding rapidly down-modulates CXCR1 and CXCR2 due to the internalization of the ligand-receptor complex and continuous stimulation leads to receptor desensitization. There is evidence that the carboxyl terminal domain of CXCR1 and CXCR2 is involved in IL-8-mediated receptor desensitization, signaling, and internalization. It is a cytokine with chemotactic, activating, and surviving functions on neutrophils and T-cells. Its other known actions in endometriosis include producing a local immuno-tolerant environment, directly affecting endometrial cell proliferation, taking part in neovascularization, promoting the vicious circle of endometrial cell attachment, and increasing matrix metalloproteinase activity and invasive capability of ESC. The increased IL-8 enhances the adhesion and invasion of ESC to peritonium partly by binding to CXCR1 on the ESC surface. Estrogen is believed to be essential for the maintenance and growth of ectopic implants, but little work has been done to investigate the biochemical mechanisms of estrogen in endometriosis.

In our present study, we found that in the mice model of endometriosis at all eighth sample group observations with the administration of genistein treatment dose of 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, and 500 mg. There was an increase in mean levels of Interleukin 8 receptor A (CXCR1) to the negative control group and positive control group there was a mean decrease in the levels of Interleukin 8 receptor A (CXCR1) from the positive control group to the treatment group administration of genistein. Mathematical mean levels of Interleukin 8 receptor A (CXCR1) decreased with increasing doses of genistein. The average value of the levels of Interleukin 8 receptor A (CXCR1) was the lower in the group treated genistein administration of 500mg. It can be said that in this study dose of 500mg genistein were considered the most rapidly reduce levels of Interleukin 8 receptor A (CXCR1) in the mice model of endometriosis. It has been suggested that genistein work from tirosin kinase inhibitor mechanism that prevent down modulating functional IL-8 from cell surface. In the classical view of signaling initiated by activation of GPCR by chemoattractants, the G_ complex activates phospholipase C _isoforms that, ultimately, results in calcium mobilization and activation of protein kinase C (PKC) that mediates the activation of NADPH oxidase complex, regulating the respiratory burst, phagocytosis, and bacterial killing in neutrophils. In addition, downstream to G proteins, other intracellular signals are triggered, including phosphatidylinositol 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK) pathways, tyrosine kinases, Rho family of small guanosine triphosphate (GTP)-binding proteins, and phosphatases that affects many aspects of neutrophil functioning, particularly chemotaxis and survival. Activation of these pathways by chemoattractants leads to protein phosphorylation, especially on tyrosine residues of several adapter proteins, which amplifies the signal transduction and priming cells to respond to adhesive interactions via integrins.

Figure 3 shown that analysis regression expression CXCR1, regression coefficient is -0.0027 with p-value 0.000. Determination coefficient (R-square) is 69.49%, that means a various expression CXCR1 is 69.49%, depend on effect of giving genistein in various doses. This have correlation with research Yavuz et al 2007 by giving 500mg genistein oral/day to mouse can show regression implant endometriosis. Genistein inhibited both the TNF-a and IL-8 pathways, implying that tyrosine kinases are involved in both TNF-a and IL-8 pathways. In studies using human monocytes and the THP-1 human monocyte cell line, cross-linking of FcγR led to phosphorylation of intracellular targets. Lane et al 2005 shows that Tyrophostin 19 (sintetic tyrosine kinase inhibitor) reduced the CXCL8 induced migration of CXCR1.

However, this research has not been able to determine the optimal dose of genistein to increase the levels of CXCR1 in peritoneal fluid of endometriosis model mice.

V. Conclusion

Based on the explain of the results above, so we suggested that genistein shows decrease of Interleukin 8 receptor A (CXCR1) level in peritoneal lesion of mice model endometriosis.

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DOI: 10.9790/0853-142894100 www.iosrjournals.org 99 | Page
The Effect Of Giving Genistein In Various Doses In Level Receptor A Interleukin...

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