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The Effect Of GivingGenistein In Various Doses In LevelReceptor A Interleukin 8 (Cxcr1) In Peritoneal Lesions Of Mice-Model Endometriosis

Rapa Yulianto*, Sutrisno, Dwijayasa Pande Made**, Wiyasa Arsana**, Nurseta Tatit*****
**Resident of Obstetrics and Gynecology Department atSaiful Anwar Hospital of Malang, Medical Faculty of Brawijaya University of Malang*
***Division of Fertility and Endocrinology, Department of Obstetrics and Gynecology Saiful Anwar Hospital of Malang, Medical Faculty of Brawijaya University of Malang*
****Division of Oncology Gynecology, Department of Obstetrics and Gynecology Saiful Anwar Hospital of Malang, Medical Faculty of Brawijaya University of Malang*

Abstract: Objective:*ToProvethe effect ofgenistein in variousdosesin Interleukin 1 receptor A level (CXCR1) in peritoneal lesion of mice model endometriosis.*
Method*: This study used atrue experimentaldesign(trueexperimental) in vivo atfemale mice(Musmusculus) withexperimentaldesignPost-Test Only With ControlGroup Design. Involveseightgroups :negative control group (healthy micewithoutgivengenistein), positive control group(mice model ofendometriosiswithoutgivengenistein) and thetreatment groupisthe group thatwas givena variety ofdifferent dosesof genistein: 50mg/day, 100mg/day, 200mg/day, 300mg/day, 400mg/dayand500mg/day. This research was conductedat the Laboratory ofPhysiologyof the Faculty ofMedicine, Universityof BrawijayaandReproductivePhysiology LaboratoryEmbryologiFaculty of Veterinary Medicine, Airlangga University Surabayasampleof a studyusingmice(Musmusculus) endo-metriosisfemalemodelsas much as32mice, with2-3 monthsof ageand body weight20-30grams. Homogenicity of peritoneum lesionis done with micro pastle continued with centrifugation and put in tubeto be processedin order tomeasurelevels 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 regretion expression CXCR1, regretion coefficient is -0,0027 with pvalue 0,000. Determination coefficient (R-square) is 69,49%, that means a various expression CXCR1 is 69,49%, depend on effect of giving ginestein 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*: Givinggenisteinshows decrease Interleukin 8 receptor A (CXCR1) level in peritoneal lesion of mice model endometriosis.*
Keywords*: Interleukin 8 receptor A (CXCR1genistein, endometriosis.*

Abstrak: Tujuan :*Membuktikan pengaruhpemberian genistein berbagai dosis terhadap kadar Reseptor A Interleukin 1 (CXCR1) padalesi peritoneal mencit model endometriosis.*
Metode: *Penelitianinimenggunakandesaineksperimenmurni (true eksperimental) secara in vivo padamencit (Musmusculus) betinadenganrancanganpenelitian Post-Test Only With Control Group Design. Melibatkan 8 kelompokyaitukelompokkontrolnegatif (mencitsehattanpadiberikangenistein), kelompokkontrolpositif (model mencit endometriosis tanpadiberikangenistein) dankelompokperlakuanyaitukelompok yang diberikangenisteinberbagaidosis yang berbeda: 50 mg/hari, 100mg/hari, 200mg/hari, 300mg/hari, 400mg/haridan 500 mg/hari.Penelitianinidilaksanakan di LaboratoriumFisiologiFakultasKedokteranUniversitasBrawijaya Malang danLaboratoriumFisiologiReproduksiEmbryologiFakultasKedokteranHewanUniversitasAirlangga SurabayaSampelpeneltianmenggunakanmencit (Musmusculus) betina model endometriosis sebanyak 32 ekor, denganusia 2-3 bulandanberatbadan 20-30 gram.Lesi peritoneum kemudian dilakukan homogenitas dengan micro pastle dilanjutkan sentrifugasi dandimasukkankedalamtabunguntukdiprosesgunapengukurankadarCXCR1 dengan pemeriksaan 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.*

Kesimpulan*:Pemberiangenisteinmenunjukan kecenderunganpenurunan kadarReseptor A Interleukin 8 (CXCR1) padaLesi peritoneal mencit model endometriosis.*

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

I. Introduction

Endometriosisbecomeone ofthe majorproblemsof re-production todaybecause ofthe incidence ofthis diseaseis quite high. Endometriosisaffects6-10% of women at reproductive agefrom allethnicand social groups. Found1 in 10women of reproductive age(15-49 years), or about 176millionwomenworldwide are infected withendometriosis.[1,2]The incidenceof endometriosisamong allpelvicsurgeryranged about 5-15%, andthat interestwas found inthe unmarried womenandyoung age. Universallyendometriosiswillcausecomplaintsof dysmenorrhea, dyspareunia, dysuria, chronicabdominalpain, pelvic painandpain ondefecation.[3,4,5]

Progression ofendometriosisimplantsis influencedby the estrogen hormone(estrogen dependent). The presenceandgrowth ofendometriosiscellsbeginsat the time ofretrograde menstruation, endometrial cellsareshedalong withmenstrual bloodandmetaboliteswill reverse direction(reflux) passes throughthe fallopian tubesthen into theperitonealcavitycausesendometrialcells andtissueattached to theperitonealsurface.[6,7]

In the development ofperitonealendometriosis, immune cellsappearin theperitoneal cavityas a result ofinflammation. Amongimmune cells, macrophages are thepredominantcell typein theperitoneal cavity,macrophagesare involved inphagocytosismainlycleaningdebrisretrogradeendometrialcells. Supposedlyperitoneal macrophagescapable to remove debrisretrogradeendometrialcells. But inthe case ofendometriosis, macrophagesfailtoperformthe function ofphagocytosisinretrogradeendometrial tissueand thus allowthe implantationand proliferation ofendometriosis lesions.[5,7]

Interleukin-8 (IL-8), alternatively known as CXCL8, is a proinflammatory CXC chemokine. Transcription of the IL-8 gene encodes for a protein of 99 amino acids that is subsequently processedto yield a signaling competent protein of either 77 amino acids in nonimmune cells or 72 amino acids in monocytes andmacrophages. 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 heterotrimeric G proteins.[8]

The activation of these G protein subunits by agonist-bound receptors triggers a typical signal transduction pathway involving activation of phospholipase C b isoforms. 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 Ca^{2+} mobilization. In addition, although chemokine receptors lack tyrosine kinase activity, they can stimulate

the phosphorylation of cytoskeletal proteins, p130 Cas and paxillin , induce the activation of the related adhesion focaltyrosine kinase (also known as Pyk2 or CAKb, mitogenactivatedprotein kinases (Erk1/2, p38, and c-Jun kinase phosphatidylinositol 3-kinase, and Janus kinase 2.p44/42 MAP kinases, also termed extracellular signal-regulatedkinases (Erk1 and Erk2), are important mediators ofgrowth 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 viavarious G protein subunits, considerable heterogeneity existsin the signaling pathways leading to Erk1/2 phosphorylationand the subsequent activation of transcription factors.[11,12]

Estrogen induces the production of pro-inflammatory cytokin (TNF-α, IL-β, TGF-β and COX2), which subsequently activates the transcription factor NF-κβ. 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]Toactivatethe transcription process, bondingof estrogenandestrogen-receptorcomplextobind to theEREco-regulatory proteinsthatco-activator proteins.[7,12]Transcription factorthat has beenactivecan bind toDNAandinducesthe transcriptional activity ofendometriosisresulting inthe synthesis ofmRNAandproteinschange theDNAinto RNAandsynthesis oftarget genesresulting ina majorincrease ininflammatory cytokines(IL-6, IL-8) angiogenesisfactor(HIF -1α, VEGF-A), matrixmetalloproteinase(MMP-2 andMMP-9), anti-apoptotic genes(Bcl-2) anda decrease inpro-apoptotic protein(Bax), increased apoptosisproteins(Caspase3) andcelladhesion molecules.[14,19]All the factors have a rolein the process ofinvasionanddifferentiation, celladhesionandtissueremodelingthroughoutectopicendometrial stromalcellsof endometriosistosurvive (cell survival)andan increase incell proliferationendometriosis. GenisteinworkedasSERMs, areantiestrogenicinhighestrogen levels. Genisteinbinding affinitytoER-α is 4%, andfor theRE-β was 87%, comparedwith estradiol.[16,18]Pre treatment of cells with PTX (100 ng/ml) or tyrosine kinase specific

inhibitors genestein (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.[11]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 endometriosisthat resultingdecreased expression levels ofInterleukin 8 Receptor A (CXCR1)in the cell with ELISA.

II. Materials And Method

This experiment used atrue experimentaldesignweredonein the laboratoryin vivo infemale mice(Musmusculus) withstudy designWithPost-Test Only ControlGroup Design.Involveseightgroups:negative control(healthy micewithoutgivengenistein), positive control group(modelmicegivenendometriosiswithoutgenistein) and thetreatment groupisthe group thatwas givena variety ofdifferent dosesof genistein: 50mg/day, 100 mg/day, 200 mg/day, 300 mg/day, 400 mg/dayand500mg/day.

This research was conductedat the Laboratory ofPhysiologyof the Faculty ofMedicine, Universityof BrawijayaandReproductivePhysiology LaboratoryEmbryologiFaculty of Veterinary Medicine, Airlangga University Surabaya. The implementationwas conducted overthreemonths fromAugust toOctober 2014, with detailsfor 1 weekdoneadaptation, 2weeksfortreatment, then usedfor the manufacture ofexaminationpreparationElissathenreadingthe results of research data(statistical test).

Samplesof a studyusingfemale mice(Musmusculus) model ofendometriosisas much as32 head, with2-3 monthsof ageandweigh20-30grams. Musmusculusobtained fromthe Laboratory ofReproductivePhysiologyEmbryologyAirlangga UniversityFaculty of Veterinary Medicine(FKH Airlangga University),Surabaya. Musmusculusselectedas the study samplebecause it is easilymaintained andisrelativelyhealthyanimalsandis suitablefor useinvarioustypesof researchexperimentsandimmunologyresponsescan be observed.Treatmentdosestoexperimental animals(MusMuculus) will be convertedbythe bodysurface areatothe humanbodyof 70 kgtomice20grams, with aconversionrate0.0026. Micemodel ofendometriosisis based onthe methodperformed onpreliminary researchconducted bySutrisnoetal, 2014. The animals that used for experimental werefemale mice(Musmuscullus) approximately 3monthsold, weighing 20-30gramswereselected based oninclusion and exclusion criteria. Afteradaptationinthe same cageandgetthe samefood anddrinkfor 1 week, doreselectionifthere aremicethat qualify asbreaking upthe testornot. Then do theinjection ofcyclosporinAin mice inthe positivecontrol groupandthe treatment group. The drug whichavailableinIndonesiaisSandimmunNovartisproduction. Oneampoulecontains 50mg/mlx 5ml. Thedose is 10mg/kg/day. In this casethe weightof micerange20-30mg, the dose is also adjusted. Afterconversioncalculation at mice and gettinga dose1,8 mg/mice.So the doseformice afterreconstitution withwaterforinjection is 0.2ccsandimunafterdiluted.Endometrial biopsymaterialtaken from the uterine operation of benign tumoruterine and storedin PBS.Dowashing2 timeswith acentrifugeat3000 rpm in temperature 4°C for 10 minutes, and then take the supernatant (containing stroma, gland, and ephitelial cell).Eachmousewillget0.1mland theninjected blind to peritonealcavityof miceslowly. Injectionsat intraperitonealendometrial tissueinthe positivecontrol groupandthe treatment group.Performedintramuscularinjection ofestrogenon days1and5.The preparationof ethinylestradiolat a doseof 30Φgr/kg.With theconversiontodosethe micewill get5,4 Φgr. Theequivalent ofl µgr equal with 10 iu. 1 vialcontaining30cccontaining20000 iu, the equivalentof 0.1cc equal with66iu. By adjustingthe doseequivalentconversion mice of5,4 Φgr equal with 54iu, the micewilleachget arounded0.095ccor0.1cc.Afterinjectingthe micewill be evaluatedwhether theentrycriteria fordroppingthe testor not.Furthermore, afteradaptation, mice weredividedinto 8 groups, one groupas thenegative control group, one groupas thepositive controlgroup, and6 groupsas the treatment group. Genisteinthat has beendissolved insesame oilwill begiven orallybythe sonde. The duration ofgenisteinin the treatment grouprefers to astudy conducted byYavuzetal(2007) on the Granting ofGenisteinonRegressionImplantsEndometriosis inRatModel. Genisteinwas givenfor 14daysand givenonce daily.

Takingmaterialinspection is doneafter 14days oftreatmentwiththe followingsteps: Mice wereterminatedbeforehand byinhalationinanesthetizedby entering the miceintoa coveredcontainer(glass jar), whichcontainscottonthat has beenspilled with ether. Thencover tightlyand wait a fewminutesuntil themicereally did notmove again. Furthermore,mice wereissuedand placedonthe baseboard with thebellyfacing up. Afterpluggingtackson the feetof mice, the abdominal wallwas openedby usingtweezersandscissorscarefully, with amid-lineincisionwas continuedto theleft and right sideonthe top and bottomand thediaphragmis opened. After that, peritoneal lesionis came to homogenitas with *micro pastle* and sentrifugation than takenandput ina tubeto be processedin order tomeasurelevels ofInterleukin 8 receptor A (CXCR1)in the Laboratoryof Physiology, Faculty ofMedicine, University ofBrawijaya, Malang.

Analysis of CXCR1 level

The level of CXCR1 in supernatant cells was measured using sandwich ELISA(Elisa kit,Elabscience Biothechnology,Hubeiprovince,P.R China). All producess were performed according 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 studythe results ofdata analysis onthe normality testperformed usingthe Shapiro-Wilktest. The criteria forthe decision, that is, whenthe Sigor thep-valueis greaterthanthe significance levelα=0.05 thennormally distributed dataandvice versawhenthe Sigor thep-valueis smallerthanthe significance levelα=0.05 thenthe datawere not normally distributed. In theShapiro-Wilktest analysiswas obtainedanddescribed in detailshown inthe table below.

Table 1. Result of normality distribution test

Variabel	Koefisien	Sig.	Distribution
CXCR1	0.960	0.444	Normal

Table 1 based onthe Shapiro-Wilktest resultsshowed thatthe datacontent ofInterleukin 8 Receptor A (CXCR1)foreach group ofobservationshave demonstratedp-valueof which arelarger thanthe significance levelα=0:05. So allthe datahas met theprerequisitesof parametrictest, the dataproved tobe normally distributed.

Table 2. Result of Homogenitas test.

Variabel	Koefisien	Sig.	Keterangan
CXCR1	1.565	0.216	Homogen

Table 2 based onthe Levenetest resultsshowed thatthe datacontent ofInterleukin 8 Receptor A (CXCR1)foreach group ofobservationshave demonstratedp-valueof which arelarger thanthe significance levelα=0:05. So allthe datahas met theprerequisitesof parametrictest, the dataproved homogen.

Table3. Results ofthe comparisoncontrol group

Group		Mean Difference (I-J)	Sig.
Negative control	Positive control	-1.598	0.000

Table3 based onthe results ofindependent samplest-test(independent sample t test)showedthatthere were significant differences(p =0.000<α) meanlevels ofCXCR1between thenegative control group(healthy micewithoutgivengenistein) withthe positivecontrol group(mice givenmodel ofendometriosiswithout given genistein).This meansthat themicemodel ofendometriosiswillshow thelevels ofCXCR1 is high when compared tohealthymice.

Based on the resultsof one-wayANOVA teston the datacontent ofCXCR1obtainednosignificant difference inthe meanlevels ofCXCR1sevengroups ofsampleobservations, as shown by thep-value=0.000<α. Furthermore,themultiplecomparison testwith Tukey HSD testis obtainedand displayedare presentedin

Table 4.Comparation of the Level of CXCR1

Groups	Mean ± SD		Sig.
K-	0.92 ± 0.15	a	0.000
K+	2.52 ± 0.15	d	
P1	1.74 ± 0.49	bc	
P2	2.19 ± 0.24	cd	
P3	1.37 ± 0.17	ab	
P4	1.34 ± 0.14	ab	
P5	1.15 ± 0.18	ab	
P6	1.01 ± 0.15	a	

Table4based onthe results ofthe multiplecomparison testwith Tukey HSD testshowedthatthere were significant differencesmeanlevels ofInterleukin 8 receptor A(CXCR1) between thepositive control group(2,52±0.15^{d}) with theadministration ofgenisteintreatment group50mg(1,74±0.49^{bc}), with100mg ofgenistein(2.19±0.24^{cd}), with200mg ofgenistein(1.37±0.17^{ab}), with300mg ofgenistein(1.34±0.14^{ab}), with400mg ofgenistein(1.15±0.18^{ab}), andalsowithgenistein500mg(1.01±0.15^{a}).Based on the mean valuethere is a decreasein the group treatedwith increaseddoses ofgenistein. This meansthat thetreatment ofgenisteinadministration of50mg, 100mg, 200mg, 300mg, 400mg, and500mg in themurinemodel ofendometriosiswill affect thelevels ofInterleukin 8 receptor A(CXCR1), which isable to reducethe levels ofInterleukin 8 receptor A(CXCR1)when

comparedthemicemodel ofendometriosiswithoutgivinggenistein.Thedifferences between the meanlevels ofInterleukin 8 receptor A(CXCR1)inthe eighthgroup ofthesampleare presentedin fullappearson the imagehistogrambelow

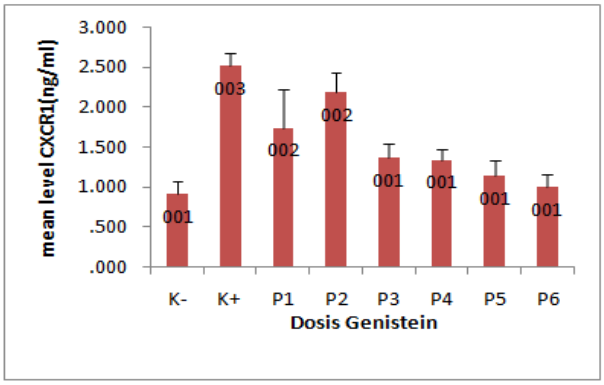

Figure 1. Histogram mean level of CXCR1.

In Figure 1 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. Looksmeanlevels ofInterleukin 8 receptor A(CXCR1)decreasedwith increasingdoses ofgenistein. Theaverage value ofthe levels ofInterleukin 8 receptor A(CXCR1) is the lowestin the group treatedgenisteinadministrationof 500mg. It canbe said thatin this studya dose of 500mg ofgenisteinwereconsidered the mostrapidlyreduce levels ofInterleukin 8 receptor A(CXCR1)in themicemodel ofendometriosis. Thetrend ofchangebetween groupsobservationsare presentedin Figure2.

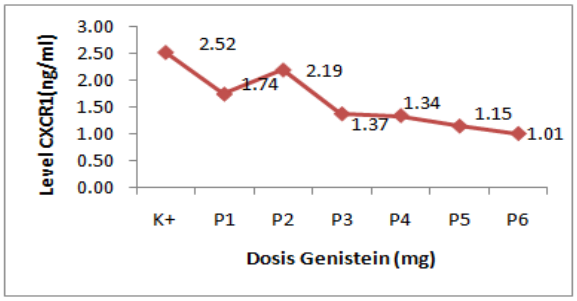

Figure 2.Trendschange inmeanlevels of CXCR1.

Shown inFigure2 showsthe trend ofincrease inthe meanlevels ofInterleukin 8 receptor A(CXCR1)fromthe negativecontrol groupto thepositive control group. Furthermore, there isa decrease inthe averagelevels ofInterleukin 8 receptor A(CXCR1)fromthe positivecontrol groupto thetreatment groupadministrationwith increaseddosesof genistein. Therefore,the average value ofthe levels ofInterleukin 8 receptor A(CXCR1)isthe lowestin the group ofgenisteinadministration of500mg sothegenisteindose500mg is a doseof the mostrapidlyreduce levels ofInterleukin 8 receptor A(CXCR1)dosage-dose compared toothers.

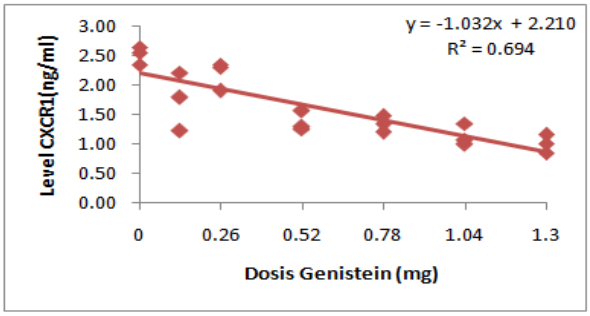

Figure 3. Scatter plot effect of genistein to CXCR1

Figure 3 shown thats analysis regretion expression CXCR1, regretion coefficient is -0,0027 with pvalue 0,000. Determination coefficient (R-square) is 69,49%, that means a various expression CXCR1 is 69,49%, depend on effect of giving ginestein 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..[12]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.[21]

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. Looksmeanlevels ofInterleukin 8 receptor A(CXCR1) decreasedwith increasingdoses ofgenistein. Theaverage value ofthe levels ofInterleukin 8 receptor A(CXCR1) is the lowestin the group treatedgenisteinadministrationof 500mg. It canbe said thatin this studya dose of 500mg ofgenisteinwereconsidered the mostrapidlyreduce levels ofInterleukin 8 receptor A(CXCR1) in themicemodel ofendometriosis. It has ben suggested that genistein work from tirosin kinase inhibitor mekanisme that prevent down mudulati functional IL-8 from cell surface.[12]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– 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.[13,15]

Figure 3 shown thats analysis regretion expression CXCR1, regretion 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 ginestein 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.[20] Genistein

inhibited both the TNF-a and IL-8 pathways, implying that tyrosine kinases are involved in both TNF-a and IL-8 pathways.[10]In studies using human monocytes and the THP-1 humanmonocyte cell line, cross-linking of FcgR led to phosphorylationof intracellular targets.Lane et al 2005 shows that Tyrphostin 19(sintetic tyrosine kinase inhibitor) reduced the CXCL8 induced migration of CXCR1.[14]

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 onthe explain of the results above, so we suggestedthatgenisteinshows decrease of Interleukin 8 receptor A (CXCR1) level in peritoneal lesion of mice model endometriosis

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