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Systematic Review/ Meta-Analysis

Genistein Effect on Estrogen Receptor especially Interleukin-6 and Tumor Necrosis Factor-α in Mice Model of Endometriosis: a Systematic Review and Meta-Analysis

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KEYWORD
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ABSTRACT

Introduction: Endometriosis is the endometrial tissue proliferation outside the uterine space. Anti-angiogenic agents from different groups of substances are currently being discussed as promising therapies for the treatment of endometriosis in the future, one of which is therapy using the phytoestrogen genistein. At the molecular level, genistein's effects on cells include inhibition of proliferation, induction of differentiation, apoptosis, and cell arrest in the cell cycle, which are related to the transforming growth factor. Genistein inhibits cell growth by modulating the signal-transforming growth factor pathway.

Methods: We searched PubMed, Scopus, Cochrane Library and Proquest from its inception to December 2022 to collect observational and interventional studies of Genistein consumption in endometriosis mice. Two authors independently screened the literature according to the inclusion and exclusion criteria, extracted data, and assessed the risk of bias. Safety analysis was assessed through TNF-α and IL-6 values of estrogen expression.

Results: No significant difference in the values of IL-6 and TNF-α in rats with endometriosis that were given genistein at these three doses. However, if analyzed further, the IL-6 outcome compared to the 0.78mg/day dose most affected the IL-6 value between the two groups, and the TNF-α output compared to the 0.78 mg/day dose most affected the TNF-α value between the two groups. So, a genistein dose of 0.78 mg/day can affect IL-6 and TNF-α in mice with endometriosis.

Conclusion: Genistein modulated estrogen expression of TNF-α and IL-6 at all doses, but the best dose for its effect was 0.78 mg/day.

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INTRODUCTION

Endometriosis is the proliferation of endometrial tissue outside the uterine cavity. Endometriosis affects 10-15% of women of reproductive age, which also accounts for 40–60% of women who experience pelvic pain and 30–50% of women who are infertile [1]. Based on World Statistics of Endometriosis data in 2014, as many as 176,000,000 women suffer endometriosis [2–4]. According to data on endometriosis patients in Indonesia, 10% of reproductive women were found to have endometriosis at the Dr. Cipto Mangukusumo Hospital in Jakarta, in the period of 2006 to 2010. Endometriosis was also prevalent in Dr. Soetomo General Hospital in Surabaya, at rate of 23,8%.

Although endometriosis is a benign mass, it exhibits characteristics of cancer due to its invasiveness and tendency to metastasize and recur [5–9]. Endometriotic lesions can be discovered in the ovaries, peritoneum, or as an endometriotic cyst [10]. These infiltrative lesions can blowout to various organs, including the bladder, intestines, and ureter [11]. Based on Sampson's(1927) implantation theory, peritoneal endometriosis lesions develop from endometrial tissue, which drains retrogradely through the fallopian tubes during menstruation [12–14].

Cell proliferation in endometriosis has been studied by various studies, but not much has been revealed

about the exact mechanism. The increased sensitivity of endometriosis to the process of cell proliferation can be one of the possible pathogeneses of this disease. Research by Subramanian and Agarwal (2010) showed a significant increase in cell proliferation in patients with endometriosis compared to non-endometriotic patients [5,6]. The activity of pro-inflammatory cytokines, Interleukin-6 (IL-6) and Tumor Necrosis Factor-α (TNF-α) triggered estrogen. Treatments for endometriosis include a non-steroidal anti-inflammatory agent. Anti-angiogenic agents from different groups of substances are currently being discussedas promising therapies for endometriosis in the future, one of which is therapy using the phytoestrogen genistein [15,16].

Genistein belongs to the isoflavone class, which can inhibit cell growth, have anti-tumor and anti-cancer properties, influence cell apoptosis, and have a good affinity for estrogen receptors [17]. The effects of genistein on cells at the molecular level include suppression of cell growth, apoptosis, induction of differentiation, and cell cycle arrest, all of which are related to the transforming growth factor [15–17].

Genistein inhibits cell growth by modulating the signal-transforming growth factor pathway. Research conducted by Sutrisno et al. (2014) reported a significant decrease in cell proliferation in endometriosis cultured cells at 6 hours after administration of genistein therapy at a dose of 50 μmol/l compared to the control group [18–20] and the study of Sutrisno et al. (2017) reported the effect of vascularization based on VEGF and HIF-1 expression [11]. As we know there is still dispute about genistein effect against endometriosis. Consequently, this study aimed to define whether genistein can modulate the estrogen receptor, angiogenesis and inhibit inflammation in the mice model of peritoneal endometriosis.

MATERIAL AND METHODS

This meta-analysis protocol was arranged according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) protocol, and the final report according to the PRISMA checklist (Appendix 1) [21].

Searching Strategy

The search strategy was carried out in consultation with experts using the boolean operator (Endometriosis) AND ((Mice) OR (Rats)) AND estrogen expression AND (((interleukin 6) OR(IL-6)) OR ((Tumor necrosis factor alpha) OR (TNF-α)) AND Genistein.This search was subjected to peer review via an Electronic Search Strategy [22–24]. The search was conducted on the following databases: PubMed, Proquest, Cochrane Library and Scopus from January 2002 to December 2022. We did not enforce any language limitations on our searches.

Eligibility Criteria

We included observational and interventional studies that examined parameters of estrogen expression in mice with endometriosis, with primary outcomes being Interleukin-6 and Tumor Necrosis Factor-α. Only mice were included in this study. Subjects (mice) were given Genistein in various doses. Studies with primary outcomes other than Interleukin-6 and Tumor Necrosis Factor-α excluded from the study.

Research Results

The primary outcomes of our study were interleukin-6 and tumor necrosis factor-a values. The results were compared from each given Genistein. Estrogen receptor expression, including TNF-α and IL-6 in peritoneal tissue, was analyzed using immunohistochemical techniques according to the previous procedure.

Study Selection Process

After compiling the list of identified ones for a literature search, duplicates were removed from the study. Titles and abstracts were assessed for inclusion by two reviewers independently.Titles or abstracts that are considered relevant are recorded and full-text articles are obtained.Two independent critics screened the articles in full to assess the eligibility of the articles.The research selection process was recorded and reported using a flowchart as suggested by PRISMA (Fig. 1).

Data Collection

Two researchers work on data concept. Each researcher objectively documented publication characteristics (i.e., year of publication, journal, and appropriate author), population (i.e.,eligibility criteria, type of animal, sex, and rat weight), details of intervention (i.e., dose and follow-up time), study design (methods, settings and sample size), and estrogen expression outcomes.

Statistic Analysis

Studies were collected using the Review Manager application (version 5.4; Biostat Inc., USA).To test the effectiveness of the dose that most affects the value of IL-6 and TNF-α with continuous (numerical test). Fixed effect odds ratios are calculated and presented with 95% confidence intervals [11,25–27]. Studies that did not provide data in a format suitable for inclusion in a meta-analysis (ie, no control group) were analyzed descriptively. Statistical heterogeneity was assessed using the I^2 statistic. I^2 values >50% are considered to represent important heterogeneity that requires further exploration.

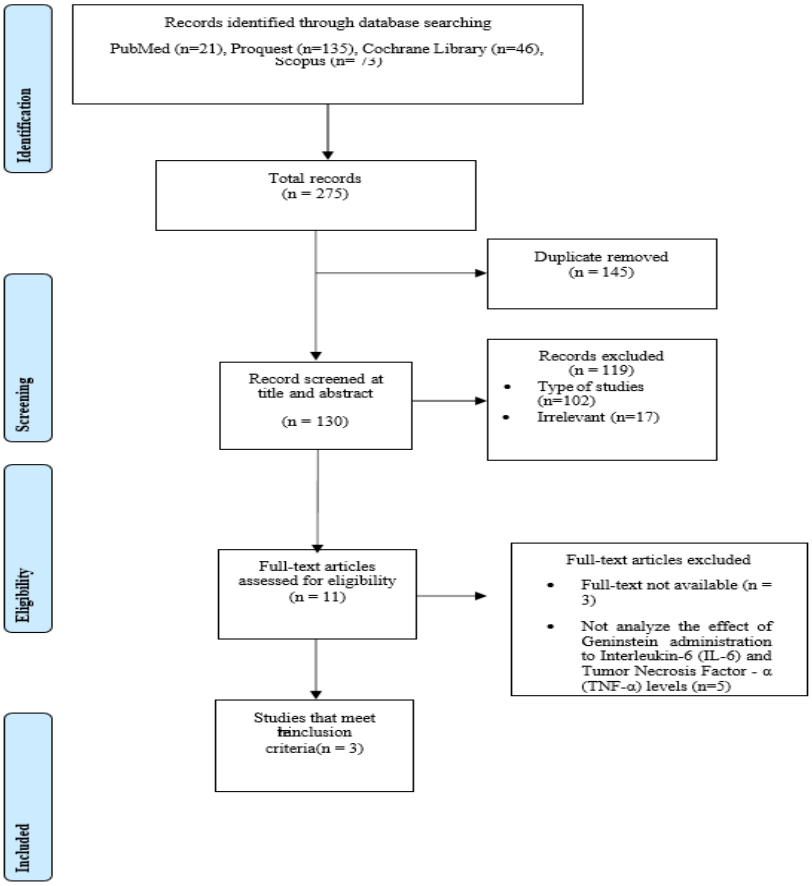


Fig. 1. Study Flow Diagram in this Review

RESULTS

A literature search identified 275 articles. Abstract and full-text screening recognized 8 studies (179 mice) for inclusion in data extraction (Fig. 1). The reasons for the exclusion of the full-textstudy are presented in Fig. 1.

Study Characteristics

Studies that meet the inclusion and exclusion criteria were 3 studies (n = 34 mice). In each study, genistein was given at various doses to mice that had endometriosis-inducing conditions. Follow-up duration ranged from 2 to 7 days (Table 1).

Intervention Characteristics

Genistein was administered in 3 doses, 0.78 mg/day, 1.04 mg/day, and 1.30 mg/day. Genistein is administered intravenously.

IL-6

a. Genistein 0.78 mg/day vs Control
   All studies included in the analysis used calculations with the mean and standard deviation. There was no statistically significant difference in IL-6 values in the group given genistein 0.78 mg/day (n=17 mice) and the group given placebo (n=17 mice). (p=0.34; I2=89%; SMD 1.38 95% CI -1.47-4.23) (Fig. 2).
b. Genistein 1.04 mg/day vs Control
   All studies included in the analysis used calculations with the mean and standard deviation. There was no statistically significant difference in IL-6 values in the group given genistein 1.04 mg/day (n=17 mice) and the group given placebo (n=17 mice). (p=0.39; I^2=63%; SMD -0.55 95% CI -1.81-0.70) (Fig. 3).
c. Genistein 1.30 mg/day vs Control
   All studies included in the analysis used calculations with the mean and standard deviation. There was no statistically significant difference in IL-6 values in the group given genistein 1.30 mg/day (n=17 mice) and the group given placebo (n = 17 mice). (p=0.91; $I^2$86%; SMD -0.13 95% CI -2.52-2.26) (Fig. 4).

Table 1. Study and Intervention Characteristic

No	Author	Number of samples	Follow-up (days)	Estrogen expression
1	Sutrisno, 2018[37]	6	5	ER-a
		6		ER-B
		6		TNF-a
		6		IL-6
		6		VEGF
		6		HIF-1a
2	Sutrisno, 2015[33]	6	7	TNF-a
		6		IL-1 B
		6		IL-6
		6		IL-8
3	Sutrisno, 2014[38]	5	2	IL-1 B
		5		TNF-a
		5		IL-6
		5		VEGF-A
		5		MMP-2

* ER (Estrogen Receptor); TNF (Tumor Necrosis Factor); IL (Interleukin); VEGF (Vascular Endothelial Growth Factor); HIF (Hypoxia-Inducible Factor).

TNF-a Outcome

a. Genistein 0.78 mg/day vs Control
All studies included in the analysis used calculations with the mean and standard deviation. There was no statistically significant difference in TNF-a values in the group given genistein 0.78 mg/day (n=17 mice) and the group given placebo (n=17 mice). (p=0.74; I^2 85%; SMD 0.36 95% CI -1.81-2.54) (Fig. 5).

b. Genistein 1.04 mg/day vs Control
All studies included in the analysis used calculations with the mean and standard deviation. There was no statistically significant difference in TNF-a values in the group given genistein 1.04 mg/day (n=17 mice) and the group was given placebo (n=17 mice). (p=0.88; I^2 87%; SMD 0.19 95% CI -2.24-2.62) (Fig. 6)

c. Genistein 1.30 mg/day vs Control
All studies included in the analysis used calculations with the mean and standard deviation. There was no statistically significant difference in TNF-a values in the group given genistein 1.30

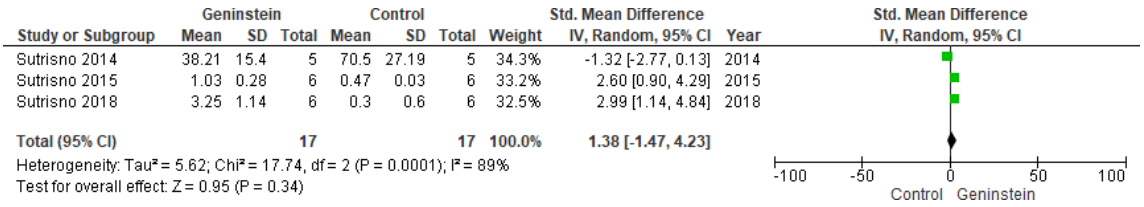


Fig. 2. Forest plot of Genistein 0.78 mg/day vs Control (IL-6 outcome)

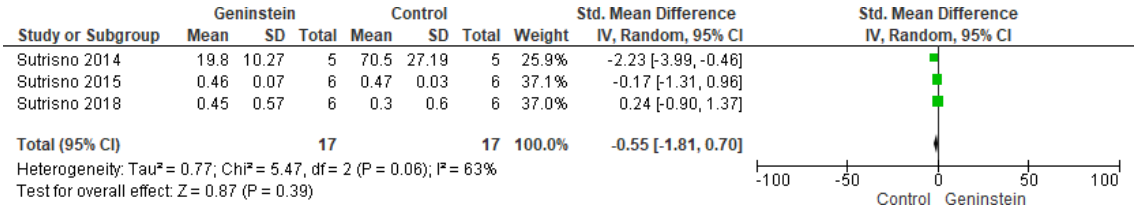


Fig. 3. Forest plot of Genistein 1.04 mg/day vs Control (IL-6 outcome)

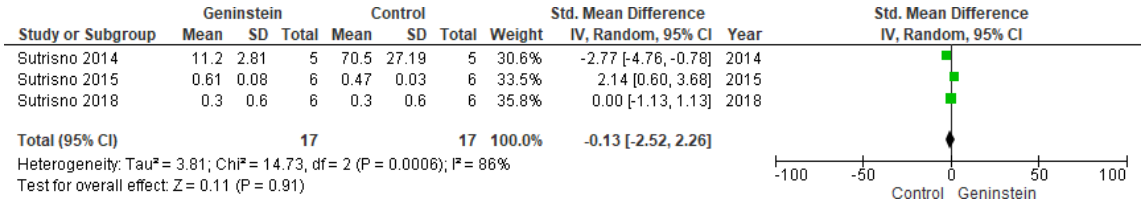


Fig. 4. Forest plot of Genistein 1.30 mg/day vs Control (IL-6 outcome)

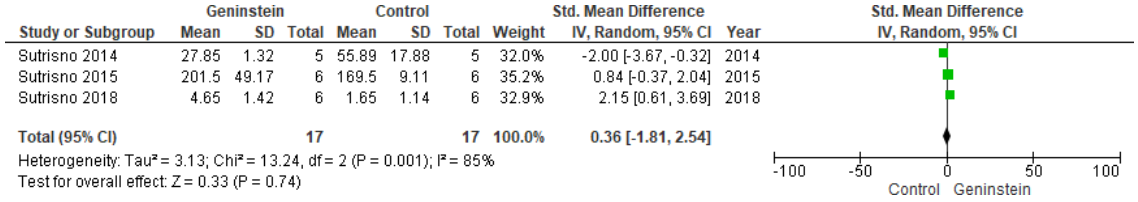


Fig. 5. Forest plot of Genistein 0.78 mg/day vs Control (TNF-a outcome)

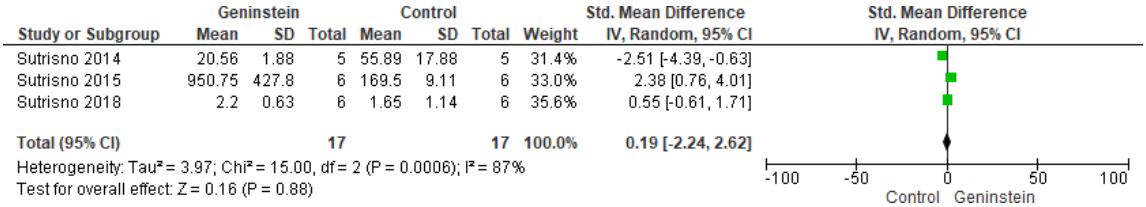


Fig. 6. Forest plot of Genistein 1.04 mg/day vs Control (TNF-a outcome)

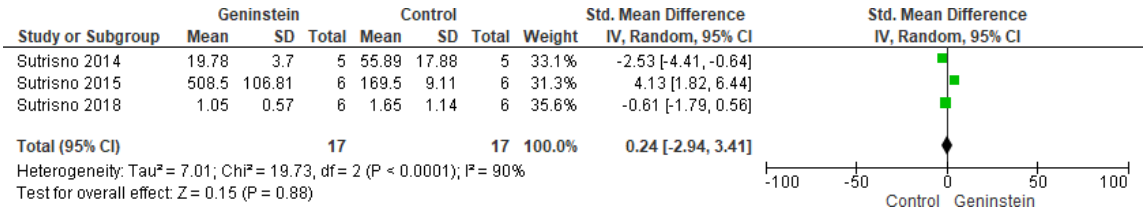


Fig. 7. Forest plot of Genistein 1.30 mg/day vs Control (TNF-a outcome)

mg/day (n=17 mice) and the group given placebo (n=17 mice). (p=0.88; I^2 90%; SMD 0.24 95% CI -2.94-3.41) (Fig. 7).

Based on the results above, there was no significant difference in the values of IL-6 and TNF-a in rats with endometriosis that were given genistein at these 3 doses.

However, if analyzed further, the IL-6 outcome compared to the 0.78mg/day dose most affected the IL-6 value between the two groups, and the TNF-a output compared to the 0.78mg/day dose most affected the TNF-a value between the two groups. So, genistein dose of 0.78mg/day can affect IL-6 and TNF-a values in mice with endometriosis.

DISCUSSION

Based on the forest plot, there was an effect on the administration of genistein between the control and treatment groups at all dose levels. Statistical tests proved that it was significantlybetter in the group given genistein at a dose of 0.78 mg/day compared to dose of 1.04 mg/dayand 1.3 mg/day. The explanation from the results of this meta-analysis is that IL-6 and TNF- α at a dose of 0.78 mg/day are the most influential compared to the control group. This is supported by data on inflammatory cytokines in these previous studies that significantly increased expression of TNF- α and IL-6 in the endometriosis group compared to the control group could be reduced by the two highest doses of up to 0.78 mg/day. Genistein has the ability to reduce pro-inflammatory cytokines such as TNF-α and IL-6

[30,31].

After genistein was given for various periods of time, many researchers found no side effects and toxic effects from genistein. There have been several studies looking at its efficacy, showing the interaction of genistein with the mechanism of action against chemotherapy so that the efficacy of chemotherapy is hampered [32]. On the other hand, the growth in the expression of RE-β is linked with a decrease in inflammatory situations (TNF-α) of endometriosis cells with the management of genistein. The decrease in inflammation is also associated with increased cell apoptosis and decreased endometriosis cell proliferation. RE-β is a potential target of treatment in the future, and more diseases will initiate RE-α. Control of RE-β will be an alternative management for endometriosis [33,34].

Genistein as an anti-proliferative agent is also supported based on research by Malloy et al. Inthis study it is proved that genistein inhibits cancer cell growth and induces cell cycle arrest in G2. The anti-proliferative mechanism induced by genistein in Malloy et al is thought to be related to several molecular targets in endometrial cancer cells studied, including inhibition of protein tyrosine kinase (EGFR/VEGFR/Her2) and modulation of ERα. Genistein-induced apoptosis and cell cycle arrest in cancer cells may be the result of targeting these signaling pathways.

Increased TNF-a, IL-1, IL-6, IL- 8, and NF-kB levels supplement this estrogen receptor expression. These findings suggest that a mice model of endometriosis upregulates NF-kB, a signalling route to produce pro-inflammatory cytokines. Estrogen receptors play an important role by mediating estrogen action and the development of eutopic or ectopic endometrium. Genistein is able to inhibit estrogen receptor expression in in-vivo studies confirmed by in vitro studies is able to inhibit estrogen receptor expression. The mechanism of this inhibition is through modification of aberrant DNA methylation status [35,36].

In addition, genistein also inhibits the activation of IL-1b, NF-kB, TNF- α, and IL-6 receptors. Previous research explained that genistein could also reduce TNF- α and IL-6 levels in the liver and serum, as well as inhibit IkB-α phosphorylation, nuclear translocation of the NF-kB p65 subunit, and activation of the C-terminal-Jun N kinase (JNK) [32,34,37]. The effect of restoring cytokine production from genistein therapy differs between cytokines. Thus, the researchers analyzed that cytokines are produced by several cells in the peritoneal fluid and tissue, and the affinity of each cell for each genistein is different. Genistein prevents an increase in pro-inflammatory cytokines. Therefore, it can provide a natural therapy to reduce inflammation and changes in estrogen receptors inendometriosis.

CONCLUSION

This meta-analysis showed that genistein could control estrogen expression of TNF- α and IL-6 at all doses, but that 0.78 mg/day was the most effective dose.

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CONFLICT OF INTEREST

The authors declare there is no conflict of interest.

REFERENCES

1. Hartati, Ocviyanti D, Amin R, Effendi Y, Hafy Z, Partan RU, et al. Gynaecologic History During Adolescence to Predict Endometriosis Earlier. Bioscientia Medicina : Journal of Biomedicine and Translational Research [Internet]. 2022 Jan 31 [cited 2023 Mar 26];6(3):1515–22. Available from: https://www.bioscmed.com/index.php/bsm/article/view/465
2. Hill CJ, Fakhreldin M, Maclean A, Dobson L, Nancarrow L, Bradfield A, et al. Endometriosis and the Fallopian Tubes: Theories of Origin and Clinical Implications. J Clin Med [Internet]. 2020 Jun 18 [cited 2023 Mar 26];9(6):1–21. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32570847
3. Sharpe-Timms KL. Endometrial anomalies in women with endometriosis. Ann N Y Acad Sci. 2001;943:131–47.
4. Sourial S, Tempest N, Hapangama DK. Theories on the pathogenesis of endometriosis. Int J Reprod Med [Internet]. 2014 [cited 2023 Mar 26];2014:1–9. Available from: https://pubmed.ncbi.nlm.nih.gov/25763392/
5. Agarwal N, Subramanian A. Endometriosis – Morphology, Clinical Presentations and Molecular Pathology. J Lab Physicians [Internet]. 2010 Jan [cited 2023 Mar 26];2(1):1. Available from: /pmc/articles/PMC3147077/
6. Burney RO, Giudice LC. Pathogenesis and pathophysiology of endometriosis. Fertil Steril [Internet]. 2012 Sep [cited 2023 Mar 26];98(3):511–9. Available from: https://pubmed.ncbi.nlm.nih.gov/22819144/
7. Signorile PG, Baldi A. Endometriosis: New concepts in the pathogenesis. International Journal of Biochemistry and Cell Biology. 2010 Jun;42(6):778–80.
8. Taylor RN, Kane MA, Sidell N. Pathogenesis of Endometriosis: Roles of Retinoids and Inflammatory Pathways. Semin Reprod Med. 2015 Jul 3;33(4):246–56.
9. Burney RO, Giudice LC. Pathogenesis and pathophysiology of endometriosis. Fertil Steril. 2012 Sep 1;98(3):511–9.

10. Leyland N, Casper R, Laberge P, Singh SS, Allen L, Arendas K, et al. Endometriosis: Diagnosis and Management. Journal of Obstetrics and Gynaecology Canada. 2010 Jul 1;32(7):S1–3.
11. Sutrisno S, Sulistyorini C, Manungkalit EM, Winarsih L, Noorhamdani N, Winarsih S. The effect of genistein on TGF-β signal, dysregulation of apoptosis, cyclooxygenase-2 pathway, and NF-kB pathway in mice peritoneum of endometriosis model. Middle East Fertil Soc J. 2017 Dec 1;22(4):295–9.
12. Luo Q, Ning W, Wu Y, Zhu X, Jin F, Sheng J, et al. Altered expression of interleukin-18 in the ectopic and eutopic endometrium of women with endometriosis. J Reprod Immunol. 2006 Dec;72(1–2):108–17.
13. Eisenberg VH, Zolti M, Soriano D. Is there an association between autoimmunity and endometriosis? Autoimmun Rev. 2012 Sep;11(11):806–14.
14. Barrier BF. Immunology of endometriosis. Clin Obstet Gynecol [Internet]. 2010 [cited 2023 Mar 26];53(2):397–402. Available from: https://pubmed.ncbi.nlm.nih.gov/20436316/
15. Spagnuolo C, Russo GL, Orhan IE, Habtemariam S, Daglia M, Sureda A, et al. Genistein and Cancer: Current Status, Challenges, and Future Directions 1,2. [cited 2023 Mar 26]; Available from: https://academic.oup.com/advances/article/6/4/408/4568643
16. Pejči´c TP, Zekovi´c MZ, Bumbaširevi´cbumbaširevi´c U, Kalaba M, Vovk I, Bensa M, et al. The Role of Isoflavones in the Prevention of Breast Cancer and Prostate Cancer. 2023 [cited 2023 Mar 26]; Available from: https://doi.org/10.3390/antiox12020368
17. Sohel M, Biswas P, Al Amin M, Hossain A, Sultana H, Dey D, et al. Genistein, a Potential Phytochemical against Breast Cancer Treatment-Insight into the Molecular Mechanisms. 2022;
18. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol [Internet]. 2016 Jul 1 [cited 2023 Mar 26];75:40–6. Available from: http://www.jclinepi.com/article/S0895435616000585/fulltext
19. Fehrmann P, Thomas J. Comprehensive computer searches and reporting in systematic reviews. Res Synth Methods. 2011 Mar;2(1):15–32.
20. Fehrmann P, Thomas J. Comprehensive computer searches and reporting in systematic reviews. Res Synth Methods. 2011 Mar;2(1):15–32.
21. Brockhaus AC, Grouven U, Bender R. Performance of the Peto odds ratio compared to the usual odds ratio estimator in the case of rare events. Biom J [Internet]. 2016 Nov 1 [cited 2023 Mar 26];58(6):1428–44. Available from: https://pubmed.ncbi.nlm.nih.gov/27546483/
22. Kobayashi H, Imanaka S, Nakamura H, Tsuji A. Understanding the role of epigenomic, genomic and genetic alterations in the development of endometriosis (review). Mol Med Rep. 2014;9(5):1483–505.
23. Iwabuchi T, Yoshimoto C, Shigetomi H, Kobayashi H. Oxidative Stress and Antioxidant Defense in Endometriosis and Its Malignant Transformation. Oxid Med Cell Longev. 2015;2015.
24. Ekarattanawong S, Tanprasertkul C, Somprasit C, Chamod P, Tiengtip R, Bhamarapravatana K, et al. Possibility of using superoxide dismutase and glutathione peroxidase as endometriosis biomarkers. Int J Womens Health. 2017 Sep 27;9:711–6.
25. Sutrisno S, Miryani I, Dwijayasa PM, Suprobo NR, Wiyasa IWA. Genistein administration increases the level of superoxide dismutase and glutathione peroxidase in the endometriosis mice model: An experimental study. Int J Reprod Biomed [Internet]. 2022 Oct 10 [cited 2023 Mar 26];20(10):873–82. Available from: http://ijrm.ir/article-1-2376-en.html
1. Hartati, Ocviyanti D, Amin R, Effendi Y, Hafy Z, Partan RU, et al. Gynaecologic History During Adolescence to Predict Endometriosis Earlier. Bioscientia Medicina : Journal of Biomedicine and Translational Research [Internet]. 2022 Jan 31 [cited 2023 Mar 26];6(3):1515–22. Available from: https://www.bioscmed.com/index.php/bsm/article/view/465
2. Hill CJ, Fakhreldin M, Maclean A, Dobson L, Nancarrow L, Bradfield A, et al. Endometriosis and the Fallopian Tubes: Theories of Origin and Clinical Implications. J Clin Med [Internet]. 2020 Jun 18 [cited 2023 Mar 26];9(6):1–21. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32570847
3. Sharpe-Timms KL. Endometrial anomalies in women with endometriosis. Ann N Y Acad Sci. 2001;943:131–47.
4. Sourial S, Tempest N, Hapangama DK. Theories on the pathogenesis of endometriosis. Int J Reprod Med [Internet]. 2014 [cited 2023 Mar 26];2014:1–9. Available from: https://pubmed.ncbi.nlm.nih.gov/25763392/
5. Agarwal N, Subramanian A. Endometriosis – Morphology, Clinical Presentations and Molecular Pathology. J Lab Physicians [Internet]. 2010 Jan [cited 2023 Mar 26];2(1):1. Available from: /pmc/articles/PMC3147077/
6. Burney RO, Giudice LC. Pathogenesis and pathophysiology of endometriosis. Fertil Steril [Internet]. 2012 Sep [cited 2023 Mar 26];98(3):511–9. Available from: https://pubmed.ncbi.nlm.nih.gov/22819144/
7. Signorile PG, Baldi A. Endometriosis: New concepts in the pathogenesis. International Journal of Biochemistry and Cell Biology. 2010 Jun;42(6):778–80.
8. Taylor RN, Kane MA, Sidell N. Pathogenesis of Endometriosis: Roles of Retinoids and Inflammatory Pathways. Semin Reprod Med. 2015 Jul 3;33(4):246–56.

9. Burney RO, Giudice LC. Pathogenesis and pathophysiology of endometriosis. Fertil Steril. 2012 Sep 1;98(3):511–9.
10. Leyland N, Casper R, Laberge P, Singh SS, Allen L, Arendas K, et al. Endometriosis: Diagnosis and Management. Journal of Obstetrics and Gynaecology Canada. 2010 Jul 1;32(7):S1–3.
11. Sutrisno S, Sulistyorini C, Manungkalit EM, Winarsih L, Noorhamdani N, Winarsih S. The effect of genistein on TGF-β signal, dysregulation of apoptosis, cyclooxygenase-2 pathway, and NF-kB pathway in mice peritoneum of endometriosis model. Middle East Fertil Soc J. 2017 Dec 1;22(4):295–9.
12. Luo Q, Ning W, Wu Y, Zhu X, Jin F, Sheng J, et al. Altered expression of interleukin-18 in the ectopic and eutopic endometrium of women with endometriosis. J Reprod Immunol. 2006 Dec;72(1–2):108–17.
13. Eisenberg VH, Zolti M, Soriano D. Is there an association between autoimmunity and endometriosis? Autoimmun Rev. 2012 Sep;11(11):806–14.
14. Barrier BF. Immunology of endometriosis. Clin Obstet Gynecol [Internet]. 2010 [cited 2023 Mar 26];53(2):397–402. Available from: https://pubmed.ncbi.nlm.nih.gov/20436316/
15. Spagnuolo C, Russo GL, Orhan IE, Habtemariam S, Daglia M, Sureda A, et al. Genistein and Cancer: Current Status, Challenges, and Future Directions 1,2. [cited 2023 Mar 26]; Available from: https://academic.oup.com/advances/article/6/4/408/4568643
16. Pejči´c TP, Zekovi´c MZ, Bumbaširevi´cbumbaširevi´c U, Kalaba M, Vovk I, Bensa M, et al. The Role of Isoflavones in the Prevention of Breast Cancer and Prostate Cancer. 2023 [cited 2023 Mar 26]; Available from: https://doi.org/10.3390/antiox12020368
17. Sohel M, Biswas P, Al Amin M, Hossain A, Sultana H, Dey D, et al. Genistein, a Potential Phytochemical against Breast Cancer Treatment-Insight into the Molecular Mechanisms. 2022;
18. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol [Internet]. 2016 Jul 1 [cited 2023 Mar 26];75:40–6. Available from: http://www.jclinepi.com/article/S0895435616000585/fulltext
19. Fehrmann P, Thomas J. Comprehensive computer searches and reporting in systematic reviews. Res Synth Methods. 2011 Mar;2(1):15–32.
20. Fehrmann P, Thomas J. Comprehensive computer searches and reporting in systematic reviews. Res Synth Methods. 2011 Mar;2(1):15–32.
21. Brockhaus AC, Grouven U, Bender R. Performance of the Peto odds ratio compared to the usual odds ratio estimator in the case of rare events. Biom J [Internet]. 2016 Nov 1 [cited 2023 Mar 26];58(6):1428–44. Available from: https://pubmed.ncbi.nlm.nih.gov/27546483/
22. Kobayashi H, Imanaka S, Nakamura H, Tsuji A. Understanding the role of epigenomic, genomic and genetic alterations in the development of endometriosis (review). Mol Med Rep. 2014;9(5):1483–505.
23. Iwabuchi T, Yoshimoto C, Shigetomi H, Kobayashi H. Oxidative Stress and Antioxidant Defense in Endometriosis and Its Malignant Transformation. Oxid Med Cell Longev. 2015;2015.
24. Ekarattanawong S, Tanprasertkul C, Somprasit C, Chamod P, Tiengtip R, Bhamarapravatana K, et al. Possibility of using superoxide dismutase and glutathione peroxidase as endometriosis biomarkers. Int J Womens Health. 2017 Sep 27;9:711–6.
25. Sutrisno S, Miryani I, Dwijayasa PM, Suprobo NR, Wiyasa IWA. Genistein administration increases the level of superoxide dismutase and glutathione peroxidase in the endometriosis mice model: An experimental study. Int J Reprod Biomed [Internet]. 2022 Oct 10 [cited 2023 Mar 26];20(10):873–82. Available from: http://ijrm.ir/article-1-2376-en.html
26. Sutrisno S, Miryani I, Dwijayasa PM, Suprobo NR, Wiyasa IWA. Genistein administration increases the level of superoxide dismutase and glutathione peroxidase in the endometriosis mice model: An experimental study. Int J Reprod Biomed. 2022 Oct 1;20(10):873–82.
27. Sutrisno S, Wulandari RCL, Sulistyowati DWW, Wulandari RF, Wahyuni ES, Yueniwati Y, et al. Effect of genistein on proinflammatory cytokines and estrogen receptor–β in mice model of endometriosis. Asian Pacific Journal of Reproduction. 2015 Jun 1;4(2):96–9.
28. Sutrisno S, Aprina H, Simanungkalit HM, Andriyani A, Barlianto W, Sujuti H, et al. Genistein modulates the estrogen receptor and suppresses angiogenesis and inflammation in the murine model of peritoneal endometriosis. J Tradit Complement Med [Internet]. 2017 Apr 1 [cited 2023 Apr 4];8(2):278–81. Available from: https://pubmed.ncbi.nlm.nih.gov/29736382/
29. Sutrisno S, Mariyani M, Herawati I, Rinata E, Jehanara J, Yueniwati Y, et al. The effects of genistein as antiinflammatory and antiangiogenesis in primary endometriosis cell culture. Asian Pacific Journal of Reproduction. 2014 Dec 1;3(4):299–304.
30. Minutolo F, Macchia M, Katzenellenbogen BS, Katzenellenbogen JA. Estrogen receptor β ligands: recent advances and biomedical applications. Med Res Rev [Internet]. 2011 May [cited 2023 Mar 26];31(3):364–442. Available from: https://pubmed.ncbi.nlm.nih.gov/19967775/
31. Paterni I, Granchi C, Katzenellenbogen JA, Minutolo F. Estrogen receptors alpha (ERα) and beta (ERβ): Subtype-selective ligands and clinical potential. Steroids. 2014 Nov 15;90:13–29.
32. Shao R, Cao S, Wang X, Feng Y, Billig H. The elusive and controversial roles of estrogen and progesterone receptors in human endometriosis. Am

J Transl Res [Internet]. 2014 [cited 2023 Mar 26];6(2):104–13. Available from: www.ajtr.org

33. Nothnick WB, Zhang X. Future targets in endometriosis treatment, targeting the endometriotic implant. Mini Rev Med Chem. 2009;9:324–8.
34. Galle PC. Clinical presentation and diagnosis of endometriosis. Obstet Gynecol Clin North Am. 1989;16:29–42.
35. Cui S, Wienhoefer N, Bilitewski U. Genistein induces morphology change and G2/M cell cycle arrest by inducing p38 MAPK activation in macrophages. Int Immunopharmacol [Internet]. 2014 Jan [cited 2023 Mar 26];18(1):142–50. Available from: https://pubmed.ncbi.nlm.nih.gov/24290959/
36. Jeong JW, Lee HH, Han MH, Kim GY, Kim WJ, Choi YH. Anti-inflammatory effects of genistein via suppression of the toll-like receptor 4-mediated signaling pathway in lipopolysaccharide-stimulated BV2 microglia. Chem Biol Interact [Internet]. 2014 Apr 5 [cited 2023 Mar 26];212(1):30–9. Available from: https://pubmed.ncbi.nlm.nih.gov/24491678/
37. Bayoglu Tekin Y, Guven S, Kirbas A, Kalkan Y, Tumkaya L, Guvendag Guven ES. Is resveratrol a potential substitute for leuprolide acetate in experimental endometriosis? European Journal of Obstetrics and Gynecology and Reproductive Biology [Internet]. 2015 Jan 1 [cited 2023 Mar 26];184:1–6. Available from: http://www.ejog.org/article/S030121151400565X/fulltext