Reduction of VEGF Levels by *Phaleria macrocarpa* Flavonoids in an Endometriosis Mouse *(Mus musculus)* Model

Amina Diarsy[1], Fany Hardiati Amalia[2], Sutrisno[2], Tatit Nurseta[2], Safrina Dewi Ratnaningrum[3]

[1]Magister of Midwifery, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia
[2]Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Brawijaya, Saiful Anwar General Hospital, Malang, Indonesia
[3]Department of Anatomy Histology, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia

*Email correspondence: aminad12@student.ub.ac.id

Track Record Article

Revised: 09 September 2025
Accepted: 11 December 2025
Published: 31 December 2025

How to cite :
Diarsy, A., Amalia, F. H., Sutrisno, Nurseta, T., & Ratnaningrum, S. D. (2025). Reduction of VEGF Levels by Phaleria macrocarpa Flavonoids in an Endometriosis Mouse (*Mus musculus*) Model. *Contagion : Scientific Periodical of Public Health and Coastal Health*, 7(3), 192–202.

Abstract

Endometriosis occurs when endometrial-like cells proliferate at ectopic sites outside the uterus. The advancement of endometriotic lesions is strongly influenced by VEGF, as it stimulates the formation of new blood vessels. In contrast, flavonoids derived from Phaleria macrocarpa extract possess inhibitory effects on both pro-inflammatory signaling molecules and pro-angiogenic pathways. This study investigated the effects of flavonoids from Phaleria macrocarpa extract on VEGF levels in the peritoneal fluid of endometriosis mouse models. This research employed a post-test-only control group experimental design. A total of thirty mice (Mus musculus) were assigned to six groups: a healthy control group, an untreated endometriosis group, and four endometriosis groups receiving isolated flavonoids from Phaleria macrocarpa extract at doses of 3.75, 7.5, 15, and 30 mg/mouse/day (n=5). Peritoneal fluid samples were collected from all groups to examine VEGF levels using ELISA. The results were expressed as mean ± SD and subsequently evaluated using a one-way ANOVA with LSD post-hoc test at a significance level of p-value < 0.05. Flavonoids at the dose of 30 mg/day significantly decreased the VEGF levels compared to the group of endometriosis mouse models (p-value=0.001). Flavonoids decreased VEGF levels as an angiogenic factor in peritoneal fluid, which may play a role in the proliferation of endometriosis tissue.

Keywords: Flavonoid, Phaleria macrocarpa, VEGF, Endometriosis

INTRODUCTION

Patients with endometriosis may experience severe pain, fatigue, depression, anxiety, and infertility, all of which affect their quality of life. Globally, endometriosis occurs in 10% of women and girls of reproductive age. The Age-specific Incidence (ASI) of endometriosis peaks in the 30-34 age group (WHO, 2023; Rowlands et al., 2021). The development of endometriotic tissue is associated with interactions involving the endocrine, immunological, pro-inflammatory, and pro-angiogenic systems. The pathophysiology and etiology of endometriosis remain uncertain; however, several theories have been proposed to explain the growth of endometrial tissue in abnormal locations, which involve processes such as backward menstrual flow, metaplastic alteration of coelomic tissue, and migration through lymphatic or circulatory routes (Zondervan et al., 2018; Zondervan et al., 2020). Endometriosis is also increasingly recognized as a disease with systemic inflammatory, hormonal, and angiogenic

involvement, driven by estrogen and immune cell signaling (Chung & Han, 2022; Li et al., 2021)**.**

Vascular Endothelial Growth Factor (VEGF) is generated and secreted by mesothelial cells, which are the predominant cell type in the peritoneum. During transdifferentiation and tumorigenesis, mesothelial cells secrete VEGF into the extracellular space (Young et al., 2015). VEGF serves as a key factor in the development of endometriosis by facilitating its ability to promote angiogenesis, which supports the growth and survival of ectopic endometrial tissue. Stimulation of endometrial cells and the endometriotic environment activates intracellular signaling pathways that enhance VEGF expression. The transcription regulator, nuclear factor-kappa B (NF-κB) functions as a mediator of inflammatory signaling cascades and increases VEGF expression, thus promoting angiogenesis in endometriosis tissue (Bo & Wang, 2024; Yoshida et al., 2013; Lousse et al., 2008). In addition to these pathways, oxidative stress has also been implicated as a major upstream regulator of VEGF expression. Oxidative stress, as shown by excessive levels of reactive oxygen species (ROS), further contributes to this process by regulating NF-κB activation in immune cells (Nanda et al., 2020)**.** Activated macrophages exposed to inflammatory stimuli also trigger NF-κB signaling, which induces the expression of pro-angiogenic genes (Khodarahmian et al., 2021).

Due to the common side effects associated with endometriosis treatments, herbal therapies are increasingly being used. *Phaleria macrocarpa*, also known as "mahkota dewa", is a plant native to Indonesia. Extracts of *P. macrocarpa* have shown anti-inflammatory, antioxidant, antibacterial, antifungal, anticancer, antidiabetic, and antihyperlipidemic properties. It contains flavonoids, alkaloids, terpenoids, polyphenols, saponins, resins, and lignans (Altaf et al., 2013). Flavonoids from mahkota dewa fruit can reduce lesion growth, proliferation, apoptosis, and angiogenesis. These flavonoids are beneficial in managing endometrial proliferation (Maharani et al., 2021; Mohamed Mahzir et al., 2018; Comalada et al., 2006). This research seeks to evaluate the administration of flavonoid fractions originating from *P. macrocarpa* extract influences on decreasing VEGF amounts in endometriosis-induced mice.

METHODS

Animals

Healthy female BALB/C mice (*Mus musculus*) aged 12 weeks, with body weights ranging from 20 to 30 grams. All thirty animals were subsequently divided into six distinct groups using a Microsoft Excel random number sequence, including a control group, an

endometriosis group, and an endometriosis group that received flavonoid derived from *P. macrocarpa* extract given at a dose of 3.75, 7.5, 15, and 30 mg/mouse/day. Each mouse was assigned a unique identification number. The group allocation corresponding to each mouse ID was placed in sequentially numbered, opaque, sealed envelopes, which were only opened immediately prior to the administration of the first treatment dose. Flavonoid isolates were provided through oral dosing by probe over a fourteen-day period. These dosing regimens were formulated with reference to previous research that reported effective ranges of flavonoids in mice and confirmed their safety without toxicity (Maharani et al., 2021).

Preparation of extract

In this study, a powdered flavonoid preparation extracted from *P. macrocarpa* was used, based on a previous study (Maharani et al., 2021). Fine powder of *P. macrocarpa* (voucher specimen no. B/430/UNI1.1.8.4/TA.00.01/2020 verified by a curator at the Department of Biology, Faculty of Mathematics and Natural Sciences, Universitas Syiah Kuala, Banda Aceh) was extracted using 96% ethanol through maceration. The resulting filtrate was subsequently separated and fractionated with n-hexane and n-butanol to enrich the flavonoid content. The solvent fractions were evaporated under controlled temperature conditions to obtain a concentrated extract, which was further dried to yield flavonoid powder. The composition of the extract was confirmed by LC-HRMS analysis. The flavonoid extracted from *P. macrocarpa* was dissolved in Phosphate-Buffered Saline (PBS) before being administered to the mouse.

Endometriosis induction and peritoneal fluid isolation

The induction to establish the endometriosis mouse model and isolation of peritoneal samples were conducted in accordance with the methods described in a prior investigation (Sutrisno et al., 2019). Female mice that fulfilled the criteria were acclimatized for 7 days before induction. On day 1, mice in the endometriosis group and treatment groups received intramuscular cyclosporin A at a dose of 0.2 mL to induce immunodeficiency, followed by intraperitoneal injection of adenomyosis tissue supernatant at 0.1 mL. Ethinyl estradiol at a dose of 0.1 mL was administered intramuscularly on days 1 and 5 to support lesion development. On day 15, a subset of mice was sacrificed to confirm endometriotic lesions, peritoneal hypervascularization, and estrogen receptor β (ERβ) expression by macroscopic evaluation and IHC.

Mice were euthanized by chloroform inhalation, and the abdominal cavity was opened through a midline incision. Peritoneal fluid was obtained by PBS injection and aspiration, while

peritoneal tissue was excised, washed with PBS, and preserved in 10% alcohol. Carcasses were buried to prevent environmental contamination.

VEGF measurement

Prior to biomarker assessment, the peritoneal fluid samples were preserved at -20°C. The quantification of VEGF levels was conducted using the Enzyme-Linked Immunosorbent Assay (ELISA) from the Mouse VEGF ELISA kit (BT Lab, China, catalog number E1184Mo).

Data Analysis

The dataset was first evaluated for normality using the Shapiro-Wilk test and homogeneity through Levene's test, with the decision criterion determined by the p-value ($p>0.05$). To compare differences among the treatment groups, a one-way Analysis of Variance (ANOVA) was applied, followed by a post hoc LSD test ($p<0.05$). This research obtained ethical authorization from the Health Research Ethics Committee of the Faculty of Medicine of Brawijaya University, number 37/EC/KEPK-S2/02/2025.

RESULT

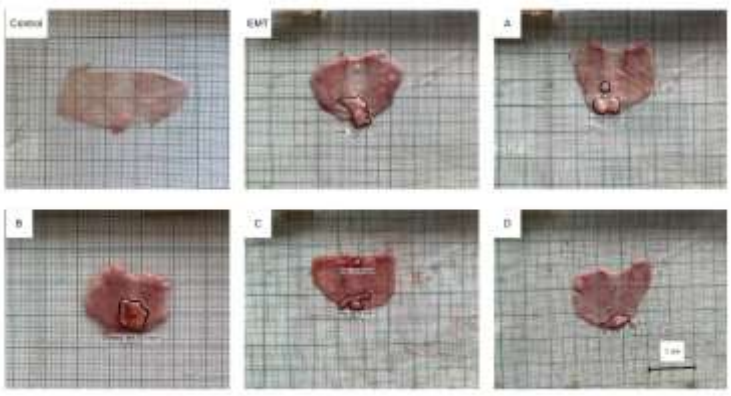

Figure 1. Endometriosis lesion

Control: without treatment; EMT: endometriosis mouse model without treatment; A: endometriosis mouse model given P. macrocarpa flavonoid extract at a dose of 3.75 mg/mouse/day; B: endometriosis mouse model given P. macrocarpa flavonoid extract at a dose of 7.5 mg/mouse/day; C: endometriosis mouse model given P. macrocarpa flavonoid extract at a dose of 15 mg/mouse/day; D: endometriosis mouse model given P. macrocarpa flavonoid extract at a dose of 30 mg/mouse/day. The black outline indicates the presence of endometriosis lesions.

The figure above shows aberrant endometrial deposits arising throughout the peritoneal cavity of each group. The control group mouse showed no visible lesions, while the EMT group mouse showed the most extensive lesions. The treatment groups showed lesions of varying extent according to each treatment.

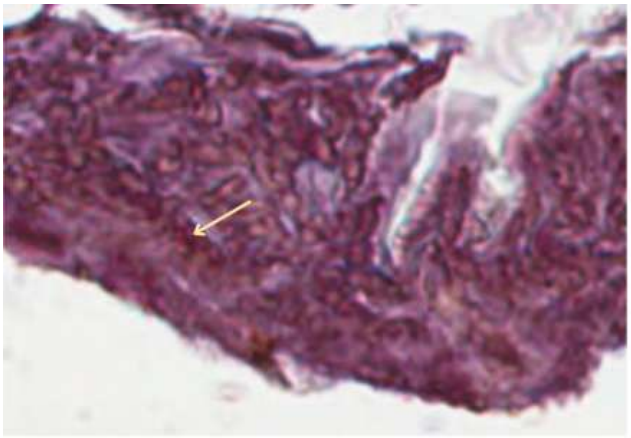

Figure 2. Immunohistochemistry of ERβ expression

The image of peritoneal tissue in endometriosis lesions shows ERβ expression in the cytoplasm of stromal cells, indicated by brown staining and marked with an arrow symbol. The observation was performed using ImageScope software from Aperio CS2 slide scanning results at 400x magnification.

Figure 2 shows ERβ expression in the cytoplasm of stromal cells in the peritoneal tissue of a mouse as a confirmation of the successful establishment of the mouse model of endometriosis that was randomly selected from the EMT group.

Table 1. Normality and homogeneity test

Groups	N	p-*value* *Shapiro-Wilk*	Data distribution	p-*value* Levene test	Data homogeneity
Control	5	0.928	Normal	0.162	Homogenous
Endometriosis	5	0.955	Normal		
3.75 mg/mouse/day	5	0.847	Normal		
7.5 mg/mouse/day	5	0.154	Normal		
15 mg/mouse/day	5	0.453	Normal		
30 mg/mouse/day	5	0.427	Normal		

Based on the normality test using Shapiro-Wilk, the VEGF level data in each group showed a p>0.05, revealing that the dataset conformed to the expected parametric assumptions. The homogeneity of variance test using Levene's test also resulted in a p-value of 0.162, indicating the values obtained were homogenous. These results confirm that the assumptions for parametric testing were satisfied; therefore, a one-way ANOVA test was performed afterward.

Table 2. One-way ANOVA

Groups	N	Mean±SD	p-*value*
Control	5	0.264±0.0384ab	0.004
Endometriosis	5	0.302±0.0258a	
3.75 mg/mouse/day	5	0.226±0.0602bc	
7.5 mg/mouse/day	5	0.290±0.0234a	
15 mg/mouse/day	5	0.250±0.0187ac	
30 mg/mouse/day	5	0.216±0.0270d	

The result showed that the endometriosis mouse model without administration of flavonoid from *P. macrocarpa* had the highest mean VEGF level compared to the other groups

(0.302±0.0258 ng/L). All treatment cohorts reflected a measurable reduction in mean VEGF levels relative to the endometriosis group. One-way ANOVA analysis revealed a statistically robust divergence in VEGF levels among the groups receiving flavonoid from *P. macrocarpa* (p-*value*=0.004).

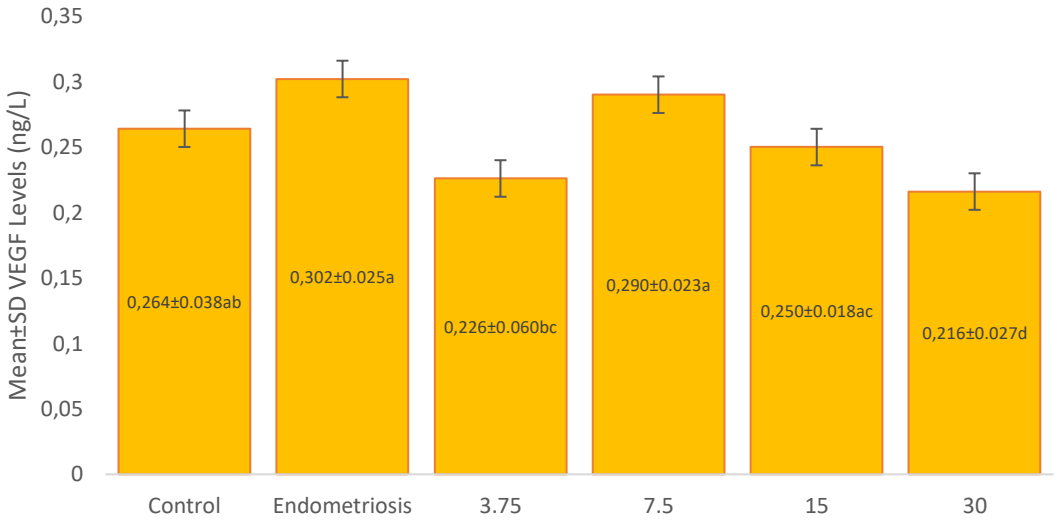

Figure 3. VEGF levels in peritoneal fluid

Control is a healthy group, an endometriosis group without treatment, and the endometriosis groups are administered with flavonoid of P. macrocarpa (3.75, 7.5, 15, and 30 mg/mouse/day). p-value <0.05 is significantly different. If there are different letter notations, it denotes a statistically significant difference.

The administration of *P. macrocarpa* flavonoid extract demonstrated a dose-dependent reduction in VEGF levels, although the pattern was not perfectly linear, with a slight increase at doses of 7.5 mg/mouse/day before decreasing at higher doses. The LSD post hoc analysis revealed that the endometriosis group had significantly higher VEGF levels compared to the control and treatment groups at 3.75, 15, and 30 mg/mouse/day ($p<0.05$), but not different from the dose of 7.5 mg/mouse/day. Based on the analysis result, administration of flavonoid at doses of 30 mg/mouse/day in the group showed results most similar to mean±SD, which is 0.216±0.027 ng/L, and this was not significantly different compared to the control group.

DISCUSSION

The findings of this study indicate that the highest VEGF levels were observed in the endometriosis mouse model that did not receive the flavonoid of *P. macrocarpa* extract. The elevation in VEGF levels observed in this experiment aligns with previous research, which reported that the peritoneal environment in endometriosis is characterized by activation that ultimately enhances VEGF expression and promotes neovascularization. Such a process not

only enables the persistence of endometriotic lesions but also contributes to their progression toward a more invasive phenotype (Zondervan et al., 2020; Liang et al., 2018).

All treatment clusters demonstrated a reduction in mean VEGF levels compared to the endometriosis group. One-way ANOVA analysis revealed a statistically significant difference in VEGF concentration among intervention sets with flavonoid of *P. macrocarpa* (p-value=0.004). These findings are consistent with in vitro studies using RL95-2 cell cultures, which found that the methanol extract of *P. macrocarpa* reduced VEGF levels through inhibition of HIF-1α transcriptional activity (Tandrasasmita et al., 2015). Similarly, an earlier examination reported that administration of flavonoids from *P. macrocarpa* extract significantly decreased VEGF levels (Sutrisno et al., 2023). In line with these results, a scientific inquiry by Sutrisno & Maharani (2024) showed that genistein, a flavonoid compound, was effective in reducing VEGF expression in an endometriosis mouse model with an optimal dose of 3.25 mg. Another flavonoid substance, luteolin, was also shown to induce apoptosis of endometriosis cells and modulate macrophages that can secrete VEGF (Woo et al., 2021).

As phytoestrogens, flavonoids possess a core structural element essential for estrogenic activity (Ilhan et al., 2019). Flavonoids are known to inhibit various biological processes, including angiogenesis, cell proliferation, inflammation, oxidative stress, and microbial activity (Rossi et al., 2013; Mustafida et al., 2014; Maharani et al., 2021; Xi et al., 2022). One of the flavonoid compounds, genistein, has demonstrated anti-inflammatory properties by reducing TNF-α levels and inhibiting NF-κB activity, thereby suppressing the expression of genes involved in endometriosis progression via angiogenic pathways. Genistein inhibits angiogenesis by reducing the accumulation of HIF-1α, a transcriptional factor critical in VEGF regulation (Sutrisno et al., 2015; Hämäläinen et al., 2007). Furthermore, flavonoids can suppress NF-κB secretion and significantly downregulate VEGF expression at both mRNA and protein levels (Mirossay et al., 2018).

VEGF levels exhibited a fluctuating pattern, indicating that their response to *P. macrocarpa* flavonoid extract is not strictly dose-dependent. This may reflect the biphasic effects of flavonoids on angiogenic pathways and their Selective Estrogen Receptor Modulators (SERMs) properties, which can stimulate or inhibit estrogen receptors depending on tissue and dose (Xi et al., 2022; Huang et al., 2010). Flavonoids may modulate VEGF via antioxidant activity by reducing ROS and inhibiting HIF-1α, or in the case of kaempferol and quercetin, by activating VEGF signaling through VEGFR2 (Wei & Zhang, 2024; Hu et al., 2020).

This study utilized *P. macrocarpa* flavonoid extract as an active compound, making it unclear which specific flavonoid subgroups were primarily responsible for the observed reductions in VEGF levels. The potential biphasic effect of the extract on VEGF in the peritoneal fluid of the endometriosis mouse model was not explored. Therefore, further studies are needed to identify the specific flavonoid subgroups responsible for these effects and to investigate the potential dose-dependent biphasic responses that regulate VEGF expression in endometriosis.

CONCLUSION

Flavonoid of *P. macrocarpa* at a dose of 30 mg/mouse/day was the most effective in decreasing the VEGF levels as an angiogenesis factor in the peritoneal fluids that might play a role in the proliferation of endometriotic tissue. Further empirical inquiry is warranted to delineate the flavonoid subclasses implicated in endometriosis progression and to characterize the biphasic modulatory effects of *P. macrocarpa*-derived flavonoid constituents on VEGF amounts in the peritoneal fluid of the endometriosis mouse model.

REFERENCES

Altaf, R., Asmawi, M. Z. Bin, Dewa, A., Sadikun, A., & Umar, M. I. (2013). Phytochemistry and medicinal properties of Phaleria macrocarpa (Scheff.) Boerl. extracts. *Pharmacognosy Reviews*, *7*(13), 73–80. https://doi.org/10.4103/0973-7847.112853

Bo, C., & Wang, Y. (2024). Angiogenesis signaling in endometriosis: Molecules, diagnosis and treatment (Review). *Molecular Medicine Reports*, *29*(3), 1–14. https://doi.org/10.3892/mmr.2024.13167

Chung, M. S., & Han, S. J. (2022). Endometriosis-Associated Angiogenesis and Anti-angiogenic Therapy for Endometriosis. *Frontiers in Global Women's Health*, *3*(April), 1–11. https://doi.org/10.3389/fgwh.2022.856316

Comalada, M., Ballester, I., Bailón, E., Sierra, S., Xaus, J., Gálvez, J., Medina, F. S. de, & Zarzuelo, A. (2006). Inhibition of pro-inflammatory markers in primary bone marrow-derived mouse macrophages by naturally occurring flavonoids: Analysis of the structure-activity relationship. *Biochemical Pharmacology*, *72*(8), 1010–1021. https://doi.org/10.1016/j.bcp.2006.07.016

Hämäläinen, M., Nieminen, R., Vuorela, P., Heinonen, M., & Moilanen, E. (2007). Anti-inflammatory effects of flavonoids: Genistein, kaempferol, quercetin, and daidzein inhibit STAT-1 and NF-κB activations, whereas flavone, isorhamnetin, naringenin, and pelargonidin inhibit only NF-κB activation along with their inhibitory effect on i. *Mediators of Inflammation*, *2007*. https://doi.org/10.1155/2007/45673

Hu, W. H., Wang, H. Y., Xia, Y. T., Dai, D. K., Xiong, Q. P., Dong, T. T. X., Duan, R., Chan, G. K. L., Qin, Q. W., & Tsim, K. W. K. (2020). Kaempferol, a Major Flavonoid in Ginkgo Folium, Potentiates Angiogenic Functions in Cultured Endothelial Cells by Binding to Vascular Endothelial Growth Factor. *Frontiers in Pharmacology*, *11*(April), 1–12. https://doi.org/10.3389/fphar.2020.00526

Huang, Z., Fang, F., Wang, J., & Wong, C. W. (2010). Structural activity relationship of

flavonoids with estrogen-related receptor gamma. *FEBS Letters*, *584*(1), 22–26. https://doi.org/10.1016/j.febslet.2009.11.026

Ilhan, M., Ali, Z., Khan, I. A., Taştan, H., & Küpeli Akkol, E. (2019). Bioactivity-guided isolation of flavonoids from Urtica dioica L. and their effect on endometriosis rat model. *Journal of Ethnopharmacology*, *243*(July). https://doi.org/10.1016/j.jep.2019.112100

Khodarahmian, M., Amidi, F., Moini, A., Kashani, L., Salahi, E., Danaii-mehrabad, S., Nashtaei, M. S., Mojtahedi, M. F., Esfandyari, S., & Sobhani, A. (2021). A randomized exploratory trial to assess the effects of resveratrol on VEGF and TNF-α 2 expression in endometriosis women. *Journal of Reproductive Immunology*, *143*(3). https://doi.org/10.1016/j.jri.2020.103248

Li, C., Zhao, H. L., Li, Y. J., Zhang, Y. Y., Liu, H. Y., Feng, F. Z., & Yan, H. (2021). The expression and significance of leukemia inhibitory factor, interleukin-6 and vascular endothelial growth factor in Chinese patients with endometriosis. *Archives of Gynecology and Obstetrics*, *304*(1), 163–170. https://doi.org/10.1007/s00404-021-05980-5

Liang, Y., Xie, H., Wu, J., Liu, D., & Yao, S. (2018). Villainous role of estrogen in macrophage-nerve interaction in endometriosis. *Reproductive Biology and Endocrinology*, *16*(1), 1–11. https://doi.org/10.1186/s12958-018-0441-z

Lousse, J. C., Van Langendonckt, A., González-Ramos, R., Defrère, S., Renkin, E., & Donnez, J. (2008). Increased activation of nuclear factor-kappa B (NF-κB) in isolated peritoneal macrophages of patients with endometriosis. *Fertility and Sterility*, *90*(1), 217–220. https://doi.org/10.1016/j.fertnstert.2007.06.015

Maharani, M., Lajuna, L., Yuniwati, C., Sabrida, O., & Sutrisno, S. (2021). Phytochemical characteristics from Phaleria macrocarpa and its inhibitory activity on the peritoneal damage of endometriosis. *Journal of Ayurveda and Integrative Medicine*, *12*(2), 229–233. https://doi.org/10.1016/j.jaim.2020.06.002

Mirossay, L., Varinská, L., & Mojžiš, J. (2018). Antiangiogenic effect of flavonoids and chalcones: An update. *International Journal of Molecular Sciences*, *19*(1). https://doi.org/10.3390/ijms19010027

Mohamed Mahzir, K. A., Abd Gani, S. S., Hasanah Zaidan, U., & Halmi, M. I. E. (2018). Development of Phaleria macrocarpa (Scheff.) Boerl Fruits Using Response Surface Methodology Focused on Phenolics, Flavonoids and Antioxidant Properties. *Molecules (Basel, Switzerland)*, *23*(4), 1–22. https://doi.org/10.3390/molecules23040724

Mustafida, R. Y., Munawir, A., & Dewi, R. (2014). Efek Antiangiogenik Ekstrak Etanol Buah MAhkota Dewa (Phaleria macrocarpa (Scheff.) Boerl.) pada Membran Korio Alantois (CAM) Embrio Ayam. *E-Jurnal Pustaka Kesehatan*, *2*(1), 4–8. https://jpk.jurnal.unej.ac.id/index.php/JPK/article/view/587/415

Nanda, A., Thangapandi, K., Banerjee, P., Dutta, M., Wangdi, T., Sharma, P., Chaudhury, K., & Jana, S. K. (2020). Cytokines, angiogenesis, and extracellular matrix degradation are augmented by oxidative stress in endometriosis. *Annals of Laboratory Medicine*, *40*(5), 390–397. https://doi.org/10.3343/alm.2020.40.5.390

Rossi, M., Edefonti, V., Parpinel, M., Lagiou, P., Franchi, M., Ferraroni, M., Decarli, A., Zucchetto, A., Serraino, D., Dal Maso, L., Negri, E., & La Vecchia, C. (2013). Proanthocyanidins and other flavonoids in relation to endometrial cancer risk: A case-control study in Italy. *British Journal of Cancer*, *109*(7), 1914–1920. https://doi.org/10.1038/bjc.2013.447

Rowlands, I. J., Abbott, J. A., Montgomery, G. W., Hockey, R., Rogers, P., & Mishra, G. D. (2021). Prevalence and incidence of endometriosis in Australian women: a data linkage cohort study. *BJOG: An International Journal of Obstetrics and Gynaecology*, *128*(4), 657–665. https://doi.org/10.1111/1471-0528.16447

Sutrisno, S., Andarini, S., Wiyasa, I. W. A., Kulsum, U., Noerhamdani, N., Suyuti, H., & Hendarto, H. (2019). The effect of implant origin differences on peritoneal endometriosis in an endometriosis mouse model. *International Journal of Women's Health and Reproduction Sciences*, *7*(1), 34–40. https://doi.org/10.15296/ijwhr.2019.06

Sutrisno, S., & Maharani, M. (2024). Genistein Ameliorated Vascular Endothelial Growth Factor-A (VEGF-A) and Estrogen Receptor-Alpha (ER- α) in Endometriosis Mice Model, in Vivo and in Silico. *Scientific World Journal*, *2024*. https://doi.org/10.1155/2024/5338212

Sutrisno, S., Noeraini, A. R., Khumairoh, R., Maharani, M., Nurseta, T., Handono, K., Wahyuni, E. S., & Khotimah, H. (2023). *The Effect of Flavonoid Isolates from Extract of Phaleria macrocarpa (Scheff.) boerl on Peritoneal Fluid of Endometriosis Mice*. https://pubs.aip.org/aip/acp/article-abstract/2634/1/020072/2871015/The-effect-of-flavonoid-isolates-from-extract-of?redirectedFrom=fulltext

Sutrisno, S., Wulandari, R. C. L., Sulistyowati, D. W. W., Wulandari, R. F., Wahyuni, E. S., Yueniwati, Y., & Santoso, S. (2015). Effect of genistein on proinflammatory cytokines and estrogen receptor-β in mice model of endometriosis. *Asian Pacific Journal of Reproduction*, *4*(2), 96–99. https://doi.org/10.1016/S2305-0500(15)30003-8

Tandrasasmita, O. M., Sutanto, A. M., Arifin, P. F., & Tjandrawinata, R. R. (2015). Anti-inflammatory, antiangiogenic, and apoptosis-inducing activity of DLBS1442, a bioactive fraction of phaleria macrocarpa, in a RL95-2 cell line as a molecular model of endometriosis. *International Journal of Women's Health*, *7*, 161–169. https://doi.org/10.2147/IJWH.S74552

Wei, Q., & Zhang, Y. H. (2024). Flavonoids with Anti-Angiogenesis Function in Cancer. *Molecules*, *29*(7). https://doi.org/10.3390/molecules29071570

Woo, J. H., Jang, D. S., & Choi, J. H. (2021). Luteolin promotes apoptosis of endometriotic cells and inhibits the alternative activation of endometriosis-associated macrophages. *Biomolecules and Therapeutics*, *29*(6), 678–684. https://doi.org/10.4062/BIOMOLTHER.2021.045

World Health Organization. (2023). *Endometriosis*. https://doi.org/ https://www.who.int/news-room/fact-sheets/detail/endometriosis

Xi, X., Wang, J., Qin, Y., You, Y., Huang, W., & Zhan, J. (2022). The Biphasic Effect of Flavonoids on Oxidative Stress and Cell Proliferation in Breast Cancer Cells. *Antioxidants*, *11*(4). https://doi.org/10.3390/antiox11040622

Yoshida, T., Hashimura, M., Mastumoto, T., Tazo, Y., Inoue, H., Kuwata, T., & Saegusa, M. (2013). Transcriptional upregulation of HIF-1α by NF-κB/p65 and its associations with β-catenin/p300 complexes in endometrial carcinoma cells. *Laboratory Investigation*, *93*(11), 1184–1193. https://doi.org/10.1038/labinvest.2013.111

Young, V. J., Ahmad, S. F., Brown, J. K., Duncan, W. C., & Horne, A. W. (2015). Peritoneal VEGF-A expression is regulated by TGF-β1 through an ID1 pathway in women with endometriosis. *Scientific Reports*, *5*(July), 1–9. https://doi.org/10.1038/srep16859

Zondervan, Krina T., D.Phil., Christian M. Becker, M. D., & and Stacey A. Missmer, S. D. (2020). Endometriosis, Review Article. *The New England Journal of Medicine*, *382*(1244), 56. https://doi.org/10.1056/NEJMra1810764

Zondervan, K. T., Becker, C. M., Koga, K., Missmer, S. A., Taylor, R. N., & Viganò, P. (2018). Endometriosis. *Nature Reviews Disease Primers*, *4*(1). https://doi.org/10.1038/s41572-018-0008-5