Therapeutic Potential of Phaleria Macrocarpa Flavonoid Extract Regulating Rantes in Endometriosis

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Abstract

Endometriosis is a long-term inflammatory disease that affects women of childbearing age. It is caused by endometrial tissue growing in places other than the uterus. RANTES (Regulated on Activation, Normal T Cell Expressed and Secreted) and other important inflammatory mediators are very important in making the inflammatory responses related to this disorder worse. The aim of this study was to evaluate the impact of the ethanolic extract of flavonoids derived from the fruit of Phaleria macrocarpa (Mahkota Dewa) on RANTES levels in a rat model of endometriosis. Thirty female rats were divided into six groups: one healthy control group, one endometriosis control group, and four treatment groups that received doses of 3.75, 7.5, 15, and 30 mg/mice/day of the extract, respectively. The endometriosis model was established by transplanting myometrial and endometrial tissues from a patient with adenomyosis into the peritoneal cavity of immunosuppressed mices. Once the model was set up, the mices got the extract every day for 15 days in a row. We used the ELISA method to measure RANTES levels and histological and immunohistochemical analyses to look at ERβ expression. The results showed that the endometriosis control group (K+) had the highest levels of RANTES (64.05 ± 1.86 pg/mL). Surprisingly, the group that got 30 mg/rat/day (P4) had the biggest drop in RANTES levels (45.95 ± 1.07 pg/mL). Moreover, an upregulation of ERβ expression was observed in mices with induced endometriosis, evidenced by intensified brown staining, succeeded by a dose-dependent reduction, signifying modulation of estrogenic activity. In summary, the administration of the ethanolic flavonoid extract from Phaleria macrocarpa significantly reduced RANTES levels in mices with endometriosis, underscoring its potential as an alternative treatment for managing inflammation related to endometriosis.

Keyword: Keywords: Phaleria macrocarpa, flavonoid, endometriosis, RANTES

INTRODUCTION

Endometriosis is a condition in which tissue that is similar to the endometrium grows in places outside the uterus, such as the ovaries, fallopian tubes, and other parts of the pelvis. The World Health Organization (WHO) says that this condition affects about 10% of women and teenage girls of reproductive age around the world (Vacaroiu et al., 2023; Salinah et al., 2020).

Even though endometriosis is very common, scientists don't fully understand how it starts or how it works. They think it's very complicated. The most widely accepted explanation is retrograde menstruation, which happens when endometrial cells move back into the peritoneal cavity through the fallopian tubes during a woman's period. But not all women with retrograde menstruation go on to develop endometriosis, so it is also thought that genetics and

the environment play a big role in its development (Chiu & Wang, 2024; Gordts et al., 2017; Saunders & Horne, 2021; Smolarz et al., 2021).

Chronic inflammation is a key component of the pathophysiology of endometriosis. RANTES (Regulated on Activation, Normal T Cell Expressed and Secreted) is a key player in this process. When inflammatory triggers like lipopolysaccharides (LPS) turn on Toll-like receptor 4 (TLR4), they start the MyD88 IKK signaling pathway, which turns on NF-κB. This activation makes the CCL5 gene more active and makes more RANTES. This chemokine works by binding to receptors like CCR1, CCR3, and CCR5 on different immune cells, which makes the inflammatory response stronger. In the case of endometriosis, high levels of RANTES help immune cells get to the lesions, which keeps the inflammation going and encourages angiogenesis and fibrogenesis, which help ectopic endometrial tissue grow and stay alive (Brun et al., 2024; Li et al., 2021; Zhang et al., 2021).

The present treatment modalities for endometriosis predominantly consist of hormonal therapy and surgical interventions. These methods can help with symptoms, but they often have bad side effects, high rates of recurrence, and don't work well over time (Petraglia et al., 2024). Consequently, there is a growing demand for safer and more efficacious alternative therapies, especially those derived from medicinal plants. Mahkota dewa, or Phaleria macrocarpa, is a plant that grows naturally in Indonesia. Phaleria macrocarpa extracts have many effects, such as anti-inflammatory, antioxidant, antibacterial, antifungal, anticancer, antidiabetic, and antihyperlipidemic effects. Flavonoids, alkaloids, terpenoids, polyphenols, saponins, resins, and lignans are just some of the bioactive compounds that this plant has a lot of. Flavonoids taken from the fruit of Phaleria macrocarpa have been shown to stop the growth of lesions, cells, and blood vessels, which makes them useful for controlling the growth of the endometrium. Maharani's study demonstrated that administration of an ethanol extract of flavonoids derived from Phaleria macrocarpa resulted in a reduction of inflammatory cytokine levels in an animal model (Ahmad et al., 2023; Maharani et al., 2021). Nonetheless, the precise effect of Phaleria macrocarpa on RANTES concerning endometriosis remains inadequately investigated. So, the goal of this study is to find out how Phaleria macrocarpa affects lowering RANTES levels in mice with an experimental endometriosis model. To do this, it will use a wider range of doses to see how well it works and how the dose affects the response.

METHODS

This research utilized a true experimental design to investigate the impact of ethanolic flavonoid extract from Phaleria macrocarpa on RANTES levels in a murine model of endometriosis. A curator at the Department of Biology, Faculty of Mathematics and Natural Sciences, Universitas Syiah Kuala, Banda Aceh, confirmed that the flavonoid extract came from plants in Langsa City, Aceh. The voucher specimen number is B/430/UNI1.1.8.4/TA.00.01/2020. Thirty liters of 96% ethanol were used to macerate 2,500 grams of Phaleria macrocarpa powder. The mixture was stirred for about 30 minutes to make sure it was well mixed, and then it was left to sit for five nights to let the sediment settle. We then used a Büchner funnel to collect the filtrate. Thirty female BALB/c mice, aged 6 to 8 weeks and weighing between 20 and 30 grams, were divided into six groups: a healthy control group, an endometriosis group, and four intervention groups that received different amounts of the extract (I1:3.75, I2:7.5, I3:15, and I4:30 mg/mice/day). Endometriosis was induced by transplanting myometrial and endometrial tissues from adenomyosis patients into the peritoneal cavity of immunosuppressed mice via cyclosporin A. After a 15-day treatment with the extract, RANTES levels were assessed in peritoneal fluid utilizing the ELISA technique. One-way ANOVA was used to compare RANTES levels across different groups, and post hoc Tukey tests were used to find significant differences between the treatment groups. The Health Research Ethics Committee (No. 130/EC/KEPK-S2/05/2025) gave this study ethical approval.

RESULTS

1. The characteristics of endometriosis

The characteristics of endometriosis in the mouse model were assessed through direct examination of the peritoneal conditions on day 15. In this study, mice in the endometriosis model group displayed hypervascularization and distinct lesions in the peritoneal region, indicating pathological changes related to the condition. In contrast, the healthy control mice showed no evidence of hypervascularization or lesions in the peritoneum, clearly highlighting the differences between the two groups, as shown in Figure 1 and Figure 2.

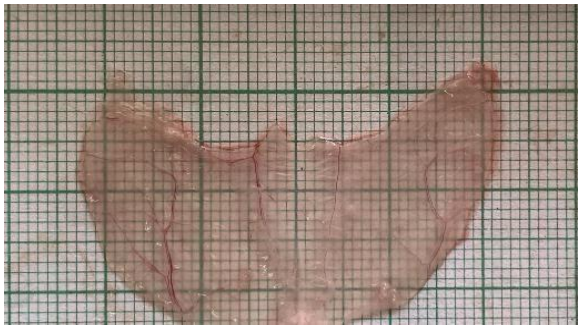

Figure 1. Peritoneal Tissue of Endometriosis Model Mice Control Group (Healthy Mice)

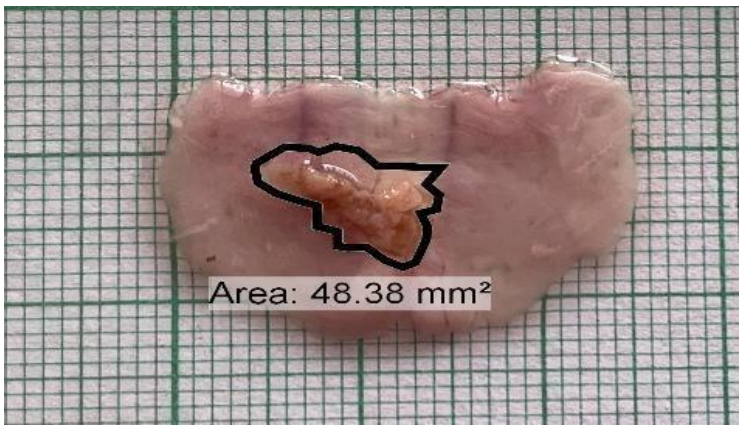

Figure 2. Peritoneal Tissue of Endometriosis Model Mice Control Group (Endometriosis Mice)

At the molecular level, immunohistochemical analysis was performed to evaluate the presence and expression levels of estrogen receptor beta (ERβ) in the endometriotic lesions, as shown in Figure 3 and Figure 4

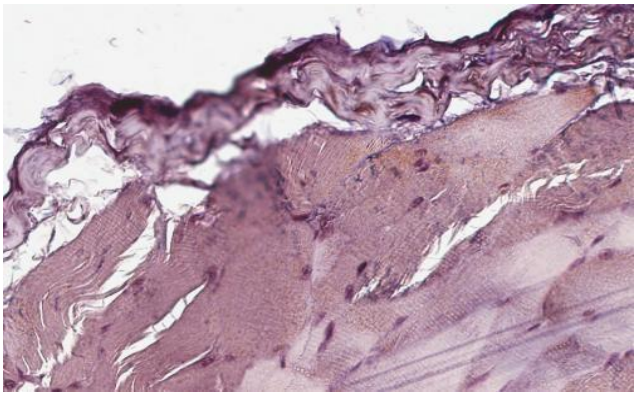

Figure 3. Expression of ERβ in Immunohistochemical Analysis (Healthy Mice)

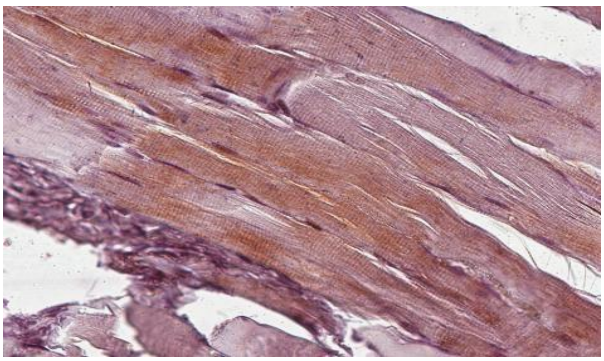

Figure 4. Expression of ERβ in Immunohistochemical Analysis (Endometriosis Mice)

In the endometriosis mouse model, treatment with the ethanol extract of flavonoids from Phaleria macrocarpa fruit was initiated on day 15, using different dosage variations. The P1 group of endometriosis-induced mice received the flavonoid ethanol extract at a dose of 3.75 mg/mouse/day, the P2 group received 7.5 mg/mouse/day, the P3 group received 15 mg/mouse/day, and the P4 group received 30 mg/mouse/day. On day 30, the mice were terminated to evaluate the effects of the flavonoid ethanol extract through ELISA-based measurement of biomarker levels and immunohistochemical examination to assess the expression of estrogen receptor beta. The surgical outcomes and immunohistochemical findings are presented in the figure 5.

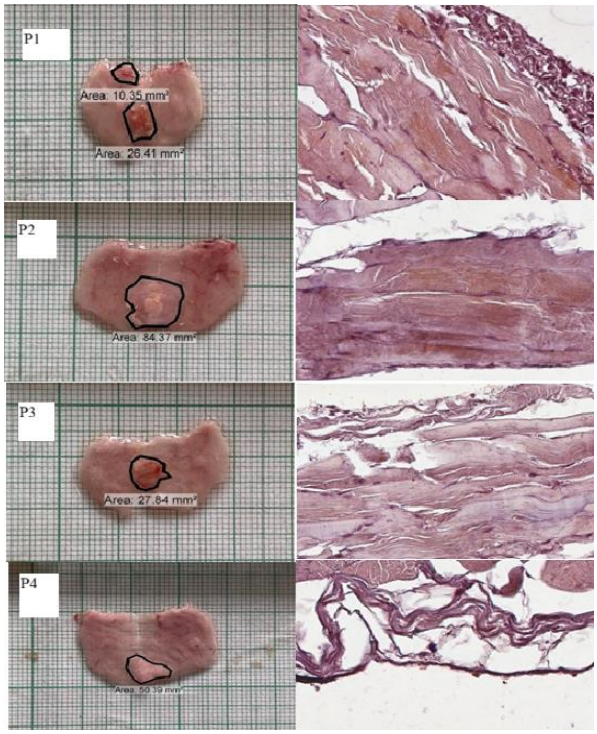

Figure 5. Peritoneal Tissue of Endometriosis Model Mice in the Treatment Groups and ERβ Expression Profile Based on Immunohistochemical Analysis

2. Level Measurement Results of Regulated On Activation, Normal T Expressed And Secreted (RANTES)

Table 1. Levels of RANTES

Group	N	Min	Max	Mean ±SD (pg/L)
Control	5	52.00	57.20	**54.88±1.85**
Endometriosis	5	61.00	66.30	**64.05±1.86**
P1	5	48.00	51.00	**50.00±1.12**
P2	5	47.00	49.10	**48.00±0.87**
P3	5	50.00	51.90	**51.17±0.63**
P4	5	44.00	47.00	**45.95±1.07**

Table 2. Assumption Testing for Data RANTES Levels

Group	P – Value Shapiro Wilk	Data Distribution	P – Value of Levene test	Data Homogenity
Control	0.941	Normal		
Endometriosis	0.756	Normal		
P1	0.265	Normal		
P2	0.447	Normal	0.250	Homogeneous
P3	0.794	Normal		
P4	0.255	Normal		

Table 3. Results of ANOVA RANTES Levels

Group	N	Mean ±SD RaANTES Levels	P- Value
Control	5	54.88±1.85	0.00
Endometriosis	5	64.05±1.86	
P1	5	50.00±1.12	
P2	5	48.00±0.87	
P3	5	51.17±0.63	
P4	5	45.95±1.07	

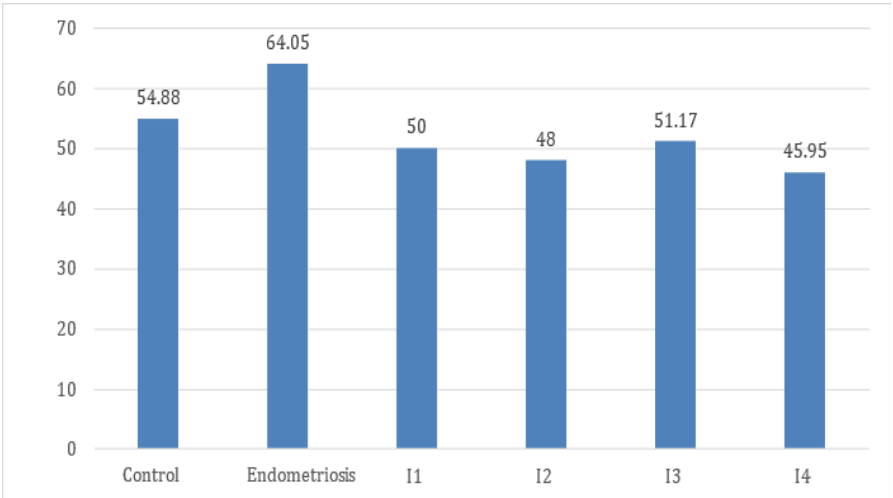

Figure 6. Bar Chart of RANTES Levels in the Control, Endometriosis, and Phaleria macrocarpa Flavonoid Extract Treatment Groups

Table 4. Results of the Tukey HSD Post Hoc Test for RANTES Levels

	Control	Endometriosis	P1	P2	P3	44
Control		0,000	0,000	0,000	0,000	0,000
Endometriosis	0,000		0,000	0,000	0,000	0,000
P1	0,000	0,000		0,123	0,648	0,000
P2	0,000	0,000	0,123		0,003	0,107
P3	0,000	0,000	0,648	0,003		0,000
P3	0,000	0,000	0,000	0,107	0,000	

DISCUSSION

The increased RANTES levels in the K+ group suggest that endometriosis induces a significant inflammatory response. The results show that giving the ethanol extract of flavonoids from Phaleria macrocarpa fruit to mice with endometriosis significantly lowered RANTES levels compared to the positive control (K+) group, which did not receive any treatment (p-value = 0.000). The K+ group had the most RANTES, with an average of 64.05 ± 1.86 pg/mL. The P4 group, which got 30 mg/mouse/day, had the least, with an average of 45.95 ± 1.07 pg/mL. This decrease in RANTES levels indicates that the flavonoids obtained from Phaleria macrocarpa demonstrate significant anti-inflammatory effects. Flavonoids are acknowledged as bioactive substances that exhibit anti-inflammatory properties via multiple biological pathways. One of their main jobs is to stop pro-inflammatory enzymes like cyclooxygenase (COX) and lipoxygenase (Abd Gani et al., 2023; Maharani & Sutrisno, 2022; Sutrisno et al., 2018). Flavonoids exhibit their effects by downregulating pro-inflammatory cytokine expression and inhibiting the NF-κB transcriptional pathway, essential for regulating inflammatory gene expression. This mechanism leads to fewer endometriotic cells growing and more of them dying by changing proteins like Bax (which causes cells to die) and Bcl-2/Bcl-XL (which stops cells from dying) (Annissa Febriani et al., 2022; Febriani et al., 2022; Kusmardi et al., 2021). NF-κB is a key regulator of RANTES expression. When NF-κB is activated, it makes more RANTES, which makes the inflammatory response stronger. In accordance with the action mechanism of flavonoids that inhibit the NF-κB transcriptional pathway, the administration of the ethanol extract of Phaleria macrocarpa flavonoids can indirectly suppress or reduce RANTES levels in a mouse model of endometriosis (Brun et al., 2024; Maharani et al., 2021; Zhang et al., 2021).

The Post Hoc Tukey test results indicated that the majority of group comparisons produced p-values < 0.05, signifying statistically significant differences in RANTES levels. These results indicate that the treatments given to each group, especially the Phaleria macrocarpa flavonoid extract, were able to change how the endometriosis mouse model

responded to inflammation. The positive control (K+) group consistently exhibited significant differences in comparison to all other groups. The p-value of 0.000 observed in nearly all comparisons confirms that endometriosis, in the absence of therapeutic intervention, results in the highest and markedly elevated RANTES levels relative to the treatment groups. This finding reinforces the understanding that endometriosis triggers significant immune activation and inflammation, primarily through the elevated expression of pro-inflammatory chemokines like RANTES, which are essential for recruiting T cells, macrophages, and other inflammatory cells to ectopic tissues. In the treatment groups (P1–P4), responses were contingent upon the dosages of the flavonoid extract administered. The P4 group, which got the most of the drug, was very different from the K+ group and had the lowest levels of RANTES, which shows a strong anti-inflammatory effect. It is interesting that comparing the treatment groups, like P1 and P2 or P2 and P3, did not show any big differences. This suggests a possible dose-effect threshold, indicating that augmenting the dosage does not consistently yield proportional anti-inflammatory advantages. This phenomenon frequently occurs with natural bioactive compounds that may attain pharmacodynamic saturation points. Additionally, the flavonoids present in the Phaleria macrocarpa extract may function as Selective Estrogen Receptor Modulators (SERMs), acting as either agonists or antagonists of estrogen receptors, contingent upon the tissue context and dosage administered (Polari et al., 2018). Flavonoids are similar in structure to estradiol, which lets them bind to ERα and ERβ receptors. In silico studies have shown that some flavonoid derivatives can bind to ER-α with affinities similar to those of tamoxifen. Flavonoids can change how estrogen-responsive genes are transcribed by binding to them. This includes genes that are part of inflammatory pathways, like NF-kB, which SERMs are known to stop from being activated in immune cells. Flavonoids may demonstrate mild agonistic effects on estrogen receptors at low doses, whereas at elevated doses, they can function as antagonists, a phenomenon referred to as a biphasic response. This variability, along with the differences in how ERα and ERβ are expressed in endometriotic tissues and how co-regulators (co-activators and co-repressors) are distributed, can lead to changes in inflammatory responses, like the different levels of RANTES seen in different treatment groups. Furthermore, the interaction between flavonoids and other signaling pathways (PI3K/Akt, MAPK) may augment or alter their anti-inflammatory effects, contingent upon particular cellular contexts. These factors bolster the notion that the disparate reductions in RANTES observed following the administration of the flavonoid extract signify the complex and context-sensitive mechanisms that govern SERM activity (Arba et al., n.d.; Dinata et al., 2025; Ikhtiarudin et al., 2022; Polari et al., 2018).

The diverse effects of flavonoids are regarded as a biological consequence of the intricate and context-sensitive mechanisms linked to SERM activity. The Repeated Tissue Injury and Repair (ReTIAR) theory elucidates the variations in RANTES levels identified in this study. The ReTIAR model posits that endometriotic lesions undergo persistent injury due to cyclic bleeding, which triggers localized inflammatory responses and activates repair mechanisms. These include the conversion of fibroblasts into myofibroblasts and the process of epithelial–mesenchymal transition (EMT) through the TGF-β/Smad signaling pathway (Habiba et al., 2023). These repeated injuries cause immune cells, like macrophages and platelets, to become active. These cells then release cytokines and chemokines, such as RANTES (CCL5), to help bring more immune cells to the site of the lesions. Because ReTIAR is a dynamic process with stages of acute injury, resolution, and remodeling, the levels of inflammatory mediators like RANTES are greatly affected by when the sample is taken in relation to the stage of the injury cycle (Gordts et al., 2017; Guo, 2020; Habiba et al., 2023). The differences in RANTES levels between the groups, even when they got the same amount of flavonoids, could mean that the flavonoids had an effect on the ReTIAR phase at the time the samples were taken. Moreover, localized platelet aggregation and immune cell activation in recurrent lesions can augment the expression of TGF-β and α-smooth muscle actin (α-SMA). This continuous process leads to fibrosis and smooth muscle metaplasia over several cycles, resulting in a microenvironment that is very pro-inflammatory and profibrotic (Liu et al., 2016; Zhang et al., 2021). In this context, the administered flavonoids may modulate the ReTIAR process by diminishing certain inflammatory mediators during the acute phase; however, their efficacy may diminish or evolve depending on the phase of lesion injury and repair. So, the changing levels of RANTES that were seen may be a sign of the complex relationship between flavonoids and the changing nature of the ReTIAR mechanism.

CONCLUSIONS

The findings of this study demonstrate that the administration of Phaleria macrocarpa flavonoid extract markedly reduced RANTES levels in mice with an endometriosis model, particularly at the maximum dosage of 30 mg/mouse/day. These results confirm that flavonoids have strong anti-inflammatory effects by changing the NF-κB signaling pathway and lowering the production of pro-inflammatory chemokines. The observed fluctuations in RANTES levels underscore the complex interplay between SERM-like flavonoid actions and the dynamic ReTIAR processes occurring in endometriotic lesions. Clinically, these insights establish the foundation for the prospective development of Phaleria macrocarpa as a herbal adjuvant

therapy intended to mitigate chronic inflammation in endometriosis. Because RANTES is involved in pain, lesion progression, and fibrosis, lowering this biomarker may lead to the development of safer and more affordable treatments for people with endometriosis.

More research is needed to find out how the extract affects important clinical factors like pain relief, lesion size, fibrosis progression, and long-term safety before these findings can be used in real life. Before this extract can be suggested as a treatment option, pharmacokinetic studies, the finding of the best doses, and well-planned clinical trials are all very important. Consequently, this research establishes a solid foundation for the advancement of novel flavonoid-based therapeutic strategies in the management of endometriosis.

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