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Original Article

Impact of Ethanol Extract of Basil Leaves (Ocimum basilicum L.) on Mast Cell Reduction and Prostaglandin E2 Levels in Female Mice as a Model for Endometriosis Development

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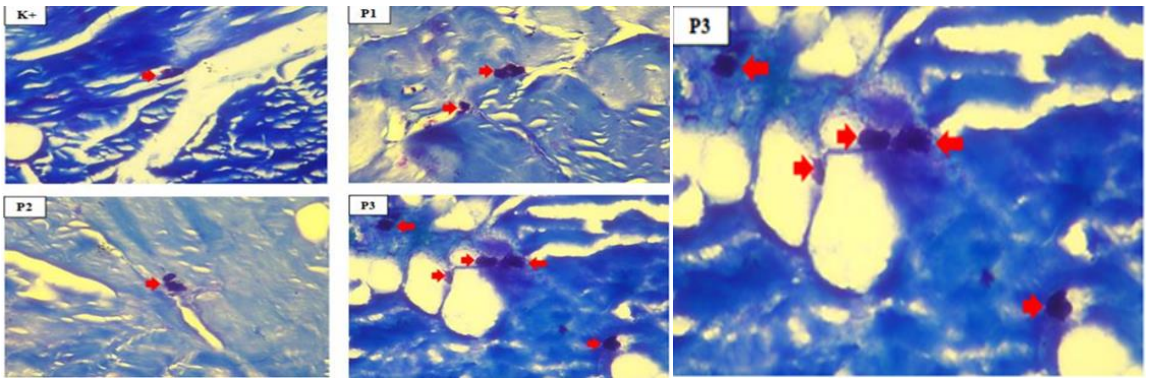
ABSTRACT

Endometriosis, a painful inflammatory condition, arises from the growth of endometrial tissue beyond the uterus. The anti-inflammatory properties of basil (Ocimum basilicum L.) suggest its potential as a treatment for endometriosis. This study aimed to examine how basil ethanol extract affects mast cells and prostaglandin E2 (PGE2) levels in endometriosis. To conduct the study, 28 female mice were divided into four groups. One group served as the untreated control, while the remaining three groups were treated with varying doses of ethanol extract from basil leaves for 14 days. On the 15th day, both endometriosis lesions and serum were collected and subjected to analysis. The group treated with basil ethanol extract exhibited a significant reduction in mast cell count when compared to the control group. However, there was no notable difference in PGE2 levels between the intervention and control groups. Therefore, the administration of ethanol extract of basil leaves has the potential to reduce mast cell numbers, but it does not significantly affect PGE2 levels. This study suggests that basil may have potential as an alternative treatment for endometriosis, but further research is needed to investigate its full potential.

GRAPHICAL ABSTRACT



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Introduction

Endometriosis is a gynecological condition characterized by the abnormal growth and dysfunction of endometrial glands, stroma, or tissue outside the uterus. This benign and estrogen-dependent disease also involves inflammatory processes, sometimes accompanied by reactive fibrosis and extrauterine muscle metaplasia [1].

Endometriosis affects 6-10% of women of childbearing age with a prevalence rate of 176-190 million women worldwide [2, 3].

Women with endometriosis often experience painful symptoms such as dysuria, dyschezia, dyspareunia, and dysmenorrhea to infertility, but endometriosis can be asymptomatic [4].

78.7% of women with endometriosis experience secondary dysmenorrhea, namely pain or cramps before or during menstruation. This symptom is one of the causes of late diagnosis [5]. Dysmenorrhea can have an impact on aspects of life including physical, psychological, sexual relations, social, economic, and reproductive functions [6].

Women with endometriosis will experience an increase in local estrogen production [7]. Estrogen production is due to the activity of prostaglandin E2 (PGE2) where the cyclooxygenase (COX)-2 enzyme induces its production [8].

Increased production of PGE2 will induce local estrogen synthesis and cause inflammation resulting in pain. Expression of COX-2 and PGE2 production can be increased in the uterus and endometriosis tissue because they are stimulated by PGE2 (autocrine action), IL-1β, VEGF, and estradiol (via the estrogen receptor), so that this complex mechanism maintains high levels of PGE2 production in endometriosis tissue [9]. Mast cells and degranulated mast cells will experience an increase in endometriosis lesions [10].

Medicinal plants and botanical products have obtained popularity in recent years as a method of complementary and alternative medicine for some gynecological disorders, such as endometriosis.

Treatment using herbal products has the advantage of being natural, comfortable, affordable, and minimal side effects, especially not interfering with ovulation [11, 12].

Basil (*Ocimum basilicum* L.) is a widely utilized culinary herb and traditional medicinal plant in Italy and Southeast Asia [13]. *Ocimum basilicum* L. has been shown to be beneficial as anti-proliferative, anti-inflammatory, anti-angiogenic, anti-microbial anti-oxidant, and immunomodulatory activity [14].

Basil leaves comprise flavonoids like quercetin, isoquercetrin, kaempferol, and rutin, as well as glycosides such as esculin and syringin which are responsible for the anti-inflammatory activity. The anti-inflammatory activity of basil leaf extract can be through various mechanisms, among which the first is through the inhibition of arachidonic acid through the lipoxygenase (LOX) and COX pathways [15], the second mechanism is influencing TLR-NF-KB signaling [16], and the third mechanism inhibits COX-2 activity and PGE2 production [17].

Given the beneficial anti-inflammatory properties of basil, it holds promise in complementary and alternative medicine for endometriosis. As such, this study seeks to assess the impact of an ethanol extract of basil leaves on PGE2 levels and mast cell counts in female mice as an experimental model.

Materials and Methods

Ethics approval

This research is an experimental study on female mice and has obtained ethical approval from the Animal Ethics Commission, Faculty of Veterinary Medicine, Airlangga University (No. 2.KEH.021.03.2022).

Animal

The research sample was twenty-eight female Balb/c mice aged two months, weighing 25-30 grams, who were not pregnant. The mice received treatment for two weeks. Adequate animal care and usage protocols were observed for the experimental mice [18].

Animals during the study were kept in cages controlled by light in the room 12 hours of

darkness and 12 hours of light. The environment where the mice were placed was regulated by temperature and humidity according to the temperature between 22-25 ºC and humidity between 45-65%. Feeding and access to drinking water during the study were given ad libitum [15, 19].

Making animal models of endometriosis

The use of endometriosis model mice refers to previous studies using heterologous techniques with a success rate of 95.7%. Endometrial tissue was collected from women who had undergone hysterectomy for non-cancerous uterine conditions and had not received hormonal therapy for a duration of three months. The collected endometrial tissue was rinsed twice with phosphate buffered saline (PBS) through centrifugation at 2,500 rpm. Subsequently, the tissue was combined as large fragments in a solution of PBS, penicillin (200 IU/ml), and streptomycin (200 µg/ml). On the first day, mice were injected intraperitoneally with 0.1 ml of endometrial wet tissue, followed by intramuscular injection of 0.2 ml of cyclosporine A, and intramuscular injection of 5.4 µg ethynil estradiol. Ethynil estradiol injection was repeated on the fifth day [20].

Preparation of ethanol extract of basil (Ocimum basilicum L.) leaves

Fresh basil (*Ocimum basilicum* L.) leaves were taken from the same area and garden, namely the Binjai garden, North Sumatra, with the same plant age and hours. Basil leaves are then dried and macerated at the Pharmacology Laboratory of Airlangga University. Fresh basil leaves were then dried for 2 days at 30-35 ºC and crushed using a blender to obtain powder. As much as 100 g of basil leaf powder was added to 100 ml of 96% ethanol solvent, put into a jar and added another 1 liter of 96% ethanol, and then closed and left for 48 hours protected from sunlight. The mixture was filtered to obtain maserate. The residue was subjected to maceration using 96% ethanol following the identical procedure. Maceration was performed with a digital shaker set at 50 rpm until a clear macerate was obtained. The liquid extract obtained was subjected to evaporation using a rotary evaporator for 2 hours at 50 ºC until a concentrated extract with a thick consistency was achieved.

Extract administration

The study involved twenty-eight mice that were randomly divided into four groups, each group consisting of seven mice. Three of the groups received treatment with ethanol extract of basil leaves, while the fourth group served as the endometriosis control group and was given a placebo. The second group was administered the extract at a dose of 0.21 mg/g-BW, the third group accpted a dose of 0.42 mg/g-BW, and the fourth group with 0.84 mg/g-BW. Because there is no standard dose of bacilli against endometriosis, the dosage we used refers to the previous studies, then carried out the conversion and implications for endometriosis inflammatory disease [15].

Sample collection

On the 1st to 7th day, the mice were acclimatized, followed by making the endometriosis model until the 14th day, then for 14 days the mice were treated. After 14 days of treatment, the mice were sacrificed using ketamine 100 mg/kgBW while intracardiac blood samples were taken for PGE2 serum examination. The rats were then terminated and continued with the opening of the peritoneal cavity to take endometriosis lesions for mast cell examination.

Toluidine blue staining

After the 14-day treatment, the endometriosis tissue underwent preparation for analysis. It was cut and stained with toluidine blue to assess the number of mast cells that had undergone degranulation. The tissue was initially fixed in 10% buffered formalin, dehydrated, and then placed in paraffin. Sections of the paraffin-embedded tissue blocks, measuring 4 µm in thickness, were obtained using a Leica RM2135 Microtome from Leica, Germany, and mounted on glass slides. The tissue was then thoroughly deparaffinized with xylene, followed by

rehydration in graded alcohol for 5 minutes per step.

Subsequently, the tissue was soaked in water for 5 minutes and exposed to toluidine blue stain in a jar for 30 minutes before being carefully removed. Finally, the tissue was immersed in absolute alcohol for 1 minute, cleaned with xylene, and mounted on a slide using Entellan. Mast cell granules appeared purple, while the rest of the tissue appeared blue. Mast cell counts were performed in all visual fields using a Nikon E100 light microscope with magnification ranging from 100x to 400x [21].

The Enzyme-Linked Immunosorbent Assay (ELISA)

was utilized in this study. Blood samples were obtained from the mice's hearts using a plain vacutainer and left to clot naturally without the use of anticoagulants. The serum was then separated from the blood by centrifugation at 1500x g for 20 minutes at 4 °C, and subsequently stored at -20 °C. PGE2 levels were determined using the Mice PGE2 ELISA Kit (Cat. No EA0028Mo, Bioassay Technology Laboratory) following the manufacturer's instructions. The optical density was measured using an ELISA reader (TC 96 microplate reader, Teco Company, Canada).

Statistic analysis

The results were presented as the mean ± standard error of the mean. Statistical analysis was carried out using a One-way ANOVA test, and then by a Tukey HSD post hoc test to determine significant variations between the groups. A significance level of $p<0.05$ was regarded statistically significant. Data analysis was performed utilizing the SPSS application.

Results and Discussion

On the twenty-eighth day, all mice from all treatment groups were still alive, had no abnormal appearance, and then were entered for examination and data analysis.

Mast cell count

Figure 1 in the study presents the count of mast cells in the control group of endometriosis tissue stained with toluidine blue. The average mast cell counts in the control group and the groups treated with ethanol extract of basil leaves at doses of 0.21 mg/g-BW, 0.42 mg/g-BW, and 0.84 mg/g-BW were (3.86 ± 1.21), (4.00 ± 2.31), (1.71 ± 1.11), and (0.86 ± 0.90), respectively, as depicted in Figure 2. The data followed a normal distribution, and a One-way ANOVA test revealed a significant difference among the groups ($p=0.001$). A Tukey's post hoc test was conducted to compare the groups, indicating that the group received dosage of 0.84 mg/g-BW of ethanol extract of basil leaves exhibited a significant distinction ($p=0.005$) compared to the control group. Furthermore, the group treated with 0.21 mg/gBW showed a significant distinction ($p=0.039$) compared to the groups administered doses of 0.42 mg/g-BW and 0.84 mg/g-BW ($p=0.003$).

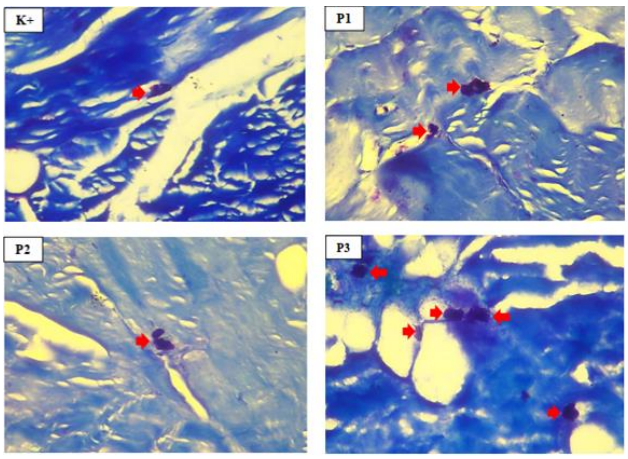

Figure 1: Histology of endometriosis tissue stained with toluidine blue staining in each group. Mast cells shown in bluish color are indicated by red arrows (Nikon E100 light microscope with 400x magnification)

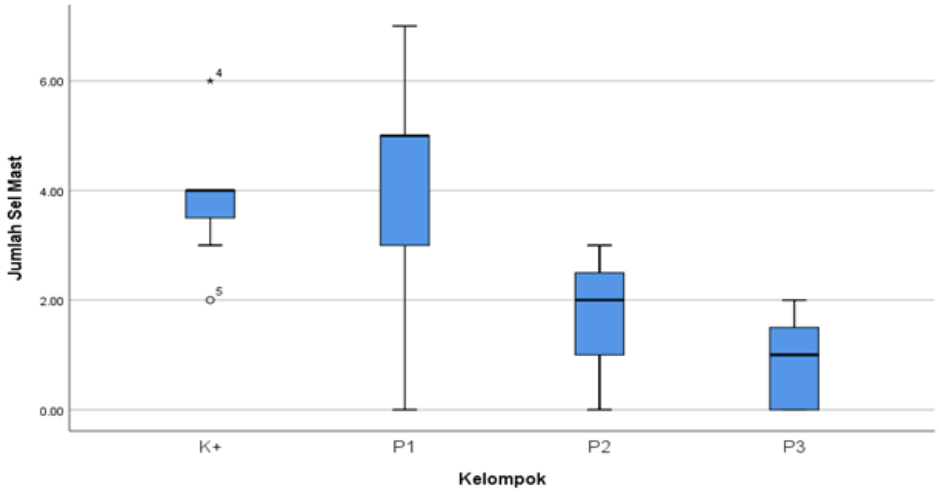

Figure 2: Mast cell count in endometriosis mice model

The One-way ANOVA analysis demonstrated a noteworthy distinction with a p-value of 0.001. The subsequent examination using Tukey's HSD test for the average mast cell count produced the following results:

(1) There was no notable distinction between the control group and the intervention group with a dose of 0.21 mg/g-BW (p=0.998), (2) A minor distinction was observed between the control group and the group treated with a dose of 0.42 mg/g-BW (p=0.057), and (3) A significant distinction was found between the control group and the intervention group of 0.84 mg/g-BW (p=0.005).

Furthermore, the following notable distinctions were observed:

(1) There existed a significant distinction between the intervention group treated with a dose of 0.21 mg/g-BW and the intervention group treated with 0.42 mg/g-BW (p=0.039), (2) A significant distinction was found between the intervention group treated with of 0.21 mg/g-BW and the intervention group treated with 0.84 mg/g-BW (p=0.003); however, (3) No significant distinction was detected between the intervention group treated with 0.42 mg/g-BW and the intervention group treated with 0.84 mg/g-BW (p=0.706).

PGE2 levels

The mean PGE2 levels in the control group, that given ethanol extract of basil leaves at doses of 0.21 mg/gBW, 0.42 mg/gBW, and 0.84 mg/gBW were (44.52 ± 11.99), (41.95 ± 5.36), (50.73 ± 4.44), and (44.39±6.53), respectively (Figure 3). The One-way ANOVA test was used because the data were normally distributed and the results showed no significant distinction between groups (p=0.199). This non-significant difference was due to variations in the expressed PGE2 values. In the control group, 2/7 rats had lower PGE2 levels than the group given ethanol extract of basil leaves with 0.21 mg/g-BW, 0.42 mg/g-BW, and 0.84 mg/g-BW. In the data proportion on PGE2 levels, the 0.42 mg/g-BW dose group had the highest average compared to the other groups. This study examined the mast cell count in the control group and observed an elevation in both degranulated and overall mast cell numbers within endometriosis lesions, indicating their involvement in inflammatory disease development [10].

Endometriosis patients displayed significantly higher mast cell counts and increased degranulation in endometriotic lesions compared to the other tissues. This phenomenon was particularly prominent in deep infiltrating lesions and regions proximate to nerve fibers [22], aligning with Kempuraj *et al*. (2004) findings of elevated mast cell density per square millimeter and 89% activation among endometriosis patients [23]. In addition, Borelli *et al*. (2020) found that mast cell degrees in the peritoneal fluid were significantly higher in women with endometriosis (2.8 ± 3.2) compared to healthy women (0.5 ± 0.5) ($p < 0.05$) [24].

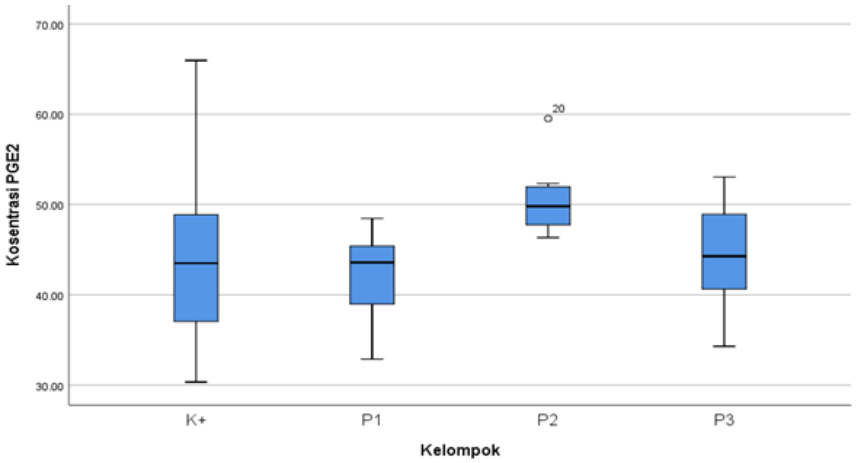

Figure 3: PGE2 levels in the endometriosis mouse model. The One-way ANOVA test exposed no significant distinction p=0.199

Endometriosis lesions contain degranulated mast cells that release proteases, leading to the production of histamine-releasing peptides and cytokines [10].

Mast cell activation is implicated in the formation of fibrous adhesions that contribute to endometriosis lesions, scarring, and fibrosis [25]. Activated mast cells also produce mediators like histamine and TNF-α that indirectly contribute to neuropathic pain by recruiting leukocytes [26]. In patients with endometriosis, the number of degranulated and activated mast cells significantly increases in deep infiltrating lesions and those located near nerves, which are the most painful lesions. Anaf *et al*. (2006) showed that deep infiltrating lesions are associated with higher pain scores, suggesting a link between mast cells and pain in endometriosis [27].

In the present study, treating the subjects with ethanol extract of basil leaves at a dosage of 0.84 mg/g-BW led to a notable decrease in mast cell count in comparison to the control group, with a significant difference observed (p=0.005). Basil leaves contain the flavonoid quercetin and rosmaniric acid, which act as mast cell stabilizers. The stabilization mechanism of mast cells in basil leaves suppresses the inhibition of IgE production in preventing cross-linking of the IgE-FcεRI complex to prevent the development of mast cell degranulation [28].

Mast cells can be activated by interacting directly with antigens (IgE-dependent pathway), where IgE production requires the release of T-helper2 (Th2) cytokines, namely IL-4, IL-5, and IL-13. Although there is increased expression of IL-4 in the peritoneal fluid of endometriosis patients, further studies regarding mast cell activation in IgE-dependent endometriotic lesions have not been confirmed [22].

The reduction in mast cell count can be characterized to the inhibitory effects of quercetin present in basil leaves. Quercetin inhibits mast cell activation by blocking calcium ion influx, suppressing the release of histamine, leukotrienes, and prostaglandins, and inhibiting protein kinase activation [29].

Release of Ca^{2+} from the extracellular matrix activates mast cells and causes NFkB to translocate to the cell nucleus, which results in cytokine transcription [30, 31].

Research conducted by Ding *et al*. (2019), proved that quercetin was significantly dose-dependent on being able to stabilize peritoneal mast cells by reducing Ca2+ expenditure [32].

Basil leaves contain a variety of antioxidants, such as vitamin C, vitamin E, carotenoids, and flavonoids, which help safeguard against oxidative stress and the harmful effects of free radicals induced by hepatotoxic substances. These substances have the potential to harm cellular structures and trigger the manufacturing of Reactive Oxygen Species (ROS) [33]. Flavonoids can reduce mast cell secretion by adding a hydroxyl group at position 2', which can interact with oxygen at position 1 to form a cyclic structure that could interfere with various biological events [34].

Furthermore, flavonoids can decrease the number of mast cells by inhibiting the activity of phosphatidylinositol-3-phosphate kinase (PI3K) enzyme and activating AMP-activated protein kinase (AMPK). This mechanism provides anti-inflammatory and anti-cancer effects. Mast-cell degranulation and activation can be through the PI3K enzyme pathway. Flavonoids contained in basil leaves such as quercetin can also inhibit mast cell degranulation in acute inflammation by inhibiting PGE2 production via arachidonic acid [35].

In a study conducted by Park *et al.* (2008), it was shown that flavonoids have inhibitory properties on mast cell degranulation and activation. These specific compounds were observed to hinder the release of histamine and inflammatory substances generated by mast cells. This inhibition resulted in the suppression of NF-Kb binding, the release of pro-inflammatory cytokines (IL-6, IL-8, TNF-α, and IL-1β), and histamine release ($p<0.05$) [36].

In patients diagnosed with endometriosis, there is an increase in macrophage count. These macrophages are responsible for enhancing the secretion of cytokines, which play a significant role in the development of lesions, angiogenesis, and proliferation. Endometriosis patients also exhibit elevated levels of proinflammatory cytokines such as interleukins-1, -8, -33, nuclear factor kappa B (NF-κB), and tumor necrosis factor alpha (TNF-α) [37].

In estrogen-induced endometriosis (E2), the signaling pathway involving cyclooxygenase-2 (COX-2), omega-3 PUFA, and IL-1β leads to an increase in NF-κB activity. Consequently, COX-2 promotes the manufacturing of prostaglandin E2 (PGE2) [38].

PGE2, in turn, regulates steroidogenesis by inducing the expression of steroidogenic acute regulatory protein (StAR) and aromatase. This enables the production of de novo estrogen from cholesterol without the need for intermediate metabolite transport from other organs. Moreover, estrogen plays an important role in angiogenesis by stimulating VEGF expression and inducing endothelial cell proliferation [7]. Prostaglandin E2 also inhibits apoptosis and increases cell proliferation by inducing the expression of fibroblast growth factor 9 (FGF-9) and matrix metalloproteinase-2 (MMP-2) [39]. Increased levels of PGE2 can cause inflammatory mediators to escape from blood vessels to local areas, causing dysmenorrhea [40].

Administration of ethanol extract of basil leaves as a complementary treatment showed no significant reduction in PGE2 levels ($p=0.199$), but in doses of 0.21 mg/g-BW (41.95±5.36) and 0.84 mg/g-BW (44.39±6.53) it reduced the average levels of PGE2 compared to the control group (44.52±11.99). Administration of ethanol extract of basil leaves at a dose of 0.21 mg/g-BW and a dose of 0.84 mg/g-BW reduced the average PGE2 level although not statistically significant. The mechanism of ethanol extract of basil leaves in reducing the average PGE2 level is by reducing the transfer of Nf-kb into the nucleus by inhibiting the Nfkb1 gene, which in turn suppresses inflammatory cytokine genes through inhibition of Nf-kB function which will affect TLR4-Nf-kB signaling [16].

The mechanism of basil leaves in anti-inflammation is through the inhibition of arachidonic acid through the lipoxygenase and cyclooxygenase pathways thereby suppressing the production of PGE2 levels [15]. Numerous studies have confirmed the efficacy of different types of flavonoids in suppressing endometriosis, a condition that impacts over 5.5 million women in the United States, and 176 million women in worldwide [41].

A meta-analysis conducted by Jalali *et al.* found that the flavonoid quercetin has the potential to decrease symptoms and levels of PGE2(42). Another study by Umar *et al.* (2014) supported this finding, demonstrating that the ethanol extract of basil leaves (Ocimum basilicum L.) could decrease PGE2 production and inhibit COX enzymes (COX-1 and COX-2) by reducing macrophage activation [17].

The group that received the ethanol extract of basil leaves with 0.42 mg/g-BW showed an abnormal increase in PGE2 levels compared to the other treatment groups, which experienced a decrease. The atypical rise can be ascribed to genetic and protein variations and mutations, leading to alterations in observable characteristics. Mutations can arise from either

inherited genetic changes passed down from parents (germline mutations) or acquired mutations that occur during an individual's lifetime (somatic mutations), with the latter being a major contributor to disease [43].

In Wang & Song's study (2015) where the genetic variation of COX-1195 is at risk for endometriosis. The COX-2 1195 AA genotype frequency and the A allele frequency were significantly higher than the control group. Allele A is consistent in the function of the -1195 G>A polymorphism, which can form a c-Myb binding site and significantly increase the activity of the COX-2 gene promoter in regulating the balance between cell division, survival, and differentiation resulting in endometriosis [44].

Administration of basil leaf extract (*Ocimum basilicum* L.) to endometriosis mice experienced an increase in PGE2 levels with increasing doses. This could be due to the content of phytochemical compounds such as euginal, euginol, sitosterol, ursolic acid, and stigmasterol in basil leaves which act as phytoandrogens or phytoestrogens [45].

Basil leaves (Ocimum basilicum L.) contain orientin, vicenin, and isoflavones which are estrogenic which can increase exogenous estrogen, bind to estrogen receptors in the body, and proliferate the uterus [19, 46, 47].

Isoflavones can cause an estrogen-raising effect in many tissues. The content of systesterol and stigmasterol in basil leaves is androgenic. Sitosterol and stigmasterol are androgen precursors that can be converted into testosterone, resulting in higher testosterone levels and suppressing the development of ovarian follicles [45].

Giving ocimum basilicum L. leaf extract which has estrogenic content has caution in the use of endometriosis treatment, where estrogen is a key hormone for the growth and persistence of endometriosis tissue as well as inflammation and pain [48].

The rise in PGE2 can also be triggered by mast cells that have been activated. When women with endometriosis lesions have activated mast cells, they produce soluble products like TNF-α, IL-4, IL-5, and IL-6. These products then stimulate fibroblasts to produce collagenase and PGE2, and induce macrophages to produce pro-inflammatory factors in the endometrium [25].

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No potential conflict of interest was reported by the authors.

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Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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References

[1]. Laganà A.S., Garzon S., Götte M., Viganò P., Franchi M., Ghezzi F., Martin D.C., The pathogenesis of endometriosis: Molecular and cell biology insights, *International journal of molecular sciences*., 2019, **20**:1 [Crossref], [Google Scholar], [Publisher]

[2]. Moen M.H., Endometriosis, an everlasting challenge, *Acta Obstetricia et Gynecologica Scandinavica*., 2017, **96**:783 [Crossref], [Google Scholar], [Publisher]

[3]. Zondervan K.T., Becker C.M., Missmer. SA. Endometriosis, Review Article, *N Engl J Med*., 2020, **382**:56 [Crossref], [Publisher]

[4]. Parasar P., Ozcan P., Terry K., Endometriosis: Epidemiology, Diagnosis and Clinical Management, *Current obstetrics and gynecology reports*., 2016, **26**:196 [Crossref], [Google Scholar], [Publisher]

[5]. Guo Y., Liu F.Y., Shen Y., Xu J.Y., Xie L.Z., Li S.Y., Ding D.N., Zhang D.Q., Han F.J., Complementary and Alternative Medicine for Dysmenorrhea

Caused by Endometriosis: A Review of Utilization and Mechanism, *Evidence-Based Complementary and Alternative Medicine*., *2021*, **2021** [Crossref], [Google Scholar], [Publisher]

[6]. Moradi M., Parker M., Sneddon A., Lopez V., Ellwood D., Impact of endometriosis on women's lives: A qualitative study, *BMC women's health*., 2014, **14**:1 [Crossref], [Publisher]

[7]. Hsiao K.Y., Wu M.H., Tsai S.J., Roles of Prostaglandin E 2 in Endometriosis, *Endometriosis: Pathogenesis and Treatment*., 2014, 125 [Crossref], [Google Scholar], [Publisher]

[8]. Tsuge K., Inazumi T., Shimamoto A., Sugimoto Y., Molecular mechanisms underlying prostaglandin E2-exacerbated inflammation and immune diseases, *International immunology*., 2019, **31**:597 [Crossref], [Google Scholar], [Publisher]

[9]. Taylor H.S., Pal L., Seli E., Speroff's Clinical Gynecologic Endocrinology and Infertility, *Connecticut: Wolters Kluwer.,* 2020, 580 [Publisher]

[10]. McCallion A., Nasirzadeh Y., Lingegowda H., Miller J.E., Khalaj K., Ahn S., Monsanto S.P., Bidarimath M., Sisnett D.J., Craig A.W., Young S.L., Lessey B.A., Koti M., Tayade C., Estrogen mediates inflammatory role of mast cells in endometriosis pathophysiology, *Frontiers in Immunology*., 2022, **13**:961599 [Crossref], [Google Scholar], [Publisher]

[11]. a) Ilhan M., Gürağaç Dereli F.T., Akkol E.K., Novel Drug Targets with Traditional Herbal Medicines for Overcoming Endometriosis, *Current Drug Delivery*., 2018, **16**:386 [Crossref], [Google Scholar], [Publisher]; b) Hamood Al-Behadili W.K., Jawad Y.M., Hasan H.J. Study the Effect of pH on Absorption and Fluorescence Spectra of Eosin Y Dye in Ethanol. *Asian Journal of Green Chemistry*, 2023, **7**:163 [Crossref], [Publisher]; c) Ahmadyousefi Y., A brief overview of plant-derived chemotherapeutic agents for cancer therapy. *Asian Journal of Green Chemistry*, 2023, **7**:175 [Crossref], [Publisher]

[12]. a) Nimesh S., Ashwlayan V.D., Rani R., Prakash O., Advantages of Herbal Over Allopathic Medicine in the Management of Kidney and Urinary Stones Diseas, *Borneo Journal of Pharmacy*., 2020, **3**:179 [Crossref], [Google Scholar], [Publisher]; b) Monjezi A., Karimian P., Yousofvand V. Therapeutic applications of Salvadora persica plant in medical sciences: a review article. *Asian Journal of Green Chemistry*, 2023, **7**:180 [Crossref], [Publisher]; c) Akbarnejad F., Dermatology Benefits of Punica granatum: A Review of the Potential Benefits of Punica granatum in Skin Disorders. *Asian Journal of Green Chemistry*, 2023, **7**:208 [Crossref], [Publisher]

[13]. Filip S., Internation f Valuable Phytonutrients, *J Clin Nutr Diet*., 2017, 3 [Crossref], [Google Scholar], [Publisher]

[14]. Shahrajabian M.H., Sun W., Cheng Q., Chemical components and pharmacological benefits of Basil (Ocimum basilicum): a review, *International Journal of Food Properties*., 2020, **23**:1961 [Crossref], [Google Scholar], [Publisher]

[15]. Eftekhar N., al Moghimi A., Mohammadian Roshan N., Saadat S., Boskabady M.H., Immunomodulatory and anti-inflammatory effects of hydro-ethanolic extract of Ocimum basilicum leaves and its effect on lung pathological changes in an ovalbumin-induced rat model of asthma, *BMC complementary and alternative medicine*., 2019, **19**:1 [Crossref], [Publisher]

[16]. Takeuchi H., Takahashi-Muto C., Nagase M., Kassai M., Tanaka-Yachi R., Kiyose C., Anti-inflammatory effects of extracts of sweet basil (Ocimum basilicum l.) on a co-culture of 3t3-l1 adipocytes and raw264.7 macrophages, *Journal of oleo science*., 2020, **69**:487 [Crossref], [Google Scholar], [Publisher]

[17]. Umar A., Zhou W., Abdusalam E., Tursun A., Reyim N., Tohti I., Moore N., Effect of Ocimum basilicum L. on cyclo-oxygenase isoforms and prostaglandins involved in thrombosis, *Journal of ethnopharmacology*., 2014, **152**:151 [Crossref], [Google Scholar], [Publisher]

[18]. Scholten D., Trebicka J., Liedtke C., Weiskirchen R., The carbon tetrachloride model in mice, *Laboratory Animals*., 2015, **49**:4 [Crossref], [Google Scholar], [Publisher]

[19]. Andriyanto A., Widi L.N., Subangkit M., Tarigan E., Irarang Y., Nengsih R.F., Manalu W., Potential use of Indonesian basil (Ocimum basilicum) maceration to increase estradiol and progesterone synthesis and secretion to improve

prenatal growth of offspring using female albino rats as an animal model, *Veterinary World*., 2022, **15**:1197 [Crossref], [Google Scholar], [Publisher]
[20]. Trisetiyono Y., Widjiati W., Hidayat S.T., Pramono N., Antioxidant Herbs Supplementation Inhibits Endometriosis Extension in Mice, *Journal of Biomedicine and Translational Research*., 2019, **5**:53[Crossref], [Google Scholar], [Publisher]
[21]. Iuvone T., Affaitati G., De Filippis D., Lopopolo M., Grassia G., Lapenna D, Negro L., Costantini R., Vaia M., Cipollone F., Ialenti A., Ultramicronized palmitoylethanolamide reduces viscerovisceral hyperalgesia in a rat model of endometriosis plus ureteral calculosis: Role of mast cells, *Pain*., 2016, **157**:80 [Google Scholar], [Publisher]
[22]. Binda M.M., Donnez J., Dolmans M.M., Targeting mast cells: a new way to treat endometriosis, *Expert opinion on therapeutic targets*., 2017, **21**:67 [Crossref], [Google Scholar], [Publisher]
[23]. Mariuzzi L., Domenis R., Orsaria M., Marzinotto S., Londero A.P., Bulfoni M., Candotti V., Zanello A., Ballico M., Mimmi M.C., Calcagno A., Functional Expression of Aryl Hydrocarbon Receptor on Mast Cells Populating Human Endometriotic Tissues, *Laboratory Investigation*., 2016, **96**:959 [Crossref], [Google Scholar], [Publisher]
[24]. Borelli V., Martinelli M., Luppi S., Vita F., Romano F., Fanfani F., Trevisan E., Celsi F., Zabucchi G., Zanconati F., Bottin C., Mast Cells in Peritoneal Fluid From Women With Endometriosis and Their Possible Role in Modulating Sperm Function, *Frontiers in Physiology*., 2020, **10** [Crossref], [Google Scholar], [Publisher]
[25]. Vallvé-Juanico J., Houshdaran S., Giudice L.C., The endometrial immune environment of women with endometriosis, *Human reproduction update*., 2019, **25**:565 [Crossref], [Google Scholar], [Publisher]
[26]. Zhu T.H., Zou G., Ding S.J., Li T.T., Zhu L.B., Wang J.Z., Yao Y.X., Zhang X.M., Mast cell stabilizer ketotifen reduces hyperalgesia in a rodent model of surgically induced endometriosis, *Journal of pain research*., 2019, **12**:1359 [Google Scholar], [Publisher]
[27]. Maddern J., Grundy L., Castro J., Brierley S.M., Pain in Endometriosis, *Frontiers in cellular neuroscience*., 2020, **14**:590823 [Crossref], [Google Scholar], [Publisher]
[28]. Sim L.Y., Rani N.Z.A., Husain K., Lamiaceae: An insight on their anti-allergic potential and its mechanisms of action, *Frontiers in pharmacology*., 2019, **10**:677 [Crossref], [Google Scholar], [Publisher]
[29]. Mlcek J., Jurikova T., Skrovankova S., Sochor J., Quercetin and its anti-allergic immune response, *Molecules*., 2016, **21**:623 [Crossref], [Google Scholar], [Publisher]
[30]. Komi D.E.A., Wöhrl S., Bielory L., Mast Cell Biology at Molecular Level: a Comprehensive Review, *Clinical reviews in allergy & immunology*., 2020, **58**:342 [Crossref], [Google Scholar], [Publisher]
[31]. Krystel-Whittemore M., Dileepan K.N., Wood J.G., Mast cell: A multi-functional master cell, *Frontiers in immunology*., 2016, **6**:1 [Crossref], [Google Scholar], [Publisher]
[32]. Ding Y., Che D., Li C., Cao J., Wang J., Ma P., Zhao T., An H., Zhang T., Quercetin inhibits Mrgprx2-induced pseudo-allergic reaction via PLCγ-IP3R related Ca 2+ fluctuations, *International immunopharmacology*., 2019, **66**:185 [Crossref], [Google Scholar], [Publisher]
[33]. Renovaldi D., Adam A.K., Potential of Sweet Basil (Ocimum basilicum) as a Hepatoprotector Agent for Liver Injury Related to Drugs, *Muhammadiyah Medical Journal*., 2020, **1**:63 [Crossref], [Google Scholar], [Publisher]
[34]. Al-Khayri J.M., Sahana G.R., Nagella P., Joseph B.V., Alessa F.M., Al-Mssallem M.Q., Flavonoids as Potential Anti-Inflammatory Molecules: A Review, *Molecules*., 2022, **27**:2901 [Crossref], [Google Scholar], [Publisher]
[35]. Shaik Y., Caraffa A., Ronconi G., Lessiani G., Conti P., Impact of polyphenols on mast cells with special emphasis on the effect of quercetin and luteolin, *Central European Journal of Immunology*., 2018, **43**:476 [Crossref], [Google Scholar], [Publisher]
[36]. Rakha A., Umar N., Rabail R., Butt M.S., Kieliszek M., Hassoun A., Aadil R.M., Anti-inflammatory and anti-allergic potential of dietary flavonoids: A review, *Biomedicine &*

Pharmacotherapy., 2022, **156**:113945 [Crossref], [Google Scholar], [Publisher]
[37]. Donnez J., Cacciottola L., Endometriosis: An Inflammatory Disease That Requires New Therapeutic Options, *International Journal of Molecular Sciences*., 2022, **23**:1518 [Crossref], [Google Scholar], [Publisher]
[38]. Lai Z.Z., Yang H.L., Ha S.Y., Chang K.K., Mei J., Zhou W.J., Qiu X.M., Wang X.Q., Zhu R., Li D.J., Li M.Q., Cyclooxygenase-2 in endometriosis, *International journal of biological sciences*., 2019, **15**:2783 [Crossref], [Google Scholar], [Publisher]
[39]. Nasry W.H.S., Rodriguez-Lecompte J.C., Martin C.K., Role of COX-2/PGE2 Mediated Inflammation in Oral Squamous Cell Carcinoma, *Cancers*., 2018, **10**:348 [Crossref], [Google Scholar], [Publisher]
[40]. Huang Q., Liu X., Guo S., Changing prostaglandin E2 (PGE 2) signaling during lesional progression and exacerbation of endometriosis by inhibition of PGE 2 receptor EP2 and EP4, *Reproductive Medicine and Biology*., 2022, **21**:12426 [Crossref], [Google Scholar], [Publisher]
[41]. Safe S., Jayaraman A., Chapkin R.S., Howard M., Mohankumar K., Shrestha R., Flavonoids: structure–function and mechanisms of action and opportunities for drug development, *Toxicological Research*., 2021, **37**:147 [Crossref], [Google Scholar], [Publisher]
[42]. Jalali M., Mahmoodi M., Moosavian S.P., Jalali R., Ferns G., Mosallanezhad A., Imanieh M.H., Mosallanezhad Z., The effects of ginger supplementation on markers of inflammatory and oxidative stress: A systematic review and meta-analysis of clinical trials, *Phytotherapy Research*., 2020, **34**:1723 [Crossref], [Google Scholar], [Publisher]
[43]. Karki R., Pandya D., Elston R.C., Ferlini C., Defining 'mutation' and 'polymorphism' in the era of personal genomics, *BMC medical genomics*., 2015, **8**:1 [Crossref], [Google Scholar], [Publisher]
[44]. Wang Y., Qu Y., Song W., Genetic variation in COX-2 -1195 and the risk of endometriosis and adenomyosis, *Clin Exp Obstet Gynecol*., 2015, **42**:168 [Google Scholar], [Publisher]
[45]. Maryanti S., Nasihun T., Amalia H., The Effect of Administering Lemon Basil (Ocimum sanctum) Leaves on FSH and LH Estrogen Levels and Size of Ovarian Antral Follicle in Female Balb / C Mice, *Sains Medika: Jurnal Kedokteran dan Kesehatan*., 2019, **10**:57 [Google Scholar], [Publisher]
[46]. Mousavi L., Salleh R.M., Murugaiyah V., Phytochemical and bioactive compounds identification of Ocimum tenuiflorum leaves of methanol extract and its fraction with an antidiabetic potential, *International Journal of Food Properties*., 2018, **21**:2390 [Crossref], [Google Scholar], [Publisher]
[47]. Farhana A., Reddy A., Bhavana K., Mutha S., Bakshi V., Assessment of Ocimum Sanctum To Normalize the Estrous Cycle in Letrazole Induced Polycystic Ovary, *World J Pharm Res*., 2018, **7**:907 [Google Scholar], [Publisher]
[48]. Antonescu A.I., Miere F., Fritea L., Ganea M., Zdrinca M., Dobjanschi L., Antonescu A., Vicas S.I., Bodog F., Sindhu R.K., Cavalu S., Perspectives on the combined effects of ocimum basilicum and trifolium pratense extracts in terms of phytochemical profile and pharmacological effects, *Plants*., 2021, **10**:1390 [Crossref], [Google Scholar], [Publisher]

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