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Review article

Phaleria macrocarpa for Endometriosis Treatment: A Review

Maharani Maharani*[1,2], Lia Lajuna[1], Cut Yuniwati[1], Nora Veri[3], Sutrisno Sutrisno[4,5]

[1] Department of Midwifery, Polytechnic of Health-Ministry of Health, Aceh, Indonesia
[2] Doctoral Program of Medical Sciences, Faculty of Medicine, University of Brawijaya, Malang, East Java, Indonesia
[3] Department of Midwifery, Polytechnic of Health-Ministry of Health, Aceh, Langsa, Indonesia
[4] Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynaecology, Faculty of Medicine, University of Brawijaya/ Saiful Anwar General Hospital, Malang, East Java, Indonesia
[5] Department of Midwifery, Magister of Midwifery, Faculty of Medicine, University of Brawijaya, Malang, East Java, Indonesia

ABSTRACT

Around 5—10% women in their productive age could suffer from endometriosis, a condition where viable endometrial tissue is present outside the uterine cavity. This disease could progress into ovarian cancer and infertility with long-lasting chronic pain. Thus, innovation for safe and efficacious management of this disease is urgent. Exploring the abilities of medicinal plants for endometriosis therapy is quite promising. Of which, *Phaleria macrocarpa* has been suggested as a strong candidate for the therapy. This review begins with explanations of endometriosis; its aetiology and pathobiology. Thereafter, we present the medicinal properties of *P. macrocarpa* for being anti-inflammatory, anti-angiogenesis, and anti-proliferation. Results from pre-clinical studies and an ongoing trial of *P. macrocarpa* as a therapy for endometriosis were also discussed in this review. Future study will explore the activity of this plant extracts against hypoxia inducible factor-1α (HIF-1α), vascular endothelial growth factor (VEGF), B-cell lymphoma 2 (Bcl-2), and Bcl-2-associated X protein (BAX).

Keywords: Anti-angiogenesis, anti-inflammation, anti-proliferation, endometrium, *Phaleria macrocarpa*

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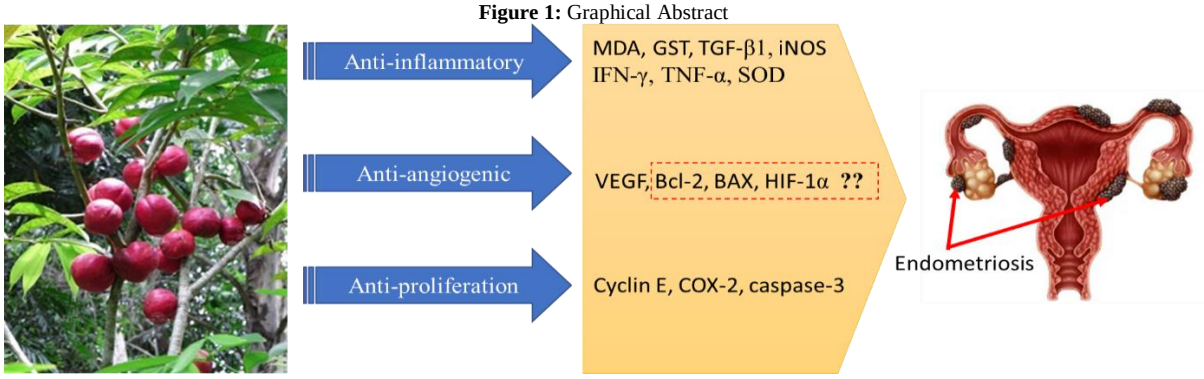
Correspondence: Maharani Maharani ✉ maharani@poltekkesaceh.ac.id, **Orcid Id**: 0000-0002-5021-1274

Department of Midwifery, Polytechnic of Health-Ministry of Health, Aceh, Indonesia.

INTRODUCTION

Plant with medicinal properties have been used as integrative medicine for multiple diseases, even it can provide significant aid tomodern medicine. For example, during the ongoing SARS-CoV-2 pandemic, natural products are intensely studied for their antiviral abilities[1]. This includes the orally bioavailable molnupiravir, which was inspired by uridine, a small compound found in human plasma [1, 2]. Extracts from the plants of *Annonaceae spp.* could work synergistically with commercially available antibiotics against multiple drugs resistant bacteria [3]. Type 2 diabetes mellitus and multiple cancers could also be treated with medicinal plants through various molecular targets [4-7]. Among the medicinal plants, *Phaleriamacrocarpa*has been recognized for its potent pharmacological properties, including but not limited to the treatments of asthma, dysentery, rheumatoid arthritis, and cutaneous diseases [8]. Research from the last few years revealed that fractions of *P. macrocarpa* extracts could be useful in the management of a proliferative endometrium [9]. Even in 2013, a phase 2/3 clinical trial has started to evaluate the efficacy of bioactive *P. macrocarpa* fraction against endometriosis (NCT01942122) [10].

Figure 1: Graphical Abstract



In 2010, the incidence of endometriosis was recorded at 5—10% among reproductive women, while its prevalence could increase to 20—50% in women with infertilityand chronic pelvic pain. The cases were predominated by individuals aged between 25 and 30 years old [11]. Clinical features of endometriosis include dyspareunia, dysuria, chronic abdominal pain, pelvic pain, pain during defecation, and menstrual pain [12]. The pain occurs due to the excessive blood outflow into the pelvic cavity stimulating peritoneum and uterine contractions following the increased levels of locally secreted prostaglandins in endometrial tissue **[12]**. Women with endometriosis could have the disease progression into ovarian cancer and infertility with long lasting chronic pain [13]. In this light, this review article provides the insights on the aetiology and pathobiology of endometriosis along with the potential of *P. macrocarpa* to act as a therapy for endometriosis.

Aetiology and pathobiology of endometriosis

Endometriosis is a gynaecological disorder that is benign but has the potential for malignancy [14]. A report stated that the presence of this disease is characterized by the presence of viable endometrial tissue outside the uterine cavity [15]. Endometriosis is considered a cancer precursor and a risk factor for ovarian cancer. There is a similar pattern in terms of local invasion, spread and responsiveness to estrogen in inducing growth signals in endometriosis and ovarian cancer [16]. The cause of endometriosis is not known with certainty and is very complex and varies from one case to another.

Retrograde theory

Retrograde theory was first reported by by John Sampson in 1927, where he describes the endometrial cells shedding along with menstrual blood returned to the peritoneal cavity and stimulate peritoneal metaplasia to invade, implant and proliferate. Furthermore, it stimulates angiogenesis, where in endometriosis lesions are often found to have increased vascularity [15].

Immunology theory

In patients with endometriosis, there is an immune system disorder characterized by reduced T cells and natural killer cell responses [17]. The immune system of patients with endometriosis shows an increase in the humoral immune response and macrophage activity [10]. The peritoneum reacts to menstrual blood fragments in the form of cessation of adhesion of viable endometrial cells to the peritoneum, which then transforms into endometrial lesions. Endometriotic lesions secrete haptoglobulin which causes macrophages instead of acting as a cleanser to remove ectopic endometrial cells, but inhibiting their cleaning function [14].

Genetic theory

Endometriosis has been observed to be closely associated with hereditary medical history.The risk 7—10 times higher in women with hereditary or family history of endometriosis in comparison to those without. Some families may carry a gene that allows abnormal cells to survive and grow in an ectopic pelvic cavity. However, little progress has been made in identifying the genetic variants that play a role in endometriosis [14].

Hormonal theory

The concept of endometriosis as an estrogen dependent disorder is supported by molecular evidence. In endometrium, increased and decreased levels were found on aromatase and 17β-hydroxysteroid dehydrogenase (17β–HSD) type 2, respectively**[12]**. The formation of estradiol in endometrial tissue occurs in 2 ways, namely the aromatase pathway by converting ovarian androstenedione to estrone (E1), and through 17β-HDS type 1, E1 is converted to significantly estrogenic E2. The next is sulfatase pathway, where sulfatase converts estrogen sulfate into E1, which will then be activated by 17β-HDS type 1 into E2**[14]**. E2 stimulates the production of PGE2 which stimulates further aromatase activity. An increase in the enzyme 20α-hydroxysteroid dehydrogenase will inactivate progesterone by converting it to a less active form, which has a low affinity for the progesterone receptor. Changes in progesterone cause local E2 effects to be more dominant in endometriosis. Hormonal changes can affect the ability of endometrial cells, mesothelium tissue to proliferate, and/or evade the immune system-mediated cleansing system [18]**.**

Coelomic metaplasia theory

Based on a report, the coelomic epithelium is found to be the origin of endometrial and peritoneal cells, allowing the transformation of one cell type into another that is affected by inflammation from the flow of refluxed menstrual blood [19]. Certain cells are pluripotent which when stimulated could change their shape into different cell types. This may explain the finding of endometriosis in women without menstrual cycles and in men.

Phaleria macrocarpa for endometriosis treatment

Phytochemical profile of Phaleria macrocarpa

Alkaloids, flavonoids, terpenoids, and saponins are usually found in *P. macrocarpa*. In detail, some of the phytocompounds identified in *P. macrocarpa* have been presented in Table 1. Phytocompounds themselves have been evaluated for their efficacies against endometriosis [20]. Phalerin and mahkoside A are identical in *P. macrocarpa***,** in which these compounds have been reported in the methanol extract [21], aqueous extract [22], and more others [23]. A phytosterol, kaempferol, was also found in *P. macrocarpa* [24]. These phytocompounds could act as anti-inflammation [25], analgesic, anti-proliferation [26], and anti-angiogenesis [27].

Anti-inflammatory properties of Phaleria macrocarpa

Inflammation reaction occurs during the endometriosis could be reduced by the extracts of *P. macrocarpa*. Several studies have shown anti-inflammatory activities of *P. macrocarpa* extracts (Table 2). The anti-inflammatory properties have been observed through the swelling reductions [24, 31].

Table 1: Phytocompounds identified in *Phaleria macrocarpa*

Year [Ref]	Sample and extraction	Phytochemical content
2022 [28]	Fruits were macerated in ethanol 96%	Alkaloids, glycosides, flavonoids, tannins, saponins
2022 [29]	Peel extraction with ultrasound assistance	Phenolic compounds, tannins, saponins, and alkaloids
2021 [9]	Hexane and n-butanol partition from the fruit ethanol extract	Eriodictyol, glycitin, 5-O-methylgenistein, (+)-catechin 7-O-beta-D-xyloside, (-)-8-prenylnaringenin, (±)-naringenin
2016[24]	Fruits and seeds were macerated using ethanol 70%	Kaempferol-3-O-β-D-glucoside, gallic acid, 29-norcucurbitacin, fevicordin A and fevicordin A glucosides, and Cucurbitacins.
2020[21]	The leaves were macerated in methanol 80%	Mahkoside A, dodecanoic acid, palmitic acid, des-acetyl flavicordin-A, flavicordin-A, flavicordin-D,Flavicordin-A glucoside, ethyl stearate, and lignans sucrose.
2020[23]	Methanolic maceration of different parts of the fruits	Phalerin, gallic acid, icaricide C, mangiferin, mahkoside A, dodecanoic acid, palmitic acid, desacetylflavicordin-A, flavicordin-A, flavicordin-D, flavicordin-A glucoside, ethyl stearate, lignans, alkaloids and saponins
2019[30]	Maceration of the fruit using ethanol 95%	Sterols, triterpenes, flavonoids, alkaloids, saponins, glycosides, and tannins.
2020[22]	Ultrasonic-assistedextraction of the leaves using methanol	Phalerin

Pro-inflammatory factors such as interferon-gamma-γ (IFN-γ), inducible nitric oxide synthase (iNOS), malondialdehyde (MDA), and tumor necrosis factor-α (TNF-α) could be reduced following the administration of *P. macrocarpa* extracts [32, 33]. Meanwhile, the increase of endogenous antioxidant such as superoxide dismutase (SOD) and glutathione-s-transferase (GST) were observed in the treatment group.

Table 2: Anti-inflammatory properties of *Phaleria macrocarpa*

Year[Ref]	Sample and extraction	Anti-inflammatory activities
2016[24]	Fruits and seeds extract with ethanol 70%	Reduce inflammation or swellingeffect
2020[23]	Methanolic maceration of different parts of the fruits	Inhibit the cascade of inflammation pathway
2018[32]	Subcritical water extraction of the fruits	Reducing MDA, TNF-α, and TGF-β1
2016 [34]	Fruits maceration using ethanol 95%	Upregulation of GST and SOD
2011 [33]	The fruits were reflux-extracted using methanol	Reduction iNOS synthesis via lipopolysaccharide and IFN-γ
2015 [31]	Combination of *Nigella sativa* seed and *Phaleria macrocarpa* fruits (1:3) was percolated using water.	Reduction of paw edema in mice model

GST: Glutathione-s-transferase, IFN-γ: Interferon-gamma-γ, iNOS: Inducible nitric oxide synthase, MDA: Malondialdehyde, SOD: Superoxide dismutase, TNF-α: Tumor necrosis factor-α, TGF- β1: Transforming growth fator-β1

Anti-angiogenic and antiproliferativeproperties of Phaleria macrocarpa

Extracts from *P. macrocarpa* have been studied for their abilities against cell proliferation, where the details of the findings have been presented in Table 3. Its leaves have been found to reduce tumor and MCF-7 cells [35, 36]. The leaf extract could also enhance the expression of Caspase-3 which is responsible for cell apoptosis [37]. Fruits samples have been reported to decrease the number of new blood vessel, suppress retinoblastoma tumor, and prevent liver fibrosis [20, 38, 39]. The ethanolic extract from *P. macrocarpa* ethanolic extract was reported for its ability in inhibiting colorectal cancer concomitant to COX-2 downregulation [40].

Table 3: Anti-angiogenic and antiproliferative properties of *Phaleria macrocarpa*

Year[Ref]	Sample and extraction	Anti-angiogenic activities
2022[35]	Maceration of the leaves using ethanol 70%	Reducing tumor volume
2019[40]	Stem barks maceration using ethanol	Inhibiting colorectal cancer cell line HCT116 via COX-2 downregulation
2014[38]	Ethanolic extract ofPhaleria macrocarpa ethanolic extract ofPhaleria macrocarpa ethanolic extract ofPhaleria macrocarpa ethanolic extract ofPhaleria macrocarpa Fruits soxhletation using ethanol 96%	Decreasing the number of new blood vessels
2021 [37]	Leaf powder was macerated with ethanol 70%.	Upregulation of Caspase-3
2020[39]	*P. macrocarpa* fruit sample of crude ethanol extract	Reducing MCM-B2 cell proliferation
2017[20]	Ethyl acetate: water fractionof the fruits (DLBS1425)	Attenuating human retinoblastoma tumor cells Y-79 via cyclin E
2017[36]	The leaves were macerated using methanol	Inhibitingbreast cancer MCF-7 cell
2018[32]	The fruits were extracted using subcritical water	Preventing liver fibrosis

COX-2: Cyclooxygenase-2

Preclinical evidence with on-going clinical trial

Preclinical studies have specifically investigated the bioactive natural products from *P. macrocarpa* for endometriosis treatment (Table 4). An in-vivo studies using *Mus muculus*suggested thatthe flavonoid isolate from *P. macrocarpa* could suppress the growth of peritoneal tissue [9]. Moreover, the isolate could improve

granulomas and increase the apoptotic index [9]. In an in vitro setting, the DLBS1442 was reported to inhibit the angiogenesis and cell migration [41]. Other hormones and pro-inflammatory factors involved during the endometriosis was also attenuated by DLBS1442 [41]. DLBS1442 itself is a bioactive fraction derived from the methanolic extract of *P. macrocarpa* [42]. An on-going clinical trial (phase II/III) even has been started to evaluate the efficacy of DLBS1442 for endometriosis management (NCT01942122). Based on the interim results, the DLBS could significantly reduce the endometrial cells (Table 4). None of the preclinical research of *P. macrocarpa* has studied on hypoxia inducible factor-1α (HIF-1α), vascular endothelial growth factor (VEGF),B-cell lymphoma 2 (Bcl-2), and Bcl-2-associated X protein (BAX) as parameters for endometriosis treatment, regardless their importance in the disease. Hence, future study should explore the activity of *P. macrocarpa* against the aforementioned molecules.

Table 4: Preclinical evidence of the potential of *Phaleria macrocarpa* in treating endometriosis

Study design,Year [Ref]	Sample	Subject	Results
In vivo, 2021 [9]	Flavonoid isolate	Female *Mus musculus* implanted with myometrial and endometrial tissues under immunodeficient condition	Suppressed the growth of peritoneal tissue, improved granulomas, and higher apoptotic index.
In silico, 2020 [43]	DLBS1442	Metabolomic studies were performed on DLBS1442 constituents against progesterone receptor	Glyceryl pentacosanoate contained in DLBS1442 otentially acts as progesterone receptor agonist
In vitro, 2015 [41]	DLBS1442	Human endometrial epithelial cell lineRL95-2	Inhibition of angiogenesis and cell migration. Upregulation of progesterone receptor and downregulation of estrogen receptor. Inhibition eicosanoid signaling pathway via downregulations of NFκB and iNOS

NFκB: Nuclear factor kappa B, iNOS: Inducible nitric oxide synthase

CONCLUSIONS

P. macrocarpa is potential for treating endometriosis by targeting multiple molecular targets. The extracts of this plant could act as anti-inflammation, anti-angiogenesis, and anti-proliferation. Composition of its phytocompounds could be ascribed to the extract activities. The bioactive fractions, named DLBS1442, has entered a clinical trial where the updated results show optimism. More research should be carried out to find a particular isolate that is potent against the development of endometrial cells. Our research group warrants the investigation of the activity of *P. macrocarpa* against HIF-1α, VEGF, Bcl-2, and BAX in-vivo.

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