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Review Article

A ROLE FOR PHALERIA MACROCARPA (SCHEFF) BOERL. EXTRACTS IN THE MANAGEMENT OF WOMEN'S PATHOLOGICAL CONDITIONS: A RESEARCH REVIEW

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ABSTRACT`

Phaleria macrocarpa (Scheff) Boerl is a medicinal plant that originates from West Papua, Indonesia. The fruit of this plant is known to contain numerous different compounds that produce different bioactivities. Many of these bioactivities are related to women pathological conditions. The purpose of this review is to evaluate the effect of *P. macrocarpa* fruit extract in the management of these conditions. Different studies have proven that *P. macrocarpa* extract helps regulate hormone imbalance in women with problems relating to their menstruation cycle, especially during premenstrual syndrome. It helps alleviate symptoms of primary dysmenorrhea and endometriosis through its bioactivity as anti-inflammation, apoptosis inducer, anti-angiogenic and anti-oxidant agent. *P. macrocarpa* fruit extract also showed selective anti-proliferative, anti-inflammatory, and anti-angiogenic activity on breast and cervical cancer cells. It regulates cancer cell progression through numerous different pathways, making it highly favourable to be developed as a cancer treatment, whether as a single treatment or as an adjunct therapy. In conclusion, *P. macrocarpa* extract has great potential to be developed into treatments for women's pathological conditions. However, further study, both preclinical and clinical studies are needed to ascertain its use in women to be effective and safe.

Keywords: *Phaleria macrocarpa*, Premenstrual syndrome, Endometriosis, Breast cancer, Cervical cancer, Hormone imbalance

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INTRODUCTION

For many years plant extracts have been used for the management of women's health conditions [1, 2]. However, scientific justifications which provide the bases for these therapeutic intents are virtualy absent. One serious problem with investigating the use of natural products for health benefits is the absence of acceptable clinical study data. Majority evidence is empirical or anecdotal involving the uncontrolled use of products of doubtful quality. Many of these traditional herbal medicines are active biologically and could be clinically beneficial. However, their real clinical effects are most likely to be dose dependent and due to the secondary metabolites contained within the product. It is likely that these active agents also cause unwanted toxicity. Without good clinical trial data and with no quality control of the product, it is unlikely that these agents would consistently provide therapeutic benefits.

The *Phaleria macrocarpa* (Scheff) Boerl plant (known locally in Indonesia as *mahkota dewa*) is a plant which originates from the West Papua area in Indonesia and is empirically used as medicine. The ripe fruits of *P. macrocarpa* have red skin, with its fruit flesh, shells and seeds located inside the fruit. It has a smooth round surface, around 3-5 cm in size. The fruit grows on the trunks and branches of the trees and suspended by short stalks. The stalk is attached to the stem and is fibrous and watery. It also has white flesh, [3].

The major ingredients of *P. marcrocapa* fruits are flavonoids, although alkaloids, saponins, tannins, and terpenoids are also found in the fruits in a much lower concentration. The n-hexane extract of *P. macrocarpa* fruit contains terpenoids, whereas the ethanol extract of *P. macrocarpa* fruit and seed contains alkaloids, flavonoids and triterpenoids. It has also been shown that the ethyl acetate extract of *P. macrocarpa* fruit contained flavonoids, triterpenoids and coumarin groups. Other isolated constituents of the fruit include Icariside C3, mangiferin and gallic acid [3].

Traditionally, the fruits of *P. macrocarpa* are frequently used as traditional medicine in conjunction with other ingredients. It is used empirically to treat a variety of chronic diseases such as diabetes mellitus, allergies, cancer, liver problem, heart disease, kidney failure, blood disease, hypertension and stroke [4, 5]. The fruits of *P. macrocarpa* are also known to have antimicrobial activities due to the presence of flavonoids [6]. An experiment which investigated the effects of *P. macrocarpa* fruit extract in diabetic animals exhibited an anti-diabetic property of the extract [7]. This is possibly due to the inhibitory activity on α-glucosidase [8]. In a separate study, it was previously reported that methanol extracts of *P. macrocarpa* caused anti-nephropathic action [9]. Many of these results suggest that the ingredients of *P. macrocarpa* may have properties to alleviate chronic diseases. In conjunction to these, other studies have show that *P. macrocarpa* fruit extracts and fractions may have pharmacological properties for women health conditions, such as premenstrual syndrome, endometriosis, breast as well as cervical cencer. Hence, this review is made based on different international publications on the effect of *P. macrocarpa* fruit extract on different women health conditions in the last 10 years**.

Premenstrual syndrome (PMS)

Since the dawn of time, history has noted that women tend to feel uncomfortable prior to the onset of menses. Unlike men, women of reproductive age have a cyclical hormonal pattern. This cyclical pattern may be associated with premenstrual syndrome (PMS) in some women. As the research of PMS continues, new evidence strongly lead to the involvement of endocrine system in the etiology. There are a number of theoretical rationales for cyclic hormonal changes causing premenstrual symptoms. PMS has been associated to include any of a number of different symptoms, both physical and emotional, which occur in a cyclic fashion just prior to the menstrual flow [10]. These symptoms should begin to lessen with the menstrual flow. Some women may get some symptoms and not others. Many patients have predominantly affective symptoms with very mild somatic symptoms, while other patients, particularly in an outpatient general gynecologic practice, may have somatic symptoms with few affective symptoms. It is not known whether these different groups have similar etiologies. However, it is entirely not clear at this moment that these cyclic changes actually cause PMS. Many women experience one or more symptoms such as depression, mood swings, sleeping disorders and pain. The imbalance of hormones which resulted in progesterone deficiency and estrogen dominance correlates with this symptom [11].

Role of estrogen and progesterone in PMS

Estrogen has been classified as regulator hormone for mood in animals and humans. However, their effects show variations of both anxiolytic and anxiogenic actions, depending on women's age and stage of the reproductive cycle [12]. It is well known that reduced estrogen levels in menopause can cause irritability, panic disorders, anxiety, cognitive dissonance, depression and even sleep disturbance [13,14]. Estrogen replacement therapy in postmenopausal women is consistently reported to improve mood and feelings of general well-being. It has also been reported that women suffering from severe premenstrual dysphoric disorder (PMDD) developed anxiety and other affective symptoms when treated with estradiol in combination with leuprolide, an agonist analog of Gonadothropin Releasing Hormone [15]. Another study was performed to measure the level of estrogen and progesterone at the onset of menstruation [16]. In this study, investigators quantified plasma estrogen and progesterone concentrations during the last six days of the menstrual cycle in women having PMS. Women with anxiety as the main symptom had significantly higher estrogen levels on day five, which was two days prior to the onset of menstruation. The ratio of estrogen to progesterone was consistently higher on day six. The PMS group also showed increased body weight during the last days of the menstrual cycle [16].

As estrogen binds to estrogen receptor (ER), it directly stimulates tissue proliferation and differentiation. ER is a member of a large family of nuclear transcriptional regulators that can stimulate the expression of several genes. ER has two isoforms, ER-ER-α and ß, encoded by two distinct genes [17]. Like that of ER, the progesterone receptor (PR) is also an intracellular steroid receptor that binds progesterone [18]. Both of these hormones have receptors which become the target for PMS treatment. When estrogen and progesterone are affected by particular agents, it may lead to a change in the activities and levels of estrogen and progesterone resulting in hormone imbalance in the body [11].

Role of neurotransmitters

Progesterone is known to induce adverse mood swings. It is hepatically metabolized into alloprenanolone and pregnanolone, both of which serve as agonists on the brain γ-aminobutyric acid A (GABA-A) receptor [19]. This complex system works as a neurotransmitting system in the central nervous system, which inhibits the impulse transmission between cell nerves. Human and animal studies suggested that in some individuals, GABA-A receptor agonists can induce negative symptoms such as anxiety, irritability, as well as aggression. These agonists have the capacity to be anxiolytic, sedative and antiepileptic in which its effects depend on its steady state concentration in the brain. It is known that progesterone metabolite alloprenanolone can serve as an agonist to GABA-A receptor agonist, having a bimodal effect on mood with an inverted U-shaped relationship between concentration and effect [20].

Estradiol concentration is also known to play a role in mood regulation by progesterone [20]. The previous study showed that estradiol treatment during the luteal phase may induce more severe negative symptoms. This indicates that simultaneously estradiol and progesterone provide different responses in the central nervous system, as opposed to when each hormone acts alone. Moreover, the estrogen receptor (ER) alpha has been shown to regulate signaling of neurotransmitter systems associated with the ethiology and treatment of PMDD [21].

Role of prostaglandins in PMS

Prostaglandins (PGs) are hormone-like compounds that function as mediators of a variety of physiological responses such as inflammation, vascular dilation and immunity. They are synthesized in virtually all cells of the body, including in the brain, breast, gastrointestinal tract, kidney and reproductive tract. The anti-inflammatory series 1 PGs are derived from linoleic acid (LA), which is converted to gamma-linolenic acid (GLA), while arachidonic acid, found in animal fats, is the precursor of the pro-inflammatory series 2 PGs and leukotrienes. Imbalances in the PGs series could produce inflammation in tissues, thus resulting into PMS [22, 23]. Studies also shown that women with PMS have abnormal serum levels of PGs and their precursors [24]. Lower levels of circulating prostaglandin E1 (PGE1) can cause increased sensitivity of reproductive tissues to estrogen, making it more vulnerable to normal ovarian hormone cycling.

Prostaglandins may be involved in some changes that occur in the premenstrual period. Symptoms such as cramps, nausea, headache, and depression occurring in the premenstrual period can be reproduced early in the cycle by administering whole blood samples taken during the late luteal phase from a previous cycle [25]. This suggests that some factors in the blood (not likely prostaglandins themselves) may stimulate prostaglandin synthesis at distant sites. Anti-PGs have been helpful for treating PMS although it is not quite effective when taken up to four days prior to menses [22, 26]. Significant improvement in tension, irritability and depression was found when mefenamic acid was administered with the onset of premenstrual symptoms to a group of women having premenstrual and menstrual symptoms [27].

***P. macrocarpa* fraction on the management of PMS**

Our previous study evaluated the efficacy and safety of DLBS1442, a proprietary and standardized semipolar bioactive extract of the *P. macrocarpa* fruit in alleviating symptoms of PMS and primary dysmenorrhea [28]. This was an open study over four menstrual cycles (with two control cycles, followed by two treatment cycles). Women with PMS and/or primary dysmenorrhea, 18–40 years** of age, and with a regular menstrual cycle were included in the study. In the treatment cycles, 100 mg of DLBS1442 was given two to three times daily (for those with mild and moderate-to-severe baseline abdominal pain, respectively), for an average of six days, i. e, three days before until the end of the first three days of the menstrual period. Throughout all four study cycles, daily self-assessment of symptoms related to PMS was made by each subject using a visual analog scale (VAS). Data were descriptively analyzed and profiled in curves of VAS score versus time point evaluation starting from day 5 before menstruation to day 5 of menstruation.

During the trial, twenty-three subjects of average age around 21 to 32 were evaluated for the intention to treat analysis [28]. Most subjects experienced primary efficacy variable (abdominal pain), peaking on days 1–2 of the menstrual phase, with a mean VAS score of 36.8±24.3 mm and 30.0±29.6 mm, respectively, during control cycles. DLBS1442 markedly reduced VAS scores by 13.76±28.27 mm (37.46%) and 13.28±29.06 mm (44.28%), respectively. Other symptoms of PMS were also markedly alleviated by DLBS1442. Some mild adverse events were observed and resolved by the end of the study. This study proved the effectiveness of DLBS1442 in alleviating primary dysmenorrhea and abdominal pain, as well as other symptoms related to PMS. It is also safe and well tolerated in women with PMS and/or dysmenorrhea [28].

Pain associated with endometriosis

Endometriosis is a non-life-threatening condition in which tissue that normally lines a woman's uterus grows in other parts of the body, particularly on peritoneal tissues, bladder, ovaries, fallopian tubes, rectum and other pelvic tissues [29]. Endometriosis has been known as the most frequent cause of pelvic pain in women during reproductive years. It is estimated that endometriosis affects up to 10% of reproductive-age women and about 70% of women with infertility or chronic pelvic pain [29]. A recent case showed that out of 2,080 women with infertility, as many as 1,263 women (60.7%) were diagnosed with endometriosis [30]. When endometriosis occurs, the eutopic endometrium experiences subtle abnormalities, including biochemical reactions that increased production of estrogen, prostaglandins, cytokines, and metalloproteinases [29]. These biological reactions resulted in pelvic pain, chronic pain and fatigue which could lead to infertility. Research to find new remedy for this condition are directed at finding a non-hormonal efficacious agent as a treatment. In this regard, the use of a natural product would be one promising method of treatment for this condition.

There are clear molecular distinctions between endometriotic tissue and normal endometrium, such as the overproduction of estrogen,

PGs and cytokines in endometriotic tissue [28]. Gene expression study of endometrium from women with endometriosis as compared with endometrium from endometriosis-free women has revealed the presence of genes related to infertility, progesterone resistance and implantation failure. Inflammation which also occurs in endometriotic tissue is associated with the overproduction of prostaglandins, chemokines, cytokines and metalloproteinases [29]. In patients with endometriosis, inflammatory and immune responses, angiogenesis and apoptosis are altered in favor of the survival and replenishment of endometriotic tissue. These basic pathological processes depend in part on estrogen and progesterone. Excessive formation of estrogen and prostaglandin and the development of progesterone resistance are regarded as essential apsects of endometriosis treatment. This is because therapeutic targeting of aromatase in the estrogen biosynthetic pathway, cyclooxygenase-2 (COX-2) in the prostaglandin pathway or the progesterone receptor helps reduce pain in the pelvic area [29].

PGs production in endometriosis

PGs are hormones involved in inflammation and pain that are important in the pathogenesis of endometriosis. In particular, prostaglandin E2 (PGE2) and prostaglandin F2 (PGF2) are produced excessively in uterine and endometriotic tissues of women with endometriosis [29-31]. The vasoconstrictive properties of PGF2, together with its ability to cause uterine contractions, contributes to dysmenorrhea, whereas PGE2 can induce pain directly [31]. These PGs are clinically relevant because the reduction of PGs formation by nonselective cyclooxygenase (COX) inhibitors decreases pelvic pain associated with endometriosis [30]. Care must be taken in the long-term administration of nonselective COX inhibitors due to its gastrointestinal side effects. Use of older COX inhibitors has been limited because of an increased risk of gastrointestinal bleeding as well as cardiovascular disease (CVD) [32].

Excessive PGE2 production during inflammation in uterine cells through coordinated induction of multiple enzymes, particularly COX-2 and microsomal prostaglandin E synthase, is believed to be the cause of pelvic pain in endometriosis cases. Endometriotic stromal cells produce large quantities of PGE2, which induce local estrogen biosynthesis and pelvic pain [29,30]. COX-2 is up-regulated to a greater degree in endometriotic stromal cells as compared with endometrial stromal cells; moreover, its expression is also increased in the endometrium of women with endometriosis as compared with that of disease-free women. Thus, increased synthesis of PGE2 in endometriotic tissue may be due to coordinated hyperactivity of COX-2 and microsomal prostaglandin E synthase [29].

Progesterone resistance in endometriosis

In contrast to the clearly unfavourable effect of estrogen on endometriosis, the role of progesterone has remained unclear. Endometriotic tissue produces large quantities of progesterone and contains much lower levels of progesterone receptors than endometrium [34]. Progesterone, induces much lower levels of prolactin expression in endometriotic cells compared to endometrial stromal cells, suggesting that progesterone resistance may lead to endometriosis. Progesterone works by increasing formation of retinoic acid, which induces 17alpha-hydroxysteroid dehydrogenase 2 (HSD17B2) expression in endometrial epithelial cells, in a paracrine fashion. However, endometriotic stromal cells fail to respond to progesterone and hence do not produce retinoic acid. In endometriotic tissue, this lack of retinoic acid leads to the lack of epithelial HSD17B2 and the failure to inactivate estradiol. Combined with high estradiol production, this results in the high levels of estradiol in endometriotic tissue. These findings suggest that eutopic endometrium of women with endometriosis also exhibits progesterone resistance. Progesterone resistance is increased by the low progesterone-receptor levels in endometriotic tissue. In endometriotic tissue, levels of progesterone receptor isoform B (PR-B) is undetectable, while that of the progesterone receptor isoform A (PR-A) isoform is markedly reduced, in endometriotic tissues [29, 34].

Effects of *P. macrocarpa* extract in endometriotic cells

In our attempts to find a natural remedy for endometriosis, *P. macrocarpa* which is commonly known as crown of god or *mahkota dewa*, our study suggested that it was a promising candidate [35, 36]. Originated from Papua, Indonesia, *P. macrocarpa* has been traditionally used by Indonesians to treat different chronic diseases ranging from diabetes, hepatitis to cancer [35-37]. However, most of the treatments using natural products are still based on the empirical information. Thus obtaining scientific proof for their biological activities will need further investigation. As described previously, our group have conducted a clinical study on the use of bioactive fraction DLBS1442 from *P. macrocarpa* to treat primary dysmenorrhea in women experiencing PMS [28]. Further study was aimed at the molecular mechanism of DLBS1442 at the cellular level of endometrial cells [38].

The effect of DLBS1442 was investigated particularly on the expression of genes that encode critical enzymes associated with the onset of endometriosis [38]. These genes include inflammatory enzymes such as cytoplasmic phospholipase A2 (cPLA2) and COX-2, angiogenic vascular endothelial growth factor (VEGF), estrogen and prostaglandin receptors and transcription factors HIF-1 and NFkB of the human endometrial epithelial cell (RL95-2). The focus of this research was to investigate the potential of *P. macrocarpa* extract in addressing the presence of the inflammatory response, cell proliferation, apoptosis inducer, angiogenesis regulation factor expression and in examining its relationship with the expression of inflammatory and sex-hormone receptor genes [38].

A dose-dependent decrease in cell viability and an increase in apoptosis of the RL95-2 cells was generated by exposure to the bioactive fraction of *P. macrocarpa*, DLBS1442, at a dose of 100 µg/ml that increased sub-G1 phase cell population from 7% to 34%. (IC50 around 100 µg/m) [38]. The expression of ERβ mRNA was suppressed by DLBS1442 in an endometrial cell line. Apoptosis-inducing effect of this bioactive fraction against endometrial cells might be correlated to the ERβ related mechanism. DLBS1442 also exhibited inhibitory activity on proliferation, migration and angiogenesis of RL95-2 cell line in a dose-dependent manner, and significantly reduced estrogen receptor level and inhibit eicosanoid signaling pathway by reducing NFκB transcript level and subsequent reduction in iNOS [38]. The free radical scavenging activity of DLBS1442 showed that it displayed strong antioxidative activity, with IC50 around 49,16 µg/ml. The result of this study proved that DLBS1442 has a significant effect on endometriosis cells, preclinically proven for its efficacy in alleviating symptoms of primary dysmenorrhea and endometriosis through its activity as an anti-inflammatory, apoptosis inducer, anti-angiogenic and anti-oxidant agent [38].

Clinical study in endometriosis

In addition to the clinical study for PMS [29] and *in vitro* study on endometiral cell [38], a pilot clinical study was conducted to evaluate the effectiveness of DLBS1442 treatment in alleviating endometriosis and/or adenomyosis-related pain [39]. Ten endometriosis and/or adenomyosis patients have recruited consecutively at Yasmin Clinic Dr. Cipto Mangunkusumo General Hospital from January to March 2013. Pain associated with menses, including PMS pain, dysmenorrhea, dyschezia and dysuria, was measured using the visual analog scale (VAS) at each of the next three menstrual cycles. Patients reporting one or more pain symptoms with a VAS score were given 100 mg of DLBS1442 three times daily for 12 w. VAS score reduction was noted in the first post-treatment menstrual cycle (approximately 5.3 w after treatment initiation) and VAS scores continued to decline over the final two cycles [39]. This study suggested that DLBS1442 was effective in alleviating endometriosis and/or adenomyosis-related pain, as demonstrated by early pain reduction after DLBS1442 consumption [39].

Breast cancer

According to the Centers for Disease Control and Prevention, breast cancer is one of the most common types of cancer in women and is the second-leading cause of cancer deaths [40]. Increasing efforts are made on identifying not only agents that selectively target cancer cells but also signaling pathways that promote or inhibit cancer progression. Targeting a specific pathway is critical to successful treatment of breast cancer as cancer cells reflect the balance between cell death and survival. The synergy between

inhibition of growth promotion and stimulation of apoptotic pathway may enhance tumor cell sensitivity to apoptosis induced by anticancer agents. Apoptosis is a form of programmed cell death which is precisely regulated and plays important roles during embryogenesis and immunology [40, 41]. Alterations in the physiological execution of apoptosis lead to the extension of cellular survival and thereby promote cancer development. Apoptotic cell death involves a series of biochemical events leading to a characteristic cell morphology, including blebbing, loss of membrane asymmetry and attachment, cell shrinkage, nuclear fragmentation, chromatin condensation and chromosomal DNA fragmentation as well as by cleavage of PARP (poly(ADP-ribose) polymerase). It is well recognized that BCL-2 family proteins are central regulators of apoptosis and act as a checkpoint through which survival and death signals must pass before the cell fate is determined. An apoptotic death stimulus activates caspases, the major executioners of this process, either directly or via the activation of the mitochondrial death program. Mitochondrial apoptosis pathway is linked to COX-2 inhibition and there has been accumulating evidence that inflammatory tissue damage proceeds the cancer development. COX which catalyzes the transformation of arachidonic acid into PGs and thromboxanes (TXs), is an important enzyme involved in mediating inflammatory process. COX-2 has been reported to be significantly overexpressed in a variety of human malignancies. Previously, it was shown that COX-2 was overexpressed in prostate cancer (41,42). It is also overexpressed in breast cancer, cervical dysplasia and cancer, hepatocellular carcinoma, pancreatic cancer, skin cancer, lung cancer, gastric cancer, and other cancer types (43-45). In human breast cancer, overexpression of HER-2/neu, which occurs in 20-30% of human breast cancer, is also associated with a poor prognosis for the patient (46).

P. macrocarpa extract effect on breast cancer cells

Anti-proliferative and induction of apoptosis conferred by a bioactive fraction of *P. Macrocarpa* DLBS1425 on breast cancer cells, MDA-MB-231 and MCF-7 cells had been investigated. DLBS1425 showed an inhibition of proliferation in both cell lines. Induction of apoptosis was shown by DNA fragmentation, activation of caspase 9, and regulation of Bax and Bcl-2 at the mRNA level. DLBS1425 downregulated COX-2, cPLA2, and VEGF-C mRNA expressions. DLBS1425 also down-regulated c-fos and HER-2/neu mRNA expression in TPA-or fatty acid-induced MDA-MB-231 cells. These findings demonstrate that DLBS1425 has anti-proliferative, anti-inflammatory and anti-angiogenic properties [47].

Another study reports that DLBS1425 exhibited inhibition of proliferative, migratory and invasive potential of MDA-MB-231 in a dose-dependent manner and significantly reduced phosphoinositide-3 (PI3)-kinase/protein kinase B (AKT) signalling by reducing PI3K transcript level and subsequent reduction in AKT phosphorylation. Further, it induced pro-apoptotic genes including BAX, Bcl-2-associated death promoter (BAD) and p35 upregulated modulator of apoptosis (PUMA) and consequently induces cellular death signal by caspase-9 activation, promoting poly ADP-ribose polymerase (PARP) cleavage and DNA fragmentation. Our results suggest that DLBS1425 is a potential anticancer agent which targets genes that are involved in both cell survival and apoptosis in MDA-MB-231 breast cancer cells [48].

P. macrocarpa extract reduces cardiotoxicity when administered with chemotherapy

Treatment of breast cancer is done through 5-fluorouracil: doxorubicin: cyclophosphamide (FAC) regimen. The use of FAC is known to generate severe toxicity. Study on mice showed that FAC regimen equivalent to the dose administered in human resulted in muscular damage of the heart. This led to animal mortality in the study. Therefore, the administration of FAC regimen on mice has to be adjusted to one-eighth of the initial dose in order for the mice to survive. On the contrary, the use of DLBS1425, a bioactive fraction from *P. macrocarpa* fruit with a dose equivalent to 300 mg three times daily did not induce any toxicity effect on the mice. Furthermore, the use of DLBS1425 in adjunct with FAC regimen is proven to exert protective property on the cardiac muscle of the mice. It also helps increase hemoglobin level in the blood. In light of these findings, DLBS1425 is a potential candidate for adjunct therapy with chemotherapy [49].

Cervical cancer

Cervical cancer is a sexually transmitted disease that results from infection with oncogenic human papillomavirus (HPV). It is the leading cause of cancer mortality in developing countries due to the high rate of HPV infection and lack of prevention steps in susceptible women. The most common HPV genotypes found in patients with invasive cervical cancer are 16, 18, 31, 33, 35, 45, 52 and 58. Out of these HPV genotypes, HPV 16 and 18 are classed as high-risk oncogenic types and are most likely to persist and progress from premalignant cervical disease to invasive cancer. These HPV types play a pivotal role in immortality and malignant transformation of infected cells [50].

The ability of HPV in generating cervical cancer is dependent on the transformative potential of its viral oncogenes. Cervical cancer formation has been proven to be dependent to the expression of high-risk HPV oncogenes, E6 and E7. These pleiotropic oncogenes are pivotal in cervical cancer formation due to their ability to reduce the intracellular availability of the host's cell cycle inhibitor (onco-suppressor) proteins; p53 and retinoblastoma (Rb). E6 proteins bind p53 and direct its rapid degradation while E7 proteins bind and inactivate the Rb protein. These led to the profound loss of function of p53 and Rb proteins that cause chromosomal instability and accumulation of oncogenic mutations resulting in cancer. Furthermore, E6 stimulates expression of HIF-1α which in turn will stimulate neoangiogenesis for tumor cells, providing the vascularization necessary for cancer formation. HIF1-α mediates angiogenesis through activation of VEGF pathway. E7 inactivates $p21^{CIP-1}$ and $p27^{KIP-1}$ which are a cell-cycle regulatory protein that interacts with cyclin-CDK2 and-CDK4, inhibiting cell cycle progression at G1. This results in growth stimulation of infected cells [50].

Early cervical cancer is treated by removing or destroying the precancerous or cancerous tissue. However, this treatment is no longer effective once the cancerous cells metastasized to other organs. The standard treatments for cervical cancer are surgery, chemotherapy and radiation therapy. These treatments can be harmful to other normal tissues and may facilitate cancer cell invasion and metastasis [51].

Effect of *P. macrocarpa* on cervical cancer

Several studies have pointed out the potential of *P. macrocarpa* as a treatment for cervical cancer. As described previously, *P. macrocarpa* is known to contain gallic acid which is inhibitory to the growth of many types of cancer cells. Study on cervical cancer cell (CaSki) showed that gallic acid, a molecule isolated from *P. macrocarpa*, is able to inhibit cell proliferation of this cell [51]. In addition, gallic acid has also shown its anti-proliferation action on human cervical cancer HeLa and HTB-35 cells, but not on normal HUVEC cells [52]. This result supported the idea that gallic acid has selective dose-dependent cytotoxicity on cervical cancer cells only. The study also evaluated the antiproliferative activity of gallic acid on cervical cancer cells which showed that it inhibited cell proliferation of both HeLA and HTB-35 cells [51].

Certain pre-invasive squamous intraepithelial lesions transform into invasive squamous cell carcinoma and spread to other areas of the body through blood and lymphocyte system. Therefore, cell migration and invasion ability is critical in the cancer progression in the body. To examine the effect of gallic acid on cell migration and cell invasion ability, wound scratch assay and matrigel™ invasion was performed on HeLa and HTB-35 cervical cancer cells [51]. The result showed that gallic acid was able to inhibit cell migration and reduce the invasiveness of both cell lines, although the result was more significant in the HeLa cells [51]. One of the most critical steps in cancer formation is angiogenesis. Gallic acid was also proven to inhibit angiogenesis in HUVEC cells. It significantly inhibited elongation of the tube in HUVEC cells compared to the untreated cells [51].

ADAMs are ectodomain shedding that function as metalloproteases. The disintegrin-metalloproteinases of the ADAM family are associated with proteolytic 'shedding' of membrane-associated proteins and hence the rapid modulation of key cell signaling pathways in the tumor microenvironment. ADAM17 is an important member of the ADAM family which is involved in the proteolysis of

collagen IV of the ECM and also the release of several integrins from the cell surface, indicating that ADAM17 affects the migration activity of a variety of cells, including cervical cancer cells. It is a primary upstream component for multiple epidermal growth factor receptor (EGFR) pro-ligands. EGFR binds with its ligands and subsequently activates downstream mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinases (ERK) and phosphatidylinositol-3-kinase (PI3K)/Akt pathways, which contribute to invasiveness and other malignant phenotypes of a tumor. EGFR is a 170-kDa transmembrane glycoprotein receptor encoded by the Her-1 proto-oncogene located on chromosome 7p12. It functions through dimerization, which activates a tyrosine kinase domain that regulates cell growth, differentiation, gene expression and development. EGFR is present in is expressed in a wide variety of solid tumors, including cervical cancer. Gallic acid helps reduce the invasiveness of cervical cancer cells through down-regulation of ADAM17 and EGFR expression and the dephosphorylation of Erk and Akt in the two cell lines which affected the cell's proliferation and invasion ability. In addition to the inhibition of protein expression, gallic acid significantly reduced ADAM17 activity [51].

Gallic acid is known to exhibit a cytotoxic effect on HPV-positive cells such as HPV-18 positive human cervical carcinoma cell line (HeLa) and human cervical epithelial cell line containing stable HPV-16 episomes (HPVep). Gallic acid showed anti-tumor activity on HeLa cells containing HPV18 genome and inhibits proliferation of HPVep cells containing stable HPV-16 episomes. Gallic acid may have a broad-spectrum antiviral activity against cells containing viruses. HPVep cells are human cervical keratinocyte cells containing stable HPV-16 episomes, and exhibited episomally replicating HPV-16 genomes at an estimated copy number between 10-50 genomes per cell. HPVep cells express HPV genes E6 and E7 stably. Compared to normal keratinocytes, HPVep cells show partial but incomplete degradation of p53. HPVep cells display features that are similar to HPV-infected human keratinocytes and appear to be a suitable model to study the mechanism by which GA reduces the viability of HPV-positive cells. GA was shown to increase apoptosis of HPVep cells significantly in a dose-dependent manner, without generating cell necrosis. It is predicted that GA induces HPVep cell death by inducing cell apoptosis. A similar result was apparent in the gallic acid treated HeLa cells. HPVep cells contain stable HPV-16 episomes and express early viral oncoproteins E6 and E7. It is known that HPV-16 E6 is targeted to degrade the tumor suppressor protein p53 through the ubiquitin pathway. Therefore, it is predicted that gallic acid may increase the p53 expression which counteracts E6 function, leading to an increase in apoptosis. Observation of the molecular mechanism of apoptosis showed that gallic acid up-regulated the pro-apoptosis protein, Bax, and induced caspase activity. It also down-regulated the expression of anti-apoptosis proteins such as Bcl-2 and x-linked inhibitor of apoptosis protein (Xiap). In contrast, delayed expression of pro-apoptosis related proteins was observable in non-cancerous cells and no reduction of survival-related protein expression was found in the non-cancerous cells [53].

CONCLUSION

Phaleria macrocarpa fruit has been proven to be potential as a treatment for many gynecological conditions such as premenstrual syndrome (PMS), endometriosis, breast cancer, and cervical cancer. It helps regulate hormone imbalance in women with problems relating to their menstruation cycle, especially during PMS. It helps alleviate symptoms of primary dysmenorrhea and endometriosis through its bioactivity as anti-inflammation, apoptosis inducer, anti-angiogenic and anti-oxidant agent. *P. macrocarpa* fruit extract also showed selective anti-proliferative, anti-inflammatory, and anti-angiogenic activity on breast and cervical cancer cells. It regulates cancer cell progression through numerous different pathways, making it highly favourable to be developed as a cancer treatment, whether as a single treatment or as an adjunct therapy. However, further study, both preclinical and clinical studies are needed to ascertain its use in women to be effective and safe.

CONFLICT OF INTERESTS

Both authors declare that there is no conflict of interest in the preparation of this manuscript.

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