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Potential of mangostin pericarp (*Garcinia mangostana Linn.*) for cancer in women: A review

Fahriani Istiqamah Jafar[1], Muchtaridi Muchtaridi[2*]
[1, 2] Department of Pharmaceutical Analysis and Medicinal Chemistry, Faculty of Pharmacy, Padjadjaran University, Sumedang, Indonesia

Abstract
Breast cancer and cervical cancer are the highest causes of women death in developed and developing countries, compared to other cancers. Currently, anticancer therapy was classified as less effective because, besides having side effects for the body, anticancer therapy is also not selective because it not only kills cancer cells but also normal cells. Mangosteen pericarp is one of the medicinal plants which become the object of research. The active compound in mangosteen is xanthone, it has activity as an anticancer. α-mangostin is able to inhibit cell proliferation and induce programmed cell death (apoptosis), through various mechanisms including α-mangostin activity in breast cancer cells through inhibition of the HER2/P13K/Akt and MPK signaling pathway against breast cancer cells, in addition, α-mangostin also has activity against cervical cancer through the mechanism of cytochrome C release, increases Bax, decreases Bcl-2 and it's able to activate caspase9 / caspase3 in cervical cancer. Several studies have been conducted to test the anticancer activity of xanhtone derivative compounds. These studies can be used as learning materials or as a basis for subsequent development to obtain compounds that have better physicochemical and bioactivity properties.

Keywords: breast cancer, cervical cancer, mangostin pericarp, xanthone

Introduction
Women's health is a parameter of the country's ability to provide health services to the community. Women play a major role in the sustainability of the nation's next generation for a country, recently there are many health problems in women, one of them is cancer. Cancer is a disease due to abnormal and uncontrolled cell growth, and it has the potential to damage or metastasize to other body parts. Some factors that increase cancer risks such as smoking, infection, radiation, lack of physical activity, poor diet, obesity and environmental pollution. Now, cancers are still becoming the world health problem, and cancers are the second leading cause of death in developing countries [13].

The World Health Organization (WHO) states that patients with cancer cases, each year more than 10 million and increase to 20%. It is estimated that in 2020 the number of cancer patients will increase to 20 million cases and in the next 10 years it is estimated up to 84 million of them will die if there is no adequate treatment. Breast cancer is one type of cancer that attacks the milk glands, glandular tracts, and breast supporting tissues that are found mostly in women. According to the American Cancer Society in 2015 there were 231,840 new cases and 40,290 cases of them causing death with a high frequency of cases per year in the world, around 1,152,161 cases [7]. Estimated in 2018, about 2.1 million new breast cancer cases are diagnosed around the world, the disease is the most often diagnosed in most countries (154 out of 185) and it's leading the cause of death in more than 100 countries [2]. Several studies have shown that there are factors associated with the increasing risk or the possibility of breast cancer. These factors are risk factors which include age, genetic risk factors, family history of breast cancer, not having children or having the first child after age 30, oral contraception, hormone therapy after menopause, earlier menstruation (before age 12) or experiencing slow menopause (after age 55), smoking, and alcohol consumption. Women are more at risk of developing breast cancer than men, because men have fewer hormones estrogen and progesterone, which can encourage the growth of breast cancer cells [9].

Cervical cancer is a type of cancer which can affect most women in productive age or women over the age of 18. Cervical cancer ranks fourth as the most diagnosed cancer and the fourth leading cause of cancer deaths in women. In 2018 estimated 570,000 cases and 311,000 deaths worldwide [2]. Based on cervical cancer research, there are several risk factors including sexual intercourse at a young age, giving birth to many children and short spacing of pregnancies, using oral contraceptives over 4 or 5 years, smoking, changing partners in sexual relations increases the likelihood of being infected with HPV. Viral infection Human papilloma virus (HPV) has various types, including types 16,18,31,33 and 35 which are often associated the relationship with moderate and severe dysplasia [17]. Cancer can be prevention by avoiding the causes, such as smoking, exposure to sunlight and UV light, exposure to radiation and other carcinogens. It's can also be prevented by adjusting to a healthy lifestyle and diet [24].

Medically, the treatments of cancers disease are carried out in several ways, namely surgery, radiation and chemical treatment (chemotherapy). However, these treatments cannot completely heal cancer. Cancer treatment with chemotherapy not only has side effects for the body but also it has a disadvantage because it kills the cancer cells and affects the normal cells instead. Therefore many research carried out on an anticancer compound from natural products, to obtain compounds that can be used as new treatments candidate that selectively kill cancer cells without affecting normal cells [11].

Research for the discovery of cancer drugs is still ongoing.

One source of the discovery of cancer drugs can be found in the mangosteen. Mangosteen (*Garcinia mangostana L.*) is a fruit that grows in Southeast Asia such as Thailand, Malaysia, Myanmar, the Philippines, Sri Lanka, and India. Mangosteen is known as The Queen of Fruits because it is one of the tropical fruits with good taste and widely liked. Mangosteen has a deep purple or reddish color, with soft and juicy white pulp, with a hint of sour and sweet taste and a fragrant aroma [14].

Mangosteen (*Garcinia mangostana L.*) is one of the plants that have potential as a medicine. The potential is in the skin of the mangosteen (pericarp), it contains compounds which able to provide a pharmacological effect for the body because there are more than 300 species of bioactive compounds such as xanthones, triterpenoids, flavonoids and benzophenones [4]. Some studies show that mangosteen pericarp contains abundant xanthones compounds such as α-mangostin, β-mangostin, γ-mangostin, gartanin, 8-deoxygartanin, and mangostanol [33]. The α-mangostin compounds in mature mangosteen have double the content compared to the young mangosteen [18]. Mangosteen pericarp is used as traditional medicine by the community for the treatment of diarrhea, trauma, wounds and skin infections [48], dysentery, festering and chronic ulcers [43].

Mangosteen Pericarp *(Garcinia mangostana Linn.)*

Some researchers have conducted research related to the pharmacological effects of mangosteen pericarp. The study found that xanthone compounds contained in the mangosteen pericarp have various pharmacological effects [36]. The xanthone compounds found in mangosteen pericarp are not only anticancer, but also analgesic [5], anti-inflammatory [3], antioxidants [47], anticonvulsants [25], antibacterial inhibitors [42], hepatoprotective [6], antimalarials [10], antimicrobial, antituberculosis [44], antifungal [15], neuroprotective [46], cardioprotective [8] and immunomodulating effects [45].

Nakatani *et al*. (2002), in his research using mouse cells, stated that five micrograms of gamma-mangostin were able to stop inflammation by inhibiting the production of the cyclooxygenase-2 enzyme that can cause inflammation. In fact, gamma-mangostin has a better anti-inflammatory effect than anti-inflammatory drugs in the market [32].

While the study by Pe'rez-Rojas, he looked at the renoprotective effect on α-Mangostin. In that study, rats were induced with Cisplatin (CDDP) so become nephrotoxicity, then for 10 days was given α-Mangostin 12.5 mg/kg/day. The results showed that α-Mangostin has a retinoprotective effect because it can help in the elimination of oxidative/nitrosative stress in the kidney and reduce kidney dysfunction. A-Mangostin compounds can also increase the expression of catalase and mRNA tumors alpha necrosis factors and beta transformation growth factors [35].

Ragavendra *et al.* (2011) conducted a study of the antioxidant activity of mangosteen extract with 1,1-diphenyl-2- picrylhydrazyl (DPPH). In his study, it was found that mangosteen pericarp had a free radical activity of 93.26 ± 0.91% at a concentration of 200 µg/mL. DPPH is a paramagnetic compound with odd electrons and has a strong absorption band at 517 nm in methanol. Absorbance decreases with color changes from purple to yellow caused by antioxidants through hydrogen administration of α-Mangostin in the formation of stable DPPH-H. Results of the study indicate that Mangosteen is a potential source of natural antioxidants [37].

Ho *et al.,* (2002) carried out extraction and purification of 6 xanthone compounds from mangosteen pericarp by partitioned chromatography. The cytotoxic effect of this compound was tested on 14 different cancer cells using the MTT method. The results showed that one of the xanthone derivatives that could be identified as garcinone e had a strong cytotoxic effect on all hepatocellular carcinomas (HCC) cells. Garcinone E can be a good potential for cancer treatment [11].

Based on research conducted by Nakagawa, at the concentration of 10 µM showed inhibition of HL60 human leukemia cells through induction of apoptosis, while at 20 µM it caused cytotoxic effects [31]. α-mangostin has antiproliferative activity and potent apoptosis in leukemia cells [26]. Alpha mangostin and gamma mangostin induce cell cycle retention and apoptosis in colon cancer DLD-1 cells [28]. α-mangostin reduces lymph node metastasis by carrying a p53 mutation [41].

Mangosteen For Woman Health

Garcinia mangostana L. (mangosteen or queen fruit) has been used for a long time as a traditional medicine for treating various medical conditions. Mangosteen has many benefits and can be used for women's health such as treating leucorrhoea, osteoporosis, anti aging, depression, reducing menstrual disorders such as dysmenorrhea and overcoming irregular menstruation [12].

Preeclampsia is the onset of hypertension accompanied by proteinuria at 20 weeks' gestation. This study was conducted to prove that mangosteen pericatp extract (MPE) can reduce NFKB, sFlt-1, TNF-α and clinical syndromes (hypertension and proteinurin). This study using preeclamptic mice (MMP) with anti-rat-Qa2 40 ng doses. The study divided into 5 groups which consisted of negative control groups, MMP groups and 3 UMK groups with doses (200 mg/kg, 400 mg/kg and 800 mg/kg). The results obtained were HIF-1α, NFkB, sFlt-1, MDA, TNF-α, blood pressure and proteinurin MMP protein higher than MPE. The results of the analysis prove that the dose of 800 mg/kg is the most effective, but it’s not significant for proteinurin. MRE as a source of antioxidants which can block free radicals, induces antioxidant enzymes for reperfusion, so it can function as an anti-inflammatory and prevent injury [38].

Skin lightening products are not only traded for cosmetic purposes but also as clinical care for treating hyperpigmentory disorders such as freckles, pregnancy marks, melasma and to even skin tone. Xanthone compounds have the potential as skin lightening to treat hyperpigmentation because they can inhibit tyrosinase enzyme activity. The purpose of this study was to determine antioxidant inhibitory activity and tyrosinase from mangosteen pericarp extract (*Garcinia mangostana L.).* The results showed that methanol (MeOH) and ethyl acetate (EtOAc) extract showed antioxidant activity at IC_{50} 0,04 mg/mL and IC_{50} 0,05 mg/mL. Mangosteen pericarp extract also inhibited tyrosinase enzyme activity in EtOAc extract with inhibition results of 61,11% at a concentration of 0,05 mg/mL. Based on the results obtained by whitening cream containing extracts of mangosteen pericarp EtOAc formulated into oil-in-water cream (O/W) and physicochemical properties such as organoleptic properties, stability, viscosity and pH were carried out [1].

Mangosteen Pericarp Bioactivity Against Breast Cancer

Mangosteen pericarp (*Garcinia mangostana L.*) with methanol extract is effective against human breast cancer SKBR3. SKBR3 is a cultured cell with various concentrations, ranging from 0–50 micrograms per ml for 48 hours. Methanol extract can inhibit the development of cancer cells in concentrations with ED (50) of 9,25 +/- 0,64 microgram/mL. Methanol extract has a significant effect on antiproliferative associated with apoptosis in breast cancer cell lines by determining changes in morphology and oligonucleosomal DNA fragments [29].

Lee *et al.* (2010) stated that the effect of α-mangostin in suppressing matrix metalloproteinase-2 (MMP-2) and matrix metalloproteinase-9 (MMP-9) induced by 12-O tetradecanoyl phorbol-13-acetate (TPA) through the extracellular regulation signal pathway (ERK) in MCF-7 breast cells. In this study, the Boyden Chamber assay and Adhesion assay methods were used. The results show that α-Mangostin can inhibit the ability of induction, invasion, and TPA migration. The evaluation results also show that α-Mangostin can inhibit signal activation from extracellular-signal regulation (ERK1/2) that involved in the regulation of enzyme, protein, and messenger RNA MMP-2 and MMP-9 activity caused by TPA [21].

Setiawati *et al.* (2012) Breast cancer have very complex morphological and molecular characteristics. Estrogen receptors are one of the biomarkers in the development of breast cancer. The results showed that mangosteen pericarp extract showed anti-proliferation activity and apoptosis induction of MCF7 cells with IC_{50} values 45 μg/mL [40].

Kritsanawong *et al.* (2016) proved that α-mangostin from mangosteen pericarp extract was able to reduce T47D cell viability at IC_{50} 7,5 ± 0,5 μM after 24-hour extract. This study stated that α-mangostin compounds were able to inhibit cell proliferation and induce T47D breast cancer cell apoptosis through the HER2/PI3K/Akt and MAPK signaling pathways [19].

Sampath & Vijayaragavan (2008) states that α-mangostin shows activities against breast cancer cells (BC-1) and oral epidermoid carcinoma. α-mangostin also maintains the integrity of the myocardial membrane. Normal cell recovery is associated with a cytoprotective role of α-mangostin [39].

Another study stated that α-mangostin can apoptosis MDA-MB231 breast cancer cells by the mechanism of P13K/Akt [20]. α-mangostin also induces apoptosis of breast cancer cells by inhibiting fatty acid synthesis [23].

Mangosteen Pericarp Bioactivity Against Cervical Cancer

The compound α-mangostin is known to have efficacy as an anticancer. However, the mechanism and activity of α-mangostin in cervical cancer is still unclear. Some studies report that α-mangostin effectively inhibits cell viability, has activity against cervical cancer through the mechanism of cytochrome C release, increases Bax, decreases Bcl-2 and can activate caspase 9/caspase 3 cascade in cervical cancer. This study shows that α-mangostin can inhibit tumor growth in cervical cancer cells by increasing the number of ROS to activate the ASK1/p38 signaling pathway and damage the integrity of mitochondria and induce apoptosis in cervical cancer cells [22].

Cervical cancer is the second leading cause of death among Mexican women. Treatment with cis diamminedichloroplatinum (II) (CDDP) has some serious side effects. α-mangostin has a protective effect against CDDP-induced nephrotoxicity and has antioxidant, antitumor, and anti-inflammatory activities. Based on the research, in-vitro and in vivo α-mangostin tests were carried out on the proliferation of cervical cancer cells combined with CDDP. The results of this study indicate that α-mangostin can be used as a neoadjuvant in cervical cancer therapy [34].

Other studies conducted cytotoxicity tests on mangosteen pericarp using fractions and isolates against HeLa cells. Mangosteen pericarp was extracted using ethanol (96%), then fractionation was carried out with n-hexane, ethyl acetate, and water. The fraction results were tested by column chromatography to obtain isolates. After obtaining Isolate, the isolates were tested to see cytotoxicity in HeLa cells with the Water Soluble Tetrazolium (WST) test. The compounds obtained from the isolation process are I-A and II-5B (ethyl acetate fraction). The results showed that IA isolates had a high cytotoxic effect on HeLa cells with IC_{50} 6,51 μg/mL then on ethyl acetate fraction 7,92 μg/ml, ethanol extract 18.09 μg / ml, n-hexane fraction 44,70 μg/mL and II-5B isolates 44,10 μg/mL. This study shows that mangosteen pericarp has a cytotoxic effect on cervical cancer [30].

Conclusion

With the rapid development of studies on new drugs, herbal plants can be used as an option in cancer treatment. Xanthone compounds found in mangosteen pericarp (*Garcinia mangostana L.*) have pharmacological activity as anti-cancer by arresting the cell cycle, inhibiting proliferation of cancer cells, inducing apoptosis and differentiation, reducing inflammation, inhibiting adhesion, invasion and cancer cell metastasis.

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