The Anticancer Properties of Guava Leaves (*Psidium guajava* L.) and Turmeric Rhizome (*Curcuma longa* L.) Against Breast Cancer: A Literature Study

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Abstract

Breast cancer, one of the most deadly diseases occurring in women, is caused by factors. In the healing process, the sufferer needs treatment, such as radiation techniques, surgery, and chemotherapy. But, these techniques have avoidable weaknesses that damage healthy cells. To date, natural sources can be utilized in medicine field. Guava (*Psidium guajava L.*) and turmeric (*Curcuma longa L.*) are two common plants obtaining compounds that inhibit the growth of cancer cells based on phytochemical properties. This study was written to review the potential both of plants as anticancer agents. Through the literature, guava leaf extract consists of flavonoids, tannins, alkaloids, saponins, terpenoids that inhibit the proliferation of cancer cells. Besides, turmeric also has tannins, alkaloids, terpenoids, flavonoids, glycosides, sterols, and curcumin. The presence of curcumin reduces histamine production which induce inflammation and decrease toxin. Because of curcumin, breast cancer cells have dehydration before apoptosis.

Keywords: apoptosis; curcumin; natural sources; phytochemical.

INTRODUCTION

Various deadly diseases always lurk in human welfare at any time worldwide. One of those diseases suffered in many countries is cancer. Cancer is the second highest cause of death after cardiovascular disease. Based on WHO data, the worldwide mortality rate due to cancer reached 13%. Every year, there were 12 million people in the world suffering from cancer and as many as 7.6 million of them died. The number of cancer patients will continue to increase. In 2030, it is estimated that the number will reach 26 million people with death is expected about 17 million (Ministry of Health 2015).

Based on Basic Health Research Data in 2007, the national rate of cancer patients in Indonesia was 4.3 per 1000 population, with higher cancer rates occurring in women than men. In women, 5.7 per 1000 people in Indonesia suffered from cancer. Meanwhile, 2.9 per 1000 male population experienced cancer (Ministry of Health of Indonesia 2013; Dewi and Hendrati 2015).

The common type of cancer attacking women is breast cancer which causes death in women. The American Cancer Society (2008) reported that as many

as 1.3 million women worldwide were diagnosed with breast cancer. Every year, approximately 465,000 women died from breast cancer. Within 25 years, the number of patients had increased by around 30% in developed countries (Wahyuni 2015).

The primary cause of breast cancer is not yet fully known, but it is believed to be multifactorial or caused by many factors. There are several factors of breast cancer, such as genetic disorders facilitating the emergence of cancer cells, chronic irritation and inflammation, radiation, exposure to certain chemical compounds, carcinogenic foods, and others (Suryaningsih and Sukaca 2009; Dewi and Hendrati 2015).

Treatments of breast cancer are usually done with radiation techniques, surgery, and chemotherapy. However, these techniques have side effects because they sometimes enhance cancer cells to spread to other parts of the body, damage healthy cells, and also trigger cancer cells to mutate. Thus, the discovery of new drugs that are safer with fewer side effects is needed in overcoming this problem (Muhartono and Subeki 2015).

It may be overcome by utilizing plants as herbal medicines as some plants produce bioactive compounds

potentially used as anticancer. Guava (*Psidium guajava L.*) and turmeric (*Curcuma longa L.*) are two common plants producing secondary metabolites such as tannins, flavonoids, alkaloids, and saponins (Correa et al. 2016). Turmeric (*Curcuma longa L.*) rhizome contains curcumin which also has anticancer properties which can inhibit carcinogenesis (Meiyanto 1999; Nurrochmad 2004). Thus, the combination of Guava (*Psidium guajava L.*) and Turmeric (*Curcuma longa L..*) can be used as an alternative to prevent breast cancer without or with fewer side effects.

METHODS

This review paper was done with a literature study. A literature study was carried out to support ideas that are based on a strong theoretical basis on several sources consisting of several leading journals. The secondary data were obtained to support the idea (Asiandu and Malayudha, 2022) and used in analyzing the usefulness of the idea to conclude the final conclusion through some stages (Sari et al. 2020). Furthermore, the benefits to be achieved from writing this scientific work are to provide information about the dangers of breast cancer and to socialize these two materials as the formation of pharmaceutical drugs to reduce the number of breast cancer patients safely.

RESULTS AND DISCUSSION

Cancer Cell
Cancer cells are normal cells that have undergone a genetic mutation causing their growth to be uncontrolled and uncoordinated with other body cells. The process of forming cancer cells is known as carcinogenesis, a somatic event, and is caused by an accumulation of genetic and epigenetic changes leading to changes in the normal regulation of molecular control of cell growth (Figure 1). These genetic changes can be in the form of activation of proto-oncogenes and/or inactivation of tumor suppressor genes which can trigger tumor formation (Kondo 1993; Nurhayati and Lusiyanti 2006).
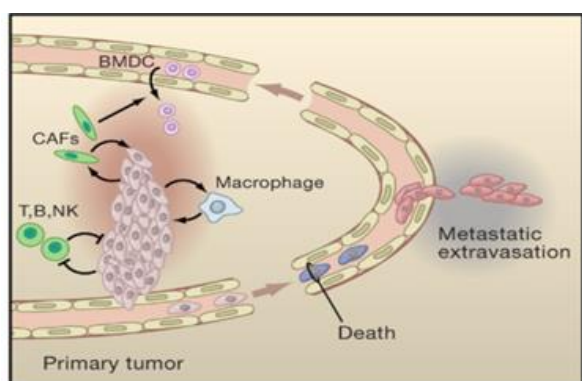

Figure 1. Cancer cell invasion (Taken from Gupta and Massague, 2006).

Generally, there are two types of cancer cells, benign, and malignant cancer. Benign cancer cells have a low growth rate and do not spread to other parts. Meanwhile, malignant cells have a rapid growth rate, invade and damage surrounding tissue, and spread to other organs. Invasion of cancer cells allows these cells to move into the blood vessels to be transported to other organs emerging new cancer in other organs (Lumongga 2008).

The general characteristic of cancer cells is the ability to grow rapidly and reduce the body's normal control mechanisms. Abnormal genes in cancer are called oncogenes (Guyton and Hall 1997; Putri et al. 2012). Cancer cells can not maintain when to stop cell division. They divide uncontrollably which will compete with normal cells using oxygen and nutrients from the body. These cells will replace normal cells and cause pain that ends in death (Nurhayati and Lusiyanti 2006).

Breast Cancer
Breast cancer is one of the most common types of cancer in women, although this cancer can also occur in men. The risk of breast cancer cases increases at the age of 40 years, which attacks more on the left breast and the upper part of the breast, close to the arm (Wijayakusuma 2008; Rahmatari 2014). According to the Indonesian Ministry of Health in 2013, breast cancer contributed 30% and was the most dominant type of cancer in Indonesia (Dewi and Hendrati 2015).

Breast cancer is a carcinoma originating from the ducts or lobules of the breast which is an international women's health issue. Breast cancer is the most common problem in developed countries and is the number two problem in developing countries after cervical cancer. Overall, breast cancer is the second leading cause of death after lung cancer (Suyatno 2010; Sumiatin, 2013).

A common symptom of breast cancer is a lump in the breast that can be felt and will get harder, irregular, and cause pain. Other symptoms are changes in size and shape, wrinkling of the breast skin that resembles an orange peel, presence of pus, blood, watery fluids, and discharge of milk in a woman who is not pregnant or breastfeeding. Breast cancer is also characterized by swelling in one breast, itchy and painful nipples, bone pain, swelling of the arms, and weight loss (Suryaningsih and Sukaca 2009; Dewi and Hendrati 2015).

Breast cancer can be caused by several factors. These factors are combined into hormonal factors which include age at menarche, age at first pregnancy, parity, history of breastfeeding, infertility, and long-term use of hormonal contraception. Early menarche or first menstruation at the age of below 12 years will increase the likelihood of breast cancer. The risk of breast cancer increases with the increasing age of women (Priyatin et al. 2013).

Breastfeeding duration affects the risk of breast cancer. Women who breastfeed in the 4-6 month range have a greater risk of breast cancer than 7-24 months. It

shows that the longer the breastfeeding time, the lower the risk of breast cancer. Meanwhile, the consumption of fatty foods also affects the high risk of breast cancer in women. In addition, passive smoking, alcohol consumption, and low physical activity also affect the occurrence of breast cancer (Yulianti et al. 2016).

Side Effects of Breast Cancer Treatment
There are several methods used to treat breast cancer. Methods of treating breast cancer include radiation, surgery, and chemotherapy. However, these methods have side effects, such as the spread of cancer cells to other organs and the mutation of cancer cells (Muhartono and Subeki 2015).

Side effects caused by chemotherapy can be in the form of physical and physiological disorders. Effects that may appear include nausea, vomiting, alopecia, and so on. Patients who feel the side effects of chemotherapy treatment, try to overcome these effects by resting or even using anti-emetic or analgesic drugs (Wahyuni 2015).

Severe side effects also often occur in post-chemotherapy patients, and often these side effects cannot be tolerated by patients which can even cause death. In addition, the side effect of post-chemotherapy patients may feel is anxiety (Setiawan 2015).

Meanwhile, radiation therapy for cancer patients also causes side effects, especially in children. Those effects can appear faster or slower and can occur locally or systemically, from small to large depending on age, location of irradiation, area of irradiation, vital organs around the tumor, and also the dose (Yunus 2008).

Therefore, the use of natural herbal ingredients is very important in preventing the growth and spread of breast cancer cells. These herbal ingredients can be derived from guava leaves (*Psidium guajava L.*) which contain secondary metabolites such as tannins, flavonoids, alkaloids, and saponins that have anticancer properties inhibiting the growth and spread of cancer cells (Correa et al. 2016). Meanwhile, turmeric rhizome (*Curcuma longa L.*) contains curcumin which has anticancer properties which can inhibit the process of carcinogenesis at the stage of initiation and promotion of cancer cell progression.

Guava Leaves (*Psidium guajava L.*) as Anticancer
Guava or Psidium guajava Linn is a tropical plant rich in vitamins A, and C, and secondary metabolites which are beneficial for health. Guava leaves contain chemical compounds such as flavonoids, quercetin, tannins, saponins, essential oils, and alkaloids used as medicines for various diseases such as coughs and diarrhea. Flavonoids are secondary metabolites of the phenol groups, efficacious as antioxidants, anti-inflammatories, and anticancer (Aziz and Djamil 2013).

Water extract from guava leaves had been reported to be able to inhibit the spread of prostate gland cancer cells. The compounds found in the extract were polyphenolic and flavonoid (Chen et al. 2007; Lee and Park 2010). Meanwhile, secondary metabolites such as tannins, alkaloids, and saponins contained in guava leaves also inhibited the growth and spread of cancer cells by inhibiting the proliferation of cancer cells (Correa et al. 2016).

Table 1. Phytochemical properties of guava leaves (*Psidium guajava L.*).

Phytochemicals	Result
Flavonoids	+
Tannins	+
Alkaloids	+
Terpenoids	+

Source: Kariawasam et al. 2017.

Guava leaf extract was reported to have considerable anticancer activity. Based on Dwitiyanti (2015), 70% ethanol extract from guava leaves had cytotoxic properties against T47D breast cancer cells with a concentration of 130.62 µg mL^{-1} capable of killing breast cancer cells by 88.52% which were incubated for 24h. Meanwhile, the concentration of 5 µg mL^{-1} was able to kill 12.49% of T47D breast cancer cells. Identification of the chemical groups contained in the 70% ethanol extract of guava leaves indicated the presence of alkaloids, flavonoids, saponins, tannins, and triterpenoids.

Also, Kaileh et al (2007), cited in Fathilah et al. (2010), stated that guava extract was effective in inhibiting the growth of MCF7 breast cancer cells within 24h with an IC50 value of 55 µg mL^{-1} mL^{-1} capable of killing cancer cells by 50%. Moreover, the extract also had immunomodulatory activity in the form of NFkB (transcription factor protein) regulated the expression of genes involved in apoptosis.

The mechanism of flavonoids in inhibiting and even killing cancer cells can be done in several ways. The first way is to act as an antioxidant which will inactivate free radicals. Then, flavonoids will also bind to electrophilic compounds, induce the work of protective enzymes conjugate activity, increase the rate of apoptosis, inhibit cell proliferation, and inhibit lipid peroxidation. Furthermore, flavonoids will also inhibit angiogenesis and inhibit DNA oxidation (Rahayu and Roosmarinto 2017).

Additionally, alkaloids have properties as antineoplastic agents that can inhibit and even kill cancer cells by inhibiting DNA synthesis and inhibiting mitosis at the metaphase and anaphase stages of cancer cells (Purwaningsih et al. 2015). Steroids function as topoisomerase II inhibitors which can prevent and inhibit the cancer cell cycle (Afandi 2006; Sahid et al. 2013). Saponin compounds also play a role in inhibiting cancer cells because they are antiproliferative, antimetastatic, and also antiangiogenesis. Saponins induce apoptosis and cell differentiation (Xu et al. 2016). Angiogenesis by tumor cells is shown in Figure 2.
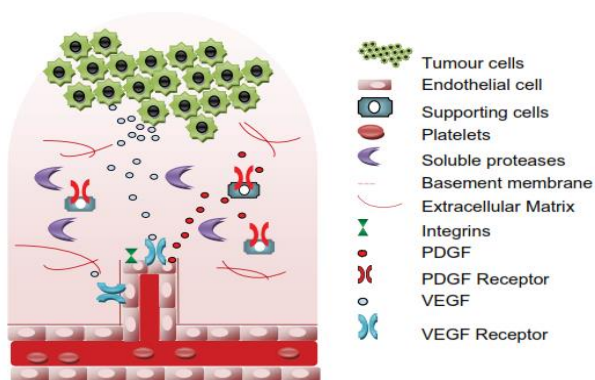
Figure 2. Angiogenesis by tumor cells (Taken from Hejmadi, 2010).

Table 2. Phytochemicals properties of turmeric water-extract (*Curcuma longa L.*).

Phytochemicals	Result
Alkaloid	+
Glycosides	-
Flavonoid	+
Tannin	+
Sterol	-
Terpenoid	-

Source: Deb et al., 2013

Turmeric Rhizome (Curcuma longa Linn.) as Anticancer

Turmeric (*Curcuma longa L.*) is a plant growing in tropical and subtropical regions. The main ingredient in turmeric is curcumin. It is a substance with antioxidant, anti-inflammatory, anti-proliferative, and cytotoxic effects that can induce apoptosis in malignant blood cells, breast, colon, liver, and ovaries (Kurniawan et al. 2016).

Curcumin is a yellow polyphenol-derived pigment found in the rhizome of the turmeric plant (Figure 3). The curcumin found in turmeric can act as an antioxidant, antiviral, antifungal, and anti-inflammatory by inhibiting several important molecules triggering inflammation. Curcumin reduces the production of histamine (a substance inducing inflammation), increases the production of cortisol which has an anti-inflammatory effect and removes toxins from the body (Hutomo et al. 2016).
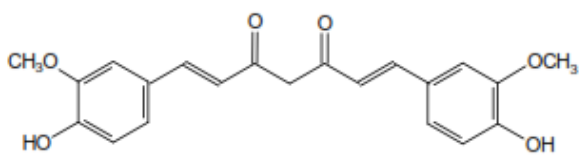

Figure 3. Structure of curcumin (Nurrochmad, 2004).

Turmeric rhizome extract suppressed the growth of MCF-7 and MDA-MB-231 breast cancer cells. Curcumin contained in turmeric rhizome extract triggered apoptosis. The rate of apoptosis of MCF-7 and MDA-MB-231 breast cancer cells correlated with the curcumin concentration. It induced the Bax protein used in cell apoptosis and inhibited Bcl-2 protein expression as an antiapoptotic protein (Lv et al. 2014).

Turmeric n-hexane extract inhibited the growth of QU-DB and T47D breast cancer cells. Data analysis on the anticancer activity of turmeric rhizome extract showed that the IC50 value for QU-DB cells was 74 µg mL^{-1} and for T47D cells the IC50 value was 57 µg mL^{-1} in the 48-hour MTT assay. The concentration of 68 µg mL^{-1} of turmeric extract was able to reduce the RTA (Relative Telomerase Activity) rate in QU-DB cells by 76.4% (Ranjbari et al. 2014).

The Curcumin induced cell cycle arrest and apoptosis through the cell-signaling pathway (Kurniawan et al. 2016). Curcumin damages cancer cells by referring to the process of apoptosis. In the event of apoptosis, cells will experience dehydration. Loss of intracellular fluid causes the cytoplasm to condense and change shape with smaller and flattened cell sizes. Cells undergoing apoptosis can be characterized by the presence of pyknosis due to chromatin condensation (Hutomo et al. 2016).

Further mechanisms of curcumin's anticancer effects may include suppression of NF-Kb activity through inhibition of Ikkb activity resulting in suppression of genes inducing tumorigenesis which include TNF, COX-2, Cyclin D1, c-myc, MMP-9, and interleukins. Curcumin also controls the cell cycle and stimulates apoptosis by regulating p16 and p53. Curcumin also acts as an autophagy modulator which is a tumor angiogenesis and metastatic inhibitor through the suppression of various growth factors including VEGF, COX-2, MMPs, and ICAMs (Wilken 2011; Kurniawan et al. 2016).

Apart from curcumin, turmeric (*C.longa L.*) rhizome also contains several compounds that play a role in inhibiting or even killing cancer cells such as alkaloids, flavonoids, and tannins with certain mechanisms. They enhance the anticancer potential of turmeric.

CONCLUSIONS

Guava leaves (*Psidium guajava Linn.*) contain several compounds that act as anticancer consisting of alkaloids, flavonoids, saponins, and steroids. Turmeric (Curcuma longa Linn.) rhizome contains curcumin and several other compounds such as alkaloids, flavonoids, and tannins which have anticancer properties. The

mechanisms of these compounds as anticancer include inhibiting the proliferation of cancer cells and inducing apoptosis of breast cancer cells. Further research is needed to determine the perfect combination of both ingredients as herbal medicine in preventing breast cancer.

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