

Management of Breast Cancer with Curcumae Rhizoma: A Therapeutic Approach

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Abstract

Breast cancer has the highest incidence in women, covering 2.3 million new cases per year and a mortality rate of 23%. Therapeutic strategies applied in breast cancer treatment include surgery, chemotherapy, endocrine therapy, and radiation. All of these therapies have relatively high side effects, so alternative therapies are needed that are more effective with minimal side effects. One of the herbs known to be effective in treating breast cancer is Curcumae Rhizoma from Curcumae longa extract. The essential components of this drug are Curcumol and Curcumin. Literature searches were obtained from various online portals such as Pubmed, Google Scholar and Science Direct using the keywords "breast cancer", "Curcumae", "Curcuma Rhizoma" and "herbal medicine". Curcuma Rhizomae can inhibit the formation and spread of cancer cells by utilizing anti-angiogenic effects, disrupting the cell proliferation cycle, and inducing apoptosis. In Indonesia, Curcumae or turmeric is commonly used as a spice ingredient. Its anti-cancer potential can be used as a breast cancer therapy in Indonesia.

Keywords: breast cancer, *Curcuma rhizome*, *herbal medicine*

1. Introduction

Breast cancer is the type of cancer with the highest incidence and is the leading cause of cancer-related deaths that occur in women, both in the world and in Indonesia¹ According to Global Cancer Statistics 2020, the incidence of breast cancer is estimated to be approximately 2.3 million new cases with deaths of approximately 685,000 cases, 23% of all cancer cases in women and 14% of cancer deaths.² The incidence of breast cancer continues to increase from year to year, both in developed and developing countries.^{3,4}

Various types of treatment are currently available, namely surgery, chemotherapy, radiation therapy, endocrine therapy, targeted therapy and immunotherapy. However, the results of treatment for breast cancer are still far from satisfactory. The high toxicity of chemotherapy drugs and the incidence of resistance are also challenges in the treatment of breast cancer. So that an

alternative is needed by using drugs from natural ingredients. These natural ingredients are expected to improve effectiveness, provide synergistic antitumour efficacy and clinical outcomes, and to reduce potential side effects during breast cancer chemotherapy.⁴

Curcumae rhizoma is a dried rhizome derived from Curcuma longa which consists of three different species of Curcuma phaeocaulis, Curcuma kwangsiensis and Curcuma wenyujin.⁵ The herb is commonly used as a colourant, spice and food additive. In addition, Curcumae has various pharmacological properties, including anti-bacterial, anti-oxidant, anti-inflammatory activities.⁶ Curcumae extract has been shown to inhibit the formation and spread of cancer cells by utilising antiangiogenic effects, inducing apoptosis and disrupting the cell proliferation cycle.⁷ Therefore, this article will

discuss Curcumae rhizome effect on breast cancer.

2. Methods

The strategy used to search for relevant articles related to the topic by searching various online portals such as Pubmed, Google Scholar, and Science Direct using keywords "keywords "breast cancer", "Curcumae", "Curcuma Rhizoma" and "herbal medicine".

3. Results and Discussions

3.1. Breast Cancer

According to its clinical subtype, breast cancer can be classified into three subtypes: HER2+ (human epidermal growth factor receptor-2 positive) subtype, HR+ (hormone receptor-positive) subtype, and TNBC (triple negative breast cancer) subtype.⁶ Several risk factors are known to increase the probability of developing breast cancer, including exogenous factors such as lifestyle, radiation, and hormonal therapy, and endogenous factors such as genetic mutations. Studies suggest that 5-10% of breast cancer cases occur as a result of gene mutations such as the BRCA1 and BRCA2 genes, PTEN gene, and p53 gene. Patients with positive gene mutations have an 80% risk of developing breast cancer, especially in the pre-menopausal age group.⁸

Currently, common therapeutic strategies applied to breast cancer cases can include surgery, chemotherapy, endocrine or hormonal therapy, radiation therapy, targeted therapy, and immunotherapy.⁶ The choice of breast cancer therapy depends on the degree of cancer, hormone receptor factors, previous therapy, side effects, and patient comfort. Chemotherapy can be given as adjuvant, preoperative (neoadjuvant), and main-palliative therapy. The principle of chemotherapy is to kill cancer cells with the ability to multiply rapidly, but normal cells around the site or in other organs can be

affected by this therapy, so it can cause side effects. Endocrine therapy can be given to breast cancer that has positive hormonal receptors with a response to therapy of 30-50% occurring within one year of therapy. Meanwhile, targeted therapy only has a 20% therapeutic response which is aggravated by the incidence of resistance within one year.⁹

Drugs from naturally isolated bioactive phytochemical compounds are one of the ideal alternative approaches to increase effectiveness, provide anti-cancer efficacy and clinical improvement, and reduce potential side effects during breast cancer chemotherapy. Curcumae exhibits anti-proliferation activity and anti-metastasis effects by inhibiting the formation of MCF-7 and MDA-MB-231, inhibiting mammosphere formation and differentiation of cancer cells. In addition, curcumin can downregulate mRNA expression and decrease protein expression of stem cell genes to inhibit breast cancer cell migration and invasion.¹⁰

3.2. Curcumae Rhizoma

Over the past few decades, more than 200 chemical constituents have been isolated and identified from Curcumae rhizoma. The essential oil (extract) of Curcumae rhizoma consists of volatile and nonvolatile compounds. The main bioactive components of volatile compounds, the largest content of Curcumae rhizoma extract, are terpenoids (including curcumol, β -element, furanodiene, furanodienone, germacrone) and curdione. Nonvolatile compounds consist of major bioactive components in the form of diphenylheptanes, such as curcumin. In addition, other elements such as Mn, Mg, Zn, P, Fe, polysaccharides, and alkaloids are also present in Curcumae rhizome.^{6,11}

3.3. The Role of Curcumae Rhizoma as Anti-Breast Cancer

Based on research, it is known that Curcumae rhizoma extract has excellent anti-

cancer activity. Bioactive components of *Curcumae rhizoma* are reported to induce tumor cell death, inhibit cell migration and increase sensitivity to chemotherapeutic drugs against breast cancer cells. Both volatile and nonvolatile components present in *Curcumae rhizoma* possess broad-spectrum anti-tumour activity through various mechanisms mostly concentrated on cell apoptosis and cytotoxicity.^{11,12}

In general, *Curcumae rhizoma* exerts anti-tumour effects through various means, including killing tumor cells, inducing apoptosis and differentiation, inhibiting cell metastasis, and affecting their cell membrane potential.^{6,13} The compound is known to induce cycle arrest and apoptosis in various breast cancer cells, which may be related to a decrease in CDC25 and CDC2, an increase in P21 protein levels, and inhibition of AKT phosphorylation, as well as activation of the mitochondrial apoptotic pathway.¹⁰ *Curcumae rhizoma* can also inhibit breast cancer cell proliferation and migration by inactivating autophagy. Recently, *Curcumae rhizoma* extract was also found to trigger ferroptosis, a mode of cell death distinct from apoptosis. Ferroptosis is a regulated form of cell death caused by oxidative disturbances in the intracellular microenvironment.¹⁴

Curcumae rhizoma not only showed obvious effects in inhibiting the survival of various types of cancer cells but also showed good effects in overcoming resistance to cancer chemotherapy. Essential oil from *Curcumae rhizoma* displays a strong inhibitory effect on the survival of chemotherapy-resistant breast cancer cells.¹²

In the use of chemotherapy drugs, anthracycline classes such as doxorubicin and epirubicin are commonly used in combination with drugs such as cyclophosphamide, epirubicin, and fluorouracil. In addition, the advent of taxane drugs with their significant anti-cancer activity against advanced breast

cancer has further enhanced the efficacy of neoadjuvant chemotherapy. Although the efficacy of neoadjuvant chemotherapy has been confirmed, clinical trial data show that neoadjuvant chemotherapy drugs for different breast cancer patients cause very different effects and drug resistance is easy to occur, especially doxorubicin, making treatment difficult.¹⁵

Various compounds in *Curcumae rhizoma* extract, such as curcumin and curcumin, play a role in improving the effectiveness of chemotherapeutic drugs through improving chemoresistance, making breast cancer cells sensitive to drugs, and enabling significant dose reduction in breast cancer therapy.¹⁶

Regulation of cell cycle, apoptosis, and metastasis regulators, accompanied by modulation of drug efflux proteins, receptors, and transcription of growth factors are involved in the potentiation of chemotherapeutic activity by curcumin and overcoming drug resistance in vitro and in vivo studies. In addition, the improvement of chemotherapy-induced side effects after combination therapy in animal models containing breast tumors also increases the potential of combination chemotherapy with curcumin in the treatment of breast cancer.¹⁶

One of the bioactive compounds from *Curcumae rhizoma* extract, curcumol, is reported to be effective against breast cancer and recent studies have shown that curcumol decreases the clonogenicity and migration of breast cancer cells by decreasing the expression of matrix metalloproteinase-9 (MMP-9).¹¹ Curcumol blocks breast cancer cell metastasis by downregulating MMP9 expression, which is mediated by JNK1/2 and AKT-dependent NF- κ B signaling pathways. In addition, curcumin inhibited the growth of p53 mutant MDA-MB-231 cells, both in vitro and in vivo. The mechanism appears to correlate with inducing G1 cycle arrest and

triggering apoptosis of MDA-MB-231 cells through activation of p73 and PUMA.^{6,17}

Curcumin, another natural polyphenol compound isolated from *Curcumae rhizoma*, also works as an anti-cancer by inhibiting MCF-7 cell proliferation through miR-19/PTEN/AKT/p53 and NF- κ B signaling pathways.⁶ In the triple negative subtype, curcumin was found to suppress cell proliferation, migration, and invasion through several pathways. Curcumin was able to inhibit MDA-MB-231 cell proliferation by inducing G2/M arrest and apoptosis while restraining migration by reducing NF- κ B p65 expression.¹⁰ Recent studies have also implicated that many molecules and pathways may be responsible for curcumin's anti-TNBC activity, such as miR-34a, the Hedgehog/Gli1 signaling pathway and the p300/miR-142-3p/PSMB5 axis.^{18,19}

Recently, given the therapeutic potential of *Curcumae rhizoma*, a series of studies have been conducted to make drugs from curcumin extracts that can be used clinically. In the United States, there are various supplements containing curcumin extract, with or without other additives. However, the safety and effectiveness of these supplements have not been significantly proven to be used as clinical therapy, especially in this case for breast cancer.²⁰

So far, curcumin samples that have been circulated, either in the form of raw extracts or capsules, have shown good quality and most have met the standard quality control criteria. Further research is needed to prove the safety and effectiveness of curcumin extracts in medicinal form.²¹

4. Conclusion

Breast cancer is the cancer with the highest mortality and morbidity in women in the world in general, and it is known that the incidence continues to increase every year. Early cancer detection programs, surgical therapy, chemotherapy, radiation, and

targeted therapy have been conducted to increase the survival rate of breast cancer patients. There is no definitive therapy in the treatment of breast cancer as the response to therapy varies in each patient and resistance can still occur. Supportive therapy can be done by utilizing natural materials to support the immune system of breast cancer patients and become an alternative treatment if resistance to conventional therapy occurs.

Curcumae rhizoma has the potential as an anti-breast cancer agent. Active ingredients contained in *Curcumae rhizoma*, such as curcumin and curcumin, have been shown to have anti-breast cancer effects through various molecular mechanisms, including inhibiting cell proliferation, migration, invasion, and stemness, as well as reversing resistance to chemotherapy and inducing cell apoptosis. However, further and in-depth research is needed to understand in more detail the direct targets of action of these active ingredients and to overcome the problem of resistance to chemotherapy. In addition, further research on appropriate drug formulation and delivery is also needed to improve the effectiveness and safety of using *Curcumae Rhizoma* in the treatment of breast cancer.

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