



Effect of Moringa Oleifera Extract on Erythrocyte Sedimentation Rate And SF-36 Scores In Aromatase Inhibitor-Associated Musculoskeletal Syndrome Breast Cancer Patients

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ABSTRACT:

Aromatase inhibitors (AIs) are key components in chemoprevention and treatment of hormone receptor-positive (HR+) breast cancer. AIs are associated with musculoskeletal adverse effects known as the aromatase inhibitor-associated musculoskeletal syndrome (AIMSS), in which the estrogen levels decrease. One of the effects of estrogen is anti-inflammatory. The mechanism of this anti-inflammatory effect is by reducing the synthesis of inflammatory cytokines. Moringa oleifera is a traditional plant that contains glucosinolates, which when hydrolyzed will produce a component called isothiosyanates. The benefit of isothiosyanates studied in this article is inhibition of the inflammatory mediator, which is measured by the variables of decrease serum ESR levels and increase SF-36 scores. The outcome of this study is improvement in patient's quality of life. The aim to elaborate the effects of the Moringa Oleifera extracts on inflammation process. This research is experimental research of 40 post-menopausal breast cancer patients with ER positive and PR positive were included as study subjects divided into two groups, K (control) and P1 (treatment). The P1 group was given moringa oleifera 600 mg/day for 1 month, all patients were taken blood samples (ESR) and interviewed to measure the SF-36 score. This experimental research will be conducted for 30 days. The difference between the pretest



and posttest of ESR serum level in the control group and the treatment group ($p < 0,001$) and between the treatment and control groups ($p < 0,001$) showed significant results. The difference between the pretest and posttest of SF-36 all aspects score in the control group and the treatment group ($p < 0,001$) and between the treatment and control groups ($p < 0,001$) also showed significant results. Moringa Oleifera extracts improve quality of life of on aromatase inhibitor induced arthralgia by decreased ESR serum and improve SF-36 scoring with outcome increasing quality life.

KEYWORDS: Moringa oleifera, Aromatase Inhibitor, AIMSS, ESR, SF-36

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INTRODUCTION :

Breast cancer or commonly referred to as mammary carcinoma (Ca mammae) is an abnormal growth of a group of cells originating from breast tissue. The number of breast cancer cases in the world with more than 1,000,000 cases occurring worldwide every year and a trend of increasing cases both in the world and in Indonesia.^{1,2} In 2018, 2 million breast cancer cases were diagnosed and 600,000 breast cancer patients died all over the world. Death from breast cancer is 6.6% of all cancer-related deaths worldwide and ranks number 1 for women. The Ministry of Health stated that the number of breast cancer in Indonesia reached 42.1 people per 100,000 population. The average death rate from this cancer reaches 17 people per 100,000 population.¹⁻⁵

Breast cancer therapy modalities include: surgery, radiotherapy, cytostatic, immunotherapy, and hormonal therapy.^{6,7} Postmenopausal patients with positive hormone receptors will be given hormonal therapy with aromatase inhibitors. Aromatase inhibitor side effects are often associated with significant joint and muscle symptoms; Symptoms are commonly referred to as aromatase inhibitor-associated musculoskeletal syndrome (AIMSS) which often affects the hands, wrists, and knees. These symptoms will immediately

disappear when the AI therapy is stopped and will appear immediately when the therapy is given again. AIMSS has a negative impact on the quality of life of many patients related to health, and reduces adherence to breast cancer treatment with AI, and increases inflammation in the blood, one of which is an increase in ESR.⁶⁻⁹

The SF-36 is an instrument that has been used in various countries and is used as the gold standard in assessing the quality of life because this instrument consists of 36 short questions covering 8 aspects, namely physical aspects, emotional aspects, social aspects, physical health aspects, emotional health aspects, aspects of emotional health, and social aspects. pain, fatigue and general health aspects. The use of SF 36 for breast cancer patients started from breast cancer survivors in the United Kingdom. Vitality and pain assessment using the SF 36 has been used to measure fatigue and pain associated with cancer. The advantage of using the SF 36 form is that it can differentiate the patient's quality of life.

This research is focused on the development of anti-pain and anti-inflammatory compounds by exploring new compounds derived from medicinal plants. The use of medicinal plants in most cases is based exclusively on traditional without sufficient scientific



evidence. Many medicinal plant derivatives are known to be effective against joint pain, one of which is Moringa leaf (*Moringa oleifera*). *Moringa oleifera* is a plant that lives in the tropics and is widely used as traditional medicine, one of which is as an anti-inflammatory drug to treat pain.

Many studies have reported that 100 grams of *Moringa oleifera* contains 12 times vitamin C than oranges, 10 times vitamin A than carrots, 9 times Moringa protein than yogurt, 15 times potassium than bananas, 17 times calcium than milk and 25 times iron than spinach. This nutrient content is very important role in the biochemical processes of humans and animals. *Moringa oleifera* is rich in compounds containing simple sugars, rhamnose, and a unique group of compounds called glucosinolates and isothiocyanates. Isothiocyanates from *Moringa oleifera* are thought to inhibit inflammation produced by cyclooxygenase-2 (COX-2) and induced by nitric oxide synthase (iNOS).^{10,11}

This study wanted to see the effectiveness of *Moringa oleifera* extract as an adjuvant to the administration of aromatase inhibitors in postmenopausal breast cancer patients with ER (+), PR (+) to see differences in short form 36 (SF 36) scores and erythrocyte sedimentation rate (ESR) as markers of inflammation. . The results of this study are expected to support the use of *Moringa oleifera* as an adjuvant for the administration of aromatase inhibitors in postmenopausal breast cancer patients with ER (+), PR (+).^{12,13}

MATERIALS AND METHODS:

Study Design

This study is an experimental study with a two groups parallel pretest and posttest control group design which was approved

by the medical research and ethics committee of RSUP Dr. Kariadi Semarang. A total of 40 post-menopausal breast cancer patients with ER (+) and PR (+) were included as subjects in this study.

Research Sample Selection Criteria

40 post-menopausal breast cancer patients with ER (+) and PR (+) were included as study subjects. In this study, the selection of subjects was based on inclusion criteria, namely (1) non-metastatic breast cancer patients, (2) post-menopause based on medical records, (3) ER (+) immunohistochemistry, PR (+) based on medical records, (4) received aromatase inhibitor therapy for 2 months, (5) experienced arthralgia post aromatase inhibitor therapy, (6) agreed to participate in the study. The exclusion criteria in this study were (1) emergency situations requiring surgery, (2) refusal to be included in the study.

Time and Location of Research

Research and data collection will be carried out for 2 months. The treatment of breast cancer patients was carried out at the Kasuari Polyclinic, Dr. Kariadi Hospital, Semarang, Central Java. Examination of CRP levels was carried out at the Clinical Pathology Laboratory, Dr. Kariadi Hospital, Semarang

Research Variable

The independent variable of this research is *Moringa oleifera* extract with dose 600 mg / day and the dependent variable are ESR serum level and SF-36 score.

Data Collection Method

This experimental research will be conducted for 30 days. The research subjects were divided into two groups, namely the control and treatment groups (given *Moringa* leaf extract at a dose of



300 mg/capsule 2 times a day). Before giving treatment, all patients were taken blood samples and interviewed to measure the SF-36 score. Then the treatment therapy according to the research group for 30 days. On the 31st day, SF-36 data and blood samples were taken to measure the patient's ESR after therapy. Monitoring of side effects is carried out regularly every week on patients. After 30 days, data were collected on ESR serum levels and the second SF-36 score was measured again.

Statistical analysis

Data analysis in this study will use the help of SPSS software for Windows 26.0. Hypothesis testing of differences in pretest and posttest of ESR levels and SF-36 scores using paired t-test if the data is normally distributed or Wilcoxon test if the data is not normally distributed. Differences in serum ESR levels and SF-36 scores between the treatment and control groups will be tested using the unpaired t-test if the distribution is normal or the Mann-Whitney test if the data is not normally distributed. Hypothesis testing in the study was continued by using independent t-test, if the data were normally distributed. However, if the data are not normally distributed, hypothesis testing will be performed using the Mann-Whitney U test. The value is considered significant if $p < 0.05$.

Research Ethical Requirements

Before the research, we received ethical clearance from the Dr. Kariadi Hospital's Institution Review Board. Prospective research subjects will be given an explanation of the research conducted, its objectives, benefits, research protocol and side effects that can occur. Prospective subjects have the right to

refuse participation without any consequences and continue to receive health services in accordance with the protocol of patient's disease. Subjects have the right to leave the study at their own will. Prospective subjects who agree to be included in the study will be asked for written consent (informed consent). The personal identity of all research subjects will be kept confidential and will not be published without the subject's consent.

RESULT:

This research is experimental research of 40 post-menopausal breast cancer patients with ER (+) and PR (+) were included as study subjects divided into two groups. Characteristic subjects are the mean age of the sample in the treatment group was 55.9 years, compared to 53.85 years in the control group. The highest education level in the treatment group was elementary school, while the control group was senior high school.

Statistical test of serum ESR levels using the Shapiro-Wilk test. From the normality test, group P1 delta serum ESR levels pretest and posttest were normally distributed, while groups K and P1 pretest, group K and P1 posttest, and group K delta serum ESR levels pretest and posttest were not normally distributed.

Hypothesis testing of differences in serum ESR levels pretest and posttest using the Wilcoxon test obtained significant results in the treatment group (<0.001) and in the control group (0.008). While the difference in serum ESR levels between the treatment and control groups using the Mann Whitney test also showed significant results (<0.001).

The average score of the physical component and the mental component of



the post-treatment control group was below the standard average score of 40.9 and 49.1. The Moringa oleifera group showed scores above the average, namely the physical component was 60.6 and the mental component was 61.8.

DISCUSSION:

Aromatase inhibitor-associated musculoskeletal syndrome" (AIMSS), is frequently cited as the leading cause of premature discontinuation; approximately 50% of patients will report new onset or worsening joint pain 1-6 month after therapy initiation. approximately 30% of patients discontinue therapy after 6 month, and only 50%–68% of patients remain fully compliant with therapy after 3 years. This leads to an increasing risk of breast cancer relapse and mortality. The exact pathophysiology behind this syndrome is not fully understood, but the prevailing theories point to estrogen deprivation as the key factor leading to degradation of bone and cartilage leading to development of the syndrome. Estrogen decreases osteoclast maturation and overall decreases osteoclast lifespan, as well as promoting osteoblast maturation and maintaining their lifespan. Estrogen also has an anti-inflammatory effect on the body by decreasing the synthesis of inflammatory cytokines such as tumour necrosis factor (TNF- α) and interleukin (IL)-1 β , and increased levels of ESR, eotaxin, and monocyte chemoattraction protein 1 (MCP-1) have been detected in patients.^{6,7}

This study intends to prove Moringa oleifera extract in reducing inflammatory status through ESR values and improving quality of life as assessed by the SF-36 score of postmenopausal breast cancer patients with ER (+), PR (+) undergoing aromatase inhibitor therapy.

In the results of this study, ESR levels decreased with the consumption of Moringa oleifera extract for 1 month. In statistical tests, it was found that there was a significant decrease in ESR levels in patients receiving Moringa oleifera extract compared to the control group. This shows that Moringa oleifera extract can reduce inflammation in breast cancer patients who experience Aromatase inhibitor-associated musculoskeletal syndrome (AIMSS).^{9,10}

Aromatase inhibitors work by inhibiting the expression of estrogen formation in women. According to Burstein HJ, decreased estrogen production in postmenopausal women will affect the number of cytokines, changes in macrophage activity and cell adhesion molecule activity, all of which contribute to inflammation and joint pain. According to Shovman, estrogen has an anti-inflammatory effect on the body by decreasing the synthesis of inflammatory cytokines such as tumor necrosis factor (TNF- α) and interleukin (IL)-1 β , as well as increasing levels of ESR, eotaxin, and monocyte chemoattraction protein 1 (MCP-1) has been detected in the patient.^{10,11}

According to Patel S. and Al Asmari, Moringa oleifera contains many substances, one of which is glucosinolates which can produce isothiocyanates compounds, these substances have anti-inflammatory properties used in this study. Isothiocyanates work by inhibiting the inflammatory mediator NF- and expressing pro-inflammatory mediators such as tumor necrosis factor (TNF- α), COX-2, PGE synthase, iNOS, IL-1 and IL-6.^{13,14}

Isothiocyanates inhibit the inflammatory mediators of NF- and express pro-



inflammatory mediators such as tumor necrosis factor (TNF-), IL-1 and IL-6 by significantly reducing the intracellular translocation of the pro-inflammatory nuclear factor transcription factor NF-. Isothiocyanates also target other mediators of the inflammatory response, including the COX-2 enzyme, PGE synthase, and iNOS. Isothiocyanates inhibit the expression of NF-B, IL-6, TNF-, and COX-2, as well as the production of NO and PGE2. In vitro, isothiocyanates have also been shown to increase NF-B inhibitor degradation, IB translocation, and/or NF-B transcriptivity. Leona A said that the body's response to inflammation is reduced as a result of inhibition of inflammation from the isothiocyanates mechanism. Increased inflammation which is characterized by increased serum ESR levels also causes a decrease in quality of life. According to Laroche et al in their study involving 1350 human samples, increased levels of ESR caused by inflammation, including chronic inflammation, have been shown to reduce quality of life. This mechanism is in line with the decrease in the initial ESR levels in patients from (62.3) to (22.3) in the group given moringa oleifera. In the control group which was compared with the moringa group, there were also significant differences, namely in the control group (22,3) and in the moringa group (52,8).^{14,16}

Assessment of Quality of life SF-36 score is divided into 2 assessment components, namely a summary of the mental component and a summary of the physical component. According to Bosworth, et al and Rahman, et al, the calculation of the quality of life score uses the average value of each physical component and mental component to determine the final score of quality of life. The results showed that

the average score of the physical component in the treatment group increased from 40.9 to 60.6 and the mental component of the treatment group also increased from 61.8 to 49.1. The results of this study are in accordance with Arafa and Rabah that most patients with breast cancer who have complaints of arthralgia have a low average quality of life score in almost every domain of quality of life both physically and mentally.¹⁵

The reliability of the Indonesian version of the SF-36 score has been studied by several researchers, including Berliana et al said that the results of the study showed a Cronbach's alpha value of 0.767 (> 0.6), which indicated that the question for measuring the physical domain and mental domain of health workers scored SF-36. 36 Indonesian versions are valid and reliable.¹⁵

Moringa leaf extract has high anti-inflammatory potential in postmenopausal breast cancer patients with ER (+), PR (+) and aromatase inhibitor therapy which in this study can be seen from the ESR value and SF-36 score. Its anti-inflammatory potential will improve the quality of life of breast cancer patients, improve treatment adherence, and, in the long term, will greatly assist breast cancer therapy and outcomes.

The author realizes that there are many limitations in this research that need to be improved and completed so that it can complete this research. Where possible, this study could be scaled up to a larger population and to other cancer patients.

CONCLUSION:

Moringa Oleifera extracts decrease ESR serum and improve SF-36 scoring by downregulating inflammation process.



CONFLICT OF INTEREST:

The authors have no conflicts of interest regarding this research.

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