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Effect of *Moringa oleifera* Extract on Inflammatory Status in Cancer Patients with Aromatase-Induced Arthralgia

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Abstract

BACKGROUND: Aromatase inhibitor therapy is commonly used for breast cancer patients with characteristics of positive estrogen and progesterone receptors test without metastases. Thus, this kind of therapy generally gives side effects of aromatase-induced arthralgia (AIA). Moringa oleifera has a strong anti-inflammatory substance that has the potential to reduce inflammation and pain in a patient with AIA.

AIM: This study aims to assess the effect of M. oleifera extract administration on pain response and inflammatory status in breast cancer with aromatase inhibitor-induced arthralgia patients.

METHODS: Forty-two patients breast cancer patients with estrogen and progesterone receptor-positive in Dr. Kariadi General Hospital were assessed for pain response and inflammatory status before and after the treatment with *M. oleifera* leaf extract for one month. Assessment of pain response is using the Australian Canadian osteoarthritis hand index (AUSCAN) questionnaire and inflammation is measured by ANA serum level. This study is experimental with two parallel pre-test and post-test group.

RESULTS: In the treatment group, there was a significant decrease of the AUSCAN score 13.5 ± 5.11 ($p \leq 0.001$), while in the control group, there was an increase in the AUSCAN score 2.7 ± 4.96 ($p = 0.022$). In the measurement of ANA serum level, a significant decrease of the treatment group found 0.3 ± 0.40 ($p \leq 0.001$).

CONCLUSIONS: *Moringa oleifera* extract can help reduce pain response and inflammatory status of patients with chronic inflammation as an additional therapy.

Introduction

Nowadays, studies reveal that more than 250.000 women are diagnosed with invasive breast cancer each year. This rate is increasing each year, as the data observed previously. In cases of hormone-receptive breast cancer in postmenopausal women in various settings, aromatase inhibitor (AI) was indicated as part of cancer management. The previous studies have shown the effectiveness of aromatase inhibitor therapy when used as adjuvant therapy to chemotherapy and surgery in metastatic estrogen-dependent breast cancer [1]. Usually, it takes up to 10 years for aromatase inhibitor therapy orally for estrogen-sensitive breast cancer patients [2]. However, these drugs can lead to syndrome of arthralgia and musculoskeletal symptoms, which have been characterized in several reviews [3], [4], [5]. The incidence of this syndrome in trials has been reported to be up to 36.5% in women taking AI, while in the community, the rate has been reported to be as high as 80% [3]. It is implicated that these side effects cause 12.8% of discontinuation of AI therapy at 12-month follow-up and 28.1% of switching AIs [6]. The precise mechanism and etiology of the disease are still under commencing debate [7]. Although estrogen depletion may be responsible [8]. Thus, Aromatase-Inhibitor Arthralgia can affect patients' quality of life due to prolonged pain and unstoppable inflammatory response [7].

The principal management of AIA is to alleviate the pain response and reduce the inflammatory response due to AIA. *Moringa oleifera* is a well-known traditional medicine, that has strong anti-inflammatory properties, such as triterpenoid, flavonoid, saponin, and tannin [9], [10]. Saponin, one of the active substances in *Moringa oleifera*, has a strong anti-inflammatory response that can inhibit inflammatory mediators, such as histamine, serotonin, and prostaglandin [9]. Studies have shown the effectiveness of *Moringa oleifera* in the inhibition of chronic inflammatory response [11], [12], [13], [14], but no studies have shown the effectiveness of *Moringa oleifera* in reducing pain responses and chronic inflammation in *Moringa oleifera*.

This study aims to assess the analgesic and anti-inflammatory effect of *Moringa oleifera leaf* extract on breast-cancer AIA patients.

Methods

Study oversight

The study was conducted in Dr. Kariadi General Hospital and was approved by appropriate individual review boards. Study participants were informed of the investigational nature of the study and provided informed consent.

Patients and randomization

Forty-two breast-cancer patients during the study period were included in this study, with the inclusion criteria such as post-menopausal women, estrogen and progesterone receptor-positive breast cancer, undergo at least 2-months treatment of aromatase-inhibitor therapy, and consented to participate in this study. While breast-cancer patients with mentioned criteria: HER2-positive and *Moringa oleifera* extract hypersensitivity patients were excluded from this study. Patients who cannot be followed up within 30 days and received analgesic therapy besides the analgesic that the procedure provided were drop-out from this study. All patients who matched the study criteria were included in this study and randomized into two groups, treatment and control groups.

This study has followed the institutional guidelines and protocol of Health Research Ethics Committee of Dr. Kariadi General Hospital, Semarang. (No.1138/EC/KEPK-RSDK/2022).

Trial procedures

All patients who matched the study criteria were included in this study and randomized into two groups, treatment and control groups. The treatment group received a 300 mg capsule of *Moringa* leaf extract with a daily dose of 600 mg and diclofenac sodium 100 mg/day for analgesia. The control group received a placebo capsule of 2 capsules/day and sodium diclofenac 100 mg/day for analgesia. Treatment was given for 30 days.

End points

On the last day of treatment, the patients were assessed the following criteria of Australian Canadian osteoarthritis hand index (AUSCAN) score and blood sample was taken. A blood sample was taken before and after 30-days of treatment to measure the ANA serum level of both groups.

ANA serum level was determined using screening ezyme-linked immunosorbent assay, and all positive samples underwent immunofluorescence testing on Hep-2 cells (Quest Laboratories, Van Nuys, California).

Statistical analysis

Data analysis included descriptive analysis and hypothesis testing. In the descriptive analysis, nominal scale data are expressed as frequency and percentage. Numerical scale data are expressed as the mean and standard deviation for normally distributed data. For abnormal distribution, data are expressed as the median and the maximum minimum value. The normality of the data distribution was assessed using the Shapiro–Wilk test. Hypothesis testing for differences in the degree of AUSCAN pain and ANA serum levels before and after the treatment was tested using paired sample t-test for the normal distribution, or the Wilcoxon test for the abnormal distribution. The hypothesis test of the difference in the degree of AUSCAN pain and ANA serum level between the treatment group and the control group was tested with an unpaired t-test for the normal distribution or the Mann–Whitney test for the normal distribution. p-value is considered significant if $p < 0.05$.

Results

The collected sample was 42 postmenopausal cancer patients with positive estrogen and progesterone receptors immunohistochemistry who received outpatient treatment at the Kasuari Installation, Dr. Kariadi General Hospital Semarang, and experienced pain due to the administration of Aromatase inhibitors.

Table 1: Average AUSCAN score in the control and treatment groups

AUSCAN	Groups		p
	Treatment n=21	Control n=21	
Pre-test	52.1 ± 4.25	52.9 ± 4,50	0.770‡
Post-test	38.5 ± 3.49	55.7 ± 5.15	<0.001‡*
Δ	–13.5 ± 5.11	2.7 ± 4.96	<0.001‡*
p-value	<0.001†*	0.022†*	

In the AUSCAN pre-test scoring assessment (Table 1 and Figure 1), the treatment group was 52.1 ± 4.25, and the control group 52.9 ± 4.50 with a $p = 0.770$. The AUSCAN post-test score in the treatment group was 38.5 ± 3.49, and in the control group 55.7 ± 5.15, the $p \leq 0.001$ showed significant results, it can be concluded that the AUSCAN score decreased after receiving additional *Moringa oleifera* extract therapy. With the difference between the pre-test and post-test, the treatment group scoring AUSCAN -13.5 ± 5.11 and the control group 2.7 ± 4.96 with $p \leq 0.001$ which showed

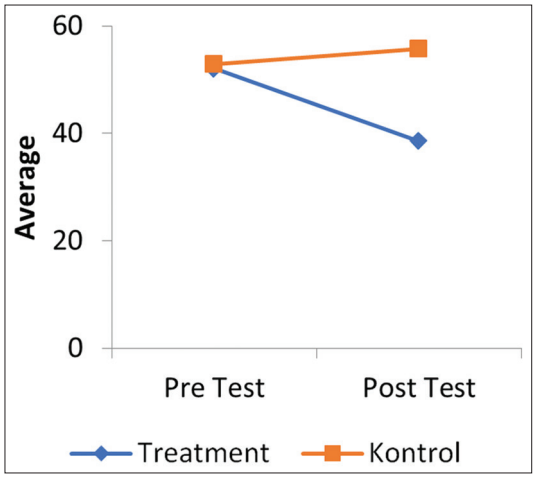

Figure 1. Graph of the AUSCAN scores of the treatment and control groups

significant results, we conclude that the decrease of the AUSCAN score in the treatment group was larger than control group.

Table 2: Average ANA serum level in the treatment and control groups

ANA	Groups		p
	Treatment (n=21)	Control (n=21)	
Pre-test	0.5 ± 0.47	0.5 ± 1.32	0.003‡*
Post-test	0.1 ± 0.18	0.4 ± 0.47	0.002‡*
Δ	–0.3 ± 0.40	–0.1 ± 1.41	<0.001‡*
p value	<0.001†*	0.170†	

In the laboratory measurement (Table 2 and Figure 2), ANA serum level in the pre-test of treated group was 0.5 ± 0.47 and in the pre-test of control group 0.5 ± 1.32 with p = 0.003. ANA serum level in the post-test of treated group was 0.1 ± 0.18 and in the post-test control group 0.4 ± 0.47 with p = 0.002 which showed significant results. Therefore, we conclude that there was a decrease in ANA serum level after received additional *Moringa oleifera* extract therapy.

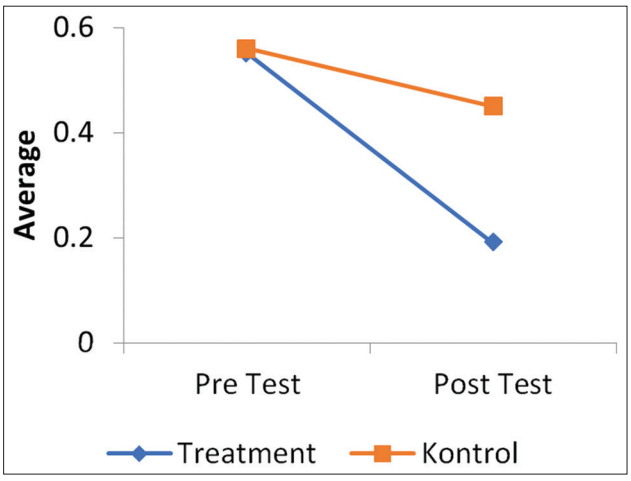

Figure 2. Graph of ANA serum level in control and treatment groups

The difference between the pre-test and post-test of the treated group was –0.3 ± 0.40 and the difference between the pre-test and post-test of the control group was –0.1 ± 1.41 with p ≤ 0.001 which shows significant results and concluded that the decrease of ANA serum level in the treated group is larger than the control group.

From the graph above, the mean ANA serum level in treated group decreased significantly from 0.5 ± 0.47 to 0.1 ± 0.18. In the control group, there was a non-significant decrease from 0.5 ± 1.32 to 0.4 ± 0.47.

Discussion

Pain in arthralgia patients is related to the inflammatory response. In the AUSCAN scoring method, complaints of pain, hand stiffness, and physiological function are assessed. The study showed that decreased of the AUSCAN score in the treatment group, indicating that *Moringa oleifera* has a significant effect on reducing pain in AIA patients. Claudia *et al*. in their study reveal the observed that enteral administration of both non-polar and polar extracts of *Moringa oleifera* leaves demonstrated significant antinociception in the neurogenic and inflammatory phases of the formalin test [15]. This study also reinforce antinociceptive effects of *Moringa oleifera* seeds using hot plate and tail immersion test in rats, where no only central action but also peripheral inhibition of the prostaglandins-mediated potential of analgesic action of bradykinin were involved [16].

Decreased inflammatory status is associated with decreased arthralgia pain caused by chronic inflammation which can be seen from the mean value of the difference between pre-test and post-test ANA serum levels, which found a decrease of 0.35 and proved the minor hypothesis of the study.

Moringa leaf extract has the potential as an anti-inflammatory. One of the components in *Moringa oleifera* which is believed to have an anti-inflammatory role is thiocyanates which inhibit the activity of COX-2 and lead to prostaglandin synthesis inhibition.

Conclusions

Moringa oleifera extract and/or diclofenac sodium can significantly reduce inflammatory status based on ANA serum level and reduce pain response assessed by the AUSCAN score.

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