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**“Effect of Moringa Oleifera Extract on CRP Serum and Quality of Life
on Aromatase Inhibitor Associated Musculoskeletal Syndromes of
Breast Cancer Patients”**

Running title : Moringa oleifera in Breast Cancer Patients

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No	Name	Conflict of interest
1.	Sugeng Pramono	<ul style="list-style-type: none"> - Help develop research concepts and designs - Get the sample and analysing results
2.	Yan Wisnu Prajoko	<ul style="list-style-type: none"> - Drafting concepts and designs study - Dividing the task - Arranging research funding - Analysing the findings - Writing research reports
3.	Hardian	<ul style="list-style-type: none"> - Help develop research concepts and designs - Analysing results
4.	Trilaksana Nugroho	<ul style="list-style-type: none"> - Write research's report and article - Help develop research concepts and designs - Analysing results
5.	Yora Nindita	<ul style="list-style-type: none"> - Write research's report and article - Help develop research concepts and designs - Analysing results

ABSTRACT

Background Breast cancer is the most frequent type of cancer in Indonesia, and it also has the highest mortality rate for women worldwide. Aromatase inhibitors will be used in hormonal therapy for postmenopausal individuals with positive hormone receptors but it can cause arthralgia. This study determined the increased impact of moringa oleifera extract therapy on pain quality as measured by serum CRP levels and HAQ-DI scores in breast cancer patients taking aromatase inhibitor therapy

Methods This research is experimental research with two groups parallel pretest and posttest control group design. 40 breast cancer patients were randomly divided into: K (control) and P1 (treatment). The P1 group was given moringa oleifera 600 mg/day for 1 month. CRP levels and HQ-Scores were measured both before and after treatment.

Results Average age of samples is 54.88 years, with a median of 53.5 years. The difference between the pretest and posttest of CRP 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 HAQ-DI 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.

Conclusion Moringa oleifera extract improve quality of life of on aromatase inhibitor induced arthralgia of postmenopausal breast cancer patients with ER (+), PR (+) by reduced inflammatory status as assessed by serum CRP levels and HAQ-DI score.

Keywords: Moringa oleifera, Breast cancer, Aromatase inhibitor, Quality of Life

INTRODUCTION

Deaths from breast cancer top the list for women, which is responsible for 6.6% of all cancer-related fatalities globally.¹ Breast cancer accounted for 58,256 cancer cases in Indonesia in 2018, or 16.7% of all cancer cases, according to data from the World Health Organization (WHO). According to the Indonesia Ministry of Health, 42.1 out of every 100,000 people in Indonesia have breast cancer. The average number of deaths from this cancer is 17 per 100,000 individuals.²

For people with breast cancer, there are numerous therapy options. One of them is hormonal therapy with aromatase inhibitors. Aromatase inhibitors are used in hormonal therapy for postmenopausal breast cancer patients who have positive hormone receptor tests. However, musculoskeletal syndromes like arthralgia is a side effect of aromatase inhibitor therapy that frequently manifests.³⁻⁴

Arthralgia was found to have a detrimental effect on the quality of life of breast cancer patients by increasing pain, raising blood inflammation, and decreasing adherence to hormonal treatment.³⁻⁴

The Health Assessment Questionnaire Disability Index (HAQ-DI) was developed to measure the quality of life in the population, including those with breast cancer. While CRP has also been used as part of measuring the presence of inflammation in the body. The HAQ-DI score and serum CRP levels will have an impact on the state of arthralgia brought on by the administration of aromatase inhibitors.⁵⁻⁶

There is no algorithm for treating aromatase inhibitors associated musculoskeletal syndromes. Painkillers like diclofenac sodium, which reduces the severity of symptoms but has serious gastrointestinal side effects like dyspepsia and gastrointestinal bleeding, are frequently prescribed to patients. The development of analgesic and anti-inflammatory compounds natural herbal is the main goal of this research. One of the many plant derivatives from which joint pain relief is known to be effective is *Moringa oleifera*.⁷⁻⁹

Since olden days, moringa oleifera has been widely used as traditional medicine, including as an anti-inflammatory medication to treat pain. This tropical plant can be easily found in Indonesia. It is believed that the isothiocyanates found in Moringa oleifera counteract inflammation. Moringa oleifera is expected to reduce the use of diclofenac sodium so that it can reduce the side effects it causes.⁷⁻⁹

This study wanted to see the effectiveness of Moringa oleifera extract in improving the quality of life as an adjuvant to the administration of aromatase inhibitors in postmenopausal breast cancer patients with ER (+), PR (+).

METHODS

Research Design

This research is experimental research with two groups parallel pretest and posttest control group design. The research group was divided into 2 groups, group K (Control) is postmenopausal breast cancer patients with ER (+) and PR (+), who received aromatase inhibitor therapy and diclofenac sodium 100 mg / day if pain, and treatment group 1 (P1 is postmenopausal breast cancer patients with ER (+) and PR (+), who received aromatase inhibitor therapy, sodium diclofenac 100 mg / day if pain and Moringa oleifera extract at a dose of 600 mg / day.

Research Sample

The research sample was breast cancer patients who were treated at Dr. Kariadi Semarang, and met the inclusion criteria, that are non-metastatic breast cancer patients with immunohistochemical results ER (+), PR (+), post menopause, received aromatase inhibitor therapy for at least 2 months, had arthralgia after receiving aromatase inhibitor therapy, and agreed to participate in the study. This is by signing the informed consent form

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 CRP serum level and HAQ-DI score.

Research Implementation

A total of 40 samples that met the inclusion criteria and exclusion criteria and had signed an informed consent were used as research subjects. The research subjects were randomized and divided into 2 research groups, namely the control group (K) and the treatment group (P1). Data were collected on CRP serum levels and HAQ-DI scores. The measurement of the HAQ-DI score was done by interviewing the subject directly by the researcher. Data on CRP levels were obtained from the subject's medical records. Administration of therapy according to the study group for 30 days. Monitoring of adverse effects will be carried out periodically every week or research subjects can immediately contact the researcher without waiting for the monitoring schedule. Monitoring is carried out by contacting the subject via WhatsApp application, or telephone by asking the progress during the treatment. After 30 days, data were collected on CRP serum levels and the second HAQ-DI score was measured again.

Data Analysis

Data cleaning, coding, and tabulation are done after the data is gathered. Analysing data also involves testing hypotheses and descriptive analysis. CRP levels and HAQ-DI scores were presented in descriptive analysis as median, minimum range, and maximum range, or as mean and standard deviation (SD) if the data were normally distributed. Because the sample size was less than 50, the data normality test was then performed using the Shapiro-Wilk test. Hypothesis testing of differences in pretest and posttest of CRP levels and HAQ-DI scores using paired t-test if the data is normally distributed or Wilcoxon test if the data is not normally

distributed.

Differences in serum CRP levels and HAQ-DI 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.

The difference is considered significant if the p value <0.05 with 95% confidence interval.

Data analysis was performed using SPSS Ver software. 26.0 for Windows.

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.

RESULTS

Forty samples that meet the inclusion and exclusion criteria and have signed an informed consent, follow the research according to the research flow and the planned method. The average age is 54.88 years, with a median of 53.5 years, as seen in the table below

Table 1. Characteristics of Research Sample Data

Variable	n	%	Mean \pm SD	Median (min – max)
Group				
Treatment (P1)	20	(50,0)		

Control (K)	20	(50,0)	
Age		54,9 ± 9,23	53,5 (38 – 18)

The graph below shows the outcomes of the study on serum CRP levels.



Figure 1. Graph shows decrease in Serum CRP Level

From the graph above, the mean serum CRP levels in the treatment group decreased from 0.4 ± 0.17 to 0.2 ± 0.13

The statistic test between the groups will be presented in table 1 as follows:

Table 2. Statistic test between CRP groups

CRP	Kelompok				p
	Perlakuan (n=20)		Kontrol (n=20)		
	Mean ± SD	Median (Min – Max)	Mean ± SD	Median (Min – Max)	

Pre test	0,4 ± 0,17	0,4 (0,26 – 0,91)	0,5 ± 0,55	0,3 (0,18 – 2,69)	– 0,045 ^{‡*}
Post test	0,2 ± 0,13	0,2 (0,12 – 0,72)	0,6 ± 0,74	0,4 (0,18 – 2,69)	– <0,001 ^{‡*}
Δ	-0,2 ± 0,12	0,2 (0,02 – 0,50)	0,2 ± 0,53	0,1 (0,07 – 2,37)	– <0,001 ^{‡*}
p	<0,001 ^{†*}		0,002 ^{†*}		

Note : *significant (p < 0,05); ‡ Mann Whitney; † Wilcoxon

From the table above, the difference between the pretest and posttest of serum CRP levels in the control group and the treatment group showed significant results. In the assessment of the CRP between the treatment and control groups also showed significant results.

The graph below shows the outcomes of the study on HAQ-DI score.

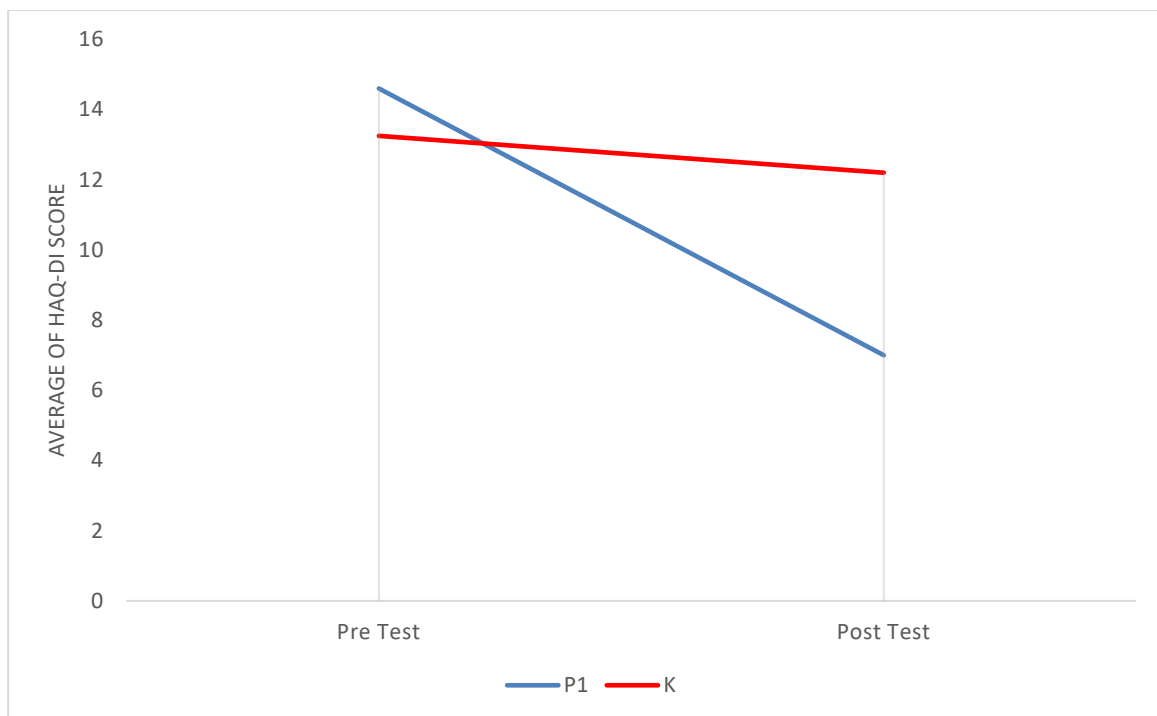


Figure 1. Graph shows decrease in HAQ-DI Score

From the graph above, the mean HAQ-DI score in the treatment group decreased from 14,6 ± 1,57 to 7,0 ± 1,84.

The statistic test between the groups will be presented in table 2 as follows:

Table 3. Statistic test between HAQ-DI groups

HAQ-DI	Groups	p
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	P1 (n=20)	K (n=20)	
	Mean \pm SD	Mean \pm SD	
Pre test	14,6 \pm 1,57	13,3 \pm 2,43	0,034 ^{‡*}
Post test	7,00 \pm 1,84	12,2 \pm 2,24	<0,001 ^{‡*}
Δ	-7,6 \pm 2,14	-1,1 \pm 1,67	<0,001 ^{§*}
p	<0,001 ^{†*}	0,011 ^{†*}	

Note : * significant (p < 0,05); § Independent t; ‡ Mann Whitney; † Wilcoxon

From the table above, the difference between the pretest and posttest HAQ-DI scores in the control group and the treatment group showed significant results. In the assessment of the HAQ-DI score between the treatment and control groups also showed significant results.

DISCUSSION

This study aims to prove the effect of *Moringa oleifera* extract in reducing CRP serum and improving the quality of life of postmenopausal breast cancer patients with ER (+), PR (+) who had aromatase inhibitor associated musculoskeletal syndrome (AIMSS).

According to April et al., postmenopausal women's decreased estrogen production will have an impact on the quantity of cytokines, adjustments in macrophage activity, and changes in cell adhesion molecule activity, all of which contribute to inflammation and joint pain. Aromatase inhibitors work by inhibiting the expression of estrogen formation in women, and that worsening the symptoms of AIMSS.¹⁰

Previous studies have shown that *Moringa oleifera* inhibits the COX-2 enzyme, which is crucial for inflammation. Isothiocyanates, which block COX-2 activity and prostaglandin formation, are one of the *Moringa oleifera* components thought to have anti-inflammatory effects. Isothiocyanates control the activity of nuclear factor-B (NF-B) and nuclear erythroid 2-related factor 2 (Nrf2), which reduces the body's inflammatory response.¹¹⁻¹⁴

This is consistent with this study, which found that after using aromatase inhibitors for arthralgia, patients' inflammatory status, as measured by serum CRP levels, decreased.

A lower quality of life is also a result of increasing inflammation, as shown by higher serum CRP levels. Increased levels of CRP brought on by inflammation, including chronic inflammation, have been found to lower quality of life, according to Roediger's research including 1225 human samples. Chronic pain is caused on by AI inhibitors. Chronic pain and inflammation are side effects of AI inhibitor medication, which is also linked to lower drug adherence, a poorer quality of life, and depression when used daily for years. Using the HAQ-DI questionnaire, it was discovered that the treatment group's quality of life had improved. *Moringa oleifera* extract has been shown to lower CRP levels in the blood. There was less pain and more patients in the therapy group.¹⁵⁻¹⁷

In postmenopausal breast cancer patients who have received aromatase inhibitor therapy and have ER (+), PR (+), *Moringa oleifera* extract has a significant deal of potential as an anti-inflammatory. Because of its anti-inflammatory properties, it will help breast cancer patients live longer, take their medications more consistently, and in the long run, it will significantly enhance their therapy and outcomes.

CONCLUSION

Moringa oleifera extract improve quality of life of on aromatase inhibitor induced arthralgia of postmenopausal breast cancer patients with ER (+), PR (+) by reduced inflammatory status as assessed by serum CRP levels and HAQ-DI score.

CONFLICT OF INTEREST

There is no conflict of interest

ACKNOWLEDGEMENTS

There is no acknowledgements

FUNDING DISCLOSURE

This research was funded using researcher's funds

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel R, Torre L, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2018;394–424.
2. Assi HA, Khoury KE, Dbouk H, Khalil LE, Mouhieddine TH, El Saghir NS. Epidemiology and prognosis of breast cancer in young women. *J Thorac Dis* 51. 2013;52–8
3. Tenti S, Correale P, Cheleschi S, Fioravanti A, Pirtoli L. Aromatase Inhibitors—Induced Musculoskeletal Disorders: Current Knowledge on Clinical and Molecular Aspects. *Int J Mol Sci.* 2020;21(5625):1–38.
4. Roberts K, Rickett K, Greer R, Woodward N. Management of aromatase inhibitor induced musculoskeletal symptoms in postmenopausal early Breast cancer: A systematic review and meta-analysis. *Elsevier.* 2017;111:66–80.
5. Mcandrew NP, Bottalico L, Mesaros C, Blair IA, Tsao PY, Rosado JM, et al. Effects of systemic inflammation on relapse in early breast cancer. *Nat Partn Journals.* 2021;7(7):1–10.
6. Rencz F, Dobos A, Baji P. Musculoskeletal Science and Practice Musculoskeletal health and capability wellbeing: Associations between the HAQ-DI, ICECAP-A and ICECAP-O measures in a population survey. *Musculoskelet Sci Pract.* 2021;55:2468–7812.
7. Jameel H, Abdul N, Khan K, Zaini M, Asmawi B, Mahmud R, et al. In vivo anti-arthritic and anti-nociceptive effects of ethanol extract of *Moringa oleifera* leaves on complete Freund's adjuvant (CFA) -induced arthritis in rats. *Integr Med Res.* 2018;7(1):85–94.
8. Borgonovo G, Petrocellis L De, Moriello AS, Bertoli S, Leone A, Battezzati A, et al. Moringin, A Stable Isothiocyanate from *Moringa oleifera* , Activates the Somatosensory and Pain Receptor TRPA1 Channel In Vitro. *Molecules.* 2020;25(976):1–12.
9. Martínez-gonzález CL, Martínez L, Martínez-ortiz EJ, González-trujano ME, Déciga-campos M, Ventura-martínez R, et al. *Moringa oleifera*, a species with potential analgesic and anti-inflammatory activities. *Biomed Pharmacother.* 2017;87:482–8.

10. April Au, Anita Feher, Lucy McPhee, Ailya Jessa, Soojin Oh, Gillian Einstein. Estrogens, Inflammation and Cognition. *Frontiers in Neuroendocrinology* 2016;40:87-100
11. Kumar G, Tuli HS, Mittal S, Shandilya JK, Tiwari A, Sandhu SS. Isothiocyanates: a class of bioactive metabolites with chemopreventive potential. *Tumour Biol.* 2015;36(6):4005-4016
12. Esteve M (2020) Mechanisms underlying biological effects of cruciferous glucosinolate-derived isothiocyanates/indoles: a focus on metabolic syndrome. *Front Nutr* 7:111
13. Saleh HA, Yousef MH, Abdelnaser A (2021) The anti-inflammatory properties of phytochemicals and their effects on epigenetic mechanisms involved in TLR4/NF- κ B-Mediated Inflammation. *Front Immunol* 12:489
14. Lucarini, Elena & Micheli, Laura & Mannelli, Lorenzo & Ghelardini, Carla. (2022). Naturally occurring glucosinolates and isothiocyanates as a weapon against chronic pain: potentials and limits. *Phytochemistry Reviews*. 21. 10.1007/s11101-022-09809-0.
15. Kumar G, Tuli HS, Mittal S, Shandilya JK, Tiwari A, Sandhu SS. Isothiocyanates: a class of bioactive metabolites with chemopreventive potential. *Tumour Biol.* 2015;36(6):4005-4016
16. Saleh HA, Yousef MH, Abdelnaser A (2021) The anti-inflammatory properties of phytochemicals and their effects on epigenetic mechanisms involved in TLR4/NF- κ B-Mediated Inflammation. *Front Immunol* 12:489
17. Lucarini, Elena & Micheli, Laura & Mannelli, Lorenzo & Ghelardini, Carla. (2022). Naturally occurring glucosinolates and isothiocyanates as a weapon against chronic pain: potentials and limits. *Phytochemistry Reviews*. 21. 10.1007/s11101-022-09809-0.
18. de Almeida Roediger M, de Fátima Nunes Marucci M, Duim EL, Santos JLF, de Oliveira Duarte YA, de Oliveira C. Inflammation and quality of life in later life: findings from the health, well-being and aging study (SABE). *Health Qual Life Outcomes*. 2019 Feb 6;17(1):26. doi: 10.1186/s12955-019-1092-2. PMID: 30728031; PMCID: PMC6366117.



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Thank you for Submitting your manuscript into **Teikyo Medical Journal**. We are Pleased and honored to inform you that your paper **""Effect of Moringa Oleifera Extract on CRP Serum and Quality of Life on Aromatase Inhibitor Associated Musculoskeletal Syndromes of Breast Cancer Patients""** has been accepted by our Editorial board for the next issue of Teikyo Medical Journal.

The current condition of the paper is fully ok and need no further edit for the publications. The editor is really pleased to see this kind of paper and the research applications. In order to proceed for publication, kindly send the Application process charge of the publication within 7 days and submit the completed copyright Agreement paper into your Author Dashboard or through the mail. you can submit it as soon as your payment is done.

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Breast cancer is the most frequent type of cancer in Indonesia, and it also has the highest mortality rate for women worldwide. Aromatase inhibitors will be used in hormonal therapy for postmenopausal individuals with positive hormone receptors but it can cause arthralgia. This study determined the increased impact of moringa oleifera extract therapy on pain quality as measured by serum CRP levels and HAQ-DI scores in breast cancer patients taking aromatase inhibitor therapy. This research is experimental research with two groups parallel pretest and posttest control group design. 40 breast cancer patients were randomly divided into: K (control) and P1 (treatment). The P1 group was given moringa oleifera 600 mg/day for 1 month. CRP levels and HQ-Scores were measured both before and after treatment. Average age of samples is 54.88 years, with a median of 53.5 years. The difference between the pretest and posttest of CRP 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 HAQ-DI 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 extract improve quality of life of on aromatase inhibitor induced arthralgia of postmenopausal breast cancer patients with ER (+), PR (+) by reduced inflammatory status as assessed by serum CRP levels and HAQ-DI score.



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“Effect of Moringa Oleifera Extract on CRP Serum and Quality of Life on Aromatase Inhibitor Associated Musculoskeletal Syndromes of Breast Cancer Patients”

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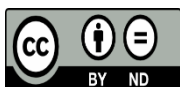


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1. INTRODUCTION

Deaths from breast cancer top the list for women, which is responsible for 6.6% of all cancer-related fatalities

globally [1]. Breast cancer accounted for 58,256 cancer cases in Indonesia in 2018, or 16.7% of all cancer cases, according to data from the World Health Organization (WHO). According to the Indonesia Ministry of Health, 42.1 out of every 100,000 people in Indonesia have breast cancer. The average number of deaths from this cancer is 17 per 100,000 individuals [2].

For people with breast cancer, there are numerous therapy options. One of them is hormonal therapy with aromatase inhibitors. Aromatase inhibitors are used in hormonal therapy for postmenopausal breast cancer patients who have positive hormone receptor tests. However, musculoskeletal syndromes like arthralgia is a side effect of aromatase inhibitor therapy that frequently manifests [3], [4].

Arthralgia was found to have a detrimental effect on the quality of life of breast cancer patients by increasing pain, raising blood inflammation, and decreasing adherence to hormonal treatment [3], [4].

The Health Assessment Questionnaire Disability Index (HAQ-DI) was developed to measure the quality of life in the population, including those with breast cancer. While CRP has also been used as part of measuring the presence of inflammation in the body. The HAQ-DI score and serum CRP levels will have an impact on the state of arthralgia brought on by the administration of aromatase inhibitors [5], [6].

There is no algorithm for treating aromatase inhibitors associated musculoskeletal syndromes. Painkillers like diclofenac sodium, which reduces the severity of symptoms but has serious gastrointestinal side effects like dyspepsia and gastrointestinal bleeding, are frequently prescribed to patients. The development of analgesic and anti-inflammatory compounds natural herbal is the main goal of this research. One of the many plant derivatives from which joint pain relief is known to be effective is *Moringa oleifera* [7- 9].

Since olden days, *moringa oleifera* has been widely used as traditional medicine, including as an anti-inflammatory medication to treat pain. This tropical plant can be easily found in Indonesia. It is believed that the isothiocyanates found in *Moringa oleifera* counteract inflammation. *Moringa oleifera* is expected to reduce the use of diclofenac sodium so that it can reduce the side effects it causes [7- 9].

This study wanted to see the effectiveness of *Moringa oleifera* extract in improving the quality of life as an adjuvant to the administration of aromatase inhibitors in postmenopausal breast cancer patients with ER (+), PR (+).

2. METHODS

2.1 Research Design

This research is experimental research with two groups parallel pretest and posttest control group design. The research group was divided into 2 groups, group K (Control) is postmenopausal breast cancer patients with ER (+) and PR (+), who received aromatase inhibitor therapy and diclofenac sodium 100 mg / day if pain, and treatment group 1 (P1 is postmenopausal breast cancer patients with ER (+) and PR (+), who received aromatase inhibitor therapy, sodium diclofenac 100 mg / day if pain and *Moringa oleifera* extract at a dose of 600 mg / day.

2.2 Research Sample

The research sample was breast cancer patients who were treated at Dr. Kariadi Semarang, and met the inclusion criteria, that are non-metastatic breast cancer patients with immunohistochemical results ER (+), PR (+), post menopause, received aromatase inhibitor therapy for at least 2 months, had arthralgia after

receiving aromatase inhibitor therapy, and agreed to participate in the study. This is by signing the informed consent form.

2.3 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.

2.4 Research Variable

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

2.5 Research Implementation

A total of 40 samples that met the inclusion criteria and exclusion criteria and had signed an informed consent were used as research subjects. The research subjects were randomized and divided into 2 research groups, namely the control group (K) and the treatment group (P1). Data were collected on CRP serum levels and HAQ-DI scores. The measurement of the HAQ-DI score was done by interviewing the subject directly by the researcher. Data on CRP levels were obtained from the subject's medical records. Administration of therapy according to the study group for 30 days. Monitoring of adverse effects will be carried out periodically every week or research subjects can immediately contact the researcher without waiting for the monitoring schedule. Monitoring is carried out by contacting the subject via WhatsApp application, or telephone by asking the progress during the treatment. After 30 days, data were collected on CRP serum levels and the second HAQ-DI score was measured again.

2.6 Data Analysis

Data cleaning, coding, and tabulation are done after the data is gathered. Analysing data also involves testing hypotheses and descriptive analysis. CRP levels and HAQ-DI scores were presented in descriptive analysis as median, minimum range, and maximum range, or as mean and standard deviation (SD) if the data were normally distributed. Because the sample size was less than 50, the data normality test was then performed using the Shapiro-Wilk test.

Hypothesis testing of differences in pretest and posttest of CRP levels and HAQ-DI scores using paired t-test if the data is normally distributed or Wilcoxon test if the data is not normally distributed.

Differences in serum CRP levels and HAQ-DI 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.

The difference is considered significant if the p value <0.05 with 95% confidence interval. Data analysis was performed using SPSS Ver software. 26.0 for Windows.

2.7 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.

3. RESULTS

Forty samples that meet the inclusion and exclusion criteria and have signed an informed consent, follow the research according to the research flow and the planned method. The average age is 54.88 years, with a median of 53.5 years, as seen in the table below

Table 1. Characteristics of Research Sample Data

Variable	n	%	Mean \pm SD	Median (min – max)
Group				
Treatment (P1)	20	(50,0)		
Control (K)	20	(50,0)		
Age			54,9 \pm 9,23	53,5 (38 – 18)

The graph below shows the outcomes of the study on serum CRP levels.

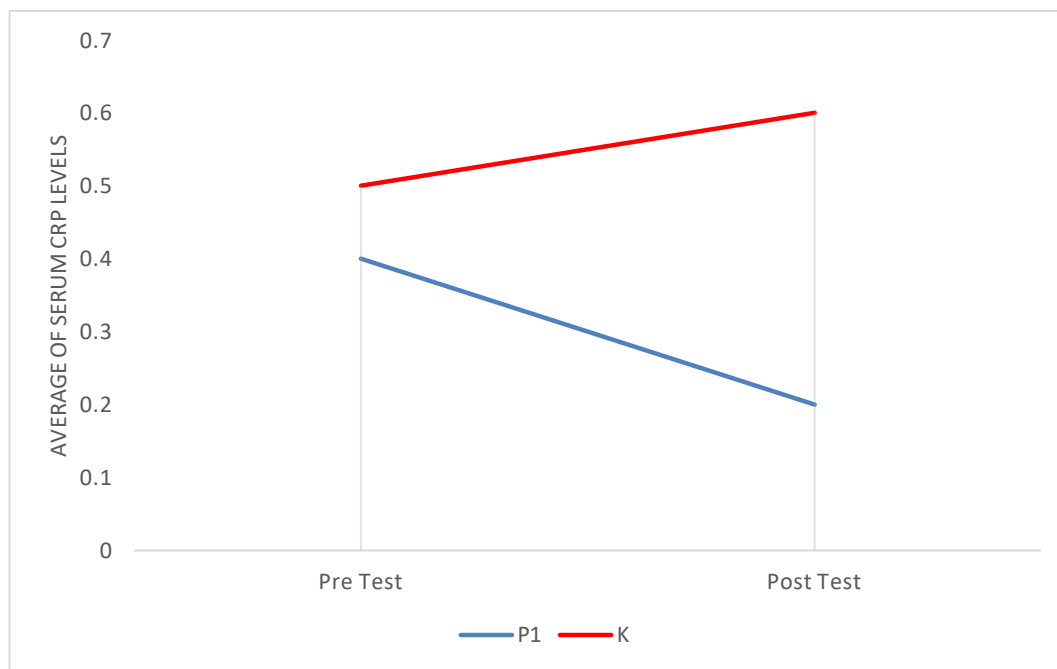


Figure 1. Graph shows decrease in Serum CRP Level

From the graph above, the mean serum CRP levels in the treatment group decreased from 0.4 ± 0.17 to 0.2 ± 0.13

The statistic test between the groups will be presented in table 1 as follows:

Table 2. Statistic test between CRP groups

CRP	Kelompok	p
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	Perlakuan (n=20)		Kontrol (n=20)		
	Mean \pm SD	Median (Min – Max)	Mean \pm SD	Median (Min – Max)	
Pre test	0,4 \pm 0,17	0,4 (0,26 – 0,91)	0,5 \pm 0,55	0,3 (0,18 – 2,69)	0,045 ^{‡*}
Post test	0,2 \pm 0,13	0,2 (0,12 – 0,72)	0,6 \pm 0,74	0,4 (0,18 – 2,69)	<0,001 ^{‡*}
Δ	-0,2 \pm 0,12	0,2 (0,02 – 0,50)	0,2 \pm 0,53	0,1 (0,07 – 2,37)	<0,001 ^{‡*}
p	<0,001 ^{†*}		0,002 ^{†*}		

Note: *significant ($p < 0,05$); [‡] Mann Whitney; [†] Wilcoxon

From the table above, the difference between the pretest and posttest of serum CRP levels in the control group and the treatment group showed significant results. In the assessment of the CRP between the treatment and control groups also showed significant results.

The graph below shows the outcomes of the study on HAQ-DI score.

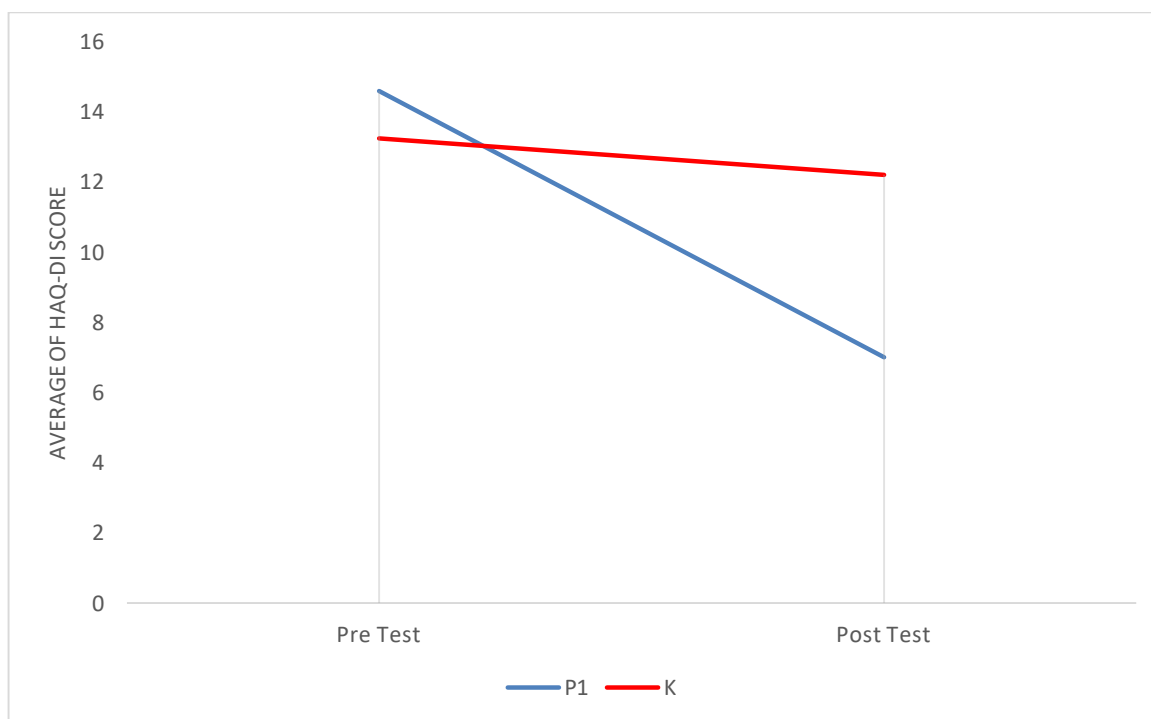


Figure 1. Graph shows decrease in HAQ-DI Score

From the graph above, the mean HAQ-DI score in the treatment group decreased from 14,6 \pm 1,57 to 7,0 \pm 1,84.

The statistic test between the groups will be presented in table 2 as follows:

Table 3. Statistic test between HAQ-DI groups

HAQ-DI	Groups		p
	P1 (n=20)	K (n=20)	

	Mean ± SD	Mean ± SD	
Pre test	14,6 ± 1,57	13,3 ± 2,43	0,034 ^{‡*}
Post test	7,00 ± 1,84	12,2 ± 2,24	<0,001 ^{‡*}
Δ	-7,6 ± 2,14	-1,1 ± 1,67	<0,001 ^{§*}
p	<0,001 ^{†*}	0,011 ^{†*}	

Note: * significant ($p < 0,05$); § Independent t; ‡ Mann Whitney; † Wilcoxon

From the table above, the difference between the pretest and posttest HAQ-DI scores in the control group and the treatment group showed significant results. In the assessment of the HAQ-DI score between the treatment and control groups also showed significant results.

4. DISCUSSION

This study aims to prove the effect of *Moringa oleifera* extract in reducing CRP serum and improving the quality of life of postmenopausal breast cancer patients with ER (+), PR (+) who had aromatase inhibitor associated musculoskeletal syndrome (AIMSS).

According to [10] postmenopausal women's decreased estrogen production will have an impact on the quantity of cytokines, adjustments in macrophage activity, and changes in cell adhesion molecule activity, all of which contribute to inflammation and joint pain. Aromatase inhibitors work by inhibiting the expression of estrogen formation in women, and that worsening the symptoms of AIMSS.

Previous studies have shown that *Moringa oleifera* inhibits the COX-2 enzyme, which is crucial for inflammation. Isothiocyanates, which block COX-2 activity and prostaglandin formation, are one of the *Moringa oleifera* components thought to have anti-inflammatory effects. Isothiocyanates control the activity of nuclear factor-B (NF-B) and nuclear erythroid 2-related factor 2 (Nrf2), which reduces the body's inflammatory response [11- 14].

This is consistent with this study, which found that after using aromatase inhibitors for arthralgia, patients' inflammatory status, as measured by serum CRP levels, decreased.

A lower quality of life is also a result of increasing inflammation, as shown by higher serum CRP levels. Increased levels of CRP brought on by inflammation, including chronic inflammation, have been found to lower quality of life, according to Roediger's research including 1225 human samples. Chronic pain is caused on by AI inhibitors. Chronic pain and inflammation are side effects of AI inhibitor medication, which is also linked to lower drug adherence, a poorer quality of life, and depression when used daily for years. Using the HAQ-DI questionnaire, it was discovered that the treatment group's quality of life had improved. *Moringa oleifera* extract has been shown to lower CRP levels in the blood. There was less pain and more patients in the therapy group [15- 17].

In postmenopausal breast cancer patients who have received aromatase inhibitor therapy and have ER (+), PR (+), *Moringa oleifera* extract has a significant deal of potential as an anti-inflammatory. Because of its anti-inflammatory properties, it will help breast cancer patients live longer, take their medications more

consistently, and in the long run, it will significantly enhance their therapy and outcomes.

5. CONCLUSION

Moringa oleifera extract improve quality of life of on aromatase inhibitor induced arthralgia of postmenopausal breast cancer patients with ER (+), PR (+) by reduced inflammatory status as assessed by serum CRP levels and HAQ-DI score.

6. REFERENCES

- [1] Bray F, Ferlay J, Soerjomataram I, Siegel R, Torre L, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2018;394–424.
- [2] Assi HA, Khoury KE, Dbouk H, Khalil LE, Mouhieddine TH, El Saghir NS. Epidemiology and prognosis of breast cancer in young women. *J Thorac Dis* 51. 2013;52–8
- [3] Tenti S, Correale P, Chelleschi S, Fioravanti A, Pirtoli L. Aromatase Inhibitors—Induced Musculoskeletal Disorders: Current Knowledge on Clinical and Molecular Aspects. *Int J Mol Sci.* 2020;21(5625):1–38.
- [4] Roberts K, Rickett K, Greer R, Woodward N. Management of aromatase inhibitor induced musculoskeletal symptoms in postmenopausal early Breast cancer: A systematic review and meta-analysis. *Elsevier.* 2017;111:66–80.
- [5] Mcandrew NP, Bottalico L, Mesaros C, Blair IA, Tsao PY, Rosado JM, et al. Effects of systemic inflammation on relapse in early breast cancer. *Nat Partn Journals.* 2021;7(7):1–10.
- [6] Rencz F, Dobos A, Baji P. Musculoskeletal Science and Practice Musculoskeletal health and capability wellbeing: Associations between the HAQ-DI, ICECAP-A and ICECAP-O measures in a population survey. *Musculoskelet Sci Pract.* 2021;55:2468–7812.
- [7] Jameel H, Abdul N, Khan K, Zaini M, Asmawi B, Mahmud R, et al. In vivo anti-arthritic and anti-nociceptive effects of ethanol extract of *Moringa oleifera* leaves on complete Freund's adjuvant (CFA) - induced arthritis in rats. *Integr Med Res.* 2018;7(1):85–94.
- [8] Borgonovo G, Petrocellis L De, Moriello AS, Bertoli S, Leone A, Battezzati A, et al. Moringin, A Stable Isothiocyanate from *Moringa oleifera*, Activates the Somatosensory and Pain Receptor TRPA1 Channel In Vitro. *Molecules.* 2020;25(976):1–12.
- [9] Martínez-gonzález CL, Martínez L, Martínez-ortiz EJ, González-trujano ME, Déciga-campos M, Ventura-martínez R, et al. *Moringa oleifera*, a species with potential analgesic and anti-inflammatory activities. *Biomed Pharmacother.* 2017;87:482–8.
- [10] April Au, Anita Feher, Lucy McPhee, Ailya Jessa, Soojin Oh, Gillian Einstein. Estrogens, Inflammation and Cognition. *Frontiers in Neuroendocrinology* 2016;40:87-100
- [11] Kumar G, Tuli HS, Mittal S, Shandilya JK, Tiwari A, Sandhu SS. Isothiocyanates: a class of bioactive metabolites with chemopreventive potential. *Tumour Biol.* 2015;36(6):4005-4016

- [12] Esteve M (2020) Mechanisms underlying biological effects of glucosinolate-derived isothiocyanates/indoles: a focus on metabolic syndrome. *Front Nutr* 7:111
- [13] Saleh HA, Yousef MH, Abdelnaser A (2021) The anti-inflammatory properties of phytochemicals and their effects on epigenetic mechanisms involved in TLR4/NF- κ B-Mediated Inflammation. *Front Immunol* 12:489
- [14] Lucarini, Elena & Micheli, Laura & Mannelli, Lorenzo & Ghelardini, Carla. (2022). Naturally occurring glucosinolates and isothiocyanates as a weapon against chronic pain: potentials and limits. *Phytochemistry Reviews*. 21. 10.1007/s11101-022-09809-0.
- [15] Kumar G, Tuli HS, Mittal S, Shandilya JK, Tiwari A, Sandhu SS. Isothiocyanates: a class of bioactive metabolites with chemopreventive potential. *Tumour Biol*. 2015;36(6):4005-4016
- [16] Saleh HA, Yousef MH, Abdelnaser A (2021) The anti-inflammatory properties of phytochemicals and their effects on epigenetic mechanisms involved in TLR4/NF- κ B-Mediated Inflammation. *Front Immunol* 12:489
- [17] Lucarini, Elena & Micheli, Laura & Mannelli, Lorenzo & Ghelardini, Carla. (2022). Naturally occurring glucosinolates and isothiocyanates as a weapon against chronic pain: potentials and limits. *Phytochemistry Reviews*. 21. 10.1007/s11101-022-09809-0.
- [18] de Almeida Roediger M, de Fátima Nunes Marucci M, Duim EL, Santos JLF, de Oliveira Duarte YA, de Oliveira C. Inflammation and quality of life in later life: findings from the health, well-being and aging study (SABE). *Health Qual Life Outcomes*. 2019 Feb 6;17(1):26. doi: 10.1186/s12955-019-1092-2. PMID: 30728031; PMCID: PMC6366117.