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**Manuscript Needs Revision (#JMCS-2305-2087 (R1))**

2 messages

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18 June 2023 at 03:56



Manuscript ID: JMCS-2305-2087

Manuscript Title: **THE EFFECT OF MORINGA OLEIFERA EXTRACT ON CPK AND QUALITY OF LIFE OF BREAST CANCER PATIENTS RECEIVING AROMATASE INHIBITOR THERAPY**

Authors: Yan Wisnu Prajoko, Sugeng Pramono, Agung Hartanto, Mada Aji Prakoso

Dear Mr. Yan Wisnu Prajoko

Evaluation process of the above mentioned manuscript has been reviewed. The comments of the reviewer(s) are included at the bottom of this letter.

The reviewer(s) have recommended publication, but also suggest some revisions to your manuscript. Therefore, I invite you to respond to the reviewer(s) comments and revise your manuscript within the period of defined time.

Because we are trying to facilitate timely publication of manuscripts submitted to journal, your revised manuscript should be uploaded as soon as possible. If it is not possible for you to submit your revision in a reasonable amount of time, we may have to consider your paper as a new submission.

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Reviewer 1

The work is of acceptable quality. However, the following major corrections must be made to improve the quality of this manuscript:

- The title can be simply modified to the following: Effects of Moringa oleifera Extract on CPK and Quality of Life in Breast Cancer Patients Receiving Aromatase Inhibitor Therapy.
- The full term of the abbreviation FACT-B, Functional Assessment of Cancer Therapy-Breast, must be included in the abstract.
- Reference 4 must be replaced by the following: Chemotherapeutic applications of folate prodrugs: A review. NeuroQuantology 2021; 19(8): 99-112. <http://dx.doi.org/10.14704/nq.2021.19.8.NQ21120>
- The fourth paragraph of the introduction must become the third, and at least two references must be added.

In the introduction, the paragraph about medicinal plants must be cited by the following:

<https://doi.org/10.22092/ARI.2021.356100.1776>

<https://doi.org/10.26655/JMCHEMSCI.2022.6.10>

In the materials and methods, what is the full term of KEPK?

What is the AI drug used in this study? And what is the dose?

The methodology used to investigate the CPK must be added.

Reference 5 must be replaced by the following:

Hymecromone and its products as cytotoxic candidates for brain cancer: A brief review. NeuroQuantology 19(7):175-186. <http://dx.doi.org/10.14704/nq.2021.19.7.NQ21101>

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<https://doi.org/10.1016/j.clnesp.2022.04.019>

I proposed that the institution's help to the authors as well as that of its staff be acknowledged.

The ethical approval must be added before the references section.

## Reviewer 2

The manuscript JMCS-2305-2087 is devoted to the actual problem of Medicinal chemistry, especially Journal of Medicinal and Chemical Sciences. The reviewed article is interesting and theme of the article meets the scope of the journal. Work is performed at sufficient scientific level and has good quality; the results of investigation are professionally interpreted. However, it needs minor revision before publication.

1. Abstract must be enriched via valuable results which pave the way for understanding the audiences.

2. The authors should more clearly emphasise the novelty of their work in the introduction of the manuscript.

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# EFFECTS OF MORINGA OLEIFERA EXTRACT ON CPK AND QUALITY OF LIFE IN BREAST CANCER PATIENTS RECEIVING AROMATASE INHIBITOR THERAPY

## Abstract

Aromatase inhibitors (AI) are commonly used adjuvant therapy drugs for women with hormone receptor-positive postmenopausal breast cancer. Frequently AI associated side effects include severe joint and muscle pain. Aromatase Inhibitor - Associated Musculoskeletal Syndrome (AIMSS) is a condition that primarily affects the hands, wrists, and knees. This study aimed to determine the efficacy of Moringa oleifera extract as an adjuvant when taken with AI to postmenopausal breast cancer patients with ER (+), PR (+) and observe the CPK levels as inflammation indicators. The Functional Assessment of Cancer Therapy-Breast (FACT-B) can assess subjects emotional, physical, functional well-being, social and also the breast cancer subscale. The research sample consisted of 40 postmenopausal cancer patients with ER(+) PR(+) immunohistochemistry and as outpatients at the Kasuari facility, Dr. Kariadi Semarang, who experienced pain due to the administration of aromatase inhibitors. The results of the changes in CPK and FACT-B scores in the group that received additional therapy with Moringa oleifera extract were obtained in this study. The treatment group showed CPK level of post-test lower than pre-test ( $105.30 \pm 50.19$  vs  $88.10 \pm 48.24$ ,  $p < 0.001$ ). The treatment group also showed lower FACT-B score than control group ( $83.45 \pm 5.11$  vs  $75.25 \pm 4.05$ ,  $p < 0.001$ ). Moringa oleifera extract has a strong anti-inflammatory effect especially for patient with postmenopausal breast cancer who received ER (+), PR (+), and aromatase inhibitor treatment. Its anti-inflammatory properties will upgrade breast cancer patient's quality of life, treatment adherence, long period of breast cancer therapy and outcomes.

## Keywords

Breast cancer, Aromatase inhibitor, AIMSS, CPK, FACT-B

## Introduction

Cancer is an uncontrolled cell proliferation that can penetrate and spread throughout the human body [1]. The prevalence and the number of fatalities from cancer are rising quickly worldwide. There is a 3.1% increase in the incidence of breast cancer every year. Around 2 million new cases of breast cancer were identified in 2018, with 600,000 dying from the disease globally. Breast cancer death accounts for 6.6% of all cancer-related fatalities globally. It becomes major cause of mortality case in female [2]. Breast cancer accounted for 58,256 instances, or 16.7% of all cancer cases reported in Indonesia in 2018, according to World Health Organization (WHO) data [3].

Breast cancer treatment modalities include surgery, radiation therapy, cytotoxic drugs, immunotherapy, and hormone therapy [3, 4]. Aromatase inhibitor is used in hormone treatment for postmenopausal women who tested positive for hormone receptors. Significant joint and muscular problems are frequently linked to the side effects of AI, affecting the hands, wrists, and knees, also called Aromatase Inhibitor - Associated Musculoskeletal Syndrome (AIMSS). Stopping AI medication would lead to the cessation of these symptoms, but as soon as it is started again, these symptoms will reappear. AIMSS negatively impacts many patients' quality of life in terms of health, impairs adherence to AI breast cancer treatment, increases blood inflammation, and raises creatine phosphokinase levels (CPK). This study focuses on developing novel chemicals derived from medicinal plants that act as analgesics and anti-inflammatory agents. In most cases, the use of medicinal plants is based solely on tradition, without sufficient scientific evidence. Moreover, derived medicinal plants are known to treat joint pain effectively. One is Moringa oleifera, a tropical plant widely used in traditional medicine, including anti-inflammatory drugs for treating pain [5,6].

Multiple researches for Moringa oleifera gave information that 100 grams of Moringa oleifera contains twelve times the vitamin C in oranges, ten times the vitamin A in carrots, nine times the protein in yogurt, fifteen times the potassium in bananas, seventeen times the milk, ten times the calcium, and twentyfive times the iron of 100 grams of beef and spinach. In both human and animal metabolic processes, this nutritional content is crucial. Monosaccharide-containing, rhamnase-containing, glucosinolate, and isothiocyanate chemicals are abundant in the Moringa oleifera plant. Cyclooxygenase 2 (COX2) produces isothiocyanate, which reduces inflammation brought on by nitric oxide synthase (i-NOS).

This study aimed to investigate the impact of *Moringa oleifera* extract as a supplementary treatment alongside aromatase inhibitors on postmenopausal breast cancer patients with ER (+) and PR (+), specifically focusing on the variations in CPK levels, an indicator of inflammation. The study also measured the subjects' well-being using the FACT-B scale, which assessed their physical, social, emotional, functional, and breast cancer subscale well-being. The research findings are expected to promote the use of *Moringa oleifera* as a beneficial addition to aromatase inhibitor therapy for ER (+) and PR (+) postmenopausal breast cancer patients.

## **Martials and Methods**

This study is experimental research with two groups parallel pretest and a post-test control group design. Breast cancer patients who met the research criteria and received treatment at RSUP Dr. Kariadi Semarang during the study period made up the research sample. As soon as the Institutional review board permission is given, research and data collection will begin until the minimum number of samples is reached. The Biochemistry Laboratory of the Sido Muncul Ungaran factory produced the *Moringa oleifera* extract. Patients with breast cancer were treated at Dr. Kariadi's Kasuari Installation. The Clinical Pathology Laboratory, headed by Dr. Kariadi, conducts the laboratory examination process. Breast cancer patients who had undergone menopause, tested positive for ER and PR immunohistochemistry, had undergone aromatase inhibitor therapy (Anastrozole, 1 mg) and had consented to participate in the study met the inclusion criteria. While emergency cases needing surgery and unwillingness to participate in the study were exclusion factors in this study. Dropout criteria in this study were being unable to follow up for 30 days after the study began and obtaining therapy in addition to the research method. These calculations show that 44 research subjects are required since each group requires 22 postmenopausal breast cancer patients with ER (+) and PR (+).

The stages in this research are patients with inclusion and exclusion criterias and already gave permission to join as research subjects. These subjects were randomized and divided into 2 groups. 1 group for intervention and the other for control group. The therapy was given according to the research group for 30 days.

A 10 ml venous blood sample was taken from each patient after 12–14 h fasting at the baseline and at the end of the study. Serum was separated by centrifugation at 3000 rpm and frozen at  $-80^{\circ}\text{C}$  until the end of the study. Serum levels of Creatine phosphokinase (CPK) was accomplished by the ELISA method at baseline and after 30 days of treatment. Subjects were also assessed using the FACT-B to measure emotional, physical, social, functional well-being and also the breast cancer subscale.

After the data is collected, data cleaning, coding, and also tabulation are carried out after the data is collected. Data that being analyzed are descriptive analysis and hypothesis testing. CPK levels and FACT-B scores as the mean,  $\pm$  SD if the data is normally distributed, or the minimum, median and maximum range if the data distribution is abnormal was presented by descriptive analysis. In this research, there were more than 50 samples, the Kolmogorov-Smirnov test was done for determining whether the data were normal. If the research data were regularly distributed, the paired t-test was employed to test this hypothesis, or else Wilcoxon test was used for non-normally distributed data.

Differences in CPK levels and FACT-B assessment between the treatment and control groups will be tested using an unpaired t-test for normal data distribution and the Mann-Whitney test for abnormal data distribution. The difference is considered significant for  $p < 0.05$  with 95% confidence interval. Then data analysis was performed with software application SPSS Ver 26.0 for Windows.

## **Results and Discussion**

Aromatase inhibitors (AI) are frequently used as adjuvant therapy for postmenopausal breast cancer patients with positive hormone receptor malignancy. Numbers of aromatase inhibitor side effects include arthralgia, fractures, and a reduction in bone mineral density (BMD). Postmenopausal onset and natural aging may contribute to joint

issues. Twenty to seventy percent of postmenopausal women who use an aromatase inhibitor will experience joint pain [7-9].

Our study used experimental methodologies and a parallel pre- and post-test control group design with two groups. Forty postmenopausal cancer patients with ER(+) PR(+) immunohistochemistry treated as outpatients at the Kasuari facility by Dr. Kariadi Semarang and with discomfort complaints after receiving aromatase inhibitors made up the research sample. Before conducting the study, the sample complied with the inclusion and exclusion criteria and provided written consent. The mean age of all subjects is  $54.88 \pm 9.23$  y.o and senior high school (32.5%) is the most populated education (Table. I). Both group showed no significant difference on mean age and education ( $p > 0.005$ , Table II).

**Table I.** Characteristics of subject

Variable	F	%	Mean $\pm$ SD	Median (min-max)
Group				
Treatment(P1)	20	50.0		
Control (K)	20	50.0		
Age			$54.88 \pm 9.23$	53.5 (38 – 18)
Education				
No school	1	2.5		
Primary school	10	25.0		
Junior high school	6	15.0		
Senior high school	13	32.5		
Graduate	10	25.0		

**Table II.** Characteristics of data by treatment group and placebo

Variable	Group		p
	Control (20)	Treatment (20)	
Age	$53.85 \pm 9.60$	$55.90 \pm 8.97$	0.490 <sup>§</sup>
Education			0.300 <sup>‡</sup>
No school	0 (0%)	1 (100%)	
Primary school	3 (30%)	7 (70%)	
Junior high school	4 (66.7%)	2 (33.3%)	
Senior high school	8 (61.5%)	5 (38.5%)	
Graduate	5 (50%)	5 (50%)	

The management of AI-induced arthralgia puts a greater emphasis on counseling and education. Therapy using this regimen is administered for 5 years. Since arthralgia side effects can start to manifest as early as 2 months after therapy and last as long as 6 months after that, patients are advised to undergo follow-up every 2 or 6 months. Additionally, patients can strengthen their muscles by adopting healthy lifestyle changes, including decreasing weight and engaging in regular exercise. To relieve pain, acetaminophen/ibuprofen or other NSAIDs may be used. Opioids or tricyclic antidepressants may assist people with higher VAS scales to feel less pain [10].

The manifestation of pain is one of the adverse effects frequently reported due to using aromatase inhibitor medication (AIA - Aromatase Inhibitor-associated Arthralgia). Aromatase inhibitors are believed to reduce estrogen production, and this drop in estrogen will result in lower pain thresholds. As a result, during regular activities, the pain sensation may happen independently[11]. Due to the adverse effects of AI medication, Moringa oleifera extract with sodium diclofenac can reduce inflammation and, subsequently pro-inflammatory cytokines. Serum CPK levels can be used to measure decreased pro-inflammatory cytokine levels [12].



**Table III.** Statistic Test of CPK levels

CPK	Group		p
	Treatment (20)	Control (20)	
Pretest	105.30 ± 50.19	100.10 ± 38.67	0.808 <sup>‡</sup>
Post-test	88.10 ± 48.24	102.60 ± 39.40	0.091 <sup>‡</sup>
P	<0.001 <sup>†*</sup>	0.015 <sup>†*</sup>	
Δ	-17.20 ± 16.60	2.50 ± 24.19	<0.001 <sup>‡*</sup>

Description: \* Significant ( $p < 0.05$ ); <sup>‡</sup> Mann Whitney; <sup>†</sup> Wilcoxon

Data from the table III showed paired difference test in the treatment and control groups is significant. In the unpaired difference test, the CPK pre and post-CPK were not significant, while the difference in CPK was significant. Creatine phosphokinase (CPK) is one of the enzyme that can catalyze the creatine and adenosine triphosphate (ATP) to become phosphocreatine and adenosine diphosphate (ADP). This enzyme can be found in muscle tissue. The study by Leverenz et al. found that the rheumatological cause of most cases of elevated CPK was idiopathic inflammatory myopathies (IIMS). IIMS is a group of diseases who manifested as abnormal inflammation in muscle tissue that constituted a large proportion of musculoskeletal problems. Additional Moringa oleifera extract has proven to reduce blood levels of CPK in patients using Aromatase Inhibitors.

**Table IV.** Statistic test of FACT-B

FACT-B	Group		p
	Treatment (20)	Control (20)	
Pretest	69.85 ± 3.27	73.90 ± 4.68	0.012 <sup>‡*</sup>
Post-test	83.45 ± 5.11	75.25 ± 4.05	<0.001 <sup>§*</sup>
p	<0.001 <sup>†*</sup>	0.009 <sup>¶*</sup>	
Δ	13.60 ± 4.48	1.35 ± 2.06	<0.001 <sup>‡*</sup>

Description: \*Significant ( $p < 0.05$ ); <sup>§</sup> Independent t; <sup>‡</sup> Mann Whitney; <sup>¶</sup> Paired t; <sup>†</sup> Wilcoxon

Data from the table IV are significant paired difference tests on Group Treatment and control. The FACT-B pre, FACT-B post and FACT-B differences were significant in the unpaired difference test. Subjects were assessed with FACT-B for both before and after administration of Moringa oleifera extract. FACT-B will assess emotional, physical, functional well-being, social and the breast cancer subscale. In the unpaired difference test, the FACT-B pre, FACT-B post and FACT-B differences were significant, indicating an upgrade for subject's quality of life in the treatment group.

Moringa leaf extract shows a solid anti-inflammatory potential in patients with postmenopausal breast cancer receiving ER (+), PR (+), and aromatase inhibitor therapy. Its anti-inflammatory properties will enhance patients' quality of life, increase medication adherence, and, over time, significantly aid breast cancer treatments and outcomes. The author is aware that several gaps in this research must be filled for it to be finished. This study could be expanded to include more people and cancer patients where feasible.

## Conclusions

It has been demonstrated that using Moringa oleifera extract as an additional therapy can lower serum CPK levels. By preventing prostaglandin synthesis, cyclooxygenase-2 (COX-2) activity, and the nuclear translocation of anti-inflammatory nuclear transcription factor (NF) factors, Moringa oleifera extract reduces inflammation. Pro-inflammatory cytokines, which prevent inflammation, are decreased by -B. It was discovered that an upgrade in subject's quality of life for Group Treatment in the FACT-B for both before and after administration of Moringa oleifera extract.

## Acknowledgements:

We thank to our institution, doctor, nurse, and staff who took care our subjects during treatment. We also thank to our subjects who voluntary contributed to our study.

## Ethical Approval

This study was obtained an ethical approval from Institutional Review Board of RSUP Dr. Kariadi Semarang No. 1126/EC/KEPK-RSDK/2022.

## References:

- [1]. Lim WF, Mohamad Yusof MI, Teh LK, Salleh MZ. *Nutrients*, 2020, **12**:2993. (DOI Link: <https://doi.org/10.3390/nu12102993>)
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- [12]. Leverenz D, Zaha O, Crofford LJ, Chung CP. *Clinical rheumatology*, 2016, **35**:1541-7. (DOI Link: <https://doi.org/10.1007/s10067-016-3242-9>)

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*A 10 ml venous blood sample was taken from each patient after 12–14 h fasting at the baseline and at the end of the study. Serum was separated by centrifugation at 3000 rpm and frozen at – 80° C until the end of the study. Serum levels of Creatine phosphokinase (CPK) was accomplished by the ELISA method at baseline and after 30 days of treatment. Subjects were also assessed using the FACT-B to measure emotional, physical, social, functional well-being and also the breast cancer subscale.*

- h. Reference 5 must be replaced by the following:  
Hymecromone and its products as cytotoxic candidates for brain cancer: A brief review. NeuroQuantology 19(7):175-186. <http://dx.doi.org/10.14704/nq.2021.19.7.NQ21101>

We thank reviewer for the comment, we have edited the reference section.

- i. I proposed that the institution's help to the authors as well as that of its staff be acknowledged.

We thank reviewer for the comment, we have edited in the acknowledged section.

- j. The ethical approval must be added before the references section.

We thank reviewer for the comment, we have edited the ethical approval section.

#### Reviewer 2

The manuscript JMCS-2305-2087 is devoted to the actual problem of Medicinal chemistry, especially Journal of Medicinal and Chemical Sciences. The reviewed article is interesting and theme of the article meets the scope of the journal. Work is performed at sufficient scientific level and has good quality; the results of investigation are professionally interpreted. However, it needs minor revision before publication.

1. Abstract must be enriched via valuable results which pave the way for understanding the audiences.

We thank reviewer for the comment, we have revised in the abstract section.

*The treatment group showed CPK level of post-test lower than pre-test ( $105.30 \pm 50.19$  vs  $88.10 \pm 48.24$ ,  $p < 0,001$ ). The treatment group also showed lower FACT-B score than control group ( $83.45 \pm 5.11$  vs  $75.25 \pm 4.05$ ,  $p < 0,001$ ).*

2. The authors should more clearly emphasise the novelty of their work in the introduction of the manuscript.

We thank reviewer for the comment, we have revised in the introduction section.

*This study aimed to investigate the impact of Moringa oleifera extract as a supplementary treatment alongside aromatase inhibitors on postmenopausal breast cancer patients with ER (+) and PR (+), specifically focusing on the variations in CPK levels, an indicator of inflammation. The study also measured the subjects' well-being using the FACT-B scale, which assessed their physical, social, emotional, functional, and breast cancer subscale well-being. The research findings are expected to promote the use of Moringa oleifera as a beneficial addition to aromatase inhibitor therapy for ER (+) and PR (+) postmenopausal breast cancer patients.*

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**The Effect of Moringa Oleifera Extract on CPK and Quality of Life of Breast Cancer Hpatinnts Reseiving Aromatase Inhibitor Therapy**

**Yan Wisnu Prajoko<sup>a\*</sup>, Sugeng Pramono<sup>b</sup>, Agung Hartanto<sup>b</sup>, Mada Aji Prakoso<sup>b</sup> Q1**

<sup>a</sup>Staff of the Sub Division of Surgical Oncology at Diponegoro University, RSUP Dr. Kariadi Hospital, Semarang  
<sup>b</sup>General Surgery Resident at Diponegoro University, RSUP Dr. Kariadi Hospital, Semarang

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**Invoice and Scientific Acceptance Letter (JMCS-2305-2087 (R1))**

Dear Mr. Yan Wisnu Prajoko

All Authors: Yan Wisnu Prajoko, Sugeng Pramono, Agung Hartanto, Mada Aji Prakoso

ID: JMCS-2305-2087 (R1)

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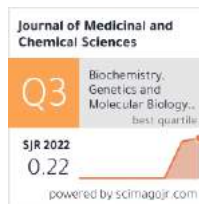
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## Acceptance Letter



Dear Authors: **Yan Wisnu Prajoko\***,

Your co-workers: **Yan Wisnu Prajoko\***, Sugeng Pramono, Agung Hartanto, Mada Aji Prakoso,

We are pleased to inform you that your manuscript entitled: **EFFECTS OF MORINGA OLEIFERA EXTRACT ON CPK AND QUALITY OF LIFE IN BREAST CANCER PATIENTS RECEIVING AROMATASE INHIBITOR THERAPY**" (**JMCS-2305-2087**), has been passed the peer-review process and accepted for publication in the forthcoming issue (Volume 6, Issue 11, 2023) of "**Journal of Medicinal and Chemical Sciences**" Online ISSN: 2651-4702

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