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The effect of *Moringa oleifera* leaves nanoparticles extract on hematology profile in breast cancer patients of chemotherapy programs

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Abstract
Background: Breast cancer is a leading cause of cancer deaths in women (15.0%). One of the problems in breast cancer patients during chemotherapy was the risk of infection and 86.3% had anemia. This occurs because excessive free radicals are formed due to chemotherapy which are toxic and cause oxidative stress resulting in disturbances and decreased hematological profiles. Herbal plants that have been shown to have good activity in the human hematology system and as a source of antioxidants are Moringa Oleifera plants.
Method: True Research Experiments with single blind and pre-test-post test with control group designs. Sampling by simple random sampling was used to get 40 respondents divided into two groups. The intervention group was given treatment of extracts of Moringa Oliefera leaf doses of 28.57 mg / kg BW / day and antianemia while the control group was given antianemia alone for 21 days.
Result: Tests between groups showed p value <0.05 which means that there was a significant effect after administration of Moringa Oleifera leaf extract to increase hemoglobin levels, hematocrit levels and the number of erythrocytes of breast cancer patients undergoing chemotherapy programs while the number of leukocytes only increase but not significant. This change is caused by the content of Moringa leaves such as iron, folic acid, B12, Vitamin C and flavonoids which trigger an increase in hematological profile and Moringa leaf extract in the form of 0.208µm nanoparticles increasing the absorption of the content.
Conclusion: The Moringa leaf nanoparticles extract significantly increases hematological profile in breast cancer patients can be made one of the supporting therapies that support the improvement of patient's health during chemotherapy.

Keywords: moringa oleifera leaves nanoparticles extract, hematology profile, breast cancer, chemotherapy

1. Introduction

Cancer is a non-communicable disease which is a health problem in the world, both in developed and developing countries. Cancer is categorized as one of the malignancies that pose a threat to everyone including women. Breast cancer is a cause of pain and suffering in women [1].

The incidence of breast cancer increases 1-2% each year in most countries, so that an average of 2000 women each year suffer from this disease. As many as 78% of breast cancers occur in women aged 50 years and over, while 6% of them are less than 40 years old. However, in recent years many women aged 30 suffer from this deadly disease [2]. Data from the World Health Organization (WHO) in 2018 show that breast cancer ranks second out of the three most cancers that cause morbidity and mortality, 6.6% or 627,000 cause deaths from all types of cancer. Breast cancer is also the most frequently diagnosed cancer (24.2%) and is the leading cause of cancer deaths in women (15.0%) [3].

Cancer prevalence in Indonesia shows an increase from 1.4 per 1000 population in 2013 to 1.8 in 2018 [4]. The incidence of breast cancer ranks highest among cancer in women with a proportion of 240 among 1000 female population. The incidence of breast cancer is also a type of cancer that ranks first in hospitalized patients throughout Indonesia (28.7%) and is the leading cause of death due to cancer in women who are hospitalized [5]. Breast cancer also experienced an increase in Central Java Province from 2127 sufferers in 2017 to 2645 patients in 2018, and 65% of sufferers were women aged 45-65 years [6].

Breast cancer is a disorder of the breast that is most feared by women. This is because this cancer is difficult to cure if found at an advanced stage [7]. Management or treatment of breast cancer, namely local therapy, in the form of surgery and radiation and systemic therapy. Types of systemic therapy in cancer are chemotherapy with cytotoxic drugs, hormonal therapy and molecular target therapy [8]. At an advanced stage, surgery cannot be done again but by radiation. If surgery and radiation are no longer possible then chemotherapy is done [9].

Chemotherapy is the use of a chemical agent that can stop or inhibit the growth of cancer cells [10]. Chemotherapy drugs are used to destroy cancer cells by not harming normal cells, but the use of cancer drugs causes side effects, namely the formation of free radicals. Excessive free radicals are toxic, which damage normal cells in the body including bone marrow cells which results in suppression of the blood cell formation system. Other consequences are physiological changes including hair loss, weak body, feeling tired, shortness of breath, easy to bleed, easily infected, blue / black, dry, and itchy skin, dry mouth and throat and other physical complaints that are felt as an effect of chemotherapy [11].

Disorders in the formation of red blood cells, white blood cells and platelets that circulate in the body, will be more at

risk of infection. In addition, suppression of the bone marrow also causes disruption of erythrocyte production and formation so there is a decrease in hemoglobin in patients undergoing chemotherapy. Decreased blood hemoglobin causes hematological disorders in the form of anemia [12].

Anemia in cancer patients receiving chemotherapy is a problem that needs to be addressed because it is associated with increased morbidity, mortality and maintenance costs [13]. Signs and symptoms that can arise due to anemia are fatigue, depression, dyspnea, tachycardia, and dizziness also occur shortening the age of red blood cells which is 60-90 days, shorter than the age of red blood cells in normal people where about 120 days. In addition, it will result in a delay in the schedule and a decrease in the dose of chemotherapy which results in the patient's condition getting worse and decreasing the quality of life of the patient [14, 15]. The response to therapy can also reduce, the risk of infection increases as well as the survival of patients [16]. 86.3% of breast cancer patients had anemia during chemotherapy which included grade 1 anemia (61.0%), grade 2 anemia (33.3%), grade 3 anemia (5.3) and grade 4 anemia (0.4).[13] Previous research showed that 41% of breast cancer patients had anemia before chemotherapy, then the incidence of anemia increased by 43.1% when getting the therapy. The results of the study were similar to other studies which showed that breast cancer patients had anemia before chemotherapy but increased by 54.1% after the third cycle of chemotherapy [17].

Anemia due to the side effects of chemotherapy is handled through several methods, namely Red Blood Cell Transfusion, Erythropnoetyn Stimulating Agent (ESA) and iron supplementation, both oral via intravenous. According to the National Comprehensive Cancer Network (NCCN) guidelines, the treatment of anemia due to cancer has advantages and disadvantages. Blood transfusion can increase hemoglobin levels and the number of hematocrit quickly, but can cause many side effects, namely antigen-antibody reactions to anaphylactic reactions, transfusion reactions, increased thrombolytic events and decreased survival. In addition to transfusion, Erythrophoetyn Stimulating Agent (ESA) therapy is used for correction of anemia with Hb target> 12 g / dL, use of ESA can improve anemia symptoms gradually but still shows a decrease in life expectancy, increased risk of thrombolytic events and limitations in the use of treatment [18]. Therefore, the choice of treatment takes precedence over the benefits compared to the risks that will be caused [10].

Nursing is a form of professional service in the form of fulfilling basic human needs given to healthy and sick individuals who experience physical, psychological, and social disorders in order to achieve optimal health status. Forms of fulfilling basic needs can be in the form of increasing the ability that exists in individuals, preventing, improving, and doing rehabilitation from a condition that is perceived by the individual as sick.[19]Giving nursing care to cancer patients who get chemotherapy aims to provide supportive therapy and prevention of problems experienced by patients after receiving chemotherapy. The condition of anemia and the decrease in blood cells that occur can cause the immune system to decrease so that the risk of infection can increase [20]. Cancer patients who get chemotherapy need adequate nutritional intake by completing the micronutrients needed for the formation of blood cells that aim to increase endurance.

Treatment of anemia in cancer patients by providing adequate nutritional intake through the provision of essential micronutrient that is iron [21]. Iron supplementation can be given orally or intravenously. How many things have been done naturally to increase iron intake is the consumption of carrot juice during chemotherapy but there was no significant increase in hemoglobin levels before and after treatment in the intervention group ($p = 0.764$) [22] then giving a mixture of mung bean and guava juice during chemotherapy, the results showed an increase in hemoglobin levels but had not reached normal values [23].

In addition to meeting the adequate nutritional intake, efforts to prevent anemia are needed because of the side effects of chemotherapy through protection of blood cells from toxic substances due to chemotherapy. Chemotherapy drugs are systemic and cause cell damage due to the radical oxygen species (ROS) produced by the drug. Chemotherapy drugs that have been shown to produce ROS include anthracyclines, alkylating agents, platinum coordination complexes, epipodophyllotoxins and camptothecins [24]. ROS in a certain amount is needed in cell metabolism, but if the amount increases and endogenous antioxidants are not able to inhibit this increase there will be damage to normal cells around the tumor including bone marrow cells [25].

Breast cancer patients given chemotherapy experience excessive oxidative stress causing hematological disorders in the form of anemia and reducing antioxidant status, which is revealed by a decrease in total plasma antioxidant capacity. Under these conditions, the mechanism of cellular antioxidants may not be able to prevent the adverse effects of ROS, so antioxidant intake from outside the body is needed through supplementation of synthetic and natural antioxidants [25]. But concerns about the side effects of synthetic antioxidants make natural antioxidants an option [26].

Herbal plants that have been shown to have good activity in the human hematology system and as a source of antioxidants are Moringa Oleifera plants. According to the results of the study, Moringa leaves contain vitamin A, vitamin C, vitamin B, calcium, potassium, iron, folic acid, B12 and protein, in very high amounts which are easily digested and realized by the human body. The nutritional comparison of fresh Moringa leaves and powder, with several other nutritional sources, amounts to many times that of food sources that have been used as a source of nutrition for nutrition improvement in many parts of the country. Moringa is known to contain more than 40 antioxidants and contains 539 compounds known in traditional medicine [27].

Moringa leaves based on previous research, have an effect on hematopoietic cells and increase hemoglobin levels in the blood in rats exposed to radiation, it is evident that Moringa leaves can protect hematopoetic cells from radiation damage because it has a lot of antioxidants, namely flavonoids and important micronutien play a role in the formation of blood cells [28]. Flavonoids in Moringa leaves are found in the most amount with the benefit of protecting cell structures and have a positive effect in protecting cells from chronic degenerative diseases. Other studies also revealed that Moringa leaf extract has a protective effect through its antioxidant potential against oxidative stress due to chemotherapy [29].

Research on wistar rats induced by cycloposphamide chemotherapy drugs and myelosuppression revealed that

there was an increase in hemoglobin levels, the number of hematocrit, the number of RBC (Red Blood Cell) and TWBC (Total White Blood Cell) after being given Moringa leaf extract of 48 mg / kg BB but the dosage is not significant so a higher dose is needed [30]. The use of Moringa leaf extract is also a food source that has the highest iron content and has been shown to be able to significantly increase the blood profile in iron deficiency anemia patients with a given dose of 1400 mg / day but has not measured the amount of leukocytes [31]. Other studies show that the dose of Moringa leaf extract is significant for increasing leukocytes by administering 27.70 mg / kg BW. [32]

Based on the background above, it is necessary to do research on the effect of Moringa Oleifera leaf extract nanoparticles on hematological profiles in breast cancer patients on chemotherapy programs.

2. Methods

This research is a True Experiment study with a single blind and a pre test - post test with control group design. Researchers arranged two groups, namely the intervention group given treatment of extracts of Moringa Oliefera leaf doses of 28.57 mg / kg BB and antianemia while the control group given anianemia alone. Giving extract of Moringa Oliefera leaf nanoparticles was given for 21 days with a dose of 28.57 mg / kg BW. The hematological profile examination was carried out before and after the treatment aimed to determine hemoglobin levels, hematocrit levels, the number of erythrocytes and the number of leukocytes by using hematology analizers, while making extracts of Moringa leaf nanoparticles was carried out in Food Technology Laboratory with particle size of nanoparticle extract was 0.208µm.

The population in this study were breast cancer patients with chemotherapy programs who received antianemia with probability sampling techniques simple random sampling method and based on inclusion and exclusion criteria as many as 40 respondents were divided into two groups.

In this study researchers conducted data collection by observing, identifying, interviewing and filling out the questionnaire. The collected data were analyzed through statistical programs with parametric difference tests (Paired t test and Independent t test). The processed data is used as the basis for the discussion which is then presented in table form so that conclusions can be drawn.

3. Result

Based on the table above shows that the average age of respondents in the intervention group is 50 years and in the control group the average age of respondents is 51 years. Characteristics of respondents based on age showed no significant difference between the intervention group and the control group with a p value of 0.315, which means that the proportion of respondents in the intervention group and controls were equal or homogeneous.

While respondent characteristics based on breast cancer stage, respondents who experienced stage I breast cancer were 6 respondents (30%) in the intervention group and 5 respondents (25%) in the control group. Respondents who experienced stage II breast cancer were 9 respondents (45%) in the intervention group and 8 respondents (40%) in the control group. And respondents who experienced stage III breast cancer were 5 respondents (25%) in the intervention group while 7 respondents (35%) in the control group. Based on the homogeneity test results there was no difference between the proportion of breast cancer stage in the intervention group and the control group with a p value of 0.687. In the chemotherapy cycle showed that respondents in this study received more chemotherapy in the third cycle of chemotherapy in the intervention group (30%) and the control group (20%). Based on the homogeneity test results showed the proportion of chemotherapy cycles between the intervention group and the equivalent or homogeneous control group with a p value of 0.803.

Table 1: Frequency and distribution of respondents based on age, breast cancer stage and chemotherapy cycle based on demographic data

Variable	Respondent Groups				P value
	Intervention		Control		
	N	%	N	%	
Age					
Mean ±SD	50.95±2.548		51.15±2.023		0.315
(Min –Maks)	(30-77)		(33-69)		
Breast Cancer Stage					
Stage I Breast Cancer	6	30	5	25	0.687
Stage II Breast Cancer	9	45	8	40	
Stage III Breast Cancer	5	25	7	35	
Total	20	100	20	100	
Chemotherapy Cycle					
Cycle 1	3	15	2	10	0.803
Cycle 2	5	25	5	25	
Cycle 3	6	30	4	20	
Cycle 4	1	5	5	25	
Cycle 5	3	15	3	15	
Cycle 6	2	10	1	5	
Total	20	100	20	100	

[*] *Homogeneity Test*

Table 2: Differences in hematological profiles before and after treatment in the intervention and control groups

Variable	Groups	Measurement	Mean±SD	Mean difference	P Value
Hemoglobin levels	Intervention	Pre-test	10.2950±0.22284	2.05	0.000
		Post-test	12.3450±0.22082		
	Control	Pre-test	10.2000±0.19561	0.99	0.004
		Post-test	11.1900±0.18409		
Hematocrit levels	Intervention	Pre-test	31.9350±1.52256	4.77	0.000
		Post-test	36.7050±0.61638		
	Control	Pre-test	32.0300±1.74087	3.44	0.005
		Post-test	35.4700±1.86522		
The number of erythrocytes	Intervention	Pre-test	3.6520±0.11450	0.767	0.001
		Post-test	4.4190±0.12746		
	Control	Pre-test	3.6940±0.10613	0.19	0.047
		Post-test	3.8840±0.08280		
Leukocyte count	Intervention	Pre-test	3.9035±0.84816	1.6095	0.003
		Post-test	5.5130±0.31184		
	Control	Pre-test	3.9820±0.25349	0.4995	0.005
		Post-test	4.4815±0.21699		

*Paired T tes*t*

Based on the table above shows that there are differences in mean hemoglobin levels before and after treatment in the intervention group and the control group with each p value 0,000 and 0,004. Then hematocrit levels showed differences in mean before and after treatment in the intervention group with a significant 0,000 and also in the control group showed a difference in mean hematocrit levels with a significant 0.005. The mean value of erythrocytes in the intervention group before and after treatment showed a significant difference with p value 0.001 and in the control group also showed the same thing. Then the mean value of leukocytes showed significant differences before and after treatment in the intervention group and the control group with each p value of 0.003 and 0.005.

Table 3: Analysis of differences in hematological profiles between the intervention group and the control group

Variable	Measurement	Groups	n	Min-Max	Mean±SD	P Value
Hemoglobin levels	Pre-Test	Intervention	20	9.03-11.54	10.2950±0.99656	0.750
		Control	20	9.00-11.90	10.2000±0.87479	
	Post-Test	Intervention	20	10.90-14.20	12.3450±0.98754	0.000
		Control	20	9.80-12.80	11.1900±0.82328	
Hematocrit levels	Pre-Test	Intervention	20	29.60-34.70	31.9350±1.52256	0.855
		Control	20	29.90-35.60	32.0300±1.74087	
	Post-Test	Intervention	20	32.80-42.80	36.7050±2.75652	0.010
		Control	20	32.50-38.90	35.4700±1.86522	
The number of erythrocytes	Pre-Test	Intervention	20	2.90-4.50	3.6520±0.51205	0.789
		Control	20	2.82-4.60	3.6940±0.47463	
	Post-Test	Intervention	20	3.12-5.66	4.4190±0.57003	0.001
		Control	20	3.10-4.53	3.8840±0.37031	
Leukocyte count	Pre-Test	Intervention	20	1.93-5.63	3.9035±0.84816	0.806
		Control	20	1.82-6.32	3.9820±1.13365	
	Post-Test	Intervention	20	3.70-8.68	5.5130±1.39460	0.105
		Control	20	3.00-6.02	4.4815±0.97042	

*Independent T test

Based on the table above shows that there is no difference in mean hemoglobin value in the pre-test between the intervention group and the control group with p value 0.750 while there are differences in the mean post-test hemoglobin values in the intervention group and the control group with p value 0,000. Then there was no difference in the mean hematocrit in the pre-test between the intervention group and the control group with p value 0.855 while there were significant differences in the post-test hematocrit mean value with p value 0.010. The mean erythrocyte value in the pre-test between the intervention group and the control group showed no difference with p value 0.789 while in the post-test there was a difference with p value 0.001. Then the mean value of leukocytes in the pre-test between the intervention group and the control group did not differ with p value 0.806 and there was no difference also in the post-test with p value 0.105.

4. Discussion

The mean value of hemoglobin in the intervention group before treatment was 10.2950 gr / dl and after treatment was given to 12.3450 gr / dl whereas in the control group before treatment the mean hemoglobin was 10.2000 gr / dl and after treatment it was 11,1900 gr / dl , the mean value of hemoglobin level before treatment in the intervention group and control group had been tested for normality and previous homogeneity with the results of $p > \alpha$ 0.05, which meant that the mean hemoglobin level of the two groups before treatment was equivalent.

The mean hematocrit in the intervention group before treatment was 31.9350 ± 1.52256 and after treatment 36.7050 ± 0.61638 with p value based on paired sample test

was 0,000 while in the control group the hematocrit value before treatment 32,0300 ± 0,38927 to be 35.4700 ± 0.41708 after the treatment with the p value of the paired sample test result is 0.004. In the intervention group and the control group had a significant p value. The mean value of hematocrit levels in both groups had the same increase, although in the intervention group the hematocrit mean value had increased to near the normal value of hematocrit levels of 36.7050 and the normal value of hematocrit was 37%.

The mean number of erythrocytes in the intervention group and the control group, the mean value of erythrocytes before treatment is 3.6520 ± 0.11450 then becomes 4.4190 ± 0.12746 after treatment with p value 0.001 which means that there are significant differences in the number of erythrocytes before and after given antianemia and Moringa leaf extract (moringa oleifera) whereas, in the control group the mean value of erythrocytes before treatment was 3.6940 ± 0.10613 and after treatment 3.8840 ± 0.08280 with p value 0.047 which means there was a significant difference in the number of erythrocytes before and after treatment. The number of erythrocytes after being given treatment in the intervention group and the clinical control group had reached the normal value of erythrocytes ie 3.8 - 5.8 x106 / µl.

The leukocyte value in the intervention group before treatment was 3.9035 ± 0.84816 and after treatment 5.5130 ± 0.31184 with p value 0.003 while in the control group the leukocyte mean value before treatment was 3.9820 ± 0.25349 and after treatment 4.4815 ± 0.21699 with p value 0.005 . This means that the intervention group and the same control group showed significant results before and after treatment.

From the analysis of the differences in unpaired samples between the intervention group and the control group, it was found that there were significant differences in the mean values of hemoglobin, hematocrit, and erythrocytes between the intervention group and the control group with a p value <0.05.

Chemotherapy is the use of a chemical agent that can stop or inhibit the growth of cancer cells but the use of chemotherapy also causes side effects on normal cells in the body. Cell damage occurs due to the influence of free radicals / ROS produced by chemotherapy. ROS in a certain amount is needed in cell metabolism, but if the amount increases and endogenous antioxidants are not able to inhibit this increase there will be damage to the normal cells around the tumor including the hemopoietic system cells so that it can cause a decrease in the number of blood cells.[33, 34]

In cancer patients who get chemotherapy experience side effects of normal cell damage due to the effect of radical oxygen species (ROS) produced by chemotherapy. Biologically reactive oxygen compounds (O2, H202, OH, HOCl) are always formed in the body and will produce free radicals that function to kill germs. Antioxidants can capture various types of reactive oxygen to prevent the formation of dangerous free radicals or by repairing damage that occurs. But the imbalance between free radicals and antioxidants will cause unwanted oxidative stress. Oxidative stress can arise from the use of chemotherapy drugs.[29]

One of the functions of antioxidants is being able to bind antioxidants, such as Fe2 + and Cu2 +, the antioxidants that play a role are flavonoids, which are found in Moringa leaves. Flavonoids prevent oxidative stress in the body so that it can protect blood cells from apoptosis. The results showed that administration of Moringa leaves in mice given previous chemotherapy drugs increased hemoglobin, erythrocyte and hematocrit levels in mice that experienced oxidative stress due to chemotherapy.[29]

Moringa leaves contain active flavonoid compounds of 422,917 mg / 100 g which can increase IL-2 activity, and can activate other cytokines in the immune response. The role of the imulator is also played by other Moringa leaf extract active ingredients in the form of calcium (Ca) and saponin because it can induce an increase in the expression of IL-2 which plays a role in increasing Th cell proliferation. IL-2 compounds are referred to as "T-lymphocyte growth factor" because they play an important role in the proliferation factor of lymphocyte cells. In the results of previous studies showed a significant increase after administration of Moringa Oleifera leaf extract on heamatological parameters, namely the number of leukocytes, platelets, neutrophils, lymphocytes, monocytes and TLC when compared with controls, due to the use of Moringa leaves can stimulate humoral mediated immunity and cellular, thus, this shows that Moringa leaves have a positive immunomodulatory effect, although the exact mechanism of Moringa leaf compounds involved in stimulating cellular immunity and humoral immunity is unclear. The results of the study also showed that Moringa leaf extract can reduce myelosuppression and leukopenia.[35]

Management of anemia in breast cancer patients is one of them by supplementing substances that play a role in the formation of blood cells in the body. In this study, breast cancer patients who were included in the intervention group received treatment in the form of antianemia which is the standard of service provided to patients after receiving chemotherapy, as well as respondents given Moringa leaf extract (moringa oleifera) for 21 days so that the measurement of hemoglobin levels, hematocrit was obtained , respondent erythrocytes and leukocytes after treatment in the intervention group showed significant differences with the value of p value <0.05 while in the control group after treatment there was no significant difference p value> 0.05. Clinically, the mean value of hemoglobin, hematocrit, erythrocytes and leukocytes in the intervention group approached normal values when compared to the control group.

In a related study showed that giving 300 mg / kg BB Moringa leaf extract for 14 days in mice that had received chemotherapy showed an increase in red blood cells, white blood cells, hemoglobin and hematocrit.[30] Other studies also showed that there were significant differences in the mean hematocrit levels in the intervention group after administration of Moringa leaf extract (moringa oleifera), which was 38.3867 ± 1.14759 compared to the control group 33.8133 ± 4.83142 with p value 0.002.36 but at other studies not in accordance with this study showed no significant differences in the mean value of hematocrit levels between the intervention groups 35.4 ± 1.58 with the control group 36.3 ± 2.65 with p value 0.133.[37]

In addition, other related studies also showed an increase in the number of erythrocytes after being given Moringa leaf extract (moringa oleifera) from 3.8 ± 0.38 in the pre-test to 4.01 ± 0.28 but in the study it did not show significant results.[37] Similar other studies showed significant differences in the number of erythrocytes between the intervention groups given Moringa leaf extract (moringa

oleifera) 4.30137 ± 3.95675 and the control group 3.78206 ± 8.04105 with p value 0.017.[36]

Other studies also showed an increase in the number of leukocytes after being given Moringa leaves in mice given previous chemotherapy, this is because Moringa leaves contain several minerals, flavonoids, amino acids, vitamin B, vitamin C, and several other vitamins, namely A, D, E which plays a role in enhancing immunity.[32]

5. Conclusion

Moringa Oleifera leaf extracts of 28.57 mg / kg body weight / day for 21 days in breast cancer patients who received antianemia affects the increase in hemoglobin levels, hematocrit levels of erythrocytes and leukocyte counts.

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