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Effectiveness of *Artemisia Vulgaris* as Supplementation Against Chemotherapy of Mammary Adenocarcinoma to Reduce Expression of NF- κ B and CD 34 (Study in C3H Mice Given Chemotherapy Adriamycin - Cyclophosphamide)

Bayu Teguh Saputro¹

ABSTRACT

Introduction: Breast cancer is a significant healthcare problem worldwide. Surgery remains the treatment of choice combined with other modalities such as chemotherapy, radiation, and immunotherapy such as *Artemisia vulgaris* (AV). Selective cytotoxicity of AV is intended as a supplementation to Adriamycin- Cyclophosphamide, improving the response rate of chemotherapy in adenocarcinoma mammary. **Method:** This study used a "Post-test only control group design" on 24 female C3H mice that were randomly selected and divided into four groups: group K (control), P1 (chemotherapy), P2 (extract), and P3 (combination). Adenocarcinoma mammary come from the inoculation of donor mice. Chemotherapy of Adriamycin 60 mg / m² and Cyclophosphamide 600 mg / m² were given in two cycles. AV 13 mg (0.2 ml) was given once daily orally. NF- κ B expression and CD34 were evaluated using immunohistochemical staining. **Result:** The expression of NF- κ B and microvascular density of CD 34 were obtained in groups of K, P1, P2, P3. Statistical analysis showed significant decrease in the expression of NF- κ B between groups K and P1, P2, P3. Correlation analysis between NF- κ B expression with CD 34 was found to have significant correlation ($p = 0,039$ and $r = 0,897$). **Conclusion:** *Artemisia vulgaris* can reduce angiogenesis by decreasing NF- κ B expression and the microvascular density CD34 of adenocarcinoma mammary of C3H mice treated with Adriamycin-Cyclophosphamide chemotherapy and can improve the effectiveness.

1. Introduction

Cancer is one of the leading causes of death worldwide with approximately 8.2 million people in 2012. (1) Breast cancer is still a significant health problem for women worldwide. Data from the International Agency for Research on Cancer (IARC) GLOBOCAN in 2012 noted that 1.7 million women were diagnosed with breast cancer or about 11.9% of all cancer incidence. Meanwhile, WHO data shows that the prevalence of breast cancer worldwide reached 6.3 million at the end of 2012, spreading across 140

countries. (2) The increase prevalence in people with breast cancer is directly proportional to the rise of mortality rate. Most breast cancer occurs at the age of more than 50 years, and the estimated incidence rate is around 2 in 1000 women per year (3,4,5,6).

The cause of cancer is not known with certainty, but it can be understood that malfunctioning to control cell growth causes this cancer. Cancer, in general, can be caused by disruption of the transcription process at the cellular level, which results in cell division out of

control. In this case, Nuclear Factor-Kappa B (NF- κ B) has a vital role in regulating regulation, including processes from inflammatory reactions, growth, and vascularity formation to oncogenesis. (7)

Incorrect regulation of NF- κ B is associated with the incidence of malignancy. (8) In previous studies, NF- κ B was a regulator of cell proliferation and protected cells against conditions that lead to apoptosis. (9) NF- κ B binds to deoxyribonucleic acid (DNA) and causes transcription of genes that will cause oncogenesis processes, such as inflammation, anti-apoptosis, and increased cell proliferation activity metastasis, and angiogenesis. (8,10)

Angiogenesis factor plays a vital role in the growth of cancer cells, progression, and metastasis. The microvascular tissue complex of cancer guarantees an adequate supply of tumor cells with good nutrition, oxygen, and metabolite drainage. (11) Tissues that undergo vascular growth occur due to the activation of transcription factors by the Vascular Endothelial Growth Factor (VEGF) and its receptor services and will show increased microvascular density. The development of primary tumor cells and metastatic tumor growth also depends on the neovascularization or microvascular density that is formed. The process of forming new blood vessels can be identified as a clinical parameter of microvascular density through the expression of glycosylated transmembrane proteins, namely Capillarity Density (CD34) protein with a molecular weight of 116 kDa. The CD34 protein can differentiate hematopoietic cells from endothelial cells and lymphatic cells. (12)

The angiogenesis process involves NF- κ B, an important angiogenic growth factor that stimulates cancer cells to grow and causes the tumor's metastasis. (13) NF- κ B and VEGF are the primary growth factors in the blood vessels around cancer and can cause metastasis (14) and associated with providing the nutrients needed for tumor growth, invasion, and metastasis. (15) In general, tumors cannot grow bigger than 1-2 mm in size without angiogenesis. The angiogenesis process in tumors begins with the formation of capillary endothelial cells, which are

typically not found in normal cells. NF- κ B can be used as an independent prognostic marker because these vascular endothelial cells in tumor cells are more stable than normal cells. It could be a promising therapeutic target in a new strategy for cancer therapy. (16)

In the process of breast cancer management, surgery is the primary therapeutic modality. Other modalities include adjuvant therapy in radiation and chemotherapy, especially when there is inadequate resection or metastases. Some chemotherapy regimens commonly used for breast cancer are CAF / CEF (Cyclophosphamide, Adriamycin / Epirubicin, and 5-Fluorouracil), CMF (Cyclophosphamide, methotrexate, and 5-Fluorouracil), E-CMF (a combination of Epirubicin with CMF), MMM (Methotrexate), mitoxantrone, mitomycin). The response rate of each of the CAF regimens for all new therapies ranges from 20-40%, but there has been no therapy that can achieve a 100% response. (3) Efforts should be made to increase the effectiveness of therapy so that the response rate Rate is increased so the survival rate can be improved.

Many studies have been conducted to find effective and efficient solutions in the treatment of breast cancer patients. Researches are carried out at the level of molecular biology. It is necessary to research to get anticancer therapy in the form of herbal treatment, in which the medicinal plants used are known to have anticancer substances. The *Artemisia vulgaris* plant contains artemisinin compounds which are known to have anti-cancer properties. Artemisinin was isolated and extracted from the dried leaves and flower buds of *Artemisia vulgaris*. Artemisinin is a sesquiterpene lactone compound that contains an endoperoxide radical without containing a nitrogen atom in its chemical structure. (17,18) Previous research was carried out on C3H mice with liver carcinoma at a dose of 100 mg/kg per day of artemisinin showing anticancer activity (19).

The mechanism of action of artemisinin compounds as anticancer is anti-angiogenic, anti-inflammatory, anti-metastatic, and inhibiting cancer cell growth. It is known that artemisinin contains an endoperoxide moiety that can react with iron to form cytotoxic free

radicals (20,21).

Although it is toxic, artemisinin has an advantage of being used as an anticancer because it has particular toxic properties.(20) This is an essential consideration in terms of safety for its users. The selective cytotoxic nature of *Artemisia vulgaris* is a supporting factor for preliminary studies at the pre-clinical stage. The study will use a dose of artemisinin 13 mg/times per day, a chemotherapy dose of Adriamycin 0.18 mg/time, a dose of Cyclophosphamide 1.8 mg/times intravenously. This study was conducted to determine the effectiveness of *Artemisia vulgaris* extract as supplementation against mammary adenocarcinoma in terms of NF- κ B expression and CD34 microvascular density carried out on C3H mice given Adriamycin- Cyclophosphamide chemotherapy.

2. Method

Research design

This research is an experimental laboratory study with the design "Post-test only control group design." The research group was divided into 4, namely the control group (K), treatment 1 (P1), treatment 2 (P2), and treatment 3 (P3). The division of treatment groups is as follows:

K : Control group, tumor inoculated mice.

P1 : Treatment group 1, mice inoculated with tumors, after developing tumors, received chemotherapy Adriamycin - Cyclophosphamide.

P2 : Treatment group 2, mice that were inoculated with tumors, after the cancer arose, they received *Artemisia vulgaris* extract 13 mg/times per day.

P3 : Treatment group 3, mice inoculated with tumors, after tumor arising, received AC chemotherapy and *Artemisia vulgaris* 13 mg/times per day.

Research samples

The experimental animal was the C3H strain mice (*Mus musculus*). Inclusion criteria: Female mice aged eight weeks, inoculated with mammary adenocarcinoma, bodyweight 20-30 grams after acclimatization, no anatomical abnormalities were seen. Exclusion criteria: no tumor growth after

inoculation, during inoculation and treatment, the mice looked sick (the movement was not active). The sample size according to WHO for each group is at least five animals with a reserve of 10%. In this study the number of samples used per group was six mice. (11)

Time and location of research

Research and data collection was carried out for five months. The extract of *Artemisia vulgaris* was made at LPPT I, Faculty of Medicine, Gajah Mada University. The treatment of mice and taking the tissue was carried out at LPPT IV, Faculty of Medicine, Gajah Mada University. Making paraffin blocks, HE staining, and immunohistochemical staining were carried out at the Anatomical Pathology Laboratory, Faculty of Medicine, Sebelas Maret University, Surakarta.

Research variable

The independent variable in this study was the administration of *Artemisia vulgaris* extract with a combination of chemotherapy Adriamycin and Cyclophosphamide.

The dependent variables in this study were the expression of NF- κ B and the microvascular density CD34.

Operational definition

Administration of *Artemisia vulgaris*: *Artemisia vulgaris* extract is an extract derived from the leaves extracted with ethanol solvent using the soxhletation method, with a dose of *Artemisia vulgaris* 100mg / kg body weight / day orally (13 mg/time). Administration of Adriamycin intravenously at a dose of 0.18 mg/time. Cyclophosphamide administration is intravenously 1.8 mg / time.

Expression of NF- κ B was calculated according to a modified method used by Chattopadhyay et al., wherein immunohistochemically stained preparations, cells expressing NF- κ B in 5 hot spots with a weak enlargement (200x) were counted. Positive NF- κ B was measured on the chrome-colored portion of tumor cells. The expression NF- κ B (EI) is calculated by the formula Extent of staining (E) x Intensity of staining (I). (22) The variable scale is the ratio.

The microvascular density of CD34 tumors is a light brown color that appears on the tumor capillaries after CD34 staining. The way to do the calculation is through the number of micro blood vessels per field of view, which is calculated on five areas of view using 400x magnification. The variable scale is a ratio.

Research materials and tools

During the experiment, the experimental animals were placed in cages and given food and drink ad libitum. Before treatment, mice underwent an adaptation period of one week.

Tumors in donor C3H mice will be inoculated in experimental animals for research and histopathological examination. Simplisia *Artemisia vulgaris* was obtained from the Biopharmaca Cultivation Conservation Unit, Center for Biopharmaca Studies, Bogor Agricultural University. The material used is *Artemisia vulgaris* extract, which is obtained by

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- a. One kg of dried leaves of *Artemisia vulgaris* is finely ground. The powder is put into a socket device (capacity of 50 mg), and the extraction is carried out by soaking using ethanol solvent with a cycle of 8- 10 times.
- b. The extract was put into a rotary evaporator flask, and vacuum distillation was carried out until it became concentrated (temperature 40°C).
- c. The extract was dried in an oven at 40°C for 1 hour to evaporate the ethanol.
- d. The results obtained were 5.5 mg of extract for every 1 kg of material (0.55%), and the products were diluted with aquabidest until a concentration of 0.2 mg/ml was reached.

Tumors containing adenocarcinoma cells from donor C3H mice were transplanted into recipient mice. Tumors from donor mice will be incised with a biopsy, and a histopathological examination will be performed to confirm the type of tumor.

Data analysis

After the data was collected, data coding, and tabulation was carried out. The data was processed and presented in tables and box plots to see the distribution

of data. To determine the normality of the data, a normality test was performed using the Shapiro-Wilk test. The data were normally distributed, then continued with the ANOVA test to see if there were differences in the expression of NF-κB and CD34 and the four groups. The magnitude of the differences in each treatment group was further analyzed by using the Post Hoc Test. The Pearson's correlation test tested the correlation test between the expression variables NF-κB and CD34 if the normal distribution was obtained. The degree of significance limit was $p = 0.05$ with a 95% confidence interval. Data analysis was performed with SPSS Ver software. 21.0. for Windows.

Ethical requirements

The research applies animal ethics and was approved by the Ethics Commission for Health Research, Faculty of Medicine, Diponegoro University.

3. Results

Descriptive analysis

Description of NF-κB expression data

The highest mean NF-κB expression was found in the K group, while the lowest average NF-κB expression was found in the P3 group.

CD34 data description

For each group, K, P1, P2, P3, preparations were made to determine the tumor's microvascular density by staining CD34. The results of measuring the average microvascular density value of the tumor can be seen in table 2.

The highest CD34 average was found in the control group, namely $69.50 \pm 1.63\%$, while the lowest average CD34 was found in the P3 group, namely $40.74 \pm 1.39\%$. Likewise, the highest and lowest medians were found in the control group and the P3 group, namely 61.50% and 35.60%, respectively. In the P1 and P3 groups with a population of C3H mice who received AC chemotherapy, the average was $39.70 \pm 2.00\%$ and $35.26 \pm 2.06\%$, respectively.

Data distribution

Normality and homogeneity tests of NF-κB expression and CD34 microvascular density for each NF-κB expression group using the Shapiro-Wilk test can be seen in Tables 5 and 6.

The normality and homogeneity test of groups K, P1, P2, P3, showed a value of $p > 0.05$. These results can be interpreted that the variable NF-κB expression and CD34 microvascular density in C3H mice with mammary adenocarcinoma in each group were normally distributed, and the data were homogeneous.

Statistic test

Expression of NF-κB. The Shapiro-Wilk test showed that the NF-κB expression data were normal and homogeneous, so it was continued with the One Way ANOVA difference test.

The results of statistical tests using One Way ANOVA showed a significant difference in CD34 between groups ($p = 0.000$), so it was followed by a post hoc test with a significance value of $p < 0.05$. The results of the post hoc test showed a significant difference between group K and group P1, P2, P3 ($p = 0.000$; $p = 0.038$; $p = 0.000$), group P1 with groups P2 and P3 ($p = 0.000$; $p = 0.002$) and group P2 with P3 ($p = 0.000$).

Microvascular density CD 34.

The Shapiro-Wilk test showed that the CD34 data were normal and homogeneous, so it was continued with the One Way ANOVA statistical test, with the following results:

From the results of the One Way ANOVA test, it was found that the value of $p = 0.000$, because $p < 0.05$, it can be concluded that there is a significant difference in CD34 in the four groups. Henceforth, the Post Hoc test was used to determine the differences between groups. From the Post Hoc test results, it was found that there was a significant difference between each group with a value of $p < 0.05$.

Correlation of NF-κB expression with CD34

Assessment of the relationship between NF-κB and CD34 was carried out using the Pearsons correlation test. The Pearsons test revealed a solid relationship between the expression of NF-κB and CD34 ($p = 0.039$ and $r = 0.897$). Because the p-value < 0.05 , it was concluded that there was a significant relationship between the expression of NF-κB and CD34. The relationship between the expression of NF-κB and CD34 is positive.

Tabel 1. Characteristics of NF-κB expression data

Group	N	Min (%)	Max (%)	Average ± SD (%)	Median (%)
K	5	67.40	71.70	69.50 ± 1.63	69.50
P1	5	42.60	47.20	45.10 ± 1.81	45.10
P2	5	65.30	67.60	66.52 ± 1.03	66.70
P3	5	39.10	42.60	40.74 ± 1.39	40.80

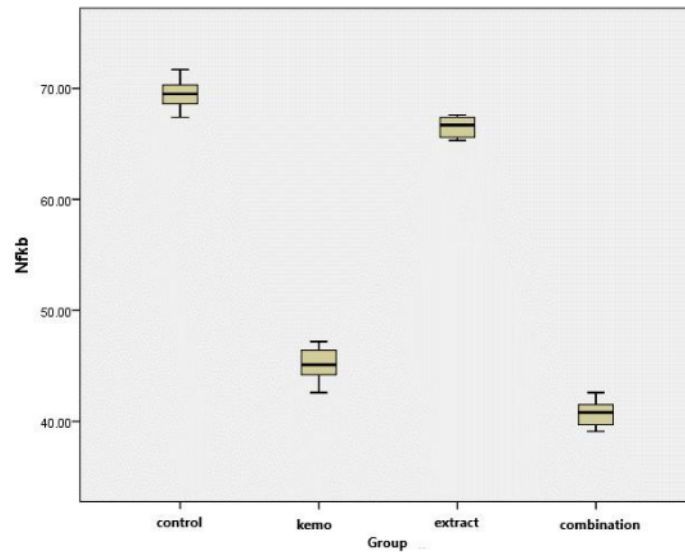


Figure 1. Box plot of NF-κB expression

Table 2. Characteristics of CD34 data

Group	N	Min (%)	Max (%)	Average \pm SD (%)	Median (%)
K	5	58.70	62.30	60.76 \pm 1.53	61.50
P1	5	36.70	41.60	39.70 \pm 2.00	39.70
P2	5	55.50	58.40	57.10 \pm 1.29	57.20
P3	5	32.40	37.70	35.26 \pm 2.06	35.60

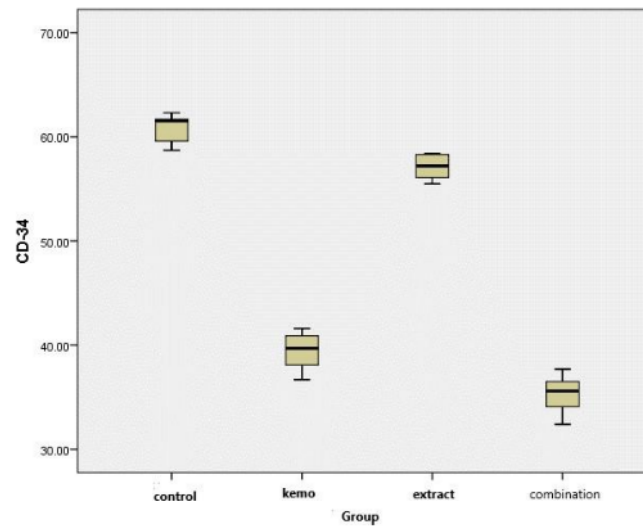


Figure 2. Characteristics of CD34 data

Tabel 3. Test for normality and homogeneity of NF-κB expression data

Group	Shapiro-Wilk			Levene test
	Statistic	Df	Sig. (p)	
K	0.998	5	0.999	0.784
P1	0.978	5	0.926	
P2	0.895	5	0.381	
P3	0.976	5	0.910	

Tabel 4. Test for normality and homogeneity of CD34 data

Group	Shapiro-Wilk			Lavene test
	Statistic	Df	Sig. (p)	
K	0.895	5	0.384	0.624
P1	0.957	5	0.787	
P2	0.902	5	0.422	
P3	0.982	5	0.945	

Tabel 5. Analysis of differences in NF-κB expression between treatment groups

Group	NF-κB Expression (%) (Mean ± SD)	P
K	69.50 ± 1.63	0.001*
P1	45.10 ± 1.81	
P2	66.52 ± 1.03	
P3	40.74 ± 1.39	

* One Way ANOVA test (significant if p < 0.05)

Tabel 6. Analysis of differences in NF-κB expression between treatment groups

Group	P1	P2	P3
K	0.001	0.038	0.001
P1	-	0.001	0.002
P2		-	0.001

* Bonferroni test (significant if p < 0.05)

Tabel 7. Analysis of CD34 differences between treatment groups

Group	Microvascular Density (Mean ± SD)	P
K	60.76 ± 1.53	0.001*
P1	39.40 ± 2.00	
P2	57.10 ± 1.29	
P3	35.26 ± 2.06	

* One Way ANOVA test (significant if p < 0.05)

Table 8. Post hoc analysis of CD34 microvascular density

Group	P1	P2	P3
K	0.001*	0.027	0.001*
P1	-	0.001	0.011
P2		-	0.001*

* Bonferroni test (signifikan $p < 0.05$)

Table 9. Pearsons correlation test

Variable	P	R
NF-Kb Expression		
CD34	0.039*	0.897

4. Discussion

The first hypothesis test obtained an F count of 260.18 with $p < 0.01$. These results showed that the expression of NF- κ B in C3H mice with mammary adenocarcinoma treated with AC chemotherapy combined with *Artemisia vulgaris* extract was lower than that which was not combined. Thus, the first hypothesis is accepted. The Post Hoc test showed a significant difference in comparing the P1 and P3 groups ($p < 0.05$). Data analysis of the variable NF- κ B expression was lower in the group (P3) than in the group (P1). From these data, it can be concluded that the effect of *Artemisia vulgaris* extract can reduce the expression of NF- κ B and can have a synergistic therapeutic effect on the administration of AC chemotherapy.

The benefits of *Artemisia vulgaris* extract as an anticancer are caused by the activity of artemisinin compounds. This potential activity is related to the endoperoxide bonding of the artemisinin compound. The peroxide bridge of artemisinin will react with ferrous ions from tumor cells to produce free radicals or ROS. ROS will also induce oxidative DNA cell damage leading to apoptosis. (23,24) This cell DNA damage is evidenced by decreased expression of NF- κ B. NF- κ B is a complex protein that acts as an important regulator of various cellular processes, including immune response, differentiation, cell proliferation, anti-apoptosis, and angiogenesis. (25) The reduced expression of NF- κ B will decrease cellular activity. This

process is caused by obstructed translocation activity of NF- κ B towards the cell nucleus, then the recruitment of other proteins (coactivators and RNA polymerases) will also be inhibited.[26]

Artemisinin compounds are part of polyphenols that have potential antioxidant properties that increase the enzyme superoxide dismutase (SOD) levels, which catalyzes the process of superoxide dismutation into oxygen and hydrogen peroxidase. The hydrogen peroxidase molecule formed is an antioxidant that will then react with free radicals, which are the trigger factors for the I κ B Kinase (I κ K) complex. I κ K plays a role in phosphorylating the NF- κ B - I κ B bonds in the cytoplasm. (27) This barrier blocks the release of NF- κ B so that it does not enter the cell nucleus. This is what causes a decrease in the expression of NF- κ B at the time of examination (28,29).

Polyphenol compounds in medicinal plants have the ability to inhibit NF- κ B. (30) Polyphenol compounds work to inhibit kinases by preventing phosphorylation or ubiquitination, which causes degradation of I κ B. This process further inhibits the translocation process of NF- κ B to the cell nucleus(31) resulting in inhibition of NF- κ B in the NF- κ B-DNA complex. (32)

The significant difference in the expression value of NF- κ B in the P3 group compared with the P1 group showed a significant synergistic effect on AC chemotherapy and *Artemisia vulgaris* extract. Adriamycin activity can occur through several mechanisms, namely:

(a) The binding of Adriamycin to the proteasome inhibits protease activity and inhibits the degradation of proteins involved in cell growth and metabolism, thereby inducing apoptosis. (b) Interaction with DNA binding protein. The regulation of gene expression by inhibiting or promoting, transcription factor binding plays a role in the cytotoxicity of Adriamycin by involving the potential of SP-1 transcription factor as a specific target for this agent. (33) (c) Intercalation of DNA into DNA leads to inhibition of macromolecular synthesis. (d) Induction of the apoptotic mechanism. Adriamycin has been shown to induce p53 binding to DNA (34) (e) Free Radical Production. The addition of one electron in the quinone portion of the C ring of Adriamycin causes the formation of semiquinone, which regenerates the quinone again by reducing oxygen to reactive oxygen species such as superoxide anions and hydrogen peroxide. (35) Adriamycin forms complexes with iron, and this complex is capable of producing hydroxyl ions. (36) (f) The anti-angiogenic mechanism of Adriamycin is shown by inhibiting the transcription factor HIF-1 by binding to the DNA of hypoxic human cells, causing a decrease in VEGF expression. Stromal Cell-Derived Factor, thereby causing a reduction in tumor vascularization. Pharmacologically, Cyclophosphamide is an alkylating agent. This agent will be metabolized in the liver and produce phosphoramidate mustard metabolites which will bind to DNA and cause DNA to become damaged, which will cause the cell to fail in mitosis and cell death. (37)

In the second hypothesis test, it is obtained F count 476.89 with $p < 0.01$. These results indicated that the CD34 microvascular density in C3H mice with mammary adenocarcinoma treated with Adriamycin-Cyclophosphamide chemotherapy combined with *Artemisia vulgaris* extract was lower than that which was not combined. Data analysis of the CD34 microvascular density variable data was lower in the P3 group than in the P1 group. Thus, the second hypothesis is accepted.

In the Post Hoc test on a population of C3H mice with mammary adenocarcinoma receiving AC

chemotherapy, P1 and P3, it was obtained $p < 0.05$. These results indicate that there is a significant difference in the comparison between the P1 and P3 groups. Using the Pearson's correlation analysis between the expression of NF- κ B in the P1 and P3 groups, the correlation coefficient $r = 0.897$ with $p < 0.05$ was obtained. There is a solid relationship between the expression of NF- κ B and CD34 in C3H mice with mammary adenocarcinoma given combination chemotherapy. Adriamycin-Cyclophosphamide and *Artemisia vulgaris* extract. Thus, the third hypothesis is accepted.

From these data, it can be concluded that the effect of *Artemisia vulgaris* extract can reduce CD34 microvascular density and has a therapeutic effect that is synergistic in giving AC chemotherapy. Other studies suggest that artemisinin compounds and their derivatives can inhibit angiogenesis by inhibiting cell proliferation, migration, and tube formation in endothelial cells. (38) The inhibition process which reduces the microvascular density of tumors is triggered by inhibition of the NF- κ B pathway, which causes downregulation of VEGFR2. VEGF and VEGFR2 are significant regulators of the angiogenesis process. The blockade of the NF- κ B pathway by artemisinin against the VEGFR2 promoter will inactivate transcription activity so that proteins that play a role in angiogenesis are not formed. (39)

The expression of NF- κ B and CD34 has a very strong relationship. NF- κ B is a protein that functions to regulate the formation of blood vessels when they translocate into the cell nucleus. The transcription factor NF- κ B is activated when there are pro-inflammatory cytokines including TNF- α , which will activate NF κ B, causing VEGF production and VEGFR expression to increase with clinical parameters in the form of increased CD34 microvascular density (25,40,41).

The results showed that the administration of *Artemisia vulgaris* extract had a synergistic effect on the administration of AC chemotherapy in a population of C3H adenocarcinoma mammae mice. This suggests that *Artemisia vulgaris* can be given as a supplement to

AC chemotherapy.

5. Conclusion

Artemisia vulgaris extract improves chemotherapy response in breast adenocarcinoma of C3H mice given Adriamycin-Cyclophosphamide. There is a synergistic effect on the administration of *Artemisia vulgaris* extract and Adriamycin-Cyclophosphamide in reducing NF- κ B expression in C3H mice with mammary adenocarcinoma. There is a synergistic effect on the administration of *Artemisia vulgaris* extract and Adriamycin-Cyclophosphamide in reducing the microvascular density of CD34 in C3H mice with mammary adenocarcinoma. There is a strong relationship between the expression of NF- κ B and CD34 in C3H mice with mammary adenocarcinoma given combination chemotherapy Adriamycin-Cyclophosphamide and *Artemisia vulgaris* extract.

6. Conflict of interest and funding.

The author has not received funding or profits from the industry or elsewhere for conducting this research.

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