

Efficacy of *Allium sativum*, *Curcuma longa* and *Zingiber officinale* Extract on Cancer Antigen 15-3 (CA 15-3) Levels of Breast Cancer Patients

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ABSTRACT

Introduction: Breast cancer is the most common malignancy in women. Progressivity of breast cancer evaluated through examination of tumor markers. Serum Ca 15-3 is tumor markers used to assess the progression. Various treatments have been developed to suppress the progression, one of which the provision of plant extractions. Extracts of *Allium sativum*, *Curcuma longa* and *Zingiber officinale* considered useful as anti-cancer, but no research discusses the combined benefits of extracts against breast cancer, especially Ca 15 -3.

Method: Open label clinical trial study with one group pretest posttest design was conducted at USU hospital on June 28, 2021 to July 18, 2021. Population came from breast cancer survivor community in Medan, consecutive sampling technique. Samples that met inclusion and exclusion criteria were examined for Ca 15 -3 before and after administration of extract *Allium sativum*, *Curcuma longa* and *Zingiber officinale* with dose 500 mg twice a day for 28 days. Data were analyzed using SPSS version 22.

Results: Of 20 breast cancer patients analyzed with mean age of 52.7 years, majority stage III A or III B breast cancer (30%). Median CA 15-3 before administration of extracts of *Allium sativum*, *Zingiber* and *Curcuma longa* 12.82 (3.29-45.81) g/mL and after administration of extracts 8.24 (2.83-47.46) g/mL, decrease but not statistically significant.

Conclusion: There was decrease in median CA 15-3 before and after extraction, but not statistically significant.

Keywords: Breast Cancer, CA 15-3, *Allium sativum*, *Curcuma longa* and *Zingiber officinale*

INTRODUCTION

Incidence and mortality of breast cancer increase every year. One of the highest mortality rates from cancer that most often affects women is breast cancer, approximately 2.1 million people suffering from breast cancer and a mortality rate of 627,000 cases. In 2018, IARC data, the average mortality from breast cancer in women was around 15%.^[1] Data in Indonesia, breast cancer occupying 8th ranks in Southeast Asia with an increasing incidence every year around 1.4 per 1000 population in 2013 and 1.79 per 1000 population in 2018.^[2] Mortality is higher in developing countries than in industrial countries, this difference due to late diagnostic, treatment and poor prognosis in developing countries compared to industrial countries.^[3]

Breast cancer originally due to excessive proliferation of the lobular and ductal epithelium of the breast. Assessment of breast cancer progression can be assessed through serum tumor markers, namely CA 15 -3. Tumor marker CA 15 - 3 was used to assess breast cancer progression and assessment of therapeutic success. The value of the tumor marker ca 15 -3 will increase as the tumor progression. Various treatments that have been applied for the management of breast cancer include

surgery, radiotherapy, chemotherapy, hormonal therapy, nutrition and various types of plant extracts. [4,5]

Several types of plant extracts include *Allium sativum*, *Curcuma longa* and *Zingiber officinale* considered to have benefits as an anti-cancer. [6,7,8] Molecular targets of watersheds for anti-cancer include modulation of enzyme metabolic activity, modulation of the immune and inflammatory systems, inhibition of angiogenesis, apoptosis induction, cell cycle regulation and antioxidant activity. [9,10,11]. However, no research about the combination of extracts *Allium sativum*, *Curcuma longa* and *Zingiber officinale* on the serum marker CA-15 in breast cancer patients. Therefore, the purpose of this study was to determine the combined benefits of the three extractions on serum marker CA-15 in breast cancer patients.

MATERIALS AND METHODS

Trial Designs & Participants

This study was an open label clinical trial with a one group pretest posttest design with 20 samples that were analyzed. Location of this study was at USU Hospital in Medan, Indonesia and hold on June 28, 2021 – July 18, 2021. All patients from the breast cancer survivor community in Medan city, Indonesia. The inclusion criteria in this study were breast cancer survivor who has finished all the treatment of breast cancer and age ≥ 18 years old. Exclusion criteria was pregnant women, suffering from hepatitis B and C, cirrhosis, hemangiomas, receiving breast cancer therapy (radiotherapy, chemotherapy, hormonal therapy or surgery) and patients who were not willing to be research subjects.

Trial Procedures

This clinical trial was conducted for 28 days on breast cancer survivor who met the inclusion and exclusion criteria. Patients who were willing must be asked for approval an informed concern then demography data was taken by history, a physical examination was carried out in the

form of measuring height and body weight. In addition, researchers searched medical records to find breast cancer diagnosis data and other diseases data. Examined laboratory test for viral markers hepatitis B and hepatitis C if data was not obtained from medical records. Before and after administration of extract *Allium sativum*, *Curcuma longa* and *Zingiber officinale* breast cancer survivors who has finished all the treatment of breast cancer was examined the laboratory test such as liver function, kidney function, albumin, and serum Ca 15-3 levels. All participants were given supplements of *Allium sativum* extract, *Curcuma longa*, and *Zingiber officinale* with dose 500 mg capsules containing a mixture of *Allium sativum* extract 200 mg, *Curcuma longa* 150 mg, and *Zingiber officinale* 150 mg twice a day for 4 weeks and monitoring of adherence to drinking was carried out drug. If there were disturbing side effects and something wanted to ask from the participant, the researcher had given phone number that can be contacted at any time. On day 29, the patient returned to USU hospital for laboratory tests after administration of the extract.

This research will be started if it has obtained permission to conduct research from the research supervisor, approval from the Health Research Ethics Commission of the USU Faculty of Medicine.

Extraction chemical material

The ingredients used in this study were extracts of *Allium sativum*, *Curcuma longa*, and *Zingiber officinale* in capsule form. Each capsule contains 200 mg *Allium sativum* extract, 150 mg *Curcuma longa*, and 150 mg *Zingiber officinale*.

The tools used in this study include: height meter, weight scale for anthropometry data, blood lancet, blood tube, Elecsys CA15-3 reagent (CA15-3 reagent), Elecsys CA15-3 II Calset (CA15-3 Calibrator), Precicontrol tumor marker (Control CA15-3), and ELISA tool for chemical laboratory test.

Statistical Analysis

Data were analyzed by SPSS version 22.0. Univariate analysis was carried out to assess demographics and bivariate analysis using paired T test or Wilcoxon test to analyse differences in numerical variables in the study group before and after administration of *Allium sativum*, *Curcuma Longa* and *Zingiber officinale* extracts. Differences were considered statistically significant if $P < 0.05$.

RESULT

This study was followed by as many as 21 participants but 1 person lost to follow-up due to side effects that disturbing of nausea after consuming the extract. The number of subjects who followed the study was 20 people. The mean age of the participants, breast cancer patients, was 52.7 years. Based on occupation, the majority was housewives around 45%. The majority of the stages of breast cancer suffered were Stage IIIA or IIIB (30%). From the immunohistochemical examination of the type of breast cancer experienced, namely Luminal B as many as 10 people (50.0%). The results of the anthropometric examination of the average body weight of the participants was 58.7 kg, the average height of the participants was 155.1 cm and the average BMI of the participants was 24.39 kg/mm².

Table 1 Characteristics of Participants

Characteristics	N=20
Age, (years)	52.7±8.47
Occupation, n(%)	
Housewife	9 (45.0)
Entrepreneur	2(10,0)
Government employee	7 (35.0)
Health – worker	2(10,0)
Stadium, n(%)	
IIB	4(20,0)
IIIA	6 (30,0)
IIIB	6 (30,0)
IV	4(20,0)
Immunohistochemistry, n(%)	
Luminal A	4(20,0)
Luminal B	10 (50.0)
Negative Triple	2(10,0)
HER-2 Overexpression	4 (20,0)
Body weight, (kg)	58.7±7.66
Height, (cm)	155.1±4.22
BMI, (kg/mm ²)	24.39±3.17

Characteristics laboratory examination before and after administration

of extraction *Allium sativum*, *Curcuma longa* and *Zingiber officinale* has listed in table 2. There was a statistically significant increase in the median albumin with a value of $p=0.001$. Before the intervention the median value of albumin was 4.25 (3.70-4.50) and after intervention the median value of albumin was 4.5 (3.50-4.70). Liver function and kidney function has changed after administration of the extract but the changing was not significant that was showed in Table 2.

On examination of CA 15 – 3 the median CA 15-3 before administration of extracts of *Allium sativum*, *Zingiber* and *Curcuma longa* was 12.82 (3.29-45.81) g/mL, median CA 15-3 after administration of extracts of *Allium sativum*, *Zingiber* and *Curcuma longa* was 8.24 (2.83-47.46) g/mL, there was a decrease in the median CA 15-3 but not statistically significant with $p>0.05$ ($p=0.332$).

Table 2. Characteristics Laboratory Parameters of Patients Before and After Therapy

Parameter	Pre-Intervention	Post-Intervention	p value
SGOT	22.5 (17.00-98.00)	21.5 (14.00-54.00)	0.218
SGPT	18.5 (11.00-113.00)	20.5 (11.00-75.00)	0.948
Albumin	4.25 (3.70-4.50)	4.5 (3.50-4.70)	0.001*
urea	20.15 (16.40-32.40)	20.9 (15.00-29.00)	0.667
Creatinine	0.65 (0.49-0.99)	0.66 (0.45-6.00)	0.343
CA 15-3	12.82 (3.29-45.81)	8.24 (2.83-47.46)	0.332

Numerical data is presented in the form of mean ± standard deviation if the data is normally distributed, presented in the form of median (minimum value-maximum value) if the data is not normally distributed. *Wilcoxon non-parametric test.

DISCUSSION

On examination of liver function, statistically significant differences were found in the effect of *Allium sativum*, *Zingiber* and *Curcuma longa* extracts on median albumin ($p=0.001$) from this study. While the effect of giving the extract on the median SGOT and SGPT gave a difference but not statistically significant ($p = 0.218$ and $p = 0.948$ respectively). The

hepatoprotective effect of *Zingiber officinale* extract reported in another study was evident from a significant reduction in elevated serum levels of liver enzymes (AST, ALT) in obese diabetic rats.^[12]

Albumin is known to function as a carrier for many small molecules including drugs. ALT and AST are considered as sensitive indicators of hepatocellular damage, and these values provide a quantitative indication of the degree of liver damage due to drug administration.^[13] In this study was a statistically significant increase in the median albumin with a value of $p=0.001$. Before the intervention the median value of albumin was 4.25 (3.70-4.50) and after intervention the median value of albumin around 4.5 (3.50-4.70). This study is similar to a previous study which *Zingiber officinale* extract was given to rats showing a significant increase in albumin values in the two groups given extracts of 20 mg/kg body weight/48 hours and 40 mg/kg body weight/48 hours compared to the control group.^[14]

In this study renal function examination, there was a difference but not statistically significant in the administration of the extract *Allium sativum*, *Zingiber officinale* and *Curcuma longa* median urea ($p=0.667$) and creatinine ($p=0.343$). Previous studies in humans, did not find the effect of oral administration of *Zingiber officinale* extract on serum biochemical tests for renal function (BUN, creatinine). This finding showed no side effects on the kidneys.^[15]

Median CA15-3 after administration of extracts of *Allium sativum*, *Zingiber officinale* and *Curcuma longa* decrease but not statistically significant ($p=0.332$). This study is similar from the previous studies regarding trials of combination therapy with docetaxel (100 mg/day) and curcumin in patients with advanced and metastatic breast cancer. The study found that CA15-3 levels remained constant (not significant), while CEA levels decreased significantly. This could be due to the diminished benefits of curcumin due to its poor oral bioavailability,

lipophilic features, and extensive metabolism.^[16] However, the results of this study contradict a case report in Korea by Han et al. (2017) regarding the administration of a combination of *Zingiber officinale* and Gemcitabine-Cisplatin chemotherapy in a 46-year-old woman with recurrent breast cancer. The study found a decrease in the tumor marker CA 15-3 from 16.7 ng/ml to 13.8 ng/mL after receiving the combination therapy for 2 months.^[17] This may be due to the limited number of research samples so that they are less representative of the population of breast cancer patients. In addition, the duration of the study which is not long also causes the results of the study to be less than optimal.

Serum CA 15-3 levels in the blood are influenced by several things, including the presence of GATA binding protein-3, breast cancer subtypes and the degree of histopathology.^[18,19] Expression of GATA binding protein-3 can predict the progression of breast cancer, which a high expression shows a much better clinical and pathological picture but in this study did not examine the Expression of GATA binding protein-3.^[20]

There are some limitations to this research. The sample community has not been able to represent the population of this study due to the small number of research samples. The short duration of this study caused results that were not optimal for the participants both in terms of benefits and side effects. Another limitation of this study was that it did not use the control group as a comparison so that the results of the study could not be compared with the control group.

CONCLUSION

Median CA 15-3 before administration of *Allium sativum*, *Zingiber officinale* and *Curcuma longa* extracts was 12.82 (3.29-45.81) g/mL, median CA 15-3 after administration of *Allium sativum*, *Zingiber officinale* and *Curcuma longa* extracts was 8, 24 (2.83-47.46) g/mL, there

was a decrease in the median CA 15-3 but not statistically significant.

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