Original Research Article

The Effect of Allium Sativum, Curcuma Longa and Zingiber Officinale Extract on Carcinoembryonic Antigen (CEA) Levels of Breast Cancer Patients

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ABSTRACT

Introduction: Breast cancer is global problem and commonly in women. Tumor markers can assess tumor progression and response therapy. CEA is used as diagnostic, progression and response therapy. The treatment aims to suppress tumor development. Traditional medicine is considered beneficial and has minimal effect in suppressing tumor. Recent study, extracts of *Allium sativum, Curcuma longa* and *Zingiber* officinale consider useful as anti-cancer. However, no studies that discuss combined extraction *Allium sativum, Curcuma longa* and *Zingiber* of CEA levels.

Method: Open label clinical trial with one group pretest posttest design, held on June 28, 2021 – July 18, 2021, was conducted at USU Hospital and the population was breast cancer survivor community in Medan. Samples were taken by consecutive sampling. Those who met inclusion and exclusion criteria will be measured for CEA before and after administration of extract *Allium sativum, Curcuma longa and Zingiber officinale* with dose 500 mg twice a day for 28 days. T test or Wilcoxon test was used to measure comparison and analyzed with SPSS version 22th.

Results: 21 subjects who participated, only 20 subjects were analyzed with mean age of 52.7 years, majority stage III A or IIIB (30%). Median CEA before intervention 2.05 (0.70-12.20) g/mL and after intervention of 2.7 (0.8-12.40) g/mL, increasing value and not statistically significant with p>0.05 (p=0,238).

Conclusion: Median CEA value increased before and after intervention and not statistically significant.

INTRODUCTION

Breast cancer is one of the burdens of the global community and ranks 2nd around 25% accounting for the number of new cases of cancer in women worldwide in 2012). [1] Approximately 2 million cases of breast cancer are diagnosed each year with more than 600,000 deaths. [2] The highest incidence of breast cancer in women in low- and middle-income countries is due to lifestyle changes and growing urbanization. [3] In 2014 the incidence of breast cancer was around 50,000 in Indonesia with 20,000 deaths and increased in 2018 with an incidence of 58,000 and deaths of 22,000. [2,4]

Carcinoembryonic antigen(CEA) is a tumor marker that was first isolated from colorectal cancer tissue in 1965 by Gold and Freedman. CEA is a fetal glycoprotein and is usually not produced after birth.[5] CEA is elevated in several pathological conditions, especially breast cancer. CEA in breast cancer is to assess diagnose, clinical staging, to detect recurrence in patients who have undergone surgery, and to monitor therapeutic response in patients undergoing chemotherapy or radiotherapy. [6]

Traditional medicine has been widely studied, especially in breast cancer because traditional medicines are generally considered safety and easier to accept by the

community, coupled with relatively fewer side effects. Some examples of these combine extraction are *Allium sativum, Curcuma longa,* and *Zingiber officinale* which are thought to have anti-cancer benefits. [7] Seeing the potential benefits of these three extracts on breast cancer, therefore the aim of this study to assess the benefits of extracts *of Allium sativum, Curcuma longa* and *Zingiber officinale* in breast cancer patients assessed through CEA levels.

MATERIALS & METHODS
Patients & Design
An open label clinical trial study with a one group pretest posttest design in which researchers and participants know the intervention given. This research was located at USU Hospital which had been held on June 28, 2021 – July 18, 2021. The population of this study came from the breast cancer survivor who has finished all the treatments of breast cancer community in Medan, Indonesia. The sampling technique in this study used consecutive sampling.

Patients who have met the inclusion and exclusion criteria as research subjects will be get intervention in the form of administration of extracts of *Allium sativum, Curcuma longa* and *Zingiber officinale* for 4 weeks. The inclusion criteria in this study were breast cancer survivor who has finished all the treatments of breast cancer and age ≥18 years. Meanwhile, the exclusion criteria for this research were pregnant women, have hepatitis B and C disease, cirrhosis, sepsis, other primary malignancies, and patients who are not willing to be research subjects.

Trial Procedures
Each participant who was willing to take part and fulfill the inclusion and exclusion criteria must fill out an informed concern for written consent to participate in the study. Participants who took part in this study were about 21 participants. This study lasted for 28 days. Each participant who has

filled in the information concern will be interviewed to find out the demographic data of the participants. After that, an anthropometric examination was carried out to measure height (m) and weight (Kg). Furthermore, the author would search of the participants' medical records to get a diagnosis of breast cancer and other diseases. If the medical record did not contain an examination for hepatitis b and c, the participant would be examined for hepatitis b and c. Participants would be given extract *Allium sativum, Curcuma longa* and *Zingiber officinale* with a dose of 500 mg twice a day for 28 days. Before administering the extract, the participants would be examined the laboratory test such as liver function, kidney function, and examination of CEA levels.

In monitoring side effects on participants, the researcher provided a mobile number that could be contacted at any time if participants experienced side effects or had something to ask. On day 29, participants were required to return to the hospital for laboratory examinations after administration of the extract.

This research was conducted as a result of has ethical clearance and has obtained permission to conduct research from the research supervisor, approval from the Health Research Ethics Commission of the USU Faculty of Medicine.

Chemical Materials
Extraction given by participants in the form of capsules that have the composition contains 200 mg *Allium sativum*, 150 mg *Curcuma longa*, and 150 mg *Zingiber officinale*. The tools used in this study include: blood lancet, blood tube, CEA reagent, and ELISA device.

Statistical Analysis
The software used for the analysis was SPSS version 20.0. Data were analysed univariate and bivariate. Univariate to determine the characteristics of research participants. Numerical data was presented in the form of mean ± standard deviation if

the data was normally distributed, presented in the form of median (minimum value-maximum value) if the data was not normally distributed.

Bivariate analysis was used to assess the differences in variables before and after administration of *Allium sativum, Curcuma Longa* and *Zingiber officinale* extracts with the dependent T test or Wilcoxon test if the data were not normally distributed. The difference was considered statistically significant if p<0.05.

RESULTS

Of 21 breast cancer survivors who took part in this study but 1 person had a disturbing side effect of nausea so was not included in the study. Only 20 people were analyzed in this study. The average age of the participants was 52.7 years. Based on occupation, the majority of the participants were housewives by 45%. The most common breast cancer stages experienced in this study was stage III A or III B, about 30%. From the immunohistochemistry examination, the majority types of breast cancer suffered was Luminal B as many as 10 people (50.0%) which was listed in Table 1.

Tables. 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/mm2)	24.39±3.17

Table 2 shows the results of the research characteristic of laboratory before and after the administration of therapy. From table 2, it can be seen that the median albumin before administration of *Allium*

sativum, Curcuma longa and *Zingiber officinale* extracts was 4.25 (3.70-4.50), the median albumin after administration of *Allium sativum, Curcuma longa and Zingiber officinale* extracts was 4.5 (3, 50-4.70), there was a statistically significant increase in median albumin with p<0.05. Not only Median liver function (SGOT and SGPT) has changed in this study but also not statistically significant. Renal function (ureum & creatinine) also has changed the median value and the changing was not statistically significant.

Based on tumor marker examination, the median CEA before *Allium sativum, Curcuma longa* and *Zingiber officinale* extracts was 2.05 (0.70-12.20) g/mL, the median CEA after administration of *Allium sativum, Curcuma longa* and *Zingiber officinale* extracts was 2.7 (0.8-12.40) g/mL, there was an increase but not statistically significant with p>0.05 (p=0.238).

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	8:15pm (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
CEA	2.05 (0.70-12.20)	2.7 (0.8-12.40)	0.238

*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

In this study, statistically significant differences were found in the effect of *Allium sativum, Curcuma longa* and *Zingiber officinale* extracts on the median albumin (p=0.001). While the effect of giving these extracts on the median SGOT and SGPT gave a difference but not statistically significant (p = 0.218 and p = 0.948 respectively). This study is similar to previous studies regarding the ex vivo and in vivo antioxidant effects of *Zingiber officinale* in humans. the effect of oral administration of the extract on serum

biochemical tests for liver function (AST, ALT, Albumin) showed no side effects on the liver. [8]

On renal function test, there was a changing but not significant difference in before and after administration of extracts *Allium sativum, Curcuma longa* and *Zingiber officinale* with median urea (p=0.667) and creatinine (p=0.343). A toxicity test of Allium sativa in rats, found a significant increase in serum urea after administration. This finding is thought to be caused by an increase in protein catabolism (Lawal et al., 2016). However, in Bilto and Alabdallat study the administration of *Zingiber officinale* extract could reduce serum BUN levels without any effect on creatinine, thus indicating a possible beneficial effect for removing urea from plasma in uremic patients. [8] From the results of this study, found that the *Allium sativum, Curcuma longa* and *Zingiber officinale* drugs did not have toxicity to the kidneys.

CEA is a tumor marker for colorectal, gastrointestinal, lung and breast cancers. Persistently elevated CEA levels in breast cancer may explain either cancer not responding to treatment, or recurrence after treatment. However, CEA can be used to aid diagnosis, clinical staging, to detect recurrence in patients who have undergone surgery, and to monitor therapeutic response in patients undergoing chemotherapy or radiotherapy. [9]

On examination of tumor markers, the median CEA before administration of the extract *Allium sativum, Curcuma longa* and *Zingiber officinale* was 2.05 (0.70-12.20) g/mL, median CEA after extract administration *Allium sativum, Curcuma longa* and *Zingiber officinale* extract was 2.7 (0.8-12.40) g/mL, there was an increase but not statistically significant (p = 0.238). The results of this study different from the research of Jafarpour-Sadegh et al. (2015) regarding the effect of administering the *Allium* plant (100-160 g/day) in breast cancer patients undergoing Doxorubicin chemotherapy. Their study found significant reductions in plasma levels of CEA and CA-125. [10] Likewise, a human study, which found that administration of docetaxel (100 mg/m2) and curcumin (500 mg/day) gave a promising biologic response in terms of chemoprevention, as shown by their ability to reduce tumor markers of CEA. [11] The difference between the results of this study and the other two studies may be due to the use of the extract combined with chemotherapy drugs, causes a decrease in CEA levels. In addition, the high stage of breast cancer in this study may be a factor that causes an insignificant effect on the administration of this extract. In a mouse study, *Zingiber officinale* was able to ameliorate the increase in CEA induced by the procarcinogen 1,2-dimethylhydrazine (DMH). This finding strengthens the hypothesis of the extract's ability to suppress plasma CEA levels. [12]

There are some limitations to this study. The sample community has not been able to represent the population of this study and the number of research samples was too small. The short duration in this study caused results that were not optimal for the research subjects both in terms of benefits and side effects. A longer time study is needed to get more real results from the effect of *Allium sativum, Curcuma Longa and Zingiber Officinale* extracts, especially because the selected research sample was Breast Cancer stage 3 and 4 patients. Another limitation of this study was that it did not use a control group as a comparison so the results of the study could not be compared with the control group.

CONCLUSION

The median CEA before administration of *Allium sativum, Zingiber officinale* and *Curcuma longa* extracts was 2.05 (0.70-12.20) g/mL, the median CEA after administration of Allium sativum, Zingiber officinale and Curcuma longa extracts was 2.7 (0, 8-12.40) g/mL. There is no significant difference in median CEA

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