International Journal of Research and Review
DOI: https://doi.org/10.52403/ijrr.20211053
Vol.8; Issue: 10; October 2021
Website: www.ijrrjournal.com
Original Research Article *E-ISSN: 2349-9788; P-ISSN: 2454-2237*

Efficacy of Allium Sativum, Curcuma Longa and Zingiber Officinale Extract on Serum Vasculoendothelial Growth Factors Levels of Breast Cancer Patients

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ABSTRACT

Introduction: Breast cancer requires high nutrition, oxygen and metabolism where VEGF-triggered angiogenesis is needed. VEGF is triggered via the HIF-1 pathway and also via the NF-Kappa B pathway. VEGF is associated with tumor growth and metastasis. Some plant extracts have anti-angiogenesis effects such as Curcuma longa, Allium sativum and Zingiber officinale.
Objective: To determine serum levels of SGOT, SGPT, ureum, creatinine, albumin and VEGF before and after administration of Curcuma longa, Allium sativum and Zingiber officinale extracts
Method: An open label clinical trial study with a one group pretest posttest design involving 21 patients from breast cancer community in Medan collected by consecutive sampling from June – July 2021 in USU hospital where these patients met the inclusion criteria. All patients were tested for complete blood count, urea, creatinine, SGOT, SGPT, albumin, serum VEGF before and after being given a combination extract of Curcuma longa 150 mg, Allium sativum 200 mg and Zingiber officinale 150 mg twice daily for 28 days. Statistical analysis was performed by paired analytical T test or Wilcoxon.
Results: The study involved 20 subjects. From the examination of kidney function obtained results before and after the administration of a combination extract VEGF results before and after the administration of the combination (1110(760-7893) µg / ml vs. 864 (532-5650 µg / ml, p = 0.001).
Conclusion: VEGF serum breast cancer patients had a significant reduction after being given a combination of extracts of Allium sativum, Curcuma longa and Zingber officinale.

Keywords: VEGF, Allium sativum, Curcuma longa, Zingiber officinale

INTRODUCTION

Cancer is the second highest cause of death worldwide. In 2018, Newly diagnoses cases reached 18.1 million, death cases reached around 9.6 million. Breast cancer was the second highest caused (11.6%).[1] (Bray 2018). In United States, breast cancer was found on adult women between 29 and 49 years old. Only 1 percent of total cases was found in men. In Indonesia, Breast cancer incidence was 0.5 per 1000 women. Newly diagnosed cases were 819 persons and death cases reached 217 persons.[2]

Breast cancer was uncontrolled growth of epithelial cells from ductal or lobules of breast. In order to support the growth of tumor cells, angiogenesis is the key for the cells to get nutrition, oxygen and metabolize. Angiogenesis is induced by vasculo endothelial growth factors(VEGF). The most abundant VEGF is VEGF A, which are produce by endothelial cells and can bind to VEGFR2 to induce pathological

angiogenesis in tumor. Meanwhile, VEGF C and D involved in lymphogenesis, which is needed for metastasis process.[3][4] In tumor cells, production of VEGF was induced by hypoxic state of tumor cells which cause mutation of Von Hippen Lindau gene. Then, hypoxic inducible factor alpha(HIF- alpha 1) will combine with HIF-1 Beta, which will translocate to nucleus and induce VEGF promotor to produce VEGF.[5] VEGF is also induced by inflammatory pathway, NF-Kappa B, in breast cancer patient.[5]

There are alternative medicine which has proven anti cancer effect. Few of them were Curcuma longa, Allium sativum, and Zingiber officinale. Curcuma longa which have curcumin as its active substance, reduces angiogenesis through inhibition of NF-KB and has anti cancer effect by stopping the cell cycle and induce apoptosis in breast cancer cell culture MBA-MB-231 and MCF-7.[6] Allium sativum consist of alliin, Diallyl Thiosulphate, Diallyl Disuphide which have anti cancer effect by halting the cell cycle.[7] Zingiber officinale contains 6-shaogaol, 6 -gingerol, 8-gingerol as its active phenolics. The phenolics are able to halt phase G1 cell cycle, induce apoptosis and down regulate cIAP-1 in cell culture HepG2.[8] Each of the herbals extract has been analyzed individually through experimental to cancer cell culture and cancer inoculated mice. Currently there is no experimental in analyzing effect of combination of three extract in cancer patient.

MATERIALS AND METHODS

Trial design and patient

An open label, one group pretest posttest trial was conducted in Medan from June – July 2021. The subjects were from a Breast cancer community in Medan. The trial has been approved by Medical Ethics commitee of Universitas Sumatera Utara. Samples were collected base on consecutive sampling. Patients who were older than 18 years old, breast cancer patient who has finished all the treatment of breast cancer, were signing informed consent and recruited. Pregnancy, infected by hepatitis B or C virus, cirrhotic, diabetic, coronary heart disease patient, other cancer patient were excluded in this trial.

Trial procedures

21 patients blood sample were assessed for their antropometry data (body weight, height) drawn for measuring their pretest laboratory test(ureum, creatinine, serum VEGF, SGOT, SGPT) in Sumatera Utara Medical Faculty laboratory for the serum VEGF and in Universitas Sumatera Utara Hospital Laboratory for the others. Patient has to consume the extract 1 capsule twice daily for 28 days. Patients were followed up for 28 days. Side effect will be noted and treated. Any miss dose of the capsule will be noted. During the trial, patients were prohibited to consume other drugs. Serum VEGF were measured by enzyme-linked immunosorbent assay. After 28 days, patients' blood will be drawn for post test laboratory test(ureum, creatinine, serum VEGF, SGOT, SGPT).

Clinical material

We provide capsules that contain Allium sativum extract 200 mg, Curcuma longa extract 150 mg, Zingiber officinale extract 150 mg. Allium sativum (garlic), Zingiber officinale (ginger), Curcuma longa (tumeric) were extract using water extraction method. The liquid extract were evaporated and crystallized using Saccharum lactis until a stable crystal mass was formed. The process continued with grinding or crushing techniques and was sifted with mesh 120 to obtain particle sizes of 10 - 125 μm.

Antioxidant activity test

Antioxidation activity tests of Curcuma longa extract, Zingiber officinale, and Allium sativum have been conducted by the radical damping method DPPH (1,1-diphenyl-2-picrylhydrazyl) by observation using visible spectrophotometry. The antioxidant activity of Curcuma longa extract, Zingiber officinale, and Allium

sativum was obtained from the results of DPPH absorbance measurement in the 60th minute with the addition of test solution with concentrations of 2 ppm, 4 ppm, 6 ppm, and 8 ppm compared to DPPH control (without the addition of test solution). The results showed a decrease in the absorbance value of DPPH which was tested against control at each increase in concentration, indicating greater antioxidant activity.

Acute toxicity assessment

Acute toxic effect testing was conducted on male rats based on the Organization for Economic Co-operation and Development (OECD) guidelines for Testing of Chemicals number 423 with fixed dose method.[9] In this study extracts curcuma longa, zingiber officinale, and allium sativum were used at doses of 500 mg / kgBB, in addition to a combination of doses (4:3: 3) with observations made for 14 days against toxic symptoms that occur both qualitatively and quantitatively. Based on this test, no toxic symptoms were noted.

Statistical analysis

We use SPSS 24 software to analyze all of the data. We calculated mean and median value of the laboratory parameter. Numerical data is presented in the form of mean ± standard deviation if the data distribution is normal and in the form of a median (maximum minimum-value value) if the data distribution is not normal. We used paired T-test to detect significant difference between ureum, creatinine, VEGF, SGOT, SGPT pre test and post test.

RESULT

This study involved 21 subjects. However, 1 person lost to follow up due to having nausea after the consumption of the extract, so the number of subjects who participated in the study to completion was 20 people.

Mean age of the study subjects were 52.7 years. Majority of the study subjects were housewives (45%), civil servants (35%), self-employed and health workers at 10% each. Based on the stage of breast cancer, study subjects who had stage IIB breast cancer as many as 4 people (20%), stage IIIA as many as 6 people (30%), stage IIIB as many as 7 people (30%), and stage IV were 4 people (20%).

Table 1. Demographic characteristic of subjects

Characteristic	N=20
Age (years)	52,7±8,47
Occupation, n(%)	
Housewives	9 (45,0)
Enterpreneur	2 (10,0)
Government employee	7 (35,0)
Medical staff	2 (10,0)
Stage, n(%)	
IIB	4 (20,0)
IIIA	6 (30,0)
IIIB	6 (30,0)
IV	4 (20,0)
Imunohistochemistry, n(%)	
Luminal A	4 (20,0)
Luminal B	10 (50,0)
Tripel Negatif	2 (10,0)
HER-2 Overexpression	4 (20,0)
Bodyweight, (kg)	58,7±7,66
Height, (cm)	155,1±4,22
Body mass index, (kg/mm^2)	24,39±3,17

Based on immunohistochemical examination (IHC), the majority of the subjects had Luminal B breast cancer as many as 10 (50.0%), Luminal A as many as 4 (20.0%), HER-2 Overexpression as many as 4 (20.0%), negative triples as many as 2 (10.0%). Based on anthropometric measurement, the average body weight of the subjects was 58.7 kg, the mean height of the study subjects was 155.1 cm, the mean body mass index of the subjects was 24.39 kg / mm^2.

The median SGOT before the administration of Allium sativum, Zingiber and Curcuma longa extracts is 22.5 (17.00-98.00) U /L, the median SGOT after the administration of Allium sativum, Zingiber and Curcuma longa extracts is 21.5 (14.00-54.00), there is no significant difference statistically (p=0.218). The median SGPT before the administration of Allium sativum, Zingiber Officinale and Curcuma longa extracts is 18.5 (11.00-113.00) U/L, the median SGPT after the administration of Allium sativum, Zingiber and Curcuma longa extracts which are 20.5 (11.00-75.00),

the result show no significant difference statistically(p=0,948).

Table 2. Laboratory parameter characteristic pre and post intervention

	Pre-Intervention	Post-Intervention	p
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
Ureum	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
VEGF	1110 (760-7893)	864 (532-5650)	<0,001*

Non parameteric : Wilcoxon

The median ureum before the administration of Allium sativum, Zingiber and Curcuma longa extracts was 20.15 (16.40-32.40) mg/dl, the median ureum after the administration of Allium sativum, Zingiber and Curcuma longa extracts was 20.9 (15.00-29.00) mg/dl, there was no significant difference statistically(p=0.667).

The median creatinine before the administration of Allium sativum, Zingiber and Curcuma longa extracts was 0.65 (0.49-0.99) mg/dl, the median creatinine after the administration of Allium sativum, Zingiber and Curcuma longa extracts was 0.66 (0.45-6.00) mg/dl, there was no significant difference statistically (p=0.343).

The median VEGF before the administration of Allium sativum, Zingiber and Curcuma longa extracts was 1110 (760-7893) µg/mL, the median OF VEGF after the administration of Allium sativum, Zingiber and Curcuma longa extracts was 864 (532-5650) µg/mL, there was a significant difference statistically (p=0.001).

DISCUSSION

In order to identify the side effect of the combined extract (Allium sativum, Curcuma longa and Zingiber officinale) to the liver, FDA suggest elevation of SGPT or SGOT is the sign of hepatocellular injury.[10] In this study, both SGOT and SGPT after the subjects consuming combined extract of Allium sativum, Curcuma longa and Zingiber offiicinale still in normal range after the subjects consumed the extract for 28 days. In fact, Curcuma longa decreased SGOT(156.8U/L vs 150.3) and SGPT(249.8U/L vs 237.5U/L) in mice with paracetamol toxicity.[11] Allicin and Aliin showed antioxidant effect which decrease oxidative stress and prevent increment in SGOT and SGPT.[12] Bachri (2011) conclude that Zingiber officinale also decreased SGOT and SGPT and had antioxidant also. These implied that the combination of the three extracts showed no side effect to Liver.[13]

In this study, we found ureum and creatinine of subjects after taking the combined extract of Allium sativum, Curcuma longa, and Zingiber officnale were still in normal range. In previous study, Allium sativum improved creatinine clearance and decreased serum creatinine in nefrectomized mice. It has renal protective effect by decreasing oxidative stress and hypertension.[14] Hamed et al concluded that Zingiber officinale significantly decreased ureum and creatinine compare to control group. Curcumin showed anti oxidant, anti inflammation and anti apoptosis effect in renal structure which decrease creatinine clearance.[15] Based on these evidences, Combination of Allium sativum, Curcuma longa, and Zingiber officinale showed no side effect to the kidney.

VEGF is an angiogenic factor that is very important for tumor in getting nutrients and growing. VEGF increase concomitantly with increament of stage and size of breast cancer.[16] In present study, serum VEGF in breast cancer patients decrease significantly after administration of combination of Allium sativum, Curcuma longa and Zingiber officinale extract(1110(760-7893) µg/ml vs 864(532-5650 µg/ml, p=0.001). Alliin showed supressive effect of VEGF in Hepatocellular carcinoma culture cell.[17] Alhasan et al reported allicin administration on cancer cell culture for 24 hours also reduce VEGF.[18] 6-Shaogaol decreased VEGF through NF-KB pathway downregulation. Curcumin was able to inhibit growth of breast cancer through inhibition of VEGF , Matrix Metaloproteinase -2(MMP-2),

MMP-9.[19] It concludes that the result of this study is consistent with the previous study.

CONCLUSION

Our study showed combination of Allium sativum, Curcuma longa, Zingiber officinale extract significantly decrease serum VEGF in breast cancer patients.

Acknowledgement: None

Conflict of Interest: None

Source of Funding: None

Ethical Approval: Approved

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How to cite this article: Yang M, Gatot D, Mardia AI. Efficacy of allium sativum, curcuma longa and zingiber officinale extract on serum vasculoendothelial growth factors levels of breast cancer patients. *International Journal of Research and Review*. 2021; 8(10): 396-401. DOI: *https://doi.org/10.52403/ijrr.20211053*

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