

Supplementation in suppressing Troponin I and NT-proBNP level in breast cancer patients with 5- fluorouracil, adriamycin, and cyclophosphamide chemotherapy



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ABSTRACT

Background: Breast cancer is a malignancy originating from breast tissue, where chemotherapy is one of the choice therapy. Doxorubicin, 5-fluorouracil, and cyclophosphamide (FAC) are the most commonly used combination of chemotherapy. One of the side effects of chemotherapy is cardiotoxicity. Multiflora honey prevents cardiotoxic effects through its flavonoids and polyphenols compounds. The aim of this research is to analyze the effectiveness of adding honey in preventing cardiotoxic effects in breast cancer patients receiving FAC chemotherapy.

Methods: An experimental study with double-blind randomized pre and post-test with control group design. Ductal invasive breast cancer patients were divided into 2 groups, the control group, who received FAC chemotherapy (n=18) and the treatment group, who received chemotherapy and 90 ml/day honey consumption for 14 days (n=18). The patient's Troponin I and NT-proBNP enzyme levels before and after 14 days of the study were assessed.

Results: Post-treatment, there was an increase in Troponin I levels from the treatment group (0.22 ± 0.07 vs. 0.24 ± 0.07) vs. control (0.25 ± 0.11 vs. 0.34 ± 0.20) with a significant difference. ($p = 0.031$). There was a decrease in NT-proBNP levels in the treatment group (461.0 ± 610.4 vs. 215.6 ± 260.3) and an increase in NT-proBNP levels (275.9 ± 392.4 vs. 315.4 ± 293.9) with a significant difference ($p = 0.006$).

Conclusion: Multiflora honey can prevent cardiotoxic effects in breast cancer patients receiving FAC chemotherapy.

Keywords: breast cancer, cardiotoxic induced chemotherapy, chemotherapy FAC, multiflora honey.

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INTRODUCTION

Breast cancer is a malignancy case with the 2nd highest mortality rate in Indonesia. According to WHO data, in 2018, there were 58,256 (16.7%) cases of breast cancer from 348,809 new malignancies found in Indonesia.¹⁻³ In general, the treatment of breast cancer includes surgery, chemotherapy, hormonal therapy, therapeutic targets and radiotherapy.^{1,4} Chemotherapy that can be given to malignant breast cancer patients could be a systemic hormones therapy, chemotherapy combination or both.⁵ First-line therapy for patients who receive chemotherapy is based on the protocol from *Perhimpunan Ahli Bedah Onkologi Indonesia* (PERABOI) using a 5-Fluorouracyl - Adriamycin (doxorubicin) - cyclophosphamide (FAC) / 5-Fluorouracyl - Epirubicin -

cyclophosphamide (FEC).^{1,6}

During chemotherapy, the patient was also monitored through laboratory tests and often gave a sign of cardiotoxicity.⁷ FAC/FEC is the line first in chemotherapy patients with breast cancer that shows the cardiotoxicity effect.⁸ Several studies have shown that drug-induced toxicity is often reversible and has been classified as type 2 cardiotoxic.^{8,9} Redox stress, due to the overproduction of reactive oxygen species (ROS) and reactive nitrogen species (RNS), can directly or indirectly induce cardiac injury. Inhibitors of intracellular signaling (e.g., tyrosine kinase inhibitors) block pathways that are major regulators of myocardial function.⁹ In a study of an angiotensin-converting enzyme inhibitor (ACE-inhibitor) as a preventive of chemotherapy-induced cardiotoxicity, it was found that 114

patients showed an increase in troponin I from 473 patients who received high doses of chemotherapy. In the group with elevated troponin I, 50 patients (44%) had troponin I level persisting for up to 1 month after chemotherapy and followed by a progressive decrease in LVEF and an increase in end-diastolic and end-systolic volumes only in control subjects who were not given ACE- inhibitors. During the study, 31 patients in the group that experienced an increase in troponin I also experienced heart problems such as cardiac death, acute pulmonary edema, heart failure and arrhythmias.¹⁰

Over the past few decades, the use of cardiac biomarkers has been investigated as a new tool that can be used for the early identification of chemotherapy drug-induced cardiotoxicity. Cardiac biomarkers have the advantages of being

minimally invasive, cheap, easy to re-evaluate, and operator independent. Most studies using cardiac biomarkers in chemotherapy-induced cardiotoxicity monitoring recommend troponin, which is associated with cardiomyocyte injury, and N-terminal pro-brain natriuretic peptide (NT-proBNP) released from the heart in response to volume expansion and increased wall pressure.^{8,11,12}

Honey is a natural ingredient that is easily available and has the potential to reduce cardiotoxic effects.¹³ Research by Hassan *et al.* showed an increase in CK-BM activity in experimental animals given paclitaxel, while the group receiving Royal Jelly honey showed reduced CK-BM activity after 28 days of chemotherapy and Royal jelly honey. Royal Jelly at doses of 100 and 150 mg/kg also significantly reduced lipid peroxidase levels.¹⁴

Honey induces cell apoptosis in various types of cancer cells through mitochondrial membrane depolarization.^{15,16} Honey increases caspase 3 activation and the breakdown of poly-(ADP-ribose) polymerase (PARP) in colorectal malignancies, which are associated with high levels of tryptophan and phenolics in honey.¹⁷ Honey produces p53 to modulate the expression of pro and anti-apoptotic proteins such as Bax and Bcl-2.¹⁸

Honey affects the termination of cancer cell cycle division and modulates the activity of Tumor Necrosis Factor (TNF), which has been shown to mediate cancer cell progression, growth, and development.^{19,20} The proinflammatory effect of TNF is related to its ability to activate NF- κ B, which leads to the expression of proinflammatory genes such as lipoxygenase-2 (LOX-2), cyclooxygenase-2 (COX-2), cell adhesion molecules, chemokines, inducible nitric oxide synthase (iNOS), and inflammatory cytokines.²¹⁻²⁴

Based on the description of the potential effects of honey as a natural substance, it has been stated that honey has immunomodulatory, anti-carcinogenic, anti-proliferative, apoptotic, antioxidant and anti-inflammatory properties.^{15,25,26} The aim of this study was to know the effect of honey given during chemotherapy treatment in order to prevent and reduce cardiotoxic effects in breast cancer patients.

METHOD

This research is an experimental study with a *Double-Blind, Randomized Pre and Post test design with a Control Group Design*. In this study, the research subjects (breast cancer patients who met the inclusion criteria) were divided into two groups, the control group and the treatment group, which previously carried out random allocation.

The research was conducted at the Surgical Oncology Clinic, Chemotherapy Room and the Dr. Kariadi Semarang central hospital laboratory from August to October 2020.

The sample in this study were women with invasive ductal breast cancer aged 30-60 years who were treated at Dr. Kariadi Semarang central hospital during the research period. The research subjects were selected by *consecutive sampling*. Patients who match the study inclusion criteria will be used as research subjects. The inclusion criteria are women aged 30 – 60 years old, Karnofsky index ≥ 70 , and willing to contribute as research subjects. The subjects will be excluded if they undergo radiotherapy, have several systemic diseases before chemotherapy, such as chronic heart disease, congenital heart disease, or heart valve disease, are malnourished, are diabetic, use another derivative during chemotherapy, and are allergic to honey. Sampling was stopped after the number of samples was achieved. The minimum total sample is 18 people in the control group and 18 people in the treatment group.

The independent variable in this study was the administration of honey. The dependent variable in this study was the levels of Troponin I and levels of NT-proBNP. Confounding variable is patient age, body mass index, nutrition status, chronic heart function disorders, kidney function disorders and radiation.

Demographic characteristics data were patient age, body mass index (BMI), education, occupation, BSA, and breast cancer stage. Data are presented in tables and graphs. All collected data were analyzed using SPSS Statistic 25 software. Before the analysis was carried out, the Shapiro-Wilk normality test was performed because the number of data was less than 50. Analysis of the pre and

post-difference test in the control group and the treatment group used a Pair t-test on data that were normally distributed or homogeneous. If the data is not normally distributed or homogeneous, the pre and post-difference test analysis in the control group and the treatment group use the Wilcoxon test. Analysis between control group delta and treatment group delta was analyzed by Independent t-test if the data were normally distributed or using the Mann-Whitney test if the data were not normally distributed. All analyzes were performed on a computer using a statistical program for windows. The difference was declared significant if the p-value was ≤ 0.05 .

The implementation of this research follows the ethics of human research. Before it was implemented, a proposal exam was carried out, followed by submitting ethical clearance through the Ethics Commission of the Faculty of Medicine, Universitas Diponegoro / Dr. Kariadi central hospital Semarang and request for permission from the Director of Dr. Kariadi central hospital Semarang.

RESULTS

Descriptive Characteristics

The sample in this study were 18 patients in the treatment group, who were given FAC chemotherapy and honey for 14 days and 18 patients in the control group, who received only FAC chemotherapy.

Analysis of Troponin I level

The results showed an insignificant increase in the average posttest Troponin I levels in the treatment group was 0.22 to 0.24. In the control group, there was a significant increase in the posttest Troponin I levels mean score, from 0.25 to 0.34 (Table 2).

The mean levels of Troponin I in both groups used the Wilcoxon test because it was not normally distributed. The difference in Troponin I levels between the treatment and control groups was analyzed using the independent t test because it was normally distributed. Based on statistical tests, there was a significant difference in Troponin I levels between the two groups of research subjects, namely 0.031 ($p < 0.05$) (Figure 1).

Analysis of NT-proBNP level

The results showed a significant decrease in the posttest NT-proBNP levels in the treatment group, from 461.0 to 215.6. In the control group, there was an insignificant increase in the mean posttest NT-proBNP levels, from 275.9 to 315.4 (Table 3).

The mean pre-test and post-test NT-

proBNP levels in both groups used the Wilcoxon test because the distribution was not normal. The difference between the pre-test and post-test NT-proBNP levels between the treatment and control groups was analyzed using the Mann-Whitney test because the distribution was not normal. Based on statistical tests, there was a significant difference in NT-proBNP

levels between the pre-test and post-test groups. It was 0.006 ($p < 0.05$) (Figure 2).

DISCUSSION

This study showed a significant difference between Troponin I levels in the control and treatment groups. However, there was an insignificant increase in Troponin I levels in the treatment group, as well as in the control group. There was an increase in Troponin I levels. The increase in Troponin I in the control group was higher than in the treatment group. This illustrates that the administration of FAC chemotherapy without the administration of honey does worse myocardial damage.

Cosimo *et al.* mention in their study that Troponin I is a sensitive biomarker of the cardiotoxic effects of chemotherapy in breast cancer patients. Changes in Troponin I levels can also be assessed in a short time and can be used as an indicator in diagnosing myocardial injury.²⁷ Based on this study, although there was an increase in Troponin I in the treatment group, this increase was so minimal that it indicated that the myocardial damage was less severe due to the cardioprotective effect of honey.

Khalil *et al.*, in their study on the evaluation of cardiac enzymes in myocardial infarction in the rat model and Talulang honey administration, showed a decrease in Troponin I, CK-MB, and LDH levels after administration of honey. Khalil *et al.* stated that when an infarction occurs, there will be an insufficiency of oxygen supply to the tissues, causing the cardiac membrane to become permeable or even rupture, resulting in leakage of cytosolic enzymes into the bloodstream and an increase in the production of free radicals.²⁸ The flavonoid compounds in honey, such as catechins and kaempferol, phenolic acids, and ascorbic acid, are important antioxidants, all of which can work synergistically to eliminate free radicals.²⁹ Redox stress, due to the overproduction of reactive oxygen species (ROS) and reactive nitrogen species (RNS), can directly or indirectly induce cardiac injury. Inhibitors of intracellular signaling (e.g., tyrosine kinase inhibitors) block pathways that are major regulators of myocardial function.⁹ Daily consumption of honey at 1.2 g/kg body weight has been shown to increase

Table 1. Demographic characteristics of two study groups.

Variable	Groups		p
	Honey Group	Control	
BMI	24,18 ± 4,83	25,39 ± 2,67	0,355 [§]
BSA	1,46 (1,22 – 1,83)	1,5 (1,34 – 1,73)	0,116 [‡]
Ductal Invasive			
Grade II	13 (72,2%)	15 (83,3%)	0,691 [¥]
Grade III	5 (27,8%)	3 (16,7%)	
Age	53,56 ± 9,87	52,17 ± 7,56	0,639 [§]
Occupation			
Work	10 (55,6%)	5 (27,8%)	0,091 [¥]
Unemployment	8 (44,4%)	13 (72,2%)	
Education			
SD	13 (72,2%)	5 (27,8%)	0,056 [¥]
SMP	2 (11,1%)	6 (33,3%)	
SMA	3 (16,7%)	6 (33,3%)	
PT	0 (0%)	1 (5,6%)	

Note: ¥ Chi-square; § Independent t; ‡ Mann-Whitney

Table 2. Differences in the mean of Troponin I level.

Troponin I	Groups		p
	Honey Group	Control	
Pre-test	0,22 ± 0,07	0,25 ± 0,11	0,680 [‡]
Post-test	0,24 ± 0,07	0,34 ± 0,20	0,254 [‡]
p	0,484 [†]	0,013 ^{*¥}	
Delta	0,02 ± 0,07	0,10 ± 0,14	0,031 ^{§*}

Note: * Significant ($p < 0,05$); § Independent t; ‡ Mann whitney; † Wilcoxon

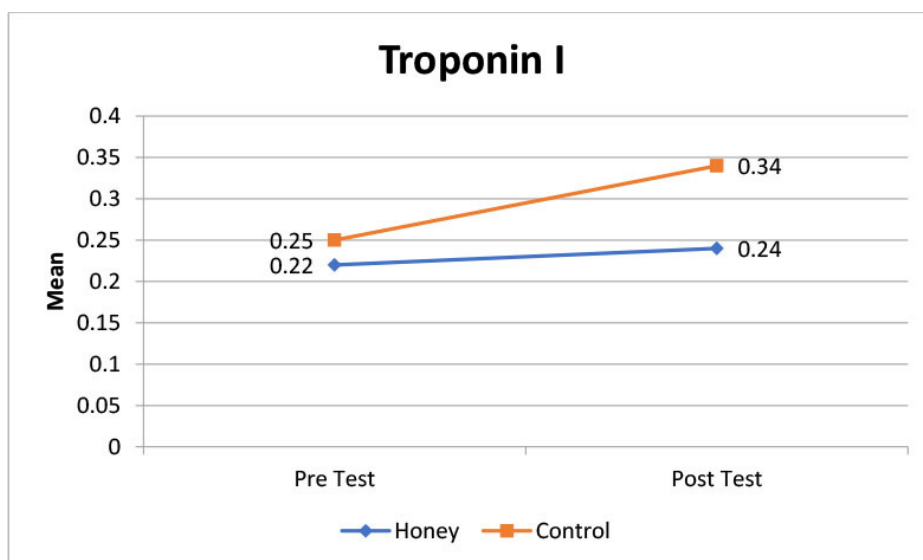
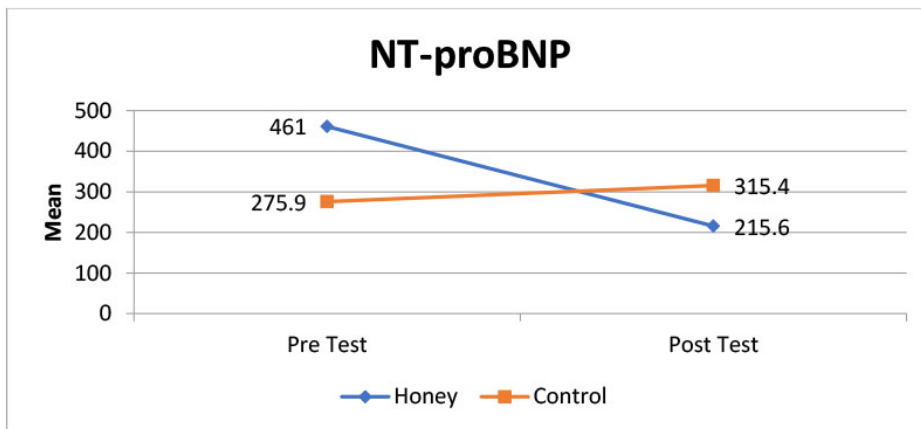


Figure 1. Graphic of Troponin I levels mean of the two study groups.

Table 3. Differences in mean levels of NT-proBNP.

Troponin I	Groups		P
	Honey	Control	
Pre-test	461,0 ± 610,4	275,9 ± 392,4	0,242‡
Post-test	215,6 ± 260,3	315,4 ± 293,9	0,110‡
p	0,034†*	0,053†	
Delta	-245,4 ± 430,7	39,5 ± 218,19	0,006‡*

Note: * Significant ($p < 0,05$); ‡ Mann Whitney; † Wilcoxon

**Figure 2.** Graphic of NT-proBNP levels mean in both study groups.

the amount and activity of antioxidant agents such as beta-carotene, vitamin C, glutathione reductase, and uric acid.¹⁵ Therefore, the presence of an antioxidant effect in honey may help to protect against ROS-induced cardiac injury, thereby limiting the leakage of enzymes from the myocardium.

This study showed a significant difference between the levels of NT-proBNP in the control group and the treatment group. There was a significant improvement in the levels of NT-proBNP in the treatment group. However, in the control group, there was an increase in the levels of NT-proBNP. Decreased levels of NT-proBNP in the treatment group indicated that honey administration could prevent cardiotoxic effects in patients receiving FAC chemotherapy.

Several studies have shown that N-terminal pro-brain natriuretic peptide (NT-proBNP) is released from the heart in response to volume expansion and increased wall pressure due to chemotherapy-induced cardiotoxicity.^{8,11,12} This hormone plays an important role in the maintenance of cardiovascular homeostasis, vasodilation, natriuresis, kaliuresis, inhibition of the renin-angiotensin-aldosterone system and

inhibition of the sympathetic pathway. NT-proBNP can be used as a useful biological marker in the diagnosis and prognosis of patients with heart failure.¹¹

Zidane *et al.* in his study reported that there was a significant increase in NT-proBNP levels in Hodgkin's lymphoma cancer patients treated with Doxorubicin. Not only NT-proBNP levels but also found a significant correlation between abnormal NT-proBNP levels and right ventricular peak myocardial velocities using tissue Doppler imaging. Patients with elevated NT-proBNP levels showed significantly lower systolic and diastolic rates in all segments of the right ventricular free wall, as well as myocardial velocity in the posterior left ventricular wall.³⁰ Thus, in this study, the effect of chemotherapy in patients given honey consumption showed a decrease in NT-proBNP levels which indicated that honey had a cardioprotective effect on patients.

Hossen *et al.*, in their research, revealed that polyphenol compounds in honey affect the progression of cardiovascular disease. Polyphenol compounds found in honey are quercetin, caffeic acid, kaempferol, and apigenin. The mechanisms of polyphenols in this cardioprotective effect include protection as antioxidants,

preventing platelet aggregation, lowering blood pressure, improving endothelial function, reducing inflammatory responses, reducing oxidative stress, increasing coronary artery vasodilation and reducing low-density lipoprotein (LDL) oxidation.³¹ Chemotherapy agents can cause inflammatory mechanisms in the heart through the ROS pathway. Apigenin compounds in honey polyphenols play an important role in the anti-inflammatory process through the mechanism of inhibiting the expression of cyclooxygenase-2 (COX-2) induced lipopolysaccharide (LPS); nitric oxide (NO) suppression; macrophage production; and suppression of TNF-induced by vascular cellular adhesion molecule-1 (VCAM-1), intracellular adhesion molecule-1 (ICAM-1) and E-selectin mRNA to the basal level.³² The current study is heavily influenced by the increasing conditions of COVID-19 cases in the current study area, thus affecting the number of a patient visiting the hospital, a limited number of chemotherapy patients in a day, and causing samples that enter the exclusion criteria due to being confirmed by COVID-19 so that they experience a change in chemotherapy schedule. The possibility of myocarditis due to COVID-19 cannot be ruled out, but all samples did not experience signs and symptoms of COVID-19 even though an antigen swab was not performed.

CONCLUSION

Thus, the administration of multiflora honey can prevent cardiotoxic effects in breast cancer patients receiving FAC chemotherapy. These results are evidenced by the lower levels of Troponin I in BREAST cancer patients after receiving multiflora honey compared to those without honey administration and a significantly lower level of NT-proBNP in breast cancer patients after receiving honey compared to those without multiflora honey administration.

ETHICAL CLEARANCE

This research has been ethically approved by Health Research Ethic Committee RSUP DR. Kariadi Semarang No 658/EC/KEPK-RSDK/2020. It is declared to be

ethically appropriate in accordance with 7 (seven) WHO 2011 standards: 1) Social Values, 2) Scientific Values, 3) Equitable Assessment and Benefits, 4) Risks, 5) Persuasion/Exploration, 6) Confidentiality And Privacy, and 7) Informed Consent, referring to the CIOMS Guidelines. This is indicated by the fulfillment of the indicator of its standard.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest working on this research.

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AUTHOR CONTRIBUTION

SS conceived the research, collected all the samples, analyzed and interpreted the data, and wrote the first manuscript. SB and SN gave systematic suggestions throughout this research according to their expertise. All authors critically revised and approved the final manuscript.

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