DOI Number: 10.37506/v11/i1/2020/ijphrd/193957

Effectiveness of Dorsata Honey Suplement on Interleukin-3 Levels in Breast Cancer Patients Who Underwent Chemotherapy

Aji Kurniawan[1], Daniel Sampepajung[1], Salman Ardy Syamsu[1], Prihantono Prihantono[1]

[1]*Department of Surgery, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia*

Abstract

Chemotherapy causes debilitating side effects include a decrease in blood cell counts. Interleukin-3 (IL-3) is a hematopoietic growth factor with extensive and multipotent activity. Honey is a natural product that has been widely used and researched for its therapeutic effects including increase the formation of blood cells. The purpose of this study was to determine the effect of honey supplement to IL-3 levels in breast cancer patients who underwent chemotherapy. The study sample included all populations diagnosed with breast cancer by the clinician in the Surgical Oncology Department of Dr. Wahidin Sudirohusodo Hospital Makassar who met the criteria for the period September to November 2018, divided into two groups, intervention and control. The intervention group was given honey orally three times a day at a dose of 15 ml (2 tablespoons) for 15 days. Examination of blood samples to measure IL-3 levels through ELISA. The statistical analysis performed is descriptive statistic calculation, frequency distribution and Chi Square statistical test, Independent-t and Paired-t test, with $P < 0.05$. The results of this study showed a significant increase in mean IL-3 levels in the group that received honey which was 70.07 pg/dL compared to 143.46 pg/dL with an average increase of 73.4 pg/dL (104.7%; $p < 0.05$), while the group that did not get honey did not experience a statistically significant change of 88.88 pg/dL compared to 84.36 pg/dL, the mean decrease was 4.52 pg/dL (5.1%; $p > 0.05$). Conclusion: Honey supplementation increases IL-3 levels in breast cancer patients underwent chemotherapy.

Keywords: *Breast Cancer, Chemotherapy, Interleukin-3, dorsata, honey.*

Introduction

Breast cancer is the most malignancy in women and affects the lives of one in 10 women. Breast cancer is the leading cause of death in women worldwide, representing 38 million (23%) of total new cancer cases and 458,400 (14%) of total cancer deaths in 2008.[1] In 2015 an estimated 231,840 new breast cancer cases were found in women and 40,730 deaths due to breast cancer occurring in the United States. [2]

Breast cancer therapy requires multiple therapeutic modalities, each of which has its own advantages and disadvantages. Some of them are surgery, chemotherapy, radiotherapy, hormonal therapy and molecular therapeutic targeting. As one of the modalities in the treatment of breast cancer, chemotherapy still has a major role in the treatment of patients with breast cancer. Widely used as adjuvant therapy after patients undergo surgical removal of tumors for healing or preventing recurrence and as palliative therapy in patients with metastatic disease. Chemotherapy causes a wide range of effects that cause symptoms that weaken and greatly affect the quality of life of patients. Nausea, vomiting, hair loss and a decrease in the number of blood cells are the most frequent acute side effects. Decreasing the number of blood cells can be a decrease in the number of erythrocyte cells (anemia), platelets (thrombocytopenia) and white blood cells (leukopenia). In chemotherapy, neutropenia associated with chemotherapy doses is at risk for infection. Thrombocytopenia is another problem with the toxicity of chemotherapy which can lead to delayed chemotherapy, reduction in dosage and requiring platelet transfusion

Interleukin-3 (IL-3) is a hematopoietic growth factor with clear thrombopoietic activity and extensive

and multipotent activity. IL-3 is a glycoprotein which is produced mainly by activated T cells. IL-3 regulates the proliferation and differentiation of pluripotent stem cells and progenitor cells from various hematopoietic lineages, including megakaryocytes, granulocytes, and erythrocytes. IL-3 also stimulates the function of several adult cells, including neutophils, eosinophils and monocytes. Available for clinical trials since 1993, IL-3 has been used by more than two thousand patients. From the research data so far it has been shown that IL-3 alone or in combination with other cytokines has become the first thrombopoietic factor available for clinical use which allows patients to undergo chemotherapy at intervals and doses according to standards that are expected to increase recovery rates. Recombinant human (rh) IL-3 has been evaluated in patients undergoing cancer chemotherapy, after bone marrow transplantation, bone marrow failure, for blood mobilization and hematopoietic progenitor cell transplantation and in combination with other Colony-stimulating factors (CSF) including Granulocyte -macrophage (GM) -CSF and granulocyte (G) -CSF. Results from stage I-II studies indicate that IL-3 alone or in combination with G- or GM-CSF can reduce or eliminate the duration and severity of thrombopenia and reduce neutropenia. [3]

Honey is a natural product that has been widely used for its therapeutic effects. It has been reported that honey contains more than 200 substrates. Its main composition is glucose and fructose but also contains fructo-oligosaccharides and many amino acids, mineral vitamins and enzymes. The composition of honey varies depending on the plant's nectar source. But almost all honey contains flavanoids (such as apigenin, pinocembrin, kaemferol, quercetin, galangin, chrysin and hesperin), phenolic acids (such as ellagic, caffeic, p-coumaric and ferulic acid), ascorbic acid, tocopherols, catalase (CAT), superocside dismutase (SOD), reduced glutathione (GSH), Milard reaction products and peptides. Most of these components work together to provide a synergistic antioxidant effect. Honey has long been used in health, both as a supplement and in medicine. Because of its potential, research on honey has begun to be carried out.[4] Flavanoids and polyphenols are the two main bioactive molecules present in honey. According to modern scientific literature, honey has a protective effect for therapy in various conditions such as diabetes, respiratory, gastrointestinal, cardiovascular and nervous systems, even useful in cancer therapy. Honey should be considered a natural therapeutic agent for disease conditions and therefore the use of honey in clinical care is highly recommended.[5] Some studies have mentioned the effects of honey as an antioxidant, natural antimicrobial, immune booster, anti-inflammatory, potentially in cancer therapy and can increase the formation of blood cells. From studies it has been found that there is an increase in CD4, CD8, erythrocytes, leukocytes, platelets, neutrophil counts and lymphocytes after 30 days of honey intake.[6] This is important because CD4, CD8 and lymphocytes are the main sources of IL-3. From other studies honey is also effective in reducing the incidence of anemia in 64% of patients and decreases the incidence of severe neutropenia, although 40% of patients still need CSFs.[7]

From the above, it is necessary to study the effects of honey on the levels of Interleukin-3 breast cancer patients who are undergoing chemotherapy because Interleukin-3 greatly affects the process of hematopoiesis, especially in breast cancer patients who underwent chemotherapy with the potential for interference. The purpose of this study was to determine the effect of giving honey to IL-3 levels in breast cancer patients who underwent chemotherapy

Materials and Method

Collection of Samples: This study was a experimental study using the pretest-posttest group control model, the experimental effects were measured before and after treatment. The study sample was the population of breast cancer patients, diagnosed by the clinician in the Surgical Oncology Department of RSUP Dr. Wahidin Sudirohusodo Makassar, from September to November 2018.

Inclusion criteria: Adult women diagnosed with locally advanced breast cancer by the clinician in the Surgical Oncology Departement and confirmed by histopathological examination, had never received breast cancer therapy, were willing to take part in the study by signing an informed consent.

Exclusion criteria: Lipemic, jaundice or hemolysis specimens, patients detected with other primary malignancies.

The study began with random sample selection for the control group and intervention group. Each informed consent was given, for the treatment group, dorsata honey was given orally three times a day (morning/ afternoon/night) at a dose of 15 ml (2 tablespoons) for

15 days. And for the control group recommends patients to take vitamin supplements and nutritious foods. Blood sampling as inspection is done twice, before the start of the intervention (day 0 chemotherapy), and then continued the examination of 2nd samples on day 16th (post chemotherapy). Interleukin-3 levels were measured from blood plasma samples and measured by ELISA.

Data Analysis: All collected data are grouped according to the purpose and type of data, then analyzed using SPSS version 22. The statistical analysis performed is descriptive statistic calculation, frequency distribution and Chi Square statistical test, Independent-t and Paired-t test, with P <0.05.

Ethical Clearance: Ethical approval for this study was obtained from the Research Ethics Committee, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia. Number; 732/H4.8.4.5.31/ PP36-KOMETIK/2018.

Results

Sample Characteristics: The samples analyzed were 30 breast cancer patients, consisting of groups who received honey supplements (intervention) and groups that did not get honey supplements (controls), each of them 15 people. The age of subjects was 23-61 years with a mean of 47.3 ± 7.5 years (median 47 years). The results of IL-3 measurements before chemotherapy varied between 11.78-350.00 pg/dL with a mean of 79.47 ± 70.70 pg/dL (median 63.6), whereas after chemotherapy had a value between 35.64-350.00 with an average of 113.91 ± 87.54 pg/dL showed in Table 1.

Table 1. Age and IL-3 Descriptive Statistics (n = 30)

Variable	Min (pg/dL)	Max (pg/dL)	Median	Mean	SD
Age	23	61	47,00	47,30	7,51
IL-3 Before Chemotherapy	11,78	350,00	63,60	79,47	70,70
IL-3 After Chemotherapy	35,64	350,00	82,83	113,91	87,54

The distribution of samples based on chemotherapy regimens, histopathology grading and stadium showed that most subjects received TAC (docetaxel, adriamicin, cyclophosphamide) chemotherapy (76.7%), grade moderate (83.3%) and stage III B (73, 3%) showed in Table 2.

Table 2. Distribution of Chemotherapy Regiment, Histopathological Results, Grading and Stage of Carcinoma Mammae

Variable		n	%
Chemotherapy Regiment	TAC (Docetaxel, Adriamycin, Cyclophosphamide)	23	76,7
	CAF (Cyclophosphamide, Adriamycin, Fluorouracil)	7	23,3
Grade	Low	1	3,3
	Moderate	25	83,3
	High	4	13,3
Stadium	III A	2	6,7
	III B	22	73,3
	III C	6	20,0

Comparative Analysis of IL-3 Levels by Group: The mean IL-3 level before chemotherapy was found to be higher in the control group than in the intervention group, which was 88.88 pg/dL compared with 70.07 pg/dL, although it was not statistically significant (p> 0.05). showed in table 3.

Table 3. Distribution of Chemotherapy Regiment, Histopathological Results, Grading and Stage of Carcinoma Mammae

Variable	Group	N	Mean	SD	P
IL-3 Before Chemotherapy	Intervention Control	15 15	70.07 88.88	69.45 73.08	0.476
IL-3 After Chemotherapy	Intervention Control	15 15	143.46 84.36	112.20 37.61	0.070

The mean IL-3 levels after chemotherapy were found to be higher in the intervention group than in the control group, namely 143.46 pg/dL compared to 84.36 pg/dL, although it was not statistically significant ($p > 0.05$). showed in table 3.

In the intervention group, there was a significant increase in IL-3 levels after chemotherapy compared to before chemotherapy, which was 143.46 pg/dL compared to 70.07 pg/dL ($p <0.05$). The mean increase in IL-3 after chemotherapy was 73.4 pg/dL or increased by 104.7%. showed in table 4.

Table 4. Comparison of IL-3 levels before and after chemotherapy

Group	Variable	N	Mean	SD	P
Intervention	IL-3 Before Chemotherapy IL-3 After Chemotherapy	15 15	70.07 143.46	69.45 112.20	0.01
Control	IL-3 Before Chemotherapy IL-3 After Chemotherapy	15 15	88.88 84.36	73.08 37.61	0.84

In the control group, there was a decrease in IL-3 levels after chemotherapy compared to before chemotherapy, namely 84.36 pg/dL compared to 88.88 pg/dL, but not statistically significant ($p> 0.05$). The mean reduction in IL-3 after chemotherapy was 4.52 or decreased 5.1%. showed in table 4.

Discussion

In this study, there were 30 samples of breast cancer patients where 15 were given treatment and 15 were controls. The age of subjects was 23-61 years with a mean of 47.3 ± 7.5 years (median 47 years). From this study, the average age of respondents was 47 years. This is in line with the journal presented by Irwan in 2014 which stated that the incidence of breast cancer was more in patients over the age of 40 years. The Partini study in 2016 showed the same pattern.[8]

Based on grade, the highest was moderate grade (83.3%). This is in line with the intensive study in 2010 where it was stated that moderate grade was the most common tumor grading. Research data by Irwan also showed the same thing.[7,8]

Stage III B (73.3%) is the most common stadium found in this study. Partini in 2016 stated that the most stadiums were stage III B. So this study had stadium distribution conformity with the research.[10]

The mean IL-3 level before chemotherapy was found to be higher in the control group than in the intervention group, which was 88.88 pg/dL compared with 70.07 pg/dL, although it was not statistically significant ($p> 0.05$). This shows that although the average IL-3 level before chemotherapy in the control state is higher than the intervention group does not have a statistical effect.

The mean IL-3 levels after chemotherapy were found to be higher in the intervention group than in the control group, namely 143.46 pg/dL compared with 84.36 pg/dL, although it was not statistically significant ($p> 0.05$). This shows that although the rate of IL-3 levels after chemotherapy in the intervention group was higher than the control group did not have statistical effect. When viewed from changes in IL-3 levels between before and after chemotherapy, in the control group there was a decrease in the mean IL-3 levels in the control group 84.36 pg/dL compared to 88.88 pg/

dL, but not statistically significant (p> 0.05). The mean reduction in IL-3 after chemotherapy was 4.52 pg/dL or decreased 5.1%.

According to Verma et al .'s study, it was said that T lymphocyte levels, B lymphocytes and NK cells decreased significantly within 2 weeks after chemotherapy even especially B cells and CD4 T cells remained significantly decreased in 9 months post chemotherapy. [11] In another study, Mackall said that although the number of neutrophils, monocytes and platelets consistently improved due to therapy at the end of each cycle, the number of lymphocytes did not improve in the same period of time. Because CD4, CD8 and lymphocytes are the main sources of IL-3, of course this affects the IL-3 levels.[12]

Whereas in the intervention group there was an increase in the mean IL-3 level of 143.46 pg/dL compared to 70.07 pg/dL (p <0.05). The mean increase in IL-3 after chemotherapy was 73.4 pg/dL or increased by 104.7%. Honey supplementation according to Heidari in his research led to an increase in CD4, CD8, erythrocytes, leukocytes, platelets, neutrophil counts and lymphocytes after 30 days of honey intake. [6] In addition, Porcza in a review of his study said that consumption of honey 1.2 g/kg body weight dissolved in 250 cc of water could produce a 50% increase in the number of peripheral monocytes and slightly increase the presentation of lymphocytes and eosinophils. [13] This increase in cells can increase IL-3 levels according to this study. Even honey supplements are also given to reduce the incidence of anemia in 64% of patients and reduce the incidence of severe neutropenia in chemotherapy patients whose treatment is by giving CSFs including human IL-3, although 40% of patients still need CSFs.[7]

Conclusion

The result of this study shows that honey supplementation increases IL-3 levels in breast cancer patients underwent chemotherapy. Suggested to for honey supplements in breast cancer patients undergoing chemotherapy so that the patient's IL-3 levels are maintained.

Acknowledgments: We give our gratitude to Hasanuddin University Hospital staff and also for breast cancer patients who supported and participated in this research.

Funding: Self Funding

Conflicts of Interest: The authors had no conflicts of interest to declare.

References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA: A Cancer Journal for Clinicians [Internet]. 2011 [cited 2018Jan7];61(2):69–90. Available from: http://www.cancer.org
2. Harvey J, Down S, Bright-Thomas R, Winstanley J, Bishop H. Breast cancer—facts and figures. Breast Disease Management [Internet]. 2013 [cited 2017Aug18];:34–40. Available from: http://www.cancer.org
3. Gianella-borradori A. Present and future clinical relevance of interleukin 3. Stem Cells. 1994;12(S1):241–8.
4. Eteraf-Oskouei T, Najafi M. Traditional and Modern Uses of Natural Honey in Human Diseases: A Review. Iranian Journal of Basic Medical Sciences. 2013;16(6):731–42.
5. Samarghandian S, Farkhondeh T, Samini F. Honey and Health: A Review of Recent Clinical Research. Pharmacognosy research. 2017;9(2):121–7.
6. Heidari A, Heidari N, Amiri G, Afsahi S, Sarahroodi S. Has The Natural Raw Honey Any Effect on HIV Infection? International Journal of Pharmaceutical Research and Bio-Science. 1(5):205–10.
7. Zidan J, Shetver L, Gershuny A, Abzah A, Tamam S, Stein M, et al. Prevention of Chemotherapy-Induced Neutropenia by Special Honey Intake. Medical Oncology. 2006;23(4):549–52.
8. Irwan I, Azamris A, Bachtiar H. Perbandingan Prognosis Subtipe Molekuler Kanker Payudara Antara Pasien Kanker Payudara Wanita Usia Muda Dan Tua Di Rsup Dr. M. Djamil Padang. Majalah Kedokteran Andalas. 2016;38(4):208.
9. Albrektsen G, Heuch I, Thoresen SØ. Histological type and grade of breast cancer tumors by parity, age at birth, and time since birth: a register-based study in Norway. BMC Cancer. 2010;10(1).
10. Partini PDO, Niryana IW, Adiputra PAT. Karakteristik kanker payudara usia muda di Sub Bagian Bedah Onkologi Rumah Sakit Umum Pusat Sanglah tahun 2014-2016. Intisari Sains Medis. 2018;9(1):76–9.
11. Verma R, Foster RE, Horgan K, Mounsey K, Nixon H, Smalle N, et al. Lymphocyte depletion

and repopulation after chemotherapy for primary breast cancer. Breast Cancer Research. 2016;18(1).

12. Mackall CL, Fleisher TA, Brown MR, Magrath IT, Shad AT, Horowitz ME, et al. Lymphocyte Depletion During Treatment With Intensive Chemotherapy for Cancer. Blood jurnal [Internet]. 1994Oct1 [cited 2018Nov14];84(7):2221–8. Available from: http://www.bloodjurnal.org
13. Porcza L, Simms C, Chopra M. Honey and Cancer: Current Status and Future Directions. Diseases. 2016Sep30;4(4).