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The effect of Apis dorsata honey as complementary therapy on IL-37 levels and fatigue in breast cancer patients undergoing chemotherapy

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Abstract.
OBJECTIVE: The purpose of this study is to determine the effect of Apis dorsata Honey as a complementary therapy on IL-37 levels and fatigue in breast cancer patients undergoing chemotherapy.
METHOD: The study used a quasi-experimental pretest-posttest design with a control group. A total of 30 subjects were recruited using a concurrent sampling technique. The intervention group consisted of 15 subjects who received oral honey at a dose of 13 ml (1 tablespoon × 3) for 15 days, and the control group consisted of 15 subjects. The groups' samples were chosen at random. The Fatigue Symptom Inventory (FSI) was used to assess the side effects of chemotherapy.
RESULTS: Although the effect of Apis dorsata Honey on IL-37 levels was not statistically significant ($p > 0.05$), the group given honey experienced a clinically significant increase in IL-37 levels, with a mean before (632.37514.93) and post (632.37514.93). (1,003.021,248.88). Fatigue decreased statistically significantly in the group given mean honey values prior to 13.205.59 and after 11.805.07 ($p = 0.004$).
CONCLUSION: Honey administration increases IL-37 levels clinically, though the increase is not statistically significant. Giving honey to patients with breast cancer can help alleviate fatigue caused by chemotherapy.

Keywords: Honey, IL-37, breast cancer, chemotherapy, side effects

1. Introduction

Breast cancer has been the most well-known cancer, particularly for women, throughout the world, both in developed and developing countries. Two-point one million new breast cancer cases were diagnosed in 2018 [1]. Early detections might reduce cancer deaths [2]. However, a study in Poland mentioned the fear of being diagnosed as a cause of late diagnosis of breast cancer [3], resulting in many deaths. Predictions of deaths from breast cancer throughout the world recorded more than 508,000 women in 2011 [4]. It occupies the fifth rank of death in 2015 [5]. It becomes the second cause of death worldwide after lung cancer, with 11.6% of people in 2018 [1]. For women, breast cancer cases rank the first as the cause of death [1]. In Indonesia, breast cancer also ranks first for the largest population (30.9%), new cases of cancer (16.7%), and the second leading cause of death (11.0%) after heart cancer [6].

The high incidence of breast cancer causes people to look for alternative treatments in complementary therapies for treatment. Honey is known as one of the complementary therapeutic ingredients that inhibits

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cancer development [7]. Honey is known to have anticancer effects through several cell-signaling pathways, such as encouraging apoptosis, antioxidants, antiproliferative pathways, and modulating the immune system [8]. The molecules found in honey, such as flavonoids and phenolics, are reported to block the G0/G1 phase [9]. Besides, honey has a higher phenolic and more robust tryptophan content which can inhibit cancer cell proliferation [10]. Some proteins in honey stimulate macrophages to release cytokines, such as TNF-α, IL-1β, and IL-6 [7]. IL-1 has a derivative, namely IL-37, known to have an antitumor effect [11]. This study aims to examine the impact of Honey on IL-37 levels in breast cancer cases.

In addition to efforts to inhibit the development of breast cancer through the body's defense mechanisms, chemotherapy is one of the main treatments for breast cancer (the other main treatments are surgery and radiation). Chemotherapy has a beneficial effect on the prognosis of breast cancer. On the other hand, it is feared that it can cause side effects [12]. A study on the side effects of chemotherapy revealed that most breast cancer patients experience hair loss, chapped lips/dry mouth, vomiting, loss of appetite, and fatigue [13]. Patients who experience fatigue reported stress, anxiety, depression, pain, significant sleep disturbance, and lower quality of life [14]. A study reported that honey administration could reduce Cancer-related fatigue (CRF) [15]. Therefore, this study aims to examine the effect of honey on fatigue, which is a side effect of chemotherapy in breast cancer patients.

2. Method

This quasi-experimental research employed the pretest-posttest control group design model in which the effects of experiments are measured before and after treatment. The honey does not go through a chemical process, but the honey is only deposited in a dark room for 72 hours so that the impurities can settle and get the honey in clean conditions.

The sampling technique used consecutive sampling techniques, subjects for the groups were selected randomly. The location of the study was at the Dr. Wahidin Sudirohusodo Hospital oncology surgery room. The place for examining samples to measure IL-37 levels is carried out at the Hasanuddin University laboratory. The 30 subjects were divided into two groups; 15 subjects for the intervention group were given honey orally for 15 days with a dose of 13 ml (1 tablespoon × 3), and 15 subjects were in the control group.

The inclusion criteria were breast cancer patients undergoing second cycle chemotherapy without complications of heart, kidney, and diabetes mellitus. Demographic data were obtained through direct observations. Routine blood examination data were obtained from the participant's medical records, and the side effects of chemotherapy were measured by the Fatigue Symptom Inventory (FSI) instrument. This study received an Ethics license No. 596/H4.8.4.5.31/PP36-KOMETIK/2017.

Table 1
Demographic characteristics of breast cancer patients with chemotherapy at Dr. Wahidin Sudirohusodo central general hospital Makassar

Variable	Intervention group *n* (%)	Control group *n* (%)
Age (year) (mean ± SD)	46.18 ± 10.24	47.6 ± 8.08
Min-max	32–68	35–64
Education		
Elementary school	3 (17.65)	3 (20)
Middle school	4 (23.53)	6 (40)
High school	7 (41.18)	6 (40)
College	3 (17.65)	0 (0)
Duration (Year) (mean ± SD)	1.24 ± 0.4	1.2 ± 0.4
Min–Max	1–6	1–6
1–3 year	13	12
4–6 year	4	3
Marital status		
Mate	12 (80.0)	14 (93.3)
Divorce	1 (6.67)	0 (0.0)
Single	2 (13.3)	1 (6.67)

3. Results

This research was conducted from July to November 2018 at the Outpatient Installation of Dr. Wahidin Sudirohusodo Central General Hospital. The average age of the subjects was 46 years in the intervention group and 47 years in the control group; most of them graduated from high school (41.2%) in the intervention group and (40%) in the control group. They are mostly married. They had an average breast cancer duration of 1.24 years, and they had had cancer for 1–3 years (Table 1).

Routine blood tests on breast cancer patients undergoing chemotherapy reveal that values were classified as abnormal in accordance with the reference, namely a

Table 2
Routine blood frequency distribution for breast cancer patients with chemotherapy at Dr. Wahidin Sudirohusodo central general hospital Makassar

	Mean (±SD)	Reference value	Unit
WBC	7.71 (±5.406)	4.00–10.0	10^3/µl
RBC	3.99 (±0.515)	4.00–6.00	10^6/µL
HGB	11.18 (±1.098)	12.0–16.0	gr/dl
HCT	34.96 (±3.491)	37.0–48.0	%
MCV	87.96 (±6.077)	80.0–97.0	fL
MCH	28.21 (±2.347)	26.5–33.5	pg
MCHC	41.96 (±52.738)	31.5–35.0	gr/dl
PLT	346.43 (±130.183)	150–400	10^3/µl
RDW_CV	15.54 (±2.687)	10.0–15.0	
PDW	9.79 (±1.280)	10.0–18.0	fL
MPV	9.35 (±0.648)	6.50–11.0	fL
PCT	0.34 (±1.292)	0.15–0.50	%
NUET	49.5 (±17.840)	52.0–75.0	%
LYMPH	31.82 (±11.008)	20.0–40.0	%
MONO	15.04 (±8.953)	2.00–8.00	10^3/µl
EO	3.08 (±3.449)	1.00–3.00	10^3/µl
BASO	0.73 (±0.319)	0.00–0.10	10^3/µl

Table 3
Frequency distribution of general complaints of breast cancer sufferers with chemotherapy at Dr. Wahidin Sudirohusodo Central General Hospital Makassar (n = 30)

General complaints	n	%
Itchy	1	3.1
Hair loss	13	40.6
Vomiting and hair loss	1	3.1
Nausea, itching	1	3.1
Nausea decreased appetite	1	3.1
Nausea and hair loss	6	18.8
Hair loss and decreased appetite	5	15.6
Itching, Fever, Decreased appetite	1	3.1
Vomiting, hair loss, appetite down	1	3.1
Total	30	100.0

decrease in the average value of RBCs (3.9957) 106/µL, mean Hb levels (11.186) gr/dl, and hematocrit (34.96) percent, and an increase in monocyte levels (15.043) 103/µl (Table 2).

Observations related to complaints of clinical symptoms felt by breast cancer patients undergoing chemotherapy indicate that they mostly experienced hair loss (40.6%) (Table 3).

IL-37 concentrations increased in both the intervention and control groups, with the mean pre (632.37 514.93) and post (1,003.02 1,248.88) in the intervention group, and the mean pre (368.25 233.50) and post (942.03 1,431.50) in the control group, but the increase was less in the intervention group. Although not statistically significant in either group, p = 0.266 (p > 0.005) for the intervention group and p = 0.221 (p > 0.005) for the control group (Table 4).

Table 4
Analysis of the effectiveness of the administration of honey to levels of interleukin 37 in the intervention group and the control group (n = 25)

		Concentration Mean (±SD)	p-value
Intervention	Pre	632.37 (±514.93)	0.266*
	Post	1,003.02 (±1,248.88)	
Control	Pre	368.25 (±233.50)	0.221*
	Post	942.03 (±1,431.50)	
		p-value	0.914**

Clinically and statistically, in assessing the effects of chemotherapy in the form of fatigue, there were significant differences before and after honey administration. The mean before the administration was 13.20 pg/dl, and the mean after the administration was 11.80 pg/dl with a significance value of 0.004 (p < 0.05). The level of fatigue in patients with breast cancer. Whereas in the control group there was no statistical difference p = 0.468 (p > 0.005) (Table 5).

4. Discussion

Research on the effects of honey as a complementary therapy in breast cancer patients has been widely done in animal and human trials. Research on the effect of honey on breast cancer in 7,12-dimethylbenz (α) anthracene (DMBA)-induced mice show much slower tumor development, smaller size, and fewer tumor counts in rats treated with honey than in rats without treatment/control [16]. Honey acts as an estrogen antagonist, inhibiting cell proliferation, inducing apoptosis and decreasing the mitochondrial membrane potential in breast cancer cells (MCF-7) & MB-231 MDA-MB-231 [17,18]. Honey possesses anticancer properties, as evidenced by its anti-estrogen activity and ability to induce mitochondrial membrane depolarization and apoptosis in breast cancer cells. Additionally, honey's antiproliferative and antimetastatic properties are demonstrated by its ability to inhibit tumorigenesis and reduce the size and number of tumors in mice with DMBA-induced breast cancer [19]. Honey

Table 5
Analysis of the effectiveness of the administration of honey to the side effects of chemotherapy in the intervention and control groups

		Fatigue level Mean (±SD)	*p*-value
Intervention	Pre	13.20 (±5.59)	0.004*
	Post	11.80 (±5.07)	
Control	Pre	10.00 (±2.16)	0.468*
	Post	10.30 (±1.76)	
		p-value	0.381**

It is also been shown to be cytotoxic to human breast cancer cells MCF-7 and MDA-MB-231 but not to normal breast cells (MCF-10A) [17]. This proves that honey only works as a cytotoxic in breast cancer cells and may not be owned by other treatments such as chemotherapy.

This study evaluates the effect of giving Honey on Il-37 levels in breast cancer patients. Certain proteins in honey can induce macrophages to release pro-inflammatory cytokines such as TNF-α, IL-1, and IL-6 [7]. Honey may exert anti-inflammatory effects via two inflammatory pathways that are frequently activated in cancer, namely the mitogen-activated protein kinase (MAPK) and the nuclear factor kappa B (NF-kB) pathways. MAPK activation and/or NF-kB activation result in the production of several pro-inflammatory proteins and genes, including cyclooxygenase-2 (COX-2), reactive protein C (CRP), lipoxygenase-2 (LOX-2), and pro-inflammatory mediators or cytokines such as interleukin 1 (IL-1), IL-6, and TNF–α [19]. Il37 is an Il-1 derivative with antitumor activity, and its receptors may serve as novel targets for the study, diagnosis, and treatment of immune-related diseases and tumors [11]. Il-37 exists in five distinct isoforms, each of which functions as an immunosuppressive factor capable of suppressing excessive immune responses [11]. IL-37 plays a role in inhibiting cancer development in cases of colon cancer and serves as a new prognostic indicator and potential therapeutic target [20]. So, we assume that if the protein in honey can stimulate the release of IL-37, where IL-37 can inhibit the development of colon cancer which may be the same thing in the case of breast cancer.

In assessing the effects of chemotherapy in the form of fatigue using the FSI instrument, it was found that the administration of honey for two weeks can reduce fatigue in breast cancer. This finding is in line with other studies that report significant decreases in fatigue severity scale (FSS) and visual analog fatigue scale (VPSS) after two weeks of intervention with honey with royal jelly and decreases after four weeks. In addition, the comparison of the severity scale of basal fatigue with the scale measured at 2 and 4 weeks after the intervention showed that subjects in the intervention group had lower fatigue scores, and this difference was more pronounced after the fourth week of the intervention [15]. The above recommendations can reduce the use of antidepressants which may be more detrimental to cancer prognosis.

5. Limitation

Supervision of drinking honey is done indirectly via telephone, and it is difficult to control the subject's food.

6. Conclusion

Clinically, honey therapy increases IL-37 levels. Honey can help patients with breast cancer who are experiencing fatigue as a side effect of chemotherapy.

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Conflicts of interest

None.

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