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Impact of *Jollab* on Blood Parameters in Patients with Breast Cancer Undergoing Chemotherapy: A Pilot Randomized Controlled Trial

Bahareh Ahadi [1,2], Mehdi Pasalar [3], Hamid Reza Mirzaei [4], Reyhaneh Gharehgozlou [4], Ali Tavakoli [3], Ghazaleh Heydarirad [2,5]✉

[1] School of Medicine, Semnan University of Medical Sciences, Semnan, Iran
[2] Department of Traditional Medicine, School of Traditional Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[3] Research Center for Traditional Medicine and History of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran
[4] Cancer Research Center, Shohadae Tajrish Hospital, Department of Radiation Oncology, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[5] Traditional Medicine and Materia Medica Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Abstract

Background: In cancer patients, a prominent side effect of chemotherapy drugs is bone marrow suppression, which leads to decreased blood cell production. Herbal remedies and natural substances such as honey may fulfill a role in relieving this complication. The present study aimed to determine the efficiency of *Jollab* (a honey-based syrup) in the prevention of pancytopenia in female patients with breast cancer undergoing chemotherapy. **Materials and Methods:** In a pilot double-blinded, randomized, placebo-controlled clinical trial, 70 patients were examined in terms of leukocyte count, platelet count, and hemoglobin level at the Shohaday-e Tajrish Cancer Clinic (Tehran, Iran) in 2020. The intervention group consumed 10 ml of *Jollab* syrup three times a day for four weeks, while the control group took a placebo with the same prescription. The independent sample t-test and chi-squared test were used for data analysis in this trial. **Results:** Our data revealed that the total number of leukocytes, hemoglobin levels, and platelet counts have no significant differences between the two groups at the end of the study, but significant changes were discovered for hemoglobin and platelet levels in intragroup analysis for both intervention and placebo groups. **Conclusion:** Although the use of *Jollab* was not found to be effective in augmenting the levels of blood cell parameters in women with breast cancer undergoing chemotherapy, future studies of higher quality may demonstrate its supportive role provided the present limitations are addressed. **[GMJ.2021;10:e1972]** **DOI:10.31661/gmj.v10i0.1972**

Keywords: *Jollab*; Breast Cancer; Chemotherapy; Honey; Bone Marrow Suppression; Persian Medicine

Introduction

Among cancer patients, bone marrow suppression represents one of chemotherapy's most common side effects, leading to pancytopenia [1]. This adverse effect is dependent on the severity and protocol of chemotherapy and can potentially be life-threat-

✉ **Correspondence to:**
Ghazaleh Heydarirad, School of Traditional Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
Telephone Number: +982188776027
Email Address: ghazalrad@yahoo.com

ening [2]. Honey is chiefly composed of sugar and water but contains a diverse range of vitamins, minerals, enzymes, and organic compounds [3]. Limited studies have elucidated the positive impact of honey on the prevention of febrile neutropenia (FN) in both children and adults [2, 4], though no effects on red blood cell (RBC) and platelet levels have been discovered among adults. The medicinal effects of honey depend to some extent on the plants from which the bee derives its pollen [2]. Therefore, the preparation of honey samples with special therapeutic properties is of interest in complementary and alternative medicine [5]. In Persian medicine (PM), one of the most emphasized combinations of honey is *Jollab* syrup, composed of honey, rose water, and saffron. In studies on various diseases, some of the medicinal effects of *Jollab* have been confirmed [6, 7]. Considering the constituents of this syrup and the problem at hand concerning the adverse effects of chemotherapy drugs on cancer patients, including pancytopenia, investigations on any potential effects of *Jollab* in preventing these complications are vital. Prior studies cannot be relied upon as they include many limitations like the lack of control groups and a high level of differences between patients in parameters such as the primary site of cancer, lesion pathology, treatment history, gender, and ethnicity. The present study aimed to investigate the impact of *Jollab* syrup on the prevention of pancytopenia in female patients with breast cancer undergoing chemotherapy.

Materials and Methods

Study Design

This study took the form of a pilot two-arm, double-blinded, parallel-group, placebo-controlled, randomized clinical trial. Women with breast cancer referring to Shohaday-e Tajrish Cancer Clinic (Tehran, Iran) who were under chemotherapy were recruited from February to March 2020. In this study, a honey-based syrup (*Jollab*) was prepared according to the documented PM manuscripts as described in a previous study [8]. Informed consent was obtained from all participants prior to their enrollment. In order to blind the investigator, the medications were coded with "A" for *Jollab* and "B" for the placebo. A randomized block design was preferred in the trial using computer software (Research Randomizer (version 4, 2013, Social Psychology Network) by the research assistant. Block size of 5 and 7 blocks were done, one patient assigned to the intervention group and one patient to the placebo one (allocation ratio 1:1). The patients were unaware of the type of drug that they were given. Group A patients consumed 10 ml of *Jollab* syrup three times per day for four weeks, while group B patients received the same regimen of the placebo. Furthermore, the bottle of the placebo syrup was identical to that of the *Jollab* syrup in terms of color, size, and shape. The groups were entered into statistical analysis with codes "A" and "B". A research assistant who was not involved in the trial listed the codes. The trial was performed in compliance with the Declaration of Helsinki (2013 revision). The study was approved by the Shahid Beheshti University of Medical Sciences Ethics Committee and was registered in a valid primary database registry (ClinicalTrials.gov; NCT04426435).

Inclusion and Exclusion Criteria

The inclusion criteria included an age of between 18-70 years, a hemoglobin (Hb)level of at least 10 g/dl, a white blood cell (WBC) count of at least 5000/µl, a platelet count (PLC) of at least 100,000/µl, a hematocrit level of at least 30%, and a normal thyroid stimulating hormone level. The exclusion criteria included heart disease with an unstable condition, disabling pulmonary disease and/or history of asthma, severe kidney disease, a creatinine level greater than 2 mg/dl, proteinuria, a liver enzyme level above thrice the normal threshold, a bilirubin level greater than 2 mg/dl, a positive history of hypersensitivity to saffron, rose water, or honey, severe infection, systemic disease, a positive history of gout or high levels of uric acid, use of antidepressants due to depression, simultaneous use of drugs that stimulate blood production, and unwillingness to participate in the study.

Outcome

The primary outcomes were the changes in Hb level, total leukocyte count (TLC), and PLC. A complete blood count was obtained by run-

ning a blood sample before and after the intervention period on an automated cell counter (Sysmex XP-300™ Automated Hematology Analyzer). The results included RBC count, Hb level, TLC, and PLC. The secondary outcome was to assess the presence of any side effects. All the participants were requested to record any side effects in a diary, especially gastrointestinal problems and allergic reactions. They were followed-up by a physician every week to detect the drug's possible adverse effects.

Data Analysis

All data were described by the mean ± standard deviation (SD) or number (percentage). The independent sample t-test and chi-squared test were used for comparisons of the baseline characteristics. The independent sample t-test was also used to compare the changes in outcomes between the two groups. The paired t-test was applied to compare the intragroup changes at the beginning and the end of the trial. All the data were analyzed using Statistical Package for the Social Sciences (SPSS) software, version 15 (IBM SPSS, Chicago, IL, USA). It should be remarked that "intention-to-treat analysis" was chosen as the statistical method in the current study. P-values less than 0.05 were considered significant.

Results

Eighty-eight patients were evaluated for eligibility, 18 of whom were excluded for various reasons (Figure-1). Finally, 70 female patients with invasive ductal carcinoma were treated in the intervention or placebo groups. The patients' demographic characteristics are outlined in Table-1. The protocol for adjuvant therapy was the same for both groups. The main chemotherapy prescription was CEF (cyclophosphamide, epirubicin, 5-fluorouracil) in the intervention and placebo groups (n=30 vs. 28, respectively). In the intervention group, three patients received Vinorelbine

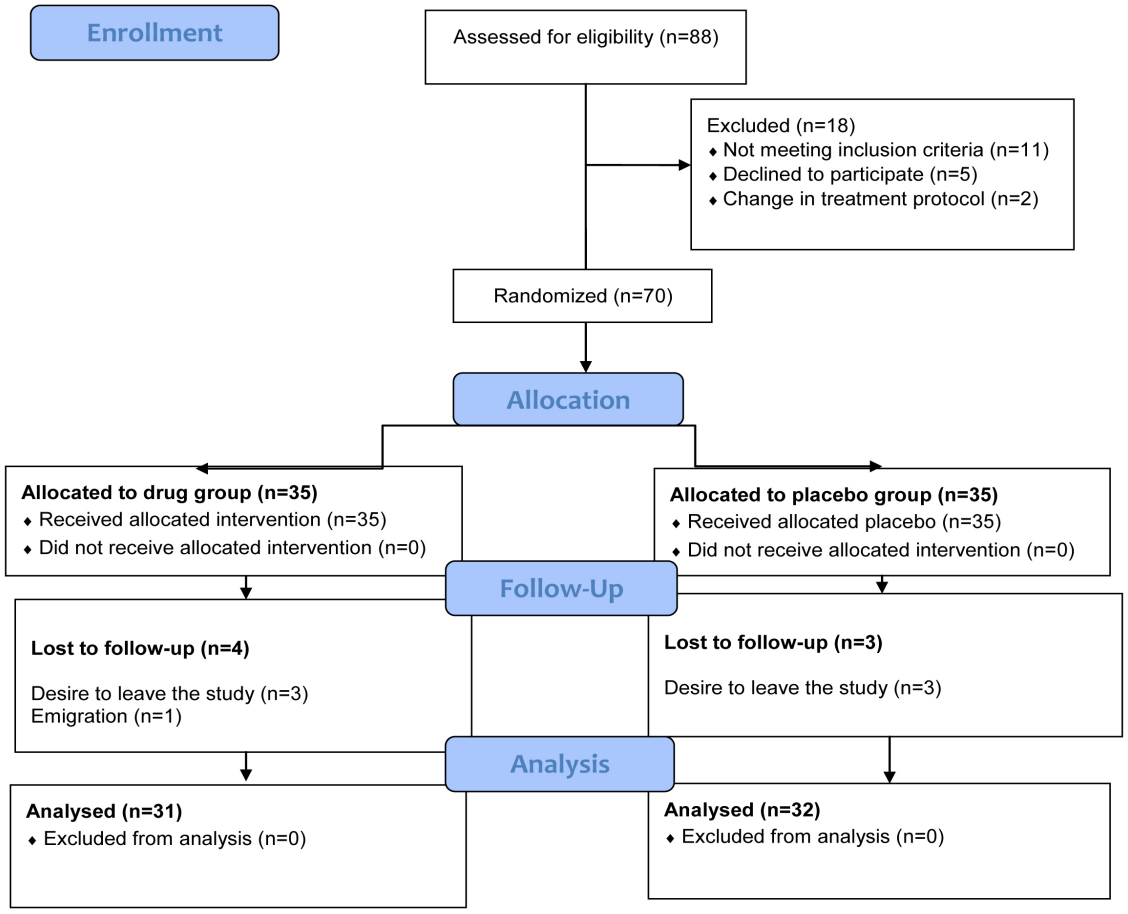

Figure 1. Flow diagram of the study.

(brand name: Navelbine) and two were given Taxol, whereas in the placebo group, four received the former and three received the latter (P=0.727). Intergroup analysis of patients for TLC, PLC, and Hb level in the intervention group did not show any statistically significant changes at the end of the trial compared to the placebo group (Table-2).

On the other hand, intragroup analysis of the intervention (P=0.166) and placebo (P=0.051) groups for TLC was also not statistically different. The mean PLC of the intervention (P=0.001) and placebo (P=0.04) groups and Hb level of the intervention (P=0.001) and placebo (P<0.001) groups, however, changed significantly throughout the study period.

Safety

The safety profile was also checked as a secondary endpoint. Although two patients in the intervention group complained of mild throat burning sensations, they did not accept to cease consuming their syrup as it was not bothering.

Discussion

The effectiveness of *Jollab*, a syrup containing honey, saffron, and sugar, in preventing the lowering of blood parameter levels (TLC, PLC, Hb) in women with breast cancer with chemotherapy was evaluated in the form of a pilot, double-blinded, randomized clinical trial with a placebo group. The results showed that *Jollab* had no effect on preventing pancytopenia in the intervention group compared with the placebo group over the intervention period, though intragroup analysis revealed that the Hb level and PLC underwent significant differences in each group. Specifically, the PLC followed an upward trend while the Hb level decreased. No severe or dangerous side effects were observed following the consumption of the PM syrup. The present study was similar to that of Abdulrhman *et al.*, which examined the effect of honey on FN in children in 2013 [4]. They discovered a lack of a remarkable rise in TLC at the end of the intervention, though there were signif-

Table 1. Demographic Characteristics of Female Patients with Breast Cancer

Variables	Intervention group n=35	Placebo group n=35	P-value
Age, y (Mean±SD)	49.03±9.13	50.67±9.44	0.961*
Ethnicity, n (%)	Fars 22 (62.9)	Fars 24 (68.6)	0.635**
	Lor 8 (22.9)	Lor 9 (25.7)	
	Turk 4 (11.4)	Turk 2 (5.7)	
	Kord 1 (2.8)	Kord 0 (0)	
Chemotherapy Rx, n (%)	CEF 30 (85.7)	CEF 28 (80.0)	0.727 **
	Navelbine 3 (8.6)	Navelbine 4 (11.4)	
	Taxol 2 (5.7)	Taxol 3 (8.6)	

* Independent Samples t-test

** Chi-square test

Table 2. Blood Parameter Levels before and after Treatment with Jollab. Data Were Presented as Mean±SD

Parameters	Intervention group		Placebo group		P-value*
	Before	After	Before	After	
Leucocyte count	11086±1153	7222±620	12042±704	7043±560	0.904
Hemoglobin level	11.6±1.1	10.9±0.8	11.9±1.2	11.1±1.1	0.409
Platelet count	224868±75195	279000±69545	246953±67533	275718±66287	0.849

* Independent Samples T-test (comparing the results after the trial)

icant differences in the study population, duration, disease type and gender between the treatment and control groups [4]. About 80% of honey is constituted by sugar, and the flavor, color, and taste of honey vary depending on the plants used by bees during production [9]. Perhaps one of the reasons for the ineffectiveness of honey in augmenting the TLC was the lack of the nectar being derived from a fixed plant during honey preparation in both the present work and in that of Abdulrahman *et al.* [4, 10]. Our results are comparable with the findings of Zidan *et al.* [2], who showed a positive effect of honey on the prevention of pancytopenia caused by chemotherapy in 30 cancer patients; we observed a significant increase in platelet numbers in both the intervention and placebo groups [2]. In line with the recent findings, the safety of honey was also confirmed in our research [11, 12].

To our knowledge, this was the first double-blinded randomized clinical trial to examine the effect of *Jollab* on blood parameters in female patients with breast cancer undergoing chemotherapy. However, other researchers have examined other effects of this PM syrup for various conditions [8, 13, 14]. According to PM sources, this syrup helps improve the process of digestion, and since digestion fulfills a major role in a person's health from the perspective of PM, its effectiveness is attributed to this mechanism [15-17]. Also, *Jollab* components like saffron have shown chemo-protective properties due to their anti-mutagenic, immuno-modulating, and radical-scavenging features [18]. It is plausible that the reason for the lack of effect of *Jollab* in the present study was that the patients' diets were left uncontrolled. *Jollab* has also been shown to induce positive effects on mental factors [7], which were not examined in the present work. These limitations may have been influential in the observed ineffectiveness of *Jollab* in the prevention of pancytopenia among patients with breast cancer undergoing chemotherapy. Recent studies have also revealed the strengthening effect of *Jollab* ingredients on the central nervous and cardiovascular systems [19-22]. Given the effects of the interaction of the various body systems on an individuals' overall health and considering the holistic approach of PM [23], the consumption of this Persian formula by cancer patients seems rational when taking into account the fact that various body systems are weakened during chemotherapy. The ineffectiveness of *Jollab* observed in the present study can perhaps be attributed to the short treatment course and the modest amount of syrup administered. Furthermore, the use of a plant that possesses a warm temperament from the perspective of PM (such as the *Ziziphus spina-christi* (L.) Willd.) [24] may give rise to a honey product that can boost blood cell levels in patients with chemotherapy-induced bone marrow suppression.

Conclusion

Although the present study revealed the ineffectiveness of *Jollab* in boosting blood parameters in female patients with breast cancer undergoing chemotherapy, it can, as a pilot study, develop a platform for more accurate studies with larger sample sizes. It is hoped that by overcoming the limitations of this pilot study, positive results are achieved for ameliorating the complications of cancer and its therapies.

Conflict of Interest

The authors have no conflicts of interest to declare.

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References

1. Nurgalieva Z, Liu C-C, Du XL. Chemotherapy use and risk of bone marrow suppression in a large population-based cohort of older women with breast and ovarian cancer. Med Oncol 2011; 28(3): 716-25.
2. Zidan J, Shetver L, Gershuny A, Abzah A, Tamam S, Stein M, et al. Prevention of chemotherapy-induced neutropenia by special honey intake. Med Oncol. 2006; 23(4): 549-52.
3. Krishnakumar GS, Mahendiran B, Gopalakrishnan S, Muthusamy S, Malarkodi Elangovan S. Honey based treatment strategies for infected wounds and burns: A systematic review of recent pre-clinical research. Wound Med. 2020; 30: 100188.
4. Abdulrhman MA, Hamed AA, Mohamed SA, Hassanen NA. Effect of honey on febrile neutropenia in children with acute lymphoblastic leukemia: A randomized crossover open-labeled study. Complement Ther Med. 2016; 25: 98-103.
5. Singh M, Chourasia H, Agarwal M, Malhotra A, Sharma M, Sharma D, et al. Honey as complementary medicine:-a review. Int Pharma Bio Sci. 2012; 3(2).
6. Sadr S, Kaveh S, Choopani R, Bayat H, Mosaddegh M. Efficacy and Safety of Iranian Poly Herbal Formulation (Compound Honey Syrup) in Pediatric Patients with Mild to Moderate Asthma: A Randomized Clinical Trial. Galen Med J. 2017; 6(4): 291-301.
7. Pasalar M, Choopani R, Mosaddegh M, Kamalinejad M, Mohagheghzadeh A, Fattahi MR, et al. Efficacy of jollab in the treatment of depression in dyspeptic patients: a randomized double-blind controlled trial. J Evid Based Complementary Altern Med. 2015; 20(2): 104-8.
8. Pasalar M, Choopani R, Mosaddegh M, Kamalinejad M, Mohagheghzadeh A, Fattahi MR, et al. Efficacy and safety of jollab to treat functional dyspepsia: a randomized placebo-controlled clinical trial. Explore (NY). 2015; 11(3): 199-207.
9. Evans JD, Spivak M. Socialized medicine: individual and communal disease barriers in honey bees. J Invertebr Pathol 2010; 103(Suppl): S62-72.
10. Yaghoubi M, Gh G, Satari R. Antimicrobial activity of Iranian propolis and its chemical composition. Daru. 2007; 15(1): 45-8.
11. Paramasivan S, Drilling AJ, Jardeleza C, Jervis-Bardy J, Vreugde S, Wormald PJ. Methylglyoxal-augmented manuka honey as a topical anti-Staphylococcus aureus biofilm agent: safety and efficacy in an in vivo model. Int Forum Allergy Rhinol. 2014; 4(3): 187-95.
12. Afrin S, Haneefa SM, Fernandez-Cabezudo MJ, Giampieri F, Al-Ramadi BK, Battino M. Therapeutic and preventive properties of honey and its bioactive compounds in cancer: an evidence-based review. Nutr Res Rev. 2020: 33(1): 50-76.
13. Norouzian R, Ghafari S, Heydarirad G, Fahimi S. Development of a honey based tonic syrup for cancer-related fatigue. Res J Pharmacogn 2017; 4(Suppl): 60.
14. Afsari Sardari F, Mosleh G, Azadi A, Mohagheghzadeh A, Badr P. Traditional and Recent Evidence on Five Phytopharmaceuticals from Rosa damascena Herrm. Res J Pharma. 2019; 6(3): 77-84.
15. Sina HA. Al-Qanun fi al-Tibb [The Canon of Medicine]. Beirut, Lebonan: Alaalami Library; 2005.
16. Jorjani SE. Zakhireye Kharazm Shahi (Treasure of Kharazm Shah) Tehran: Iranian Medical Academy; 2001.
17. Arzani MA. Mofareh Al-Gholub. Lahoor: salim lahoor; 1915.
18. Bhandari PR. Crocus sativus L. (saffron) for cancer chemoprevention: A mini review. J Tradit Complement Med. 2015; 5(2): 81-7.
19. Shah ZA, Mir R, Matoo JM, Dar MA, Beigh M. Medicinal importance of saffron: A review. J Pharma Phytochem. 2017; 6(5): 2475-8.
20. Moazen-Zadeh E, Abbasi SH, Safi-Aghdam H, Shahmansouri N, Arjmandi-Beglar A, Hajhosseinn Talasaz A, et al. Effects of Saffron on Cognition, Anxiety, and Depression in Patients Undergoing Coronary Artery Bypass Grafting: A Randomized Double-Blind Placebo-Controlled Trial. J Altern Complement Med. 2018; 24(4): 361-8.
21. Boskabady MH, Shafei MN, Saberi Z, Amini S. Pharmacological effects of rosa damascena. Iran J Basic Med Sci. 2011; 14(4): 295-307.
22. Mahboubi M. Rosa damascena as holy ancient herb with novel applications. J Tradit Complement Med. 2016; 6(1): 10-6.

23. Aghili Shirazi MH. Moalejat-e Aghili (Persian). Tehran: Institute of Meical History, Islamic Medicine and Complementary Medicine; Iran Medical University; 2008.
24. Aghili Shirazi MH. Makhzan-al-advia (Persian). Tehran: Tehran University of Medical Sciences; 2009.