Original Article Open Access

Archives Of Breast Cancer

DOI: 10.32768/abc.202293358-363

Assessing Honey Jell® as a Treatment for Reducing Cancer-Related Fatigue in Breast Cancer Patients Undergoing Radiotherapy: Double Blind Phase III Clinical Trial

Hossein Rezaeizadeh**[a], Masoumeh Najafi**[b], Farnaz Amouzegar Hashemi[c], Fatemeh Jafari[c,d], Amin Jahanbakhshi[b], Peiman Haddad[c], Mahdi aghili[c], Bita Kalaghchi*[c]

[a]*School of Persian Medicine ,Tehran University of Medical Sciences, Tehran, Iran*

[b]*Skull Base Research Center, Neurosurgery Department, Iran University of Medical Sciences, Tehran, Iran*

[c]*Radiation Oncology Research Center, Cancer Institute, Tehran University of Medical Sciences, Tehran, Iran*

[d]*Department of Radiation Oncology, Cancer Institute, Tehran University of Medical Sciences, Tehran, Iran*

***: The mentioned authors made equal cooperation in this manuscript and jointly considered as first author.*

ARTICLE INFO

Received:
12 December 2021
Revised:
31 March 2022
Accepted:
31 March 2022

Keywords:
Cancer-related fatigue, Honey Jell ®, Royal jelly, Ziziphus zizyphus, ADH, Breast Surgery, High Risk Upgrade

ABSTRACT

Background: Cancer-Related Fatigue (CRF) is one of the most common complaints among cancer patients, which is experienced by 50-90% of them. It can affect several physical, emotional, and social aspects of cancer patients' lives and reduce their quality of life. In recent decades, the number of studies has increased in this regard, and several different ways for CRF management have been introduced. We aimed to assess the effect of Honey Jell ® on reducing cancer-related fatigue among breast cancer patients undergoing cancer treatment.

Methods: The current study was a 9-week, double-blind, randomized phase III clinical trial, which was carried out on 40 breast cancer patients at the Cancer Institute of Iran. The participants were randomly assigned to two groups by the Balanced-Block Randomization method. The study group received Honey Jell ® (natural product based on honey, royal jelly, and extract of Ziziphus zizyphus) while we used ordinary honey as a placebo for the control group. We assessed CRF at baseline, 2 and 4 weeks after the start of the study and four weeks after finishing the intervention using three different approaches. The mean score of fatigue was compared between the study groups during the study period using the T-test.

Results: Mean of fatigue score for intervention and control cases was 39.80 (±9.6) and 38.4 (±11.1) at the baseline (P-value= 0.698). The figure reduced to 31.55 (±6.08) for the intervention group in the 2nd week, while for controls, it was 35.55 (±8.2) (P=0.041). The mean score of fatigue continuously reduced to 30.65 (±6.86) in the fourth week in the intervention cases, which was considerably lower than the figure for controls (36.05±5.20) (P=0.024). The mean score of CRF in the intervention group increased 31.80 (±6.91) four weeks after the end of the study, while it was almost unchanged for controls (36.64±6.13) and the observed difference was not statistically significant (P=0.148).

Conclusion: Honey Jell ® could be considered as an effective treatment to alleviate cancer-related fatigue. However, more studies are required in this regard.

***Address for correspondence:**
Bita Kalaghchi, M.D.,
Department of Radiation Oncology, Cancer Institute, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran
Tel: +98-216-658-1535
Email: bitakalaghchi@gmail.com

INTRODUCTION

Permanent fatigue is one of the cancer patients' chief complaints who receive cancer treatment, such as radiotherapy.[1,2] It could be either due to cancer or its treatment. This kind of fatigue is different from sport or work - related fatigue and is not resolved by sleeping.

It involves both subjective and objective parts leading to physical signs, pain, depression, and other social and cognitive problems.[3,4] The prevalence of Cancer Related Fatigue (CRF) is relatively high, and it has been reported to be between 50-90% in different studies.[1,5] CRF is one of the most annoying symptoms of cancer, as it is always accompanied by pain, stress, anemia, and sleep disturbances; it will affect many different aspects of the patient's life and, consequently, reduce the quality of life. CRF is curable and can be managed.[6,7] However, the treatment of CRF must be initiated as soon as possible after diagnosis to prevent it from turning into a chronic problem.[2]

The etiology of CRF remains unknown. However, several possible factors, such as cytokines, physiological distress, metabolic problems, melatonin disorders, and serotonin levels have been known in relation to CRF.[8] It has also been reported that poor diet, anemia, hypothyroidism, treatments of comorbidities, stress, and depression could increase the severity of CRF.[8,9] It has been shown in previous studies that cancer treatments such as radiotherapy increase CRF in cancer patients.[10,11] Accordingly, treatment and management of CRF have been investigated in several clinical trial studies, and the efficiency of some medications as well as psychological interventions and food supplements has been shown.[12–15] However, there is still inconsistency in the best possible CRF management.

Royal jelly is a kind of honey bee that contains water, protein, monosaccharide, fat-soluble vitamins, some enzymes, antibiotic components, and fatty acids.[16] This product was previously used as a food supplement to reduce swimming-related fatigue in mice, and it seems to have the same effect on CRF in humans.[17] Moreover, it has been shown to be an antioxidants, anti-inflammatory, and anti-tumoral material in previous studies.[18–20] As there is a lack of evidence in the role of Royal jelly and honey in reducing CRF, we aimed to assess the effect of Royal jelly and honey on CRF among breast cancer patients who underwent radiotherapy.

METHODS

The current study was a nine-week, double-blind, phase III randomized clinical trial that compared the effect of Royal jelly and processed honey versus placebo on reducing CRF among breast cancer women. Written informed consent was completed for all participants before the study participation. The participants (according to the sample size formula provided below) were randomly assigned to Honey Jell ® (natural product based on simple honey, royal jelly, and extract of Ziziphus zizyphus) (n=20) or placebo (simple honey) groups (n=20). We used the Balanced Block Randomization method to allocate the participants. The block size was four, consisting of an equal number of each treatment, and there were six possible ways for the allocation of participants into each arm of the study. The treatment group received the jelly twice daily (1 dose 2.5cc per 12hours, with a total dose of 210cc) and we used matched placebo of the study drug (simple honey) for the control group. The study was double-blinded, and none of the patients and medical staff knew who was in the treatment or placebo groups. The placebo was identical in size, shape, color, and weight compared to the Royall jelly and honey.

Sample size calculation was performed using the folowing formula:

$$n = \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2 \times (S_1^2 + S_2^2)}{d^2}$$

α=0.05/power:0.95
Z (1-β) =1.6449/Z (1-α/2) = 1.96

Inclusion and exclusion criteria

Before enrollment in the study, participants were assessed if they met the inclusion criteria. The inclusion criteria were age over 18, hemoglobin level>8g/dl, Hematocrit>30%, level of Serum Glutamic Oxaloacetic Transaminase (SGOT) SGOT<3 times higher than normal level, Bilirubin level<2mg/dl, Creatinine<2mg/dl and normal thyroid exam result. Those patients who had an unstable cardiovascular condition, disabling pulmonary diseases such as Asthma, uncontrolled pain, severe infection, pregnancy, major depression, and simultaneous use of drugs that could affect fatigue were removed from the study.

Fatigue assessment

The fatigue assessment has been done in 4 different circumstances, including the start of the study, 2 and 4 weeks after starting the study, and one month after finishing the study.

The Visual Analogue Scale (VAS), Fatigue Severity Scale (FSS), and Eastern Cooperative Oncology Group (ECOG) were three different approaches that we used to assess fatigue among cases and controls. In FFS approaches, we completed a 9-items Likert-scale questionnaire for each patient, which varied from 1 (the lowest score) to 7 (the highest score).

Statistical analysis

We provided frequency tables, percentages, means, and associated standard deviations (SD) of outcomes over the study period. We also compared the estimated mean score of fatigue using all the three approaches at the baseline, 2 and 4 weeks after starting the study and one month after finishing the study

between cases and controls using the T-test. The mean score of fatigue was analyzed using the intention-to-treat approach, and for lost to follow-up cases, no data imputation was done. All statistical analysis was performed using Stata (ver. 11, College Station, Texas, USA).

RESULTS.

This study was carried out on 40 women admitted to the Cancer Institute of Iran for breast cancer. Mean age (±SD) of the participants in the intervention and control groups were 53.6 (6.5) and 56.5 (7.2), respectively. In general, 17.5% of the participants were diagnosed at stage I, and percentages of patients at stage II and stage III were 47.5% and 35.0%, respectively, and there was no statistical difference in stage distribution between case and control groups (P-value>0.005). Among the participants, 12 patients received MRM and chemoradiation (30.0%), 23 patients underwent Breast Conservative Surgery (BCS) and chemoradiation (57.5%), and for the five remaining patients, the treatment plan was Chemoradiation and MRM (12.5%). No significant difference was observed between the groups at the baseline (Table 1).

Table 2 presents the CRF of the participants in both case and control groups by three different methods, including ECOG, VAS, and FSS. Based on the ECOG scale, for both the case and control groups, the highest mean of fatigue was recorded in the last fatigue assessment 4 weeks after the study ended, which was 1.13 (±0.5) for the intervention group and 1.18 (±0.4) for controls; however, the difference between intervention cases and the control group was not statistically significant (P=0.878). Accordingly, the lowest mean was observed in the 2nd week, which was 0.90 (±0.4) for intervention cases and 0.95 (± 0.3) for controls. No significant difference was observed between the two arms of the cases and controls (P=0.841).

We also reported the mean score of fatigue using the VAS approach. At the start of the study, it was 5.30 (±1.97) for intervention cases and 5.10 (±1.97) for controls. No statistically significant difference was observed (P=0.799). The lowest mean score in both arms was observed in the 2nd week, while the difference between the groups was not statistically significant (P=0.698).

FFS approach was also used to assess the mean score of CRF. The mean fatigue score for intervention cases and controls was 39.80 (±9.6) and 38.4 (±11.1) at the baseline (P-value=0.698). This score was reduced to 31.55 (±6.08) for the case intervention group in the 2nd week, while for controls, it was 35.55 (±8.2). It was significantly lower in the intervention group (P=0.041). The mean score of fatigue continuously decreased to 30.65 (±6.86) in the fourth week of the study in intervention cases which was considerably lower than the figure for controls (36.05±5.20) (P=0.024). Finally, after the intervention, the mean score of CRF in the case group increased again to 31.80 (±6.91) four weeks after the end of the study, while it was almost unchanged for controls (36.64±6.13) and the observed difference was not statistically significant (P=0.148) (Table 2).

Table 1. Study participants' characteristic in the intervention and control groups

Variable		Case Intervention	Control
	Sub groups	N (%)	N (%)
Gender	Female	20 (100)	20 (100)
Stage at diagnosis			
	Stage I	4 (20)	3 (15)
	Stage II	10 (50)	9 (45)
	Stage III	6 (30)	8 (40)
Treatment			
	MRM + Chemo	5 (25)	7 (35)
	BCS + Chemo	12 (60)	11 (55)
	Chemo + MRM	3 (15)	2 (10)
Age	Mean (SD)	53.6 (6.5)	56.5 (7.2)

MRM: Modified Radical Mastectomy, BCS: Breast Conservative Surgery,
SD: Standard Deviation

DISCUSSION

The current study investigated the anti-fatigue effect of Honey Jell ® (natural product based on simple honey, royal jelly, and extract of Ziziphus zizyphus) among breast cancer patients. This study was a nine-week double-blind, randomized clinical trial in which the CRF of the participants was compared between intervention cases and controls for four times during the study period using three different approaches. According to the results, the mean score of CRF for controls was almost unchanged, while among patients in the intervention group that had been given Honey Jell ®, it was constantly reduced until the third time of fatigue assessment 4 weeks after initiating the study, and then after finishing the intervention it partially increased again.

The etiology of CRF remains unknown, and there is no clear understanding of how it could be treated. This is a multi-factorial phenomenon, and several possible etiologies and mechanisms have been suggested for its progress.[8,9]

Table 2. Comparison of mean score of CRF among case and control groups at baseline, at 2, 4 and 9 weeks of the study

Characteristics	Visit time	Case Intervention	Control	
		Mean ± SD	Mean ± SD	P- Value
FSS	Baseline	39.80 ± 9.61	38.40± 11.16	0,698
	2nd Week	31,55 ± 6.08	35.55 ± 8.23	0,041
	4th Week	30.65 ± 6.86	36.05 ± 5.20	0,024
	9th Week	31.80 ± 6.91	36.64 ± 6.13	0.148
ECOG	Baseline	1.10 ± .64	0.90 ± 0.64	0.398
	2nd Week	0.90 ± 0.44	0.95 ± 0.60	0.841
	4th Week	1.00 ± 0.32	1.10 ± 0.44	0.620
	9th Week	1.13 ± 0.51	1.18 ± 0.40	0.878
VAFS	Baseline	5.30 ± 1.49	5.10 ± 1.97	0.799
	2nd Week	4.40 ± 1.18	4.60 ± 0.88	0.698
	4th Week	4.80 ± 1.19	4.95 ± 0.94	0.841
	9th Week	4.53 ± 0.74	4.73 ± 0.64	0.574

Hence, different pharmaceutical approaches and food supplements have been already assessed in order to find the best CRF management. Ginseng, Coenzyme Q10, L-carnitine, and guarana are some examples which have been already investigated in previous studies.[12,15] Mofid *et al*. assessed the effect of Royal jelly and processed honey on reducing CRF and reported that Royal jelly could considerably reduce the mean score of fatigue in cancer patients.[16] In another study, the anti-fatigue effect of Royal jelly on sport-related fatigue was investigated in male mice. This study showed that Royal jelly could be considered as a supplement to decrease physical fatigue, which is in line with our findings.[17] Other studies have shown promising results for herbal prescriptions in terms of CRF treatment and management.[21] Anti-cancer characteristics of honey have also been investigated in other studies, showing that Tualang honey had an anti-cancer effect on cervical and breast cancer epithelial cell line.[21] Moreover, in some other studies, immune-modulatory and anti-oxidant features have been reported for Royal jelly, showing that it can be an effective herbal treatment to improve the severity of CRF.[22]

The current study is one of the first attempts to assess the effect of adding royal jelly and Ziziphus zizyphus extract to simple honey for CRF treatment. However, there were some limitations that could affect our findings. Although patients' compliance was high and all the patients were compliant regarding the routine follow up and exact drug usage and we recruited more cases than needed in each arm of our study, the number of participants was quite small. Thus, the effect of Honey Jell ® on CRF should be investigated in studies with more participants. Also, there is insufficient evidence on assessing the anti-fatigue effect of Royal jelly, which reduces the comparability of our findings.

CONCLUSION

Regarding our study results, using the natural product based on simple honey, royal jelly, and extract of Ziziphus zizyphus is an effective herbal approach to reducing CRF, and it could be considered a traditional prescription to ameliorate fatigue among cancer patients. However, more studies must be carried out to support its the anti-fatigue effect on CRF treatment.

ACKNOWLEDGEMENTS

The paper was part of the first author's thesis conducted in the Cancer Institute of Iran, Tehran University of Medical Sciences. The authors would like to thank all the staff at the Cancer Institute of Iran and study participants who contributed to this study.

ETHICAL CONSIDERATIONS

Ethical approval code: IR.TUMS.IKHC.REC.1396.4287. Trial Registration Number: IRCT20161112030841N3, date of registration: 2021-03-08.

FUNDING

This study was supported financially by the Vice Chancellor of Tehran University of Medical Sciences.

CONFLICT OF INTEREST

None.

REFERENCES

1. Gupta D, Lis CG, Grutsch JF. The Relationship Between Cancer-Related Fatigue and Patient Satisfaction with Quality of Life in Cancer. *Journal of Pain and Symptom Management*. 2007;34:40–7. doi: 10.1016/j.jpainsymman.2006.10.012.
2. Stone P, Richardson A, Ream E, Smith AG, Kerr DJ, Kearney N. Cancer-related fatigue: Inevitable, unimportant and untreatable? Results of a multi-centre patient survey. *Annals of Oncology*. 2000;11:971–5. doi: 10.1023/A:1008318932641.
3. Jereczek-Fossa BA, Santoro L, Alterio D, Franchi B, Fiore MR, Fossati P, et al. Fatigue During Head-And-Neck Radiotherapy: Prospective Study on 117 Consecutive Patients. *International Journal of Radiation Oncology*Biology*Physics*. 2007;68:403–15. doi: 10.1016/j.ijrobp.2007.01.024.
4. Atkins MB, Mier JW, Parkinson DR, Gould JA, Berkman EM, Kaplan MM. Hypothyroidism after Treatment with Interleukin-2 and Lymphokine-Activated Killer Cells. *New England Journal of Medicine*. 1988;318:1557–63. doi: 10.1056/nejm198806163182401.
5. Campos MPO, Hassan BJ, Riechelmann R, Del Giglio A. Cancer-related fatigue: A practical review. *Annals of Oncology*. 2011:1273–9. doi: 10.1093/annonc/mdq458.
6. Patient, caregiver, and oncologist perceptions of cancer-related fatigue: results of a tripart assessment survey. The Fatigue Coalition - PubMed. Available at: https://pubmed.ncbi.nlm.nih.gov/9253778/ [accessed March 17, 2021].
7. Lis CG, Rodeghier M, Grutsch JF, Gupta D. Distribution and determinants of patient satisfaction in oncology with a focus on health related quality of life. *BMC Health Services Research*. 2009;9. doi: 10.1186/1472-6963-9-190.
8. Horneber M, Fischer I, Dimeo F, Rüffer JU, Weis J. Tumor-assoziierte Fatigue: Epidemiologie, pathogenese, diagnostik und therapie. *Deutsches Arzteblatt International*. 2012;109:161–72. doi: 10.3238/arztebl.2012.0161.
9. Wang XS. Pathophysiology of cancer-related fatigue. *Clinical Journal of Oncology Nursing*. 2008;12:11–20. doi: 10.1188/08.CJON.S2.11-20.
10. Hofman M, Ryan JL, Figueroa-Moseley CD, Jean-Pierre P, Morrow GR. Cancer-Related Fatigue: The Scale of the Problem. *The Oncologist*. 2007;12:4–10. doi: 10.1634/theoncologist.12-s1-4.
11. Passos CS, Ribeiro Sady ER, Passos Neves RV, Piovezani Carvalho BE, Santos Rodrigues Costa T, Haro AS, et al. Cancer and radiotherapy-related fatigue: implications and therapies integratives. *Journal of Medical Oncology and Therapeutics*. 2018;03. doi: 10.35841/medical-oncology.3.1.9-14.
12. Barton DL, Soori GS, Bauer BA, Sloan JA, Johnson PA, Figueras C, et al. Pilot study of Panax quinquefolius (American ginseng) to improve cancer-related fatigue: A randomized, double-blind, dose-finding evaluation: NCCTG trial N03CA. *Supportive Care in Cancer*. 2010;18:179–87. doi: 10.1007/s00520-009-0642-2.
13. Moraska AR, Sood A, Dakhil SR, Sloan JA, Barton D, Atherton PJ, et al. Phase III, randomized, double-blind, placebo-controlled study of long-acting methylphenidate for cancer-related fatigue: North Central Cancer Treatment Group NCCTG-N05c7 trial. *Journal of Clinical Oncology*. 2010;28:3673–9. doi: 10.1200/JCO.2010.28.1444.
14. Roscoe JA, Morrow GR, Hickok JT, Mustian KM, Griggs JJ, Matteson SE, et al. Effect of paroxetine hydrochloride (Paxil®) on fatigue and depression in breast cancer patients receiving chemotherapy. *Breast Cancer Research and Treatment*. 2005;89:243–9. doi: 10.1007/s10549-004-2175-1.
15. Jeong JS, Ryu BH, Kim JS, Park JW, Choi WC, Yoon SW. Bojungikki-tang for cancer-related fatigue: A pilot randomized clinical trial. *Integrative Cancer Therapies*. 2010;9:331–8. doi: 10.1177/1534735410383170.
16. Mofid B, Rezaeizadeh H, Termos A, Rakhsha A, Rezazadeh Mafi A, Taheripanah T. Effect of Processed Honey and Royal Jelly on Cancer-Related Fatigue: A Double-Blind Randomized Clinical Trial. *Electron Physician*. 2016;8:2475–82. doi: 10.19082/2475.
17. Kamakura M, Mitani N, Fukuda T, Fukushima M. Antifatigue effect of fresh royal jelly in mice. *Journal of Nutritional Science and Vitaminology*. 2001;47:394–401. doi: 10.3177/jnsv.47.394.
18. Pourahmad M, Sobhanian S. Effect of Honey on the Common Cold. *Archives of Medical Research*. 2009:224–5. doi: 10.1016/j.arcmed.2009.01.001.
19. Nakaya M, Onda H, Sasaki K, Yukiyoshi A, Tachibana H, Yamada K. Effect of royal jelly on bisphenol A-induced proliferation of human breast cancer cells. *Bioscience, Biotechnology and Biochemistry*. 2007;71:253–5. doi: 10.1271/bbb.60453.
20. Karadeniz A, Simsek N, Karakus E, Yildirim S, Kara A, Can I, et al. Royal jelly modulates oxidative stress and apoptosis in liver and kidneys of rats treated with cisplatin. *Oxidative Medicine and Cellular Longevity*. 2011;2011. doi: 10.1155/2011/981793.

21. Fauzi AN, Norazmi MN, Yaacob NS. Tualang honey induces apoptosis and disrupts the mitochondrial membrane potential of human breast and cervical cancer cell lines. *Food and Chemical Toxicology*. 2011;49:871–8. doi: 10.1016/j.fct.2010.12.010.

22. Erem C, Deger O, Ovali E, Barlak Y. The effects of royal jelly on autoimmunity in Graves' disease. *Endocrine*. 2006;30:175–83. doi: 10.1385/ENDO:30:2:175.

How to Cite This Article

Rezaeizadeh H, Najafi M, Amouzegar Hashemi F, Jafari F, Jahanbakhshi A, Haddad P, et al. Assessing Honey Jell ® as a Treatment for Reducing Cancer-Related Fatigue in Breast Cancer Patients Undergoing Radiotherapy: Double Blind Phase III Clinical Trial. Arch Breast Cancer. 2022; 9(3): 358-63.
Available from: https://www.archbreastcancer.com/index.php/abc/article/view/508