Original Article
Middle East Journal of Cancer; October 2019; 10(4): 333-340

Effect of Omega-3 Fatty Acid Supplements on Cancer-related Fatigue in an Outpatient Setting: A Randomized Controlled Trial

Hourieh Ansari*, Mohammad Nouranian*, Ali Hajigholami♦, Ahmad Mahmudian***

*Department of Family and Community Medicine, Faculty of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran
**Department of Internal Medicine, Faculty of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

Abstract

Background: Fatigue, as one of the most common side effects of cancer and its associated treatments, induces a distressing, persistent, and inward feeling. This study aimed to investigate the synergistic effect of the omega-3 supplement as an unconfirmed effect on conventional ginseng treatment with a possible effect on this side effect in cancer patients.

Method: This clinical trial was conducted in 2018 on 70 cancer patients referring to outpatient clinics affiliated to Isfahan University of Medical Sciences. Patients were included in the study by the convenience sampling method and were randomly divided into control and intervention groups. Patients in the treatment group received an omega-3 supplement and usual treatment. For patients in the control group, only the usual intervention was administered. Data were collected using the Multidimensional Fatigue Inventory questionnaire. The duration of intervention was 6 weeks. The primary outcome was the improvement of fatigue scores measured by the questionnaire.

Result: There was a significant difference in both groups concerning the mean total fatigue score in three times; i.e., 0, 3, and 6 weeks after the intervention (P <0.001). Mean value of total fatigue score at the beginning of the study was 77.8±6.6 in the intervention group and 76.8±9.7 in the control group. After 3 weeks of the study, it was 49.2±6.8 and 57.5±9.5 and after 6 weeks it was 25.3±7.8 and 37.2±8.4 in the intervention group and in the control group, respectively.

Conclusion: This study revealed that omega-3 supplement can reduce cancer-related fatigue in outpatient cancer patients compared with the control group.

Keywords: Cancer-related fatigue, Omega-3 supplement, Chemotherapy, RCT

♦Corresponding Author:
Ali Hajigholami, MD
Department of Hematology-Oncology, Isfahan University of Medical Sciences, Hezar Jerib St., Isfahan, Iran
Email:
alihajigholami@med.mui.ac.ir

Middle East Journal of Cancer

Received: August 06, 2018; Accepted: June 11, 2019

Introduction

According to the World Health Organization (WHO), cancer is a chronic health problem. Today, there is a significant increase in the number of deaths from cancer worldwide. Cancer is accounted for 12.5% of all death globally and is estimated to afflict 24.6 million people by 2020.[1,2] Cancer-related fatigue (CRF) is a distressing subjective feeling that can be either physical or mental. CRF is cognitive tiredness or exhaustion related to cancer or cancer treatment. This health issue significantly interferes with normal functions and can affect mood, work, and daily activities, self-care, and communication.[3, 4]

Fatigue is the most common side-effect of cancer treatment and often occurs without any warning. CRF can persist for months or years and often continue after treatment discontinuation.[4] CRF is a common clinical problem for more than 10 million cancer patients worldwide. CRF includes physical, psychosocial, occupational aspects[5] and may even be one of the first symptoms of malignant disease. Indeed, all patients experience fatigue during cancer treatment. More specifically, about 90% of radiotherapy patients and 80% of patients are undergoing chemotherapy experience fatigue.[5-10] Recently, more attention has been dedicated to the screening and treatment of CRF in supportive care. Clinical guidelines and expert groups recommend that screening for fatigue should be performed at the initiation of cancer treatment, during disease progression, and at all cycles of chemotherapy.[11-13]

Various factors can be effective in CRF incidence, including disease nature, treatment methods, and a set of physical or psychological accompanying conditions such as anemia, pain, depression, anxiety, cachexia, sleep disturbances, and inactivity.[12,13] To our knowledge, mechanisms responsible for CRF, except chemotherapy-induced anemia, have not been fully understood. Medicines with different effect mechanisms including psychostimulants, Phytotherapeutic agents, growth factors, and corticosteroids are employed to treat CFR.[14,15] Acupuncture and biofield healing would significantly reduce CRF following cancer treatment. Recently, it has been evidenced that multivitamins are ineffective in reducing CRF. However, studies in this regard are different in quality, and most of them are methodologically weak.[16] Today, dietary supplements are a common therapeutic approach for illness without an effective treatment, including CRF. Among many plants used through popular culture and traditional usage as a solution to fatigue, none is as famous as ginseng around the world. ginseng is a substance that can maintain the body's balance and homeostasis and is commonly known as an adaptogen in traditional Chinese medicine.[17] Evidence has shown that ginseng may be beneficial in treating CRF. In this context, in vitro studies have reported anti-inflammatory properties and regulatory effects of this plant on cortisol.[18,19]

Omega-3 long-chain unsaturated fatty acids such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have beneficial effects on the inflammatory process by modulating the immune system, increasing phagocytic activity, stopping TLR signaling cascade, and producing anti-inflammatory eicosanoids.[19] It has been evidenced that omega-3 fatty acids rich diet can be beneficial for cancer patients by modifying the proliferation of cancer cells, inflammation, psychosocial function, and quality of life.[20] Moreover, the anti-tumor effects of omega-3 fatty acids can be through controlling angiogenesis and metastasis. These supplements can be used as adjuvants for chemotherapy and may have direct anti-cancer effects and may improve some side-effects of cancer.[20,21]

Considering the CRF's effect on the quality of life, its annoying feeling, and multifactorial nature, and lack of extensive studies based on reliable findings, on one hand, and considering the specific effects of the omega-3 supplement on the pathophysiology of cancer, on the other hand, it is necessary to review this health issue in patients with CRF. This study aimed to evaluate the synergistic effect of the omega-3 supplement as an unconfirmed effect and conventional ginseng therapy with a possible effect on CRF.

Materials and Methods

To perform this randomized clinical trial, the secretary of oncology clinic introduced the patients to the oncologist using a randomized grouping and the oncologist provided treatments for both groups according to the grouping done. The investigator, in collaboration with the oncologist, supervised the patient's use of the drug. Given that the grouping procedure is strictly confidential, the data provided by patients were analyzed by a statistician. After obtaining an approval code from the Medical Ethics Committee, patients who had the inclusion criteria, filled informed consent paper for participation in the study. The inclusion criteria for the study were: age 30-60 years, definitive diagnosis of cancer with chemotherapy indication, having a score of 40 and above in the questionnaire, the literacy to read and write, the ability to take oral medications, not taking Omega-3 supplement in the last three months, not having allergy to fish and soy, not using anticoagulants (except aspirin), and not having anemia. A multidimensional fatigue inventory (MFI) was used to measure fatigue-induced cancer. The questionnaire was comprised of 20 questions and was scored based on the 5 points Likert Scale and included the levels of general fatigue, physical fatigue, decreased activity, mental fatigue, and decreased motivation. The questionnaire was completed in a self-administered manner. Validity and reliability of the questionnaire have been assessed and proven in various demographic groups. In this study, Cronbach's alpha was estimated to be 74% for total fatigue score, 73% for general fatigue, 71% for physical fatigue, 82% for mental fatigue, and 75% for decreased activity and motivation. The response rate was 100% (Figure 1).

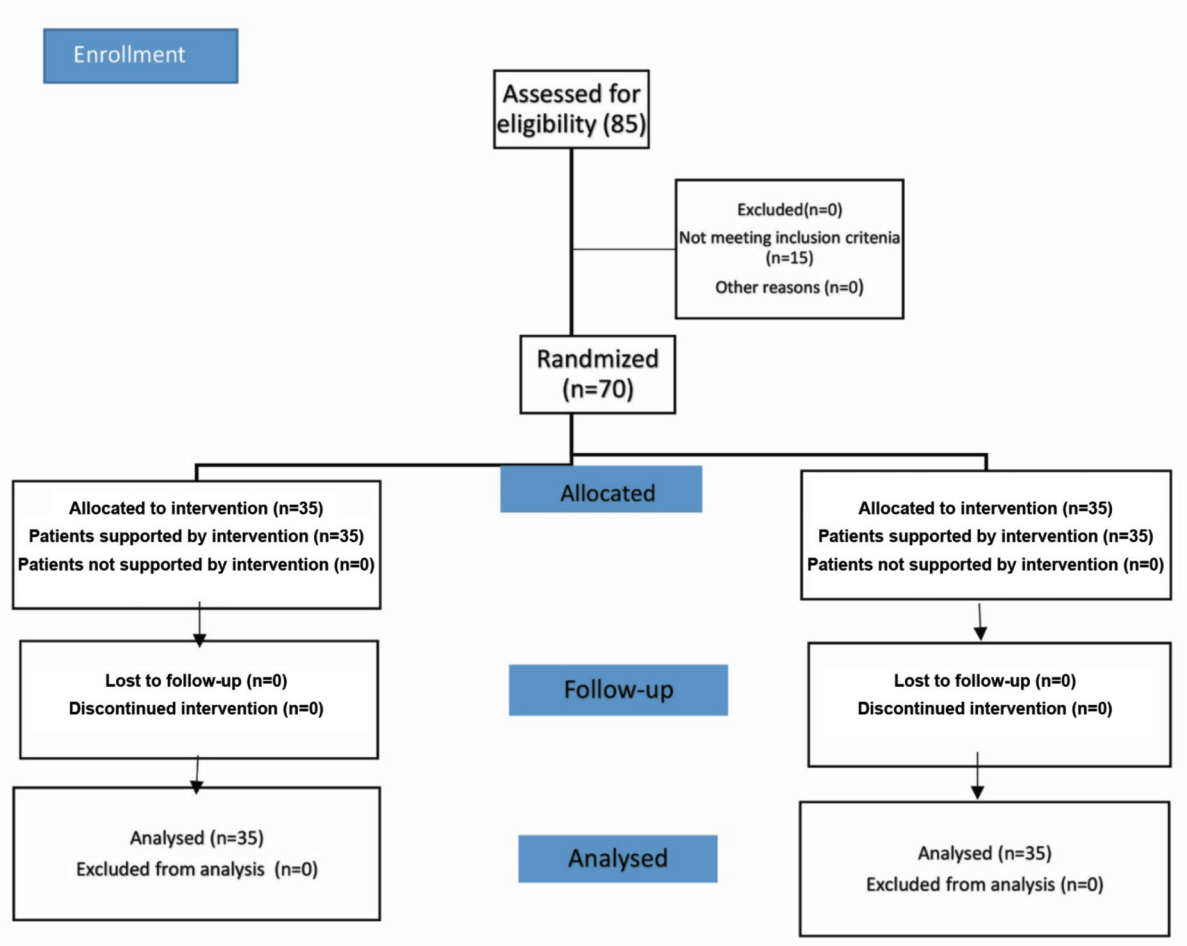

Figure 1. Flow chart of subjects through the trial; No patient was excluded from the two groups; after 3 and 6 weeks of the trial, the number of the participants was equal (n=35).

Table 1. Frequency distribution of gender and level of education in both control and experimental groups

Variable	Experimental group		Control group		*P*-value
	No.	%	No.	%	
Gender					
Man	15	41.7	13	37.1	0.7
Woman	21	58.3	22	62.9	
Level of education					
No high school diploma	20	55.6	14	40	0.22
High school diploma	10	27.8	13	37.1	
Academic degree	6	16.7	8	22.9	
Type of cancer					
Type 1*	14	38.9	9	25.7	0.29
Type 2**	9	25	7	20	
Type 3***	13	36.1	19	54.3	

Types of cancer were adapted from ICD-10, 2017

*Malignant neoplasms, except lymphoid and hematopoietic; ** Malignant neoplasms lymphoid and hematopoietic; *** Other neoplasms

For patients in the treatment group, the omega-3 capsules (GMV Omega 3, Australia) were purchased from Ferdows Pharmaceuticals Company, Iran, and was prescribed 1000 mg daily.[22] This supplement was also provided free for the patients in the intervention group. Patients in the control and treatment group received 1000 mg ginseng (Goldaru Pharmaceuticals Company, Iran) with their doctor's prescription. Patients in the control group received only the ordinary intervention. Patients completed the MFI questionnaire three and six weeks after the initiation of the study to follow up and measure the weakness of patients in both groups. Questionnaires completed for less than 20% were removed from the study and another patient was replaced. The attrition rate was zero. It means that no one excluded from the study. No patient withdrew or died during the course of the study (dropout rate was zero). The present study started in July and continued until November. Chemotherapy continued during the study for all patients.

1) The research followed the tenets of the declaration of Helsinki. Informed consent was obtained from the patient. The study was approved by the Ethics Committee of Isfahan University of Medical Sciences, with an ethics code of IR.MUI.REC.1396.3.182, IRCT code of IRCT20170308032957N2, and proposal number of 396182.

Statistical Analysis

All statistical methods were analyzed using SPSS software version 20. Descriptive statistics including frequency, percentage, mean, standard deviation, and statistical difference between these values were reported with 95% confidence interval for publishing the findings. Normality of variables was measured before analysis by Kolmogorov-Smirnov statistical test. Independent t-test, repeated measures ANOVA, Chi-square test, and ANCOVA were employed to analyze the hypotheses. Our approach falls in the category of intention-to-treat analysis. The level of significance established for a two-tailed t-test was 0.05.

Results

The age range of subjects in experimental group was 30-60 with a mean age of 48.4±9.1 years and in the control group it was 30-60 with a mean age of 48±7.6 years. There was no statistically significant difference in the mean age of the two groups (P=0.85).

There was no significant difference in the frequency distribution of gender (P=0.7), level of education (P=0.22), and type of cancer (P=0.29) between the two groups (Table 1).

There was no significant difference in the mean value of total fatigue score at the initiation of intervention between the two groups (P=0.6). By modifying the initial value of the total fatigue score at the initiation of intervention, the mean

Table 2. Mean value of total fatigue score at different times in both control and experimental groups

time	Experimental group		Control group		*P*-value
	mean	SD	mean	SD	
Initiation of intervention	77.8	6.6	76.8	9.7	0.6
3 weeks after the initiation of intervention	49.2	6.8	57.5	9.5	<0.001
6 weeks after the initiation of intervention	25.3	7.8	37.2	8.4	<0.001

SD: Standard deviation

value of total fatigue score at three weeks and six weeks after the intervention in the experimental group was significantly lower than that of the control group ($P<0.001$). The mean value of total fatigue score in both groups was significantly different among these three times ($P<0.001$). The mean value of total fatigue score in both groups was decreased over time ($P<0.001$) (Table 2).

Also, the results of this study showed that there was no significant difference in the mean value of all subscales of fatigue score at the initiation of intervention between the two groups ($P>0.05$). By modifying the initial value of the subscales of fatigue score at the initiation of intervention, the mean value of all subscales of fatigue score at three and six weeks after the intervention in the experimental group was significantly lower than that of the control group ($P<0.05$). In all three separate analyses, a significant difference in the mean value of all subscales of fatigue score was observed ($P<0.001$). The mean value of all subscales of fatigue score in both groups decreased with the passage of time ($P<0.05$) (Table 3).

Discussion

The current study aimed to investigate the effects of ginseng alone and in association with an omega-3 supplement in controlling CRF symptoms in a patient under the chemotherapy. The results showed that the scores of weakness and fatigue were approximately less than half of the average after six weeks in the intervention group. Two groups were similar in terms of age, sex, and levels of education. The rate of improvement in the different parameters of weakness after three and six weeks was almost the same, but less improvement was observed in decreased activity and was somewhat more prominent in decreased motivation and mental fatigue. This improvement was lower in the control group compared with the experimental group in each parameter. Overall, the results of this study indicate the positive effect of the omega-3 supplement on cancer-induced fatigue. In this regard, there are a limited number of studies concerning the effects of omega-3 on cancer-related fatigue.

In a study on the effects of prostate cancer on cell proliferation, inflammation and quality of life, Guertin et al. recommended investigating the effects of omega-3 fatty acids in prospective RCTs in prostate cancer.[20] Evidence suggests that hypnosis and ginseng may prevent an increase in CRF. In a study on American ginseng, Barton et al. (2013) showed that the effect of American ginseng (2 g daily) after eight weeks was statistically significant. The results of this study, which was generally based on various parameters of weakness, showed a decrease in weakness after four and eight weeks; which are rather consistent with the results of the present study.[23] According to WHO, the recommended daily dose of Panax ginseng is about 2-3 gr/day of dry matter or 300-800 mg/day of a standardized extract (containing 4-7% Ginsenosides).[24]

The administrated doses of Panax ginseng in different studies have been lower compared with the current study. For example, Yennurajalingam et al., in a study to achieve a safe dose for CRF, reported the highest dose of 800 mg, which is lower than that of the present study.[24] This difference can be one of the reasons for the better effects of ginseng in this study.

Regarding whether ginseng interferes with the activity of chemotherapy agents, no study has been conducted on humans. However, preclinical findings suggest that American ginseng does not

Table 3. Mean value of subscales of fatigue score at different times in both control and experimental groups

subscales	time	Experimental group		Control group		*P*-value
		mean	SD	mean	SD	
General fatigue						
	Initiation of intervention	18.2	1.4	18.1	2.01	0.81
	3 weeks after the initiation of intervention	11.6	1.8	14	1.9	<0.001
	6 weeks after the initiation of intervention	5.4	2.2	8.4	1.9	<0.001
Physical fatigue						
	Initiation of intervention	17.4	2.1	17.11	2.6	0.96
	3 weeks after the initiation of intervention	11.2	2.2	13.4	2.7	<0.001
	6 weeks after the initiation of intervention	5.4	2.2	8.6	1.9	<0.001
Decreased activity						
	Initiation of intervention	11.6	2.7	11.5	4.02	0.88
	3 weeks after the initiation of intervention	7	2.1	8.7	2.8	<0.001
	6 weeks after the initiation of intervention	4.6	1.5	5	2.1	<0.001
Mental fatigue						
	Initiation of intervention	14.1	2.6	13.8	3.3	0.67
	3 weeks after the initiation of intervention	8.6	2.4	9.7	3.1	0.003
	6 weeks after the initiation of intervention	4.5	0.9	6.5	2.4	<0.001
Decreased motivation						
	Initiation of intervention	16.8	1.7	16.3	2.6	0.37
	3 weeks after the initiation of intervention	10.7	2.1	11.7	2.6	0.006
	6 weeks after the initiation of intervention	5.2	2.4	7.7	2.6	<0.001

SD: Standard deviation

interact with tamoxifen, doxorubicin, cyclophosphamide, paclitaxel, fluorouracil, and Methotrexate. Additionally, administering ginseng with these drugs has synergistic inhibitory effects on breast cancer cell lines.[25-27] Omega-3 supplement in cancer patients can increase the effectiveness of ginseng in improving fatigue and may also affect it independently. Therefore, selecting high-quality trials similar to this study on various types of cancer is necessary to prove the effectiveness of this supplement. Considering depression as comorbidity associated with cancer and an effective element in increasing CRF (mood and mental fatigue), in future studies, the use of pharmacological interventions in association with non-pharmacological interventions such as CBT (cognitive behavioral therapy) to control comorbidity such as depression and determining its effects on CRF may lead to promising results. In subsequent studies, the use of these methods in a wider range of patients with other types of cancers or specific age ranges, such as children or specific comorbidities such as chronic diseases as RA or diabetes, can be considered for a complete and better analysis of this information.[28]

In our study, there was no screening for isolating patients with depression and no classification based on the severity of depression. As a result, it would be difficult to interpret the results of the response to treatment, improve various components of weakness, and discuss the degree of adherence to treatment in these groups. Comparing the effect of ginseng on patients in our study with those from South and East Asian

countries, who use more ginseng, may lead to misleading results because the higher usage of ginseng in these cultures can interfere with its role as a drug. To deal with this issue, some researchers recommend a one-week withdrawal after three weeks to one month of taking medicine, because continuous use of the medicine causes the body to recognize it as a food, which influences its medicinal effect. Researchers also believe that taking this medicine for more than two months can reverse its effects in the body and disrupt the homeostatic even hormone balance.[17]

Another important point to consider in our study is that the average per capita consumption of fish and omega-3 in our country is lower than European and American countries, which can indicate and justify its significant impact compared with ginseng, as well as its relative impact compared with European and American studies. The classification of patients into two groups (in one group biological agents are involved in the exacerbation and creation of CRF and in the other group behavioral factors and expectations are considered) can lead to better CRF management. Non-pharmacologic interventions are more effective in the group that non-biological agents are responsible. Therefore, in subsequent studies, it is recommended applying an omega-3 supplement instead of other biological treatments in patients with less emotional disturbances and better coping mechanisms.[28]

Conclusion

This study revealed that omega-3 supplement can reduce cancer-related fatigue in cancer outpatients compared with a control group. Thus, it is recommended that well-designed clinical trials and other special target groups be included in future studies.

In the subgroup that has a mild or no grade of anxiety and depression scale, in order to have a better interpretation of the results, the prescription of omega-3 supplement should be administered before, during, and after the initiation of therapy, and should be followed by a longer follow-up period. To provide definitive conclusions about pharmacologic factors that may be effective in the field of CRF and to declare certainty about its effect, extensive cohort studies and meta-analyses are needed. Due to the lack of extensive studies based on standard and reliable findings, and considering the specific effects of omega-3 supplement in the pathophysiology of cancer, further clinical investigations should be considered based on various types of cancer to prove the effectiveness of this supplement

Financial support

This research was supported by Isfahan University of Medical Sciences, Isfahan, Iran.

Conflicts of Interest

None declared.

References

1. World Health Organization. [Internet] Global Status Report on Noncommunicable Diseases 2010. Geneva, Switzerland: World Health Organization; 2011. Available at: http://www.who.int/nmh/publications/ncd_report_full_en.pdf. *Accessed date*: October 20, 2015.
2. Gulzar K, Ahmed M, Junejo AM. Frequency of electrolyte imbalance associated with cisplatin in oral cancer patients; a tertiary care experience from Pakistan. *J Nephropharmacol.* 2018;7(2):126-30.
3. Bower JE, Bak K, Berger A, Breitbart W, Escalante CP, Ganz PA, et al. Screening, assessment, and management of fatigue in adult survivors of cancer: an American Society of Clinical Oncology clinical practice guideline adaptation. *J Clin Oncol.* 2014;32(17):1840-50. doi: 10.1200/JCO.2013.53.4495.
4. Gupta D, Lis CG, Grutsch JF. The relationship between cancer-related fatigue and patient satisfaction with quality of life in cancer. *J Pain Symptom Manage*. 2007;34(1):40-7.
5. Dagnelie PC, Pijls-Johannesma MC, Lambin P, Beijer S, De Ruysscher D, Kempen GI. Impact of fatigue on overall quality of life in lung and breast cancer patients selected for high-dose radiotherapy. *Ann Oncol.* 2007;18(5):940-4.
6. Kangas M, Bovbjerg DH, Montgomery GH. Cancer-related fatigue: a systematic and meta-analytic review of non-pharmacological therapies for cancer patients. *Psychol Bull.* 2008;134(5):700-41. doi: 10.1037/a0012825.
7. Davoodi M, Bahadoram S, Barahman M, Barahman M, Khazaei Z, Amiri M. Impact of cancers on the kidney function and structure; an ignored entity. *J Renal Inj*

Prev. 2018;7 (3):112-5. DOI: 10.15171/jrip.2018.26.
8. Mousavi Movahhed SM, Beladi Mousavi SS, Hayati F, Shayanpour S, Halili SA, Sabetnia L, et al. The relationship between chronic kidney disease and cancer. *J Nephropathol*. 2018;7(3):115-6. DOI: 10.15171/jnp.2018.26.
9. Norouzirad R, Khazaei Z, Mousavi M, Adineh HA, Hoghooghi M, Khabazkhoob M, et al. Epidemiology of common cancers in Dezful county, southwest of Iran *Immunopathol Persa*. 2018;4(1):e10.
10. Dehghan Shahreza F. From oxidative stress to endothelial cell dysfunction. *J Prev Epidemiol.* 2016;1(1):e04.
11. Dy SM, Lorenz KA, Naeim A, Sanati H, Walling A, Asch SM. Evidence-based recommendations for cancer fatigue, anorexia, depression, and dyspnea. *J Clin Oncol.* 2008;26(23):3886-95. doi: 10.1200/JCO.2007.15.9525.
12. Wang XS. Pathophysiology of cancer-related fatigue. *Clin J Oncol Nurs.* 2008;12(5 Suppl):11-20. doi: 10.1188/08.CJON.S2.11-20.
13. Horneber M, Fischer I, Dimeo F, Rüffer JU, Weis J. Cancer-related fatigue: epidemiology, pathogenesis, diagnosis, and treatment. *Dtsch Arztebl Int.* 2012;109(9):161-71; quiz 172. doi: 10.3238/arztebl.2012.0161.
14. Bruera E, Roca E, Cedaro L, Carraro S, Chacon R. Action of oral methylprednisolone in terminal cancer patients: a prospective randomized double-blind study. *Cancer Treat Rep.* 1985;69(7-8):751-4.
15. Weis J. Cancer-related fatigue: prevalence, assessment and treatment strategies. *Expert Rev Pharmacoecon Outcomes Res.* 2011;11(4):441-6. doi: 10.1586/erp.11.44.
16. Finnegan-John J, Molassiotis A, Richardson A, Ream E. A systematic review of complementary and alternative medicine interventions for the management of cancer-related fatigue. *Integr Cancer Ther.* 2013;12(4):276-90. doi: 10.1177/1534735413485816.
17. Mani N. Natural standard. *J Med Libr Assoc.* 2005; 93(4): 507-9.
18. Freitas RDS, Campos MM. Protective effects of omega-3 fatty acids in cancer-related complications. *Nutrients*. 2019 26;11(5). pii: E945. doi: 10.3390/nu11050945.
19. de Pablo MA, Alvarez de Cienfuegos G. Modulatory effects of dietary lipids on immune system functions. *Immunol Cell Biol.* 2000;78(1):31-9.
20. Guertin MH, Robitaille K, Pelletier JF, Duchesne T, Julien P, Savard J, et al. Effects of concentrated long-chain omega-3 polyunsaturated fatty acid supplementation before radical prostatectomy on prostate cancer proliferation, inflammation, and quality of life: study protocol for a phase IIb, randomized, double-blind, placebo-controlled trial. *BMC Cancer.* 2018;18(1):64. doi: 10.1186/s12885-017-3979-9.
21. Nabavi SF, Bilotto S, Russo GL, Orhan IE, Habtemariam S, Daglia M, et al. Omega-3 polyunsaturated fatty acids and cancer: lessons learned from clinical trials. *Cancer Metastasis Rev*. 2015;34(3):359-80. doi: 10.1007/s10555-015-9572-2.
22. Bays HE. Safety considerations with omega-3 fatty acid therapy. *Am J Cardiol.* 2007;99(6A):35C-43C.
23. 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. *Support Care Cancer*. 2010;18(2):179-87. doi: 10.1007/s00520-009-0642-2.
24. Yennurajalingam S, Reddy A, Tannir NM, Chisholm GB, Lee RT, Lopez G, et al. High-dose Asian ginseng (Panax ginseng) for cancer-related fatigue: A preliminary report. *Integr Cancer Ther*. 2015;14(5):419-27. doi: 10.1177/1534735415580676.
25. King ML, Murphy LL. American ginseng (*Panax quinquefolius L.*) extract alters mitogen-activated protein kinase cell signaling and inhibits proliferation of MCF-7 cells. *J Exp Ther Oncol.* 2007;6(2):147-55.
26. King ML, Adler SR, Murphy LL. Extraction-dependent effects of American ginseng (*Panax quinquefolium*) on human breast cancer cell proliferation and estrogen receptor activation. *Integr Cancer Ther.* 2006;5(3):236-43.
27. Duda RB, Zhong Y, Navas V, Li MZ, Toy BR, Alavarez JG. American ginseng and breast cancer therapeutic agents synergistically inhibit MCF-7 breast cancer cell growth. *J Surg Oncol.* 1999;72(4):230-9.
28. Bower JE. Cancer-related fatigue--mechanisms, risk factors, and treatments. *Nat Rev Clin Oncol.* 2014;11(10):597-609. doi: 10.1038/nrclinonc.2014.127.