

Journal of **Nutrition and Food Security**

Shahid Sadoughi University of Medical Sciences School of Public Health Department of Nutrition Nutrition & Food Security Research Center



eISSN: 2476-7425 pISSN: 2476-7417 JNFS 2022; 7(3): 379-387 Website: jnfs.ssu.ac.ir

Effectiveness of Co-Administration of Camelina Oil and Caloric Restriction on Cardiometabolic Risk Factors, Liver Function and Mental Health in Patients with Non-Alcoholic Fatty Liver Disease: A Blinded Randomized Controlled Trial Protocol

Vali Musazadeh; MSc1, Parvin Dehghan; PhD *2 & Sodeif Azadmard-Damirchi, PhD 3

- ¹ Student research committee, School of Nutrition and Food Science, Tabriz University of Medical Sciences, Tabriz, Iran.
- ² Nutrition Research Center, School of Nutrition and Food Science, Tabriz University of Medical Sciences, Tabriz, Iran.
- ³ Department of Food Science and Technology, School of Agriculture, University of Tabriz, Tabriz, Iran.

ARTICLE INFO

PROTOCOL ARTICLE

Article history:

Received: 28 May 2021 Revised: 22 Aug 2021 Accepted: 22 Sep 2021

*Corresponding author:

dehghan.nut@gmail.com Nutrition Research Center, Faculty of Nutrition and Food Science, Tabriz University of Medical Sciences, Iran

Postal code: 5166614711 Tel: +98 4133376229

ABSTRACT

Background: Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease (CLD). Omega-3 fatty acids and antioxidants cosupplementation have been considered as an alternative treatment in NAFLD. This trial will evaluate camelina sativa oil (CSO) effects as a rich source of omega-3 fatty acids and antioxidants on cardiometabolic risk factors, metabolic endotoxemia, liver enzymes, hepatic steatosis, and mental health in NAFLD patients. **Methods:** Forty-six patients with NAFLD will be randomly assigned to either a CSO supplementation or placebo for 12 weeks. Both groups will receive a weight-loss diet too. Insulin resistance, oxidative stress, anti/inflammatory biomarkers, lipid profile, adiponectin, lipopolysaccharide (LPS), anthropometric indices, liver enzymes, hepatic steatosis, and cortisol will be assessed all patients at baseline and post-intervention. DASS and GHQ questionnaires will be completed for all patients at baseline and postintervention. Results: The CSO is expected to reduce hepatic steatosis and improve cardiometabolic risk factors, liver function, and mental health compared to the placebo group after 12 weeks. Conclusion: The CSO as a phytopharmaceutical drug may improve cardiometabolic risk factors, metabolic endotoxemia, liver enzymes, hepatic steatosis, and mental health in patients with NAFLD.

Keywords: Fatty acids omega-3; Camelina oil; Oxidative stress; Inflammatory biomarkers; Non-alcoholic fatty liver disease

This paper should be cited as Musazadeh V, Dehghan P, Azadmard-Damirchi S. Effectiveness of Co-Administration of Camelina Oil and Caloric Restriction on Cardiometabolic Risk Factors, Liver Function and Mental Health in Patients with Non-Alcoholic Fatty Liver Disease: A Blinded Randomized Controlled Trial Protocol. Journal of Nutrition and Food Security (JNFS), 2022; 7(3): 379-387.

Introduction

The most common chronic liver disease (CLD) the non-alcoholic fatty liver disease (NAFLD) that is characterized by a high hepatic triglyceride content (over 5%) and the histological feature of simple steatosis, with no evidence of alcohol abuse (Hardy et al., 2016). NAFLD has a broad pathological spectrum that ranges from simple steatosis to Non-alcoholic steatohepatitis (NASH) with varying degrees of fibrosis and cirrhosis (Chalasani et al., 2012). Approximately 30% of developed countries adults are considered to develop NAFLD (Younossi et al., 2018), and between 20% to 30% of them will subsequently develop NASH (Reccia et al., 2017), leading to cirrhosis and its complications, such as portal hypertensive bleeding, hepatocellular carcinoma, and hepatic decompensation (McCarthy and Rinella, 2012). According to a report, the NAFLD prevalence is 33.9% in Iran as a developing country (Younossi et al., 2018). Currently, the multiple-hit model has shown that genetic, epigenetic, environmental, or nutritional factors, including higher age, inactivity, obesity, and high energy intake, are the most critical risk factors for fatty liver, resulting in fat accumulation in the liver and the induction of the disease via increasing insulin resistance (Utzschneider and Kahn, 2006), oxidative stress (Pereira et al., 2008), and inflammatory factors (Hu et al., 2004). However, no definitive pharmacological treatment has been approved for the treatment of NAFLD. NAFLD therapeutic approaches are substantially focused on lifestyle modification, especially nutritional and exercise interventions. A systematic review found that diet and exercise interventions in NAFLD patients modulated liver fat, liver aminotransferase level, and insulin sensitivity, all of which strongly correlate with weight loss (Hannah and Harrison, 2016, Thoma et al., 2012). Among nutritional interventions, n-3 PUFAs supplementation is a potential way to treat and prevent NAFLD due to low n-3 PUFAs dietary intake and the higher hepatic n-6/n-3 ratio in NAFLD patients (Araya et al., 2004). Omega-3 PUFA sources might help

alleviate the NAFLD complications by improving beta-cell function, lipid profile, serum inflammatory markers, oxidative stress. endothelial function, and the gut microbiota composition (Parker et al., 2012). However, due to recent concerns about the animal sources of omega-3 like fish oil, including the contamination possibility with heavy metals, such as mercury and dioxins, the unpleasant odor of the oil, the possible side effects, and also the lack of interest in consuming animal-derived products vegetarianism and veganism, the plant sources of omega-3 PUFA has attracted many researchers and physicians' attention (Mendes et al., 2009, Raghukumar, 2008).

The Camelina sativa (CS) is a flowering plant belonging to the family Brassicaceae that is recognized as false flax. The Camelina sativa oil (CSO) is one of the richest dietary sources of omega-3 fatty acids, with PUFA amounts over 50%, high alpha-linolenic acid (ALA) (40% to 45%), and about 15% linoleic acid (LA), the n-3 to n-6 ratio (1.79-2.17), low saturated fatty acid (SFA) content (about 9%), high contents of antioxidants, including tocopherols (55.8-76.1 mg/100 g) (Zubr and Matthäus, 2002), carotenoids (103-198 mg of carotene/kg), and phytosterols (331-442 mg/100 g) (Abramovič et al., 2007). It was reported that the high content of tocopherols in CSO inhibits extracted oil autoxidation. This significant beneficial aspect is not seen in flaxseed oil as one of the richest plant sources of omega-3 fatty acid. It has been reported that CS oil (CSO) may also have less fertilizer contamination than other oils (Ergönül and Özbek, 2020). The limited trials have investigated the effect of CSO supplementation on the modulation of the lipid profile, oxidative stress, and immune system (de Mello et al., 2019, Erkkilä et al., 2019, Schwab et al., 2018). To best of the authors' knowledge, the effects of CSO intake on insulin resistance, anti/inflammatory biomarkers, oxidative stress, and hepatic steatosis in patients with NAFLD have not been investigated. Therefore, the current study will examine the effects of dietary intake of CSO as one of the richest plant sources of omega-3 fatty acids and antioxidants in combination with a weight loss program on some parameters. They include insulin resistance, lipid profile, oxidative stress, anti/inflammatory biomarkers, adiponectin, Lipopolysaccharides (LPS), anthropometric indices, liver enzymes, hepatic steatosis, and mental health in patients with NAFLD.

Materials and Methods

Study design and participants: This is a placebocontrolled, triple-blind, randomized clinical trial to evaluate the CSO effects on insulin resistance. oxidative stress, anti/inflammatory biomarkers, lipid profile, adiponectin, LPS, anthropometric indices, liver enzymes, and hepatic steatosis in patients with NAFLD. This study will be conducted in the Valiasr hospital of Tabriz, Iran, and clinics of Tabriz via advertisements and posters. Fig. 1 depicts an overview of the research. This study also will be reported the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement. A SPIRIT diagram revealing details of the timing of enrolment, interventions, and assessments is provided in Fig. 2. A completed SPIRIT checklist is also provided in Additional file 1. Any methodological changes in the study design or sample size that may affect the safety or study procedures of the participants will be discussed with the ethics committee before starting the study.

Eligibility of criteria: The inclusion criteria include NAFLD diagnosis by a specialist using an ultrasound examination, aged 20-50 years old, body mass index (BMI) ranged 25–35 kg/m², gender, adherence to a fixed diet, regular physical activity level (PAL), and willingness to participate. The exclusion criteria also include a history of biliary disease, hepatitis B and C, copper and iron storage disease, cardiovascular, gastrointestinal, and renal disease, pancreas disorders, thyroid disorders, cancer, smoking, pregnancy, lactation, post-menopausal period, intake of lipid-lowering and fatty liver medications, currently antibiotics consumption, antacids intake, antidiarrheal, anti-

inflammatory or laxative medicines, and patients with special diets or dietary limitations. Patients will also be asked to consume the minimum amount of nuts and fish and not take antioxidants and omega-3 supplements. All the patients will sign an informed consent at the baseline visit after receiving a complete explanation of the study protocol.

Randomization and blinding: After a 2-week run-in period, the eligible patients will be randomly assigned to the supplementation (n=23) or the placebo group (n=23) for 12 weeks. The randomization will be done based on a blocking procedure matched for age, sex, and BMI. Random allocation software will be used to perform allocation sequencing. A third person will assign the subjects to the study groups to ensure the concealing process of research elements. Until the end of the analysis, the statistical consultant and the main researcher will be blinded regarding the subjects' groups.

Sample size: The sample size was calculated regarding the changes in SOD level as one of the primary outcomes using the Pocock formula with a 90% power and 95% confidence interval (n=21). Additional participants will be recruited until the required number is achieved (n = 23) per group to account for the estimated drop-out rate of 10% (Pocock, 2013).

Intervention: Two trained researchers will explain the study to the participants before starting the study. The patients will be requested to keep their usual PAL and follow the designed diet until the end of the intervention. A low-calorie diet (-500 kcal) will be designed for patients in both groups (the energy distribution: 50-55% from carbohydrates, 15-20% from protein, 30-35% from fat, <300 mg from dietary cholesterol per day) based on the Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults from the National Institutes of Health and recommendations by the North American Association for the Study of Obesity (North American Association for the Study of Obesity, 2000). A dietitian will explain the diet and give each patient an exchange list to enhance the diet's adherence during the 12-week intervention.

The intervention group (IG) will receive a 15% of the daily total fat intake (~20g) from CSO (Jahan, Tabriz, Iran). The placebo group (PG) will receive a similar amount of sunflower oil (SFO) as a PG for 12 weeks. CSO and SFO will be delivered to the patients in similar bottles. A 10 ml measuring cup will be provided for the participants to add two cups of oil per day to rice or salads at the time of consumption. The CSO will provide about one-third of the daily oil requirements of the participants. The rest of the diet oil will be acquired from low-fat meats, dairy, and cooking oil. After a full explanation of the diet, the patients will receive an exchange list to facilitate adherence to the designed diet during the intervention. A checklist will also be provided for the participants to mark after each consumption of the prescribed oil to evaluate for cases of non-compliance. Furthermore, with a 15-day follow-up and anthropometric measurements, and completion of a 3-day questionnaire, it will be estimated that all the patients adhered to the diet at the end of the study. Furthermore, the extracted data percentage for macronutrients of Nutritionist 4 software will approve this issue. Oils will be delivered to the patients at baseline and 45 days after starting the study. To emphasize on maintaining physical activity and designed diet, resolve problems with how to take supplements and to ensure compliance, all the participants will be contacted two times per week by a dietitian.

Primary and secondary outcomes: The primary outcomes of the present study are lipid profile, enzymes, glycemic indices, resistance, high-sensitivity C-reactive protein (hs-CRP), Interleukin 10 (IL10), Interleukin 6 (IL6), Tumor necrosis factor-alpha (TNFa), LPS, total antioxidant capacity (TAC), superoxide dismutase glutathione peroxidase (SOD), (GSH-Px), catalase, malondialdehyde (MDA), uric acid, and 8-iso-prostaglandin F2a $(8-iso-PGF2\alpha)$, adiponectin and cortisol in NAFLD patients. While

the secondary outcomes are anthropometric indices, body composition, blood pressure, dietary intake, and mental health.

Questionnaires: At the baseline, the participants will receive a full explanation of the study and then will ask to fulfill a demographic questionnaire containing variables including age, sex, PAL, and the current medications. Weight will be measured barefoot and in light clothing to the nearest 0.5 kg using a reliable scale (Seca, Hamburg, Germany). Height measurement will be done without shoes using a centimeter tape with a precision of 0.1 cm. Waist circumference (WC) will obtain using an inelastic tape at the midpoint between the lowest rib and the upper iliac crest. Neck circumference (NC) will obtain below the cricoid cartilage. Hip circumference (HC) will measure around the widest portion of the buttocks without pressing the skin, with the tape parallel to the floor. BMI will compute by dividing weight (kg) by the square of the height (m).

A 3-day food diary will be used to assess dietary intake (two weekdays and one weekend) before starting the low-calorie diet and supplements and at the end of the study. Dietary intake data will be analyzed by "Nutritionist 4" (First Databank Inc., Hearst Corp., San Bruno, CA, USA). The subjects' PAL will assess using the International Physical Activity Questionnaire (Vasheghani-Farahani et al., 2011) before and after the intervention. The mental health data of patients will be collected using the depression, anxiety, and stress scale (DASS) and general health questionnaires (GHQ). The DASS consists of 14 items divided into three subscales to assess depression, anxiety, and stress (Sahebi et al., 2005). Four other subscales, including somatic symptoms, anxiety, insomnia, social dysfunction, and severe depression, were also assessed by 28-item GHQ (Yaghubi et al., 2012).

Assessments and measurements: Following an overnight fast, a venous blood sample (10 ml) will be collected from the patients. Plasma samples will be used to analyze the parameters, including insulin, fasting plasma glucose (FPG), MDA,

TAC, uric acid, hs-CRP, and 8-iso-PGF2α. FPG and uric acid will be measured via an autoanalyzer using kits via the enzymatic method. Plasma insulin will be measured using a chemiluminescent immunoassay method. TAC, GSH-Px, and SOD activity levels will be measured through a colorimetric method by an automatic analyzer. **MDA** level will be determined spectrofluorimeter, and the Aebi method will be applied to determine catalase activity (Aebi, 1974). An enzyme-linked immunosorbent assay (ELISA) will be used to measure the circulating adiponectin, cortisol, LPS, IL10, IL6, and TNF-α. According to the American Heart Association guidelines, the blood pressure will be determined with a well-validated automated digital blood pressure monitor (Beurer, Germany, BM 85). Total cholesterol, triglycerides, HDL-c, and liver enzymes, including ALT, AST, GGT, and ALP will be measured using automated enzymatic methods.

The insulin resistance will calculate using a homeostatic model assessment for insulin resistance (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI) via the following formula:

HOMA-IR = [fasting insulin (mU/l) \times fasting blood glucose (mg/dl)] / 405

QUICKI = 1/(log (insulin, U/ml) + log (FPG, mg/dl)) (Gutch *et al.*, 2015)

All of the assessments will be done before and after the intervention.

Chemical analysis of oils: The fatty acid compositions of CSO and SFO will be determined using gas chromatography (Budin *et al.*, 1995).

Ethical conciderations: Trial registration number: IRCT20150205020965N5, 13 December 2019, Intervention registration.

Data analysis: SPSS version 24.0 will use to analyze the data. The results will be shown as mean (SD) and frequency (percent) for quantitative and qualitative data. The intention-to-treat approach will be used to include data of subjects who discontinued the trial. The Kolmogorov-Smirnov test will be used to determine the normality distribution of data. An unpaired sample student ttest and Chi-square test will be applied to assess between-group quantitative and qualitative data differences, respectively. Analysis of covariance (ANCOVA) will be applied to compare the quantitative variables between groups after the intervention. A paired sample student t-test will also be used to compare the differences between baseline and post-intervention groups. Percentage changes will be calculated as [100 × (IG values -PG values)/placebo values] to determine the differences between groups. P < 0.05 will consider statistically significant.

Results

CSO is expected to reduce hepatic steatosis and improve cardiometabolic risk factors, liver function, and mental health compared to the PG after 12 weeks. Over the past few years, the benefits of omega-3 (Janczyk *et al.*, 2013) and antioxidants (Musso *et al.*, 2013) have been reported in managing NAFLD complications. CSO supplementation, as one of the richest dietary sources of omega-3 fatty acids and antioxidants, may be an effective complementary therapy in NAFLD patients.

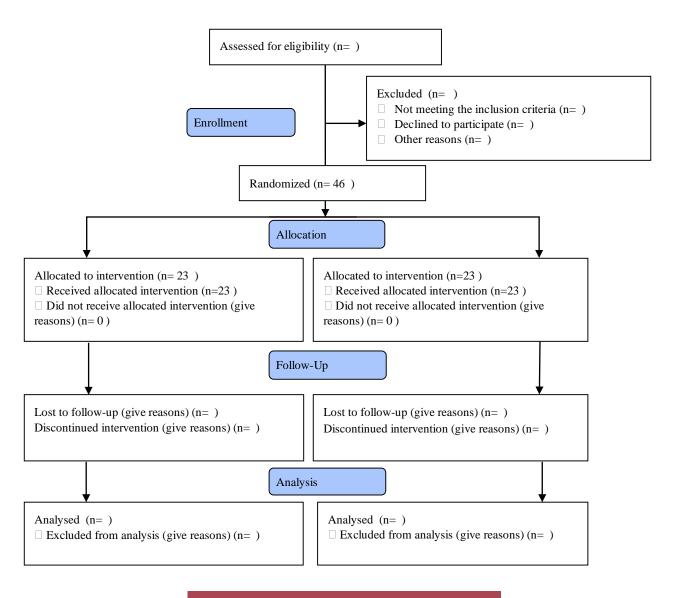


Figure 1. The overview of the study flowchart.

Figure 2. Template of recommended content for the schedule of enrolment, interventions, and assessment.

	STUDY PERIOD					
	Enrolment	Allocation	Post-allocation			Close-out
Time point	-t ₁	0	+1 Month	+1.5 Months	+2 Months etc.	+3 Months
Enrolments						
Eligibility screen	X					
Informed consent	X	X				
General questionnaire		X				
24 hours food recall		X		X		X
SF-IPAQ questionnaire		X				X
Anthropometrics		X				X
Other questionnaires		X				X
Blood taking		X				X
Allocation		X				
Interventions						
Intervention A			X	X	X	
Intervention B			X	X	X	
Assessments						
Dietary status		X		X		X
Blood pressure		X		X		X
Physical activity status		X				X
Lipid profile		X				X
Liver enzymes		X				X
Hepatic steatosis		X				X
Anthropometrics		X		X		X
Inflammatory factors		X				X
Insulin		X				X
Oxidative stress		X				X
Adiponectin		X				X
LPS		X				X

SF-IPAQ: Short-Form International Physical Activity Questionnaire, LPS: Lipopolysaccharide

Discussion

Today, no definite pharmacological treatment for NAFLD has been approved. The majority of NAFLD treatment approaches focus on lifestyle modification, including nutritional and exercise interventions. In addition to nutritional and exercise interventions, supplementation has recently been proposed as an efficient therapeutic approach in NAFLD. Omega-3 and antioxidants, such as vitamin E have longly been recommended as the most common supplements for NAFLD treatment. It should be noted that the cellular pathways and mechanisms related to this issue are not clear. However, as a rich source of omega-3 and antioxidants, CSO has probably had beneficial effects in alleviating liver steatosis due to its antiantioxidant, anti-inflammatory obesity, and properties. The current study aims to assess the impacts of CSO on insulin resistance, oxidative stress, anti/inflammatory biomarkers, lipid profile, adiponectin, LPS, anthropometric indices, liver enzymes, hepatic steatosis, and mental health in NAFLD patients. If the results of the present study are confirmed by more randomized controlled trials, CSO, as one of the richest dietary sources of omega-3 fatty acids, can be recommended as a complementary therapy in NAFLD patients.

Strengths and limitations of the study

- 1. This study is the first to evaluate CSO's impact on glycemic indices, inflammatory and oxidative stress parameters, and metabolic endotoxemia in NAFLD patients.
- 2. This study will not assess gut and fecal microbial composition, serum SCFA, glucose clamp, free fatty acids, and other inflammatory/oxidative stress biomarkers due to

financial constraints.

Authors' contributions

Dehghan P and Musazadeh V contributed to the conception, design, statistical analysis, and drafting of the manuscript. Dehghan P, Musazadeh V, Azadmard-Damirchi S contributed to the conception, data collection, and manuscript drafting. All authors confirmed the final version for submission.

Additional file

Additional file 1: SPIRIT Checklist.

Conflict of interest statement

Both authors declare that there is no conflict of interest.

Funding statement

This study will be financially supported by the Vice-Chancellor for Research Affairs of Tabriz University of Medical Sciences (grant number: 65932).

Acknowledgments

The authors would like to acknowledge patients and the dedication and commitment of the staff at Nutrition Research.

References

- Abramovič H, Butinar B & Nikolič V 2007. Changes occurring in phenolic content, tocopherol composition and oxidative stability of Camelina sativa oil during storage. *Food chemistry.* **104** (3): 903-909.
- **Aebi H** 1974. Catalase. In *Methods of enzymatic analysis*, pp. 673-684. Elsevier.
- **Araya J, et al.** 2004. Increase in long-chain polyunsaturated fatty acid n- 6/n- 3 ratio in relation to hepatic steatosis in patients with non-alcoholic fatty liver disease. *Clinical science*. **106 (6)**: 635-643.
- Budin JT, Breene WM & Putnam DH 1995. Some compositional properties of camelina (Camelina sativa L. Crantz) seeds and oils. *Journal of the American oil chemists' society.* 72 (3): 309-315.
- **Chalasani N, et al.** 2012. The diagnosis and management of non-alcoholic fatty liver disease:

- practice guideline by the American Gastroenterological Association, American Association for the Study of Liver Diseases, and American College of Gastroenterology. *Gastroenterology*. **142** (7): 1592-1609.
- de Mello VD, et al. 2019. The effect of different sources of fish and camelina sativa oil on immune cell and adipose tissue mRNA expression in subjects with abnormal fasting glucose metabolism: a randomized controlled trial. *Nutrition & diabetes.* 9 (1): 1-12.
- Ergönül PG & Özbek ZA 2020. Cold pressed camelina (Camelina sativa L.) seed oil. In *Cold pressed oils*, pp. 255-266. Elsevier.
- **Erkkilä AT, et al.** 2019. Camelina sativa oil, fatty fish, and lean fish do not markedly affect urinary prostanoids in subjects with impaired glucose metabolism. *Lipids*. **54** (**8**): 453-464.
- Gutch M, Kumar S, Razi SM, Gupta KK & Gupta A 2015. Assessment of insulin sensitivity/resistance. *Indian journal of endocrinology and metabolism.* 19 (1): 160.
- **Hannah WN & Harrison SA** 2016. Lifestyle and dietary interventions in the management of nonalcoholic fatty liver disease. *Digestive diseases and sciences.* **61 (5)**: 1365-1374.
- Hardy T, Oakley F, Anstee QM & Day CP 2016. Nonalcoholic fatty liver disease: pathogenesis and disease spectrum. *Annual review of pathology: mechanisms of disease.* 11: 451-496.
- Hu FB, Meigs JB, Li TY, Rifai N & Manson JE 2004. Inflammatory markers and risk of developing type 2 diabetes in women. *Diabetes*. **53** (3): 693-700.
- **Janczyk W, et al.** 2013. Omega-3 fatty acids for treatment of non-alcoholic fatty liver disease: design and rationale of randomized controlled trial. *BMC pediatrics.* **13** (1): 1-11.
- McCarthy EM & Rinella ME 2012. The role of diet and nutrient composition in nonalcoholic fatty liver disease. *Journal of the Academy of nutrition and dietetics.* 112 (3): 401-409.
- Mendes A, Reis A, Vasconcelos R, Guerra P & da Silva TL 2009. Crypthecodinium cohnii with emphasis on DHA production: a review. *Journal of applied phycology.* **21** (2): 199-214.

- **Musso G, Anty R & Petta S** 2013. Antioxidant therapy and drugs interfering with lipid metabolism: could they be effective in NAFLD patients? *Current pharmaceutical design.* **19** (**29**): 5297-5313.
- North American Association for the Study of Obesity 2000. National Heart, Lung, Blood Institute and NHLBI Obesity Education Initiative, the Practical Guide: Identification, Evaluation, and Treatment of Overweight and Obesity in Adults.
- **Parker HM, et al.** 2012. Omega-3 supplementation and non-alcoholic fatty liver disease: a systematic review and meta-analysis. *Journal of hepatology*. **56 (4)**: 944-951.
- **Pereira EC, et al.** 2008. Biomarkers of oxidative stress and endothelial dysfunction in glucose intolerance and diabetes mellitus. *Clinical biochemistry.* **41** (**18**): 1454-1460.
- **Pocock SJ** 2013. Clinical trials: a practical approach. John Wiley & Sons.
- **Raghukumar S** 2008. Thraustochytrid marine protists: production of PUFAs and other emerging technologies. *Marine biotechnology*. **10** (**6**): 631-640.
- **Reccia I, et al.** 2017. Non-alcoholic fatty liver disease: a sign of systemic disease. *Metabolism*. **72**: 94-108.
- Sahebi A, Asghari MJ & Salari RS 2005.
 Validation of depression anxiety and stress scale (DASS-21) for an Iranian population. *Journal of developmental psychology*. 1 (4).

- Schwab US, et al. 2018. Camelina sativa oil, but not fatty fish or lean fish, improves serum lipid profile in subjects with impaired glucose metabolism—a randomized controlled trial. *Molecular nutrition & food research.* 62 (4): 1700503.
- **Thoma C, Day CP & Trenell MI** 2012. Lifestyle interventions for the treatment of non-alcoholic fatty liver disease in adults: a systematic review. *Journal of hepatology.* **56** (1): 255-266.
- **Utzschneider KM & Kahn SE** 2006. The role of insulin resistance in nonalcoholic fatty liver disease. *Journal of clinical endocrinology & metabolism.* **91** (12): 4753-4761.
- Vasheghani-Farahani A, et al. 2011. The Persian, last 7-day, long form of the International Physical Activity Questionnaire: translation and validation study. *Asian journal of sports medicine*. 2 (2): 106
- Yaghubi H, Karimi M & Omidi A 2012. Validity and Factor Structure f the General Health Questionnaire (GHQ-12) In University Students. *International journal of behavioral sciences.* 6 (2).
- **Younossi Z, et al.** 2018. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. *Nature reviews gastroenterology & hepatology.* **15** (1): 11-20.
- **Zubr J & Matthäus B** 2002. Effects of growth conditions on fatty acids and tocopherols in Camelina sativa oil. *Industrial crops and products.* **15** (2): 155-162.