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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

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ABSTRACT

Background: Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease (CLD). Omega-3 fatty acids and antioxidants co-supplementation 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 post-intervention. **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

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Introduction

The most common chronic liver disease (CLD) is 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, serum lipid profile, 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 in 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 placebo-controlled, 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, liver enzymes, glycemic indices, insulin resistance, high-sensitivity C-reactive protein (hs-CRP), Interleukin 10 (IL10), Interleukin 6 (IL6), Tumor necrosis factor-alpha (TNF α), LPS, total antioxidant capacity (TAC), superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), catalase, malondialdehyde (MDA), uric acid, and 8-iso-prostaglandin F 2α (8-iso-PGF 2α), 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-PGF2 α . 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 by 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:

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

$$\text{QUICKI} = 1/(\log(\text{insulin, U/ml}) + \log(\text{FPG, mg/dl})) \text{ (Gutch et al., 2015)}$$

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 considerations: 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 t-test 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 $[100 \times (\text{IG values} - \text{PG values}) / \text{placebo values}]$ 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.

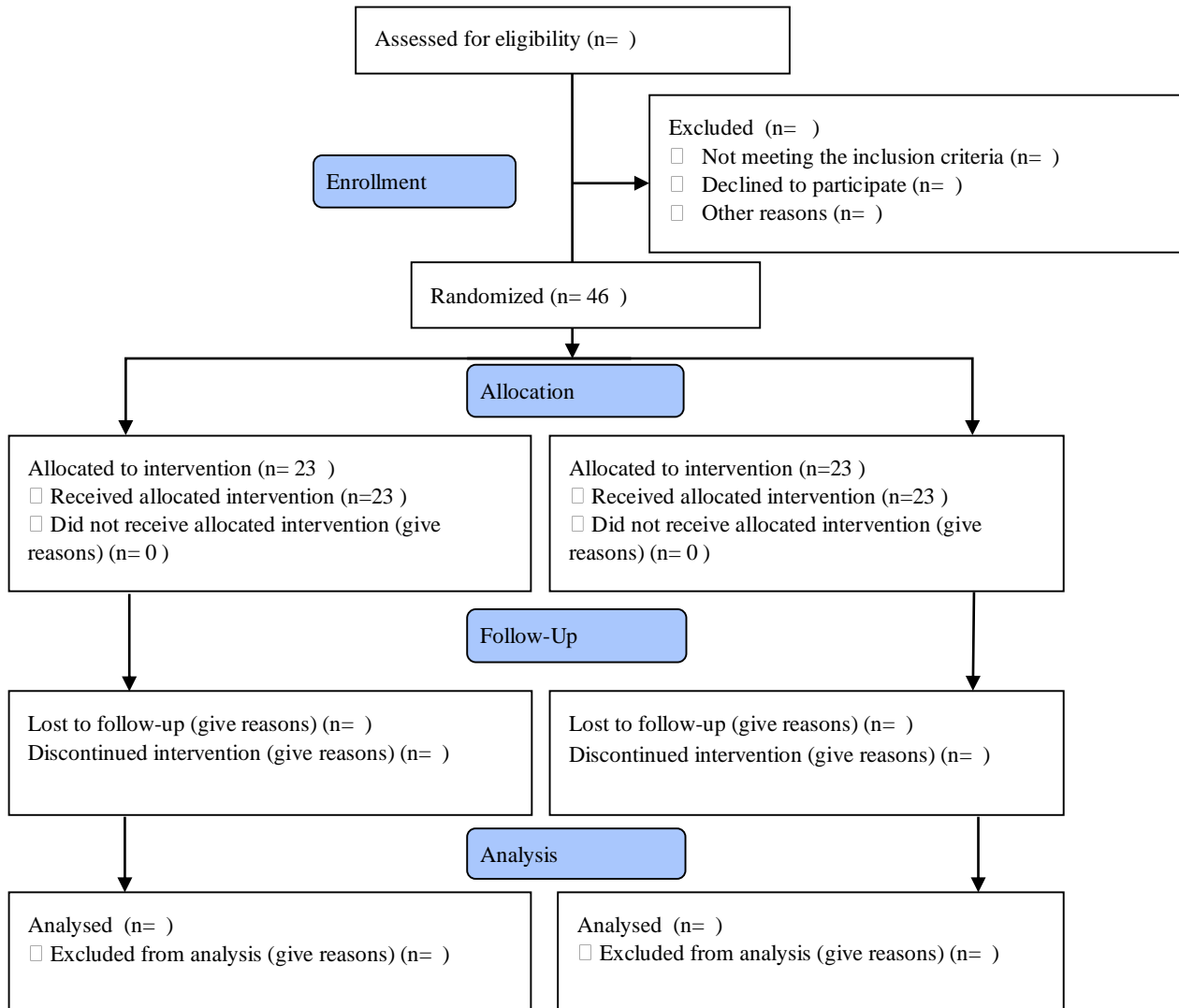


Figure 1. The overview of the study flowchart.

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

Time point	Enrolment -t ₁	Allocation 0	STUDY PERIOD			Close-out +3 Months
			+1 Month	Post-allocation +1.5 Months	+2 Months etc.	
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 anti-obesity, antioxidant, and anti-inflammatory 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.

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