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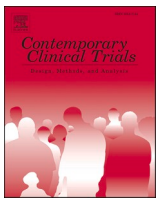

Effects of an intervention with EVOO and physical exercise in systemic lupus erythematosus patients: Efinutriles trial protocol

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ABSTRACT

Background: Health-related lifestyle management could improve related symptoms and adverse events in patients with systemic lupus erythematosus (SLE). The phenolic compounds in extra virgin olive oil (EVOO) and physical exercise (PE) have both shown benefits for autoimmune conditions, but no intervention has synergised the two approaches.
Aim: To analyse the effects of an intervention combining EVOO and a multicomponent health promotion and PE programme on disease activity, clinical characteristics, cardiovascular risk, physical fitness, and the molecular level in SLE sufferers.
Methods: Three-arm prospective randomised controlled 24-week clinical trial. 90 participants will be randomised into one of three groups: control; EVOO supplements; or EVOO and multicomponent health promotion and PE programme.
Results: Pre-, mid- and post-intervention assessments will record disease activity, clinical characteristics, nutritional evaluation, cardiovascular risk assessment, physical condition and functioning, and molecular markers.
Conclusions: The proposed trial will help clarify whether a combined intervention adding an EVOO supplement to a Mediterranean Diet intake pattern and adherence to an active-healthy lifestyle are beneficial for SLE patients, as well as the need for health and pharmacological care, increasing knowledge of the organic mechanisms mediated by EVOO and PE adherence, allowing new useful biomarkers to be characterised at the diagnostic/prognostic level.

1. Background

Systemic lupus erythematosus (SLE), one of the most characteristic autoimmune diseases [1], is a complex condition with a great deal of clinical heterogeneity and a high morbidity-mortality rate. Its aetiology is still unknown to the scientific community, although it has been linked to an interaction between hormonal, genetic, immunological and environmental factors that trigger a systemic autoimmune response

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characterised by immune system activation (especially exaggerated B and T cells) and a loss of tolerance to self-antigens [2,3].

Patients suffer from several clinical manifestations ranging from mild symptoms (e.g., fatigue, cutaneous-mucosal symptoms, and joint pain) to severe and life-threatening ones (e.g., cardiovascular, neuropsychiatric, and renal conditions), having a huge impact in terms of socioeconomic and health costs to patients, families, and health economies. It is widely established that the therapeutic target is to induce clinical remission over time or, if this is not possible, a state of low inflammation disease activity [4], achieved by decreasing the autoimmunity status using a combination of antimalarial hydroxychloroquine, glucocorticoids, and immunosuppressive agents over long periods; this approach, despite its effectiveness, is accompanied by an increase in adverse effects and long-term damage, resulting in poor adherence to therapeutic regimens, a higher risk of flare ups, and morbidity-mortality [5].

Appropriately managing *health-related lifestyles* (adequate dietary patterns, regular physical exercise, and stress control) could be crucial in SLE as this has been proven to balance, among other things, physiological status (microbiota dysbiosis, skin damage, immune response); fitness (body composition, physical and functional capacity) and mood (fatigue, anxiety and depression symptoms), having a positive impact on the clinical course of SLE and quality of life [6].

The Mediterranean Diet (MD), a plant-based diet characterised by the use of Extra Virgin Olive Oil (EVOO), has shown to provide a protective effect against chronic diseases and decrease mortality [7]. The molecular basis of these benefits is still poorly understood, but it seems that the MD and its components modulate intestinal microbiome, miRNA expression, oxidative stress, and the production of immune and inflammatory markers [8].

Previous studies have suggested that most of the benefits of this diet could be attributed to the phenolic compounds in EVOO, which are anti-inflammatory, antimicrobial and antioxidant [9]. Although there is strong evidence to suggest the beneficial effects of EVOO supplements and adherence to the MD on health outcomes in general populations, there is limited evidence in autoimmune disease cohorts. The results of the LyDIMED study revealed how greater adherence to the MD decreases cardiovascular risk and improves the clinical course of SLE (disease activity and organ damage) [10], in line with other cross-sectional non-interventional studies [11]. For this reason, longitudinal studies would help establish causal relationship between the MD, EVOO and the clinical course of SLE.

Adherence to moderate-intensity physical exercise (PE) programmes is safe and feasible in SLE patients [12], producing improvements not only in aerobic capacity but also cardiovascular status, functional ability, fatigue, depression, and quality of life [13,14]. Despite this, published results show certain contradictions [14] due to the heterogeneity of the interventions, as well as disease activity variability in study participants. It is therefore necessary to run further studies to explore how adherence to PE affects overall health and disease activity over time in SLE sufferers.

Current evidence shows both the protective effect of EVOO supplements and adherence to PE on the progression of SLE and the risks associated with it, but no intervention has ever combined the two approaches. Consequently, a combined strategy could be effective in enhancing improvements in SLE patient quality of life, as a complement to pharmacological approaches. Additionally, it is important to consider how such a multidisciplinary intervention could directly impact nursing care, as nursing professionals are the gateway to the healthcare system, and indirectly improve healthcare systems and the costs related to caring for people with chronic conditions. The implementation of strategies such as the one outlined above, if successful, could help reduce direct workloads and staff turnover, increase retention of professionals, foster resilience, and also inspire nurses to follow similar self-care practices and take an active role in managing their health status and symptomatology.

Considering everything explained above, the main objective of this study protocol is to analyse the effect of an intervention combining EVOO supplements with a multicomponent health promotion and PE programme on disease activity in SLE sufferers. The secondary objectives are to analyse the effect of the intervention in terms of clinical characteristics, cardiovascular risk, physical fitness, and the molecular level (MiRNA expression and microbiome).

2. Methods

2.1. Design

The study protocol involves a three-arm prospective randomised controlled 24-week clinical trial that will be developed following the recommendations of the following standard protocol items: Recommendation for Interventional Trials, the Consolidated Standards of Reporting Trials Statement, and the Template for Intervention Description and Replication Checklist. The clinical trial has been registered at ClinicalTrials.gov (Identifier NCT05261529). The materials and workspaces required will be provided by the nursing department and physiotherapy lab at the Sport and Health University Research Institute (iMUDS), unit BIO277 (CUIDATE) at the University of Granada.

2.2. Study setting and sampling

The study population will comprise SLE patients attending the outpatient clinic in the Systemic Autoimmune Diseases Unit at Hospital Universitario Clínico San Cecilio and Hospital Universitario Virgen de las Nieves (Granada, Spain), following the revised American College of Rheumatology (ACR), SLICC or ACR/EULAR criteria from 2019.

To achieve a statistical power of at least 80 % in order to determine significant changes with a threshold value of $p = 0.05$ in intermediate disease phenotypes (using a SLEDAI difference of 1.5 between groups as a reference), a sample of 24 participants per group is necessary. Considering an expected 20 % loss rate, a total of 90 subjects (30 per group) will be recruited (calculation performed using Power and Sample Size Calculations Version 2.1.23.).

2.3. Inclusion and exclusion criteria

The inclusion criteria will be: [1] an SLE diagnosis from at least one year prior; [2] stable SLEDAI-2 K (no flares or new symptomatology reported between annual medical check-ups) and no treatment modifications over the preceding 3 months; [3] subjects who are sedentary, inactive or not taking part in structured PE (+5 h sitting or less than 300 min of weekly physical activity, or < 60 min structured PE per week); and [4] medium (8–11 points) to high (12–14 points) adherence to the MD as measured by the 14-point MD adherence scale of the PREDIMED study [15].

The exclusion criteria will include: [1] SLE in the terminal stages; [2] serum creatinine levels ≥1.5 mg /dl; [3] type 1 diabetes mellitus; [4] infection, trauma or surgery six months prior to the intervention; [5] SLICC rating of >5 points; [6] pregnancy or breastfeeding; [7] diagnosis of other autoimmune/inflammatory diseases occurring independently of SLE or its associated damage or comorbidities; [8] participation in other guided PE programmes; [9] contraindication for PE: psychiatric or cognitive disorders, acute or chronic conditions (advanced lung disease, high requirements, stenosis>70 %); and [10] a body mass index of ≥40 kg/m^2.

2.4. Randomisation and allocation

After it has been checked that the potential participants meet the inclusion criteria ($-t_1$), they will be called to the University of Granada where the baseline (t_0) and consecutive (t_1,t_2) face-to-face assessments and PE intervention will take place.

As part of the baseline assessment and before allocation, a more than 5 years of experience nutrition specialist with specific expertise in MD and autoimmune conditions will remind the participants of the basic principles of the MD. This will involve a 1-h non-face-to-face session to ensure adequate levels of adherence to the MD throughout the intervention. Subsequently, the patients will be randomised and allocated to a group (Fig. 1) using the computer-supported centralised OxMar system (Oxford Minimization and Randomisation®, O'Callaghan CA) in a 1:1:1 distribution: control group (CG); intervention group 1 (IG1); or intervention group 2 (IG2). The data will be analysed by a blinded researcher. However, the patients and research staff responsible for performing the intervention will not be blinded.

2.5. Intervention

The participants in the CG will maintain their habitual lifestyle, therefore they will be encouraged to not to change their physical activity pattern, including physical exercise performance, daily physical activity, nutritional daily intake, tobacco or alcohol consumption, or sleep routine. The participants in IG1 will add a daily supplement of 40 ml of EVOO, in a single dose, to their habitual lifestyle, preferably taken at breakfast, over a 24-week period. The EVOO will have a fixed polyphenol content and stable composition. The participants allocated to IG2 will follow the same supplementation as IG1 and, after 12 weeks of EVOO supplements, they will start a multicomponent health promotion and PE programme lasting 12 weeks (see Fig. 2).

The EFINUTRILES programme is a multicomponent health promotion and PE programme developed with the main objective of improving overall health status by promoting participant adherence to an active healthy lifestyle and self-management. To achieve this, there are two well-defined components: a home-based daily physical activity promotion and health education programme, and a PE programme. The EFINUTRILES programme and its different parts are shown in Table 1. The intervention will be delivered by a nursing specialist with more than 5 years of solid experience on the influence of appropriate lifestyle management on clinical course and health outcomes of chronic conditions.

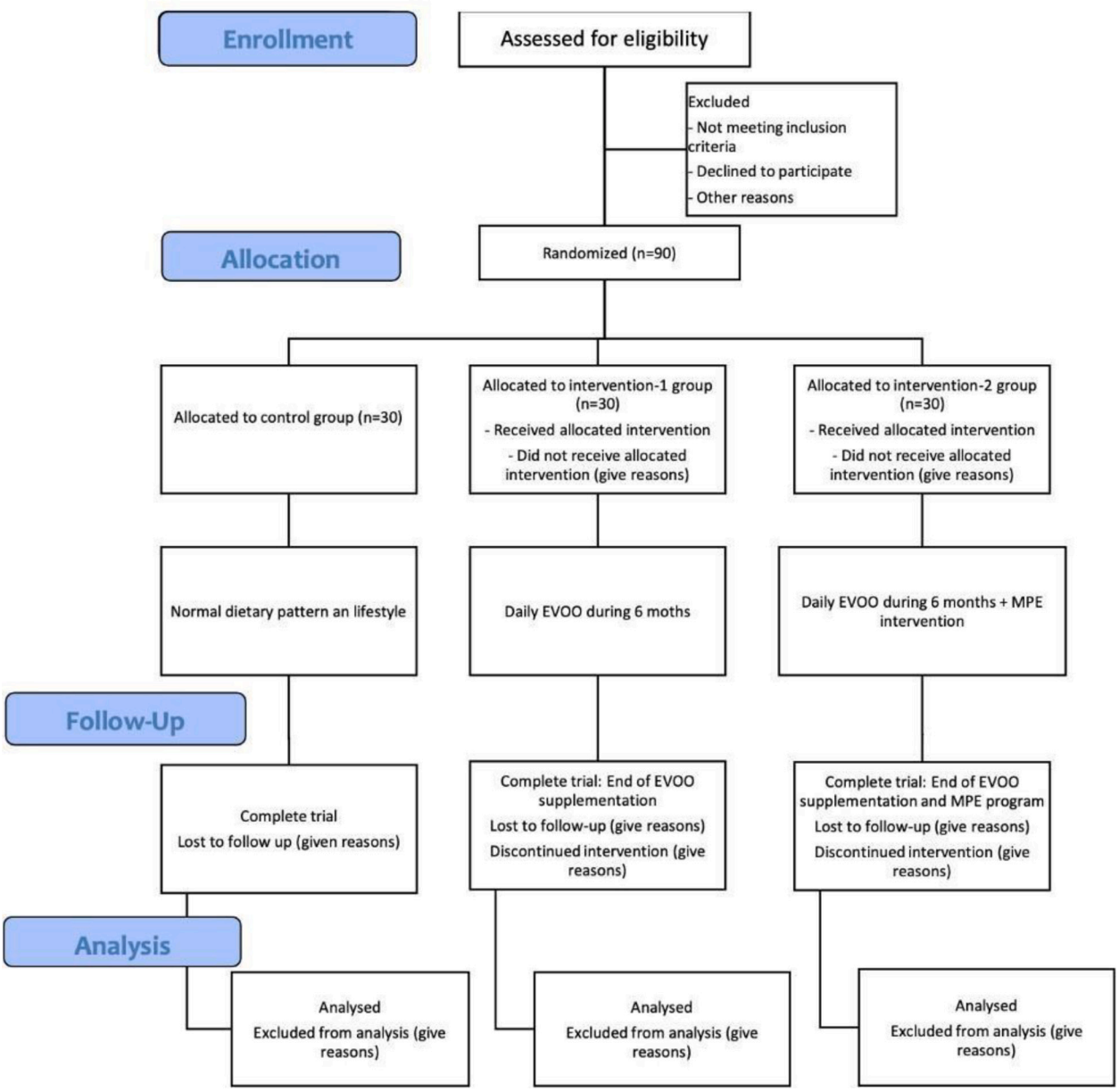

Fig. 1. The proposed CONSORT diagram of enrollment, allocation, follow-up, and analysis through the study for each arm (adapted). Abbreviations: EVOO= Extra Virgin Olive Oil; MPE: multicomponent health promotion and physical exercise programme.

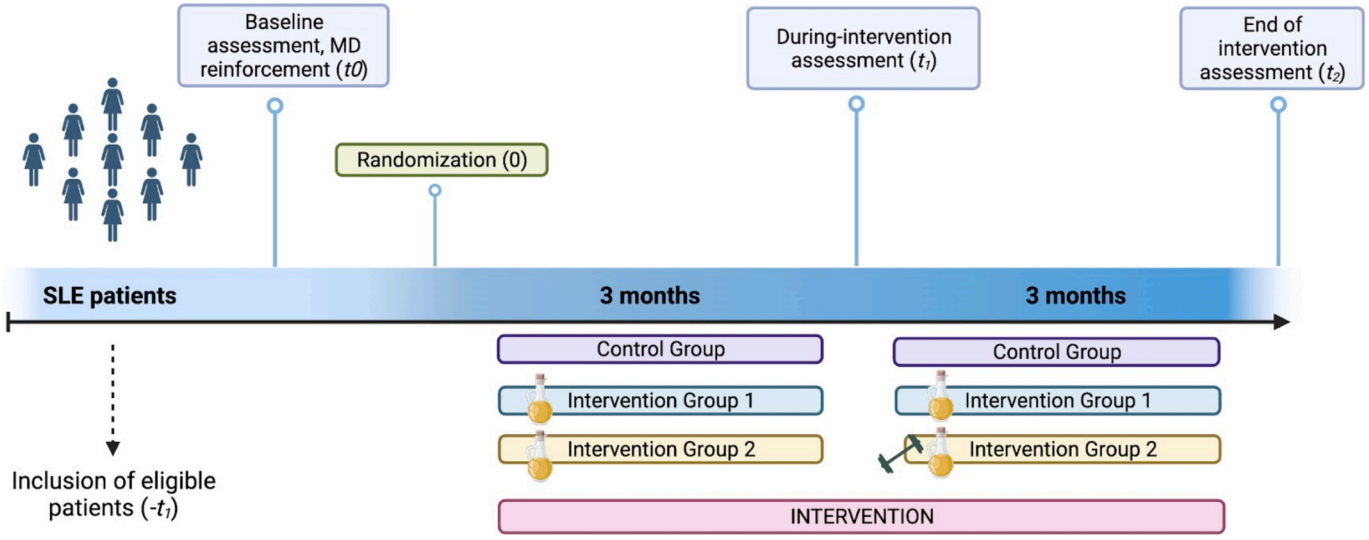

Fig. 2. EFINUTRILES programme timing. Created with BioRender.com

Table 1
EFINUTRILES programme

Objectives:	
- Getting introduced to sitting time reduction strategies and physical activity promotion. - Learn proper and safe exercise executions. - Internalize lumbopelvic control motor work. - Understand the use of parameters and tools for intensity control (Borg CR-10 scale, RIR, HRR) to enhance systemic adaptation to PE and training loads. - Improve bone density and physiological status. - Foster adherence to an active lifestyle and self-care practices.	
1. Home-based daily physical activity promotion and health education programme: Steps per day strategy + Daily recording of active time and sedentary behaviour + weekly digital infographics regarding essencial aspects of health-related lifestyles and impact on SLE's clinical course.	
Frequency	7 days per week
Intensity	Light
Time	The one required to get into the daily minimal steps
Type	Steps per day strategy controlled with FITBIT® bracelets and daily Google Forms self-administered questionnaires
Volume	Goal of reaching ≥ 12.000 daily steps
Progression	Weekly individualized % daily increase progression according to baseline steps evaluation [16].
2. PE programme	
Frequency	3 times a week (2 face-to-face / 1 home-based)
Intensity	Light to intense
Time	1 h 15 min per session
Type	Aerobic, strength, high-impact, motor control exercises, myofascial techniques and breathing exercises
Volume	Lineal prescription
Progression	Linear prescription with weekly increases of 5 % for small muscle group strength work, motor control, and high-impact; 10 % weekly increase for locomotor skills and large muscle group strength in terms of number of repetitions, number of sets, and intensity.

Abbreviations: HRR = heart rate reserve; PE = physical exercise; RIR = repetitions in reserve, SLE: Systemic Lupus Erythematosus.

In terms of the PE intervention, the EFINUTRILES PE programme is a multimodal exercise programme that includes aerobic, strength, high-impact, motor control exercises, and vagal activation techniques with an instructor trained by an physiotherapist expert in therapeutic exercise with more than 10 years of experience working with people with chronic conditions, who will help in the supervision, feedback and adjustment of exercise execution, individualization and prescription. It comprises three weekly sessions on non-consecutive days (two in a face-to-face group format and one home-based session) over 12 weeks with a total duration of 75 min/session. A linear prescription will be used according to the FITT-VP method (frequency, intensity, time, type, volume, and progression) with a gradual weekly adjustment in duration or intensity. Details of the EFINUTRILES PE programme are displayed in Table 2.

Table 2
EFINUTRILES PE programme components in detail.

M1: Mesocycle 1- General preparatory phase (4 weeks)		M2: Mesocycle 2- Specific Phase (8 weeks)	
Components		Time (min) or volume	Intensity
Warm up (8-10 min)	Mobility exercises	10 repetitions	Light (<50HRR)
	Locomotor skills	5–8 min	50–70 % HRR [17] RPE: 4–6 [18]
	Joint Mobility	10–15 repetitions	40–50 % RM
	Myofascial elasticity	1–2 sets of 10–15 repetitions	Last 5° of subjects' individual RoM
Skill and fitness activities (45 min)	Strength and power	**M1:** 8 all body exercises, 1–2 sets of 8–15 repetitions (Flanagan et al., 2014)	RPE 5–6 RIR ≥ 6
		M2: 8 all body exercises, 3–5 sets of 6–10 repetitions (Flanagan et al., 2014)	RPE 7–8 RIR 2–3
	High-impact	**M1**: 4 exercises, 1–3 sets of 10 repetitions at 10-15 cm height **M2:** 4 exercises, 1–3 sets of 10 repetitions at 15-25 cm height	RPE 6–7 [19]
	Motor control	2 exercises (lumbopelvic-cervico/scapular) of 60–90s	RPE 1–2
Cool- down/ VAT (10-15 min)	Myofascial stretching	4 exercises of 15–30s	To the point of tightness
	Myofascial release	2 exercises of 2–3 min	Slow rhythm 30–60 s/ structure
	Breathing exercises	8–10 min	–

Abbreviations: HRR = heart rate reserve; PE = physical exercise; RIR = repetitions in reserve; RM = repetition maximum; RoM = range of motion; RPE = rating of perceived exertion; VAT = vagal activation techniques.

2.6. Outcome measures

2.6.1. Main outcome: systemic lupus erythematosus disease activity index 2000 (SLEDAI2-K)

The SLEDAI-2 K index is an improved version of the original SLEDAI index for assessing disease activity using a combination of data from clinical records, physical examinations, organ-specific functional tests, and serological studies over the preceding 30 days, which is recognized as a suitable assessment for use in clinical trials and SLE prognosis studies [20].

2.6.2. Clinical characteristics

Clinical characteristics, including the date of the SLE diagnosis, cumulative manifestations, pharmacological prescription (immunosuppressants, glucocorticoids, calcium and vitamin D supplements, bisphosphonates, and biologic drugs), basal biochemistry blood analysis results (glucose, urea, creatinine levels, lipid profile), inflammatory markers (creatine kinase, haemoglobin, leukocytes, lymphocytes, platelets, C-reactive protein), and immunological markers (anti-phospholipid antibodies, anti-double-stranded DNA antibodies, and complement fractions C3 and C4).

Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index for Systemic Lupus Erythematosus (SLICC/ACR) Index: this index will also be recorded. It was developed by the ACR as a validated measure of SLE damage since its onset, resulting from either the disease process or its sequelae, including items in 12 organ systems. It is capable of detecting differences among patients ($p > 0.001$) with no inter-observer differences ($p = 0.933$) [21].

2.6.3. Cardiovascular risk

Cardiovascular risk factors and endothelial function will be assessed by portable arteriography (TensioMed Arteriograph Tl2, Tensiomed LTd., Budapest, Hungary), which has proven to provide adequate reliability and validity [22], registering: the brachial systolic blood pressure (mmHg), brachial diastolic blood pressure (mmHg), heart rate (beats/min), mean arterial pressure (mmHg), brachial pulse pressure (mmHg), ankle-brachial index (ABI), brachial augmentation index (%), central augmentation index (%), left ventricle ejection duration (m/s), return time (m/s), aortic pulse wave velocity (PWVao, m/s), SD PWVAo (m/s), central pulse pressure (PPao, mmHg), diastolic reflection area (DRA), systolic area index (%), and the diastolic area index (%). Additionally, other recognized traditional risk factors such as tobacco or alcohol compsumption and metabolic or cardiovascular comorbidities will be recorded through clinical interview, and Framingham risk score, as a validated tool for predicting a person's risk of cardiovascular event over time, will be calculated.

If additional funding is obtained, human vascular cell adhesion molecule-1 concentration (VCAM-1), intercellular adhesion molecule-1 concentration (ICAM-1) and *E*-selectin concentration will be assessed through plasma samples by using commercially available ELISA kits (Proteintech®, Proteintech Europe, Manchester, United Kingdom; Invitrogen, Life Technologies Corporation, Carlsbad, CA, USA).

2.6.4. Nutritional status

2.6.4.1. Anthropometry. Waist, hip and mid-upper arm (MUAC) circumferences in centimetres (cm) will be measured using an inelastic tape (Lufkin W606PM®, Parsippany, NJ, USA). Waist circumference will be measured at the midpoint between the last rib and the upper edge of the iliac crest; the participants will be asked to breathe normally and the measurement will be taken at the end of the breath. Hip circumference will be measured at the greater trochanter level. MUAC will be measured to the nearest 0.1, at the midpoint between the acromion and olecranon processes on the shoulder blade and the ulna of the arm, respectively.

2.6.4.2. Body composition. Weight (kg), skeletal muscle mass (kg), body fat mass (kg), body mass index (kg/m^2), body fat percentage (%), obesity degree (%), body cell mass (kg), bone mineral content (kg), basal metabolic rate (kcal), and visceral fat area will be estimated using an InBody 720 impedance meter (Biospace, Seoul, South Korea), which has shown reliable results and low standard errors of measurement for this purpose [23].

2.6.4.3. Mediterranean diet adherence. MD adherence levels will be assessed at baseline, in the 3rd month of the intervention, and post intervention, using the 14-point MD adherence scale from the PREDIMED study [15], which comprises 12 items relating to food consumption frequency and consumption habits regarding foods considered characteristic of the MD. Each item is scored either 0 or 1, and the higher score, the greater adherence to the MD.

2.6.4.4. Food frequency consumption. The food frequency questionnaire (FFQ) consists of a finite list of foods and beverages with categorical responses to indicate the usual frequency of consumption over a concrete period, usually lasting 6 months or a year. The Spanish version has 136 items and has proven to be a valid and reproducible tool in nutritional epidemiology [24].

2.6.5. Physical condition and functioning

2.6.5.1. Cardiorespiratory fitness. This will be evaluated via a cardiopulmonary exercise treadmill ergometric test using a Medisoft 870 treadmill (Medisoft S.A, Belgium) and Jaeger MasterScreen CPX gas analyser (CareFusion, Germany) through a linearly increased loading incremental test following a proven and reliable protocol for determining VO2 max under chronic conditions [25]. Oxygen consumption will be calculated as the highest VO2 value in litres per minute during the exercise. The minimal clinically important difference will be set at 6 % of the VO2 peak [26].

2.6.5.2. Functional capacity. The 6-min walking test (6MWT) will be used for this purpose. It is a widely validated measure of general physical functioning and mobility. Following the instructions from the American Thoracic Society [27] all the participants will be tested by the same clinician in standardised conditions. The patients will be instructed to walk between 2 markers set 30 m apart as many times as they can for 6 min. Fatigue level, blood pressure, heart rate and oxygen saturation (SpO_2) will be determined using the Borg CR-10 scale, a sphygmomanometer (Omrom M3 Confort®, HEM-7134-E, Omrom, Healthcare, Kyoto, Japan), and a pulse oximeter (Beurer-PO 30, Beurer GmbH, Germany). The greater the distance achieved, the greater the mobility and general functioning. Based on previous studies of an SLE population [28], desaturation will be defined as a decrease in SpO_2 of at least 4, and walking distance limited to <400 m.

2.6.5.3. Strength. Handgrip muscle strength tests will be performed using a TKK5101 Grip-D dynamometer (Takeya, Tokyo, Japan) according to a standardised protocol [29]. The patients will be asked to grip and squeeze the device as hard as possible three times, with breaks of at least 1-min between attempts. The values will be determined in kilograms, with the mean value obtained for each side being considered.

2.6.6. Molecular markers

2.6.6.1. MiRNA analysis. The miRNA expression profile will be quantified prior to and after intervention by collecting 3 ml blood samples in Tempus tubes (Applied Biosystems TM, Foster City, California, USA) and creating a small RNA library from the extracted RNA samples using the NETflex Small RNAseq kit v3, followed by size selection using acrylamide gels to include only miRNA fragments (~150 bp). Then, miRNA

mass sequencing will be performed using NGS technology, with the NextSeq 500 (Illumina) with endpoint reads (final coverage of approximately 5 million reads per library).

2.6.6.2. Microbiome. approximately 600 mg of faecal samples will be self-collected using an all-in-one specific system (OMNIgene.gut OM-200, DNAgenotek, Ottawa, Ontario, Canada). The taxonomic groups will be identified through metagenomic sequencing using the NexteraXT library preparation kit (Illumina) on the NovaSeq-6000 platform. To analyse the taxonomy of the microbiota, the RAST platform (Meyer F,

	STUDY PERIOD				
	Enrolment	Baseline	Allocation	During Intervention	End of Intervention
TIMEPOINT	$-t_1$	$t0$	0	t_1	t_2
ENROLMENT:					
Eligibility screening	X				
Informed consent	X				
MD Reinforcement		X			
Allocation			X		
INTERVENTIONS:					
Control Group (GC)					
Intervention 1 group (IG1)				X	
Intervention 2 group (IG2)				X	
ASSESSMENTS:					
SLEDAI-2K Index		X			X
SLICC/ACR Index		X			X
Clinical characteristics		X			X
Cardiovascular risk factors		X		X	X
Endothelial function		X		X	X
Anthropometry		X		X	X
Body composition		X		X	X
Mediterranean Diet adherence		X		X	X
Cardiorespiratory fitness		X			X
Functional capacity		X		X	X
Bone status		X			X
Strength		X		X	X
MiRNA analysis		X		X	X
		X			X
Microbiome		X			X
Oxidative stress		X			X

Fig. 3. Details of enrolment, intervention, and assessments according to SPIRIT diagram. Abbreviations: SLEDAI-2 K: Systemic Lupus Erythematosus Disease Activity 2000; SLICC/ACR: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index for Systemic Lupus Erythematosus.

BMC Bioinformatics 2008) will be used to classify the reads into different operational taxonomic units (OTUs). QIIME wrapper scripts (v1.9.1) will be used to classify the reads into OTUs and identify taxa that differ in abundance between groups.

2.6.6.3. Oxidative stress. By taking fasting blood samples, systemic oxidative damage to proteins, DNA and lipids will be assessed through the erythrocyte content of thiobarbituric acid reactive substances, glutathione reductase and peroxidase, and advanced oxidation protein products. The analyses will be performed using commercially available ELISA kits (Enzo Life Sciences, Inc., Farmingdale, NY, USA; Cell Biolabs, San Diego, CA, USA) with high sensitivity and reproducibility based on the information data sheets provided by manufacturers.

2.7. Data collection

All participants will be assessed at the baseline (t0), 1 week after taking EVOO supplements for three months (just prior to beginning the EFINUTRILES programme in the case of the IG2 group) (t1), and after six months of intervention (t2) (Fig. 3). All the assessments will be carried out by a single blinded researcher with 5 years of experience. All the evaluations will take place according to the same timetable and conditions.

2.8. Data analysis

All the analyses will be performed by a blinded researcher using the IBM Statistical Program for Social Sciences (IBM SPSS Statistics Version 25, IBM Corp., Armonk, NY, USA). A confidence interval (CI) of 95 % will be set. The results will be considered significant at $p \leq 0.05$. The baseline sociodemographic and clinical data of the participants at the baseline will be described using preliminary descriptive analyses, these results being presented as mean and standard deviation (m ± SD) for continuous data, and frequencies and percentages (n, %) for categorical data. The normal distribution of the variables will be checked using the Kolmogorov-Smirnov test and visual inspection. A baseline comparison will be made to test the homogeneity between the groups using the Student's t/Mann–Whitney *U* tests as appropriate. Multivariate logistic regression analyses will be carried out to test the effects of the intervention on disease indexes, clinical characteristics, cardiovascular risk, nutritional status, physical condition and functioning, and molecular markers. The magnitude of difference between the groups will be calculated using Cohen's effect size values, categorising these as [30]: 0 to 0.19, negligible; 0.20 to 0.49, small; 0.50 to 0.79, moderate; and ≥ 0.8, large. The data analysis will be based on the intention-to-treat principle, using imputation methods for any missing data.

2.9. Ethical considerations

The study has been approved by the Biomedical Research Ethics Committee of Granada, Spain (*2099-N-21)* and follows the principles of the Helsinki Declaration for biomedical research. The study will be carried out in accordance with the Spanish Data Protection Law (3/2018). All the participants will provide informed consent prior to their participation, choosing whether they want their data to be anonymised or coded.

3. Results

The study hypotheses are novel and of interest for clinical and basic research into SLE. If they are confirmed, the applicability of the project is foreseeable, by implementing combined strategies that include nutritional and PE interventions in patients with SLE, alongside the usual drug treatment.

To our knowledge, this pragmatic randomised control trial is the first study to develop a combined intervention including EVOO supplements and a physical activity and health promotion multicomponent programme in patients with SLE.

The use of a robust study and evidenced based design intervention guided by a strong theoretical framework will provide further knowledge of the effects of a nutritional intervention (specifically, EVOO supplements) and a multicomponent physical activity and health promotion intervention in SLE patients.

The expected results could have a huge positive social and economic impact, improving health system sustainability and the quality of care provided by health professionals, particularly nursing care. Furthermore, these kinds of approaches arising from primary healthcare settings are necessary and can reduce the burden on health professionals, as the Political Declaration of the 2019 UN High-Level Meeting on Universal Health Coverage [31] reaffirmed health as an essential precondition for sustainable development and equity, as well as the role of primary healthcare as a cornerstone of universal health coverage for reducing the workload of health professionals and improving patient well-being.

Potential limitations include the feasibility of the intervention as it has not previously been tested. Patients will be offered the greatest possible availability of morning and evening sessions to enable them to participate without disrupting their usual routine.

DCOOP (S. Coo. And) agri-food corporation laboratory tests will ensure the EVOO has a fixed, stable composition, and that all patients go under the same supplementation, reducing the potential confounding bias or mixing effects. Each patient will be provided with 10 l of EVOO, enough to cover the intervention and provide an additional amount for the family. Reminders like pictograms or drinking cups will be provided. Group messages on instant messaging platforms will allow patients to receive weekly reminders to take their supplements and will help solve any issues.

One limitation of the study is the inability to blind the patients in the intervention groups; this should be counteracted by the randomisation and allocation process which will be undertaken by investigators not involved in the assessments. It is true that patients who are in the intervention groups may reveal this information to the researcher during the assessments, but valid, reliable objective instruments are being used, which should eliminate any risk of response bias.

4. Conclusion

The proposed trial should help clarify whether EVOO supplements combined with a multicomponent physical activity and health promotion programme exert a beneficial effect on SLE sufferers at a number of levels, including disease clinical course, health outcomes, and molecular mechanisms, providing novel scientific evidence with potential application in SLE management.

CRediT authorship contribution statement

R. Gil-Gutiérrez: Methodology, Investigation, Data curation, Writing – review & editing, Writing – original draft. **I. Medina-Martínez:** Methodology, Investigation, Data curation. **C. Ballesteros-Rubio:** Methodology, Investigation, Data curation. **F.J. De La Hera-Fernández:** Resources, Project administration, Investigation. **R. Ríos-Fernández:** Methodology, Investigation, Funding acquisition. **J.L. Callejas-Rubio:** Project administration, Funding acquisition. **M. Zamora-Pasadas:** Resources, Investigation. **I. Cantarero-Villanueva:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Conceptualization. **M. Correa-Rodríguez:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Funding acquisition, Formal analysis, Conceptualization. **N. Ortego-Centeno:** Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **B. Rueda-Medina:** Writing – review &

editing, Writing – original draft, Validation, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could influence the work reported in this paper. This work is part of R. Gil-Gutiérrez's doctoral work at the Clinical Medicine and Public Health doctoral studies programme at the University of Granada, Granada, Spain.

Data availability

On completion of the trial, the data supporting the findings obtained will be available on appropriate request from the corresponding author. The data will not be publicly available for ethical reasons.

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