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Review

Scoping Review of Nutraceuticals Use in Mediterranean Diet

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Abstract

Mediterranean diet, considered key to varied diets, raises whether it is necessary to supplement it with compounds like nutraceuticals to obtain more benefits. A scoping review was conducted. Nine articles were selected that compared the effects of nutraceuticals on biochemical markers (such as total cholesterol (TC), low-density lipoprotein cholesterol (LDLc)), weight, and blood pressure in various studies to the results observed in groups only exposed to the Mediterranean diet. The aim was to assess the impact of the Mediterranean diet with and without nutraceutical supplementation. The studies showed that, following nutraceutical intake, there were significant changes in subjects' lipid profile, specifically decreases in TC and LDLc. We did not observe systematic information regarding blood pressure and weight changes in response to the Mediterranean diet with and without nutraceuticals. No adverse effects related to nutraceutical consumption were reported in any study. Nutraceuticals can be used to reinforce the basis of the Mediterranean diet and

promote a reduction in lipid profile parameters like TC and LDLc. No significant information about triglycerides, blood pressure, or glucose levels is reported.

Keywords
Nutraceuticals; food products; mediterranean diet; health prevention; dietary supplement

1. Introduction

Mediterranean diet has been presented as one of Western culture's most beneficial nutritional patterns. The advice provided by this diet has been recognized as a strategy for a healthy lifestyle and has been attributed to benefits for both cardiovascular and metabolic health [1]. Nutritional diversity and the different ways of treating food for consumption have made it one of the top diets to follow in the population at large [2]. Mediterranean diet originates from this geographical area and shows differences depending on location, but has many common characteristics, such as a high intake of vegetables (including fresh fruit, vegetables, legumes, nuts, especially nuts, seeds, and cereals, which are not refined). Olive oil is presented as the primary type of fat and is combined with a low intake of saturated fats. Fish intake is moderate to high, depending on proximity to the sea, while meat and poultry consumption is low, with moderate alcohol consumption, mainly wine, during meals. Dairy food consumption is moderate to low, primarily in the form of cheese and yogurt [3]. Research indicates that its main nutritional principles are having a satisfactory impact on the people who follow it [4].

Despite the benefits of Mediterranean diet on health, there is an increase in nutraceutical intake. One reason for this is that many people end up self-medicating such products to gain theoretical benefits without the need for a doctor's prescription (9), but following their beliefs. The marketing of such products plays a role in how they reach consumers, who are influenced by the supposed benefits they seek to achieve *via* their intake [5].

The definition of nutraceuticals has been modified from De Felice's recommendation in 1995 to the present day. Numerous studies on the functions and effects on human health of compounds labeled as nutraceuticals have come up with up to 25 different definitions, as studied by Palthur et al. in 2010. These researchers defined the term as "A nutraceutical is a food or part of a food whose oral administration has demonstrated safety and health benefits beyond basic nutritional functions to supplement the diet, presented in a non-food matrix or unconventional food formats, in an amount that exceeds those that could be obtained from normal foods and at a frequency necessary to obtain such properties and is labeled as a 'nutraceutical" [6].

Food products for nutritional purposes are not regulated in the same way as medicinal products that are licensed and, even when sold as supplements, they are not submitted to the same control [7]. The public tends to view natural products as healthy, and some groups of the general public are encouraged to explore dietetic choices to enhance their health, e.g., cancer patients, the aged or athletes [8-10]. The choice of nutraceuticals as a preventive strategy to improve vitamin deficiency or to enhance physical performance must be based on scientific evidence that should be studied and compared with alternatives such as following a varied and balanced diet. The most appropriate

selection of products should be clear and precise and according to the prevention that needs to be considered.

The pharmaceutical sector has greatly benefited from the nature of these compounds, and approximately one-third of the drugs approved by the Food and Drug Administration (FDA) in the last 20 years derive from natural products or their analogs [11].

Due to the population's considerable use of and keen interest in nutraceuticals, it is important to collect available scientific evidence on the therapeutic benefits of nutraceutical supplements in the Mediterranean diet. The present scoping review asks what the effects of nutraceutical supplementation are in a varied Mediterranean diet context. This work aimed to study if nutraceutical use provides benefits in a well-balanced Mediterranean diet.

To do so, nine articles were selected, and the effects of nutraceuticals on the biochemical, weight, and blood pressure parameters reported in the different studies were compared to the results in the groups only exposed to the Mediterranean diet.

2. Analysis and Results

2.1 Research and Selection of Articles

A literature search was conducted from 1990 to January 2022 in the following bibliographic databases: PubMed, Web of Science, Cochrane, and Google Scholar.

The keywords included in the research were "nutraceuticals", "Mediterranean diet" and "humans". The nutraceuticals terms were searched in the title of articles to make the findings more accurate. The other keywords were searched for in either the title or abstract of articles. These research searches were carried out in January 2022(Figure 1).

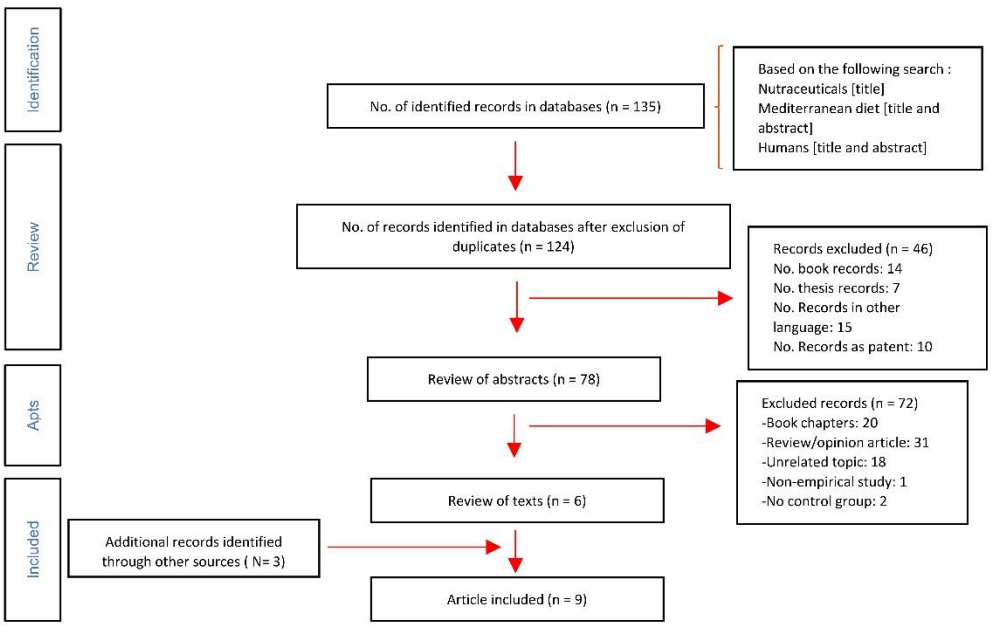

Figure 1 Systematic search flow chart according to the PRISMA methodology (n (number)).

The PICO (Population, Intervention, Comparison, Outcome) test was used to establish the article selection protocol. Therefore, we included articles that:

1) included a population with a cardiovascular risk indicator (CVR) or healthy people who formed part of a control group of an empirical study.
2) involved using nutraceuticals accompanied by an intervention that included adherence to the Mediterranean diet.
3) used nutraceuticals in conjunction with the Mediterranean diet in a sample, compared to another sample that received only Mediterranean diet intervention.
4) included variables showing changes or differences in the benefits or harm of nutraceutical supplementation in the Mediterranean diet: biochemical parameters, Body Mass Index (BMI), and Blood Pressure (BP).
5) had a variable period between comparison studies ranging from 12 weeks to 18 months, with consumption of nutraceuticals and/or a Mediterranean diet.
6) were clinical trials.

We excluded those articles in which the nutraceutical was not part of the intervention as well as those that constituted books or book chapters, doctoral theses, studies written in languages other than English and Spanish, patents, opinion articles, non-empirical studies, studies without a control group as well as unrelated topics.

2.2 Selected Articles

The current review was conducted by PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [12].

As shown in Figure 1, the selection stage of this review followed the PRISMA flow diagram. After checking for duplicates, articles were identified for selection according to the established inclusion and exclusion criteria. One researcher was involved in the initial selection process by screening all the titles and abstracts of the remaining articles to define any potentially relevant literature for this review. This researcher excluded irrelevant papers or those that did not fulfilling the specified inclusion criteria. Two researchers then assessed the selected articles independently using the titles and abstracts based on the inclusion and exclusion criteria.

3. Results

Figure 1 shows the total number of records obtained corresponding to 135 scientific articles. Papers were available in the following databases: 8 in PubMed, 90 in Google Scholar, 9 in Cochrane, 28 in Web of Science. After setting the search criteria, three additional articles were included after reviewing the bibliography of the selected articles. We concluded with nine articles, which we analyzed.

3.1 Socio-Demographic Characteristics

The sample consisted of a total of 597 participants. The arithmetic mean age of the subjects who participated in the studies was 54.26 years. Among participants who received the intervention, 20.4% were male compared to 22.6% female. For those in the control group, 21.6% were male versus 22.1% female. Two studies were identified where the gender of participants was not considered when

assigning them to control and intervention groups, and another two where gender was not specified in the sample distribution. The patients enrolled in the studies had a history of metabolic syndrome (MetS) and hypercholesterolemia in six of the nine studies [13-18], the subjects with pre-hypertensive status or diagnosed with primary hypertension in one of the nine studies [14], the patients with pre-diabetes in only one of the nine studies [19] and one with type 2 diabetes mellitus were enrolled [20].

3.2 Duration of Intervention

The time taken to study the effects of the published studies ranged from 12 weeks to 18 months. Five studies were carried out between 12 and 13 weeks [13, 15-18], three between 16 and 24 weeks [14, 19, 21], and only one lasted 18 months [20]. The number of participants in the studied papers who completed the entire study with all its phases corresponded to 665 subjects, of whom 356 were in the nutraceutical intervention group, and 309 were in the control group. The distribution of the experimental and control groups was comparable regarding the number of individuals who participated; only one work was observed in which groups were unbalanced [20]. Groups were grouped into those with several participants less than or equal 30, and four of the nine studies presented this characteristic *versus* those that did not [14, 16, 17]; those between 30 and 50 subjects accounted for two of the nine articles [13, 15, 18, 21], and those with more than 100 subjects accounted for two of the nine works [19, 20].

3.3 Characteristics of the Mediterranean Diet Intervention

The Mediterranean diet, found across the different articles, appeared in three of the nine in which the Mediterranean diet with a low glycemic load was used in both the nutraceutical and control groups [13, 15, 16]. A study showing phytochemicals with a low glycemic index (GI) were added to the Mediterranean diet [16]. Macronutrient accounting was carried out in three of the nine studies. However, the macronutrient proportion of the nutraceutical compounds delivered where the proportion of protein and fiber was higher in the intervention group in only one study [16]. In the Mediterranean diets using the GI reduction strategy, only one study specified 34% additional carbohydrate reduction and a 54% increase in protein compared to the previous intervention study [13]. The dietary training period consisted of giving the dietary recommendations established by the study. Two of the nine publications indicated that subjects were given a dietary guide with the permitted foods and their portions. In both these studies, they were allowed to consume one glass of red wine daily [15, 16]. However, as part of the identical low glycemic load diets, alcohol was not permitted in one work [13]. There were no references made in the other studies about wine consumption. Two articles with a low glycemic load diet specified that participants could eat to their maximum, with no calorie restrictions [15, 16]. Two diets included in the low glycemic load guidelines specified that wholegrain cereals were allowed in one serving per day in their diet [15, 16]. There was one study in which no Mediterranean diet education was offered, and it only evaluated whether the included subjects were good followers according to their adherence to Mediterranean diet with the PREDIMED survey [1] and by classifying subjects as having good adherence to Mediterranean diet (GAMD) or poor adherence to Mediterranean diet (PAMD). However, this measure did not relate to treatment effects in either of the two groups [20]. Only one study was found in which the Mediterranean diet incorporated an energy restriction of 1500

kilocalories (kcal) for women and 1800 kcal for men by moderating fat intake, increasing vegetable choices, and modifying poultry *versus* lamb and beef [19]. The dietary recommendations given to participants were to follow qualitative Mediterranean nutritional guidelines [13, 14, 17, 18] and avoid salty products, dairy, and meat or processed products during the study period [14, 21]. This period for training in the task was not counted as intervention time [18]. Only studies where the Mediterranean diet was compared to the Mediterranean diet supplemented with nutraceuticals were included in this paper.

3.4 Follow-Up of the Implemented Intervention

The study schedule consisted of a longitudinal follow-up of the participants during the trial course. Data were recruited at the beginning and end of each scheduled treatment. However, we found studies in which "extra" follow-up visits were implemented. In studies 7 and 4, there were two extra visits in the middle of the established period, one of which was individualized in study 7 [13]. In study 4, extra telephone calls were added [20]. In study 8, a mid-term control visit was made [21], and in studies 1 and 2, there were 3 follow-up visits during the 12-week intervention period; in the last-mentioned work, the diet diaries submitted in advance were evaluated, as were as questionnaires on fullness, food cravings and physical activity (PA) [15, 16]. Three of the nine studies mentioned that advice was given with the supervision of a nutritionist or medical specialist [17, 19, 21]. It was observed from the follow-up results that one of the nine studies specified that samples did not involve the continuous follow-up of the prescribed norms by the participating subjects [13]. However, other studies found that compliance with the project was specified to be 100% [21]. Three of the nine studies considered the need for a previous stabilization period in terms of prescribed diet and PA [14, 17, 18]. Although in some, the stabilization period was considered the study time [17], in others, it was not taken into account [18, 19]. Four of the nine selected studies referred to cases of participants leaving the study, which was not observed in five of the nine studies. The adverse effects of groups were not significant, although many aimed to evaluate the safety of the nutraceuticals in use. Only one study mentioned adverse effects, corresponding to one of the low glycemic load diets. These effects were bloating, flatulence, and self-limited constipation [13], although these effects were not documented in the other two diets with the same low glycemic load characteristics [15, 16].

3.5 Physical Exercise

Performing PA was recommended in seven of the nine studies, in which recommendations were offered regarding frequency of activity, duration, and intensity. In one study, the evaluation was conducted during follow-up visits [16], while no indication or control was offered in two [13, 19].

3.6 Nutraceuticals and Their Relationship to Health Outcome Parameters

The nutraceuticals that were administered in the different studies were very generic. The different studies aimed to evaluate their safety, tolerability, and efficacy in humans. In them all, interest lay in the synergic combination between components to achieve a preventive and therapeutic attitude in patients with a well-established pathology. The objectives maintained in all the studies were associated with reducing risk factors in subjects with cardiovascular risk,

prediabetes stage or diagnosed type 2 diabetes mellitus patients. Six of the nine reported studies observed a clinical effect on lipid parameters. Although the studies that evaluated parameters intended to know their impact on glucose metabolism, they offered contradictory data. One study reported an increase in glycosylated hemoglobin levels in patients with type 2 diabetes mellitus [20], while another study reported a decrease in this parameter in pre-diabetic patients [19]. Although nutraceuticals with hypoglycemic functions were used, these effects were not significant in the studies evaluated for the patients with MetS.

3.7 Nutraceutical Formulation

The presentation of nutraceuticals mainly was in a solid form, such as tablets or pills, powder preparations, and syrup, and two studies did not detail its presentation [19]. Three of the nine studies were supplemented with protein shakes and nutraceutical tablets (13, 15, 16). The dose pattern of nutraceuticals in terms of subjects' anthropometric characteristics was not specified in the reviewed studies. All subjects' doses were specified, and Table 1 summarizes the daily dose of the different administered compounds. The recommended daily intake (RDI) was not specified in the studies; this concept appeared only in study 2, which indicated that the RDI was not established [16]. The nutraceutical components administered to achieve cardiometabolic effect were supplemented with phenols, phytosterols, carotenoids, amino acids, vitamins, minerals, probiotics, omega-3 fatty acids, and a Mediterranean diet with a low glycemic load. The dose patterns of nutraceuticals were once or twice a day for the different compounds (Table 1).

Table 1 Key aspects of the studies included in the literature review.

STUDY	NUTRACEUTICALS (used in the intervention group/day)	COMMON CHARACTERISTICS OF THE STUDY FOR BOTH GROUPS	INTERVENTION (intake of nutraceuticals (NTR))	CONTROL	RESULTS			
					PARAMETER	INTERVENTION GROUP (%)	CONTROL G. (%)	p-value between arms
			n = 23 (NTR)	n = 18 (MED)	TC[5]	-14.5	-6.3	p = 0.03*
					LDLc[6]	-17.3	-8.4	p = 0.11
					LDLp[7]	-11.9	-7	p = 0.26
					TG[8]	-35.2	-14.3	p = 0.03*
1. Lerman & cols. 2008.		n = 41			HDL[9]	7	2.7	p = 0.18
"Enhancement of a modified Mediterranean-style, low glycemic load diet with specific phytochemicals improves cardiometabolic risk factors in subjects with metabolic syndrome and hypercholesterolemia in a randomized trial"	UltraMeal Plus ®(UMP) contains: 34 g soy isoflavones 4 g phytosterols (B-sitosterol) 1 powdered beverage BID[1] + 150 mg RIAA[2] (Humulus lupulus) 30 mg PAC[3] 1 tablet, BID	Period:12 weeks Training in Mediterranean diet (MED) with a low glycemic index (GI) max. Consumption of red wine at 1 glass/day, whole grains only one serving/day. Recommendation: physical activity (PA) and eating to satiety.	Diagnosis: Metabolic syndrome (MetS) and hypercholesterolemia. Age: 25-80 (52.5) Dropout: 8 subjects (3 NTR/5 MED) Side effects: NO Follow-up: 2, 4, 8 and 12 weeks HbA1c[4] baseline MED > PED baseline Randomized Clinical Trial		No-HDLc[10]	-18.2	-8	p = 0.02*
					TC/HDL	-19.5	-8.9	p = 0.01*
					TG/HDL	-42.7	-17.6	p = 0.02*
					Apo A[11]	-2.1	-4.3	p = 0.24
					Apo B[12]	-17.5	-9.9	p = 0.09
					Apo B/Apo A	-15.4	-6.3	p = 0.07
					FBG[13]	-2.2	-4.8	p = 0.85
					HOMA score[14]	-29.7	-24.9	p = 0.61
					HbA1c%	-2.6	-3.8	p = 0.82
					Weight	-5.9 kg	-5.7 kg	No reported (nr)
					SBP[15]	123.4 ± 2.7 mmHg	128.1 ± 1.8 mmHg	nr
					DBP[16]	82.0 ± 2 mmHg**	84.4 ± 1.6 mmHg	nr
					MetS	-43	-22	nr
					CVR[17]	9.6 ± 1.4	13.1 ± 2.7	nr

2. Lerman & cols. 2009 "Subjects with elevated LDL cholesterol and metabolic syndrome benefit from supplementation with soy protein, phytosterols, hops rho iso-alpha acids, and Acacia nilotica proanthocyanidins"	PharmaSoy ® contains: soy proteins with plant sterols (campesterol, stigmasterol, brassicasterol, sitostanol) 2 g powdered beverage BID + 4 g dietary fiber 150 mg RIAA + 60 mg PAC 1 table, BID	n = 21 Period: 12 weeks Training: MED with foods low GI, no caloric restriction + dietary fiber Recommendation: 150 min aerobic exercise each week	N = 10 N = 11 Diagnosis: MetS and hypercholesterolemia. Age: 25-80 years (54.35) Dropout: 2 NUTRA/1 MED Side effects: NO Follow up: 2,4,8 y 12 weeks Randomized Clinical Trial	TC LDLc LDLp TG HDL No-HDLc CT/HDL TG/HDL Apo A Apo B Apo B/ApoA1 Fasting blood Glucose HbA1c% HOMA score HOMOC Weight BMI Waist circunference SBP DBP	-22.3** -26.5** -368.8** -23.3 8.5 -27.4** -27.9** -27 -0.1 -29.9** -29.3** -1 -1.1 2.5 -3.7 -6.8 -6.7 -5.9 -5.2 -3.7	-7.8 -10.9 -107.6 0.6 1.6 -9.3 -8.6 -0.4 -5.6 -12.3 -6.8 -3.8 -3 -27.9 14** -5.2 -5.2 -5.4 -4.7 -1.7	p < 0.01 p < 0.03 p < 0.03 p = 0.07 p = 0.33 p < 0.01 p < 0.01 p < 0.05 p = 0.25 p < 0.01 p < 0.01 p = 0.30 p = 0.25 p = 0.14 p < 0.01 p = 0.57 p = 0.48 p = 0.92 p = 0.97 p = 0.51
3. Cicero & cols. 2013 "Red yeast rice improves lipid pattern, high-sensitivity C-reactive protein, and	Contains: 10 mg monacolin + 10 mg de coenzyme Q10 1 tablet every day	n = 25 Period: 12 weeks Training: Qualitative MED, avoid excess dairy products, red	N = 12 N = 13 Diagnosis: MetS and untreated moderate hypercholesterolemia Age: 18-70 years (52.42) Dropout: NO	TC LDLc No-HDLc	-12.45 -21.99 -14.67	nr nr nr	nr nr nr

vascular remodeling parameters in moderately hypercholesterolemic Italian subjects"		meat and red meat by products The amount of macronutrients is measured at the beginning and end of the study. Recommendation: Increase vigorous PA 20 to 30 minutes 3 to 5 days per week.	Side effects: NO Follow up: end of each treatment, after the washout period and after the second treatment. Clinical Crossover Trial	MMP-2 MMP-9 hs-CRP	-28.05 -27.19 -23.77	nr nr nr	nr nr nr
4.Roig & cols. (2015) "Enhanced Oxidative Stress and Other Potential Biomarkers for Retinopathy in Type 2 Diabetics: Beneficial Effects of the Nutraceutic Supplements"	NUTROF OMEGA contains: DHA vitamins (E, C, B1, B2, B3, B6, B9 y B12) luteine zeaxanthin glutathione hydroxytyrosol trace elements (Se, Mn, Zn y Cu). 1 table every day	n = 208 Period: 18 moths Training: No (MED adherence scale that groups them into good adherence of the MED (GAMD) or poor adherence of MED (PAMD). Recommendation: No	N = 130 N = 78 Diagnosis: Diabetes Mellitus (DM) with diabetic retinopathy Age: 25-80 years old (63.7) Abandonment: 57 subjects Side effects: NO Follow up: each 6 moths and telephone calls.	nr			
5. A. Cicero&cols march (2016) "Effects of a Combined	500 mg artichoke extract 10 mg monacoline	n = 30 Period: 18 weeks (4 stabilization)	Nutr1/Plc2 = 15 Plc1/Nutr2 = 15 Diagnosis: MetS and moderate hypercholesterolemia	TC LDLc	-13.6 -18.2	nr nr	nr nr

Nutraceutical on Lipid Pattern, Glucose Metabolism and Inflammatory Parameters in Moderately Hypercholesterolemic Subjects: A Double-blind, Cross- over, Randomized Clinical Trial"	K 75 mg banaba extract 50 mg coenzyme Q10 9 mg vitamin B3 1.4 mg vitamine B6 0.83 µg vitamineB12 110 µg folic acid 1 table every day	Training: Qualitative MED avoiding excess dairy products and red meat, correction of unhealthy habits and inappropriate behavior. Recommendation: AP vigorous 20-30 min, 3-5 days per week	Age: 25-75 years (52.2) Drop out: NO Side effects: NO Follow up: end of each treatment, after rising period and after 2nd treatment.	No-HDLc hs-CRP GOT GPT	-15 -18.2 -10 -30.9	nr nr nr nr	nr nr nr nr
6. A. Cicero & cols. (2017) "Short- Term Effects of a Combined Nutraceutical on Lipid Level, Fatty Liver Biomarkers, Hemodynamic Parameters, and Estimated Cardiovascular Disease Risk: A Double-Blind, Placebo- Controlled Randomized Clinical Trial"	ColesiaTM (píldora) contains: 10 mg monacoline 800 mg phytosterols 5 mg L tyrosine	n = 50 Period: 12 week (4 stabilization) Training: qualitative MED avoiding excess consumption of dairy, red meat and processed foods Recommendation: PA vigorous 20-30 min, 3-5 days per week	N = 25 N = 25 Diagnosis: polygenic hypercholesterolemia resistant to MED, obesity Age: 35-69 years (50.2) Drop out: NO Side effects: NO Follow up: at the end	TC LDLc HSI ALT AST HSI SBP FMD URIC ACID CVR	-16.3 -23.4 -2.8 -27.7 -13.8 -2.8 -5.6 -13.2 -12.3 1.19	-9.9 -13.2 -1.8 nr r -1.8 nr nr nr nr	p < 0.001* p < 0.001* nr nr nr nr nr nr nr nr
7. Dahlberg & cols (2017) "A 13-week low glycemic load diet and	40 g high protein shakes (soybean, pea, whey)	N = 32 Period: 13 weeks Training: Modified	N = 15 N = 17 Diagnosis: overweight, MetS + 2 FCVR	TC LDLc TG	-17.5 -18.6 -50.8	-7.7 -10.3 -30.6	p < 0.01* p < 0.01* p < 0.05*

lifestyle modification program combining low glycemic load protein shakes and targeted nutraceuticals improved weight loss and cardio-metabolic risk factors"	4 g phytosterols 2 capsules antioxidant formulation (CardioxLDL®) 2 capsules probiotic colonies 2 g capsules fish oil capsules (Super Omega3®) 1 g berberine 4 tablets of vitamins and minerals distributed over the 5 meals	MED with low GI foods, 5 meals/day, limited coffee or tea. Cognitive-behavioral program Recomendation: PA	Age: 27-64 (46.5) Drop out: 6/6 Side effects: YES Follow up: 3 visits (discontinued)	HDL	-2.6	-5.7	nr
				No-HDLc	-22.7	-8	p < 0.01
				CT/HDL	-15.9**	-4.3	p < 0.01
				TG/HDL	-47	-26	p < 0.05*
				Apo A	-6.8	-5.1	nr
				Apo B	-19.7	-9.2	p < 0.01
				Apo B/Apo A	-9.7**	0	p < 0.01
				Fasting blood Glucose	-2	-2	nr
				HbA1c	-1.8	0	p < 0.05
				HOMA score	-31.3	-29.6	p < 0.05
				hs-CRP	-25.6**	-5.2	p < 0.05
				Weight	93	66	nr
				Weist c.	-11.5	-8.4	nr
				BMI	-11.9	-7.8	p < 0.05*
				Fat mass	-21.5	-13.7	p < 0.01*
				SBP	-11.2	-5	nr
				DBP	-12.1	-7.4	nr
				CVR	-40	-16.7	p < 0.05
8. Cicero & cols. (2018) "Is it Possible to Significantly Modify Blood Pressure with a Combined Nutraceutical on Top of a Healthy Diet? The Results of a Pilot	BPLN®: 500 mg dry beet extract 300 mg magnesium 400 mg vitamine C 25 mg vitamine B1 25 µg vitamine D 1 time per day	n = 36 Period: 16 weeks (4 stabilization weeks) Training: MED avoidance of salt and excesses; choice of suitable food (qualitative)	Nutra1/Place2 = 18 Place1/Nutra2 = 18 Diagnosis: untreated pre-hypertensive or primary hypertension, moderate CVR Age: 47-63 years (55) Dropout: NO Side effects: NO	CT	nr	nr	nr
				SBP morning	nr	nr	nr
				DBP morning	nr	nr	nr
				SBP night	nr	nr	nr
				DBP night	nr	nr	nr

Clinical Trial"		Recomendation: vigorous AP (3-5 days per week)	Follow up: 2 visits	CVR	4.2 ± 1.0	4.7 ± 1.0	p < 0.05*
9. Colleta y cols. (2020) "Lifestyle and silymarin: a fight against liver damage in NAFLD associated - prediabetic disease"	210 mgr Silybum marianum and Morus alba BID	n = 212 Period: 6 moths Training: nutritional guide and nutritionist Follow up: MED with caloric restriction and moderate fat 1500-1800 kcal Recommendation: Consumption of vegetables and poultry to replace lamb and beef	N = 108 N = 104 Diagnosis: prediabetics without treatment in the previous 12 weeks with HbA1c between 5.7-6.4%, BMI 25-29, and liver fibrosis Age >= 18 years Dropout: NO Side effects: NO	HbA1c	nr	nr

1 twice a day; 2 rho iso-alpha acids; 3 proanthocyanidin; 4 glycosylated hemoglobin; 5 total cholesterol; 6 low-density lipoprotein cholesterol; 7 low-density lipoprotein particle; 8 Triglycerides; 9 high-density lipoprotein; 10 non-high-density lipoprotein; 11 Apolipoprotein A; 12 Apolipoprotein B; 13 fasting blood glucose; 14 homeostasis model assessment; 15 sistolic blood pressure; 16 diastolic blood pressure; 17 cardiovascular risk; 18 "+"onset/progression of DR (Diabetic Retinopathy) with + DR ; 19 "+"onset/progression of DR (Diabetic Retinopathy) with – DR; 20 Malondialdehyde; 21 Total antioxidant activity (*) significant difference within group (**) significant difference between groups

3.8 The Nature of Nutraceutical Compositions

The composition of the nutraceuticals administered in the different studies was quite variable. No single nutraceutical compound was used in any study; rather, a combination of antioxidants, probiotics, vitamins, minerals, or amino acids, and in amounts that, while specified in all the studies, resulted in two of the nine studies as "nonspecific" data, as specified in Table 1 [13, 20]. The reviewed studies revealed that polyphenols, phytosterols, and stanols were the main constituents in the formulation of nutraceuticals and were part of all preparations. The names of the commercial formulations and the used extracts were added in those cases in which the article named them. Only 4 out of 9 studies added vitamins to the compounds extracted. They are referenced in Table 1. in addition to their indications and principal actions. In the compounds that were extracted, water-soluble vitamins, such as C [20, 21], B1 [20, 21], B2 [20], B3, B6, B9, and B12 [14, 20], were added. Furthermore, some nutraceutical compounds had fat-soluble vitamins like vitamin D [21]. Mineral compounds, such as Selenium, Magnesium, Manganese, Zinc, and Copper, were added [20, 21]. In one of the nine studies, it was noticed that probiotics had been added as part of the strategy created by the study [22]. Amino acids like L-tyrosine [18] and glutathione were added [20]. The compounds found in the present study varied, such as polyphenols, phytosterols and their stanols, red yeast-fermented rice, and coenzyme Q10.

The analytical values obtained from the different studies can be grouped into categories and summarized in Table 1.

3.9 Anthropometric Measures

Weight, body mass index (BMI), and fat mass were variables that significantly decreased in one of the nine observed studies. In addition to nutraceutical supplementation, this study included a Mediterranean diet with a low glycemic load in both the comparison groups. Although this decrease occurred in both arms of the intervention in study 7, the drop in these parameters in the group treated with nutraceuticals was maintained over time in the control group, which entered a plateau state in which weight reduction was lower [13]. The result of this study was not specified as significant. However, the BMI result did indicate significance at $p < 0.05$. In the other studies, which also applied a Mediterranean diet with a low glycemic load, no significant decrease in the aforementioned anthropometric parameters was observed [15, 16].

3.10 Clinical Measures

In three of the nine studies, blood Pressure (BP) levels significantly lowered after nutraceutical consumption. Systolic blood pressure (SBP) decreased in two studies, and diastolic blood pressure (DBP) dropped in two others. Only one study detailed that this decrease occurred in both variables simultaneously [21], and it did not remain constant in the other studies.

3.11 Serum Lipid and Apoprotein Values Results

TC decreased in four of the nine studies [13, 15, 16, 18]. LDLc levels lowered in three of the nine studies [15, 17, 20]. Very Low-Density lipoprotein (VLDL) levels were reported to decrease in only one study, and the result was not presented in the paper (15). This omission occurred because the

measurements reported in that study were presented in absolute values, from which the percentage change cannot be estimated. The effects on triglycerides (TG) were reported in two of the nine studies where a Mediterranean diet with a low glycemic load was used [13, 15]. Non-HDL cholesterol was significantly lower in three of the nine studies that used a Mediterranean diet with a low glycemic load [13, 15, 16]. The lipid parameter value ratios in the different studies were not homogeneous: cholesterol/HDL, triglycerides/HDL ratios decreased in three of the nine studies [13, 15, 16]. Regarding the values of lipid particles, a decrease in this parameter was reported in only one of the nine articles [16]. Apolipoprotein B and apolipoprotein B/apolipoprotein A ratio decreased in two of the nine articles that used a Mediterranean diet with a low glycemic load [13, 16]. In one of the nine studies, serum high-sensitivity C-reactive protein (Hs-CRP) decreased [13]. CVR measured on the Framingham scale at 10 years was reduced in two of the nine articles where this parameter was assessed [13, 21]. Matrix metalloproteinase (MMP) was reported in only one of the nine studies, where its decrease was documented [17]. The lipid profile parameters in the modified Mediterranean diets with a low glycemic load, when accompanied by nutraceuticals, showed consistency in the reduction of values such as TC, LDLc, TG, non-HDL cholesterol, COLEST/HDL, and TG/HDL ratio [13, 15, 16].

Significant effects on MetS reduction were observed in one of the nine studies [15], although the TG/HDL parameter (MetS marker) decreased in three of the nine studies [13, 15, 16]. This reduction in MetS was associated with a drop in the CVR according to the Framingham equation at 10 years in one study [13]. No other research showed any combined significance of this type. This reduction was not associated with weight loss or reduced SBP [15].

Two of the nine studies showed a significant decrease in uric acid levels [14, 18].

The effects on the variables related to fasting glucose showed effects in one of the nine studies on both arms [19], while HbA1c was observed as high in one of the nine studies [20].

Nutraceutical consumption in subjects with type 2 diabetes mellitus and diabetic retinopathy lowered the lipid peroxidation values, which reduced lipid oxidative stress and increased antioxidant status in the plasma values compared to the subjects who did not take nutraceuticals. The progression of diabetic macular edema (DME) increased to 31% in patients who did not receive treatment. Meanwhile, 26% of subjects who did not have DMA at baseline and did not take nutraceuticals progressed to this condition by the end of the study. Malondialdehide (MDA) levels were lower in the treated DM2 group than in the untreated group at baseline. Treatment affected MDA levels in the group with positive diabetic retinopathy of the DM group. Total Antioxidant Activity (TAA) increased in the DM groups that received treatment [20].

4. Discussion

The review of the effects of supplementation with nutraceuticals in the Mediterranean diet showed that it was an appropriate strategy in lipid profile alteration cases. Nutraceuticals were also associated with reduced CVR variability between 12 weeks and 18 months. However, the observed studies did not provide any consistency in other variables, such as SBP or HDLc, which could be attributed to the factors discussed below. It is crucial to indicate that the studied samples required previous training in their diet despite living in Mediterranean regions. The variability in their clinical characteristics was different and not consistent across studies. Consequently, nutraceuticals provide benefits for the Mediterranean diet according to certain clinical variables.

Mediterranean diet and nutraceuticals were associated with reductions in CVR variability. This was reflected in its effect on various indicators. TC and LDLc showed a more uniform reduction than other indicators like BMI and fat mass. Previous studies have reported a relationship between nutraceuticals use and reductions in BMI and fat mass [23], which did not appear to be the case in those studies in which the Mediterranean diet was combined. These findings suggest that the Mediterranean diet context could condition the effects of nutraceuticals on specific parameters in other studies that did not include the Mediterranean diet [1, 24]. However, this conclusion needs another review to compare the effects of nutraceuticals with those of different diets. None of the studies in this review included a different diet from the Mediterranean diet as a condition to make a comparison, in addition to nutraceuticals, or studies that have related greater effectiveness of the Mediterranean diet in reducing LDLc levels compared to a low-fat diet [1]. These results were confirmed in the studies carried out with three different diets in three groups without nutraceutical supplements: a Mediterranean diet, a low carbohydrate diet, and a low-fat diet. The study evaluated weight loss and, consequently, cardiovascular parameters. In the low-carbohydrate diet and Mediterranean diet, groups were able to reduce and maintain LDLc levels after 2 intervention years [25].

Guidelines for dyslipidemia treatment were identified about 15 years ago with nutraceuticals and functional foods for their cholesterol-lowering action and a means to control lipid levels in lower-risk patients [26]. However, this type of approach has not yet been developed [21].

Reduced high-sensitivity C-reactive protein (hs-CRP) has been proposed as an essential factor affecting CVD risk [13, 14, 17]. The hs-CRP parameter is a biomarker of inflammation used to predict myocardial infarction, stroke, and peripheral arterial disease. It is known that hs-CRP plays a role in improving leukocyte reactivity, complement binding, activation of platelets, and removing cellular debris from sites of active inflammation. A consistent decrease in hs-CRP levels has been observed with monacolin k treatment [17], but this reduction has also been reported in another study in which monacolin k did not form part of the used nutraceutical, but omega-3 from fish oil was present as an adjuvant with other nutraceuticals and phytosterols [27]. The explanation could be that monacolin k may control chronic inflammation through an indirect anti-inflammatory effect resulting from lipid-lowering and other processes that reduce stimulants rather than from a direct anti-inflammatory effect of natural statin-like elements [17].

According to the Framingham equation, at 10 years, Nutraceuticals showed a reduction in CVR by reducing variables like TC. However, the results of other variables in this index, such as HDLc or SBP, were not consistent with other observed studies, which have indicated that nutraceuticals alone achieve a reduction in CVR. To measure CVR, the applied screening methods, such as the Framingham index at 10 years, classify risk factors as nonmodifiable (age, sex, genetic factors/family history) and modifiable, where preventive action can be taken: smoking, hypertension, hypercholesterolemia, diabetes mellitus, and overweight and obesity (specifically abdominal or visceral obesity), together with physical inactivity. These modifiable data are closely associated with CVD [28, 29]. Other factors associated with an increased risk of CVD are low HDLc, high TG, and dense and small LDL particles, which can be associated with MetS, high blood glucose, BP, and abdominal obesity [29]. The NCEP (National Cholesterol Education Program) incorporated hyperglycemia or insulin resistance, visceral obesity, atherogenic dyslipidemia, and hypertension into the MetS definition. It has been specified that the concurrence of three of these factors is considered a valid diagnosis of MetS [29].

Three of the nine studies explicitly reported parameters like TC, HDLc, and SBP, which formed part of the Framingham risk equation at 10 years [13, 15, 21]. In two of these studies, the significant change could be attributed mainly to the decrease in TC, whereas in a third, it could be explained by a change in the reduction of BPS. In the other studies, the Framingham index was not explicitly estimated, although significant reductions in cholesterol were observed in four studies and SBP in one more study [14, 16-18]. Several studies observed that TC and LDLc reduced after adhering to a Mediterranean diet and consuming nutraceuticals. These administered nutraceuticals included compounds with elements, such as monacolin k from red rice yeast or phytosterols, and other active components that impacted extravascular functions, such as magnesium and vitamin D, were also included [21, 30].

Quantitatively more marked reductions in combined factors, such as cholesterol, SBP, and DBP, were the main factors to promote the reduction in the CVD risk for the subjects treated with nutraceuticals, where a decrease in the CVD risk was evidenced. Nutraceuticals were also proposed as an aid to reduce the MetS risk. Most of the reviewed studies manifested the intention of reducing this parameter's risk as one of their hypotheses [15]. However, only one study reported a significant reduction in MetS, while others reflected reductions in the indices associated with MetS. For example, decreases in TG/HDL were observed in three studies [13, 15, 16]. This decrease only coincided with a reduction of MetS in one of them. These results may allow us to consider whether the study of MetS should be approached as a whole or as a series of disaggregated indicators that are associated but not always modified as a whole, even if each one was to a different extent.

No consistency was found in the reviewed studies in the nutraceutical compounds used to modify the other studied variables. More than 40 nutraceutical substances have been studied to improve lipid metabolism, and some clinical trials have demonstrated cholesterol-lowering activity, improved glucose metabolism, and inflammatory parameters, as well as a possible positive influence on cardiovascular prognosis [14, 31]. However, this review's main elements of the nutraceuticals corresponded mainly to products extracted from plants. The concentration and variety of these compounds vary in each study. It could be stated that polyphenols, phytosterols, and their stanols represent essential values in nutraceuticals due to their representativeness among various compounds. We can find compounds like monacolin k used in three of the studies, which report coinciding results in the reduction of TC, LDLc, and Hs-CRP [13, 14, 17]. However, in the studies in which this compound was used, neither a significant decrease on the Framingham CVR scale at 10 years nor a decrease in MetS was observed. Nevertheless, as nutraceuticals were not used as single compounds and studies did not pay attention to the proportions of the components they included, no conclusions could be drawn in this direction from the reviewed studies.

The strategy employed in three of the studies herein collected included a modification of the Mediterranean diet with a low-GI carbohydrate intake in favor of increased protein intake and nutraceuticals supplementation. Although low GI diets have been documented as a target for weight [32], BMI, and fat mass reduction, this parameter was only observed in one of the related studies with the same characteristics [13]. Consistency was observed in variables such as TC, LDLc, TG, nonHDL cholesterol, COLEST/HDL, TG/HDL, Apo B, and Apo B/ApoA-1, where a significant decrease was appreciated in those groups treated with nutraceuticals. Still, no significant reduction was documented for MetS, except in one. This should make us consider if this type of strategy could effectively reduce CVR [33] and in what circumstances its use would be recommended. Perhaps a case-by-case approach should discuss the framework of general risk indicators.

NonHDL cholesterol is considered a strong predictor of CVD and mortality risk and, together with LDLc, was added by the NCEP to treat hypercholesterolemia in adults as a secondary target of therapy [34-36]. Apo B indicates the total number of atherogenic lipoprotein particles, and apo A1, an essential lipoprotein in HDL, plays a critical role in cholesterol transport. The Apo B/ Apo A-1 ratio and Apo B concentration have been suggested as a risk factor for cardiovascular disease. Multiple studies have observed that the apo B/apo A-1 ratio predicts CVR, with lower ratios indicating lower risk. Some studies have considered it a better predictor than LDLc and lipid ratios [37, 38].

Final glycation products (the result of transforming proteins or lipids when exposed to sugars) induce cell damage. Together with lipid peroxidation, these products are associated with the development of diabetic retinopathy, the accumulation (elevation) of the end products of their degradation in ocular tissue by increasing cell permeability, angiogenesis, and retinal barrier alteration [20]. MMP levels in circulation are high in patients with acute myocardial infarction, unstable angina, and after coronary angioplasty. Their reduction benefited after consuming monacolin k and coenzyme Q10. This parameter has not been documented in other studies in which monacolin k has been administered. Nor is it noted in the other nutraceuticals where coenzyme Q10 has been administered [14, 17, 20]. In the present work, only one study was reported in which treatment with nutraceuticals was carried out in diabetic subjects in whom no significant drop in glucose values was observed. Still, an increase in HbA1c was noted [20]. No lipid peroxidation measurement was found as a parameter to be evaluated in the other reviewed studies.

Although the other studies included glucose as a parameter, none showed a significant reduction in value after nutraceutical consumption. In some studies, proanthocyanidin (PAC), a component studied as a decrease in insulin sensitivity, was administered. However, significant results were shown in the glucose levels between patients treated with PAC *versus* those adhering to the Mediterranean diet [15, 16]. More interventions should be made in this regard.

The education on the Mediterranean diet offered to study subjects was based on teaching or instructing them to follow it qualitatively. Some groups also provided recommendations about which products to avoid or reduce, such as excessive dairy products or processed meat [18].

The combination of different nutraceuticals was often used in commercial products to take advantage of the potential synergistic effects of distinct agents on cholesterol metabolism [31, 39]. One major limitation of the studies that investigated the effect of nutraceutical combinations on lipids should be borne in mind because most of the trials were short, performed by single centers, often open-label, and with not a very large number of patients.

Finally, safe nutraceutical consumption was an objective proposed in the different studies. Adverse effects related to nutraceutical consumption were only mentioned by one of the nine evaluated studies [13]. However, the dose for such effects to occur was not addressed. The RDI rates of the used nutraceuticals were not specified in any study.

5. Study Limitations

This review has some limitations. Firstly, to compile the study's objective, the numbers of papers included is low. Of the reviewed studies, several limitations can be identified:

The nutraceutical expression describes a wide range of products, but no broad consensus of its definition appears in the scientific literature [7]. Hence, several nutraceutical compounds combined

in different formulations are designed to affect the biochemical markers used in other studies, especially for those that aim to reduce lipid profile alterations.

Various names of nutraceutical compounds can be found in the scientific literature, which have not been entered into the database.

In most reviewed studies, no precision was observed when evaluating subjects' adherence to the Mediterranean diet. Adherence to the Mediterranean diet was assessed only in the work of Roig, in which groups were divided into correct and not correct followers of the Mediterranean diet [20]. This classification was adequate to help differentiate the groups that followed the guidelines and to visualize whether the results were under such adherence. However, no other study had such a consideration taken into account.

Dietary choices in the countries that border the Mediterranean Sea have varied considerably since Ancel Keys' study, even within a country itself, which suggests that there is no unique Mediterranean diet (5).

The variability of the pathology of the study groups did not remain constant within the observed studies. The final sample in some of the studies was small and not very varied, which did not allow the results to be extrapolated to larger populations [13, 14, 18]. Albeit with adequate statistical power, this factor also had the effect of not being able to observe the capacity of nutraceuticals to individualize their impact at the individual level [16].

The complex nature of the components studied and the dosages used in the different studies do not allow for their comparison. Only one study omits quantifying the elements that constitute the nutraceutical used [20].

None of the studies considered the possibility of dosing according to the anthropometric parameters of the subjects studied.

The strategies included in the studies did not allow us to identify whether the effects observed in the parameters that were not found to be frequent, such as TG and VLDL, were the result of nutraceutical supplementation alone or of additive interactions among diet, lifestyle modifications and PA performance.

The follow-up period in the observed studies was short, although only one lasted 18 months, and the rest did not exceed 18 weeks. There was no follow-up after the intervention study to evaluate adherence to the changes observed. There was no standardized follow-up of patients beyond two or three check-ups or telephone calls. This characteristic does not allow us to evaluate the effects of the different treatments in a comparable unit of time.

Supplements were used that are not included in the Mediterranean diet, such as banaba extract from Southeast Asia. For this reason, it could not be compared to foods typical of the Mediterranean geography. Other foods, such as artichoke, have offered benefits for inhibiting cholesterol synthesis and are accessible to Mediterranean people [40].

No randomized clinical trials were related to the topic discussed in this study. Likewise, there was no comparison of the exposed groups to another arm where the same study was carried out using another diet type, such as a low-fat diet.

The variety of nutraceutical compounds studied in these nine articles was wide. However, studies were not at all comparable in terms of the employed nutraceutical type or the variables analyzed to study effects. It is difficult to conclude what nutraceutical can be used in certain circumstances.

6. Conclusions

This study aims to understand the effect of nutraceutical intake while following a Mediterranean diet.

The papers reported in the present study examined nutraceutical compounds and the benefits of lowering lipid levels in subjects with cardiovascular pathology or MetS. As nutraceutical compounds provided in the Mediterranean diet context were varied, the results also had some variations. The reduction in lipid markers, such as TC, HDLc, and SBP, at the laboratory level allowed a decrease in the CVR score on the Framingham index at 10 years to be reported, even though not all the presented studies were able to conclude that these circumstances are present as a whole. The other collected values, such as non HDL cholesterol, cholesterol/HDL, TG/HDL, and Hs-CRP, were also found to reduce the CVR risk. MetS was only reported to decrease significantly in one of the studies. How to manage these variables, individually or by finding a combination method, must be asked to approach preventive measures or treatments for those parameters must be asked. Suppose the combined action is more beneficial than the individualized one, as this study assumes. In that case, a series of lifestyle modifications should be prescribed in addition to nutraceutical intake, including adherence to the Mediterranean diet and PA.

We did not find any treatment based on a single compound that improves a function. Instead, we used synergies between nutraceuticals to achieve this end, varying from employing nutraceutical compounds to modifying low-GI Mediterranean diet to performing PA.

Despite the wide variability discussed above, nutraceuticals comprise main elements, such as phenolic compounds, phytosterols, and stanols. The doses applied in the different studies were not calculated according to anthropometric variables, and RDIs were not established in any study.

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Author Contributions

María del Valle del Olmo de Dios, and Laura Laguna Cruañes collaborated equally in the present work, sharing the first place. Alfonso Barrós-Loscertales contributed in writing in critical review of the manuscript.

Competing Interests

The authors have declared that no competing interests exist.

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