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Original Article

Effects of Chios Mastiha essential oil on cholesterol levels of healthy volunteers: A prospective, randomized, placebo-controlled study (MASTIHA-OIL)

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ABSTRACT

Introduction: Chios Mastiha essential oil (CMO) is a natural product extracted from the resin of Mastiha, possessing antioxidant, anti-microbial, anti-ulcer, anti-neoplastic, and cholesterol-lowering capabilities in vitro, and its hypolipidemic effect was confirmed in animal studies. Yet, there are no randomized, placebo-controlled clinical studies in the literature regarding CMO's hypolipidemic effects in humans. A prospective, randomized, placebo-controlled study was designed to study the hypolipidemic effect of CMO capsules on healthy volunteers with elevated cholesterol.

Methods: 192 healthy volunteers were screened and 160 of them with total cholesterol> 200 mg/dl participated in the study. They were randomized with a 2:1 ratio of receiving CMO capsules (200 mg mastiha-oil/capsule) and placebo for 8 weeks respectively. 113 patients received CMO and 47 were randomized in the control group, and all of them completed the follow-up period.

Results: After 8 weeks of CMO administration, total and LDL cholesterol were significantly lower in the CMO compared to the placebo group 215.2 ± 27.5 vs 237.0 ± 27.9 mg/dl ($p < 0.001$) and 135.0 ± 26.1 vs 153.0 ± 23.3 mg/dl ($p < 0.001$) respectively. No gastrointestinal adverse events or liver or renal toxicity were reported. Additionally, in the CMO group total cholesterol was significantly decreased by 20.6 mg/dl (9%), LDL by 18.1 mg/dl (12%), triglycerides by 21.8 mg/dl (15%), and glucose by 4.6 mg/dl (5%) and HDL was increased by 2.4 mg/dl (5%), compared to their baseline values.

Conclusion: The MASTIHA-OIL study showed the efficacy and safety of CMO in reduction of total and LDL cholesterol after 8 weeks of administration in healthy volunteers with elevated cholesterol levels.

1. Introduction

Cardiovascular disease (CVD) is a leading cause of death worldwide. Several cardiovascular risk factors result in the progress of atherosclerosis, the main pathological process leading to CVD, with dyslipidemia being a major factor[1]. Thus, total and LDL cholesterol drastic reduction is a major aim in the primary and secondary prevention of CVD[1-3].

Chios mastic gum (Mastiha Chia) is a natural resin that is excreted from the trunk and branches of the mastic tree (Pistacia

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Lentiscus var. Chia of the Anacardiaceae family). For thousands of years, the southern part of Chios Island has been the only place on the planet where mastic trees are systematically cultivated, and mastic gum is produced. Chios mastic gum possesses many beneficial biological activities – anti-indigestion, anti-ulcer (acting against Helicobacter pylori), antimicrobial, antioxidant, hypolipidemic, anti-inflammatory, anti-Crohn's disease, and anti-neoplastic, as reported by many clinical studies[4-13].

Chios Mastiha essential oil (CMO) is a natural product extracted from the resin of Mastiha, possessing antioxidant, anti-microbial, anti-ulcer,anti-neoplastic, and cholesterol-lowering capabilities in vitro, and its hypolipidemic effect was confirmed in animal studies. Yet, there are no randomized, placebo-controlled clinical studies in the literature regarding CMO's hypolipidemic effects in humans[14-19].

1.1. Aim of the study

We designed a prospective, placebo-controlled, randomized clinical study to evaluate the hypolipidemic effect and safety of CMO in healthy volunteers with elevated cholesterol levels, who were not receiving or had no indication for other lipid-lowering medications according to the current guidelines.

2. Methods

2.1. Endpoints

The primary endpoint was to record changes in cholesterol (total, HDL, LDL-directly measured) and triglyceride levels after continuous administration of capsules containing 200 mg of CMO for 8 weeks. Secondary endpoints included changes in other serum biochemical parameters, such as electrolytes, alanine aminotransferase (ALT), aspartate aminotransferase (AST), urea, creatinine, uric acid, glucose and C-reactive protein (CRP), and any adverse events.

2.2. Eligibility criteria

Our study received approval from the hospital's Ethics Committee and Scientific Council (approval number 4-19/02/2020) and written informed consent was obtained from all participants. The study has been registered in ClinicalTrials.gov (ID: NCT05858372). The recruitment period was between 1 July 2022 and 30 September 2022. Inclusion criteria were increased total cholesterol >200 mg/dl, in adult volunteers (≥18 years old) of any gender, not amenable or not willing to receive pharmaceutical therapy. The exclusion criteria were: participation in any other study during the recruitment period, contribution to the design or accomplishment of the study, known cardiovascular disease (coronary artery disease, carotid artery disease, peripheral vascular disease, stroke, diabetes mellitus, aortic aneurysm), patients in high or very high risk of CVD according to SCORE2, subjects amenable to pharmaceutical lipid-lowering regimens according to current guidelines, or any other pharmaceutical regimen with hypolipidemic effects.

2.3. CMO formulation and administration

The CMO capsule was kindly provided by the Chios Gum Mastic Growers Association. It was a soft gel capsule containing 200 mg of CMO and 100 mg of other excipients being medium chain triglycerides, while the shell was made of bovine gelatin and glycerol, with life expectancy of 2 years. The recommended dosage was 1 capsule per day, 30 minutes before dinner with water or juice, given to participants as casual advice. Moreover, participants were advised not to use other Mastiha-containing products during their participation in the study. The subjects stored the capsules in a cool and dry place at temperatures not exceeding 25°C. The substance of placebo capsules was the same with CMO capsules without mastiha-oil and thus, were aromatized with mastiha-oil.

2.4. Study sample

Our study took place at the Cardiology Department of the "Skylitseion" General Hospital of Chios. Based on our previous pilot study of the effect of Chios mastic gum (total mastic) on cholesterol levels (total and LDL cholesterol) of healthy volunteers[4] and a prespecified 2:1 randomization, a total sample size of about 150 volunteers would provide an 80% power to detect a difference of at least 10 mg/dl at total or LDL cholesterol between CMO and placebo.192 volunteers were screened and 160 of them met the inclusion criteria and participated in the study. They were randomized with a 2:1 ratio of receiving CMO capsules and placebo (control) for a total of 8 weeks respectively. Out of the 160 patients 113 received CMO and 47 were randomized in the control group, and all of them completed the follow-up period. No specific dietary or exercise instructions were given to the study participants.

2.5. Statistical Analysis

Statistical analysis was performed with the software IBM SPSS Statistics for Windows, version 24.0 (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was used for normality tests. Nominal variables were compared with the chi-square test. Comparisons of continuous variables between CMO and placebo groups were performed with the t-test for independent samples. Differences in continuous variables for each group between the baseline and the follow-up visit were performed with the paired-samples t-test. Statistical significance was defined as $p < 0.05$.

3. Results

The baseline characteristics and the biochemical parameters of the study population (Visit 1) are presented in Table 1. Volunteers in the CMO group were more overweight and had higher baseline values of total and LDL cholesterol, triglycerides, and glucose, while the HDL cholesterol was lower than the placebo group. The biochemical parameters for the placebo and CMO groups after 8 weeks of treatment (follow-up Visit 2) are provided in Table 2.

At 8 weeks, total and LDL cholesterol were significantly lower in the CMO compared to the placebo group 215.2 ± 27.5 vs 237.0 ± 27.9 mg/dl ($p < 0.001$) and 135.0 ± 26.1 vs 153.0 ± 23.3 mg/dl ($p < 0.001$) respectively (Table 2, Fig. 1). There was also a significant difference in uric acid although considered not clinically significant, due to the very small absolute difference (0.2 mg/dl). No gastrointestinal adverse events or liver or renal toxicity were reported.

Furthermore, comparisons between the baseline (0 weeks) and 8 weeks were performed for the CMO group (Table 3, Fig. 2). CMO administration for 8 weeks decreased significantly total cholesterol by 20.6 mg/dl (9%) and LDL by 18.1 mg/dl (12%) ($p < 0.001$). Also, a decrease in triglycerides by 21.8 mg/dl (15%) and glucose by 4.6 mg/dl (5%) and an increase in HDL by 2.4 mg/dl (5%) was observed.

4. Discussion

MASTIHA-OIL is the first human in vivo, prospective, randomized, placebo-controlled study regarding the hypolipidemic effect of CMO in healthy volunteers with elevated cholesterol levels.

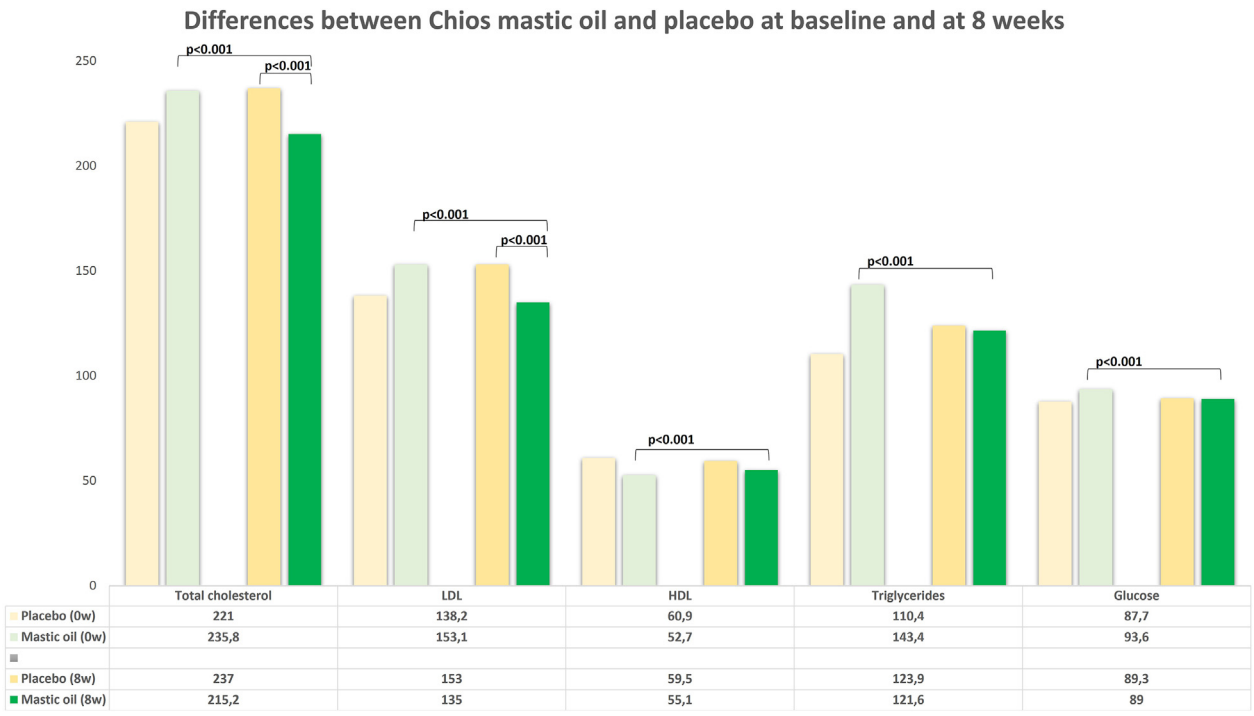

Figure 1. Differences between Chios mastic oil (CMO) and placebo at baseline (0w) and at 8 weeks (8w). At 8 weeks only total and LDL cholesterol were significantly different between CMO and placebo. Regarding the CMO group, all parameters showed statistically significant differences between baseline and 8 weeks. (LDL: low-density lipoprotein, HDL: high-density lipoprotein).

4.1. Mechanisms of action and in vitro studies of Mastic Oil

CMO possesses hypolipidemic, anti-ulcer, antioxidant, and anti-inflammatory action. More than 60 CMO constituents have been identified including monoterpenes: a-pinene, b-pinene, and myrcene. These monoterpenes are absorbed by humans and are bioavailable in human plasma already after 0,5 h post-ingestion of a single dose[16].

Table 1
Baseline characteristics of the study population (Visit 1 − 0 weeks).

Variable	Total sample (n = 160)	Placebo (n = 47)	Mastic oil (n = 113)	p
Age (years)	52 ± 9	51 ± 10	53 ± 10	0.216
Gender				0.462
Female	102 (63.8%)	32 (68.1%)	70 (61.9%)	
Male	58 (36.2%)	15 (31.9%)	43 (38.1%)	
Height (m)	1.68 ± 0.1	1.69 ± 0.1	1.67 ± 0.1	0.334
Weight (kg)	79.1 ± 15.2	74.5 ± 13.1	81.1 ± 15.6	0.012
BMI (kg/m^2)	28.1 ± 5.2	26.1 ± 4.1	29.0 ± 5.4	0.001
Arterial Hypertension	13 (8.1%)	2 (4.3%)	11 (9.7%)	0.248
Family History CAD	27 (16.9%)	6 (12.8%)	21 (18.6%)	0.371
Smoking				0.846
Never	101 (63.1%)	30 (63.8%)	71 (62.8%)	
Ex	21 (13.1%)	7 (14.9%)	14 (12.4%)	
Active	38 (23.8%)	10 (21.3%)	28 (24.8%)	
Total cholesterol (mg/dl)	231.4 ± 23.9	221.0 ± 18.3	235.8 ± 24.6	<0.001
LDL (mg/dl)	148.7 ± 23.8	138.2 ± 19.1	153.1 ± 24.3	<0.001
HDL (mg/dl)	55.1 ± 13.7	60.9 ± 16.0	52.7 ± 12.0	0.002
Triglycerides (mg/dl)	133.7 ± 61.2	110.4 ± 41.9	143.4 ± 65.4	<0.001
Glucose (mg/dl)	91.9 ± 13.0	87.7 ± 16.0	93.6 ± 11.2	0.008
SGOT (AST) (U/L)	20.5 ± 6.5	21.5 ± 8.6	20.1 ± 5.3	0.311
SGPT (ALT) (U/L)	19.9 ± 9.5	20.0 ± 9.3	19.9 ± 9.7	0.925
gGT (U/L)	22.1 ± 18.1	20.5 ± 14.3	22.7 ± 19.4	0.490
BUN ((mg/dl)	32.4 ± 9.4	30.1 ± 6.6	33.4 ± 10.2	0.045
Creatinine (mg/dl)	0.8 ± 0.2	0.8 ± 0.1	0.8 ± 0.2	0.094
Sodium (mEq/L)	140.2 ± 2.1	140.0 ± 2.1	140.0 ± 2.0	0.387
Potassium (mEq/L)	4.5 ± 0.4	4.4 ± 0.3	4.5 ± 0.4	0.694
CRP (mg/dl)	0.3 ± 0.6	0.2 ± 0.2	0.3 ± 0.7	0.367
Uric acid (mg/dl)	5.1 ± 1.3	4.8 ± 1.2	5.2 ± 1.4	0.064

BMI: body mass index, CAD: coronary artery disease, LDL: low-density lipoprotein, HDL: high-density lipoprotein, SGOT: serum glutamic oxaloacetic transaminase, AST: aspartate transaminase, SGPT: serum glutamic pyruvic transaminase, ALT: alanine transaminase, gGT: gamma-glutamyl transferase, BUN: blood urea nitrogen, CRP: c-reactive protein.
Nominal variables are expressed as n(%). Continuous variables are expressed as mean ± SD.

Table 2
Differences between groups at 8 weeks (Visit 2)

Variable	Total sample (n = 160)	Placebo (n = 47)	Mastic oil (n = 113)	p
Total cholesterol (mg/dl)	221.6 ± 29.3	237.0 ± 27.9	215.2 ± 27.5	<0.001
LDL (mg/dl)	140.3 ± 26.5	153.0 ± 23.3	135.0 ± 26.1	<0.001
HDL (mg/dl)	56.4 ± 13.8	59.5 ± 16.1	55.1 ± 12.5	0.07
Triglycerides (mg/dl)	122.3 ± 51.6	123.9 ± 47.1	121.6 ± 53.5	0.793
Glucose (mg/dl)	89.1 ± 12.1	89.3 ± 15.7	89.0 ± 10.4	0.866
SGOT (AST) (U/L)	20.3 ± 5.3	20.4 ± 4.0	20.3 ± 5.8	0.927
SGPT (ALT) (U/L)	19.4 ± 9.3	19.4 ± 8.1	19.4 ± 9.8	1.0
gGT (U/L)	20.9 ± 19.1	19.1 ± 14.8	21.7 ± 20.6	0.441
BUN (mg/dl)	31.3 ± 8.3	30.3 ± 6.5	31.7 ± 8.9	0.258
Creatinine (mg/dl)	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.2	0.307
Sodium (mEq/L)	140.0 ± 2.0	140.3 ± 2.1	140.0 ± 1.9	0.166
Potassium (mEq/L)	4.5 ± 0.4	4.5 ± 0.4	4.5 ± 0.4	0.280
CRP (mg/dl)	0.3 ± 0.6	0.2 ± 0.3	0.3 ± 0.7	0.585
Uric acid (mg/dl)	4.9 ± 1.3	4.5 ± 1.2	5.0 ± 1.3	0.03

LDL: low-density lipoprotein, HDL: high-density lipoprotein, SGOT: serum glutamic oxaloacetic transaminase, AST: aspartate transaminase, SGPT: serum glutamic pyruvic transaminase, ALT: alanine transaminase, gGT: gamma-glutamyl transferase, BUN: blood urea nitrogen, CRP: c-reactive protein.
Nominal variables are expressed as n (%). Continuous variables are expressed as mean ± SD.

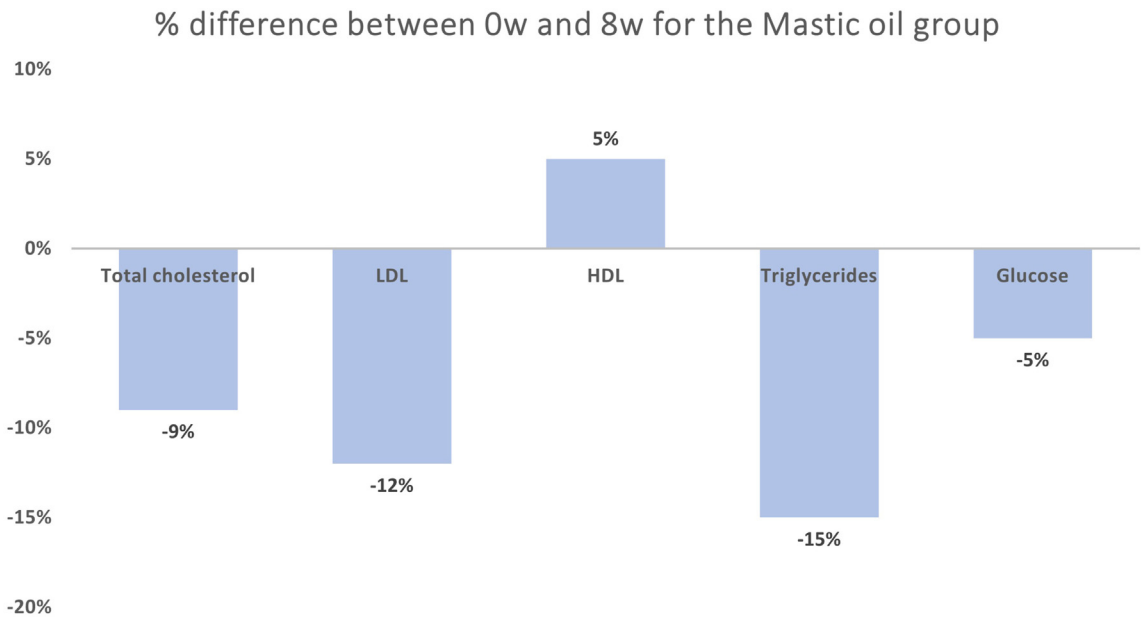

Figure 2. Effect of Chios mastic oil on cholesterol and glucose levels at 8 weeks. (LDL: low-density lipoprotein, HDL: high-density lipoprotein).

Another monoterpene, camphene, was studied as a hypolipidemic factor in both naïve and rats susceptible to detergent-induced hyperlipidemia[14]. Camphene was proved to be a dose-depended lipid-lowering agent having a synergistic action with other CMO components, reducing plasma cholesterol and triglycerides independently of HMG-CoA reductase inhibition, which is the main pathway of action of statins.

Sterol regulatory element-binding proteins (SREBPs) are membrane-bound transcription factors that regulate the synthesis of cholesterol. SREBP-1a targets genes involved in both cholesterol and triglyceride pathways including the LDL receptor gene (increasing the LDL receptor expression and scavenging of circulating LDL), SREBP-1c regulates genes of fatty acid and triglyceride metabolism, while SREBP-2 regulates the genes of cholesterol

Table 3
Significant differences in biochemical parameters of the Chios mastic oil group between baseline (Visit 1 − 0 weeks) and 8 weeks.

Chios mastic oil	Week 0 (mean)	Week 8 (mean)	Absolute difference	% difference	p
Total cholesterol (mg/dl)	235,8	215,2	−20,6	−9	<0.001
LDL (mg/dl)	153,1	135	−18,1	−12	<0.001
HDL (mg/dl)	52,7	55,1	2,4	5	<0.001
Triglycerides (mg/dl)	143,4	121,6	−21,8	−15	<0.001
Glucose (mg/dl)	93,6	89	−4,6	−5	<0.001
BUN (mg/dl)	33,4	31,7	−1,7	−5	0.004
Creatinine (mg/dl)	0,8	0,78	−0,02	−3	0.036
Uric acid (mg/dl)	5,2	5	−0,2	−4	<0.001

LDL: low-density lipoprotein, HDL: high-density lipoprotein, BUN: blood urea nitrogen.

metabolism. Vallianou et al studied the effect of camphene on SREBPs, microsomal triglyceride transfer protein (MTP), and apolipoprotein AI (apoAI) the critical protein component of HDL. Camphene significantly increased apoAI expression, while reducing MTP expression. Camphene treatment upregulated the expression of both SREBP-1a and SREBP-1c implying that camphene triggers the proteolytic process of SREBP-1 precursor form which then activates the transcription of target genes in the nucleus[14,20].

4.2. Animal studies

Administration of CMO at a dose of 30 μg/gr of body weight in hyperlipidemic rats resulted in a reduction of total cholesterol, LDL cholesterol, and triglycerides. This is the only available animal study using CMO in the literature so far carried out by Vallianou et al. The authors suggested that the hypolipidemic action of CMO was independent of HMG-CoA reductase activity[20].

4.3. Safety of Chios Mastic gum and CMO

Chios Mastic gum consumption is generally considered safe, although the long-term safety has not been sufficiently investigated, and the maximum safe dose remains still unknown. High doses of mastic have also been well tolerated in clinical trials, and no adverse effects have been recorded[4,22]. Regarding CMO Papada et al 2020, show for the first time that MO consumption at the dose of 1 mL is safe, since there were no adverse effects, and the parameters of renal and hepatic function were within the normal range after MO consumption[16]. Vlastos et al 2015, provide evidence of the lack of genotoxic, mutagenic, or recombinogenic activities of CMO under in vitro and in vivo conditions[23]. Furthermore, no interactions between Mastiha gum or CMO and other medications are known from the literature.

4.4. Effects of CMO capsules in our study

In our study, the administration of CMO capsules for 8 weeks resulted in a significant reduction of both total and LDL cholesterol. Slight elevation of HDL and reduction of triglycerides and glucose were observed (Table 3, Fig. 2). When compared to placebo at 8 weeks only total and LDL cholesterol showed significant differences (Table 2, Fig. 1).

No specific dietary or exercise instructions were given to the study participants, except for the avoidance of consumption of Mastiha-containing products, who were encouraged to follow their daily routine. As a result, the net clinical benefit on cholesterol levels of CMO was studied. Significantly, total- and LDL cholesterol levels were elevated in the placebo group from baseline, while in the CMO group, LDL was decreased by 12% from baseline with an absolute difference of 18 mg/dl from the placebo group ($p < 0.001$). This is explained by the fact that our trial took place during the summer period with no COVID-19 restrictions, and people participating in many wedding ceremonies and other social occasions.

The hypolipidemic effect of CMO was already known from animal studies, but data on its efficacy and safety of its use in humans were lacking in the literature. CHIOS MASTIHA OIL was the first human, placebo-controlled trial to study the hypolipidemic effect of CMO on healthy volunteers with real-world data. CMO proved to be effective in cholesterol-lowering with a significant reduction of LDL of 12% in 8 weeks, and safe with no adverse events. This could establish CMO as a lipid-lowering agent for CVD prevention, given its high efficacy in total and LDL cholesterol reduction[21]. A dose-related LDL-reducing effect of CMO looks appealing and cannot be excluded by the current study, since only 1 dose of CMO was tested. However, based on a previous study with Chios Mastic gum (CMG) the dose of 2gr did not offer any significant benefit regarding LDL lowering compared to the 1gr of CMG[4].

5. Future perspectives

Given the establishment of the Chios Mastiha Foundation 3 months ago, more multicenter clinical trials with larger sample sizes are planned to be initiated to further investigate the efficacy of CMO as a cholesterol-lowering agent. Moreover, different doses of CMO should be tested in order to investigate any correlation between the dose of CMO and its hypolipidemic effect, and potential toxicities. Possible interactions of CMO with other drugs should be tested initially in a pre-clinical level and then recorded systematically in a clinical trial.

6. Conclusions

In conclusion, the MASTIHA-OIL study showed the efficacy and safety of CMO in reduction of total and LDL cholesterol in healthy volunteers with elevated cholesterol levels. Based on the 12% LDL reduction from baseline, CMO could be a promising choice as a natural lipid-lowering supplement in patients with dyslipidemia. Further multicenter studies should be organized to confirm its role as a hypolipidemic agent.

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Conflicts of interest

The authors declare that they have no conflict of interest.

Informed consent

Written informed consent for participation in the study and publication of the manuscript was obtained by all participants.

Author contribution

1) Kartalis Athanasios: Conception and design of the analysis, paper writing, and supervising.
2) Dimitrios Afendoulis: Conception and design of the analysis, data collection, data contribution, paper writing, and analysis performance.
3) Didagelos Matthaios: Conception and design of the analysis, data collection, paper writing, analysis performance, and analysis tools.
4) Ampeliotis Michail: data collection, paper writing, analysis performance.
5) Moutafi Maria: data collection, data contribution.
6) Voutas Petros: data collection, conception, and design of the analysis.
7) Smyrnioudis Nikolaos: data collection.
8) Papagiannis Nikolaos: data collection.
9) Garoufalis Stefanos: data collection.
10) Boula Eirini: biochemistry analysis.
11) Smyrnioudis Ilias: conception and design of the study, manuscript review.
12) Vlachopoulos Charalambos: final review of the manuscript.

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