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Review

A network meta-analysis on the comparative effect of nutraceuticals on lipid profile in adults

Tadeusz Osadnik [a], Marcin Goławski [a], Piotr Lewandowski [a], Jakub Morze [b], Kamila Osadnik [a], Natalia Pawlas [a], Mateusz Lejawa [a], Grzegorz K. Jakubiak [a,c], Agnieszka Mazur [a], Lucas Schwingschackl [d], Mariusz Gąsior [e], Maciej Banach [f,*]

[a] Department of Pharmacology, Faculty of Medical Sciences in Zabrze, Medical University of Silesia, Katowice, Poland
[b] Department of Human Nutrition, Faculty of Food Sciences, University of Warmia and Mazury, Olsztyn, Poland
[c] Department and Clinic of Internal Medicine, Angiology, and Physical Medicine, Faculty of Medical Sciences in Zabrze, Medical University of Silesia, Poland
[d] German Institute for Evidence in Medicine, Faculty of Medicine and Medical Center, University of Freiburg, Freiburg, Germany
[e] 3rd Department of Cardiology, Faculty of Medical Sciences in Zabrze, Medical University of Silesia, Katowice, Poland
[f] Department of Preventive Cardiology and Lipidology, Medical University of Lodz (MUL), Lodz, Poland

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ABSTRACT

It is estimated that 2.6 million deaths worldwide can be attributed to hypercholesterolemia. The main reason for non-adherence to statin therapy are the statin-associated muscle symptoms (including nocebo/drucebo effect). In this case, apart from ezetimibe, nutraceuticals are prescribed. We aimed to assess the comparative efficacy of different nutraceuticals in terms of lowering low density lipoprotein cholesterol (LDL-C) and improving lipid profile. Electronic and hand searches were performed until February 2021. The inclusion criteria were the following: (1) randomized trial with any of the reportedly LDL-C lowering nutraceutical: artichoke, berberine, bergamot, garlic, green tea extract, plant sterols/stanols, policosanols, red yeast rice (RYR), silymarin or spirulina. (2) outcome either LDL-C (primary outcome), total cholesterol (TC), high density lipoprotein cholesterol (HDL-C) or serum triglycerides (TG). Random effects network meta-analysis (NMA) was performed to rank the effect of each intervention using frequentist approach. Finally, a total of 131 trials enrolling 13,062 participants were included. All analysed nutraceuticals except for policosanols were more effective in lowering LDL-C (−1.21 [−46.8 mg/dL] to −0.17 [−6.6 mg/dL] mmol/l reduction) and TC (−1.75 [−67.7 mg/dL] to −0.18 [7 mg/dL] mmol/l reduction) than placebo/no intervention. The most effective approaches in terms of LDL-C- and TC-lowering were bergamot and RYR (−1.21 [−46.8 mg/dl] and −0.94 [−36.4 mg/dl] mmol/l) reduction respectively. In conclusion, bergamot and RYR appear to be the most effective nutraceuticals in terms of LDL-C and TC reduction. Evidence for bergamot effect was based on relatively small study group and may require further investigations. Policosanols have no effect on the lipid profile.

1. Introduction

There is a worldwide trend toward unfavourable changes in lipid profiles [1]. According to data from the World Health Organization (WHO), the global prevalence of elevated (>190 mg/dl; 4.9 mmol/l) total cholesterol (TC) was 39% and was the highest in Europe (54%) [2]. Recent data suggest that only one out of three of patients in Europe have values of low-density lipoprotein cholesterol (LDL-C) within the recommended range, with an even lower prevalence (24%) in Central and Eastern Europe (CEE) [3]. It is also estimated that over 2.6 million deaths worldwide can be attributed strictly to hypercholesterolemia [2]. Additionally, the disability caused by cardiovascular diseases (CVD) places a heavy burden on healthcare and insurance systems both in high middle- and low-income countries [4].

Lipid-lowering therapy (LLT) with statins as a first-line treatment is a mainstay of hypercholesterolemia treatment [5]. Randomized controlled trials (RCTs) have indicated the efficacy and safety of statin treatment in primary and secondary prevention of CVD [6,7]. Despite the fact that nonadherence to statin treatment results in an increased risk for progression of atherosclerosis and a higher risk of CVD events [8,

* Correspondence to: Department of Preventive Cardiology and Lipidology, Medical University of Lodz (MUL), Rzgowska 281/289, 93-338 Lodz, Poland.
E-mail address: maciej.banach@icloud.com (M. Banach).

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9], half of patients discontinue statin therapy after 12–24 months of treatment [10] and less than 20% of high-risk patients reach target LDL-C levels [11]. The main reason for primary nonadherence (patients never taking prescribed statins) is the desire to test alternatives before starting a statin along with worrying about possible statin-related adverse effects [11]. Statin-associated muscle symptoms (SAMS), defined usually as musculoskeletal complaints that are reported in 9.1% of patients on statins [12], are, on the other hand, the main cause of therapy discontinuation. It is, however, worth mentioning that "drucebo effect" is suspected to play a significant role [13–17]. Higher frequency of statin-related adverse events in real world as compared to clinical trials might be also a result of disinformation on statin treatment [18].

Some studies and meta-analyses showed the efficacy of various nutraceuticals as lipid-lowering agents [19–23]; however, many of them yielded conflicting results, e.g., regarding policosanols [24,25], where the results of RCTs from outside of Cuba differ substantially from those conducted in Cuba [26]. Importantly, in the last few years, critical comprehensive position papers from the International Expert Lipid Panel (ILEP) on nutraceuticals regarding the treatment of dyslipidaemia, including among statin-intolerant patients, have been published [27–29]. European Society of Cardiology (ESC) recommends application of various nutraceuticals including red yeast rice and phytosterols/-stanols as a part of lifestyle intervention to reduce TC and LDL-C levels [30]. Despite the vast amount of data regarding nutraceutical interventions that allowed the experts to make the recommendations, the question of the comparative efficacy of such nutraceuticals remains unanswered, as there is a paucity of head-to-head trials comparing various nutraceuticals. A network meta-analysis (NMA) approach that enables simultaneous comparison of interventions could provide indirect evidence of the comparative efficacy of particular nutraceuticals [31]. To the best of our knowledge, no study has been performed that simultaneously compared different nutraceuticals in terms of lipid-lowering efficacy. Therefore, the aim of our analysis was to compare the effect of different nutraceuticals used in clinical practice and addressed in a recent position paper [27] on lipid profiles in a systematic review with NMA.

2. Methods

NMA integrates data from direct evidence (head-to-head trials between different interventions) and indirect evidence (evidence derived from comparisons between studied nutraceuticals and common comparators). This review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) [32]. An extensive protocol for this meta-analysis was published in August 2020 [33]. There were some changes with regard to the published protocol. List of changes is presented in the Supplementary Material.

The present meta-analysis was planned according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and its extensions [34,35].

2.1. Search strategy

Three databases, PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials, were searched to identify eligible studies through 28 February 2021. There were no restrictions regarding the language or date of publication. Searches were conducted by the selected co-authors (KO, ML, GJ, MG, PL, AM), and disagreements were resolved through extensive discussion (TO, JM, NP, MG, PL). Additionally, the list of references from the available meta-analyses on studied nutraceuticals was carefully checked. A detailed search strategy is provided in the Supplementary Material.

2.2. Eligibility criteria

The nutraceuticals were selected to the network meta-analysis based on the recommendations of ILEP on the use of nutraceuticals in statin intolerant patients [27], where two main indications for nutraceuticals in hypercholesterolemic patients were covered: LDL-C lowering properties and effectiveness and safety in case of nonadherence/intolerance. Studies were included if they met the following criteria:

(i) RCTs – parallel or crossover between different nutraceuticals, comparing the efficacy of a nutraceutical with another nutraceutical (head-to-head trials) or the efficacy of a nutraceutical with a placebo:
   a) Artichoke—extracts from Cynara scolymus and C. cardunculus;
   b) Berberine—isoquinoline alkaloids isolated from barberry (Berberis vulgaris), tree turmeric (B. aristata), goldenseal (Hydrastis canadensis) or Oregon grape (B. aquifolium);
   c) Bergamot—extract from Citrus bergamia;
   d) Garlic—extract from Allium sativum;
   e) Green tea—extract from Camellia sinensis;
   f) Plant sterols and stanols;
   g) Policosanols (not Cuban);
   h) Cuban policosanols;
   i) Red yeast rice—extracts from Oryza sativa fermented by yeast from the genus Monascus;
   j) Silymarin—extracts from Silybum marianum;
   k) Spirulina—microalgae including the species Spirulina platensis, S. maxima and S. fusiformis;
(ii) Nutraceuticals were administered in the form of a capsule, pill or tablet;
(iii) Patients were $\geq$ 18 years of age;
(iv) The primary outcome was LDL-C. The secondary outcomes were TC, high-density lipoprotein cholesterol (HDL-C) or TG (triglycerides).

Studies that met the following criteria were excluded:

i) Dietary or exercise cointerventions were not applied in the intervention and placebo groups;
ii) Lipid-lowering drugs were used in any trial arm;
iii) Studies that included children and/or adolescents.

We did not include omega-3 fatty acids, as it has been shown that they do not lower LDL-C levels and therefore cannot be considered as an alternative to statin therapy in statin-intolerant patients [5,27]. They also have established roles in the treatment of hypertriglyceridemia [36]. The search strategy is described in detail in the Supplementary Material.

2.3. Data extraction and missing data

A standardized form was created to extract data for synthesis. The data extracted included the name of the first author, study date, study origin, length of follow-up, age, sex, BMI, concomitant diseases, nutraceutical studied, cointervention (if any), and study design, including the number of arms. Risk of bias was assessed using a Cochrane revised tool for assessing risk of bias in RCTs [37]. Data were extracted by five co-authors (KO, ML, GJ, PL, MG) and double checked (MG, PL, JM, TO, NP). We attempted to contact the authors to request missing baseline, change and outcome data (MG and PL).

2.4. Evaluation of synthesis assumptions

2.4.1. Assessment of transitivity

The transitivity assumption means that there are no systematic differences between populations of the analysed studies with the exception of compared treatments. To evaluate whether the assumption of transitivity is violated, we compared the distribution of treatment effect

modifiers across direct comparisons. Potential treatment modifiers considered were baseline TC, LDL-C, HDL-C, and TG levels as well as age, body mass index (BMI) and length of follow-up.

2.5. Statistical analysis

The random-effects NMA was performed using a frequentist approach [38]. The measure of the treatment effect was the change score adjusted for baseline measurements with the corresponding standard deviation (SD). Data on changes in lipid levels were not available for the majority of the studies; therefore, change scores were calculated using simple subtraction using baseline and final data, and change score standard deviations were calculated in line with the Cochrane Handbook recommendations [39]. As this sort of calculation requires an assumption of correlation coefficients [39], an attempt was made to calculate these coefficients for 14 studies for which sufficient data were available (Table S4).

We also attempted to contact the authors to request missing baseline, change and outcome data (MG and PL). In cases where only medians with IQRs are reported, the mean and SD were estimated using the method described by Wan et al. [40].

Network estimates along with their 95% confidence intervals are presented in the league tables. We also analysed the contribution of direct and indirect evidence used for each estimated comparison. Nutraceuticals were ranked according to the P-score, which is a frequentist analogue of their treatment effects as measured by the surface under the cumulative ranking curve (SUCRA). A nutraceutical with a higher P-score indicates a greater probability of better effectiveness in terms of lowering LDL-C, TC, and TG and elevating HDL-C. Differences in treatment effect modifiers between direct comparisons were assessed using Tukey's honest difference test. All analyses were conducted in R 3.6.0 software using *metafor* [41] and *netmeta* [42]packages.

2.6. Network geometry

The network geometry is presented using network plots. The size of the nodes reflects the frequency of a particular treatment used, while the thickness of connecting lines reflects the number of studies for a particular comparison.

2.7. Assessment of inconsistency

Local and global approaches for inconsistency testing were employed. Local approaches included loop-specific approaches and side-splitting approaches [43]. Global approaches test for inconsistency jointly from all sources within the network. For this purpose, a design-by-treatment interaction model was used.

2.8. Subgroup and sensitivity analysis

We performed subgroup analyses by considering study duration (>2 months vs. ≤ 2 months), sample size (<100 vs. ≥ 100) and patients with mean baseline TC >5.2 mmol/l (200 mg/dL) vs. those with mean TC $\leq$ 5.2 mmol/l (200 mg/dL). Sensitivity analysis was performed by analysing only studies with a low risk of bias.

2.9. Detection of small study effects and publication bias

Apart from assessment based on expert knowledge with regard to possible risk of publication bias, we produced comparison-adjusted funnel plots with the Thompson-Sharp test to examine whether publication bias could be a reason for the small study effect [44].

2.10. Certainty of the evidence

The quality of the most clinically important outcome was assessed in accordance with JCE GRADE guidelines [45]. Each direct estimate was evaluated according to the following criteria: risk of bias, indirectness, imprecision, inconsistency, presence of large affect and publication bias. The extension of the GRADE system for the assessment of the credibility of evidence for NMA was used. We applied the approach described by Brignardello-Petersen et al. [46]. The network estimate assessments were based on direct certainty with downrating in cases when serious intransitivity was established.

3. Results

3.1. Selection and characteristics of the relevant studies

Literature searches in PubMed, Cochrane and Embase and additional sources identified 4151 (Fig. S1) records. After duplicate removal and title and abstract screening, 383 full-text articles were assessed in detail. Of those, 234 were excluded because they were deemed irrelevant, assessed as duplicate publications, had no full text available, or included an inappropriate nutraceutical form due to a change in protocol. A reference list of excluded studies based on the full text is given in the supplementary material. Reasons for the exclusion of studies based on the full text are given in Table S1.

Finally, 148 studies met the eligibility criteria and were included in the qualitative and quantitative synthesis. Seventeen of those studies were studies on policosanols carried out in Cuba, which, for reasons stated in the methods section, were not included in the main analysis. A total of 131 studies were analysed in the primary analysis. As some of the studies included clinically different groups, they were entered as separate study arms, resulting in 136 records. Of those records, 134 (98.5%) had data on TC, 125 (91.9%) on LDL-C, 127 (93.3%) on HDL-C, 129 (94.9%) on TG, and 117 (86.0%) had complete data on all lipid parameters. A reference list of the included studies is presented in the Supplementary Material.

The included studies enrolled a total of 13,062 patients, out of whom 12,979 completed follow-up. Out of the 131 studies included in the main analysis, 78 were carried out in Asia, 18 in North America, 32 in Europe, two in Australia, one in South America and one in Africa. The study duration was between 1 week and 168 weeks, with a mean time of 13.9 weeks. The mean age of the study participants was 47.0 $\pm$ 10.9 years. The mean BMI was 27.7 $\pm$ 3.5 kg/m^2. The mean LDL-C level at baseline was 3.56 $\pm$ 0.77 mmol/l (138 $\pm$ 30 mg/dL), while the mean TC, TG and HDL-C levels at baseline were 5.61 $\pm$ 0.84 mmol/l (217 $\pm$ 32 mg/dL), 1.80 $\pm$ 0.55 mmol/l (160 $\pm$ 49 mg/dL), and 1.26 $\pm$ 0.24 mmol/l (49 $\pm$ 9.3 mg/dL), respectively. The main characteristics of the included studies are given in Table S2.

3.2. Risk of bias assessment of the included studies

Fifty-one (38.9%) trials were judged to have a low risk of bias, 53 (40.5%) trials were classified as having a high risk of bias, and 27 (20.6%) trials were classified as "some concerns". Regarding the specific items of the risk of bias assessment tool by the Cochrane Collaboration, out of the 131 studies included in the main analysis, 88 (67.2%) of the included studies indicated a low risk of bias for the randomization process, 118 (90.1%) for deviation from intended interventions, 91 (69.5%) for missing outcome data, 131 (100%) for measurement of the outcome and 120 (91,6%) for selective reporting. Out of crossover trials (seven), two (28.6%) were deemed to have a low risk of bias due to period and carryover effects. Detailed results of the risk of bias assessment are given in the Supplementary Material (Tables S3.1 and S3.2; Figs. S2.1 and S2.2).

Most of the 136 study arms compared the intervention with a placebo (119 ([87.5%)); only one comparison was a head-to-head comparison between berberine and silymarin; and in 16 (11.8%) study arms, a nutraceutical was compared against no intervention. Fig. 1 shows the network diagrams of direct comparisons for LDL-C, TC, HDL-C and TG.

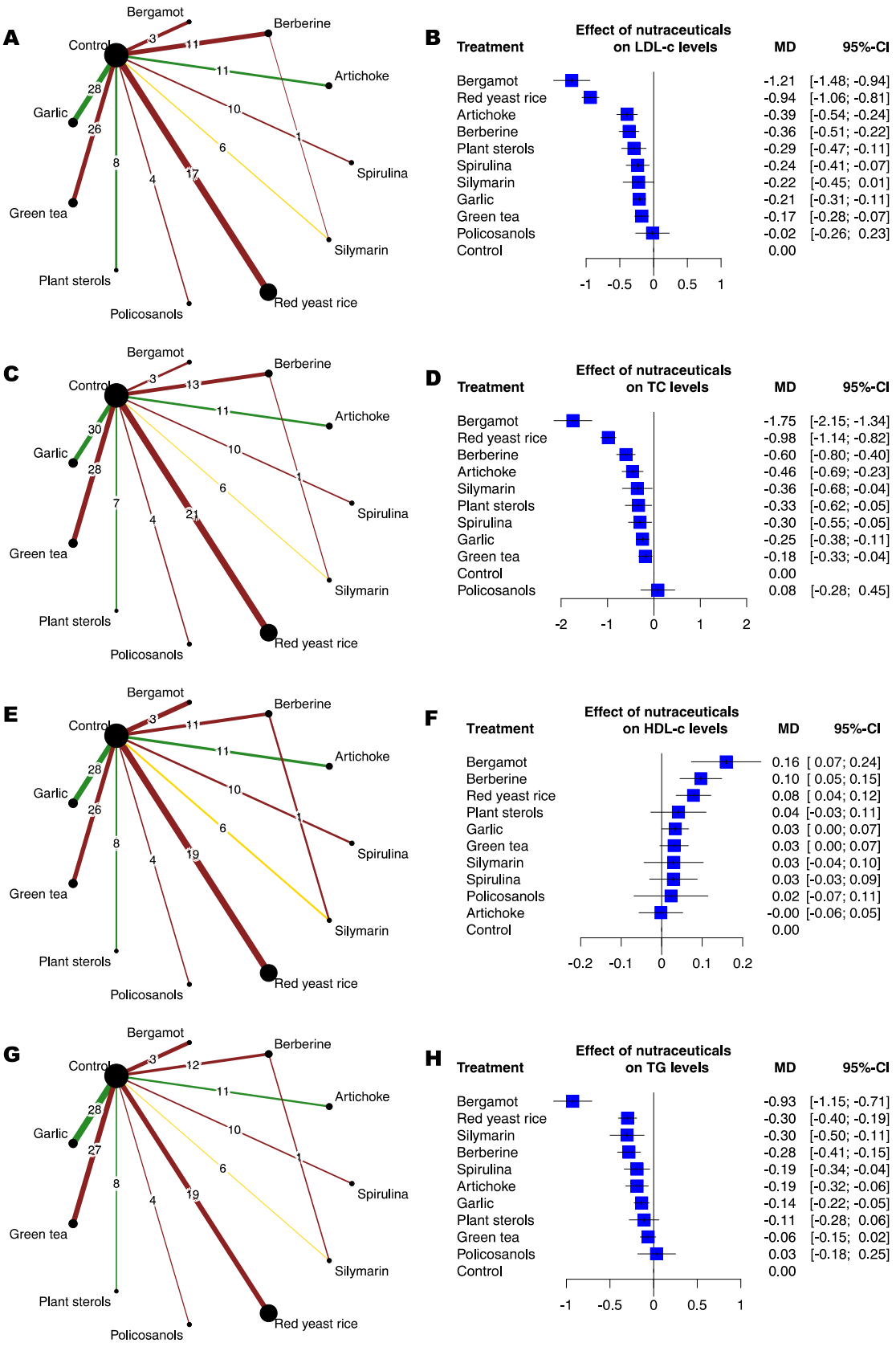

Fig. 1. A-D. Network diagram for LDL-C, TC, HDL-C, and TG. Mean difference (MD) and 95% confidence interval (95% CI) are provided as (mmol/l). The size of the nodes reflects the total number of participants allocated to treatment with each nutraceutical. The thickness of the lines is proportional to the number of studies addressing each pairwise comparison. The colour of the line reflects the most prevalent risk of bias (RoB) for pairwise comparisons. Red indicates that for a given comparison, most trials were assessed as having a high RoB, yellow indicates that most trials were described to be of some concern with regard to RoB assessment, and green indicates that most of the trials for a given comparison were assessed to have a low RoB. Fig. 1 E-G. Treatments are ranked according to their P-score values.

The largest number of trials was available for garlic (29), green tea extract (27), and red yeast rice (21).

3.3. Study consistency and heterogeneity

Comparisons of the hypolipemic effect between different nutraceuticals except berberine and silymarin were based solely on indirect evidence. This was because, with the exception of one study comparing the lipid-lowering effect of silymarin and berberine, no head-to-head studies between analysed nutraceuticals were conducted. Direct evidence contribution plots are provided in the supplementary materials (Fig. S3.1 - Fig. S3.4).

The distributions of follow-up length and BMI were similar across comparisons (Fig. S4.1 and S4.2). There were differences in age distribution ($p < 0.0001$). A post hoc test revealed that there were significant differences in age distribution between trials assessing the effectiveness of green tea extracts and red yeast rice (adjusted p value <0.0001) (Fig. S4.3). Baseline TC levels, LDL-C levels, and were differentially distributed between the comparisons ($p < 0.001$, p) (Figs. S4.4 and S4.5). *Post hoc* tests revealed that patients included in green tea extract trials and spirulina trials had significantly lower TC levels than patients enrolled in garlic and policosanol trials. Baseline LDL-C levels were significantly lower for patients included in trials on green tea extracts than for patients in garlic and policosanol trials. No other significant differences with regard to baseline TC or LDL-C levels were detected. *A* post hoc test did not reveal any differences with regard to HDL-c distribution (Fig. S4.6). Baseline TG levels were similar across studies, with the exception of bergamot trials, for which TG levels were higher than in patients enrolled in the green tea extract, spirulina and sterols/stanols trials (Fig. S7).

3.4. Effects of nutraceuticals on lipid parameters

The effect size estimates for the comparison of the effectiveness of every nutraceutical in terms of reducing LDL-C and TC levels are presented in Table 1. The assessed effectiveness of the studied nutraceuticals in terms of HDL-C increase and TG reduction is presented in Table 2**.** Nutraceuticals ranked according to their P-score values are presented in forest plots (Fig. 1). Exact P-score values are given in Table S6. All analysed nutraceuticals, with the exception of policosanols (based on data from trials from outside Cuba), were more effective in lowering LDL-C (−1.21 [−46.8 mg/dL] to −0.17 [−6.6 mg/dL] mmol/l reduction) and TC (−1.75 [−67.7 mg/dL] to - 0.18 [7 mg/dL] mmol/l reduction) than placebo/no intervention (Fig. 1, Table 1). The most effective approaches in terms of LDLC- and TC-lowering were bergamot, red yeast rice and berberine (Fig. 1, Table 1). Bergamot, silymarin and red yeast rice also showed significant effects on TG reduction: − 0.93 [− 82 mg/dl], 0.3 [− 27 mg/dl] and 0.3 [− 27 mg/dl] mmol/l, respectively (Fig. 1, Table 2). Three of the studied nutraceuticals, bergamot, berberine and red yeast rice, significantly influenced the levels of HDL-c, although this effect was modest (Fig. 1, Table 2).

The side-splitting approach did not reveal any inconsistencies regarding changes in LDL-C or HDL-C; however, there was only one head-to-head trial that compared silymarin and berberine. To assess inconsistency due to random effects, the between-design Q-statistic was calculated based on a full design by an interaction random effect model. The full design-by-treatment interaction random effect models showed no significant inconsistencies between designs for LDL-C ($p = 0.27$), TC ($p = 0.37$), HDL-C ($p = 0.50$) or TG ($p = 0.15$).

3.5. Subgroup analysis

A summary of the results of the subgroup analysis is presented in

Table 1
Results of NMA comparing the effects (mean difference; MD) of all nutraceuticals and 95% confidence intervals (95% CI). The values in the upper triangle correspond to the MD and 95% CI of TC (mmol/l). The values in the lower triangle correspond to the MD of LDL-C (mmol/l).

TC (mmol/l)										
Bergamot	-0.76 (−1.20; −0.32)	-1.29 (−1.75; −0.82)	-1.14 (−1.60; −0.69)	-1.41 (−1.91; −0.92)	-1.45 (−1.93; −0.97)	-1.39 (−1.91; −0.87)	-1.50 (−1.93; −1.07)	-1.56 (−2.00; −1.13)	-1.83 (−2.38; −1.28)	-1.75 (−2.15; −1.34)
-0.28 (−0.57; 0.02)	Red yeast rice	-0.52 (−0.80; −0.25)	-0.38 (−0.64; −0.12)	-0.65 (−0.98; −0.32)	-0.68 (−0.98; −0.39)	-0.63 (−0.99; −0.27)	-0.74 (−0.95; −0.53)	-0.80 (−1.02; −0.58)	-1.07 (−1.47; −0.67)	-0.98 (−1.14; −0.82)
-0.82 (−1.13; −0.51)	-0.54 (−0.74; −0.35)	Artichoke	0.14 (−0.16; 0.45)	-0.13 (−0.49; 0.24)	-0.16 (−0.50; 0.18)	-0.10 (−0.50; 0.29)	-0.21 (−0.48; 0.05)	-0.28 (−0.55; −0.01)	-0.54 (−0.97; −0.11)	-0.46 (−0.69; −0.23)
-0.85 (−1.16; −0.54)	-0.57 (−0.76; −0.38)	-0.03 (−0.24; 0.18)	Berberine	-0.27 (−0.62; 0.08)	-0.30 (−0.62; 0.01)	-0.25 (−0.60; 0.11)	-0.36 (−0.60; −0.12)	-0.42 (−0.67; −0.17)	-0.69 (−1.11; −0.27)	-0.60 (−0.80; −0.40)
-0.92 (−1.24; −0.60)	-0.64 (−0.86; −0.42)	-0.10 (−0.34; 0.13)	-0.07 (−0.30; 0.16)	Plant sterols	-0.03 (−0.41; 0.34)	0.02 (−0.40; 0.45)	-0.09 (−0.40; 0.23)	-0.15 (−0.47; 0.17)	-0.42 (−0.88; 0.05)	-0.33 (−0.62; −0.05)
-0.98 (−1.29; −0.66)	-0.70 (−0.91; −0.49)	-0.16 (−0.38; 0.07)	-0.13 (−0.35; 0.10)	-0.06 (−0.30; 0.19)	Spirulina	0.06 (−0.35; 0.46)	-0.05 (−0.34; 0.23)	-0.12 (−0.41; 0.17)	-0.38 (−0.83; 0.06)	-0.30 (−0.55; −0.05)
-0.99 (−1.34; −0.64)	-0.71 (−0.97; −0.45)	-0.17 (−0.44; 0.10)	-0.14 (−0.39; 0.11)	-0.07 (−0.36; 0.22)	-0.01 (−0.30; 0.27)	Silymarin	-0.11 (−0.46; 0.24)	-0.17 (−0.53; 0.18)	-0.44 (−0.93; 0.05)	-0.36 (−0.68; −0.04)
-1.00 (−1.29; −0.72)	-0.72 (−0.88; −0.57)	-0.18 (−0.36; 0.00)	-0.15 (−0.33; 0.02)	-0.08 (−0.29; 0.12)	-0.03 (−0.22; 0.17)	-0.01 (−0.26; 0.24)	Garlic	-0.06 (−0.26; 0.14)	-0.33 (−0.72; 0.06)	-0.25 (−0.38; −0.11)
-1.04 (−1.33; −0.75)	-0.76 (−0.92; −0.60)	-0.22 (−0.40; −0.04)	-0.19 (−0.37; −0.01)	-0.12 (−0.32; 0.09)	-0.06 (−0.26; 0.14)	-0.05 (−0.30; 0.20)	-0.04 (−0.18; 0.10)	Green tea	-0.27 (−0.66; 0.13)	-0.18 (−0.33; −0.04)
-1.20 (−1.56; −0.83)	-0.92 (−1.20; −0.64)	-0.38 (−0.67; −0.09)	-0.35 (−0.64; −0.06)	-0.28 (−0.58; 0.03)	-0.22 (−0.52; 0.08)	-0.21 (−0.54; 0.13)	-0.20 (−0.46; 0.07)	-0.16 (−0.43; 0.11)	Policosanols	0.08 (−0.28; 0.45)
-1.21 (−1.48; −0.94)	-0.94 (−1.06; −0.81)	-0.39 (−0.54; −0.24)	-0.36 (−0.51; −0.22)	-0.29 (−0.47; −0.11)	-0.24 (−0.41; −0.07)	-0.22 (−0.45; 0.01)	-0.21 (−0.31; −0.11)	-0.17 (−0.28; −0.07)	-0.02 (−0.26; 0.23)	Control
LDL-C [mmol/L]										

Table 2
Results of NMA comparing the effects (mean difference; MD) of all dietary nutraceuticals and 95% confidence intervals (95% CI). The values in the upper triangle correspond to the MD and 95% CI of TG (mmol/l). The values in the lower triangle correspond to the MD of HDL-C (mmol/l).

TG [mmol/L]										
Bergamot	-0.63 (−0.87; −0.39)	-0.74 (−0.99; −0.48)	-0.65 (−0.90; −0.39)	-0.82 (−1.10; −0.54)	-0.74 (−1.00; −0.47)	-0.62 (−0.92; −0.33)	-0.79 (−1.03; −0.55)	-0.86 (−1.10; −0.63)	-0.96 (−1.27; −0.65)	-0.93 (−1.15; −0.71)
0.08 (−0.02; 0.18)	Red yeast rice	-0.11 (−0.27; 0.06)	-0.02 (−0.18; 0.15)	-0.19 (−0.39; 0.01)	-0.11 (−0.29; 0.07)	0.01 (−0.21; 0.23)	-0.16 (−0.29; −0.03)	-0.23 (−0.37; −0.10)	-0.33 (−0.57; −0.09)	-0.30 (−0.40; −0.19)
0.16 (0.06; 0.26)	0.08 (0.01; 0.15)	Artichoke	0.09 (−0.09; 0.28)	-0.08 (−0.29; 0.13)	0.00 (−0.19; 0.19)	0.11 (−0.12; 0.35)	-0.05 (−0.21; 0.10)	-0.13 (−0.28; 0.03)	-0.22 (−0.48; 0.03)	-0.19 (−0.32; −0.06)
0.06 (−0.04; 0.16)	-0.02 (−0.08; 0.05)	-0.10 (−0.17; −0.02)	Berberine	-0.17 (−0.39; 0.04)	-0.09 (−0.29; 0.10)	0.02 (−0.19; 0.24)	-0.14 (−0.30; 0.01)	-0.22 (−0.38; −0.06)	-0.32 (−0.57; −0.06)	-0.28 (−0.41; −0.15)
0.12 (0.01; 0.23)	0.04 (−0.04; 0.12)	-0.04 (−0.13; 0.04)	0.06 (−0.03; 0.14)	Plant sterols	0.08 (−0.14; 0.31)	0.20 (−0.06; 0.45)	0.03 (−0.16; 0.22)	-0.05 (−0.24; 0.15)	-0.14 (−0.42; 0.13)	-0.11 (−0.28; 0.06)
0.13 (0.03; 0.23)	0.05 (−0.02; 0.12)	-0.03 (−0.11; 0.05)	0.07 (−0.01; 0.15)	0.01 (−0.08; 0.10)	Spirulina	0.11 (−0.13; 0.36)	-0.05 (−0.22; 0.12)	-0.13 (−0.30; 0.04)	-0.23 (−0.49; 0.04)	-0.19 (−0.34; −0.04)
0.13 (0.02; 0.24)	0.05 (−0.04; 0.13)	-0.03 (−0.12; 0.06)	0.07 (−0.02; 0.15)	0.01 (−0.09; 0.11)	-0.00 (−0.09; 0.09)	Silymarin	-0.17 (−0.38; 0.05)	-0.24 (−0.45; −0.03)	-0.34 (−0.63; −0.05)	-0.30 (−0.50; −0.11)
0.13 (0.03; 0.22)	0.05 (−0.01; 0.10)	-0.04 (−0.10; 0.03)	0.06 (0.00; 0.12)	0.01 (−0.07; 0.08)	-0.00 (−0.07; 0.06)	-0.00 (−0.08; 0.08)	Garlic	-0.07 (−0.20; 0.05)	-0.17 (−0.41; 0.06)	-0.14 (−0.22; −0.05)
0.13 (0.04; 0.22)	0.05 (−0.01; 0.10)	-0.03 (−0.10; 0.03)	0.07 (0.00; 0.13)	0.01 (−0.07; 0.09)	-0.00 (−0.07; 0.07)	-0.00 (−0.08; 0.08)	0.00 (−0.05; 0.05)	Green tea	-0.10 (−0.33; 0.13)	-0.06 (−0.15; 0.02)
0.14 (0.01; 0.26)	0.06 (−0.05; 0.16)	-0.03 (−0.13; 0.08)	0.07 (−0.03; 0.18)	0.02 (−0.10; 0.13)	0.01 (−0.10; 0.11)	0.01 (−0.11; 0.12)	0.01 (−0.09; 0.11)	0.01 (−0.09; 0.11)	Policosanols	0.03 (−0.18; 0.25)
0.16 (0.07; 0.24)	0.08 (0.04; 0.12)	-0.00 (−0.06; 0.05)	0.10 (0.05; 0.15)	0.04 (−0.03; 0.11)	0.03 (−0.03; 0.09)	0.03 (−0.04; 0.10)	0.03 (0.00; 0.07)	0.03 (0.00; 0.07)	0.02 (−0.07; 0.11)	Control
HDL-C [mmol/L]										

Table 3
Nutraceuticals with a statistically significant effect on lipid profile in subgroup analysis. Nutraceuticals are listed from highest to lowest P-score value. Details including estimated magnitude of effect are presented in Supplementary material (Fig. S7).

	Length of follow-up [weeks]		Number of participants		Initial TC level [mmol/l]	
	≤ 8	> 8	≤ 100	> 100	≤ 5.2	> 5.2
LDL-C	• Bergamot • Red yeast rice • Artichoke • Spirulina • Plant sterols • Berberine	• Red yeast rice • Bergamot • Berberine • Garlic • Green tea extract	• Bergamot • Red yeast rice • Berberine • Artichoke • Plant sterols • Garlic • Spirulina • Silymarin • Green tea extract	• Red yeast rice • Artichoke • Berberine	• Bergamot • Red yeast rice • Berberine • Artichoke • Plant sterols • Garlic • Spirulina • Silymarin • Green tea extract	• Bergamot • Red yeast rice • Artichoke • Berberine • Spirulina • Plant sterols • Green tea extract • Garlic
TC	• Bergamot • Red yeast rice • Artichoke • Plant sterols • Spirulina	• Bergamot • Red yeast rice • Berberine • Garlic • Green tea extract	• Bergamot • Red yeast rice • Berberine • Artichoke • Silymarin • Plant sterols • Spirulina • Garlic • Green tea extract	• Red yeast rice	• Red yeast rice • Berberine • Spirulina	• Bergamot • Red yeast rice • Berberine • Artichoke
HDL-C	• Bergamot • Red yeast rice	• Bergamot • Berberine • Green tea extract	• Bergamot • Berberine • Red yeast rice	• Berberine	• Garlic	• Bergamot • Berberine • Red yeast rice • Green tea extract
TG	• Bergamot • Silymarin • Red yeast rice • Berberine • Artichoke • Garlic • Spirulina	• Bergamot • Berberine • Silymarin • Red yeast rice	• Bergamot • Red yeast Rice • Silymarin • Berberine • Artichoke • Spirulina • Garlic	• Berberine • Red yeast rice	• Bergamot	• Bergamot • Silymarin • Red yeast rice • Berberine • Artichoke • Garlic

Table 3. Details are given in Figs. S7.1, Fig. S11. In the subgroup analyses of study duration, smaller sample size and TC level at baseline, we showed that red yeast rice was the most effective or ranked second best to bergamot in reducing LDL-C and TC levels (Table 3, Figures: S7.1, S7.2, S8.1, S8.2, S9.1, S9.2). In general, red yeast rice effectively lowered LDL-C and TC in all subgroup analyses, while bergamot was effective in all trials, except for larger trials where there were no suitable data for bergamot (Table 3. Figs. S7.1, S7.2, S8.1, S8.2, S9.1, S9.2).

The lipid-lowering effect of artichoke, berberine, plant sterols and stanols was also quite consistent across subgroup analysis, with some exceptions for LDL-C assessed in trials with longer follow-up (plant sterols/stanols and artichoke) and studies including more than 100 participants (plant sterols/stanols) or patients with TC levels lower than 5.2 mmol/l (200 mg/dL) (Figs. S7.1, S8.1, S9.1).

Bergamot and berberine significantly but modestly increased HDL-c across all subgroups except in larger trials and trials that enrolled patients with mean TC levels lower than 5.2 mmol/l (200 mg/dL), where only garlic appeared to increase HDL-C (Table 3, Figs. S7.3, S8.3, S9.3). A significant effect for red yeast rice was also observed in trials among participants with baseline TC $\geq$ 5.2 mmol (200 mg/dL) (Table 3, Fig. S9.4).

Bergamot was most effective for TG reduction across all subgroups except for larger trials (no suitable data for bergamot) (Table 3, Figs. S7.4, S8.4, S9.4, S11).

Sensitivity analysis that included only low risk of bias trials confirmed the results of the main analysis, with one notable exception in which red yeast rice did not influence HDL-C significantly (Table 3, Fig. S11).

Consistently across the main and subgroup analyses policosanols had no significant effect on TC, LDL-C, HDL-C or TG levels. When trials on policosanols carried out in Cuba were incorporated, however, Cuban policosanols appeared to be second most effective in reducing TC and LDL-C levels, most effective in increasing HDL-c levels and moderately effective in reducing TG levels (Figs. S10A, S10B, S10C, S10D).

3.6. Certainty of evidence assessment (GRADE)

For direct estimates, only evidence from sterol and stanol studies was judged as high quality, and evidence of berberine, spirulina, silymarin and garlic was assessed as very low quality. The evidence for remaining nutraceuticals was assessed as low quality. The mark was downgraded mostly due to high and very high risk of bias and less often due to inconsistency or imprecision. Two marks were increased for large effects comparable to statin usage (bergamot and red yeast rice). Dose-response gradients were not assessed due to the inability to reliably compare doses of nutraceuticals. The result estimate assessments are included in the summary of the findings (Table 4 and Fig. 2). Justification for the assessment of each criterion is provided in the supplementary material.

4. Discussion

Attaining optimal lipoprotein levels is one of the goals for reducing cardiovascular risk. According to the meta-analysis by Khan et al., each 1 mmol/l decrease in LDL-C levels reduced the risk of cardiovascular mortality by 15% [47]. Due to statin intolerance and increasing disinformation on statin side effects, many patients insist on changing their statin treatment to a nutraceutical. Irrespective of statin intolerance that affects 10% of patients treated with statins [13], it is assumed that 5–10% of patients are not willing to use statin therapy [16,48]. This raises the question about the lipid-lowering potential of available nutraceuticals. By conducting an NMA of 131 trials, we ranked the effect of ten nutraceuticals (artichoke, berberine, bergamot, garlic, green tea extract, plant sterols and stanols, spirulina and silymarin) addressed in a recent position paper [27] on lipid parameters. The ranking according to P-score values revealed that all analysed nutraceuticals, with the exception of policosanols (in trials carried out outside of Cuba), were

Table 4
Summary of findings for the main comparison (LDL-C).

Patients, interventions, comparators	Participants (studies), follow-up†	Certainty of the evidence (GRADE)	Intervention vs. comparator mean difference (95% CI)
Hypercholesterolemia (LDL-C)			
Bergamot vs. placebo	144 participants (3 studies), 4–13 weeks (weighted mean = 6.8)	●●○○ **Low**[1,2,3]	-1.21 (95% CI: −1.48, −0.94) mean difference lower LDL-c
Red yeast rice vs. placebo	5868 participants (17 studies), 4–168 weeks (weighted mean = 141.4)	●●○○ **Low**[1,2,3]	-0.94 (95% CI: −1.06, −0.81) mean difference lower LDL-c
Artichoke vs. placebo	775 participants (11 studies), 4–12 weeks (weighted mean = 8.7)	●●○○ **Low**[2]	-0.39 (95% CI: −0.54, −0.24) mean difference lower LDL-c
Berberine vs. placebo	992 participants (13 studies), 4–16 weeks (weighted mean = 10.9)	●○○○ **Very low**[4,5]	-0.36 (95% CI: −0.51, −0.22) mean difference lower LDL-c
Plant sterols vs. placebo	297 participants (8 studies), 3–12 weeks (weighted mean = 7.7)	●●●● **High**	-0.29 (95% CI: −0.47, −0.11) mean difference lower LDL-c
Spirulina vs. placebo	420 participants (8 studies), 6–16 weeks (weighted mean = 10.7)	●○○○ **Very low**[4,5]	-0.24 (95% CI: −0.41, −0.07) mean difference lower LDL-c
Silymarin vs. placebo	346 studies (6 studies), 6.4–48 weeks (weighted mean = 25.4)	●○○○ **Very low**[1,5,6]	-0.22 (95% CI: −0.45, 0.01) mean difference lower LDL-c
Garlic vs. placebo	1620 participants (26 studies), 2–48 weeks (weighted mean = 13.7)	●○○○ **Very low**[1,2]	-0.21 (95% CI: −0.31, −0.11) mean difference lower LDL-c
Green tea vs. placebo	1487 participants (25 studies), 1–72 weeks (weighted mean = 13.6)	●●○○ **Low**[1,5]	-0.17 (95% CI: −0.28, −0.07) mean difference lower LDL-c
Policosanols vs. placebo	309 participants (4 studies), 8–12 weeks (weighted mean = 9.9)	●●○○ **Low**[1,7]	-0.02 (95% CI: −0.26, 0.23) mean difference lower LDL-c

† Included only studies where LDL-c was measured
[1] Downgraded by one due to risk of bias: less than 50% of the studies had a low risk of bias
[2] Downgraded by two due to inconsistency: I2 value > 90%
[3] Upgraded by one due to large effect: effect was comparable to that associated with statin usage
[4] Downgraded by two due to risk of bias: more than 50% of the studies had a high risk of bias
[5] Downgraded by one due to inconsistency: I2 value > 45%

[6] Downgraded by two due to imprecision: Optimal Information Criterion not met (power=67%) and CI does not exclude no effect

[7] Downgraded by one due to imprecision: CI does not exclude no effect

more effective in lowering LDL-C than placebo. Bergamot, red yeast rice, artichoke and berberine were most effective in lowering LDL-C and TC levels. Bergamot had the highest P-score values that reflect LDL-C, TC and TG reduction; however, the credibility of the evidence of its effectiveness for LDL-C reduction was rated very low for bergamot, as opposed to red yeast rice, which was ranked as second best in terms of effectiveness for LDL-C reduction.

In line with our observations, a meta-analysis of 15 high-quality RCTs showed that red yeast rice significantly reduced TC and LDL-C and increased the level of HDL-C [49]. Red yeast rice, a traditional Chinese medicine, contains monacolins, in particular monacolin K, which is chemically identical to lovastatin [50]. It is commonly used as a lipid-lowering dietary supplement, particularly in Asia, and recently, it has been gaining popularity in Europe. The results from the meta-analysis performed by Pengfan et al. concluded that red yeast rice was comparable to regular statin treatment regarding LDL-C reduction, less effective in terms of TC reduction and more effective regarding TG reduction [49]. The positive effect of red yeast rice on the lipid profile is associated with the statin-like mechanism of action, which is the inhibition of hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase by monacolin K. Despite some safety concerns with regard to the statin-like mechanism of action [49], the frequency of side effects was demonstrated to be very low [51,52]. In the present meta-analysis, we did not assess the side effects of the analysed nutraceuticals, as reliable data are almost exclusively available only for red yeast rice, and this topic is well studied. This is also reflected by the fact that red yeast rice is regarded as an option in patients who are likely to suffer side effects from regular statin therapy (class I, level of evidence A recommendation) [27,51–53].

Bergamot extract contains polyphenols with various mechanisms of action, including neoericitrin, neohesperidin, naringin, rutin, neodesmin, rhoifolin, poncirin and melitidin, which inhibit the oxidation of LDL-C, activate adenosine-monophosphate-kinase and show potential scavenging mechanisms and, most importantly, statin-like inhibition of HMG-CoA reductase [54]. This mechanism of action explains the LDL-C-, TC-, and TG-reduction effect and the significant increase in HDL-C levels. The magnitude of bergamot's effect on the lipid profile should be interpreted with caution since there were only three trials available, and the certainty of evidence as assessed by GRADE was low. Nonetheless, our results are in line with recommendations included in recent guidelines based on a IIa level of evidence recommending bergamot while acknowledging a lack of data on the strength of the hypolipemic effect of bergamot and lower certainty of evidence compared to that for red yeast rice. Bergamot allegedly has many additional health benefits that are not related to the lipid profile, such as reduction in glucose level, reduction in biomarkers of vascular oxidative damage and decreased atherogenic sdLDL [55]. This may suggest a potential use of bergamot in patients with dyslipidaemia and metabolic syndrome with non-alcoholic fatty liver disease, although high-quality clinical trials are needed.

Berberine and artichoke proved to be almost equally effective at reducing LDL-C and TC. This result also confirms the validity of the 2018 recommendations of the International Expert Lipid Panel that categorize berberine and artichoke as class I and IIa, respectively, for use in statin-intolerant patients as a monotherapy or co-administered with ezetimibe [27,56]. Our NMA helped to assess their strength compared to red yeast rice and bergamot and ranked them as slightly less effective than red yeast rice and bergamot. Nonetheless, berberine has a unique mechanism of action; through ubiquination and subsequent degradation of hepatocyte nuclear factor 1 alpha (HNF-1 alpha), it inhibits proprotein convertase subtilisin/kexin type 9 (PCSK9) and upregulates receptors for LDL-c [54,57]. Therefore, there is a potential for combination therapy with red yeast rice that has a statin-like mechanism of action. Berberine is also a component of over the counter (OTC) drugs containing silymarin. There was only one head-to-head trial between

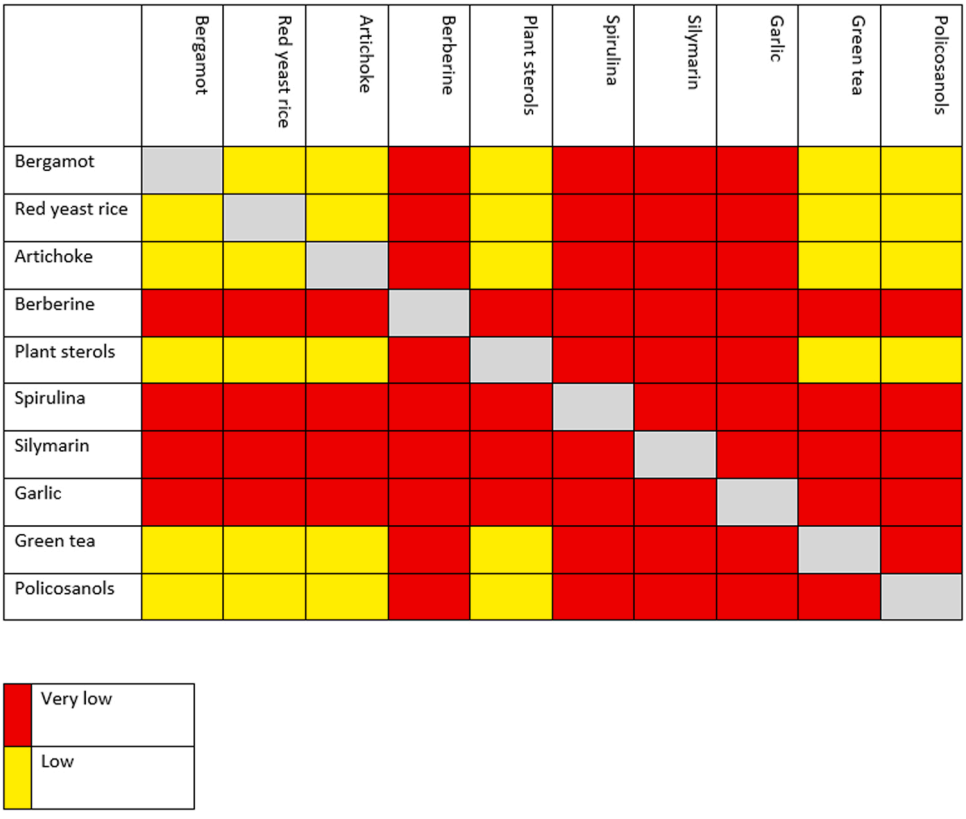

Fig. 2. Certainty of NMA estimates. Red indicates that for a given comparison certainty is very low, yellow indicates that for a given comparison is low.

berberine and silymarin, which showed a greater reduction in LDL-C for berberine. Silymarin was ranked as slightly more effective than berberine in TG reduction; in contrast, berberine had no effect on HDL-C.

The lipid-lowering effects of plant sterols have been shown in several meta-analyses indicating marked reductions in LDL-C and TC [58]. We confirmed these findings, but the effect on LDL-C and TC was modest, and plant sterols/stanols were ranked fifth in terms of TC and LDL-C reduction. Nonetheless, due to different mechanisms of action, including inhibition of intestinal absorption, they might be effective in combination with other nutraceuticals [56]. It was also reported that plant sterols and stanols can lower TG levels and that this effect is modest at best and dependent on the initial TG concentration [59]. We did not confirm those findings in the main analysis or in the subgroup analyses, including the analysis of trials of patients with a mean initial TC level greater than 5.2 mmol/l (200 mg/dl). Importantly, plant sterols/stanols had the highest certainty of evidence as assessed by GRADE. It was also reflected in recent guidelines that give IIa recommendations acknowledging moderate effects and a level of evidence acknowledging the quality of trials.

Additionally, it must be emphasized that our meta-analysis confirmed that the results of Cuban trials on policosanols are almost certainly flawed – an issue that has been widely discussed [26]. Strikingly, when we included only the results of trials with policosanols conducted outside of Cuba, there was no effect on the lipid profile. In sensitivity analysis, after inclusion of trials carried out in Cuba, policosanols appeared to be more effective even than red yeast rice in terms of LDL-C reduction. Because of the very different results from other academic centres, it is unlikely that this is a real effect.

4.1. Strengths and limitations

This is the first network meta-analysis that aimed to compare the lipid-lowering effects of various nutraceuticals. We used state-of-the-art NMA methods. Additional strengths are comparison of the effectiveness of nutraceuticals that were mentioned in recent guidelines [27] regarding the use of nutraceuticals in statin-intolerant patients, the comprehensive literature search, the published study protocol, the identification of inconsistency and the assessment of the credibility of evidence.

A limitation of the review lies mainly in the quality of the studies included, as almost 53% of trials were at high risk of bias. Sensitivity analysis including only trials with a low risk of bias in general confirmed the important findings of the main analysis. Another important limitation is that the majority of included trials were rather small, including less than 100 participants, with relatively short follow-up (mean follow-up was 13.9 weeks) and that there was, with one exception, no head-to-head trials between different nutraceuticals. The paucity of head-to-head trials between various nutraceuticals was, however, also the main reason to conduct this meta-analysis. There was also some inconsistency between the baseline clinical characteristics. Bearing in mind the number of trials and different nutraceuticals studied, those differences did not appear to be very large, especially as most differences could be attributed to participants enrolled in studies related to garlic, green tea extract and spirulina.

5. Conclusions

Bergamot and red yeast rice appear to be the most effective nutraceuticals in terms of LDL-cC reduction. Evidence for bergamot effect was based on relatively small study group and may require further investigations. Policosanols have no effect on the lipid profile. These findings should be interpreted with caution due to the low quality of the majority of RCTs on nutraceuticals as well as the paucity of head-to-head trials.

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T.O.: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Roles/Writing – original draft. **M.G., P.L., J. M., K.O., N.P., M.L., G.K.J., A.M., L.S.**: Data curation, Formal analysis, Investigation, Methodology, Validation, Roles/Writing – original draft. **M.G.:** Supervision, Writing – review & editing. **M.B.:** Conceptualization, Methodology, Project administration, Supervision, Visualization, Roles/Writing – original draft, Writing – review & editing.

Data Availability

Extensive data is provide in the supplementary material.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.phrs.2022.106402.

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