A REVIEW ON NATURAL CHOLESTEROL LOWERING SUPPLEMENTS SOLD IN SOUTH AFRICAN PHARMACIES

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A research report in the publication submissible format submitted to the Faculty of Health Science, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Science.

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DECLARATION

I, Hyeon Bok Lee, student number [360981], declare that this Research Report is my own work and that I contributed adequately towards research findings published in the article stated below which are included in my research report. This research report is being submitted in fulfilment for the degree of Master of Science in Pharmaceutical Affairs at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

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Agreement by co-authors: By signing this declaration, the co-authors listed below agree to the use of the article by the student as part of his Research Report.

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Contribution per author:

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- Data analysis
- Interpretation of the results.
- Writing of article.

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ABSTRACT

Background:

Dyslipidaemia is defined as elevated total or low-density lipoprotein (LDL) levels or low levels of high-density lipoprotein (HDL). Patients may often make use of natural cholesterol lowering supplements (NCLS) available at the pharmacy, however, limited information on these supplements is readily available. Pharmacists should be knowledgeable about NCLSs to ensure that the use of these supplements is supported by evidence and to provide appropriate advice to patients for desirable therapeutic outcomes.

Aim:

This study aimed to identify the NCLS being sold in South African pharmacies and review the scientific evidence for each of the ingredients in these NCLSs.

Methods:

Seventeen NCLS products were identified, and the Joanna Briggs Institute (JBI) scoping review methodology was used to conduct a literature review of NCLSs.

Results:

From the ingredients reviewed it is evident that coenzyme Q10, probiotics, and sterols have sufficient evidence supporting their use. However, there is still limited scientific evidence available to validate the rest of the ingredients.

Conclusion:

Further research on NCLSs will provide practicing pharmacists and practitioners with a guide to the evidence available on the various ingredients in NCLSs.

Contribution:

This study provides a review of the available literature on the NCLSs being sold in the pharmacies across South Africa to provide pharmacists with a collated document of the evidence behind these popular supplements to assist them in making evidence based informed decision regarding natural products for cholesterol.

Keywords: LDL, HDL, Natural, Supplements, Cholesterol

PUBLICATION

At the time of submission, the article had been submitted to the journal, Health SA Gesondheid, 14 December 2022, and is presented in its submissible format.

A review on natural cholesterol lowering supplements sold in South African pharmacies

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Introduction:

Cardiovascular diseases (CVDs) are a prominent leading cause of death worldwide, accounting for approximately 17.9 million deaths in 2019, which represents 32% of all deaths that year (World Health Organization, 2021). In South Africa cardiovascular death accounts for nearly a fifth of total adult deaths (Statistics South Africa, 2015). A close link between CVDs and dyslipidemia exists (Carson et al., 2020). Although cholesterol is a vital biological molecule in the human body, excessive cholesterol is directly related to CVDs, and such levels are easily attained with an unhealthy diet (Lin et al., 2015).

Lipoproteins are responsible for transporting cholesterol in the bloodstream. The two primary types of lipoproteins that transport cholesterol in the body are low-density

lipoprotein (LDL) and high-density lipoprotein (HDL) (Lin et al., 2015). LDL is known as "bad" cholesterol, while HDL is referred to as "good" cholesterol (Elshourbagy et al., 2014). HDL carries cholesterol to the liver, where it is removed from the bloodstream before it accumulates in the arteries. On the other hand, LDL transports cholesterol directly to the arteries, leading to the development of atherosclerosis, which is the buildup of plaque contributing to cardiovascular diseases (Goldstein and Brown, 2015).

Cholesterol is necessary for healthy cell function, but too much of it in the bloodstream can harm the body and increase the risk of premature cardiovascular disease. High LDL-cholesterol levels lead to hypercholesterolemia, which further increases the risk of cardiovascular disease. (Huff et al., 2023)

Dyslipidemia is defined as elevated total or low-density lipoproteins (LDL) cholesterol and triglyceride levels, or low levels of high-density lipoprotein (HDL) cholesterol (Goldstein and Brown, 2015). Dyslipidemia can be present irrespective of race, gender, genes, genetic predisposition, and age if lifestyle and dietary habits have deteriorated (Fodor, 2011; García-Giustiniani and Stein, 2016). The occurrence of cardiovascular events such as myocardial infarction or stroke is associated with low HDL levels and high LDL levels (Goldstein and Browns, 2015). Patients who experienced a myocardial infarction were reported to have a significant increase in the cholesterol-carrying LDL, and a reduced level of HDL (Goldstein and Browns, 2015). Thus, controlling dyslipidemia is essential in preventing and managing cardiovascular-related diseases.

Treatment of dyslipidemia consists of lifestyle modification and drug treatment (AHA, 2020). Although there is positive research and clinical trial data supporting the efficacy of cholesterol-lowering medications, patient compliance can be challenging due to the potential side effects or personal preference (Ward et al., 2019). Most cholesterol-lowering medicines decrease blood cholesterol levels with few side effects such as headache, dizziness, and myalgia (Raal et al., 2011). Experienced by 5-10% of patients undergoing HMG-CoA reductase inhibitor therapy, also known as statin therapy, myalgia is one of the most frequently encountered side effects (Marais, 2016). However, the type and severity of side effects vary from person to person (Raal et al., 2011).

Due to side effects and the desire to be on natural supplements, patients may seek an alternative treatment available at the pharmacy (Marais, 2016). A case report of a 49-year-old man taking a statin for the past three years showed improved cholesterol levels and eventually reaching an acceptable cholesterol range. However, the patient continued to experience myalgia, and a pharmacist advised discontinuing statin therapy and starting an over-the-counter supplement. After being on natural supplements for nearly two months, a significant increase in LDL was noted (Marais, 2016). Recommending a natural cholesterol lowering supplement (NCLS) product with insufficient evidence can be harmful to a patient.

In accordance with the Good Pharmacy Practice (GPP) guidelines of South Africa, the well-being of the patient is the primary concern of a pharmacist (GPPSA, 2017). Therefore, the objective of a pharmacist in providing medication therapy is to achieve appropriate therapeutic outcomes that enhance patient health and quality of life. A pharmacist cannot suggest an alternative treatment without consulting with the doctor when conventional treatments, which are prescribed substances, are available. When there is no scientific evidence of the effectiveness of supplements, a pharmacist must not give patients the impression that the product is effective (GPPSA, 2017). Hence, a pharmacist must have thorough knowledge and provide impartial information to patients while being aware of the various types of non-conventional treatments available in the market.

Although NCLSs do not need to be regulated by SAHPRA (SAFLII, 2020), pharmacists are responsible for knowing the evidence behind the products being sold at the pharmacy (GPPSA, 2017). There is a critical need to review the evidence behind NCLS as pharmacists should be able to provide adequate information on what medications are safe and effective. However, due to limited information about NCLSs, limited advice is given to the patients (Fourie et al., 2017).

This review aimed to evaluate the evidence behind the NCLS available in South African pharmacies and provide practicing pharmacists and practitioners with a guide to the evidence available on the NCLS. The objectives was to identify and list the ingredients in the natural cholesterol-lowering supplements available in South African pharmacies, compare the ingredients in the health supplements against scientific literature available and determine whether ingredients effectively lower serum cholesterol levels, and

lastly, to evaluate the claims made by the manufacturer regarding health supplement's dosage, dosing regimen, and its therapeutic effect of lowering cholesterol levels.

Methodology:

A selection of supplements claiming to reduce cholesterol was collected from randomly chosen pharmacies in South Africa. Each products's name was recorded, along with the ingredients, dosage and instructions. Product names were allocated pseudoname. A total of seventeen NCLS products (50 ingredients) were identified in South African pharmacies (Table 1). The information on selected products was tabulated in Microsoft Excel 365. All ingredients mentioned in various supplements were reviewed and the article summary can be found in supplementary data from Table S1 to S13.

A scoping review study was guided by the JBI scoping review methodology (The Joanna Briggs Institute, 2015). This review aimed to provide descriptive evidence behind the NCLS available in South African pharmacies. This study design was chosen to allow the researcher to describe available evidence on NCLSs sold in South African pharmacies. The analyzed papers were selected from three different electronic databases: PubMed, ScienceDirect, and Scopus, accessed during the period 2020–2022. Additionally, unpublished literature obtained from Opengrey and Grey Literature Report was also utilized. The filters used included the terms 'natural cholesterol supplement,', 'cholesterol', 'lowering cholesterol,' 'cholesterol supplement,' 'triglycerides' 'LDL,' 'HDL,' and the scientific or common name for each ingredient listed in Table 1.

Inclusion criteria included the following:

(i) Literature specific to the specific ingredients identified.
(ii) *In vitro* studies
(iii) Animal studies
(iv) Systemic reviews
(v) Meta-analysis
(vi) All clinical trials
(vii) Case reports

Exclusion criteria included the following:

(i) Lack of access to the complete paper

(ii) If the article was not available in English

(iii) Papers that were dated earlier than 2010

The researchers used a three-step search strategy to ensure a comprehensive search (The Joanna Briggs Institute, 2015). The search strategy aimed to identify all included sources of information, both published and unpublished literature. The researchers searched for all sources of evidence simultaneously which should result in greater sensitivity (The Joanna Briggs Institute, 2015). The researcher made use of a reference manager, Mendeley, to assist with this process. The key information extracted during the study was recorded in a table. This included information related to the authors, year of publication, study method, outcome, and interpretation. Titles and abstracts were screened for eligibility by two authors, and where disagreement existed, a third was asked.

Results:

Table 1: Investigative products with ingredients and dosage.

	Product	**Ingredient**	**Strength**	**Dosage**	**Sufficient dosage****
1	Product A	Co-enzyme Q10 ***	150 mg	Take 1 capsule	120 mg
		Magnesium	150 mg	daily, 2 hours	N/D*
		Vitamin D3	1000 IU	before supper.	1000 IU
2	Product B	Bergamot extract	200 mg	Take 1 tablet daily,	N/D
		Plant sterols ***	120 mg	at night.	1.5 g to 3 g
		Artichoke extract	80 mg		N/D
		Vitamin C ***	20 mg		500 mg
3	Product C	*Lactobacillus Fermentum* ME3	8 billion CFU	Take 1 capsule daily.	6 billion CFU
4	Product D	Berberine HCl	500 mg	Take 2 capsules 3	N/D
		Origine 8®	25 mg	times daily, before	N/D
		Phytophare® green tea extract	15 mg	or with a meal.	N/D
			10 mg		N/D
		Phosphatidylcholine complex	25 ug		N/D
		Chromium ***			
5	Product E	Co-enzyme Q10 ***	150 mg	Take 1 capsule 1-2	120 mg
		L-carnitine fumarate ***	100 mg	times daily,	750 mg
		Vitamin C ***	75 mg	preferably with a meal.	500 mg
6	Product F	Co-enzyme Q10 ***	150 mg	Take 1 capsule daily.	120 mg
7	Product G	Omega 3 fish oil ***	750 mg	Take 1 capsule	500 mg
		EPA ***	375 mg	daily.	N/D
		DHA ***	45 mg		N/D
		Co-enzyme Q10 ***	10 mg		120 mg

	Product	Ingredient	Strength	Dosage	Sufficient dosage**
8	Product H	Vitamin A	2.27 mg	Take 1-4 sachets	N/D
		Vitamin B6	50 mg	daily.	N/D
		Vitamin C ***	3000 mg		500 mg
		Vitamin E (50%)	282 mg		N/D
		Folic Acid ***	400 mg		0.8 mg
		L-Arginine	200 mg		N/D
		L-Lysine	3000 mg		N/D
		L-Proline	500 mg		N/D
9	Product I	Betaine HCL ***	250 mg	Take 1-2 tablets	4 g
		Magnesium	100 mg	daily.	N/D
		Vitamin E acetate	14 IU		N/D
		Vitamin B2	12 mg		N/D
		Vitamin B6	12 mg		N/D
		Policosanol ***	10 mg		10 mg
		Zinc	7.5 mg		N/D
		Folic Acid ***	0.2 mg		0.8 mg
		Vitamin B12	0.012 mg		N/D
10	Product J	Barberry root extract 60% (*Berberis vulgaris*)	40 mg	Take 2 tablets 2-3 times daily, with	10 g
		Phytosterols ***	350 mg	meals.	459 mg
		Apple polyphenols 30% extract	150 mg		N/D
		Nicotinamide	12.6 mg		N/D
		Co-enzyme Q10 ***	15 mg		120 mg
11	Product K	Phytosterols ***	400 mg	Take 2 tablets 1-3	459 mg
		Co-enzyme Q10 ***	15 mg	times daily.	120 mg
		Beta-carotene	195 ug		N/D
		Niacin (nicotinic acid)	5 mg		N/D
12	Product L	Co-enzyme Q10 ***	150 mg	Take 1 capsule	120 mg
		Bioperine	5 mg	daily.	N/D
13	Product M	Policosanol ***	20 mg	Take 1 tablet daily,	10 mg
		Folic acid ***	400 ug	at night	0.8 mg
14	Product N	Niacin (Vitamin B3)	35 mg	Take 1 tablet daily, after food.	N/D
15	Product O	Co-enzyme Q10 ***	150 mg	Take 1 capsule daily.	120 mg
16	Product P	*Apium graveolens*	7 mg	Take 1-2 tablets 4	N/D
		Coriandrum sativum	6 mg	times daily.	N/D
		Purified *Ferula foetida*	7 mg		N/D
		Cuminum cyminum	7 mg		N/D
		Embelia ribes	10 mg		N/D
		Piper longum	15 mg		N/D
		Zingiber officinale	15 mg		N/D
		Curcuma longa	15 mg		N/D
		Cyperus rotundus	15 mg		250 mg
		Allium sativum	25 mg		N/D
		Emblica officinalis ***	25 mg		500 mg
		Terminalia belerica	25 mg		25 mg
		Terminalia chebula	25 mg		25 mg
		Bauhinia variegate	25 mg		N/D
		Plumbago zeylanica	30 mg		N/D
		Pterocarpus marsupium	50 mg		N/D
17	Product Q	Nicotinamide (Vit B3)	16 mg	Take 1 tablet daily,	N/D
		Beta-Phytosterols	150 mg	after a meal.	459 mg
		Inulin (*Fructooligosaccharides*)	200 mg		N/D
		Soy lecithin	20 mg		N/D

*(N/D: Not Defined).

**(Sufficient dosage: a specific dosage that is deemed appropriate according to the scientific literature for achieving a therapeutic outcome based on the literature review)

*** Ingredients in NLCSs with substantial evidence.

Description of Studies

Single ingredients

After the initial database search, 1854 articles were screened. Duplicates were removed, which reduced the number of articles countdown to 148, after which the abstracts were then screened, and additional articles were excluded based on not meeting the inclusion criteria. A total of 110 articles were read and reviewed. The process that was followed is summarized in the Prisma diagram in Figure 1. Of the 110 articles, 28 were *in vitro / in vivo* studies, 64 clinical trials, and 18 reviews (Figure 2).

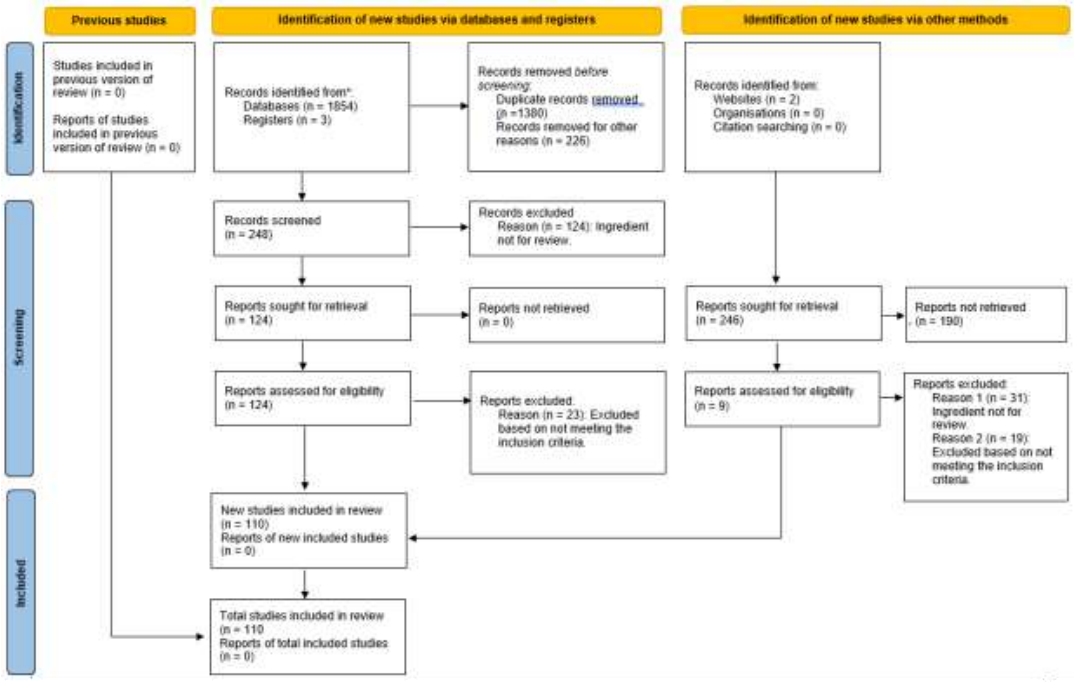


Figure 1: PRISMA diagram: Summarizing the flow of information for this research report. Total of 110 articles reviewed for this study.

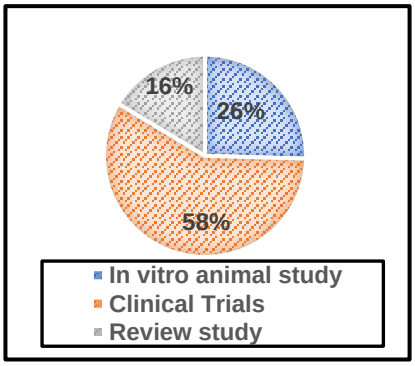


Figure 2: Overview of Study Types: *In vitro* studies, clinical trials, and review studies.

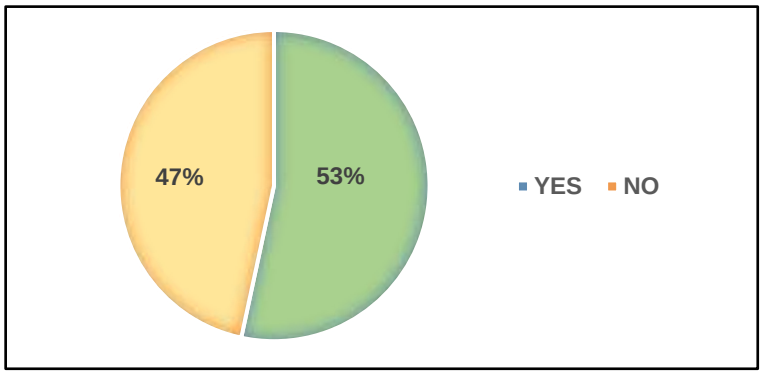
Combination products

Articles containing multiple ingredients were reviewed, and a total of 24 articles were identified for this investigation. The reviewed article included ingredients not mentioned in the study, however, contains one or more ingredients from the current study as shown in Table S1 of supplementary data.

Categorizing of Scientific Evidence

Each article reviewed was categorized into either ’yes’ or ‘no’ as illustrated in Figure 3, based on the level of evidence. The determination of the level of evidence for each study was based on the type of scientific evidence presented. Studies that included systematic reviews and meta-analyses of human trials were allocated a 'yes', while those that only included animal studies or human trials with limited evidence of beneficial effects were allocated a 'no'. There was 47% of reviewed articles categorized as ‘no’, and 53% of articles were categorized as ‘yes’.

Figure 3: Article categorization based on level of scientific evidence being sufficient: Yes or No



Discussion:

Of the 17 NCLSs products identified, a total of 50 ingredients were identified as presented in Table 1. Each ingredient was classified into different categories as summarized in Figure 4. Different class of ingredients were then categorized into either ‘yes’ or ‘no’ based on the level of evidence in Figure 5. Of 17 NCLSs products, four products had a single ingredient, while the rest were a combination of various ingredients. The most common types of ingredients found in the supplements were extracts with 22 different ingredients found in 5 different products, followed by vitamins

with 10 different ingredients found in 10 different products. For the various ingredients, the minimum dose required for an effect was tabulated (Table 1).

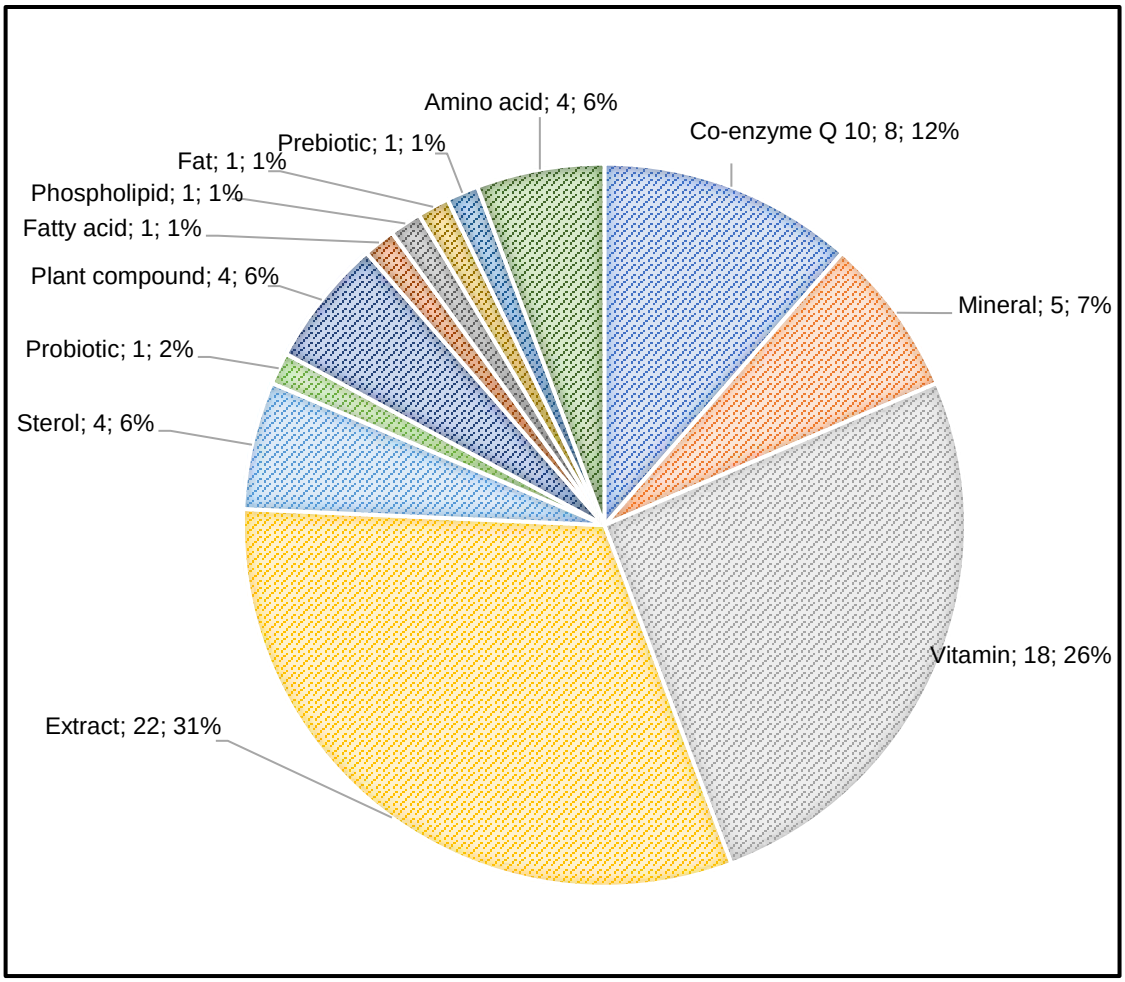


Figure 4: Graph summarizing different classes of ingredients in various products (Class of ingredient; Number of counts; %)

A summary of scientific evidence studied for each class of ingredients is given in Figure 5. Of 148 articles reviewed, 79 articles (53%) include systemic reviews and various randomized clinical trials to support its use as NCLS. However, not enough evidence is available to support its use as an alternative to statins. A total of 69 (47%) articles did not have sufficient scientific evidence to support the claims of cholesterol-lowering effects due to their study being a small-scale trial or being limited to in vivo studies.

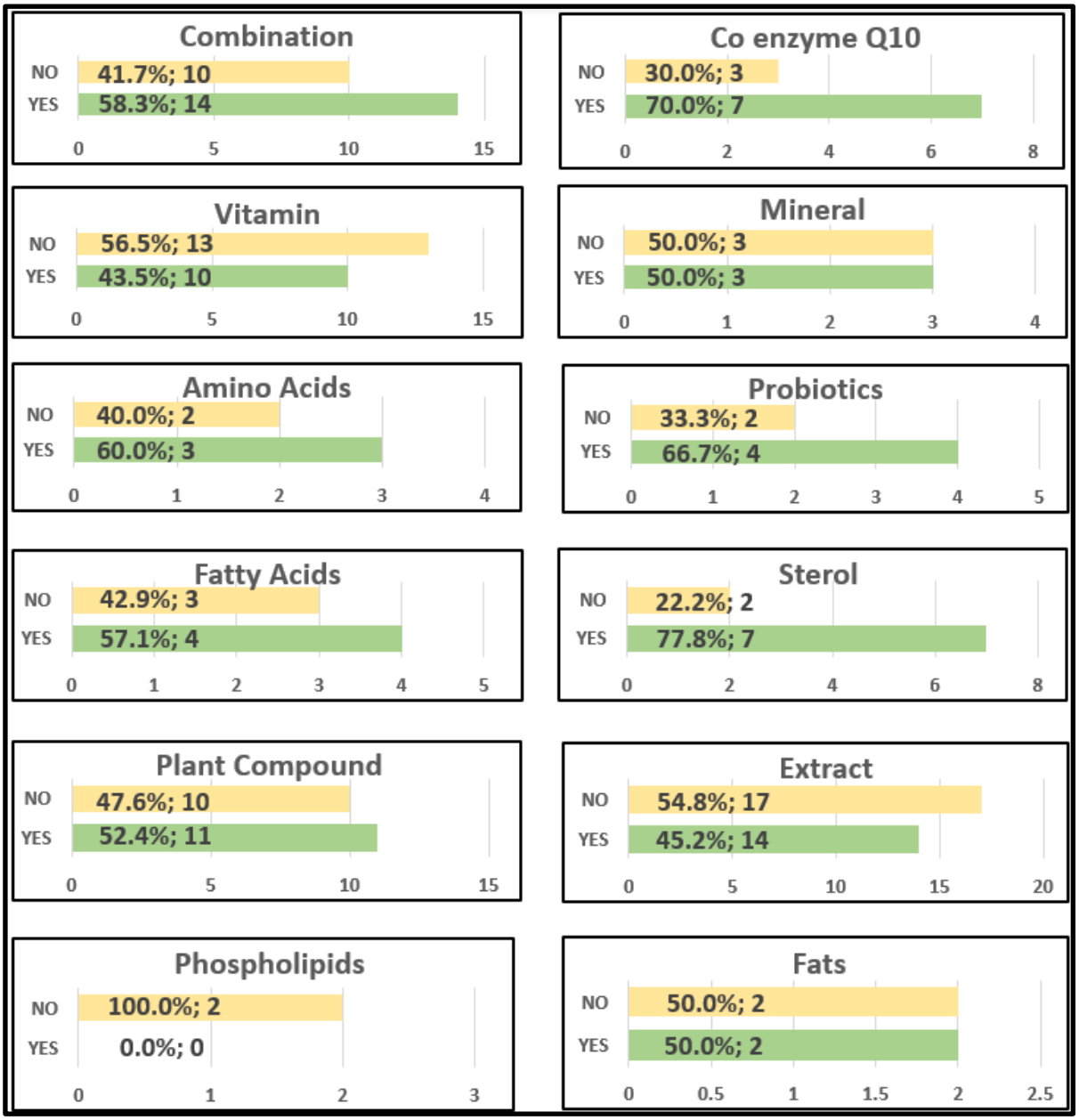


Figure 5: Summary of scientific evidence studied for each class of ingredients. The **X-axis** represents the count, while the **Y-axis** article categorization based on level of scientific evidence: Yes or No, Refer to Categorizing of Scientific Evidence.

Co-enzyme Q 10

Co-enzyme Q10 is a vital substance needed for the correct functioning of the various organs and chemical reactions in the body. Aging and the use of statins lead to coenzyme Q10 deficiency, and supplementation of coenzyme Q10 may ease cardiovascular-related diseases (Aaseth et al., 2021). Co-enzyme Q10 has been widely used to assist in lowering cholesterol levels (Fan et al., 2017), it was noted that two products contained Co-enzyme Q10 as the only ingredient, and six products included Co-enzyme Q10 in combination with other ingredients. Co-enzyme Q10 was

shown to have a beneficial effect in lowering cholesterol levels as well as decreasing the risk of CVDs at a dosage of 120 mg daily (Fan et al., 2017; Tóth et al., 2017; Choi and Chae, 2018; Jorat et al., 2018; Magno et al., 2018; Sabbatinelli et al., 2020; Zhang et al., 2018a; Zhang et al., 2018b). Additionally, when a co-enzyme Q10 is added to the statin therapy, the intensity of the statin side effects is significantly reduced (Qu et al.,2018), this further assists in patient adherence to statin treatment.

Vitamins

Vitamins are essential micronutrients that the body needs for adequate performance and well-being (Semba, 2012). Vitamins are present in almost all foods, however, supplementation of certain Vitamins such as Vitamin D has a beneficial effect on reducing serum total cholesterol, LDL cholesterol, and triglyceride levels at a dosage of 1000 IU to 1500 IU daily (Yin et al., 2015; Tavakoli et al., 2016; Dibaba, 2019; Alves et al., 2021; Holt et al., 2022). A combination of Vitamin D (400 IU) and calcium (1,000 mg) was beneficial in improving lipid profiles in postmenopausal women with dyslipidemia (Schnatz et al., 2014). Of the seventeen supplements investigated, a total of nine products contained vitamins as a combination, and one product contained Niacin (Vitamin B3) as the only ingredient. Niacin (1-3 g/day) is beneficial in increasing HDL and reducing LDL, triglyceride, and total cholesterol levels; however, possible side effects (flushing, liver damage) should be taken into consideration (Julius, 2015; Dwyer et al., 2018). Vitamins were the most common types of ingredients found in the NCLSs after extracts.

Extracts

This category includes Artichoke extract, Barberry (*Berberis vulgaris*) root extract 60%, and Bergamot extract. The extracts derived from various plants were mentioned twenty-two times and seen in five different investigative products, making extracts the most common ingredients used on the South African market. Commonly used extracts such as garlic (*Allium sativum*) and red yeast rice (*Monascus purpureus*) have been demonstrated to lower serum cholesterol (Barrat et al., 2013; Zadhoush et al., 2021). Red yeast rice is not included into investigative products; however, it is found through rice fermentation by the fungus *Monascus purpureus*, contains monacolin K which is chemically identical to lovastatin and can cause the same types of side effects and drug interactions as lovastatin (Nguyen et al., 2017). Red yeast rice containing 2 mg Monacolin K significantly reduces LDL in patients with unsatisfactory LDL (Minamizuka

et al., 2021). The use of RYR can lead to gastrointestinal effects and potentially result in myopathy, hepatotoxicity, rhabdomyolysis, and anaphylaxis, which are comparable to the adverse effects associated with statin usage (Nguyen et al., 2017). Lovastatin is a structurally similar derivative of simvastatin that is less potent, with a daily dose of 20 mg reducing cholesterol by 25-30% compared to 10 mg of simvastatin (Muscas et al., 2019). Patients who supplemented with 800 mg and above of garlic showed a decrease in total cholesterol and LDL, as well as an increase in HDL (Alobaidi, 2014; Aslani et al., 2016). Despite the scientific claims of hypolipidemic effects associated with most extracts, there is insufficient evidence to support these claims. It is important to note that the maximum daily intake of these extracts as a supplement only reaches tens of milligrams, which is significantly lower than the therapeutic dosage required for the hypolipidemic effect. Therefore, taking these extracts as a supplement is unlikely to have a significant impact on reducing cholesterol levels

Sterols

Plant stanols and sterols, also known as phytosterols, are cholesterol-like compounds that are found naturally in a range of plant-based foods (BDA, 2021). The cholesterol lowering effect of phytosterols is recognized to result from the inhibition of intestinal cholesterol absorption (Trautwein et al., 2018). Daily intake of phytosterols alone at 1.5 g to 3 g daily lowers LDL-cholesterol and triglyceride by 7.5% to 12% and 8.3% respectively (Smet et al., 2012; Demonty et al., 2013; Han et al., 2016; Trautwein et al., 2018; Blom et al., 2019). While the LDL-cholesterol lowering effect of phytosterols has been established, the evidence for an additional triglyceride lowering effect is still scarce (Demonty et al., 2013). A study by Han et al. (2016) found that supplementation of 2.5 g daily of phytosterols in patients treated with statins led to a significant decrease in LDL-cholesterol and total cholesterol levels by 0.30 mmol/L each, compared to statins alone. However, the impact of phytosterols on preventing cardiovascular disease lacks randomized data according to the same study. The LDL cholesterol is a known risk factor for arteriosclerotic CVD and a reduction in LDL-C concentration can be achievable with phytosterols intake (Ference et al., 2017). Based on the evidence, in patients that do not respond adequately to single statin therapy, stanols or sterols can be added as a complementary medicine with low statin doses to avoid possible adverse effects (Párraga-Martínez, et al., 2015).

Probiotics

Probiotics are live micro-organisms intended for health benefits when consumed. Lactobacillus fermentum ME-3 is a unique strain of Lactobacillus species, having health benefits, including cholesterol-lowering effects on humans, and lowering the risk of CVDs by reducing the formation of oxidized LDL and triglyceride when 8 billion CFUs of Lactobacillus fermentum ME-3 is consumed (Mikelsaar et al., 2015; Wang et al., 2018). Probiotics promote LDL-C and triglyceride reduction by reducing the intestinal cholesterol absorption (Magno et al., 2018). Probiotics such as Lactobacillus species, when used as a supplement, were found to be effective from a dose of 5 billion CFUs or higher (Kligler and Cohrssen, 2008). Supplementation of Lactobacillus fermentum ME-3 may also help to prevent risk, alleviate the symptoms, and treat metabolic related conditions such as diabetes (Kullisaar et al., 2016). Only 1 product on the South African market contained 8 billion CFUs of Lactobacillus fermentum ME-3 as a single ingredient which is sufficient to have cholesterol-lowering effects.

Plant compounds

Berberine and policosanol are two bioactive compounds that fall under this category. Berberine, which can be extracted from various plants, has been found to have lipid-lowering and insulin-resistance properties at a dose greater than 500 mg daily (Investigative product D), according to several studies (Hu et al., 2012; Cicero and Baggioni, 2016; Koppen et al., 2017; Spigoni et al., 2017; Zhao et al., 2021). When taken alone or in combination with other ingredients, berberine has been shown to lower average LDL cholesterol levels by 20% to 30%, which is comparable to the effectiveness of moderate-intensity statins that lower LDL cholesterol by 30% to 50% (Koppen et al., 2017). Policosanol, on the other hand, is a sugar cane extract that contains aliphatic alcohols that assist in down-regulating cholesterol synthesis (Park et al., 2019). A study conducted in Cuba found that a daily dose of 10 mg of policosanol led to a significant reduction in total cholesterol, LDL, and triglycerides, as well as an increase in HDL (Park et al., 2019). Supplementation with these plant compounds could serve as an alternative for patients who are intolerant to statins.

Fatty acid (Omega-3)

Omega-3 fatty acids are a group of polyunsaturated fatty acids found in seafood that is required for numerous functions in the body. A study suggests that the long-chain fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) can reduce blood triglyceride levels and slightly improve HDL (Nicholls et al., 2018). The

recommended daily dosage of EPA and DHA for heart-healthy diet is 250 mg to 500 mg daily, however, no strong evidence on the protective effect against the heart disease is available (Peters et al., 2012; Siscovick et al., 2017; Choi and Chae, 2018). The supplementation of Omega-3 increases the levels of LDL and may also increase the risk of prostate cancer, therefore whether Omega-3 supplements are beneficial is uncertain (Tóth et al., 2017). Thus, statin and omega-3 fatty acid combination should be cautiously recommended, considering the safety issues associated with its use.

Fat (Soy protein)

The cholesterol-lowering effect of soy is well-known and led to regulatory approval of a health claim relating to soy protein reducing the risk of cardiovascular diseases (Ramdath et al., 2017). However, soy contains additional ingredients such as isoflavones, lecithins, saponins and fiber that may improve cardiovascular health through separate mechanisms (Ramdath et al., 2017). The supplementation of soy food products (25g) decreased the total and LDL cholesterol by 0.23 mmol/L and 0.18 mmol/L respectively. (Jung et al., 2021). No scientific evidence was available for its beneficial effect as a combination with statins or other ingredients.

Prebiotic (Inulin (Fructooligosaccharides))

Prebiotics are non-digestible food components that selectively stimulate the growth or activity of desirable microorganisms (probiotics). Inulin is a carbohydrate belonging to a class of compounds known as fructans and is known to lower serum cholesterol at a daily dosage of more than 2 g (Kassaian et al., 2019). However, from the scientific evidence reviewed there were no significant effects of the prebiotic supplementation on serum Total cholesterol, LDL, and HDL (Taghizadeh et al., 2014), thus their only benefit would be promoting the growth of probiotics.

Amino acids

Amino acids are referred to as the building block proteins. The amino acid L-arginine has received much attention due to its numerous beneficial effects of significantly improving lipid profiles (Hadi et al., 2019). However, L-arginine supplementation has not been proven to significantly change the concentrations of total cholesterol, or HDL (Hadi et al., 2019). The study conducted by Hadi et al. (2019) found that there was only a decrease in triglyceride levels, which suggests inadequate evidence to support the cholesterol-lowering effects of the amino acids. In general, amino acids are consumed

alongside various other components, often including vitamins found in Investigative product H.

Overview

High cholesterol levels are a major risk factor for cardiovascular diseases such as coronary heart diseases and stroke and may require specific intervention with the prescription of an appropriate drug like statins (Magno et al., 2018). However, despite statins' cardiovascular benefits, all statins are associated with myopathy, ranging in severity from minor muscle aches to fatal rhabdomyolysis (Egan and Colman, 2011). Hence, there are NCLSs that can be recommended as either substitutes or supplements to statins. These NCLSs may be particularly useful for patients who are intolerant to statins or prefer to take natural alternatives.

The beneficial role of NCLS should not be underestimated. In general, any food has the potential to be used as a drug or supplement depending on the content of its active compounds. The finding of the current review showed that supplementation of sterols, coenzyme Q 10, and probiotics can improve lipid profiles and reduce statin-related side effects. According to a meta-analysis of 12 randomized controlled trials, patients taking statins who supplemented with Coenzyme Q10 experienced a significant reduction in the incidence of muscle pain (Bookstaver et al., 2012; Kumar et al.,2012). A meta-analysis of 15 randomized clinical trials, involving over 500 participants, has demonstrated the effectiveness of sterol supplementation in neutralizing the intestinal absorption of cholesterol caused by statin therapy (Poli et al., 2021). Consuming 8 billion CFUs of Lactobacillus fermentum ME-3 probiotic has been found to help decrease the production of oxidized LDL and triglycerides by decreasing the absorption of cholesterol in the intestines (Mikelsaar et al., 2015; Wang et al., 2018).

Of the seventeen NCLS products identified and investigated, thirteen products were a combination of multiple ingredients. The products with multiple ingredients may influence the cholesterol levels directly or indirectly by triggering more than one mechanism. However, certain ingredients may have the potential to negate each other's effects, and since there is insufficient evidence regarding their combination, the effectiveness of these supplements cannot be conclusively determined. A reduction in cholesterol may be achieved either by inhibition of cholesterol synthesis in the liver or by reduction of intestinal cholesterol absorption (Magno et al., 2018).

Side effects and drug interactions

Those who are taking NCLS should be advised to have regular follow-ups with a medical professional to monitor for potential side effects and interactions with ingredients from the supplements and drugs. Common ingredients such as Allium sativum (Garlic), green tea extract, policosanol, and fish oil should be taken with care as they may interact with some blood-thinning medications (Zadhoush et al., 2021). Common gastrointestinal side effects such as diarrhea, nausea, and vomiting can be experienced in ingredients such as berberine, fish oil, and green tea extracts (Zhao et al., 2021). Red yeast rice is used as a dietary supplement to lower cholesterol levels, however, it should not be taken with statins, because it may enhance their effect and increase the risk of liver damage (Farkouh and Baumgärtel, 2019).

Conclusion:

After reviewing 50 ingredients, sterols (with 77% of sufficient scientific evidence), co-enzyme Q10 (70%), and probiotics (*Lactobacillus fermentum* ME-3) (66%) were noted as having evidence demonstrating cholesterol lowering effects when taken at the correct dosage. It was noted that various NCLSs may be effective in lowering cholesterol levels when taken alone or in combination. However, due to the limited information available to pharmacists and practitioners relating to NCLSs, there are challenges when it comes to recommending the most suitable NCLSs to a patient. Different factors need to be considered, as some ingredients may cause side effects or may interact with other medications leading to undesirable therapeutic outcomes.

The limited scientific evidence on certain ingredients, having one study or several small studies with no comparison group, may lead the products to be less known to the public. The scientific literature for minerals, amino acids, and extracts lacks evidence in clinical trials, and further studies on ingredients and various combinations need to be studied, whether the collaboration of different ingredients is synergic and effective, along with the logical rationale for the selection of specific combinations. Despite some of the ingredients containing sufficient scientific evidence if used alone, future studies should demonstrate cholesterol-lowering effects and cardiovascular disease prevention through pharmacological action as well as providing the subsequent dosages required for the products to be efficacious.

Pharmacists play a crucial role in recommending and advising on the use of NCLS product. However, it is essential for them to exercise caution and thorough evaluation when considering the recommendation of such products. This evaluation should involve assessing the available evidence regarding the ingredients used in the NCLS product, determining the minimum effective dose required for its desired effects, and being mindful of potential side effects.

By taking these precautions, pharmacists can ensure that they provide informed and responsible guidance to individuals seeking NCLS products. It allows them to make well-informed decisions based on scientific evidence, weighing the benefits and risks associated with the specific product. Ultimately, this approach promotes patient safety and helps pharmacists fulfill their professional responsibility of delivering high-quality healthcare advice.

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SUPPLEMENTARY DATA

Table S1: Summary of articles containing multiple ingredients.

Combination

No	Ingredients	Year	Title	Type of study	Method/Design of study	Control / Placebo	Outcome	Interpretation	Comment	Available at	Reference	Scientific Evidence
1	Vitamin C & E	2016	Vitamin E (α-Tocopherol) and Vitamin C (Ascorbic Acid) Supplementation on Cholesterol and Triglyceride Blood Profile of Male Native Muscovy	Animal study	Eighty four muscovy duck were rationed to seven (7) treatments	Control	vitamin E and vitamin C supplementation decreased blood cholesterol level.	Result showed that treatments significantly affected blood cholesterol level but did not significantly affect HDL, LDL and Triglyceride levels of muscovy blood.	In male muscovy, HDL was increased with Vitamin C and E supplementation.	http://medpub.litbang.pertanian.go.id/index.php/proceedings/article/view/1502/1376	Tugiyanti, E., Zuprizal, Z., & Rusman, R. (2016). Vitamin E (α-Tocopherol) and Vitamin C (Ascorbic Acid) Supplementation on Cholesterol and Triglyceride Blood Profile of Male Native Muscovy. 370–377. https://doi.org/10.14334/proc.intsem.lpvt-2016-p.370-377	No
2	bergamot extract (120-mg flavonoids), phytosterols, vitamin C, and chlorogenic acid	2019	Three-arm, placebo-controlled, randomized clinical trial evaluating the metabolic effect of a combined nutraceutical containing a bergamot standardized flavonoid extract in dyslipidemic overweight subjects	Double-blind, placebo-controlled, parallel-group, dose-escalation, clinical trial	90 overweight dyslipidemic subjects. Participants were randomly allocated to treatment with two pills of either active treatment or placebo, or a combination of both (a pill per treatment).	Placebo	After 8 weeks, all active-treated groups experienced a significant improvement in triglycerides (TG) versus placebo and in low-density lipoprotein cholesterol (LDL-C) versus baseline and placebo treatments. In the high-dose-treated group, also total cholesterol (TC), significantly decreased.	The tested nutraceutical showed to improve lipid and glucose metabolism, adipokines pattern, and systemic inflammation in dyslipidemic overweight subjects.	All patients allocated to either low-dose or high-dose active treatment experienced a significant decrease in TG, LDL-C, and homeostatin model assessment of insulin resistance.	https://pubmed.ncbi.nlm.nih.gov/31225673/	Cicero, A. F. G., Fogacci, F., Bove, M., Giovannini, M., & Borghi, C. (2019). Three-arm, placebo-controlled, randomized clinical trial evaluating the metabolic effect of a combined nutraceutical containing a bergamot standardized flavonoid extract in dyslipidemic overweight subjects. Phytotherapy Research : PTR, 33(8), 2094–2101. https://doi.org/10.1002/PTR.6402	Yes
3	red yeast rice, policosanols and artichoke leaf extracts	2013	A combined natural supplement lowers LDL cholesterol in subjects with moderate untreated hypercholesterolemia: a randomized placebo-controlled trial	Randomized, double-blind, placebo-controlled trial.	natural cholesterol-lowering supplement (NCLS) containing red yeast rice, policosanols and artichoke leaf extracts on blood lipid concentrations as well as on safety parameters when given over 16 weeks in 100 volunteers with untreated moderate hypercholesterolemia	Placebo	Reduction of primary outcome low-density lipoprotein cholesterol as well as total cholesterol were observed after 16 weeks of supplementation with NCLS.	The NCLS was effective in reducing low-density lipoprotein cholesterol in subjects with moderate hypercholesterolemia, without modifying safety parameters.	No significant changes were observed in high-density lipoprotein, triacylglycerol, creatine kinase, lactate dehydrogenase and coenzyme Q10 levels, as well as in markers of liver and renal function.	https://pubmed.ncbi.nlm.nih.gov/23815518/	Barrat, E., Zair, Y., Ogier, N., Housez, B., Vergara, C., Maudet, C., Lescuyer, J. F., Bard, J. M., Carpentier, Y. A., Cazaubiel, M., & Peltier, S. L. (2013). A combined natural supplement lowers LDL cholesterol in subjects with moderate untreated hypercholesterolemia: a randomized placebo-controlled trial. International Journal of Food Sciences and Nutrition, 64(7), 882–889. https://doi.org/10.3109/09637486.2013.809405	Yes
4	**Extract** - Red yeast rice (RYR), sugar cane-derived policosanols (SCdP) and artichoke leaf extracts (ALEs)	2013	LDL-cholesterol-lowering effect of a dietary supplement with plant extracts in subjects with moderate hypercholesterolemia	Double-blind, randomized, parallel controlled study	39 subjects from 21 to 55 years with moderate hypercholesterolemia without drug treatment were assigned to 2 groups and then consumed either a DS containing RYR, SCdP and ALEs or a placebo over a 16-week period.	Placebo	LDL-cholesterol and TC were reduced by, respectively, 21.4 % (95 % CI, −13.3 to −24.9 %, p < 0.001) and 14.1 % (95 % CI, −10.1 to −18.0 %, p < 0.001) at week 16 in the DS group compared with baseline.	Daily consumption of this new DS decreased LDL-cholesterol and TC and is therefore an interesting, convenient aid in managing mild to moderate hypercholesterolemia.	N/A	https://link.springer.com/article/10.1007/s00394-012-0357-x	Ogier, N., Amiot, M.-J., Georgé, S., Maillot, M., Mallmann, C., Maraninchi, M., Morange, S., Lescuyer, J.-F., Peltier, S. L., & Cardinault, N. (2013). LDL-cholesterol-lowering effect of a dietary supplement with plant extracts in subjects with moderate hypercholesterolemia. European Journal of Nutrition, 52(2), 547–557. https://doi.org/10.1007/s00394-012-0357-x	Yes
5	**Extract** - red yeast rice extract, policosanol and artichoke leaf extract	2013	Effect on LDL-cholesterol of a large dose of a dietary supplement with plant extracts in subjects with untreated moderate hypercholesterolaemia: a randomised, double-blind, placebo-controlled study	Randomised, double-blind, placebo-controlled clinical trial.	Forty-five healthy subjects (15 per group), with untreated hypercholesterolaemia, were included for this trial	Placebo	After 4 weeks of supplementation, LDL-C was significantly lower in 6-TAB (−0.21 g/l; 95 % CI −0.38 to −0.03 g/l; p = 0.0217) and 3-TAB (−0.25 g/l; 95 % CI −0.42 to −0.07 g/l; p = 0.0071) compared to Placebo, although no difference in LDL-cholesterol was observed between the two groups, while no effect was seen on triacylglycerol and HDL-cholesterol.	After 4 weeks of supplementation, LDL-C was significantly lower in TWICE DAILY DOSE (6 TABLET INSTEAD OF 3)	Supplementation with twice the recommended dose of the DS was effective in reducing LDL-cholesterol and appeared safe, but according to the present results, no additional benefit could be achieved compared to the recommended dose.	https://link.springer.com/article/10.1007/s00394-012-0486-2	Barrat, E., Zair, Y., Sirvent, P., Chauveau, P., Maudet, C., Housez, B., Derbord, E., Lescuyer, J.-F., Bard, J.-M., Cazaubiel, M., & Peltier, S. L. (2013). Effect on LDL-cholesterol of a large dose of a dietary supplement with plant extracts in subjects with untreated moderate hypercholesterolaemia: a randomised, double-blind, placebo-controlled study. European Journal of Nutrition, 52(8), 1843–1852. https://doi.org/10.1007/s00394-012-0486-2	Yes
6	Coriandrum sativum and Allium sativum	2018	Supplementation of garlic and coriander seed powder: Impact on body mass index, lipid profile and blood pressure of hyperlipidemic patients	Randomized controlled trial	Eighty patients were partitioned into 4 groups, each group consisting of twenty patients. The groups were randomly assigned to three supplements i.e. garlic powder (GP), coriander seed powder (CSP) and mixture (1:1 dry weight basis) of GP and CSP at a dose rate of 2 g/day. The fourth group was kept as placebo. The patients were examined for serum lipid profile, BMI and blood pressure at the start (0 day), 20, 40 and 60th day of supplementation.	Placebo	The results indicated that all the supplements significantly ($p<0.05$) influenced the BMI, HDL, total cholesterol, triglycerides, LDL and systolic blood pressure of the patients. Among the supplements, GP had the highest influenced on BMI, TC, LDL and HDL whereas the impact of GP-CSP and CSP was more pronounced on TGL and blood pressure of the patients, respectively.	It was concluded that consumption of garlic, coriander and their mixture at a dose rate of 2 g/day is improving the lipid parameters of the patients.	All the parameters decreased with supplementation except HDL, which increased with the consumption of supplements.	https://pubmed.ncbi.nlm.nih.gov/30150192/	Zeb, F., Safdar, M., Fatima, S., Khan, S., Alam, S., Muhammad, M., Syed, A., Habib, F., & Shakoor, H. (2018). Supplementation of garlic and coriander seed powder: Impact on body mass index, lipid profile and blood pressure of hyperlipidemic patients. Pakistan Journal of Pharmaceutical Sciences, 31(5), 1935–1941. https://pubmed.ncbi.nlm.nih.gov/30150192/	No
7	red yeast rice with monacolin K	2021	Low dose red yeast rice with monacolin K lowers LDL cholesterol and blood pressure in Japanese with mild dyslipidemia: A multicenter, randomized trial	A multicenter, randomized trial	Eighteen patients without known cardiovascular disease and unsatisfactory low-density lipoprotein cholesterol (3.96±0.19 mmol/L) controlled only by diet therapy were randomly allocated to receive low dose red yeast rice (200 mg/day) containing 2 mg monacolin K or diet therapy alone for 8 weeks.	Control	Low-density lipoprotein cholesterol decreased significantly in the red yeast rice group than in the diet therapy group. The red yeast rice group also exhibited significant decreases in total cholesterol, apolipoprotein B, and blood pressure.	We found that patients in the red yeast rice group exhibited significant reductions in lowdensity lipoprotein cholesterol, total cholesterol, apolipoprotein B, and blood pressure without any recognised adverse effect. This suggests that low daily dose red yeast rice could reduce cardiovascular risk in patients with dyslipidemia.	No severe treatment-related adverse effects on muscles, liver, or renal function were observed.	https://pubmed.ncbi.nlm.nih.gov/34587702/	Minamizuka, T., Koshizaka, M., Shoji, M., Yamaga, M., Hayashi, A., Ide, K., Ide, S., Kitamoto, T., Sakamoto, K., Hattori, A., Ishikawa, T., Kobayashi, I., Maezawa, Y., Kobayashi, K., Takemoto, M., Inagaki, M., Endo, A., & Yokote, K. (2021). Low dose red yeast rice with monacolin K lowers LDL cholesterol and blood pressure in Japanese with mild dyslipidemia: A multicenter, randomized trial. Asia Pacific Journal of Clinical Nutrition, 30(3), 424–435. https://doi.org/10.6133/APJCN.202109_30(3).0009	No
8	Coenzyme Q10, Vitamin C, monacolin K, and L-arginine.	2018	LDL-cholesterol lowering effect of a new dietary supplement: An open label, controlled, randomized, cross-over clinical trial in patients with mild-to-moderate hypercholesterolemia	This was a single center, controlled, randomized, open-label, cross-over clinical study	20 Caucasian outpatients aged 18–75 years with serum LDL-C between 130 and 180 mg/dL. Patients assumed two different dietary supplements (A and N) both containing monacolin K 10 mg for 8 weeks each, separated by a 4-week wash-out period.	Control	LDL-C decreased by 23.3% during treatment with N and by 25.6% during treatment with A . **Total-C** decreased significantly within each treatment period. **HDL-C** increase was negligible during **A** whereas it was significant during **N**. **TG** diminished markedly during **A** and non-significantly during **N**. The difference between treatments was not statistically significant for all variables.	Our results confirm the clinically meaningful LDL-C lowering properties of **monacolin K**. At variance witha supplement already in the market (**N**), the novel association (**A**) of **monacolin K** with **L-arginine**, **coenzime Q10** and **ascorbic acid** also produces a significant reduction of triglycerides without significant effects on HDL.	Results confirm the clinically meaningful LDL-C lowering properties of monacolin K	https://pubmed.ncbi.nlm.nih.gov/29793488/	Magno, S., Ceccarini, G., Pelosini, C., Jaccheri, R., Vitti, J., Fierabracci, P., Salvetti, G., Airoldi, G., Minale, M., Saponati, G., & Santini, F. (2018). LDL-cholesterol lowering effect of a new dietary supplement: An open label, controlled, randomized, cross-over clinical trial in patients with mild-to-moderate hypercholesterolemia. Lipids in Health and Disease, 17(1). https://doi.org/10.1186/s12944-018-0775-8	Yes
9	Coenzyme Q10 and Omega-3	2017	Addition of omega-3 fatty acid and coenzyme Q10 to statin therapy in patients with combined dislipidemia	Pilot randomized double-blind trial	105 subjects who met the criteria of combined dislipidemia and elevated TAG levels were randomly divided into three groups. In the control group, unaltered statin therapy was indicated. In the second and third groups, omega-3 PUFA 2.52 g/day (Zennix fa Pleuran) and omega-3 PUFA 2.52 g+CoQ10 200 mg/day (Pharma Nord ApS) were added, res//. At the end of the 3-month period (±1 week), all patients were evaluated.	Control	Significant reduction of hepatic enzymes activity, systolic blood preasure, inflammatory markers and TAG levels were detected in both groups in comparison to the control group.	Coenzyme Q10 addition significantly reduced most of the abovementioned parameters (systolic blood preasure, total cholesterol, LDL, hsCRP, IL-6, SOD) in comparison with the statin+omega-3 PUFA group.	The results of this pilot study suggest the possible beneficial effects of triple combination on the lipid and non-lipid paramaters related to atherogenesis and side effects of statin treatment.	https://pubmed.ncbi.nlm.nih.gov/28541926/	Tóth, Š. Šaity, M., Pekárová, T., Mughees, A., Štefanič, P., Katz, M., Spišáková, K., Pella, J., & Pella, D. (2017). Addition of omega-3 fatty acid and coenzyme Q10 to statin therapy in patients with combined dyslipidemia. Journal of Basic and Clinical Physiology and Pharmacology, 28(4), 327–336. https://doi.org/doi:10.1515/jbcpp-2016-0149	Yes
10	Sterols and fish oil	2018	A low-fat spread with added plant sterols and fish omega-3 fatty acids lowers serum triglyceride and LDL-cholesterol concentrations in individuals with modest hypercholesterolaemia and hypertriglyceridaemia	Randomized, double-blind, placebo-controlled, parallel group design	Following a 2-week placebo run-in period, 260 healthy individuals with modestly elevated blood TG (≥ 1.4 mmol/L) and LDL-C (≥ 3.4 mmol/L) concentrations consumed either the placebo or intervention spread for 4 weeks. The intervention spread contained 2.0 g/day PS and 1.0 g/day eicosapentaenoic acid (EPA) + docosahexanoic acid (DHA) from fish oil.	Placebo	Four-week consumption of the intervention spread resulted in significantly lower TG and LDL-C concentrations as compared to placebo. Total cholesterol non-HDL-C concentrations were also significantly lower, as compared to placebo.	Four-week consumption of the intervention spread led to significant and clinically relevant decreases in serum TG, LDL-C and other blood lipid concentrations.	No significant treatment effects were found for HDL-cholesterol, ApoAI, ApoCIII, Apo E or ApoB/ApoAI.	https://pubmed.ncbi.nlm.nih.gov/29725824/	Blom, W. A. M., Koopenol, W. P., Hiemstra, H., Stojakovic, T., Scharnagl, H., & Trautwein, E. A. (2019). A low-fat spread with added plant sterols and fish omega-3 fatty acids lowers serum triglyceride and LDL-cholesterol concentrations in individuals with modest hypercholesterolaemia and hypertriglyceridaemia. European Journal of Nutrition, 58(4), 1615–1624. https://doi.org/10.1007/S00394-018-1706-1	Yes
11	phytosterols (800 mg) and red yeast rice, standardized to contain 5 mg of monacolins from Monascus purpureus, with added niacin (27 mg) and policosanols (10 mg) (LEVELIP DUO®)	2020	A Randomized, Double-Blinded, Placebo-Controlled, Clinical Study of the Effects of a Nutraceutical Combination (LEVELIP DUO ®) on LDL Cholesterol Levels and Lipid Pattern in Subjects with Sub-Optimal Blood Cholesterol Levels (NATCOL Study)	A Randomized, Double-Blinded, Placebo-Controlled, Clinical Study	randomizing 88 moderately hypercholesterolemic subjects to treatment with a combined nutraceutical or placebo.	Placebo	The mean LDL-Cholesterol (LDL-C) change at Week 8 was -32.5 ± 30.2 mg/dL (-19.8%) in the combined nutraceutical group and 2.5 ± 19.4 mg/dL (2.3%) in the placebo group. Total Cholesterol (TC), non-HDL cholesterol (non-HDL-C), Apolipoprotein B, TC/HDL-C and LDL-C/HDL-C improved in a similar way in the combined nutraceutical group only.	In conclusion, the tested combined nutraceutical was well tolerated, while significantly reducing the plasma levels of LDL-C, TC, non-HDL-C, ApoB, TC/HDL-C and LDL-C/HDL-C ratios in mildly hypercholesterolemic patients.	N/A	https://pubmed.ncbi.nlm.nih.gov/33066334/	Cicero, A. F. G., D'addato, S., & Borghi, C. (2020). A Randomized, Double-Blinded, Placebo-Controlled, Clinical Study of the Effects of a Nutraceutical Combination (LEVELIP DUO ®) on LDL Cholesterol Levels and Lipid Pattern in Subjects with Sub-Optimal Blood Cholesterol Levels (NATCOL Study). Nutrients, 12(10), 1–10. https://doi.org/10.3390/NU12103127	Yes
12	Berberine, Red Yeast Rice and Chitosan	2017	Effects of a New Nutraceutical Formulation(Berberine, Red Yeast Rice and Chitosan) onNon-HDL Cholesterol Levels in Individuals withDyslipidemia: Results from a Randomized,Double Blind, Placebo-Controlled Study	Randomized,Double Blind, Placebo-Controlled Study	The aim ofthe study is to test the efficacy of the nutraceutical formulation (one daily) in lowering non-HDLcholesterol vs. placebo at 12 weeks in individuals with non-HDL-cholesterol levels≥160 mg/dL.39 subjects (age 52±11 years; 54% females; body mass index 27±4 kg/m2) were randomized(3:1) in a double blind phase II placebo-controlled study.	Placebo	The intervention significantly decreased non-HDL cholesterol (−30 ± 20 mg/dL), LDL cholesterol (−31 ± 18 mg/dL) and apolipoprotein (Apo) B (−14 ± 12 mg/dL) levels compared to the placebo.	In conclusion, the tested nutraceutical formulation was effective in the reduction of non-HDL/LDL-C levels at 4 and 12 weeks thus representing a possible therapeutic strategy in dyslipidemic individuals in primary prevention.	new combination of nutraceuticals (berberine 200 mg, monacolin K 3 mg, chitosan 10 mg andcoenzyme Q 10 mg)	https://www.mdpi.com/1422-0067/18/7/1498	Spigoni, V., Aldigeri, R., Antonini, M., Michell, M. M., Fantuzzi, F., Fratter, A., Pellizzato, M., Derlindati, E., Zavaroni, I., Bonadonna, R. C., & Dei Cas, A. (2017). Effects of a new nutraceutical formulation (Berberine, red yeast rice and chitosan) on non-HDL cholesterol levels in individuals with dyslipidemia: Results from a randomized, double blind, placebo-controlled study. International Journal of Molecular Sciences, 18(7). https://doi.org/10.3390/ijms18071498	Yes
13	Berberine, red yeast rice, plant sterols, fibers	2018	Cholesterol-Lowering Nutraceuticals Affecting Vascular Function and Cardiovascular Disease Risk	Review	The aim of this review is to provide an update on the effects of the dietary supplementation with cholesterol-lowering nutraceuticals and nutraceutical combinations affecting vascular function and CV risk in clinical interventional studies.	Not Applicable - NA	Current evidence supports the mild-to-moderate cholesterol-lowering efficacy of red yeast rice, berberine, plant sterols, fibers, and some nutraceutical combinations whereas data on the individual cholesterol-lowering action of other nutraceuticals are either less striking or even	There is also promising evidence on the vascular protective effects of some of the aforementioned nutraceuticals.	However, except for red yeast rice, clinical interventional studies have not investigated their impact on CV outcomes.	https://link.springer.com/article/10.1007/s11886-018-0994-7#citeas	Bianconi, V., Mannarino, M. R., Sahebkar, A., Cosentino, T., & Pirro, M. (2018). Cholesterol-Lowering Nutraceuticals Affecting Vascular Function and Cardiovascular Disease Risk. Current Cardiology Reports, 20(7), 53. https://doi.org/10.1007/s11886-018-0994-7	No

14	cinnamon-, chromium- and magnesium-formulated honey	2016	The effect of a cinnamon-, chromium- and magnesium-formulated honey on glycaemic control, weight loss and lipid parameters in type 2 diabetes: an open-label cross-over randomised controlled trial	An open-label cross-over randomised controlled trial	Twelve individuals with type 2 diabetes received 53.5 g of a formulated honey and a control (non-formulated) kanuka honey in a random order for 40 days, using cross-over design. Fasting glucose, insulin, HbA1c, lipids and anthropometric measures were measured at baseline and end of treatment. A meal tolerance test was performed at baseline to assess acute metabolic response.	Control	There was a statistically significant reduction in total cholesterol by -0.29 mmol/L (95 % CI -0.57 to -0.23), LDL cholesterol by -0.29 mmol/L (95 % CI -0.57 to -0.23) and weight by -2.2 kg (95 % CI -4.2 to -0.1). There was a trend towards increased HDL and reduced systolic blood pressure in the intervention treatment.	The addition of cinnamon, chromium and magnesium supplementation to kanuka honey was not associated with a significant improvement in glucose metabolism or glycaemic control in individuals with type 2 diabetes.	Use of the formulated honey was associated with a reduction in weight and improvements in lipid parameters, and should be investigated further.	https://pubmed.ncbi.nlm.nih.gov/25986159/	A Whitfield, P., Parry-Strong, A., Walsh, E., Weatherall, M., & Krebs, J. D. (2016). The effect of a cinnamon-, chromium- and magnesium-formulated honey on glycaemic control, weight loss and lipid parameters in type 2 diabetes: an open-label cross-over randomised controlled trial. European Journal of Nutrition, 55(3), 1123–1131. https://doi.org/10.1007/S00394-015-0926-X	No
15	NutraforChol®, a nutraceutical product containing red yeast rice extract, guggulipid extract and chromium picolinate	2020	Efficacy and tolerability of a nutraceutical combination of red yeast rice, guggulipid, and chromium picolinate evaluated in a randomized, placebo-controlled, double-blind study	Randomized, placebo-controlled, double-blind study	NutraforChol®, a nutraceutical product containing red yeast rice extract, guggulipid extract and chromium picolinate, was evaluated on subjects who had total cholesterol level 200-239 mg/dL and LDL cholesterol level 100-159 mg/dL. In this study, a randomized, placebo-controlled, double-blind study which consisted of 4 weeks run-in period and 8 weeks treatment period was performed.	Placebo	NutraforChol® effectively decreased total cholesterol (-15.9 %) and LDL level (-19.9 %) after two weeks consumption. The total cholesterol and LDL reduction were maintained during 8 weeks study period. At study termination (week 8), there was a significant difference between total cholesterol level of NutraforChol® treated group (173.5 ± 21.7 mg/dL) and placebo-treated group (204.5 ± 22.8 mg/dL) (p < 0.05).	Thus, NutraforChol® may be considered as a complementary or alternative safe nutraceuticals for the treatment of mild dyslipidemic subjects.	In addition, there was a significant difference between LDL level at week 8 in NutraforChol® group (115.5 ± 22.2 mg/dL) and placebo-treated group (145.1 ± 23.7 mg/dL) (p < 0.05).	https://pubmed.ncbi.nlm.nih.gov/31987238/	Iskandar, I., Harahap, Y., Wijayanti, T. R., Sandra, M., Prasaja, B., & Cahyaningsih, P. (2020). Efficacy and tolerability of a nutraceutical combination of red yeast rice, guggulipid, and chromium picolinate evaluated in a randomized, placebo-controlled, double-blind study. Complementary Therapies in Medicine, 48. https://doi.org/10.1016/J.CTIM.2019.102282	Yes
16	probiotic Bifidobacterium longum BB536 and red yeast rice extract	2019	Nutraceutical approach for the management of cardiovascular risk - a combination containing the probiotic Bifidobacterium longum BB536 and red yeast rice extract: results from a randomized, double-blind, placebo-controlled study	Randomized, double-blind, placebo-controlled study	A 12-week randomized, parallel, double-blind, placebo-controlled study. Thirty-three subjects (18-70 years) in primary CV prevention and low CV risk (SCORE: 0-1% in 24 and 2-4% in 9 subjects; LDL-C: 130-200 mg/dL) were randomly allocated to either nutraceutical (N = 16) or placebo (N = 17).	Placebo	Twelve-week treatment with the nutraceutical combination, compared to placebo, significantly reduced TC (- 16.7%), LDL-C (- 25.7%), non-HDL-C (- 24%) (all p < 0.0001), apoB (- 17%, p = 0.003).	A 12-week treatment with a nutraceutical combination containing the probiotic Bifidobacterium longum BB536 and RYR extract significantly improved the atherogenic lipid profile and was well tolerated by low CV risk subjects.	No adverse effects and a 97% compliance were observed.	https://pubmed.ncbi.nlm.nih.gov/30795775/	Ruscica, M., Pavanello, C., Gandini, S., Macchi, C., Botta, M., Dall'Orto, D., del Puppo, M., Bertolotti, M., Bosisio, R., Mombelli, G., Sirtori, C. R., Calabresi, L., & Magni, P. (2019). Nutraceutical approach for the management of cardiovascular risk - a combination containing the probiotic Bifidobacterium longum BB536 and red yeast rice extract: results from a randomized, double-blind, placebo-controlled study. Nutrition Journal, 18(1). https://doi.org/10.1186/S12937-019-0438-2	Yes
17	Armolipid Plus (AP) (berberine 500 mg, red yest rice, monacolin K 3 mg and policosanol 10 mg)	2019	Efficacy of a nutraceutical combination on lipid metabolism in patients with metabolic syndrome: a multicenter, double blind, randomized, placebo controlled trial	A multicenter, double blind, randomized, placebo controlled trial	One hundred and fifty eight patients, aged between 28 and 76 years old, were enrolled and randomized to receive either one tablet of AP or placebo (PL) once daily for 24 weeks.	Placebo	After 24 weeks of treatment, the analysis performed on 141 subjects (71 in AP arm and 70 in PL arm), showed a significant improvement of lipid profile in the AP group, with reduction in tot-C (- 13.2 mg/dl), LDL-C (- 13.9 mg/dl) and NHDL-C (- 15.3 mg/dl) and increase in HDL-C (+ 2.0 mg/dl). These changes were equally significant compared with placebo	The results of this study, applicable to a specific local population show that, in a population of subjects affected by MetS, treatment with AP improves the lipid profile and the most atherogenic factors, thus suggesting a reduction in the risk of development and progression of atherosclerosis, particularly in subjects with high atherogenic risk, due to the presence of sdLDL-C.	Although no significant difference was observed between the two arms in the reduction of HDL-C nevertheless it increased significantly in the AP group (AP + 2 mg/dL p < 0.05, PL 0.13 mg/dL).	https://pubmed.ncbi.nlm.nih.gov/30885221/	Galletti, F., Fazio, V., Gentile, M., Schillaci, G., Pucci, G., Battista, F., Mercurio, V., Bosso, G., Bonaduce, D., Brambilla, N., Vitalini, C., D'Amato, M., & Giacovelli, G. (2019). Efficacy of a nutraceutical combination on lipid metabolism in patients with metabolic syndrome: a multicenter, double blind, randomized, placebo controlled trial. Lipids in Health and Disease, 18(1). https://doi.org/10.1186/S12944-019-1002-Y	Yes
18	inulin and phytosterols	2015	Effect of phytosterols and inulin-enriched soymilk on LDL-cholesterol in Thai subjects: a double-blinded randomized controlled trial	Double-blinded randomized controlled trial	Two hundred and forty subjects who were 18 years old or older and had a baseline LDL-c of 130 mg/dl or higher were enrolled into the double-blinded randomized controlled trial study. Subjects were randomly assigned into the study group that received 2 g/day of phytosterols and 10 g/day of inulin-enriched soymilk or into the control group that received standard soymilk. The lipid profile was measured every 2 weeks for 8 weeks.	Control	At the end of the study, the median LDL-c levels decreased significantly from 165 (132, 254) mg/dl to 150 (105, 263) mg/dl in the study group (p < 0.001) and from 165 (130, 243) mg/dl to 159 (89, 277) mg/dl in the control group (p = 0.014). The LDL-c reduction was significantly better in the study group (-10.03%, (-37.07, 36.00) vs -1.31% (-53.40, 89.73), p < 0.001). TC also reduced significantly by 6.60% in the study group while it reduced only by 1.76% in the control group (p < 0.001).	Daily consumption of soymilk containing 2 g of phytosterols and 10 g of inulin reduced TC and LDL-c better than standard soymilk.	It had no effect on TG and HDL-c levels compared to standard soymilk.	https://pubmed.ncbi.nlm.nih.gov/26553006/	Kietsiriroje, N., Kwankaew, J., Kitpakornsanti, S., & Leelawattana, R. (2015). Effect of phytosterols and inulin-enriched soymilk on LDL-cholesterol in Thai subjects: a double-blinded randomized controlled trial. Lipids in Health and Disease, 14(1). https://doi.org/10.1186/S12944-015-0149-4	No
19	Inulin, Pomegranate extract	2017	Cholesterol-lowering effects of dietary pomegranate extract and inulin in mice fed an obesogenic diet	Animal study	Male C57BL/6 J mice were fed high-fat/high-sucrose [HF/HS (32% energy from fat, 25% energy from sucrose)] diets supplemented with PomX (0.25%) and inulin (9%) alone or in combination for 4 weeks.	Control	Feeding the HF/HS diet supplemented with PomX and inulin individually resulted in a significant decrease in serum TC compared HF/HS control.	inulin mainly targeted hepatic cholesterol de novo synthesis and fecal cholesterol and bile acid excretion involving changes in the metabolism of the intestinal microbiome.	Supplementation with PomX and inulin together resulted in lower hepatic and serum total cholesterol compared to individual treatments. PomX showed a trend to decrease liver triglyceride (TG) levels, while inulin or PomX-inulin combination had no effect on either serum or liver TG levels.	https://www.sciencedirect.com/science/article/pii/S0955286316308294	Yang, J., Zhang, S., Henning, S. M., Lee, R., Hsu, M., Grojean, E., Pisegna, R., Ly, A., Heber, D., & Li, Z. (2018). Cholesterol-lowering effects of dietary pomegranate extract and inulin in mice fed an obesogenic diet. Journal of Nutritional Biochemistry, 52, 62–69. https://doi.org/10.1016/J.JNUTBIO.2017.10.003	No
20	Artichoke and Bergamot	2021	Artichoke and Bergamot Phytosome Alliance: A Randomized Double Blind Clinical Trial in Mild Hypercholesterolemia	Randomized placebo-controlled trial.	600 mg of bergamot phytosome® (from Citrus Bergamia Risso) and 100 mg of artichoke leaf standardized dry extract (from Cynara cardunculus L.). Sixty overweight adults were randomized into two groups: 30 were supplemented and 30 received a placebo. The metabolic parameters and DXA body composition were evaluated at the start, after 30 and 60 days.	Placebo	Between the two groups, total and LDL cholesterol in the supplemented group (compared to placebo) showed significant decreases overtime.	In conclusion, the synergism between Citrus Bergamia polyphenols and Cynara cardunculus extracts may be an effective option and may potentially broaden the therapeutic role of botanicals in dyslipidemic patients.	A significant reduction of waist circumference and visceral adipose tissue (VAT) was recorded in the supplemented group (compared to placebo), even in subjects who did not follow a low-calorie diet.	https://pubmed.ncbi.nlm.nih.gov/35010984/	Riva, A., Petrangolini, G., Allegrini, P., Perna, S., Giacosa, A., Peroni, G., Faliva, M. A., Naso, M., & Rondanelli, M. (2021). Artichoke and Bergamot Phytosome Alliance: A Randomized Double Blind Clinical Trial in Mild Hypercholesterolemia. Nutrients, 14(1). https://doi.org/10.3390/NU14010108	Yes
21	Artichoke and bergamot	2022	Artichoke and bergamot extracts: a new opportunity for the management of dyslipidemia and related risk factors.	Review	this review aimed to describe the effects of artichoke and bergamot in modifying the lipid and inflammatory parameters described in in vitro, in vivo and clinical studies.	Not Applicable - NA	significant presence of polyphenols in their extracts, can exert this action associated with a number of other complementary inflammation and oxidation benefits.	The available data support the use of standardized compositions of artichoke and bergamot extracts, alone or in combination, in the treatment of mild to moderate dyslipidemia	significant presence of polyphenols in their extracts, can exert this action associated with a number of other complementary inflammation and oxidation benefits.	https://europepmc.org/article/med/35313442	Arnaboldi, L., Corsini, A., & Bellosta, S. (2022). Artichoke and bergamot extracts: a new opportunity for the management of dyslipidemia and related risk factors. Minerva Medica, 113(1), 141–157. https://doi.org/10.23736/S0026-4806.21.07950-7	No
22	lysine, vitamin B(6), and carnitine		Effect of lysine, vitamin B(6), and carnitine supplementation on the lipid profile of male patients with hypertriglyceridemia: a 12-week, open-label, randomized, placebo-controlled trial	Randomized, placebo-controlled clinical trial	This 12-week, randomized, placebo-controlled clinical trial. A total of 85 hypertriglyceridemic [TG> 150 mg/dL] male patients were randomized to 1 of 5 groups and given supplements of lysine (1 g/d), vitamin B(6) (50 mg/d), lysine (1 g/d) + vitamin B(6) (50 mg/d), carnitine (1 g/d), or placebo for 12 weeks. The lipid profile (TG, total cholesterol, LDL-C, and HDL-C) and fasting plasma glucose levels were assessed at baseline and at 6 and 12 weeks.	Placebo	Vitamin B(6) supplementation was associated with a significant reduction in total cholesterol and HDL-C of ~10%. In addition, plasma TG was reduced by 36.6 mg/dL at 6 weeks, whereas levels in the placebo group increased by 18 mg/dL	Vitamin B(6) supplementation in these male patients with hypertriglyceridemia reduced plasma total cholesterol and HDL-C concentrations.	No major changes in the lipid profile were observed in the lysine and carnitine groups or when lysine was added to vitamin B(6).	https://pubmed.ncbi.nlm.nih.gov/22818869/	Hlais, S., Reslan, D. R. A., Sarieddine, H. K., Nasreddine, L., Taan, G., Azar, S., & Obeid, O. A. (2012). Effect of lysine, vitamin B(6), and carnitine supplementation on the lipid profile of male patients with hypertriglyceridemia: a 12-week, open-label, randomized, placebo-controlled trial. Clinical Therapeutics, 34(8), 1674–1682. https://doi.org/10.1016/J.CLINTHERA.2012.06.019	No
23	omega-3 fatty acids and vitamin E	2015	A randomized-controlled clinical trial investigating the effect of omega-3 fatty acids and vitamin E co-supplementation on markers of insulin metabolism and lipid profiles in gestational diabetes	Randomized, double-blind, placebo-controlled clinical trial	60 patients with GDM. Patients were randomly allocated to take either 1000-mg omega-3 fatty acids from flaxseed oil plus 400-IU vitamin E supplements (n = 30) or placebo (n = 30) for 6 weeks. Fasting blood samples were obtained from at the beginning of the study and after 6-week intervention to quantify related variables.	Placebo	After 6 weeks of intervention, Changes in serum triglycerides (+10.8 ± 41.5 vs +34.2 ± 35.5 mg/dL, P = .02), VLDL-cholesterol (+2.1 ± 8.3 vs +6.8 ± 7.1 mg/dL, P = .02), low-density lipoprotein (LDL)-cholesterol (+11.6 ± 18.8 vs +1.7 ± 15.9 mg/dL, P = .03) and HDL-cholesterol concentrations (+1.9 ± 8.7 vs -2.4 ± 7.7 mg/dL, P = .04) were significantly different between the supplemented women and placebo group.	Overall, we demonstrated that omega-3 fatty acids and vitamin E co-supplementation in GDM women had beneficial effects on glucose homeostasis parameters, serum triglycerides, VLDL-cholesterol, and HDL-cholesterol concentrations, but it did not influence total-cholesterol and LDL-cholesterol levels.	However, after controlling for baseline total cholesterol levels, maternal age, and BMI at baseline, the changes in serum LDL-cholesterol concentrations were not significantly different between the 2 groups. We did not find any significant effect of joint omega-3 fatty acids and vitamin E supplementation on total cholesterol concentrations.	https://pubmed.ncbi.nlm.nih.gov/27055970/	Taghizadeh, M., Jamilian, M., Mazloomi, M., Sanami, M., & Asemi, Z. (2016). A randomized-controlled clinical trial investigating the effect of omega-3 fatty acids and vitamin E co-supplementation on markers of insulin metabolism and lipid profiles in gestational diabetes. Journal of Clinical Lipidology, 10(2), 386–393. https://doi.org/10.1016/J.JACL.2015.12.017	No
24	Magnesium and Vitamin E	2018	The effects of magnesium and vitamin E co-supplementation on parameters of glucose homeostasis and lipid profiles in patients with gestational diabetes	Randomized, double-blinded, placebo-controlled trial	60 subjects diagnosed with gestational diabetes (GDM) , aged 18-40 years. Subjects were randomly allocated into two groups to receive 250 mg/day magnesium oxide plus 400 IU/day vitamin E supplements or placebo (n = 30 each group) for 6 weeks. Participants' blood samples were taken to determine their metabolic profiles.	Placebo	magnesium plus vitamin E supplementation resulted in a significant reduction in serum triglycerides, VLDL, LDL and total-/HDL-cholesterol ratio compared with placebo. Magnesium and vitamin E co-supplementation did not affect HDL-cholesterol levels.	Overall, magnesium and vitamin E co-supplementation for 6 weeks in women with GDM significantly improved lipid profiles, except for HDL-cholesterol levels.	Magnesium and vitamin E co-supplementation did not affect HDL-cholesterol levels.	https://pubmed.ncbi.nlm.nih.gov/30025522/	Maktabi, M., Jamilian, M., Amirani, E., Chamani, M., & Asemi, Z. (2018). The effects of magnesium and vitamin E co-supplementation on parameters of glucose homeostasis and lipid profiles in patients with gestational diabetes. Lipids in Health and Disease, 17(1). https://doi.org/10.1186/S12944-018-0814-5	Yes

Table S2: Summary of articles containing Coenzyme Q10.

Co enzyme Q10

No	Ingredients	Year	Title	Type of study	Method/Design of study	Control / Placebo	Outcome	Interpretation	Comment	Available at	Reference	Scientific Evidence
1	Co enzyme Q10	2018	Coenzyme Q10 protects against hyperlipidemia-induced cardiac damage in apolipoprotein E-deficient mice	Animal study	Eight-week-old male – mice were randomly divided into four groups: mice fed a normal diet ; mice fed a normal diet + CoQ10 ; Apolipoprotein (ApoE−/−) E-deficient mice fed a high-fat diet, and ApoE−/− mice fed a high-fat diet + CoQ10. All groups were fed the different diets for 16 weeks.	Control	The metabolic parameters such as total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-c), and triglycerides (TG) levels were lower in ApoE−/− HD + CoQ10 mice than in ApoE−/− HD mice.	These results indicate that CoQ10 is a potential therapeutic target for cardiac damage caused by hyperlipidemia	CoQ10 contributes to the mitigation of hyperlipidaemic cardiac damage, findings provide new insights into the role of CoQ10 in hyperlipidemia-induced cardiac damage and raise the possibility of a novel therapeutic intervention for treatment of CVDs.	https://link.springer.com/content/pdf/10.1186/s12944-018-0928-9.pdf	Zhang, X., Liu, H., Hao, Y., Xu, L., Zhang, T., Liu, Y., Guo, L., Zhu, L., & Pei, Z. (2018). Coenzyme Q10 protects against hyperlipidemia-induced cardiac damage in apolipoprotein E-deficient mice. Lipids in Health and Disease, 17(1). https://doi.org/10.1186/s12944-018-0928-9	No
2	Co enzyme Q10	2020	The effects of coenzyme Q10 supplementation on lipid profiles among patients with coronary artery disease: a systematic review and meta-analysis of randomized controlled trials	Systematic review	a systematic review and meta-analysis of randomized controlled trials. A total of eight trials (267 participants in the intervention group and 259 in placebo group) were included in the current meta-analysis.	Not Applicable - NA	This meta-analysis demonstrated the promising effects of CoQ10 supplementation on lowering lipid levels among patients with CAD, though it did not affect triglycerides, LDL-cholesterol and Lp(a) levels.	CoQ10 supplementation significantly improved some of the parameters of lipid profile including total cholesterol and HDL-cholesterol levels in patients with CAD	CoQ10 deficiency usually occurs with aging and mayincrease the risk of CVD. Meta-analysis conducted byPirro et al. [18] showed that taking a nutraceutical com-bination of red yeast rice, berberine, policosanol, astax-anthin, CoQ10 and folic acid significantly reducedserum triglycerides, total-, LDL-and HDL-cholesterollevels.	https://lipidworld.biomedcentral.com/track/pdf/10.1186/s12944-018-0876-4.pdf	Jorat, M. V., Tabrizi, R., Mirhosseini, N., Lankarani, K. B., Akbari, M., Heydari, S. T., Mottaghi, R., & Asemi, Z. (2018). The effects of coenzyme Q10 supplementation on lipid profiles among patients with coronary artery disease: A systematic review and meta-analysis of randomized controlled trials. In Lipids in Health and Disease (Vol. 17, Issue 1). BioMed Central Ltd. https://doi.org/10.1186/s12944-018-0876-4	Yes
3	Co enzyme Q10, Vitamin C, monacolin K, and L-arginine.	2018	LDL-cholesterol lowering effect of a new dietary supplement: An open label, controlled, randomized, cross-over clinical trial in patients with mild-to-moderate hypercholesterolemia	Single center, controlled, randomized, open-label, cross-over clinical study	20 Caucasian outpatients aged 18–75 years with serum LDL-C between 130 and 180 mg/dL. Patients assumed two different dietary supplements (A and N) both containing monacolin K 10 mg for 8 weeks each, separated by a 4-week wash-out period.	Control	LDL-C decreased by 23.3% during treatment with N and by 25.6% during treatment with A . **Total-C** decreased significantly within each treatment period. **HDL-C** increase was negligible during **A** whereas it was significant during **N**. **TG** diminished markedly during **A** and notsignificantly during **N**. The difference between treatments was not statistically significant for all variables.	Our results confirm the clinically meaningful LDL-C lowering properties of **monacolin K**. At variance witha supplement already in the market (**N**), the novel association (**A**) of **monacolin K** with **L-arginine**, **coenzime Q10** and **ascorbic acid** also produces a significant reduction of triglycerides without significant effects on HDL.	Results confirm the clinically meaningful LDL-C lowering properties of monacolin K	https://pubmed.ncbi.nlm.nih.gov/29793488/	Magno, S., Ceccarini, G., Pelosini, C., Jaccheri, R., Vitti, J., Fierabracci, P., Salvetti, G., Airoldi, G., Minale, M., Saponati, G., & Santini, F. (2018). LDL-cholesterol lowering effect of a new dietary supplement: An open label, controlled, randomized, cross-over clinical trial in patients with mild-to-moderate hypercholesterolemia. Lipids in Health and Disease, 17(1). https://doi.org/10.1186/s12944-018-0775-8	Yes
4	Co enzyme Q10	2017	Effects of coenzyme Q10 supplementation on inflammatory markers: A systematic review and meta-analysis of randomized controlled trials	Systematic review	A systematic review and meta-analysis of **seventeen randomized controlled trials.** The aims of this meta-analysis is to evaluate the effects of coenzyme Q10 (CoQ10) supplementation on inflammatory mediators including C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) by analyzing published randomized controlled trials (RCTs).	Not Applicable - NA	CoQ10 supplementation significantly reduced the levels of circulating CRP , IL-6 and TNF-α.	meta-analysis of RCTs suggests significant lowering effects of CoQ10 on CRP, IL-6 and TNF-α.	However, results should be interpreted with caution because of the evidence of heterogeneity and limited number of studies.	https://www.sciencedirect.com/science/article/abs/pii/S1043661816312804?via%3Dihub	Fan, L., Feng, Y., Chen, G. C., Qin, L. Q., Fu, C. ling, & Chen, L. H. (2017). Effects of coenzyme Q10 supplementation on inflammatory markers: A systematic review and meta-analysis of randomized controlled trials. Pharmacological Research, 119, 128–136. https://doi.org/10.1016/J.PHRS.2017.01.032	Yes
5	Co enzyme Q10	2018	Treatment of coenzyme Q10 for 24 weeks improves lipid and glycemic profile in dyslipidemic individuals	Randomized, double-blinded, placebo-controlled trial	randomized, double-blinded, placebo-controlled trial, 101 dyslipidemic subjects without taking any hypoglycemic or hypolipidemic drugs were administrated to 120 mg CoQ10 or placebo daily for 24 weeks.	Placebo	Coenzyme Q10 treatment for 24 weeks reduced triglycerides to 12.6%, low-density lipoprotein cholesterol to 7.6% and increased ApoA-I to 7.7%.	The versatility and safety of CoQ10 makes it a potential candidate for the primary prevention of CVD.	Twenty-four-week treatment of CoQ10 ameliorates multiple CVD risk factors.	https://www.sciencedirect.com/science/article/abs/pii/S193328741730541X	Zhang, P., Yang, C., Guo, H., Wang, J., Lin, S., Li, H., Yang, Y., & Ling, W. (2018). Treatment of coenzyme Q10 for 24 weeks improves lipid and glycemic profile in dyslipidemic individuals. Journal of Clinical Lipidology, 12(2), 417-427.e5. https://doi.org/10.1016/J.JACL.2017.12.006	Yes
6	Co enzyme Q10 and Omega-3	2017	Addition of omega-3 fatty acid and coenzyme Q10 to statin therapy in patients with combined dyslipidemia	Pilot randomized double-blind trial	105 subjects who met the criteria of combined dislipidemia and elevated TAG levels were randomly divided into three groups. In the control group, unaltered statin therapy was indicated. In the second and third groups, omega-3 PUFA 2.52 g/day (Zennix fa Pleuran) and omega-3 PUFA 2.52 g+CoQ10 200 mg/day (Pharma Nord ApS) were added, res//. At the end of the 3-month period (±1 week), all patients were evaluated.	Control	Significant reduction of hepatic enzymes activity, systolic blood preasure, inflammatory markers and TAG levels were detected in both groups in comparison to the control group.	Coenzyme Q10 addition significantly reduced most of the abovementioned parameters (systolic blood preasure, total cholesterol, LDL, hsCRP, IL-6, SOD) in comparison with the statin+omega-3 PUFA group.	The results of this pilot study suggest the possible beneficial effects of triple combination on the lipid and non-lipid parameters related to atherogenesis and side effects of statin treatment.	https://pubmed.ncbi.nlm.nih.gov/28541926/	Tóth, Š. Šajty, M., Pekárová, T., Mughees, A., Štefanič, P., Katz, M., Spišáková, K., Pella, J., & Pella, D. (2017). Addition of omega-3 fatty acid and coenzyme Q10 to statin therapy in patients with combined dyslipidemia. Journal of Basic and Clinical Physiology and Pharmacology, 28(4), 327–336. https://doi.org/doi:10.1515/jbcpp-2016-0149	Yes
7	Co enzyme Q10	2017	Treatment of coenzyme Q10 for 24 weeks improves lipid and glycemic profile in dyslipidemic individuals	Randomized, double-blinded, placebo-controlled trial,	101 dyslipidemic subjects without taking any hypoglycemic or hypolipidemic drugs were administrated to 120 mg CoQ10 or placebo daily for 24 weeks. Anthropometric parameters, lipid and glycemic profile, biomarkers of inflammation, and antioxidant capacity were evaluated before and after 12 and 24 weeks of intervention.	Placebo	All 101 subjects were included in the analysis. On the 12th week, compared to placebo, CoQ10 supplementation decreased systolic (P = .010) and diastolic pressure (P = .001) and increased serum total antioxidant capacity (TAC; P = .003). On the 24th week, compared to placebo, CoQ10 supplementation further lowered blood pressure and TAC, reduced triglyceride (P = .020) and low-density lipoprotein cholesterol (P = .016).	Twenty-four-week treatment of CoQ10 ameliorates multiple CVD risk factors. The versatility and safety of CoQ10 makes it a potential candidate for the primary prevention of CVD.	led to significant decrease of non-high-density lipoprotein cholesterol in CoQ10 group compared to placebo (P = .031).	https://pubmed.ncbi.nlm.nih.gov/29454678/	Zhang, P., Yang, C., Guo, H., Wang, J., Lin, S., Li, H., Yang, Y., & Ling, W. (2018). Treatment of coenzyme Q10 for 24 weeks improves lipid and glycemic profile in dyslipidemic individuals. Journal of Clinical Lipidology, 12(2), 417-427.e5. https://doi.org/10.1016/J.JACL.2017.12.006	Yes
8	Co enzyme Q10	2020	Ubiquinol Ameliorates Endothelial Dysfunction in Subjects with Mild-to-Moderate Dyslipidemia: A Randomized Clinical Trial	Randomized, double-blind, single-center trial	Fifty-one subjects with low-density lipoprotein (LDL) cholesterol levels of 130-200 mg/dL, not taking statins or other lipid lowering treatments, moderate (2.5%-6.0%) endothelial dysfunction as measured by flow-mediated dilation (FMD) of the brachial artery, and no clinical signs of cardiovascular disease were randomized to receive either ubiquinol (200 or 100 mg/day) or placebo for 8 weeks.	Placebo	48 participants who completed the study demonstrated a significantly increased FMD in both treated groups compared with the placebo group (200 mg/day, +1.28% ± 0.90%; 100 mg/day, +1.34% ± 1.44%; p < 0.001) and a marked increase in plasma CoQ10, either total (p < 0.001) and reduced (p < 0.001). Serum NOx increased significantly and dose-dependently in all treated subjects (p = 0.016), while LDL oxidation lag time improved significantly in those receiving 200 mg/day (p = 0.017). Ubiquinol significantly ameliorated dyslipidemia-related endothelial dysfunction.	This effect was strongly related to increased nitric oxide bioavailability and was partly mediated by enhanced LDL antioxidant protection.	N/A	https://pubmed.ncbi.nlm.nih.gov/32326664/	Sabbatinelli, J., Orlando, P., Galeazzi, R., Silvestri, S., Cirilli, I., Marcheggiani, F., Dludla, P. v., Giuliani, A., Bonfigli, A. R., Mazzanti, L., Olivieri, F., Antonicelli, R., & Tiano, L. (2020). Ubiquinol Ameliorates Endothelial Dysfunction in Subjects with Mild-to-Moderate Dyslipidemia: A Randomized Clinical Trial. Nutrients, 12(4). https://doi.org/10.3390/NU12041098	No
9	Co enzyme Q10 and fatty acid	2017	Addition of omega-3 fatty acid and coenzyme Q10 to statin therapy in patients with combined dyslipidemia	Pilot randomized double-blind trial	105 subjects who met the criteria of combined dislipidemia and elevated TAG levels were randomly divided into three groups. In the control group, unaltered statin therapy was indicated. In the second and third groups, omega-3 PUFA 2.52 g/day (Zennix fa Pleuran) and omega-3 PUFA 2.52 g+CoQ10 200 mg/day (Pharma Nord ApS) were added, res//. At the end of the 3-month period (±1 week), all patients were evaluated.	Control	Coenzyme Q10 addition significantly reduced most of the abovementioned parameters (systolic blood preasure, total cholesterol, LDL, hsCRP, IL-6, SOD) in comparison with the statin+omega-3 PUFA group.	The results of this pilot study suggest the possible beneficial effects of triple combination on the lipid and non-lipid parameters related to atherogenesis and side effects of statin treatment.	The intensity of statin adverse effects were significantly reduced in the group with the addition of CoQ10.	https://pubmed.ncbi.nlm.nih.gov/28541926/	Tóth, Š. Šajty, M., Pekárová, T., Mughees, A., Štefanič, P., Katz, M., Spišáková, K., Pella, J., & Pella, D. (2017). Addition of omega-3 fatty acid and coenzyme Q10 to statin therapy in patients with combined dyslipidemia. Journal of Basic and Clinical Physiology and Pharmacology, 28(4), 327–336. https://doi.org/10.1515/JBCPP-2016-0149	No
10	Co enzyme Q10	2018	Comparison of efficacy and safety of combination therapy with statins and omega-3 fatty acids versus statin monotherapy in patients with dyslipidemia: A systematic review and meta-analysis	Systematic review and meta-analysis	We performed a systematic review and meta-analysis of published data to compare the safety and efficacy of combination therapy with statins and omega-3 fatty acids versus statin monotherapy in patients with dyslipidemia. Six articles were assessed in the present meta-analysis (quantitative assessment) and qualitative assessment.	Not Applicable - NA	the combination treatment afforded a significantly greater reduction in total cholesterol/high-density lipoprotein cholesterol than statin alone did. However, there was no significant difference in low-density lipoprotein (LDL) cholesterol between the 2 groups. Combination therapy with statins and omega-3 fatty acids was generally more effective on lipid concentration than statin monotherapy.	We suggest that combination therapy with statins and omega-3 fatty acids enhances lipid profile, except LDL cholesterol, compared with statin monotherapy.	Nevertheless, statin and omega-3 fatty acid combination should be cautiously recommended, taking into account the clinical importance of LDL cholesterol and safety issues associated with their concomitant use.	https://pubmed.ncbi.nlm.nih.gov/30558030/	Choi, H. D., & Chae, S. M. (2018). Comparison of efficacy and safety of combination therapy with statins and omega-3 fatty acids versus statin monotherapy in patients with dyslipidemia: A systematic review and meta-analysis. Medicine, 97(50). https://doi.org/10.1097/MD.0000000000013593	Yes

Table S3: Summary of articles containing vitamins.

Vitamin												
No	**Ingredients**	**Year**	**Title**	**Type of study**	**Method/Design of study**	**Control / Placebo**	**Outcome**	**Interpretation**	**Comment**	**Available at**	**Reference**	**Scientific Evidence**
1	Vitamin D	2016	Vitamin D Supplementation and High-Density Lipoprotein Cholesterol: A Study in Healthy School Children	Controlled clinical trial	47 healthy children (23 boys) aged 10 - 14 years, students of Birjand (Iran) elementary schools, were selected and randomly divided into two groups. The study group received a vitamin D supplement (1000 mg capsule) daily for one month, and placebo tablets were prescribed to the controls. Before and after the treatment course, the serum HDL-C and 25-hydroxy vitamin D levels of both groups were measured.	Placebo	Forty children completed the study. The mean serum levels of both HDL-C and vitamin D showed a significant rise following the treatment in the study group, whereas both variables decreased slightly in the control group. There was no statistically significant difference in the mean serum levels of HDL-C and vitamin D between the two groups after the intervention	Vitamin D supplements seem to have a positive impact on serum HDL-C levels and may be effective in reducing the risk of cardiovascular diseases in the long term.	Despite the small sample size, the present study provides consistent support for a relationship between vitamin D and HDL-C, indicating that vitamin D supplementation results in increased blood levels of HDL and that it can be regarded as a protective factor to reduce the risk of cardiovascular disease.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5045666/pdf/ijp-26-04-3311.pdf	Tavakoli, F., Namakin, K., & Zardast, M. (2016). Vitamin D supplementation and high-density lipoprotein cholesterol: A study in healthy school children. Iranian Journal of Pediatrics, 26(4). https://doi.org/10.5812/ijp.3311	No
2	Vitamin D	2021	Effects of Calcium and Vitamin D Co-supplementation on the Lipid Profile: A Systematic Review and Meta-analysis	A Systematic Review and Meta-analysis	Controlled Trials, and clinical trial registry databases was conducted to identify placebo-controlled RCTs that were published through September 2020 and that evaluated the impact of calcium and vitamin D co-supplementation on total cholesterol (TC), triglycerides (TGs), low- and very-low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol (HDL-C). Standardized mean differences (SMDs) were pooled using random-effects meta-analysis models.	not applicable	Thirteen studies in a total of 2304 participants met the inclusion criteria. Calcium and vitamin D co-supplementation was associated with significant reductions in both TC and TGs, and with a significant increase in HDL-C. However, calcium and vitamin D co-supplementation were not found to be associated with significantly decreased low-density lipoprotein cholesterol	The findings from the present systematic review and meta-analysis suggest that calcium and vitamin D co-supplementation has a beneficial effect on TC, TG, and HDL-C.	Larger-scale, well-designed RCTs are needed to clarify the effect of calcium and vitamin D co-supplementation on all lipid-profile components.	https://www.sciencedirect.com/science/article/abs/pii/S0149291821002605	Morvaridzadeh, M., Agah, S., Alibakhshi, P., Heydari, H., Hoseini, A. S., Palmowski, A., Toupchian, O., Abdollahi, S., Rezamand, G., & Heshmati, J. (2021). Effects of Calcium and Vitamin D Co-supplementation on the Lipid Profile: A Systematic Review and Meta-analysis. Clinical Therapeutics, 43(9), 274–296. https://doi.org/10.1016/J.CLINTHERA.2021.07.018	Yes
3	Vitamin D	2018	Vitamin D supplementation and lipoprotein metabolism: A randomized controlled trial	Post hoc analysis of the single-center, double-blind, randomized, placebo-controlled Styrian Vitamin D Hypertension Trial	Vitamin D supplementation significantly increased total cholesterol, triglycerides, very-low-density lipoprotein (VLDL) triglycerides, low-density lipoprotein (LDL) triglycerides, high-density lipoprotein (HDL) triglycerides, There was a nonsignificant increase in LDL cholesterol.	Placebo	Vitamin D supplementation significantly increased total cholesterol, triglycerides, very-low-density lipoprotein (VLDL) triglycerides, low-density lipoprotein (LDL) triglycerides, high-density lipoprotein (HDL) triglycerides, There was a nonsignificant increase in LDL cholesterol.	The effects of vitamin D on lipid metabolism are potentially unfavorable.	They require further investigation in view of the wide use of vitamin D testing and treatment.	https://www.sciencedirect.com/science/article/abs/pii/S1933287417307277	Schwetz, V., Scharnagl, H., Trummer, C., Stojakovic, T., Pandis, M., Grübler, M. R., Verheyen, N., Gaksch, M., Zittermann, A., Aberer, F., Lerchbaum, E., Obermayer-Pietsch, B., Pieber, T. R., März, W., Tomaschitz, A., & Pilz, S. (2018). Vitamin D Supplementation and lipoprotein metabolism: A randomized controlled trial. Journal of Clinical Lipidology, 12(3), 588–596.e4. https://doi.org/10.1016/J.JACL.2018.03.079	Yes
4	Vitamin D	2021	Effect of vitamin D supplementation on markers of cardiometabolic risk in children and adolescents: A meta-analysis of randomized clinical trials	A meta-analysis of randomized clinical trials	Eligible randomized controlled trials (RCTs) were identified by searching PubMed, EMBASE and Web of Science. The results of this study are synthetized and reported in accordance with the PRISMA statement. GRADE system was used to assess the certainty of evidence. A total of 9 RCTs were identified and included in the meta-analysis.	not applicable	However, vitamin D supplementation showed a beneficial effect on fasting glucose (MD, −1.54 mg/dl, 95% CI -2.98 to −0.10) and TG (MD, −24.76 mg/dl, 95% CI -37.66 to −11.86) in the sub-group analysis of total vitamin D supplementation ≥ 200,000 IU.	Vitamin D supplementation appeared to have a beneficial effect on reducing fasting glucose and TG level when total vitamin D supplementation ≥200,000 IU but not HDL-C, LDL-C TC, blood pressure and waist circumferences levels in children and adolescents. Further studies are needed to address this issue.	When total vitamin D supplementation ≥200,000 IU, it reduces TG level. Vitamin D supplementation does not affect HDL-C, LDL-C or TC. Vitamin D supplementation does not affect BP and waist circumferences and BMI.	https://www.sciencedirect.com/science/article/pii/S0939475321001290	Cai, B., Luo, X., Zhang, P., Luan, Y., Cai, X., & He, X. (2021). Effect of vitamin D supplementation on markers of cardiometabolic risk in children and adolescents: A meta-analysis of randomized clinical trials. Nutrition, Metabolism and Cardiovascular Diseases, 31(10), 2800–2814. https://doi.org/10.1016/J.NUMECD.2021.06.013	No
5	Vitamin D	2021	Vitamin D supplementation reduces serum lipids of children with hypertriacylglycerolemia: A randomized, triple-masked, placebo-controlled crossover trial	A randomized, triple-masked, placebo-controlled crossover trial	44 Brazilian children with hypertriacylglycerolemia, age 4 to 11 y. The sample included eutrophic and overweight/obese children according to body mass index for age, with sufficient and insufficient vitamin D basal levels. The intervention lasted 34 wk, with two periods of 12 wk each separated by a 10-wk washout. The two groups, supplemented and placebo, received five drops of cholecalciferol (equivalent to 1000 international unit/d) and five drops of sunflower oil, respectively, daily for 12 wk.	Placebo	There was a reduction in serum total cholesterol (P < 0.001), low-density lipoprotein cholesterol (P < 0.001), nonhigh-density lipoprotein cholesterol (P < 0.001), total cholesterol/high-density lipoprotein cholesterol (P = 0.001), and low/high-density lipoprotein cholesterol ratios (P < 0.001) in the supplemented group compared with the placebo group.	Cholecalciferol supplementation improved the lipid profile of children with hypertriacylglycerolemia without altering body composition.	N/A	https://www.sciencedirect.com/science/article/abs/pii/S0899900720721001581	Alves, A. G. P., Cruvinel, B. A. C., Schincaglia, R. M., Godoi, L. S., & Silva, M. S. (2021). Vitamin D supplementation reduces serum lipids of children with hypertriacylglycerolemia: A randomized, triple-masked, placebo-controlled crossover trial. Nutrition, 89, 111296. https://doi.org/10.1016/J.NUT.2021.111296	Yes
6	Vitamin D	2022	Vitamin D Supplementation Improves Fasting Insulin Levels and HDL Cholesterol in Infertile Men	A single-center, double-blinded, randomized clinical trial	A total of 307 infertile men were randomly assigned (1:1) to a single dose of 300 000 IU cholecalciferol followed by 1400 IU cholecalciferol + 500 mg of calcium daily (n = 151) or placebo (n = 156) for 150 days.	Placebo	men in the vitamin D group had higher high-density lipoprotein (HDL) cholesterol levels (1.38 vs 1.32 mmol/L, P = .008) compared with the placebo group.	High-dose vitamin D supplementation has beneficial effects on glucose homeostasis and HDL cholesterol levels in infertile men.	At the end of the trial, men receiving vitamin D supplementation had 13% lower fasting serum insulin concentrations compared with the placebo-treated group (65 vs 74 pmol/L, P = .018) and 19% lower HOMA-IR (2.2 vs 2.7, P = .025).	https://pubmed.ncbi.nlm.nih.gov/34508607/	Holt, R., Petersen, J. H., Dinsdale, E., Knop, F. K., Juul, A., Jørgensen, N., & Blomberg Jensen, M. (2022). Vitamin D Supplementation Improves Fasting Insulin Levels and HDL Cholesterol in Infertile Men. The Journal of Clinical Endocrinology and Metabolism, 107(1), 98–108. https://doi.org/10.1210/CLINEM/DGAB667	No
7	Vitamin D	2015	Vitamin D Protects Against Atherosclerosis via Regulation of Cholesterol Efflux and Macrophage Polarization in Hypercholesterolemic Swine	Animal study	placebo-controlled trial, Yucatan microswine were fed with Vitamin D-deficient (0 IU/d), VD-sufficient (1000 IU/d), or Vitamin D-supplemented (3000 IU/d) high-cholesterol diet for 48 weeks. Serum lipids and 25(OH)-cholecalciferol levels were measured biweekly	CONTROL	Vitamin D protects against atherosclerosis in hypercholesterolemic swine via controlling cholesterol efflux and macrophage polarization via increased CYP27A1 activation.	VD deficiency exacerbates the lipid accumulation and atherosclerosis in hypercholesterolemic microswine. clinical studies suggest that Vitamin D deficiency is related to a higher risk for cardiovascular disease,	the exact role of Vitamin D in the progression of cardiovascular diseases has not been well defined	https://www.ahajournals.org/doi/full/10.1161/ATVBAHA.115.306132	Yin, K., You, Y., Swier, V., Tang, L., Radwan, M. M., Pandya, A. N., & Agrawal, D. K. (2015). Vitamin D Protects Against Atherosclerosis via Regulation of Cholesterol Efflux and Macrophage Polarization in Hypercholesterolemic Swine. Arteriosclerosis, Thrombosis, and Vascular Biology, 35(11), 2432–2442. https://doi.org/10.1161/ATVBAHA.115.306132	No
8	Vitamin D	2018	Lower Vitamin D intake is associated with low hdl cholesterol and Vitamin D insufficiency/deficiency in brazilian children	A cross-sectional study carried out with a representative sample.	378 children 8–9-year-old age group. Bloodwas collected after 12 h of fasting. Laboratory tests were performed to determinetotal cholesterol, HDL cholesterol (HDL-C), LDL cholesterol, TAG, apoB, apoA1,25-hydroxyvitamin D and parathyroid hormone. Dietary intake was evaluated by a24 h recall.	CONTROL	study has found that Brazilian children have a high prevalence of inadequate vitamin D intake, dyslipidaemia and 25(OH)D insufficiency/deficiency.	The inadequate vitamin D intake was associated with higher prevalence of low HDL-C and vitamin D insufficiency/ deficiency	it is important to develop specific actions in food and nutritional education as well asprogrammes that stimulate and facilitate access to vitamin D food sources,	https://www.cambridge.org/core/journals/public-health-nutrition/article/lower-vitamin-d-intake-is-associated-with-low-hdl-cholesterol-and-vitamin-d-insufficiencydeficiency-in-brazilian-children/BD79973DA4ECE61D8ED6347F99BF2320	de Santis Filgueiras, M., Suhett, L. G., Silva, M. A., Rocha, N. P., & de Novaes, J. F. (2018). Lower Vitamin D intake is associated with low hdl cholesterol and Vitamin D insufficiency/deficiency in brazilian children. Public Health Nutrition, 21(11), 2004–2012. https://doi.org/10.1017/S1368980018000204	No
9	Vitamin C	2021	Red Dragon Fruit (Hylocereus Polyrhizus) to Reduce Cholesterol Level in People With Excessive Nutritional Status	Experimental approach with a pretest and post-test control group design	The sample consisted of 2 groups, namely the control group and the intervention group, with 50 respondents in each group. The sample was taken using purposive sampling. The intervention group got red dragon fruit juice for seven days. Blood cholesterol levels are measured by laboratory tested using intravenous blood.	CONTROL	The difference mean posttest-pretest control group and intervention groups were 13.56 mmHg and -13.06 mmHg.	The results showed that red dragon fruit effectively reduced total cholesterol levels in people	This study's results can further increase the intake of healthy nutrients from fruit to keep cholesterol levels regular.	https://www.researchgate.net/publication/354401954_Red_Dragon_Fruit_Hylocereus_Polyrhizus_to_Reduce_Cholesterol_Level_in_People_With_Excessive_Nutritional_Status	Fadiliah, S., Sucipto, A., Judha, M., Dede, C., Nekada, Y., Amestiasih, T., Mindarsih, E. & Pramana, C. (2021). Red Dragon Fruit (Hylocereus Polyrhizus) to Reduce Cholesterol Level in People With Excessive Nutritional Status Herbal Therapies to Prevent Diabetes Mellitus View project Obstetric Gynecology View project Red Dragon Fruit (Hylocereus Polyrhizus) to Reduce Cholesterol Level in People With Excessive Nutritional Status. In Article in Journal of Forensic Medicine and Toxicology (Vol. 15, Issue 4). https://www.researchgate.net/publication/354401954	No
10	Vitamin C	2008	Vitamin C supplementation lowers serum low-density lipoprotein cholesterol and triglycerides: a meta-analysis of 13 randomized controlled trials	Meta-analysis used a random-effects model	Thirteen randomized controlled trials published between 1970 and June 2007 were identified. From the 13 trials, 14 separate group populationswith hypercholesterolemia and who were supplemented with at least 500 mg/d of vitamin C forbetween 3 and 24 weeks were entered into the meta-analysis.	CONTROL	The pooled estimate of effect for vitamin C supplementation on LDL and HDLcholesterol was−7.9 mg/dL and1.1mg/dL, respectively. The pooled estimate of effect for vitamin Csupplementation on triglycerides was−20.1 mg/dL.	Supplementation with at least 500 mg/d of vitamin C, for a minimum of 4 weeks, can result in a significant decrease in serum LDL cholesterol and triglyceride concentrations	n this current meta-analysis, vitamin C supplemen-tation provided a significant reduction in both LDLcholesterol and triglycerides, but failed to provide asignificant increase in HDL cholesterol	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2682928/	McRae, M. P. (2008). Vitamin C supplementation lowers serum low-density lipoprotein cholesterol and triglycerides: a meta-analysis of 13 randomized controlled trials. Journal of Chiropractic Medicine, 7(2), 48–58. https://doi.org/10.1016/J.JCME.2008.01.002	Yes
11	Vitamin C & E	2016	Vitamin E (α-Tocopherol) and Vitamin C (Ascorbic Acid) Supplementation on Cholesterol and Triglyceride Blood Profile of Male Native Muscovy	Animal study	Eighty four muscovy duck were rationed to seven (7) treatments	CONTROL	vitamin E and vitamin C supplementation decreased blood cholesterol level.	Result showed that treatments significantly affected blood cholesterol level but did not significantly affect HDL, LDL and Triglyceride levels of muscovy blood.	In male muscovy, HDL was increased with Vitamin C and E supplementation.	http://medpub.litbang.pertanian.go.id/index.php/proceedings/article/view/1502/1376	Tugiyanti, E., Zuprizal, Z., & Rusman, R. (2016). Vitamin E (α-Tocopherol) and Vitamin C (Ascorbic Acid) Supplementation on Cholesterol and Triglyceride Blood Profile of Male Native Muscovy. 370–377. https://doi.org/10.14334/proc.intsem.ipvt-2016-p.370-377	No
12	Vitamin C	2015	Beetroot Juice Supplementation Increases High Density Lipoprotein-Cholesterol and Reduces Oxidative Stress in Physically Active Individuals	Controlled clinical trial	A group of randomly selected 30 infantry soldiers participated in the study. participants were supplemented with 400ml beetroot juice (consumed twice daily) for 15 days. Body composition of participants, at baseline and after 15 days of supplementation, was analyzed .	CONTROL	Beetroot juice supplementation beneficially influenced the lipid profile by significantly increasing the levels of high-density lipoprotein cholesterol (HDL-C) from 42.9 ± 8.3 mg/dl to 50.2 ± 9.8 mg/dl and decreasing low-density lipoprotein cholesterol (LDL-C) from 129.7 ± 82.3 mg/dl to 119.5 ± 79.2 mg/dl	Beetroot juice consumption improves plasma lipid profile. A significant increase in plasma total antioxidant capacity and vitamin C levels was observed after beetroot juice intake for 15 days.	Beetroot juice consumption improves plasma lipid profile and antioxidant status, encouraging further evaluation on a population with higher cardiovascular disease risk.	https://web.archive.org/web/20200307024503id_/https://www.lifesciencesglobal.com/media/zj_fileseller/files/JPANSV5N3A2-Singh.pdf	Singh, A., Kumar Verma, S., Singh, V. K., Nanjappa, C., Roopa, N., Raju, P. S., & Singh, S. N. (2015). Beetroot Juice Supplementation Increases High Density Lipoprotein-Cholesterol and Reduces Oxidative Stress in Physically Active Individuals. Journal of Pharmacy and Nutrition Sciences, 5, 179–185. https://web.archive.org/web/20200307024503id_/https://www.lifesciencesglobal.com/media/zj_fileseller/files/JPANSV5N3A2-Singh.pdf	No

13	Vitamin E and Omega 3	2019	Effect of Omega-3 and vitamin E co-supplementation on serum lipids concentrations in overweight patients with metabolic disorders: A systematic review and meta-analysis of randomized controlled trials	A systematic review and meta-analysis of randomized controlled trials	A systematic search was performed to find the related articles, up to April, 2019. There was no language and time limitation. Meta-analyses were carried out using both the random and fixed effects model where appropriate, and I2 index was used to evaluate the heterogeneity.	not applicable	Search yielded 1236 publications. Five RCTs with 254 patients were eligible. Results of the meta-analysis indicated that omega-3 and vitamin E co-supplementation significantly reduced the serum concentrations of TG and LDL, whereas, it had no significant effect on the serum levels of TC and HDL in overweight patients with MS.	Present systematic review and meta-analysis revealed that omega-3 and vitamin E co-supplementation have beneficial effects on lipid profile of overweight patients with MS. It significantly reduced the serum levels of TG and LDL in such patients.	N/A	https://www.sciencedirect.com/science/article/abs/pii/S1871402119303844	Asbaghi, O., Choghakhori, R., & Abbasnezhad, A. (2019). Effect of Omega-3 and vitamin E co-supplementation on serum lipids concentrations in overweight patients with metabolic disorders: A systematic review and meta-analysis of randomized controlled trials. Diabetes & Metabolic Syndrome: Clinical Research & Reviews, 13(4), 2525–2531. https://doi.org/10.1016/J.DSX.2019.07.001	Yes
14	Vitamin E	2016	Dietary vitamin E supplementation on cholesterol, vitamin E content, and fatty acid profile in chicken muscles	Animal study	Chickens (420 cocks) were randomlydivided into two feeding groups (210 birds each). The control group wasfed with standard diet containing 44 mg kg−1 of vitamin E, whereas the experimental group was supplemented with extra 200 mg kg−1of vitamin E.	CONTROL	The dietary addition of vitamin E caused a significant increase in its content in the muscles, witha higher value noted in the leg muscles.	Meat of chickens fed with the higher dose of vitamin E was also character-ized by a lower cholesterol level.	The addition of vitamin E as well as type of the muscles had a significant effect on the fatty acid profile.	https://cdnsciencepub.com/doi/pdf/10.1139/cjas-2015-0103	https://cdnsciencepub.com/doi/pdf/10.1139/cjas-2015-0103	No
15	bergamot extract (120-mg flavonoids), phytosterols, vitamin C, and chlorogenic acid	2019	Three-arm, placebo-controlled, randomized clinical trial evaluating the metabolic effect of a combined nutraceutical containing a bergamot standardized flavonoid extract in dyslipidemic overweight subjects	Double-blind, placebo-controlled, parallel-group, dose-escalation, clinical trial	90 overweight dyslipidemic subjects. Participants were randomly allocated to treatment with two pills of either active treatment or placebo, or a combination of both (a pill per treatment).	Placebo	After 8 weeks, all active-treated groups experienced a significant improvement in triglycerides (TG) versus placebo and in low-density lipoprotein cholesterol (LDL-C) versus baseline and placebo treatments. In the high-dose-treated group, also total cholesterol (TC), significantly decreased.	The tested nutraceutical showed to improve lipid and glucose metabolism, adipokines pattern, and systemic inflammation in dyslipidemic overweight subjects.	All patients allocated to either low-dose or high-dose active treatment experienced a significant decrease in TG, LDL-C, and homeostatin model assessment of insulin resistance.	https://pubmed.ncbi.nlm.nih.gov/31225673/	Cicero, A. F. G., Fogacci, F., Bove, M., Giovannini, M., & Borghi, C. (2019). Three-arm, placebo-controlled, randomized clinical trial evaluating the metabolic effect of a combined nutraceutical containing a bergamot standardized flavonoid extract in dyslipidemic overweight subjects. Phytotherapy Research : PTR, 33(8), 2094–2101. https://doi.org/10.1002/PTR.6402	Yes
16	Coenzyme Q10, Vitamin C, monacolin K, and L-arginine.	2018	LDL-cholesterol lowering effect of a new dietary supplement: An open label, controlled, randomized, cross-over clinical trial in patients with mild-to-moderate hypercholesterolemia	This was a single center, controlled, randomized, open-label, cross-over clinical study	20 Caucasian outpatients aged 18–75 years with serum LDL-C between 130 and 180 mg/dL. Patients assumed two different dietary supplements (A and N) both containing monacolin K 10 mg for 8 weeks each, separated by a 4-week wash-out period.	control	LDL-C decreased by 23.3% during treatment with N and by 25.6% during treatment with A . **Total-C** decreased significantly within each treatment period. **HDL-C** increase was negligible during **A** whereas it was significant during **N**. **TG** diminished markedly during **A** and notsignificantly during **N**. The difference between treatments was not statistically significant for all variables.	Our results confirm the clinically meaningful LDL-C lowering properties of **monacolin K**. At variance witha supplement already in the market (**N**), the novel association (**A**) of **monacolin K** with **L-arginine**, **coenzime Q10** and **ascorbic acid** also produces a significant reduction of triglycerides without significant effects on HDL.	Dietary supplement containing **monacolin K, L-arginine, coenzyme Q10 and ascorbic acid**, named **Argicolina (A)**, compared to a commercially available product containing **monacolin K and coenzyme Q10, Normolip 5 (N).** results confirm the clinically meaningful LDL-C lowering properties of monacolin K	https://pubmed.ncbi.nlm.nih.gov/29793488/	Magno, S., Ceccarini, G., Pelosini, C., Jaccheri, R., Vitti, J., Fierabracci, P., Salvetti, G., Airoldi, G., Minale, M., Saponati, G., & Santini, F. (2018). LDL-cholesterol lowering effect of a new dietary supplement: An open label, controlled, randomized, cross-over clinical trial in patients with mild-to-moderate hypercholesterolemia. Lipids in Health and Disease, 17(1). https://doi.org/10.1186/s12944-018-0775-8	Yes
17	FOLIC ACID	2016	Folic Acid Therapy Reduces the First Stroke Risk Associated With Hypercholesterolemia Among Hypertensive Patients	Double-blind, randomized controlled trial.	A total of 20 702 hypertensive adults without a history of major cardiovascular disease were randomly assigned to a double-blind daily treatment of an enalapril 10-mg and a folic acid 0.8-mg tablet or an enalapril 10-mg tablet alone. The primary outcome was first stroke.	control	Folic acid supplementation significantly reduced the risk of first stroke among participants with high total cholesterol (4.0% in the enalapril-only group versus 2.7% in the enalapril-folic acid group; hazard ratio, 0.69; 95% confidence interval, 0.56-0.84; P<0.001; number needed to treat, 78; 95% confidence interval, 52-158), independent of baseline folate levels and other important covariates. By contrast, among participants with low total cholesterol, the risk of stroke was 2.6% in the enalapril-only group versus 2.5% in the enalapril-folic acid group (hazard ratio, 1.00; 95% confidence interval, 0.75-1.30; P=0.982). The effect was greater among participants with elevated total cholesterol (P for interaction=0.024).	Elevated total cholesterol levels may modify the benefits of folic acid therapy on first stroke. Folic acid supplementation reduced the risk of first stroke associated with elevated total cholesterol by 31% among hypertensive adults without a history of major cardiovascular diseases.	N/A	https://pubmed.ncbi.nlm.nih.gov/27729579/	Qin, X., Li, J., Spence, J. D., Zhang, Y., Li, Y., Wang, X., Wang, B., Sun, N., Chen, F., Guo, J., Yin, D., Sun, L., Tang, G., He, M., Fu, J., Cai, Y., Shi, X., Ye, P., Chen, H., … Huo, Y. (2016). Folic Acid Therapy Reduces the First Stroke Risk Associated With Hypercholesterolemia Among Hypertensive Patients. Stroke, 47(11), 2805–2812. https://doi.org/10.1161/STROKEAHA.116.014578	Yes
18	FOLIC ACID	2016	Folic Acid Therapy Reduces the First Stroke Risk Associated With Hypercholesterolemia Among Hypertensive Patients	A double-blind, randomized controlled trial.	A total of 20 702 hypertensive adults without a history of major cardiovascular disease were randomly assigned to a double-blind daily treatment of an enalapril 10-mg and a folic acid 0.8-mg tablet or an enalapril 10-mg tablet alone. Participants were scheduled for follow-up every 3 months.		The primary outcome was first stroke. The secondary outcomes included first ischemic stroke (fatal or nonfatal), first hemorrhagic stroke (fatal or nonfatal), and a composite of cardiovascular events consisting of cardiovascular death, myocardial infarction, and stroke.	The median treatment duration was 4.5 years. For participants not receiving folic acid treatment (enalapril-only group), high total cholesterol (≥200 mg/dL) was an independent predictor of first stroke when compared with low total cholesterol. Folic acid supplementation significantly reduced the risk of first stroke among participants with high total cholesterol	Folic acid supplementation reduced the risk of first stroke associated with elevated total cholesterol by 31% among hypertensive adults without a history of major cardiovascular diseases.	https://www.ahajournals.org/doi/epub/10.1161/STROKEAHA.116.014578	Qin, X., Li, J., Spence, J. D., Zhang, Y., Li, Y., Wang, X., Wang, B., Sun, N., Chen, F., Guo, J., Yin, D., Sun, L., Tang, G., He, M., Fu, J., Cai, Y., Shi, X., Ye, P., Chen, H., … Huo, Y. (2016). Folic acid therapy reduces the first stroke risk associated with hypercholesterolemia among hypertensive patients. Stroke, 47(11), 2805–2812. https://doi.org/10.1161/STROKEAHA.116.014578	Yes
19	lysine, vitamin B(6), and carnitine		Effect of lysine, vitamin B(6), and carnitine supplementation on the lipid profile of male patients with hypertriglyceridemia: a 12-week, open-label, randomized, placebo-controlled trial	Randomized, placebo-controlled clinical trial	This 12-week, randomized, placebo-controlled clinical trial. A total of 85 hypertriglyceridemic (TG> 150 mg/dL) male patients were randomized to 1 of 5 groups and given supplements of lysine (1 g/d), vitamin B(6) (50 mg/d), lysine (1 g/d) + vitamin B(6) (50 mg/d), carnitine (1 g/d), or placebo for 12 weeks. The lipid profile (TG, total cholesterol, LDL-C, and HDL-C) and fasting plasma glucose levels were assessed at baseline and at 6 and 12 weeks.	placebo	Vitamin B(6) supplementation was associated with a significant reduction in total cholesterol and HDL-C of ~10%. In addition, plasma TG was reduced by 36.6 mg/dL at 6 weeks, whereas levels in the placebo group increased by 18 mg/dL	Vitamin B(6) supplementation in these male patients with hypertriglyceridemia reduced plasma total cholesterol and HDL-C concentrations.	No major changes in the lipid profile were observed in the lysine and carnitine groups or when lysine was added to vitamin B(6).	https://pubmed.ncbi.nlm.nih.gov/22818869/	Hlais, S., Reslan, D. R. A., Sarieddine, H. K., Nasreddine, L., Taan, G., Azar, S., & Obeid, O. A. (2012). Effect of lysine, vitamin B(6), and carnitine supplementation on the lipid profile of male patients with hypertriglyceridemia: a 12-week, open-label, randomized, placebo-controlled trial. Clinical Therapeutics, 34(8), 1674–1682. https://doi.org/10.1016/J.CLINTHERA.2012.06.019	No
20	omega-3 fatty acids and vitamin E	2015	A randomized-controlled clinical trial investigating the effect of omega-3 fatty acids and vitamin E co-supplementation on markers of insulin metabolism and lipid profiles in gestational diabetes	Randomized, double-blind, placebo-controlled clinical trial	60 patients with GDM. Patients were randomly allocated to take either 1000-mg omega-3 fatty acids from flaxseed oil plus 400-IU vitamin E supplements (n = 30) or placebo (n = 30) for 6 weeks. Fasting blood samples were obtained from at the beginning of the study and after 6-week intervention to quantify related variables.	placebo	After 6 weeks of intervention, Changes in serum triglycerides (+10.8 ± 41.5 vs +34.2 ± 35.5 mg/dL, P = .02), VLDL-cholesterol (+2.1 ± 8.3 vs +6.8 ± 7.1 mg/dL, P = .02), low-density lipoprotein (LDL)-cholesterol (+11.6 ± 18.8 vs +1.7 ± 15.9 mg/dL, P = .03) and HDL-cholesterol concentrations (+1.9 ± 8.7 vs -2.4 ± 7.7 mg/dL, P = .04) were significantly different between the supplemented women and placebo group.	Overall, we demonstrated that omega-3 fatty acids and vitamin E co-supplementation in GDM women had beneficial effects on glucose homeostasis parameters, serum triglycerides, VLDL-cholesterol, and HDL-cholesterol concentrations, but it did not influence total-cholesterol and LDL-cholesterol levels.	However, after controlling for baseline total cholesterol levels, maternal age, and BMI at baseline, the changes in serum LDL-cholesterol concentrations were not significantly different between the 2 groups. We did not find any significant effect of joint omega-3 fatty acids and vitamin E supplementation on total cholesterol concentrations.	https://pubmed.ncbi.nlm.nih.gov/27055970/	Taghizadeh, M., Jamilian, M., Mazloomi, M., Sanami, M., & Asemi, Z. (2016). A randomized-controlled clinical trial investigating the effect of omega-3 fatty acids and vitamin E co-supplementation on markers of insulin metabolism and lipid profiles in gestational diabetes. Journal of Clinical Lipidology, 10(2), 386–393. https://doi.org/10.1016/J.JACL.2015.12.017	No
21	Magnesium and Vitamin E	2018	The effects of magnesium and vitamin E co-supplementation on parameters of glucose homeostasis and lipid profiles in patients with gestational diabetes	Randomized, double-blinded, placebo-controlled trial	60 subjects diagnosed with gestational diabetes (GDM) , aged 18-40 years. Subjects were randomly allocated into two groups to receive 250 mg/day magnesium oxide plus 400 IU/day vitamin E supplements or placebo (n = 30 each group) for 6 weeks. Participants' blood samples were taken to determine their metabolic profiles.	placebo	magnesium plus vitamin E supplementation resulted in a significant reduction in serum triglycerides, VLDL, LDL and total-/HDL-cholesterol ratio compared with placebo. Magnesium and vitamin E co-supplementation did not affect HDL-cholesterol levels.	Overall, magnesium and vitamin E co-supplementation for 6 weeks in women with GDM significantly improved lipid profiles, except for HDL-cholesterol levels.	Magnesium and vitamin E co-supplementation did not affect HDL-cholesterol levels.	https://pubmed.ncbi.nlm.nih.gov/30025522/	Maktabi, M., Jamilian, M., Amirani, E., Chamani, M., & Asemi, Z. (2018). The effects of magnesium and vitamin E co-supplementation on parameters of glucose homeostasis and lipid profiles in patients with gestational diabetes. Lipids in Health and Disease, 17(1). https://doi.org/10.1186/S12944-018-0814-5	Yes
22	(vitamin B3 or niacin	2013	Effect of Nicotinic Acid (Vitamin B3 or Niacin) on the lipid profile of diabetic and non – diabetic rats	Animal study	A total of 50 rats were included in the study. Nicotinic acid was administered to a hypercholesterolemic group and a hypercholesterolemic + diabetic Group of Albino rats for 42 days and response to therapy was recorded on day 21 and day 42 of the experiment.	control	Lipid profile of the hypercholesterolemic group as well as hypercholesterolemic + diabetic group as compared with the control groups showed highly significant improvement on the day 21 and day 42 of the experiment. The values of serum total cholesterol (TC), triglycerides (TG), low density lipoprotein (LDL) cholesterol and total lipids (TL) showed highly significant decrease whereas serum high density lipoprotein (HDL) cholesterol showed highly significant increase.	Nicotinic acid is the most effective agent available in increasing HDL cholesterol and lowering serum TC, triglycerides (TG), LDL cholesterol and TL in hypercholesterolemic Diabetic and hypercholesterolemic non-diabetic Albino rats.	Nicotinic acid decreased the levels of serum total cholesterol, serum Triglycerides, serum low density lipoprotein cholesterol and serum Total lipids and it increased the high density lipoprotein cholesterol in both the diabetic as well as non-diabetic rats.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3858911/	Shah, T. Z., Ali, A. B., Jafri, S. A., & Qazi, M. H. (2013). Effect of nicotinic acid (vitamin B3 or niacin) on the lipid profile of diabetic and non - Diabetic rats. Pakistan Journal of Medical Sciences, 29(5). https://doi.org/10.12669/pjms.295.4193	No
23	(vitamin B3 or niacin	2015	Niacin as antidyslipidemic drug	Review	review	No control indicated	niacin was shown to have beneficial effects on cardiovascular end-points; but in recent years, two major studies performed in patients whose LDL cholesterol levels had been optimized by a statin therapy did not demonstrate an additional significant effect on these end-points in the groups where niacin was administered. Both studies have several drawbacks that suggest that they are not representative for other patients. Thus, niacin still plays a role either as an additive to a statin or as a substitute for a statin in statin-intolerant patients.	patients with elevated triglyceride and low HDL cholesterol levels and patients with elevated lipoprotein(a) concentrations will possibly benefit from niacin, although currently the study evidence for these indications is rather poor.	Niacin may be useful for compliant patients, however possible side effects (flushing, liver damage) and contraindications should be taken into consideration.	https://cdnsciencepub.com/doi/abs/10.1139/cjpp-2014-0478	Julius, U. (2015). Niacin as antidyslipidemic drug. Canadian Journal of Physiology and Pharmacology, 93(12), 1043–1054. https://doi.org/10.1139/cjpp-2014-0478	No

Table S4: Summary of articles containing minerals.

Mineral												
No	Ingredients	Year	Title	Type of study	Method/Design of study	Control / Placebo	Outcome	Interpretation	Comment	Available at	Reference	Scientific Evidence
1	Cinnamon, chromium and magnesium formulated honey	2016	The effect of a cinnamon-, chromium- and magnesium-formulated honey on glycaemic control, weight loss and lipid parameters in type 2 diabetes: an open-label cross-over randomised controlled trial	An open-label cross-over randomised controlled trial	Twelve individuals with type 2 diabetes received 53.5 g of a formulated honey and a control (non-formulated) kanuka honey in a random order for 40 days, using cross-over design. Fasting glucose, insulin, HbA1c, lipids and anthropometric measures were measured at baseline and end of treatment. A meal tolerance test was performed at baseline to assess acute metabolic response.	Control	There was a statistically significant reduction in total cholesterol by -0.29 mmol/L, LDL cholesterol by -0.29 mmol/L and weight by -2.2 kg. There was a trend towards increased HDL and reduced systolic blood pressure in the intervention treatment.	The addition of cinnamon, chromium and magnesium supplementation to kanuka honey was not associated with a significant improvement in glucose metabolism or glycaemic control in individuals with type 2 diabetes.	Use of the formulated honey was associated with a reduction in weight and improvements in lipid parameters, and should be investigated further.	https://pubmed.ncbi.nlm.nih.gov/25986159/	A Whitfield, P., Parry-Strong, A., Walsh, E., Weatherall, M., & Krebs, J. D. (2016). The effect of a cinnamon-, chromium- and magnesium-formulated honey on glycaemic control, weight loss and lipid parameters in type 2 diabetes: an open-label cross-over randomised controlled trial. European Journal of Nutrition, 55(3), 1123–1131. https://doi.org/10.1007/S00394-015-0926-X	No
2	Chromium	2021	Effects of chromium supplementation on lipid profile in patients with type 2 diabetes: A systematic review and dose-response meta-analysis of randomized controlled trials	Dose-response meta-analysis of randomized controlled trials	A systematic search was performed in Scopus, Embase, Web of Science, the Cochrane library and PubMed databases to find randomized controlled trials (RCTs) related to the effect of chromium supplementation on lipid profile in patients with T2DM, up to June 2020. Meta-analyses were performed using the random-effects model, and I2 index was used to evaluate heterogeneity.	Not Applicable - NA	The primary search yielded 725 publications. 24 RCTs (with 28 effect size) were eligible. Our meta-analysis indicated that chromium supplementation resulted in a significant decrease in serum levels of triglyceride (TG) and total cholesterol (TC). chromium significantly increases high-density lipoprotein (HDL) level. However, chromium supplementation did not have significant effects on low-density lipoprotein (LDL) level.	Chromium supplementation may significantly improve lipid profile in patients with T2DM by decreasing TG and TC and increasing HDL.	However, based on our analysis, chromium failed to affect LDL. It should be noted that the lipid-lowering properties of chromium supplementation were small and may not reach clinical importance.	https://www.sciencedirect.com/science/article/abs/pii/S094667 2X21000316	Asbaghi, O., Naeini, F., Ashtary-Larky, D., Moradi, S., Zakeri, N., Eslampour, E., Kelishadi, M. R., & Naeini, A. A. (2021). Effects of chromium supplementation on lipid profile in patients with type 2 diabetes: A systematic review and dose-response meta-analysis of randomized controlled trials. Journal of Trace Elements in Medicine and Biology, 66, 126741. https://doi.org/https://doi.org/10.1016/j.jtemb.2021.126741	Yes
3	Magnesium and Vitamin E	2018	The effects of magnesium and vitamin E co-supplementation on parameters of glucose homeostasis and lipid profiles in patients with gestational diabetes	Randomized, double-blinded, placebo-controlled trial	60 subjects diagnosed with gestational diabetes (GDM) , aged 18-40 years. Subjects were randomly allocated into two groups to receive 250 mg/day magnesium oxide plus 400 IU/day vitamin E supplements or placebo (n = 30 each group) for 6 weeks. Participants' blood samples were taken to determine their metabolic profiles.	Placebo	magnesium plus vitamin E supplementation resulted in a significant reduction in serum triglycerides, VLDL, LDL and total-/HDL-cholesterol ratio compared with placebo. Magnesium and vitamin E co-supplementation did not affect HDL-cholesterol levels.	Overall, magnesium and vitamin E co-supplementation for 6 weeks in women with GDM significantly improved lipid profiles, except for HDL-cholesterol levels.	Magnesium and vitamin E co-supplementation did not affect HDL-cholesterol levels.	https://pubmed.ncbi.nlm.nih.gov/30025522/	Maktabi, M., Jamilian, M., Amirani, E., Chamani, M., & Asemi, Z. (2018). The effects of magnesium and vitamin E co-supplementation on parameters of glucose homeostasis and lipid profiles in patients with gestational diabetes. Lipids in Health and Disease, 17(1). https://doi.org/10.1186/S12944-018-0814-5	Yes
4	Magnesium	2020	Oral Magnesium Supplementation Improved Lipid Profile but Increased Insulin Resistance in Patients with Diabetic Nephropathy: a Double-Blind Randomized Controlled Clinical Trial	Double-Blind Randomized Controlled Clinical Trial	A total of 80 hypomagnesemic patients diagnosed with type 2 diabetes and early-stage nephropathy were recruited. Subjects received either daily magnesium oxide or placebo for 12 weeks.	Placebo	No significant changes were observed in serum total cholesterol, triglycerides, HDL, LDL, and total cholesterol/HDL cholesterol ratio.	No significant changes were observed in serum total cholesterol, triglycerides, HDL, LDL, and total cholesterol/HDL cholesterol ratio.	Oral magnesium supplementation slightly improved microalbuminuria but resulted in increased insulin resistance in patients with diabetic nephropathy.	https://link.springer.com/article/10.1007/s12011-019-01687-6	Sadeghian, M., Azadbakht, L., Khalili, N., Mortazavi, M., & Esmaillzadeh, A. (2020). Oral Magnesium Supplementation Improved Lipid Profile but Increased Insulin Resistance in Patients with Diabetic Nephropathy: a Double-Blind Randomized Controlled Clinical Trial. Biological Trace Element Research, 193(1), 23–35. https://doi.org/10.1007/s12011-019-01687-6	No
5	Magnesium	2016	Serum magnesium status among obese children and adolescents	A cross-sectional study	50 obese subjects of ages 2–16 years and 50 healthy normal weight subjects of matched age and sex as controls were consecutively enrolled. Fasting total serum magnesium, total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides were measured.	Not Applicable - NA	Obese cases compared to normal weight controls showed significantly lower serum magnesium and HDL-cholesterol levels and significantly higher total cholesterol, LDL-cholesterol, triglycerides, systolic and diastolic blood pressures.	Serum magnesium showed a significant, strong inverse correlation with the degree of obesity ($r = -0.8$, $p < 0.001$); significant, moderate inverse correlation with total cholesterol and LDL-cholesterol; and non-significant correlation with triglycerides and HDL-cholesterol.	Serum magnesium levels are inversely correlated with the degree of obesity, and is related to an unfavorable serum lipid profile in obese children and adolescents, who also show a trend to higher systemic blood pressure.	https://www.sciencedirect.com/science/article/pii/S111066381 5000592	Zaakouk, A. M., Hassan, M. A., & Tolba, O. A. (2016). Serum magnesium status among obese children and adolescents. Egyptian Pediatric Association Gazette, 64(1), 32–37. https://doi.org/https://doi.org/10.1016/j.epag.2015.11.002	No
6	Zinc	2018	Zinc supplementation in prediabetes: A randomized double-blind placebo-controlled clinical trial	A randomized double-blind placebo-controlled clinical trial	A randomized double-blind placebo-controlled Phase 2 clinical trial was conducted over a 12-month period in 200 subjects, randomly assigned to the treatment or control group.The treatment group received zinc (20 mg daily). Subjects were evaluated at baseline and at 1, 3, 6, and 12 months. The primary outcome was the change in glycemic control from baseline.	Placebo	During the 12-month follow-up, a significantly higher percentage of participants developed type 2 diabetes in the control compared with zinc-treated group. total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C) were significantly lower in the treated group	supplementation reduced disease progression to diabetes and had beneficial effects on TC and LDL-C.	Zinc supplementation reduced blood glucose and insulin resistance while improving β-cell function.	https://pubmed.ncbi.nlm.nih.gov/29072815/	Ranasinghe, P., Wathurapatha, W. S., Galappatthy, P., Katulanda, P., Jayawardena, R., & Constantine, G. R. (2018). Zinc supplementation in prediabetes: A randomized double-blind placebo-controlled clinical trial. Journal of Diabetes, 10(5), 386–397. https://doi.org/10.1111/1753-0407.12621	Yes

Table S5: Summary of articles containing amino acids.

Amino acid												
No	Ingredients	Year	Title	Type of study	Method/Design of study	Control / Placebo	Outcome	Interpretation	Comment	Available at	Reference	Scientific Evidence
1	Coenzyme Q10, Vitamin C, monacolin K, and L-arginine.	2018	LDL-cholesterol lowering effect of a new dietary supplement: An open label, controlled, randomized, cross-over clinical trial in patients with mild-to-moderate hypercholesterolemia	Single center, controlled, randomized, open-label, cross-over clinical study	20 Caucasian outpatients aged 18–75 years with serum LDL-C between 130 and 180 mg/dL. Patients assumed two different dietary supplements (A and N) both containing monacolin K 10 mg for 8 weeks each, separated by a 4-week wash-out period.	Control	LDL-C decreased by 23.3% during treatment with N and by 25.6% during treatment with A . **Total-C** decreased significantly within each treatment period. **HDL-C** increase was negligible during **A** whereas it was significant during **N**. **TG** diminished markedly during **A** and notsignificantly during **N**. The difference between treatments was not statistically significant for all variables.	Our results confirm the clinically meaningful LDL-C lowering properties of **monacolin K**. At variance witha supplement already in the market (**N**), the novel association (**A**) of **monacolin K** with **L-arginine**, **coenzime Q10** and **ascorbic acid** also produces a significant reduction of triglycerides without significant effects on HDL.	Results confirm the clinically meaningful LDL-C lowering properties of monacolin K	https://pubmed.ncbi.nlm.nih.gov/29793488/	Magno, S., Ceccarini, G., Pelosini, C., Jaccheri, R., Vitti, J., Fierabracci, P., Salvetti, G., Airoldi, G., Minale, M., Saponati, G., & Santini, F. (2018). LDL-cholesterol lowering effect of a new dietary supplement: An open label, controlled, randomized, cross-over clinical trial in patients with mild-to-moderate hypercholesterolemia. Lipids in Health and Disease, 17(1). https://doi.org/10.1186/s12944-018-0775-8	Yes
2	l-Carnitine	2015	l-Carnitine supplementation improved clinical status without changing oxidative stress and lipid profile in women with knee osteoarthritis	Randomized double-blind, placebo-controlled trial	72 overweight or obese women with mild to moderate knee OA were randomly allocated into 2 groups to receive 750 mg/d l-carnitine or placebo for 8 weeks. Dietary intake was evaluated using 24-hour recall for 3 days. Lipid profile were assessed before and after supplementation.	Placebo	l-Carnitine supplementation resulted in significant reductions in serum total cholesterol, and low-density lipoprotein cholesterol levels compared with baseline, whereas these parameters increased in the placebo group. Serum triglyceride, high-density lipoprotein cholesterol, and TAC levels did not change significantly in both groups	l-carnitine improved clinical status without changing oxidative stress and lipid profile significantly in women with knee OA.	There were significant intragroup and intergroup differences in pain intensity and patient global assessment of disease status after supplementation.	https://www.sciencedirect.com/science/article/abs/pii/S0271531715001372	Malek Mahdavi, A., Mahdavi, R., Kolahi, S., Zemestani, M., & Vatankhah, A.-M. (2015). l-Carnitine supplementation improved clinical status without changing oxidative stress and lipid profile in women with knee osteoarthritis. Nutrition Research, 35(8), 707–715. https://doi.org/https://doi.org/10.1016/j.nutres.2015.06.003	Yes
3	Lysine, vitamin B(6), and carnitine		Effect of lysine, vitamin B(6), and carnitine supplementation on the lipid profile of male patients with hypertriglyceridemia: a 12-week, open-label, randomized, placebo-controlled trial	Randomized, placebo-controlled clinical trial	This 12-week, randomized, placebo-controlled clinical trial. A total of 85 hypertriglyceridemic (TG> 150 mg/dL) male patients were randomized to 1 of 5 groups and given supplements of lysine (1 g/d), vitamin B(6) (50 mg/d), lysine (1 g/d) + vitamin B(6) (50 mg/d), carnitine (1 g/d), or placebo for 12 weeks. The lipid profile (TG, total cholesterol, LDL-C, and HDL-C) and fasting plasma glucose levels were assessed at baseline and at 6 and 12 weeks.	Placebo	Vitamin B(6) supplementation was associated with a significant reduction in total cholesterol and HDL-C of ~10%. In addition, plasma TG was reduced by 36.6 mg/dL at 6 weeks, whereas levels in the placebo group increased by 18 mg/dL	Vitamin B(6) supplementation in these male patients with hypertriglyceridemia reduced plasma total cholesterol and HDL-C concentrations.	No major changes in the lipid profile were observed in the lysine and carnitine groups or when lysine was added to vitamin B(6).	https://pubmed.ncbi.nlm.nih.gov/22818869/	Hlais, S., Reslan, D. R. A., Sarieddine, H. K., Nasreddine, L., Taan, G., Azar, S., & Obeid, O. A. (2012). Effect of lysine, vitamin B(6), and carnitine supplementation on the lipid profile of male patients with hypertriglyceridemia: a 12-week, open-label, randomized, placebo-controlled trial. Clinical Therapeutics, 34(8), 1674–1682. https://doi.org/10.1016/J.CLINTHERA.2012.06.019	No
4	L-lysine	2019	Dietary supplementation with L-lysine affects body weight and blood hematological and biochemical parameters in rats	Animal study	Male Sprague–Dawley rats at 10 weeks of age were assigned to ten diet groups (eight rats/group) and fed diets containing either 7% or 20% casein and supplemented with either 0% (Control), 1.5%, 3%, 6% Lys, or 6% Lys + 3% arginine for 1 week.	Control	Rats fed 7% casein with ≥ 1.5% Lys supplementation had lower serum albumin and leptin and higher LDL cholesterol (LDLC), ratios of total cholesterol (TC):HDL cholesterol (HDLC) and LDLC:HDLC than those fed 7% casein Control diet. Addition of 6% Lys in 7% casein caused significant BW loss and altered additional parameters. No major changes in the lipid profile were observed in the lysine and carnitine groups or when lysine was added to vitamin B(6).	these results show that Lys supplementation affects BW, food intake and a number of hematological and biochemical parameters. These effects of Lys supplementation were confined primarily in diets with lower levels of dietary protein	In the context of a low protein diet (7% casein), levels of Lys supplementation ≥ 1.5% may exert adverse health effects in rats.	https://link.springer.com/article/10.1007/s11033-018-4492-1#citeas	Xiao, C.-W., Wood, C., & Bertinato, J. (2019). Dietary supplementation with l-lysine affects body weight and blood hematological and biochemical parameters in rats. Molecular Biology Reports, 46(1), 433–442. https://doi.org/10.1007/s11033-018-4492-1	No
5	L-arginine	2019	The effect of L-arginine supplementation on lipid profile: a systematic review and meta-analysis of randomised controlled trials	A systematic review and meta-analysis of randomised controlled trials	twelve studies were included in the systematic review.	Not Applicable - NA	The meta-analysis revealed that L-arginine supplementation did not significantly change the concentrations of total cholesterol, or HDL. A significant reduction was observed only in serum TAG levels	This meta-analysis concludes that L-arginine supplementation can significantly reduce blood TAG levels; however, there is insufficient evidence to support its hypocholesterolaemic effects.	There is a need for more well-controlled trials targeting exclusively patients with dyslipidaemia.	https://www.cambridge.org/core/journals/british-journal-of-nutrition/article/effect-of-larginine-supplementation-on-lipid-profile-a-systematic-review-and-metaanalysis-of-randomised-controlled-trials/F9FE43B86AD15C869CA4364F45978CC2	Hadi, A., Arab, A., Moradi, S., Pantovic, A., Clark, C. C. T., & Ghaedi, E. (2019). The effect of l-arginine supplementation on lipid profile: a systematic review and meta-analysis of randomised controlled trials. British Journal of Nutrition, 122(9), 1021–1032. https://doi.org/10.1017/S0007114519001855	Yes

Table S6: Summary of articles containing probiotics.

Probiotic											
No	**Ingredients**	**Year**	**Title**	**Type of study**	**Method/Design of study**	**Control / Placebo**	**Outcome**	**Interpretation**	**Comment**	**Available at**	**Reference**	**Scientific Evidence**
1	Probiotic	2019	The effect of probiotic supplementation on glycemic control and lipid profile in patients with type 2 diabetes: A randomized placebo controlled trial	Randomized double blind controlled trial	This randomized double blind controlled trial was performed among 60 patients; individuals were randomly assigned into 2 groups of 30 participants in order to take either probiotic supplements or placebo for 6 weeks. The probiotic supplement consisted of 7 viable strains Lactobacillus, Bifidobacterium and Streptococcus. Nutrient intakes were estimated using a 3-day and 24 hour-dietary recall at the beginning and end of study. Fasting blood samples were taken before and after intervention to measure the levels of FPG, plasma insulin and lipid profiles.	Placebo	Within group comparisons showed significant decrease and increase in the levels of FPG and HDL-C in probiotic group, respectively. No significant alterations were observed for within and between group comparisons in the levels of insulin, triglycerides, total cholesterol, insulin resistance and anthropometric measurements, including weight, waist circumference and body mass index.	This study showed a significant decrease in FPG level by multi-strain probiotic supplements in within group comparison	further studies are needed to confirm results	https://pubmed.ncbi.nlm.nih.gov/30641692/	Razmpoosh, E., Javadi, A., Ejtahed, H. S., Mirmiran, P., Javadi, M., & Yousefinejad, A. (2019). The effect of probiotic supplementation on glycemic control and lipid profile in patients with type 2 diabetes: A randomized placebo controlled trial. Diabetes & Metabolic Syndrome, 13(1), 175–182. https://doi.org/10.1016/J.DSX.2018.08.008	Yes
2	Probiotic	2016	The use of probiotic L. fermentum ME-3 containing Reg'Activ Cholesterol supplement for 4 weeks has a positive influence on blood lipoprotein profiles and inflammatory cytokines: an open-label preliminary study	An open-label preliminary study	Forty-five clinically asymptomatic participants consumed an RAC (Reg'Activ Cholesterol (RAC)) containing an antioxidative and antiatherogenic probioticLactobacillus fermentumME-3 (LFME-3) for 4 weeks.	Control	The reduction of total cholesterol (from 6.5 ± 1.0 to 5.7 ± 0.9 mmol/L) and HDL cholesterol level rose from 1.60 ± 0.31to 1.67 ± 0.34mml/l.	The consumption of RAC capsules in asymptomatic vol-unteers with borderline values of risk factors for cardio-vascular disease (BMI, HbA1c%, LDL cholesterol) for 4 weeks had a positive effect on blood lipoprotein, oxidative stress and inflammatory profile.	The level of total cholesterol and LDL decreased significantly in all participants and HDL cholesterol showed a tendency of improvementafter 4 weeks of consumption of LFME3 containing food supplement RAC	https://www.researchgate.net/publication/309772788_The_use_of_probiotic_L_fermentum_ME-3_containing_Reg'Activ_Cholesterol_supplement_for_4_weeks_has_a_positive_influence_on_blood_lipoprotein_profiles_and_inflammatory_cytokines_an_open-label_preliminar/link/5fc3ab46299bf104cf905e78/download	https://www.researchgate.net/publication/309772788_The_use_of_probiotic_L_fermentum_ME-3_containing_Reg'Activ_Cholesterol_supplement_for_4_weeks_has_a_positive_influence_on_blood_lipoprotein_profiles_and_inflammatory_cytokines_an_open-label_preliminar/link/5fc3ab46299bf104cf905e78/download	No
3	probiotic Bifidobacterium longum BB536 and red yeast rice extract	2019	Nutraceutical approach for the management of cardiovascular risk - a combination containing the probiotic Bifidobacterium longum BB536 and red yeast rice extract: results from a randomized, double-blind, placebo-controlled study	Randomized, double-blind, placebo-controlled study	A 12-week randomized, parallel, double-blind, placebo-controlled study. Thirty-three subjects (18-70 years) in primary CV prevention and low CV risk (SCORE: 0-1% in 24 and 2-4% in 9 subjects; LDL-C: 130-200 mg/dL) were randomly allocated to either nutraceutical (N = 16) or placebo (N = 17).	Placebo	Twelve-week treatment with the nutraceutical combination, compared to placebo, significantly reduced TC (- 16.7%), LDL-C (- 25.7%), non-HDL-C (- 24%) (all p < 0.0001), apoB (- 17%, p = 0.003).	A 12-week treatment with a nutraceutical combination containing the probiotic Bifidobacterium longum BB536 and RYR extract significantly improved the atherogenic lipid profile and was well tolerated by low CV risk subjects.	No adverse effects and a 97% compliance were observed.	https://pubmed.ncbi.nlm.nih.gov/30795775/	Ruscica, M., Pavanello, C., Gandini, S., Macchi, C., Botta, M., Dall'Orto, D., del Puppo, M., Bertolotti, M., Bosisio, R., Mombelli, G., Sirtori, C. R., Calabresi, L., & Magni, P. (2019). Nutraceutical approach for the management of cardiovascular risk - a combination containing the probiotic Bifidobacterium longum BB536 and red yeast rice extract: results from a randomized, double-blind, placebo-controlled study. Nutrition Journal, 18(1). https://doi.org/10.1186/S12937-019-0438-2	Yes
4	lactobacillus fermentum	2015	Regulation of plasma lipid profile by lactobacillus fermentum (probiotic strain ME-3 DSM14241) in a randomised controlled trial of clinically healthy adults	Randomised, double-blind, placebo-controlled, parallel design, two-armed study	One hundred sixty four participants meeting the inclusion criteria were included. Participants were randomised to receive 200 ml/day kefir, either with probiotic(PG) or without probiotic (CG). The probiotic contained fermentum ME-3. At 4 weeks and at 8 weeks, evaluation of anthropologic, blood biochemical indices, and the faecal temporal persistence of the probiotic strain was done by real-time PCR.	Placebo	After 4 weeks, the lipid profiles were mostly similar between groups: only the values of oxidised LDL (ox-LDL) and TG were significantly reduced. After 8 weeks, the PG group exhibited reductions in LDL-C, ox-LDL, TG. Next, the ratio of LDL-C to HDL-C was decreased only in the PG while in the CG it was significantly increased.	Eight weeks of consuming probiotic L fermentum ME-3, reduced serum LDL-C, ox-LDL and TG values in clinically healthy volunteers with borderline-high lipid profile indices.	L. fermentum ME-3 has potential to lower the risk of CVD that is tightly associated with maintenance of plasma lipid profile.	https://link.springer.com/content/pdf/10.1186/s40795-015-0020-z.pdf	Mikelsaar, M., Sepp, E., Štšepetova, J., Hütt, P., Zilmer, K., Kullisaar, T., & Zilmer, M. (2015). Regulation of plasma lipid profile by lactobacillus fermentum (probiotic strain ME-3 DSM14241) in a randomised controlled trial of clinically healthy adults. BMC Nutrition, 1(1). https://doi.org/10.1186/s40795-015-0020-z	Yes
5	Probiotic	2018	The effects of probiotics on total cholesterol A meta-analysis of randomized controlled trials	A meta-analysis of randomized controlled trials	Thirty-two RCTs including 1971 patients met the inclusion criteria. The curative effects of probiotics on the reduction of TC were assessed using mean difference (MD), as well as their 95% confidence interval (CI). RevMan software (version 5.3) was used to carry out this meta-analysis.	Not Applicable - NA	Results of this analysis showed that compared with the control group serum TC was significantly reduced in probiotics group. In addition, specific strains also significantly reduced serum TC, L acidophilus and B lactis	Available evidence indicates that probiotics supplements can significantly reduce serum TC. Furthermore, higher baseline TC, longer intervention time, and probiotics in capsules form might contribute to a better curative effect.	Subgroup analysis indicated that the difference of baseline TC, probiotics forms and intervention duration might have a significant impact on the results. However, strains and doses of probiotics had no significant influence on curative effects.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5805418/	Wang, L., Guo, M. J., Gao, Q., Yang, J. F., Yang, L., Pang, X. L., & Jiang, X. J. (2018). The effects of probiotics on total cholesterol: A meta-analysis of randomized controlled trials. Medicine, 97(5). https://doi.org/10.1097/MD.0000000000009679	Yes
6	Probiotic and Prebiotic	2010	Cholesterol-Lowering Effects of Probiotics and Prebiotics: A Review of in Vivo and in Vitro Findings	A Review	A Review	Not Applicable - NA	In conclusion, the mechanisms proposed for mediating hypocholesterolemic effect by probiotics and/or prebiotics are numerous. Although those hypotheses were proved via in vitro studies, the mechanisms are not firmly established and demonstrated in in vivo studies. Therefore, more in vivo studies are needed to explore the underlying mechanism of cholesterol-lowering effects by probiotics and/or prebiotics in order to have a better understanding of the mechanisms and better formulations for human consumption.	Probiotic and/or prebiotics have been widely assessed for their effects on lipid profiles such as total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides. However, not all trials have yielded conclusive results.		https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2904929/	Ooi, L. G., & Liong, M. T. (2010). Cholesterol-Lowering Effects of Probiotics and Prebiotics: A Review of in Vivo and in Vitro Findings. International Journal of Molecular Sciences, 11(6), 2499. https://doi.org/10.3390/IJMS11062499	No

Table S7: Summary of articles containing prebiotic.

Prebiotic												
No	Ingredients	Year	Title	Type of study	Method/Design of study	Control / Placebo	Outcome	Interpretation	Comment	Available at	Reference	Scientific Evidence
1	inulin and phytosterols	2015	Effect of phytosterols and inulin-enriched soymilk on LDL-cholesterol in Thai subjects: a double-blinded randomized controlled trial	Double-blinded randomized controlled trial	Two hundred and forty subjects who were 18 years old or older and had a baseline LDL-c of 130 mg/dl or higher were enrolled into the double-blinded randomized controlled trial study. Subjects were randomly assigned into the study group that received 2 g/day of phytosterols and 10 g/day of inulin-enriched soymilk or into the control group that received standard soymilk. The lipid profile was measured every 2 weeks for 8 weeks.	Control	At the end of the study, the median LDL-c levels decreased significantly from 165 mg/dl to 150 mg/dl in the study group and from 165 mg/dl to 159 mg/dl in the control group. The LDL-c reduction was significantly better in the study group. TC also reduced significantly by 6.60% in the study group while it reduced only by 1.76% in the control group.	Daily consumption of soymilk containing 2 g of phytosterols and 10 g of inulin reduced TC and LDL-c better than standard soymilk.	It had no effect on TG and HDL-c levels compared to standard soymilk.	https://pubmed.ncbi.nlm.nih.gov/26553006/	Kietsiriroje, N., Kwankaew, J., Kitpakornsanti, S., & Leelawattana, R. (2015). Effect of phytosterols and inulin-enriched soymilk on LDL-cholesterol in Thai subjects: a double-blinded randomized controlled trial. Lipids in Health and Disease, 14(1). https://doi.org/10.1186/S12944-015-0149-4	No
2	Inulin, Pomegranate extract	2017	Cholesterol-lowering effects of dietary pomegranate extract and inulin in mice fed an obesogenic diet	Animal study	Male C57BL/6 J mice were fed high-fat/high-sucrose [HF/HS (32% energy from fat, 25% energy from sucrose)] diets supplemented with PomX (0.25%) and inulin (9%) alone or in combination for 4 weeks.	Control	Feeding the HF/HS diet supplemented with PomX and inulin individually resulted in a significant decrease in serum TC compared HF/HS control.	inulin mainly targeted hepatic cholesterol de novo synthesis and fecal cholesterol and bile acid excretion involving changes in the metabolism of the intestinal microbiome.	Supplementation with PomX and inulin together resulted in lower hepatic and serum total cholesterol compared to individual treatments. PomX showed a trend to decrease liver triglyceride (TG) levels, while inulin or PomX-inulin combination had no effect on either serum or liver TG levels.	https://www.sciencedirect.com/science/article/pii/S0955286316308294	Yang, J., Zhang, S., Henning, S. M., Lee, R., Hsu, M., Grojean, E., Pisegna, R., Ly, A., Heber, D., & Li, Z. (2018). Cholesterol-lowering effects of dietary pomegranate extract and inulin in mice fed an obesogenic diet. Journal of Nutritional Biochemistry, 52, 62–69. https://doi.org/10.1016/j.jnutbio.2017.10.003	No
3	Inulin	2022	Physical activity enhances the improvement of body mass index and metabolism by inulin: a multicenter randomized placebo-controlled trial performed in obese individuals	Randomized, single-blinded, multicentric, placebo-controlled trial	(placebo: n = 31, prebiotic: n = 30). trial was conducted in obese participants who received 16 g/day native inulin versus maltodextrin, coupled to dietary advice to consume inulin-rich versus -poor vegetables for 3 months, respectively,	Placebo	Obese subjects who increased PA during a 3 months intervention with inulin-enriched diet exhibited several clinical improvements such as reduced BMI (- 1.6 kg/m2), decreased liver enzymes and plasma cholesterol, and improved glucose tolerance.	We conclude that PA level is an important determinant of the success of a dietary intervention targeting the gut microbiota.	N/A	https://pubmed.ncbi.nlm.nih.gov/35351144/	Rodriguez, J., Neyrinck, A. M., van Kerckhoven, M., Gianfrancesco, M. A., Renguet, E., Bertrand, L., Cani, P. D., Lanthier, N., Crop, M., Paquot, N., Thissen, J. P., Bindels, L. B., & Delzenne, N. M. (2022). Physical activity enhances the improvement of body mass index and metabolism by inulin: a multicenter randomized placebo-controlled trial performed in obese individuals. BMC Medicine, 20(1). https://doi.org/10.1186/S12916-022-02299-Z	No
4	Inulin , Lactobacillus sporogenes	2013	Synbiotic food consumption reduces levels of triacylglycerols and VLDL, but not cholesterol, LDL, or HDL in plasma from pregnant women	Randomized, double-blind, controlled clinical trial	52 primigravida pregnant women, aged 18 to 35-year-old at their third trimester. After a 2-week run-in period, subjects were randomly assigned to consume either a synbiotic (n = 26) or control food (n = 26) for 9 weeks. The synbiotic food consisted of a probiotic viable and heat-resistant Lactobacillus sporogenes (1 × 10^7 CFU) and 0.04 g inulin (HPX)/g as the prebiotic. Patients were asked to consume the synbiotic and control foods two times a day.	Placebo	Consumption of a synbiotic food for 9 weeks resulted in a significant reduction in serum TAG (P = 0.04), VLDL (P = 0.04) and a significant rise in plasma GSH levels (P = 0.004) compared to the control food.	No significant effects of the synbiotic food consumption on serum TC, LDL, HDL and plasma TAC levels (P > 0.05) were observed.	N/A	https://pubmed.ncbi.nlm.nih.gov/24271261/	Taghizadeh, M., Hashemi, T., Shakeri, H., Abedi, F., Sabihi, S. S., Alizadeh, S. A., & Asemi, Z. (2014). Synbiotic food consumption reduces levels of triacylglycerols and VLDL, but not cholesterol, LDL or HDL in plasma from pregnant women. Lipids, 49(2), 155–161. https://doi.org/10.1007/S11745-013-3867-2	Yes
5	Inulin	2018	Probiotic and synbiotic supplementation could improve metabolic syndrome in prediabetic adults: A randomized controlled trial	Double-blind, placebo-controlled randomized parallel-group clinical trial.	articipants were randomized to a multi-species probiotic or inulin-based synbiotic or placebo. Blood samples and anthropometric measures were collected at baseline, 12 and 24 weeks after treatment.	Placebo	A significant trend for a reduction in the prevalence of hyperglycemia in probiotic and synbiotic groups (p = 0.01 and 0.005 respectively), and hypertension in probiotic group (p = 0.04) was found. The decreases in metabolic syndrome prevalence were significant after taking probiotic and synbiotic supplementation as compared with placebo (p = 0.02). Also, the prevalence of low HDL-cholesterol level was decreased during the study in the probiotic group compared with placebo (p = 0.02).	The potential benefits of using probiotic and synbiotic for metabolic syndrome management in prediabetes have been supported by the results in the current study which might provide an important strategy to combat metabolic syndrome-associated diseases.	N/A	https://pubmed.ncbi.nlm.nih.gov/30076087/	Kassaian, N., Feizi, A., Aminorroaya, A., & Amini, M. (2019). Probiotic and synbiotic supplementation could improve metabolic syndrome in prediabetic adults: A randomized controlled trial. Diabetes & Metabolic Syndrome, 13(5), 2991–2996. https://doi.org/10.1016/J.DSX.2018.07.016	Yes

Table S8: Summary of articles containing fatty acid.

Fatty Acid

No	Ingredients	Year	Title	Type of study	Method/Design of study	Control / Placebo	Outcome	Interpretation	Comment	Available at	Reference	Scientific Evidence
1	Fatty acid	2018	Assessment of omega-3 carboxylic acids in statin-treated patients with high levels of triglycerides and low levels of high-density lipoprotein cholesterol: Rationale and design of the STRENGTH trial	Randomized, double-blind,placebo-controlled trial	13 086 patients were randomized to Epanova 4 g or placebo daily in addition to standard medical therapy. The trial will continue until 1600 patients reach the primary endpoint, with a median duration of therapy of 3 years. STRENGTH study will determine whether Epanova 4 g daily will reduce cardiovascular events in statin-treated high-risk patients with hypertriglyceridemia and low HDL-C levels.	Placebo	STRENGTH will permit the opportunity to determine the effects of administrationof Epanova 4 g daily, a much higher dose than evaluated in many stud-ies	While omega-3 fattyacids are of interest as a potential preventive therapy, most studieshave used suboptimal doses and formulations with variable bioavail-ability for non-HDL-C reduction and failed to evaluate their impact inpatients who are most likely to derive potential benefit	The trial will continue until 1600 patients reach the primary end point .The primary efficacy outcome is time tofirst event of cardiovascular death, myocardial infarction, stroke, coronary revascularization orhospitalization for unstable angina.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6489732/pdf/CLC-41-1281.pdf	Nicholls, S. J., Lincoff, A. M., Bash, D., Ballantyne, C. M., Barter, P. J., Davidson, M. H., Kastelein, J. J. P., Koenig, W., McGuire, D. K., Mozaffarian, D., Pedersen, T. R., Ridker, P. M., Ray, K., Karlson, B. W., Lundström, T., Wolski, K., & Nissen, S. E. (2018). Assessment of omega-3 carboxylic acids in statin-treated patients with high levels of triglycerides and low levels of high-density lipoprotein cholesterol: Rationale and design of the STRENGTH trial. Clinical Cardiology, 41(10), 1281–1288. https://doi.org/10.1002/clc.23055	Yes
2	Fatty acid	2013	Omega 3 Fatty Acids Promote Macrophage ReverseCholesterol Transport in Hamster Fed High Fat Diet	Animal study	Three groups of hamsters (n = 6/group) were studied for 20 weeks: 1) control diet: **Control**, 2) HFD group: **HF** and 3) HFD group supplemented with v3PUFA (EPA andDHA): **HFv3**.	Control	Liver TG content was higher in HF compared to Control group (14.2 +/- 2.1 mg/g vs. 8.5 +/- 1.1mg/g) and lower in HFv3 (11.1 +/- 2.6 mg/g) compared to HF group.	In conclusion, EPA andDHA supplementation improved macrophage to feces reverse cholesterol transport in hamster fed HFD.	In the present study performed in hamster, we showed that v3PUFA prevented the increase of plasma TG and cholesterol by decreasing VLDL TG and HDL cholesterol concentrations respectively. These changes were related to increase of RCTefficiency as showed by a higher fecal bile acid and cholesterol elimination.	https://journals.plos.org/plosone/article/file?id=10.1371/journal.pone.0061109&type=printable	Kasbi Chadli, F., Nazih, H., Krempf, M., Nguyen, P., & Ouguerram, K. (2013). Omega 3 Fatty Acids Promote Macrophage Reverse Cholesterol Transport in Hamster Fed High Fat Diet. PLoS ONE, 8(4). https://doi.org/10.1371/journal.pone.0061109	No
3	Coenzyme Q10 and Omega-3	2017	Addition of omega-3 fatty acid and coenzyme Q10 to statin therapy in patients with combined dyslipidemia	Pilot randomized double-blind trial	105 subjects who met the criteria of combined dislipidemia and elevated TAG levels were randomly divided into three groups. In the control group, unaltered statin therapy was indicated. In the second and third groups, omega-3 PUFA 2.52 g/day (Zennix fa Pleuran) and omega-3 PUFA 2.52 g+CoQ10 200 mg/day (Pharma Nord ApS) were added, res//. At the end of the 3-month period (±1 week), all patients were evaluated.	Control	Significant reduction of hepatic enzymes activity, systolic blood preasure, inflammatory markers and TAG levels were detected in both groups in comparison to the control group.	Coenzyme Q10 addition significantly reduced most of the abovementioned parameters (systolic blood preasure, total cholesterol, LDL, hsCRP, IL-6, SOD) in comparison with the statin+omega-3 PUFA group.	The results of this pilot study suggest the possible beneficial effects of triple combination on the lipid and non-lipid parameters related to atherogenesis and side effects of statin treatment.	https://pubmed.ncbi.nlm.nih.gov/28541926/	Tóth, Š., Šajty, M., Pekárová, T., Mughees, A., Štefanič, P., Katz, M., Spišáková, K., Pella, J., & Pella, D. (2017). Addition of omega-3 fatty acid and coenzyme Q10 to statin therapy in patients with combined dyslipidemia. Journal of Basic and Clinical Physiology and Pharmacology, 28(4), 327–336. https://doi.org/doi:10.1515/jbcpp-2016-0149	Yes
4	fish oil EPA DHA	2012	The effect of a 12-week course of omega-3 polyunsaturated fatty acids on lipid parameters in hypertriglyceridemic adult HIV-infected patients undergoing HAART: a randomized, placebo-controlled pilot trial	Randomized, placebo-controlled pilot trial	A double-blind, placebo-controlled, randomized, multicenter pilot study was undertaken in 48 evaluable HIV-infected patients undergoing HAART, with fasting triglyceride levels of 3.39 to 11.3 mmol/L. Patients were allowed fibrate or niacin but not statins and were randomized to polyunsaturated fatty acids (PUFA) 4 g daily versus placebo for 12 weeks. The primary end point was mean fasting triglyceride levels.	Placebo	PUFA reduced triglycerides by a median of 1.75 mmol/L versus a 0.41 mmol/L increase for the placebo group	PUFA therapy with DHA/EPA reduced triglyceride levels significantly compared with placebo in HIV-infected patients with HAART-associated hypertriglyceridemia.	N/A	https://pubmed.ncbi.nlm.nih.gov/22212377/	Peters, B. S., Wierzbicki, A. S., Moyle, G., Nair, D., & Brockmeyer, N. (2012). The effect of a 12-week course of omega-3 polyunsaturated fatty acids on lipid parameters in hypertriglyceridemic adult HIV-infected patients undergoing HAART: a randomized, placebo-controlled pilot trial. Clinical Therapeutics, 34(1), 67–76. https://doi.org/10.1016/J.CLINTHERA.2011.12.001	Yes
5	fish oil EPA DHA	2013	Effect of fish oil supplementation on serum triglycerides, LDL cholesterol and LDL subfractions in hypertriglyceridemic adults	Double-blind, parallel design, placebo controlled trial	This was a secondary analysis from a double-blind, parallel design, placebo controlled trial with 42 adults that experienced significant TG lowering and modest increases in total LDL-C concentrations	Placebo	42 adults that experienced significant TG lowering and modest increases in total LDL-C concentrations after 12 weeks of 4 g/d EPA + DHA.	In this population of hypertriglyceridemic adults, dietary supplementation with fish oil resulted in an increase in total LDL-C concentration	N/A	https://pubmed.ncbi.nlm.nih.gov/21924882/	Oelrich, B., Dewell, A., & Gardner, C. D. (2013). Effect of fish oil supplementation on serum triglycerides, LDL cholesterol and LDL subfractions in hypertriglyceridemic adults. Nutrition, Metabolism, and Cardiovascular Diseases : NMCD, 23(4), 350–357. https://doi.org/10.1016/J.NUMECD.2011.06.003	No
6	Sterols and fish oil	2018	A low-fat spread with added plant sterols and fish omega-3 fatty acids lowers serum triglyceride and LDL-cholesterol concentrations in individuals with modest hypercholesterolaemia and hypertriglyceridaemia	Randomized, double-blind, placebo-controlled, parallel group design	Following a 2-week placebo run-in period, 260 healthy individuals with modestly elevated blood TG (≥ 1.4 mmol/L) and LDL-C (≥ 3.4 mmol/L) concentrations consumed either the placebo or intervention spread for 4 weeks. The intervention spread contained 2.0 g/day PS and 1.0 g/day eicosapentaenoic acid (EPA) + docosahexanoic acid (DHA) from fish oil.	Placebo	Four-week consumption of the intervention spread resulted in significantly lower TG and LDL-C concentrations as compared to placebo. Total cholesterol non-HDL-C concentrations were also significantly lower, as compared to placebo.	Four-week consumption of the intervention spread led to significant and clinically relevant decreases in serum TG, LDL-C and other blood lipid concentrations.	No significant treatment effects were found for HDL-cholesterol, ApoAI, ApoCII, Apo E or ApoB/ApoAI.	https://pubmed.ncbi.nlm.nih.gov/29725824/	Blom, W. A. M., Koppenol, W. P., Hiemstra, H., Stojakovic, T., Scharnagl, H., & Trautwein, E. A. (2019). A low-fat spread with added plant sterols and fish omega-3 fatty acids lowers serum triglyceride and LDL-cholesterol concentrations in individuals with modest hypercholesterolaemia and hypertriglyceridaemia. European Journal of Nutrition, 58(4), 1615–1624. https://doi.org/10.1007/S00394-018-1706-1	Yes
7	Co enzyme Q10 and fatty acid	2017	Addition of omega-3 fatty acid and coenzyme Q10 to statin therapy in patients with combined dyslipidemia	Pilot randomized double-blind trial	105 subjects who met the criteria of combined dislipidemia and elevated TAG levels were randomly divided into three groups. In the control group, unaltered statin therapy was indicated. In the second and third groups, omega-3 PUFA 2.52 g/day (Zennix fa Pleuran) and omega-3 PUFA 2.52 g+CoQ10 200 mg/day (Pharma Nord ApS) were added, res//. At the end of the 3-month period (±1 week), all patients were evaluated.	Control	Coenzyme Q10 addition significantly reduced most of the abovementioned parameters (systolic blood preasure, total cholesterol, LDL, hsCRP, IL-6, SOD) in comparison with the statin+omega-3 PUFA group.	The results of this pilot study suggest the possible beneficial effects of triple combination on the lipid and non-lipid parameters related to atherogenesis and side effects of statin treatment.	The intensity of statin adverse effects were significantly reduced in the group with the addition of CoQ10.	https://pubmed.ncbi.nlm.nih.gov/28541926/	Tóth, Š., Šajty, M., Pekárová, T., Mughees, A., Štefanič, P., Katz, M., Spišáková, K., Pella, J., & Pella, D. (2017). Addition of omega-3 fatty acid and coenzyme Q10 to statin therapy in patients with combined dyslipidemia. Journal of Basic and Clinical Physiology and Pharmacology, 28(4), 327–336. https://doi.org/10.1515/JBCPP-2016-0149	No

Table S9: Summary of articles containing phospholipids.

Phospholipids												
No	**Ingredients**	**Year**	**Title**	**Type of study**	**Method/Design of study**	**Control / Placebo**	**Outcome**	**Interpretation**	**Comment**	**Available at**	**Reference**	**Scientific Evidence**
1	Phospholipids	2018	Effect of dietary cholesterol and phospholipids on feed intake, growth performance and cholesterol metabolism in juvenile turbot (Scophthalmus maximus L.)	Animal study	examined the effect of dietary cholesterol and phospholipids on feed intake, growth performance and cholesterol metabolism in juvenile turbot (Scophthalmus maximus L.) (initial body weight 5.18 ± 0.01 g) during a 10-week period. Nine isonitrogenous and isolipidic diets were formulated to contain 0.0, 1.0 and 2.0% cholesterol (LC, MC and HC), and each with 0.0, 2.0 and 4.0% phospholipids (LP, MP and HP), respectively.	Control	Cholesterol transport was significantly affected by the interaction between dietary cholesterol and phospholipids. Except for total cholesterol, free cholesterol and cholesterol ester, both high-density lipoprotein cholesterol (HDL-C) (P = 0.012) and low-density lipoprotein cholesterol (LDL-C) (P = 0.002) in serum were significantly affected by the interaction between dietary cholesterol and phospholipids.	In conclusion, there is a significant interaction between dietary cholesterol and phospholipids on the growth performance and the HDL-C and LDL-C involved in cholesterol transport, while no significant interaction was found on the feed intake in juvenile turbot.	Interaction between dietary cholesterol and phospholipids on the growth performance was found in terms of weight gain rate.	https://www.sciencedirect.com/science/article/abs/pii/S004484861732567X	Zhu, T., Mai, K., Xu, W., & Ai, Q. (2018). Effect of dietary cholesterol and phospholipids on feed intake, growth performance and cholesterol metabolism in juvenile turbot (Scophthalmus maximus L.). Aquaculture, 495, 443–451. https://doi.org/10.1016/J.AQUACULTURE.2018.06.002	No
2	Phospholipids	2018	Effect of dietary phospholipid levels on growth, lipid metabolism, and antioxidative status of juvenile hybrid snakehead (Channa argus×Channa maculata)	Animal study	The study was conducted to evaluate the effect of dietary phospholipids (PLs) on growth, lipid metabolism, and antioxidative status of hybrid snakehead (Channa argus × Channa maculata). Five isonitrogenous and isolipidic diets with graded levels of PLs (8.5, 19.3, 30.7, 41.5, and 50.8 g kg-1) were fed to triplicate groups of juveniles (initial body weight 12.6 ± 0.23 g) for 8 weeks.	Control	Results showed that dietary PL supplementation significantly improved growth of juveniles. The final body weight (FBW) and specific growth rate (SGR) significantly increased with dietary PLs increasing from 8.5 to 41.5 g kg-1 ($P < 0.05$). Fish fed with the diet containing 8.5 g kg-1 PLs showed higher feed conversion ratio (FCR) compared to the other treatments ($P < 0.05$). Liver lipid contents, serum triglyceride (TG), and low-density lipoprotein cholesterol (LDL-C) contents significantly decreased with the increasing levels of dietary PLs ($P < 0.05$). However, serum total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C) contents and HDL-C/TC and HDL-C/LDL-C value significantly increased with increasing dietary PL levels ($P < 0.05$).	These results confirmed that dietary PL supplementation has beneficial effects on growth performance and antioxidant capacity of juvenile hybrid snakehead. Dietary PLs might reduce lipid deposition in the liver of juvenile hybrid snakehead.	N/A	https://pubmed.ncbi.nlm.nih.gov/29147969/	Lin, S. M., Li, F. J., Yuangsoi, B., & Doolgindachbaporn, S. (2018). Effect of dietary phospholipid levels on growth, lipid metabolism, and antioxidative status of juvenile hybrid snakehead (Channa argus×Channa maculata). Fish Physiology and Biochemistry, 44(1), 401–410. https://doi.org/10.1007/S10695-017-0443-3	No

Table S10: Summary of articles containing sterols.

Sterol											
No	Ingredients	Year	Title	Type of study	Method/Design of study	Control / Placebo	Outcome	Interpretation	Comment	Available at	Reference	Scientific Evidence
1	bergamot extract (120-mg flavonoids), phytosterols, vitamin C, and chlorogenic acid	2019	Three-arm, placebo-controlled, randomized clinical trial evaluating the metabolic effect of a combined nutraceutical containing a bergamot standardized flavonoid extract in dyslipidemic overweight subjects	Double-blind, placebo-controlled, parallel-group, dose-escalation, clinical trial	90 overweight dyslipidemic subjects. Participants were randomly allocated to treatment with two pills of either active treatment or placebo, or a combination of both (a pill per treatment).	Placebo	After 8 weeks, all active-treated groups experienced a significant improvement in triglycerides (TG) versus placebo and in low-density lipoprotein cholesterol (LDL-C) versus baseline and placebo treatments. In the high-dose-treated group, also total cholesterol (TC), significantly decreased.	The tested nutraceutical showed to improve lipid and glucose metabolism, adipokines pattern, and systemic inflammation in dyslipidemic overweight subjects.	All patients allocated to either low-dose or high-dose active treatment experienced a significant decrease in TG, LDL-C, and homeostatin model assessment of insulin resistance.	https://pubmed.ncbi.nlm.nih.gov/31225673/	Cicero, A. F. G., Fogacci, F., Bove, M., Giovannini, M., & Borghi, C. (2019). Three-arm, placebo-controlled, randomized clinical trial evaluating the metabolic effect of a combined nutraceutical containing a bergamot standardized flavonoid extract in dyslipidemic overweight subjects. Phytotherapy Research : PTR, 33(8), 2094–2101. https://doi.org/10.1002/PTR.6402	Yes
2	Sterols and fish oil	2018	A low-fat spread with added plant sterols and fish omega-3 fatty acids lowers serum triglyceride and LDL-cholesterol concentrations in individuals with modest hypercholesterolaemia and hypertriglyceridaemia	Randomized, double-blind, placebo-controlled, parallel group design	Following a 2-week placebo run-in period, 260 healthy individuals with modestly elevated blood TG (≥ 1.4 mmol/L) and LDL-C (≥ 3.4 mmol/L) concentrations consumed either the placebo or intervention spread for 4 weeks. The intervention spread contained 2.0 g/day PS and 1.0 g/day eicosapentaenoic acid (EPA) + docosahexanoic acid (DHA) from fish oil.	Placebo	Four-week consumption of the intervention spread resulted in significantly lower TG and LDL-C concentrations as compared to placebo. Total cholesterol non-HDL-C concentrations were also significantly lower, as compared to placebo.	Four-week consumption of the intervention spread led to significant and clinically relevant decreases in serum TG, LDL-C and other blood lipid concentrations.	No significant treatment effects were found for HDL-cholesterol, ApoAI, ApoCII, Apo E or ApoB/ApoAI.	https://pubmed.ncbi.nlm.nih.gov/29725824/	Blom, W. A. M., Koppenol, W. P., Hiemstra, H., Stojakovic, T., Scharnagl, H., & Trautwein, E. A. (2019). A low-fat spread with added plant sterols and fish omega-3 fatty acids lowers serum triglyceride and LDL-cholesterol concentrations in individuals with modest hypercholesterolaemia and hypertriglyceridaemia. European Journal of Nutrition, 58(4), 1615–1624. https://doi.org/10.1007/S00394-018-1706-1	Yes
3	Sterols	2018	Plant sterols lower LDL-cholesterol and triglycerides in dyslipidemic individuals with or at risk of developing type 2 diabetes; a randomized, double-blind, placebo-controlled study	Double-blind, randomized, placebo-controlled, parallel study	161 individuals at increased risk of and with established T2DM, consumed low-fat spreads without or with added PS (2 g/d) for 6 weeks. Fasting serum/plasma total cholesterol (TC), LDL-C, TG, high-density lipoprotein cholesterol (HDL-C), glucose and insulin were measured at baseline and after 6 weeks.	Placebo	PS intake significantly lowered fasting LDL-C and TG with no significant changes in HDL-C, glucose or insulin.	In individuals at risk of and with established T2DM and with elevated TG and LDL-C, 2 g/d of PS results in dual LDL-C plus TG lowering.	ostprandial lipid or glycemic responses did not differ between PS and control treatment.	https://pubmed.ncbi.nlm.nih.gov/29795368/	Trautwein, E. A., Koppenol, W. P., de Jong, A., Hiemstra, H., Vermeer, M. A., Noakes, M., & Luscombe-Marsh, N. D. (2018). Plant sterols lower LDL-cholesterol and triglycerides in dyslipidemic individuals with or at risk of developing type 2 diabetes: a randomized, double-blind, placebo-controlled study. Nutrition & Diabetes, 8(1). https://doi.org/10.1038/S41387-018-0039-8	Yes
4	Sterols	2017	Interindividual variability in the cholesterol-lowering effect of supplementation with plant sterols or stanols	Review	This review focuses on the interindividual variability in response todietary supplementation with plant sterols and stanols.	Not Applicable - NA	Dietary plant sterols andstanols have no significant effects on LDL-C in substantial numbers of individuals.Higher responses, in absolute value and percentage of LDL-C, are observed in individuals with higher cholesterol absorption and a lower rate of cholesterol synthesis.	Dietary plant sterols andstanols have no significant effects on LDL-C in substantial numbers of individuals	Plant sterolsand stanols compete with cholesterol for absorption in the intestine and induce anaverage decrease in LDL-C by 5% to 15% in a dose-dependent manner, but not inall individuals.	https://doi.org/10.1093/nutrit/nuw059	Fumeron, F., Bard, J.-M., & Lecerf, J.-M. (2017). Interindividual variability in the cholesterol-lowering effect of supplementation with plant sterols or stanols. Nutrition Reviews, 75(2), 134–145. https://doi.org/10.1093/nutrit/nuw059	Yes
5	Sterols	2017	Plant sterol ester diet supplementation increases serum plant sterols and markers of cholesterol synthesis, but has no effect on total cholesterol levels	Double-blind, randomized, placebo-controlled, cross-over intervention-study	Sixteen volunteers, average age 34 years, with no or mild hypercholesterolemia were subjected to a 4 week period of daily intake of 3 g plant sterols per day supplied via a supplemented margarine on top of regular eating habits. To evaluate the effects of plant sterol ester supplemented margarine on cholesterol, non-cholesterol sterols and oxidative stress in serum and monocytes.	Placebo	consumption of plant sterol ester supplemented margarine results in increased concentrations of plant sterols and cholesterol synthesis markers without affecting total cholesterol in the serum, activation of circulating monocytes or redox state.	Cholesterol serum levels, however, were not changed significantly	in a population of healthy volunteers with no or mild hypercholesterolemia, consumption of plant sterol ester supplemented margarine results in increased concentrations of plant sterols and cholesterol synthesis markers without affecting total cholesterol in the serum,	https://pubmed.ncbi.nlm.nih.gov/27473562/	Weingärtner, O., Bogeski, I., Kummerow, C., Schirmer, S. H., Husche, C., Vanmierlo, T., Wagenpfeil, G., Hoth, M., Böhm, M., Lütjohann, D., & Laufs, U. (2017). Plant sterol ester diet supplementation increases serum plant sterols and markers of cholesterol synthesis, but has no effect on total cholesterol levels. The Journal of Steroid Biochemistry and Molecular Biology, 169, 219–225. https://doi.org/10.1016/J.JSBMB.2016.07.016	Yes
6	Sterols	2018	LDL-Cholesterol Lowering of Plant Sterols andStanols—Which Factors Influence Their Efficacy?	Review	This review summarizes evidence for the impact of various factors potentiallyinfluencing the LDL-C-lowering efficacy of plant sterols/stanols (PSS).	Not Applicable - NA	Numerous clinical studies have shown that the intake of PSS lowers LDL-C concentrations by7.5 to 12% with daily intakes of 1.5 to 3 g.	Compared to multiple daily intakes,once-a-day intake of PSS, especially in the morning with light breakfast, leads to a sub-optimal LDL-Clowering.	In conclusion, PSS are efficacious in all foods andfood supplements; for optimal efficacy they should be consumed with a (main) meal and twice daily.	https://pubmed.ncbi.nlm.nih.gov/30205492/	Trautwein, E. A., Vermeer, M. A., Hiemstra, H., & Ras, R. T. (2018). LDL-cholesterol lowering of plant sterols and stanols—which factors influence their efficacy? In Nutrients (Vol. 10, Issue 9). MDPI AG. https://doi.org/10.3390/nu10091262	Yes
7	phytosterols (800 mg) and red yeast rice, standardized to contain 5 mg of monacolins from Monascus purpureus, with added niacin (27 mg) and policosanols (10 mg) (LEVELIP DUO®)	2020	A Randomized, Double-Blinded, Placebo-Controlled, Clinical Study of the Effects of a Nutraceutical Combination (LEVELIP DUO ®) on LDL Cholesterol Levels and Lipid Pattern in Subjects with Sub-Optimal Blood Cholesterol Levels (NATCOL Study)	A Randomized, Double-Blinded, Placebo-Controlled, Clinical Study	randomizing 88 moderately hypercholesterolemic subjects to treatment with a combined nutraceutical or placebo.	Placebo	The mean LDL-Cholesterol (LDL-C) change at Week 8 was -32.5 ± 30.2 mg/dL (-19.8%) in the combined nutraceutical group and 2.5 ± 19.4 mg/dL (2.3%) in the placebo group. Total Cholesterol (TC), non-HDL cholesterol (non-HDL-C), Apolipoprotein B, TC/HDL-C and LDL-C/HDL-C improved in a similar way in the combined nutraceutical group only.	In conclusion, the tested combined nutraceutical was well tolerated, while significantly reducing the plasma levels of LDL-C, TC, non-HDL-C, ApoB, TC/HDL-C and LDL-C/HDL-C ratios in mildly hypercholesterolemic patients.	N/A	https://pubmed.ncbi.nlm.nih.gov/33066334/	Cicero, A. F. G., D'addato, S., & Borghi, C. (2020). A Randomized, Double-Blinded, Placebo-Controlled, Clinical Study of the Effects of a Nutraceutical Combination (LEVELIP DUO ®) on LDL Cholesterol Levels and Lipid Pattern in Subjects with Sub-Optimal Blood Cholesterol Levels (NATCOL Study). Nutrients, 12(10), 1–10. https://doi.org/10.3390/NU12103127	Yes
8	Phytosterols	2010	Dose effects of dietary phytosterols on cholesterol metabolism: acontrolled feeding study	Placebo-controlled, crossover feeding trial	18 adults received a phytosterol-deficient diet (50 mg phytosterols/2000 kcal)plus beverages supplemented with 0, 400, or 2000 mg phytosterols/d for 4wk each, in random order.	Placebo	Phytosterol intakes (diet plus supplements) averaged 59, 459, and 2059 mg/d during the 3 diet periods. Relative to the 59-mgdiet, the 459- and 2059-mg phytosterol intakes significantly (P,0.01) increased total fecal cholesterol excretion (36 +/- 6% and 74 +/- 10%, respectively) and biliary cholesterol excretion (38 +/- 7% and77 +/- 12%, respectively) and reduced percentage intestinal cholesterol absorption(-10 +/- 1%and - 25 +/- 3%,respectively). Serum LDL cholesterol declined significantly only with the highest phytosteroldose (- 8.9+/- 2.3%).	Dietary phytosterols in moderate and high doses favorably alter whole-body cholesterol metabolism in a dose-dependent manner.	A moderate phytosterol intake (459 mg/d) canbe obtained in a healthy diet without supplementation.	https://academic.oup.com/ajcn/article/91/1/32/4597163?login=true	Racette, S. B., Lin, X., Lefevre, M., Spearie, C. A., Most, M. M., Ma, L., & Ostlund, R. E. (2010). Dose effects of dietary phytosterols on cholesterol metabolism: A controlled feeding study. American Journal of Clinical Nutrition, 91(1), 32–38. https://doi.org/10.3945/ajcn.2009.28070	No
9	Inulin and phytosterols	2015	Effect of phytosterols and inulin-enriched soymilk on LDL-cholesterol in Thai subjects: a double-blinded randomized controlled trial	Double-blinded randomized controlled trial	Two hundred and forty subjects who were 18 years old or older and had a baseline LDL-c of 130 mg/dl or higher were enrolled into the double-blinded randomized controlled trial study. Subjects were randomly assigned into the study group that received 2 g/day of phytosterols and 10 g/day of inulin-enriched soymilk or into the control group that received standard soymilk. The lipid profile was measured every 2 weeks for 8 weeks.	Control	At the end of the study, the median LDL-c levels decreased significantly from 165 (132, 254) mg/dl to 150 (105, 263) mg/dl in the study group ($p < 0.001$) and from 165 (130, 243) mg/dl to 159 (89, 277) mg/dl in the control group ($p = 0.014$). The LDL-c reduction was significantly better in the study group (-10.03%, (-37.07, 36.00) vs -1.31% (-53.40, 89.73), $p < 0.001$). TC also reduced significantly by 6.60% in the study group while it reduced only by 1.76% in the control group ($p < 0.001$).	Daily consumption of soymilk containing 2 g of phytosterols and 10 g of inulin reduced TC and LDL-c better than standard soymilk.	It had no effect on TG and HDL-c levels compared to standard soymilk.	https://pubmed.ncbi.nlm.nih.gov/26553006/	Kietsiriroje, N., Kwankaew, J., Kitpakornsanti, S., & Leelawattana, R. (2015). Effect of phytosterols and inulin-enriched soymilk on LDL-cholesterol in Thai subjects: a double-blinded randomized controlled trial. Lipids in Health and Disease, 14(1). https://doi.org/10.1186/S12944-015-0149-4	No

Table S11: Summary of articles containing plant compounds.

Plant compound											
No	Ingredients	Year	Title	Type of study	Method/Design of study	Control / Placebo	Outcome	Interpretation	Comment	Available at	Reference	Scientific Evidence
1	red yeast rice, policosanols and artichoke leaf extracts	2013	A combined natural supplement lowers LDL cholesterol in subjects with moderate untreated hypercholesterolemia: a randomized placebo-controlled trial	Randomized, double-blind, placebo-controlled trial.	natural cholesterol-lowering supplement (NCLS) containing red yeast rice, policosanols and artichoke leaf extracts on blood lipid concentrations as well as on safety parameters when given over 16 weeks in 100 volunteers with untreated moderate hypercholesterolemia	Placebo	Reduction of primary outcome low-density lipoprotein cholesterol as well as total cholesterol were observed after 16 weeks of supplementation with NCLS.	The NCLS was effective in reducing low-density lipoprotein cholesterol in subjects with moderate hypercholesterolemia, without modifying safety parameters.	No significant changes were observed in high-density lipoprotein, triacylglycerol, creatine kinase, lactate dehydrogenase and coenzyme Q10 levels, as well as in markers of liver and renal function.	https://pubmed.ncbi.nlm.nih.gov/23815518/	Barrat, E., Zaïr, Y., Ogier, N., Housez, B., Vergara, C., Maudet, C., Lescuyer, J. F., Bard, J. M., Carpentier, Y. A., Cazaubiel, M., & Peltier, S. L. (2013). A combined natural supplement lowers LDL cholesterol in subjects with moderate untreated hypercholesterolemia: a randomized placebo-controlled trial. International Journal of Food Sciences and Nutrition, 64(7), 882–889. https://doi.org/10.3109/09637486.2013.809405	Yes
2	**Extract** - Red yeast rice (RYR), sugar cane-derived policosanols (SCdP) and artichoke leaf extracts (ALEs)	2013	LDL-cholesterol-lowering effect of a dietary supplement with plant extracts in subjects with moderate hypercholesterolemia	Double-blind, randomized, parallel controlled study	39 subjects from 21 to 55 years with moderate hypercholesterolemia without drug treatment were assigned to 2 groups and then consumed either a DS containing RYR, SCdP and ALEs or a placebo over a 16-week period.	Placebo	LDL-cholesterol and TC were reduced by, respectively, 21.4 % (95 % CI, −13.3 to −24.9 %, p < 0.001) and 14.1 % (95 % CI, −10.1 to −18.0 %, p < 0.001) at week 16 in the DS group compared with baseline.	Daily consumption of this new DS decreased LDL-cholesterol and TC and is therefore an interesting, convenient aid in managing mild to moderate hypercholesterolemia.	N/A	https://link.springer.com/article/10.1007/s00394-012-0357-x	Ogier, N., Amiot, M.-J., Georgé, S., Maillot, M., Mallmann, C., Maraninchi, M., Morange, S., Lescuyer, J.-F., Peltier, S. L., & Cardinault, N. (2013). LDL-cholesterol-lowering effect of a dietary supplement with plant extracts in subjects with moderate hypercholesterolemia. European Journal of Nutrition, 52(2), 547–557. https://doi.org/10.1007/s00394-012-0357-x	Yes
3	**Extract** - red yeast rice extract, policosanol and artichoke leaf extract	2013	Effect on LDL-cholesterol of a large dose of a dietary supplement with plant extracts in subjects with untreated moderate hypercholesterolaemia: a randomised, double-blind, placebo-controlled study	Randomised, double-blind, placebo-controlled clinical trial.	Forty-five healthy subjects (15 per group), with untreated hypercholesterolaemia, were included for this trial for 4 weeks of supplementation.	Placebo	After 4 weeks of supplementation, LDL-C was significantly lower in 6-TAB (−0.21 g/l; 95 % CI −0.38 to −0.03 g/l; p = 0.0217) and 3-TAB (−0.25 g/l; 95 % CI −0.42 to −0.07 g/l; p = 0.0071) compared to Placebo, although no difference in LDL-cholesterol was observed between the two groups, while no effect was seen on triacylglycerol and HDL-cholesterol.	After 4 weeks of supplementation, LDL-C was significantly lower in TWICE DAILY DOSE (6 TABLET INSTEAD OF 3)	Supplementation with twice the recommended dose of the DS was effective in reducing LDL-cholesterol and appeared safe, but according to the present results, no additional benefit could be achieved compared to the recommended dose.	https://link.springer.com/article/10.1007/s00394-012-0486-2	Barrat, E., Zaïr, Y., Sirvent, P., Chauveau, P., Maudet, C., Housez, B., Derbord, E., Lescuyer, J.-F., Bard, J.-M., Cazaubiel, M., & Peltier, S. L. (2013). Effect on LDL-cholesterol of a large dose of a dietary supplement with plant extracts in subjects with untreated moderate hypercholesterolaemia: a randomised, double-blind, placebo-controlled study. European Journal of Nutrition, 52(8), 1843–1852. https://doi.org/10.1007/s00394-012-0486-2	Yes
4	Berberine	2022	Combined berberine and probiotic treatment as an effective regimen for improving postprandial hyperlipidemia in type 2 diabetes patients: a double blinded placebo controlled randomized study	Double blinded placebo controlled randomized study	Blood PL (120 min after taking 100 g standard carbohydrate meal) was examined in 365 participants with T2D from the Probiotics and BBR on the Efficacy and Change of Gut Microbiota in Patients with Newly Diagnosed Type 2 Diabetes	Placebo	study proved the therapeutic effect of a combined treatment of oral administration of probiotics with berberine on improving PL in patients newly diagnosed with T2D and proposed a new gut microbiome related remedy for managing dyslipidemia, covering both PL and FL, in patients with T2D.	Prob+BBR was superior to BBR or Prob alone in improving postprandial total cholesterol (pTC) and low-density lipoprotein cholesterol (pLDLc) levels	N/A	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8726654/	Wang, S., Ren, H., Zhong, H., Zhao, X., Li, C., Ma, J., Gu, X., Xue, Y., Huang, S., Yang, J., Chen, L., Chen, G., Qu, S., Liang, J., Qin, L., Huang, Q., Peng, Y., Li, Q., Wang, X., … Wang, W. (2022). Combined berberine and probiotic treatment as an effective regimen for improving postprandial hyperlipidemia in type 2 diabetes patients: a double blinded placebo controlled randomized study. Gut Microbes, 14(1), 2003176. https://doi.org/10.1080/19490976.2021.2003176	Yes
5	Berberine	2013	The effects of berberine on blood lipids: a systemic review and meta-analysis of randomized controlled trials	Systemic review	eleven randomized controlled trials (including a total of 874 participants) were included in this study.	Not Applicable - NA	The final analysis showed that administration of berberine produced a significant reduction in total cholesterol , triglycerides , and low-density lipoprotein cholesterol	berberine may have beneficial effects in the control of blood lipid levels. However, the efficacy of berberine in treating hyperlipidemia should be further evaluated by more randomized controlled trials in a larger population of patients.	No serious adverse effects of berberine have been reported.	https://pubmed.ncbi.nlm.nih.gov/23512497/	Dong, H., Zhao, Y., Zhao, L., & Lu, F. (2013). The effects of berberine on blood lipids: a systemic review and meta-analysis of randomized controlled trials. Planta Medica, 79(6), 437–446. https://doi.org/10.1055/S-0032-1328321	No
6	Berberine	2021	Effect of Berberine on Cardiovascular Disease Risk Factors: A Mechanistic Randomized Controlled Trial	Randomized, double-blind, placebo-controlled, parallel trial	In total, 84 eligible Chinese men with hyperlipidemia were randomized to berberine (500 mg orally, twice a day) or placebo for 12 weeks. CVD risk factors (lipids, thromboxane A2, blood pressure, body mass index and waist-hip ratio) and testosterone were assessed at baseline, and 8 and 12 weeks after intervention.	Placebo	Men randomized to berberine had larger reductions in total cholesterol and high-density lipoprotein cholesterol after 12 weeks. Considering changes after 8 and 12 weeks together, berberine lowered total cholesterol and possibly low-density lipoprotein-cholesterol.	Changes in triglycerides, thromboxane A2, blood pressure, body mass index and waist-hip ratio after the intervention did not differ between the berberine and placebo groups.	Berberine is a promising treatment for lowering cholesterol. Berberine did not lower testosterone but instead may increase testosterone in men, suggesting sex-specific effects of berberine.	https://pubmed.ncbi.nlm.nih.gov/34444711/	Zhao, J. v., Yeung, W. F., Chan, Y. H., Vackova, D., Leung, J. Y. Y., Ip, D. K. M., Zhao, J., Ho, W. K., Tse, H. F., & Schooling, C. M. (2021). Effect of Berberine on Cardiovascular Disease Risk Factors: A Mechanistic Randomized Controlled Trial. Nutrients, 13(8). https://doi.org/10.3390/NU13082550	Yes
7	Berberine	2019	Efficacy and Safety of Berberine Alone or Combined with Statins for the Treatment of Hyperlipidemia: A Systematic Review and Meta-Analysis of Randomized Controlled Clinical Trials	Systematic Review and Meta-Analysis of Randomized Controlled Clinical Trials	A total of 11 RCTs involving 1386 patients were finally included.	Not Applicable - NA	The results of meta-analysis showed that compared with the placebo group, berberine could significantly reduce the total cholesterol and low-density lipoprotein levels and elevate the high density lipoprotein level. Compared with the simvastatin group, berberine was effective only in reducing the level of triglyceride	Compared with the simvastatin group, berberine plus simvastatin was more effective in reducing the level of triglyceride and total cholesterol. This study suggests that berberine is effective for hyperlipidemia.	In terms of adverse reactions, the incidence of adverse reactions including transaminase elevation and muscle aches was lower in the berberine alone or combined with simvastatin group than that in the control group,	https://pubmed.ncbi.nlm.nih.gov/31094214/	Zhang, L.-S., Zhang, J.-H., Feng, R., Jin, X.-Y., Yang, F.-W., Ji, Z.-C., Zhao, M.-Y., Zhang, M.-Y., Zhang, B.-L., & Li, X.-M. (2019). Efficacy and Safety of Berberine Alone or Combined with Statins for the Treatment of Hyperlipidemia: A Systematic Review and Meta-Analysis of Randomized Controlled Clinical Trials. The American Journal of Chinese Medicine, 47(4), 751–767. https://doi.org/10.1142/S0192415X19500393	No
8	Berberine	2014	Berberine (BBR) decreases cholesterol levels in rats through multiple mechanisms, including inhibition of cholesterol absorption	Animal study	Male Sprague–Dawley rats were fed the AIN-93G diet (normal control) or modified AIN-93G diet containing 28% fat, 2% cholesterol and 0.5% cholic acid with treatment of 0 (atherogenic control), 50, 100, and 150 mg/kg·d of BBR, respectively by gavaging in water for 8 weeks.	Control	Treatment with BBR in rats on the atherogenic diet reduced plasma total cholesterol and nonHDL cholesterol levels by 29%–33% and 31%–41%, respectively, with no significant differences being observed among the three doses. The fractional dietary cholesterol absorption rate was decreased by 40%–51%. Rats fed the atherogenic diet showed lower plasma triacylglycerol levels, and no changes were observed after the BBR treatment.	In conclusion, BBR lowered blood cholesterol levels in dietinduced hypercholesterolemic rats at least in part through inhibiting intestinal cholesterol absorption.	due to the differences in diet composition and cholesterol metabolism between humans and rats, it is not possible to conclude that the NC diet is a better approach than the AC plus BBR in humans. Generally, the NC diet does not apply in humans, as people, even vegetarians, eat diets containing cholesterol and have high cholesterol absorption rates.	https://www.sciencedirect.com/science/article/abs/pii/S0026049514001620	Wang, Y., Yi, X., Ghanam, K., Zhang, S., Zhao, T., & Zhu, X. (2014). Berberine decreases cholesterol levels in rats through multiple mechanisms, including inhibition of cholesterol absorption. Metabolism, 63(9), 1167–1177. https://doi.org/10.1016/J.METABOL.2014.05.013	No
9	Berberine	2012	Lipid-lowering effect of berberine in human subjects and rats	Clinical trial	In this pilot study, obese human subjects (Caucasian) were given 500 mg berberine orally three times a day for twelve weeks. The efficacy and safety of berberine treatment was determined by measurements of body weight, comprehensive metabolic panel, blood lipid and hormone levels, expression levels of inflammatory factors, complete blood count, and electrocardiograph. A Sprague-Dawley rat experiment was also performed to identify the anti-obesity effects of berberine treatment.	Not Applicable - NA	The results demonstrate that berberine treatment produced a mild weight loss (average 5 lb/subject) in obese human subjects. But more interestingly, the treatment significantly reduced blood lipid levels (23% decrease of triglyceride and 12.2% decrease of cholesterol levels) in human subjects. The lipid-lowering effect of berberine treatment has also been replicated in the rat experiment (34.7% decrease of triglyceride and 9% decrease of cholesterol level).	this study demonstrates that berberine is a potent lipid-lowering compound with a moderate weight loss effect,	Tests of hematological, cardiovascular, liver, and kidney function following berberine treatment showed no detrimental side effects to this natural compound.	https://pubmed.ncbi.nlm.nih.gov/22739410/	Hu, Y., Ehli, E. A., Kittelsrud, J., Ronan, P. J., Munger, K., Downey, T., Bohlen, K., Callahan, L., Munson, V., Jahnke, M., Marshall, L., Nelson, K., Huizenga, P., Hansen, R., Soundy, T. J., & Davies, G. E. (2012). Lipid-lowering effect of berberine in human subjects and rats. Phytomedicine : International Journal of Phytotherapy and Phytopharmacology, 19(10), 861–867. https://doi.org/10.1016/J.PHYMED.2012.05.009	No
10	Berberine	2010	Berberine and plant stanols synergistically inhibit cholesterol absorption in hamsters	Animal study	Male Golden Syrian hamsters wererandomly divided into 4 groups (n=15/group) and fed a cornstarch–casein–sucrose-based diet contain-ing 0.15% cholesterol and 5% fat. Three treatment groups were supplemented with 0.17% (equivalentto 100mgkg−1d−1) BBR, 1% PS, or a combination of both (BBRPS) for 4wk	Control	Berberine(BBR), plant stanols (PS), and BBRPS supplementations significantly decreased(p<0.0001) plasma T-C and nonHDL-C levels as compared with the control group. These three treatments lowered plasma T-C by 22%, 30%, and 43% and nonHDL-C by 28%, 45%, and 63%, respectively.	BBR lowered plasma cholesterol and nonHDL-cholesterol levels possibly through a combination of inhibition ofcholesterol absorption and stimulation of bile acid synthesis.	Moreover, we have observed that BBR and PS actedsynergistically to inhibit fractional cholesterol absorption whenthey were administered in combination. The significant correla-tion between fractional cholesterol absorption rates and plasmatotal cholesterol or nonHDL-cholesterol concentrations providesadditional support to the important role of cholesterol absorp-tion in reducing plasma cholesterol levels after the BBR, PS andBBRPS treatments, respectively.	https://reader.elsevier.com/reader/sd/pii/S0021915009007126?token=8A38EEEB89874E2296753385D19C4D771C6F71E2D1235DFA85910B084AC0E1A55974D2E467F7A5491D98376C1E1682F5&originRegion=eu-west-1&originCreation=20220209190006	Wang, Y., Jia, X., Ghanam, K., Beaurepaire, C., Zidichouski, J., & Miller, L. (2010). Berberine and plant stanols synergistically inhibit cholesterol absorption in hamsters. Atherosclerosis, 209(1), 111–117. https://doi.org/10.1016/j.atherosclerosis.2009.08.050	No

11	Berberine, Red Yeast Rice and Chitosan	2017	Effects of a New Nutraceutical Formulation(Berberine, Red Yeast Rice and Chitosan) onNon-HDL Cholesterol Levels in Individuals withDyslipidemia: Results from a Randomized,Double Blind, Placebo-Controlled Study	Randomized,Double Blind, Placebo-Controlled Study	The aim ofthe study is to test the efficacy of the nutraceutical formulation (one daily) in lowering non-HDLcholesterol vs. placebo at 12 weeks in individuals with non-HDL-cholesterol levels≥160 mg/dL.39 subjects (age 52±11 years; 54% females; body mass index 27±4 kg/m2) were randomized(3:1) in a double blind phase II placebo-controlled study.	Placebo	The intervention significantly decreased non-HDL cholesterol (−30 ± 20 mg/dL), LDL cholesterol (−31 ± 18 mg/dL) and apolipoprotein (Apo) B (−14 ± 12 mg/dL) levels compared to the placebo.	In conclusion, the tested nutraceutical formulation was effective in the reduction of non-HDL/LDL-C levels at 4 and 12 weeks thus representing a possible therapeutic strategy in dyslipidemic individuals in primary prevention.	new combination of nutraceuticals (berberine 200 mg, monacolin K 3 mg, chitosan 10 mg andcoenzyme Q 10 mg)	https://www.mdpi.com/1422-0067/18/7/1498	Spigoni, V., Aldigeri, R., Antonini, M., Micheli, M. M., Fantuzzi, F., Fratter, A., Pellizzato, M., Derlindati, E., Zavaroni, I., Bonadonna, R. C., & Dei Cas, A. (2017). Effects of a new nutraceutical formulation (Berberine, red yeast rice and chitosan) on non-HDL cholesterol levels in individuals with dyslipidemia: Results from a randomized, double blind, placebo-controlled study. International Journal of Molecular Sciences, 18(7). https://doi.org/10.3390/ijms18071498	Yes
12	Berberine, red yeast rice, plant sterols, fibers	2018	Cholesterol-Lowering Nutraceuticals Affecting Vascular Function and Cardiovascular Disease Risk	Review	The aim of this review is to provide an update on the effects of the dietary supplementation with cholesterol-lowering nutraceuticals and nutraceutical combinations affecting vascular function and CV risk in clinical interventional studies.	Not Applicable - NA	Current evidence supports the mild-to-moderate cholesterol-lowering efficacy of red yeast rice, berberine, plant sterols, fibers, and some nutraceutical combinations whereas data on the individual cholesterol-lowering action of other nutraceuticals are either less striking or even inconclusive.	There is also promising evidence on the vascular protective effects of some of the aforementioned nutraceuticals.	However, except for red yeast rice, clinical interventional studies have not investigated their impact on CV outcomes.	https://link.springer.com/article/10.1007/s11886-018-0994-7#citeas	Bianconi, V., Mannarino, M. R., Sahebkar, A., Cosentino, T., & Pirro, M. (2018). Cholesterol-Lowering Nutraceuticals Affecting Vascular Function and Cardiovascular Disease Risk. Current Cardiology Reports, 20(7), 53. https://doi.org/10.1007/s11886-018-0994-7	Yes
13	Betaine	2018	Metabolic Effects of Betaine: A Randomized Clinical Trial of Betaine Supplementation in Prediabetes	Randomized, double-masked, placebo-controlled trial	Persons with obesity and prediabetes (N = 27) were randomly assigned to receive betaine 3300 mg orally twice daily for 10 days, then 4950 mg twice daily for 12 weeks, or placebo.	Placebo	Betaine tended to reduce fasting glucose levels but had no other effect on glycemia. Serum total cholesterol levels increased after betaine treatment compared with placebo	Betaine had little metabolic effect. Additional studies may elucidate mechanisms contributing to differences between preclinical and human responses to betaine	N/A	https://pubmed.ncbi.nlm.nih.gov/29860335/	Grizales, A. M., Patti, M. E., Lin, A. P., Beckman, J. A., Sahni, V. A., Cloutier, E., Fowler, K. M., Dreyfuss, J. M., Pan, H., Kozuka, C., Lee, A., Basu, R., Pober, D. M., Gerszten, R. E., & Goldfine, A. B. (2018). Metabolic Effects of Betaine: A Randomized Clinical Trial of Betaine Supplementation in Prediabetes. The Journal of Clinical Endocrinology and Metabolism, 103(8), 3038–3049. https://doi.org/10.1210/JC.2018-00507	No
14	Betaine	2016	Long term betaine supplementation regulates genes involved in lipid andcholesterol metabolism of two muscles from an obese pig breed	Animal study	fourteen purebred AL pigs surgically castrated, Pigs wererandomly assigned into two experimental groups, Group C(n= 6), consuming the C diet, and Group CB (n= 8), consuming the Cdiet supplemented with betaine (1 g kg−1)	Control	Total intramuscular lipids from both muscles were significantlyhigher (Pb0.05) on CB (C diet supplemented with betaine;)- when compared to (commercial) C-fed pigs, mainly due to higher contents on intramuscular neutral lipids	This study examined the effect of a long term betaine supplementa-tion (1 g kg−1) on the regulation of genes involved in lipid and choles-terol metabolism. Betaine supplementation did not affect the FA profile of neutral in-tramuscular lipids fromL. lumborumandB. femorisof AL pigs	Betaine consumption by AL obese pigs led to an increase in (intramuscular fat) IMF of both muscles analyzed.	https://www.sciencedirect.com/science/article/pii/S0309174016304260	Albuquerque, A., Neves, J. A., Redondeiro, M., Laranjo, M., Félix, M. R., Freitas, A., Tirapicos, J. L., & Martins, J. M. (2017). Long term betaine supplementation regulates genes involved in lipid and cholesterol metabolism of two muscles from an obese pig breed. Meat Science, 124, 25–33. https://doi.org/10.1016/j.meatsci.2016.10.012	No
15	Betaine	2021	Effects of betaine supplementation on cardiovascular markers: A systematic review and Meta-analysis	Systematic review and Meta-analysis	This systematic review and meta-analysis compared the effects of betaine supplementation on cardiovascular disease (CVD) markers. Betaine supplementation had a significant effect on concentrations of betaine	Not Applicable - NA	Betaine supplementation had a significant effect on concentrations of betaine , total cholesterol (TC) , low-density lipoprotein (LDL), homocysteine , dimethylglycine , methionine. Moreover, our analysis indicated that betaine supplementation did not affect serum concentrations of triglyceride (TG), high-density lipoprotein (HDL), fasting blood glucose (FBG), C-reactive protein (CRP), liver enzymes, and blood pressure.	In conclusion, the present systematic review and meta-analysis supports the advantage of a lower dose of betaine supplementation (<4 g/d) on homocysteine concentrations without the lipid-augmenting effect observed with a higher dosage.	Studies examining betaine supplementation on CVD markers published up to February 2021 were identified through PubMed, the Cochrane Library, Web of Science, Embase, and SCOPUS.	https://www.tandfonline.com/doi/full/10.1080/10408398.2021.1902938?scroll=top&needAccess=true	Ashtary-Larky, D., Bagheri, R., Ghanavati, M., Asbaghi, O., Tinsley, G. M., Mombaini, D., Kooti, W., Kashkooli, S., & Wong, A. (2021). Effects of betaine supplementation on cardiovascular markers: A systematic review and Meta-analysis. Critical Reviews in Food Science and Nutrition, 1–18. https://doi.org/10.1080/10408398.2021.1902938	Yes
16	Betaine	2021	Effects of dietary betaine on cholesterol metabolism and hepatopancreas function in gibel carp (Carassius gibelio) fed with a high-fat diet	Animal study	This research aimed to investigate the role of dietary betaine in high-fat diet in cholesterol metabolism in gibel carp. Fish were randomly allocated to five groups and fed with basic diet, high-fat diet and high-fat diet with 1 g/kg, 4 g/kg and 16 g/kg betaine, respectively. The feeding trial lasted 10 weeks.	Control	The results showed that though betaine addition decreased fish final body weight, it alleviated lipid metabolism disorder caused by high-fat diet according to serum TC, TG, LDLC and HDLC levels. More importantly, betaine supplementation enhanced cholesterol synthesis as well as conversion of cholesterol to bile acid by promoting expression of HMGCR and CYP7A1 genes.	betaine supplementation not only promoted bile acid efflux and increased total bile acid level in the intestine but also improved intestinal lipase activity.	Dietary betaine supplementation was beneficial to alleviate high-fat feeding-induced lipid metabolism disorder, promote cholesterol conversion to bile acid and enhance hepatopancreas function in gibel carp.	https://onlinelibrary.wiley.com/doi/full/10.1111/anu.13316	Dong, X., Qin, W., Fu, Y., Ji, P., Wang, J., Du, X., Miao, S., & Sun, L. (2021). Effects of dietary betaine on cholesterol metabolism and hepatopancreas function in gibel carp (Carassius gibelio) fed with a high-fat diet. Aquaculture Nutrition, 27(6), 1789–1797. https://doi.org/https://doi.org/10.1111/anu.13316	No
17	policosanol	2018	Consumption of Cuban Policosanol Improves Blood Pressure and Lipid Profile via Enhancement of HDL Functionality in Healthy Women Subjects: Randomized, Double-Blinded, and Placebo-Controlled Study	Randomized, Double-Blinded, and Placebo-Controlled Study	consumption of policosanol for 8 weeks in healthy female subjects	Control	Consumption of policosanol for 8 weeks enhanced plasma antioxidant activity. In the policosanol group, plasma total cholesterol (TC) and triglyceride (TG) levels were reduced up to 20% and 14%, respectively, and HDL-C level was elevated up to 1.3-fold compared to that at week 0. TG/HDL-C and cholesteryl ester transfer protein (CETP) activities were reduced up to 36% and 20%, respectively.	In conclusion, consumption of policosanol for 8 weeks in healthy female subjects resulted in lowered blood pressure and CETP activity via elevation of HDL/apoA-I contents and enhancement of HDL functionalities, including cholesterol efflux and insulin secretion.	These functional enhancements of HDL can contribute to the prevention of aging-related diseases, hypertension, and stroke.	https://pubmed.ncbi.nlm.nih.gov/29854085/	Cho, K. H., Kim, S. J., Yadav, D., Kim, J. Y., & Kim, J. R. (2018). Consumption of Cuban Policosanol Improves Blood Pressure and Lipid Profile via Enhancement of HDL Functionality in Healthy Women Subjects: Randomized, Double-Blinded, and Placebo-Controlled Study. Oxidative Medicine and Cellular Longevity, 2018. https://doi.org/10.1155/2018/4809525	Yes
18	policosanol	2019	Short-Term Consumption of Cuban Policosanol Lowers Aortic and Peripheral Blood Pressure and Ameliorates Serum Lipid Parameters in Healthy Korean Participants: Randomized, Double-Blinded, and Placebo-Controlled Study	Randomized, Double-Blinded, and Placebo-Controlled Study	A total of 84 healthy participants were randomly allocated to three groups receiving placebo, 10 mg of policosanol, or 20 mg of policosanol for 12 weeks.	Placebo	The policosanol groups showed significant reductions of total cholesterol (TC) of 9.6% and 8.6% and low-density lipoproteins (LDL-C) of 21% and 18% for 10 mg and 20 mg of policosanol, respectively.	In conclusion, 12-week consumption of policosanol resulted in significant reductions of peripheral SBP and DBP, aortic SBP and DBP, mean arterial pressure (MAP), and serum TC and LDL-C with elevation of % HDL-C.	Between group comparisons using repeated measures ANOVA showed that the policosanol (10 mg and 20 mg) groups at 12 weeks had a significant reduction of TC (p = 0.0004 and p = 0.001) and LDL-C (p = 0.00005 and p = 0.0001) and elevation of %HDL-C (p = 0.048 and p = 0.014).	https://pubmed.ncbi.nlm.nih.gov/30841655/	Park, H. J., Yadav, D., Jeong, D. J., Kim, S. J., Bae, M. A., Kim, J. R., & Cho, K. H. (2019). Short-Term Consumption of Cuban Policosanol Lowers Aortic and Peripheral Blood Pressure and Ameliorates Serum Lipid Parameters in Healthy Korean Participants: Randomized, Double-Blinded, and Placebo-Controlled Study. International Journal of Environmental Research and Public Health, 16(5). https://doi.org/10.3390/IJERPH16050809	Yes
19	policosanol	2016	Effects of long-term supplementation of policosanol on blood cholesterol/glucose levels and 3-hydroxy-3-methylglutaryl coenzyme a reductase activity in a rat model fed high cholesterol diets	Animal study	The Wistar rats were assigned randomly to high-cholesterol diets (1.25% cholesterol) with or without policosanol (8.0 mg/kg body weight) for 6 weeks.	Control	Compared with the control group, dietary treatment with policosanol resulted in a significant decrease of blood cholesterol (p<0.01), blood glucose (p<0.01), triglyceride (p<0.001), and low density lipoprotein-cholesterol levels	These results indicate that policosanol decreases blood cholesterol levels by suppressing cholesterol biosynthesis via decrease of HMG-CoA activity.	Policosanol has the potential to be developed into an effective dietary strategy for both postprandial hyperglycemia and hypercholesterolemia.	https://link.springer.com/article/10.1007/s10068-016-0147-y#citeas	Lee, J.-Y., Choi, H.-Y., Kang, Y.-R., Chang, H.-B., Chun, H.-S., Lee, M.-S., & Kwon, Y.-I. (2016). Effects of long-term supplementation of policosanol on blood cholesterol/glucose levels and 3-hydroxy-3-methylglutaryl coenzyme a reductase activity in a rat model fed high cholesterol diets. Food Science and Biotechnology, 25(3), 899–904. https://doi.org/10.1007/s10068-016-0147-y	No
20	policosanol	2017	Consumption of policosanol enhances HDL functionality via CETP inhibition and reduces blood pressure and visceral fat in young and middle-aged subjects	Controlled clinical study	analyzed serum parameters in young non-smoker (YN; n=7, 24.0±2.4 years), young smoker (YS; n=7, 26.3±1.5 years), and middle-aged subjects (MN; n=11, 52.5±9.8 years) who consumed policosanol daily (10 mg/day) for 8 weeks.	Control	Serum triglyceride (TG) levels decreased to 28 and 26% from initial levels in the YN and MN groups, respectively. The percentage of high-density lipoprotein-cholesterol (HDL-C) in total cholesterol was elevated in all subjects (YN, 36%; YS, 35%; MN, 8%) after 8 weeks of policosanol consumption.	Electron microscopy revealed that the size and number of HDL particles increased after 8 weeks, and the YS group showed a 2-fold increase in particle size. Daily consumption of policosanol for 8 weeks resulted in lowered blood pressure, reduced serum TG level and CETP activity, and elevated HDL-C contents.	These functional enhancements of HDL can prevent and/or attenuate aging-related diseases, hypertension, diabetes and coronary heart disease.	https://www.spandidos-publications.com/10.3892/ijmm.2017.2907	Kim, J. Y., Kim, S. M., Kim, S. J., Lee, E. Y., Kim, J. R., & Cho, K. H. (2017). Consumption of policosanol enhances HDL functionality via CETP inhibition and reduces blood pressure and visceral fat in young and middle-aged subjects. International Journal of Molecular Medicine, 39(4), 889–899. https://doi.org/10.3892/ijmm.2017.2907	No
21	Armolipid Plus (AP) (berberine 500 mg, red yest rice, monacolin K 3 mg and policosanol 10 mg)	2019	Efficacy of a nutraceutical combination on lipid metabolism in patients with metabolic syndrome: a multicenter, double blind, randomized, placebo controlled trial	Multicenter, double blind, randomized, placebo controlled trial	One hundred and fifty eight patients, aged between 28 and 76 years old, were enrolled and randomized to receive either one tablet of AP or placebo (PL) once daily for 24 weeks.	Placebo	After 24 weeks of treatment, the analysis performed on 141 subjects (71 in AP arm and 70 in PL arm), showed a significant improvement of lipid profile in the AP group, with reduction in tot-C (- 13.2 mg/dl), LDL-C (- 13.9 mg/dl) and NHDL-C (- 15.3 mg/dl) and increase in HDL-C (+ 2.0 mg/dl). These changes were equally significant compared with placebo	The results of this study, applicable to a specific local population show that, in a population of subjects affected by MetS, treatment with AP improves the lipid profile and the most atherogenic factors, thus suggesting a reduction in the risk of development and progression of atherosclerosis, particularly in subjects with high atherogenic risk, due to the presence of sdLDL-C.	Although no significant difference was observed between the two arms in the reduction of HDL-C nevertheless it increased significantly in the AP group (AP + 2 mg/dL p < 0.05, PL 0.13 mg/dL).	https://pubmed.ncbi.nlm.nih.gov/30885221/	Galletti, F., Fazio, V., Gentile, M., Schillaci, G., Pucci, G., Battista, F., Mercurio, V., Bosso, G., Bonaduce, D., Brambilla, N., Vitalini, C., D'Amato, M., & Giacovelli, G. (2019). Efficacy of a nutraceutical combination on lipid metabolism in patients with metabolic syndrome: a multicenter, double blind, randomized, placebo controlled trial. Lipids in Health and Disease, 18(1). https://doi.org/10.1186/S12944-019-1002-Y	Yes

Table S12: Summary of articles containing extract.

Extract

No	Ingredients	Year	Title	Type of study	Method/Design of study	Control / Placebo	Outcome	Interpretation	Comment	Available at	Reference	Scientific Evidence
1	bergamot extract (120-mg flavonoids), phytosterols, vitamin C, and chlorogenic acid	2019	Three-arm, placebo-controlled, randomized clinical trial evaluating the metabolic effect of a combined nutraceutical containing a bergamot standardized flavonoid extract in dyslipidemic overweight subjects	Double-blind, placebo-controlled, parallel-group, dose-escalation, clinical trial	90 overweight dyslipidemic subjects. Participants were randomly allocated to treatment with two pills of either active treatment or placebo, or a combination of both (a pill per treatment).	Placebo	After 8 weeks, all active-treated groups experienced a significant improvement in triglycerides (TG) versus placebo and in low-density lipoprotein cholesterol (LDL-C) versus baseline and placebo treatments. In the high-dose-treated group, also total cholesterol (TC), significantly decreased.	The tested nutraceutical showed to improve lipid and glucose metabolism, adipokines pattern, and systemic inflammation in dyslipidemic overweight subjects.	All patients allocated to either low-dose or high-dose active treatment experienced a significant decrease in TG, LDL-C, and homeostatin model assessment of insulin resistance.	https://pubmed.ncbi.nlm.nih.gov/31225673/	Cicero, A. F. G., Fogacci, F., Bove, M., Giovannini, M., & Borghi, C. (2019). Three-arm, placebo-controlled, randomized clinical trial evaluating the metabolic effect of a combined nutraceutical containing a bergamot standardized flavonoid extract in dyslipidemic overweight subjects. Phytotherapy Research : PTR, 33(8), 2094–2101. https://doi.org/10.1002/PTR.6402	Yes
2	red yeast rice, policosanols and artichoke leaf extracts	2013	A combined natural supplement lowers LDL cholesterol in subjects with moderate untreated hypercholesterolemia: a randomized placebo-controlled trial	Randomized, double-blind, placebo-controlled trial.	natural cholesterol-lowering supplement (NCLS) containing red yeast rice, policosanols and artichoke leaf extracts on blood lipid concentrations as well as on safety parameters when given over 16 weeks in 100 volunteers with untreated moderate hypercholesterolemia	Placebo	Reduction of primary outcome low-density lipoprotein cholesterol as well as total cholesterol were observed after 16 weeks of supplementation with NCLS.	The NCLS was effective in reducing low-density lipoprotein cholesterol in subjects with moderate hypercholesterolemia, without modifying safety parameters.	No significant changes were observed in high-density lipoprotein, triacylglycerol, creatine kinase, lactate dehydrogenase and coenzyme Q10 levels, as well as in markers of liver and renal function.	https://pubmed.ncbi.nlm.nih.gov/23815518/	Barrat, E., Zair, Y., Ogier, N., Housez, B., Vergara, C., Maudet, C., Lescuyer, J. F., Bard, J. M., Carpentier, Y. A., Cazaubiel, M., & Peltier, S. L. (2013). A combined natural supplement lowers LDL cholesterol in subjects with moderate untreated hypercholesterolemia: a randomized placebo-controlled trial. International Journal of Food Sciences and Nutrition, 64(7), 882–889. https://doi.org/10.3109/09637486.2013.809405	Yes
3	polyphenol	2019	Chronic consumption of a low calorie, high polyphenol cranberry beverage attenuates inflammation and improves glucoregulation and HDL cholesterol in healthy overweight humans: a randomized controlled trial	Randomized, double-blind, placebo-controlled, parallel design trial.	78 overweight or obese men and women (30-70 years; BMI 27-35 kg/m2) with abdominal adiposity (waist: hip > 0.8 for women and > 0.9 for men; waist: height ≥ 0.5) consumed 450 mL placebo or low calorie, high polyphenol cranberry extract beverage (CEB) daily for 8 week . Blood and urine samples were collected after overnight fast at baseline and after 8 weeks of daily beverage consumption.	Placebo	CEB consumption for 8 week also reduced serum insulin and increased HDL cholesterol compared to placebo (P < 0.05).	An acute dose of low calorie, high polyphenol cranberry beverage improved antioxidant status, while 8 week daily consumption reduced cardiovascular disease risk factors by improving glucoregulation, downregulating inflammatory biomarkers, and increasing HDL cholesterol.	N/A	https://pubmed.ncbi.nlm.nih.gov/29476238/	Chew, B., Mathison, B., Kimble, L., McKay, D., Kaspar, K., Khoo, C., Chen, C. Y. O., & Blumberg, J. (2019). Chronic consumption of a low calorie, high polyphenol cranberry beverage attenuates inflammation and improves glucoregulation and HDL cholesterol in healthy overweight humans: a randomized controlled trial. European Journal of Nutrition, 58(3), 1223–1235. https://doi.org/10.1007/S00394-018-1643-Z	Yes
4	Apple polyphenols 30% extract	2020	Two apples a day lower serum cholesterol and improve cardiometabolic biomarkers in mildly hypercholesterolemic adults: a randomized, controlled, crossover trial	Randomized, controlled, crossover, intervention study.	Healthy mildly hypercholesterolemic volunteers (23 women, 17 men), consumed 2 apples/d (Renetta Canada, rich in proanthocyanidins (PAs)) or a sugar- and energy-matched apple control beverage (CB) for 8 wk each, separated by a 4-wk washout period.	Control	Whole apple (WA) consumption decreased serum total (WA: 5.89 mmol/L; CB: 6.11 mmol/L; P = 0.006) and LDL cholesterol (WA: 3.72 mmol/L; CB: 3.86 mmol/L; P = 0.031), triacylglycerol (WA: 1.17 mmol/L; CB: 1.30 mmol/L; P = 0.021),	These data support beneficial hypocholesterolemic and vascular effects of the daily consumption of PA-rich apples by mildly hypercholesterolemic individuals.	N/A	https://pubmed.ncbi.nlm.nih.gov/31840162/	Koutsos, A., Riccadonna, S., Ulaszewska, M. M., Franceschi, P., Trošt, K., Galvin, A., Braune, T., Fava, F., Perenzoni, D., Mattivi, F., Tuohy, K. M., & Lovegrove, J. A. (2020). Two apples a day lower serum cholesterol and improve cardiometabolic biomarkers in mildly hypercholesterolemic adults: a randomized, controlled, crossover trial. The American Journal of Clinical Nutrition, 111(2), 307–318. https://doi.org/10.1093/AJCN/NQZ282	No
5	**Extract** - Red yeast rice (RYR), sugar cane-derived policosanols (SCdP) and artichoke leaf extracts (ALEs)	2013	LDL-cholesterol-lowering effect of a dietary supplement with plant extracts in subjects with moderate hypercholesterolemia	Double-blind, randomized, parallel controlled study	39 subjects from 21 to 55 years with moderate hypercholesterolemia without drug treatment were assigned to 2 groups and then consumed either a DS containing RYR, SCdP and ALEs or a placebo over a 16-week period.	Placebo	LDL-cholesterol and TC were reduced by, respectively, 21.4 % (95 % CI, −13.3 to −24.9 %, p < 0.001) and 14.1 % (95 % CI, −10.1 to −18.0 %, p < 0.001) at week 16 in the DS group compared with baseline.	Daily consumption of this new DS decreased LDL-cholesterol and TC and is therefore an interesting, convenient aid in managing mild to moderate hypercholesterolemia.	N/A	https://link.springer.com/article/10.1007/s00394-012-0357-x	Ogier, N., Amiot, M. J., Georgé, S., Maillot, M., Mallmann, C., Maraninchi, M., Morange, S., Lescuyer, J.-F., Peltier, S. L., & Cardinault, N. (2013). LDL-cholesterol-lowering effect of a dietary supplement with plant extracts in subjects with moderate hypercholesterolemia. European Journal of Nutrition, 52(2), 547–557. https://doi.org/10.1007/s00394-012-0357-x	Yes
6	**Extract** - red yeast rice extract, policosanol and artichoke leaf extract	2013	Effect on LDL-cholesterol of a large dose of a dietary supplement with plant extracts in subjects with untreated moderate hypercholesterolaemia: a randomised, double-blind, placebo-controlled study	Randomised, double-blind, placebo-controlled clinical trial.	Forty-five healthy subjects (15 per group), with untreated hypercholesterolaemia, were included for this trial	Placebo	After 4 weeks of supplementation, LDL-C was significantly lower in 6-TAB (−0.21 g/l; 95 % CI −0.38 to −0.03 g/l; p = 0.0217) and 3-TAB (−0.25 g/l; 95 % CI −0.42 to −0.07 g/l; p = 0.0071) compared to Placebo, although no difference in LDL-cholesterol was observed between the two groups, while no effect was seen on triacylglycerol and HDL-cholesterol.	After 4 weeks of supplementation, LDL-C was significantly lower in TWICE DAILY DOSE (6 TABLET INSTEAD OF 3)	Supplementation with twice the recommended dose of the DS was effective in reducing LDL-cholesterol and appeared safe, but according to the present results, no additional benefit could be achieved compared to the recommended dose.	https://link.springer.com/article/10.1007/s00394-012-0486-2	Barrat, E., Zair, Y., Siryent, P., Chauveau, P., Maudet, C., Housez, B., Derbord, E., Lescuyer, J.-F., Bard, J.-M., Cazaubiel, M., & Peltier, S. L. (2013). Effect on LDL-cholesterol of a large dose of a dietary supplement with plant extracts in subjects with untreated moderate hypercholesterolaemia: a randomised, double-blind, placebo-controlled study. European Journal of Nutrition, 52(8), 1843–1852. https://doi.org/10.1007/s00394-012-0486-2	Yes
7	Coriandrum sativum and Allium sativum	2018	Supplementation of garlic and coriander seed powder: Impact on body mass index, lipid profile and blood pressure of hyperlipidemic patients	Randomized controlled trial	Eighty patients were partitioned into 4 groups, each group consisting of twenty patients. The groups were randomly assigned to three supplements i.e. garlic powder (GP), coriander seed powder (CSP) and mixture (1:1 dry weight basis) of GP and CSP at a dose rate of 2 g/day. The fourth group was kept as placebo. The patients were examined for serum lipid profile, BMI and blood pressure at the start (0 day), 20, 40 and 60th day of supplementation.	Placebo	The results indicated that all the supplements significantly (p<0.05) influenced the BMI, HDL, total cholesterol, triglycerides, LDL and systolic blood pressure of the patients. Among the supplements, GP had the highest influenced on BMI, TC, LDL and HDL whereas the impact of GP-CSP and CSP was more pronounced on TGL and blood pressure of the patients, respectively.	It was concluded that consumption of garlic, coriander and their mixture at a dose rate of 2 g/day is improving the lipid parameters of the patients.	All the parameters decreased with supplementation except HDL, which increased with the consumption of supplements.	https://pubmed.ncbi.nlm.nih.gov/30150192/	Zeb, F., Safdar, M., Fatima, S., Khan, S., Alam, S., Muhammad, M., Syed, A., Habib, F., & Shakoor, H. (2018). Supplementation of garlic and coriander seed powder: Impact on body mass index, lipid profile and blood pressure of hyperlipidemic patients. Pakistan Journal of Pharmaceutical Sciences, 31(5), 1935–1941. https://pubmed.ncbi.nlm.nih.gov/30150192/	No
8	**Extract** - garlic (Allium sativum)	2014	Effect of Nigella sativa and Allium sativum coadminstered with simvastatin in dyslipidemia patients: a prospective, randomized, double-blind trial	Randomized, double-blind, placebo controlled	study consisted of 4 week diet stabilization period that included a 4 week base line evaluation phase, followed by an 8 week treatment period. The study comprised men (n=127) and women (n=131) aged 24 to 57 years, who met the NCEP ATP III criteria for drug treatment of hyperlipidemia and dietary intervention. Three hundred patients were randomized to treatment and 258 completed the study.	Placebo	There were no significant differences between the two treatment groups at the baseline for triglyceride, HDL, Non-HDL, LDL and total cholesterol. Following 8 weeks treatment with simvastatin and placebo the reduction in Non-HDL, triglyceride, LDL and total cholesterol following treatment course was statistically highly significant (P= <0.01).	This study suggests that the evaluated combination was effective in correction of dyslipidemia. Large scale clinical trials comparing different doses are warranted.	However, the increase in HDL was significant (P=0.02). Patients who received simvastatin, plus black seed and garlic for 8 weeks of treatment show significant differences between baseline and after treatment course for all tested profiles (P=<0.01).	https://pubmed.ncbi.nlm.nih.gov/23848231/	AH, A. A. (2014). Effect of Nigella sativa and Allium sativum coadminstered with simvastatin in dyslipidemia patients: a prospective, randomized, double-blind trial. Anti-Inflammatory & Anti-Allergy Agents in Medicinal Chemistry, 13(1), 68–74. https://doi.org/10.2174/18715230113129990013	Yes
9	**Extract** - garlic (Allium sativum)	2021	The effect of garlic (Allium sativum) supplementation on the lipid parameters and blood pressure levels in women with polycystic ovary syndrome: A randomized controlled trial	Randomized, double-blinded control trial,	conducted on 80 PCOS patients. Participants were taught to intake either a total 800 mg/day garlic supplement or an identical placebo (starch) after lunch for 8 weeks. Physical activity, diet intake, anthropometric measures, and blood pressure were evaluated at baseline and end of the study.	Placebo	Garlic supplementation significantly reduced serum total cholesterol (change mean difference: -8.05, 95% CI: -15.47, -0.62) and LDL-C (change mean difference: -7.67, 95%CI: -14.64, -0.70) levels in comparison to the control group.	The present study suggested that garlic supplementation might be effective on lipid markers improvement. Further studies are needed to confirm our findings.	In addition, a trend to a significant decrease was found in serum triglyceride levels and Systolic blood pressure; however, no significant difference was observed between two groups in HDL-C and diastolic blood pressure levels.	https://pubmed.ncbi.nlm.nih.gov/34496450/	Zadhoush, R., Alavi-Naeini, A., Feizi, A., Naghshineh, E. & Ghazvini, M. R. (2021). The effect of garlic (Allium sativum) supplementation on the lipid parameters and blood pressure levels in women with polycystic ovary syndrome: A randomized controlled trial. Phytotherapy Research : PTR, 35(11), 6335–6342. https://doi.org/10.1002/PTR.7282	Yes
10	**Extract** - garlic (Allium sativum)	2019	Combination effect of voluntary exercise and garlic (Allium sativum) on oxidative stress, cholesterol level and histopathology of heart tissue in type 1 diabetic rats	Animal study	Thirty-five male Wistar rats were randomly assigned into five experimental groups Control, Diabetes, Diabetes+Garlic, Diabetes+Exercise, Diabetes+Garlic+Exercise groups: Animals received garlic homogenate (250 mg/kg) by oral gavage or subjected to voluntary exercise alone or together for 6 weeks. At the end of intervention blood and heart tissue samples were obtained and used for measurement of glycosylated haemoglobin (HbA1c), cholesterol, total antioxidant capacity (TAC), malondialdehyde (MDA) levels and histological analysis.	Control	significant increase in MDA level (P < 0.001) in the heart and serum of the diabetic group compared with the control group. However, 6 weeks treatment of the diabetic animals with garlic or exercise alone (P < 0.01) and in combination (P < 0.001) significantly decreased serum MDA level in comparison to the group with diabetes.	improved blood glucose, cholesterol, total antioxidant capacity, and MDA levels were established in both Diabetes+Garlic and Diabetes+Exercise groups.	The findings indicated that combination therapy with garlic and voluntary exercise may present more beneficial effects in heart histological remodeling in diabetic rats than the use of garlic or voluntary exercise alone	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6477110/	Ghyasi, R., Mohaddes, G., & Naderi, R. (2019). Combination effect of voluntary exercise and garlic (Allium sativum) on oxidative stress, cholesterol level and histopathology of heart tissue in type 1 diabetic rats. Journal of Cardiovascular and Thoracic Research, 11(1), 61–67. https://doi.org/10.15171/jcvtr.2019.10	No
11	cinnamon-, chromium- and magnesium-formulated honey	2016	The effect of a cinnamon-, chromium- and magnesium-formulated honey on glycaemic control, weight loss and lipid parameters in type 2 diabetes: an open-label cross-over randomised controlled trial	an open-label cross-over randomised controlled trial	Twelve individuals with type 2 diabetes received 53.5 g of a formulated honey and a control (non-formulated) kanuka honey in a random order for 40 days, using cross-over design. Fasting glucose, insulin, HbA1c, lipids and anthropometric measures were measured at baseline and end of treatment. A meal tolerance test was performed at baseline to assess acute metabolic response.	Control	There was a statistically significant reduction in total cholesterol by -0.29 mmol/L (95 % CI -0.57 to -0.23), LDL cholesterol by -0.29 mmol/L (95 % CI -0.57 to -0.23) and weight by -2.2 kg (95 % CI -4.2 to -0.1). There was a trend towards increased HDL and reduced systolic blood pressure in the intervention treatment.	The addition of cinnamon, chromium and magnesium supplementation to kanuka honey was not associated with a significant improvement in glucose metabolism or glycaemic control in individuals with type 2 diabetes.	Use of the formulated honey was associated with a reduction in weight and improvements in lipid parameters, and should be investigated further.	https://pubmed.ncbi.nlm.nih.gov/25986159/	A Whitfield, P., Parry-Strong, A., Walsh, E., Weatherall, M., & Krebs, J. D. (2016). The effect of a cinnamon-, chromium- and magnesium-formulated honey on glycaemic control, weight loss and lipid parameters in type 2 diabetes: an open-label cross-over randomised controlled trial. European Journal of Nutrition, 55(3), 1123–1131. https://doi.org/10.1007/S00394-015-0926-X	No
12	NutraforChol®, a nutraceutical product containing red yeast rice extract, guggulipid extract and chromium picolinate	2020	Efficacy and tolerability of a nutraceutical combination of red yeast rice, guggulipid, and chromium picolinate evaluated in a randomized, placebo-controlled, double-blind study	Randomized, placebo-controlled, double-blind study	NutraforChol®, a nutraceutical product containing red yeast rice extract, guggulipid extract and chromium picolinate, was evaluated on subjects who had total cholesterol level 200-239 mg/dL and LDL cholesterol level 100-159 mg/dL. In this study, a randomized, placebo-controlled, double-blind study which consisted of 4 weeks run-in period and 8 weeks treatment period was performed.	Placebo	NutraforChol® effectively decreased total cholesterol (-15.9 %) and LDL level (-19.9 %) after two weeks consumption. The total cholesterol and LDL reduction were maintained during 8 weeks study period. At study termination (week 8), there was a significant difference between total cholesterol level of NutraforChol® treated group (173.5 ± 21.7 mg/dL) and placebo-treated group (204.5 ± 22.8 mg/dL) (p < 0.05).	Thus, NutraforChol® may be considered as a complementary or alternative safe nutraceuticals for the treatment of mild dyslipidemic subjects.	In addition, there was a significant difference between LDL level at week 8 in NutraforChol® group (115.5 ± 22.2 mg/dL) and placebo-treated group (145.1 ± 23.7 mg/dL) (p < 0.05).	https://pubmed.ncbi.nlm.nih.gov/31987238/	Iskandar, I., Harahap, Y., Wijayanti, T. R., Sandra, M., Prasaja, B. & Cahyaningsih, P. (2020). Efficacy and tolerability of a nutraceutical combination of red yeast rice, guggulipid, and chromium picolinate evaluated in a randomized, placebo-controlled, double-blind study. Complementary Therapies in Medicine, 48. https://doi.org/10.1016/J.CTIM.2019.102282	Yes

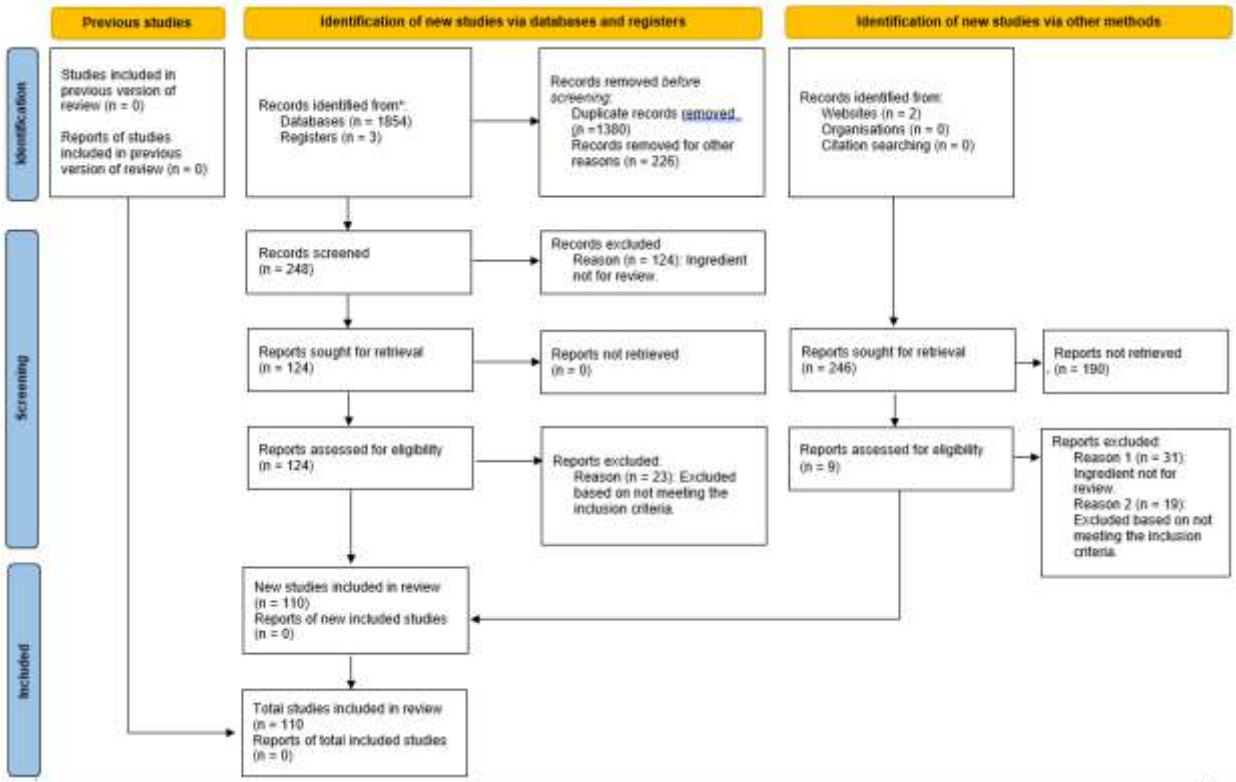
13	probiotic Bifidobacterium longum BB536 and red yeast rice extract	2019	Nutraceutical approach for the management of cardiovascular risk - a combination containing the probiotic Bifidobacterium longum BB536 and red yeast rice extract: results from a randomized, double-blind, placebo-controlled study	Randomized, double-blind, placebo-controlled study	A 12-week randomized, parallel, double-blind, placebo-controlled study. Thirty-three subjects (18-70 years) in primary CV prevention and low CV risk (SCORE: 0-1% in 24 and 2-4% in 9 subjects; LDL-C: 130-200 mg/dL) were randomly allocated to either nutraceutical (N = 16) or placebo (N = 17).	Placebo	Twelve-week treatment with the nutraceutical combination, compared to placebo, significantly reduced TC (- 16.7%), LDL-C (- 25.7%), non-HDL-C (- 24%) (all p < 0.0001), apoB (- 17%, p = 0.003).	A 12-week treatment with a nutraceutical combination containing the probiotic Bifidobacterium longum BB536 and RYR extract significantly improved the atherogenic lipid profile and was well tolerated by low CV risk subjects.	No adverse effects and a 97% compliance were observed.	https://pubmed.ncbi.nlm.nih.gov/30795775/	Buscica, M., Pavanello, C., Gandini, S., Macchi, C., Botta, M., Dall'Orto, D., dei Puppo, M., Bertolotti, M., Boisio, R., Mombelli, G., Sirtori, C. R., Calabresi, L., & Magni, P. (2019). Nutraceutical approach for the management of cardiovascular risk - a combination containing the probiotic Bifidobacterium longum BB536 and red yeast rice extract: results from a randomized, double-blind, placebo-controlled study. Nutrition Journal, 18(1). https://doi.org/10.1186/S12937-019-0438-2	Yes
14	Inulin, Pomegranate extract	2017	Cholesterol-lowering effects of dietary pomegranate extract and inulin in mice fed an obesogenic diet	Animal study	Male C57BL/6 J mice were fed high-fat/high-sucrose [HF/HS (32% energy from fat, 25% energy from sucrose)] diets supplemented with PomX (0.25%) and inulin (9%) alone or in combination for 4 weeks.	Control	Feeding the HF/HS diet supplemented with PomX and inulin individually resulted in a significant decrease in serum TC compared HF/HS control.	inulin mainly targeted hepatic cholesterol de novo synthesis and fecal cholesterol and bile acid excretion involving changes in the metabolism of the intestinal microbiome.	Supplementation with PomX and inulin together resulted in lower hepatic and serum total cholesterol compared to individual treatments. PomX showed a trend to decrease liver triglyceride (TG) levels, while inulin or PomX-inulin combination had no effect on either serum or liver TG levels.	https://www.sciencedirect.com/science/article/pii/S0955286316308294	Yang, J., Zhang, S., Henning, S. M., Lee, R., Hsu, M., Grojean, E., Pisegna, R., Ly, A., Heber, D., & Li, Z. (2018). Cholesterol-lowering effects of dietary pomegranate extract and inulin in mice fed an obesogenic diet. Journal of Nutritional Biochemistry, 52, 62–69. https://doi.org/10.1016/j.jnutbio.2017.10.003	No
15	artichoke leaf extract	2013	Beneficial effects of artichoke leaf extract supplementation on increasing HDL-cholesterol in subjects with primary mild hypercholesterolaemia: a double-blind, randomized, placebo-controlled trial	Double-blind, randomized, placebo-controlled trial	artichoke leaf extract (ALE) supplementation (250 mg, 2 b.i.d.) . clinical trial was performed on 92 overweight subjects with primary mild hypercholesterolaemia for 8 weeks. Forty-six subjects were randomized to supplementation (age: 54.2 ± 6.6 years, body mass index (BMI): 25.8 ± 3.9 kg/m(2), male/female: 20/26) and 46 subjects to placebo (age: 53.8 ± 9.0 years, BMI: 24.8 ± 1.6 kg/m(2), male/female: 21/25).	Placebo	Verum supplementation was associated with a significant increase in mean high-density lipoprotein (HDL)-cholesterol (p < 0.001) and in mean change in HDL-cholesterol (HDL-C) (p = 0.004). A significantly decreased difference was also found for the mean change in total cholesterol (p = 0.033), low-density lipoprotein (LDL)-cholesterol (p < 0.001), total cholesterol/HDL ratio (p < 0.001) and LDL/HDL ratio (p < 0.001), when verum and placebo treatment were compared.	These results indicate that ALE could play a relevant role in the management of mild hypercholesterolaemia, favouring in particular the increase in HDL-C, besides decreasing total cholesterol and LDL-cholesterol.	N/A	https://pubmed.ncbi.nlm.nih.gov/22746542/	Rondanelli, M., Giacosa, A., Opizzi, A., Faliva, M. A., Sala, P., Perna, S., Riva, A., Morazzoni, P., & Bombardelli, E. (2013). Beneficial effects of artichoke leaf extract supplementation on increasing HDL-cholesterol in subjects with primary mild hypercholesterolaemia: a double-blind, randomized, placebo-controlled trial. International Journal of Food Sciences and Nutrition, 64(1), 7–15. https://doi.org/10.3109/09637486.2012.700920	Yes
16	Artichoke and Bergamot	2021	Artichoke and Bergamot Phytosome Alliance: A Randomized Double Blind Clinical Trial in Mild Hypercholesterolemia	Randomized placebo-controlled trial.	600 mg of bergamot phytosome® (from Citrus Bergamia Risso) and 100 mg of artichoke leaf standardized dry extract (from Cynara cardunculus L.). Sixty overweight adults were randomized into two groups: 30 were supplemented and 30 received a placebo. The metabolic parameters and DXA body composition were evaluated at the start, after 30 and 60 days.	Placebo	Between the two groups, total and LDL cholesterol in the supplemented group (compared to placebo) showed significant decreases overtime.	In conclusion, the synergism between Citrus Bergamia polyphenols and Cynara cardunculus extracts may be an effective option and may potentially broaden the therapeutic role of botanicals in dyslipidemic patients.	A significant reduction of waist circumference and visceral adipose tissue (VAT) was recorded in the supplemented group (compared to placebo), even in subjects who did not follow a low-calorie diet.	https://pubmed.ncbi.nlm.nih.gov/35010984/	Riva, A., Petrangolini, G., Allegrini, P., Perna, S., Giacosa, A., Perpoi, G., Faliva, M. A., Naso, M., & Rondanelli, M. (2021). Artichoke and Bergamot Phytosome Alliance: A Randomized Double Blind Clinical Trial in Mild Hypercholesterolemia. Nutrients, 14(1). https://doi.org/10.3390/NU14010108	yes
17	Artichoke and bergamot	2022	Artichoke and bergamot extracts: a new opportunity for the management of dyslipidemia and related risk factors.	Review	this review aimed to describe the effects of artichoke and bergamot in modifying the lipid and inflammatory parameters described in in vitro, in vivo and clinical studies.	Not Applicable - NA	significant presence of polyphenols in their extracts, can exert this action associated with a number of other complementary inflammation and oxidation benefits.	The available data support the use of standardized compositions of artichoke and bergamot extracts, alone or in combination, in the treatment of mild to moderate dyslipidemia	significant presence of polyphenols in their extracts, can exert this action associated with a number of other complementary inflammation and oxidation benefits.	https://europepmc.org/article/med/35313442	Arnaboldi, L., Corsini, A., & Bellosta, S. (2022). Artichoke and bergamot extracts: a new opportunity for the management of dyslipidemia and related risk factors. Minerva Medica, 113(1), 141–157. https://doi.org/10.23736/s0026-4806.21.07950-7	No
18	Curcuminis	2012	Effects of Supplementation with Curcuminoids onDyslipidemia in Obese Patients: A RandomizedCrossover Trial	Randomized Crossover Trial	Participants(n= 30) were treated with curcuminoids (1 g/day), or placebo in a randomized, double-blind, placebo-controlled,crossover trial. Serum concentrations of total cholesterol, triglycerides, low-density lipoprotein cholesterol andhigh-density lipoprotein cholesterol, together with anthropometric parameters and high-sensitivity C-reactiveprotein were measured before and after each treatment period.	Placebo	erum triglycerides were significantly reducedfollowing curcumin supplementation (p= 0.009)	the findings of the present study indicated that curcuminoid supplementation (1 g/day for 30 days) leads to a significant reduction in serum triglycerides concentrations but do not have a significant influence on other lipid profile parameters as well as body mass index and body fat.	curcuminoids were not found to affect serum levelsof total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and high-sensitivityC-reactive protein (p>0.05)	https://onlinelibrary.wiley.com/doi/epdf/10.1002/ptr.4715	Mohammadi, A., Sahebkar, A., Iranshahi, M., Amini, M., Khojasteh, R., Ghayour-Mobarhan, M., & Ferns, G. A. (2013). Effects of supplementation with curcuminoids on dyslipidemia in obese patients: A randomized crossover trial. Phytotherapy Research, 27(3), 374–379. https://doi.org/10.1002/ptr.4715	yes
19	Apium graveolens	2019	The Effect of Celery (Apium graveolens L.) Leaf Infusion on Blood Cholesterol Levels in White Male Rat (Rattus norvegicus) Induced by Alloxan	Animal study	The sample used in this study were 25 white male rats Wistar strained aged 3-4 months with a bodyweight of 150-200 grams. The design used are were unidirectional pattern of completely randomized design with 5 treatments and 5 replications. Treatment 1 (P1) rats were given with the standard feed. Treatment 2 P2),rats were induced by alloxan. Treatment 3 (P3) rats were induced by alloxan and given 2 ml of 5% celery leaf infusion therapy. Treatment 4 (P4) rats were induced by alloxan and given 2 ml of 10% celery leaf infusion therapy. Treatment 5 (P5) rats were induced by alloxan and given 2 ml of 15% celery leaf infusion therapy. Celery leaf infusion was given every morning and evening. Administration of alloxan with a single dose of 150 mg / kg in IP and celery leaf infusion therapy were given for 14 days.	Control	The results showed that the infusion of celery leaves was not showing any effect (P> 0.05) on blood cholesterol levels of white male rats induced by alloxan.	Administration of celery leaves (Apium graveolens L.) infusion for 14 days with a concentration of 5%, 10% and 15% have no effect on blood cholesterol levels in male rats induced byalloxan.	Administration of celery leaves (Apium graveolens L.) infusion for 14 days with a concentration of 5%, 10% and 15% have no effect on blood cholesterol levels in male rats induced byalloxan.	http://202.4.186.66/JMV/article/view/4309/11584	Moelviani, K., & Armansyah, T. T. (2019). The Effect of Celery (Apium graveolens L.) Leaf Infusion on Blood Cholesterol Levels in White Male Rat (Rattus norvegicus) Induced by Alloxan. Jurnal Medika Veterinaria Februari, 13(1), 108–113. https://doi.org/10.21157/j.med.vet.v1	No
20	*Bauhinia variegata*	2019	Antidiabetic, anti-hyperlipidemic and antioxidant activities of Bauhinia variegata flower extract	Animal study	Ethanolic extract of B. variegata was administered orally to Streptozotocin (STZ) induced diabetic rats once daily for 21 days. Blood glucose levels were estimated at day 0, 7, 14 and 21 by glucometer (one touch) and lipid profile and histopathological examination of isolated organs (kidney, liver and pancreas) were also estimated on 21 day.	Control	The levels of triglycerides, total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), very low density lipoprotein (VLDL) were restored while administrating B. variegata.	it can be concluded from the present study that B. variegata possesses significant antidiabetic, anti-hyperlipidemic and antioxidant activities.	To evaluate antidiabetic, anti-hyperlipidemic and antioxidant activities of ethanolic extract of Bauhinia variegata flower.	https://www.sciencedirect.com/science/article/abs/pii/S1878818119302506	Tripathi, A. K., Gupta, P. S., & Singh, S. K. (2019). Antidiabetic, anti-hyperlipidemic and antioxidant activities of Bauhinia variegata flower extract. Biocatalysis and Agricultural Biotechnology, 19, 101142. https://doi.org/https://doi.org/10.1016/j.bcab.2019.101142	No
21	Coriandrum Sativum	2021	The Effectiveness of Coriander Seed Extract (Coriandrum Sativum) on Lowering Cholesterol Levels in Elderly Patients with Hypercholesterolemia	Quasi-experimental study with coriander seed extract as a treatment.	The treatment group was given an intervention in the form of coriander seed extract for 14 days which was recorded on the observation sheet while the control group was given health education about healthyeating patterns and lifestyles. This study was 15 elderly people per group. The data analysis technique used an independent T test.	Control	The results showed that the significance value of the treatment group and the control group before was 0.063, while the significance value after treatment was 0.038.	Based on the results of the independent t test, the significance value in the treatment group and the control group before being given coriander seed extract was 0.063 (p value > 0.05), which means there was no difference in cholesterol levels between the treatment group and the control group. Meanwhile, the significance value in thetreatment group and the control group after treatment was 0.038 (p value <0.05), which means that there was a difference in cholesterol levels between the treatment group and the control group.	Based on the results of the study above, it shows that there is a significant effect of coriander seed extract on cholesterol reduction in the elderly withhypercholesterolemia with p-value before 0.063 and p-value after 0.038.	https://jurnal.uns.ac.id/placentum/article/view/54727	Setyowati, A., & Ulya, matul. (2021). The Effectiveness of Coriander Seed Extract (Coriandrum Sativum) on Lowering Cholesterol Levels in Elderly Patients with Hypercholesterolemia. PLACENTUM Jurnal Ilmiah Kesehatan Dan Aplikasinya, 9(3). https://jurnal.uns.ac.id/placentum/article/view/54727	Yes
22	*Curcuma longa*	2020	Antidyslipidaemic and cardioprotective effects of turmeric (Curcuma longa) in rat fed a high cholesterol diet	Animal study	Twenty (20) rats were randomly grouped into four groups: A-D of five animals per group. Groups A-C received HCD (2000mg/kg, oral) and carbimazole (60mg/kg, oral) daily for eight weeks. Group A served as negative control. Group B (positive control) was treated with atorvastatin (20mg/kg), while group C served as treatment group and received Curcuma longa (400mg/kg) daily for eight weeks. Group D served as normal control and received no treatment. After the administration, biochemical markers of Lipid profiles (total cholesterol (TC), triglycerides (TG) and high density lipoprotein cholesterol (HDL-C)) were assayed using standard methods.	Control	Curcuma longa significantly induced hypolipidaemia and stabilized lipid biochemical markers (p<0.05 or p<0.01); and protected the cardiac muscle fibres from injuries.	Curcuma longa significantly induced hypolipidaemia and stabilized lipid biochemical markers (p<0.05 or p<0.01); and protected the cardiac muscle fibres from injuries. Tumeric (Curcuma longa) has antidyslipidaemic and cardioprotective effects.	This study showed that the aqueous extract of Curcuma longa(AECL) has effect on lipid metabolism and prevents cardiomyopathy in albino rats fed a high cholesterol diet and high doseCarbimazole.	http://www.jddtonline.info/index.php/jddt/article/view/3869	Uchendu, I. K., Ekeigwe, I. B., & Nnedu, E. B. (2020). Antidyslipidaemic and cardioprotective effects of turmeric (Curcuma longa) in rat fed a high cholesterol diet. Journal of Drug Delivery and Therapeutics, 10(1-s), 178–181. https://doi.org/10.22270/jddt.v10i1-s.3869	No
23	Cyperus rotundus	2015	Hypolipidemic Properties of Ethanol Extract of Cyperus rotundus Rhizome	Animal study	This study investigated the effect of ethanol extract of Cyperus rotundus rhizome on hyperlipidemia induced with carbimazole and cholesterol in male wister rats. Hyperlipidemia was induced using 400 mg/kg cholesterol and 2 mg/kg carbimazole. The lipemic control group was administered cholesterol and carbimazole but not the normal control group.	Control	Cholesterol and carbimazole administration caused a significant (p = 0.05) increase in the Total Cholesterol, Triglyceride (TG), Low Density Lipoprotein (LDL), non-High Density Lipoprotein (non-HDL) Cholesterol and LDL/HDL ratio and a significant (p = .05) decrease in the levels of HDL cholesterol in the lipemic control when compared to the normal control.	Treatment with ethanol extract of Cyperus rotundus at 250 mg/kg, 500 mg/kg and the standard hypolipidemic drug (simvastatin) at 5mg/kg significantly (p = 0.05) reduced total cholesterol, TG, LDL, LDL/HDL ratio, total non-HDL Cholesterol and also significantly (p=.05) increased the level of HDL cholesterol when compared to the non-treatment group (the lipemic control group).	Results of the present study indicate that Cyperus rotundus rhizome contains principles that have hypolipidemic potentials and which compare effectively with standard clinically used therapeutic Hypolipidemic agent, simvastatin	https://www.researchgate.net/profile/Ujowundu-Cosmas/publication/276456633_Hypolipidemic_Properties_of_Ethanol_Extract_of_Cyperus_rotundus_Rhizome/links/5abf614945851584fa7258b1/Hypolipidemic-Properties-of-Ethanol-Extract-of-Cyperus-rotundus-Rhizome.pdf	Okwu, G., Abanobi, S., Nnadi, U., Ujowundu, C., & Ene, A. (2015). Hypolipidemic Properties of Ethanol Extract of Cyperus rotundus Rhizome. International Journal of Biochemistry Research & Review, 7(3), 132–138. https://doi.org/10.9734/ijbcrr/2015/17158	No

24	Embelia ribes	2013	Anti-obesity effect of standardized ethanol extract of Embelia ribes in murine model of high fat diet-induced obesity	Animal study	In this study, a total of 50 rats were used and divided into five groups of 10 rats each. Group I: normal healthy control rats fed with rodent chow diet and administered 1% gum acacia [1 ml/kg, body weight (bw)] for the period of 28 days (NC). Group II: rats fed with HFD for the period of 28 days (HFD). Group III: rats fed with HFD for the period of 28 days + from 8th day, treated with ERE (100 mg/kg, bw) for period of 21 days (HFD + ERE). Group IV: rats fed with HFD for the period of 28 days + from 8th day, treated with Orlistat (10 mg/kg, bw) for period of 21 days (HFD + ORL). Group V: rats fed with rodent chow diet for the period of 28 days + from 8th day, treated with ERE (100 mg/kg, bw) for period of 21 days. Changes in body weight gain, body mass index (BMI), blood pressure, serum parameters, and myocardial oxidative stress parameters were measured.	Control	ERE showed a preventive effect on body weight gain, visceral fat accumulation and elevated blood pressure.	The extract treatment elicited a significant reduction in total cholesterol by 18%, and triglycerides by 24% while HDL-C level increased by 31%.	Furthermore, ERE treatment decreased the myocardial lipid peroxidation and increased antioxidant levels in obese rats.	https://reader.elsevier.com/reader/sd/pii/S2213434413000108?token=6F5B858D3DC9E1B257112AB2C974F9C9CC385870E72A335EF5410A07738DD0B8EB520DF467E8668AEA43C58617FF8DF3&originRegion=eu-west-1&originCreation=20220407163201	Bhandari, U., Chaudhari, H. S., Bisnoi, A. N., Kumar, V., Khanna, G., & Javed, K. (2013). Anti-obesity effect of standardized ethanol extract of Embelia ribes in murine model of high fat diet-induced obesity. PharmaNutrition, 1(2), 50–57. https://doi.org/10.1016/j.phanu.2013.01.001	No
25	Emblica officinalis	2019	A randomized, double blind, placebo controlled, multicenter clinical trial to assess the efficacy and safety of Emblica officinalis extract in patients with dyslipidemia	Randomized, double blind, placebo controlled, multicenter clinical trial	A total of 98 dyslipidemic patients were enrolled and divided into amla and placebo groups. Amla extract (500 mg) or a matching placebo capsule was administered twice daily for 12 weeks to the respective group of patients. The patients were followed up for 12 weeks and efficacy of study medication was assessed by analyzing lipid profile.	Placebo	In 12 weeks, the major lipids such as total cholesterol (TC) (p = 0.0003), triglyceride (TG) (p = 0.0003), low density lipoprotein cholesterol (LDL-C) (p = 0.0064) and very low density lipoprotein cholesterol (VLDL-C) (p = 0.0001) were significantly lower in amla group as compared to placebo group. Additionally, a 39% reduction in atherogenic index of the plasma (AIP) (p = 0.0177) was also noted in amla group.	The Amla extract has shown significant potential in reducing TC and TG levels as well as lipid ratios.	A single agent to reduce cholesterol as well as TG is rare. Cholesterol reduction is achieved without concomitant reduction of Co Q10, in contrast to what is observed with statins.	https://link.springer.com/content/pdf/10.1186/s12906-019-2430-y.pdf	Upadya, H., Prabhu, S., Prasad, A., Subramanian, D., Gupta, S. & Gopel, A. (2019). A randomized, double blind, placebo controlled, multicenter clinical trial to assess the efficacy and safety of Emblica officinalis extract in patients with dyslipidemia 11 Medical and Health Sciences 1103 Clinical Sciences. BMC Complementary and Alternative Medicine, 19(1). https://doi.org/10.1186/s12906-019-2430-y	Yes
26	Piper longum	2012	Hypolipidemic effects of a new piperine derivative GB-N from Piper longum in high-fat diet-fed rats	Animal study	rats were randomly divided into six groups, each group consisting of 10 rats. Except the control group, other groups were switched to high-fat rodent chow (modified from standard rodent chow, including 10% lard, 3% cholesterol, 0.5% sodium tauroglycocholate and 86.5% standard chow by weight) and they had free access to food and water throughout the experimental period (14 days).	Control	Compared with model rats, oral administration of GB-N at doses of 2.5–10 mg/kg to hyperlipidemic rats could significantly decrease the levels of serum TG from 1.54 mmol/L in hyperlipidemic rats to 0.94–1.02 mmol/L, with an increase in serum HDL-C levels from 0.40 mmol/L in hyperlipidemic rats to 1.21–2.26 mmol/L.	Over a period of 14 days of treatment, compared with model group, GB-N could significantly decrease the serum levels of TC, TG and LDL-C. GB-N could improve serum lipid profile in high-lipid diet-induced hyperlipidemic rats	GB-N had hypolipidemic activity via regulating lipid metabolism pathways in liver of hyperlipidemic rats and could be explored as a potential agent for the prevention of hyperlipidemia diseases.	https://www.tandfonline.com/doi/full/10.3109/13880209.2012.654395	Bao, L., Bai, S., & Borjihan, G. (2012). Hypolipidemic effects of a new piperine derivative GB-N from Piper longum in high-fat diet-fed rats. Pharmaceutical Biology, 50(8), 962–967. https://doi.org/10.3109/13880209.2012.654395	No
27	Plumbago zeylanica	2009	Antihyperlipidemic effect of aqueous extract of Plumbago zeylanica roots in diet-induced hyperlipidemic rat	Animal study	Healthy male albino rats (250-300 g) of Wistar strain were obtained from Bharat Serum, Thane, India. The rats were divided into seven groups, each group containing six rats. The group 1 (normal control) animals were retained on standard laboratory animal diet. However, the remaining animals in groups 2 to 7 were fed with a high fat diet for a period of 10 days. The group 2 animals (high fat diet control) received high fat diet with sodium carboxymethyl cellulose (drug vehicle) for 15 days. Group 3 and group 4 hyperlipidemic animals were orally administered with standard drugs atorvastatin (8mg kg−1, p.o.) and fenofibrate (20mg kg−1 p.o.) respectively, for 15 days. The animals of groups 5 to 7 were administered the aqueous extract of Plumbago zeylanica by oral gavage at the doses of 20, 40 and 80mg kg−1 p.o., respectively, for 15 days	Control	Administration of aqueous extract for a treatment period of 15 days at the dose of 40 and 80 mg kg−1 demonstrated a significant ($p < 0.05$) reduction in triglyceride and cholesterol levels with respect to the high fat diet control group. However, at the low dose of 20 mg kg−1 the aqueous extract was found to significantly decrease the triglyceride levels, but failed to exhibit significant cholesterol lowering activity	The rats fed with a high fat diet demonstrated a significant increase in triglyceride and total cholesterol. These elevated lipid levels were significantly reduced by aqueous extract at the dose of 40 and 80mg kg−1.	However, at the low dose of 20mg kg−1 the aqueous extract failed to significantly reduce cholesterol levels while a significant triglyceride lowering activity was demonstrated.	https://www.tandfonline.com/doi/pdf/10.1080/13880200902973779?needAccess=true	Pendurkar, S. R., & Mengi, S. A. (2009). Antihyperlipidemic effect of aqueous extract of Plumbago zeylanica roots in diet-induced hyperlipidemic rat. Pharmaceutical Biology, 47(10), 1004–1010. https://doi.org/10.1080/13880200902973779	No
28	Pterocarpus marsupium	2011	Antidiabetic, Antihyperlipidaemic and Antioxidant activity of Pterocarpus marsupium Roxb. in alloxan induced diabetic rats.	Animal study	In the investigation, a total of 24 rats (18 diabetic surviving rats and 6 normal rats) were taken and divided in to four groups of 6 rats each. Group I: Normal, untreated rats. Group II: Diabetic control rats GroupIII:Diabetic rats given ethanol extract of Pterocarpus marsupium wood(150 mg/kg of body weight). GroupIV:Diabetic rats given ethanol extract of Pterocarpus marsupium bark(150 mg/kg of body weight). GroupV:Diabetic rats given standard drug glibenclamide (600µg/kg of body weight). GroupVI: Diabetic rats given combined ethanol extract of Pterocarpus marsupium wood and bark(150+150 mg/kg of body weight).	Control		The glibenclamide and ethanol extracts of P. marsupium treated rats showed a significant decrease in the content of lipid profiles when compared with diabetic induced rats. Similarly HDL-C level decreased in alloxan induced diabetic rats when compared to normal rats.	In conclusion, the present study has shown that the ethanol extract of P. marsupium wood, bark and combined extracts have antidiabetic and antihyperlipidaemic and antioxidant effects.	https://www.researchgate.net/profile/Veerabahu-Mohan/publication/265977630_Antidiabetic_Antihyperlipidaemic_and_Antioxidant_activity_of_Pterocarpus_marsupium_Roxb_in_alloxan_induced_diabetic_rats/links/55267f2d0cf2628d5afe1484/Antidiabetic-Antihyperlipidaemic-and-Antioxidant-activity-of-Pterocarpus-marsupium-Roxb-in-alloxan-induced-diabetic-rats.pdf	Maruthupandian, A., Maruthupandian, A., & Mohan, V. R. (2011). Antidiabetic, Antihyperlipidaemic and Antioxidant activity of Pterocarpus marsupium Roxb. in alloxan induced diabetic rats. In Article in International Journal of PharmTech Research (Vol. 3, Issue 3). https://www.researchgate.net/publication/265977630	No
29	Terminalia chebula, Terminalia belerica and Emblica officinalis	2011	Hypolipidemic effect of triphala (Terminalia chebula, Terminalia belerica and Emblica officinalis) on female albino rats.	Animal study	Six groups (5rat/group) of female albino rats (Rattus albinus) were used. The 1st group used as control, in the 2 nd group hyperlipidemia (25% fat & 2% cholesterol) was induced for 3 weeks only then sacrified , the 3rd group was hyperlipidemic rats for 3 weeks then left for other 3 weeks without any additional treatment as a recovery period, the 4th group served as hyperlipidemic group for 3 weeks then treated with triphala for another 3 weeks (25 mg/100 gm b. wt.), the 5th group was hyperlipidemic (25% fat & 2% cholesterol) for 6 weeks and the 6th group served as hyperlipidemic rats for 6 weeks, and at the same time given triphala (25 mg/100 gm b. wt.) by oral administration.	Control	In the current investigation, triphala significantly turned back liver total lipids to the normal values.	Results of the present study showed that triphala has hypolipidemic action specially when used with fat free diet for treating hyperlipidemia.	It is recommended to use triphala in diets for hyperlipidemic patients or those people who have hyperlipidemic family history.	https://journals.ekb.eg/article_16780_ce52a249eab791c15556d673d178e0cf.pdf	Ahmed Eid, F., Helal, E. G., & Salah El-Din Ahmed El-Wahsh, A. M. (2011). Hypolipidemic effect of triphala (Terminalia chebula, Terminalia belerica and Emblica officinalis) on female albino rats. In The Egyptian Journal of Hospital Medicine (Vol. 43). https://journals.ekb.eg/article_16780_ce52a249eab791c15556d673d178e0cf.pdf	No
30	Triphala (Terminalia chebula, Terminalia belerica, and Phyllanthus emblica)	2021	Guggulu and Triphala for the Treatment of Hypercholesterolaemia: A Placebo-Controlled, Double-Blind, Randomised Trial	Placebo-Controlled, Double-Blind, Randomised Trial	90 individuals at low-moderate cardiovascular risk. Subjects were administered either Guggulu and Triphala or placebo three times daily for 3 months, with 3 months of follow-up after the end of treatment.	Placebo	At intention-to-treat analysis, from baseline to 3 months, total serum cholesterol decreased by 1.9% in the placebo (n = 44) and 3.3% (p = 0.01) in the intervention (n = 46) group. Serum LDL-C decreased by 4.9% (p = 0.03) and 4.8% (p = 0.02) in the placebo and intervention group, respectively, without differences between them.	Three months of treatment with Guggulu and Triphala did not show better effects than placebo on serum levels of total and LDL cholesterol	N/A	https://www.karger.com/Article/Abstract/510985#	Donato, F., Raffetti, E., Tonin elli, G., Festa, A., Scarcella, C., & Castellano, M. (2021). Guggulu and Triphala for the Treatment of Hypercholesterolaemia: A Placebo-Controlled, Double-Blind, Randomised Trial. Complementary Medicine Research, 28(3), 216–225. https://doi.org/10.1159/000510985	No
31	Ginger	2011	Ginger Enhances Antioxidant Activity and Attenuates Atherogenesis in Diabetic Cholesterol-Fed Rats	Animal study	Sprague-Dawley male rats were divided into three main groups of eight animals each. The animals of the first group were fed on a commercial pellet diet and served as control. Diabetes was induced in both second and third group of animals by intraperitoneal injection with one dose of streptozotocin (60 mg/kg) and fed on the same pellet diet mixed with 0.5% cholesterol. The animals of the third group were daily administered by ginger (25 mg/kg body weight) using oral gavages. After six weeks of the experimental period, different blood lipid parameters, lipid peroxidation and anti-oxidant activities were analyzed in all groups.	Control	a significant increase in plasma triglycerides, total cholesterol, LDL-cholesterol and HDL-cholesterol was observed in diabetic cholesterol-fed animals as compared to control group.	The results revealed that ginger produced a decline in blood glucose and significant decrease of triglyceride levels, but could not restore the increase of cholesterol and low density lipoprotein cholesterol levels of diabetic cholesterol-fed rats.	The data of the present study indicated that antiatherogenic effect of ginger could be attributed to its vital role in regulation of per-oxidation process, antioxidant activity and inhibition of monocyte migration and interaction accompanied with endothelial dysfunction.	http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.1078.635&rep=rep1&type=pdf	Al-Azhary, D. B. (2011). Ginger Enhances Antioxidant Activity and Attenuates Atherogenesis in Diabetic Cholesterol-Fed Rats. Australian Journal of Basic and Applied Sciences, 5(12), 2150–2158. http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.1078.635&rep=rep1&type=pdf	No

Table S13: Summary of articles containing fat.

Fat											
No	Ingredients	Year	Title	Type of study	Method/Design of study	Control / Placebo	Outcome	Interpretation	Comment	Available at	Reference	Scientific Evidence
1	soy lecithin	2016	Effect of soy lecithin on total cholesterol content, fatty acid composition and carcass characteristics in the Longissimus dorsi of Hanwoo steers (Korean native cattle)	Animal study	Hanwoo steers (24 head) were fed two diets: Control (CON) (concentrate + alcohol-fermented feed (AFF)) and soy lecithin treatment (CON + soy lecithin at 0.5% of the AFF).	Control	A lower cholesterol concentration was found in the Longissimus dorsi for the soy lecithin diet compared to the CON diet.	Soy lecithin supplementation would alter the total cholesterol content, polyunsaturated fatty acid profile and meat quality of Longissimus dorsi.	N/A	https://onlinelibrary.wiley.com/doi/abs/10.1111/asj.12660	Li, X. Z., Park, B. K., Hong, B. C., Ahn, J. S., & Shin, J. S. (2017). Effect of soy lecithin on total cholesterol content, fatty acid composition and carcass characteristics in the Longissimus dorsi of Hanwoo steers (Korean native cattle). Animal Science Journal, 88(6), 847–853. https://doi.org/https://doi.org/10.1111/asj.12660	No
2	soy lecithin	2018	Protective role of soybean lecithin in reducing hypercholesterolemia and DNA fragmentation inducing by high cholesterol in adult male rats	Animal study	Thirty two adult male rats have been used in this study, were randomly selected and equally divided in to four groups as follows C, T1 , T2, T3 for 42 days. C:control group, were given distilled water by gavage needle, rats of this group were given soybean lecithin only (430mg\kg\day). T2:rats of this groups were given only cholesterol (10gm\day). T3: rats of this groups were given soybean lecithin (430mg\kg\day).	Control	The daily supplementation of soybean lecithin induces a significant decrease (p > 0.05) in total cholesterol (TC) and triglyceride (TG) in both intact and hypercholesterolemic infected rats respectively.	oybean lecithin supplementation to rats has an important protective role on cardiovascular system and liver in hypercholesterolemic infected rats.	This supplementation can overcome the deleterious effect of hypercholesterolemia on heart and liver basically.	https://journals.uokufa.edu.iq/index.php/kjvs/article/view/7403	Alshammary, S. M., & Khaleel, L. W. (2018). Protective role of soybean lecithin in reducing hypercholesterolemia and DNA. Kufa Journal for Veterinary Medical Sciences, 9(1), 35–45. https://journals.uokufa.edu.iq/index.php/kjvs/article/view/7403	No
3	soy product	2021	A Non-Probiotic Fermented Soy Product Reduces Total and LDL Cholesterol: A Randomized Controlled Crossover Trial	Randomized Controlled Crossover Trial	In a randomized, crossover, intervention study, 27 men and women (aged 29-75 y) exhibiting at least two risk factors, consumed two packets (12.5 g each) daily of a fermented powdered soy product, or an isoenergic control powder made from germinated brown rice for 12 weeks each.	Control	The consumption of the fermented soy product resulted in a significantly greater mean change from baseline (compared to the germinated rice, all p < 0.05) in total cholesterol of -0.23 mmol/L (CI: -0.40, -0.06) compared with 0.14 mmol/L (CI: -0.03, 0.31), respectively; and low density lipoprotein (LDL) cholesterol -0.18 mmol/L (CI: -0.32, -0.04) compared with 0.04 mmol/L (CI: -0.01, 0.018) respectively.	The fermented soy powder consumed by participants in this study without implementing other changes in their typical diets, decreased the total and LDL cholesterol, and may serve as a dietary strategy to manage blood lipids.	N/A	https://pubmed.ncbi.nlm.nih.gov/33562090/	Jung, S. M., Haddad, E. H., Kaur, A., Sirirat, R., Kim, A. Y., Oda, K., Rajaram, S., & Sabaté, J. (2021). A Non-Probiotic Fermented Soy Product Reduces Total and LDL Cholesterol: A Randomized Controlled Crossover Trial. Nutrients, 13(2), 1–16. https://doi.org/10.3390/NU13020535	Yes
4	Soy Product	2016	Probiotic Soy Product Supplemented with Isoflavones Improves the Lipid Profile of Moderately Hypercholesterolemic Men: A Randomized Controlled Trial	Randomized placebo-controlled double-blind trial	49 male healthy men with total cholesterol (TC) >5.17 mmol/L and <6.21 mmol/L Intervention: The volunteers have consumed 200 mL of the probiotic soy product (group SP-10(10) CFU/day), isoflavone-supplemented probiotic soy product (group ISP-probiotic plus 50 mg of total isoflavones/100 g) or unfermented soy product (group USP-placebo) for 42 days in a randomized, double-blind study.	Control	fter 42 days, the ISP consumption led to improved total cholesterol, non-HDL-C (LDL + IDL + VLDL cholesterol fractions) and electronegative LDL concentrations (reduction of 13.8%, 14.7% and 24.2%, respectively, p < 0.05). The ISP and SP have prevented the reduction of HDL-C level after 42 days. The C-reactive protein and fibrinogen levels were not improved. The equol production by the ISP group subjects was inversely correlated with electronegative LDL concentration.	The results suggest that a regular consumption of this probiotic soy product, supplemented with isoflavones, could contribute to reducing the risk of cardiovascular diseases in moderately hypercholesterolemic men, through the an improvement in lipid profile and antioxidant properties.	N/A	https://pubmed.ncbi.nlm.nih.gov/26797632/	Cavallini, D. C. U., Manzoni, M. S. J., Bedani, R., Roselino, M. N., Celiberto, L. S., Vendramini, R. C., de Valdez, G. F., Abdalla, D. S. P., Pinto, R. A., Rosetto, D., Valentini, S. R., & Rossi, E. A. (2016). Probiotic Soy Product Supplemented with Isoflavones Improves the Lipid Profile of Moderately Hypercholesterolemic Men: A Randomized Controlled Trial. Nutrients, 8(1). https://doi.org/10.3390/NU8010052	Yes

Table S14: Full Prisma Flow Diagram



Full Prisma flow diagram showing identification of studies via databases (Page et al., 2020).

Appendix A: Research protocol

CANDIDATE'S SURNAME: **LEE**		FIRST NAME/S: **HYEON BOK**	STUDENT NUMBER: **360981**
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DEGREE FOR WHICH PROTOCOL IS BEING SUBMITTED: **MSC IN PHARMACEUTICAL AFFAIRS**			
PART-TIME OR FULL-TIME: **PART-TIME**			
FIRST REGISTERED FOR THIS DEGREE:	TERM : **JAN 1ST**	YEAR: **2020**	
DEPARTMENT: **Pharmacy and Pharmacology**			
TITLE OF PROPOSED RESEARCH: **A REVIEW ON NATURAL CHOLESTEROL LOWERING SUPPLEMENTS SOLD IN SOUTH AFRICAN PHARMACIES**			
CANDIDATE'S SIGNATURE:			DATE: **19/01/2022**
SUPERVISOR 1 (NAME & SURNAME): **Dr Ané Orchard**			% Supervision **33.3%**
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SYNOPSIS OF RESEARCH:

Cardiovascular diseases (CVDs) are the most prominent leading cause of death, accounting for approximately 17.9 million deaths in 2019, representing 32% of all deaths globally. Approximately 1 in 6 deaths in South Africa every year are cardiovascular-related. High blood cholesterol or dyslipidemia is defined as elevated total or low-density lipoprotein (LDL) cholesterol level or low high-density lipoprotein (HDL) levels. Dyslipidaemia increases the risk of arterial blockage, and therefore lowering the serum cholesterol level is essential in preventing or managing a disease due to high blood cholesterol. The most well-known drug for lowering cholesterols are HMG-CoA reductase inhibitors. This class of cholesterol-lowering drugs lowers the serum LDL level. Despite promising clinical outcomes, many patients seek an alternative option for managing high serum cholesterol. Many natural cholesterol-lowering supplements (NCLS) claiming to be effective in managing high blood cholesterol are available in South African pharmacies. This study aims to collate the list of products and review it's evidence for their use in dyslipidaemia. The different ingredients will be reviewed for their safety and efficacy. This review will provide practicing pharmacists with a guide to the evidence available on the NCLS.

Introduction

Cardiovascular diseases (CVDs) are the most prominent leading cause of death worldwide, accounting for approximately 17.9 million death in 2019, which represents 32% of all deaths that year (WHO, 2021). The most common risk factors for CVDs include low physical activity, an unhealthy diet, smoking, and excessive alcohol use (WHO, 2021). A close link between CVDs and dyslipidemia exists (Carson *et al., 2020).* Although cholesterol is a vital biological molecule in the human body, excessive cholesterol is directly related to CVDs, and such levels are easily attained with an unhealthy diet (Lin *et al*., 2015).

Cholesterol in the body comes from two sources. The liver produces majority of the cholesterol the body needs from various nutrients, mainly from saturated fats. The remainder of the cholesterol in the body comes from eating animal products. Cholesterol is transported in the blood by lipoproteins. The two main types of lipoproteins that carry cholesterol throughout the body are low-density lipoprotein (LDL) and high-density lipoprotein (HDL) (Lin *et al*., 2015). The HDL is known as good cholesterol, while LDL is known as bad cholesterol. The HDL takes cholesterol to the liver, which is separated from the bloodstream before it builds up in arteries, while LDL takes cholesterol directly to arteries, this can result in atherosclerosis, a plaque buildup that contributes to CVDs (Goldstein and Browns, 2015).

Dyslipidemia is defined as elevated total or low-density lipoproteins (LDL) cholesterol level or low levels of high-density lipoprotein (HDL) cholesterol (Goldstein and Browns, 2015). Dyslipidemia can be present irrespective of race, gender, genes, and age, if lifestyle and dietary habits have deteriorated (Fodor, 2010; García-Giustiniani and Stein, 2016). The correlation exists between low HDL levels, high LDL levels, and myocardial infarction or stroke (Goldstein and Browns, 2015). Patients who experienced a myocardial infarction were reported to have a significant increase in the cholesterol-carrying LDL, and a reduced level of HDL (Goldstein and Browns, 2015). Thus, controlling dyslipidemia is essential in the prevention and management of cardiovascular-related diseases.

Treatment of dyslipidemia consists of lifestyle modification and drug treatment (AHA, 2020). As part of lifestyle modification in lowering cholesterol level, healthy eating, smoking cessation, weight loss, and becoming more physically active is advised (AHA, 2020). People with high cholesterol levels are usually advised to modify their diet by reducing saturated and trans-fat intake. This can be achieved by limiting red meat, fried food, and dairy products made from whole milk (AHA, 2020).

The most well-known and widespread group of cholesterol-lowering drugs are called HMG CoA reductase inhibitors (colloquially referred to as statins). These are

cholesterol-lowering drugs that inhibit HMG CoA reductase, thereby lowering the serum LDL level (Bansal and Cassagno, 2021). Statins also contribute to anti-inflammatory effects, antioxidant effects, and prevention of platelet aggregation (Kavalipati *et al*., 2015). However, despite the availability of positive research and clinical trial data regarding cholesterol-lowering medicines, patient compliance is a challenge due to side effects and other personal reasons (Rosenthal, 2000). Most of the cholesterol-lowering medicines decrease blood cholesterol levels with few side effects such as headache, dizziness, and myalgia (Raal *et al*., 2011). Myalgia is one of the most common side effects experienced by patients on HMG CoA reductase inhibitor therapy, and it occurs in 5-10% of the patients (Marais, 2016). However, the type and severity of side effects vary from person to person (Raal *et al*., 2011).

Due to side effects and the desire to be on natural supplements, patients may seek an alternative treatment available at the pharmacy (Marais, 2016). A case report of a 49-year-old man taking a statin for the past three years showed improved cholesterol levels and eventually reaching an acceptable cholesterol range. However, the patient continued to experience myalgia, and a pharmacist advised discontinuing statin therapy and starting an over-the-counter supplement. After being on the natural supplements for nearly two months, a significant increase in LDL was noted (Marais, 2016). However, this is a weak evidence with insufficient data. Recommending a natural cholesterol lowering supplement (NCLS) product with insufficient evidence can be harmful to a patient. Thus, a review of the efficiency/ data available on the NCLS will provide practicing pharmacists with information that will benefit the patients.

According to Good Pharmacy Practice (GPP) of South Africa, Part 1: Rules relating to the code of conduct, the pharmacist’s primary concern must always be for the wellbeing of the patient. Therefore, the pharmacist's goal in providing medication therapy should be to accomplish suitable therapeutic outcomes that contribute to patient health and quality of life. When there is no evidence of efficacy on supplements, a pharmacist must not give an impression to a patient that the product is efficacious (GPPSA, 2017). Therefore, a pharmacist needs to be knowledgeable and provide non-biased information to patients while being aware of the different types of NCLS available in the market.

There is a critical need to review the evidence behind NCLS. Medical professionals should be able to provide adequate information on what medications are safe and effective. However, due to limited information about NCLS, limited advice is given to the patients (Fourie *et al*., 2017). Therefore, enough must be learned about complementary and alternative medicines so that professionals can make informed decisions on the use of NCLS. The Good Pharmacy Practice Section 2.22 outlines the minimum standard for the provision of complementary medicine and being able to provide appropriate information about the use and effectiveness of complementary medicine, as well as the possibility of adverse events, drug or food interactions, and the appropriateness of the stated claims (GPPSA, 2017). Thus, this review will provide practicing pharmacists with a guide to the evidence available on the NCLS. In addition, it will benefit patients seeking pharmacist's advice related to NCLS.

Aim

The project aims to review the evidence behind the natural cholesterol-lowering supplements (NCLS) available in South African pharmacies against the claims made by the manufacturer.

Objectives

1. To identify and list the ingredients in the natural cholesterol-lowering supplements available in South African pharmacies (Appendix A).
2. To compare the ingredients in the health supplements against scientific literature available and determine whether ingredients effectively lower serum cholesterol levels.
3. To evaluate the claims made by the manufacturer regarding health supplement’s dosage, dosing regimen, and its therapeutic effect of lowering cholesterol levels (Appendix B).

Methodology

1. Type of study

A scoping review study will be conducted and will be guided by the JBI scoping review methodology (The Joanna Briggs Institute, 2015). This review aims to provide descriptive evidence behind the natural cholesterol-lowering supplements (NCLS) available in South African pharmacies. The PRISMA-ScR was also reviewed as a guideline to ensure all aspects of the study were considered at the protocol development stage (Tricco et al., 2018b). This study design was chosen to allow the researcher to describe available evidence on the topic of a review on natural cholesterol lowering supplements sold in South African pharmacies. A scoping review is therefore valuable in examining the emerging evidence base and understanding around this topic. Studies will be included if they use the term 'natural cholesterol supplement,', 'cholesterol', 'lowering cholesterol,' 'cholesterol supplement,' 'triglycerides' 'LDL,' 'HDL' or related term in the title or abstract. Studies in English will be included; this will include publications that have been translated to ensure the researcher is able to complete an accurate and comprehensive review. Studies will be included from inception to 2022 as the aim of the study is to identify all available evidence. During the initial stage of the search strategy, if the number of publications that meet the inclusion criteria is too large, the researcher may choose to limit the timeframe accordingly to the most recent evidence such as the last 10 years i.e. 2012-2022.

2. Types of sources

The source of information will be published and unpublished (grey) literature including literature specific to the specific ingredients identified, *in vitro* studies, animal studies, randomized control trials, real-world trials, clinical trials, systematic reviews, monographs, papers that are dated after 2010, and meta-analyses. Sources which are not scientific, such as opinion papers, will be excluded due to the nature of the concept being studied as well as the aims and objectives of the study.

3. Search strategy

The researcher will use a three-step search strategy as recommended by the JBI guideline to ensure a comprehensive search (The Joanna Briggs Institute, 2015). The search strategy will aim to be comprehensive to identify all included sources of

information, published and unpublished literature. The researcher will search for all sources of evidence simultaneously which should result in greater sensitivity (The Joanna Briggs Institute, 2015).

Step (1): This will include a limited search of the identified databases; ScienceDirect, Scopus, Google Scholar, PubMed, ResearchGate, and Microsoft Academic Search.

The researcher will search the terms “natural cholesterol supplement” AND/OR “cholesterol” AND/OR “lowering cholesterol” AND/OR “cholesterol supplement” AND/OR “triglycerides’” AND/OR “LDL” AND/OR “HDL”.

Step (2): Following the initial search the researcher will examine text words present in the title and abstract of the retrieved studies (The Joanna Briggs Institute, 2015). This will include reviewing the index terms used to label the articles (The Joanna Briggs Institute, 2015). The researcher will also consider inclusion of synonyms, antonyms, homonyms, alternative spellings, different terminology, abbreviations, and different word endings. Once the keywords and index terms have been identified; the researcher will use the keywords and terms to conduct a second search across all included databases. Included databases: Academic Search Complete (EBSCO), Education Research Information Center (ERIC), ProQuest, Science Direct, CINAHL Plus (EBSCO), Clinical Key, Cochrane Library and Web of Science (The Joanna Briggs Institute, 2015).

Step (3): The researcher will search the reference list of all identified reports and articles to identify additional studies (The Joanna Briggs Institute, 2015). If applicable, the researcher may also contact authors of studies or reviews for further information (The Joanna Briggs Institute, 2015). As the search progresses, and the researcher becomes more familiar with the evidence base; additional keywords, terms or sources may be included in the search strategy (The Joanna Briggs Institute, 2015). The researcher may consult with an experienced librarian at the University of the Witwatersrand to inform protocol development and will continue to do so, during the study, as and when necessary, to review the search process.

4. Extraction of the results

The data extraction process will provide a means to chart the information to provide a clear summary that relates to the research question, aim and objectives (The Joanna Briggs Institute, 2015). Once the researcher has completed the search; full texts will be extracted, and the information will be managed.

The researcher will make use of a reference manager, Mendeley, to assist with this process. The key information extracted during the study will be recorded in a table. This will include information related to the authors, year of publication, study population and key findings. A provisional table for charting results has been included (Appendix C) and will be continually updated or refined as the search progresses (The Joanna Briggs Institute, 2015). The key information will be rigorously considered during the initial search to ensure all relevant results are extracted as the review process progresses.

5. Presentation of results

The results of the study will be presented in a tabular, graphic and/or diagrammatic format which charts the information relevant to the topic, research question, aims and objectives. An example of the table for charting results with relevant headings is included as Appendix C. The results will be descriptive, and this may include frequencies, measures of central tendency (mean, median or mode) and/or plots related to population group or date of study. The PRISMA flow diagram will be used (Appendix D) to indicate the search strategy and resultant articles selected (Suri et al., 2020). In addition, a description and explanation that relates to the review topic will be provided. The PRISMA-ScR checklist and explanation will also be used during the results and reporting phase to ensure comprehensive and transparent reporting of the review process and results.

Data Analysis

This research will use a quantitative approach. It will utilize the information from the collected information with the findings with other data sources. This research aims to provide information regarding the existing natural cholesterol-lowering supplements (NCLS) in South Africa. The information from the selected supplements will be tabulated in Microsoft 365 Excel, and the graph will be used to illustrate the difference in the selected products better. In addition, the pharmacological effect, the concentration of active ingredients, and the recommended dosage of the selected NCLSs will also be tabulated to analyze whether an adequate therapeutic level would be reached, thereby assisting to lower cholesterol levels. From this data gathered, it is possible to evaluate whether the product's claims are valid and not misleading.

Ethics

A scoping review does not require human participants. However, an Ethics Waiver is available (Appendix E). The use of the pseudo name will conceal the product's identity to avoid bias (Appendix A).

Funding

This is a low-cost self-funded research project. The primary resource needed for the project will be internet costs, printing costs, and stationery costs (Table 1).

Table 1: Cost summary

Type of cost	Cost in Rand
Internet (Data)	R 405.00 (Vodacom 5GB)
Printing	R 150.00 (50c per page)
Stationery	R 50.00
Total	**R 605.00**

Timeline

The timing for this project to be carried out is shown in Table 2.

Table 2: Timing summary

	2021					2022		
Research timeline	**Aug**	**Sep**	**Oct**	**Nov**	**Dec**	**Jan**	**Feb**	**Mar**
Literature review								
Writing protocol and submission								
Ethics waiver application								
Product Identification and evaluation								
Comparison to literature								
Data analysis								
Presentation and write up								

Reference

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Appendix B: Ethics clearance

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Human Research Ethics Committee (Medical)

Research Office Secretariat:
Faculty of Health Sciences, Phillip Tobias Health Sciences Building, 3rd Floor, Office 301/2/4, 29 Princess of Wales Terrace, Parktown, 2193
Private Bag 3, Wits 2050
Office email: HREC-Medical ResearchOffice@wits.ac.za
Website: www.wits.ac.za/research/about-our-research/ethics-and-research-integrity/

Ref: W-CBP-211025-01 25/10/2021

TO WHOM IT MAY CONCERN:

Waiver:	This certifies that the following research does not require clearance from the Human Research Ethics Committee (Medical)
Investigator:	Mr Hyeon Bok Lee
Supervisors:	Dr Anè Orchard, Mr Muhammed Vally and Ms Razeeya Khan
Department:	Pharmacy and Pharmacology
Project title:	A review on natural cholesterol lowering supplements sold in South African pharmacies
Reason:	A review of information in the public domain. No human participants will be involved in the study.

Dr CB Penny

Chairperson: Human Research Ethics Committee (Medical)

Copy – HREC (Medical) Secretariat: Ms Zanele Ndlovu, Ms Mapula Ramaila and Mr Rhulani Mkansi

Appendix C: Approval letter from assessors committee

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

Private Bag 3 Wits, 2050
Fax: 027117172119
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Reference: Mrs Sandra Benn
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25 October 2022
Person No: 360981
PAG

Mr HB Lee
15 Boschendal Estate
Wellington Crescent
Lonehill
2191
South Africa

Dear Mr Hyeon Bok Lee

Master of Science in Medicine: Approval of Title

We have pleasure in advising that your proposal entitled *A review on natural cholesterol lowering supplements sold in South African Pharmacies* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences