Invited Review

Natural compounds as anti-atherogenic agents: Clinical evidence for improved cardiovascular outcomes.

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Abstract

Atherosclerosis, a chronic progressive inflammatory condition characterized by the formation of lipid-laden lesions in arterial walls, is associated with substantial morbidity (including ischaemic stroke and myocardial infarction) and mortality. Risk factors for atherosclerosis are well understood and can be ameliorated by evidence-based and guideline-directed pharmaceutical agents (e.g. the reduction of circulating concentrations of low-density lipoprotein cholesterol by statins). Additionally, many natural products (usually food derivatives) and 'nutraceuticals' (pharmaceutical formulations prepared from components of foods) have also been shown to have favourable effects on risk factors for atherosclerotic cardiovascular disease. This literature review summarises the evidence for anti-atherogenic natural compounds. The article focuses on agents which are discussed in international guidelines and are supported by extensive high-quality randomized-controlled trial (RCT) data. We focus on micronutrients (compounds present in food in small quantities) and nutraceuticals, in particular, phytosterols, polyunsaturated ω-3 fatty acids and red-yeast rice. We conclude that the 'nutraceutical approach' (identify the active ingredients in natural products; produce high-quality products according to Good Manufacturing Practice guidelines; evaluate them in ling-term outcomes trials) is the mechanism by which the domains of natural product research and evidence-based medicine can move closer together.

Keywords: Atherosclerosis, natural products, cholesterol, lipoproteins, nutraceuticals

Key Points:

- A wide variety of nutraceutical agents have favourable effects on lipid and inflammatory risk factors for cardiovascular diseases, however long-term trials with 'hard' outcomes are rare.
- Phytosterols reduce blood cholesterol levels and are well tolerated, however the effects on CVD risk are conflicting.
- Polyunsaturated ω-3 fatty acids have been extensively evaluated in long-term clinical trials for their triglyceride-lowering effects. High--dose, high-purity eicosapentaenoic acid reduces cardiovascular events.
- Red-yeast rice contains the active ingredient monacolin K, which is chemically identical to lovastatin, reduced cardiovascular events in long-term trials.
- Nutraceuticals containing natural products are safe and well-tolerated, but they might harm patients owing to variations in product quality and composition, toxic contaminants, and the unknown long-term effects of some agents.

Table of Abbreviations

AE	Adverse effects
AHA	American Heart Association
AMPK	Adenosine-monophosphate-kinase
CVD	Cardiovascular disease
DHA	Docosahexaenoic acid
EACPR	European Association for Cardiovascular Prevention & Rehabilitation
EPA	Eicosapentaenoic acid
ESC	European Society of Cardiology
FDA	U.S. Food and Drug Administration
FMD	Flow mediated dilation
GI	Gastro-intestinal
HDL-C	High-density lipoprotein cholesterol
HMGCR	3-hydroxy-3-methyl-glutaryl-coenzyme A reductase
ILEP	International Lipid Expert Panel
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
MI	Myocardial infarction
NICE	National Institute for Health and Care Excellence
PUFA	Polyunsaturated fatty acids
PWV	Pulse-wave velocity
RCT	Randomized-controlled trial
TC	Total Cholesterol

1. Introduction

Atherosclerosis is a chronic, progressive, inflammatory condition characterized by the formation of lipid-laden lesions in arterial walls[1]. Cardiovascular complications of atherosclerosis include myocardial infarction (MI) and angina. Cerebrovascular complications result in ischaemic stroke and transient ischaemic attacks. Other life-threatening complications include abdominal aortic aneurisms[1]. All organs and tissues can be adversely affected by acute or chronic flow-limiting obstructions caused by atherosclerotic plaques, and atherosclerosis is responsible for substantial morbidity and mortality. The World Health Organisation, in their Global Burden of Disease report, estimated that 17.9 million deaths in 2017 were attributable to cardiovascular disease [2].

This seemingly bleak outlook is to some extent compensated by the considerable advances made in recent years in the prevention of atherosclerosis and its cardiovascular and cerebrovascular sequelae. The Framingham Heart Study, both introduced the general concept of 'risk factors' for diseases [3], leading to the development of risk-prediction tools[4] and confirmed earlier observations by Gofman [5] of an association between low-density lipoprotein cholesterol (LDL-C) and cardiovascular disease (CVD). The observation that dietary saturated fat was associated with CVD led Ancel Keys to promote the 'Mediterranean Diet' in which saturated fats are largely replaced with polyunsaturated fats. This recommendation remains valid half a century later [6].

Complementing the interest of scientists, clinicians and the public in the avoidance of foods which promote heard disease, an enormous body of work has investigated the potential of the constituents of food, and other natural products to prevent cardiovascular diseases. The volume of such research can be illustrated by a search of Google Scholar®, using the terms *(nutraceutical OR food OR natural product) AND (heart OR cardiovascular OR cardiac OR*

myocardial) which returns 5.4 million results (August 2020). These publications describe investigations into a very wide range of whole foods, and specific natural products with putative anti-atherosclerotic actions. The foods and substances have been identified by a variety of mechanisms, including studies comparing dietary patterns (and disease prevalence) between different countries, from determining the constituents of traditional remedies, and from experimental studies which have identified effects of natural products on biological targets involved in the pathogenesis of atherosclerosis[7-9].

When particular foods are consumed as part of the normal diet because of a presumed health benefit from consumption, the intervention can be considered to be a 'functional food'. When some chemical component (or a mixture of components) of food are processed and presented in a pharmaceutical formulation, such as tablets, capsules, suspensions, then the term 'nutraceutical' is used [10]. Despite the huge scientific and public interest in the potential for nutraceuticals and functional foods to prevent and treat disease, and notwithstanding the enormous volume of publications in the field, this field of study is less well supported by evidence-based medicine than conventional pharmaceuticals. This situation is the result of several difficulties. RCTs of dietary interventions are very hard to conduct in a rigorous manner, and there are rarely any clear economic or regulatory drivers to perform such studies[11]. RCTs of nutraceuticals are technically easier, however, because natural products are not patentable in many jurisdictions, studies are often conducted on a low budget. Frequently studies are conducted using relatively small sample sizes, and short durations of follow-up relying on surrogate biomarkers, rather than patient-orientated outcomes. Product manufacturers may also be reluctant to perform studies, which might make their product appear like a pharmaceutical, because such studies may complicate a marketing approach, which relies upon consumer perception of natural products as ‘mild’ and ‘safe’. Observational studies investigating relationships between reported dietary consumptions and health outcomes are

common but are limited by residual confounding, meaning that they cannot establish causal relationships[12]. The fact that individuals who eat healthily or take nutritional supplements are likely to be generally health-conscious is a particular problem for investigators evaluating the health benefits of an individual dietary component. However, carefully an observational study is planned; it cannot eliminate all possible confounders. For these reasons, natural products, functional foods and nutraceuticals have received relatively little attention in international guidelines, which require high standards of evidence (ideally RCTs) in order to make practice recommendations. Nevertheless, this topic is increasingly being addressed by guideline committees[13-17].

2. Aim

This review aims to summarise the evidence for anti-atherogenic natural compounds. We will focus on agents which are a) discussed in international guidelines and b) are supported by extensive high-quality RCT data. We will focus on micronutrients (compounds present in food in small quantities) rather than macronutrient (e.g. protein, carbohydrate, triglyceride) components of the diet for which comprehensive reviews exist [18-21]. Established and putative mechanisms of actions for natural products have been extensively detailed elsewhere [14]. These will not be repeated in detail here, but the interested reader will be directed to relevant sources of information.

This paper is based upon data from major relevant international guidelines (and the references they cite) in addition to database searches to identify RCT investigating long-term effects of nutraceuticals on hard outcomes relating to atherosclerosis (e.g mortality, stroke, MI, heart failure, acute coronary syndromes).

3. Mechanism of action of anti-atherogenic natural products

Many natural products contain multiple active ingredients, and may act *via* multiple mechanisms. The International Lipid Expert Panel Position (ILEP) Position Paper: 'Lipid lowering nutraceuticals in clinical practice' has summarised the mechanisms for a large number of nutraceuticals [14]. These are briefly summarised here in Table 1. Some general trends can be observed. Many natural products (e.g. phytosterols) are thought to reduce the absorption of cholesterol in the gut, or to increase the excretion of cholesterol by preventing enterohepatic recycling of bile acids (e.g. soluble fibres). Several compounds (pantethine, bergamot flavonoids) are reported to reduce the hepatic production of cholesterol. In some cases, this is achieved by inhibition of the enzyme 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMGCR), the target of 'statin' drugs. The compound 'monacolin K', obtained from red yeast rice, is chemically identical to lovastatin. Several natural compounds, including policosanols and polyphenols, increase the activity of adenosine-monophosphate-kinase (AMPK) and thereby increase the rate of ß-oxidation of fatty acids. Constituents of berberine have been demonstrated to reduce the activity of proprotein convertase subtilisin/kexin type 9 (PCSK9), thereby increasing expression of LDL-receptors (LDL-R) on hepatocytes and enhancing the clearance of LDL from plasma. PCSK9 is the target of the monoclonal antibody therapies alirocumab and evolocumab, which result in substantial reductions of circulating LDL-C and cardiovascular outcomes[22]. Soy acts through modulation of sterol regulatory element-binding proteins (SREBP), SREBP-1 and SREBP-1 to reduce the secretion of lipoproteins from the liver, reduce cholesterol synthesis, increase cholesterol clearance from the blood and increase excretion of bile salts in the faeces. Interested releasers are directed to the International Lipid Expert Panel (ILEP) position paper for more detailed descriptions of the mechanisms [14].

4. Outcomes in the evaluation of anti-atherogenic natural products

As described above, RCTs of nutraceuticals are often limited by short durations of follow up, and the use of surrogate biomarkers. This is problematic because it is not known whether beneficial effects on biomarkers are sustained over time, and even if they are, whether they result in improvements in hard outcomes. Furthermore long-term safety has not been established for many products (See Section 8, below). Typical biomarkers employed in clinical trials include standard constituents of lipid panels (e.g. total cholesterol (TC), LDL-C, HDL-C, non-HDL-C, TG). Many trials also measure functional parameters of blood vessels (e.g. flow mediated dilation (FMD) and pulse-wave velocity (PWV)) or circulation concentrations of inflammatory markers (e.g. high-sensitivity C-reactive protein (hs-CRP) and tumour necrosis factor-alpha (TNF-alpha) (**Table 1**). The recent Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS)[23] provided the first definitive evidence of the hypothesis that inflammation is an important contributor to the pathogenesis of atherosclerotic disease [24] and provides a compelling rationale for the exploration of potential anti-inflammatory nutraceuticals in this conditions. Nevertheless, seemingly favourable changes in biomarkers must be treated with caution, as they do not guarantee favourable clinical outcomes. For example, whilst treatment with canakinumab, an anti-IL-1β monoclonal antibody reduced hs-CRP and cardiovascular events[23], methotrexate, had no effect on outcomes in a high-risk secondary prevention population [25]. Similarly, whilst circulating concentrations of HDL-C are inversely correlated with CVD risk at a population level, interventions to increase HDL-C have little or no effect on outcomes. Indeed, high levels of 'dysfunctional' HDL-C may be harmful [26], and there is an increasing recognition of the importance of the 'quality' rather than the 'quantity' of HDL-C [27]. Similarly, whilst LDL-C is strongly correlated with CVD risk in population studies, only LDL-C-lowering interventions which upregulate LDL-receptors appear to reduce the risk of CV events [28]. These observations illustrate the difficulties of

interpreting the short-term outcomes on biomarkers typically measured in studies of anti-atherogenic natural products.

5. Anti-atherogenic natural products in clinical guidelines and position papers

Recommendations relating to nutraceuticals in major international guidelines are discussed below:

5.1. International Lipid Expert Panel

The most extensive recommendations for the use of nutraceuticals in the context of the prevention of atherosclerotic disease have been produced by the ILEP. In 2017, ILEP published their position paper 'Lipid-lowering nutraceuticals in clinical practice' [14] which provides a comprehensive description of the mechanism of action of a wide range of nutraceuticals, and describes their effects on important biomarkers. The information presented in the paper is summarised here in Table 1. For each nutraceutical of group of nutraceuticals, the class of recommendation (See Table S1 for explanation) and Level of Evidence (See Table S2 for explanation) have been summarised. Further ILEP opinion articles and position papers have discussed the evidence supporting the use of nutraceuticals in a range of conditions and specialist patient groups. These include: patients with elevated lipids, but low overall risk of CVD [29]. Patients at high risk of CVD who fail to meet lipid treatment goals with conventional phrmaceuticals[8], athletes and patients performing regular intense exercise[30], patients with heart failure[15] and individuals who experience statin intolerance[13, 17]. These are discussed further in Part 9, below.

5.2. European Society of Cardiology (ESC) / European Atherosclerosis Society (EAS)

The 2019 ESC/EAS Guidelines for the management of dyslipidaemias discuss a range of lifestyle techniques to reduce the risk of cardiovascular disease. These recommendations

include dietary recommendations (both relating to macronutrients and micronutrients) (Table 2). As with the ILEP position paper, the ESC/EAS guidelines classify the evidence supporting a range of interventions. Three natural products relevant to this discussion are given a 'Class A' recommendation. These are phytosterol-enhanced foods and red yeast rice nutraceuticals to reduce LDL-C and polyunsaturated ω-3 fatty acid supplements to reduce TG-rich lipoproteins. The high rating of the evidence for these interventions reflects the fact that, compared with many other nutraceuticals, larger, longer trials have been conducted with these agents, and in some cases CVD outcomes have been reported. The evidence supporting these three interventions is discussed in more detail in Section 7, below. The ESC/EAS guidelines also discuss a range of other natural product interventions, including policosanols, berberine, soy, although they highlight the lack of evidence supporting the use of these interventions.

5.3. American College of Cardiology / American Heart Association

American guidelines for the primary prevention of cardiovascular disease[31] and the management of blood cholesterol [32] do not endorse natural products for the prevention of atherosclerotic disease.

5.4. National Institute for Health and Care Excellence (NICE) guidelines (United Kingdom)

The most recent NICE guidelines do not endorse any natural products for the prevention of atherosclerosis and cardiovascular disease[33]. Furthermore, the guidelines advise against the use of coenzyme Q10 or vitamin D (which some studies have reported improve adherence to statin therapy [34, 35]), nicotinic acid (niacin) and ω-3 fatty acid compounds. [33]

6. Specific natural products with 'Level A' Evidence in ESC Guidelines

6.1. Polyunsaturated ω-3 fatty acids

Polyunsaturated ω-3 fatty acids provide a case study of the ideal situation whereby natural products can be standardised, produced to pharmaceutical quality standards and rigorously assessed in randomized outcomes trials. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) reduce circulating triglycerides [36] and have been recently evaluated in a range of trials. The Nutrition Committee of the American Heart Association (AHA) recommends preparations should contain 460 mg EPA, 380 mg DHA [37]. However it is important to note that the majority of pharmaceutical preparations of 'fish oil' or polyunsaturated fatty acids (PUFAs) available for sale in shops and pharmacies typically contain a variety of ingredients, usually including relatively low concentrations of EPA and DHA, and may contain contaminants, including mercury. Recent clinical trial evidence has demonstrated that the dose and purity of the ingredients appear to be very important in determining outcomes.

The ASCEND trial[38] and VITAL study[39] were placebo-controlled randomized two-by-two factorial evaluation of a preparation corresponding the AHA formula. ASCEND included a high-risk, population of 15,480 participants with diabetes whereas VITAL recruited 25,871 individuals, including men over the age of 50 years, and women 55 years or older. Both studies employed composite cardiovascular primary outcomes. No difference in outcomes was observed between treatment and controls over a mean follow-up of 7.4 years in ASCEND, or 5.3 years in VITAL. Another trial, STRENGTH, which used a mixture of EPA and DHA to reduce hypertriglyceridemia in statin-treated patients with high levels of triglycerides and low levels of high-density lipoprotein cholesterol was recently halted due to futility [40 41].

In contrast to these three 'negative' results, the REDUCE-IT randomized, placebo-controlled trial evaluated icosapent ethyl, a high dose (4g) preparation of pure EPA in 8179 participants.

Over a median five-year follow-up, there was a remarkable 25% relative reduction (HR 0.75 95% [CI] 0.68 -0.83 p < 0.001) in first CV events (a composite of cardiovascular death, MI, stroke, coronary revascularization and unstable angina) in the treatment group compared to control [42]. Whereas many outcomes trials only consider the first events, a pre-specified analysis of REDUCE-IT investigated subsequent ischaemic events, which were also reduced by icosapent ethyl [43]. Icosapent ethyl was generally well-tolerated, although treatment was associated with an increased risk of serious bleeding events (2.7% v. 2.1%, $p = 0.06$) and atrial fibrillation or flutter (3.1% vs. 2.1%, $p = 0.004$)[42]. These results were consistent with the findings of the earlier JELIS study which evaluated an intervention consisting of 1.8g of EPA daily in 18 645 patients with a total cholesterol of 6.5 mmol/L or greater, in Japan, where fish is a large part of the diet. In secondary prevention subset of the population, EPA reduced major coronary events were reduced by 19% (p=0.048). In primary prevention, EPA reduced major coronary events by 18%, although this was not statistically significant[44]. In an analysis presented at American Heart Association Annual Congress in 2019, we showed that EPA and DHA might also have beneficial properties for the reduction of cardiometabolic risk, and using Mendelian Randomization we showed that alfa-linolenic acid is also linked to reduced risk of coronary heart disease and myocardial infarction[20].

ILEP recommendations have rated the evidence supporting the recommendation to use polyunsaturated ω-3 fatty acids for lipid-lowering as I A[14], with a IIa B rating in a statin-intolerant population[13].

6.2. Phytosterols

Phytosterols (plant sterols) are chemically similar to cholesterol and occur widely in plants. In human diets, nuts, grains, vegetable oils, and fresh vegetables are the most prominent source of phytosterols. Phytosterols compete with cholesterol for transporters in the gut and thus

reduce cholesterol absorption. The NPC1L1 transporter (the target of ezetimibe) absorbs both cholesterol and phytosterols, and the ABCG5/8 transporter returns them to the intestinal lumen by excreting them in bile and thereby plays an important role in preventing the accumulation of phytosterols and cholesterol [45]. Phytosterols are frequently added to food products, such as margarines, and consumption of 2g/ day can reduce LDL-C by 8-10%, and (as with ezetimibe which also prevents cholesterol absorption) this reduction is additional to that achieved by statins (which act by reducing endogenous production of cholesterol by inhibiting HMGCR) [46]. A meta-analysis of 113 randomized placebo-controlled trials of plant sterols found the LDL-lowering effects of sterols to follow a dose-response relationship, with potentially larger reductions achievable at doses higher than 2g/day.[47] No data on hard CVD outcomes are available [16].

Although plant sterols are generally well-tolerated in trials [46] [47], recent findings suggest that caution may be required before recommending phytosterols to some individuals. Loss-of-function sequence variants in ABCG5/8 increase the absorption of both cholesterol and phytosterols and double the risk of coronary artery disease (OR = 1.54, 95% CI 1.49–1.59). Clearly, supplementation with phytosterols in individuals with this variant is undesirable, and the demonstration that phytosterols can contribute to atherogenesis may have wider implications for the safety of supplements [45].

ILEP recommendations have rated the evidence supporting the recommendation to use phytosterols for lipid-lowering as IIa A[14], with a IIa C rating in a statin-intolerant population[13].

6.3. Monacolin and red yeast rice

Red-yeast rice is a traditional ingredient of Chinese foods. The strongly coloured pigment is produced by fermentation of rice (*Oryza sativa*) by *Monascus purpureus*, *M. pilosus*, *M.*

floridanus or *M. ruber* .[14] The fermentation process a range of molecules *including polyketides such as monacolins*[14] One such compound, monacolin K is chemically identical to lovastatin, and is thus an inhibitor of HMGCR and reduces endogenous cholesterol production and lowers LDL-C [48]. Whilst this is an attractive approach to CV risk reduction, it is complicated by the fact that preparations of red-yeast rice preparations vary by as much as 30-fold and may contain contaminants such as citrinin, which is hepatotoxic[49]. Therefore, the extraction and purification of the active ingredient are necessary steps to produce a product for therapeutic use. Interestingly, a large RCT, including nearly 5000 participants in China, compared a partially purified extract of red yeast rice with placebo on CV endpoints. The intervention group experiences a 45% relative reduction in cardiovascular events [50]. This extremely promising finding should prompt further studies to investigate whether similar benefits are achievable in other populations.

RYR therapy is very safe. However, some patients, especially those at the risk of statin intolerance, who receive red-yeast rice preparations might report statin-like adverse effects [51, 52]. However, taking into account the very small dose of natural lovastatin (usually up to 3 mg based on the recent EFSA recommendations), this risk is very low (less than 1‰ based on the unpublished nutrivilligance data)[53]. Adverse effects may be less severe than for a similar dose of statin in a conventional formulation, because of differences in pharmacokinetic profiles and bioavailability.

ILEP recommendations have rated the evidence supporting the recommendation to use red-yeast-rice products for lipid-lowering as IA in all patients (including those with statin intolerance) [13, 14].

7. Safety considerations

Safety data for a wide range of nutraceuticals has been summarised by the International Lipid Expert Panel [14]. Most nutraceuticals are well-tolerated, with only minor adverse effects being reported. Nevertheless, practitioners should consider Hippocrates maxim "*primum non nocere*" when discussing natural products with their patients, and indeed there a number of plausible mechanisms by which natural products may cause harm, which may not be apparent in the typically short studies employed in the evaluation of these agents.

From a safety perspective, the short duration of many trials excludes the possibility of evaluating the long-term effects of treatment. Hypothetically, agents which reduce the absorption of cholesterol and other lipids, may also result in malabsorption of fat-soluble vitamins and other important dietary components. This may not result in short-term harm, but might be a problem with long-term use.

The relatively light regulatory environment for natural products (in comparison to conventional pharmaceuticals) means that the quantity of active ingredients in preparations may vary markedly between manufacturers, and even between batches produced by a single manufacturer [49]. This is a particular concern when the identity of the active ingredient in a preparation is not certain. Perhaps more concerning is the fact that contaminants in unregulated products may be harmful to health[49].

Finally, harm may be caused if patients do not commence treatment, or cease taking guideline-directive therapy because they consider nutraceuticals to be an equivalent alternative. Clearly, patient autonomy, and patient-centred decision making is crucial to the prevention and treatment of long-term diseases. Nevertheless, studies have shown that most patients[54] and even practitioners[55, 56] are very poor at quantitatively estimating the benefits and risks of a wide range of medicines. This may be a particular problem in the context of CVD prevention, because the day-to-day inconveniences associated with medicine use are immediately apparent

to the patient, whereas the benefits (avoidance of a future counterfactual event) are intangible. Furthermore, mass-media often publishes alarmist and inaccurate reports about the harms of statins [57]. This may contribute to poor adherence; in one study, only 61% of people given a prescription for a statin were adherent at 3 months [58]. When patients expect to experience an adverse effect, there is an increased likelihood that they will report the relevant symptom (the 'drucebo' effect)[59] . Additionally, 'alternative' preparations are often promoted uncritically in the lay press, and patients believe natural products to be safe and effective, and prefer them to conventional pharmaceuticals [60]. In this context, the advice of ILEP is crucially important *"it is simultaneously critical to emphasize that nutraceuticals, both in patients with good adherence to statin therapy as well as with statin intolerance, cannot replace pharmacological therapy, but might help achieve treatment targets".* Ideally, patients would be provided with accessible quantitative and individualised information about potential benefits and risks before making any decisions about treatments. This is particularly true if they plan to replace statins (for which there is excellent long-term efficacy and safety data) with nutraceuticals (which have very little long-term data).

8. Future roles for natural compounds as anti-atherogenic agents

Position papers from ILEP have outlined the evidence supporting a range of emerging uses for nutraceuticals. Of particular interest is the population of individuals considered by most current guidelines to be at 'low risk' of CVD. Currently, most international guidelines use risk calculators such as the SCORE 10-year risk calculation [61, 62], QRISK [63, 64], or the pooled-cohort equations to evaluate 10-year risk [65, 66]. However, it is increasingly clear that the risk of CVD is strongly associated with lifetime exposure to LDL-C [67]. A young individual with raised LDL-C may be at low 10-year risk (and therefore not fulfil criteria for statin therapy), but

nevertheless have appreciable lifetime CVD risk. ILEP experts have proposed nutraceutical strategies to avoid missing opportunities to intervene early and manage risk factors in these individuals [29]. One interesting approach to this is the use of polypill [68] preparations, which combine low or moderate doses of several lipid-lowering nutraceuticals in a single quality-controlled preparation. One such product, Armolipid Plus ®, has been demonstrated to reduce TC by 11-21% and LDL-C by 15-31%, a response similar to that expected with low-dose statins [69, 70] (albeit without long-term follow-up data on outcomes). At the other end of the risk spectrum, ILEP experts have outlined how nutraceuticals might be used in high risk who cannot achieve treatment targets with statins and conventional therapies, and for whom more potent agents such PCSK9 inhibitors may not be affordable or appropriate [8]. ILEP have also produced advice on the management of statin intolerance, which may include the use of nutraceuticals, especially in the vast majority of cases where intolerance is 'partial' (i.e. individuals can tolerate statin therapy, but not at a sufficiently high dose as recommended by evidence-based guidelines). In this situation, low-dose statin therapy can be supplemented with nutraceuticals [13, 17]. Recent ILEP recommendations concern statin treatment in athletes and patients performing regular intense exercise. If these individuals experience treatment-related muscle symptoms, nutraceuticals may be considered as part of the lipid-lowering regimen[30]. Finally, ILEP have produced guidance on the use of nutraceuticals in heart failure, the end-stage of coronary atherosclerotic disease processes[15].

9. Summary and conclusions

A wide range of natural products have apparently beneficial effects on biomarkers and risk factors for cardiovascular disease. International guidelines make relatively few recommendations relating to natural products because many agents have not been evaluated in

long-term outcomes trials, and the composition and safety of commercially available products cannot always be assured. Nevertheless, the value and potential of natural products have been demonstrated in the REDUCE-IT trial of icosapent ethyl (high-dose, high-purity) eicosapentaenoic acid. The current state of evidence and expert opinion on the use of anti-atherosclerotic nutraceuticals is clearly summarised in position papers of ILEP. This 'nutraceutical approach' (identify the active ingredients in natural products; produce high-quality products according to Good Manufacturing Practice guidelines; evaluate them in ling-term outcomes trials) is the mechanism by which the domains of natural product research and evidence-based medicine can move closer together.

Conflicts of interest:

PEP owns four shares in AstraZeneca PLC and has received honoraria and/or travel reimbursement for events sponsored by AKCEA, Amgen, AMRYT, Link Medical, Napp and Sanofi. MB has received research grant(s)/support from Amgen, Sanofi, Mylan and Valeant, and has served as a consultant for Akcea, Amgen, Daiichi-Sankyo, Esperion, Freia Pharmaceuticals, KRKA, MSD, Mylan, Novartis, Polfarmex, Polpharma, Resverlogix, Sanofi-Aventis and Servier.

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Table 1: Summary of ILEP guidance and clinical evidence relating to nutraceuticals in the context of lipid modification to reduce cardiovascular risk. Data (with the exception of long-term outcomes data from RCTs) are taken from 'Lipid lowering nutraceuticals in clinical practice: position paper from an International Lipid Expert Panel '[14]. Explanations of classes of recommendation in the ILEP position paper can be found in Table S1, and explanation of levels of evidence can be found in Table S2.

Active compound	Natural source	Predominant Putative mechanism	Class of Recommendation	Level of Evidence	Active Daily Doses	Expected effects on LDL-C	Effects on other CV risk biomarkers	Direct vascular effects	Safety	Long-term outcomes data from RCTs
Phytosterols and stanols	Almost all plants (esp. nuts, vegetable oils, legumes, seeds)	↓ intestinal absorption of cholesterol	IIa	A	400–3000 mg	–8% to –12%	↓ hs-CRP	Not demonstrated	Good safety data up to 2 years	[45] [46] [47]
Soluble fibres (ß-glucan	β-glucan : plant cell walls, algae, fungi, bacteria, yeast;	↓ intestinal absorption of	IIa	A	5–15 g	–5% to –15%	↓ TG, glycemia, HOMA	↓ CVD risk (epidemiological data on	No serious adverse	None

Psyllium, Glucomannan)	Psyllium: blonde psyllium seed; Glucomannan: *Amorphophallus konjac* (konjac root)	cholesterol; ↑excretion bile acid					index, body weight	fibre-rich foods)	effects of psyllium up to 20 g/day. Glucomannan may cause some gastrointestinal side effects and interfere with absorption of lipophilic drugs and vitamins	

Chitosan	Shellfish and sea crustaceans	↓ intestinal absorption of cholesterol	IIb	A	1–6 g	–5%	↓ Body weight, glucose, HOMA index	Not demonstrated	Transient GI AE reported	None
Probiotics	Many inc. *Lactobacillus acidophilus*, *L. bulgaricus, Bifidobacterium lactis* and *L. plantarum*.	Unclear, may ↓ intestinal absorption of cholesterol	IIb	B	Strain dependent	–5% (strain dependent)	None (at least none with a lipid-lowering effect)	Not demonstrated	No evidence of serious AE reported	None
Monacolins, esp. monacolin K	Red yeast rice	↓ hepatic cholesterol production by inhibition	I	A	3–10 mg (monacolin K)	–15% to –25%	↓ ApoB, hs-CRP, MMP-2, MMP-9	↑ FMD, ↓ PWV ↓ CV events in secondary prevention	Statin-like A/E may be observed. Citrinin, present in many	[48, 50, 71]

		of HMGCR							products is nephrotoxic	
Allicin (diallyl thiosulfinate)	Garlic (*Allium sativum)*	May may ↓ intestinal absorption and hepatic production of cholesterol	IIa	A	5–6 g (extract)	–5% to –10%	↓ Blood pressure, platelet aggregation	Not demonstrated	Transient GI AE reported	None
Panthenine	Derived from vitamin B_5 (pantothenic acid)	↓fatty acid synthesis ↓HMGCR	IIa	A	600–900 mg	NA	ND	ND	Good tolerability inc. in children and dialysis patients	None

Bergamot flavonoids	*Citrus bergamia Risso*	↓HMGCR ↓ACAT	IIa	B	500–1000 mg (BPF)	–15% to –40%	↓ sdLDL, hs-CRP, TNF-α	Not demonstrated	No AE detected (500 - 1500 mg/day)	None
Policosanols	sugarcane wax (*Saccharum officinarum L*)	↓HMGCR ↓bile acid absorption ↑AMPK	III	A	10-80 mg	ND	None	ND	Good tolerability	None
Berberine	Roots of *Coptis* (*Coptis chinensis*, *Coptis japonica*), *Hydrastis* (*Hydrastis canadensis*) and *Berberis* (*Berberis aristata*, *Berberis vulgaris*, *Berberis croatica*)	↓ PCSK9; directly ↑ LDL-receptor	I	A	500–1500 mg	–15% to –20%	↓ ApoB, TG, hs-CRP, IL-6, MCP-1, ICAM-1, VCAM-1, MMP-9,	ND	Mild GI AE reported	None

							glucose, HOMA index, blood pressure			
Polyphenols (catechins, epigallocatechin-3-gallate (EGCG))	Green-tea extract	↓HMGCR ↑AMPK	IIa	A	25-100g	-5%	↓ Blood pressure	↑ FMD, ↓ PWV (tea)	GI AEs, rash and ↑ BP reported. ↓Intestinal absorption of folate and iron.	None

Bioactive peptides inc. conglutin-γ	Soy and lupin	↓ SREBP-1	IIb	A	25-100g	–3% to –10%	ND (humans)	↑ FMD (soy with isoflavones)	Long-term soy use may affect fertility, thyroid function and absorption of minerals. Lupin is well-tolerated	None
Polyunsaturated ω-3 fatty acids	Fish oils	↓ VLDL suynthesis ↓ TG synthesis (ω-3 are	I	A	1–4 g	NA	↓ sdLDL, TG, hs-CRP, TNF-α, ↓ adhesion	↑ FMD, ↓ PWV, ↓ post-MI sudden death risk	Mild GI side-effects	[38-43]

		false substrates) ↑β-oxidation of fatty acids					molecules, ↓ blood pressure			
γ-oryzanol	Rice bran oil	↓HMGCR	IIb	B	300mg (γ-oryzanol)	–5% to –10%	↓ ApoB, ↑ HDL-C	Not demonstrated	None reported	None
Spirulina	*Arthrospira platensis*	↑heme oxygenase-1	IIa	B	400–800 UI	–5%	↓ TG, ↑ HDL-C	ND	Well-tolerated	None
Curcumin	Turmeric (rhizome of *Curcuma longa*)		IIa	B	1–3 g	–5%	↓ TG, Lp(a), glucose, HbA1c, HOMA	↑ FMD, ↓ PWV	Well-tolerated	None

							index, hs-CRP, TNF-α, IL-6, ↑ adiponectin, HDL-C			
L-carnitine		↑β-oxidation of fatty acids	IIb	B	1–2 g	NA	↓ hs-CRP, ↓ Lp(a), ↓ body weight	Not demonstrated	No concerns reported, but data is limited	None
Artichoke	Cynara scolymus, Cynara cardunculus	↓HMGCR ↓ SREBPs	IIa	B	1-3g	–5% to –15%	↓ TG ↓ AST, ALT, glucose	ND	Well-tolerated	None

Vitamin E		↑peroxisome proliferator-activated receptor activity ↓HMGCR	IIb	B	400-800UI	≤ –5%	↓ ApoB, ↑ HDL-C	↑ FMD, ↓ PWV, ↓ risk of MI		None
Anthocyanins	Blueberries, black rice, purple cabbage, raspberries, purple grapes and cherries	Various	IIb	B	100-450mg	–5% to 10%	↓ oxLDL, TG, glucose, HbA1c, HOMA index, ↑ adiponectin, HDL-C	ND	Well-tolerated at dosages ≤ 640 mg/day.	None

Silymarin	Silybum marianum	↓LDL peroxidation	III	C	NA	ND	↓ oxLDL, AST, ALT, γGT, glucose, HbA1c	ND	Limited safety data are available	None
Conjugated linoleic acid	Fatty tissues and milk of ruminant animals	Various	III	C	1–6 g	–5%	ND	↓ FMD (Worsened)	Categorised as safe by FDA in 2008	None

Abbreviations: AE, adverse effects; NA, not applicable; ND, not demonstrated

Table 2: Summary of ESC guidance in the impact of nutraceuticals and functional foods in the context of lipid modification to reduce cardiovascular risk[16]

	Magnitude of reduction	**Level of Evidence**
Natural products to ↓ LDL-C and TC		
Phytosterol-enhanced foods	**5-10%**	**A**
Red yeast rice nutraceuticals	**5-10%**	**A**
Natural products to ↓ TG-rich lipoproteins		

Polyunsaturated ω-3 fatty acid supplements	**5-10%**	**A**

Supplementary Tables

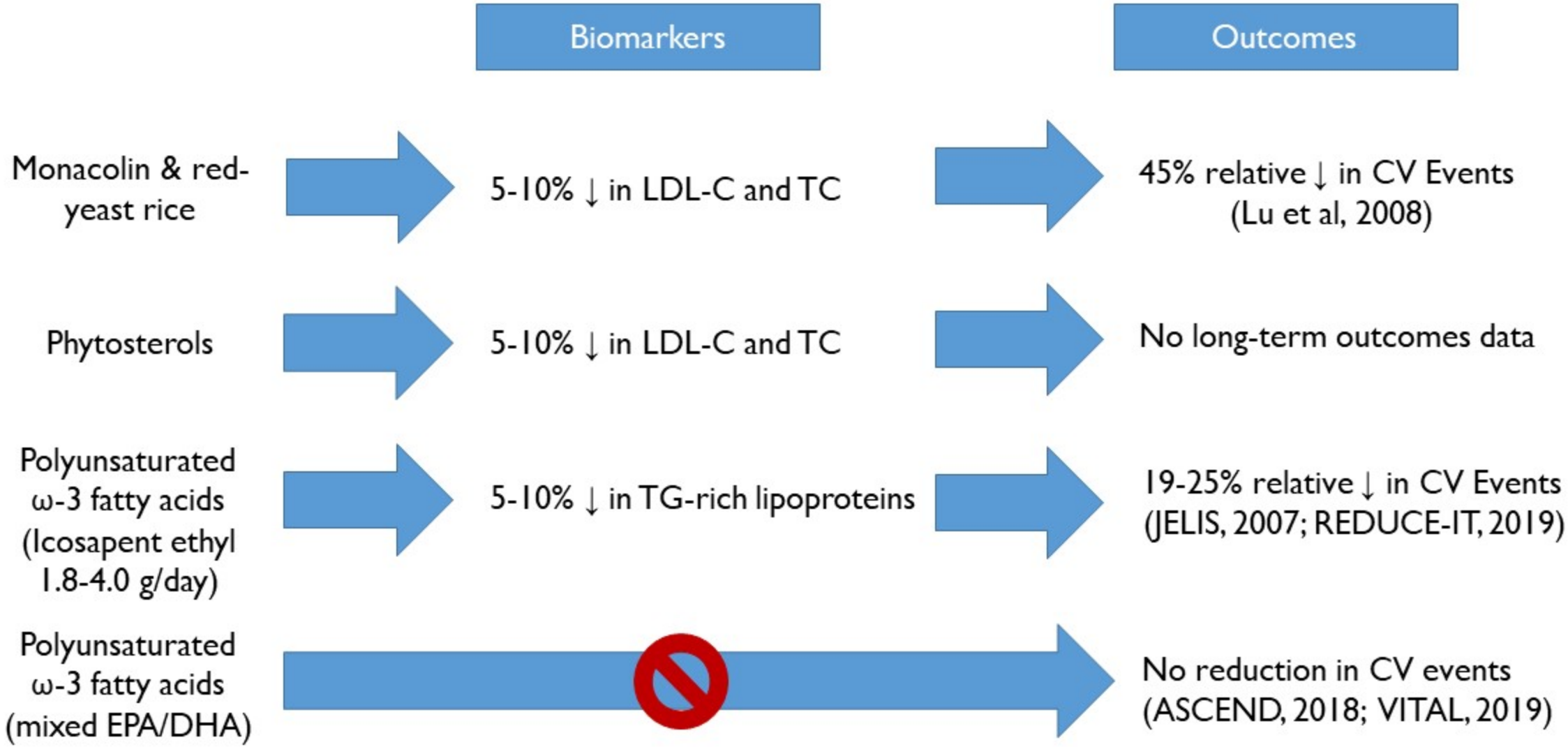
Table S1: Classes of recommendation

Class of recommendation	**Definition**	**Suggested wording**
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective	Is recommended/Is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure	
Class IIa	Weight of evidence/ opinion is in favour of usefulness/efficacy	Should be considered
Class IIb	Usefulness/efficacy is less well established by evidence/opinion	May be considered

Class of recommendation	Definition	Suggested wording
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective and in some cases may be harmful	Is not recommended (no efficacy on lipid profile)

Table S2: Levels of evidence

Level of evidence	Definition
Level A	Data derived from multiple randomized clinical trials or their meta-analysis
Level B	Data derived from single randomized clinical trial or large non-randomized studies
Level C	Consensus or opinion of experts and/or small studies, retrospectives studies, registries


Biomarkers
Outcomes
Monacolin & red-yeast rice
5-10% ↓ in LDL-C and TC
45% relative ↓ in CV Events (Lu et al, 2008)
Phytosterols
5-10% ↓ in LDL-C and TC
No long-term outcomes data
Polyunsaturated ω-3 fatty acids (Icosapent ethyl 1.8-4.0 g/day)
5-10% ↓ in TG-rich lipoproteins
19-25% relative ↓ in CV Events (JELIS, 2007; REDUCE-IT, 2019)
Polyunsaturated ω-3 fatty acids (mixed EPA/DHA)
No reduction in CV events (ASCEND, 2018; VITAL, 2019)