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Nutraceuticals and dyslipidaemia: Beyond the common therapeutics

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ABSTRACT

Dyslipidaemia accelerates the atherosclerotic process and its morbid consequences; statins represent the evidence-based treatment of choice for reducing low-density lipoprotein cholesterol levels and decreasing cardiovascular events. Unfortunately, statins are frequently not available for several reasons, including intolerance, side effects or, simply, patient preference. Nutraceuticals and functional food ingredients that are beneficial to vascular health may represent useful compounds that are able to reduce the overall cardiovascular risk induced by dyslipidaemia by acting parallel to statins or as adjuvants in case of failure or in situations where statins cannot be used. The mechanisms underlying such actions are not fully understood but may be related to reducing 7α-hydroxylase, increasing faecal excretion of cholesterol, decreasing 3-hydroxy-3-methylglutaryl-CoA reductase mRNA levels or reducing the secretion of very low-density lipoprotein. This contribution provides an overview of the mechanism of action of nutraceuticals and functional food ingredients on lipids and their role in the management of lipid disorders.

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1. Introduction

Dyslipidaemia is a main cardiovascular risk factor for coronary heart disease (CHD) incidence and mortality, as already demonstrated by several studies (Gillespie et al., 2012; Heron, 2012; Roger et al., 2012). Lipid disorders can accelerate the atherosclerosis process and its consequences, such as heart failure and coronary atherosclerosis (Ebong et al., 2013; Paramsothy et al., 2010), whereas the control of fasting lipid blood levels leads to a reduction in the cardiovascular risk profile of individuals (Cziraky et al., 2011).

Nevertheless, failure to achieve an optimal reduction of lipid levels can often be observed in real life. Martin et al. (2013) recently noted that patients with acute myocardial infarction (AMI) often failed to reach the target level of low-density lipoprotein (LDL)-cholesterol <100 mg/dL at 6-month follow-ups after discharge from the hospital. Among their 336 AMI patients, 33% ($n = 121$ patients) did not attain the lipid levels goal, and this was due to the absence of statin therapy prescription at discharge, reduced adherence to therapy, lack of cardiac rehabilitation participation and/or diet/activity counselling. Many other studies have confirmed the previous findings (Collins & Altman, 2012; Ludman et al., 2011; Pittman et al., 2012).

Thus, other interventions had already been considered to promote healthy control of dyslipidaemia. In 1989, DeFelice hypothesised the occurrence of biological interventions not related to pharmacological methods and wrote about "*nutraceutical*" products, i.e., "*a food (or part of a food) that provides medical or health benefits, including the prevention and/or treatment of a disease*" (DeFelice, 1995; Kalra, 2003). The original hypothesis was that these foods can protect human body from adverse events because of the beneficial effects of some phytochemicals. Several studies have reported the validity of this idea in clinical practice (Estruch et al., 2013; Massaro et al., 2010). In particular, the Mediterranean diet, which may be considered on top of the list, can improve the overall outcome and prognosis of the general population by reducing major cardiovascular risk events (myocardial infarction, stroke, or death from cardiovascular causes) rates (Estruch et al., 2013). This positive action may be related to several mechanisms such as endothelial function amelioration (Zuchi et al., 2010), atherosclerosis burden reduction (Badimon, Vilahur, & Padro, 2010), antithrombotic activities (Chakrabarti & Freedman, 2010), decreases in diabetes and metabolic syndrome incidence and evolution (Davì, Santilli, & Patrono, 2010) and improving dyslipidaemia (Houston, 2012) via lipid metabolism mechanisms (such as improving paraoxonase activities) (Rahimi-Ardabili et al., 2012).

The present contribution provides a detailed overview of nutraceutical action on dyslipidaemia to highlight the role of functional food ingredients in overcoming the negative effects of lipid disorders beyond pharmacological interventions.

2. Methods

The database consulted was MEDLINE. The main keywords adopted were nutraceuticals, functional foods, dyslipidaemia, hypercholesterolaemia, cardiovascular diseases and cardiovascular mortality/morbidities. All terms were combined to obtain the maximum selection of relevant articles. One physician analysed all the studies from MEDLINE, combining each term to generate a complete overview of the literature. The period considered was from 1989 until November 2013. More than 454 studies were evaluated; they were collected according to aims, and the more relevant studies (according to the population considered, the strength of the results and the relationship with paragraph aims) were included in the final version. Duplicates and ongoing trials were excluded from the analysis. At the end, considering reviews and original articles involving children and adolescents, only 104 articles were considered for the final evaluation (Fig. 1). All the main features of animals and human studies considered in this overview are summarised in Tables 1 and 2.

3. Nutraceuticals: definition and classification

According to DeFelice's definition, a "nutraceutical" is "*a food (or part of a food) that provides medical or health benefits, including the prevention and/or treatment of a disease*", as already noted (DeFelice, 1995; Kalra, 2003). The term is tightly related to "functional food", defined by the US Institute of Medicine's Food and Nutrition Board as "*any food or food ingredient that may provide a health benefit beyond the traditional nutrients it contains*" (Ross, 2000). These are broad and not specific definitions that include a myriad of compounds that are more or less widespread in common diets.

The Bureau of Nutritional Sciences of the Food Directorate of Health Canada (Health Canada, 1998) tried to provide more accurate definitions of both nutraceuticals and functional foods:

- *Nutraceutical*: "a product isolated or purified from foods that is generally sold in medicinal forms not usually associated with food. It is demonstrated to have a physiological benefit or provide protection against chronic disease."

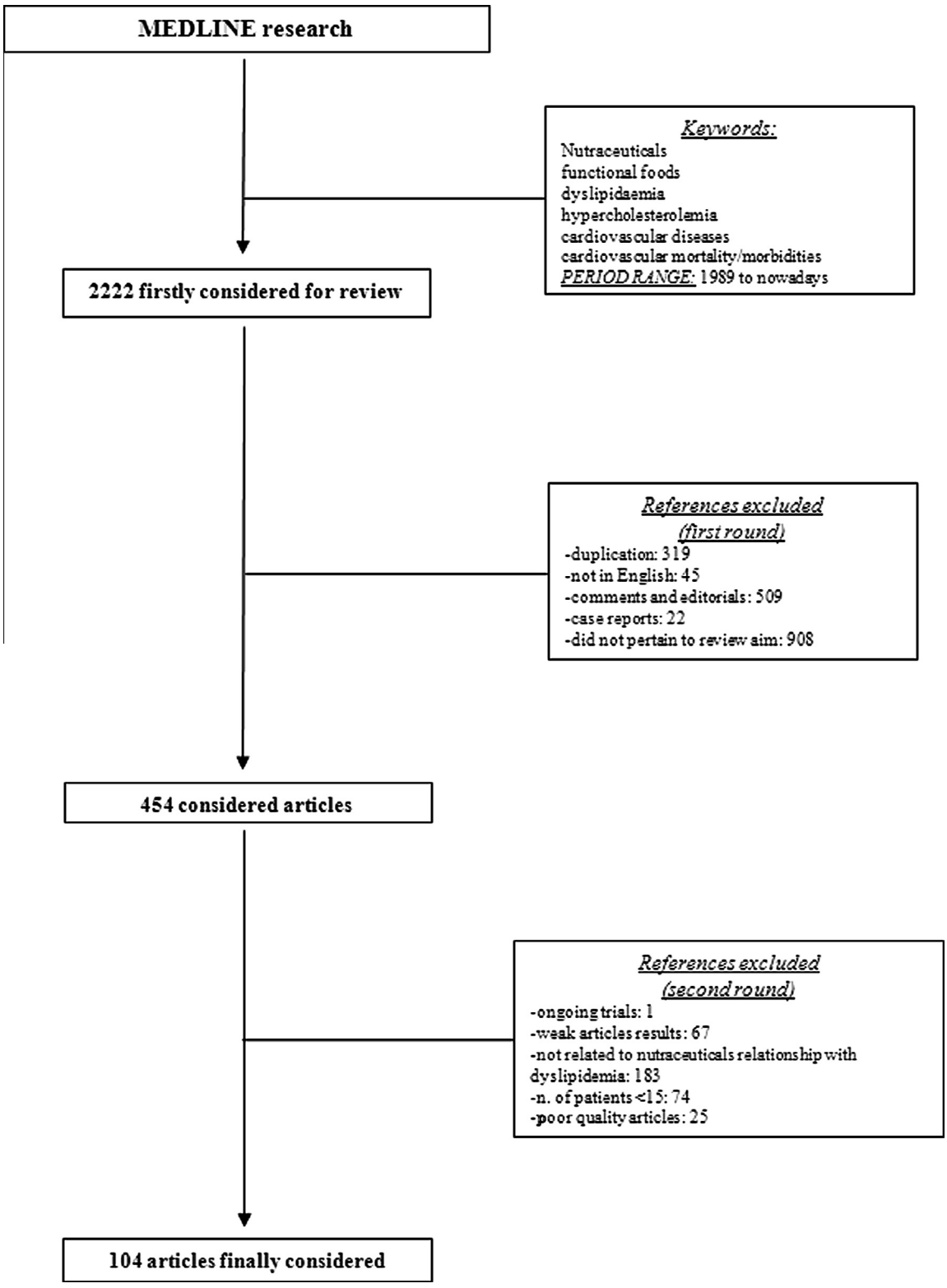

Fig. 1 – Study flow chart.

– *Functional food*: "it is similar in appearance to, or may be, a conventional food, consumed as part of a usual diet, and demonstrated to have physiological benefits and/or reduce the risk of chronic disease beyond basic nutritional functions."

Because of the large number of compounds, it is quite difficult to classify all nutraceuticals in a systematic manner. Singh and Sinha (2012) attempted to order and classify them. We attempt to offer a schematic approach to nutraceutical classification in Fig. 2. At a glance, we can divide

Table 1 – Features of the main literature of in vivo/in vitro experimental researches about nutraceuticals.

Source	N.	Pts	Nutraceutical	Approach used	Aims	Results	Time
Kumar et al. (2012)	15 Mice/130 embryos	8 week old	Zinc	Three groups: (a) control, (b) diabetes, and (c) diabetes + zinc (5 mg/kg body weight).	Protective role of zinc on diabetic embryonic rat cardio-myoblast cells	Both cytosolic and mitochondrial SOD activity was lower in embryos from the diabetic group than control and zinc-supplemented groups. Zn inhibited oxidative stress- induced damage and inhibition of ROS generation	N/A
Kukongviriyapan et al. (2012)	Male ICR mice	6–8 week old	Quercetin	Quercetin (50 or 100 mg/kg) administered before or after LPS (10 mg/kg; i.p.) injection.	Antioxidant effects of quercetin on LPS-induced oxidative stress	Quercetin preserved vascular function, blood pressure, heart rate and vascular responsiveness to stress. It up-regulated eNOS expression, reduced oxidative stress, and maintained blood glutathione redox ratio	N/A
Chen et al. (2012)	30 Male C57BL/6J mice	38-week-old	Resveratrol	Three groups: (1) ND; (2) HFD; (3) HFD + resveratrol (200 mg/kg diet/day)	Resveratrol influence on hypercholesterolemia, hepatic cholesterol accumulation and bile acid synthesis in vitro/vivo.	Resveratrol-fed mice had lower TC and LDL-C, higher HDL-C, lower LDL-C/HDL-C ratio than HFD group; hepatic accumulation of cholesterol was reduced by 46% compared with HFD group ($p < 0.05$). CYP7α1 mRNA and protein levels and enzyme activity in liver from resveratrol-treated mice were higher than ND and HFD groups	8 weeks
Kato et al. (2009)	48 Female Wistar rats	6 month old	Water-insoluble fish protein	Rats subjected to sham-operation or ovariectomy, and fed casein or IFP as a protein source	IFP from Alaska pollock (*Theragra chalcogramma*) influence on hypercholesterolaemia related to ovarian hormone deficiency.	IFP diet significantly decreased TC, VLDL, LDL-C levels and 3-hydroxy-3-methylglutaryl-CoA reductase protein mRNA in the ovariectomised rats	4 weeks
Quesada et al. (2012)	Male Wistar rats	N/A	Grape seed proanthocyanidin extract	Two groups: (1) GSPE fed rats (250 mg/kg body weight); (2) control rats	GSPE hypotriacylglycerolaemic action	GSPE markedly reduced plasma TG (22% reduction in the area under the curve) 1.5 h after administration. GSPE reduced chylomicrons/VLDL content of TG and inhibited (30%) VLDL-TG secretion	N/A
Quesada et al. (2009)	12 Female rats	N/A	Grape seed proanthocyanidin extract	Three groups: (1) GSPE + HFD (25 mg/kg of body weight); (2) HFD; (3) controls	GSPE effects in dyslipidemia induced by HFD	GSPE decreased TG (204.0 ± 2.3 vs 129.4 ± 12.3 mg/dL, $p < 0.05$) and LDL-C (15.2 ± 2.0 vs 6.6 ± 1.0 mg/dL, $p < 0.05$) than HFD rats and improved HDL-C/LDL-C ratio	13 weeks

Baiges et al. (2010)	18 Female Wistar rats	N/A	Grape seed proanthocyanidin extract	Three groups: (1) GSPE + HFD (25 mg/kg of body weight); (2) HFD; (3) controls	GSPE effects on the liver proteome of rats suffering from metabolic syndrome	Proteins exhibited similar expression in the HFD + GSPE and control groups, thus GSPE corrected HFD effects. Some of these proteins are related to lipid metabolism (pyruvate kinase; ATP-citrate lyase isoform 1; fatty-acid synthase; glycerol-3-phosphate dehydrogenase 1; mitochondrial acyl-CoA thioesterase 2 and butyryl-CoA synthetase 1 protein)	13 weeks
Alshatwi et al. (2011)	42 Male Wistar rats	8 week old	Black/green tea	Six groups: (I) ND; (II) HCD; (III) ND + black tea (7 g/L); (IV) HCD + black tea (7 g/L); (V) ND + green tea (7 g/L); (VI) HCD + green tea (7 g/L)	Effect of black or green tea on lipid status and lipid peroxidation	Group III/V had decreased ($p < 0.001$) TC and LDL-C. Group V rats showed a TG ($p < 0.001$) and TC/LDL-C ($p < 0.01$) decrease and HDL-C increase ($p < 0.05$) than group III. Group VI showed a decrease in TC, TG, and LDL cholesterol ($p < 0.001$) and an increase ($p < 0.01$) in HDL-C, HCD group. Group VI showed a decrease in TC/TG ($p < 0.001$) and LDL-C ($p < 0.01$), an HDL-C increase ($p < 0.05$) than group IV	5 weeks
Huang and Lin (2012a)	30 Male Wistar rats	5 week-old	Green, oolong, black and pu-erh teas.	Six groups: (1) C: chow; (2) F: fructose + chow; (3) FG: fructose + chow + green tea; (4) FB: fructose + chow + black tea; (5) FO: fructose + chow + oolong tea; 6) FP: fructose + chow + pu-erh tea	Green, oolong, black and pu-erh teas effects on dyslipidaemia	Green, oolong, black and pu-erh teas significantly reduced serum TG (FG: 80.1 ± 27.1 mg/dL; FB: 92.3 ± 26.4 mg/dL; FO: 87.6 ± 23.1 mg/dL; FP: 66.8 ± 14.1 mg/dL) than group F (175.4 ± 24.6 mg/dL; $p < 0.05$). Green, black and pu-erh teas significantly reduced serum TC (FG: 59.1 ± 3.6 mg/dL; FB: 67.7 ± 3.4 mg/dL; FP: 67.8 ± 6.0 mg/dL) than group F (75.3 ± 3.9 mg/dL; $p < 0.05$). Green, oolong, black and pu-erh teas normalized the serum TG and TC concentrations	12 weeks
Chen et al. (2008)	Male Wistar rats	6–8 week old	Red mold rice (RMR)	(I) Control; (II) HFD; (III) HFD + 1.43 mg/kg/day lovastatin; (IV) HFD + 0.4% rice; (V) HFD + 0.4% RMR; (VI) HFD + 2% RMR	Influences of red mold rice (RMR) on obesity, dyslipidaemia and related metabolic abnormalities	RMR significantly reduced serum TC, LDL-C, LDL HDL-C ratio in the HFD group. The HFD + 2% red mold rice protocol significantly increased serum HDL-C	6 weeks

(*continued on next page*)

Table 1 – (*continued.*)

Source	N.	Pts	Nutraceutical	Approach used	Aims	Results	Time
Dvir et al. (2009)	24 Male Sprague-Dawley rats	N/A	Algal biomass and isolated algal polysaccharide of Porphyridium sp.	Four groups: (1) algal biomass fed; (2) algal polysaccharide fed; (3) pectin-fed; (4) control	Algal biomass and isolated algal polysaccharide (AP) of Porphyridium sp. effects in hypercholesterolemic rats	Biomass or AP significantly reduced: TC (22–34%; $p < 0.001$), TG and VLDL-C v (12–39%) and LDL-C (32–53%; $p < 0.005$) compared with control or pectin-fed rats. HDL/LDL-C ratio was higher (31–60%; $p < 0.001$) in the AP and biomass groups vs. the pectin and control diets	15 days
Metzger et al. (2009)	54 Swine	6-month old	Pectin, polyphenols, phytosterols	Treatment diets (pectin, polyphenols, phytosterols, all combinations of pectin, polyphenols, and phytosterols) vs lovastatin vs controls	To compare nutritional supplements (pectin, polyphenols, and phytosterols) to lovastatin to reduce serum cholesterol	All, except pectin, reduced TC more than control/lovastatin. LDL-C was reduced 22%, 19%, 20%, 17%, 18%, and 17% by polyphenols, phytosterols, pectin + polyphenols, pectin + phytosterols, polyphenols + phytosterols, and pectin + polyphenols + phytosterols, respectively, compared to control (8%) and lovastatin (40%)	8 weeks
Yang (2010)	48 Male Wistar rats	32-month-old	Powder of mulberry (*Morus alba* L.) fruit	Six groups: (1) ND: normal diet; (2) NDM I: ND + 5% MFP; (3) NDM II: ND + 10% MFP; (4) HFD; (5) HFM I: HFD + 5% MFP; (6) HFM II: HFD + 10% MFP	Hypolipidaemic and antioxidant effects of MFP in hyperlipidaemic rats	HFM II group showed a decrease of 16.2% for TC, 35.7% for TG, 23.5% for LDL-C and 43.4% for AI compared than HF. Liver TC decreased by 17.0% and liver TG by 54.3%, while HDL-C increased by 33.0%. HFM I did not show significantly differences than HF group, except for serum TG (18.6% decrease).	4 weeks
Bremer et al, (2013), in press	19 Rhesus monkeys	12–20 years	Fish oil	Two groups: (1) standard chow plus 75 g fructose/day (control); (2) standard chow, 75 g fructose/day, and 4 g fish oil (16% EPA/11% DHA)/day	Evaluate the effects of fish oil on dyslipidaemia	Fasting TG and apo CIII concentrations higher in controls than patients ($p = 0.005$). Controls showed an increased fasting TG (+71 ± 25%) and apo CIII (+28 ± 8%), while no change was detected in daily fish oil supplemented patientsCholesterol concentrations increased slightly in the control group (+4 ± 3%), while decreasing in treated one (-8 ± 5%) (P = 0.025).	6 months
Huff et al. (1992)	6 Miniature pigs	N/A	Fish oil	Crossover design: first diet containing fish oil 30 g/day for 3 weeks; then of lovastatin 1.2 mg/kg body weight/day for a further 3 weeks	Effect of Lovastatin to the fish oil diet combination to lipids	Combined therapy reduced VLDL apo B production (26%, $p < 0.005$). Conversion of VLDL apo B to LDL was reduced by 48% ($p < 0.005$), It determined a 38% ($p < 0.002$) decrease in LDL production	6 weeks
Wakutsu et al. (2012)	16 KKAy mice	5 week old	Fish oil	Three groups: (1) beef tallow diet ad libitum (BA); (2) beef tallow diet restricted (BR); (3) fish oil diet; (4) controls	Effects of fish oil on lipids levels	TG and TC plasma as well as liver concentrations tended to decrease in obese KKAy mice fed fish oil. A reduced expression of fatty acid synthase mRNA was noticed in fish oil mice as compared to controls	6 weeks

Gunathilake et al. (2013)	60 Male rats	N/A	Polyphenols-rich fruit-based functional beverage	Five groups: normal control; HFD; and HFD with three different beverage dosages (0.5X, 1X, 2X), where X is the equivalence of two portion sizes for an adult (X = 10 ml/kg body weight/day) after dose translation	Polyphenols-rich fruit-based functional beverage action on serum and liver lipid profiles in vivo	Rats treated with 1X or 2X had significantly ($p < 0.05$) lower total and free cholesterol levels than HFD alone group and than group fed with 0.5X 1X and 2X supplementation doses reversed the serum lipid as compared to HFD alone treated	4 weeks
Jin et al. (2013)	40 Male SD rats	4-week-old	Theaflavins (polyphenols)	Five groups: (1) ND; 2) HFD; (3) HFD + BTE; (4) HFD + TFs; (5) HFD + TF1	Evaluate theaflavins effects on lipid levels.	TC levels in the HFD + TFs group was reduced by 26.5% (i < 0.05). BTE, TFs and TF1 significantly reduced TG by 56.9%, 50.8% and 52.3% as compared to HFD control group, respectively ($p < 0.05$). They BTE, TFs and TF1 decreased LDL-C by 69.6%, 71.7% and 43.5%, respectively, as compared to HFD controls (i < 0.05)	30 days
Kwok et al. (2013)	32 Male Sprague–Dawley rats	N/A	Ethanolic extract of dried fruit of *Crataegus pinnatifida*, hawthorn (Shan Zha)	Four groups: (1) control; (2) HCD; (3) low dose Shan Zha 80% ethanolic extract (30 mg/kg/day, p.o.) (HCD + SA); (4) high dose Shan Zha 80% ethanolic extract (100 mg/kg/day, p.o.) (HCD + SB)	Evaluate *Crataegus pinnatifida*, hawthorn (Shan Zha) on cholesterol plasma concentrations	SA/SB suppress the increased plasma TC ($p < 0.05$) and LDL-lipoprotein ($p < 0.05$) induced by the HCD. Liver lipids increased ($p < 0.001$) in the HCD, HCD + SA and HCD + SB groups as compared to controls. SB significantly enhanced the suppressed mRNA expression level up to about 90% of the Control level ($p < 0.05$)	4 weeks
Hsu et al. (2013)	32 Syrian golden hamster	6-weeks old	Ankaflavin	Four groups: (a) normal diet (control); (b) HFD; (c) HFD + AK (5 mg/kg body weight/day); and (d) HFD + AK + GW9662 (PPARγ antagonist; 5 mg/kg body weight/2 days	Potential mechanism of AK-regulated dyslipidaemia.	AK was found to suppress increases in plasma TC levels in HFD hamsters.	6 weeks
Srinivasan and Pari (2013)	24 Male albino Wistar rats	N/A	Diosmin	Four groups: (1) controls; (2) normal rats + diosmin (100 mg/kg b.w.; (3) diabetic; (4) diabetic rats + diosmin (100 mg/kg body weight	Investigate antihyperlipidemic effects of diosmin	Diosmin significantly ($p < 0.05$) reduced cholesterol, TG, free fatty acids and phospholipids in plasma and tissues as compared to diabetic rats It decreased VLDL and increased HDL levels ($p < 0.05$) It significantly ($p < 0.05$) decreased the activity of 3-hydroxy 3-methylglutaryl coenzyme A as compared to diabetic control rats	45 days

AK: ankaflavin; BTE: black tea extract; CYP7α1: cholesterol 7α-hydroxylase; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; GSPE: grape seed proanthocyanidin extract; HCD: high-cholesterol diet; HDL-C: high-density lipoprotein-cholesterol; HFD: high fat diet; IFP: water-insoluble fish protein; LDL-C: low-density lipoprotein-cholesterol; LPS: lipopolysaccharide; MFP: powder of mulberry fruit; N/A: not applicable; ND: normal diet; RMR: red mold rice; ROS: reactive oxygen species; SOD: superoxide dismutase; TC: total cholesterol; TF1: theaflavin; TFs: theaflavins mixture; TG: triglycerides; VLDL-C: very low density lipoprotein-cholesterol.

Table 2 – Features of the main literature studies involving humans about nutraceuticals role in dyslipidaemia treatment.

Source	N.	Age (years)	Design	Nutraceutical	Approach used	Aims	Results	Time
Estruch et al. (2013)	7447	55–80	Parallel-group, multicenter, randomized trial	Mediterranean diet supplemented with extra-virgin olive oil or nuts	Three groups: – Mediterranean diet + extra-virgin olive oil – A Mediterranean diet + nuts – Controls	Mediterranean diets (+ extra-virgin olive oil or nuts) efficacy on primary cardiovascular prevention	Primary end-point events occurred in 288 participants. The multivariable-adjusted hazard ratios for primary endpoints were 0.70 (95% CI, 0.54 to 0.92) and 0.72 (95% CI, 0.54–0.96) for extra-virgin olive oil and nuts groups. Mediterranean diet reduces incidence of major cardiovascular events	4.8 years
Rahimi-Ardabili et al. (2012)	60	N/A	Double-blind randomized controlled trial	Zinc	100 mg/day zinc vs placebo	Effects of zinc supplementation on PON enzyme activity	No change were in TC, TG, LDL-C, and Apo-B levels. HDL-C, Apo-AI, and PON activity were significantly increased ($p = 0.02$) than controls	2005–2007
Sheikholeslami Vatani and Ahmadi Kani Golzar (2012)	30	23.4 ± 3.6	Single-blind research protocol	Whey	Three groups: (1) resistance training + whey (RW); (2) resistance training + placebo; (3) control group	Effects of whey protein supplementation and resistance training in overweight young men	In the post-test TC decreased significantly only in the RW group ($p < 0.05$). HDL-C levels increased significantly in the RW group pretest to post-test ($p < 0.05$). LDL-C/TG decreased in experimental groups in the post-test ($p < 0.05$).	6 weeks
Marazzi et al. (2011)	80	82.4 ± 4.4	Randomize, prospective, parallel group, single-blind	Berberine, policosanol, red yeast rice, folic acid, coenzyme Q10, astaxanthin	Nutraceutical-combined pill (berberine 500 mg, policosanol 10 mg, red yeast rice 200 mg, folic acid 0.2 mg, coenzyme Q10 2.0 mg, and astaxanthin 0.5 mg) vs placebo	Nutraceuticals effects in elderly hypercholesterolemic patients (>75 years of age) previously intolerant to statins and refusing other pharmaceutical treatments	TC (−20%, $p < 0.001$) and LDL-C (−31%, $p < 0.001$) decreased significantly in the treated group; no significant change in placebo group; significant between-group differences ($p = 0.008$ and $p = 0.002$,respectively) No significant changes for plasma HDL cholesterol	12 months
Tomé-Carneiro et al. (2012)	75	62 ± 9	Triple-blind, randomized, placebo-controlled trial	Grape seed proanthocyanidin extract and resveratrol	Three groups: (1) resveratrol-enriched grape extract (GE-RES); (2) grape extract (GE); (3) placebo (maltodextrin).	Effect of GSPE plus resveratrol on statin-treated patients in primary cardiovascular disease prevention	GE-RES decreased ApoB (−9.3 mg/dL, 95% CI −16.4, −2; $p = 0.014$), LDLox (−14.5 U/L, 95% CI −19.5, −9.5; $p = 0.001$), LDLc (−5 mg/dL, 95% CI −14, 4; $p = 0.04$), LDLox/ApoB (−0.01 U/mg, 95% CI −0.015, −0.005; $p = 0.000$), while increased non-HDL-C/ApoB ratio (0.12, 95% CI 0.04, 0.13; $p = 0.046$)	6 months

Qin et al. (2009)	120	40–65	Double-blind, randomized, placebo-controlled trial	Anthocyanin	Two groups: (1) anthocyanin (two 80-mg anthocyanin capsules twice daily); (2) placebo (2 capsules twice daily)	Effects of pure anthocyanins on the serum lipid profile in dyslipidemic patients	Anthocyanin increased HDL-C [13.7% (95% CI: 10.4%, 16.9%) vs 2.8% (95%CI: 21.6%, 7.2%), $p < 0.001$] and decreased LDL-C [−13.6% (95% CI: 10.1%, 17.1% vs +0.6% (95% CI: 24.1%, 5.2%), $p < 0.001$] compared to controls [between group difference: $p < 0.001$]. Anthocyanin decreased CETP mass [−10.4% (95% CI: 6.7%, 14.1%) vs +3.5% (95% CI: 23.6%, 10.5%)] compared to controls [between group difference: $p < 0.001$] CETP activity decreased in the anthocyanin group than control [6.3% (95% CI: 4.6%, 8.0%) vs 1.1% (95% CI: 21.6%, 4.0%), $p = 0.001$]. In the anthocyanin group, HDL-C change was negatively correlated with CETP activity change (rs = 20.330, $p = 0.010$); LDL-C change was positively correlated with CETP mass change (rs = 0.354, $p = 0.005$)	04/2007–10/2008
Becker et al. (2009)	62	60.5 ± 9.3	Randomized, controlled trial	Red yeast rice / RYR)	Two groups: (1) RYR, (1800-mg/day); (2) placebo	RYR in dyslipidemia in statin-intolerant patients	LDL-C decreased from baseline in RYR group [−27.3 ± 16.4% at week 12 and −21.3 ± 22.7% at week 24]. LDL-C significantly differed between the RYR and placebo groups (week 12: $p < 0.001$; week 24: $p = 0.011$) as well as TC (week 12: $p < 0.001$; week 24.$p = 0.016$)	09/2006–03/2007.
Rayman et al. (2011)	501	60–74	Double-blind, placebo-controlled, study	Selenium.	Four groups: (1) placebo; (2) 100 mcg selenium/day; (3) 200 mcg selenium/day; (4) 300 mcg selenium/day	Selenium supplementation action on TC, HDL and non-HDL-C	In longitudinal analyses, selenium decreased TC, non-HDL-C levels, and TC/HDL-C ratio, with increasing HDL-C levels	06/2000–07/2001
Wofford et al. (2012)	352	>22	Randomized double-blind, 3-phase crossover trial	Soy protein and milk protein	Three sequences: (A) soy protein → milk protein → complex carbohydrate; (B) milk protein → carbohydrate → soy protein; (C) carbohydrate → soy protein → milk protein	Effects of soy protein, milk protein and complex carbohydrate supplementations on serum lipids and lipoproteins	Soy protein reduced TC by 3.97 mg/dL (95% CI, −7.63 to −0.31; $p = 0.03$) and TC/HDL-C ratio by 0.12 (95% CI, −0.23 to −0.01; $p = 0.03$) compared with carbohydrate- Soy protein increased HDL by 1.54 mg/dL (95% CI, 0.63 to 2.44; P = 0.0009) and reduced TC/HDL-C ratio by 0.14 (95% CI, -0.22 to -0.05; P = 0.001) compared with milk protein.	09/2003–04/2008
Wong et al. (2010)	23	59.6 ± 7.7	Randomized controlled crossover trial	Soy protein and probiotics	Three groups: (1) prebiotic alone; (2) soy plus prebiotic; (3) soy without prebiotic	Soy and a prebiotic influence on serum lipid	Soy + prebiotic reduced LDL-C (−0.18 ± 0.07 mmol/L, $p = 0.042$), LDL-C/HDL-C (−0.28 ± 0.11, $p = 0.041$), TC/HDL-C (−9.2% ± 2.7%, $p = 0.004$), LDL/HDL-C (−12.2% ± 3.4%, $p = 0.003$), while increased HDL-C (0.06 ± 0.02 mmol/L, $p = 0.029$) more than prebiotic	09/2003–03/2004

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Table 2 – (*continued*)

Source	N.	Age (years)	Design	Nutraceutical	Approach used	Aims	Results	Time
Casas-Agustench et al. (2012)	43	49 ± 13	Randomized placebo-controlled, crossover study	Plant sterol esters	Three groups: (1) placebo (skimmed milk, SM); (2) plant sterol-enriched skimmed milk (PS-SM); (3) plant sterol-enriched semi-skimmed vegetable fat-enriched milk (PS-VFM.	PS esters and vegetable fat in hypercholesterolaemic subjects	PS-SM and PS-VFM reduced TC and LDL-C ($p < 0.015$) by 7.8% and 6.3% and by 8.0% and 7.4%, respectively. HDL-C rose by 3.8% with PS-VFM milk ($p < 0.05$) compared to PS-SM milk. TG decreased by 18·7% in PS-VFM group ($p < 0.01$) than PS-SM	16 weeks
Demonty et al. (2006)	21	30–65	Semi-randomized, single-blind, 4-period crossover study	Fish-oil fatty acid esters of plant sterols (FO-PS)	Three treatment: (1) Fish oil (2) Fish oil + FO-PS (3) Low-fat SU-PS margarine	Effect of fish-oil supplement containing PS esterified to fish-oil fatty acids on the lipid profile of overweight, hyperlipidemic subjects	FO-PS and SU-PS reduced LDL-C ($p = 0.0031$ and 0.041, respectively) more than controls. Fish oil and FO-PS resulted in TG levels 40% ($p = 0.0004$) and 46% ($p = 0.0002$) lower, respectively, than controls ones. FO-PS and fish oil resulted in TG levels 39% ($p < 0.0001$) and 32% ($p = 0.0001$) lower, respectively, than SU-PS	8 weeks
Gonçalves et al. (2006)	37	30–45	Crossover study	Plant sterol-enriched milk	Two groups: (1) PS-enriched milk (2 mg/day); (2) controls (milk without PS)	Effect of PS milk in hypercholesterolemia	TC decreased from 245 to 223 mg/dL after 15 days of PS-milk intake and from 248 to 229 mg/dL after 30 days ($p < 0.05$), as well as LDL-C (from 156 to 138 mg/dL after 15 days and from 157 to 143 mg/dL after 30 days, $p < 0.05$)	30 days
Guardamagna et al. (2011)	58	8–16	Open-label intervention study	Plant sterols	Children evaluated before and after a 12-week treatment with PS	PS effects in children with different forms of primary hyperlipidemias	PS significantly decreased in TC, LDL-C and apoB. LDL-C decreased about 15% in Familial Combined Hyperlipidemia and Undefined Hypercholesterolemia children; about 10% in familial hypercholesterolemia patients	12 weeks
Garaiova et al. (2013)	25	16	Crossover study	Plant sterols, fish oil and B vitamins	Children evaluated before and after PS esters (1300 mg), fish oil, vitamins B12 (50 μg), B6 (2.5 mg), folic acid (800 μg) and coenzyme Q10 (3 mg) use	Effects of a combination of PS, fish oil and B vitamins on lipids profile of hypercholesterolemic children and adolescents	TC, LDL-C, VLDL-C, subfractions LDL-2, IDL-1, IDL-2 and plasma homocysteine levels were significantly reduced at the end of the intervention period ($p < 0.05$)	16 weeks

Maki et al. (2012)	32	21–79	Randomized placebo-controlled, crossover trial	Plant sterols and stanols	Treatment period I: 5 weeks, non-esterified sterol/stanol tablets, 0.45 g per tablet) vs placebo. Treatment period II: 6 weeks, cross over to receive the opposite product	PS and stanols action in primary hypercholesterolaemia	LDL-C (2 4.9%), non-HDL-C (2 3.6%) and TC (2 2.8%) significantly decreased after plant sterol/stanol administration ($p < 0.05$).	11 weeks
Zhao et al. (2011)	82	35–70	Randomized crossover trial	Plant sterols	Patients consuming spreads with or without 2 g/d of PS for two 4-week periods, each separated by a 4-week washout	PS action in individuals with high versus low basal circulatory PS concentrations	Cholesterol absorption index was positively correlated with campesterol ($r = 0.5864$, $p < 0.0001$) and b-sitosterol ($r = 0.4676$, $p < 0.0001$) one. PS reduced absorption indices of campesterol, b-sitosterol, and cholesterol by 36.5 ± 2.7%, 39.3 ± 2.9%, and 34.3 ± 1.9%, respectively, but increased cholesterol fractional synthesis rate by 33.0 ± 3.3% relative to control	12 weeks
Dulin et al. (2006)	40	47.4 ± 10.8	Double-blind, randomized controlled trial	Sugar cane–derived policosanol	Two groups: (1) oral policosanol (20 mg) once daily; (2) placebo	Sugar cane–derived policosanol in mildly hypercolesterolemic patients	No change was in LDL-C, HDL-C, TG between groups No change wad in LDL particle number, LDL particle size, or any other lipoprotein variable	01/2005–06/2005
Becker et al. (2008)	74	55.9 ± 8.4	Randomized primary prevention trial	Red yeast rice	Group 1: simvastatin (40 mg/d) group Group 2: fish oil and RYR.	RYR + fish oil vs statin in lipid lowering therapy	LDL-C significantly decreased in both groups but no significant differences were noted between groups. Groups 2 showed a more pronounced decrease in TG (−29% vs −9.3%; 95% confidence interval, −61 to −11.7; $p = 0.003$) than simvastatin group	05/2006–06/2006
Panahi et al. (2011)	100	52.9 ± 7.8	Randomized open-label, clinical trial	*Heracleum persicum*	Group 1): *H. persicum* (500 mg/day) + atorvastatin (10 mg/day); Group 2) atorvastatin alone (20 mg/day)	*Heracleum persicum* influence on atorvastatin therapy in dyslipidemic subjects	TC and LDL-C reduced both in the *H. persicum* ($p = 0.001$) and atorvastatin ($p < 0.001$) groups No HDL-C, not TG change in the *H. persicum* group ($p > 0.05$).Atorvastatin alone was not superior to combination therapy in lipid lowering therapy.	06/2009–06/2010
Bays et al. (2012)	177	53.2 ± 9.0	Randomized placebo-controlled, study	Icosapent ethyl	Three groups: (1) IPE 4 g/day; (2) IPE 2 g/day; (3) placebo	Effects of IPE on lipoprotein particle concentration and size	IPE 4 g/day reduced large VLDL (−27.9%; $p = 0.0211$), total LDL (−16.3%; $p = 0.0006$), small LDL (−25.6%; $p < 0.0001$), total HDL (−7.4%; $p = 0.0063$) levels, and VLDL particle size (−8.6%; $p = 0.0017$)	12 weeks

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Table 2 – (*continued*)

Source	N.	Age (years)	Design	Nutraceutical	Approach used	Aims	Results	Time
Chan et al. (2002)	52	53 ± 1	Randomized, placebo-controlled, 2 × 2 factorial intervention trial	Fish oil	Two groups: (1) atorvastatin (40 mg/day); (2) fish oil (4 g/day)	Effects of fish oil on plasma lipids and lipoproteins	Fish oil significantly decreased TG (−0·38 ± 0·11 mmol/L, $p = 0.002$) and increased HDL-C (+0·07 ± 0·04 mmol/L, $p = 0.041$). No significant interactions were between atorvastatin and fish oil treatments	6 weeks
Khandelwal et al. (2013)	200	35–55	Double-blind, placebo-controlled, trial	Fish oil and Plant sterols	Four groups: (1) both placebo; (2) active omega-3; (3) active plant sterol; (4) both active	Effects of omega-3 fatty acids from fish oil and PS on LDL-C and non-HDL-C levels	PS significantly decreased LDL-C 4.5%; ($p = 0.017$) and non-HDL-C (7.9%; $p = 0.0019$) levels. No effects were detected for fish oil omega-3 fish oil	4 weeks
Oelrich (2013)	57	52 ± 10	Double-blind, parallel design, placebo controlled trial	Fish oil	Four groups: (1) placebo; (2) fish oil 4 g/day of combined EPA and DHA provided as 90% TG formulation (TG90); (3) fish oil 4 g/day of combined EPA and DHA provided as 60% TG formulation (TG60); (4) fish oil 4 g/day of combined EPA and DHA provided as ethyl esters (EE) (i.e., 0% TG).	Examine the changes in serum concentrations of four subclasses of LDL particles as well as shifts in LDL phenotype patterns among hypertriglyceridemic adults	EPA + DHA supplementations significantly reduced TG modestly increased LDL-C (26 ± 4% and 13 ± 3%, $p < 0.0001$) LDL1, LDL2, LDL3 concentrations changes were all significant ($p < 0.05$).	12 weeks
Schmidt et al. (2012)	20	N/A	Controlled, parallel group intervention study	Fish oil	Two groups: normo- and dyslipidemic men both supplemented with 6 fish oil capsules per day	Investigate n-3 fatty acids effects on lipid expression of metabolism-related genes	Up-regulation of peroxisome proliferator-activated receptor α (PPARα) in dyslipidaemic patients undergone n-3 fatty acids supplementation; enhanced lipoprotein lipase -mediated catabolism of VLDL and reduced VLDL production by repression of apo CIII and apo B expression. Down regulation of Apo CII expression by n-3 fatty acids supplementation. Triacylglycerols clearance improved in treated patients. Reduced mRNA expression of MOGAT3, MOGAT2 and DGAT1, (genes involved in triacylglycerols synthesis) in n-3 fatty acids supplemented patients. Down-regulation of LDL receptor	12 weeks
Kong et al. (2004)	91	N/A	Randomized, placebo-controlled trial	Berberine	Two groups: (1) berberine; (2) placebo	Berberine effects in dyslipidaemia	Berberine reduced serum cholesterol by 29%, TG by 35% and LDL-C by 25%	3 months
Lee et al. (2013)	51	18–80	Randomized, open-label, multicenter, parallel groups, phase IV study	Omega-3 fatty acids	Patients were randomized to omega-3 fatty acid 4, 2 g, or no drug while continuing statin therapy	Omega-3 fatty acids effects on lipids	LDL size and TG levels' changes were greater in patients undergone 4 g omega-3 fatty acid assumption than no drug group (2.8 ± 3.1% vs 2.3 ± 3.6%, $p = 0.024$; −41.0 ± 24.1% vs −24.2% ± 31.9%, $p = 0.049$)	8 weeks

Schneider et al. (2011)	20	20–34	Randomized, placebo-controlled trial	Oyster mushrooms	Two groups: (1) 30 g dried oyster mushrooms; (2) tomato soup (placebo)	Oyster mushrooms influence on lipid profile	Oyster mushroom decreased TG (0.44 mmol/L; $p = 0.015$) and oxidized LDL-C (7.2 U/mL; $p = 0.013$).	21 days
Zamora-Ros et al. (2008)	40685	35–64	Crossover study	Resveratrol	Usual food intake was assessed by interviews	Estimate the dietary intake of resveratrol and piceid (R&P) present in foods, and to the principal dietary sources of these compounds in the Spanish population	Median and mean R&P intake were 100 and 933 mg/d, respectively. Compounds were distributed like this: trans-piceid = 53.6%, trans-resveratrol = 20.9%, cis-piceid = 19.3%, cis-resveratrol = 6.2%. The most important source of R&P was wines (98.4%) and grape and grape juices (1.6%); less peanuts, pistachios and berries (0.01%)	N/A

CETP: cholesteryl ester transfer protein; CI: confidence interval; FO-PS: Fish-oil fatty acid esters of plant sterols; GSPE: grape seed proanthocyanidin extract; HDL-C: high-density lipoprotein-cholesterol; IPE: Icosapent ethyl; LDL-C: low-density lipoprotein-cholesterol; N/A: not applicable; PS: plant sterols; PON: paraoxonase; RYR: Red yeast rice; SU-PS: sunflower oil plant sterol; TC: total cholesterol; TG: triglycerides; VLDL-C: very low density lipoprotein-cholesterol.

nutraceuticals into two categories: traditional and non-traditional. The first set includes all the substances naturally contained in foods, not changed by biotechnological techniques, industrial improvements and/or *de novo* synthesis. On the opposite side, we include non-traditional nutraceuticals that are externally added to the foods by bio-engineering actions.

4. Nutraceutical actions in cardiovascular diseases

Nutraceuticals are effectively able to reduce the burden of the atherosclerosis process and coronary heart disease development as already demonstrated in the literature (Ciccone et al., 2013; Garcia-Rios et al., 2013; Giordano et al., 2012; Kukongviriyapan et al., 2012; Kumar et al., 2012; Mitjavila & Moreno 2012; Raatz et al., 2013; Sheikholeslami Vatani & Ahmadi KaniGolzar, 2012; Voloshyna, Hussaini, & Reiss, 2012; Zhang et al., 2013). The main mechanisms that explain such a positive action on the cardiovascular system are not well understood. Carotenoids, the fat-soluble pigments produced by plants and microorganisms and highly present in fruits, vegetables, seaweeds and some seafoods and a fundamental component of Mediterranean foods, are already known to decrease the incidence and prevalence of cardiovascular events, perhaps by means of their antioxidant action on free radicals or by acting as anti-inflammatory molecules (i.e., by modulating the lipoxygenase enzyme activity) (Giordano et al., 2012). Izzo et al. (2010) found amelioration in calculated Framingham Risk Score in patients suffering from metabolic syndrome and undergoing nutraceutical administration. This result supports the hypothesis about the use of nutraceuticals in primary cardiovascular prevention protocols to reduce the overall burden of cardiovascular disease morbidity and mortality. Nevertheless, further studies are needed to implement the actual findings associated with this hypothesis.

5. Nutraceutical effects on dyslipidaemia: action mechanisms

Nutraceuticals play a peculiar role in ameliorating human dyslipidaemia (Marazzi et al., 2011; Sirtori et al., 2009). The exact pathophysiological mechanism is still unknown. Functional food ingredients can act on several biochemical pathways able to influence lipid disorders in the human body. Physicians have attempted to identify the mechanisms responsible for nutraceuticals actions (Baiges et al., 2010; Chen et al., 2012; Kato et al., 2009; Quesada et al., 2009, 2012). The benefits from red wine consumption (i.e., the "French paradox") (Renaud & de Lorgeril, 1992) are already known and are ascribed to its resveratrol and polyphenol contents.

Resveratrol (trans-3,4′,5-trihydroxystilbene) is a phytoalexin produced by more than 70 plant species, whose major concentrations are detected in grapes, berries, peanuts/pistachios (Tokuşoglu, Unal, & Yemiş, 2005), and red wine (Augustin, Sanguansri, & Lockett, 2013; Maier-Salamon et al., 2013). According to Zamora-Ros et al. (2008), a rough estimation of resveratrol content in common foods indicates that

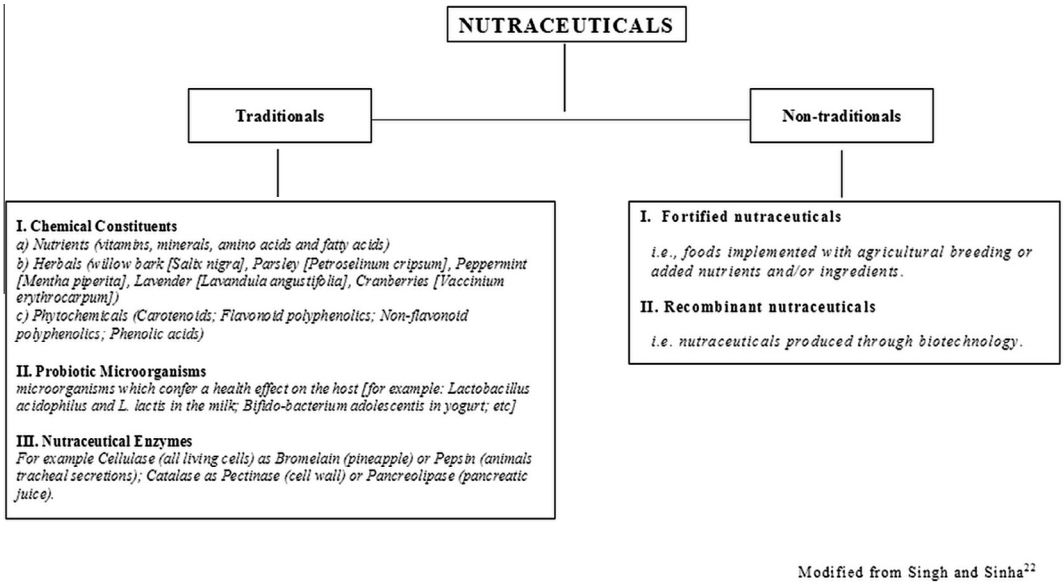

Fig. 2 – Nutraceuticals' classification.

higher concentrations of resveratrol are in red wine (0.847 mg/100 g) and itadori tea (0.974 mg/100 g), followed by wine, grapes, grape juice and peanut butter (range from 0.08 to 0.547 mg/100 g) and peanuts, pistachios and berries (0.01 mg/100 g).

Chen et al. (2012) hypothesised the role of resveratrol in counteracting hypercholesterolaemia. They fed mice a hypercholesterolaemic diet and resveratrol (200 mg/kg/day) for 8 weeks, observing a reduction in main serum lipid parameters. The inner mechanism underlying such an effect appears to involve cholesterol 7α-hydroxylase (CYP7A1), which is an enzyme able to mediate the conversion of cholesterol in 7α-hydroxycholesterol and, subsequently, in cholic acid. Bile acids genesis contributes to the elimination of cholesterol from plasma. Chen et al. (2012) demonstrated increased CYP7A1 mRNA transcription, protein production and activity. In particular, CYP7A1 increased liver X receptor alpha (LXRα) activation. This nuclear receptor mediates transcriptional up-regulation of CYP7A1 by binding to an LXR regulatory element in the CYP7A1 promoter (Chen et al., 2012). Thus, resveratrol enhances the metabolism of lipids, and this action ameliorates hypercholesterolaemia in experimental models. Nevertheless, a recent meta-analysis from Sahebkar (2013 in press) revealed no effect of resveratrol on dyslipidaemia in human models. The blood concentrations of every lipid parameter were not affected by the intake of such a compound, contradicting the previous experimental model results from Chen et al. (2012). This may be attributable to the metabolism of resveratrol in human body that results in small final bioavailability in tissues. An analysis performed by Sahebkar (2013 in press) outlined that no dose-response relationship or durations of supplementation affected the plasma concentrations of resveratrol. The hepatic first-pass metabolism greatly reduces its plasma concentrations, and its metabolites appear not to succeed in reaching good and optimal concentrations in blood. Thus, resveratrol has been supposed to exert a positive role in humans via down-regulating proinflammatory conditions or by inhibiting LDL oxidation. Studies are needed to obtain definite results in regard to this issue.

The polyphenols contained in mulberry leaf appear to corroborate the results from studies about resveratrol (Wu et al., 2013 in press). They appear to effectively reduce liver fatty acid storage and may be counteracting the activity of enzymes involved in lipid creation, such as fatty acid synthetase, acetyl-CoA carboxylase, or 3-hydroxy-3-methylglutaryl-CoA reductase. Theaflavins, the major polyphenols in black tea, have been demonstrated to have lipid-lowering effects (Jin et al., 2013). Furthermore, Gunathilake, Wang, and Vasantha Rupasinghea (2013) recently demonstrated that a polyphenol-rich fruit-based functional beverage was able to significantly lower liver cholesterol and total and non-HDL-cholesterol levels in spontaneously hypertensive rats fed a cholesterol-rich diet.

Water-insoluble fish proteins (IFP) from Alaska Pollock (*Theragra chalcogramma*) have been considered as optimal nutraceuticals in dyslipidaemia management. Kato et al. (2009) administered such compounds in ovariectomised rats fed a cholesterol-free diet. The results indicated that IFPs were able to increase CYP7A1 activities. Furthermore, IFPs increased bile acids in intestine and thus increased faecal excretion of cholesterol. The 3-hydroxy-3-methylglutaryl-CoA reductase mRNA levels were decreased by IFPs, providing a further genetic mechanism able to explain the overall reduction in plasma cholesterol by means of IFPs (Kato et al., 2009).

Grape seed reduces lipid plasma levels (Quesada et al., 2012). One of its components, i.e., proanthocyanidins (polyphenols widespread in other compounds of human diet), appear to play the major role in this process. Proanthocyanidins act on triacylglycerol levels by reducing their concentration in chylomicrons and very low-density lipoprotein (VLDL). The hypothesis is that proanthocyanidins can reduce the secretion of chylomicrons and VLDL, and this action reduces the

triacylglycerol level in plasma. Quesada et al. (2012) outlined that grape seed proanthocyanidin extracts can primarily improve the activity and expression of carnitine palmitoyltransferase 1a (CPT-1a), a mitochondrial enzyme that is fundamental in long-fatty acids metabolism, which, in turn, results in reduced triacylglycerol formation and thus reduced VLDL and chylomicrons concentrations. Furthermore, proanthocyanidins reduce hepatic CD36 action, a protein involved in fatty acids uptake by the liver. Its lower activity decreases the availability of fatty acids for VLDL lipid contents, which thus reduces the levels of plasma triacylglycerols (Quesada et al., 2012). Proanthocyanidins may modulate transcription of genes involved in VLDL synthesis. In fact, transcription factor sterol regulatory element-binding protein 1 (SREBP1), microsomal transfer protein (MTP) and diacylglycerol O-acyltransferase 2 (DGAT2) are all repressed by grape seed proanthocyanidin extracts. These are all fundamental in production and genesis of VLDL and thus in triacylglycerol synthesis and secretion in the blood. The reduction in their transcription process leads to reduction of dyslipidaemia in rats (Baiges et al., 2010; Quesada et al., 2009).

Curcumin, extracted from *Curcuma Longa*, is able to prevent macrophage transformation in foam cells (Zhao et al., 2012) by inhibiting scavenger receptor class A, a membrane protein able to induce internalisation of oxidised LDL in macrophages and initialise foam cells transformation. Furthermore, it promotes up-regulation of ATP-binding cassette transporter A1, which is a protein involved in cholesterol efflux from macrophage foam cells to apo-AI.

Furthermore, Rahimi-Ardabili et al. (2012) recently demonstrated that zinc can enhance paraoxonase enzyme activity in patients on haemodialysis (paraoxonase activity significantly increased [$p = 0.02$] in zinc-treated group rather than controls). Paraoxonases are enzymes located on HDL that are involved in the reduction of cardiovascular disease incidences via a suggested role in preventing LDL oxidation (Li, Liu, & Liang, 2003). Thus, they reduce the first moments of atherosclerotic process development, avoiding LDL-oxidation. This could be another fundamental mechanism by which nutraceuticals and functional food ingredients can prevent the negative effects of dyslipidaemia on the cardiovascular system.

Fish oil is safely employed in dyslipidaemia treatment. Fish oil is defined in the British Pharmacopoeia (2012 online) as "*Purified, winterised and deodorised fatty oil obtained from fish of families such as Engraulidae, Carangidae, Clupeidae, Osmeridae, Scombridae (except the genera Thunnus and Sarda) and Ammodytidae (type I) or from the genera Thunnus and Sarda within the family Scombridae (type II)*". It contains large amounts of unsaturated fatty acids, above all omega-3 fatty acids (eicosapentaenoic [EPA] and docosahexaenoic [DHA] acid), which are already known to exert protective effects on the cardiovascular system and, therefore, on the cardiovascular risk profile of individuals (Ciccone et al., 2013; Kris-Etherton et al., 2002; Stone, 1996). In particular, omega-3 fatty acids supplementation has hypotriglyceridaemic effects. Their use reduces triacylglycerol levels from 25% to 30%, although they can increase the serum concentrations of LDL cholesterol (Kris-Etherton et al., 2002). Physicians have attempted to explain the molecular mechanisms involved in the hypotriglyceridaemic effects of fish oil and its omega-3 fatty acid content. Schmidt et al. (2012) identified up-regulation of peroxisome proliferator-activated receptor α (PPARα) in dyslipidaemic patients receiving n-3 polyunsaturated fatty acids (PUFA) supplementation: the administration of these latter compounds enhanced lipoprotein lipase (LPL)-mediated catabolism of VLDL and reduced VLDL production by repressing apo CIII and apo B expression. Such an action enhances the hypotriglyceridaemic effects of these compounds. Apo CII (a regulator of lipoprotein lipase activation) expression was down-regulated in n-3 PUFA supplemented patients. Therefore, triacylglycerols clearance was improved in treated patients. In addition, reduced triacylglycerols synthesis was the result of lower mRNA expression of MOGAT3, MOGAT2 and DGAT1, which are the three fundamental genes involved in triacylglycerol synthesis. Nevertheless, an increased VLDL conversion to LDL and down-regulation of LDL receptor in dyslipidaemic patients treated with fish oil supplementation could be detected (Schmidt et al., 2012). In addition, ankaflavin, a yellow pigment isolated from Monascus-fermented product, appears to modulate the action of PPAR-γ and, therefore, lipid and glucose metabolism (Hsu et al., 2013).

Other nutraceutical and functional food ingredients can exert a role in controlling lipid metabolism (Kwok, Li, Cheng, et al. 2013; Srinivasan & Pari 2013), but further trials are needed to corroborate the experimental results.

6. Nutraceutical role in dyslipidaemia: experimental indications

Many studies have evaluated the potential role of nutraceuticals in the prevention of dyslipidaemia both in animal models (Alshatwi et al., 2011; Chen et al., 2008; Dvir et al., 2009; Huang & Lin, 2012a, 2012b) and in humans (Becker et al., 2009; Casas-Agustench et al., 2012; Demonty et al., 2006; Dulin et al., 2006; Garaiova et al., 2013; Gonçalves et al., 2006; Guardamagna et al., 2011; Izzo et al., 2010; Maki et al., 2012; Marazzi et al., 2011; Párraga et al., 2011; Qin et al., 2009; Rayman et al., 2011; Sirtori et al., 2009; Tomé-Carneiro et al., 2012; Weingärtner, Böhm, & Laufs, 2009; Wofford et al., 2012; Wong et al., 2010; Zhao et al., 2011).

Tomé-Carneiro et al. (2012) managed a triple-blind, randomised, placebo-controlled trial in 75 patients consuming resveratrol-enriched grape extract, grape extract alone, or placebo for at least 6 months. Resveratrol-enriched grape extract induced a significant decrease in the low-density lipoprotein (LDL) cholesterol, apoB, oxidised LDL and oxidised LDL/apoB ratio (LDLc, −4.5%, $p = 0.04$; −9.8%, $p = 0.014$; −20%, $p = 0.001$; −12.5%, $p = 0.000$, respectively) compared with placebo and grape extract groups. Considering the homogenous consumption of statins by all individuals enrolled in the three groups, these data revealed impressive results: resveratrol reduces hypercholesterolaemia, and, more importantly, it reduces the overall burden of oxidation of lipids and thus can be safely adopted in the primary prevention of cardiovascular disease in association with statins.

Anthocyanins, water-soluble pigments widespread in the plant kingdom, influence LDL- and high density lipoprotein

(HDL) cholesterols. The influence of berry-derived anthocyanin supplements on serum lipid profile was evaluated in dyslipidaemic patients by Qin et al. (2009). They observed a significant reduction in LDL cholesterol concentrations in the berry-derived anthocyanin supplement group after 12 weeks of treatment [−13.6% (95% CI: −10.1% to −17.1%)], whereas the placebo group displayed an increase in LDL cholesterol [0.6% (95% CI: −4.1% to 5.2%)]. The difference between groups was significant ($p < 0.001$) and was related to the inhibition of cholesteryl ester transfer protein (Qin et al., 2009). Thus, dyslipidaemic patients could benefit from such compounds to ameliorate their lipid state and their consequential cardiovascular risk profile.

An interesting work about this latest subject comes from Becker et al. (2009). Although limited by a small sample size (only 62 patients involved), this research attempted to evaluate the influence of red yeast rice on plasma lipids in patients suffering from statins discontinuation. After a 24-week observational period, physicians observed a 21.3% decrease in LDL cholesterol, which was a significant decrease as compared with the placebo group (8.7%, $p = 0.011$). The same results were obtained with total cholesterol levels (−14.9 ± 15.9% vs −5.3 ± 11.4%, $p = 0.016$). Nevertheless, the question about the lipid-lowering properties of red yeast rice is complex. Red yeast rice was already described in the Chinese Tang Dynasty in 800 AD, where it was used as herbal medication (Becker et al., 2008). It is obtained by fermenting the yeast *Monascus purpureus* over red rice. The process generates substances called "monacolins" whose major characteristic is the inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase. Therefore, they are able to negatively act on lipid formation in the same manner as statins. In particular, monacolin K is the same substance synthetically isolated from *Aspergillus terreus* and approved for pharmacological treatment of dyslipidaemia with the name lovastatin. Such considerations reveal that red yeast rice is a real functional food that is able to reduce lipid levels because of its statin contents. Thus, red yeast rice consumption can be compared with the daily intake of synthetically prepared statins. Becker et al. (2008, 2009) outlined that they adopted levels of red yeast rice containing a monacolin K (i.e., lovastatin) dose that was inferior to those of commercial tablets of the statin. This is partially true because the bioavailability of lovastatin contained in red yeast rice is higher than that coming from the intake of lovastatin tablets (Chen et al., 2013). Nevertheless, the normal side effects of statins appear to be reduced by red yeast rice (Becker et al., 2008, 2009), perhaps due to the presence of other compounds in the red yeast rice not fully discovered, and are able to synergistically reduce lipids levels with monacolin K, resulting in the substance not reaching toxicity levels. It has been supposed that adding selenium to yeast could further positively affect lipid profile, although the data coming from international studies (Rayman et al., 2011) should be better addressed and confirmed before full statements are drawn about this subject.

Nutraceutical and functional food ingredients can be added to common pharmacological treatments for dyslipidaemia, such as statin therapy, to improve and positively influence lipid profile by combining the effects of drug therapy and those of nutraceuticals. Furthermore, they can be considered as a helpful tool when standard therapy cannot be adopted because of intolerance. That is, they are not a total substitute for all well-standardised pharmacological treatments but can surely improve the outcome of the patients suffering from lipid disorders.

Soy milk and its derivatives in the common diet (Sirtori et al., 2009; Wofford et al., 2012; Wong et al., 2010) can effectively enhance the therapeutic goals of pharmacological treatment of dyslipidaemias. Soy milk significantly reduces plasma concentrations of all lipids (total cholesterol, LDL-cholesterol and triacylglycerols), with an average of 2% decrease in total and LDL cholesterol as compared with carbohydrate or milk protein administration and a mean 3.6% reduction in total/HDL cholesterol ratio (Wofford et al., 2012). Wong et al. (2010) confirmed such results and reported a reduction of approximately 8–10 mg/dL in LDL cholesterol when soy was added to prebiotics. The LDL/HDL cholesterol ratio was also affected in a negative manner: soy plus prebiotics could effectively reduce this ratio, which means a reduction in the cardiovascular risk profile of individuals (Wong et al., 2010).

As many studies (Casas-Agustench et al., 2012; Demonty et al., 2006; Garaiova et al., 2013; Gonçalves et al., 2006; Guardamagna et al., 2011; Maki et al., 2012; Párraga et al., 2011; Weingärtner et al., 2009; Zhao et al., 2011) have already indicated, plant sterols are able to actively influence lipid profile. The mean LDL-cholesterol reduction after consumption of plant sterol-supplemented foods ranges from 5.9% to 10.4% (Casas-Agustench et al., 2012). Thus, these nutraceuticals effectively improve hypercholesterolaemia. Although the mechanisms of action of such compounds is not fully known, they appear to be able to selectively act on LDL-cholesterol formations and, to some extent, on triacylglycerol concentrations in the blood, whereas little or no action had been observed with HDL-cholesterol (Demonty et al., 2006; Gonçalves et al., 2006; Maki et al., 2012). An interesting study by Maki et al. (2012) indicated the difference in response of approximately 4.9% ($p = 0.002$) in LDL-cholesterol when plant sterols were introduced into the diet compared with the placebo. This result was associated with a difference in response of approximately −3.6% ($p = 0.008$) in non-HDL-cholesterol (Maki et al., 2012). Khandelwal et al. (2013) reported no influence of fish-oil omega-3 PUFAs (2 g/day) on LDL and non-HDL cholesterol levels, whereas plant sterols appeared to succeed in lowering LDL and non-HDL cholesterol levels by 4.5% and 7.9%, respectively.

Fish oil and n-3 fatty acids deserve particular mention in this connection. Their role in dyslipidaemia has been evaluated in several studies. Triacylglycerols appear to be the preferred target of the action of fish oil and n-3 fatty acids (Schmidt et al., 2012). Bremer et al. (2013 in press) considered adult (aged 12–20 years) rhesus monkeys fed a high-fructose diet or a high-fructose diet plus 4 g fish oil (16% EPA/11% DHA)/day for 6 months. Fasting triacylglycerols and apo C3 concentrations were significantly lower in the fish oil group as compared with controls ($p = 0.005$). Triacylglycerols and total cholesterol plasma concentrations tended to decrease in obese KKAy mice fed fish oil (Wakutsu et al., 2012). The statistical trend was maintained in the liver where triacylglycerols and total cholesterol continued to reach lower levels in the fish oil group than controls (Wakutsu et al., 2012). The reason for similar results appears to lie in the reduced expression of fatty

acid synthase mRNA in fish oil mice as compared with controls, whereas no effect could be detected related to 3-hydroxy-3-methylglutaryl coenzyme A reductase mRNA among groups (Wakutsu et al., 2012). Effectively, it is known that fish oil can slightly increase LDL cholesterol. Thus, if one combines fish oil with statin therapy, a beneficial effect on triacylglycerols blood concentrations can be observed, followed by a parallel decrease in LDL levels. Huff, Telford, and Barrett (1992) observed that miniature pigs fed fish oil plus lovastatin had reduced VLDL and LDL apo B concentrations, primarily due to lower production rates. Nevertheless, the use of icosapent ethyl, a high-purity prescription form of eicosapentaenoic acid ethyl ester appears to overcome the limitations of normal fish oil and omega-3 fatty acids with LDL particles. Bays et al. (2012) demonstrated that, in fact, a reduced total LDL particle concentration (IDL particles, small LDL particles, and large LDL particles) of approximately 16.3% ($p = 0.0006$), whereas the small LDL particle concentrations were reduced by approximately 25.6% ($p < 0.0001$) and 12.8% ($p = 0.0274$) when administering 4 and 2 g/day of icosapent ethyl, respectively.

A good idea on the feasible application of nutraceuticals comes from Guardamagna et al. (2011). They attempted to explore the influence of plant sterols on hypercholesterolaemia in children suffering from primary hyperlipidaemia. In their open-label research, they enrolled 32 children with heterozygous familial hypercholesterolemia (FH), 13 children with familial combined hyperlipidemia (FCH) and 13 children with undefined hypercholesterolemia (UH). After 12 weeks of treatment with a plant sterol–enriched yoghurt, the results were positive. The total cholesterol was significantly reduced from baseline in each group (FH: 7.55 ± 1.09 mmol/L at baseline vs 6.90 ± 1.06 mmol/L after treatment, $p < 0.05$; FCH: 5.90 ± 0.65 mmol/L at baseline vs 5.20 ± 0.75 mmol/L after treatment, $p < 0.05$; UH: 6.15 ± 0.83 mmol/L at baseline vs 5.35 ± 0.93 mmol/L after treatment, $p < 0.005$), as well as LDL-cholesterol (FH: 5.61 ± 1.06 mmol/L at baseline vs 5.04 ± 1.06 mmol/L after treatment, $p < 0.005$; FCH: 3.96 ± 0.57 mmol/L at baseline vs 3.34 ± 0.70 mmol/L after treatment, $p < 0.005$; UH: 4.11 ± 0.93 mmol/L at baseline vs 3.36 ± 0.70 mmol/L after treatment, $p < 0.005$). These results are very important because of the poor tools that physicians have when treating children diseases. Garaiova et al. (2013) corroborate the evaluations of Guardamagna et al. (2011) by outlining that the early administration of nutraceuticals in hypercholesterolaemic children could really improve their lipid levels.

7. Nutraceuticals versus lipid lowering drugs in dyslipidaemia treatment

Nutraceuticals reduce dyslipidaemia burden. This action is fundamental when considering patients who are intolerant to statins although suffering from severe lipid disorders or whose statin treatment is not able to obtain good results. Nutraceuticals could be safely adopted in these individuals to prevent dyslipidaemia development.

Because of their direct reductive action on triacylglycerols, fish oil supplementation has always been considered for hypertriacylglycerolaemic states to improve lipid profile (Bremer et al., 2013; Schmidt et al., 2012). Nevertheless, it is already known that they are able to slightly increase LDL particle concentrations (Bremer et al., 2013; Schmidt et al., 2012). In a double-blind, parallel design, placebo controlled trial, 42 patients underwent 12 weeks of administration of 4 g/day omega-3 fatty acids (i.e., eicosapentaenoic acid and docosahexaenoic acid). Oelrich, Dewell, and Gardner (2013) observed a reduction in serum triacylglycerols of 26 ± 4% ($p < 0.0001$) and an increase in total LDL cholesterol of 13 ± 3% ($p < 0.0001$). For this reason, it has been supposed a combination therapy of fish oil supplementation and statins in which the former decreases triacylglycerols and increase HDL and the latter acts on LDL particles by reducing their serum concentration and cholesterol content would be useful. Chan et al. (2002) and Lee et al. (2013) confirmed such considerations by demonstrating a better lipid profile of patients suffering from dyslipidaemia when fish oil supplementation was added to standard statin therapy. Nevertheless, a recent work by de Lorgeril et al. (2013) indicated some doubts about such combined treatments. According to the authors, omega-3 supplementation and statins can negatively interact with each other, leading to a reduction in the final action on dyslipidaemia. Icosapent ethyl can potentially reduce the need for statins, as it has been demonstrated to actively reduce both triacylglycerols and total LDL particle (IDL, small LDL, large LDL) concentrations (Bays et al. 2012). Nevertheless, further studies are needed to confirm these findings.

Pectin (30 g/day), polyphenols (20 g/day), and phytosterols (6 g/day) have demonstrated comparable lipid lowering effects as lovastatin in hypercholesterolaemic swine (Metzger, Barnes, & Reed, 2009). Some authors (Schneider et al., 2011) have proposed edible mushrooms as good foods endowed with lipid-lowering properties. Their levels of n-3 fatty acids and, additionally, mevinolin (lovastatin) may explain the effects of such natural foods on lipids.

Berberine is a novel natural compound able to reduce plasma lipids. It is an alkaloid derived from Huanglian (*Coptis chinensis*), and its chemical structure is a benzyltetrahydroxyquinoline (Kong et al., 2004). Its administration deeply reduced serum cholesterol by increasing LDL receptor mRNA expression independent of circulating cholesterol by stabilising the post-transcriptional products of the gene involved in LDL receptor mRNA genesis (Kong et al., 2004). This finding is truly important because of the discovery of a substance that acts with a different mechanism than statins. Thus, statins and berberine could be combined to achieve a better control of LDL cholesterol levels in dyslipidaemic patients. Kong et al. (2008) found major efficacy of such a combined therapy (simvastatin plus berberine) as compared with mono-therapy, with a LDL cholesterol reduction of 31.8% ($p < 0.05$ vs berberine alone, $p < 0.01$ vs simvastatin alone) and similar results were observed for total cholesterol and triacylglycerols levels. Thus, nutraceuticals could be added to standard statin therapy. According to the literature, this combination is safe for patients and produces no side effects (Eussen et al., 2010). Even when patients are intolerant to statins, nutraceuticals can have a fundamental role in treating dyslipidaemia (Micallef & Garg, 2009; Sikka et al., 2011; Stock, 2012). Panahi et al. (2011) demonstrated that *Heracleum persicum* supplementation of atorvastatin at 10 mg allowed comparable reduction in lipid plasma levels to atorvastatin at 20 mg. *H. persicum* can be

added to traditional lipid lowering therapy to reduce the dosage and, consequentially, the side effects related to statin administration (Panahi et al., 2011).

8. Doubt about nutraceutical administration

Despite enthusiastic results reported in the literature, a recent review from Weingartner et al. (2009) generated concerns about nutraceuticals in clinical practice as useful compounds in dyslipidaemia management.

In particular, the authors dealt with the effective role of phytosterols in dyslipidaemia management and their relationship with the overall cardiovascular risk burden of individuals, gathering information coming from literature. Plant sterols are the main component of plant cell membranes. Their biochemical structure is tightly related to that of cholesterol: an extra ethyl group (sitosterol and stigmasterol) or methyl (campesterol) group at C-24 of the sterol side chain is responsible for the difference as compared with the cholesterol chemical formula (Othman, Myrie, & Jones, 2013; Weingartner et al., 2009). The absence of a double bond in the sterol ring, that is, the saturation of carbon atoms in the sterol ring, generates the corresponding plant stanols. The role of phytosterols in lipid metabolism has raised questions because of the uncertainty in the exact mechanisms involved. In particular, plant sterols and stanols appear to decrease the plasma concentration of cholesterol by reducing its absorption at the enterocyte level. It is possible that the higher lipophilic properties of phytosterols displace cholesterol from absorption. This would reduce the concentration of cholesterol into chylomicrons, and, therefore, there would be less introduction of cholesterol with diet (De Smet, Mensink, & Plat, 2012). Furthermore, it would be possible for phytosterols to favour the excretion of cholesterol from enterocytes to the intestinal lumen by means of adenosine triphosphate binding cassette G 5 (ABCG5) and G 8 (ABCG8) transporters (De Smet et al., 2012). Thus, cholesterol absorption is reduced and, although the endogenous production rate of cholesterol is increased, the net result is a final reduction in plasma concentration of cholesterol (Jones & AbuMweis, 2009). Phytosterols can properly be adopted as lipid lowering nutraceuticals, and can be safely added to other pharmaceuticals. Thus, their ability to reduce cholesterol concentration in plasma also indicates an ability to reduce cardiovascular risk in patients. Nevertheless, Weingartner et al. (2009) had doubts about the real effect of phytosterols on cardiovascular risk. Phytosterols can favour LDL uptake in vessels and tissues, as demonstrated by xanthomatosis in patients suffering from sitosterolaemia. Thus, although they reduce LDL plasma concentrations, they cannot prevent atherosclerosis development. Furthermore, plant sterols can be incorporated in cell membranes altering their function and structure, which induces an unstable condition that enhances organ damage (Weingartner et al., 2009).

Dulin et al. (2006) evaluated the efficacy of sugar cane-derived policosanol in healthy adults with mild hypercholesterolemia, but they failed to demonstrate a reduction in total and LDL-cholesterol and in triacylglycerols in this type of patients. Thus, policosanol cannot be considered as being able to influence the cardiovascular risk profile of individuals. Policosanols are long-chain fatty alcohols ranging from 24 to 34 carbons in length. As Jones, Kassis, and Marinangeli (2009) already indicated, literature data about policosanol efficacy on lipids is quite confusing and unclear. They revealed that although a few reports have highlighted the possible role of policosanols in reducing LDL cholesterol by suppressing its biosynthesis, when translating such experimental results to human studies, the endpoints were not reached. This limits the full consideration of such compounds for adoption in dyslipidaemic patients as lipid-level controllers.

Overall, the role of nutraceuticals in cardiovascular risk protection is still under debate. Several trials are needed to establish their exact real role for such a purpose.

9. Future directions in functional food and nutraceutical implementation

Ongoing trials (Párraga et al., 2011) intend to elucidate the influence of sterols and, broadly, of nutraceuticals on lipid lowering. Surely, functional food and nutraceuticals have the potential to become the future of primary prevention in dyslipidaemia treatment in particular and, secondarily, in cardiovascular disease prevention because of their demonstrated actions in past studies. Marinangeli and Jones (2013) supposed an important role for them in human diet and cardiovascular risk reduction, but, correctly, they noted that such a role may be greatly increased and become more reliable in clinical practice with only increased trust by industrial producers in these products. The researchers hoped that manufacturers will be able to devote resources to nutraceutical development, but the economic crisis has limited such an effort.

An ongoing area of focus is the influence of genetics on the lipid levels of individuals beyond lipid-lowering treatment (Rudkowska et al., 2013). This is an aspect that should be taken into account when evaluating and treating a patient. Although it is too early to introduce genetic evaluation into clinical practice and treatment guidelines, future studies should aim first to develop drugs that are able to attack several pathway of lipid metabolism. For this purpose, nutraceuticals appear to guarantee the success of such research. As previously noted (Garcia-Rios et al., 2013; Giordano et al., 2012; Kukongviriyapan et al., 2012; Li et al., 2003; Mitjavila & Moreno, 2012; Sheikholeslami Vatani & Ahmadi Kani Golzar, 2012; Voloshyna et al. 2012; Zhang et al. 2013; Zhao et al. 2012), nutraceuticals are able to interact with several biochemical pathways in lipid metabolism, and thus, they have the potential to overcome the genetic variability of individuals. Many features should still be defined such as the exact mechanisms of action of nutraceuticals, the perfect dosages to be used in clinical practice, the dose-response relationships, the duration of effects, and other such related features (Brownawell et al., 2012). Thus, we are still waiting for future studies to explain the exact pharmacokinetics and pharmacodynamics of nutraceuticals to better adopt these molecules as therapeutics in dyslipidaemia treatment.

Conflict of interest

None declared.

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