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A Review on Lipid-Lowering Effects of Nutraceuticals

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Abstract

Hyperlipidemia is a prevalent disease and an important risk factor for Cardiovascular Diseases (CVDs). When it occurs with other CVDs and diseases like diabetes and hypertension, the morbidity and mortality rate is enhanced. Throughout the years, nutraceuticals have been studied to prevent or reduce hyperlipidemia, many of which are found in natural sources. For this review we explored published clinical trials and papers on Nutraceuticals fulfilling our eligibility criteria. Drug therapy when combined with Nutraceuticals work in synergy and helps in lowering total cholesterol, triglycerides and other lipoproteins. Furthermore, combination therapy reduces the required dose of conventional drugs, thus reducing side effects. The aim of this review is to aid physicians in understanding the lipid lowering potential of certain nutraceuticals in primary hyperlipidemia.

Key words: Hyperlipidemia; Nutraceuticals; Total Cholesterol; Lipoproteins

Introduction

Cardiovascular Diseases (CVDs) cause 31% of deaths globally. Globally almost 17.9 million people died due to CVDs in the year 2016 [1]. Hyperlipidemia is identified as the main risk factor for Coronary Atherosclerosis and other CVDs [2]. Hyperlipidemia is characterized by elevated serum Total Cholesterol (TC), Low Density (LDL), and Very Low-Density Lipoprotein (VLDL) and decreased High-Density Lipoprotein (HDL) levels. According to the ICMR INDIAB study restricted to urban and rural populations in India, hypercholesterolemia was seen in 13.9%, high triglycerides in 29.5%, low HDL cholesterol in 72.3% and high LDL cholesterol in 11.8% of the population. 79% men and women had abnormalities in at least one of the lipid parameters [3]. Hyperlipidemia can be classified into two types: Primary and Secondary. Lipid lowering drugs are effective in the treatment of primary hyperlipidemia while management of underlying disease is necessary in secondary hyperlipidemia. As hyperlipidemia is an important risk factor for CVDs, its dramatic increase highlights the importance of controlling it. Diet and exercise are the first line of prevention & treatment of hyperlipidemia. When these recommended lifestyle changes fail to control the disease, physicians' resort to cholesterol-lowering agents. Prolonged use of statins, fibrates, bile acid sequestrants may cause severe adverse effects [4,5]. Hence it is necessary to find an alternative adjuvant treatment for hyperlipidemia which is well tolerated by the patients. Herbal drugs have always been an important source for finding new medications for human health problems. Traditionally, many herbs have been recommended for lipid lowering and their hypolipidemic effects have been reported by many researchers.

Research Methodology

The literature survey was done using the databases of Google Scholar, Medline and Science Direct, using the key terms hyperlipidemia, lipid lowering agents, bioactive constituents, nutraceuticals and clinical trials.

Lipid targets

The clinical targets in treating hyperlipidemia are decreasing the LDL levels and increasing the HDL levels. Patients can be categorized according to their LDL level to assess CVD risk: Low Risk (<130 mg/dL); Moderate risk (130–160 mg/dL); High risk (>160 mg/dL). Patients with HDL levels <40 mg/dL are also at high risk of CVDs [6]. These targets

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can be achieved by the following mechanisms depicted in TABLE 1.

- Inhibition of hepatic cholesterol synthesis,
- Inhibition of cholesterol absorption,
- Enhancers of cholesterol excretion and by
- Acting on fatty acids.

TABLE 1. **Other mechanism of nutraceutical intervention. ABCA1: ATP-Binding Cassette Transporter A1; ACAT: Acyl Coenzyme A Cholesterol Acyltransferase; NPC1L1: Niemann-Pick C1-Like 1**

Sr. No.	Mechanism/Category	Nutraceutical Intervention
1	Inhibtion of NPC1L1 transported and ABCA1	Curcumin
2	Inc cholesterol faecal excretion	Plant sterols/stanols
3	Inhibition of cholesterol absorption	Bergamot, berberine, gamma-oryzanol, policosanols, psyllium, soluble fibres
4	Inc bile salts excretion	Berberine, bergamot, lupin, psyllium, probiotics, soluble fibres, soy
5	Inhibition of the formation of cholesterol esters (ACAT inhibition)	Artichoke, bergamot, plant sterols/stanols
6	Inhibition of the formation of solubilised micelles	Green tea, plant sterols/stanols, probiotics

Artichoke

From the acquired data, it is established that Artichoke Leaf Extract (ALE) has hypolipidemic effect. ALE contains the flavonoids (1%), which include the glycosides luteolin 7β-rutinoside (scolymoside), luteolin-7β-D-glucoside and luteolin-4β-D-glucoside [7,8].

Lipid lowering mechanism: Luteolin inhibits the enzyme HMG-CoA reductase, which is an important enzyme in liver cholesterol biosynthesis thus it reduces the cholesterol production. It also increases the cholesterol elimination in bile secretions and inhibits the LDL oxidation.

Clinical trials: Bundy et al. appraised the hypolipidemic potential of ALE in 38 hyperlipidemic patients with recently diagnosed mild to moderate hyperlipidemia. In comparison with the patients of Placebo group 4.2% decrease of TC was seen in the patients consuming 1280 mg/day of ALE for 12 weeks [9]. Englisch et al. evaluated that 69 patients of the treatment group who administered 1800 mg/day ALE for 6 weeks showed a significant decrease in TC, LDL, and LDL/HDL ratio *i.e.* 18.5%, 22.9% and 20% respectively in comparison with the placebo group [10]. In another study Rondanelli et al. treated 46 hyperlipidemic patients with ALE 1000 mg/day and 46 patients with placebo. A significant increase in HDL was seen $p<0.001$ and a significant decrease was found in TC and LDL *i.e.* $p<0.033$ and $p<0.001$ respectively [11]. In all investigations ALE didn't show any serious side effect in some cases minor and ephemeral gastrointestinal effects were observed. Thus, it indicates that ALE has good tolerability and is safe for use.

Konjac

Glucomannan is a soluble fibre derived from Amorphophallus konjac commonly known as Konjac root. It is a polysaccharide comprising of glucose and mannose in the ratio of 1:1.6 and is bound with β-1,4-glycosidic bond, in Traditional Chinese Medicine (TCM) it is used for detoxification, tumour-suppression, blood stasis alleviation and phlegm liquefaction [12,13].

Lipid lowering mechanism: Glucomannan; it decreases the absorption of cholesterol and bile acids from jejunum and

ileum respectively yielding into improvements in the levels of LDL and Apolipoprotein B. Also it boosts the activity of the enzyme 7α-hydroxylase which converts cholesterol into bile acids [14].

Clinical trials: Anders Arvill and Lennart Bodin found that subjects who administered glucomannan 3900 mg/day for four weeks showed reduction in the concentrations of TC, LDL and TG by 10%, 7.2% and 23% respectively [15]. In another trial O. Guardamagna et al. revealed that glucomannan consumption of about 2000 or 3000 mg/day in 36 hypercholesteraemic children significantly reduced the TC by 8%, LDL by 7.3% and non HDL cholesterol by 7.2% compared to the placebo [16]. From a study F. Martino et al. estimated that in hypercholesteraemic children Step one diet and glucomannan (dose 2000 or 3000 mg/day depending upon the weight of the children) showed synergistic effects in significantly reducing the TC and LDL levels by 18% ($p=0.042$) and 23% ($p=0.026$) respectively[17]. Glucomannan consumption did not cause any severe side effects; diarrhoea, flatulence and abdominal discomfort were seen in some cases.

Psyllium

It is a source of concentrated fibres derived from the husk of Psyllium seeds. Psyllium increases the excretion of bile acids by stimulating 7α-hydroxylase.

Lipid lowering mechanism: It reduces the absorption of intestinal cholesterol and also brings about reduction of hepatic cholesterol synthesis *via* the short-chain fatty acid by-products of fibre fermentation [18].

Clinical trials: Sprecher et al. investigated the Antihyperlipidemic effects of psyllium 5100 mg/day in patients with mild to moderate hypercholesteremia; it reduced the TC by 5.8% ($p<0.05$) and LDL by 7.2% ($p<0.05$) in patients consuming High fat died while It reduced the TC by 4.2% ($p<0.05$) and LDL by 6.2% ($p<0.05$) in patients consuming Low fat diet[19]. Also psyllium works in synergy with other hypolipidemic agents like Simvastatin. Wilson et al. found that the patients who received the combination of Simvastatin 10 mg/day and Psyllium 5100 mg/day showed significant reduction in TC by 26% and LDL by 35.6% levels compared to patients receiving Simvastatin 20 mg/day showed decrease in TC by 24% and LDL by 35% [20]. Murray et al. concluded that a combination of 2.5 g of psyllium and 2.5 g of colestipol was better tolerated than and as effective as either 5 g of colestipol alone. The combination therapy and colestipol alone did not differ significantly with respect to changes in individual lipid values. Both showed significant decrease in TC ($p<0.05$) and LDL ($p<0.05$) when compared with the placebo group [21]. Psyllium showed mild and transient gastrointestinal irritations, no severe adverse effects were reported this indicates that Psyllium has a good safety profile.

Red Yeast Rice (RYR)

Monascus purpureus, M. pilosus, M. floridanus or M. ruber are some varieties of Yeasts which are used in the preparation of RYR. It is obtained by fermentation of rice with yeast of the above-mentioned species. The fermentation process yields the red colour in rice and also enriches the rice with hypolipidemic active constituents known as Monacolins. Many subtypes of Monacolins such as Monacolin J, K, L, M and X have been identified depending upon the strain of the yeast used and the process of fermentation. Monacolin K is structurally identical to Lovastatin [22,23].

Lipid lowering mechanism: RYR reversibly inhibits the enzyme HMG-CoA reductase which is a key enzyme in endogenous cholesterol synthesis and there by exhibits its lipid lowering effect.

Clinical trials: In a study comprising of 42 mild to moderate hyperlipidemic patients Bogsrud et al. discovered that the treatment group receiving RYR 2400 mg/day showed a significant decrease in the levels of TC by 15% and LDL by 23% with $p<0.001$ in comparison with the patients treated with placebo ; while Steven et al. observed that statin intolerant hyperlipidemic patients treated with 4800 mg/day of RYR showed a reduction of 23% & 30% in TC & LDL levels respectively and the patients treated with Pravastatin 40 mg/day decreased the TC by 19% & LDL levels by 27% [24,25]. RYR was well tolerated in all the patients it didn't revealed any side effects. Alterations in the plasma concentrations of Monacolin K can be caused by the inhibitors and inducers of the enzyme CYP450. CYP450 inhibitors like cyclosporine, niacin, fibrates, coumarin, verapamil, antifungals, macrolides, nefazodone, HIV protease inhibitors may increase the risk of myotoxic side effects.

Probiotics

Probiotics are vital microorganisms which grant health benefits when consumed in adequate amounts. Lactobacillus acidophilus, Bifidobacterium bifidum, Lactobacillus reuteri and Lactobacillus plantarum are some strains of probiotics which have shown antihyperlipidemic effects.

Lipid lowering mechanism: Lactobacillus acidophilus and L. bulgaricus contain the enzymes cholesterol dehydrogenase/isomerase. These enzymes transform cholesterol into cholest-4-en-3-one, an intermediate cofactor in the con-

version of cholesterol to coprosterol or coprostanol, which are directly excreted in the faeces [26]. Lactobacilli and Bifidobacterium reduce the enterohepatic circulation of bile salts through activity of Bile Salt Hydrolase (BSH) enzymes; they deconjugate bile acids enzymatically, thereby increasing their excretion rates and attracting greater mobilization of systemic cholesterol to the liver for *de novo* synthesis of bile salts [27].

Clinical trials: Sanguansak Rerksuppaphol & Lakkana Rerksuppaphol found that in a study consisting of 70 hyperlipidemic patients; patients treated with the probiotics (Lactobacillus acidophilus+Bifidobacterium bifidum) for a short duration of six weeks showed decreased TC LDL and TG levels by 10%, 4.2% and 15% respectively as compared to the placebo group [28]. In another study Fuentes et al. appraised the lipid lowering potential of probiotic Lactobacillus plantarum as its consumption for 12 weeks reduced the TC, LDL and TG levels by 13%, 14% and 16% respectively also it increased the HDL levels by 11% [29]. In an trial Jones et al. investigated that administration of probiotic Lactobacillus reuteri for a short duration of six weeks lowered the TC levels by 10% and LDL levels by 7.5% compared to patients who received placebo [30].

Nigella Sativa

Nigella sativa seeds are also known as black seeds. It has been widely used by Unani physicians and Ayurvedic practitioners for the treatment of several disorders like obesity, dyslipidaemia, hypertension etc. Many studies have reported that Nigella sativa has shown antioxidant and hypoglycaemic effects [31]. Thymoquinone and ω-6 linoleic acid are the two active constituents present in Nigella sativa seeds responsible for its hypolipidemic effect.

Lipid lowering mechanism: The hypolipidemic effect is exhibited by the inhibition of the enzyme HMG-CoA reductase which is a key enzyme in hepatic cholesterol synthesis [32].

Clinical trials: In a trial Qureshi et al. evaluated that patients in the treatment group receiving 2000 mg/day for 6 weeks showed decrease of 10%, 11% and 14% in the levels of TC, LDL and TG respectively as compared to the placebo group [33]. In comparison with the patients receiving placebo Mohammad et al. revealed that the patients administering 2000 mg/day of nigella for 4 weeks showed a significant decrease of 4.78%, 5.6% and 16% in the levels of TC, LDL and TG respectively [34]. Amina Hamed Ahmad Alobaidi discovered that Nigella (500 mg/day) in combination with Simvastatin (10 mg/day) and Garlic oil (250 mg/day) gives synergistic effect and showed reduction of 18%, 29% and 21% in the levels of TC, LDL and TG respectively while it showed significant increase in the HDL levels by 21% [35]. Nigella was well tolerated in all the patients and didn't produce any severe side effects (TABLE 2).

TABLE 2. **Clinical data of nutraceuticals in Hyperlipidemia. a: p<0.05, b: p<0.01**

Sr. No.	Drug	Author & ref	N	Study design	Intervention dose & duration	Results
1.	Artichoke	R Bundy et al.	75	Randomised, double blind, placebo controlled, parallel	1280 mg/day (Tablets) For 8 weeks	4% decrease in TC [a] While LDL and TG decreased by 6%.
2.		Englisch et al.	113	Randomised, double blind, placebo controlled, parallel	1800 mg/day (Capsule) For 6 weeks	18.5% decrease in TC [b] LDL showed a decrease of 22.9% and TG decreasedby 6%. LDL/HDL ratio was decreased by 20.2%
3.		Rondanelli et al.	92	Randomised, double blind, placebo controlled	1000 mg/day (Tablets) For 8 weeks	Significant decrease in TC was observed [a] LDL decreased [b] LDL/HDL ratio reduced [b]

4.	Red Yeast	Martin et	40	Double-blind, Randomized,	2400 mg/day	14% reduction in TC [b]
	Rice	al.		Placebo-controlled	(Capsule) For 16 weeks	29% reduction in LDL [b] and 11% decrease in TG [b] Apo B reduced by 22% [b] while Apo A-I increased by 10% [a] HDL increased by 6%
5.		Steven et al.	43	Randomized controlled trial	4800 mg/day (Capsule) For 12 weeks	TC decreased by 23%. While LDL showed a decrease of 30% TGs decreased by 7.8%.
6.	Probiotics	Sanguansak Rerksupphol & Lakkana Rerksupphol	70	Randomized, Double-blind, Placebo-controlled	(Capsule) For 6 weeks	TC was decreased by 10% ($p<0.001$). While LDL showed a decrease of 3.6% ($p<0.01$) TG decreased by 15%.
7.		Fuentes et al.	60	Randomized, Double-blind, Placebo-controlled	(Capsule) For 12 weeks	TC was decreased by 13%. While LDL showed a decrease of 14% Also, the TGs decreased by 16%. LDL/HDL ratio decreased by 19% HDL increased by 11%
8.		Jones et al.	114	Randomized, Double-blind, Placebo-controlled	(Capsule) For 6 weeks	10% reduction in TC [a] 7.8% reduction in LDL [a]

Conclusions

Nutraceuticals are food supplements obtained from natural sources and have been studied for Hyperlipidemia since many decades. Conventional lipoid lowering drugs have side-effects and its prolonged use causes tolerance in the patients there is need for an effective anti-hyperlipidemic nutraceutical. Artichoke, Konjac, Psyllium, Red Yeast Rice, Probiotics, Nigella sativa have good mechanism and efficacy in hyperlipidemia braced by good quality clinical trials and animal studies. Lipid lowering effects of these drugs are attributed by their ability to inhibit the hepatic cholesterol synthesis, inhibit cholesterol absorption and enhancing cholesterol excretion. Combination of these nutraceuticals and conventional lipid lowering agents could potentially reduce its dose and adverse effects associated with the long-term use of the conventional drug therapy. Thus, physicians can use these nutraceuticals to treat borderline hyperlipidemia and as adjuvant treatment in treating Sever hyperlipidemia.

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