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Natural Approaches to Managing Dyslipidemia: a review of nutraceuticals for lipid regulation and clinical applications

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ABSTRACT

The hallmarks of dyslipidemia, a major risk factor for cardiovascular disorders, are aberrant lipid levels that fuel atherosclerosis. Alternative therapeutic techniques are necessary because of the potential negative effects of standard lipid-lowering medications, including statins, despite their widespread use. By inhibiting the absorption of cholesterol, up regulating LDL receptors, and exhibiting antioxidant activity, natural products such as phytochemicals, polyphenols, flavonoids, and omega-3 fatty acids have shown notable lipid-lowering effects.

The function of several plant-based substances and their mechanisms of action in the treatment of dyslipidemia are examined. This review looks at the roles played by a number of plant-based compounds and how they work to treat dyslipidemia. The therapeutic potential of functional foods, medicinal plants, and bioactive compounds is highlighted through evidence from preclinical and clinical studies. A full understanding of these natural compounds may contribute to the development of safer, innovative treatments for dyslipidemia. These bioactive compounds, synergistic effects, dosage adjustment, and clinical validation should be the main topics of future research..

Keywords: *Dyslipidemia, Hypercholesterolemia, Lipoproteins, Natural products, Nutraceuticals, Phytochemicals, Polyunsaturated fatty acids.*

1. INTRODUCTION

Cholesterol is an essential component of cell membranes; it preserves the structure and functionality of cells. Furthermore, vitamin D, corticosteroids, and sex hormones are all precursors of cholesterol. This vitamin affects the immune system, controls gene expression, and aids in the creation of bones. It is possible to catabolize cholesterol into bile acids, which are essential for the digestion and absorption of fat-soluble vitamins and fat-based diets.

The cells obtain their cholesterol from two sources:

1) Endogenous, which comes from the liver's production (80%), and
2) Exogenous, which comes from the diet (20%).

When cholesterol binds to particular proteins and lipids to create lipoproteins, it is carried throughout the bloodstream [11]. There are six different kinds of lipoproteins in the blood that carry cholesterol:

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- Chylomicrons
- Low-density lipoprotein (LDL), often known as "bad cholesterol,"
- high-density lipoprotein (HDL), sometimes known as "good cholesterol,"
- very low density lipoproteins (VLDL)
- Lipoproteins with an intermediate density (IDL)
- Lipoprotein (a) [5].

High total cholesterol (TC), high triglyceride (TG) levels, low HDL-C, and high LDL-C are examples of lipid imbalances that describe dyslipidemia, an aberrant lipid profile [8]. One or more of these anomalies may cause other types of dyslipidemia, such as hypertriglyceridemia, are linked to acute pancreatitis and non-alcoholic fatty liver disease, but dyslipidemia, particularly elevated LDL-C, and is a major risk factor for CVD [7].

Inadequate management of dyslipidemia may result in progressive cardiovascular harm. Approximately 40% of the world's population suffers from elevated plasma cholesterol levels, according to the World Health Organization[6]. The most common kind of dyslipidemia is hypercholesterolemia, which is linked to a higher risk of CVD. In 2019, elevated LDL-C values were the eighth most important risk factor for death worldwide [7]. The primary form of dyslipidemia in the globe is caused by circulating non-optimal cholesterol, which includes elevated low-density lipoprotein cholesterol (LDL-C) and residual cholesterol carried by triglyceride-rich lipoproteins. It is also a known risk factor for atherosclerotic cardiovascular disease (ASCVD) [4].

Epidemiology:

A total of 34.0% of Chinese individuals suffer from dyslipidemia, according to numerous epidemiological research [6]. Only a few research on the epidemiology of cholesterol and other lipoprotein lipids on sizable samples have been conducted in India during the past 30 years [3]. According to our evaluation of current population-based epidemiological research, there are only six multisite studies with sample sizes ranging from 2000 to 16,000 that concentrate on cardiovascular risk factors, such as cholesterol levels. None of the studies from 14 to 19 are representative of the country [3]. The incidence of hypercholesterolemia varies by location in India [3]. These studies show that the prevalence of hypercholesterolemia ranges from 10–15% in rural populations to 25–30% in urban ones. Dyslipidemias linked to cholesterol, such as hypercholesterolemia and elevated LDL cholesterol, were more common in developed states [3]. According to National Family Health Surveys, the more developed Indian states had higher rates of obesity, diabetes, and hypertension, three cardio metabolic risk factors. Big interstate and interregional heterogeneity in hypercholesterolemia and other dyslipidemias was reported by data from the recent ICMR-INDIAB research (2023). Prevalence of high total cholesterol was lowest in Jharkhand (4.6%), Assam (7.9%), and Bihar (9.7%), and highest in Kerala (50.3%), Goa (45.6%), and Himachal (39.6%). The prevalence of several dyslipidemias (higher LDL and total cholesterol, triglycerides, and low HDL cholesterol) in all of the major Indian states is described in depth.[3] There are very few population-based studies from India that have assessed the epidemiology of LDL-C. In LDL-C epidemiological investigations, the lack of information on the small-dense LDL component is a significant factor that is particularly pertinent to South Asian populations. High levels of qualitatively aberrant LDL-C particles with a lower density and smaller size have been found to be indicative of a unique atherogenic dyslipidemia among South Asian emigrants in the United States. Low HDL cholesterol and elevated triglycerides are additional factors contributing to this atherogenic dyslipidemia. In India, more research is needed to determine which LDL-C subfraction is crucial to the pathophysiology of CAD [3].

Prevalence:

Over the past three decades, dyslipidemia has become more common and is now regarded as a global health burden [7]. Because it raises the risk of coronary heart disease later in life, an increased prevalence of dyslipidemia in young adults is concerning. About 50% of young adults with high total cholesterol may be five times more likely to have coronary heart disease and nine times more likely to have a myocardial infarction than those with low total cholesterol who are between the ages of thirty and forty [7]. Identifying the prevalence of dyslipidemia and associated risk factors in these particular population groups will be a crucial first step in raising awareness and preventing dyslipidemia and its associated health consequences [7]. The prevalence of hypertriglyceridemia in India has not been extensively studied using population-based data. Indians and South Asian immigrants have been shown to have lower levels of total cholesterol and higher triglyceride levels than people in the UK and Europe. The prevalence of hypertriglyceridemia has been reported to be around 10% in European countries, with significant regional differences; this is far lower than in India. Mild-to-moderate hypertriglyceridemia is as common as type 2 diabetes and obesity. Extremely high triglyceridemia. The prevalence of dyslipidemia varies according to socioeconomic class, age, gender, and place of residence. In India, the prevalence of different dyslipidemias varies by region [3]. The incidence of elevated triglycerides was higher in eastern and southern states, but elevated total and LDL-C were more common in northern and western Indian towns. Hypertriglyceridemia was more common in cities with lower human development indices, while total and LDL-C levels were greater in those with higher

indices [3]. The prevalence of dyslipidemia in T2DM patients is very high. The following factors were linked to an increased risk of dyslipidemia patterns: female gender, overweight or obesity, hypertension, prolonged duration of type 2 diabetes, poor glycemic control, and diabetic vascular complications [9].

Global trends and clinical research:

The prevalence of hypercholesterolemia has been the subject of only a few cross-sectional research regarding changing patterns [3]. Over the course of 25 years, from 1991 to 2015, Jaipur Heart Watch study carried out a number of cross-sectional studies to find patterns in the different cardiovascular risk factors among Indian metropolitan residents. Hypercholesterolemia (≥200 mg/dl) prevalence throughout this time period is trending slightly upward. Cross-sectional research with time intervals from different parts of India, such as Delhi, Punjab, Vellore, etc., has revealed comparable patterns [3].

NHDL cholesterol was identified in the PURE study as a significant cardiovascular risk factor in high-, middle-, and low-income nations. In fact, it is the most major risk factor for CAD, accounting for 17% of the population, which is far greater than risk factors like diabetes, smoking, and hypertension. Additionally, in groups with NHDL cholesterol levels of 155 mg/dl for CVD incidence and mortality as well as IHD incidence and mortality, the study found that cardiovascular risk increased as NHDL cholesterol levels increased. According to numerous researches conducted worldwide, NHDL cholesterol is one of the more significant CAD risk factors besides PURE. In India, NHDL cholesterol has only been recorded in a small number of epidemiological investigations [3].

Clinical and epidemiologic studies have shown that elevated triglyceride levels are a biomarker of cardiovascular (CV) risk. Nonetheless, icosapent ethyl (highly refined eicosa pantenoic acid) has been shown to be a significant CAD risk factor in the Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT).Long-term use of icosapent ethyl was linked to a lower risk of later cardiovascular events in people with elevated triglyceride levels (>200 mg/dl), According to one study (the mechanisms behind this advantage are debatable).[3] The most significant predictor of CAD is lipid abnormalities, a prevalent clinical disease that causes an excess of potentially atherogenic lipids and lipoproteins. Important dyslipidemias that satisfy the Bradford Hill criteria for CAD causation include elevated triglycerides, total cholesterol, LDL cholesterol, and NHDL cholesterol [3].

According to the study, hypertriglyceridemia and low HDL are common, although elevated total and LDL cholesterol are most common in the nation's more developed states (Kerala, Goa, Delhi, etc.). Although they require further research, dietary issues may be significant. Since India has the greatest number of CAD patients worldwide, additional national representative survey studies are needed to evaluate dyslipidemias. Awareness-building, lipid abnormality screening, risk stratification, and therapy initiation should all be intensified. Our nation's cardiovascular mortality and morbidity will decline if people follow the World Heart Federation's recommendations for well-designed population-based and individual-level interventions to lower dyslipidemia [3]. As a result, non-HDL-C and LDL-C have been often employed as lipid-lowering targets. Further ASCVD incidents have decreased proportionately to the absolute decrease in LDL-C thanks to effective treatment options that lower LDL-C, such as statin monotherapy, statin with ezetimibe, or statin with proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors [4]. LDL-C reduction lowers the risk of ASCVD and its clinical consequences, according to numerous clinical investigations [1]. However, despite improvements in the management of dyslipidemia in many nations, ASCVD continues to be the leading cause of death worldwide. Understanding the worldwide epidemiologic characteristics and developments in dyslipidemia management is crucial for determining the main problems or obstacles to reducing the present and future burdens of diseases linked to dyslipidemia. At the national or regional level, numerous studies have documented the epidemiological patterns of dyslipidemia and its management; only a small number of studies have examined lipid levels and changes over time on a worldwide scale [4]. Preclinical and clinical data demonstrating the safety and effectiveness of some lipid-lowering nutraceuticals support their usage. However, unless prescribed by international criteria, the usage of nutraceuticals should never be used in place of traditional medications [1]. According to clinical studies, a number of nutraceuticals work in concert with lipid-lowering medications to reduce side effects and allow statin dosages to be lowered without compromising TC and LDL-C reduction outcomes. However, the majority of the combinations that have been provided have only been tried in one study, and the results gained have not yet been validated, thus recommendations cannot be made [1].

Pathogenesis with associated diseases:

The etiology of atherosclerotic cardiovascular disease (ASCVD) is largely influenced by lipid abnormalities. Unesterified and esterified cholesterol, phospholipids, triglycerides, and Apo lipoproteins in varying proportions, densities, and sizes make up lipoproteins [5]. It might be argued that nutraceuticals have little role in the treatment of people at high risk of ASCVD given the astonishing variety of lipid-lowering medications available [2].

Nutraceuticals can actually perform five distinct roles:

- Reducing the risk that remains from lipids other than LDL-C.
- Taking care of residual risk that is not mediated by fat.

- The best way to treat LDL-C in patients with statin sensitivity and when statin add-on medications are unavailable.
- The lifestyle choices of people who have a high lifetime risk of atherosclerotic cardiovascular disease (ASCVD) [2].

Triglycerides contribute to the pathophysiology of CAD by a number of direct and indirect pathways, including as coagulation, endothelial dysfunction, transport proteins, enzymes, and other lipoprotein metabolism. Diet, age, lifestyle, a number of medical problems, medication, and metabolic disorders are some of the variables that might impact triglyceride levels. Triglyceride levels that are not fasting have been suggested to be a more accurate indicator of CAD occurrences than fasting values [3].

Natural products for dyslipidemia:

Nutraceuticals is a combination of the words "Pharmaceutical" and "Nutrient." DeFelice used the phrase for the first time in 1989 when he described a nutraceutical as "food, or parts of a food, that provide medical or health benefits, including the prevention and treatment of discomfort." The distinction between nutraceuticals and functional foods has been made more recently. The former are "similar in appearance to conventional foods … consumed as part of a usual diet," while the latter are "made from foods but sold in pills, powders, (potions), and other medicinal forms not generally associated with food" [2]. As a result, nutraceuticals offer a way to benefit from naturally occurring biologically active, health-promoting compounds while maintaining control over dosage, formulation quality, and composition, much like traditional medications. Thus, it is not surprising that patients and doctors alike are very enthusiastic about the use of nutraceuticals in the prevention and treatment of many illnesses, including dyslipidemias [2]. Herbal medicine, often known as plant medicine, botanical medicine, or herbs, is a widely used treatment all over the world. In addition to their nutritional applications in food and nutrition, herbal products have a special role in the treatment of a number of illnesses. The plant's flowers, fruits, seeds, leaves, berries, bark, and roots are among the parts that can be utilized to make herbal medicine. 80% of people are thought to rely on herbs for their basic medical requirements [10]. Herbal medicine has been used for thousands of years, as evidenced by numerous scientific investigations and a body of literature that is growing in popularity in the region. Approximately 75% of herbal remedies and 25% of pharmaceutical medications were derived from traditional medicinal plants, according to reports. Numerous components or formulations of the medication were taken from medicinal plants, which are being used to treat a variety of illnesses today. Commercial pharmaceutical treatments today owe a great deal to those therapeutic plants [10]. Natural substances that can safely alter lipid patterns are gaining popularity. Although several lipid-lowering nutraceuticals have been found and put through clinical testing, there are differences in their effectiveness and acceptability. Reviewing the safety and effectiveness of the most researched lipid-modifying nutraceuticals in this context, as well as their correlations, can help them prescribe the most evidence-based medication [1].

Natural products as drugs:

Nuts, Olive Oil(*Olea Europaea*),Rapeseed Oil, Guggul(*Commiphora Mukul*), Nutshell Of Semecarpus Anacardium, Legumes, Tomato (*Solanum Lycopersicum*) And Carrot (*Daucus Carota*), Cocoa (*Theobroma Cocoa*), Saponin, Fungal Polysaccharides, Aspergillus Tereus, Soybean Protein, Whole Grains, Dietary Fiber, Garlic (*Allium Sativum*), Red Yeast Rice (*Monascus Purpureus*), Kiwifruit (*Actinidia Arguta*), Grapes(*Vitis Vinifera*), Dill (*Anethum Graveolens*), Turmeric Rhizome(*Curcuma Longa*), Fish Oil, Pumpkin (*Cucurbita Indica*), Nutmeg Fruit (*Myristica Fragrans*), Citrus Fruits, Tea (*Camellia Sinensis*), Fenugreek Seeds (*Trigonella Foenumgraecum*), Cinnamon (*Cinnamomum Cassia*), Flaxseed/Flaxseed Oil (*Linum Usitatissimum*), Sesame Oil (*Sesamum Indicum*), Ginger Rhizome (*Zingiber Officinale*). Furthermore, a lot of functional foods and nutritional supplements have several or ambiguous modes of action [12].

Lipid-lowering nutraceuticals can be divided into three categories based on how they work: (i) Inhibitors of intestinal cholesterol absorption,

(ii) Inhibitors of hepatic cholesterol production, and
(iii) LDL-C excretion enhancers [1].

i) Inhibitors of Intestinal Cholesterol Absorption

Plant Sterols and Stanols: Similar in structure to cholesterol, plant sterols can be found in nearly every vegetable source, but are especially found in vegetable oils, nuts, seeds, legumes, and fat spreads. Plant stanols can also be found in plants. Less than 500 mg of PS (plant sterols + stanols) are typically consumed daily in a typical diet. By reducing intestinal absorption of exogenous cholesterol micelles in the gastrointestinal lumen and their interaction with the brush border membrane and substrate of the Niemann Pick C1-Like 1 (NPC1L1) transporter, PS mostly lowers LDL-C levels [1].

Soluble Fibers: A wide range of substances derived from vegetables that are resistant to enzymatic digestion in the gastrointestinal tract is together referred to as dietary fiber. Certain soluble fibers, such as pectin, guar gum, mucilages, oats, and psyllium, have been shown in tests to have lipid-lowering qualities. Soluble fibers have a variety of lipid-lowering modes of action, such as a longer stomach emptying time, increased satiety, blocked hepatic cholesterol synthesis, and increased excretion of cholesterol and bile salts in the feces. The type of fiber, dosages, and patients treated, research size, and various

diets all affect how much cholesterolemia is reduced by soluble fibers. Three servings of oatmeal, each containing 28 g of soluble fiber, can reduce LDL cholesterol by about 0.13 mmol/L. Glucomannan, psyllium, and oat-based fibers, however, may have a greater impact [1].

β-Glucan: In order to lower blood cholesterol, international guidelines for the treatment of dyslipidemia recommend consuming 5–15 g (European guidelines) or 10–25 g (US guidelines) of soluble fibers made from oats, which are high in β-glucan. The soluble fiber known as β-glucan is found in the walls of several plant cells, bacteria, algae, fungus, and yeasts. Because of its high viscosity, β-glucan has the ability to decrease cholesterol [1].

Psyllium: Psyllium is a natural source of concentrated fibers derived from the husks of blonde psyllium seed. The mechanisms of action of psyllium are similar to those of other fibers already discussed, including an increased excretion of bile acids (stimulating 7-α-hydroxylase) and a reduced absorption of intestinal cholesterol [1].

Glucomannan:

The soluble fiber known as glucomannan is obtained from the konjac root, or Amorphophallus konjac. Glucomannan appears to decrease the absorption of bile acids in the ileum and cholesterol in the jejunum, but it does not bind bile acids like other fibers do. Additionally, it boosts 7-α-hydroxylase activity, which turns cholesterol into bile acids [1].

Probiotics:

Probiotics are essential bacteria that, when consumed in sufficient quantities, boost the host's health. The idea of using certain microbial strains as potential medicinal agents to decrease cholesterol has been bolstered by a few clinical investigations conducted in recent years. However, the wide range of research in terms of treatment duration, probiotic strain type, dosage, participant clinical features, and administration form/vehicle still makes it challenging to draw definitive conclusions. One of the hypothesized lipid-lowering processes is that probiotics may interact with intestinal cholesterol by attaching to or integrating it into the membranes of the bacteria [1].

ii) Inhibitors of Liver Cholesterol Synthesis

Red Yeast Rice Extract

White rice is fermented with a certain yeast (usually *Monascus purpureus*) to make red yeast rice (RYR), a nutraceutical. Pigments from secondary fermentative metabolism give the rice its red hue. A combination of compounds with significant lipid-lowering properties, such as polyketides like monacolins, is added to the rice by the yeast during the fermentation process. Red yeast rice's primary mechanism of lowering cholesterol is the reversible inhibition of 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase. This subtype of monacolin, known as monacolin K (MonK), is structurally identical to lovastatin and is determined by the yeast strain and fermentation conditions. Despite having the same structure, the pharmacokinetic characteristics and bioavailability of lovastatin and MonK vary. Since lovastatin has a 31% bioavailability in humans when taken as a single active ingredient in a traditional pharmaceutical form, MonK is merely one of the RYR components that may interact to alter the drug's usual pharmacokinetic profile [1].

Garlic:

Garlic (*Allium sativum*) lowers cholesterol because it contains allicin, which is made from the non-proteinogenic amino acid alliin in a reaction that is catalysed by alliinase. Allicin actually inhibits acetyl-Coenzyme A (acetyl CoA) synthetase, squalene-monooxygenase, and HMG-CoA reductase. The stimulation of bile acid excretion is another potential way that garlic may work [1].

Bergamot (Citrus bergamia)

Citrus bergamia Risso is often known as bergamot. Its composition sets it apart from other citrus fruits, especially its abundance of flavonoids (such as neoeriocitrin, neohesperidin, naringin, rutin, neodesmin, rhoifolin, and poncirin). Specifically, the bergamot peel contains the 3-hydroxy-3-methyl-glutaryl flavanones enriched fraction (brutieridin, melitidin, and neoeriocitrin), which function as statins by blocking HMG-CoA reductase and Acyl-CoA cholesterin acyltransferase (ACAT), which lowers the formation of apo B lipoproteins and cholesterol esters. Bergamot also contains naringin, which, like neoeritrocitrin, meltidin, and rutinit, activates adenosine monophosphate kinase (AMPK) and prevents LDL-C from oxidizing. Additionally, bergamot may decrease intestine absorption, improve bile acid turnover and excretion, and boost fecal cholesterol excretion. Clinical research on bergamot's ability to lower cholesterol reveals that polyphenols derived from bergamot (500–1500 mg/day) can lower tumornecrosis factor alpha (TNF-α), triglycerides, non HDL-C, malonyldialdehyde, fasting plasma insulin, leptin, leptin/adiponectin ratio, hs-CRP, and LDL-C in a dose-dependent manner that varies greatly depending on the level of extract purification [1].

Artichoke:

Clinical studies have suggested that the extract from artichoke leaves (*Cynara scolymus*, *Cynara cardunculus*) may have hepatoprotective and hypolipidemic effects. These effects are primarily ascribed to caffeic acid, volatile sesquiterpene,

flavonoids, and mono- and dicaffeoylquinic acid (cynarin and chlorogenic acid). Artichoke appears to have two main lipid-lowering mechanisms: the interaction of luteolin with HMG-CoA reductase and the liver's sterol regulatory element-binding protein (SREBP) and ACAT regulatory pathways [1].

iii) Inducers of LDL Cholesterol Excretion

Berberine:

The quaternary benzylisoquinoline alkaloid berberine (BBR) is found in the root, rhizome, stem, fruit, and bark of various plant species, including Hydrastis (Hydrastis canadensis), Berberis (Berberis aristata, Berberis vulgaris, and Berberis croatica), and Coptis (Coptis chinensis, Coptis japonica). Through the ubiquitination and degradation of hepatocyte nuclear factor 1 alpha (HNF-1α), BBR inhibits proprotein convertase subtilisin/kexin type 9 (PCSK9), leading to elevated levels and decreased lysosomal degradation of hepatic LDL receptors (LDLR). Additionally, BBR directly affects LDLR expression through two known processes. One of these mechanisms is a post-transcriptional mechanism that stabilizes LDLR messenger ribonucleic acid (mRNA), which leads to an up regulation of the receptors. According to recent research, BBR also decreases intestinal cholesterol absorption, which increases fecal output and encourages the liver's cholesterol turnover and bile acid production. Additionally, BBR is an AMPK activator, which promotes fatty acid oxidation and suppresses lipogenic gene expression. Lastly, it effectively inhibits oxidative stress caused by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase [1].

Due to weak intestinal absorption, limited permeability of the molecule, and intestinal and hepatic first-pass metabolism (43.5% and 0.14%, respectively), BBR has a bioavailability of less than 1% [1].

Green Tea Extracts:

Tea (*Camellia sinensis*) has been shown to prevent foreign lipids from being absorbed. Green tea was found to have a significant impact on fat metabolism in lab settings by lowering food intake and preventing lipid emulsification and absorption. Through heat production, fat oxidation, and fecal lipid excretion, green tea may also raise energy expenditure, according to further study findings. [10] Polyphenol antioxidants are especially abundant in green tea. Green tea contains a significant amount of catechins, such as epigallocatechin-3-gallate (EGCG), which are polyphenols. It is plausible that green tea disrupts micellar solubilisation and cholesterol absorption in addition to its antioxidant properties from polyphenols and its ability to lower lipid peroxidation. Both HMG-CoA reductase and AMPK are activated by green tea, which promotes lipogenesis. The ileal apical sodium-dependent bile acid transporter (ASBT) is inhibited by tea catechins, which decreases bile acid reabsorption. They also increase the expression of LDLR in the liver and the excretion of cholesterol in the biliary system [1].

Soy Proteins:

The beneficial effects of soy proteins on the lipid profile are supported by preclinical and clinical data. Isoflavones, which are bioactive peptides found in soy, may be a factor in this action. Several mechanisms have been proposed to lower cholesterol in soy: activation of SREBP-2 (with increased LDLR expression and blood cholesterol clearance), decrease of cholesterol biosynthesis, an increase in bile salt excretion in the feces, and down regulation of the expression of the hepatic transcription factor SREBP-1 via the phosphatidylinositol 3-kinase/protein kinase B/glycogen synthase kinase-3β (PI3K/Akt/GSK3β) pathways [1].

Other lipid-lowering nutraceuticals with mixed mechanisms of action:

Polyunsaturated Omega-3 Fatty Acids: Polyunsaturated fatty acids (PUFAs) with a double bond at position 3 at the end of the carbon chain are known as omega-3 (ώ-3) fatty acids. Omega-3 is found naturally in both plant (algae, flaxseed, walnut, edible seeds, clary sage, and seed) and animal (fish, krill, egg, and squid) sources [1].

Omega-3 reduces TG through the following mechanisms: (1) decrease in hepatic VLDL synthesis; (2) decrease in available substrate for TG synthesis (omega-3s are false substrata); (3) decrease in TG-synthesizing enzyme activity (diacylglycerol acyltransferase or phosphatidic acid phosphohydrolase); (4) increase in fatty acid β-oxidation; and (5) decrease in endogenous fatty acid synthesis and increase in phospholipid synthesis [1].

Spirulina:

The filamentous microalga Spirulina (*Arthrospira platensis*) has a known ability to decrease cholesterol, although its exact mode of action is unknown. High levels of PUFAs and antioxidants are found in spirulina. An important enzyme in the heme catabolic pathway in endothelial cells, atheroprotective heme oxygenase-1 (HMOX-1), can be activated by the phycocyanobilin found in C-phycocyanin, a specific critical pigment of spirulina. Phycocyanin has also been shown to have anti-inflammatory, antioxidant, and radical-scavenging qualities [1].

Nutraceuticals to manage residual risk associated with lipids other than LDL-C:

Long-chain omega-3 polyunsaturated fatty acids (PUFAs) and oily fish consumption improve cardiovascular disease risk

factors and biomarkers in a way that is consistent with our understanding of the biological actions of PUFAs, particularly the triglyceride-lowering effects of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). Pharmaceutical forms of "fish oil" or "PUFAs" can be purchased over-the-counter or with a prescription in the majority of nations. EPA and DHA are frequently among the several components found in these treatments [2].

Risk factors:

Inadequate physical activity, obesity, diabetes, and advanced age were all substantially associated with an elevated risk of dyslipidemia [8]. The type of job and the workplace may have an impact on dyslipidemia. There are a lot of characteristics of employment that include stress on the body and mind, poor nutrition, and less physical activity. In general, employed people spend a large amount of their lives at work, and the stress and demands of the job can have an impact on their lifestyle, daily exercise patterns, and eating habits, all of which can have an impact on their general fitness [7].

Currently, pharmaceutical therapy and lifestyle modifications in food and exercise patterns are the mainstays of treatment, contingent on the severity of dyslipidemia and cardiovascular risk [1].

Lifestyle modification:

An energy-balanced Mediterranean diet, low in saturated fat (less than 7% of total energy), moderate to high-intensity physical exercise (more than 150 minutes per week), and weight loss (5–10% of body weight) are all key components of lifestyle management for hypercholesterolemia. Additionally, one must avoid being around tobacco smoke, either actively or passively. Improvements in lifestyle typically result in a 5–15% decrease in LDL-C. There may be a significant decrease in the risk of CVD if these reductions are sustained over time. Triglyceride (TG) levels can be lowered in patients with hypertriglyceridemia by implementing lifestyle changes such as limiting alcohol, simple sugars, and refined carbohydrates, exercising (≥150 minutes per week of moderate or higher intensity activity), and losing weight if overweight or obese (initially aiming for loss of 5–10% of body weight in order to relieve insulin resistance) [1].

Comparing the effectiveness with conventional lipid –lowering drugs:

It is well established from genetic, pathologic, observational, and therapeutic research that dyslipidemia, particularly hypercholesterolemia, plays a significant role in the development of cardiovascular disorders associated with atherosclerosis. International standards suggest lowering low-density lipoprotein cholesterol (LDL-C) to the lowest level achievable in order to avoid the onset and progression of atherosclerosis. This can be achieved by altering lifestyle choices and using medications that share this objective. The most common medications for enhancing lipid profiles and reducing LDL-C levels are statins; nevertheless, their usage is restricted due to their adverse effects and drug interactions. Statin intolerance is one of the primary causes of statin discontinuation, poor adherence, and the subsequent failure of lipid-lowering treatment. Although complete statin intolerance is thought to affect less than 5% of the population, the number of people who are intolerant to conventional treatment varies from 45,000 to 290,000 annually worldwide [9].

The recommendations also state that these medications have a favourable benefit-risk ratio for both primary and secondary prevention of cardiovascular diseases in those with high or extremely high overall cardiovascular risk. Most patients, however, who have just moderately elevated LDL-C values and are not at high cardiovascular risk, have an unfavourable ratio. Therefore, there is an unmet therapeutic need in two participant classes: individuals with high cardiovascular risk who cannot or will not take cholesterol-lowering medication, and health-conscious individuals with low cardiovascular risk who wish to lower their LDL-C levels but are ineligible for pharmacological therapy [9].

Numerous studies have been conducted on nutraceuticals, showing that they have the ability to decrease cholesterol. However, it's crucial to stress once more that while nutraceuticals can enhance lipid-lowering therapy (cutting CV residual risk), they cannot take its place. It appears that this therapy may be particularly important to consider for patients with mixed dyslipidemia, particularly atherogenic dyslipidemia in patients with diabetes and metabolic syndrome, for patients with low to moderate hypercholesterolemia that is not at the LDL-C goal, and for all patients with statin-associated side effects that cannot be treated with statins or appropriate doses of statins and are at a higher risk of cardiovascular events, given the influence of some of the presented nutraceuticals on various lipid parameters. However, the primary problem remains which of the lipid-lowering benefits of nutraceuticals are clinically significant, sustained over time, and potentially linked to a reduction in the risk of CVD. Combos of lipid-lowering nutraceuticals may increase their safety by lowering the doses of the individual components, but their effectiveness has rarely been examined in several studies or RCTs, and some of the evaluated nutraceutical combos included components that were under dosed. Conversely, it has been shown that both individual ingredients and certain combinations—specifically, red yeast rice, berberine, and policosanol—maintain their effectiveness over an extended period of years, improve certain vascular aging markers (such as endothelial function and pulse wave velocity), and have a beneficial effect on CVD risk factors other than LDL-C [1].

The effectiveness of conventional pharmaceutical therapies has been demonstrated to be considerably increased by certain nutraceuticals. Given this, using lipid-lowering nutraceuticals in a therapeutic setting with an evidence-based strategy may enhance treatment quality, including therapy adherence and the attainment of the LDL-C objective. The fact that there are currently no outcome trials demonstrating that nutraceuticals can reduce CVD morbidity or death in a primary preventive

setting must be emphasized, nevertheless.

Despite being the preferred medication for individuals with elevated LDL-C levels and moderate to high cardiovascular risk, high-intensity statin treatment increases adverse effects, which are linked to decreased therapy compliance and adherence. Conversely, even in patients at high and very high risk, the LDL-C targeted values may not be reached, even with good statin medication tolerability, for 30 to 70% of patients (depending on risk), even when ezetimibe is taken in addition. For most patients, there are numerous safe and tolerated nutraceutical choices that can be used either alone or in conjunction with statins to help them achieve approved goals [1].

Statins have been linked to PUFAs, soluble fibers, plant sterols, bergamot, tocotrienols, garlic, and vitamin D, with some evidence of their additive efficacy. The combination with policosanol, berberine, and RYR has increased the effectiveness of ezetimibe. The use of lipid-lowering nutraceuticals, either by themselves or in conjunction with pharmaceutical therapy, may be considered if adequate progress is not made toward reaching atherogenic cholesterol goals. These nutraceuticals are recommended for patients with borderline lipid values (above target) or who are drug intolerant [1].

2. CONCLUSION:

The study concludes that with moderate hypercholesterolemia, 100 mL of dietary supplementation with standardized kiwi, Annurca apple, bergamot and grape juice extracts with phytosterols, red yeast rice, and berberine complexed with cyclodextrin safely results in notable improvements in serum lipids. Although polyphenols have been shown to have therapeutic benefits and the ability to prevent disease in the literature, this was the first study to use this unusual combination [9]. In addition, more research is required to determine the function of the polyphenols found in fruit-by-product extracts in lowering cholesterol and preventing cardiovascular disease [9]. The cornerstones of ASCVD prevention for the worldwide population are promoting a healthy lifestyle, comprehending the harm caused by dyslipidemia, and preventing the onset of dyslipidemia in its early stages [4].

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