Hypercholesterolemia

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Hypercholesterolemia is a widespread hereditary metabolic disease caused by elevated serum levels of low-density lipoprotein cholesterol (LDL-c), leading to premature coronary artery disease. Hypercholesterolemia is one of the leading causes of CVD, and when treated appropriately, it can reduce the risk of CVD-related morbidity and death.

Keywords: hypercholesterolemia ; probiotics ; cardiovascular disease ; cholesterol

1. Introduction

Hypercholesterolemia is a widespread hereditary metabolic disease caused by elevated serum levels of low-density lipoprotein cholesterol (LDL-c), leading to premature coronary artery disease [1]. The Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program (NCEP) recommends LDL-c levels of 100 mg/dL are optimal and >160 is high [2]. It is predominantly caused by the mutation in low-density lipoprotein receptor (LDLR), apolipoprotein B-100 and proprotein convertase subtilisin/Kexin 9 (PCSK9), which leads to decreased LDL-c receptor absorption and evacuation from the circulation [3][4][5]. Due to the emphasis on lifestyle changes, most patients must use medications to achieve a sufficient decline in LDL-c levels. It also implies that any cholesterol-lowering medication should focus on LDL-c as the primary goal [6]. Statins are the most often prescribed treatment for hypercholesterolemia. Studies have shown that statins lower the risk of heart attack and mortality by 30–40% and lower LDL-c levels by 25–40% [7][8]. Statins are also combined with other small molecules such as ezetimibe, proprotein convertase subtilisin-kexin type 9 inhibitors, bempedoic acid, angiopoietin-like 3 protein inhibitors, and nutraceuticals to treat hypercholesterolemic patients. At the same time, it develops intolerance [9][10][11][12]. However, statin usage is now widely known to be linked to various side effects and symptoms, including myositis, myalgia, rhabdomyolysis, cognitive impairment, liver dysfunction, neuropathy, pancreatitis, sexual development, and semen parameters [13][14][15].

Ayurveda is one of the oldest well-known medical practices in the world. Ayurvedic formulations are prepared based on the patient's diet, behavioral changes, patient assessment, detoxification, and rejuvenation condition [16][17][18]. The most widely used herbs to reduce cholesterol are garlic, guggulu, and arjuna [19][20][21]. However, there is no clear evidence for the direct correlation between herbs and hypercholesterolemia [21]. The extracts of red yeast rice (RYR) are currently the most effective cholesterol-lowering nutraceuticals, containing monacolin K, a reversible inhibitor of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase. It improves the reduction of LDL-c associated with the improved function of the endothelium and arterial stiffness in CVD [22][23]. The prevalent use of RYR medications is still specific, and they should not be included in place of statins or other LDL-c lowering pharmacological approaches as the mainstay potential therapy for efficiently lowering CVD risk, especially in patients with high or very high CVD risk, as current guidelines highly suggested [24]. Due to medications' highest prices and side effects, the desire to use probiotics or mix probiotics treatment as an efficient solution.

In 2002, the World Health Organization described probiotics as "live microorganisms that, when consumed in sufficient quantities, offer the host a therapeutic benefit." Several scientists from the International Scientific Association formally approved the definition for probiotics and prebiotics [25]. There may be some advantages of daily consumption of microorganisms, such as general health protection and disease prevention [26]. The first microorganism-rich diet is breast milk, containing up to 10 7 microbes per milliliter [27]. The emergence of chronic diseases has been attributed to decreasing everyday consumption of microbial-rich foods [28][29]. According to growing research, probiotics have been shown to decrease LDL-c and enhance the LDL/HDL ratio and lower blood pressure, inflammatory cytokines, insulin sensitivity, and mass index [30][31]. The administration of Lactobacillus , a well-known probiotic, may be considered as the essential treatment method for lipid-lowering effects and urinary tract infections [32][33]. As an adjuvant and complementary medicine, probiotics are often supplemented in the diet to manage metabolic and intestinal diseases [34]. The probiotic bacteria Bifidobacteria and lactobacilli may be used as prophylactic or therapeutic agents towards lowering cholesterol levels, enteric pathogens, and control of metabolic disorders in infants and adults. Several strains of the Lactobacillus acidophilus , L. plantarum, and Lactococcus lactis led to a reduced serum cholesterol level due to their ability to assimilate

cholesterol available in vitro [35]. The evidence supporting probiotic microorganisms being given prophylactically to preterm newborns to avoid necrotizing enterocolitis, late-onset infection, and mortality is substantial. Still, it's restricted to the L. reuteri DSM 17938 species [36].

Probiotic preparations with or without pharmaceutical formulations have been shown to enhance the health of menopausal women [37]. Therefore, probiotic bacteria may benefit human health and maintain a healthy microbial gut [38]. However, additional research is needed to understand how probiotics may benefit the cardiovascular system by decreasing LDL-c substantially and figure out any potential detrimental health effects [39].

2. The Administration of Probiotics against Hypercholesterolemia

S. boulardii var. *boulardii* CNCM I-1079 supplementation lowered remnant lipoprotein. TG-rich lipoproteins are linked to the incidence and development of coronary artery disease, regardless of LDL-c levels [40]. However, the precise lipoprotein lowering mechanisms of *S. boulardii* is undisclosed, and the safety and tolerance of the strain were also not evaluated in this study. The safety risk management criteria are required to measure the safety of probiotics. However, due to the wide variety of microorganisms, it is also important to determine the unique hazards connected with each probiotic, including the risk factors associated with the host and the complex interaction between the probiotic, host, and nutrition constituents [41][42].

L. reuteri NCIMB 30242 was found to raise bloodstream bile acid levels involved in several metabolic activities, including energy balance, lipid metabolism, and inflammatory control [43][44]. The administration of *Bifidobacterium* species claimed to be involved in the control of dyslipidemia in hypercholesterolemic children by improving lipid profile [45]. However, to elucidate the precise molecular mechanisms of action of *Bifidobacterium* in dyslipidemic children, further studies and clinical examination are needed.

L. reuteri NCIMB lowers cholesterol and reduced sterol absorption. Authors have also analyzed the increased circulation of 25-hydroxyvitamin D in serum during *L. reuteri* NCIMB administration and found that the level of vitamin D was increased at the end of the study. The increased vitamin D level improves the proper intestinal colonization of probiotics, prevents pathogenic bacterial invasion, reduces chronic inflammation, and maintains enterocyte cell integrity [46][47][48]. Women who consumed yogurt containing *L. acidophilus* 145 and *B. longum* 913 regularly for six months had higher HDL-c levels and improved LDL-c/HDL-c ratio [49]. Fukushima and Nakano reported that a probiotic mixture diet containing Bacillus, Lactobacillus, Streptococcus, Clostridium, Saccharomyces, and Candida decreased cholesterol synthesis in rats' liver. The *L. acidophilus* strains removed cholesterol by binding to the intestine surface area, making it less obtainable for absorption in the intestine [50]. Likewise, *L. plantarum* KCTC3928 and *L. acidophilus* ATCC 43121 enhanced the conversion of HMG-CoA and cholesterol to mevalonate and bile acid, respectively, reducing the LDL-c level in hypercholesterolemic patients [51][52][53].

The probiotic mixture of *L. plantarum* CECT 7527, 7528, and 7529 improves the cholesterol profile and reduces the CVD risk in hypercholesteremic patients [45]. However, the over-growth probiotics mixture may lead to gut dysbiosis, affecting physiology, gut-brain axis function, and other secondary disease outcomes in the host [54][55]. Further studies are needed to warrant the tolerance and safety of long-term consumption of a mixture of *L. plantarum* strains. The consumption of *L. acidophilus*, *B. bifidum,* and oligofructose increases the HDL-c level, reduces CVD risk, and significantly reduces the blood sugar level [56]. Ataie-Jafari et al. stated that probiotic yogurt consumption significantly decreases the total lipid content and reduces the CVD risk [57].

The administration of *E. faecium* M-74 enriched with selenium reduces the LDL-c level. However, no significant changes were noted in HDL-c and TG levels. Further studies are required to meet the safety and tolerance criteria [58].

The yogurt fermented with *B. longum* BL1 has the highest efficacy in lowering serum cholesterol in moderately hypercholesterolemic subjects [59]. However, there are no significant changes in HDL-c, TC, and TG levels. Furthermore, studies are needed to warrant the efficacy of *B. longum* BL1. Therefore, probiotics are the natural replacements that could be beneficial to improve the lipid profile and reduce the CVD risk without causing adverse effects, unlike statin drugs.

3. Conclusions

Probiotics against hypercholesterolemia could act as an alternative medicine to reduce the CVD risk and other diseases. The obtained clinical trailed data confirm the positive effect of probiotic consumption against hypercholesterolemia. As a result, additional research is needed to understand how probiotics can benefit the cardiovascular system and perhaps other ailments and test out any potential adverse health effects.

It appears that the potential of probiotics to decrease cholesterol depends on species and strain. L. acidophilus was found to reduce cholesterol levels. Similarly, a fermented milk product containing B. longum 913 and BL1 reduced the LDL-c cholesterol levels in the blood. The L. plantarum and L. reuteri lowers LDL-c levels while increasing vitamin D synthesis.

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