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Corrigendum

Corrigendum to "Effects of Probiotics, Prebiotics, and Synbiotics on Hypercholesterolemia: A Review"

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The article titled "Effects of Probiotics, Prebiotics, and Synbiotics on Hypercholesterolemia: A Review," was found to contain material from the authors' published work [1]. The article has been revised as follows.

Abstract

Cholesterol is important for both humans and animals to maintain their normal health. However, increased serum cholesterol level can cause several cardiovascular diseases. Higher cholesterol in the blood will develop a plaque in the walls of artery. Numerous pharmacological and non-pharmacological methods have been used to decrease the blood cholesterol. Various drugs have been developed to treat hypercholesterolemia, and the most common drugs include atorvastatin and rosuvastatin (statin drugs). However, prolonged usage of these drugs causes severe side effects. During the past decades, various scientists reported that the ingestion of several fermented products with probiotic bacteria decreases the serum cholesterol level. Probiotics are viable microorganisms that promote various health benefits upon consumption, while prebiotics are nondigestible food ingredients, which promote the growth of probiotic microorganisms in the human gut. The cholesterol reduction mechanism of probiotic bacteria is not well understood; however, most of the probiotic bacteria reduce the serum cholesterol level by using the bile salt deconjugation method. Herein, we review the cholesterol-reducing capability of probiotics, prebiotics, and synbiotics and use them as an alternative for cholesterol-reducing drugs which is used for hypercholesterolemia.

1. Introduction

Increased serum cholesterol level can cause several cardiovascular diseases (CVDs) including coronary heart diseases, atherosclerosis, and hypertension. According to the World Health Organization (WHO) survey by 2030, CVD will be one of the major causes of death, and worldwide, 23.6 million people will be affected [1]. Many researchers reported that even a 1% reduction in the serum cholesterol level might reduce the coronary heart disease by 2-3% [2]. During the period of 1999 to 2003, 45% of Western Europe and 35% Central and Eastern Europe populations are affected by heart attacks caused by hypercholesterolemia [3, 4]. Elevated serum cholesterol level may increase the heart attack risk by three times compared with people having normal serum cholesterol level. Unhealthy diets such as foods rich in sugar, salt, oil, and fat or food with low fiber content are the major causes of cardiovascular diseases [5].

1.1. Good and Bad Cholesterol. Generally, cholesterol is a waxy, fat-like substance present in the human and animal cells and referred as "good" and "bad" cholesterol. Actually, these descriptions refer to the substances called lipoproteins that carry cholesterol throughout the body in the bloodstream. Lipoproteins are a combination of varying amounts of fats and proteins.

"Good" cholesterol is associated with high-density lipoproteins (HDLs). HDLs are believed to remove excess cholesterol from the body; therefore, higher levels of HDLs are also believed to be associated with lower rates of heart disease. "Bad" cholesterol is associated with low-density lipoproteins (LDLs). LDLs carry cholesterol in the blood to body cells. High levels of

LDLs are usually associated with elevated blood cholesterol and an increased risk of heart disease due to cholesterol and fat being deposited in the arteries. These fatty deposits decrease the interior size of the arteries so the blood supply is reduced, thus increasing the risk of heart disease and stroke.

Several drugs have been developed to treat hypercholesterolemia. Nowadays, numerous nonpharmacological approaches (including dietary ones) have been used to reduce the serum cholesterol. Recently, probiotics and prebiotics are considered as a remedy to reduce the serum cholesterol level.

2. Probiotics

The word "probiotic" is derived from Greek word "pro bios" which literally means "for life," which is opposite to the meaning of "antibiotics" which is translated to "against life." Greek and Romans began the probiotic history by consuming the fermented foods [6, 7]. In 1908, the Nobel laureate Elie Metchnikoff proposed the probiotic bacteria has a beneficial effect on human health. Metchnikoff observed Bulgarian peoples consuming milk which is fermented with rod-shaped *Lactobacillus* spp. and thus improved their health. And also, he suggested that these probiotic bacteria have positive effects in the gut microflora and exclude the intestinal pathogens in the human intestine [6, 8, 9].

In 1965, Lilly and Stillwell first used the term "probiotic" to define any substance which kindles the growth of beneficial microorganisms. Later, "probiotic" was also used in different interpretations based on their mechanism and their beneficial effects on human health. Few years later (1974), Parker defined "probiotic" as "substances and microorganisms which contribute to intestinal microbial balance" [10]. In 1989, definition of probiotics was improved by Fuller [11]. Generally, probiotic microorganisms not only present or act in the large intestine but also in other organs, either by modulating immunological parameters, intestinal permeability, bacterial translocation or also by providing bioactive substances or regulatory metabolites. Hence, extensive definitions for probiotics were suggested by many researchers and organizations. Schrezenmeir and de Vrese [12] and the International Life Sciences Institute (ILSI) in Europe defined probiotic as "a viable microbial food supplement which beneficially influences the health of the host" [13]. In normal human intestines, approximately 400 different bacterial species exist, which is a more complex ecosystem, since it includes both facultative anaerobic and anaerobic microorganisms [14]. Generally, the gut microflora is constant but it is affected by numerous factors including age, diet, environment, medication, and stress. *Lactobacillus* and *Bifidobacterium* species constitute the majority of probiotic bacteria. Apart from this, several other bacteria and some yeasts are also considered as a probiotic since it has demonstrated some probiotic properties (Table 1). In humans and animals, Gram-positive, lactic acid-producing bacteria such as *Lactobacilli* and *Bifidobacteria* are the most common intestinal microflora [15].

Lactobacilli are non-spore-forming bacteria, rod-shape, strictly fermentative, anaerobic, aciduric, or acidophilic bacterial species and require complex nutrition for their growth. Generally, *Lactobacilli* are found in various habitats including carbohydrate-rich substrates (i.e., fermented milk), plant products, mucosal membranes of both humans and animals, rotten food items, and sewage [15].

Table 1: Probiotic microorganisms which are used to feed both humans and animals.

Lactobacillus species	*Bifidobacterium* species	Others
L. acidophilus	*B. bifidum*	*Enterococcus faecalis*
L. rhamnosus	*B. animalis*	*Enterococcus faecium*
L. gasseri	*B. breve*	*Streptococcus salivarus*
L. casei	*B. infantis*	subsp.
L. reuteri	*B. longum*	*thermophilus*
L. delbrueckii subsp.	*B. lactis*	*Lactococcus lactis* subsp.
bulgaricus	*B. adolascentis*	*lactis*
L. crispatus		*Lactococcus lactis* subsp.
L. plantarum		*cremoris*
L. salivarus		*Propionibacterium*
L. johnsonii		*freudenreichii*
L. gallinarum		*Pediococcus acidilactici*
L. plantarum		*Saccharomyces boulardii*
L. fermentum		*Leuoconostoc mesenteroides*
L. helveticus		*Weissella cibaria*
L. oris		*Weissella confusa*

Both human and animal intestinal microflora predominantly comprise of several Bifidobacterial species during their lifetime. Normally, the *Bifidobacteria* populations in the healthy adult colon are about 10^{10}-10^{11} CFU/g and thus will decrease with age. Most of the Bifidobacterial species are strictly anaerobic, nonmotile, and nonsporulating rods with varying morphological appearance [15].

2.1. Sources of Probiotics. Fermented milk products are the major sources of probiotics including cultured buttermilk, yoghurt, and cheeses. Buttermilks are prepared by fermenting the milk with lactic acid-producing bacteria which is the reason for its sourness. In cheese industry, probiotic bacteria were used for the maturation of cheese. Kefir is one of the most popular fermented milk products. Generally, yoghurt was fermented by one or two bacterial species, whereas kefir was fermented by more than one probiotic bacterium. Other foods that are either produced by bacterial fermentation are Japanese miso, tempeh, sauerkraut, beer, sour dough, bread, chocolate, kimchi, olives, and pickles [16]. Due to the lower pH of fermented yogurt and milk, they are the major food vehicles for probiotics [17]. However, many studies show probiotics strains are also found in non-dairy-fermented substrates [12]. Some of the non-dairy probiotic products are cereal, legume, cabbage, maize, pearl millet, vegetable, sorghum, etc [18].

2.2. Health Benefits of Probiotics. Probiotic bacteria have several health benefits in various medical conditions such as irritable bowel syndrome, diarrhea, *Helicobacter pylori* infections, inflammatory bowel disease, gastroenteritis, depressed immune function, infant allergies, cancer, hepatic diseases, hyperlipidemia, and others [19]. The overall health benefits of probiotic microorganism are represented in Figure 1.

The probiotic mechanisms that have been reported include effects on mucin secretion, receptor competition, and immunomodulation of gut-associated lymphoid tissue, decreased proinflammatory mediators, and increased immunosuppression [20]. Probiotic microbes exert beneficial effects through many actions. These include production of antimicrobial substances, inhibition of adhesion and colonization of intestinal pathogens, promoting the local and peripheral immunity, detoxification, promoting the activity of brush border enzymes, microbial translocation prevention, and stimulating the production of secretory IgA. Generally, normal intestinal microflora has the ability to inhibit the colonization of harmful, enteric pathogens; this phenomenon was referred to as colonization resistance. This colonization resistance ability was attained by the complex interactions among the bacterial community [21]. The inhibitory chemical substance bacteriocin is defined as protein antibiotics of the type of colicin, i.e., substance characterized by lethal biosynthesis, killing activity of predominant intraspecies, and its adsorption to specific receptors on the surface of bacteriocin-sensitive cells [22].

3. Prebiotics

The term "prebiotic" was first used by Gibson and Roberfroid in 1995 [23]. Prebiotics are defined as "indigestible fermented food substrates that selectively stimulate the growth, composition, and activity of microflora in gastrointestinal tract and thus improve hosts' health and well-being" [24]. Lactulose was used 50 years ago as a prebiotic formula supplement to increase the numbers of *Lactobacillus* strains in infants' intestines [25].

Several prebiotics have been identified such as oligofructose, fructooligosaccharides, lactulose, inulin, and galactooligosaccharides. These prebiotics are resistance to gastric acidity and hydrolysis by mammalian enzymes. Also human gastrointestinal microflora can digest these prebiotics; hence, it promotes the growth of these probiotic microorganisms. Various new compounds which have gut-resistant characteristics and selective fermentability by intestinal microorganisms have been identified and developed as prebiotics and include oligosaccharides (lactosucrose, isomaltooligosaccharides, xylooligosaccharides, and glucooligosaccharides), sugar alcohols, and polysaccharides (starch, modified starch, and resistant starch) [26–28].

Fermentation of oligofructose in the colon is due to the presence of intestinal microflora, which confers the beneficial effects to the humans via. increasing the probiotic populations in gastrointestinal microflora, increasing the calcium absorption and fecal weight, shortening the gastrointestinal transit time, and more importantly lowering the serum cholesterol level.

3.1. Sources of Prebiotics. Generally, the prebiotics are abundant in foods including yacon, soybeans, oats, unrefined wheat, and barley, and inulin was abundant in Jerusalem artichoke, chicory root, and jicama. Apart from this, human breast milk also contains large quantities of oligosaccharides, which promote the health and immune system in infants. Breast-feeding infants contain normal microflora majorly composed of *Lactobacilli* and *Bifidobacteria*. These microflora act as a primary defense layer against the invading pathogens and also promote the immune system [29, 30]. The oligosaccharides present in the breast milk nurtured these beneficial microflora and hence are regarded as original and natural prebiotics. Recently, several peptides, proteins, and lipids are also considered as potential prebiotics. However, indigestible carbohydrates, particularly oligosaccharides, gained attraction among the researchers [31].

4. Synbiotics

Synbiotics are referred to as usage of both probiotics and prebiotics together. The combination of suitable probiotics and prebiotics drastically improves the activity of the probiotic microorganism. The example for synbiotics is a combination of a FOS and a *Bifidobacterium* strain or lactitol with *Lactobacillus* strains [23]. Administration of prebiotics and probiotics in combination may provide the synergistic effects and promotes the growth, survival, and adhesion of both probiotic and already existing beneficial bacteria in the colon.

5. Mechanism of Cholesterol Reduction

Numerous cholesterol lowering mechanisms by *Lactobacillus* strains have been proposed. The cholesterol-reducing effect of probiotic bacteria might be due to their ability to bind the cholesterol present in the small intestine. One of the most important mechanisms is through the bile salt hydrolase (BSH) enzyme. The BSH enzyme plays a major role in the deconjugation of bile salt in the enterohepatic circulation. This enzyme hydrolyzes conjugated glycodeoxycholic acid and taurodeoxycholic acid and releases the glyco- and tauro-bile acids. BSH enzyme was identified in several lactic acid bacterial (LAB) species isolated from the gastrointestinal tracts of both humans and animals [32–35]. Many researchers proposed that BSH activity should be considered as a prerequisite characteristic during the selection of probiotic bacteria along with other cholesterol reducing properties [36]. Over the last few years, the possibility of using bile salt deconjugation by LAB species to treat hypercholesterolemia in humans has gained more attention [37, 38]. The major source of cholesterol in human body includes biosynthesis and absorption by the liver and intestines, respectively. These two attributes determine the overall cholesterol level. Many researchers have found that diverse pathways are involved in the mechanism, which governs the cholesterol-reducing properties of probiotics, but so far these mechanisms are not clearly understood. The overall cholesterol reduction mechanism of probiotic microorganism is represented in Figure 2.

5.1. Effects of Probiotics on Cholesterol Reduction. In 1974, Mann and Spoerry first reported the serum cholesterol

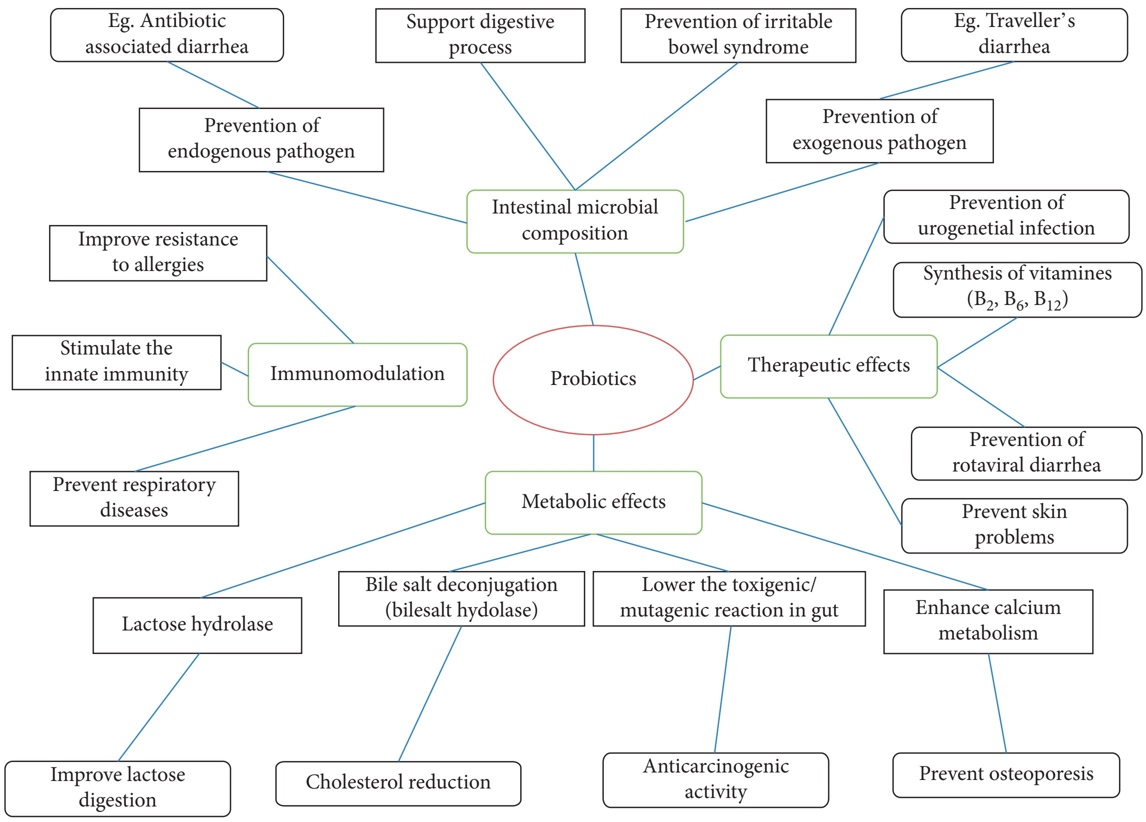

Figure 1: Overall health benefits of probiotic bacteria on human health.

reduction by LAB and they witnessed the serum cholesterol level of Masai and Sambura tribes was reduced by 18% and their diet was primarily composed of fermented milk containing *Lactobacillus* [39] Anderson and Gilliland reported that *Lactobacillus acidophilus* reduces the blood cholesterol by two mechanisms including breakdown the cholesterol and bile salt deconjugation. They also reported that the effects of consumption of yoghurt could reduce the serum cholesterol level significantly [40].

Anderson and Gilliland also examined the effect of milk fermented with *L. acidophilus* L1 on the serum cholesterol level in hypercholesterolemic subjects. Forty-eight volunteers whose serum cholesterol level ranged from 5.40 mmol/L to 8.32 mmol/L were involved in the randomized, double-blind, crossover, and placebo-controlled study for about ten weeks. Results showed that the consumption of 200 grams of *L. acidophilus* L1 containing yogurt after dinner significantly ($P < 0.05$) reduced the serum cholesterol level when compared to the placebo group [40]. Liong and Shah isolated 11 different *Lactobacilli* strains and screened for BSH activity and coprecipitation of cholesterol along with deconjugated bile salt. They reported that *Lactobacillus acidophilus* strains had higher deconjugation potential compared with the *L. casei* and the cholesterol coprecipitation with deconjugated bile was increased at lower pH [41].

Similarly, Xiao et al. used thirty-two volunteers to examine the cholesterol-reducing capacity of a low-fat yoghurt comprising 10^8 CFU/g of *Bifidobacterium longum* BL1 strains. Results showed that the levels of serum total cholesterol, triglycerides, and LDL cholesterol significantly ($P < 0.05$) decreased after 4 weeks. Interestingly, HDL cholesterol level increased by 14.5% compared to that in the control patients who consumed yoghurt without *Bifidobacterium longum* BL1 [42].

The probiotic microorganisms isolated from fermented milk reduce the cholesterol in presence of 0.3% bile salt ranging from 28% to 83%. And some strains were able to reduce cholesterol more than 70% [43]. Kim and coworkers demonstrated the cholesterol reduction mechanism of *Lactobacillus acidophilus* ATCC 43121. They have demonstrated the cholesterol reduction using the cell-free culture supernatant (CFCS) of *L. acidophilus* ATCC 43121 [44].

In another study, the cholesterol reduction of *Lactobacillus reuteri* CRL 1098 was demonstrated using the mice fed with the 10^4 cells/day probiotic cells for 7 days. Results showed the 38% reduction in total cholesterol and among them, 40% were triglycerides. Surprisingly, administration of *L. reuteri* CRL 1098 increased the high-density lipoprotein by 20% [45].

5.2. Effects of Prebiotics on Cholesterol Reduction. Prebiotics or their cofactors act as good alternative for probiotics. These prebiotics are defined as nondigestible or low-digestible food components which would selectively stimulate the growth and activity of probiotic microorganisms present in the colon of host organism [31, 46, 47]. Brighenti et al. conducted a 12-week trial using twelve

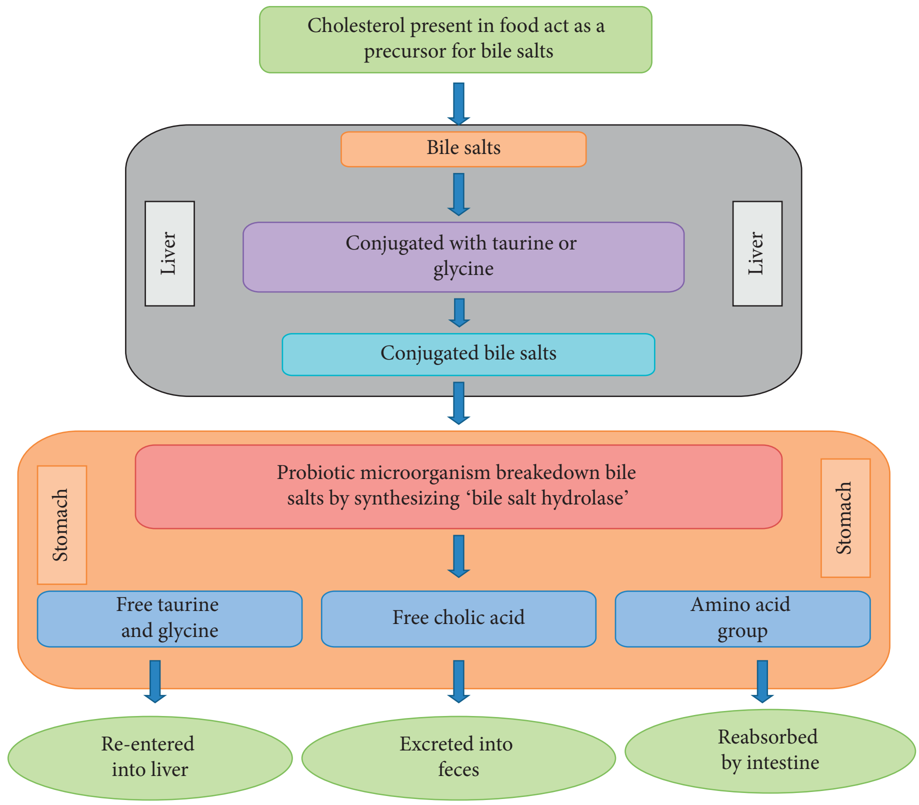

Figure 2: Cholesterol reduction mechanism of probiotic microorganisms.

healthy persons (male) in which the researchers found that the daily consumption of rice-based ready-to-eat cereal (50 g) comprising 18% inulin significantly ($P < 0.05$) decreased total cholesterol and triacylglycerol present in the plasma by 7.9% (±5.4) and 21.2% (±7.8), respectively, when compared to control [48].

Fernandez et al. used male Hartley guinea pigs (300–400 g body weight) to study the effect of resistant starch in the plasma cholesterol reduction. This study reported that the administration of 10 g/100 g of resistant starch (obtained from the Meer Corporation) to sixteen male Hartley guinea pigs for about four weeks resulted in the significant reduction ($P < 0.001$) of plasma cholesterol by 27.4% and LDL cholesterol concentration by 28.0% when compared with the control group [49].

Causey et al. performed a randomized, double-blind, and crossover study using twelve hypercholesterolemic men patients to evaluate the inulin (extracted from chicory roots) effects on blood cholesterol levels of patients. Twelve men were randomly assigned to two different groups, viz., the control group (consumed one pint of vanilla ice cream without inulin) and the inulin group (consumed one pint of vanilla ice cream containing 20 g of inulin). As a result of a 3-week study, the researchers found that the daily ingestion of 20 g of inulin significantly ($P < 0.05$) decreased triglycerides present in the serum [50].

Mortensen et al. reported that when forty male mice were administered with a purified diet containing 10% of long-chained fructan for 16 weeks, the fructan present in the diet significantly decreased the concentration of blood cholesterol by 29.7% ($P < 0.001$), LDL cholesterol concentration by 25.9% ($P < 0.01$), VLDL cholesterol concentration by 37.3% ($P < 0.05$), and the level of IDL cholesterol by 39.4% ($P < 0.001$) compared to the control group [51].

Favier et al. conducted a 21-day trial study in ten male Wistar rats (body weight of 150 g) to evaluate the hypocholesterolemic effects of β-cyclodextrin in a randomized, placebo-controlled, and parallel design trial. The researchers reported that the daily consumption of β-cyclodextrin (25 g/kg) significantly ($P < 0.05$) reduced the level of cholesterol and triacylglycerols present in the plasma by 25.9% and 35.0%, respectively, compared to the control group [52].

5.3. Effects of Synbiotics on Cholesterol Reduction. Liong and Shah examined the effect of 3 synbiotic diets ((a) diet containing *Lactobacillus casei* ASCC 292 and fructooligosaccharides (LF diet), (b) diet containing *L. casei* ASCC 292 and maltodextrin (LM diet), and (c) diet containing *L. casei* ASCC 292, maltodextrin (LFM diet), and fructooligosaccharides) on the reduction of serum cholesterol in male Wistar rats. The authors reported that the synbiotic diet containing *L. casei* ASCC 292, maltodextrin, and fructooligosaccharide reduced the cholesterol levels and a healthier bowel microbial population was developed without translocation of *Lactobacilli* to the nearby or other organs [53].

Schaafsma et al. performed a trial study comprising thirty volunteers who were aged between 33 and 64 years and their body weight ranged about 66.5–98.0 kg with an average total cholesterol of 5.23 ± 1.03 mmol/L and LDL cholesterol of 3.42 ± 0.94 mmol/L. Results from this study showed that the daily intake of 375 mL of synbiotic milk (made of 10^7-10^8 CFU/g *Lactobacillus acidophilus* and 2.5% (g/100 g) fructooligosaccharides) resulted in a significant decrease in total cholesterol level ($P < 0.001$), LDL cholesterol concentration ($P < 0.005$), and LDL/HDL ratio ($P < 0.05$) of 4.4%, 5.4%, and 5.3%, respectively [54].

6. Conclusion and Future Prospects

Probiotics, prebiotics, and their combinations have been found to be clinically effective for a large number of disorders which include hypercholesterolemia. The use of any probiotic and prebiotic substances for the enrichment of fermented products provides its delivery into the human gastrointestinal tract and thus stimulates beneficial health effects. Several probiotic-mediated cholesterol removal mechanisms have been suggested, including cholesterol assimilation by growing cells, cholesterol binding to the cell surface, incorporation of cholesterol into the cellular membrane, bile salt deconjugation via bile salt hydrolase, and cholesterol coprecipitation with deconjugated bile. But the exact mechanisms remain unclear and controversial. Much work has already been accomplished to help us to understand probiotics and the manner in which they function. Nevertheless, some concerns like viability and dosage of probiotic strains, safety aspects, and industrial standardization are essential to be studied in detail. In recent times, cholesterol reduction, cancer prevention, and immunology are the major research subjects on probiotics and prebiotics. Genetic engineering and other similar methods are being used to increase the beneficial effects of probiotic strains. Supplementation of promising probiotic strains may indulge better solution to reduce the high cholesterol level issue in human beings. However, broad research is essential for the screening of potent probiotic strains and to evaluate the effective management of good and bad cholesterol present in the body and the sustainability of the desired results obtained by the probiotic strains. The combination of probiotics and prebiotics significantly reduces the serum cholesterol level and that can be used as an alternative remedy for hypercholesterolemic problems without any side effect to the consumers.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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