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REVIEW ARTICLE

Cholesterol-Lowering Effects of *Lactobacillus* Species

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Abstract
Probiotics are the living and non-pathogenic microbial supplements which, upon administration in adequate quantities, influence the host organism positively by improving gut health and enhancing intestinal mucosal integrity. They suppress potentially pathogenic microorganisms by competing with them for nutrients as well as space for gut adherence. *Lactobacillus* species are the most commonly used bacteria in the probiotic preparations and studies show that they have cholesterol-lowering effects on the hosts. Lipids are biological molecules that are insoluble in water and bile salts play a major role in their digestion as they are synthesized and conjugated to taurine or glycine in the liver. Bile salt hydrolase deconjugates taurine or glycine from bile salts. Cholesterol metabolism is influenced by the effect of *Lactobacillus* species on microbial populations as well as overall metabolic activity of human intestinal microflora. Deconjugation of bile salt, concentration of short-chain fatty acids and molar proportion of propionate constitute the major processes by which cholesterol lowering is brought about by *Lactobacillus* species. This review summarizes the cholesterol-lowering properties of this species. A significant number of *Lactobacillus* strains have been known to display substantial bile salt hydrolase activities and identifying those strains for use in therapeutic purposes can be a great advancement. Here, this identification is done using phylogenetic relationship for different identified potential probiotic *Lactobacillus* strains.

Introduction

Probiotics are live microbial entities having beneficial roles towards the host which involve improvement of the microbial balance inside the host's intestine. They are essentially live and non-pathogenic microbes which, upon administration in sufficient dosage, confer beneficial effects on the health of the host organism [1]. They are also referred as "good microorganisms" and can be found in the form of oral consumer products such as dietary supplements, chocolates, yogurts and many others [2].

The father of probiotics, Elie Metchnikoff proposed in "*The Prolongation of Life: Optimistic Studies*", that ingestion of microbes might have significant benefits for human health, and this led to the emergence of the concept of probiotics, at the start of the twentieth century [3]. The gastrointestinal tract of humans has a surface area higher than 400 m^2 and this is where the commensal microbes have the highest concentration. Moreover, the GI tract comprises a rich microflora having higher than 500 species of bacteria, out of which several show beneficial roles towards human health. These benefits broadly include normalizing intestine, providing better immune response and enhancement of metabolic effect of our body [4]. Benefits of probiotics also include improvement of gut health, enhancement of intestinal mucosal integrity, suppression of potentially pathogenic microorganisms through competition for nutrients and space for gut adherence, antihypertensive effects, reduction in allergic symptoms, prevention of cancer, facilitation of mineral absorption, cholesterol-lowering effects, amelioration of arthritis and reduction of dermises symptoms [5].

A high degree of viability of cells and resistance to acidic conditions are the major requirements for a microorganism to be used as a probiotic. The properties of persistence of the cells in the intestine and adhesion to gut epithelium to reduce the flushing effects of peristalsis is also desired [6]. Probiotics should also be able to interact with and send signals to immune cells, having association with gut and resistance towards processing and must have the capacity to influence local metabolic activities. It should be kept in mind that the majority of probiotics are of human origin and are non-pathogenic (Fig. 1) [7].

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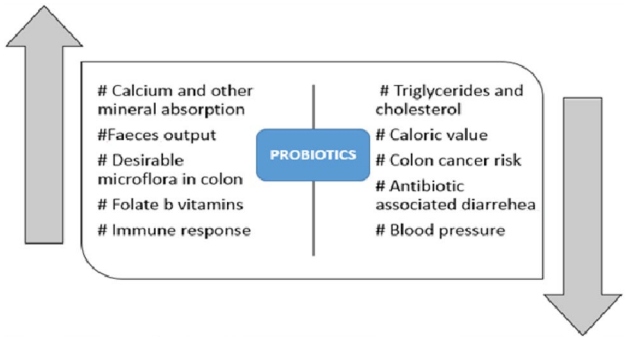

Fig. 1 The effects of probiotics

Probiotic formulations are mostly prepared from the genera of *Lactobacillus*, *Streptococcus thermophilus*, *Bifidobacterium*, *Escherichia coli* (*E. coli*) Nissle (EcN) 1917, *Enterococcus* and *Bacillus*. Few strains of the yeast genus *Saccharomyces* have also been used as probiotics [8]. Bifidobacteria are among the very first colonizers of human intestinal tract after birth and they are the predominant group in breast-fed infants' colonic microbiota [9]. Different strains of probiotics are administered in different dosages like for *Lactobacillus* sp. 1 to 20 CFU per day and for *Saccharomyces boulardii* 250 to 500 mg per day is sufficient [10]. Using antibiotics or immunosuppressive therapies might cause some alterations in the gut composition and can affect the microbiota of the gastrointestinal tract. Introduction of such beneficial bacterial species of probiotics to the GI tract is a promising option to re-establish microbial equilibrium of gut and prevent diseases [11].

The mechanisms by which probiotics help in achieving health benefits involve modifying the composition or function of the gut microbiota, reducing the colonic pH, improving immune response, stimulating cell development, bolstering intestinal barrier function, inhibiting gut pathogens and fostering nutrient absorption [12]. This review summarizes the cholesterol-lowering properties of *Lactobacillus* species.

Mechanism Involved in Lowering of Cholesterol

Cholesterol

In aqueous environments, biological molecules such as lipids display properties of insolubility, since they constitute a hydrophobic region, which is non-polar in nature and thus prevent their dissolution in water [13]. Eukaryotic and bacterial cells have phospholipids and glycolipids. In lipoproteins, HDL (high-density lipoproteins), vLDL (very low-density lipoproteins), chylomicrons and LDL (low-density lipoproteins) are formed by the arrangement of lipid and protein units in varying concentrations [14]. The protein amount increases from chylomicrons to HDL. Chylomicrons are responsible for the deliverance of fat that we have absorbed in our diet to the body tissues while HDL removes excess of cholesterol from the tissues and transfer them back to the liver [15].

According to the World Health Organization, cardiovascular ailments have been estimated to become the major cause of death by the year 2030, and will affect approximately 23 million human beings worldwide [16]. It has been reported that hypercholesterolemia resulted in 45% of heart attacks in Western Europe and 35% in Central and Eastern Europe, since 2000 [17]. People with hypercholesterolemia have a three times higher risk of suffering from heart attack than people with normal levels of lipid profile [18].

Biosynthesis of Cholesterol

Our diet contains fats, carbohydrates and proteins. These get digested and then absorbed in the duodenum of small intestine. On the apical side of small intestine there is sodium glucose transmitter which takes 1 glucose for 2 molecules of sodium. Glucose is then reabsorbed in the blood [19]. The fat in the diet form lipid droplets which are digested and emulsified to micelles, which are then absorbed into intestinal cells as monoglycerides, fatty acids and cholesterol. These when coated with apoproteins make chylomicrons. They are absorbed in the blood via lymph and circulate in the body as circulating lipids. The remaining arrive at the liver and bind to the LDL receptor and brought to the hepatic cells [20].

Glucose undergoes glycolysis to form pyruvic acid and further acetyl co-A which via HMG co-A reductase enzyme forms cholesterol (Fig. 2). The glycerol thus obtained along with malonyl co-A forms monoglycerol and then triglycerol. These are packaged with cholesterol apoprotein in golgi apparatus from where vLDL transports them to the tissues for energy or storage. The vLDL liberates fatty acids by action of lipases to form ILDL(intermediate LDL) and then to LDL which reaches liver and is excreted through bile or recycled in golgi apparatus to make more lipoproteins. Excess of cholesterol is secreted through bile. The empty HDL enters into circulation and picks up cholesterol from tissues containing excess and returns them to the liver or they are excreted depending upon how much cholesterol is needed by the body [21].

Bile Salt Deconjugation

Bile is a liquid secretion of the liver having a yellowish-green color. Bile's major functions include fat digestion and absorption. It also serves as a means for excretion of waste products from the blood. Major constituents are bile acids,

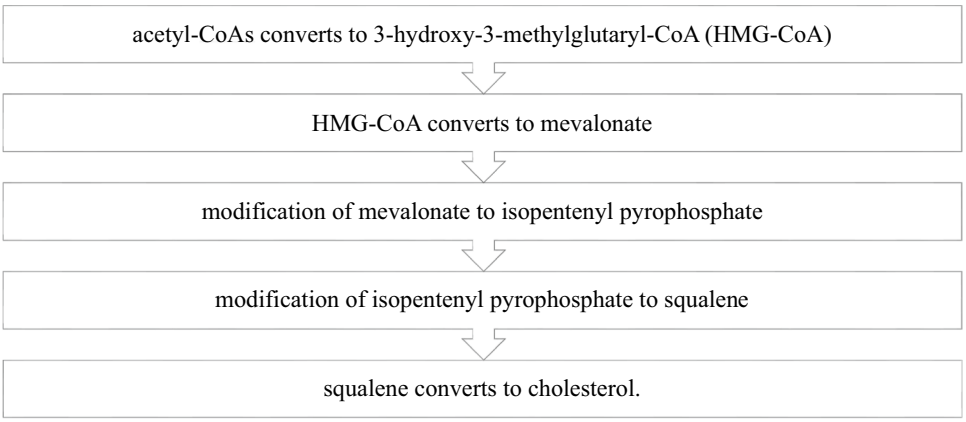

Fig. 2 The stages in biosynthesis of cholesterol

cholesterol, phospholipids, bile pigments, ions and water [22]. Bile acids are produced from cholesterol inside the liver. Cholic as well as chenodeoxycholic acids are primary forms of bile acids that are synthesized by hepatocytes. Secretions of bile acids constitute conjugates with glycine or taurine. Bacteria act on primary bile acids and convert them to secondary bile acids by dehydroxylation [23].

Bile Salt Hydrolase

The intestinal microbiota secrete an important enzyme known as bile salt hydrolase (BSH). This enzyme aids in the catalysis of deconjugation of bile salts linked with glycine or taurine. Glycine or taurine are liberated from the core of a steroid, when amide bonds undergo hydrolysis by BSH enzymes. The resulting acids are known as unconjugated or deconjugated bile acids [24]. It has been shown that *Lactobacillus, Bifidobacterium, Enterococcus* and *Clostridium* sp. possess BSH activity. At low pH, the glycoconjugated bile salts are toxic in nature. BSH enzymes play an essential role in alleviating these toxic effects of glycoconjugated bile salts, by letting bile enter into the intestinal duodenum or microenvironments, when the pH gets low due to lactic acid bacteria [25].

The selection criterion for probiotic microbes having the properties of decreasing the levels of cholesterol, must include BSH activity. BSH enzyme is responsible for bile salt deconjugation during enterohepatic circulation. Deconjugation is catalyzed by BSH enzyme which hydrolyses amide bonds and glycine or taurine groups are released from the core of the steroid [26]. Deconjugated bile salts have low solubility and are absorbed with lesser efficiency as compared to their conjugated counterparts from inside the lumen of intestine, as a result of which, an excess of free bile is excreted in fecal matter. Free bile salts display lower efficiency in solubilising and absorbing lipids inside the intestine [26]. Thus, serum cholesterol is reduced due to deconjugation of bile salts, as there is an increased requirement for cholesterol during the pathway for de novo synthesis (Fig. 3) [27].

Lactobacillus Species as Probiotic and Strains Mediating Cholesterol Reduction

The use of *Lactobacillus* species in disease prevention and treatment is very common. It is also used for health restoration and maintenance. However, recently, there has been a shift in the use of these strains as probiotics. According to in vitro utilization in human data, these strains can only be considered as good probiotics for humans [28].

The properties such as adherence to cells, reduction in adherence to pathogens, persistence and multiplication, formation of hydrogen peroxide and bacteriocins (that show antagonism to pathogenic proliferation), safe and non-invasive nature as well as non-pathogenicity and non-carcinogenicity are essential for a strain to be a good probiotic [29].

The adhesion properties of the species of *Lactobacillus* have been studied by various experiments. Scientists have explicated the cell wall protein mechanisms and cell wall bonded exopolysaccharides for *Lactobacillus delbrueckii*. Antikainen et al. [30] have categorized the adhesion proteins from *Lactobacillus* into five categories, namely anchorless housekeeping proteins, surface layer proteins, LPXTG-motif proteins, transporter proteins and other proteins. Bacterial auto-aggregation and the hydrophobic nature of the cell surface play key factors in the adhesion and colonization capabilities possessed by probiotic species. These also influence the adhesion characteristics and prevent the binding of pathogens to the gut lining [31].

Significant reduction in the amount of serum cholesterol, after consumption of large quantities of fermented milk containing *Lactobacillus* or *Bifidobacterium* or both was observed by Mann and Spoerry [32]. The adhesive abilities possessed by these species to mucosal surfaces of the intestine for a long- or short-term colonization result in a

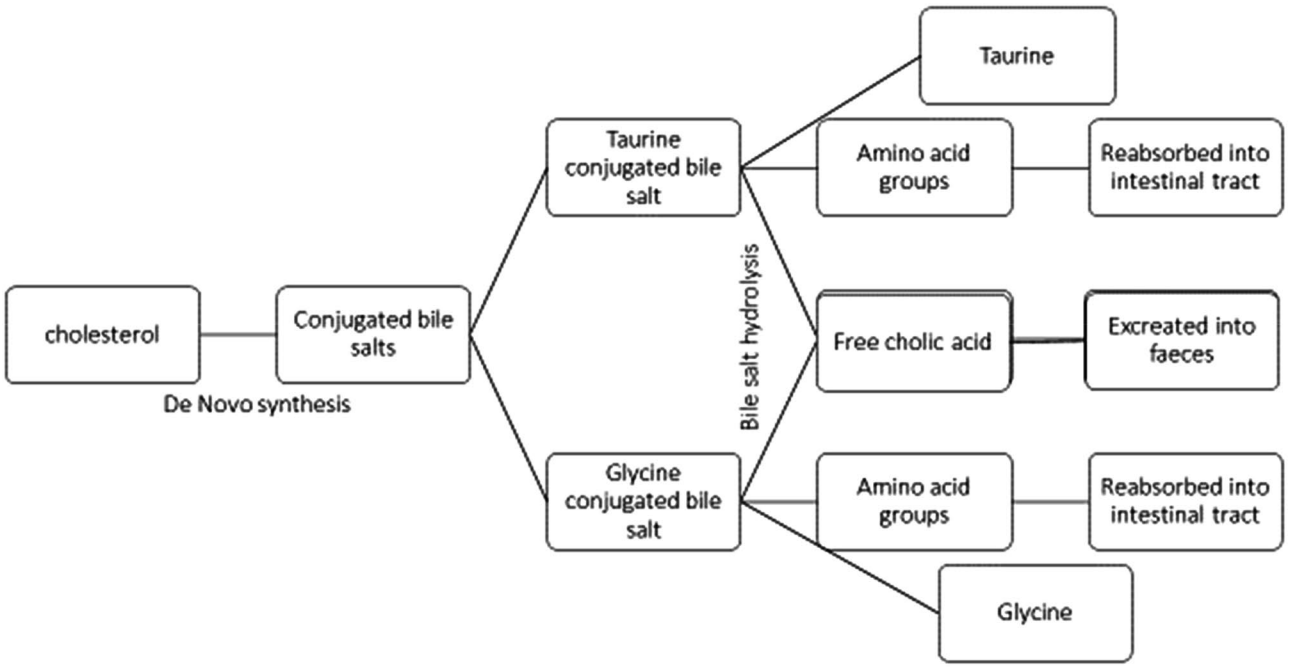

Fig. 3 Cholesterol as the precursor for new bile acid synthesis and the role of bile salt hydrolase in hypocholesterolemia [8, 19]

Table 1 BSH homologs in genomes of probiotic strains of *Lactobacillus* [35–39]

Strain	*bsh homolog(s),* (accession no.)
Lactobacillus johnsonii NCC533	*LJ1412, (AAS09178)*
	LJ1147, (AAS08969)
	LJ0056, (AAS08038)
Lactobacillus plantarum WCFS1	*lp_3536 (bsh 1),* (Q06115)
	lp_0067 (bsh 2), (CCC77632)
	lp_3362 (bsh 3), (YP_004890864)
	lp_2572 (bsh 4), (YP_004890239)
Lactobacillus reuteri JCM 1112	*(BAG25217.1)*
Lactobacillus acidophilus NCFM ATCC700396	*LBA1078 (bshB), (YP_193954)*
	LBA0892, (YP_193782)
Lactobacillus casei LOCK919	*(KTE98348.1)*
Lactobacillus fermentum NCDO394	*bsh1, (AEZ06356)*
Lactobacillus fermentum F1	*bsh2, (ADZ55761)*
Lactobacillus salivarius NRRL B-30514	*(5HKE_B)*
Lactobacillus helveticus CIRM-BIA 951	*(CDI59344.1)*
Lactobacillus rhamnosus	*(AEP69108.1)*

biofilm formation and subsequently have many benefits such as hypo-cholesteremic effect [33].

Experiments have shown that the increase in the deconjugation of the bile acids results in the greater excretion of bile salts from the intestinal tract which triggers synthesis of replacement of bile salts from the cholesterol. This provides potential to reduce the cholesterol levels significantly in the body [34]. The effect of *Lactobacillus* species on triglycerides is due to the action of lipase from *Lactobacilli* which actually breaks the larger molecules of fat into simpler and easy to digest substrates such as, fatty acids and glycerol. Apart from this experiment, studies show that the mix of the *L. acidophilus* and *S. faecalis* decreased the synthesis of cholesterol and shows effects on LDL, VLDL and HDL cholesterol [10]. Further, it was shown that *L. acidophilus* can enhance the reduction of serum cholesterol

Table 2 Major outcomes of cholesterol reduction mediated by probiotic *Lactobacillus* species [40]

Probiotic Species used	Experimental system used	Major outcomes	References
Lactobacillus acidophilus	Culture medium	Removal of cholesterol In cholesterol media—survival rate increased	[40]
Lactobacillus reuteri	Mice	Reduced blood cholesterol Decreased triglycerides	[41]
Lactobacillus bulgaricus	Human	Decreased cholesterol	[42]
Lactobacillus sporogenes	Human	Reduced cholesterol Decreased LDL-cholesterol	[43]
Lactobacillus reuteri	Human	Decreased LDL-cholesterol Reduction in total cholesterol Reduced non-HDL-cholesterol	[44]

in hypercholesteremic rats. The feasibility of *Lactobacillus* strain in the human gut and ultimately colonizing in the small intestine remains the most important aspect for the hypocholesteremic results of the probiotics as most of the absorption of the cholesterol takes place in the same area [35].

The strains listed in Table 1 represent strains fulfilling the criteria of discussion along with their *bsh* homologs. The second table (Table 2) shows the major findings for different probiotic *Lactobacillus* species in various experimental setups mediating the cholesterol reduction as a result.

The strains that are listed in Table 1 fulfill the criteria as potential probiotic for cholesterol-lowering effects. To determine the phylogentic relationship of these strains their *bsh* homologs were extracted and used to construct a phylogentic tree (Fig. 4) depicting the degree of gene similarity

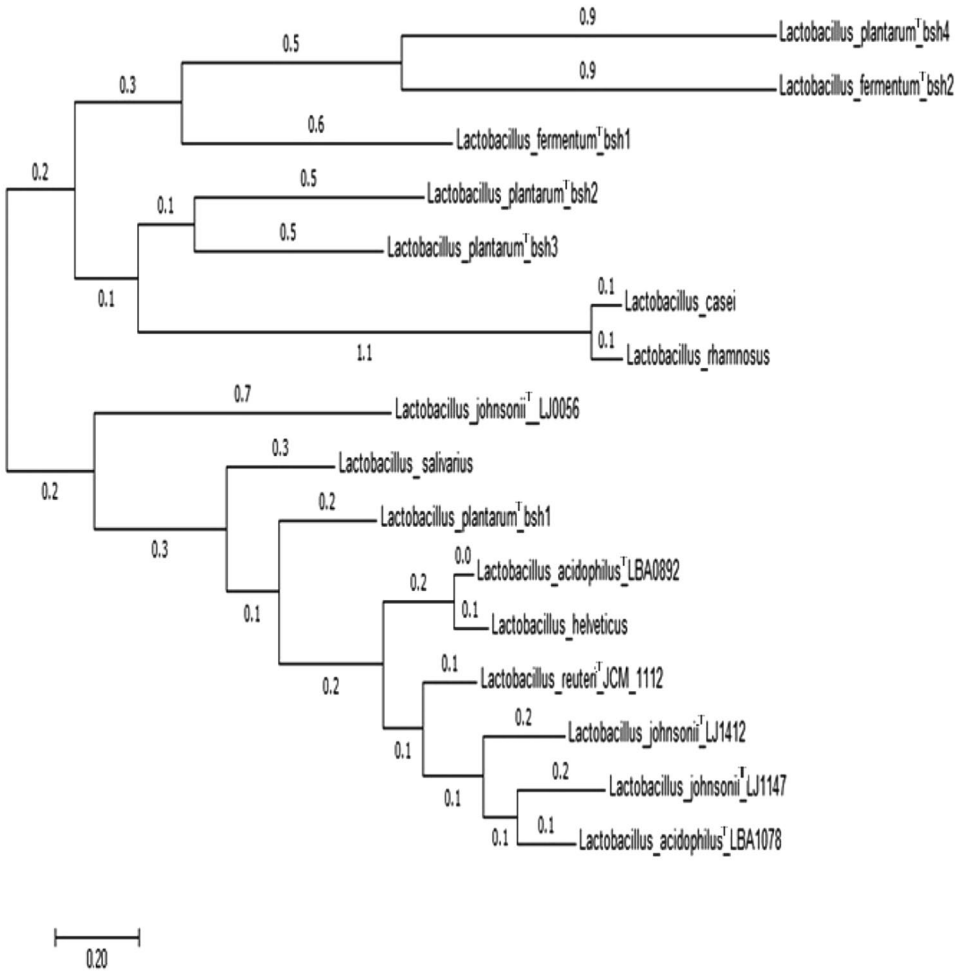

Fig. 4 Molecular phylogenetic analysis of bsh sequences by Maximum Likelihood method for *Lactobacillus* species (Refer Table 1 for accession no. and strain no.)

of different strains with each other. Table 2 was constructed showing the major findings as to what is the mechanism of action and effects by every probiotic *Lactobacillus* species in various experimental setups mediating the cholesterol reduction as a result.

Maximum likelihood method, which is based on the JTT matrix-based model, was used to draw inference on the evolutionary history [45]. The tree with the highest log likelihood (− 3805.3813) is shown. To obtain the initial tree(s) for the heuristic search, neighbor-join as well as BioNJ algorithms were applied to matrices of pairwise distances predicted utilizing a JTT model, and then selection of a topology with superior likelihood value for log was done. The tree was then drawn, which was to scale, and the branch lengths were measured in the number of substitutions per site. Sixteen amino acid sequences were used in the analysis. Elimination of all positions containing gaps along with missing 0 data was carried out. In the final dataset, a total of 133 positions were obtained. MEGA7 was used to carry out evolutionary analyses [46].

Conclusion

Probiotics having many health benefits are attaining much attention. Their benefits include decreasing the cholesterol serum levels; improving the lactose intolerance, digestion and showing superior resistant capacity towards the infections in GI tract and cancer inhibition. Many studies have been conducted on potential hypocholesterolemic properties of different probiotic strains administered to humans. Numerous pathways for the removal of cholesterol by *Lactobacillus* strains have been hypothesized which include assimilating cholesterol inside growing cells, attachment of cholesterol to cell surface, incorporating cholesterol inside cell membrane, utilizing bile salt hydrolase to deconjugate bile, and then precipitation of cholesterol along deconjugated bile. More recently, it has been discovered that many probiotic *Lactobacillus* strains show elevated BSH activities and identifying those strains for using in therapeutic purposes can be a great advancement.

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Compliance with Ethical Standards

Conflict of interest The authors declare no conflict of interest.

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