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# The Effect of Probiotics on Lipid Metabolism

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## 1. Introduction

Probiotics are defined as viable microorganisms that exhibit beneficial effects on the health of the host [1]. Now, probiotics are known to possess physiological functions such as inhibition to pathogens, assisting digestion, immunoregulatory activity and antitumor activity [2]. Here, we discuss the effects of probiotic on lipid metabolism from seven main aspects including history, antioxidant effect, impact on lipoprotein, microflora view, hormones, receptors and new mechanisms.

### 1.1. Past and present

As early as in 1974, Mann and Spoerry observed that inhabitants from African Maasai tribes maintained a lower level of blood lipids due to a high fermented milk intake [3]. Further perspective suspected that live Lactobacilli included in fermented milk may contribute to reducing cholesterol [4]. The cholesterol-reducing effect of probiotic has become more apparent with the discovery of bile salt deconjugating and cholesterol assimilating ability of *Lactobacillus* [5] [6]. Thereafter, a set of screening procedures both *in vitro* and *vivo* was established for evaluation of cholesterol-reducing probiotics [7]. Many probiotic strains mostly *L. acidophilus* were screened out with cholesterol-reducing property [8].

A new study by Lye et al showed that there existed five possible probiotic mechanisms including assimilation of cholesterol during growth, binding of cholesterol to cellular surface, disruption of cholesterol micelle, deconjugation of bile salt and bile salt hydrolase (BSH) activity [9]. Now with the development of molecular biology, we can judge cholesterol-lowering effect firstly by detection of BSH gene and its expression in a probiotic genome. A recent study by Sridevi et al showed that *Lactobacillus buchneri* ATCC 4005 exhibited a great cholesterol-lowering property through an optimal condition of bile salt hydrolase production [10]. In conclusion from a meta-analysis, administration of probiotic can exact benefits on total cholesterol and LDL-cholesterol level of human [11].

There are some reports that fermented soy milk by probiotics also showed favorable function of regulating lipids level [12]. The advantages of fermented soy milk are that undesirable soybean oligosaccharides can be hydrolysed which provide nutritional components for probiotic and a large variety of peptides and amino acids are produced as well as active aglycon form of isoflavones [13]. An improved cholesterol profile was observed with daily intake of a probiotic soy product [14]. It seems possible that living probiotics and functional isoflavones cooperated in regulating lipid profile.

## 2. Antioxidant effect

Probiotic originated from longevity research by the well-known Eli Metchnikoff. As we all known, various published evidence suggested reduction of oxidative stress led to longevity-promoting consistent with Harman's Free Radical Theory of Aging [15]. These two observations inspired the investigation of antioxidant ability of probiotics.

Oxidative stress induced by obesity tend to produce surplus reactive oxygen species (ROS) which may cause further damage by free radical chain reaction mechanism [16]. ROS have some deleterious effects on polyunsaturated lipids in cell membrane leading to damage of cell structure and malondialdehyde (MDA), which was also toxic to DNA and protein and formed as a marker of lipid peroxidation at the same time [17] [18]. As for the oxidative stress, human body has its own antioxidant defense system including superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px) , glutathione (GSH) and so on [19]. Many *Lactobacillus* strains with antioxidative effects were not only reducing MDA level, but also enhance the antioxidants production (Table1).

Strains	Model	Antioxidant effects	Renferences
Probiotic yoghurt containing <i>Lactobacillus acidophilus</i> La5 and <i>Bifidobacterium lactis</i> Bb12	Type 2 diabetic patients	Serum MDA concentration significantly decreased	[20]
Probiotic yoghurt containing <i>Lactobacillus acidophilus</i> LA-5 and <i>Bifidobacterium</i> BB-12	Pregnant Women	Increased erythrocyte glutathione reductase levels, plasma glutathione and 8-oxo-7,8-dihydroguanine levels	[21]
<i>Lactobacillus casei</i> Zhang	High-fat fed rat	A decrease of MDA and increase of SOD and GSH-Px in serum and liver	[22]
<i>Lactobacillus fermentum</i>	pigs	Increased total antioxidant capacity, SOD and GSH-Px activity in serum as well as hepatic CAT and muscle SOD; Decreased MDA level in serum and muscle	[23]

Strains	Model	Antioxidant effects	References
Probiotic yoghurt containing <i>Lactobacillus acidophilus</i> LA-5 and <i>Bifidobacterium</i> BB-12	human	An increase of SOD and catalase activity	[24]
<i>Bacillus polyfermenticus</i>	Rats with colon carcinogenesis	Lower plasma lipid peroxidation levels and higher plasma total antioxidant levels	[25]
Probiotic dahi containing <i>Lactobacillus acidophilus</i> and <i>Lactobacillus casei</i>	High fructose fed rats	Lower values of TBARS and higher values of glutathione in liver and pancreatic tissues	[26]
<i>Lactobacillus fermentum</i> ME-3	human	Enhanced total antioxidative status	[27]
<i>Bacillus polyfermenticus</i> SCD	High-Fat and cholesterol fed rat	An increase in total radical trapping antioxidant potential (TRAP) and a decrease in conjugated dienes in plasma	[28]
<i>Streptococcus thermophilus</i> YIT 2001	Iron overloaded mice	A significant decrease of lipid peroxide in the colonic mucosa	[29]
VSL#3	ob/ob mice	Lower fatty acid beta-oxidation	[30]
<i>L. acidophilus</i>	rats	Higher GSH-Px activity in red blood cells	[31]
<i>L. rhamnosus</i> SBT 2257	rats	Inhibition of hemolysis of red blood cell under the condition of vitamin E deficient	[32]

**Table 1.** Antioxidative effects of probiotics

### 3. Impact on lipoprotein

Lipoprotein transport play an important role in accumulation of host lipopolysaccharide level (LPS) [33]. Studies by Cani et al showed that elevated LPS level was considered as a trigger factor involved in the pathogenesis of obesity and metabolic risk via innate immune mechanism [34]. LPS-binding protein (LBP) and lipoproteins exert a synergistic effect on reducing the toxic LPS level[35].

Several fermented milk containing probiotics were demonstrated to reduce low-density lipoprotein cholesterol(LDL-c) level and very-low-density lipoprotein cholesterol (VLDL-c) in animal and human [26] [36] [37].Recently, *L. casei* Shirota had been proved a plasma LBP-lowering effect in obesity mice and *L. reuteri* NCIMB 30242 yoghurt could improve ApoB-100 level in hypercholesterolaemic subjects, suggesting that probiotic possess LPS-reducing function to delay the obesity risk [38] [39].

#### 4. The whole microflora view

Intestinal microbes not only *Lactobacillus* could also exhibit a bile salt deconjugating effect [40], suggesting that other microbes had lipid-reducing potential. Thus, overall intestinal microflora was taken into account for lipid metabolism evaluation. In the past few years, research has focused on new areas of microflora and lipid metabolism with the development of culture-independent methods for understanding the total microbial diversity [41].

The human gut is consisting of a microbial community of  $10^{14}$  bacteria with at least 1000 species and the whole microbiome is more than 100-fold the human genome [42]. These researches highlight the significance of the whole gut microbiome contribute to energy harvest and the relationship between obesity and changes of gut microbiome [43]. More detailed, obese is mainly characterized by elevated *Firmicutes/Bacteroidetes* ratio in gut [44]. Probiotics serve as one of effective agents for regulation of gut microflora, they can exert benefits on lipid metabolism through downregulating the ratio of *Firmicutes/Bacteroidetes*. Other bacteria such as *Methanobrevibacter smithii* are also at low level in obese people [45]. Interestingly, atherosclerotic disease, which caused by accumulation of cholesterol and inflammation, was recently found its atherosclerotic plaque microbiota was associated with oral and gut microbiota through high throughput 454 pyrosequencing of 16S rRNA genes [46].

Besides, such a huge microflora provide a large reservoir of LPS molecules to circulation through colonizing of Gram-negative bacteria in the gut [47]. A recent study showed *Bifidobacteria* with genes encoding an ATP-binding-cassette-type carbohydrate transporter could protect against Gram-negative *E. coli* O157:H7 colonization in gut due to acetate production [48]. Thus, probiotic can restrict LPS-related microbial communities in the gut.

The whole gut microflora is also known as a target for drug metabolism because of diverse microbial transformations [49]. Manipulation of commensal microbial composition through antibiotics, probiotics or prebiotics was thought to enhance the metabolic activity and production of effective metabolites [50]. Simvastatin, which is an inhibitor of HMG-CoA and widely used for regulating hepatic cholesterol production, was proposed to possess altered pharmacological properties by microflora degradation via changing its capacity to bind to the corresponding receptors [51]. It is indicated that probiotics have potential to influence the metabolism of lipid-regulating drugs in gut.

#### 5. Regulation of leptin, adiponectin and osteocalcin

Hormones such as leptin, adiponectin and osteocalcin play an important role in lipid metabolism. Obese population was characterized by significant lower levels of osteocalcin and adiponectin as well as high leptin level (leptin-resistant) which have been reported in literature. It is now increasingly accepted that leptin can regulate food intake and energy expenditure through hypothalamus and adiponectin can enhance tissue fat oxidation to downstream fatty acids levels and tissue triglyceride content associated with insulin sensitivity [52]. As for osteocalcin, leptin assumed to modulate osteocalcin bioactivity and osteocalcin could stimulate the adiponectin synthesis [53] [54].

### 5.1. Leptin

Leptin, an antiobesity hormone produced by adipose tissue, has been reported to regulate body weight by controlling food intake and energy expenditure [55]. However, obesity tend to display markedly higher serum leptin level with a leptin-resistant symptom. Several studies reported a decrease of leptin by probiotic administration. In high-fat fed mice, Lee et al confirmed that *Lactobacillus rhamnosus* PL60 exhibited a reduction in leptin level and anti-obesity effect due to production of conjugated linoleic acid [56]. Moreover, serum leptin concentration was reduced by *Lactobacillus gasseri* SBT205 in lean Zucker rats linked with lowered adipocyte size [57]. Another study also report leptin level was reduced by a combined bifidobacteria (*B. pseudocatenulatum* SPM 1204, *B. longum* SPM 1205, and *B. longum* SPM 1207) in obese rats [58]. Interestingly and controversially, direct injection of *Lactobacillus acidophilus* supernatants (germ free) into the brains of rats lead to weight loss with an increase in leptin expression in neurons and adipose tissue [59].

Leptin-lowering effect of probiotics was also observed in human. Similarly, Naruszewicz et al investigated whether oral administration of *L. plantarum* 299v exert beneficial effect on smokers by detection of cardiovascular risk factors [60]. In this study, smokers showed a great decrease in plasma leptin concentrations and anti-inflammatory properties when supplement of probiotic. Discouragingly, two months of *Lactobacillus acidophilus* and *Bifidobacterium longum* consumption failed to lower plasma leptin levels in male equol excretors [61].

### 5.2. Adiponectin

As an adipocyte-derived serum protein, adiponectin play an important role in glucose and lipid metabolism since adiponectin deficiency are associated with insulin resistance, inflammation, dyslipidemia and risk of atherogenic vascular disease [62]. In parallel, adiponectin has also been shown to suppress macrophage foam cell formation in atherosclerosis [63]. Several studies showed that probiotic therapy improved adiponectin level or adiponectin gene expression. One comparative research performed in normal microflora (NMF) and germ-free (GF) mice revealed that adiponectin gene expression (Adipoq) was up-regulated in the groups of *Lactobacillus*-treated germ free mice [64]. Moreover, Higurashi et al reported a probiotic cheese could prevent abdominal adipose accumulation and maintained serum adiponectin concentrations in high-calorie fed rats [65]. However, *Lactobacillus plantarum* strain No. 14 exert a white adipose-reducing effect in high-fat fed mice with no change of adiponectin [66].

Kadooka et al used a probiotic *L. gasseri* SBT2055 to regulate abdominal adiposity in obese adults, where the probiotic treatment involved a significant reduction in abdominal visceral and subcutaneous fat areas from baseline and significantly increased high-molecular weight adiponectin in their serum [67]. Furthermore, a recent large scale clinical study conducted by Luoto et al confirmed that pregnant women with a consumption of combined *Lactobacillus rhamnosus* GG and *Bifidobacterium lactis* probiotics possessed higher colostrum adiponectin concentration compared to placebo which was correlated inversely with maternal weight gain during pregnancy [68].



### 5.3. Osteocalcin

In recent years, osteocalcin secreted by osteoblasts has aroused great interest linked to  $\beta$  cell function, adiponectin production, energy expenditure and adiposity [69]. In humans, fat individuals kept a low level of serum osteocalcin [70]. The only study by Naughton et al showed that osteocalcin levels was slightly increased in middle aged rats by consumption of inulin-rich milk fermented by *Lactobacillus* GG and *Bifidobacterium lactis* [71]. It is interesting that osteocalcin is an vitamin K-dependent protein and two main types including vitamin K1 and vitamin K2 are respectively produced from dietary vegetable and microflora [72]. As an effective way to alter microflora, probiotics have potential to enhance vitamin K2 production and related osteocalcin level through changing the microflora.

## 6. Interaction with receptors

Various Receptors are involved in regulating important genes in lipid transport and metabolism and selected as potential therapeutic targets for dyslipidemia and atherosclerosis. Recent studies have focused on nuclear receptors (NRs), G protein-coupled receptor (GPRs) and Toll-like receptors (TLRs) as factors regulated by probiotics administration. But the crosstalk among NRs,TLRs and GPRs have not been clearly elucidated. The only investigation about crosstalk of NRs,TLRs and microflora between specific pathogen-free (SPF) mice and germ-free (GF) mice have revealed that LXR alpha, ROR gamma and CAR expression were reduced while TLR-2 and TLR-5 increased in SPF compared with GF mice [73].

### 6.1. Nuclear receptors

According to the stated above, some probiotics were found to be effective in reducing blood cholesterol level and one possible mechanism is enhanced fecal bile acids level. As one of important lipid mediators, bile acids have been confirmed to influence a series of NRs including farnesoid X receptor (FXR), pregnane-X-receptor (PXR), constitutive androstane receptor (CAR), peroxisome proliferator-activated receptor (PPAR), liver X receptor (LXR), glucocorticoid receptor (GR) and vitamin D receptor (VDR) [74-76].

Recently, *Lactobacillus acidophilus* ATCC 4356 could act as a liver X receptor (LXR) receptor agonist and inhibited the cellular uptake of micellar cholesterol in Caco-2 cells [77]. A similar study conducted with Yoon et al using a combination of *L. rhamnosus* BFE5264 and *L. plantarum* NR74 also showed a up-regulating the expression of LXR and promotion of cholesterol efflux in Caco-2 cells [78]. This is identical to effect of bile acid sequestrants drug which can also induce an increase of LXR activity in liver[79].

As we all known, PPARs play a key role in inflammation and blood glucose metabolism. Some studies have indicated that probiotic regulated the expression of PPARs in experimental inflammatory model [80]. In fact, PPARs is also a target gene of energy homeostasis and adipogenesis [81]. Linked to ApoE gene transcription, PPAR- $\gamma$  need LXR pathway for regulating adipocyte triglyceride balance [82]. Avella et al reported that dietary

probiotics could modify the expression of PPAR- $\alpha$ , PPAR- $\beta$ , VDR- $\alpha$ , RAR- $\gamma$  and GR in a marine fish, suggesting extensive crosstalk among NRs activated by probiotic [83]. Concerning about NRs and lipid metabolism linked with probiotic, Aronsson et al observed that *L. paracasei* F19 could reduce the fat storage associated with the drastic changes of PPARs [84]. One most recent study by Zhao et al have also demonstrated probiotic *Pediococcus pentosaceus* LP28 could also acted as a PPAR- $\gamma$  agonist concomitantly with the great reduction of triglyceride and cholesterol in obese mice [85].

## 6.2. Toll-like receptors

As important pattern recognition receptors, TLRs participate in distinguishing and recognizing a range of microbial components such as peptidoglycan (TLR2) and LPS (TLR4) to activate immune responses [86]. Up to date, the relationship between TLRs and lipid metabolism is mainly from two aspects. On one hand, TLRs signaling can directly contact and interfere with cholesterol metabolism in macrophages [87]. On the other hand, TLRs signaling (mainly TLR4) are involved in interaction LPS with fatty acid, lipoprotein and organ injury (especially liver and intestine). There is evidence that low dose of LPS can boost *de novo* fatty acid synthesis and lipolysis and lipoprotein production in liver which leading to hepatic hypertriglyceridemia [88]. In mice, moderately higher LPS level could be increased by a fat-enriched diet and contributed to low grade inflammation [34]. In rabbits, high cholesterol intake plus with low dose LPS accelerated the development of atherosclerosis [89]. These two studies are considered as the result of crosstalk between LPS and TLRs leads to intestinal mucosal injury associated with inflammatory response. Besides, foam cell formation in atherosclerosis has been shown to be mediated by TLR2 and 4 and other TLRs such as TLR3, 7, and 9 may also participate in atherosclerosis [90] [91].

TLR4 appears to be tightly linked to high-fat intake, LPS and inflammation. Probiotics are known to reduced LPS-containing gram-negative organisms (such as *E. coli*) in the gut and influx of LPS into circulation [92] [93]. A great number of probiotics are also able to specifically modulate the NF- $\kappa$ B pathway (one of most important inflammatory pathways) in intestinal epithelial cells and macrophages [94].

Due to TLR4 deficiency with anti-obesigenic effects and susceptible to colitis, little information about influence of probiotic on lipid metabolism is obtained in TLR4 knockout model whereas protective effect of probiotic VSL#3 from inflammation was observed in TLR4 knockout mice [95] [96]. With regard to the role of TLR4 in the development of metabolic disorders, Andreassen et al have considered that *L. acidophilus* NCFM may reduce overflow of LPS from the gut to the circulation and downregulate the TLR4 signalling and pro-inflammatory cytokines in human subjects [97].

Immunity homeostasis also have important effect on lipid metabolism. In general, it is well accepted that probiotic bacteria are able to maintain the Th1 and Th2 balance of immunity through regulating pro-inflammatory and anti-inflammatory cytokines [98]. In addition, Agrawal et al documented that TLR2-derived signaling mainly enhance Th2-cytokine release, while TLR4 triggered by LPS stimulates Th1-type responses [99]. Interestingly,



Voltan et al found that *L. crispatus* M247 could increase TLR2 mRNA level and reduced TLR4 mRNA and protein levels in the colonic mucosa, suggesting that *L. crispatus* M247 maintain the Th1 / Th2 homeostasis through TLR2 / TLR4 balance [100].

### 6.3. G protein-coupled receptors

It has been well-established that probiotic bacteria exert beneficial effects on the intestine especially the antimicrobial property by producing organic acids or regulating the organic acid-producing flora [93]. It has been also reported that GPR41 and GPR43 can be activated by short-chain fatty acids (SCFAs) [101]. Thus, it is possible that probiotic may affect GPRs through production of SCFAs in gut. However, this relationship among these have not yet been well-established. Study performed in Gpr41-deficient mice under germ free or conventional environment revealed that presence of microflora was associated with harvest of short-chain fatty acids from the diet which control the degree of adiposity [102].

By our knowledge, only one study has investigated the effect of prebiotic which can specifically increase intestinal probiotic bifidobacteria on GPR43 expression through modified lipid profile [103]. Using a high-fat fed rodent model, the authors studied the effects of prebiotic on changes of microflora, adipose fatty acid profile and receptors expression. High fat diet is able to increase GPR43 and TLR4 expression as well as PPAR- $\gamma$  expression due to oleic acid and  $\alpha$ -linolenic acid production, while prebiotic decreases GPR43 and TLR4 overexpression.

## 7. New mechanisms exploration

In the past recent years, new mechanisms of probiotics on lipid metabolism were proposed. A research by Khedara et al showed lower nitric oxide level has been responsible for hyperlipidemia since endogenous nitric oxide can reduce fatty acid oxidation [104]. Some probiotics had ability to induce nitric oxide synthesis through activation of inducible nitric oxide synthase [105] [106]. Thus, modified NO availability by probiotics play an important role in lipid metabolism.

Moreover, Tanida et al demonstrated that *Lactobacillus paracasei* ST11 could increase adipose tissue lipolysis through enhancing the autonomic nerve activity [107]. In liver, probiotics also exhibited lipid-reducing effects [108]. Ma et al demonstrated that VSL#3 probiotics could increase hepatic NKT cell numbers to attenuate high fat diet-induced steatosis [109]. Huang et al found that *L. acidophilus* 4356 could downregulate the Niemann-Pick C1-Like 1 (NPC1L1) level in the duodenum and jejunum of high-fat fed rats [110]. Another recent study by Aronsson et al revealed a new mechanism of *Lactobacillus paracasei* F19 to reduce fat storage by up-regulating levels of Angiopoietin-Like 4 Protein (ANGPTL4) in mice [84].

Omics technology provide a new insight into the mechanisms of lipid metabolism influenced by probiotics. Lee et al demonstrated that gene *ccpA* (encodes catabolite control protein A) had function in cholesterol reduction in vivo by comparison of cholesterol-reducing strain *L. acidophilus* A4 and the BA9 mutant strain with no lipid-lowering effect

[111]. In addition, six main different expressed proteins involved in these two different strains *in vitro* were identified by proteomic analysis including transcription regulator, FMN-binding protein, major facilitator superfamily permease, glycogen phosphorylase, YknV protein, and fructose/tagatose bisphosphate aldolase.

Microarray analysis of probiotic *L. casei* Zhang effect on liver of high fat diet-fed rats revealed that *L. casei* Zhang administration promote the  $\beta$ -oxidation of fatty acid metabolism through up-regulating five genes expression (*Acs11*, *Hadh*, *Acaa2*, *Acads*, and *gcdH*). Moreover, *L. casei* Zhang could strongly activate expression of glucocorticoid receptor (*NR3C1* gene) which might be related to protect against high-fat induced low grade inflammation [112].

Recently, small intestinal proteomes in weanling piglets that respond differently to probiotic (*Lactobacillus fermentum* I5007) and antibiotic (Aureomycin) supplementation in terms of lipid metabolism have shown that probiotic enhanced mucosal SAR1B abundance could prevent weanling piglets from fat malabsorption. More importantly, high mucosal abundance of EIF4A and KRT10 in probiotic-treated piglets may contribute to improve overall gut integrity, suggesting a potential reduction of LPS influx [113].

## 8. Conclusion

In conclusion, probiotic is a better prevention and treatment strategy for regulating lipid homeostasis with the high prevalence of obesity, burden of amazing overweight and developing chronic diseases in the modern world. Despite the fact that people too pay attention to the thin result to neglect the drug side effect, probiotic can avoid this to achieve a healthy weight. Enhancing bile acids enflux and gut cholesterol assimilation was considered as the classic theory for cholesterol-reducing probiotics. Nevertheless, recent studies focus on antioxidant activity and interaction with lipoprotein, hormones and the whole microbiota. Besides, crosstalk among NRs, GPRs and TLRs by probiotics is new frontiers for mechanical research. However, further investigations are needed to identify various responses related to lipid metabolism influenced by probiotics.

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