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Review 综 述

基于肠道微生态改善的益生菌抗糖尿病作用机制研究进展

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摘　要：2 型糖尿病(type 2 diabetes, T2D)会引起糖脂代谢紊乱，严重危害人类健康，为了防治这一流行病，急需寻找安全和无副作用的抗糖尿病的方法，其中，基于微生物方法治疗 T2D 最常见的策略是补充益生菌，其可通过对不同组织和代谢通路的调节来实现抗糖尿病的功效。益生菌摄入可通过降低慢性低度炎症，减少氧化应激，调节肠道菌群，增加短链脂肪酸含量来达到调控血糖的目的；通过增加胆固醇与胆盐的共沉淀作用，胆固醇在胃肠道内转化为粪甾醇，降低肝脏中 3-羟基-3-甲基戊二酸单酰辅酶 A 还原酶活性，降低胆固醇转运体的表达及对脂肪细胞的调节来达到降脂的目的。本综述系统总结了益生菌抗糖尿病现状和基于肠道微生态的抗糖尿病分子机制，以期为益生菌作为降糖降脂等保健产品的开发利用提供理论依据。

关键词：2 型糖尿病；肠道微生态；益生菌；降血脂；降血糖

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Anti-diabetes mechanism of probiotics based on intestinal microecology

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Abstract: Type 2 diabetes (T2D) is a metabolic disorder characterized by the imbalance in the levels of blood glucose and lipid, threatening human health. Therefore, it is an urgent task to find a safe therapy with no side effects. Probiotics top the microbial therapies against T2D, which exert the anti-diabetes effect by regulating different tissues and metabolic pathways. To be specific, they modulate blood glucose by reducing chronic low-grade inflammation, alleviating oxidative stress, regulating intestinal flora, and increasing the content of short-chain fatty acids. They regulate blood lipids by enhancing the coprecipitation of cholesterol and bile salt and the transformation of cholesterol into fecal sterol in the gastrointestinal tract, reducing the activity of 3-hydroxy-3-methylglutaryl coenzyme A reductase in the liver, lowering the expression of cholesterol transporter, and regulating adipocytes. In this review, we summarized the current status of probiotics against diabetes and the anti-diabetes mechanisms based on intestinal microecology, hoping to lay a theoretical basis for developing hypoglycemic and lipid-lowering products with probiotics.

Keywords: type 2 diabetes; intestinal microecology; probiotics; lowering blood lipid; hypoglycemic

2 型糖尿病(type 2 diabetes, T2D)是严重威胁人类健康的慢性非传染性疾病，已成为全球性的公共健康问题[1]。根据世界卫生组织报道，目前 T2D 影响到全世界约 3.82 亿人，预计到 2035 年将达到 5.92 亿人[2]。另外，研究发现已有 2 型糖尿病的新冠肺炎(corona virus disease 2019, COVID-19)患者的死亡率更高[3]。然而，目前临床上尚无根治 T2D 的方法，一旦确诊，就需要长期使用降糖药物治疗。因此，探寻有效延缓甚至逆转 T2D 进展的新疗法对 T2D 治疗至关重要。

自人体肠道元基因组计划(human intestinal metagenome, MetaHIT)提出，大量研究报道了肠道微生态系统在维持宿主生理方面发挥重要作用，人类的许多重要功能依赖于肠道菌群，其组成、多样性及代谢产物的改变会引发一系列的生理紊乱，增加了发生 T2D 的风险[4]。研究发现，肠道菌群在很大程度上参与宿主的代谢、营养、生理和免疫功能，还产生与宿主代谢相互作用的药理活性信号分子[5-7]，如短链脂肪酸(short chain fatty acids, SCFAs)是由肠道细菌发酵膳食纤维产生的，影响脂肪细胞和胰岛素的敏

感性，从而改善血糖血脂的水平[8]。以上研究表明，肠道菌群组成的变化可导致人类疾病的发生，揭示微生物是治疗 T2D 的潜在重要靶点。

随着对肠道菌群研究的深入，国内外学者研究发现补充益生乳酸菌可以调节菌群紊乱[9-11]。首先，益生菌可以直接到达胃肠道(1 级)，例如直接调节肠道菌群，或改变酶活性。其次，可直接与肠道黏液层和上皮细胞相互作用(2 级)，从而影响肠道屏障功能和黏膜免疫系统。第三，益生菌可以在胃肠道外发挥作用(3 级)，例如对全身免疫系统和其他器官发挥作用，如肝脏和大脑。虽然临床研究正在开展，但大多数益生菌的机理研究都是在体外或借助动物模型进行的，特定益生菌的体外活性不一定与预期的体内临床疗效相关。值得注意的是，每一种益生菌都有其独特的特性。一种益生菌对健康的益处不能推及其他益生菌或多种益生菌的混合。即使是同一物种亲缘关系密切的微生物菌株也可能具有不同的生理效应[12-13]。此外，研究发现益生菌可通过调节肠道菌群来达到治疗某种疾病的作用，特别是肠道特定菌株的选择和肠道微生态系统的改善，是控制能量摄入、降低肥胖和代谢综合征患病率的一种潜在的治疗方法，表明益生菌具有调节血脂和改善胰岛素抵抗的作用[14]。但是目前，益生菌改善肠道微生态发挥降糖降脂作用的机制尚无定论。为此，本实验室通过采集国内(内蒙古、新疆和西藏)及国外(南非、埃及和斯里兰卡)传统发酵食品(发酵乳制品[15]，发酵豆制品[16]和发酵果蔬制品[17])，利用高通量测序联合传统的分离培养技术，构建了包含超过两万株的益生菌菌种资源库及其对应的基因组数据库，并且对其利用多组学联合进行其功能挖掘及机制探讨，目前已挖掘出一批能缓解高血脂[18]、高血糖、高血压、高尿酸血症、抗氧化以及抑菌[19]的益生菌。

本文系统综述了基于肠道微生态的 2 型糖尿病的发生机制，益生菌的降糖降脂作用研究现状，以及对益生菌是如何通过改善肠道微生态进而达到预防和治疗 2 型糖尿病的作用机制进行了归纳和总结，为临床研究提供参考。

1 基于肠道微生态的 2 型糖尿病发生机制

越来越多的证据表明，2 型糖尿病的发生与宿主遗传和环境因素相关，肠道菌群作为一种主要的环境因素，其与 2 型糖尿病的发生与发展有着密切的联系[20]。其中，慢性低度炎症是导致 2 型糖尿病发生的驱动因素，炎症反应的触发因子包括内质网应激、炎症小体激活和 Toll 样受体[21]。

1.1 与糖尿病有关的细菌结构成分

肠道菌群能够通过特定的细胞膜或激活模式识别受体(pattern recognition receptors, PRRs)参与宿主的代谢活动。这些 PRRs 参与识别特定细菌和其他微生物的分子模式，称为病原相关分子模式(pathogen associated molecular patterns, PAMP)，其中 Toll 样受体(Toll-like receptors, TLRs)是研究最多的 PRRs，刺激 TLR4 可导致炎症反应的发生[22]。

研究表明，脂多糖(lipopolysaccharide, LPS)是细菌毒素，正常情况下，脂多糖存在于肠道内，如果发生“肠漏”，或通过与乳糜微粒结合，就会进入血液，进而引发炎症因子的产生，导致疾病的发生发展。2007 年，研究首次发现肠道菌群通过增加血浆脂多糖(LPS) (代谢性内毒素血症)而导致了胰岛素抵抗和 2 型糖尿病的发生[23]。同时，在肥胖和 2 型糖尿病动物模型中，代谢性内毒素血症与肠道菌群组成的改变和肠道通透性的增加有关[24]。一些临床研究报告也指出脂多糖或脂多糖结合蛋白水平的增加与 2 型糖尿病有关[25]。

综上所述，肠道菌群、炎症和代谢紊乱(包括高血糖)之间紧密相关。此外，其他细菌成分，如肽聚糖，其与核苷酸结合的寡聚化域蛋白 2 受体(NOD2)结合，在控制胰岛素抵抗和肥胖方面发挥重要作用。在喂食高脂饮食的 Nod2$^{-/-}$小鼠中，抑制肽聚糖信号通路会引起机体的失调，促进黏膜中的细菌粘附和肝脏中的细菌积聚，从而导致全身炎症、胰岛素抵抗和肥胖[26]。类似地，TLR5-缺陷小鼠对肠道黏膜中的细菌鞭毛蛋白失去反应，表现出轻度丧失血糖控制的能力，这可能是由胰岛素抵抗所驱动的。

1.2 细菌代谢产物和葡萄糖稳态

肠道菌群产生的代谢物也可能与胰岛素抵抗和 2 型糖尿病的发生或调控相关。一些代谢物可以通过调节肠道内分泌功能，影响葡萄糖稳态。

研究表明，SCFAs 是肠道菌群产生的影响宿主代谢的最广泛研究的代谢物之一。这些分子是由肠道菌群通过不同的代谢途径对特定的低聚糖或多糖(即不可消化的碳水化合物)进行发酵产生的[27]。SCFAs 对胰岛素敏感性和能量代谢有着深远的影响，能够改变参与葡萄糖代谢、肠道屏障功能和能量稳态的几种肠肽的水平[28]。例如，丁酸和丙酸可以抑制高脂饮食诱导的肥胖小鼠的体重增加，醋酸可以减少健康小鼠的食物摄入量[29]。研究表明 SCFAs 的作用是由 G 蛋白偶联受体家族的成员介导的，该家族包括 G 蛋白偶联受体(G protein coupled receptor, GPR) 43 和 41 (分别为 GPR43 和 GPR41)[30]。SCFAs 与 GPR43 和 GPR41 结合后，血浆胰高血糖素样肽-1 (glucagon like peptide1, GLP-1)和酪酪肽(peptide YY, PYY)水平升高，调节葡萄糖稳态，食欲下降[31]。研究表明，丁酸可通过 cAMP 依赖机制激活肠内糖异生相关基因的表达，而丙酸可通过参与 GPR41 的肠脑神经回路促进肠内糖异生基因的表达[32]。

最近大量数据表明，肠道菌群从色氨酸中产生的代谢物吲哚也可能促进肠内内分泌细胞分泌 GLP-1[33]。Chimerel 等[34]发现吲哚可以抑制电压门控的 K^+通道，从而改变 L 细胞的动作电位特性，导致 Ca^{2+}进入，从而促进 GLP-1 的分泌[34]。更重要的是，研究发现，在较长时间的刺激下，吲哚作为一种线粒体代谢抑制剂，导致细胞内 ATP 浓度降低，对 ATP 敏感的 K^+ (K_{ATP})通道打开，从而使质膜超极化，减缓 GLP-1 释放[34]。有趣的是，研究发现，在那些喝酒的具有较高肠道通透性和较高代谢内毒素血症的人体内吲哚和 3-甲基吲哚的含量较低[35]。综上所述，吲哚可促进 GLP-1 的分泌，增强肠道屏障功能，且由 L 细胞共同分泌的 GLP-1 与 GLP-2 受吲哚的控制[36]。

研究表明胆汁酸不仅在膳食脂质消化中起重要作用，而且在能量、葡萄糖和脂质代谢中起信号分子的作用[37]。最近的一项研究表明，初级共轭胆汁酸(牛磺胆酸)水平的增加可作为促进 GLP-1 分泌和宿主葡萄糖稳态的关键调节器[38]。G 蛋白胆汁酸偶联受体 5 (takeda G-protein-coupled receptor 5, TGR5)主要定殖于肠内分泌细胞，最初通过肠道菌群由次生胆汁酸激活产生(胆石酸和脱氧胆酸)[39]。研究发现表达硫酸盐还原酶的细菌可以产生 H_2S，它可以抑制 TGR5 的活化，对 GLP-1 和 PYY 的产生具有抑制作用[39]。

因此，虽然肠道菌群对能量代谢的影响是多因素的，但近年来的研究重点是涉及菌群或特定代谢产物，为基于细菌来源或其代谢产物寻找新的治疗靶点提供理论基础。

2 基于肠道微生态改善的益生菌降糖降脂作用

2.1 益生菌降糖作用

近年来，益生菌的保健作用越来越受到人

们的关注。益生菌是活的微生物，当摄入充足的数量时，能给予宿主健康作用，一直被认为是具有改善代谢紊乱的功能。

在动物模型中(表 1)，益生菌可以通过改善炎症降低血糖，防止胰岛 β 细胞的损坏[50]。乳酸菌和双歧杆菌已经被证明可以改善葡萄糖耐受和胰岛素抵抗[51]，且双歧杆菌(*Bifidobacterium* spp.)可以改善高脂饮食诱导的小鼠的葡萄糖稳态[52]。研究表明，在用于治疗 2 型糖尿病的细菌中，嗜黏液菌(*Akkermansia muciniphila* MucT) ATTC BAA-835 被证明对葡萄糖代谢具有直接有益作用[40]。首先，嗜黏液菌可以通过阻止 G6pc (葡萄糖-6-磷酸酶) mRNA 的表达来抑制高脂饮食诱导的 2 型糖尿病小鼠空腹血糖的升高。

在人体研究中(表 2)，益生菌干预研究已经揭示了其对葡萄糖代谢的积极作用。其中，乳

表 1　益生菌干预抗糖尿病动物模型研究

Table 1　Intervention of probiotics in animal models of diabetes mellitus

Probiotic type	Dosage	Animal model	Duration	Outcome indexes	Reference
Akkermansia muciniphila	1×10^{10} CFU/mL	STZ induced SD rats	4 weeks	HDL-C↑ Liver glycogen, plasminogen activator inhibitor-1, TNF-α, lipopolysaccharide, malondialdehyde, glucagon-like peptide-1↓	[40]
Lactobacillus plantarum HAC01	1×10^{9} CFU/mL	STZ induced C67BL/6J	10 weeks	Insulin-positive beta cell area of the islet↑ FBS, HbA1c, OGTT and HOMA-IR↓	[41]
Lactobacillus sakei Probio65 *Lactobacillus plantarum* Probio-093	1×10^{8} CFU/mL	STZ induced C67BL/6J	8 weeks	— Blood glucose, α glucosidase and α amylase↓	[42]
Lactobacillus gasseri *Lactobacillus johnsonii*	1×10^{9} CFU/mL	Western diet induced C57BL/6J	8 weeks	Serum glutathione and bilirubin↑ Blood glucose, blood lipids↓	[43]
Heat-Inactivated *Lactobacillus reuteri* GMNL-263	1×10^{9} CFU/mL	STZ induced Wistar rats	4 weeks	Activate the IGF1R cell survival pathway↑ —	[44]
Lactobacillus fermentum MCC2759 and MCC2760	1×10^{9} CFU/mL	STZ induced Wistar rats	12 weeks	OGTT, Insulin, IL-10, ZO-1, GLP-1↓ —	[45]
Lactobacillus plantarum SCS2	—	KM Mice	12 weeks	Insulin, antioxidant enzyme↑ HbA1c, ROS	[46]
Lactobacillus fermentum TKSN041	—	STZ induced Wistar rats	—	FBS, TC, TG, LDL-C, IL-1β, IL-6, IL-10↓	[47]
Lactobacillus plantarum 9-41-A, *Lactobacillus fermentum* M1-16	2×10^{9} CFU/mL	SD rats induced by high fat diet	6 weeks	TC, TG, LDL-C↓	[48]
Lactobacillus plantarum LS/07 *Lactobacillus plantarum* LP96	1.5×10^{9} CFU/mL	SD rats induced by high fat diet	10 weeks	TC, TG, LDL-C↓	[49]

FBS: Fasting blood sugar; HbA1c: Glycated hemoglobin; HOMA-IR: Homeostasis model assessment of insulin resistance; TC: Total cholesterol; TG: Triglycerides; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; TNF-α: Tumor necrosis factor α; ROS: Reactive oxygen species; —: Not reported.

表 2　益生菌干预抗糖尿病临床研究

Table 2　Clinical study of probiotics in the treatment of diabetes

Probiotic type	Dosage	Animal model	duration	Outcome indexes	Reference
L. paracasei HII01	50×10^9 CFU/d	T2D	12 weeks	FBS, LPS, TNF-α, IL-6 and hsCRP↓	[53]
L. salivarius UBLS22, *L. casei* UBLC42, *L. plantarum* UBLP40, *L. acidophilus* UBLA34, *B. breve* UBBr01, and *B. coagulans*	3.0×10^{10} CFU/mL	T2D	12 weeks	FBS/HbA1c/insulin/HOMA-IR/TC/TG/LDL-C↓ HDL-C↑ FBS/HbA1c/insulin/HOMA-IR/TC/TG/LDL-C↓ HDL-C↑	[54]
Lactobacillus casei	10^8 CFU/mL	T2D	8 weeks	FBS/HbA1c/insulin/HOMA-IR↓	[55]
Lacidophilus+*L. casei*+ *L. rhamnosus*+ *L. bulgaricus*+*B. breve*+ *B. longum*+*Streptococcus thermophilus*	3.9×10^{10} CFU/mL	T2D	6 weeks	FBS/insulin/ HOMA-IR/TC/TG/LDL-C↓ HDL-C↑	[56]
Lactobacillus+ *Lactococcus*+ *Bifidobacterium*+ *Propionibacterium*+ *Acetobacter*	10 g/d	T2D	8 weeks	FBS/HbA1c/insulin/TNF-α↓	[57]
B. bifdum W23, *B. lactis* W52, *L. acidophilus* W37, *L. brevis* W63, *L. casei* W56, *L. salivarius* W24, *L. lactis* W19 and *L. lactis* W58	5×10^9 CFU/d	T2D	12 weeks	Glucose/insulin/HOMA-IR/TC/TG/LDL-C↓ HDL-C↑	[58]
L. acidophilus, *L. casei*, *B. bifdum*	2×10^9 CFU/mL	T2D	12 weeks	FBS/insulin/HOMA-IR/TC/TG/LDL-C↓ HDL-C↑	[59]
L. acidophilus, *L. casei*, *L. lactis*, *Bifdobacterium*, *Actinobacteria*, *B. bifdum*, *B. longum* and *B. infantis*	10^{10} CFU/mL	T2D	12 weeks	FBS/HbA1c/insulin/HOMA-IR/TC/TG/LDL-C/CRP↓ HDL-C↑	[60]
L. reuteri DSM 17938	10^{10} CFU/d	T2D	12 weeks	FBS/HbA1c/insulin/TC/TG/LDL-C/CRP↓ HDL-C↑	[61]

FBS: Fasting blood sugar; HbA1c: Glycated hemoglobin; HOMA-IR: Homeostasis model assessment of insulin resistance; TC: Total cholesterol; TG: Triglycerides; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; TNF-α: Tumor necrosis factor α; CRP: C-reactive protein.

酸菌和双歧杆菌的降血糖作用已在多项人体研究中得到了证实[62-64]。例如，在一项对 60 名超重健康印度人进行的 6 周随机安慰剂对照研究中，VSL#3 益生菌组合降低了全身葡萄糖和胰岛素水平[65]。研究表明，益生菌的摄入可预防或降低糖尿病或非糖尿病患者的血糖升高[66]。Akbari 等[67]研究发现，补充益生菌可显著降低胰岛素抵抗、空腹血糖(fasting blood glucose, FBG)及糖化血红蛋白(glycosylated hemoglobin, HbA1c)水平。Ruan 等[68]报道称，益生菌的摄入显著降低空腹血糖、空腹血浆胰岛素和胰岛素抵抗指数(homeostatic model assessment insulin resistance index, HOMA-IR)水平，且混合益生菌补充剂可以减少肝脏转氨酶、肿瘤坏死因子 TNF-α 和胰岛素抵抗水平[69]。

本团队在前期研究发现植物乳杆菌 84-3 可

显著降低 2 型糖尿病大鼠空腹血糖、总胆固醇和甘油三酯的水平。目前，益生菌改善 2 型糖尿病可能是由菌株特异性产生的，同一物种的不同菌株可能产生不同的效果。且在大多数情况下，多菌株益生菌比单一菌株更有效，这可能是由于多菌株产物中不同菌株之间的协同作用[70]，此外，益生菌抗糖尿病作用的证据还有待证实。因此，益生菌的摄入对肠道菌群组成的变化以及对宿主疾病与健康的影响作用复杂，有待于进一步研究。

2.2 益生菌降脂作用

脂肪组织是人体重要的代谢调节器官[71]，肠道菌群通过与脂肪组织的相互作用促进宿主代谢[72]。最近的一项研究表明，与常规饲养的小鼠相比，无菌饲养的小鼠褐色脂肪组织的分解增加，脂肪生成减少，这表明肠道菌群刺激褐色脂肪组织的脂质代谢[73]。

近年来，益生菌对脂质代谢的影响引起了越来越多的关注。大量研究发现添加益生菌菌株可以降低大鼠的总胆固醇(total cholesterol, TC)和甘油三酯(total triglycerides, TG)浓度[48,74]。Salaj 等[49]报道称植物乳杆菌可降低高脂饮食大鼠的 TC 和低密度脂蛋白胆固醇(low-density lipoprotein cholesterol, LDL-C)。Kim 等[75]表明，发酵豆浆中柠檬明串珠菌(*Leuconostoc citreum*)和植物乳杆菌(*Lactobacillus plantarum*)可降低大鼠 LDL-C 水平，抑制 3T3-L1 脂肪细胞分化。

而在人体研究中，对于益生菌对脂质谱的影响尚未达成共识。研究表明，每天饮用含嗜酸乳杆菌 L1 的牛奶 200 mL，3 周后可以降低高胆固醇脂血症患者的 TC 水平。此外，Fuentes 等[76]报道称，高胆固醇脂血症患者每天服用含有 1.2×10^9 CFU/mL 的植物乳杆菌，12 周后可显著降低 TC 和 LDL-C 浓度。益生菌干预还可以通过调节肠道菌群组成的变化，显著降低体重、体脂百分比，改善胰岛素敏感性、低度慢性炎症和脂质代谢水平[77]。对 13 项随机对照试验的荟萃分析表明，益生菌的摄入能够有效降低 TC 和 LDL-C 水平。Choi 等[78]研究表明，利用双歧杆菌对异黄酮苷元进行发酵，可有效抑制脂质吸收。据报道，食用加氏乳酸菌 SBT2055 可降低腹部脂肪、体重、体重指数和腰臀围[79]。此外，补充 *Lactis* 420 可减少肠杆菌科革兰氏阴性菌的易位，使脂肪组织炎症正常化[80]。然而，Hove 等[81]报道，2 型糖尿病患者摄入用瑞士乳杆菌(*L. helveticus*)发酵的牛奶，12 周后对血脂没有影响。

本团队在前期研究发现屎肠球菌 132 和副干酪乳杆菌 201 均显著降低了大鼠血清总胆固醇、低密度脂蛋白胆固醇、甘油三酯、肝脏总胆固醇和甘油三酯水平，升高了粪便总胆固醇、总胆汁酸水平。因此，对于益生菌对动物和人体脂质代谢的影响有待于进一步研究。

3 基于肠道微生态改善的益生菌降糖降脂机制

研究表明，肠道菌群在维持宿主体内稳态以及糖尿病的发病机制中起着关键作用[52]。益生菌缓解及治疗糖尿病主要作用机制包括调节免疫反应和改善肠屏障，改变肠道菌群，增加短链脂肪酸含量，降低氧化应激及抗氧化作用，抑制与葡萄糖吸收相关的酶的活力，增加胆盐水解酶活性和吸收或吸附胆固醇，并且各个机制是相互关联作用共同达到抗糖尿病的功效(图 1)。

3.1 调节免疫反应和改善肠屏障

众所周知，葡萄糖稳态的改变与肠道微生物源性脂多糖或内毒素促进的低度慢性炎症呈负相关[82]，且脂多糖对小鼠肝脏胰岛素抵抗有

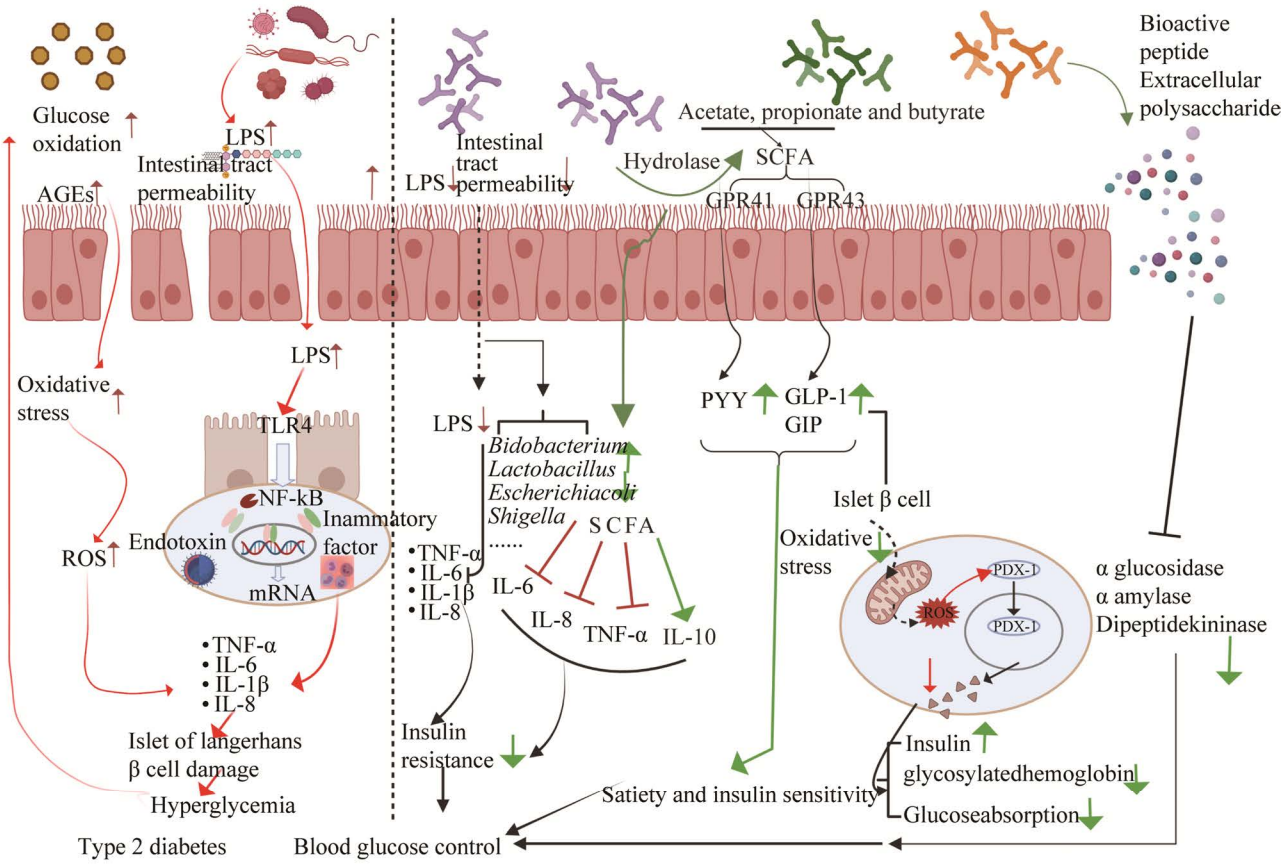

图 1　益生菌降糖的主要作用机制[52,82,90,97]

Figure 1　The main mechanism of hypoglycemic action of probiotics[52,82,90,97].

影响。研究发现，益生菌可以降低肠道内毒素水平，且双歧杆菌能够降低脂多糖水平[83]。在动物模型中，口服双歧杆菌(婴儿双歧杆菌，两歧双歧杆菌)可降低肠道内毒素浓度，提高葡萄糖耐受性[84]，缓解胰岛素抵抗，从而调控血糖。乳酸菌可增加其在肠道上皮内的定殖，以及对葡萄糖的利用，从而减少肠道对葡萄糖的吸收[85]。本团队在前期研究发现植物乳杆菌 84-3 显著降低了糖尿病大鼠的促炎因子水平(C 反应蛋白、内毒素、TNF-α 和白介素-6)；同时，研究也发现长双歧杆菌 070103 可增加小鼠肠道组织 ZO-1 和 Claudin-1 的水平。因此，调节代谢内毒素水平(血浆脂多糖水平较高)和肠道通透性被认为是降血糖作用的靶点。

3.2　改变肠道菌群

目前，益生菌改善肠道菌群和宿主代谢在糖尿病等代谢疾病中已被广泛研究[42]。益生菌混合制剂 VSL#3，已经被证明可以通过改变肠道菌群的组成来抑制体重增加和胰岛素抵抗[86]。Park 等[87]研究发现，用弯曲乳酸杆菌 HY7601 和植物乳杆菌 KY1032 处理后，高脂饮食(high fat diet, HFD)喂养的肥胖小鼠体重增加减少，肠道菌群也发生了变化。Tsai 等[88]研究发现喂养植物乳杆菌 NTU101 6–9 周后，与对照组相比，小鼠粪便中产气荚膜梭菌(*Clostridium perfringens*)数量明显减少，双歧杆菌和乳酸菌的数量明显增加。在最近的一项研究中，小鼠被喂以低脂或高脂饮食，并用万古霉素唾液乳杆菌 UCC118

Bac+或细菌素阴性株唾液乳杆菌治疗，研究发现，产万古霉素和细菌素的益生菌都改变了饮食诱导肥胖小鼠的肠道菌群，然而，与非产细菌素对照组相比，只有产细菌素的益生菌导致拟杆菌门(*Bacteroidetes*)和变形菌门(*Proteobacteria*)数量增加，放线菌门(*Actinobacteria*)数量减少[89]。本团队在前期通过对不同乳酸菌进行体外模拟人体粪便发酵和体内大鼠动物实验，研究发现，在体外，植物乳杆菌 84-3 可促进乳杆菌属和布氏杆菌属等短链脂肪酸产生菌的生长；在体内可增加粪杆菌属、副拟杆菌属、另枝菌属和厌氧原体属等短链脂肪酸产生菌，降低有害菌大肠埃希菌和志贺氏菌的丰度；另外，我们研究发现长双歧杆菌 070103 显著降低厚壁菌门与拟杆菌门的比值，增加双歧杆菌的丰度，因此，我们推测植物乳杆菌 84-3 和长双歧杆菌 070103 可能是通过改变肠道菌群的组成来达到降糖降脂的目的。以上结果表明，益生菌能够通过改善肠道菌群的组成，增加有益菌，抑制有害菌，对糖尿病等代谢性疾病的发生和发展具有一定的预防作用。

3.3 增加短链脂肪酸含量

肠道菌群产生与宿主代谢相互作用的药理活性信号分子，如短链脂肪酸是由肠道细菌发酵膳食纤维产生的，包括丁酸、醋酸和丙酸等。这些短链脂肪酸不仅是一种重要的能量来源，而且在调节能量摄入方面发挥着重要作用[90]。它们与 G 蛋白偶联受体(G protein-coupled receptors, GPCRs)的相互作用影响脂肪细胞和周围器官的胰岛素敏感性[91]。益生菌对动物炎症通路、体重增加和葡萄糖代谢的影响很大程度上归因于短链脂肪酸(SCFA)的产生[92]。SCFAs 与结肠免疫细胞中的 GPCRs (如 GPR41 和 GPR43)相互作用，促进结肠上皮中特定趋化因子的表达[93]。在白细胞中，SCFAs 抑制 NF-κB 并影响促炎因子的产生，如 IL-6、IL-8 和 TNF-α[94]。SCFAs 通过增加上皮细胞中酪酪肽(peptide YY, PYY)和原胰高血糖素的合成，抑制瘦素等神经内分泌因子的表达，增强饱腹感[95]。其他研究表明益生菌对肠道健康和炎症的影响也受肠内分泌 L 细胞中胰高血糖素样肽(GLP-1 和 GLP-2)水平的介导[96]，增加胰岛素的敏感性，进而降低 2 型糖尿病的血糖水平。本团队在前期研究发现，在体外，植物乳杆菌 84-3 可显著增加乙酸、丙酸和丁酸的产生，同时，在体内可显著增加 GLP-1 的含量，增加大鼠粪便中乙酸、丙酸和丁酸的含量，因此，我们推测植物乳杆菌 84-3 可能是通过增加短链脂肪酸的产生来达到降糖降脂的目的。

3.4 降低氧化应激及抗氧化作用

研究表明，氧化损伤和抗氧化能力在糖尿病的发病机制中发挥很重要的角色[97]，益生菌的抗氧化活性已在以往的实验中得到证实。Zhang 等[98]报道称益生菌对葡萄糖代谢的影响可以通过降低氧化应激来发挥作用。本团队在前期研究发现屎肠球菌 132 和副干酪乳杆菌 201 可显著降低大鼠肝脏谷丙转氨酶、谷草转氨酶水平。Yadav 等[85,99]研究表明益生菌通过抑制脂质过氧化，提高糖尿病大鼠谷胱甘肽、超氧化物歧化酶、过氧化氢酶和谷胱甘肽过氧化物酶的抗氧化含量，从而降低氧化损伤[100]，增加胰岛素的分泌，降低糖化血红蛋白水平，降低肠道对葡萄糖的吸收，从而使血糖恢复至正常水平，缓解 2 型糖尿病的发展。

3.5 抑制与葡萄糖吸收相关酶的活力

益生菌可通过产生生物活性肽和胞外多糖来抑制引起加快肠道对葡萄糖吸收的 α 葡萄糖苷酶、二肽激肽酶和淀粉酶 α 的含量，即益生菌的降糖作用可能是由于这些细菌的代谢产物影响生物信号通路，调节泛素化酶和蛋白酶基因，改

变自主神经活性[101-103]，从而抑制或延迟肠道对葡萄糖的吸收。本团队在前期研究发现植物乳杆菌 84-3 可降低肝脏二肽激肽酶 DPP-4 和小肠 α 葡萄糖苷酶的酶活，且发现长双歧杆菌 070103 可显著激活葡萄糖激酶的表达。由于糖尿病是一种多因素的疾病，益生菌抗糖尿病作用的确切机制尚未完全建立，需要进一步研究完善。

3.6 增加胆盐水解酶活性和吸收或吸附胆固醇

研究表明，益生菌降低胆固醇的可能机制有以下几种(图 2)：(1) 部分细菌分泌胆汁盐水解酶，导致粪便中胆汁酸排泄量增加[104]，从而降低胆固醇水平；(2) 胆固醇与共轭胆盐的共沉淀作用，减少可吸收的胆固醇量[105-106]；(3) 胆固醇可与细菌细胞表面[107]结合，或与细菌细胞膜结合[108]；(4) 由乳酸菌产生的胆固醇还原酶转化为粪甾醇[109]，然后通过粪便排泄；(5) 降低胆固醇转运蛋白(niemann pick C1 like 1, NPC1L)的表达，从而抑制肠道对胆固醇的吸收[110]；(6) 益生菌选择性发酵难消化的食物产生的短链脂肪酸可降低血浆胆固醇水平[111]；(7) 益生菌可调节脂肪细胞组织中 PPARγ 的表达，促进脂联素的生成和白色脂肪细胞的凋亡；另外，益生菌摄入可增加粪便含水量，具有通便的潜力，刺激肠道蠕动，从而缩短胆固醇在肠道吸收的转运时间[56]。

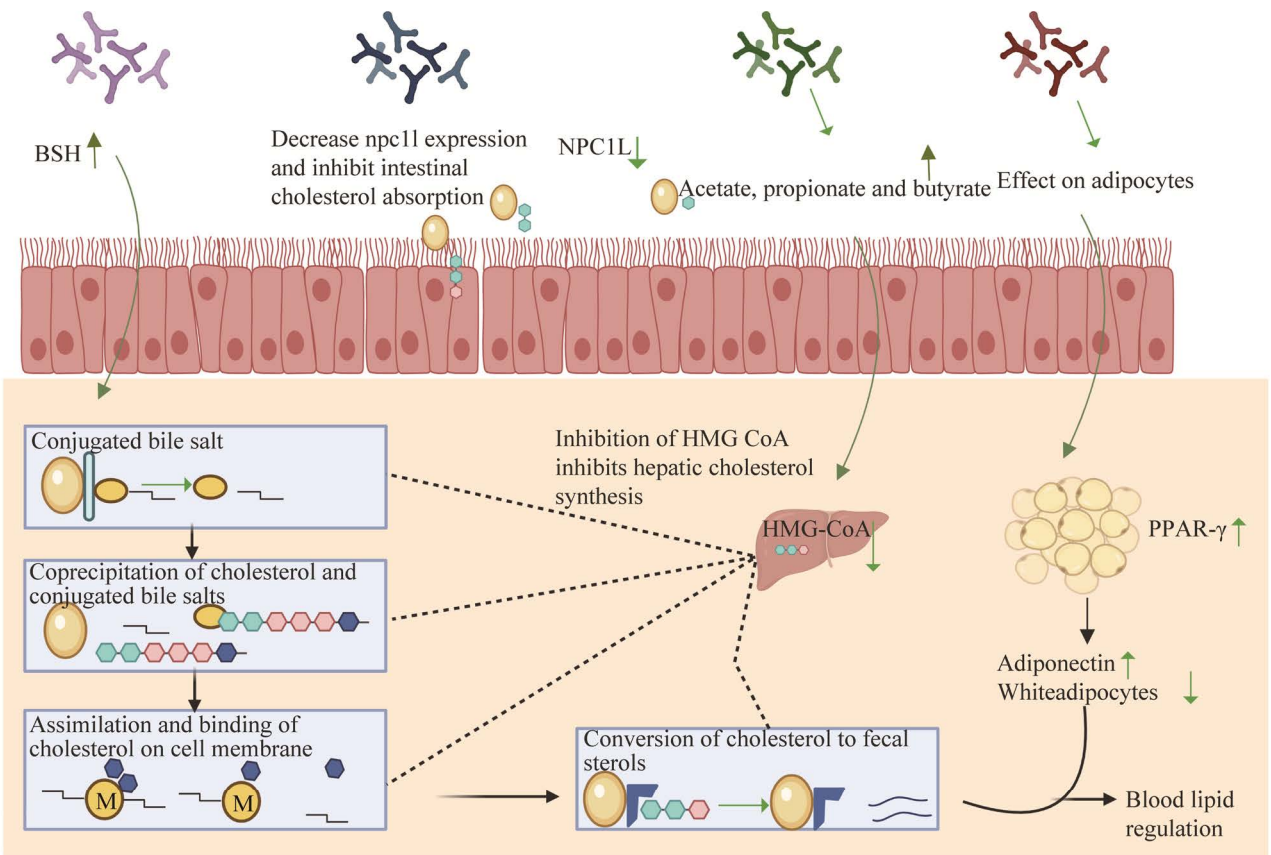

图 2　益生菌降脂的主要作用机制[104-111]

Figure 2　The main mechanism of probiotics reducing lipid[104-111].

本团队在前期研究发现植物乳杆菌 84-3 显著增加了大鼠粪便中短链脂肪酸的产生，屎肠球菌 132 和副干酪乳杆菌 201 显著增加了乙酸和丙酸的含量，且屎肠球菌 132 和副干酪乳杆菌 201 显著增加粪便中胆固醇的含量，因此，我们推测植物乳杆菌 84-3、屎肠球菌 132 和副干酪乳杆菌 201 可能是通过多条通路来达到降脂的目的，后续有待于进一步研究。

4 结论

综上所述，肠道菌群作为治疗 2 型糖尿病的一个潜在的干预新靶标，可能通过多种机制参与能量代谢的调节，即通过细菌结构成分、细菌代谢产物来调控 2 型糖尿病的发生。而通过摄入具有降糖降脂的益生菌，可降低慢性低度炎症，调节肠道菌群，增加肠道代谢产物短链脂肪酸的产量，减少氧化应激，增加细菌性生物活性肽/胞外多糖，进而抑制与葡萄糖吸收相关的酶，从而实现调控血糖的目的；通过增加分泌胆盐水解酶活性，增加胆固醇与胆盐的共沉淀作用，胆固醇在胃肠道内转化为粪甾醇，降低肝脏中 3-羟基-3-甲基戊二酸单酰辅酶 A 还原酶活性，降低胆固醇转运体的表达及对脂肪细胞的调节来达到降脂的目的。

随着科学研究的不断深入，研究者们将进一步探索益生菌在 2 型糖尿病患者中的降糖降脂的应用价值。近年来，益生菌在降糖降脂方面的作用机制还不是完全清楚，自身也存在一定的缺陷，如摄入益生菌以后其在肠道中能否定殖，还是只是“穿肠而出”，以及在使用抗生素后再次摄入益生菌延长了肠道菌群恢复的时间，对于益生菌的保健功效今后必须加强研究，使其能够更好地发挥作用为人类造福。另外，益生菌对于糖尿病的有益作用虽然已经在细胞水平、动物实验和临床上被探究，其产业化应用仍需要进一步开发。因此，在目前的基础上，我们还需要通过应用宏组学技术及其联合应用深入探索益生菌对 2 型糖尿病的降糖降脂机制，开发更多新型微生物制剂来达到预防和治疗 2 型糖尿病的目的。

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