益生菌: 代谢性疾病调控新靶向

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摘要 代谢综合征是一种代谢异常性疾病, 近年来随着其发病率逐年升高, 严重影响个人的生活质量, 成为世界性公共卫生问题. 代谢紊乱性疾病的流行与近几十年来膳食中大量营养素摄入量的动态变化和生活方式的改变有关. 肠道微生物群失调被认为是代谢紊乱发生的影响因素之一, 如何通过调节肠道菌群改善代谢综合征已成为目前的研究热点. 益生菌作为一种广泛应用于食品中对人类健康有益的活的微生物, 通过调节肠道微生物群起到改善血糖、调节血脂和降低胰岛素抵抗及胆固醇的作用. 本文综述了益生菌在肥胖、2型糖尿病及高血压等代谢性疾病方面的具体作用效果及相关机制, 提出在其应用过程中将面临的问题, 为益生菌在未来的产业发展及应用提供新的思路.

关键词 益生菌, 代谢性疾病, 肠道菌群, 作用机制

代谢性疾病包括肥胖、2型糖尿病(type 2 diabetes mellitus, T2DM)、高血脂、高血压和心血管疾病等, 近年来在各国发病率不断攀升, 已经成为一个严重的社会问题. 与健康人相比, 代谢性疾病患者病死率是前者的2倍, 心脏病和卒中的发生率也提高了3倍^[1]. 因此, 有必要深入了解代谢性疾病背后的诸多成因, 饮食习惯、运动量、睡眠质量、遗传因素和肠道微生物群等都与代谢性疾病密切相关^[2]. 肠道微生物群是由数千种微生物组成的共生群落. 随着测序技术和生物信息学的发展, 研究者能够从动物和人类样品中提取DNA完成测序和分析, 从而清晰地揭示出宿主的微生物群变化^[3]. 研究已证明, 肠道微生物群具有重要的生理功能, 可直接影响宿主的代谢、肠道黏膜屏障的发育以及局部和全身的免疫功能^[4]. 最近, 科学界认为, 肠道菌群组成改变是代谢性疾病发展最可能的因素之一^[5]. 基于

此, 针对肠道菌群采取有效的预防和治疗策略来降低代谢性疾病的发生率和病死率是十分重要的. 已有研究发现, 二甲双胍、益生菌、益生元以及一些传统中药(小檗碱、葛根芩连汤)等通过调节肠道菌群, 发挥降低体重、减轻胰岛素抵抗的积极作用, 但有研究也发现, 小檗碱和二甲双胍等会引起胃肠不适, 具有一定的副作用^[6~9]. 而以益生菌为主流的膳食疗法安全性高, 对机体副作用小, 正越来越多的引起人们广泛关注.

益生菌是指摄入足够量会对宿主健康产生有益作用的活的微生物^[10]. 大量研究表明, 益生菌可通过平衡体内细菌的数量和促进良好的新陈代谢来创造健康的肠道环境, 被认为是预防和治疗代谢性疾病的一种有前途的工具^[4,11]. 然而, 目前大多数研究都集中关注益生菌与代谢性疾病之间的相关性, 对二者因果关系探讨甚少^[12]. 究其原因, 不仅是各类代谢性疾病病因复

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杂,而且益生菌存在菌株特异性,对不同人群、不同代谢性疾病作用机制等也不尽相同^[12,13]。鉴于以上所述,本综述旨在概述益生菌在预防和治疗代谢性疾病中的主要作用,指出它们在临床应用中的最新进展以及迄今为止所述的作用机制,并展望了未来相关研究的方向。

1 益生菌与代谢性疾病

1.1 传统益生菌在代谢性疾病中的应用

益生菌的使用历史悠久,最早可追溯到公元前3000年。然而,它们的重要性直到最近几十年才被逐渐发现^[14]。市场上常见的益生菌是乳酸杆菌属(*Lactobacillus*)和双歧杆菌属(*Bifidobacterium*),而芽孢杆菌属(*Bacillus*)、肠球菌属(*Enterococcus*)和酵母菌(*Saccharomyces*)相对较少。由于这些微生物具有悠久的历史和安全保证,常被归为传统益生菌^[15]。有研究表明,益生菌可促使它们暂时或永久地与肠道微生物群结合,除了调节肠道微生物群落组成和多样性外,还通过影响患者体重和脂肪含量、葡萄糖稳态、减少炎症水平和脂肪肝变性而发挥改善代谢性疾病作用^[16,17]。一些菌株已被证实可以改善高血压、肥胖、炎症、葡萄糖稳态紊乱和血脂水平异常等代谢疾病,其中两歧双歧杆菌(*Bifidobacterium bifidum*)、干酪乳杆菌(*Lactobacillus casei*)、植物乳杆菌(*Lactobacillus plantarum*)和嗜酸乳杆菌(*Lactobacillus acidophilus*)等在这些疾病中发挥着关键作用^[18-21]。

1.2 下一代益生菌在代谢性疾病中的应用

一般来说,双歧杆菌、乳酸菌等传统益生菌大多数具有生物安全性,对疾病具有改善作用,但其不能针对特定的疾病。基于此,需要挖掘与鉴定疾病特异性的下一代益生菌(next generation probiotics, NGP)^[22]。随着分子生物学技术的突破,新的测序技术具有高通量、高分辨率和低成本特点,加速了新一代益生菌的发现^[23]。基于微生物组分析新发现的细菌,可称为NGP,具体是指各类尚未得到应用的肠道非典型益生菌以及基因改良微生物^[15],主要包括古氏副拟杆菌(*Parabacteroides goldsteinii*)、粪便普雷沃氏菌(*Prevotella copri*)、脆弱拟杆菌(*Bacteroides fragilis*)、嗜黏蛋白阿克曼氏菌(*Akkermansia muciniphila*)和普氏栖粪杆菌(*Faecalibacterium prausnitzii*)等^[24]。*Akkermansia muciniphila*

是一种在黏膜层定居的肠道共生体,被认为是很有前途的益生菌候选物,在大多数动物实验和临床研究中,一致发现*Akkermansia muciniphila*在改善宿主代谢方面有积极作用,其丰度普遍与代谢紊乱呈负相关,其中*Akkermansia muciniphila*的数量降低导致空腹血糖、皮下脂肪细胞直径和腰臀比等指标的升高^[25]。研究发现,粪便普雷沃氏菌具有调控胰岛素抵抗的作用,可能是通过胆汁酸代谢和对法尼醇X受体通路干预实现的,古氏副拟杆菌和多形拟杆菌(*Bacteroides thetaiotaomicron*)能减轻肥胖和胰岛素抵抗,脆弱拟杆菌具有减少炎症和抗癌作用^[24]。NGP对代谢性疾病具有积极作用,然而微生物组是一个复杂的生态系统,特定的菌株和宿主之间的相互作用及潜在机制有待揭示。未来的研究需要侧重于临床试验以及益生菌的作用机制,为不同的益生菌菌株提供更多的基础研究数据。通过前沿的高通量测序技术和生物信息学技术平台筛选和分离NGP,对其进行严格的功能验证。总体而言,下一代益生菌对代谢性疾病的干预效果仍需进一步探索。

2 益生菌对常见代谢性疾病的影响

2.1 益生菌对肥胖症的影响

肥胖是指体内异常或过量的脂肪积累,可能会损害健康状况^[26]。饮食习惯的改变和高热量食物的增加使超重和肥胖成为这个时代最严重的健康问题^[27]。肥胖的发生与遗传因素、新陈代谢、激素水平和环境条件有关。最近的动物和人类研究表明,肠道菌群会改变以能量平衡为中心的多种代谢途径,从而影响肥胖的发生和发展^[28]。近年来,益生菌和益生元已被证明通过调节胃肠道菌群影响食物的摄入量、食欲、体重和机体代谢功能^[29]。基于此,使用益生菌(如乳酸杆菌属、双歧杆菌属、链球菌属(*Streptococcus*)和肠球菌等)和益生元(一些低聚糖)选择性调节宿主的肠道菌群,被认为是控制肥胖的重要手段。一些属于乳酸杆菌属(干酪乳杆菌、加氏乳杆菌(*Lactobacillus gasseri*)、鼠李糖乳杆菌(*Lactobacillus rhamnosus*)和植物乳杆菌等)和双歧杆菌属(婴儿双歧杆菌(*Bifidobacterium infantis*)、地衣芽孢杆菌(*Bacillus licheniformis*)、长双歧杆菌(*Bifidobacterium longum*)和短双歧杆菌(*Bifidobacterium breve*)B3等)的特定菌株,已成功地应用于治疗肥胖动物模型。与安慰剂组相比,益生菌干预后显著降低动物的体重和脂肪量^[28,30,31](表1)。有趣的是,研究发现,使

表 1 益生菌对代谢性疾病改善作用

Table 1 Ameliorative effects of probiotic on metabolic diseases

菌株(剂量)	研究对象	治疗周期	动物/受试者数目	试验设计	效果	文献
<i>Lactobacillus acidophilus</i> LA1、 <i>Lactobacillus rhamnosus</i> LR5、 <i>Bifidobacterium bifidum</i> BF3等 (1×10^7 CFU/d)	SD大鼠	8周	益生菌对肥胖的改善作用 正常饮食组: 6只 高脂饮食组: 6只 高脂饮食+益生菌组: 6只 高脂饮食+安慰剂组: 6只	对照试验	体重、炎症因子、脂蛋白和相关代谢产物↓	[30]
<i>Bacillus subtilis</i> 、 <i>Bacillus licheniformis</i> (1×10^8 CFU/d)	C57BL/6J小鼠	8周	正常饮食组: 12只 高脂饮食组: 12只 <i>Bacillus subtilis</i> 组: 12只 <i>Bacillus licheniformis</i> 组: 12只 益生菌混合物组: 12只	对照试验	<i>Bacillus licheniformis</i> 及其混合物使体重、胰岛素抵抗和脂肪沉积↓	[31]
<i>Pediococcus pentosaceus</i> LP28 (LP28)	成人	12周	活的LP28粉末组: 21人 热处理的LP28粉末组: 21人 安慰剂组: 20人	随机、双盲、安慰剂对照试验	BMI、体脂率和腰围↓	[32]
<i>Bifidobacterium breve</i> B-3 (2×10^{10} CFU/d)	成人	12周	益生菌组: 40人 安慰剂组: 40人	随机、双盲、安慰剂对照试验	体脂质量、体脂百分比↓	[33]
<i>Bifidobacterium animalis</i> sp. <i>lactis</i> CECT 8145 (Ba8145) (1×10^{10} CFU/d)	成人	3个月	益生菌组: 42人 热灭活的益生菌组: 44人 安慰剂组: 40人	随机、双盲、安慰剂对照试验	体重指数、内脏脂肪面积、舒张压、胰岛素抵抗指数↓	[34]
<i>Lactobacillus plantarum</i> Ln4 (5×10^8 CFU/d)	C57BL/6J小鼠	5周	益生菌对T2DM的改善作用 正常饮食组: 5~7只 高脂饮食组: 5~7只 高脂饮食+益生菌组: 5~7只	对照试验	葡萄糖耐量和胰岛素敏感性↑	[35]
<i>Akkermansia muciniphila</i> (2×10^8 CFU/d)	C57BL/6小鼠	5周	正常饮食组: 10只 益生菌组: 10只	对照试验	葡萄糖耐量和胰岛素敏感性↑	[36]
<i>Lactobacillus casei</i> (10^8 CFU/d)	成人	8周	益生菌组: 20人 安慰剂组: 20人	随机、平行、安慰剂对照试验	空腹血糖、胰岛素和胰岛素抵抗↓	[37]
<i>Lactobacillus acidophilus</i> (2×10^9 CFU)、 <i>Lactobacillus casei</i> (7×10^9 CFU)、 <i>Lactobacillus rhamnosus</i> (1.5×10^9 CFU)等	成人	6周	益生菌组: 30人 安慰剂组: 30人	随机、双盲、安慰剂对照试验	空腹血糖↓	[38]
<i>Lactobacillus rhamnosus</i> 、 <i>Bifidobacterium animalis</i> subspecies <i>lactis</i> ($>1 \times 10^9$ CFU/d)	孕妇	中期妊娠-孕28周	益生菌组: 207人 安慰剂组: 204人	随机、双盲、安慰剂对照试验	不能防止妊娠期糖尿病	[39]
<i>Lactobacillus plantarum</i> LP104 (1×10^9 CFU/d)	C57BL/6N小鼠	8周	益生菌对高血脂的改善作用 正常饮食组: 10只 高脂饮食组: 10只 高脂饮食+益生菌组: 10只	对照试验	体重、血清甘油三酯、总胆固醇和肿瘤坏死因子α↓	[40]

(续表1)

菌株(剂量)	研究对象	治疗周期	动物/受试者数目	试验设计	效果	文献
<i>Lactobacillus plantarum</i> FZU3013 (1×10^9 CFU/mL)	Kunming小鼠	8周	正常饮食组: 8只 高脂饮食+益生菌组: 8只 正常饮食+益生菌组: 8只 高脂饮食+辛伐他汀: 8只	对照试验	体重、血清甘油三酯、总胆固醇和低密度脂蛋白↓	[41]
<i>Bifidobacterium animalis subsp. lactis</i> MB 2409、 <i>Bifidobacterium bifidum</i> MB 109等 (均 1×10^9 CFU/d)	儿童	3月	益生菌组: 19人 安慰剂组: 19人	随机、双盲、安慰剂对照试验	总胆固醇和低密度脂蛋白胆固醇↓	[42]
<i>Lactobacillus curvatus</i> HY7601等 (均 0.5×10^{10} CFU/d)	成人	12周	益生菌组: 58人 安慰剂组: 63人	随机、双盲、安慰剂对照试验	甘油三酯↓	[43]
<i>Bacillus subtilis</i> R0179、 <i>Lactobacillus plantarum</i> HA-119、 <i>Bifidobacterium animalis subsp. lactis</i> B94	成人	18周	3个不同的益生菌组 安慰剂组	随机、双盲、安慰剂对照试验	血脂、血糖或胰岛素无影响	[44]
<i>Bifidobacterium bifidum</i> W23、 <i>Bifidobacterium lactis</i> W51、 <i>Bifidobacterium lactis</i> W52、 <i>Lactobacillus acidophilus</i> W37等 (2.5×10^9 CFU/g)	女性	12周	益生菌对高血压的改善作用 低剂量益生菌组 (2.5×10^9 CFU/d): 24人 高剂量益生菌组 (1×10^{10} CFU/d): 23人 安慰剂组: 24人	随机、双盲、安慰剂对照试验	收缩压、血管内皮生长因子、脉搏速度、白细胞介素-6和肿瘤坏死因子 α ↓	[45]
<i>Lactobacillus fermentum</i> CECT5716 (LC40)、 <i>Lactobacillus coryniformis</i> CECT5711 (K8)、 <i>Lactobacillus gasseri</i> CECT5714 (LC9) (3.3×10^{10} CFU/d)	正常/自发性高血压大鼠	5周	正常组: 10只 高血压组: 10只 高血压+LC40组: 10只 高血压+K8/LC9组: 10只	对照试验	收缩压↓	[46]
<i>Bifidobacterium breve</i> CECT7263、 <i>Lactobacillus fermentum</i> CECT5716(LC40) (1×10^9 CFU/d)	正常/自发性高血压大鼠	13周	正常组: 10只 高血压组: 10只 高血压+BMF组: 10只 高血压+LC40组: 10只 高血压+醋酸盐组: 10只 高血压+丁酸盐组: 10只	对照试验	收缩压, 内毒素↓	[47]
<i>Lactobacillus plantarum</i> DSM 15313	成人	3个月	益生菌组: 44人 越桔发酵液组: 45人 益生菌组: 46人	双盲、安慰剂对照试验	血压未降低	[48]
<i>Lactobacillus paracasei</i> LPC-37等 (1×10^9 CFU/g)	女性	8周	益生菌组: 19人 安慰剂组: 17人	随机、三盲、安慰剂对照试验	空腹血糖、胆固醇↓	[49]
<i>Bifidobacterium animalis sp. lactis</i> LKM512(6×10^9 CFU/d)	成人	12周	益生菌组: 17人 安慰剂组: 10人	平行、双盲、安慰剂对照试验	TMA浓度和BMI↓	[50]
<i>Saccharomyces boulardii</i> (1000 mg/d)	成人	3月	益生菌组: 10人 安慰剂组: 10人	随机、双盲、安慰剂对照试验	左心房内径、尿酸和肌酐值↓	[51]

益生菌对其他代谢性疾病的改善作用

用多菌株和异黄酮混合物可降低动物的体重和脂肪堆积,但单独使用益生菌却没有观察到这种作用^[52],而Bubnov等人^[53]发现,使用单菌株(动物双歧杆菌(*Bifidobacterium animalis*)VKB和动物双歧杆菌VKL)或混合菌株均可降低雌鼠体重。此外,除乳酸杆菌和双歧杆菌,其他一些益生菌在动物模型中也表现出抗肥胖作用,包括戊糖片球菌(*Pediococcus pentosaceus*)LP28和布拉氏酵母菌(*Saccharomyces boulardii*),以及下一代益生菌单形拟杆菌(*Bacteroides uniformis*)CECT 7771和*Akkermansia muciniphila*等^[28,54]。*Akkermansia muciniphila*通常被称为Akk,由Derrien等人^[55]于2004年从健康人的粪便中分离出来,研究发现,肥胖小鼠肠道中*Akkermansia muciniphila*的丰度明显降低^[56]。

基于动物模型的良好结果,一些益生菌在人类临床试验中也被广泛测试,有效降低了儿童和成人的体重、身体质量指数(body mass index, BMI)、腰围和脂肪量。一项为期8周的实验发现,服用高剂量益生菌可降低肥胖儿童的BMI和内脏脂肪^[57]。同样地,一种包含9种菌株的混合益生菌VSL#3也降低了儿童的BMI^[58]。对肥胖成年人,研究显示,乳酸杆菌和双歧杆菌的一些菌株(单独或者混合使用)以及戊糖片球菌可显著降低BMI、腰围和脂肪量,发挥抗肥胖作用^[32,33,59,60]。一项随机对照试验(randomized controlled trial, RCT)发现,腹部肥胖患者服用动物双歧杆菌后腰围和腰围/身高比等腹部肥胖指标显著降低,且舒张压和胰岛素抵抗指数也能显著改善^[34]。最近的研究发现,一种新的抗肥胖益生菌——古氏副拟杆菌(*Parabacteroides goldsteinii*),其抗肥胖作用和肠道微生物群有关,可通过粪菌移植发挥作用^[61]。此外,研究还发现,粪便中Akk菌的丰度和孕妇体重增加呈负相关^[61]。然而,近期一项荟萃分析发现,妊娠期糖尿病、超重和肥胖孕妇在孕期补充益生菌,对新生儿出生体重的降低无显著影响^[62]。虽然益生菌或可通过改变母亲肠道菌群结构对新生儿的发育带来健康效应,但是这种效应是否能够被观察以及是否具有长期健康效应,需要进一步的探索。目前,相关研究发现,益生菌抵抗肥胖的潜在机制主要集中于增加脂肪组织的氧气消耗、重塑能量代谢、改变副交感神经和自主神经的活动、调节炎症及氧化应激状态、改善肠道通透性以及改变肠道微生物群等^[13](图1(a))。毫无疑问,由于其较低的治疗成本和对患者较低的伤害风险,通过操纵肠道菌群治疗肥胖症是一个潜在的理想策略。当然,未来的研究要侧重于探究微生物群的

变化如何导致肥胖,反过来肥胖是如何影响微生物群组成变化,通过解析这种复杂的相互作用将有助于开发更有针对性的益生菌疗法,进而全面评估益生菌在预防和控制肥胖症的作用^[63]。

2.2 益生菌对T2DM的影响

T2DM是一种以高血糖、低度炎症、胰岛素抵抗和β细胞衰竭为特征的代谢紊乱型疾病^[64]。预计到2040年,成人糖尿病患病率将上升到10.4%^[65]。T2DM的病因复杂,涉及环境因素和遗传因素之间的相互作用。此外,近年来研究发现,肠道菌群也是T2DM发病的重要因素之一^[65]。特别是益生菌作为食品微生物的培养物,其对T2DM的干预作用备受关注^[66]。研究表明,T2DM患者胃肠道中的厚壁菌门细菌数量较低,而拟杆菌门和变形菌门的数量较高^[67],且存在大量的致病菌,如梭状杆菌(*Bacterium fusiformis*)、粪拟杆菌(*Bacteroides caccae*)、多枝梭菌(*Clostridium ramosum*)和大肠埃希氏菌(*Escherichia coli*)等^[68,69]。目前使用益生菌进行T2DM干预以乳酸菌为主,包括干酪乳杆菌、植物乳杆菌、路氏乳杆菌(*Lactobacillus reuteri*)和鼠李糖乳杆菌等^[16,35]。其中,植物乳杆菌MTCC5689可抑制高脂饮食小鼠胰岛素抵抗和糖尿病的发生^[70]。类干酪乳杆菌(*Lactobacillus paracasei*)NL41通过降低胰岛素抵抗、氧化应激和保护β细胞功能预防糖尿病^[71]。此外,下一代益生菌Akk、*Akkermansia muciniphila* MucT和粪便普雷沃氏菌对葡萄糖代谢也有一定的促进作用^[56,36,72]。除了单一菌株,利用乳酸菌菌株混合物或VSL#3评估混合益生菌对T2DM的影响,结果均显示,益生菌干预后,有效降低空腹血糖、增加胰岛素敏感性以及提高啮齿动物的糖耐量^[73-75]。

在临床试验中,Khalili等人^[37]发现,干酪乳杆菌显著降低T2DM患者的空腹血糖、胰岛素和胰岛素抵抗。日本T2DM患者服用发酵乳制品(含益生菌)16周后细菌易位减少,肠道菌群发生了部分改变^[76]。混合益生菌(包含乳酸杆菌、双歧杆菌和链球菌等)对T2DM患者的研究表明,多菌株益生菌补充剂可显著降低空腹血糖水平^[38]。近期的荟萃分析结果同样显示,补充益生菌显著降低空腹血糖、空腹胰岛素和总胆固醇水平,增加高密度脂蛋白胆固醇(high-density lipoprotein cholesterol, HDL-C)水平,其可能作为T2DM患者改善血脂异常和调节代谢的一种补充治疗方法^[77]。此外,一项关于411例超重/肥胖孕妇的RCT试验结果表明,孕中期使用

图 1 (网络版彩色)益生菌对代谢性疾病影响的潜在机制

Figure 1 (Color online) Potential mechanisms of probiotics action in the prevention and treatment of metabolic diseases

益生菌(鼠李糖乳杆菌和动物双歧杆菌乳亚种BB-12)干预,无法预防妊娠期糖尿病^[39]。Barengolts等人^[78]也发现,益生菌酸奶对T2DM或肥胖患者的空腹血糖、空腹胰岛素和胰岛素抵抗等指标均无显著改善作用。虽然在动物和临床实验上益生菌对糖尿病的有益作用被探究,但关于益生菌的种类、剂量以及功效等级却不同,需要进一步大样本量的临床研究验证。目前,益生菌干预T2DM的几种机制已得到广泛的认可,其有益作用可能是通过调节肠道微生物群和增加短链脂肪酸(short-chain fatty acids, SCFAs),改善肠道完整性和机体能量代谢,减轻低水平慢性炎症和氧化应激反应,改善外周胰岛素敏感性以及影响免疫应答等机制发挥调节糖代谢降低血糖作用^[16](图1(b))。未来还需要进一步的

临床试验来识别和比较不同益生菌菌株的剂量、最佳的治疗时间和疗程,为针对糖尿病的益生菌干预治疗指南奠定扎实基础。

2.3 益生菌对高血脂的影响

高脂血症是一种以血清甘油三酯(triglyceride, TG)、总胆固醇(total cholesterol, TC)、游离脂肪酸(free fatty acids, FFA)和低密度脂蛋白胆固醇(low-density lipoprotein cholesterol, LDL-C)浓度升高并伴有肝脏中TG过度积累为特征的病理状态,与高血压、糖尿病、非酒精性脂肪肝(nonalcoholic fatty liver disease, NAFLD)和心血管疾病等多种慢性疾病密切相关^[79]。截至目前,已经开发出多种降脂类药物,应用最广泛的

是他汀类药物,但它们都具有较强的副作用^[80]。益生菌安全性高、副作用小且不会引起体内有毒物质大量的积累,通过排除获得性病原体恢复正常肠道菌群,改善肠黏膜免疫屏障,减少肠道炎症^[81]。体内外研究表明,一些乳酸杆菌可以有效降低TC和LDL-C水平^[82]。其中,发酵乳杆菌(*Lactobacillus fermentum*)NCIMB 5221和NCIMB 2797在体外水平降低胆固醇,嗜酸乳杆菌通过分解胆固醇降低血液胆固醇^[83]。此外,研究发现,一些乳酸菌、双歧杆菌和肠球菌与HDL-C呈正相关^[84],较高水平的HDL-C有利于清除血液中的有害胆固醇。

多项研究表明,益生菌及其发酵制品可以调节动物和人的脂质水平。研究发现,灌胃植物乳杆菌LP104有效降低高脂饮食小鼠的血清TC、TG和LDL水平,升高肝脏HDL水平^[40];植物乳杆菌FZU3013降低NAFLD小鼠的血清TG、TC和LDL-C水平,抑制肝脏脂质的过度积累并调节脂质代谢相关基因^[41]。一项研究发现,植物乳杆菌P-8降低高脂饮食大鼠的血清TC、TG和LDL-C水平,升高HDL-C水平^[85]。此外,研究发现,下一代益生菌*Akkermansia muciniphila*也可降低肥胖小鼠的血清TG和丙氨酸转氨酶(alanine aminotransferase, ALT)水平^[86]。许多临床试验也进一步验证了益生菌对脂质的调节作用。Guardamagna等人^[42]将含有双歧杆菌的益生菌混合物用于治疗患有高脂血症的儿童,发现治疗3个月儿童的TC和LDL-C水平显著降低。Ahn等人^[43]进行的一项关于128例高甘油三酯血症非糖尿病患者的随机、双盲安慰剂对照试验发现,患者服用益生菌(弯曲乳杆菌(*Lactobacillus curvatus*)HY7601和植物乳杆菌KY1032)12周后,血清TG水平显著降低,apoA-V和LDL颗粒大小显著升高。同时,一项关于3种益生菌对肥胖人群的临床试验结果表明,不同的益生菌对机体非结合型血浆胆汁酸影响显著,但对粪便胆汁酸以及血糖血脂等无显著影响^[44]。Khalesi等人^[87]也发现,健康成人摄入益生菌后,各种血脂指标的浓度没有明显变化,提示健康成人补充益生菌以促进健康的可行性有待研究。目前,益生菌降脂的确切作用机制尚不十分明确,可能与以下几个方面有关: (1) 吸收胆固醇并黏附、渗入菌体的细胞膜或细胞壁; (2) 产生胆盐水解酶并促进胆汁酸排泄; (3) 分泌胞外多糖并与去结合型胆酸盐结合,减少肠道对胆固醇的吸收; (4) 发酵碳水化合物产生丙酸和丁酸等SCFAs,抑制脂肪酸及胆固醇合成^[88](图1(c))。未来,仍需要更合理严谨的临床实验设计来揭示益生菌降脂的潜在机制。

2.4 益生菌对高血压的影响

高血压是导致心血管疾病最主要的危险因素之一,包括心肌梗死、肾脏疾病和卒中。由于人口老龄化和其他风险因素(如不健康的饮食和缺乏锻炼等),全球高血压患病率正在上升,预计到2025年,世界人口的患病率将增加到29%^[88]。截至目前,在动物模型和人类患者中,越来越多的研究发现,肠道微生物与高血压之间存在联系。总的来说,无论是原发性高血压,还是肾素依赖型高血压,患者和动物的肠道微生物均匀度、多样性和丰富度降低,产乙酸和丁酸盐的细菌数量减少,厚壁菌门/拟杆菌门比值增加^[88,89]。有证据表明,肠道菌群通过脑-肠-肾轴、炎症因子和代谢产物等途径参与高血压的病理过程^[45]。某些益生菌(如乳酸杆菌和双歧杆菌)还可产生SCFAs、共轭亚油酸、 γ -氨基丁酸以及ACE抑制肽等参与降压过程^[90]。研究发现,鼠李糖乳杆菌GG、瑞士乳杆菌(*Lactobacillus helveticus*)、加氏乳杆菌、路氏乳杆菌和双歧杆菌在微噬细胞中诱导NO产生,增强血管舒张,降低高血压;发酵乳杆菌E-3和E-18、加氏乳杆菌和嗜热链球菌(*Streptococcus thermophilus*)产生超氧化物歧化酶从而降低血压^[91,46]。近期一项研究表明,短双歧杆菌CECT7263和发酵乳杆菌CECT5716可以预防自发性高血压大鼠的生态失调、内皮功能障碍和高血压,这些作用可能与其减少内毒素和血管中调节性T细胞(Treg)的积累有关^[47]。

益生菌对高血压患者的影响在临床上也有许多研究。一些荟萃分析关注益生菌的使用效果,发现益生菌不仅可以降低糖尿病患者的血压^[92,93],对健康人群的血压也有一定调节作用^[94,95]。一项关于846名高血压患者的荟萃分析发现,补充益生菌后患者的收缩压和舒张压降低。此效应与治疗时间、剂量和受试者年龄有关,但与单株或多株使用无关,且补充益生菌对降低BMI和血糖具有有益作用^[45]。虽然血压的下降和益生菌的摄入存在联系,但不同菌株之间仍存在差异性。Xu等人^[48]利用植物乳杆菌DSM 15313以及这株菌发酵的越桔液对142名高血压患者进行干预,发现患者服用益生菌3个月后血压没有出现下降的现象,且益生菌产品对口腔和粪便微生物群的多样性和组成均无显著影响。Romão da Silva等人^[49]将乳酸菌相关的益生菌混合物干预高血压妇女8周,发现益生菌能降低患者的空腹血糖和胆固醇水平,改善血脂和自主调节功能。越来越多的临床试验支持益生菌在降低高血压方面的作用,摄

入益生菌后血压的降低与保护宿主肠道屏障、调节免疫和炎症反应、改善胰岛素抵抗, 以及调节肾素-血管紧张素神经功能等方面存在密切的联系, 同时这些现象之间可能又存在相互联系, 构成复杂的降压机制^[91](图1(d)). 目前的研究结果表明, 益生菌的降压作用是很有前景的, 但是还需要更多细致的研究来全面理解肠道微生物群与宿主相互作用和控制高血压的生化网络关系, 为未来预防和治疗心血管疾病绘制清晰的蓝图.

2.5 益生菌对其他心血管疾病的影响

心脑血管疾病是指由于高脂血症、血液黏稠、动脉粥样硬化和高血压等所导致的心脏、大脑及全身组织发生的缺血性或出血性疾病, 严重危害人类健康. 除高脂血症和高血压, 益生菌在动脉粥样硬化、血栓和心肌缺血等方面也发挥一定的调节作用. 研究发现, 肠道微生物衍生的具有生物活性的三甲胺N-氧化物(TMAO)可导致动脉粥样硬化和血栓的形成^[5], 在ApoE缺陷型小鼠中, 植物乳杆菌ZDY04显著抑制了TMAO诱导的动脉粥样硬化的发展^[96]. 以健康志愿者为对象, 发现动物双歧杆菌乳双歧亚种LKM512通过降低肠道菌群产生的结肠三甲胺(TMA), 降低动脉粥样硬化风险^[50]. 在心肌梗死大鼠的饮用水中连续添加含有植物乳杆菌的益生菌饮料14 d, 大鼠的心肌缺血面积减少29%, 缺血后恢复速度升高23%^[97]. 心衰患者口服布拉氏酵母菌(1000 mg/d)为期3个月, 与安慰剂相比, 益生菌治疗组患者左心房内径, 尿酸和肌酐值明显减少^[51]. 表明益生菌对心脏有直接保护作用, 有利于改善心肌

缺血损伤和心功能. 此外, 一项关于46例血液透析患者持续3个月服用益生菌(嗜热链球菌、嗜酸乳杆菌和双歧杆菌)的RCT试验表明, 治疗后患者的血清尿素水平显著增加, 尿毒症毒素和炎症标志物变化不明显, 说明益生菌对慢性肾病患者治疗作用仍需进一步研究^[98]. 总体而言, 摄取一定量益生菌可改善心血管疾病患者的健康状况, 但具体临床应用效果仍存在争议, 未来需要更深入更严谨的临床研究.

3 总结与展望

近年来, 代谢性疾病已经遍布全球, 探寻预防和治疗策略对降低其发病率和病死率具有重要意义. 越来越多的证据表明, 肠道菌群可能通过影响体重、炎症因子活性、调节血脂和胰岛素抵抗等在代谢性疾病中发挥重要作用. 近年来, 益生菌被广泛用于调节肠道微生物群, 降低肠道炎症, 改善肠道屏障完整性, 从而降低血糖和血脂水平, 诱导体重减轻, 降低胰岛素抵抗^[99]. 本文从肥胖、糖尿病、高血压、高脂血症及其他心血管疾病等多个方面阐述了益生菌对代谢性疾病的干预作用, 提示使用益生菌作为饮食替代品减轻代谢性疾病的发展, 可能是未来的趋势. 同时, 益生菌还可以作为辅助性补充剂使用, 加快已经患病或正在服用药物(激素)治疗患者的康复进程. 然而, 在使用益生菌作为替代疗法之前, 还需要大量的临床研究阐明其确切机制、体内靶点、稳定性和安全性以及达到有益效果所需的最小剂量、补充期、效果的持久性甚至可能禁忌证, 从而进一步揭示益生菌在未来研究中的潜力.

参考文献

- 1 He M, Shi B. Gut microbiota as a potential target of metabolic syndrome: The role of probiotics and prebiotics. *Cell Biosci*, 2017, 7: 54
- 2 Martinez K B, Leone V, Chang E B. Western diets, gut dysbiosis, and metabolic diseases: Are they linked? *Gut Microbes*, 2017, 8: 130–142
- 3 Santos-Marcos J A, Perez-Jimenez F, Camargo A. The role of diet and intestinal microbiota in the development of metabolic syndrome. *J Nutr Biochem*, 2019, 70: 1–27
- 4 Ferrarese R, Ceresola E R, Preti A, et al. Probiotics, prebiotics and synbiotics for weight loss and metabolic syndrome in the microbiome era. *Eur Rev Med Pharmacol Sci*, 2018, 22: 7588–7605
- 5 Yoo J Y, Kim S S. Probiotics and prebiotics: Present status and future perspectives on metabolic disorders. *Nutrients*, 2016, 8: 173
- 6 Zhang Y, Gu Y, Ren H, et al. Gut microbiome-related effects of berberine and probiotics on type 2 diabetes (the PREMOT study). *Nat Commun*, 2020, 11: 5015
- 7 Gao Z, Li Q, Wu X, et al. New insights into the mechanisms of Chinese herbal products on diabetes: A focus on the “bacteria-mucosal immunity-inflammation-diabetes” axis. *J Immunol Res*, 2017, 2017: 1813086
- 8 Fatehah A A, Poh B K, Shanita S N, et al. Feasibility of reviewing digital food images for dietary assessment among nutrition professionals. *Nutrients*, 2018, 10: 984
- 9 Dujic T, Zhou K, Donnelly L A, et al. Association of organic cation transporter 1 with intolerance to metformin in type 2 diabetes: A GoDARTS

- study. *Diabetes*, 2015, 64: 1786–1793
- 10 Hill C, Guarner F, Reid G, et al. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nat Rev Gastroenterol Hepatol*, 2014, 11: 506–514
- 11 Westfall S, Lomis N, Kahouli I, et al. Microbiome, probiotics and neurodegenerative diseases: Deciphering the gut brain axis. *Cell Mol Life Sci*, 2017, 74: 3769–3787
- 12 Koutnikova H, Genser B, Monteiro-Sepulveda M, et al. Impact of bacterial probiotics on obesity, diabetes and non-alcoholic fatty liver disease related variables: A systematic review and meta-analysis of randomised controlled trials. *BMJ Open*, 2019, 9: e017995
- 13 Sivamaruthi B S, Kesika P, Suganthi N, et al. A review on role of microbiome in obesity and antiobesity properties of probiotic supplements. *Biomed Res Int*, 2019, 2019: 3291367
- 14 Chang C S, Ruan J W, Kao C Y. An overview of microbiome based strategies on anti-obesity. *Kaohsiung J Med Sci*, 2019, 35: 7–16
- 15 O'toole P W, Marchesi J R, Hill C. Next-generation probiotics: The spectrum from probiotics to live biotherapeutics. *Nat Microbiol*, 2017, 2: 17057
- 16 Sun Z, Sun X, Li J, et al. Using probiotics for type 2 diabetes mellitus intervention: Advances, questions, and potential. *Crit Rev Food Sci Nutr*, 2020, 60: 670–683
- 17 Cani P D, Van Hul M. Novel opportunities for next-generation probiotics targeting metabolic syndrome. *Curr Opin Biotechnol*, 2015, 32: 21–27
- 18 Szulińska M, Łoniewski I, Skrypnik K, et al. Multispecies probiotic supplementation favorably affects vascular function and reduces arterial stiffness in obese postmenopausal women-A 12-week placebo-controlled and randomized clinical study. *Nutrients*, 2018, 10: 1672
- 19 Bernini L J, Simão A N C, Alfieri D F, et al. Beneficial effects of *Bifidobacterium lactis* on lipid profile and cytokines in patients with metabolic syndrome: A randomized trial. Effects of probiotics on metabolic syndrome. *Nutrition*, 2016, 32: 716–719
- 20 Barreto F M, Colado Simão A N, Morimoto H K, et al. Beneficial effects of *Lactobacillus plantarum* on glycemia and homocysteine levels in postmenopausal women with metabolic syndrome. *Nutrition*, 2014, 30: 939–942
- 21 Rezazadeh L, Gargari B P, Jafarabadi M A, et al. Effects of probiotic yogurt on glycemic indexes and endothelial dysfunction markers in patients with metabolic syndrome. *Nutrition*, 2019, 62: 162–168
- 22 Bottacini F, van Sinderen D, Ventura M. Omics of bifidobacteria: Research and insights into their health-promoting activities. *Biochem J*, 2017, 474: 4137–4152
- 23 Patro J N, Ramachandran P, Barnaba T, et al. Culture-independent metagenomic surveillance of commercially available probiotics with high-throughput next-generation sequencing. *mSphere*, 2016, 1: e00057
- 24 Chang C J, Lin T L, Tsai Y L, et al. Next generation probiotics in disease amelioration. *J Food Drug Anal*, 2019, 27: 615–622
- 25 Zhou J C, Zhang X W. *Akkermansia muciniphila*: A promising target for the therapy of metabolic syndrome and related diseases. *Chin J Nat Med*, 2019, 17: 835–841
- 26 Huo Y, Lu X, Wang X, et al. *Bifidobacterium animalis* subsp. *lactis* A6 alleviates obesity associated with promoting mitochondrial biogenesis and function of adipose tissue in mice. *Molecules*, 2020, 25: 1490
- 27 Abenavoli L, Scarpellini E, Colica C, et al. Gut microbiota and obesity: A role for probiotics. *Nutrients*, 2019, 11: 2690
- 28 Cerdó T, García-Santos J, Bermúdez G M, et al. The role of probiotics and prebiotics in the prevention and treatment of obesity. *Nutrients*, 2019, 11: 635
- 29 Kobylak N, Conte C, Cammarota G, et al. Probiotics in prevention and treatment of obesity: A critical view. *Nutr Metab*, 2016, 13: 14
- 30 Shin J H, Nam M H, Lee H, et al. Amelioration of obesity-related characteristics by a probiotic formulation in a high-fat diet-induced obese rat model. *Eur J Nutr*, 2018, 57: 2081–2090
- 31 Cao G T, Dai B, Wang K L, et al. *Bacillus licheniformis*, a potential probiotic, inhibits obesity by modulating colonic microflora in C57BL/6J mice model. *J Appl Microbiol*, 2019, 127: 880–888
- 32 Higashikawa F, Noda M, Awaya T, et al. Antiobesity effect of *Pediococcus pentosaceus* LP28 on overweight subjects: A randomized, double-blind, placebo-controlled clinical trial. *Eur J Clin Nutr*, 2016, 70: 582–587
- 33 Minami J, Iwabuchi N, Tanaka M, et al. Effects of *Bifidobacterium breve* B-3 on body fat reductions in pre-obese adults: A randomized, double-blind, placebo-controlled trial. *Biosci Microbiota Food Health*, 2018, 37: 67–75
- 34 Pedret A, Valls R M, Calderón-Pérez L, et al. Effects of daily consumption of the probiotic *Bifidobacterium animalis* subsp. *lactis* CECT 8145 on anthropometric adiposity biomarkers in abdominally obese subjects: A randomized controlled trial. *Int J Obes*, 2019, 43: 1863–1868
- 35 Lee E, Jung S R, Lee S Y, et al. *Lactobacillus plantarum* strain Ln4 attenuates diet-induced obesity, insulin resistance, and changes in hepatic mRNA levels associated with glucose and lipid metabolism. *Nutrients*, 2018, 10: 643
- 36 Zhao S, Liu W, Wang J, et al. *Akkermansia muciniphila* improves metabolic profiles by reducing inflammation in chow diet-fed mice. *J Mol Endocrinol*, 2017, 58: 1–14
- 37 Khalili L, Alipour B, Asghari Jafar-Abadi M, et al. The effects of *Lactobacillus casei* on glycemic response, serum sirtuin1 and fetuin-A levels in patients with type 2 diabetes mellitus: A randomized controlled trial. *Iran Biomed J*, 2019, 23: 68–77

- 38 Razmpoosh E, Javadi A, Ejtahed H S, et al. The effect of probiotic supplementation on glycemic control and lipid profile in patients with type 2 diabetes: A randomized placebo controlled trial. [Diabetes Metab Syndr-Clin Res Rev](#), 2019, 13: 175–182
- 39 Callaway L K, McIntyre H D, Barrett H L, et al. Probiotics for the prevention of gestational diabetes mellitus in overweight and obese women: Findings from the SPRING double-blind randomized controlled trial. [Diabetes Care](#), 2019, 42: 364–371
- 40 Teng Y, Wang Y, Tian Y, et al. *Lactobacillus plantarum* LP104 ameliorates hyperlipidemia induced by AMPK pathways in C57BL/6N mice fed high-fat diet. [J Funct Foods](#), 2020, 64: 103665
- 41 Chen M, Guo W L, Li Q Y, et al. The protective mechanism of *Lactobacillus plantarum* FZU3013 against non-alcoholic fatty liver associated with hyperlipidemia in mice fed a high-fat diet. [Food Funct](#), 2020, 11: 3316–3331
- 42 Guardamagna O, Amaretti A, Puddu P E, et al. Bifidobacteria supplementation: Effects on plasma lipid profiles in dyslipidemic children. [Nutrition](#), 2014, 30: 831–836
- 43 Ahn H Y, Kim M, Chae J S, et al. Supplementation with two probiotic strains, *Lactobacillus curvatus* HY7601 and *Lactobacillus plantarum* KY1032, reduces fasting triglycerides and enhances apolipoprotein A-V levels in non-diabetic subjects with hypertriglyceridemia. [Atherosclerosis](#), 2015, 241: 649–656
- 44 Culpepper T, Rowe C C, Rusch C T, et al. Three probiotic strains exert different effects on plasma bile acid profiles in healthy obese adults: Randomised, double-blind placebo-controlled crossover study. [Benef Microbes](#), 2019, 10: 497–509
- 45 Chi C, Li C, Wu D, et al. Effects of probiotics on patients with hypertension: A systematic review and meta-analysis. [Curr Hypertens Rep](#), 2020, 22: 34
- 46 Gómez-Guzmán M, Toral M, Romero M, et al. Antihypertensive effects of probiotics *Lactobacillus* strains in spontaneously hypertensive rats. [Mol Nutr Food Res](#), 2015, 59: 2326–2336
- 47 Robles-Vera I, Toral M, De La Visitación N, et al. Probiotics prevent dysbiosis and the rise in blood pressure in genetic hypertension: Role of short-chain fatty acids. [Mol Nutr Food Res](#), 2020, 64: e1900616
- 48 Xu J, Lazou Ahrén I, Olsson C, et al. Oral and faecal microbiota in volunteers with hypertension in a double blind, randomised placebo controlled trial with probiotics and fermented bilberries. [J Funct Foods](#), 2015, 18: 275–288
- 49 Romão da Silva L F, de Oliveira Y, de Souza E L, et al. Effects of probiotic therapy on cardio-metabolic parameters and autonomic modulation in hypertensive women: A randomized, triple-blind, placebo-controlled trial. [Food Funct](#), 2020, 11: 7152–7163
- 50 Matsumoto M, Kitada Y, Shimomura Y, et al. *Bifidobacterium animalis* subsp. *lactis* LKM512 reduces levels of intestinal trimethylamine produced by intestinal microbiota in healthy volunteers: A double-blind, placebo-controlled study. [J Funct Foods](#), 2017, 36: 94–101
- 51 Costanza A C, Moscovitch S D, Faria Neto H C C, et al. Probiotic therapy with *Saccharomyces boulardii* for heart failure patients: A randomized, double-blind, placebo-controlled pilot trial. [Int J Cardiol](#), 2015, 179: 348–350
- 52 Ali A A, Velasquez M T, Hansen C T, et al. Effects of soybean isoflavones, probiotics, and their interactions on lipid metabolism and endocrine system in an animal model of obesity and diabetes. [J Nutr Biochem](#), 2004, 15: 583–590
- 53 Bubnov R V, Babenko L P, Lazarenko L M, et al. Comparative study of probiotic effects of *Lactobacillus* and *Bifidobacteria* strains on cholesterol levels, liver morphology and the gut microbiota in obese mice. [EPMA J](#), 2017, 8: 357–376
- 54 Goodrich J K, Waters J L, Poole A C, et al. Human genetics shape the gut microbiome. [Cell](#), 2014, 159: 789–799
- 55 Derrien M, Vaughan E E, Plugge C M, et al. *Akkermansia muciniphila* gen. nov., sp. nov., a human intestinal mucin-degrading bacterium. [Int J Syst Evol Microbiol](#), 2004, 54: 1469–1476
- 56 Everard A, Belzer C, Geurts L, et al. Cross-talk between *Akkermansia muciniphila* and intestinal epithelium controls diet-induced obesity. [Proc Natl Acad Sci USA](#), 2013, 110: 9066–9071
- 57 Vajro P, Mandato C, Licenziati M R, et al. Effects of *Lactobacillus rhamnosus* strain GG in pediatric obesity-related liver disease. [J Pediatr Gastroenterol Nutr](#), 2011, 52: 740–743
- 58 Alisi A, Bedogni G, Baviera G, et al. Randomised clinical trial: The beneficial effects of VSL#3 in obese children with non-alcoholic steatohepatitis. [Aliment Pharmacol Ther](#), 2014, 39: 1276–1285
- 59 Gomes A C, de Sousa R G M, Botelho P B, et al. The additional effects of a probiotic mix on abdominal adiposity and antioxidant status: A double-blind, randomized trial. [Obesity](#), 2017, 25: 30–38
- 60 Kim J, Yun J M, Kim M K, et al. *Lactobacillus gasseri* BNR17 supplementation reduces the visceral fat accumulation and waist circumference in obese adults: A randomized, double-blind, placebo-controlled trial. [J Med Food](#), 2018, 21: 454–461
- 61 Wu T R, Lin C S, Chang C J, et al. Gut commensal *Parabacteroides goldsteinii* plays a predominant role in the anti-obesity effects of polysaccharides isolated from *Hirsutiella sinensis*. [Gut](#), 2019, 68: 248–262
- 62 Wang C C, Tung Y T, Chang H C, et al. Effect of probiotic supplementation on newborn birth weight for mother with gestational diabetes mellitus or overweight/obesity: A systematic review and meta-analysis. [Nutrients](#), 2020, 12: 3477
- 63 Mazloom K, Siddiqi I, Covasa M. Probiotics: How effective are they in the fight against obesity? [Nutrients](#), 2019, 11: 258

- 64 Liang T, Wu L, Xi Y, et al. Probiotics supplementation improves hyperglycemia, hypercholesterolemia, and hypertension in type 2 diabetes mellitus: An update of meta-analysis. *Crit Rev Food Sci Nutr*, 2020, doi: 10.1080/10408398.2020.1764488
- 65 Ogurtsova K, Da Rocha Fernandes J D, Huang Y, et al. IDF diabetes atlas: Global estimates for the prevalence of diabetes for 2015 and 2040. *Diabetes Res Clin Pract*, 2017, 128: 40–50
- 66 Rad A H, Abbasalizadeh S, Vazifekhah S, et al. The future of diabetes management by healthy probiotic microorganisms. *Curr Diabetes Rev*, 2017, 13: 582–589
- 67 Roager H M, Vogt J K, Kristensen M, et al. Whole grain-rich diet reduces body weight and systemic low-grade inflammation without inducing major changes of the gut microbiome: A randomised cross-over trial. *Gut*, 2019, 68: 83–93
- 68 Larsen N, Vogensen F K, van den Berg F W J, et al. Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults. *PLoS One*, 2010, 5: e9085
- 69 Karlsson F H, Tremaroli V, Nookaew I, et al. Gut metagenome in European women with normal, impaired and diabetic glucose control. *Nature*, 2013, 498: 99–103
- 70 Balakumar M, Prabhu D, Sathishkumar C, et al. Improvement in glucose tolerance and insulin sensitivity by probiotic strains of Indian gut origin in high-fat diet-fed C57BL/6J mice. *Eur J Nutr*, 2018, 57: 279–295
- 71 Zeng Z, Yuan Q, Yu R, et al. Ameliorative effects of probiotic *Lactobacillus paracasei* NL41 on insulin sensitivity, oxidative stress, and beta-cell function in a type 2 diabetes mellitus rat model. *Mol Nutr Food Res*, 2019, 63: e1900457
- 72 De Vadder F, Kovatcheva-Datchary P, Zitoun C, et al. Microbiota-produced succinate improves glucose homeostasis via intestinal gluconeogenesis. *Cell Metab*, 2016, 24: 151–157
- 73 Yadav H, Lee J H, Lloyd J, et al. Beneficial metabolic effects of a probiotic via butyrate-induced GLP-1 hormone secretion. *J Biol Chem*, 2013, 288: 25088–25097
- 74 Memarrast F, Ghafouri-Fard S, Kolivand S, et al. Comparative evaluation of probiotics effects on plasma glucose, lipid, and insulin levels in streptozotocin-induced diabetic rats. *Diabetes Metab Res Rev*, 2017, 33: e2912
- 75 Yakovlieva M, Tacheva T, Mihaylova S, et al. Influence of *Lactobacillus brevis* 15 and *Lactobacillus plantarum* 13 on blood glucose and body weight in rats after high-fructose diet. *Benef Microbes*, 2015, 6: 505–512
- 76 Sato J, Kanazawa A, Azuma K, et al. Probiotic reduces bacterial translocation in type 2 diabetes mellitus: A randomised controlled study. *Sci Rep*, 2017, 7: 12115
- 77 Kocsis T, Molnár B, Németh D, et al. Probiotics have beneficial metabolic effects in patients with type 2 diabetes mellitus: A meta-analysis of randomized clinical trials. *Sci Rep*, 2020, 10: 11787
- 78 Barengolts E, Smith E D, Reutrakul S, et al. The effect of probiotic yogurt on glycemic control in type 2 diabetes or obesity: A meta-analysis of nine randomized controlled trials. *Nutrients*, 2019, 11: 671
- 79 Zhang Y, Wang Z, Jin G, et al. Regulating dyslipidemia effect of polysaccharides from *Pleurotus ostreatus* on fat-emulsion-induced hyperlipidemia rats. *Int J Biol Macromol*, 2017, 101: 107–116
- 80 Gotto A M Jr, Moon J E. Recent clinical studies of the effects of lipid-modifying therapies. *Am J Cardiol*, 2012, 110: 15a–26a
- 81 Tlaskalová-Hogenová H, Štěpánková R, Kozáková H, et al. The role of gut microbiota (commensal bacteria) and the mucosal barrier in the pathogenesis of inflammatory and autoimmune diseases and cancer: Contribution of germ-free and gnotobiotic animal models of human diseases. *Cell Mol Immunol*, 2011, 8: 110–120
- 82 Pereira D I A, Gibson G R. Effects of consumption of probiotics and prebiotics on serum lipid levels in humans. *Crit Rev Biochem Mol Biol*, 2002, 37: 259–281
- 83 Antony S, Leon M P D. Probiotics and its relationship with the cardiovascular system. In: Enany S, ed. *Probiotics—Current Knowledge and Future Prospects*. London: IntechOpen, 2018
- 84 Cavallini D C U, Suzuki J Y, Abdalla D S P, et al. Influence of a probiotic soy product on fecal microbiota and its association with cardiovascular risk factors in an animal model. *Lipids Health Dis*, 2011, 10: 126
- 85 Bao Y, Wang Z, Zhang Y, et al. Effect of *Lactobacillus plantarum* P-8 on lipid metabolism in hyperlipidemic rat model. *Eur J Lipid Sci Technol*, 2012, 114: 1230–1236
- 86 Kim S, Lee Y, Kim Y, et al. *Akkermansia muciniphila* prevents fatty liver disease, decreases serum triglycerides, and maintains gut homeostasis. *Appl Environ Microbiol*, 2020, 86: e03004-19
- 87 Khalesi S, Bellissimo N, Vandelanotte C, et al. A review of probiotic supplementation in healthy adults: Helpful or hype? *Eur J Clin Nutr*, 2019, 73: 24–37
- 88 Nazir Y, Hussain S A, Abdul Hamid A, et al. Probiotics and their potential preventive and therapeutic role for cancer, high serum cholesterol, and allergic and HIV diseases. *Biomed Res Int*, 2018, 2018: 3428437
- 89 Li J, Zhao F, Wang Y, et al. Gut microbiota dysbiosis contributes to the development of hypertension. *Microbiome*, 2017, 5: 14

- 90 Upadrasta A, Madempudi R S. Probiotics and blood pressure: Current insights. *Integr Blood Press Control*, 2016, 9: 33–42
- 91 Daliri E B M, Lee B H, Oh D H. Current perspectives on antihypertensive probiotics. *Probiotics Antimicrob Proteins*, 2017, 9: 91–101
- 92 Lewis-Mikhael A M, Davoodvandi A, Jafarnejad S. Effect of *Lactobacillus plantarum* containing probiotics on blood pressure: A systematic review and meta-analysis. *Pharmacol Res*, 2020, 153: 104663
- 93 Khalesi S, Sun J, Buys N, et al. Effect of probiotics on blood pressure. *Hypertension*, 2014, 64: 897–903
- 94 He J, Zhang F, Han Y. Effect of probiotics on lipid profiles and blood pressure in patients with type 2 diabetes. *Medicine*, 2017, 96: e9166
- 95 Hendijani F, Akbari V. Probiotic supplementation for management of cardiovascular risk factors in adults with type II diabetes: A systematic review and meta-analysis. *Clin Nutr*, 2018, 37: 532–541
- 96 Qiu L, Tao X, Xiong H, et al. *Lactobacillus plantarum* ZDY04 exhibits a strain-specific property of lowering TMAO via the modulation of gut microbiota in mice. *Food Funct*, 2018, 9: 4299–4309
- 97 Lam V, Su J, Koprowski S, et al. Intestinal microbiota determine severity of myocardial infarction in rats. *FASEB J*, 2012, 26: 1727–1735
- 98 Borges N A, Carmo F L, Stockler-Pinto M B, et al. Probiotic supplementation in chronic kidney disease: A double-blind, randomized, placebo-controlled trial. *J Renal Nutr*, 2018, 28: 28–36
- 99 Torres S, Fabersani E, Marquez A, et al. Adipose tissue inflammation and metabolic syndrome. The proactive role of probiotics. *Eur J Nutr*, 2019, 58: 27–43

Summary for “益生菌：代谢性疾病调控新靶向”

Probiotics: A new target for metabolic disease regulation

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Metabolic syndrome is a construct relating to a series of metabolic dysfunctions attributable to insulin resistance and obesity. In recent years, the incidence of metabolic diseases has gradually increased, which seriously affecting the quality of life of individuals, and has become a worldwide public health problem. The prevalence of metabolic disorders is associated with dynamic changes in dietary macronutrient intake and lifestyle changes during the past decades. Recently, the scientific community has considered alteration in gut microbiota composition to constitute one of the most probable factors in the development of metabolic disorders. How to improve metabolic syndrome by regulating the gut microbiota has become a research hotspot. Probiotics, as a living microorganism beneficial to human health, has been widely applied in different foods, which can improve blood glucose, regulate blood lipid and reduce insulin resistance and cholesterol by regulating gut microbiota. Animal experiments and clinical trials demonstrated that probiotics, especially *Lactobacillus* and *Bifidobacterium*, had a good effect on the improvement of metabolic syndrome, showing the features of weight loss, lowering blood lipid, blood pressure and blood sugar and so on. Studies have shown that probiotics play a regulatory role in metabolic syndrome. Firstly, the data showed that the fat synthesis had been inhibited and its dissolves had been enhanced by probiotics. Secondly, probiotics protected pancreatic islet cells, improved insulin sensitivity and accelerated glucose transport. Finally, probiotics also increased the converse of cholesterol and the excretion of bile acid, and released angiotensin converting enzyme inhibitory peptides. However, some people hold neutral or opposing views. The paper reviewed the specific effects and mechanisms of probiotics in metabolic diseases such as obesity, type 2 diabetes mellitus (T2DM) and hypertension, and the problems which will be faced in application, so as to provide new ideas for the industrial development and application of probiotics in the future.

Although probiotics have shown excellent performances in regulating metabolic diseases, there is still a long way to achieve their clinical applications. Some of the proposed experimental evidence and mechanisms specifically targeting metabolic diseases effects remain inconclusive, and differences in probiotic strains, dosages and duration of effects remain to be explored. Therefore, more specific and thorough *in vivo* and clinical trials will need to be designed in the future to improve our understanding and eliminate uncertainty. Meanwhile, there are currently no standard safety guidelines for oral probiotics and prebiotics for use in human. Therefore, each probiotics and prebiotics should be carefully evaluated to identify potential adverse reactions. Future research is needed to increase our understanding of the complex interactions between gut and ingesting microbes. Nevertheless, we still believe that probiotics are expected to play an important role in metabolic diseases in the near future.

probiotics, metabolic diseases, gut microbiota, mechanism

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