

多糖与肠道菌群相互作用及其构效关系研究进展

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摘要: 肠道菌群是一个复杂的生态系统, 影响宿主的饮食、疾病发展、药物代谢和免疫系统调节等诸多生理方面。多糖广泛存在于动物、植物及微生物中, 具有多种生理活性。肠道菌群与多糖相互作用, 消化难以消化的多糖, 多糖作为肠道菌群的重要能量来源, 促进益生菌增殖。肠道菌群紊乱导致疾病的发生, 多糖通过调节肠道菌群改善疾病。随着“人类微生物组计划”的启动和国内外学者对肠道菌群的深入研究, 多糖与肠道菌群的关系逐渐清晰, 但多糖的结构与肠道菌群之间的关系还有待进一步探究。因此, 本文综述了多糖与肠道菌群的相互作用, 并通过调节肠道菌群的组成来改善疾病, 以及从多糖的分子量、糖苷键、单糖组成三方面探讨多糖与肠道菌群的构效关系, 同时对未来研究的方向进行展望, 以期治疗疾病的深入研究提供重要参照和建议。

关键词: 肠道菌群; 多糖; 炎症性肠病; 代谢疾病; 结直肠癌; 腹泻; 肝脏疾病; 构效关系

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Interaction between polysaccharide and intestinal flora and its structure-effect relationship: a review

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Abstract: Intestinal flora is a complex ecosystem which affects many aspects of human physiology, such as diet, disease development, drug metabolism, and immune system regulation. Ubiquitous in animals, plants, and microorganisms, polysaccharides have a variety of physiological activities. Intestinal flora interacts with polysaccharides and digests indigestible polysaccharides. Polysaccharides, which are an important energy source of intestinal flora, promote the proliferation of probiotics. Disorder of intestinal flora leads to the occurrence of diseases, and polysaccharides can alleviate the diseases by regulating intestinal flora. With the launch of Human Microbiome Project and the in-depth research on intestinal flora in China and abroad, relationship between polysaccharides and intestinal flora has been gradually elucidated. However, the relationship between intestinal flora and polysaccharide structure needs to be further explored. Therefore, this article summarized the interaction between polysaccharides and intestinal flora and the alleviation of diseases through regulating intestinal flora structure, and discussed the structure-activity relationship between polysaccharides and intestinal flora from the following aspects: molecular weight of polysaccharides, glycosidic bond, and monosaccharide composition. Moreover, we summed up the future research directions, hoping to provide a reference for further research on disease treatment.

Keywords: intestinal flora; polysaccharide; inflammatory bowel disease; metabolic disease; colorectal cancer; diarrhoea; liver disease; structure-activity relationship

肠道菌群(intestinal flora)是肠道微生态的核心部分,参与碳水化合物等物质的代谢,合成维生素等人体必需营养物质,也是连接饮食和人类健康的重要桥梁,在维持人体内环境稳定方面发挥着至关重要的作用^[1]。一旦有外界因素刺激,如环境和饮食的改变或服用抗生素、激素等药物,便会诱导肠道菌群失调^[2],引发多种疾病,如炎症性肠病、代谢疾病、结直肠癌、肝脏疾病和哮喘等^[3-4]。因此,维持人体肠道菌群的内环境平衡不容忽视。多糖(polysaccharide)是由 10 个以上单糖通过糖苷键连接成的天然

高分子多聚物,广泛来源于动物、植物、藻类和微生物,是构成生命的四大基本物质之一,因具有良好的生物活性和低毒副作用,早已被运用到医学和生命科学等领域中^[5]。由于人体缺乏碳水化合物活性酶(carbohydrate-activated enzymes, CAZymes),因此大多数多糖不能被人体直接消化和吸收,但由人类肠道微生物组编码的 CAZymes 可将低聚糖和多糖转化为单糖,产生易吸收的短链脂肪酸(short chain fatty acid, SCFA)和其他代谢物;此外,不同类型的多糖可以通过增加有益肠道微生物和减少有害

肠道微生物从而发挥对宿主的有益作用^[6]。探讨多糖与肠道菌群的相互作用、建立相关的饮食干预策略已成为当今国际研究的热点,并且我国多糖资源丰富,尤其是来源于中草药的植物多糖应用历史悠久,具有巨大的开发前景。因此,本文以多糖和肠道菌群为对象,主要综述多糖与肠道菌群相互作用、多糖调节肠道菌群对疾病的预防和治疗,以及从分子量、糖苷键和单糖组成三方面阐述多糖与肠道菌群的构效关系,以期为今后治疗疾病的深入研究和开发提供理论依据。

1 肠道菌群概况

人体肠道含有大量微生物群,它们之间相互作用组成一个复杂的网络,其种类及数量在一定范围内保持动态平衡。据统计,人类胃肠道中细菌根据自然属性主要分为4个门:厚壁菌门(*Firmicutes*, 64%)、拟杆菌门(*Bacteroid*, 23%)、变形菌门(*Proteobacteria*, 3%)和放线菌门(*Actinomycetes*, 3%)^[7]。拟杆菌门和厚壁菌门是最主要的门,占整个机体发育类型的90%以上。这些庞大的细菌根据与人体的关系又大致分为三类:有益菌、有害菌和中性菌。在健康宿主中,有益菌和致病菌处于相对平衡状态。一旦肠道菌群失调后,肠内致病菌大量增殖,不同种类的致病菌将通过直接或间接的作用方式促进疾病的发生发展^[8]。具核梭杆菌(*Fusobacterium nucleatum*)作为一种共生菌存在于人类肠道中,可以通过抑制免疫细胞功能^[9]、增加肿瘤多样性^[10]和激活自噬信号^[11]促进肿瘤的生长。Chung等^[12]用脆弱拟杆菌(*Bacteroides fragilis*)定殖的Apc^{Min+}小鼠模型发现可以触发致癌的多级炎症反应,从而共同触发了远端结肠骨髓细胞依赖性肿瘤发生。然而,肠道益生菌则可通过增强肠黏膜屏障、减

少肠道炎症、抑制致病菌活性、调节细胞的增殖和凋亡反应等作用机制来维持机体胃肠道健康^[13]。Yue等^[14]研究证明每天口服植物乳杆菌(*Lactobacillus plantarum*) YYC-3悬浮液可以下调白细胞介素(interleukin, IL)-6、IL-17和IL-22的表达,抑制核因子(nuclear factor, NF)- κ B和Wnt (wingless/integrated)信号通路,防止高脂肪饮食的APC^{Min/+}小鼠结肠肿瘤和黏膜损伤的发生。Madempudi等^[15]评价了凝结芽孢杆菌(*Bacillus coagulans*)对人结肠癌细胞的体外抗癌作用,结果表明凝结芽孢杆菌通过升高促凋亡蛋白Bax,降低抗凋亡蛋白Bcl2而诱导癌细胞凋亡。

2 多糖与肠道菌群相互作用

多糖在体内的生物活性受其消化和糖酵解特性的影响,许多多糖被人体消化和发酵吸收后在细胞中发挥作用。多糖的消化可以通过体外模拟人口腔、胃和小肠的消化环境,比较消化前后相对分子质量、还原糖和游离单糖等理化性质的变化,预测多糖的消化特性。大量实验发现,在体外消化过程中,每种多糖的变化是不同的。茯砖茶^[16](Fuzhuan brick tea)多糖和红江蓼^[17](*Gracilaria rubra*)多糖的分子量、单糖和还原糖含量在体外消化过程中没有发生变化,说明它们不能被消化系统消化。然而车前草^[18](*Plantago asiatica* L.)多糖、荡皮参^[19](*Holothuria leucospilota*)多糖和灵芝^[20](*Ganoderma lucidum*)多糖的分子量在胃肠消化过程中发生了显著变化,却未检测到游离单糖。从这些实验结果不难发现,多糖难以被人体的消化液降解,难以消化的多糖随着肠道蠕动进入大肠被微生物利用。多糖与肠道菌群相互作用,肠道菌群参与多糖代谢,多糖可作为肠道菌群的重要能量来源调节肠道菌群的组成。

2.1 肠道菌群参与多糖代谢

人类基因组无法编码足够针对不同糖苷键的有效活性酶(CAZymes), 这将限制糖酵解。然而肠道微生物的基因组合大约是人类基因组补体的 150 倍, 其可以诱导数千种互补的 CAZymes, 将大分子碳水化合物分解为小分子化合物^[21]。根据 CAZymes 的不同作用可将其分为五类催化酶和一类非催化模块^[22]。催化酶分别为糖苷水解酶(glycoside hydrolases, GHs)、多糖裂解酶(polysaccharide lyases, PLs)、碳水化合物酯酶(carbohydrate esterases, CEs)、糖基转移酶(glycosyl transferases, GTs)和辅助氧化还原酶(auxiliary activities, AAs); 非催化模块即碳水化合物结合模块(carbohydrate-binding modules, CBMs)。其中有 2 种酶可以切断碳水化合物之间或碳水化合物和非碳水化合物之间的糖苷键: GHs 一般通过插入水分子(水解)来完成, 主要参与简单碳水化合物主链的降解; PLs 是一组通过消除机制降解含糖醛酸的多糖长链的酶, 常用来切断复杂的碳水化合物^[23]。多糖在肠道菌群酵解作用下产生有益代谢产物, 特别是含有乙酸、丙酸和丁酸的短链脂肪酸, 一方面影响肠道环境, 例如降低肠道 pH 值; 另一方面转化为次生代谢物(CO₂、CH₄ 和 H₂)被宿主吸收利用, 通过干预宿主能量或物质代谢过程等, 影响细胞增殖和凋亡, 改变宿主健康状况^[24]。不同肠道菌群对多糖的降解能力与其所编码的 CAZymes 数量有关, 一般来说, 多糖越复杂, 分解它所需的酶就越多。例如拟杆菌门中的菌属平均编码 137.1 个 CAZymes 基因, 能够降解多种多糖; 而厚壁菌门中的菌属平均编码 39.6 个 CAZymes 基因, 只能降解少部分特异性多糖^[25]。多糖的水解只有当它们被运送到细菌的细胞表面时才会发生。因此, 这些细菌中的 GHs 和 PLs 一定含有输出到细胞表面的信号序列。研究发现拟

杆菌门中大约 81% 的 GHs 和 PLs 具有信号序列, 而厚壁菌门中只有 19% 的 GHs 和 PLs 具有信号序列^[26]。因此, 拟杆菌门具有较强的碳水化合物代谢能力。

2.2 多糖对肠道菌群的调节作用

多糖难以被消化吸收, 但可作为肠道菌群的碳源, 通过提高机体肠道微生物多样性, 调节肠道菌群组成来改善疾病和维持生理活性。现有研究表明, 多糖对肠道菌群的调节保护作用是多方面的。在菌群组成上, 多糖可促进有益菌增殖、抑制有害菌增殖, 从而调节肠道菌群, 使之形成更平衡的菌群结构; 在菌群功能上, 多糖可上调 CAZymes 基因的表达, 提高 CAZymes 的活性, 增加 SCFA 的生成, 降低炎症因子的表达和增加紧密连接蛋白的表达^[27]。据报道, 饮食中富含植物多糖和纤维的非洲儿童的肠道生物多样性明显高于典型西方高脂饮食的欧洲儿童。与欧洲儿童相比, 非洲儿童的拟杆菌门比例明显较高, 且普氏菌属(*Prevotella*)丰富; 而某些潜在病原体如志贺氏菌属(*Shigella*)和埃希氏菌属(*Escherichia*)的比例明显低于欧洲儿童^[28]。Han 等^[29]实验证明, 口服秋葵 [*Abelmoschus esculentus* (L.) Moench]多糖可显著提高正常小鼠肠道双歧杆菌(*Bifidobacterium*)和乳酸菌(*Lactobacillus*)的丰度, 降低拟杆菌属、肠球菌属(*Enterococcus*)和埃希氏菌属的丰度, 而且结肠内乙酸、丙酸和丁酸浓度显著高于对照组; 此外, 随着小鼠粪便中总 SCFAs 水平的提高, 小鼠的结肠黏膜和肌层厚度增加, 胃肠道通过时间缩短。Zhao 等^[30]通过灌胃 ICR 小鼠黑木耳多糖(*Auricularia auricular* polysaccharide, AAP), 高通量测序显示, AAP 喂养的小鼠粪便微生物群多样性丰富, 组成发生改变, 厚壁菌门/拟杆菌门比率显著降低, 紫单胞菌科(*Porphyromonadaceae*)和拟杆菌科的相对丰度增加。

不同的多糖促进不同肠道菌群的生长,这与多糖的本身结构有关^[31]。 β -葡聚糖(来自燕麦)增加双歧杆菌和乳酸杆菌在肠道微生物群中的数量^[32],拟杆菌能有效降解果聚糖^[33],木聚糖被布氏普雷沃氏菌(*Prevotella bryantii*)有效代谢^[34]。不同种类的多糖在肠道菌群作用下产生不同类型的 SCFA 及其他代谢产物(主要包括 CH_4 、 CO_2 等),产生的 SCFA 与肠道菌群共同调节机体健康。乙酸、丙酸和丁酸是肠道中最重要的 SCFA,乙酸和丙酸主要由拟杆菌门代谢产生,而厚壁菌门代谢主要产生丁酸^[35]。现有研究发现, β -葡聚糖、菊粉和低聚果糖类多糖可引起丁酸产量显著增加^[36];富含鼠李糖、鼠李半乳糖甘露聚糖的多糖在肠道微生物作用下可使丙酸含量增加; α -葡聚糖、果聚糖和阿拉伯糖基木聚糖类多糖可使机体肠道中的乙酸含量增加^[37]。多糖的结构影响其调节肠道各种微生物群的功能,然而肠道微生物如何根据多糖的结构特点使用不同类型多糖还有待进一步研究。

3 多糖调节肠道菌群改善疾病

近年来,由于肠道菌群与各种疾病之间千丝万缕的联系逐渐浮现,导致越来越多的研究者将目光转移到肠道菌群的研究上。据报道,炎症性肠病、代谢性综合征、结直肠癌、肝脏疾病和腹泻等疾病的发病机制与肠道菌群失调有关。多糖可通过调节肠道菌群失调,促进益生菌发挥生理作用,抑制致病菌增殖,改善疾病,具体作用机制见表 1。

3.1 炎症性肠病

炎症性肠病(inflammatory bowel disease, IBD)是一种慢性和复发性肠道炎症疾病,包括溃疡性结肠炎(ulcerative colitis, UC)和克罗恩病(crohn disease, CD),其患病率和发病率正在急

剧上升,目前是一个重要的健康问题^[52]。虽然 IBD 确切的发病机制尚不清楚,但随着高通量测序的发展,近几年研究者发现,在 IBD 患者肠道中存在异常的肠道菌群(失调),而且可能是长期慢性炎症的因果或协同因素^[53]。已有实验证明,IBD 患者体内的普拉梭菌(*Faecalibacterium prausnitzii*)、双歧杆菌和拟杆菌门显著减少,变形杆菌门比例显著增加^[54]。IBD 患者体内产生丁酸的厚壁菌门和氏菌属比例降低,导致 SCFA 水平降低,调节 T 辅助细胞 17/调节性 T 淋巴细胞(Th17/Treg)平衡紊乱,这可能是触发肠道炎症的关键因素^[55]。近年研究表明,肠道某些有益菌对 IBD 的治疗则具有积极作用。普拉梭菌通过显著降低 IL-12 和干扰素(interferon, IFN)- γ 产生水平、提高 IL-10 的分泌水平、阻断 NF- κ B 的活化发挥部分抗炎作用^[56]。植物乳杆菌^[57]显著降低 IL-1 β 和肿瘤坏死因子(tumor necrosis factor, TNF)- α 的表达,上调 IL-10 水平对 UC 大鼠有明显缓解作用。由此可推论,肠道有益菌如乳酸杆菌、双歧杆菌等可下调炎症肠组织表达促炎性细胞因子,并起到调节免疫细胞的功能。因此,通过促进肠道有益菌的增殖抑制致病菌可有效改善 IBD。

越来越多的研究表明,多糖可通过调节肠道菌群丰富度,增加有益菌水平,降低肠道的 pH 值,刺激肠道中巨噬细胞和淋巴细胞对抗 IBD 的发生;此外,肠道菌群发酵多糖类物质产生的乙酸、丙酸和丁酸等 SCFA 有助于调节肠内稳态,并可能通过表观遗传调控基因表达,降低脂肪组织中促炎症因子的产生^[58]。Cui 等^[38]发现,黄芩(*Scutellaria baicalensis* Georgi)多糖 SP2-1 可减轻 UC 小鼠的体重,显著提高小鼠结肠内乙酸、丙酸和丁酸水平,通过调节细胞因子减轻炎症。Fábrega 等^[59]报道,IBD 患者的厚壁菌门与拟杆菌门的比率降低,而且厚壁菌门的比例与胃肠

表 1 多糖调节肠道菌群改善疾病及其主要作用机制

Table 1 Polysaccharide regulates intestinal flora to improve disease and its main mechanism

多糖来源	实验模型	肠道菌群变化	主要作用机制
Polysaccharide source	Experimental model	Changes in intestinal flora	Main mechanism of action
黄芩 ^[38] <i>Scutellaria baicalensis</i> Georgi ^[38]	结肠炎小鼠 Colitis mouse	增加厚壁菌门、双歧杆菌门、乳酸杆菌门和氏菌属的丰度, 抑制拟杆菌门、变形菌门和葡萄球菌的水平 Increased the abundance of <i>Firmicutes</i> , <i>Bifidobacteria</i> , <i>Lactobacillus</i> and <i>Roseburia</i> , and inhibited the level of <i>Bacteroidetes</i> , <i>Proteobacteria</i> and <i>Staphylococcus</i>	降低促炎细胞因子 IL-6、IL-1 β 和 TNF- α 的水平; 上调紧密连接蛋白表达, 修复肠道屏障; 提高乙酸、丙酸和丁酸水平 Decreased the level of pro-inflammatory cytokines such as IL-6, IL-1 β and TNF- α ; up-regulated tight junction protein (ZO-1, Occludin, Claudin-5) expression, repaired the intestinal barrier; improved acetate propionic acid and butyric acid levels
菊花 ^[39] <i>Chrysanthemum morifolium</i> Ramat ^[39]	溃疡性结肠炎大鼠 Ulcerative colitis in rats	厚壁菌门/拟杆菌门比值上升; 降低埃希氏菌属、肠球菌属和普氏菌属丰度, 升高梭菌属、乳杆菌属、双歧杆菌属、毛螺菌科水平 Increased the ratio of <i>Firmicutes/Bacteroidetes</i> ; decreased the abundance of <i>Escherichia</i> , <i>Enterococcus</i> and <i>Prevotella</i> , and increased the abundance of <i>Clostridium</i> , <i>Lactobacillus</i> , <i>Bifidobacteria</i> and <i>Lachnospiraceae</i>	增加抗炎细胞因子 IL-4、IL-10、IL-11 水平; 降低 IL-23、IL-6、IF-17、TNF- α 、IL-1 β 和 IFN- γ 等促炎细胞因子水平 Increased levels of the anti-inflammatory cytokine such as IL-4, IL-10, IL-11; decreased IL-23, IL-6, IF-17, TNF- α , IL-1 β and IFN- γ levels of pro-inflammatory cytokines
罗布麻叶 ^[40] <i>Apocynum venetum</i> ^[40]	II型糖尿病小鼠 Type 2 diabetic mice	降低克雷伯氏菌属、肠球菌属和气球菌属的丰度; 降低厚壁菌门与拟杆菌门比率 Reduced the abundance of <i>Klebsiella</i> , <i>Enterococcus</i> and <i>Aerococcus</i> ; decreased the ratio of <i>Firmicutes/Bacteroidetes</i>	降低空腹血糖、血清胰岛素、糖化血清蛋白水平和血脂水平, 显著改善氧化损伤 Decreased fasting blood glucose, serum insulin, glycosylated serum protein level and lipid level, significantly improved oxidative damage
姬松茸 ^[41] <i>Agaricus blazei Murrill</i> ^[41]	高脂血症大鼠 Hyperlipidemia rats	降低厚壁菌门/拟杆菌门比例; 增加消化链球菌科、丹毒丝菌科和梭菌科丰度 Decreased the ratio of <i>Firmicutes/Bacteroidetes</i> ; increased the abundance of <i>Peptostreptococcaceae</i> , <i>Erysipelaceae</i> and <i>Clostridium</i>	调节脂质代谢, 改善肝小叶紊乱和肝细胞脂肪变性 Egulated lipid metabolism, improved hepatic lobule disorder and hepatic cell steatosis
藜麦 ^[42] <i>Chenopodium quinoa Willd.</i> ^[42]	高脂饮食大鼠 High fat diet rats	降低厚壁菌门和拟杆菌门的比例; 降低变形菌门和脱硫弧属的相对丰度 Decreased the ratio of <i>Firmicutes/Bacteroidetes</i> ; reduced the relative abundance of <i>Proteobacteria</i> and <i>Desulfovibrio</i>	改善肝脏中转氨酶(AST、ALT)异常水平; 降低肝脏脂质积累和降低 TG、LDL-C、MDA 水平 Improved the abnormal level of AST and ALT in liver; decreased lipid accumulation and decreased level of TG, LDL-C and MDA in liver

(待续)

(续表 1)

枣 ^[43] <i>Ziziphus jujuba</i> Mill. ^[43]	结肠炎肿瘤小鼠 Colitis tumor mice	增加拟杆菌门的相对丰度, 减少厚壁菌门的相对丰度; 厚壁菌门与拟杆菌门的比率降低 The relative abundance of <i>Bacteroidetes</i> were increased and that of <i>Firmicutes</i> were decreased; decreased the ratio of <i>Firmicutes/Bacteroidetes</i>	影响细胞组分基因, 包括细胞质、细胞质膜和膜的整体组分; 调节免疫系统 Genes that affected cellular components, including cytoplasm, cytoplasmic membrane and membrane components; regulated the immune system
苹果 ^[44] <i>Malus pumila</i> Mill. ^[44]	结直肠癌小鼠 Colorectal cancer mice	降低厚壁菌门丰度, 增加拟杆菌门丰度 The abundance of <i>Firmicutes</i> were decreased and the abundance of <i>Bacteroidetes</i> were increased	减少 T 细胞和巨噬细胞数量, 抑制 β -catenin 核聚集, 抑制结肠组织 Wnt 通路的激活 The number of T cells and macrophages were decreased, the aggregation of β -catenin nucleus was inhibited, and the activation of Wnt pathway in colon tissue was inhibited
地木耳 ^[45] <i>Nostoc commune</i> Vaucher ^[45]	结肠炎肿瘤小鼠 Colitis tumor mice	减少拟杆菌门丰度, 增加厚壁菌门、丁酸弧菌属、丁酸蓖麻单胞菌、毛罗菌科和布劳特氏菌属丰度 The abundance of <i>Bacteroidetes</i> were decreased and the abundance of <i>Firmicutes</i> , <i>Butyrivibrio</i> , <i>Butyricimonas</i> , <i>Lachnospiraceae</i> and <i>Blautia</i> were increased	降低结肠肿瘤发生率 Reduced the incidence of colon tumors
人参 ^[46] <i>Panax ginseng</i> C. A. Meyer ^[46]	抗生素相关性腹泻小鼠 Antibiotic associated diarrhea in mice	增加厚壁菌门的相对丰度, 降低拟杆菌门、变形菌门和放线菌门的相对丰度; 在属水平上, 增加乳杆菌属和链球菌属的相对丰度 The relative abundance of <i>Firmicutes</i> were increased and that of <i>Proteobacteria</i> and <i>Actinomycetes</i> were decreased; at the genus level, the relative abundance of <i>Lactococcus</i> , and <i>Streptococcus</i> were increased	调节碳水化合物、氨基酸和能量代谢过程; 促进黏膜结构的恢复 Regulated carbohydrate, amino acid and energy metabolism process; promoted the recovery of mucosal structure
紫薯 ^[47] <i>Ipomoea batatas</i> (L.) Lam ^[47]	抗生素相关性腹泻小鼠 Antibiotic associated diarrhea in mice	增加拟杆菌门的丰度, 降低厚壁菌门和变形菌门(包括大肠杆菌和克雷伯氏菌)的丰度 Increased the abundance of <i>Bacteroidetes</i> and decreased the abundance of <i>Firmicutes</i> and <i>Proteobacteria</i> (including <i>Escherichia coli</i> and <i>Klebsiella</i>)	降低 IL-1 β 、IL-6 和 TNF- α 水平, 提 IL-10 水平, 平衡脂肪酸代谢 Decreased IL-1 β , IL-6 and TNF- α levels, increased IL-10 levels; balanced fatty acid metabolism
枸杞 ^[48] <i>Lycium barbarum</i> L. ^[48]	高脂饮食诱导非酒精性脂肪肝大鼠 Nonalcoholic fatty liver disease induced by high fat diet in rats	增加拟杆菌门和丁酸蓖麻单胞菌的丰度, 降低变形菌门和厚壁菌门的比例 The abundance of <i>Bacteroidetes</i> and <i>Butyricimonas</i> were increased, and the proportion of <i>Proteobacteria</i> and <i>Firmicutes</i> were decreased	增加紧密连接蛋白表达, 恢复结肠和回肠紧密连接; 下调肝脏肠源性脂多糖、炎症因子及炎症通路相关指标 Increased tight junction protein expression and restored tight junction between colon and ileum; down-regulated of liver and intestinal lipopolysaccharide, inflammatory factors and inflammatory pathway related indicators

(待续)

(续表 1)

长牡蛎 ^[49] <i>Crassostrea gigas</i> ^[49]	酒精性肝损伤小鼠 Alcoholic liver injury in mice	显著提高罗伊氏乳杆菌和氏菌属的含量, 降低了埃希氏菌属的水平 Significantly increased the contents of <i>Lactobacillus reuteri</i> and <i>Roseburia</i> , and reduced the level of <i>Escherichia</i>	提高紧密连接蛋白的表达和抑制炎症反应; 激活 AMPK α /SREBP1c 通路和升高 SCFA 水平; 恢复肠道屏障, 减少脂质积累 Enhanced tight junction protein expression and inhibited inflammatory response; activated AMPK α /SREBP1c pathway and increased SCFA level; restored intestinal barrier and reduced lipid accumulation
灵芝 ^[50] <i>Ganoderma lucidum</i> (Curtis) P. Karst. ^[50]	慢性胰腺炎小鼠 Chronic pancreatitis mice	降低拟杆菌门的相对丰度, 增加厚壁菌门的相对丰度; 属水平上, 提高乳酸菌属、氏菌属和毛螺菌属等有益菌的相对丰度 The relative abundance of <i>Bacteroidetes</i> were decreased and that of <i>Firmicutes</i> were increased; at the genus level, the relative abundance of beneficial bacteria such as <i>Lactobacillus</i> , <i>Roseburia</i> and <i>Lachnospira</i> were increased	降低脂肪酶、IFN- γ 和 TNF- α 水平, 提高超氧化物歧化酶(SOD)和总抗氧化活性 The levels of lipase, IFN- γ and TNF- α were decreased, and superoxide dismutase (SOD) and total antioxidant activity were increased
车前子 ^[51] Plantain seed ^[51]	膜性肾病大鼠 Membranous nephropathy in rats	有害菌厚壁菌门丰度降低, 有益菌拟杆菌门丰度升高 The abundance of the harmful fungus <i>Firmicutes</i> were decreased while the abundance of the beneficial fungus <i>Bacteroidetes</i> were increased	降低 TNF- α 和 IL-1 β 蛋白表达, 恢复受损肠道屏障 Decreased TNF- α , IL-1 β protein expression and restored the damaged intestinal barrier

道炎症呈负相关。然而, 经 SP2-1 治疗后小鼠肠道中厚壁菌门、双歧杆菌、乳酸菌和罗氏菌属(*Roseburia*)丰度显著增加, 拟杆菌属、变形杆菌属和葡萄球菌属(*Staphylococcus*)的水平受到抑制^[38]。Tao 等^[39]通过 UC 大鼠模型评估菊花(*Chrysanthemum morifolium* Ramat)多糖对肠道微生物群的影响。对大鼠结肠内容物进行 16S rRNA 基因测序, 随着菊花多糖的增加, 大鼠肠道中厚壁菌门与拟杆菌门的比值也逐渐上升; 菊花多糖可改善 UC 大鼠肠道微生物多样性和群落丰富度, 并可恢复模型组肠道菌群的组成; 致病菌(埃希氏菌属、肠球菌属和普氏菌属)的丰度降低, 益生菌[梭菌属(*Clostridium*)、乳杆菌属、双歧杆菌属、毛螺菌科(*Lachnospiraceae*)等]的水平平均不同程度升高; 此外, 大鼠肠道菌群与生化

因子的相关性分析表明, 益生菌的相对丰度与抗炎细胞因子 IL-4、IL-10、IL-11 水平呈正相关, 致病菌与促炎细胞因子 IL-23、IL-6、TNF- α 、IL-1 β 和 IFN- γ 呈正相关。这些研究表明, 肠道菌群与机体内细胞因子的分泌和表达密切相关, 并相互作用调节免疫功能, 多糖类物质能够影响肠道菌群及其代谢产物降低炎症因子的表达进而有效预防 IBD, 但其具体机制仍需进一步探索。

3.2 糖尿病

糖尿病(diabetes mellitus, DM)是一种长期的糖代谢紊乱疾病, 严重影响患者的健康和生活质量。研究发现, 肠道菌群失调是导致 DM 发生的重要因素, 其主要通过干预 SCFA 代谢、胆汁酸代谢和脂多糖(lipopolysaccharides, LPS)分泌

等途径促进 DM 的发生与发展^[60]。传统的治疗药物在降血糖的同时会带来许多副作用,而一些具有降血糖作用的植物多糖因其来源广泛、毒副作用小,引起了国内外研究人员的关注。多糖的降糖作用与肠道菌群密切相关,肠道中的细菌可以分解多糖并产生 SCFA, SCFA 有益地调节脂肪组织和肝组织功能,从而改善葡萄糖稳态和胰岛素敏感性^[61]。此外, SCFA 平衡位于黏膜上皮和固有层的致糖尿病的 Treg 细胞,进一步影响肠道和胰腺免疫环境,防止自身免疫性糖尿病的发展^[62]。与此同时,多糖通过调节肠道菌群发挥降血糖的作用机制也逐渐完善,其可能是通过增加 SCFA 产生菌的丰度,同时减少 LPS 产生菌的数量,促进紧密连接蛋白的表达,增强肠道屏障完整性,促进 Treg 细胞的生成,减少全身炎症,促进胰高血糖素样肽(glucagon-like peptide, GLP)-1的释放,从而发挥降低血糖的功能^[63]。

在一项研究中, II型糖尿病(type 2 diabetes mellitus, T2DM)的研究患者与健康个体相比,患者肠道中厚壁菌门丰度显著上升,而拟杆菌门的丰度显著降低,厚壁菌门与拟杆菌门的比例显著升高^[64]。杨明琛等^[65]探讨黄精多糖对 T2DM 小鼠肠道菌群的调节作用,通过对酵解物进行 16S rRNA 基因序列分析,发现 T2DM 小鼠的肠道菌群经过黄精多糖的酵解后,从菌门水平上比较,其厚壁菌门的相对丰度显著降低,变形菌门和拟杆菌门的相对丰度显著上升;从菌属水平上比较,乳酸菌属的相对丰度显著降低,韦荣氏球菌属(*Veillonella*)、埃希氏菌属和克雷伯氏菌属(*Klebsiella*)的相对丰度显著上升。Yuan 等^[40]研究了罗布麻叶(*Apocynum venetum*)多糖对链脲佐菌素(streptozotocin, STZ)诱导 T2DM 小鼠的降血糖作用及其对肠道菌群的影响,结果表明,罗布麻叶多糖可显著降低空腹血糖、血清胰岛素和

糖化血清蛋白水平,以及包括总胆固醇(total cholesterol, TC)、低密度脂蛋白胆固醇(low density lipoprotein cholesterol, LDL-C)和非酯化脂肪酸在内的血脂水平,并显著改善了氧化损伤;此外,通过对小鼠肠道微生物群落结构进行 OTU 聚类分析,在门水平上,厚壁菌门与拟杆菌门比率降低,且变形菌门降低至正常水平。因此,多糖可以用作肠道菌群靶向益生元,以防止肠道菌群失调,改善 II型糖尿病的发生与发展。

3.3 高血脂

高血脂(hyperlipemia)是由脂质代谢失调引发的体内血脂升高的一类代谢疾病。在动物和人类研究中,肠道微生物组的丰富度、多样性失调与高血脂密切相关,大致分为三种:第一种为肠道菌群中双歧杆菌含量异常变化,引起肠道内 LPS 水平升高,增加促炎因子的分泌,诱发高脂血症^[66];第二种为双歧杆菌和拟杆菌门比例变化使腺苷酸激活蛋白激酶(AMP-activates protein kinase, AMPK)能量代谢路径受阻,从而导致 SCFA 含量下降,加速肝脏胆固醇合成并且抑制了胆汁酸的分泌,引发高脂血症^[67];第三种为肠道菌群中拟杆菌门的含量异常,导致三酰甘油生成增多,肝脏中脂肪的堆积,引起高脂血症^[68]。目前大量研究发现,多糖可以通过促进肠道内益生菌的增殖、抑制有害菌的生长,改善肠道菌群,发挥调节脂质代谢的作用,但其调节脂质代谢的具体机理还未能确定和统一。据报道,多糖可以通过上调有益菌的含量影响 AMPK 通路激活乙酰辅酶 A 羧化酶(acetyl-CoA carboxylase, ACC)因子的表达促进短链脂肪酸合成,从而抑制肝脏内胆固醇的合成及促进胆汁酸分泌达到调节脂质代谢的作用;不仅如此,多糖能够上调肠道内环境中益生菌比例,使 NF- κ B、丝裂原活化蛋白激酶(mitogen activated protein kinase, MAPK)和 PI3K/Akt 等信号通路中断及相关炎症因子被抑

制,从而减少炎症反应,为维持脂质代谢稳态起到了积极的作用^[69]。

多糖可增加肠道菌群中益生菌水平、降低致病菌的比例,其主要调节以厚壁菌门、双歧杆菌和拟杆菌门等为代表的肠道菌群丰度,并通过增加短链脂肪酸的含量和降低炎症反应达到调节脂质代谢的功能。Li 等^[41]研究结果表明,姬松茸 (*Agaricus blazei* Murrill. polysaccharides, ABPs) 多糖可调节高脂血症大鼠的血脂异常,显著降低大鼠血清 TC、甘油三酯(triglyceride, TG) 和 LDL-C 水平,提高高密度脂蛋白胆固醇(high density lipoprotein cholesterol, HDL-C)水平,改善肝小叶紊乱和肝细胞脂肪变性;菌群多样性分析表明,经 ABPs 处理后,小鼠肠道中厚壁菌门/拟杆菌门的比例降低,消化链球菌科(*Peptostreptococcaceae*)、丹毒丝菌科(*Erysipelotrichaceae*)和梭菌科(*Clostridiaceae*)等相对丰度增加。Cao 等^[42]研究发现,藜麦(*Chenopodium quinoa* Willd.)多糖通过降低 TG、LDL-C、丙二醛(malondialdehyde, MDA)的水平,显著缓解高脂肪饮食(high fat diet, HFD)大鼠血脂异常并恢复紊乱的肠道微生物群;16S rRNA 基因测序显示,藜麦多糖降低小鼠厚壁菌门和拟杆菌门的比例,降低变形菌门和脱硫弧属(*Desulfovibrio*)的相对丰度。

3.4 结直肠癌

结直肠癌(colorectal cancer, CRC)是一种发生在人体下消化道结肠或直肠的恶性肿瘤,其发病率和死亡率仅次于胃癌和肝癌。CRC 病因研究指出饮食、遗传、炎症等因素与其发病密切相关,近年来众多研究表明肠道菌群失衡在 CRC 的发展中可能发挥着重要作用,其可能通过肠道细菌对肠道上皮细胞 DNA 直接造成损伤、诱发肠管慢性炎症反应、干扰免疫反应信号通路诱导炎症因子释放或产生有毒代谢产物及影响 CRC

患者化疗药物疗效等作用促进肿瘤发生^[70]。目前已有大量研究表明核梭杆菌、产肠毒脆弱拟杆菌(*Enterotoxigenic Bacteroides fragilis*, ETBF)和大肠杆菌是 CRC 相关的重要致病菌^[71]。核梭杆菌通过形成炎症微环境促进癌症生长,触发 CRC 细胞中的几个重要信号通路(NF- κ B)^[9];大肠杆菌的致病菌株可合成各种毒素,通过 DNA 酶活性诱导细胞 DNA 损伤,并刺激 NF- κ B 促炎反应^[72]。脆弱拟杆菌具有高度的炎症潜能,可引起 T17 细胞和 Treg 细胞的增加,通过诱导髓样细胞分化为髓样源性抑制细胞促进早期肿瘤生长^[73]。

目前,临床上治疗 CRC 的放疗和化疗手段具有明显的局限性,对正常组织、器官副作用大。然而研究发现,多糖因成本低、副作用小且能通过调节肠道菌群,从而抑制致病菌增殖、促进有益菌生长,降低肠道炎症,在一定程度上可减轻 CRC 症状。Ji 等^[43]研究了枣(*Jujube polysaccharide*, JP)多糖对偶氮甲烷(azoxymethane, AOM)/葡聚糖硫酸钠(dextran sulfate sodium, DSS)诱导的结肠炎肿瘤小鼠的影响;经 JP 治疗后缓解了小鼠的体重减轻现象,抑制了结肠肿瘤的数量和大小;高通量测序分析其肠道菌群结构发现拟杆菌门的相对丰度显著增加,而厚壁菌门的相对丰度显著减少,厚壁菌门与拟杆菌门的比率降低。Li 等^[44]研究苹果多糖(apple polysaccharide, AP)是否可以通过调节肠道微生物群紊乱来预防 CRC,ICR 小鼠灌胃给予 AP 15 周后结果发现,AP 处理后显著减少了小鼠结肠组织中 T 细胞和巨噬细胞数量,抑制了结肠组织中 Wnt 通路的激活;此外,AP 组小鼠的厚壁菌门数量显著减少、拟杆菌数量显著增加,使小鼠肠道微生物丰度恢复到对照组水平。Guo 等^[45]评估地木耳多糖(*Nostoc commune* Vaucher polysaccharides, NVPS)对小鼠结肠肿瘤发生的保护作用及其对肠道微

生物群的影响,小鼠灌胃给予 NVPS 14 周显著减少了肿瘤数量和大小;利用 16S rRNA 基因测序和 qPCR 技术分析小鼠粪便样本的细菌组成,结果表明 NVPS 显著增加了厚壁菌门的丰度、减少了拟杆菌门丰度,从而改变了厚壁菌门与拟杆菌门的比例;此外,在 NVPS 干预后产生 SCFA 的细菌属大幅增加,包括丁酸弧菌属(*Butyrivibrio*)、丁酸蓖麻单胞菌(*Butyricimonas*)、毛罗菌科(*Lachnospiraceae*)和布劳特氏菌属(*Blautia*)。多糖预防 CRC 有降低肿瘤复发率的作用,而针对多糖调节肠道菌群,临床试验表明多糖具有提升肠道益生菌、抑制肠道有害菌、改善肠道炎症环境、减少有毒致癌物质释放及影响腺瘤形成的信号通路的作用,进而抑制肠道肿瘤的发生;此外,肠道菌群酵解多糖的代谢物 SCFA 可以抑制肿瘤细胞的增殖、诱导黏蛋白(mucoprotein, MUC)的合成,加强上皮细胞之间的紧密连接,从而预防炎症,最终抑制肠道肿瘤的增长^[74]。目前对多糖调节肠道菌群抑制 CRC 的研究主要集中于多糖对益生菌的促进作用,而多糖通过调节肠道菌群改善 CRC 的具体作用机制还有待进一步深入研究。

3.5 腹泻

腹泻主要分为病毒性腹泻、细菌性腹泻和营养性腹泻等。其中对动物危害最严重的是细菌性腹泻,大肠杆菌(*Escherichia coli*)、沙门氏菌(*Salmonella*)是引起动物细菌性腹泻的常见病原体。大肠杆菌寄生于动物肠道内,处于正常范围内的大肠杆菌不会致病,当环境条件改变或动物免疫力下降时,大肠杆菌种群数量会发生改变,引发一系列的动物胃肠道问题^[75];沙门氏菌入侵肠道黏膜时,以淋巴组织为环境进行大量繁殖,从而破坏宿主免疫系统^[76]。

多糖可改变肠道菌群的种类,修复肠道上皮细胞和肠相关淋巴组织来预防和治疗肠道菌群

失衡,减少致病性大肠杆菌的数量,降低腹泻发生率。任多多等^[77]提取得到水溶性西洋参多糖(water-soluble *Panax quinquefolius* polysaccharide, WQP),通过灌胃克林霉素磷酸酯建立抗生素相关腹泻模型,利用 WQP 干预后大鼠腹泻症状减轻,改善了结肠组织水肿,恢复肠道菌群多样性;在门水平上,可降低厚壁菌门和变形菌门的相对丰度,增加拟杆菌门的相对丰度;在属水平上,可降低拟杆菌属和梭菌属的相对丰度。Li 等^[46]探讨了人参多糖(*Panax ginseng* polysaccharide, WGP)对盐酸林可霉素诱导腹泻小鼠肠道微生物多样性的影响,与腹泻小鼠相比, WGP 增加厚壁菌门的相对丰度,降低拟杆菌门、变形菌门和放线菌门的相对丰度;在属水平上,增加了乳杆菌属、乳球菌属(*Lactococcus*)和链球菌属(*Streptococcus*)的相对丰度,降低了拟杆菌属的丰度;此外, WGP 还能使碳水化合物、氨基酸和能量代谢恢复到正常水平,从而促进黏膜结构的恢复,改善腹泻症状。Bie 等^[47]从紫薯中提取了非淀粉多糖(purple sweet potato polysaccharide, PSPP),体内实验表明 PSPP 可改善盐酸林可霉素对小鼠回肠的结构损害,增加 SCFA 的含量,并在一定程度上缓解腹泻症状; β 多样性分析表明, PSPP 增加了拟杆菌门的丰度,降低了厚壁菌门和变形菌门(包括大肠杆菌和克雷伯氏菌)的丰度,减少肠道炎症的发生。

3.6 肝脏疾病

肠道微生物群最近发展成为许多肠道和肠外疾病病理生理学中的一个新的重要角色。由于肝脏和肠道通过门静脉相连,使肝脏更容易暴露于易位的细菌和炎症介质中。在某些病理条件下,肠道屏障的破坏可导致致病菌易位和免疫系统的异常活化,引发肝脏炎症和损伤,各种肝脏疾病如酒精性肝病、非酒精性肝病和原发性硬化性胆管炎等,均与微生物组改变有关^[78]。

非酒精性脂肪肝(nonalcoholic fatty liver disease, NAFLD)是一种常见的临床综合征,是由除饮酒或任何其他公认的肝损伤以外的因素引起肝内脂肪过量堆积的慢性疾病。研究表明,肠道菌群主要通过干预脂质代谢、改变肠道通透性、产生内源性乙醇等机制促进 NAFLD 发展^[79]。临床上有专门针对非酒精性脂肪肝治疗的药物,但目前饮食和生活方式干预是比较好的治疗方式。近年来,研究发现多糖可以通过调节机体肠道菌群结构,从而保护和改善 NAFLD。多糖进入肠道后,通过肠道菌群酵解能够有效补充肠道有益菌,在肠道内与肠道致病革兰阴性菌竞争,减少脂多糖(革兰阴性菌细胞壁的主要组成部分)的含量,并激活肠道 FXR-FGF15 通路^[80],减轻肝组织的炎症反应及氧化应激;此外,有益菌促进肠道紧密连接蛋白表达,提高肠黏膜屏障的完整性,降低血液循环中肠源性内毒素水平,减轻肝损伤及脂肪沉积,减少胆固醇的生成,降低 NAFLD 发病率^[81]。与此同时,肠道菌群代谢产物中的短链脂肪酸通过降低肠道 pH 值、改善肠道通透性、调节肠道上皮的渗透性及其功能,从而阻止肠道细菌过度生长和细菌移位,减少 NAFLD 并发症^[82]。Gao 等^[48]实验发现,枸杞多糖(*Lycium barbarum* polysaccharide, LBP)通过改善肠道菌群紊乱、上调 SCFA 和紧密连接蛋白水平、修复肠道上皮屏障、阻止肠道源性细菌缓解了 HFD 小鼠的肝脏损伤;肠道微生物群的 β 多样性分析表明, LBP 组小鼠呈现出较高的肠道菌群丰度和多样性,增加了部分拟杆菌门和短链脂肪酸,降低了变形菌门和厚壁菌门的比例,同时增加了丁酸萆麻单胞菌的丰度。韩琳^[83]用 16S rRNA 基因高通量测序技术研究大豆 [*Glycine max* (Linn.) Merr.]皮多糖对 CCl₄ 致小鼠肝损伤的肠道菌群的影响,研究结果表明, CCl₄ 处理的小鼠肠道菌群中厚壁菌门含量降低,拟杆菌门

含量显著上升;此外,大豆皮多糖干预还可显著降低拟杆菌门含量,提高厚壁菌门含量,同时增加双歧杆菌、乳酸杆菌和阿克曼菌(*Akkermansia*)的含量,通过调节 Nrf2 信号通路调节细胞内氧化还原状态,提高肝细胞抗氧化应激能力,发挥肝脏损伤保护作用。

酒精性肝病(alcoholic liver disease, ALD)是由于长期大量饮酒导致的中毒性肝病,严重危害自体健康。研究表明,酒精会破坏肠道微生物群,使拟杆菌门减少、变形菌门和放线菌门增加,改变肠道屏障,导致细菌及细菌产物易位,细菌内毒素(如 LPS、细菌 DNA)释放到肝,引发炎症反应^[84]。各种饮食和益生元等疗法可能通过调节肠道菌群增加短链脂肪酸生成,缓解 ALD 的肠道菌群紊乱,改善肠屏障功能及炎症反应,保护肝脏损伤。范颖等^[85]研究了大蒜多糖对急性酒精性肝损伤小鼠肠道菌群失调的影响, PCR-DGGE 结果显示,急性 ALD 的小鼠肠道菌群多样性指数降低,优杆菌属(*Eubacterium*)和乳酸菌属细菌明显减少,大蒜多糖组的多样性指数和均匀度指数最高,优杆菌属和乳酸菌属细菌增多。Jiang 等^[49]证明,长牡蛎多糖(*Crassostrea gigas* polysaccharides, RPS)可降低 ALD 小鼠肝脏中脂质和促炎细胞因子的积累,显著提高罗伊氏乳杆菌(*Lactobacillus reuteri*)和氏菌属的含量;微生物代谢产物,尤其是丙酸和丁酸显著增加;在目前的研究中,乙醇增加了大肠杆菌的丰度和肝脏促炎细胞因子(TNF- α 和 IL- β)的水平,经 RPS 处理后,大肠杆菌水平均受到抑制。

3.7 其他疾病

Li 等^[50]研究了灵芝多糖 S3 (*Ganoderma lucidum* polysaccharide S3, GLP S3)对小鼠慢性胰腺炎治疗及肠道菌群调节的作用, GLP S3 通过降低脂肪酶、IFN- γ 和 TNF- α 水平显著减轻了小鼠胰腺炎症状;高通量测序分析表明, GLP S3

降低了拟杆菌门的相对丰度,增加了厚壁菌门的相对丰度;在属水平上,提高了乳酸菌属、氏菌属和毛螺菌属(*Lachnospiraceae*)等有益菌的相对丰度。赵宏等^[51]研究车前子多糖(Plantain seed polysaccharide, PSP)对膜性肾病大鼠肾损伤的保护作用及对肠道菌群的影响,16S rRNA 基因测序结果显示,给予 PSP 后大鼠肠道中有害菌厚壁菌门丰度降低、有益菌拟杆菌门丰度升高,可有效缓解大鼠的肾损伤、降低炎症因子的表达、改善受损的肠道屏障。崔芳等^[86]探讨枸杞多糖(*Lycium barbarum* polysaccharide, LBP)对过敏性哮喘小鼠肠道菌群的影响,测序分析结果表明,LBP 显著影响了肠道菌门水平的厚壁菌门和拟杆菌门,在菌群属水平上显著影响了乳酸菌属、梭菌属和拟杆菌属。

4 多糖调节肠道菌群的构效关系

多糖的化学结构是其生物活性的基础,不同化学结构的多糖其生物活性具有较大的差异。由于多糖结构的复杂性,截至目前,多糖与肠道菌群的构效关系研究并不完善。本文通过总结近几年国内外实验研究,主要从多糖分子量、糖苷键和单糖组成进行讨论。

4.1 分子量

相对分子质量是影响多糖生物活性的一个重要因素。研究表明,多糖的相对分子质量需要在合适的范围内才能发挥最佳活性。相对分子质量越大,多糖分子体积也越大,其跨膜阻力也将随之增大,因此不利于吸收利用,从而影响活性的发挥;但相对分子质量太低,则多糖无法形成具有活性的结构,从而降低其活性^[87]。

不同来源的多糖产生生物活性的最佳相对分子质量范围也不同。王莹^[88]实验证明,高分子量(120.74×10^4 Da)的枸杞多糖可改善免疫抑制小鼠菌群多样性,提高双歧杆菌、乳杆菌、拟

杆菌的相对丰度。Deng 等^[89]对低、中、高分子量的魔芋葡甘露聚糖(konjac glucomannan, KGM)探究了理化性质、降糖作用及机制分析,结果表明,中等分子量的 KGM (KGM-M₁: 757.1 kDa; KGM-M₂: 252.7 kDa)对小鼠增重、降低空腹血糖、胰岛素抵抗、TC 和 LDL-C 水平、增强胰腺和结肠完整性的作用优于高分子量(KGM-H: 1 129.5 kDa)和低分子量(KGM-L: 87.3 kDa)的 KGM;此外, KGM-M₁ 和 KGM-M₂ 增加了肠道菌群多样性,包括拟杆菌门/厚壁菌门比值,降低了罗姆布茨菌(*Romboutsia*)和克雷伯氏菌,改善了 6 种糖尿病相关代谢产物。KGM-H、KGM-M₁、KGM-M₂ 和 KGM-L 组的拟杆菌门数分别增加了 6.14%、24.2%、18.38%和 12.28%。然而有些来源的多糖,分子量小则更有利于活性的发挥。石丹等^[90]研究发现 7 组不同分子量段的蒲公英(*Traxacum mongolicum* Hand.-Mazz.)多糖均能改善林可霉素灌胃导致的小鼠菌群失调,显著增加双歧杆菌和乳酸杆菌数量、减少肠杆菌和肠球菌数量,其中较低相对分子质量(>100 000、6 000–10 000)的作用最明显。董嘉琪^[91]实验发现低分子量(19.420 kDa)的红芪多糖更有利于调节小鼠失调的肠道菌群,保护肠道健康。

4.2 单糖组成

大量研究发现,多糖的益生活性与其单糖组成密切相关,多糖的单糖组成不同可能导致其对肠道菌群的影响也不同。表 2 总结了部分具有调节肠道菌群活性的多糖的单糖组成。

从表 2 可以看出,大部分具有调节肠道菌群活性的多糖都具有甘露糖、葡萄糖、鼠李糖、半乳糖和阿拉伯糖,少数具有半乳糖醛酸、葡萄糖醛酸、岩藻糖和木糖。葡萄糖含量更高,则益生菌活性更强。孔秋红等^[97]研究了 4 种不同方法提取的羊栖菜多糖(*Sargassum fusiforme*

表 2 具有调节肠道菌群活性的部分多糖的单糖组成

Table 2 Monosaccharide composition of partial polysaccharides that regulate the activity of the gut microbiota

多糖来源 Polysaccharide sources	实验模型 Experimental models	肠道菌群变化 Changes in intestinal flora	单糖组成及比例 Composition and proportion of monosaccharides
黄芩 ^[45] <i>Scutellaria baicalensis</i> Georgi ^[45]	DSS 诱导小鼠结肠炎模型 DSS induced mouse colitis model	增加厚壁菌门、双歧杆菌门、乳酸杆菌门和氏菌属的丰度,抑制拟杆菌门、变形菌门和葡萄球菌的水平 Increased the abundance of <i>Firmicutes</i> , <i>Bifidobacteria</i> , <i>Lactobacilli</i> and <i>Roseburia</i> , and inhibited the level of <i>Bacteroidetes</i> , <i>Proteobacteria</i> and <i>Staphylococcus</i>	甘露糖、核糖、鼠李糖、葡萄糖醛酸、葡萄糖、木糖、阿拉伯糖(摩尔比为 5.06:21.24:1.00:20.25:3.49:50.90:228.77:2.40) Mannose, ribose, rhamnose, glucuronic acid, glucose, xylose, arabinose (the mole ratio was 5.06:21.24:1.00:20.25:3.49:50.90:228.77:2.40)
紫甘薯 ^[92] <i>Ipomoea batatas</i> (L.) Lam ^[92]	DSS 诱导小鼠溃疡性结肠炎模型 DSS induced mouse model of ulcerative colitis	变形菌门相对丰度显降低,厚壁菌门水平明显升高;厚壁菌门与拟杆菌门的比值显著升高 The relative abundance of <i>Proteobacterias</i> were decreased and <i>Firmicutes</i> were increased; The ratio of <i>Firmicutes</i> to <i>Bacteroidetes</i> increased significantly	鼠李糖、阿拉伯糖、木糖、甘露糖、葡萄糖(摩尔比为 2.8:1.9:1.0:7.6:53.3) Rhamnose, arabinose, xylose, mannose, glucose (the mole ratio was 2.8:1.9:1.1:7.6:53.3)
长裙竹荪 ^[93] <i>Dictyophora indusiata</i> (Vent. Pers.) Fisch. ^[93]	抗生素致小鼠肠道菌群失调 Antibiotic induced intestinal microflora disorder in mice	增加有益菌群,包括乳酸杆菌科和瘤胃菌科,减少肠球菌、拟杆菌和变形杆菌等有害细菌 Increased beneficial bacteria, including <i>Lactobacilli</i> and <i>Ruminococcaceae</i> , and reduced harmful bacteria such as <i>Enterococcus</i> , <i>Bacteroides</i> and <i>Proteobacteria</i>	甘露糖、核糖、鼠李糖、葡萄糖醛酸、葡萄糖、半乳糖、木糖、阿拉伯糖、岩藻糖(摩尔比为 23.55:0.46:0.043:1.014:59.84:12.95:0.36:0.17:0.58) Mannose, ribose, rhamnose, glucuronic acid, glucose, galactose, xylose, arabinose, fucose (the mole ratio was 23.55:0.46:0.043:1.014:59.84:12.95:0.36:0.17:0.58)
金针菇 ^[94] <i>Flammulina velutipes</i> ^[94]	正常小鼠 Normal mice	厚壁菌门水平明显升高,拟杆菌门水平降低;厚壁菌门与拟杆菌门的比值升高 <i>Firmicutes</i> were increased significantly while <i>Bacteroidetes</i> were decreased; The ratio of <i>Firmicutes</i> to <i>Bacteroidetes</i> was increased	甘露糖、葡萄糖、木糖、阿拉伯糖、岩藻糖(摩尔比为 6.6:27.8:18:1.5:5.2) Mannose, glucose, xylose, arabinose, fucose (the mole ratio was 6.6:27.8:18:1.5:5.2)
茯砖茶 ^[95] Fuzhuan brick tea ^[95]	HFD 小鼠 HFD mice	厚壁菌门相对丰度降低,拟杆菌门相对丰度增加;厚壁菌门与拟杆菌门的比值降低 The relative abundance of <i>Firmicutes</i> were decreased while that of <i>Bacteroidetes</i> were increased; The ratio of <i>Firmicutes</i> to <i>Bacteroidetes</i> was decreased	甘露糖、核糖、鼠李糖、葡萄糖醛酸、半乳糖醛酸、葡萄糖、半乳糖、阿拉伯糖(摩尔比为 3.66:1.69:12.11:1.41:28.17:21.97:19.15:11.83) Mannose, ribose, rhamnose, glucuronic acid, galacturonic acid, glucose, galactose, arabinose (the mole ratio was 3.66:1.69:12.11:1.41:28.17:21.97:19.15:11.83)
蛹虫草 ^[96] <i>Cordyceps militaris</i> (L. ex Fr.) Link. ^[96]	醋酸铅(Pb ²⁺)致小鼠肝、肾损伤模型 Liver and kidney injury model induced by lead acetate (Pb ²⁺) in mice	厚壁菌门相对丰度降低,梭状芽孢杆菌和拟杆菌相对丰度增加 The relative abundance of <i>Firmicutes</i> were decreased, while the relative abundance of <i>Clostridium</i> and <i>Bacteroidetes</i> were increased	鼠李糖、半乳糖、葡萄糖、半乳糖醛酸、葡萄糖醛酸(摩尔比为 0.130:47.687:40.784:1.795:0.48) Rhamnose, galactose, glucose, galacturonic acid, glucuronic acid (the mole ratio was 0.130:47.687:40.784:1.795:0.48)
枸杞 ^[79] <i>Lycium barbarum</i> L. ^[79]	HFD 小鼠诱导 NAFLD 模型 HFD mice induce NAFLD	降低厚壁菌门和拟杆菌门的比例,增加丁酸菌单胞菌的丰度 The proportion of <i>Firmicutes</i> and <i>Bacteroidetes</i> were decreased and the abundance of <i>Butyricimonas</i> was increased	甘露糖、鼠李糖、葡萄糖、半乳糖、阿拉伯糖(摩尔比为 1.00:0.93:12.55:0.31:0.53) Mannose, rhamnose, glucose, galactose, arabinose (the mole ratio was 1.00:0.93:12.55:0.31:0.53)

polysaccharide, SFP)的理化性质及益生活性, 结果表明, 由热水提取(H-SFP)、超声辅助水提法(U-SFP)、脉冲电场辅助水提法(P-SFP)和纤维素酶辅助水提法(E-SFP)得到的4个多糖主要由岩藻糖、葡萄糖、半乳糖、甘露糖和木糖组成, 岩藻糖和半乳糖是主要成分, 其中酶助辅水提羊栖菜多糖的单糖组成中葡萄糖的含量较其他3个多糖的高, 达到了19.57%, 对乳杆菌的增殖活性也最佳, 可能的原因是肠道菌群主要通过代谢产物调控糖代谢, 其代谢产生的SCFA, 尤其是丁酸和丙酸在能量平衡及对葡萄糖代谢稳态方面有重要意义^[98]。此外, 单糖组成越复杂, 促益生菌增殖的作用越明显。王轶帆等^[99]发现龙眼多糖和燕麦多糖作为碳源均能促进干酪乳杆菌(*Lactobacillus casei*)、嗜酸乳杆菌(*Lactobacillus acidophilus*)、植物乳杆菌(*Lactobacillus plantarum*)和粪肠球菌(*Enterococcus faecalis*)的增殖, 然而两者的促增殖作用明显不同, 龙眼多糖的促增殖作用显著优于燕麦多糖; 进一步分析发现, 龙眼多糖的单糖组成为葡萄糖、甘露糖和阿拉伯糖等, 而燕麦多糖的单糖组成主要为葡萄糖, 而且与燕麦多糖相比, 龙眼多糖单糖组成结构更复杂。

4.3 糖苷键

多糖通常由各种单糖通过糖苷键连接而成。根据连接糖基的方式不同, 可将糖苷键分为不同的类型。大多数研究结果表明, 具有调节肠道菌群活性的多糖大部分以(1→3)糖苷键连接。Shao等^[100]从猴头菌(*Hericium erinaceus*)中分离出一种独特的多糖组分EP-1, 主链以 α -(1→3)-D-葡萄糖和 β -(1→3)-D-葡萄糖为主, 显著增加了大鼠肠道菌群的多样性和丰富度, 恢复了乙酸和丁酸比例, 对醋酸诱导的UC大鼠有明显的缓解作用。Zhao等^[101]研究发现, 木耳[*Auricularia auricular-judae* (Bull.)]多糖主链由 β -(1→3)糖苷

键组成, 不仅改善了结肠炎小鼠的体重减轻、结肠损伤和黏膜炎症, 而且还改变了肠道菌群的组成, 降低致病菌的丰度; 此外, 以(1→4)和(1→6)糖苷键为主链的多糖也具有调节肠道健康的活性。Zeng等^[102]从肉苁蓉(*Cistanche deserticola* Ma.)中提取了中性多糖CDA-0.05, 主链以 α -(1→4)-D-葡萄糖为主, 生物活性试验结果表明, CDA-0.05能显著促进拟杆菌和脆弱杆菌的生长; 同时, CDA-0.05还能促进干酪乳杆菌、植物乳杆菌和罗伊氏乳杆菌等益生菌的生长。主链以(1→4)和(1→6)糖苷键为主的霍山石斛(*Dendrobium huoshanense*)^[103]多糖通过增加拟杆菌门丰度, 降低厚壁菌与拟杆菌的比率, 改善宿主健康。

5 展望

随着对多糖调节肠道菌群的不断深入研究, 人们逐渐认识到多糖在治疗疾病中的重要性。本文综述了肠道菌群紊乱与疾病发生的关系, 总结了多糖与肠道菌群相互作用改善疾病, 并从分子量、单糖组成和糖苷键三方面探讨了多糖调节肠道菌群的构效关系。然而, 尽管许多研究表明多糖作为天然药物通过调节肠道菌群可以预防和缓解疾病的发生, 仍有一些方面可进一步提高。

(1) 关注多糖调节肠道菌群与其他疾病之间的关系

众所周知, 肠道菌群主要存在机体肠道中, 其数量和组成的紊乱会严重影响宿主的生理健康, 从而诱发多种疾病。然而国内外学者大多数只关注肠道菌群与肠道疾病如CRC、IBD、UC的发生发展。最近, Song等^[96]发现重金属铅(Pb^{2+})可通过增加厚壁菌门丰度, 降低拟杆菌门丰度进而诱导小鼠肝、肾损伤; Xie等^[104]实验证明枸杞多糖具有抗铅诱导的小鼠肾损伤作用。因此, 肠道菌群失调与非肠道疾病的发生以及多糖是

否可通过调节肠道菌群改善肠道以外其他疾病如重金属诱导的肝肾损伤、神经系统疾病、心血管疾病、过敏性疾病等还值得进一步探索。

(2) 加强多糖的结构研究及其与肠道菌群之间的关系

不同多糖在相对分子质量和聚合物长度上差异较大,这将影响多糖与微生物之间的识别和糖酵解过程。近年来已有学者致力于研究多糖调节肠道菌群的构效关系,但多糖的分子量、单糖组成、糖苷键连接方式及多糖的高级结构与其调节肠道微生态之间的关系还不够明确,仍需要进一步证实。

(3) 开展更多的临床试验,以确保多糖使用的安全有效剂量

多糖的剂量并不是越高达到的效果就越好,过高剂量的多糖摄入会导致菌群多样性下降,增加人体对多糖负荷的承受能力^[105]。虽然体外和体内动物实验已证实多糖对肠道菌群具有调节作用,但由于人与动物之间存在着特定的差异,今后还应开展更多的临床试验,根据患者的具体情况来确定个体化治疗,以确保多糖使用的安全性和有效剂量。

研究发现,传统中草药能够与肠道微生物相互作用而调节人体健康,多糖是植物的重要活性成分之一,作为天然的肠道微生态调节剂,因其资源丰富、疗效稳定和副作用小等特点,被认为是未来基于肠道菌群调控疾病预防甚至治疗选择的发展方向。现有的微生态调节剂多是益生菌产品,虽然可以在一定程度上调理肠道菌群平衡,但存在菌群数量不易控制、对储存条件要求较高等特点,而且长期使用会促使肠道逐渐丧失自身繁殖益生菌的功能^[106]。然而多糖易保存、疗效稳定,对其作用机制及相应产品的开发值得进一步深入研究和探讨。

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