

益生元在药物递送系统中的研究进展

任玲¹, 郑稳生¹, 何淑旺², 于昊杨¹, 王璐璐^{1*}

(1. 中国医学科学院、北京协和医学院药物研究所, 北京 100050; 2. 北京达因高科儿童药物研究院, 北京 101149)

摘要: 随着对肠道微生物研究的深入, 肠道菌群对人类健康的影响受到关注, 已成为当前生命科学和医学的研究热点, 也被认为是疾病治疗的重要靶点。益生元可调节肠道菌群的组成和功能从而改善宿主健康。碳水化合物是最基本的益生元, 其独特的理化性质及肠道菌调节能力可在实现药物靶向递送的同时又能促进肠道健康, 从而对疾病的治疗发挥积极作用。本文对不同种类的益生元及其肠道菌调节机制进行了阐述, 介绍了碳水化合物类益生元在药物递送系统中的研究进展, 并对其应用前景进行展望, 以期对相关研究提供参考。

关键词: 益生元; 碳水化合物; 肠道微生物; 药物递送系统; 肠道健康

中图分类号: R943 文献标识码: A 文章编号: 0513-4870(2022)07-2041-08

Research progress of prebiotics in drug delivery system

REN Ling¹, ZHENG Wen-sheng¹, HE Shu-wang², YU Hao-yang¹, WANG Lu-lu^{1*}

(1. Institute of Materia Medica, Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing 100050, China; 2. Beijing Dyne High-tech Pediatric Pharmaceutical R&D Institute, Beijing 101149, China)

Abstract: With the in-depth study on the gut microflora, the impact of intestinal bacteria on human health has attracted more and more attention. It has become a research hotspot in life science and medicine, and is considered as an important target of disease control. Prebiotics can regulate the composition and function of intestinal flora and then improve host health. Carbohydrate is the most basic prebiotic. Its unique physiochemical characteristics and gut microbiota-regulating ability make it a promising ingredient for achieving drug target delivery and intestinal health promotion. In this paper, different kinds of prebiotics and their regulation mechanism of intestinal bacteria were illuminated. Moreover, the research progress of carbohydrate prebiotics in drug delivery system was elucidated, and its application prospect is prospected, so as to provide reference for related research.

Key words: prebiotics; carbohydrate; gut microflora; drug delivery system; intestinal healthiness

人体的胃肠道内栖息着约100万亿个微生物, 是一个由细菌、真菌、古生菌和病毒等组成的复杂群落^[1]。这些微生物通过参与人体代谢、免疫等生理、病理过程而对宿主健康产生重要影响。肠道微生物拥有的一系列酶能降解难以被人体直接消化吸收的复杂碳水化合物, 还可参与蛋白质和氨基酸、脂质、胆盐和胆

碱等物质的代谢, 由此产生的多种代谢产物可在多个生理、病理过程中发挥作用^[2]。肠道微生物还通过与免疫系统的相互作用刺激其发育、调节免疫应答反应, 从而对机体进行保护^[3]。此外, 作为肠道神经系统与中枢神经系统之间沟通的“桥梁”, 肠道微生物, 特别是其代谢产物可与特定的受体相互作用, 进而刺激细胞因子及神经介质的释放, 促进多种类型神经元的发育和存活, 通过调节肠-脑轴的功能, 参与精神类疾病的发病与治疗^[4,5]。

通过调节肠道微生物的组成及功能治疗相关疾病已成为目前生命科学界研究的热点问题。其中, 益生

收稿日期: 2021-12-20; 修回日期: 2022-01-06.

基金项目: 国家科技重大专项“重大新药创制”资助项目 (2018ZX097210-03-008-026); 中国医学科学院医学与健康科技创新工程 (2021-I2M-1-070); 2019年度国家重点研发计划资助项目 (2019YFC1708901).

*通讯作者 Tel: 86-10-63165233, E-mail: wanglulu@imb.cams.cn

DOI: 10.16438/j.0513-4870.2021-1817

元被证实是肠道菌调节的有效方法之一。益生元是“一种不能消化的膳食补充剂,通过选择性地刺激肠道中对宿主具备有益作用的细菌的生长和/或活性,从而对宿主产生有益影响,改善宿主健康”^[6]。此外,益生元还可改善药物的不稳定性、分散性、溶解性等多种性质^[7,8],其在上消化道稳定、到达结肠部位后可被肠道菌产生的特异性酶降解的特点,使得益生元成为构建靶向药物递送系统的理想材料。

本文对益生元的分类及其对肠道菌的作用及机制进行了阐述,并重点总结分析了碳水化合物类益生元在药物递送系统中的研究进展,以期为进一步研究提供参考。

1 益生元的分类

最基本的益生元为碳水化合物,其他如多酚和不饱和脂肪酸等物质也可发挥益生元作用。下面进行分类介绍。

1.1 碳水化合物类

1.1.1 果聚糖 果聚糖是由果糖单元通过 β -1,2糖苷键连接而成的低聚糖/多糖,其末端常连着一个葡萄糖基团^[9]。根据聚合度的不同,果聚糖又可分为低聚果糖和菊粉^[10]。由于人体缺乏能破坏 β -1,2糖苷键的消化酶,所以这些果聚糖能完整地通过上消化道,而在结肠部位被微生物分泌的果糖水解酶降解成短链脂肪酸。Gibson等^[11]最早证明低聚果糖及菊粉在体外可特异性增加粪便中双歧杆菌的数量。低聚糖饲喂实验显示饮食中添加低聚果糖能增加实验动物肠道内双歧杆菌及厌氧菌的数量,从而改善胃肠道健康^[12]。多项临床试验表明,饮食中的低聚果糖及菊粉能改善粪便微生物的组成,由此对人体健康产生积极作用^[13,14]。基于对肠道微生物的有益作用,菊粉型果聚糖已被用于包括消化系统、免疫系统、代谢以及癌症等多种疾病预防和治疗研究^[15]。

1.1.2 低聚半乳糖 低聚半乳糖通常是利用 β -半乳糖苷酶水解乳糖得到的混合物,由2~8个糖单体通过 β -1,3或 β -1,4键连接而成,一般包含一个末端葡萄糖单元以及余下的半乳糖或二糖单元^[16]。Tanaka等^[17]早在1983年就发现反式半乳糖低聚糖在体外被双歧杆菌发酵,而在体内能促进双歧杆菌的生长,因此被称为双歧因子。体内实验进一步表明,低聚半乳糖的摄入会引起人体肠道微生物的组成变化,促进双歧杆菌、乳酸菌等细菌的增殖,进而调节代谢及免疫等功能,可用于疾病预防或治疗^[18-20]。

1.1.3 抗性淀粉 抗性淀粉又称抗酶解淀粉、难消化淀粉,在小肠中不能被酶解,吸收和进入血液都较缓慢,性质类似溶解性纤维^[21]。Zaman等^[22]对抗性淀粉

通过影响肠道微生物而产生的健康益处进行了综述,证明了其作为益生元的潜力。近几年也有临床研究证明,摄入抗性淀粉能增加中老年人肠道中双歧杆菌的数量,改变厚壁菌门/拟杆菌门的比例,从而改善肠道健康^[23]。

1.1.4 β -葡聚糖 β -葡聚糖是一种由D-葡萄糖单体通过 β -糖苷键连接而成的多糖^[24]。 β -葡聚糖在大肠中能被微生物分解代谢,相对于菊粉, β -葡聚糖能更好地促进长双歧杆菌的生长^[25]。体外分批发酵实验发现葡聚糖能显著提高乳酸杆菌及双歧杆菌等细菌的数量并促进短链脂肪酸的产生,显示出益生元的潜力^[26]。大鼠及人体中的实验也进一步表明 β -葡聚糖可通过发挥益生元效应从而调节免疫并缓解炎症^[27,28]。

1.1.5 果胶 果胶是一种来源于植物的复杂阴离子多糖,由聚半乳糖醛酸和鼠李糖半乳糖醛酸组成,也含有少量以侧链形式连接的中性糖/聚合物^[29]。果胶也被认为是一种益生元候选物,在体外能促进双歧杆菌和乳酸杆菌的生长^[30]。体外实验证实,由果胶衍生而来的低分子质量果胶低聚糖可促进乳酸杆菌及双歧杆菌的生长,具有潜在的益生元特性,甚至较果胶的活性更优^[31]。Prandi和Naqash等^[32,33]分别在综述中系统地介绍了果胶和果胶低聚糖的益生元潜力及由此对健康产生的益处。

1.1.6 壳聚糖 壳聚糖一般由甲壳素部分去乙酰化而制得,是一种天然阳离子多糖,由 β -(1-4)键连接的D-氨基葡萄糖以及随机分布在聚合物中的N-乙酰基-D-氨基葡萄糖组成^[34]。关于壳聚糖益生元活性的证据并不多,但也有实验发现壳聚糖,特别是其酶解后得到的低分子质量壳寡糖能促进肠道有益菌的生长,或对某些致病细菌产生抑制作用,表现出潜在的益生元活性^[35,36]。

1.1.7 糊精 糊精是淀粉在特定条件下部分水解的产物,其结构中的 α -1,3糖苷键不能被人体胃肠道内的淀粉酶破坏^[37]。体外培养实验表明,抗性糊精能促进双歧杆菌和乳酸杆菌等益生菌的生长,可能是潜在的益生元^[38]。益生菌是通过定殖在人体内,改变宿主某一部位菌群组成的一类对宿主有益的活性微生物^[39]。多项动物实验证实了抗性糊精对肠道菌群的数量及组成的调节作用,不仅可改善肠道健康,对于肝脏脂肪沉积/变性、肥胖及炎症等都有积极影响^[40-42]。

1.1.8 海藻多糖 海藻多糖是从海藻或微藻等中提取到的多糖,其潜在的益生元作用及应用已被广泛报道^[43]。而由海藻多糖衍生而来的低分子质量多糖也显示出益生元潜力。例如,几项体内外研究均表明海藻低聚糖能选择性刺激肠道有益菌的生长,降低致病菌

的丰度,有望用于预防或治疗肠道疾病或代谢性疾病^[44]。

1.2 非碳水化合物类

1.2.1 多酚类物质 多酚是一大类具有生物活性的植物化学物质,根据其结构可分为酚酸类、黄酮类、二苯乙烯类、单宁、木脂素等多个亚类^[45]。多酚类物质在小肠不能被完全吸收,未被吸收的多酚化合物及其代谢物在到达结肠后,能改变肠道微生物的生态,发挥健康保护作用^[46]。Shi等^[47]研究证明槲皮素可有效恢复抗生素治疗后小鼠的肠道微生物失调。实验证实,红酒多酚能显著增加人体粪便中双歧杆菌、乳酸菌和丁酸产生菌的数量,抑制有害菌数量,改善代谢相关的标志物^[48,49]。而一些富含多酚的食物或其提取物也表现出对肠道微生物的调节作用,从而对炎症、癌症或代谢疾病等产生有益影响^[50-52]。

1.2.2 多不饱和脂肪酸 目前的研究中, ω -3多不饱和脂肪酸被认为是益生元,其对肠道微生物的作用也得到了详细的综述^[53]。实验发现, ω -3多不饱和脂肪酸的干预能可逆性增加健康人体内的双歧杆菌、乳酸杆菌及罗斯杆菌等几个属的丰度^[54]。小鼠实验表明, ω -3多不饱和脂肪酸能通过调节肠道微生物的组成,而对炎症缓解、肥胖及神经行为发育等产生有益影响^[55-57]。

2 益生元对肠道微生物的作用及其机制

益生元能通过调节肠道微生物的组成、结构及代谢功能调节机体健康(图1)^[58]。

2.1 调节肠道微生物的组成/结构

大量实验研究表明益生元能选择性刺激肠道有益菌的生长,从而调节肠道菌的组成和结构,其中报道较多的有双歧杆菌和乳酸杆菌,其他肠道共生菌的生长也会受到益生元的选择性刺激^[19,20,40,44]。这种选择性作用的机制,一方面是肠道菌本身能产生相应的酶,选择性利用益生元;另一方面是益生元可促进肠道微生物群落中不同物种间的广泛相互作用,即所谓的交叉喂养^[59]。多项研究发现,在低聚果糖为唯一碳源的培养基中,双歧杆菌降解低聚果糖产生的醋酸或乳酸,以及释放的游离低聚糖,可被厌氧菌等细菌利用从而刺激其生长^[60]。此外,益生元的摄入可刺激肠道有益菌的生长,而这些占据优势的有益菌则能与肠道病原菌竞争有限的资源或分泌某些抗微生物分子而抑制病原菌的生长,进而保护宿主免受病原体的感染^[61]。如体外模型实验证实乳酸杆菌、双歧杆菌及鼠李糖乳杆菌等能通过抑制病原菌黏附,干扰病原菌的入侵,从而保护肠上皮、预防肠道感染^[62]。

2.2 影响肠道微生物的代谢

益生元对肠道菌代谢的影响主要涉及短链脂肪酸的产生,其中最重要的是乙酸、丙酸和丁酸,这些都是益生元被肠道菌发酵后产生的终产物^[63]。而这些短链脂肪酸又能从多个方面发挥有益作用,其最直接影响就是降低肠道管腔内的pH,从而抑制病原微生物的生长,此外,还能增加某些营养物质的吸收^[64,65]。值得

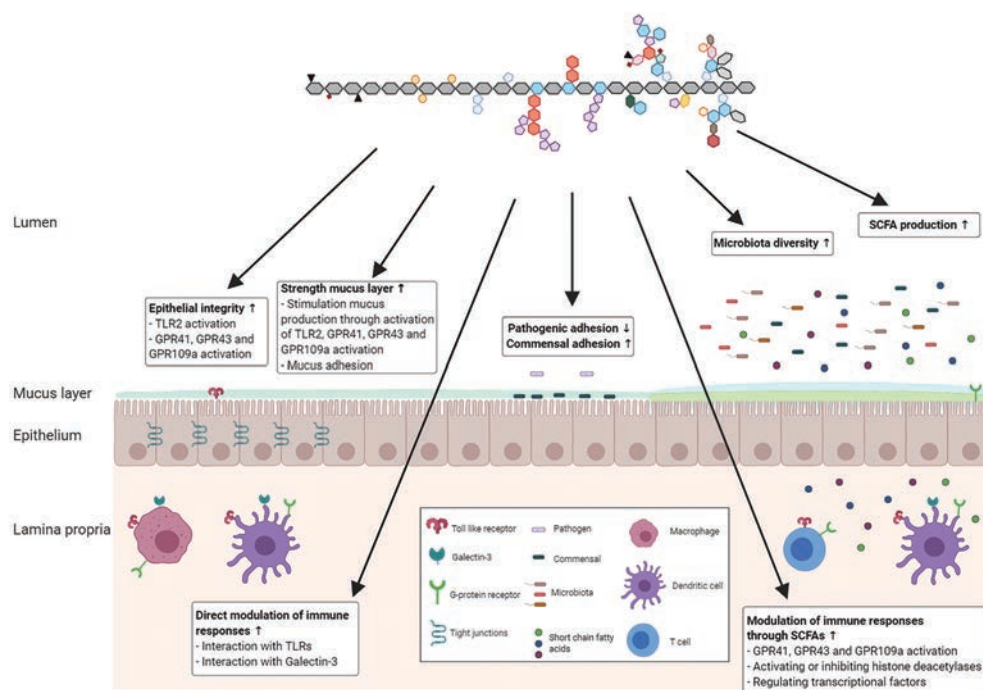


Figure 1 Prebiotics regulate intestinal health through microbial dependence (indirect effect) and non-microbial dependence (direct effect). [Adapted from Ref. 58 with permission. Copyright © 2020, The Author(s)]

注意的是,短链脂肪酸在维持肠道健康方面具有重要意义,如丁酸作为结肠上皮细胞首选的能量来源,在维持肠道屏障功能方面发挥着重要作用^[66]。一方面,丁酸能调节黏蛋白的产生,增加黏蛋白含量而提高益生菌的黏附能力,减少大肠杆菌等有害菌的黏附^[67]。另一方面,丁酸可促进紧密连接的组装,改善肠壁完整性,从而增强肠道屏障功能^[50]。

3 益生元在药物递送系统中的应用

益生元具有上消化道稳定,到达结肠后可被肠道菌产生的特异性酶生物降解的特性,是构建靶向递送系统的理想材料(图2)^[68]。此外,通过取代官能团等对益生元进行修饰,改善其性质,能更好地实现靶向给药的目的^[69]。

3.1 微球/微囊

益生元构建微球/微囊包载药物或益生菌,一方面能够实现药物的结肠靶向释放或保护益生菌的活性,另一方面其降解后又能发挥有益作用^[7,70]。Zhang等^[70]制备了纤维素-海藻酸钠微球并包埋益生菌,体外实验证明该微球能有效保护益生菌免受胃酸的影响,在模拟肠液环境下有效释放益生菌,实现肠道靶向给药。Zhao等^[71]则以海藻酸盐为外壳,包裹两种益生菌制成双核微囊,该微囊不仅能实现益生菌在肠道内的pH响

应性释放,而且可利用海藻酸盐及其降解产物的益生元作用促进肠道益生菌增殖。Morales-Burgos等^[7]发现,阿拉伯木聚糖微球为载体的递送系统能保护胰岛素在胃肠道上部不被降解并将其输送至结肠。值得注意的是,阿拉伯木聚糖在大肠发酵后能增加大鼠粪便中双歧杆菌、丙酸、醋酸等浓度,发挥预防肥胖的作用。Hufnagel等^[72]对菊粉进行修饰得到疏水性的乙酰化菊粉,并基于此制备了载有5-氨基水杨酸的微丸,该微丸可实现pH依赖的药物释放,其中菊粉可发挥潜在的益生元作用。

3.2 纳米载体

3.2.1 胶束 菊粉能被结肠中的双歧杆菌选择性降解,可用于靶向药物递送,然而,良好的水溶性不利于其包载药物^[73]。但菊粉中含有许多羟基,故可利用偶联反应制备两亲性菊粉衍生物以构建递送载体^[8]。Mandraccia等^[74]合成了菊粉-维生素E共轭物并制备出一种pH敏感型纳米胶束,该胶束可包载疏水性药物—塞来昔布并实现结肠靶向释放。Catenacci等^[75]将菊粉与 β -环糊精(β -CD)共轭连接制成胶束,其中 β -CD的疏水性空腔可用于包载疏水性药物,两种材料均可被肠道菌特异性降解,使得该载药体系可实现结肠靶向给药,其中菊粉作为益生元可进一步对肠道菌发挥

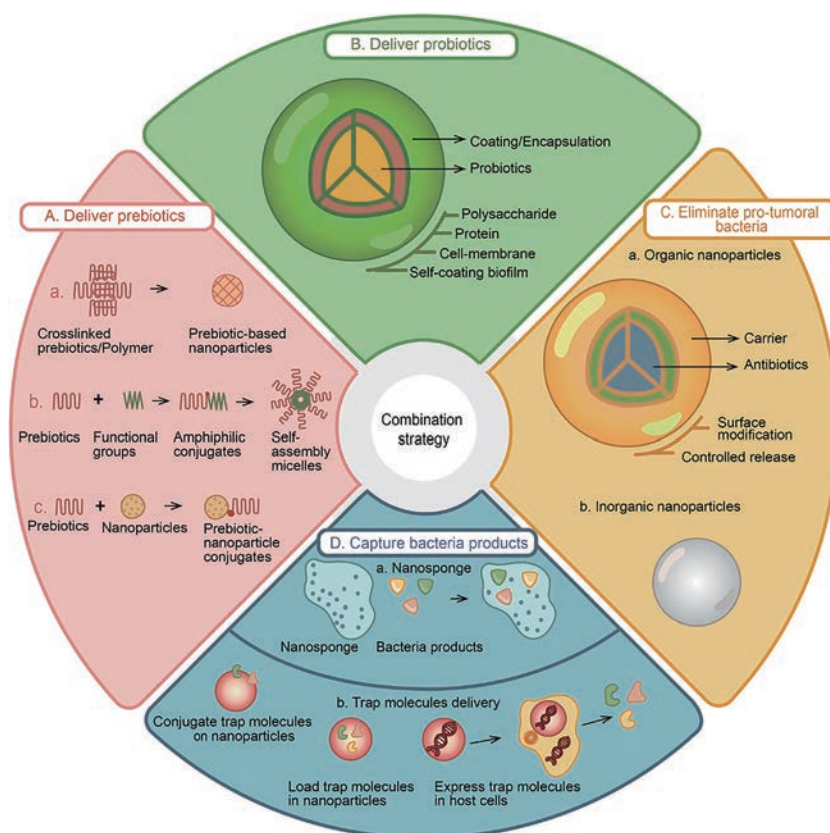


Figure 2 The application of prebiotics in the drug delivery systems. (Adapted from Ref. 68 with permission. Copyright © 2021 The Authors. Advanced Science published by Wiley-VCH GmbH)

有益作用。Jangid等^[76]则合成了菊粉-普朗尼克-硬脂酸偶联物并自组装成胶束,用于疏水性药物白藜芦醇的口服结肠递送。其中,菊粉能保护胶束在胃肠道上部不被降解,而在结肠中最大限度地释放药物。Wang等^[81]将菊粉和硫辛酸交联成两亲性聚合物并自组装成胶束,该胶束包载疏水性药物一丹参酮以治疗结肠癌,克服了药物溶解度及生物利用度差的问题。值得注意的是,该研究中的体外实验证明胶束中的菊粉成分可促进益生菌—主要为长双歧杆菌的增殖。

3.2.2 纳米粒 以益生元为载体材料构建纳米粒的相关研究较多,主要用于改善药物性质或实现靶向释药。如Fares等^[77]制备了一种姜黄素-菊粉纳米粒,可有效改善姜黄素的生物利用度。Sun等^[78]制备了一种两亲性菊粉衍生物—4-氨基噻吩-羧甲基菊粉,将其自组装成纳米粒并包载药物布地奈德,结果展现出良好的pH及还原响应性,为口服靶向治疗结肠炎提供了一种良好策略。Shivhare等^[79]将一种疏水性肽与菊粉连接成两亲性菊粉后组装形成纳米粒,其疏水核可包载药物。以奥硝唑为模型药物的体外释放实验表明该载体有很好的酶响应特性,可能成为靶向治疗结肠癌及胃肠道疾病的有效载体。而Singh等^[80]开发了一种基于瓜尔胶和黄原胶的5-氟尿嘧啶(5-FU)结肠靶向纳米粒,并与双歧杆菌联合给药,其中益生菌能调节5-FU导致的肠道菌失调,有助于载体中天然胶的降解从而使药物能在结肠中充分释放。还有研究者在合成基于益生元的载药纳米粒后,进一步利用同轴静电纺丝技术将其制成静电纤维毡,其中益生元可刺激益生菌生长,代谢产物短链脂肪酸能发挥有益的肠道调节作用^[81,82]。此外,将益生元与益生菌或噬菌体相结合,构建纳米靶向递送系统是日前较为新颖的研究。Zheng等^[83]选择目前已广泛应用的益生菌-丁酸梭菌的孢子,在其表面包裹 β -环糊精和葡聚糖的接枝物,构建出载有丁酸梭菌孢子的葡聚糖颗粒,该纳米粒可调节肠道菌群组成,其中葡聚糖作为益生元可促进肠道菌产生短链脂肪酸,发挥抗炎、抗肿瘤作用。Zheng等^[84]将载有伊立替康的葡聚糖纳米粒与核梭杆菌噬菌体相交连,该纳米药物递送系统能通过噬菌体介导药物特异性富集于结直肠肿瘤,同时噬菌体通过抑制核梭杆菌增殖而抑制肿瘤对化疗的耐受性,纳米粒中的葡聚糖发挥益生元作用增加肠道中丁酸等短链脂肪酸的含量,进一步增加药物的抗肿瘤作用。

3.2.3 聚电解质复合物 许多益生元结构中含有带电荷的基团,在适宜条件下能形成聚电解质复合物。如Guo等^[85]就利用壳聚糖和果胶之间的静电相互作用制备了一种pH/肠道菌双刺激响应纳米粒,并包载小檗

碱用于肠道靶向递送。该载体能避免小檗碱在上消化道降解,且其中果胶作为益生元,可能与小檗碱协同调节肠道菌。Liu等^[86]则利用带负电的低分子质量柑橘果胶(LCP)和带正电的壳聚糖合成了聚电解质复合物,并包载多酚类益生元—越橘花青素,该制剂一方面提高了越橘花青素的消化道稳定性,另一方面LCP作为一种益生元候选物,可能也参与调节肠道微生物。

3.3 纳米粒-益生元共轭物

有研究直接将益生元与已构建的药物递送载体相连以发挥有益作用。例如,Ren等^[87]将人参皂苷(Rg3)与已合成的 $\text{Fe}@\text{Fe}_3\text{O}_4$ 纳米粒相偶联,开发了一种新的纳米药物NpRg3,以用于肝癌的治疗。结果发现,NpRg3可能通过改变肠道微生物的结构,减轻肝癌诱导的肠道微生物变化从而促进药物抗肝癌作用。

4 总结与展望

肠道微生物与人体共同进化,并与宿主相互作用而在代谢、免疫及信号传递等方面发挥重要功能,其稳定性和多样性与人体健康密切相关。肠道微生物失调(包括其组成及功能的失衡)与胃肠道疾病、肝脏疾病、代谢及心血管疾病等息息相关^[88]。

对肠道微生物功能的深入了解也引发了人们对通过调节肠道微生物而改善健康、治疗疾病的极大兴趣。益生元是调节肠道微生物的重要方法之一。益生元种类众多,能通过选择性刺激特定肠道微生物生长或活性,影响肠道微生物的组成及功能,进而对宿主的健康与疾病治疗产生重要影响。同时,益生元本身的许多性质使其在构建药物递送系统,特别是结肠靶向递送系统方面具有许多优势。利用益生元对肠道微生物的调节并实现靶向递送而在疾病治疗上发挥“双重作用”,在未来的研究及应用中将具有十分广阔的空间。并且随着研究的深入,未来可能如通过对多酚类及多不饱和脂肪酸类益生元进行结构改造构建更多合理有效的药物递送系统。然而,益生元通过调节肠道微生物进而治疗疾病的具体分子机制仍不清楚,有待进一步的研究,其在人体中应用的安全性也需要进一步证实。

作者贡献:任玲负责文献的搜集整理及综述的撰写;王璐璐负责文稿的统筹及修改;郑稳生、何淑旺和于昊杨参与了文稿的修改。

利益冲突:所有作者声明本文不存在任何利益冲突。

References

- [1] Gill SR, Pop M, DeBoy RT, et al. Metagenomic analysis of the human distal gut microbiome [J]. *Science*, 2006, 312: 1355-1359.
- [2] Adak A, Khan MR. An insight into gut microbiota and its func-

- tionalties [J]. Cell Mol Life Sci, 2019, 76: 473-493.
- [3] Fung TC, Olson CA, Hsiao EY. Interactions between the microbiota, immune and nervous systems in health and disease [J]. Nat Neurosci, 2017, 20: 145-155.
- [4] Liu X, Cao S, Zhang X. Modulation of gut microbiota-brain axis by probiotics, prebiotics, and diet [J]. J Agric Food Chem, 2015, 63: 7885-7895.
- [5] Zhang ZW, Zhao ZX, Wang Y, et al. Research progress on the interaction of neuropsychiatric drugs with the gut microbiota [J]. Acta Pharm Sin (药 学 学 报), 2021, 56: 643-653.
- [6] Gibson GR, Roberfroid MB. Dietary modulation of the human colonic microbiota: introducing the concept of prebiotics [J]. J Nutr, 1995, 125: 1401-1412.
- [7] Morales-Burgos AM, Carvajal-Millan E, Sotelo-Cruz N, et al. Highly cross-linked arabinoxylans microspheres as a microbiota-activated carrier for colon-specific insulin delivery [J]. Eur J Pharm Biopharm, 2021, 163: 16-22.
- [8] Wang D, Sun F, Lu C, et al. Inulin based glutathione-responsive delivery system for colon cancer treatment [J]. Int J Biol Macromol, 2018, 111: 1264-1272.
- [9] Roberfroid MB, Van Loo JA, Gibson GR. The bifidogenic nature of chicory inulin and its hydrolysis products [J]. J Nutr, 1998, 128: 9-11.
- [10] Ninnes KR. Inulin and oligofructose: what are they? [J]. J Nutr, 1999, 129: 1402S-1406S.
- [11] Gibson GR, Wang X. Enrichment of bifidobacteria from human gut contents by oligofructose using continuous culture [J]. FEMS Microbiol Lett, 1994, 118: 121-127.
- [12] Campbell JM, Fahey GC, Wolf BW. Selected indigestible oligosaccharides affect large bowel mass, cecal and fecal short-chain fatty acids, pH and microflora in rats [J]. J Nutr, 1997, 127: 130-136.
- [13] Mitsuoka T, Hidaka H, Eida T. Effect of fructo-oligosaccharides on intestinal microflora [J]. Mol Nutr Food Res, 1987, 31: 427-436.
- [14] Kleessen BB, Sykura BB, Zunft HJ, et al. Effects of inulin and lactose on fecal microflora, microbial activity, and bowel habit in elderly constipated persons [J]. Am J Clin Nutr, 1997, 65: 1397-1402.
- [15] Man S, Liu T, Yao Y, et al. Friend or foe? The roles of inulin-type fructans [J]. Carbohydr Polym, 2021, 252: 117155.
- [16] Singh SP, Jadaun JS, Narnoliya LK, et al. Prebiotic oligosaccharides: special focus on fructooligosaccharides, its biosynthesis and bioactivity [J]. Appl Biochem Biotechnol, 2017, 183: 613-635.
- [17] Tanaka R, Takayama H, Morotomi M, et al. Effects of administration of TOS and *Bifidobacterium breve* 4006 on the human fecal flora [J]. Bifidobact Microflora, 1983, 2: 17-24.
- [18] Ito M, Deguchi Y, Miyamori A, et al. Effects of administration of galactooligosaccharides on the human faecal microflora, stool weight and abdominal sensation [J]. Microb Ecol Health Dis, 2009, 3: 285-292.
- [19] Vulevic J, Juric A, Walton GE, et al. Influence of galacto-oligosaccharide mixture (B-GOS) on gut microbiota, immune parameters and metabolomics in elderly persons [J]. Br J Nutr, 2015, 114: 586-595.
- [20] Cheng W, Lu J, Lin W, et al. Effects of a galacto-oligosaccharide-rich diet on fecal microbiota and metabolite profiles in mice [J]. Food Funct, 2018, 9: 1612-1620.
- [21] Englyst HN, Kingman SM, Cummings JH. Classification and measurement of nutritionally important starch fractions [J]. Eur J Clin Nutr, 1992, 46: 33-55.
- [22] Zaman SA, Sarbini SR. The potential of resistant starch as a prebiotic [J]. Crit Rev Biotechnol, 2016, 36: 578-584.
- [23] Alfa MJ, Strang D, Tappia PS, et al. A randomized trial to determine the impact of a digestion resistant starch composition on the gut microbiome in older and mid-age adults [J]. Clin Nutr, 2018, 37: 797-807.
- [24] Lam KL, Cheung PCK. Non-digestible long chain beta-glucans as novel prebiotics [J]. Bioact Carbohydr Diet Fibre, 2013, 2: 45-64.
- [25] Wang H, Chen G, Li X, et al. Yeast β -glucan, a potential prebiotic, showed a similar probiotic activity to inulin [J]. Food Funct, 2020, 11: 10386-10396.
- [26] Shi Y, Liu J, Yan Q, et al. *In vitro* digestibility and prebiotic potential of curdlan (1 \rightarrow 3)- β -D-glucan oligosaccharides in *Lactobacillus* species [J]. Carbohydr Polym, 2018, 188: 17-26.
- [27] Wilczak J, Blaszczyk K, Kamola D, et al. The effect of low or high molecular weight oat beta-glucans on the inflammatory and oxidative stress status in the colon of rats with LPS-induced enteritis [J]. Food Funct, 2015, 6: 590-603.
- [28] Mio K, Otake N, Nakashima S, et al. Ingestion of high β -glucan barley flour enhances the intestinal immune system of diet-induced obese mice by prebiotic effects [J]. Nutrients, 2021, 13: 907.
- [29] Babbar N, Dejonghe W, Gatti M, et al. Pectic oligosaccharides from agricultural by-products: production, characterization and health benefits [J]. Crit Rev Biotechnol, 2016, 36: 594-606.
- [30] Ferreira LA, Kachrimanidou V, Villamiel M, et al. *In vitro* fermentation properties of pectins and enzymatic-modified pectins obtained from different renewable bioresources [J]. Carbohydr Polym, 2018, 199: 482-491.
- [31] Gómez B, Gullón B, Yáñez R, et al. Prebiotic potential of pectins and pectic oligosaccharides derived from lemon peel wastes and sugar beet pulp: a comparative evaluation [J]. J Funct Foods, 2016, 20: 108-121.
- [32] Prandi B, Baldassarre S, Babbar N, et al. Pectin oligosaccharides from sugar beet pulp: molecular characterization and potential prebiotic activity [J]. Food Funct, 2018, 9: 1557-1569.
- [33] Naqash F, Masoodi FA, Rather SA, et al. Emerging concepts in

- the nutraceutical and functional properties of pectin—a review [J]. *Carbohydr Polym*, 2017, 168: 227-239.
- [34] Cheung RCF, Ng TB, Wong JH, et al. Chitosan: an update on potential biomedical and pharmaceutical applications [J]. *Mar Drugs*, 2015, 13: 5156-5186.
- [35] Šimůnek J, Brandysová V, Koppová I, et al. The antimicrobial action of chitosan, low molar mass chitosan, and chitooligosaccharides on human colonic bacteria [J]. *Folia Microbiol (Praha)*, 2012, 57: 341-345.
- [36] Lee HW, Park YS, Jung JS, et al. Chitosan oligosaccharides, dp 2-8, have prebiotic effect on the *Bifidobacterium bifidum* and *Lactobacillus* sp. [J]. *Anaerobe*, 2002, 8: 319-324.
- [37] Leszczynski W. Resistant starch - classification, structure, production [J]. *Pol J Food Nutr Sci*, 2004, 13: 37-50.
- [38] Sliżewska K. The citric acid-modified, enzyme-resistant dextrin from potato starch as a potential prebiotic [J]. *Acta Biochim Pol*, 2013, 60: 671-675.
- [39] Hill C, Guarner F, Reid G, et al. Expert consensus document. The international scientific association for probiotics and prebiotics consensus statement on the scope and appropriate use of the term probiotic [J]. *Nat Rev Gastroenterol Hepatol*, 2014, 11: 506-514.
- [40] Barczynska R, Jurgoński A, Sliżewska K, et al. Effects of potato dextrin on the composition and metabolism of the gut microbiota in rats fed standard and high-fat diets [J]. *J Funct Foods*, 2017, 34: 398-407.
- [41] Zhang Z, Chen X, Cui B. Modulation of the fecal microbiome and metabolome by resistant dextrin ameliorates hepatic steatosis and mitochondrial abnormalities in mice [J]. *Food Funct*, 2021, 12: 4504-4518.
- [42] Valcheva R, Hotte N, Gillevet P, et al. Soluble dextrin fibers alter the intestinal microbiota and reduce proinflammatory cytokine secretion in male IL-10-deficient mice [J]. *J Nutr*, 2015, 145: 2060-2066.
- [43] Zheng LX, Chen XQ, Cheong KL. Current trends in marine algae polysaccharides: the digestive tract, microbial catabolism, and prebiotic potential [J]. *Int J Biol Macromol*, 2020, 151: 344-354.
- [44] Li S, Wang L, Liu B, et al. Unsaturated alginate oligosaccharides attenuated obesity-related metabolic abnormalities by modulating gut microbiota in high-fat-diet mice [J]. *Food Funct*, 2020, 11: 4773-4784.
- [45] Singh AK, Cabral C, Kumar R, et al. Beneficial effects of dietary polyphenols on gut microbiota and strategies to improve delivery efficiency [J]. *Nutrients*, 2019, 11: 2216.
- [46] Kasprzak DK, Oniszczyk T, Stasiak M, et al. Beneficial effects of phenolic compounds on gut microbiota and metabolic syndrome [J]. *Int J Mol Sci*, 2021, 22: 3715.
- [47] Shi T, Bian X, Yao Z, et al. Quercetin improves gut dysbiosis in antibiotic-treated mice [J]. *Food Funct*, 2020, 11: 8003-8013.
- [48] Queipo OM, Boto OM, Murri M, et al. Influence of red wine polyphenols and ethanol on the gut microbiota ecology and biochemical biomarkers [J]. *Am J Clin Nutr*, 2012, 95: 1323-1334.
- [49] Moreno-Indias I, Sánchez AL, Pérez MP, et al. Red wine polyphenols modulate fecal microbiota and reduce markers of the metabolic syndrome in obese patients [J]. *Food Funct*, 2016, 7: 1775-1787.
- [50] Peng L, Li ZR, Green RS, et al. Butyrate enhances the intestinal barrier by facilitating tight junction assembly *via* activation of AMP-activated protein kinase in Caco-2 cell monolayers [J]. *J Nutr*, 2009, 139: 1619-1625.
- [51] Sorrenti V, Ali S, Mancin L, et al. Cocoa polyphenols and gut microbiota interplay: bioavailability, prebiotic effect, and impact on human health [J]. *Nutrients*, 2020, 12: 1908.
- [52] Anhê FF, Roy D, Pilon G, et al. A polyphenol-rich cranberry extract protects from diet-induced obesity, insulin resistance and intestinal inflammation in association with increased *Akkermansia* spp. population in the gut microbiota of mice [J]. *Gut*, 2015, 64: 872-883.
- [53] Costantini L, Molinari R, Farinon B, et al. Impact of omega-3 fatty acids on the gut microbiota [J]. *Int J Mol Sci*, 2017, 18: 2645.
- [54] Watson H, Mitra S, Croden FC, et al. A randomised trial of the effect of omega-3 polyunsaturated fatty acid supplements on the human intestinal microbiota [J]. *Gut*, 2018, 67: 1974-1983.
- [55] Kaliannan K, Wang B, Li XY, et al. A host-microbiome interaction mediates the opposing effects of omega-6 and omega-3 fatty acids on metabolic endotoxemia [J]. *Sci Rep*, 2015, 5: 11276.
- [56] Kaliannan K, Wang B, Li XY, et al. Omega-3 fatty acids prevent early-life antibiotic exposure-induced gut microbiota dysbiosis and later-life obesity [J]. *Int J Obes (Lond)*, 2016, 40: 1039-1042.
- [57] Robertson RC, Seira OC, Murphy K, et al. Omega-3 polyunsaturated fatty acids critically regulate behaviour and gut microbiota development in adolescence and adulthood [J]. *Brain Behav Immun*, 2017, 59: 21-37.
- [58] Beukema M, Faas MM, De Vos P. The effects of different dietary fiber pectin structures on the gastrointestinal immune barrier: impact *via* gut microbiota and direct effects on immune cells [J]. *Exp Mol Med*, 2020, 52: 1364-1376.
- [59] Holscher HD. Dietary fiber and prebiotics and the gastrointestinal microbiota [J]. *Gut Microbes*, 2017, 8: 172-184.
- [60] Belenguer A, Duncan SH, Calder AG, et al. Two routes of metabolic cross-feeding between *Bifidobacterium adolescentis* and butyrate-producing anaerobes from the human gut [J]. *Appl Environ Microbiol*, 2006, 72: 3593-3599.
- [61] Chiu L, Bazin T, Truchetet ME, et al. Protective microbiota: from localized to long-reaching co-immunity [J]. *Front Immunol*, 2017, 8: 1678.
- [62] Campana R, Hemert SV, WJGP Baffone. Strain-specific probiotic properties of lactic acid bacteria and their interference with human intestinal pathogens invasion [J]. *Gut Pathog*, 2017, 9: 283-287.

- [63] Ballan R, Battistini C, Xavier SD, et al. Interactions of probiotics and prebiotics with the gut microbiota [J]. *Prog Mol Biol/Transl Sci*, 2020, 171: 265-300.
- [64] Slavin J. Fiber and prebiotics: mechanisms and health benefits [J]. *Nutrients*, 2013, 5: 1417-1435.
- [65] Fooks LJ, Gibson GR. *In vitro* investigations of the effect of probiotics and prebiotics on selected human intestinal pathogens [J]. *FEMS Microbiol Ecol*, 2002, 39: 67-75.
- [66] Rivièrè A, Selak M, Lantin D, et al. Bifidobacteria and butyrate-producing colon bacteria: importance and strategies for their stimulation in the human gut [J]. *Front Microbiol*, 2016, 7: 979.
- [67] Jung TH, Park JH, Jeon WM, et al. Butyrate modulates bacterial adherence on LS174T human colorectal cells by stimulating mucin secretion and MAPK signaling pathway [J]. *Nutr Res Pract*, 2015, 9: 343-349.
- [68] Zhu R, Lang T, Yan W, et al. Gut microbiota: influence on carcinogenesis and modulation strategies by drug delivery systems to improve cancer therapy [J]. *Adv Sci (Weinh)*, 2021, 8: 2003542.
- [69] Seifert A, Kashi Y, Livney YD. Delivery to the gut microbiota: a rapidly proliferating research field [J]. *Adv Colloid Interface Sci*, 2019, 274: 102038.
- [70] Zhang H, Yang C, Zhou W, et al. A pH-responsive gel macro-sphere based on sodium alginate and cellulose nanofiber for potential intestinal delivery of probiotics [J]. *ACS Sustainable Chem Eng*, 2018, 6: 13924-13931.
- [71] Zhao C, Zhu Y, Kong B, et al. Dual-core prebiotic microcapsule encapsulating probiotics for metabolic syndrome [J]. *ACS Appl Mater Interfaces*, 2020, 12: 42586-42594.
- [72] Hufnagel B, Muellner V, Hlatky K, et al. Chemically modified inulin for intestinal drug delivery—a new dual bioactivity concept for inflammatory bowel disease treatment [J]. *Carbohydr Polym*, 2021, 252: 117091.
- [73] Akhgari A, Farahmand F, Afrasiabi Garekani H, et al. Permeability and swelling studies on free films containing inulin in combination with different polymethacrylates aimed for colonic drug delivery [J]. *Eur J Pharm Sci*, 2006, 28: 307-314.
- [74] Mandracchia D, Trapani A, Perteghella S, et al. pH-sensitive inulin-based nanomicelles for intestinal site-specific and controlled release of celecoxib [J]. *Carbohydr Polym*, 2018, 181: 570-578.
- [75] Catenacci L, Sorrenti M, Perteghella S, et al. Combination of inulin and β -cyclodextrin properties for colon delivery of hydrophobic drugs [J]. *Int J Pharm*, 2020, 589: 119861.
- [76] Jangid AK, Patel K, Jain P, et al. Inulin-pluronic-stearic acid based double folded nanomicelles for pH-responsive delivery of resveratrol [J]. *Carbohydr Polym*, 2020, 247: 116730.
- [77] Fares MM, Salem MTS. Dissolution enhancement of curcumin *via* curcumin-prebiotic inulin nanoparticles [J]. *Drug Dev Ind Pharm*, 2015, 41: 1785-1792.
- [78] Sun Q, Luan L, Arif M, et al. Redox-sensitive nanoparticles based on 4-aminothiophenol-carboxymethyl inulin conjugate for budesonide delivery in inflammatory bowel diseases [J]. *Carbohydr Polym*, 2018, 189: 352-359.
- [79] Shivhare K, Garg C, Priyam A, et al. Enzyme sensitive smart inulin-dehydropeptide conjugate self-assembles into nanostructures useful for targeted delivery of ornidazole [J]. *Int J Biol Macromol*, 2018, 106: 775-783.
- [80] Singh S, Kotla NG, Tomar S, et al. A nanomedicine-promising approach to provide an appropriate colon-targeted drug delivery system for 5-fluorouracil [J]. *Int J Nanomed*, 2015, 10: 7175-7182.
- [81] Wen Y, Wen P, Hu TG, et al. Encapsulation of phycocyanin by prebiotics and polysaccharides-based electrospun fibers and improved colon cancer prevention effects [J]. *Int J Biol Macromol*, 2020, 149: 672-681.
- [82] Wen P, Hu TG, Li L, et al. A colon-specific delivery system for quercetin with enhanced cancer prevention based on co-axial electrospinning [J]. *Food Funct*, 2018, 9: 5999-6009.
- [83] Zheng DW, Li RQ, An JX, et al. Prebiotics-encapsulated probiotic spores regulate gut microbiota and suppress colon cancer [J]. *Adv Mater*, 2020, 32: e2004529.
- [84] Zheng DW, Dong X, Pan P, et al. Phage-guided modulation of the gut microbiota of mouse models of colorectal cancer augments their responses to chemotherapy [J]. *Nat Biomed Eng*, 2019, 3: 717-728.
- [85] Guo HH, Ma C, Zheng WS, et al. Dual-stimuli-responsive gut microbiota-targeting berberine-CS/PT-NPs improved metabolic status in obese hamsters [J]. *Adv Funct Mater*, 2019, 29: 1808197.
- [86] Liu X, Wang L, Jing N, et al. Biostimulating gut microbiome with bilberry anthocyanin combo to enhance anti-PD-L1 efficiency against murine colon cancer [J]. *Microorganisms*, 2020, 8: 175.
- [87] Ren Z, Chen X, Hong L, et al. Nanoparticle conjugation of ginsenoside Rg3 inhibits hepatocellular carcinoma development and metastasis [J]. *Small*, 2020, 16:e1905233.
- [88] Lynch SV, Pedersen O. The human intestinal microbiome in health and disease [J]. *N Engl J Med*, 2016, 375: 2369-2379.