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功能性寡糖调控肠道健康的研究进展

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摘要: 功能性寡糖是不易被肠道吸收, 但却能改善肠道健康的一类碳水化合物。近年来, 人们关于功能性寡糖的生物活性, 尤其是在寡糖对肠道健康的影响方面, 开展了广泛地研究。功能性寡糖可通过提高消化酶活性、改善肠道组织及产生乳酸等方式来促进肠道对营养物质和矿物元素的吸收, 也可通过调节肠道菌群、改善肠道组织、增加短链脂肪酸的产生等途径来缓解代谢综合征、减轻炎症、增强免疫反应以及改善肠道黏膜屏障等, 为肠道提供一个良好的内部环境。本文对功能性寡糖的肠道健康调控作用进行了综述, 以期对功能性寡糖的深入研究与应用提供理论依据。

关键词: 功能性寡糖, 调控, 肠道健康, 免疫

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Research Progress of Functional Oligosaccharides on Regulating Intestinal Health

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Abstract: Functional oligosaccharide is a kind of carbohydrates which is not easily absorbed by the gut while can improve intestinal health. In recent years, extensive research has been conducted on the biological activities of functional oligosaccharides, especially on the effects of oligosaccharides on intestinal health. Functional oligosaccharides can provide a good internal environment for intestinal tract. Functional oligosaccharides can promote intestinal absorption of nutrients and mineral elements by increasing digestive enzyme activity, improving intestinal tissue and producing lactic acid. They can also alleviate metabolic syndrome, reduce inflammation, enhance immune response and improve intestinal mucosal barrier by regulating intestinal flora, improving intestinal tissue and increasing the production of short chain fatty acids. The regulatory effects of functional oligosaccharides on intestinal health are reviewed in this paper which can provide theoretical basis for the further development and application of functional oligosaccharides.

Key words: functional oligosaccharides; regulation; intestinal health; immune

寡糖又称低聚糖, 是由 2~20 个单糖通过糖苷键连接的介于单糖和多糖之间的低分子量碳水化合物。它可以从天然原料中提取, 也可以利用转移酶、

水解酶的糖基转移反应、天然高聚糖的控制性水解法和化学合成法进行制备^[1]。寡糖可分为两类: 普通寡糖和功能性寡糖。普通寡糖包括乳糖、蔗糖等, 这

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类寡糖易被肠道吸收, 为人体活动提供能量。功能性寡糖包括壳寡糖、木寡糖、果寡糖、大豆低聚糖、褐藻寡糖、甘露寡糖、低聚半乳糖等^[2]。功能性寡糖在机体内很难被吸收, 和糖类具有一些相同的特征, 但是能量很低, 摄入后不会引起肥胖。近年来, 人们对功能性寡糖在促进肠道健康方面开展了大量研究, 结果发现功能性寡糖能在保持肠道内微生态平衡的基础上促进肠道内有益菌的生长^[3]、促进短链脂肪酸的产生^[4]、改善肠道组织结构、增加肠道对营养物质的吸收^[5]、加强肠粘膜屏障^[6]、缓解肠道炎症^[7]和提高肠道免疫能力等^[8]。本文综述了功能性寡糖对肠道健康的影响及作用机制, 为寡糖的进一步研究提供理论依据。

1 功能性寡糖对肠道健康的调控

1.1 调节肠道菌群

正常人体内的肠道菌群往往维持在一种动态平衡的状态, 人体健康与肠道菌群存在密切的联系。一个成年人的肠道中细菌数量大概有 10^{14} 个, 这些细菌大致分为三类: 生理性细菌、条件致病菌和病原菌^[9]。功能性寡糖可直接进入肠道, 被肠道内的有益菌利用, 促进有益菌的增长, 减少有害产物的产生, 以改善肠道的内环境。徐海燕等^[10]模拟人体肠道环境培养微生物, 发现低聚木糖对大肠杆菌等有害菌的增长起抑制效果, 对双歧杆菌和乳杆菌等有益菌的增长起积极作用, 低聚木糖对人体肠道有较好的调节作用。也有研究表明功能性寡糖对仔猪、小鼠、鱼等动物肠道内的有益菌的生长起促进作用, 调节肠道菌群, 促进机体的生长发育^[11-13]。

肠道微生物的平衡一旦打破则会很大程度上影响机体的健康^[14]。功能性寡糖对菌群紊乱的肠道也有一定的修复作用, 赵丹莉等^[15]对小鼠连续灌胃壳寡糖 14 d 后用高通量测序技术进行肠道菌群检测, 发现壳寡糖能促进乳酸菌抑制大肠杆菌的生长, 并能增加肠道菌群的多样性; 在抗生素破坏肠道微生态平衡之后, 壳寡糖可对其进行恢复, 对肠道菌群紊乱有明显的改善作用。另有实验表明褐藻糖胶寡糖可在降低厚壁菌门丰度的同时增加拟杆菌门的丰度, 从而逆转肠道菌群失调, 特别是结肠菌群失调、缓解代谢综合征^[16]等。此外, 低聚果糖可通过改善肠道微生物来延缓衰老等相关健康问题的发生^[17]。

1.2 促进短链脂肪酸的产生

短链脂肪酸是肠道内有益菌降解不能被消化的碳水化合物得到的产物, 是由碳原子数小于 6 的有机脂肪酸组成的, 主要产物包括醋酸盐、丙酸盐、丁酸盐等^[18]。短链脂肪酸被认为是肠道中的关键微生物代谢物, 对机体有积极的影响。短链脂肪酸能促进肠道吸收, 维持肠道的正常功能^[19]; 通过促进有益菌的生长来参与免疫系统的调节^[20]; 预防肥胖及并发症^[16]; 调节脂肪组织、骨骼肌和肝组织功能^[21]等。谢洁玲等^[22]研究了人肠道微生物对不同分子量褐藻聚

糖硫酸酯的降解情况, 发现人肠道微生物能利用降解后的寡糖产生短链脂肪酸, 促进肠道健康。CHEN 等^[23]在仔虾日粮中添加低聚果糖发现低聚果糖可显著增加仔虾肠道内的短链脂肪酸含量。郑雅文等^[24]在肉鸡的日粮中添加果寡糖发现果寡糖可以提高盲肠中戊酸的含量, 从而达到对肠道微生物的调节, 为宿主提供能量。

1.3 促进矿物元素吸收

矿物元素在人体内起着重要的作用, 如参与代谢、预防慢性疾病、维持免疫力等^[25]。功能性寡糖可以促进肠道对矿物元素的吸收, 现已有研究表明其吸收机制。朱志怀等^[26]研究发现低聚果糖在大肠内被发酵成 L-乳酸, 能溶解钙、铁、镁等矿物质, 促进肠道吸收, 且低聚果糖能使钙的吸收率达到 70.18%。此研究表明肠道对矿物质的吸收可通过肠道有益菌代谢产生短链脂肪酸, 代谢产物乳酸使肠道内 pH 下降, 增加金属离子的可溶性来完成。王秀武^[27]等在肉仔鸡饲料中添加壳寡糖发现肉仔鸡的胸肌和腿肌中 Ca、Zn、Fe 和 Mn 元素的含量显著提高, 其机制也可能是消化道黏膜通透性增加, 紧密结合蛋白结构发生变化, 开放跨膜通道或借助氢键和盐键形成笼形分子来吸附金属离子, 达到对矿物元素的吸收。此外, 秦雪梅^[28]研究完全母乳喂养老婴儿的粪便发现低聚糖可促进钙、镁等矿物质的吸收, 动物实验结果显示, 低聚果糖和低聚半乳糖均能促进肠道对钙、镁、铁等矿物质的吸收。DELZENNE^[29]等研究发现低聚果糖可促进钙、镁、铁和锌的吸收, 减缓铁、钙、镁和锌稳态失调引起的症状。

1.4 改善肠道组织结构以及加强肠粘膜屏障

小肠的组织结构与营养物质的吸收有决定性的关系。小肠的内部有皱襞和皱襞上的细小突起绒毛, 它们的增长可增大肠道面积, 有利于营养物质的吸收^[30]。隐窝是指肠壁的凹陷, 绒毛是指肠壁的突起, 常用 V/C 值(小肠绒毛高度/隐窝深度)来反映肠道的吸收能力, 比值升高则表明吸收功能升高, 比值下降可能是由于肠道病变造成, 会引起腹泻的发生^[31]。有研究发现, 甘露寡糖能改善金鲷的肠道功能, 增加肠道面积和绒毛长度与密度, 影响肠道微生物物种的丰富度和多样性^[32]。寡糖对肠道组织结构的改变将有利于增加机体对营养物质的利用率, 增加对矿物质元素的吸收, 调节脂质代谢, 从而提高生产性能。仔猪在断奶后, 肠道隐窝深度随着仔猪的生长而增加, 绒毛长度显著低于出生 7 d 的, 肠道上皮屏障受损^[33]; 低聚木糖能有效降低隐窝深度, 增加绒毛长度, 改善肠道的形态结构^[34]。壳寡糖、低聚果糖、褐藻寡糖均可调节肠道屏障完整性^[5,35-36]。

肠黏膜屏障是机体黏膜屏障系统最重要的组成部分, 它能吸收营养物质以及阻止肠道内的有害物质进入机体内环境, 这种屏障是由紧密连接组成的组织良好的系统进行调节的。紧密连接是由闭合蛋白

(occludin, OCLN)和封闭蛋白(claudin, CLDNs)以及紧密连接蛋白(zonula occludens, ZO)组成的多蛋白复合物^[37]。果寡糖能显著降低小肠粘膜中活性最强的血浆二胺氧化酶(DAO)活性和代谢产物 D-乳酸的含量,增加与肠道上皮完整性紧密相关的 ZO2、OCLN 和 CLDN2 mRNA 的表达量,从而起到保护黏膜屏障的效果^[38]。WAN 等^[36]在仔猪的饲料中添加褐藻寡糖发现褐藻寡糖可上调断奶仔猪盲肠黏膜中的 OCLN 和 CLDN-1 mRNA 水平,以及结肠黏膜中的 CLDN-1 mRNA 水平,盲肠和结肠黏膜中 SCFA 浓度升高导致单磷酸腺苷活化蛋白激酶(adenosine 5'-monophosphate (AMP)-activated protein kinase, AMPK)活化,从而提高断奶仔猪肠道屏障的完整性。上皮组织的致密性、完整性由通透性和紧密连接的结构所决定。通过尤斯灌流室技术对肠黏膜屏障进行研究,发现上皮细胞跨膜电阻(trans epithelial electrical resistance, TEER)减小,表明肠道通透性增加,紧密连接结构受到破坏,肠黏膜屏障受损;荧光素标记物质的检测也可以体现出肠道的通透性,纤维寡糖能提高 TEER 和降低上皮细胞对荧光素异硫氰酸酯-葡聚糖(fluorescein isothiocyanate-dextran4, FD4)的通透性,且能促进肠道内有益菌的增加,并产生丙酸、丁酸等代谢产物保护肠道屏障^[39]。同时益生菌和寡糖的共同作用更能有效的修复肠上皮细胞损伤^[40]。

1.5 提高消化酶活性

人体的消化主要靠器官机械式运动和化学性消化完成的,消化酶的主要作用是将摄入的食物进行分解转化成机体所需要的养分,消化酶分泌不足会导致吸收能力减弱,免疫保护作用减弱,会广泛引起消化不良症候群,如腹泻、胃胀等,从而会阻碍营养物质的消化吸收。有研究表明新琼寡糖可以促进乳杆菌的生长,能对唾液淀粉酶起稳定作用和激活作用,对消化不良类的疾病具有治疗作用^[41]。WANG 等^[42]将低聚果糖加入饲料中对鲈鱼幼苗进行饲养试验,28 d 后发现饲喂低聚果糖的幼鱼体内的脂肪酶活性明显提高。潘金露^[43]在大菱鲆的饲料中分别加入褐藻酸钠寡糖和壳寡糖喂养 70 d 后发现壳寡糖和褐藻酸钠寡糖均能明显提高肠道脂肪酶、淀粉酶和蛋白酶的活性,提高饲料的消化率。除此之外,还有研究表明甘露寡糖可以提高鳗鲡肠道内的淀粉酶、胰蛋白酶和脂肪酶的活性^[44]。

1.6 改善肠道炎症

炎症是机体对于刺激的一种防御反应。炎症性肠病是一种非特异性的肠道炎症,肠黏膜屏障破损、肠道菌群失常、肠道黏膜免疫、遗传易感染、环境因素等都能影响炎症性肠病的发生,肠黏膜破损是关键的一个因素^[45],炎症性肠病会导致肠黏膜屏障损伤。

寡糖可以减轻动物模型肠道炎症反应。刘海平^[46]研究发现,壳寡糖能抑制核转录因子 NF- κ B(nuclear transcription factor- κ B, NF- κ B)的表达来

有效改善 TNBS/乙醇法诱导的溃疡性结肠炎(ulcerative colitis, UC)小鼠的肠道炎症反应。此外,壳寡糖可降低经口服脂多糖(lipopolysaccharide, LPS)诱导的仔猪中炎症细胞因子的浓度,通过抑制核转录因子 NF- κ B 的传导途径和钙敏感受体的激活改善肠道炎症^[47]。CHENG 等^[6]用热应激破坏肉鸡肠道组织形态,增加肠道炎症后在膳食中添加甘露寡糖发现十二指肠和空肠粘膜白细胞介素 1 β (Interleukin-1 β , IL-1 β)的含量降低,表明甘露寡糖可调节炎症细胞因子和免疫球蛋白的产生,从而减轻热应激引起的肉鸡肠道炎症反应。

患有炎症性肠病和结直肠癌的人粪便中的大肠杆菌和粪肠球菌的数量高于正常人,乳酸杆菌和双歧杆菌的数量明显低于正常人^[48]。功能性寡糖可通过提高双歧杆菌和乳杆菌的数量,降低大肠杆菌和肠球菌的数量,提高短链脂肪酸的产量来减轻溃疡性结肠炎的症状^[49]。短链脂肪酸中的丁酸盐能促进 IL-4 的吞噬作用来限制 IL-17A 分化的 T 细胞的产生从而来抑制结肠炎^[50]。木寡糖可以在肠道内被代谢为短链脂肪酸,其中丙酸和丁酸促进幼稚 CD4⁺T 细胞向调节性 T 细胞(regulatory T cells, Treg)分化,增加 Treg 细胞数量进而减缓炎症性肠病^[51]。

1.7 提高肠道免疫反应

免疫反应是指机体对外来成分和变异的自体成分做出的防御反应,而肠道则在免疫方面发挥了巨大的作用。肠黏膜是机体与抗原相互作用的主要场所,肠道黏膜免疫系统是机体免疫系统的第一道防线,能够对病原体或有害抗原产生免疫应答,从而达到免疫效果^[52]。低聚寡糖是一种天然活性物质,可以激活体液和细胞免疫系统,从而提高机体的免疫功能^[53]。益生菌可以通过调节肠道菌群来抑制肠上皮细胞与微生物相互作用引起的免疫失调;同时益生菌能产生免疫保护反应,其机制是与受体识别调节免疫反应从而激发机体的非特异性免疫应答^[54]。周笑犁^[55]在断奶仔猪身上进行体内体外实验发现大豆寡糖可以增加肠道内的有益菌的数量,增加血浆免疫球蛋白 G(immunoglobulin G, IgG)和 IL-10 的浓度,减少血浆中 IL-1 β 的浓度,有效调节机体免疫功能。MA 等^[56]给小鼠灌胃不同剂量的大豆低聚糖(soybean oligosaccharides, SBOs),结果发现高剂量 SBOs 提高巨噬细胞吞噬百分率和吞噬指数,促进腹腔巨噬细胞的吞噬活性,提高非特异性免疫;T 淋巴细胞的百分比显著增加,表明施用大豆寡糖促进了小鼠的细胞免疫;此外,高剂量组血清 IgA、IgG、IgM 水平明显升高,表明大豆寡糖增强了肠黏膜免疫球蛋白的分泌,从而提高了免疫功能。李元凤等^[57]饲喂母猪短链果寡糖之后,对肠系膜淋巴细胞和派式淋巴结进行刺激,发现干扰素 γ (interferon- γ , IFN- γ)、短链脂肪酸以及未受刺激的派式淋巴结细胞的分泌型 IgA 含量增加,表明果寡糖可以提升初乳免疫水平,修复仔猪

的肠道免疫系统。

2 功能性寡糖的应用与展望

目前功能性寡糖在生活中的应用越来越广泛, 主要应用在食品、农业、医药等领域。在食品领域, 果寡糖具有益生元特性, 能增加饱腹感, 限制能量的摄入, 常应用在焙烤食品中^[58]; 寡糖抗菌、抗氧化的特性, 能够使果蔬采摘之后的储存时间延长^[59]; 功能性低聚糖可以模拟母乳中低聚糖的功能, 将其加入婴儿的奶粉中, 可抵抗肠道病原菌的侵害, 维持婴儿肠道微生态的平衡^[60]。益生元被誉为人体肠道的健康卫生, 很多功能性寡糖也常被用于保健产品和功能性食品中^[61-63]。在农业领域中, 功能性寡糖对于动物的肠道也有积极地影响, 可以提高肠道对养分的吸收, 改善肠道菌群, 促进动物生长, 所以常被加入动物的饲料中^[64-66]; 将海藻寡糖混入肥料对农作物进行施肥, 结果发现海藻寡糖可以增加氮、钾和磷肥的利用率, 提高玉米的产量^[67]; 除此之外海藻酸钠寡糖可以促进光能的转化, 提高电子传递效率, 提高酶活性从而促进蔗糖的积累^[68]。在医药领域, 白芨寡糖能有效预防由高脂饮食引起的代谢紊乱症状的发生^[69]; 魔芋甘露寡糖对于小鼠肥胖有抑制作用, 同时能抑制由肥胖引发的炎症等慢性疾病^[70]; 壳寡糖也能明显减轻大鼠的体重, 降低血清总胆固醇和低密度脂蛋白胆固醇水平, 从而改善血脂情况^[71]。

目前, 由于很多功能性寡糖的结构、活性作用机制及构效关系的研究尚未完全阐明, 还需要进一步的探索与研究。但基于功能性寡糖对机体胃肠道健康的有益调控作用, 随着人们对其研究的逐步深入, 未来将有更多的功能性寡糖被应用在保健食品及医药领域, 具有很好的发展前景。

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