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· 专题综述 ·

基于肠-脑轴探讨植物多糖干预肠道菌群抗抑郁的研究进展

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摘　要: 抑郁症是一种严重的情绪障碍疾病，患者通常表现出持续显著的悲伤情绪、意志消沉等临床特征。抑郁症发病机制复杂，近年肠-脑轴理论的研究为抑郁症探索提供可能的内在机制，体现在抑郁患者肠道菌群紊乱、高炎症水平和异常的神经递质水平等方面。植物多糖具有多种生物活性，研究发现其能够基于肠-脑轴调节肠道菌群不同代谢途径缓解抑郁，但其作用机理尚未得到系统的总结。因此，本文通过调研近年相关文献资料，从肠-脑轴的角度出发探讨植物多糖通过肠道菌群调节短链脂肪酸、脂多糖水平和色氨酸代谢等途径发挥抗抑郁作用，综述了不同植物多糖改善抑郁的机制和构效关系，为阐述植物多糖抗抑郁的机制及开发抗抑郁多糖资源提供理论依据。

关键词: 多糖, 肠-脑轴, 肠道菌群, 抑郁症, 短链脂肪酸
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Exploring the Antidepressant Effects of Plant Polysaccharides on Gut Microbiota Based on the Gut-Brain Axis

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Abstract: Depression is a severe emotional disorder characterized by persistent and prominent clinical symptoms, such as sadness and a loss of interest or pleasure. The pathogenesis of depression is intricate, and in recent years, investigations into the gut-brain axis theory have offered viable endogenous mechanisms for further exploration of depression. This theory is supported by evidence of disrupted gut microbiota, elevated inflammation markers, and deviant neurotransmitter levels in individuals with depression. Plant polysaccharides exhibit various biological activities and have been shown to modulate different metabolic pathways within the gut microbiota, thus impacting depression through the gut-brain axis. Nevertheless, a comprehensive summary of their mechanisms of action is currently lacking. Therefore, this study explores the potential antidepressant effects of plant polysaccharides by examining their regulation of short-chain fatty acids, lipopolysaccharides, and tryptophan metabolism within the gut microbiota and the gut-brain axis. Through a comprehensive analysis of recent literature, this article reviews the intricate relationships between various plant polysaccharides and their mechanisms in alleviating depression. It provides a theoretical basis for understanding how plant polysaccharides act as antidepressants and for developing resources for antidepressant polysaccharides.

Key words: polysaccharide; gut-brain axis; gut microbiota; depression; short chain fatty acids

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抑郁症是一种常见的心理精神类疾病，患者会产生严重且持续的消极情绪，伴随身体疲劳、虚弱和睡眠障碍等症状，同时也会引发神经退行性异常、心血管疾病和糖尿病等重大疾病[1−2]。全球大约有3.5 亿抑郁症患者，深受抑郁和附带产生的神经障碍影响，抑郁症给社会带来巨大经济负担，给人们生活和身体造成影响[3−4]。抑郁症临床用药主要有三环类抗抑郁药、选择性 5-羟色胺（5-Hydroxytryptamine，5-HT）再摄取抑制剂、单胺氧化酶抑制剂和去甲肾上腺素再摄取抑制剂，但这些药物仍存在明显缺点，如起效慢、治愈率低、复发率高等[5]，因此抗抑郁天然产物的开发已逐渐成为热点。

抑郁症和相关风险精神疾病发病与神经信号损伤、炎症、代谢失调等有关[6−7]，现有学说以单胺理论[8]、炎症反应[9]、下丘脑-垂体-肾上腺轴（The hypothalamic-pituitary-adrenal axis，HPA axis）[10] 为主。近年来发现肠-脑轴（Gut-brain axis，GBA）与抑郁症密切相关，而肠道菌群是影响脑肠互动的关键，目前已有大量研究证明抑郁症与肠道菌群息息相关[11−13]，图 1 为肠-脑轴互动的三大途径，肠道菌群及其代谢物能够通过迷走神经、HPA 轴和免疫途径影响到大脑，菌群代谢物紊乱会降低神经递质水平并诱导神经炎症，进而引起神经元损伤引发抑郁[14−16]。另外，肠道菌群及其代谢物能够突破血脑屏障的限制[17]，增加对脑部疾病早诊断、早治疗的可能，极有可能成为抗抑郁药研发的新方向[18]。

多糖作为益生元，广泛存在于植物中，因具有抗氧化[19]、抗炎[20]、抗抑郁[21] 等药理活性而受到越来越多的关注。植物多糖在促进情绪和认知功能方面发挥着重要作用，多糖促进肠道有益菌的生长繁殖，调节肠道菌群介导的微生物代谢缓解或治疗抑郁的机制已经被逐渐认可[22−23]；然而，其抗抑郁机制和构效关系还未系统总结。因此，本文主要通过调研近年相关文献，基于 GBA 分析总结植物多糖通过肠道菌群缓解和治疗抑郁症的作用机制，系统总结植物多糖通过调节肠道菌群，改善短链脂肪酸（Short chain fatty acids，SCFAs）水平、色氨酸（Tryptophan，TRP）代谢等方面，进而调节神经递质和炎症因子水平，发挥抗抑郁作用，为阐释肠道菌群与抑郁症的关系以及植物多糖通过肠道菌群多靶点抗抑郁的作用机制提供理论依据。

1　植物多糖调节肠道菌群 SCFAs 代谢

多糖作为碳源供菌群利用，菌群也参与多糖代谢，不同多糖可以降低宿主体内有害肠道微生物和增加有益菌群，产生更多的 SCFAs[24]。正常人体结肠中乙酸、丙酸、丁酸占 SCFAs 总量的 95% 左右，抑郁症患者表现出肠道菌群的紊乱，炎症反应升高，SCFAs 浓度改变，SCFAs 数量低于正常组[25]。SCFAs 是肠道有益菌发酵碳水化合物的产物，包括乙酸、丙酸、丁酸、异丁酸、异戊酸等，主要由厚壁菌门（Firmicutes）、拟杆菌门（Bacteroidetes）和放线菌门（Actinobacteria）等菌群中的一些成员产生。在肠-脑轴理论研究中，肠道菌群对宿主的作用主要通过 SCFAs 介导[26]，SCFAs 作为结肠细胞的关键能量来源，不仅能够调控相关基因表达影响肠上皮屏障和防御功能，还可以调节免疫细胞中细胞因子来降低炎症反应，益生菌可以通过增加 SCFAs 水平或迷走神经信号转导来减少抑郁相关行为[27−28]。乙酸主要由双

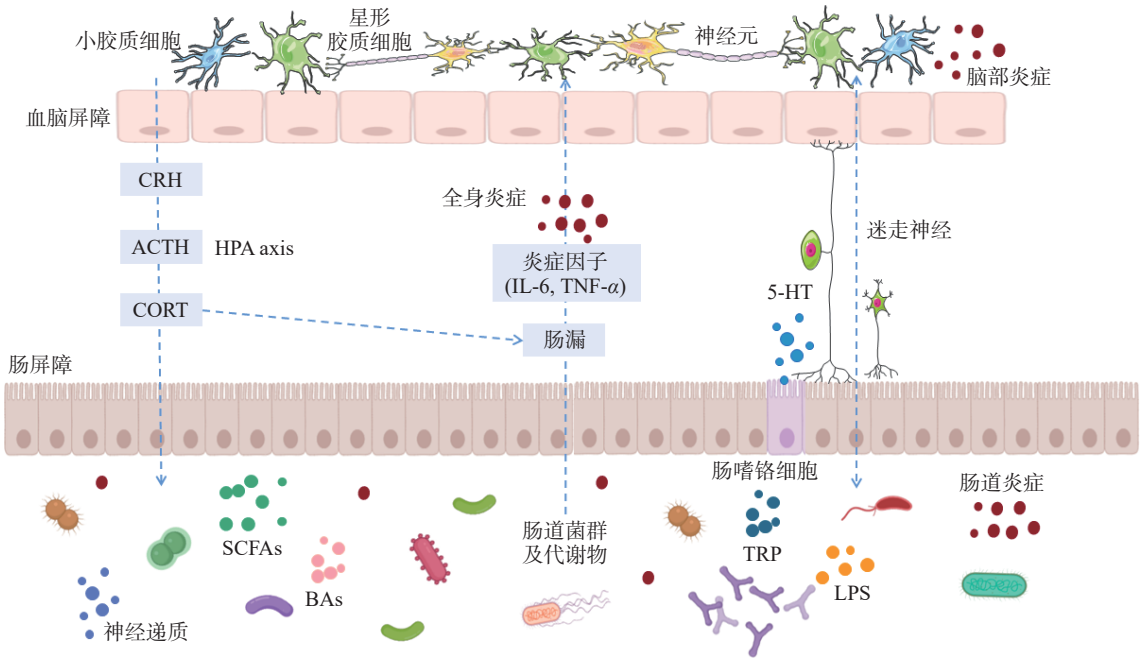

图 1　肠道菌群及其代谢物与肠脑轴的关联

Fig.1　Association between gut microbiota and its metabolites with the gut-brain axis

注：CRH：促肾上腺皮质激素释放激素；ACTH：促肾上腺皮质激素；CORT：皮质酮；IL-6：白细胞介素-6；TNF-α：肿瘤坏死因子-α；SCFAs：短链脂肪酸；Bas：胆汁酸；TRP：色氨酸；LPS：脂多糖。

歧杆菌属(*Bifidobacteriu*)、乳酸杆菌属(*Lactobacillus*)和埃希氏菌属(*Escherichia*)产生,能调节肠道 pH、促进产丁酸盐的细菌繁殖并防止病原体进入肠道;丁酸盐由罗氏菌属(*Roseburia*)和梭状芽胞杆菌属(*Clostridium*)产生,能保持肠壁的完整性来抵抗炎症,靶向肠-脑轴保护神经系统;乳酸有抗炎、减少焦虑等功能,由肠球菌属(*Bifidobacterium*)、乳酸杆菌属和梭状芽胞杆菌属产生[29−31]。

研究表明,经多糖干预后抑郁行为得到一定逆转[32−33],在慢性轻度不可预见性应激(Chronic unpredictable mild stress, CUMS)动物模型中被证实[34−35]。Yan 等[36]发现 CUMS 模型小鼠肠道厚壁菌门(Firmicutes)丰度和 SCFAs 水平降低,炎症因子显著增加,经秋葵多糖干预后调节小鼠肠道菌群组成,增加了乙酸、丙酸和丁酸水平,下调促炎因子,限制免疫反应程度并促进免疫稳态。SCFAs 能抑制 Toll 样受体 4(Toll-like receptors4, TLR4)的激活,减少其与配体的结合,从而抑制髓样分化因子激活核因子 κB(Nuclear factor kappa-B, NF-κB)信号通路,因此秋葵多糖可能通过抑制 TLR4/NF-κB 通路降低脑部炎症。CUMS 能够诱发 NOD 样受体热蛋白结构域相关蛋白 3(NOD-like receptor thermal protein domain associated protein 3, NLRP3)激活,NLRP3 炎症小体激活后产生一系列炎症反应,茯苓多糖干预后提高小鼠粪便丁酸含量并降低炎症反应,丁酸可能通过抑制 kappa B 抑制因子激酶-α(Inhibitor of kappa B kinase alpha, IKKα)的磷酸化,激活核因子 κB 抑制因子 α(Recombinant inhibitory subunit of NF kappa B alpha, IκBα),从而阻断 NF-κB 核易位诱导炎症,并调节下游 NLRP3 通路减轻神经炎症[37]。茯苓酸性多糖降低血清炎症水平的主要机制也在于调节与 NLRP3 相关 mRNA 与蛋白表达水平,抑制 NLRP3 炎症小体通路改善 CUMS 大鼠的抑郁行为[38]。铁皮石斛花醇溶性多糖显著提高了 CUMS 小鼠肠道总 SCFAs 浓度,增加了有益菌的丰度,富集的乙酸菌属通过上调 G 蛋白偶联受体(G Protein-coupled receptors, GPCRs)发挥抗神经炎症作用,从而激活脑源性神经营养因子(Brain-derived neurotrophic factor, BDNF)-酪氨酸激酶受体(BTyrosine kinase receptor B, TrkB)-环磷腺苷效应元件结合蛋白(cAMP-response element binding protein, CREB)信号通路缓解神经元损伤达到抗抑郁效果[39]。Zhang 等[40]发现黄精多糖上调了 CUMS 小鼠肠道中丁酸含量,维持肠道屏障的完整性并增加抗炎效果。逍遥散中的甘草多糖、茯苓多糖等[41]通过调节肠道总菌群与产 SCFAs 功能菌群的比例以及调控 SCFAs 的生成作为潜在的抗抑郁机制,多糖干预后调节优势菌的组成和结构,增加了产丁酸的属多样性,罗氏菌属(*Roseburia*)从 11.5% 上升至 61.1%,对降低炎症反应起到重要作用。桑叶多糖能够改善肠道菌群组成,显著提升乙酸、丙酸和正丁酸的含量,修复小鼠肠道屏障损坏,降低了炎症因子水平从而调节肠道免疫反应[42]。

大量炎症因子穿过血脑屏障后会激活小胶质细胞释放白细胞介素-6(Interleukin-6, IL-6)和肿瘤坏死因子 α(Tumour necrosis factor-α, TNF-α),这些促炎因子进一步吸引免疫细胞进入大脑,加剧神经炎症导致抑郁。植物多糖通过提高 CUMS 模型组 SCFAs 水平,降低炎症反应,保护肠道屏障,缓解神经炎症,具体机制见图 2,涉及 SCFAs 与 GPCRs 或组蛋白去乙酰化酶(Histone deacetylase, HDAC)相互作用,并通过细胞信号转导调节 NF-κB 通路、NLRP3 通路降低炎症反应。

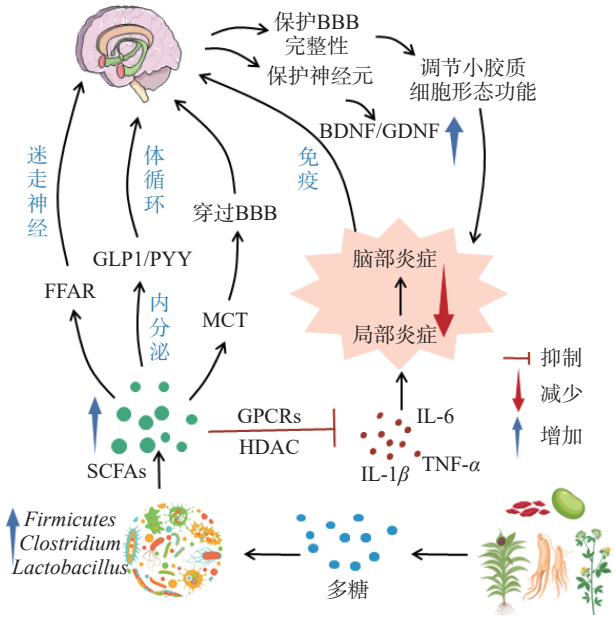

图 2 植物多糖调节 SCFAs 抗抑郁的机制[26]

Fig.2 Mechanisms of plant polysaccharides regulating SCFAs for antidepressant effects[26]

注: SCFAs: 短链脂肪酸; GPCRs: G 蛋白偶联受体; HDAC: 组蛋白去乙酰化酶; TNF-α: 肿瘤坏死因子-α; IL-1β: 白细胞介素-1; IL-6: 白细胞介素-6; FFAR: 游离脂肪酸受体; GLP1/PYY: 胰高糖素样肽-1/酪酪肽; MCT: 单羧酸盐转运蛋白; BBB: 血脑屏障; BDNF: 脑源性神经营养因子; GDNF: 胶质细胞源性神经营养因子。

2 植物多糖调节肠道菌群降低 LPS 水平

脂多糖(Lipopolysaccharide, LPS)是常见的内毒素,进入血液后可激活细胞的 TLR4、NF-κB 和丝裂原活化蛋白激酶(Mitogen-activated protein kinase, MAPK)进而诱导多种促炎细胞因子释放,引发炎症诱导抑郁[43−44]。研究发现,抑郁患者的 LPS 生物合成相关基因表达增加,血浆 LPS 显著增加,脂肪酸结合蛋白 2 显著升高,表示肠道菌群失调及肠道屏障通透性增加[45]。动物实验证明 CUMS 小鼠血清 LPS 显著高于对照组,血清中肠道通透性标志物二胺氧化酶(Diamine oxidase, DAO)结果证实 CUMS 诱导小鼠的肠道通透性增加[46]。LPS 会激活小胶质细

胞，继而上调海马体中促炎因子的表达，Wang 等[47]发现 CUMS 小鼠海马体中的 TLR4、NF-κB p65 和 p38MAPK 蛋白水平明显增加，表明 TLR4/NF-κB/MAPK 信号通路被激活，经杜仲多糖治疗后，改变小鼠肠道菌群结构组成，血清 LPS 减少，增强肠道屏障完整性，抑制了小胶质细胞介导的 TLR4/NF-κB/MAPK 信号通路激活和促炎因子表达，减轻小鼠抑郁样行为。

香菇多糖与肠道菌群协同发挥免疫调节作用，通过调节仔猪肠道菌群组成和代谢产物来减轻 LPS 诱导的肠道损伤，增加了厚壁菌门（Firmicutes）的相对丰度，修复了肠道屏障，降低仔猪肠道 LPS 水平[48]。申丰铭[49]发现在小鼠注射 LPS 后，细胞外信号调节激酶（Extracellular signal-regulate sigsignal-regulated kinases, ERK）的磷酸化水平和 NLRP3 表达升高，而黄精多糖干预后可以显著降低 ERK 磷酸化水平，通过调控活性氧（Reactive oxygen species, ROS）-钙蛋白酶（Calpain-1）介导的炎症通路来抑制 LPS 诱导的 ERK 磷酸化水平和 NLRP3 表达上升，并降低 IL-1β、TNF-α 水平，改善小鼠抑郁样行为。LPS 能诱导小鼠小胶质瘤细胞（BV2）TLR4 表达和 NF-κB 表达增加，MAPKs 通路中 ERK、p38、应激活化蛋白激酶（c-Jun N-terminal kinase, JNK）的表达增加，而秋葵多糖干预抑制了细胞 NF-κB 的表达，下调了 TLR4/NF-κB 信号通路和 MAPKs 通路，IL-1β、IL-6 和 TNF-α 的 mRNA 表达显著降低[36]。史云静等[50]发现茯苓多糖能通过调节免疫应答特征性标记物促进 LPS 诱导的 BV2 细胞由炎症性 M1 向抗炎型 M2 表型转化，显著降低了一氧化氮、ROS、TNF-α 和 IL-1β 等炎症因子水平，减轻小鼠焦虑和抑郁样行为。

抑郁可能导致肠道内 LPS 水平升高，损害肠道屏障完整性，导致肠道通透性增加。随着 LPS 进入血液，其对生物活性代谢的影响可能引发炎症，植物多糖干预的实验结果表明，它能显著降低体内 LPS 水平，同时伴随着 IL-1β、TNF-α 水平的降低，从而缓解神经炎症，对抑郁症状具有积极作用，具体机制可参见图 3。因此，降低 LPS 水平和改善肠道通透性是植物多糖基于肠-脑轴调节肠道菌群抗抑郁的重要作用机制。

3　植物多糖调节肠道菌群色氨酸代谢

色氨酸是人体不能合成的必需氨基酸，通过摄入外源性食物并经肠道菌群产生，影响肠-脑轴信号转导。色氨酸代谢分为 5-HT、犬尿氨酸（Kynurenine, KYN）和吲哚衍生物三种途径[17]。5-HT 降低是抑郁发生的关键，人体约 90% 的 5-HT 主要由肠上皮肠嗜铬细胞合成，大约有 5% 的色氨酸通过色氨酸羟化酶（Recombinant tryptophan hydroxylase, TPH）合成 5-HT，进而生成血清素、5-羟基吲哚乙酸（5-Hydroxyindole acetic acid, 5-HIAA）和褪黑素[51]。

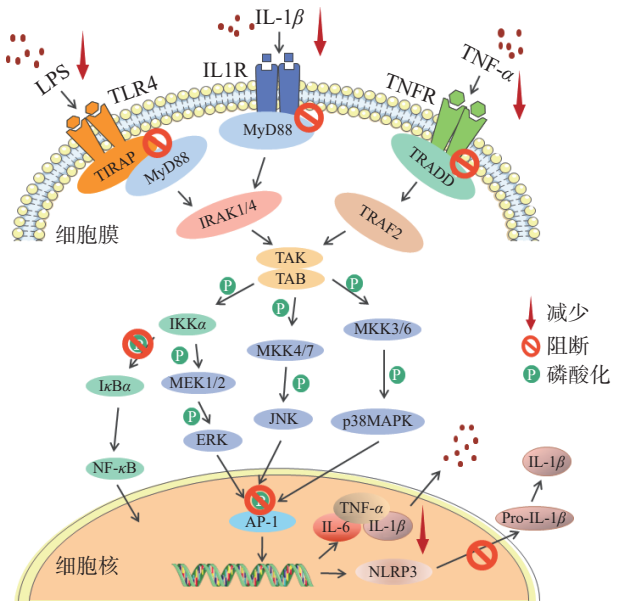

图 3　植物多糖调节 LPS 抗抑郁的机制

Fig.3　Mechanisms of plant polysaccharides regulating LPS for antidepressant effects

注：LPS：脂多糖；TLR-4：Toll 样受体 4；TIRAP：含 toll 白介素 1 受体域衔接蛋白；MyD88：髓样分化因子；TRADD：通过死亡域关联的 TNFRSF1A；IL1R：白细胞介素-1 受体；TNFR：肿瘤坏死因子受体；IRAK1/4：白介素 1 受体关联激酶 1/4；TRAF2：TNF 受体关联因子 2；TAK：转化生长因子 B 活化激酶；TAB：转化生长因子 β 活化激酶结合蛋白；IKKα：kappa B 抑制因子激酶-α；IκBα：核因子 κB 抑制因子 α；NF-κB：核因子 κB；MEK1/2：丝裂原活化蛋白激酶激酶；ERK：细胞外信号调节激酶；MKK：丝裂原活化蛋白激酶激酶；JNK：应激活化蛋白激酶；p38MAPK：p38 蛋白激酶；AP-1：激活子蛋白-1；NLRP3：NOD 样受体热蛋白结构域相关蛋白 3；Pro-IL-1β：白细胞介素-1 前体。

其余 95% 的色氨酸会沿着犬尿氨酸代谢途径（Kynurenine pathway, KP）进行，KP 代谢偏倚影响多种疾病发展[52]。TRP、KYN 和 3-羟基犬尿氨酸（3-Hydroxy-kynurenine, 3-HK）可以通过血脑屏障，被星细胞、小胶质细胞和神经元吸收，星形胶质细胞产生具有神经保护作用的犬尿酸（Kynurenic acid, KA），而小胶质细胞产生具有神经毒性的 KP 代谢物喹啉酸（Quinolinic acid, QA）[52]。抑郁症患者体内肠道菌群改变，糖皮质激素（Glucocorticoid, GC）和皮质酮（Corticosterone, CORT）过高，血浆 TRP 浓度降低，高水平的 GC 和促炎因子能增加色氨酸-2,3-双加氧酶（Tryptophan 2,3-dioxygenase, TDO）和吲哚胺-2,3-二氧化酶（Indoleamine-2,3-dioxygenase, IDO）的活性，使大量色氨酸通过 KP 代谢生成 KYN，增加 QA，减少 5-HT 和 KA 合成，最后导致抑郁[53−54]。

多糖通过重塑肠道菌群影响色氨酸代谢的主要途径为增加 5-HT 代谢和降低 KYN/3-HK 代谢。Chen 等[55]发现抑郁小鼠 IDO、TDO、GC、CORT 的表达上调，海马体谷氨酸（Glutamate, Glu）受体、γ-氨基丁酸（γ-Aminobutyric acid, GABA）受体和 BDNF 的转录水平下降，体内 TRP 代谢偏向于 KYN 途径，

海马体 5-HT 水平降低，而白术、白芍、陈皮、防风多糖能够逆转 CUMS 诱导的抑郁样行为，多糖干预改善了肠道菌群，降低海马、结肠 IDO 转录水平和血清中 KYN 水平，提高小鼠 TRP/5-HT 代谢途径，改善应激导致的 5-HT 水平紊乱。韦震等[56] 发现黄精多糖能上调抑郁模型动物脑内的单胺神经递质，下调海马 TRP 和 3-HK 水平，抑制神经炎症反应，抑制 TRP/KYN/3-HK 代谢通路，增加 TPH 活性，增加 TRP/5-HT/5-HIAA 通路的代谢，显著升高脑内多巴胺（Dopamine, DA）、5-HT 和去甲肾上腺素（Norepinephrine, NE）水平，同时降低血清中 TNF-α 水平。此外，肉苁蓉总糖苷能够显著升高 CUMS 大鼠血清 TRP 水平，降低 KYN 代谢途径，逆转了 CUMS 引起的结肠和海马中 KYN、KYN/TRP 和 IDO1 蛋白表达水平升高[57]。

KA 能够调节 Glu 水平，Glu 是抑制性神经递质 GABA 的前体，作用于 HPA 轴和自主神经系统，Glu/GABA 影响着下丘脑释放促肾上腺皮质激素释放激素（Corticotropin releasing hormone, CRH），过度激活的 HPA 轴导致 GC 增加进一步诱导 TRP/KYN 代谢。当归多糖能够升高 GABA/Glu 比率，增加 TPH1 酶活性，提高 5-HT、DA 含量，调节神经递质传导改善慢性应激模型小鼠抑郁行为[58]。刘佳蕾等[59] 发现黄芪多糖和百合多糖联用能够抑制由 CUMS 诱导的炎症反应和 HPA 轴过度激活，降低 CORT 和促肾上腺皮质激素（Adrenocorticotropic hormone, ACTH）水平，促进 5-HT 含量增加，BDNF 和 CREB 蛋白表达显著上调；5-HT 和 ACTH 作用于 G 蛋白偶联受体，从而激活腺苷酸环化酶（Adenylate cyclase, AC）催化腺苷酸（Adenosine triphosphate, ATP）水解形成环磷酸腺苷（Cyclic adenosine monophosphate, cAMP），活化蛋白激酶 A（Protein kinase A, PKA），进一步促进 CREB 调节下游 BDNF 蛋白合成，多糖通过 AC/cAMP/PKA 信号转导通路上调 BDNF 水平。黄精多糖能改变菌群结构调节小鼠 HPA 轴功能，降低 CUMS 诱导小鼠的血清 ACTH 水平和 CORT 水平[40]。植物多糖通过调节肠道菌群，对色氨酸代谢产生积极影响，从而缓解抑郁症状，具体机制参见图 4，主要表现在降低 KYN/3-HK 代谢，调节 Glu/GABA 比率协同作用于 HPA 轴，有助于提高 5-HT、DA 和 BDNF 水平，同时减轻炎症反应，保护神经元。

4 植物多糖调节肠道菌群次级胆汁酸代谢

胆汁酸（Bile acids, BAs）是胆汁的重要成分，在肠道代谢和循环与菌群密切相关。初级胆汁酸由胆固醇通过 7α-羟化酶（CYP7A1）在肝脏中合成并储存在胆囊中，摄入食物后，BAs 被释放到十二指肠沿着肠道下行，被肠上皮细胞吸收，大约 95% 的初级胆汁酸经过肠肝循环被重吸收到肝脏中，仅 5% 的初级胆汁酸（鹅去氧胆酸 CDCA、胆酸 CA）在肠道内由菌群通过胆盐水解酶（Bile salt hydrolase, BSH）转化为次级或三级胆汁酸（石胆酸 LCA、脱氧胆酸 DCA），阻止胆汁酸的重吸收，肠道菌群失衡后，具有 BSH 活性的乳杆菌、双歧杆菌等有益菌数量减少，BSH 活性降低导致次级胆汁酸生成减少，初级胆汁酸增加[60−61]。作为肠道激素，胆汁酸可以通过法尼醇

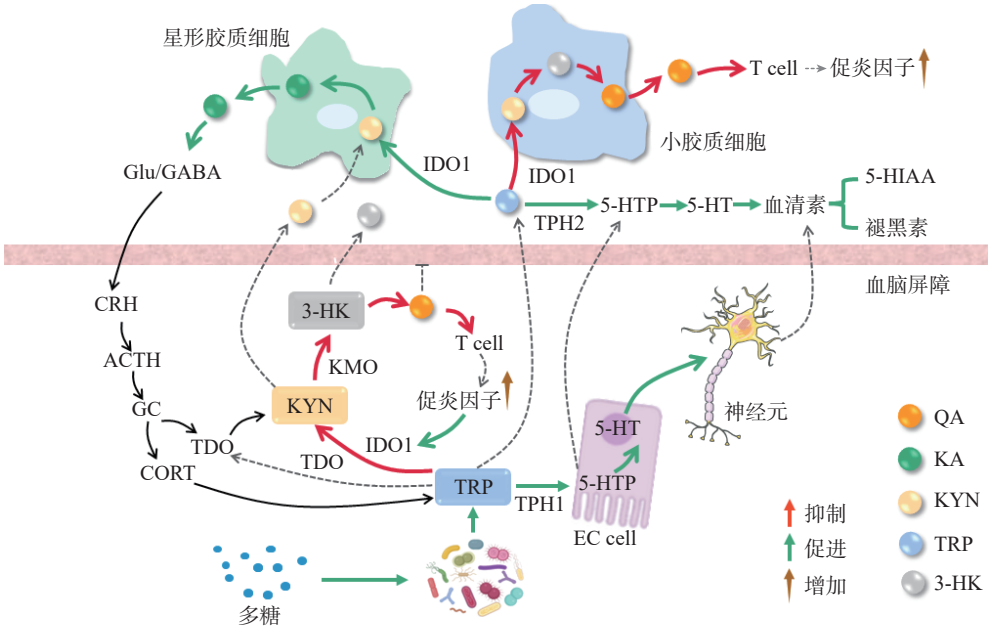

图 4 植物多糖调节色氨酸代谢抗抑郁的机制

Fig.4 Mechanism of plant polysaccharides regulating tryptophan metabolism for anti-depressant effects

注：TRP：色氨酸；TDO：色氨酸-2,3-双加氧酶；IDO1：吲哚胺-2,3-二氧化酶 1；KMO：犬尿氨酸 3-单加氧酶；KYN：犬尿氨酸；3-HK：3-羟基犬尿氨酸；CRH：促肾上腺皮质激素释放激素；ACTH：促肾上腺皮质激素；GC：糖皮质激素；CORT：皮质酮；Glu/GABA：谷氨酸/γ-氨基丁酸；5-HTP：5-羟基色氨酸；5-HT：5-羟色胺；5-HIAA：5-羟基吲哚乙酸；TPH1：色氨酸羟化酶 1；TPH2：色氨酸羟化酶 2；QA：喹啉酸；KA：犬尿酸；EC cell：肠嗜铬细胞。

X 受体(Farnesoid X receptor, FXR)和 G 蛋白偶联胆汁酸受体 TGR5 等受体影响代谢过程，直接作用于大脑。

BAs 激活肠道中的 FXR 受体向中枢神经系统发出信号，抑制 CREB 的转录，导致 BDNF 表达被抑制，CUMS 小鼠的 BDNF 异常表达与胆汁酸改变有关[60]。次级胆汁酸牛磺去氧胆酸与 TGR5 受体的结合通过抑制神经炎症改善应激小鼠抑郁表型[62]，CUMS 小鼠海马体神经元 TGR5 表达水平显著下降，敲除 TGR5 基因的小鼠出现部分抑郁样行为，上调 TGR5 后显著改善模型鼠抑郁样行为[63]。Chen 等[55] 发现 CUMS 降低小鼠结肠中牛磺胆酸(TCA)水平，而 CA 及其相关产物水平升高，白术、白芍、陈皮、防风多糖通过上调相关菌群丰度改善 BAs 代谢紊乱降低炎症反应，乳酸菌富集提高海马 BDNF 基因表达。葛根多糖和灰树花多糖能够提高 CYP7A1 的表达，促进肝脏 BAs 的生物转化，胆盐输出泵 BSEP 的激活增加了 BAs 的转录，有利于 BAs 的排泄，调控了胆汁酸的合成与吸收[64−65]。杏鲍菇多糖和龙须菜多糖均通过调节肠道菌群促进小鼠粪便中总胆汁酸的排泄，改善胆汁酸代谢紊乱[66−67]。目前，多糖调节胆汁酸抗抑郁研究还在持续进展，多糖通过调节肠道菌群组成影响胆汁酸的代谢产物，主要由 BAs-FXR/TGR5 通路与炎症和神经递质信号传导来影响抑郁行为。

5　具有抗抑郁作用植物多糖的构效关系

植物多糖的一级结构是研究各种生物活性的基础，构效关系更是当前焦点，分析多糖的构效关系对功能性食品和药物的开发至关重要，但目前因为技术有限，对多糖构效关系的研究并不完善[68−69]。多糖根据其组成可分为均多糖和杂多糖，均多糖由一种单糖组成，杂多糖则由两种以上的单糖组成，具有抗抑郁效果的多糖大多为杂多糖，多糖生物活性与其分子量、单糖组成、糖苷键类型等一级结构密切相关[70]。

分子量的功能特征与活性基团有关，分子量间接影响溶解度、粘度等理化性质，从而影响体内多糖的吸收，分子量越大的多糖体积越大，对多糖跨越细胞膜进入生物体内发挥活性作用有不利影响，而分子量过小的多糖很难形成活性空间结构。表 1 列举了部分具有抗抑郁活性植物多糖的结构特征，大多数具有肠屏障保护作用的多糖具有较高的分子量，分子量较大的多糖粘度较高，可以形成类似肠粘膜层的亲水性凝胶层与膜受体交联，维持肠屏障结构的完整性，桑叶多糖分子量为 2220 kDa，大分子量可能有助于增强肠道屏障蛋白表达，从而保护肠道菌群，进而起到抗抑郁效果[71]，目前分子量如何影响抗抑郁效果还有待深入研究。

单糖组成和糖苷键类型决定了多糖在体内与靶点的亲和力大小，一般认为单糖组成越复杂，其生物活性越好[69,72]。从表 1 可以看出大多数具有抗抑郁作用多糖的单糖组成为葡萄糖(Glc)、鼠李糖(Rha)、甘露糖(Man)、岩藻糖(Fuc)、半乳糖(Gal)、阿拉伯糖(Ara)，其中含有较高比例的葡萄糖，而这些单糖组成的多糖都具有调节肠道菌群活性的作用，葡萄糖含量更高的多糖益生菌活性更强[24,73]。研究表明，具有肠屏障保护功能的多糖中的单糖组成为 Gal、Man、Ara、Rha 和木糖(Xyl)，含有 Glc、Man、Gal、Ara 的多糖具有较强的促免疫活性，能起到抗炎作用[69,71]。多糖由各种单糖通过糖苷键连接而成，根据半缩醛(酮)羟基的构型分为 α 型和 β 型，一般认为具有 β 构型的多糖具有较高的活性[73]。具有抗抑郁活性的多糖大多含有 β-糖苷键，尤其是 β-葡聚糖，如香菇多糖[48] 和桑黄多糖[74] 主链葡聚糖通过 β-(1→3)-糖苷键相连，而具有调节肠道菌群活性的多糖大部分以(1→3)糖苷键连接，例如以 β-(1→3)-D-葡萄糖为主的猴头菇多糖能够增加大鼠肠道菌群的多样性和丰富度，提高乙酸和丁酸比例[75]。与铁皮石斛水溶性多糖相比，铁皮石斛花醇溶性多糖的糖苷键中不包括

表 1　具有抗抑郁活性植物多糖的结构特征

Table 1　Structural characteristics of anti-depression plant polysaccharide

多糖种类	分子量(kDa)	单糖组成	参考文献
秋葵多糖	626	鼠李糖:阿拉伯糖:半乳糖:葡萄糖醛酸:半乳糖酸=6.11:5.51:7.12:39.25:42.01(百分比)	[36]
铁皮石斛花醇溶性多糖	31	鼠李糖:阿拉伯糖:岩藻糖:甘露糖:葡萄糖=0.39:0.27:0.35:4.92:10.75(摩尔比)	[39]
黄精多糖	5.34	阿拉伯糖:葡萄糖:葡萄糖醛酸:半乳糖:半乳糖醛酸:甘露糖:鼠李糖:D-核糖=13.7:82.9:3.7:36.2:4.3:52.5:3.3:1.0 (摩尔比)	[40,76]
桑叶多糖	2220	甘露糖:鼠李糖:葡萄糖:半乳糖:阿拉伯糖=1.31:8.45:6.94:1.00:11.96(摩尔比)	[42]
杜仲多糖	6.22	甘露糖:鼠李糖:半乳糖醛酸:葡萄糖:半乳糖:木糖:阿拉伯糖:岩藻糖:葡萄糖醛酸=2.05:2.43:2.15:81.48:2.94:1.23:7.10:0.24:0.39(百分比)	[47]
银杏叶多糖	296.96	甘露糖:鼠李糖:葡萄糖:半乳糖:阿拉伯糖=29.73:31.54:24.81:5.72:8.30(摩尔比)	[77]
茯苓多糖	37.15	甘露糖:葡萄糖:半乳糖:岩藻糖=36.896:7.298:40.480:15.326(百分比)	[78]
灵芝多糖	107	葡萄糖:半乳糖:岩藻糖= 68.4:26.2:5.4(百分比)	[79]
金银花多糖	<1000	半乳糖酸:鼠李糖:半乳糖:阿拉伯糖:葡萄糖:甘露糖=8.7:8.2:16.2:19.5:26.9:20.5(摩尔比)	[80]
薏苡仁多糖	82.3	木糖:阿拉伯糖:半乳糖:葡萄糖=0.4:1.4:1.6:0.5(摩尔比)	[81]
桑黄多糖	20.708	鼠李糖:甘露糖:阿拉伯糖:半乳糖:木糖:葡萄糖=0.82:8.32:1.13:8.06:2.8:78.88(百分比)	[74]
石菖蒲多糖	25.1	葡萄糖=98.23(百分比)	[82]

(1→4)糖苷键，作者推测其抗抑郁活性和物理性质的差异可能是由于多糖结构不同造成[39]。

6 结论与展望

抑郁症作为一种多因素影响的疾病，应从多方面干预，使用天然物质治疗替代传统治疗备受关注，随着多糖药性机理的逐渐完善，制备药剂和相关功能性产品也有了更多参考依据。本文基于肠-脑轴理论，综述了植物多糖调节肠道菌群各方面代谢发挥抗抑郁作用的机制，显示出多糖抗抑郁具有广阔前景。天然多糖为研发高效、低毒的抗抑郁新药提供了重要途径，而探究多糖与菌群相互作用对于研究抑郁症发病机制和抗抑郁新药靶点研发具有深远意义。未来，多糖研究需要更加关注其结构和活性之间的关系，分析活性多糖的一级结构以更好解析化学信号对肠道菌群和肠-脑轴的影响。这些研究有望推动多糖药品和功能性食品的开发，例如多糖膳食补充剂和肠道菌群调节剂等。最终，多糖抗抑郁疗法有望成为需替代治疗方法的患者的全新选择。然而，为确保其安全性和有效性，后续需要进行更多的临床研究，进一步深入探讨多糖的作用机制，以促进植物多糖在临床治疗抑郁症方案中的应用，并为患者提供更多可能性和希望。

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