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专论与综述

乳酸菌对抑郁症的影响及其可能的作用机制

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摘　要：抑郁症是一种常见的精神疾病，其发病率逐年上升。近年来，使用乳酸菌治疗抑郁症得到了关注，越来越多的动物和人体研究证明了乳酸菌的抗抑郁功效。研究表明，乳酸菌可以缓解由抑郁症引起的肠道菌群失衡，进而改善宿主的行为和情绪。本文总结了乳酸菌对抑郁症的影响及其可能的作用机制，以及抗抑郁乳酸菌的分离来源，旨在为乳酸菌抗抑郁的研究提供新见解。
关键词：抑郁症；乳酸菌；肠道菌群；研究进展

Amelioration of depression by lactic acid bacteria and its possible mechanism of action

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Abstract: Depression is a prevalent mental health disorder with rising incidence annually. In

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recent years, the application of lactic acid bacteria as a therapy for depression has garnered great attention. A growing body of animal and human studies has confirmed the antidepressive efficacy of lactic acid bacteria. Studies have revealed that lactic acid bacteria can mitigate the intestinal flora imbalance induced by depression, thereby modulating the behaviors and moods of the host. This review summarized the effects and mechanisms of lactic acid bacteria on depression and discusses the sources of lactic acid bacteria isolated for treating depression, aiming to offer novel perspectives for research on the antidepressive properties of lactic acid bacteria.

Keywords: depression; lactic acid bacteria; intestinal flora; research progress

抑郁症是一种常见的有认知、行为和生理改变的精神疾病，以持续的情绪低落为主要特征，伴随着兴趣减退和愉快感的丧失，重度抑郁症患者甚至会对未来感到绝望而产生自杀的想法，严重地影响了患者的工作和生活，是当今重要的精神卫生问题[1-2]。据世界卫生组织(World Health Organization, WHO)统计，世界上大约有 3 亿抑郁症患者[3]，目前我国患抑郁症人数约为 9 500 万[4]。2019 年新型冠状病毒疫情大流行的出现明显增加了抑郁负担，使全球抑郁症患病率增加了 27.6%[5]，据 WHO 预测，到 2030 年，抑郁症将成为世界第一大负担疾病[6]。临床上可用的抗抑郁药只能使一部分患者受益，并且在过去的几十年里并未减少抑郁症的患病率。因此，需要新的干预措施。

微生物-肠-脑(microbiome-gut-brain, MGB)轴在维持体内平衡方面起着重要作用。它通过神经内分泌、神经和免疫信号通路参与肠道和大脑之间的双向通信，以维持机体平衡[7-8]。研究表明，抑郁症的发生通常伴随着肠道菌群的失调，肠道菌群通过 MGB 影响宿主的行为和情绪，继而诱发抑郁症状[9-10]。近年来，益生菌治疗抑郁症的研究越来越受到重视，越来越多的动物和人体研究证实了益生菌的抗抑郁效果。乳酸菌是补充剂中最常见的益生菌，应用最广泛的是乳杆菌属(*Lactobacillus*)和双歧杆菌属(*Bifidobacterium*)，乳酸菌可以通过上调有益菌含量、减少致病菌来缓解疾病引起的肠道菌群失衡，通过抗炎、促进 5-羟色胺(5-hydroxytryptamine or serotonin, 5-HT)合成等途径，进一步改善抑郁症症状[11-12]。

本文就乳酸菌与抑郁症的关系进行了综述(图 1)。

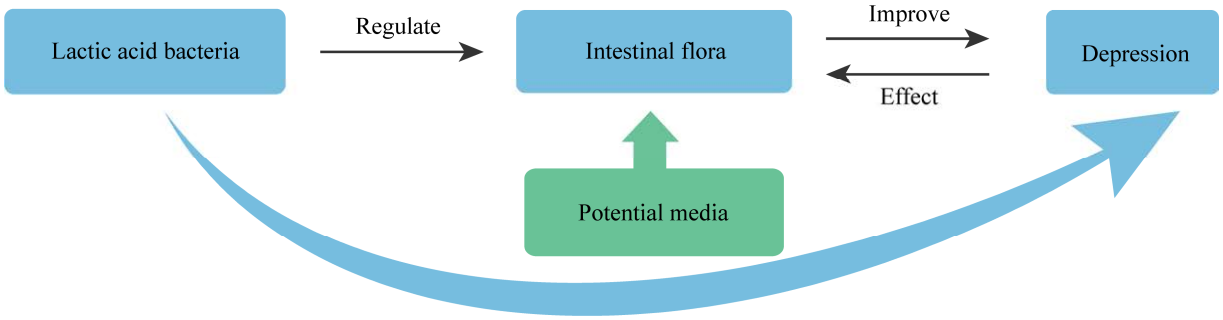

图 1　肠道菌群介导的乳酸菌和抑郁症的关系

Figure 1　Intestinal flora-mediated relationship between lactic acid bacteria and depression.

1 肠道菌群与抑郁症

中枢神经系统影响肠道菌群结构组成。研究发现，健康个体的肠道菌群环境主要由 79%厚壁菌门(*Firmicutes*)、17%拟杆菌门(*Bacteroidota*)、3%放线菌门(*Actinomycetota*)、0.9%变形菌门(*Proteobacteria*)和 0.1%疣微菌门(*Verrucomicrobiota*)组成[13]。大量研究表明，抑郁症患者的肠道菌群在门和属水平上发生了显著改变，相较于健康人群，抑郁症患者肠道中变形菌门、拟杆菌门的相对丰度增加，厚壁菌门的相对丰度减少，在属水平上，粪球菌属(*Coprococcus*)、栖粪杆菌属(*Faecalibacterium*)、戴阿利斯特菌属(*Dialister*)和萨特氏菌属(*Sutterella*)的相对丰度显著降低[14-17]。更多抑郁症患者肠道菌群变化的研究总结见表 1。

肠道菌群的组成变化或失调越来越被认为在精神疾病的发病机制中起关键作用。Li 等[23]分别将抑郁症患者和健康人群的粪便微生物区系移植到无菌(germ free, GF)小鼠体内，结果与健康微生物组小鼠相比，抑郁组小鼠强迫游泳试验和悬尾试验的不动次数显著增加，旷场试验的中心运动距离显著减少，表现出抑郁样行为。另外，适量补充益生元可以通过调节肠道菌群组成，最终减少焦虑和抑郁行为[24]。一项研究发现，低聚半乳糖通过增加有益菌如双歧杆菌的相对丰度及肠道短链脂肪酸(short-chain fatty acid, SCFA)的水平、促进神经递质的合成、降低血液中促炎细胞因子的浓度等途径有效地减轻了受试者抑郁症状[25]。而且，人们逐渐认识到中医药的抗抑郁功效也与肠道菌群的多样性和组成有关；Zhao 等[26]报道，用天麻素干预慢性不可预知温和刺激(chronic unpredictable mild stress, CUMS)诱导的抑郁小鼠，结果表明，天麻素治疗显著改善了抑郁样行为，并且提高了肠道菌群的多样性和丰富性。最新公布的《全国医疗服务项目技术规范(2023 年版)》(http://www.nhc.gov.cn/caiwusi/s7786k/202309/45dd0435bd254b1bb98a9e22836b44a4.shtml，项目编码为 KPH3M401)，把肠道菌群移植列入了医疗服务项目，为治疗肠道菌群失衡导致的多种肠道疾病(如抑郁症、炎症性肠病等)提供了强有力的支撑，这也间接说明肠道菌群稳态在调控宿主行为中起重要作用。

2 乳酸菌与抑郁症

乳酸菌是一类能利用可发酵碳水化合物产生大量乳酸的细菌的统称。它们无处不在，在

表 1 抑郁症患者肠道菌群变化

Table 1 Intestinal flora alterations of depression patients

菌群变化 Changes in intestinal flora	参考文献 Reference
Proteobacteria, *Escherichia*, *Gammaproteobacteria*, *Enterobacterales*, *Enterobacteriaceae*↑	[18]
Prevotellaceae, *Prevotella*, *Lachnospiraceae*, *Agathobacter*, *Clostridium*↓	
Alistipes, *Blautia*, *Bacteroides*, *Parabacteroides*, *Roseburia*, *Oscillibacter*, *Clostridium*, *Phascolarctobacterium*↑	[19]
Prevotellaceae, *Prevotella*, *Dialister*, *Faecalibacterium*, *Bacteroidota*, *Coprococcus*↓	
Bifidobacterium, *Escherichia coli*, *Lactobacillus*, *Bacteroides*↓	[20]
Bacteroidaceae, *Desulfovibrionaceae*, and *Enterococcaceae*↑	[21]
Firmicutes, *Streptococcus*, *Clostridiaceae*_unclassified, *Blautia*, *Lachnospiraceae*_unclassified↓	
Ruthenibacterium, *Escherichia*↑	[22]
Faecalibacterium, *Roseburia*, *Lachnospira*↓	

自然界中分布广泛。据报道，它们存在于人类和动物的不同栖息地，包括土壤、水、乳制品、肉类、蔬菜、胃肠道等，具有丰富的物种多样性[27]。根据系统分类，乳酸菌主要分布在厚壁菌门和放线菌门中。在厚壁菌门中，乳酸菌属于4个纲7个目18个科39个属；而在放线菌门中，乳酸菌属于2个纲2个目3个科12个属[28]。目前研究乳酸菌最多的菌属主要集中在乳杆菌属、双歧杆菌属、链球菌属(*Streptococcus*)、肠球菌属(*Enterococcus*)、乳球菌属(*Lactococcus*)、片球菌属(*Pediococcus*)和明串珠菌属(*Leuconostoc*)等[28]。

前期研究结果发现，相较于对照组，抑郁症患者的双歧杆菌和乳杆菌数量减少，乳酸菌逐渐进入大众视野[29]。最初将乳酸菌与抑郁症联系在一起的研究表明，乳酸菌可能是重度抑郁症治疗的辅助剂，有望采用单菌种或多菌种联合来发挥乳酸菌的抗抑郁作用[30]。目前已经有大量研究表明乳酸菌对抑郁症有改善作用。一项研究用复合乳酸菌[鼠李糖乳杆菌(*Lactobacillus rhamnosus*) GMNL-74、嗜酸乳杆菌(*Lactobacillus acidophilus*) GMNL-185和植物乳杆菌(*Lactobacillus plantarum*) GMNL-141]干预氨苄青霉素诱导的抑郁症小鼠，结果表明复合乳酸菌治疗具有抗抑郁潜力，可能是通过调节肠道微生物群的组成、降低炎症因子的水平、调节SCFA的水平、改变抑郁相关代谢途径的mRNA表达及肠道来源的5-HT水平等途径来实现[31]。另外，即使同一种属不同菌株的乳酸菌抗抑郁效果也存在着显著的差异，分离自健康小鼠派伊尔结处的罗伊特氏乳杆菌(*Lactobacillus reuteri*) L3，能够促进抗炎性细胞因子IL-10，抑制炎性细胞因子IL-6，对高脂膳食诱导的肥胖小鼠自主活动行为有促进作用，而分离自肥胖小鼠派伊尔结处的罗伊特氏乳杆菌L10，对小鼠自主活动行为反而有抑制作用[32]。可见，益生菌具有菌株特异性，后续还需要在单菌水平上对分离菌株进行比较基因组学测序，分析菌株组别间的遗传进化关系及编码不同生物特性的差异基因。表2分别罗列了不同种属来源的乳酸菌的抗抑郁作用。

表2 不同种属乳酸菌对抑郁症的改善作用

Table 2 The improvement effect of different species and genus of lactic acid bacteria on depression

属 Genus	种 Species	菌株 Strain	研究对象 Research object	改善作用 Improvement effect
乳杆菌属 *Lactobacillus*	罗伊特氏乳杆菌 *Lactobacillus reuteri*	8008[33]	雄性C57BL/6小鼠 Male C57BL/6 mice	减轻肥胖和抑郁症合并症小鼠的抑郁样行为，改善肠道紧密连接以及微生物群失调 Alleviate depressive-like behaviors and improve intestinal tight junctions as well as dysbiosis in obesity and depression comorbid mice
	Lactiplantibacillus plantarum	R6-3[34]	雄性C57BL/6J小鼠 Male C57BL/6J mice	调节肠道菌群的组成和功能，促进肠道SCFA的分泌，并激活单胺类神经递质的产生，抑制HPA轴的过度活跃 Regulates the composition and function of the intestinal microbiota, promotes the secretion of intestinal SCFA, and activates the production of monoamine neurotransmitters, inhibits the overactivity of the HPA axis
	鼠李糖乳杆菌 *Lactobacillus rhamnosus*	zz-1[35]	雄性C57BL/6小鼠	减轻CUMS诱导的抑郁症并改善应激诱导的生理问题，包括HPA轴过度活跃、神经递质缺乏和BDNF-TrkB信号传导损伤

(待续)

(续表 2)

属名 Genus	种名 Species	菌株 Strain	研究对象 Research object	改善作用 Improvement effect
			Male C57BL/6 mice	Alleviate CUMS-induced depression and ameliorate stress-induced physiological problems, including HPA axis overactivity, neurotransmitter deficiency, and BDNF-TrkB signaling impairment
	类干酪乳杆菌 *Lactobacillus paracasei*	CCFM1229[36]	雄性 C57BL/6J 小鼠 Male C57BL/6J mice	减轻小鼠由慢性应激引起的抑郁行为和神经学变化，显著升高脑血清素和 BDNF 浓度，降低血清皮质酮浓度等 Alleviate depressive behaviors and neurological changes in mice induced by chronic stress, significantly increase the concentration of brain serotonin and BDNF, and decrease the concentration of serum corticosteron
	瑞士乳杆菌 *Lactobacillus helveticus*	R0052[37]	MDD 患者 MDD patients	第 4 周观察到情感临床症状的显著改善，第 8 周观察到主观睡眠质量的显著改善 Significant improvements in affective clinical symptoms were observed by the 4th week, and significant improvements in subjective sleep quality were observed by the 8th week
乳球菌属 *Lactococcus*	乳酸乳球菌 *Lactococcus lactis*	WHH2078[38]	雄性 BALB/c 小鼠 Male BALB/c mice	减轻慢性应激小鼠的抑郁和焦虑样行为以及神经系统异常，显著降低血清皮质酮水平，并恢复了 5-HT、5-羟基色氨酸(5-hydroxytryptophan, 5-HTP)和 BDNF 水平，改善 CUMS 诱导的肠道微生物失调 Alleviate depression and anxiety-like behaviors and neurological abnormalities in chronically stressed mice, significantly reduce serum corticosterone levels, and restore 5-HT, 5-HTP and BDNF levels, and ameliorate CUMS-induced gut microbial dysbiosis
双歧杆菌属 *Bifidobacterium*	短双歧杆菌 *Bifidobacterium breve*	CCFM1025[39]	MDD 患者 MDD patients	显著减轻抑郁症状，改变肠道微生物组的色氨酸代谢 Significantly reduced depressive symptoms and altered tryptophan metabolism in the gut microbiome
	长双歧杆菌 *Bifidobacterium longum*	R0175[37]	MDD 患者 MDD patients	第 4 周观察到情感临床症状的显著改善，第 8 周观察到主观睡眠质量的显著改善 Significant improvements in affective clinical symptoms were observed by the 4th week, and significant improvements in subjective sleep quality were observed by the 8th week
粪球菌属 *Coprococcus*	普氏栖粪杆菌 *Faecalibacterium prausnitzii*	ATCC27766[40]	雄性 SD 大鼠 Male SD rats	减轻大鼠的焦虑和抑郁样行为，盲肠中 SCFA 水平以及血浆中白细胞介素 10 (IL-10)水平升高 Alleviate anxiety and depression-like behaviors in rats, with elevated levels of SCFA in the cecum and IL-10 levels in plasma

3 乳酸菌调节抑郁症可能的机制

3.1 发挥抗炎作用

炎症因子假说是抑郁症的发病机制之一，认为炎症反应是导致抑郁症发生发展的关键因素。大量荟萃分析对抑郁症炎症标志物横断面进行了研究，这些研究表明了抑郁症患者体内循环 C 反应蛋白、IL-6、IL-12、IL-1β 及肿瘤坏死因子-α (tumor necrosis factor-α, TNF-α)浓度增加，抗炎性细胞因子 IL-10 及 IL-4 浓度显著减少[41-44]。目前对于炎症反应影响抑郁症发病的机制，许多研究集中在 NLRP3 炎症小体的激活、Toll 样受体 4 对神经元炎症的影响以及吲哚胺-2,3-双加氧酶的过度表达等方面。“肠-脑”轴理论也表明了抑郁症伴随着炎症反应，患者大脑和身体产生炎症反应，炎症信号通过血液循环进入肠道，引起肠道紊乱[45]。

动物研究发现，口服罗伊特氏乳杆菌 L6 菌株能够通过抑制 TNF-α 和 IL-6 表达，有效地抑制炎症性肠病粪菌移植诱导的抑郁小鼠的抑郁相关行为[46]。一项针对健康但给予中度压力的个体的安慰剂对照研究表明，摄入植物乳杆菌 HEAL9 4 周可以改变急性应激期间的应激反应并减少新的炎症标志物[47]。有研究表明，雌激素缺乏引起的抑郁症与肠道微生物群失衡和炎症密切相关，而补充栖组织普雷沃氏菌(*Prevotella histicola*) DSM19854 能够降低炎症因子单核细胞趋化因子-1、IL-6、IL-8 和 TNF-α 等的水平，显著改善卵巢切除小鼠的抑郁样行为[48]，表明乳酸菌可以通过改善肠道菌群来修复肠漏和抑制中枢炎症，从而缓解抑郁症。

3.2 促进神经活性物质产生

3.2.1 调节脑源性神经营养因子(brain-derived neurotrophic factor, BDNF)表达

BDNF 是中枢神经系统中最重要的神经营养因子之一，参与神经系统发育和神经元重塑。BDNF 广泛分布于大脑，尤其是大脑皮层和海马区，由神经细胞、小胶质细胞和星形胶质细胞产生，已被证明在神经元细胞的生长、成熟和存活、突触可塑性和中风后恢复中发挥着关键作用。有报道称，慢性应激通过降低 BDNF 水平导致海马轴突损伤、认知功能障碍和抑郁[49]。动物研究表明，干酪乳杆菌(*Lactobacillus casei*) HY2782 和乳双歧杆菌(*Bifidobacterium lactis*) HY8002 通过抑制肠道微生物群介导的 NF-κB 激活和诱导 BDNF 表达，能有效缓解压力引起的抑郁和焦虑样行为，增加大脑中被抑制的 BDNF、血清素水平和 BDNF 阳性神经元细胞数量[50]。一项临床试验表明，在抑郁症患者中补充长双歧杆菌(*Bifidobacterium longum*) R0175 和瑞士乳杆菌(*Lactobacillus helveticus*) R0052 8 周可改善抑郁症状，显著提高血清 BDNF 水平[51]。以上证据表明乳酸菌可能通过增加 BDNF 水平进一步改善抑郁症。

3.2.2 提高 5-HT 水平

色氨酸是蛋白质合成所必需的一种氨基酸，它被降解成几种神经活性化合物，包括 5-HT，色氨酸代谢途径的改变被认为与抑郁症的发病机制有关，已知色氨酸被代谢为 5-HT 和犬尿氨酸，犬尿氨酸被进一步代谢为具有神经毒性的喹啉酸。5-HT 是一种重要的兴奋性神经递质；在调节胃肠运动、神经信息传递方面起着重要作用；大量临床及临床前研究表明，5-HT 水平下降或功能异常可能是导致抑郁症的关键因素之一，神经炎症导致代谢途径从色氨酸向犬尿氨酸转变，喹啉酸损害神经元，导致抑郁症状[52]。

有研究发现，粪菌移植修复了酒精诱导的抑郁小鼠的肠道通透性，在接受来自健康小鼠的粪便微生物群后，抑郁小鼠肠道和脑组织中的 5-HT 含量显著增加，抑郁行为得到缓解[53]。

Sun 等[54]研究表明，植物乳杆菌 WLPL04 可改善小鼠焦虑或抑郁样行为和认知功能障碍，逆转肠道菌群异常变化，改善小鼠慢性应激诱导的 5-HT、BDNF 和 TrkB 水平降低。罗伊特氏乳杆菌 ATG-F4 通过调节前额叶 5-HT 能系统缓解慢性压力引起的快感缺乏，补充 ATG-F4 后，应激小鼠内侧前额叶皮层中 Htr1a (5-HT 受体的一种亚型)的表达增加，并恢复到在未应激小鼠中所观察到的水平，从而有效逆转 CUMS 诱导的快感缺乏行为[55]。由此推测，乳酸菌可能通过调节大脑中 5-HT 的水平来缓解抑郁症。

3.2.3 提高 γ-氨基丁酸(γ-aminobutyric acid, GABA)水平

GABA 是一种非蛋白质氨基酸，由大脑中的兴奋性神经递质谷氨酸产生，在大脑的正常功能中发挥重要作用，能够增强突触可塑性和神经元兴奋性，从而改善记忆和学习等认知功能。有大量证据支持 GABA 在调节大脑压力方面的重要作用，是一种能够抑制焦虑和抑郁的神经递质[56]。研究表明，发酵黏液乳杆菌(*Limosilactobacillus fermentum*) L18 能生产高水平的 GABA，可通过增加连接蛋白浓度和调节肠道微生物群来增强肠道上皮屏障,有潜力用于治疗焦虑相关疾病[57]。另一项研究表明，产生 GABA 的鼠李糖乳杆菌 JB-1 可以减少小鼠的焦虑行为和抑郁症标志物，并改变参与调节情绪和焦虑的关键大脑区域(例如海马体和杏仁核)中 $GABA_A$ 受体亚基的表达[58]。

近年来多篇报道表明，多种乳酸菌都能产生 GABA，包括植物乳杆菌[59-61]、短乳杆菌(*Lactobacillus brevis*)[62]、发酵黏液乳杆菌(*Limosilactobacillus fermentum*)和乳酸乳球菌(*Lactococcus lactis*)[63]、鼠李糖乳杆菌[64]、罗伊特氏乳杆菌[65]、鼠乳杆菌(*Lactobacillus murine*)[65]、齿双歧杆菌(*Bifidobacterium dentium*)[66]、青春双歧杆菌(*Bifidobacterium adolescentis*)[67]以及嗜热链球菌(*Streptococcus thermophilus*)[68]等。

3.3 改善肠道屏障通透性与紧密连接

肠道通透性是指肠壁的完整性，肠壁作为屏障，选择性地允许有益的营养物质和分子通过，同时防止有害物质，如炎性细胞因子和细菌代谢物进入血液。正常情况下，胃肠道上皮细胞具有很多种功能以维持肠道稳态，肠上皮屏障的破坏会导致肠漏，使有害物质通过黏膜组织导致多种疾病，抑郁症和肠道通透性在临床前和临床研究中也显示出正相关[69]。紧密连接(tight junction, TJ)是肠上皮屏障的结构基础，由 claudin、occludin、连接黏附分子(junction adhesion molecular, JAM)，三凝胶素和带状闭合蛋白(zonula occludens 1, ZO-1)以及细胞骨架共同构成。一项研究发现副肠膜状魏斯氏菌(*Weissella paramesenteroides*) WpK4 通过促进上皮屏障的完整性和减少肠道渗漏来改善小鼠健康，并能够减少海马体中炎症细胞因子的表达，从而减少小鼠焦虑样和抑郁行为[70]。另一项研究表明，普通拟杆菌(*Bacteroides vulgatus*)通过增加血脑屏障血管内皮细胞紧密连接蛋白 claudin-5 的表达，减轻了肠道炎症，缓解了脂多糖诱导的小鼠抑郁样行为[71]。由此可以看出乳酸菌可能通过恢复肠道的通透性来改善抑郁症。

3.4 其他途径

迷走神经是自主神经系统的关键元件，参与应激反应，位于微生物群-肠-脑轴的交互界面，具有抗炎、促动力、可塑性和再生能力等特性，在抑郁症患者的肠道向大脑传递微生物信号方面发挥重要作用。有研究表明，迷走神经刺激后患者的平均抑郁严重程度评分降低 59.9%，缓解率为 87%，焦虑水平也大大降低，表明迷走神经刺激可以通过增加血脑屏障完整性和减少炎症细胞水平来调节炎症，为难治性

抑郁症的治疗提供了新途径[72]。

下丘脑-垂体-肾上腺(hypothalamic-pituitary-adrenal, HPA)轴参与了许多神经精神障碍的病理生理过程。慢性应激可观察到 HPA 轴活性增加，这在抑郁症的病理生理学中起着关键作用。HPA 轴的过度活跃发生在严重抑郁障碍中，可能导致皮质醇水平的持续升高，最终导致认知功能障碍和情绪下降。Sudo 等[73]的研究发现，对GF小鼠和无特定病原体(specific pathogen free, SPF)小鼠给予 1 h 的束缚应激后，GF 鼠血浆中促肾上腺皮质激素和皮质酮水平显著高于 SPF 鼠，HPA 轴过度活跃，接种婴儿双歧杆菌(*Bifidobacterium infantis*)后得到显著改善。Tette 等[64]应用鼠李糖乳杆菌来恢复中枢 GABA 的活性，同时减轻了抑郁诱导的 HPA 轴过度活跃，最终改善抑郁。

SCFA 包括乙酸、丁酸、丙酸等，是脂肪酸的一大类，在近端结肠中含量丰富，它们通过 G 蛋白偶联受体显著影响情绪状态和认知，这表明了 SCFA 与抑郁症的潜在机制之间存在联系。单链脂肪酸可以穿过血脑屏障到达中枢神经系统，通过肠道菌群对大脑功能产生影响。大量研究都证明了抑郁小鼠和人类粪便中单链脂肪酸的数量是减少的[74]。在 Tian 等[75]的研究中，长双歧杆菌婴儿亚种(*Bifidobacterium longum* subsp. *infantis*) E41 增加了盲肠丁酸盐水平和产生丁酸的双歧杆菌的相对丰度，海马体 5-羟基色氨酸(5-hydroxytryptophan, 5-HTP)和前额叶皮层 BDNF 水平升高，这可能是因为丁酸盐和其他单链脂肪酸能够增加内皮细胞的色氨酸羟化酶 1 活性，从而促进 5-HT 和 5-HTP 的分泌，进而改善小鼠的抑郁症状。

综上所述，乳酸菌可能是通过减少由促炎物质引起的炎症反应，促进神经活性物质释放，保护肠屏障的完整性并降低其渗透性，刺激迷走神经通路，抑制 HPA 轴的亢进，增加 SCFA 水平等多种途径缓解抑郁症的症状，可能的机制见图 2。但并不是所有研究的结果都是可观

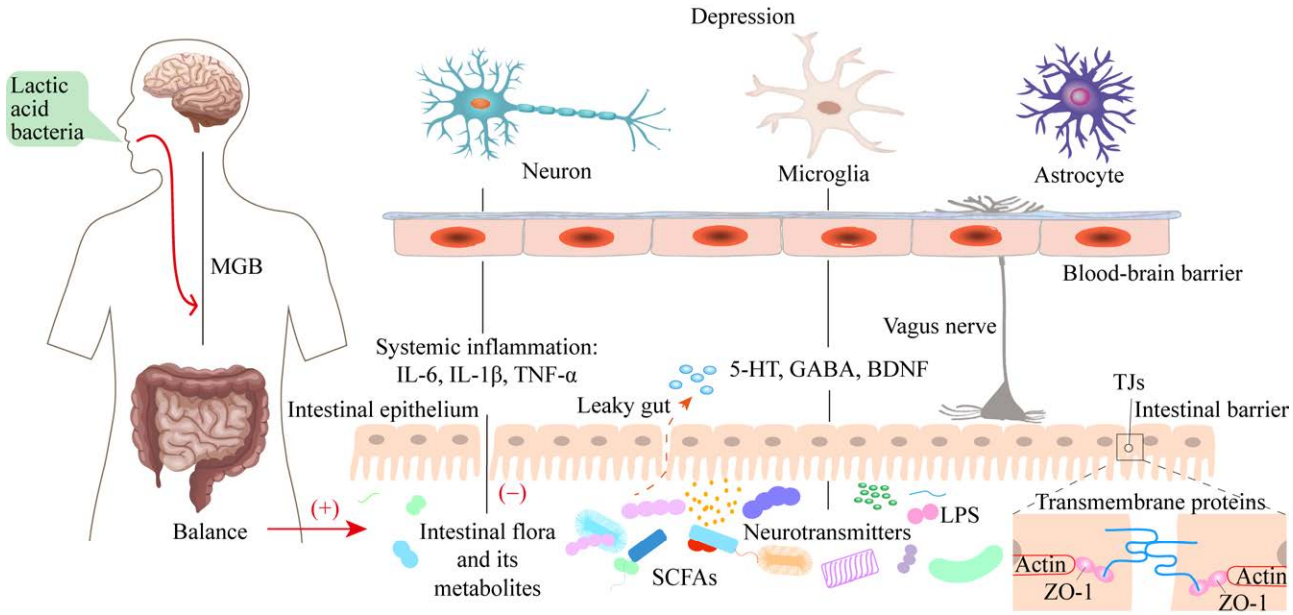

图 2　乳酸菌的抗抑郁机制

Figure 2　The antidepressant mechanisms of lactic acid bacteria.

的，一项研究[76]调查了益生菌是否可以改善情绪低落患者的情绪、压力和焦虑，结果发现没有证据表明益生菌配方可以有效治疗情绪低落或调节炎症和其他生物标志物的水平，后续的研究还需要关注乳酸菌菌株的特异性，以及乳酸菌和肠道菌群其他微生物之间的互作关系，更好地阐明乳酸菌的抗抑郁机制并挖掘乳酸菌的治疗潜力。

4 抗抑郁乳酸菌的分离

目前具有潜在抗抑郁作用乳酸菌的分离来源非常广泛，主要来源有人初乳、动物乳及乳制品、植物及其发酵制品，以及健康人体的胃肠道[77]等，它们可能通过调节肠道菌群和改变抑郁相关代谢物的水平来表现出不同程度的抗抑郁效果，更多抗抑郁乳酸菌的分离来源总结见表 3。但是益生菌行业海外企业入局早，具有领先的时间和技术优势，导致行业内海外企业的益生菌产品市场占有率较高。因此，不断发掘和拓展适合中国人肠道菌群的益生菌，构建具有自主知识产权的乳酸菌菌种资源库迫在眉睫。

5 总结与展望

抑郁症严重影响患者的健康和生活质量，传统的抗抑郁药如 5-HT 再摄取抑制剂和去甲肾上腺素再摄取抑制剂已被证明具有特殊的抗抑郁效果。然而，它们的不良影响，如恶心呕吐、体重变化、睡眠障碍和容易上瘾，也不容忽视，并且这些药物并不能对所有的抑郁症患者有效，因此亟须有效的干预措施来预防和治疗该疾病，并且这些干预措施应该成本低且副作用小。

当前的研究表明，乳酸菌通过调节微生物-肠-脑(microbiome-gut-brain, MGB)轴，在治疗抑郁症方面表现出显著的临床疗效，并且可以通过抗炎作用、促进神经活性物质产生、保护肠黏膜免疫屏障、刺激迷走神经、降低 HPA 轴的活性、增加肠道中 SCFA 的含量与降低神经炎症等多种途径对抑郁症状产生积极的影响。但是，乳酸菌对抑郁症的改善作用具有菌株特异性。未来，仍需要更多的研究来充分阐明乳酸菌不同菌株抗抑郁作用的复杂机制，从而更好地发挥乳酸菌治疗抑郁症的潜力。

目前我国乳酸菌市场使用的菌种大多都来自国外，国外厂商在乳酸菌原料市场占据较大份额，市面上常见的商品化乳酸菌很可能不适合中国人的肠道，因此，筛选安全、抗抑郁且适合中国人肠道的乳酸菌菌株显得尤为关键。未来，亟须构建专属于中国人并且适应于不同差异个体的菌株资源库。

表 3 抗抑郁乳酸菌的分离来源

Table 3 Isolated source of antidepressant lactic acid bacteria

菌株编号 Strain number	种属 Species	来源 Source	参考文献 Reference
CCFM1229	*Lactobacillus paracasei*	Pickle water	[35]
CCFM1228	*Lactobacillus rhamnosus*	Feces from healthy old people	[35]
OLL2809	*Lactobacillus paragasseri*	Healthy human feces	[78]
R0052	*Lactobacillus helveticus*	Dairy product	[79]
R0175	*Bifidobacterium longum*	Feces of healthy adult	[79]
GM11	*Lactobacillus plantarum*	Sichuan broad bean paste	[80]
JYLP-326	*Lactobacillus plantarum*	Traditionally fermented glutinous rice	[81]
CCFM1025	*Bifidobacterium breve*	Adult feces	[38]

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