肠道菌群与抑郁症相关性的研究进展

王小咪，邵云晓，王小兰，黄生权*

（仁和全域（上海）大健康研究院有限公司，上海 200000）

摘要：抑郁症是一种常见的精神疾病，通常与性别、遗传、环境或心理原因有关。肠道菌群可参与人体的众多生理调节，对情绪状态和行为认知方面发挥重要作用。健康的肠道微生物群主要以拟杆菌门和厚壁菌门为主要优势菌门，而抑郁症患者的肠道微生物丰富度和多样性较正常人相比显著降低。研究发现肠道微生物群通过神经、免疫和代谢途径直接或间接与大脑进行双向沟通，肠道菌群变化与抑郁症之间存在明显的相关性。因此，保持健康的肠道微生物群对大脑健康极其重要。该研究主要基于肠-脑轴探讨抑郁症的可能发病机制，分别从肠道菌群影响单胺类神经递质的产生、改变神经系统可塑性、诱使炎症因子水平变化以及导致下丘脑-垂体-肾上腺轴功能紊乱等 4 个方面对抑郁症的作用进行讨论。此外，该研究还总结了几种调节肠道菌群干预抑郁症的可能途径，以期为治疗抑郁症提供新的思路。

关键词：抑郁症；肠道微生物群；肠-脑轴；作用机制；调节途径

文章编号：1673-9078(2023)06-331-341 DOI: 10.13982/j.mfst.1673-9078.2023.6.0718

Research Progress on Correlation between Gut Microbiota and Depression

WANG Xiaomi, SHAO Yunxiao, WANG Xiaolan, HUANG Shengquan*

(Renhe Global (Shanghai) Grand Health Research Institute Co. Ltd., Shanghai 200000, China)

Abstract: Depression is a common mental illness that is often linked to sex, genetics, and environmental or psychological causes. The gut microbiota plays an important role in emotional state and behavioral cognition by participating in many forms of the physiological regulation of the human body. Bacteroidetes and Firmicutes are the dominant phyla in healthy gut microbiota; the richness and diversity of the gut microbiota are substantially lower in patients with depression than those in healthy people. The gut microbiota directly or indirectly communicates with the brain through neural, immune, and metabolic pathways, and a strong correlation exists between changes in the gut microbiota and depression. Therefore, maintaining a healthy gut microbiome is extremely important for brain health. This study mainly explored the possible pathogenesis of depression based on the gut–brain axis, and the effects of gut microbiota on depression were discussed from four aspects: affecting monoamine neurotransmitter production, changing the plasticity of the nervous system, inducing changes in the levels of inflammatory factors, and causing dysfunction of the hypothalamus-pituitary-adrenal axis. In addition, several possible methods of regulating the gut microbiota to intervene in depression were summarized to provide new ideas for the treatment of depression.

Key words: depression; gut microbiota; gut-brain axis; mechanism of action; regulatory pathways

引文格式：

王小咪,邵云晓,王小兰,等.肠道菌群与抑郁症相关性的研究进展[J].现代食品科技,2023,39(6):331-341.

WANG Xiaomi, SHAO Yunxiao, WANG Xiaolan, et al. Research progress on correlation between gut microbiota and depression [J]. Modern Food Science and Technology, 2023, 39(6): 331-341.

抑郁症是一种严重的精神疾病，发病年龄范围一般在 15~30 岁左右，女性患病率高于男性，患者通常表现为食欲不振，情绪低落，思维消极，悲观厌世，最后甚至有自残自杀倾向和行为[1]。据世界卫生组织统计，全球超过 3 亿人受到抑郁症影响，已成为世界第一大致残性疾病[2]。抑郁症致病因素多样，如遗传、环境、心理或代谢等，发病机理尚不明确，现有研究表明，下丘脑-垂体-肾上腺轴（Hypothalamic-Pituitary-Adrenal Axis，HPA）过度活跃、中枢单胺类神经递质或其相应受体功能低下、炎症因子水平变化、内分泌

收稿日期：2022-06-06

基金项目：上海市普陀区科技研发平台项目（2022QX01）

作者简介：王小咪（1996-），女，硕士研究生，研究方向：食品微生物学，E-mail：wangxiaomi1224@163.com

通讯作者：黄生权（1977-），男，博士，教授级高工，研究方向：食品科学与工程，E-mail：14321084@qq.com

紊乱等因素均会对抑郁症发生造成影响[3,4]。目前治疗抑郁症的方法主要有心理疗法、电痉挛疗法及药物疗法[5]。然而经过临床观察显示，这些方法不仅治疗效果缓慢，还会给患者带来失眠、恶心和性功能障碍等副作用[5]。随着科学技术研究的不断深入，研究者们发现肠道微生物群在维持胃肠道以及激素、免疫和神经稳态方面具有重要的生理作用[6]。因此，通过调控个体肠道微生物群的变化干预抑郁症成为可能。基于前人研究，本文主要综述了肠道菌群对抑郁症的作用机理，总结了几种基于调节肠道菌群干预抑郁症的可能途径，以期为抑郁症患者提供成本更低、效果更佳、副作用更小的治疗参考方法，同时也为科研人员研发抗抑郁特殊营养品提供理论依据。

1 肠道微生物群

1.1 肠道微生物群的组成、动态和功能

肠道微生物群是一个由数万亿种微生物组成的复杂多样的群落，它们生活在人类和动物的消化道中[7,8]。人体肠道微生物群主要类型包括古细菌、细菌、病毒、真核生物和寄生虫，总质量为个体体重的 0.3%，是胃肠道器官的第一道保护系统，对宿主体内的平衡起着关键作用[9,10]。人类肠道微生物群中的门主要包括厚壁菌门、拟杆菌门、梭杆菌门、放线杆菌门和变形杆菌门等，其中厚壁菌门和拟杆菌门占比最大[11,12]。肠道微生物群主要有三种类型：一是普氏菌型，具有抗炎或保护性作用；二是拟杆菌型，与促炎症、代谢性疾病等有关；三是瘤胃球菌型，其相对丰度影响抑郁症的发生[13]。总的来说，婴儿从出生到 5 岁，肠道微生物群的多样性和组成都会发生动态变化，然后渐渐趋于稳定，基本上与成年人相当[14-16]。此外，胃肠道的这种动态系统受到两方面因素的影响，一是内源性因素，例如性别、年龄、种族、民族和基因构成；二是外源性因素，例如体育锻炼、饮食、感染或疾病的暴露、抗生素的使用和药物滥用。有研究表明，保持健康的肠道菌群平衡能够提高肠上皮屏障完整性，刺激肠细胞再生，产生粘蛋白，其代谢产物短链脂肪酸（Short-Chain Fatty Acids，SCFA）还可用于粘膜滋养[17]。肠道菌群和肠内分泌细胞协同调节消化、生长和免疫防御[18]。肠道菌群还通过在生命早期调节肠道相关淋巴组织的成熟以及通过刺激局部和全身炎症反应激活获得性免疫来塑造先天免疫系统[19]。肠道菌群促进上皮细胞分泌抗菌肽，加强细胞间的紧密连接，调节激素、特定微量营养素和维生素的代谢，并在吸收、代谢和消除外源性物质方面发挥关键作用[20]。

1.2 肠道菌群的主要代谢产物及其生理功能

肠道菌群的主要代谢产物包括 SCFA、支链氨基酸、脂多糖（Lipopolysaccharide，LPS）、胆汁酸和儿茶酚胺等。其中 SCFA 通过 G 蛋白偶联受体对情绪状态和认知等发挥中枢作用，在大脑和肠道之间的双向沟通中扮演重要角色，直接或间接地参与肠-脑轴的功能性调节[21]。SCFA 中具有生物学效应的有乙酸、丙酸和丁酸，比例约为 3:1:1，其来源、分布及对宿主生理的潜在影响存在一定差异[22]。乙酸可在脂肪、肝脏和肌肉等组织中代谢并发挥调节作用，为外周组织提供能量，且血浆中的乙酸盐可能是耐力运动中重要的能量底物，并有研究发现，乙酸可影响与抑郁症密切相关的中枢神经递质 5-羟色胺（5-Hydrotryptamine，5-HT）的表达[23-25]。丙酸可增加肠源性调节性 T 细胞的数量，还可以通过增加髓鞘再生而对中枢神经系统产生积极影响，研究表明，在慢性不可预知温和应激（Chronic Unpredictable Mild Stress，CUMS）模型大鼠的直肠内给予一段时间丙酸盐可以改善其抑郁症状[26,27]。丁酸作为结肠细胞的主要能量底物，可对结肠中钠和水的吸收起到刺激作用，并对肠道细胞具有营养作用，研究显示，丁酸可增加 5-HT 浓度，促进脑源性神经营养因子（Brain-Derived Neurotrophic Factor，BDNF）表达，同时可显著改善 CUMS 模型小鼠的抑郁样行为[28,29]。

1.3 肠-脑轴

近年来，一个可能参与精神疾病的通路肠-脑轴受到广泛关注[30,31]。肠-脑轴是肠道微生物群与大脑之间的双向调节轴，其包括自主神经系统（Autonomic Nervous System，ANS），肠道内神经系统（Enteric Nervous System，ENS），中枢神经系统（Central Nervous System，CNS），HPA 轴、中枢免疫系统调控及外周等，各部分功能相互影响。肠道微生物群及其代谢产物通过神经内分泌和肠内分泌信号通路与 CNS 和 ENS 及生物屏障（如肠粘膜屏障和血脑屏障）进行沟通，或者通过 ANS 的副交感神经和交感神经成分以及 ENS（主要是 HPA 轴）直接介导[32-34]。迷走神经传入通路可协调各种应激源的适应性反应，在激活 HPA 轴中起着重要作用。此外，肠道微生物群可通过色氨酸代谢产生细菌代谢物作用于迷走神经[35-37]。HPA 激活会刺激免疫系统，进而诱发炎症因子水平改变，使得促炎因子和趋化因子数量增加[38]。综上所述，肠道微生物及其代谢物在建立肠-脑轴通讯和维持宿主体内平衡中起着关键作用。

2 肠-脑轴对抑郁症的影响

肠-脑轴是大脑和肠道之间的双向沟通通路，在情绪处理和行为方面发挥着重要作用，是干预抑郁症的新靶点[39]。本文基于肠-脑轴机制，从单胺类神经递质、脑源性神经营养因子、炎症因子以及下丘脑-垂体-肾上腺轴等四个角度阐述肠道菌群在抑郁症中的可能作用途径，其作用机理详见图 1[40]。

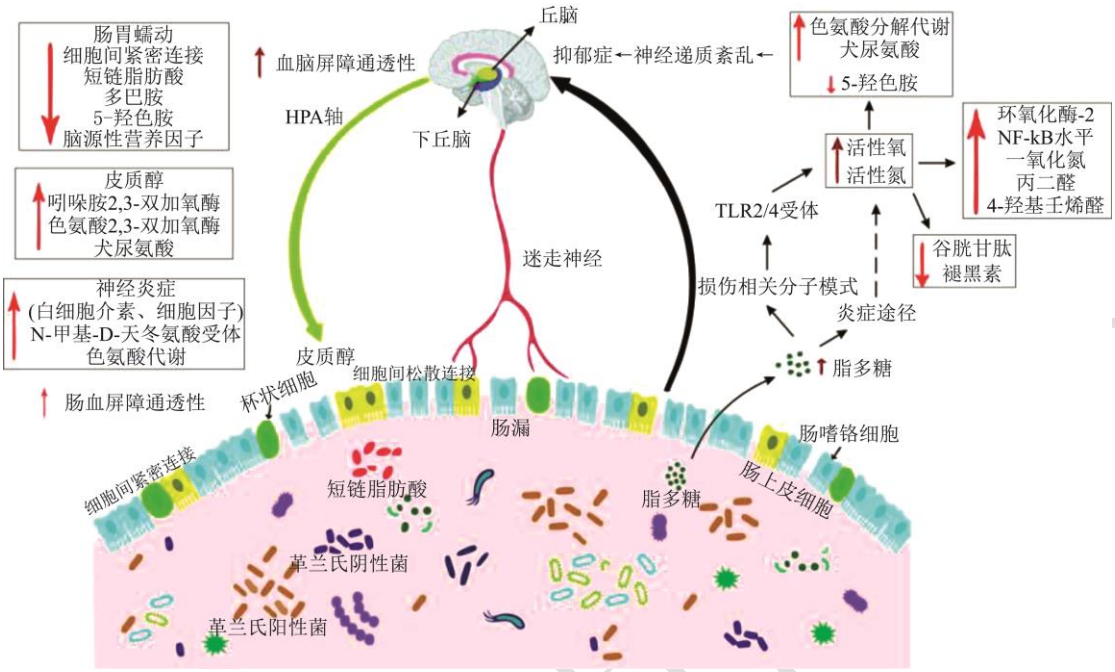

图 1 抑郁症的微生物-肠-脑轴作用机理

Fig.1 Microbiota-gut-brain axis mechanism of depression

2.1 影响单胺类神经递质的产生

神经递质是两个神经细胞之间传递信息的一种中间化学物质，包括 5-HT、去甲肾上腺素、多巴胺、γ-氨基丁酸和乙酰胆碱等[41]。研究表明，神经递质水平的高低与抑郁症的发生呈正相关，当脑内神经递质分泌不足时就会引起抑郁症状，而提高这些神经递质水平，可对抗抑郁作用产生积极影响[42]。5-HT 作为单胺类神经递质对大脑正常活动起着关键作用，人体超过 90%的 5-HT 是在肠道中产生的，大部分由肠嗜铬细胞合成并释放。色氨酸作为 5-HT 的前体，可通过犬尿氨酸途径激活吲哚胺 2,3-双加氧酶（Indoleamine 2,3-Dioxygenase，IDO）代谢，使脑内 5-HT 水平降低，最终引发抑郁症状[43]。有研究表明补充富含色氨酸的食物可对情绪状态和行为认知产生积极影响[44]。因此，肠道菌群失调可影响单胺类神经递质的产生，可通过调节肠道菌群平衡来缓解抑郁症状。

2.2 改变神经系统的可塑性

BDNF 可介导神经系统的可塑性，维持脑神经元的生长发育。在应激情况下，BDNF 水平会降低，从而导致神经元发生萎缩或凋亡，引起抑郁症状，因此，可通过减少神经凋亡、增加神经可塑性，以达到抗抑郁作用[45,46]。BDNF 水平降低还会导致海马体萎缩、细胞毒性增加及神经胶质细胞及其突触减少等，这些因素均会引起抑郁症状[47]。有研究表明，肠道菌群的变化会引起 BDNF 水平改变，将无特定病原体或喂食益生菌小鼠的粪便对无菌小鼠进行定植，分别导致无菌小鼠行为和 BDNF 水平的部分和完全正常化[48]。另有一项研究表明，对小鼠膈下迷走神经切除可降低海马区 BDNF mRNA 的表达，证明迷走神经作为肠道与大脑之间的双向通道可对海马 BDNF 的表达产生影响[49]。

2.3 诱发炎症因子水平的改变

细胞因子可分为促炎因子和抗炎因子，正常情况下两者在机体内保持动态平衡，当平衡被打破时，就会诱发炎症反应，导致疾病发生。肠道微生物与肠黏膜细胞之间相互作用，诱导促炎和抗炎细胞因子释放，当促炎因子数量显著高于抗炎因子时，就会引起炎症反应，从而导致抑郁样行为。促炎因子的增加会造成氧化性和亚硝化性脑损伤，除此之外，还通过 IDO 途径产生色氨酸分解代谢产物，使得色氨酸和 5-HT 的利用率显著降低，最终导致抑郁症[50,51]。此外，细胞因子还会影响神经递质的产生、代谢和运输以及诱导谷氨酸失调，导致兴奋性中毒，从而抑制 BDNF 的表达，诱发抑郁症[52]。肠道微生物可将色氨酸代谢为色

氨酸分解物，使其通过促进肠黏膜层、诱导 T 细胞分化来提高抗炎因子水平，使细胞因子趋于平衡，从而促进免疫稳态[53]。

2.4 导致下丘脑-垂体-肾上腺轴功能的紊乱

HPA 轴是肠-脑轴重要组成部分之一，为人体急慢性应激刺激提供主要的生物反应，在抑郁症的病理生理机制中占有重要地位[54]。HPA 轴的过度活跃和促肾上腺皮质激素释放激素（Corticotropin Releasing Hormone，CRH）的升高是导致人类抑郁和焦虑症状的主要原因。环境、情绪和生理应激可增加全身促炎细胞因子水平来触发下丘脑室旁核分泌 CRH 激活 HPA 轴，表明人体长期处于应激状态下，可导致 HPA 轴过度活跃，造成 BDNF 表达水平下降，5-HT 合成减少，谷氨酸受体表达减少，对神经可塑性和神经环路功能产生消极作用[55]。CRH 水平升高可激活促肾上腺皮质激素过度分泌，导致肾上腺皮质释放糖皮质激素，皮质醇水平过高会造成肠道失调，从而破坏肠道通透性，导致肠道渗漏和内毒素血症（革兰氏阴性细菌细胞壁释放的免疫原性 LPS 增加）[56,57]。应激诱导的肠道微生物成分变化促进了革兰氏阴性细菌的生长，导致肠道通透性增加，并通过炎症反应促进了细菌成分在肠腔中移位，大量 LPS 进入血循环，LPS 识别 Toll 样受体使促炎细胞因子产生，引起 HPA 过度活跃，进一步刺激微生物群-免疫-神经内分泌相互作用，导致抑郁行为的产生[58]。

3 基于肠道菌群干预抑郁症的可能途径

目前有许多合成药物用于治疗人类抑郁症，但是它们的疗效受多种因素影响各不相同[59]。因此，调节肠道微生物群组成变化已成为干预抑郁症研究的焦点。有临床数据证明，服用益生元、益生菌和合生元对恢复健康的肠道微生物组成和多样性有很大的帮助，可能成为改善抑郁症和其他压力相关疾病的潜在方法[60-62]。本节主要从益生菌、益生元、后生元、合生元以及多酚类物质、饮食结构、粪菌移植等 7 个方面分别总结分析了干预抑郁症的途径。

3.1 益生菌

益生菌是一类对宿主有益的肠道细菌，具有神经保护作用，被广泛用于治疗精神疾病，临床和动物实验研究均证实，补充适量的益生菌可以缓解抑郁症状，治疗效果能媲美传统抗抑郁治疗方式。已报道的具有治疗抑郁作用的益生菌主要包括干酪乳杆菌、瑞士乳杆菌和双歧杆菌[63]。在动物模型中，服用长双歧杆菌可使海马 BDNF 水平正常化，并减少炎症诱导的焦虑样行为。研究发现，通过改善健康男性志愿者的视觉空间记忆，补充长双歧杆菌 1714 可有效降低应激诱导的皮质醇释放，并降低每日自我报告的应激水平[64]。有研究表明，复合益生菌主要包括乳双歧杆菌 W52、嗜酸乳杆菌 W37、双歧杆菌 W23、短乳杆菌 W63、唾液乳杆菌 W24、干酪乳杆菌 W56 和乳酸乳球菌（W19 和 W58），在减少消极想法和行为方面显示出积极作用[65]。以上研究表明，特定益生菌可通过抗炎机制或促进 5-HT 的生成对抑郁症产生积极作用。

3.2 益生元

益生元是一种不可消化纤维，可促进特定有益肠道微生物代谢和增殖[66]。研究表明，低聚果糖和 *β*-免疫半乳低聚糖可刺激有益细菌（如长双歧杆菌）的增殖，并降低健康年轻志愿者应激诱导的 HPA 轴激活[67-69]。*β*-免疫半乳低聚糖已被证明可以减少 LPS 诱导的大鼠焦虑和抑郁样行为[70]。Crocin-I 是藏红花素的主要活性成分，可增加肠道菌群多样性和 SCFAs 水平，减少 LPS 从肠道泄漏到体循环中，同时还可增加抑郁小鼠的 BDNF 水平[10]。目前益生元对抑郁症的研究主要集中在增殖肠道有益菌方面，但益生元与肠道菌群多样性变化的关系仍需进一步明确。表 1 将最近研究中各种益生菌和益生元的有益作用进行了详细统计。

3.3 后生元

后生元是指混合或不混合代谢物（如乳酸、蛋白质、维生素和 SCFA）或细胞成分（包括菌毛、细胞壁成分）的失活微生物细胞，它们对宿主的健康有益[70]。与益生菌类似，由后生元介导的有益机制包括促进上皮屏障功能的完整性，恢复微生物群组成和多样性，调节免疫反应，以及调节肠-脑轴信号[71,72]。研究表明，给予热灭活的瑞士乳杆菌菌株 MCC1848 可减少暴露于亚慢性和轻度社交失败应激的青春期雄性 C57BL/6J（B6）小鼠的抑郁和焦虑样行为，并可改善神经元分化和发育[73]。给予热灭活粪肠球菌 EC-12 可减少抑郁和焦虑样行为，上调前额叶皮质中的神经递质受体 *Adrb3* 和 *Avpr1a* 基因表达，还增加了成年雄性 C57BL/6J 小鼠肠道中丁酸球菌和肠球菌成分的相对丰度[74]。在 241 名健康成年志愿者中，在早餐前连续 12 周服用两剂热灭活副干酪乳杆菌 MCC1849，可增强对普通感冒的抵抗力，并保持理想的情绪状态[75]。24 周内每天服用两片热灭活的格氏乳杆菌 CP2305 可减轻焦虑，提高睡眠质量，并恢复长期处于压力下的菌群多样性[76]。后生元成分容易被肠道吸收，菌体细

胞破壁后释放的代谢物可直接与小肠上皮细胞接触，从而增强利用率。对于易受活菌感染的人群，不会有菌群从肠腔转移到血液的风险。但是目前关于后生元与抑郁症的相关性研究为数不多。

3.4 合生元

合生元是益生元和益生菌的协同混合物，旨在通过促进有益的微生物活性来造福宿主。有研究表明，服用合生元会导致人体血浆中丙二醛和过氧化氢浓度显著降低[77]。此外，与男性相比，服用合生元后，女性血浆中的谷胱甘肽和游离巯基水平显著升高。这种性别差异可以用不同浓度的激素来解释，如雌二醇和睾酮，它们与心理压力有关[78,79]。最近的一项随机研究报告表明，与对照组相比，合生元（嗜酸乳杆菌 T16、双歧杆菌 BIA-6、乳双歧杆菌 BIA-7 和长双歧杆菌 BIA-8）增加了抑郁症患者的血清 BDNF 水平，改善了抑郁症症状[80]。

3.5 多酚类物质

多酚类物质具有抗炎、抗氧化、抗细胞凋亡以及正向调控海马组织中的代谢物质等作用。有研究表明，社会挫败抑郁型鼠进食含有绿茶多酚的饲料，强迫游泳不动时间、水迷宫潜伏时间显著减少，说明绿茶多酚能够改善社会挫败抑郁型小鼠抑郁症[94]。另有研究表明姜黄素中的多酚类物质可通过改变单胺氧化酶活性，来提高血清素、去甲肾上腺素和多巴胺水平，从而改善抑郁症[95,96]。表 2 总结了用于抑郁症管理或治疗的不同来源多酚的抗抑郁作用。

表 1 益生菌、益生元和后生元抗抑郁作用

Table 1 Antidepressant effects of probiotics, prebiotics and postbiotics

菌株	作用机制	文献
瑞士乳杆菌 长双歧杆菌	使海马 BDNF 水平和炎症恢复正常	[81-83]
低聚果糖 β-免疫半乳糖	刺激有益细菌，即长双歧杆菌的生长，从而减少应激诱导的 HPA 轴激活、皮质酮水平和促炎细胞因子并增加 BDNF 水平	[62,67,69,84]
婴儿双歧杆菌 35624	通过缓解 5-HT 减少抑郁样行为	[47,85,86]
短双歧杆菌	刺激大鼠肠细胞 5-HT 受体	[87]
长双歧杆菌	产生有益代谢物 SCFA 并改善抑郁患者的运动能力	[88]
植物乳杆菌	减少压力诱导的焦虑样行为	[88]
鼠李糖乳杆菌（JB-1）	减少 GABA Aα2mRNA 和皮质酮	[89]
香肠乳杆菌	防止肠道屏障渗漏，逆转心理应激诱导的 HPA 轴激活	[90,91]
干酪乳杆菌代田株	降低慢性疲劳综合征患者的焦虑评分，增加粪便样本中乳酸杆菌和双歧杆菌的丰度	[92,93]

表 2 不同来源多酚潜在抗抑郁作用

Table 2 Potential antidepressant effects of polyphenols from different sources

来源	主要成分	作用机制	文献
可可豆	儿茶素、花青素、原花青素、黄酮类、表儿茶素	预防迷走神经背侧复合体的神经炎症	[97]
蓝莓	花青素	显著增加大脑活动，改善工作记忆和抑郁样行为	[98]
咖啡豆	黄烷醇咖啡酸、绿原酸	显著提高认知能力、精神运动控制和工作记忆	[99]
草莓	菲西丁（多酚）	抑制促炎标志物，如 TNF-α	[100]
花生 红葡萄 葡萄酒	多酚	增加单胺和 BDNF 水平	[100]
姜黄素	多酚	通过改变单胺氧化酶活性，提高血清素、去甲肾上腺素和多巴胺水平	[95,96]
绿茶	表没食子儿茶素没食子酸酯（EGCG）	绿茶的自由基清除和抗氧化特性可以减少应激反应中 HPA 轴的过度活动	[101-103]
白藜芦醇	多酚	提高前额叶皮质中的 5-HT 和去甲肾上腺素水平，并上调 BDNF 水平	[104-106]

3.6 调整饮食结构

不同国家或地区由于风土人情或认知理念的不同，在饮食结构与习惯上存在一定差异，这种差异可能会对抑郁症的产生造成不同的影响[107]。因此，通过调整饮食结构不仅可辅助治疗抑郁症，还可克服药物治疗带来的毒副作用，成为治疗抑郁症的新途径。本节主要综述了几种比较常见的饮食结构，主要有生酮饮食、高蛋白饮食、高脂饮食、终止高血压饮食和素食饮食等模式。

研究表明，生酮饮食可以通过调节炎症、控制促氧化过程和抗氧化过程之间的平衡或改变肠道微生物群的组成来影响疾病的进程[108-115]。饮食中的蛋白质可通过影响 5-HT 水平诱发抑郁症，有研究表明低水平高蛋白饮食有利于提高认知能力，摄入过量的蛋白质则会引起抑郁症[116,117]。用高脂饮食饲喂小鼠并在饮用水中添加 42 g/L 的流糖，连续 14 周后，检测到大脑中能诱导葡萄糖转运蛋白在质膜上的表达和转运的胰岛素信号通路受到损伤，突触可塑性受损以及产生神经炎症[118]。研究人员发现降脂饮食能缓解抑郁症，降低抑郁的发生。植物基中含有丰富的纤维素、抗氧化剂、植物蛋白、多不饱和脂肪酸和绿原酸。有研究表明纤维素可以降低血脂，调节肠道蠕动并预防结肠癌等；绿原酸、多不饱和脂肪酸可以降低炎症的发生[119]。当大脑发生氧化应激时会产生大量的自由基，未被清除的自由基积累会损害机体，导致大脑出现细胞凋亡、大脑皮层和海马区受损、突触可塑性降低现象，长时间应激会引起 HPA 轴功能异常而导致抑郁的发生，蔬菜、水果含有丰富的抗氧化物质，可以通过清除自由基来缓解抑郁程度[120-122]。因此，健康饮食可刺激肠道有益菌的增殖并可能通过肠-脑轴来改善情绪状态和行为认知，对抑郁症的发生有着积极作用。

3.7 粪菌移植

粪菌移植是指在受损肠道内移植健康供体的粪便，以恢复受损肠道菌群[123]。有研究表明将重度抑郁患者的粪便菌群移植到缺失菌群的大鼠体内，可以诱导受体大鼠快感缺乏和类似焦虑的行为，并引起色氨酸代谢改变，由此得出，肠道微生物群对抑郁症的发生起着关键作用，并可能为抑郁症的治疗和预防提供一个可控制的靶点[124]。粪菌移植已成为各种胃肠道和神经精神疾病中最常用的方法之一[125]。临床研究报告称，IBS 和胃肠道相关问题与抑郁症有关，健康捐赠者给予患病患者的粪菌移植可缓解 IBS 患者的抑郁和焦虑样行为，以及老年人的梭菌感染[126,127]。尽管没有关于健康供体获得重度抑郁患者的粪菌移植这种反向途径的研究调查，但是与肠道菌群相关的遗传性表明粪菌移植可能对治疗重度抑郁患者具有价值[128]。目前大量研究表明合理利用粪菌移植对宿主机体是有益的，但粪便中也可能存在一些危害人体生命健康的感染因子或毒素，这使得粪菌移植的技术应用产生很大的局限性，因此需要更多的研究来降低粪菌移植对机体造成的不良影响。

4 结论

在新冠疫情大流行状态下，抑郁症患病率显著上升，抗抑郁药等经典疗法虽被广泛用于治疗抑郁症，但其疗效各不相同，且产生不可避免的不良反应。因此，对于许多患有精神疾病的患者来说，迫切需要新的治疗靶点以及开发替代方法来缓解抑郁症带来的痛苦。大量研究表明肠道菌群失调与抑郁症的发病机制呈正相关。肠道菌群失调导致肠-脑轴的失调，造成有毒微生物代谢产物的增加、肠漏、内毒素血症和免疫介质的释放。所有这些变化都会引起慢性促炎状态，进而触发血液中脑屏障、神经传递、神经炎症和行为等变化，从而导致抑郁的发生。本文从肠-脑轴机制入手，探讨了通过不同途径调节肠道菌群相对丰度和多样性来干涉抑郁症发生发展的研究进展。益生菌、益生元、后生元、合生元等靶向肠-脑轴的干预方式将成为抑郁症防治领域的重要部分，且后生元相较于活益生菌具有技术、安全和经济优势。然而，目前大多数关于肠脑轴的研究都是在实验动物模型中进行的，这就需要在抑郁症患者中进行大规模随机队列研究，以期为治疗干涉抑郁症做出重大突破。此外，对肠道微生物群进行个体化和定制能够调节个人肠道微生物群以促进健康的食物至关重要。要研发出营养美味的食品，同时又能为人类肠道微生物群和健康量身定制，需要更多学者们采用跨学科方法，来了解食物如何调节肠道微生物群以促进人类健康。

参考文献

[1] Vahia V N. Diagnostic and statistical manual of mental disorders 5: A quick glance [J]. Indian Journal of Psychiatry, 2013, 55(3): 220.

[2] Friedrich M J. Depression is the leading cause of disability around the world [J]. Jama, 2017, 317(15): 1517.

[3] Mishra S K, Srivastava M, Tiwary N K, et al. Prevalence of depression and anxiety among children in rural and suburban areas of eastern uttar pradesh: A cross-sectional study [J]. J Family Med Prim Care, 2018, 7: 21-26.

[4] 孙珊珊,刘阳,高丽娜.高脂饮食联合慢性不可预知性温和应激诱导抑郁症模型的研究进展[J].中国病理生理杂志, 2021,37(3):543-550.

[5] Li B, Guo K, Zeng L, et al. Metabolite identification in fecal microbiota transplantation mouse livers and combined proteomics with chronic unpredictive mild stress mouse livers [J]. Transl Psychiatry, 2018, 8(1): 34.

[6] Lach G, Schellekens H, Dinan T G, et al Anxiety, depressionand the microbiome: A role for gut peptides [J]. Neurotherapeutics, 2018, 15: 36-59.

[7] Gomaa E Z. Human gut microbiota/microbiome in health and diseases: A review [J]. Antonie Van Leeuwenhoek 2020, 113(12): 2019-2040.

[8] Passos M, Moraes Filho J P, Passos M, et al. Microbiota intestinal nas doen ças digestivas [J]. Arq Gastroenterol, 2017, 54: 255-262.

[9] Lozupone C A, Stombaugh J I, Gordon J I, et al. Diversity, stability and resilience of the human gut microbiota [J]. Nature, 2012, 489: 220-230.

[10] Xiao Q, Shu R, Wu C, et al. Crocin-I alleviates the depression-like behaviors probably via modulating "Microbiota-Gut-Brain" axis in mice exposed to chronic restraint stress [J]. J Affect Disord, 2020, 276(1): 476-486.

[11] Lin S, Li Q, Jiang S, et al. Crocetin ameliorates chronic restraint stress-induced depression-like behaviors in mice by regulating MEK/ERK pathways and gut microbiota [J]. J Ethnopharmacol, 2021, 268: 113608.

[12] Braniste V, AlAsmakh M, Kowal C, et al. The gut microbiota influences blood-brain barrier permeability in mice [J]. Sci Transl Med, 2014, 6(263): 158.

[13] 陈朴,赵伟,臧鹏,等.不同"肠型"人群肠道菌群结构[J].中国微生态学杂志,2020,32(10):1117-1122.

[14] De Filippo C, Cavalieri D, Di Paola M, et al. Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa [J]. Proc Natl Acad Sci USA, 2010, 107: 14691-14696.

[15] Odamaki T, Kato K, Sugahara H, et al. Age-related changes in gut microbiota composition from newborn to centenarian: A cross-sectional study [J]. BMC Microbiol, 2016, 16: 90.

[16] Yu D H, Gadkari M, Zhou Q, et al. Postnatal epigenetic regulation of intestinal stem cells requires DNA methylation and is guided by the microbiome [J]. Genome Biol, 2015, 16: 211.

[17] Burgervan Paassen N, Vincent A, Puiman P J, et al. The regulation of intestinal mucin MUC2 expression by short-chain fatty acids: implications for epithelial protection [J]. Biochem J, 2009, 420: 211-219.

[18] Konturek S J, Konturek J W, Pawlik T, et al. Brain-gut axis and its role in the control of food intake [J]. Physiol Pharmacol, 2004, 55: 137-154.

[19] Nell S, Suerbaum S, Josenhans C. The impact of the microbiota on the pathogenesis of IBD: lessons from mouse infection models [J]. Nat Rev Microbiol, 2010, 8: 564-577.

[20] Belkaid Y, Hand T. Role of the microbiota in immunity and inflammation [J]. Cell, 2014, 157: 121-141.

[21] Dinan T G, Cryan J F. The microbiome-gut-brain axis in health and disease [J]. Gastroenterology Clinics, 2017, 46(1): 77-89.

[22] Kaji I, Karaki S, Kuwaharaa. Short-chain fatty acid receptor and its contribution to glucagon-like peptide-1 release [J]. Digestion, 2014, 89(1): 31-36.

[23] Gonzalez Hearnandez M A, Canfora E E, Jocken J W E, et al. The short-chain fatty acid acetate in body weight control and insulin sensitivity [J]. Nutrients, 2019, 11(8): 1943.

[24] Okamoto T, Morino K, Ugi S, et al. Microbiome potentiates endurance exercise through intestinal acetate production [J]. American Journal of Physiology-Endocrinology and Metabolism, 2019, 316(5): E956-E966.

[25] Bhattarai Y, Schmidt B A, Linden D R, et al. Human-derived gut microbiota modulates colonic secretion in mice by regulating 5-HT3 receptor expression via acetate production [J]. American Journal of Physiology-Gastrointestinal and Liver Physiology, 2017, 313(1): G80-G87.

[26] Hirschberg S, Gisevius B, Duscha A, et al. Implications of diet and the gut microbiome in neuroinflammatory and neurodegenerative diseases [J]. International Journal of MolecularSciences, 2019, 20(12): 3109.

[27] Li J, Hou L, Wang C, et al. Short term intrarectal administration of sodium propionate induces antidepressant-like effects in rats exposed to chronic unpredictable mild stress [J]. Frontiers in Psychiatry, 2018, 9: 454.

[28] Manrique V D, Gonzalez S M E. Ácidos grasos de cadena corta (ácido but írico) y patolog ás intestinales [J]. Nutrici ón Hospitalaria, 2017, 34: 58-61.

[29] Sun J, Wang F, Hong G, et al. Antidepressant-like effects of sodium butyrate and its possible mechanisms of action in mice exposed to chronic unpredictable mild stress [J]. Neuroscience Letters, 2016, 618: 159-166.

[30] Kasai C, Sugimoto K, Moritani I, et al. Comparison of the gut

microbiota composition between obese and non-obese individuals in a Japanese population, as analyzed by terminal restriction fragment length polymorphism and next-generation sequencing [J]. BMC Gastroenterology, 2015, 15(1): 1-10.

[31] Ncd RisC. Rising rural body-mass index is the main driver of the global obesity epidemic in adults [J]. Nature, 2019, 569(7755): 260-264.

[32] Furness J B, Rivera L R, Cho H J, et al. The gut as a sensory organ [J]. Nat Rev Gastroenterol Hepatol, 2013, 10: 729-740.

[33] Nair A T, Ramachandran V, Joghee N M, et al. Gut microbiota dysfunction as reliable non-invasive early diagnostic biomarkers in the pathophysiology of parkinson's disease: A critical review [J]. Neurogastroenterol Motil, 2018, 24: 30-42.

[34] Carabotti M, Scirocco A, Maselli M A, et al. The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems [J]. Ann Gastroenterol, 2015, 28: 203-209.

[35] Forsythe P, Bienenstock J, Kunze W A. Vagal pathways for microbiome-brain-gut axis communication [J]. Adv Exp Med Biol, 2014, 817: 115-133.

[36] Cryan J F, Dinan T G. Gut microbiota: microbiota and neuroimmune signalling-metchnikoff to microglia [J]. Nat Rev Gastroenterol Hepatol, 2015, 12: 494-496.

[37] Sherwin E, Rea K, Dinan T G, et al. A gut (microbiome) feeling about the brain [J]. Curr Opin Gastroenterol, 2016, 32: 96-102.

[38] Singh V, Roth S, Llovera G, et al. Microbiota dysbiosis controls the neuroinflammatory response after stroke [J]. J Neurosci, 2016, 36: 7428-7440.

[39] 杨宇霖,刘畅.炎症性肠病脑功能变化研究进展[J].医学研究生学报,2019,32(7):755-759.

[40] Sonali S, Ray B, Ahmed Tousif H, et al. Mechanistic insights into the link between gutdysbiosis and major depression: Anextensive review [J]. Cells, 2022, 11: 1362.

[41] Kennedy P J, Cryan J F, Dinan T G, et al. Kynurenine pathway metabolism and the microbiota-gut-brain axis [J]. Neuropharmacology, 2017, 112(pt B): 399-412.

[42] Hamon M, Blier P. Monoamine neurocircuitry in depression and strategies for new treatments [J]. Prog Neuropsychopharmacol Biol Psychiatry, 2013, 45: 54-63.

[43] Gardier A M. Antidepressant activity: contribution of brain microdialysis in knock-out mice to the understanding of BDNF/ 5-HT transporter/ 5-HT autoreceptor interactions [J]. Front Pharmacol, 2013, 4: 98.

[44] Strasser B, Gostner J M, Fuchs D. Mood, food, and cognition: Role of tryptophan and serotonin [J]. Current Opinion in Clinical Nutrition & Metabolic Care, 2016, 19(1): 55-61.

[45] Huang Y J, Lane H Y, Lin C H. New treatment strategies of depression: based on mechanisms related to neuroplasticity [J]. Neural Plast, 2017, 2017: 4605971.

[46] Kraus C, Castrén E, Kasper S, et al. Serotonin and neuroplasticity-links between molecular, functional and structural pathophysiology in depression [J]. Neurosci Biobehav Rev, 2017, 77: 317-326.

[47] Campbell S, Macqueen G. The role of the hippocampus in the pathophysiology of major depression [J]. J Psychiatry Neurosci, 2004, 29(6): 417-426.

[48] Sudo N, Chida Y, Aiba Y, et al. Postnatal microbial colonization programs the hypothalamic-pituitary-adrenal system for stress response in mice [J]. J Physiol, 2004, 558(Pt1): 263-275.

[49] O'Leary O F, Ogbonnaya E S, Felice D, et al. The vagus nerve modulates BDNF expression and neurogenesis in the hippocampus [J]. Eur Neuropsychopharmacol, 2018, 28(2): 307-316.

[50] Catena Dell' Osso M, Bellantuono C, Consoli G, et al. Inflammatory and neurodegenerative pathways in depression: a new avenue for antidepressant development? [J]. Curr Med Chem, 2011, 18(2): 245-255.

[51] Słuzewska A, Rybakowski J K, Laciak M, et al. Interleukin-6 serum levels in depressed patients before and after treatment with fluoxetine [J]. Ann N Y Acad Sci, 1995, 762: 474-476.

[52] Eyre H, Baune B T. Neuroplastic changes in depression: a role for the immune system [J]. Psychoneuroendocrinology, 2012, 37(9): 1397-1416.

[53] Peirce J M, Alviña K. The role of inflammation and the gut microbiome in depression and anxiety [J]. J Neurosci Res, 2019, 97(10): 1223-1241.

[54] Sudo N. Microbiome, HPA axis and production of endocrine hormones in the gut [J]. Adv Exp Med Biol, 2014, 817: 177-194.

[55] Hryhorczuk C, Sharma S, Fulton S E. Metabolic disturbances connecting obesity and depression [J]. Front Neurosci, 2013, 7: 177.

[56] Forsythe P, Bienenstock J, Kunze W A. Vagal pathways for microbiome-brain-gut axis communication [J]. Adv. Exp Med Biol, 2014, 817: 115-133.

[57] Stilling R M, Dinan T G, Cryan J F. Microbial genes, brain &

behaviour - Epigenetic regulation of the gut-brain axis [J]. Genes Brain Behav, 2014, 13: 69-86.

[58] Ait Belgnaoui A, Durand H, Cartier C, et al. Prevention of gut leakiness by a probiotic treatment leads to attenuated HPA response to an acute psychological stress in rats [J]. Psychoneuroendocrinology, 2012, 37(11): 1885-1895.

[59] Fleshner M, Frank M, Maier S F. Danger signals and inflammasomes: Stress-evoked sterile inflammation in mood disorders [J]. Neuropsychopharmacology 2017, 42: 36-45.

[60] Guida F, Turco F, Iannotta M, et al. Antibiotic-induced microbiota perturbation causes gut endocannabinoidome changes, Hippocampal neuroglial reorganization and depression in mice [J]. Brain Behav Immun, 2018, 67: 230-245.

[61] Haghighat N, Rajabi S, Mohammadshahi M. Effect of synbiotic and probiotic supplementation on serum brain-derived neurotrophic factor level, depression and anxiety symptoms in hemodialysis patients: A randomized, double-blinded, clinical trial [J]. Nutr Neurosci, 2021, 24: 490-499.

[62] Sherwin E, Dinan T G, Cryan J F. Recent developments in understanding the role of the gut microbiota in brain health and disease [J]. Ann N Y Acad Sci, 2018, 1420: 5-25.

[63] Abildgaard A, Elfving B, Hokland M, et al. Probiotic treatment reduces depressive-like behaviour in rats independently of diet [J]. Psychoneuroendocrinology, 2017, 79: 40-48.

[64] Allen A P, Hutch W, Borre Y E, et al. *Bifidobacterium longum* 1714 as a translational psychobiotic: modulation of stress, electrophysiology and neurocognition in healthy volunteers [J]. Transl Psychiatry, 2016, 6: e939.

[65] Steenbergen L, Sellaro R, Van Hemert S, et al. A randomized controlled trial to test the effect of multispecies probiotics on cognitive reactivity to sad mood [J]. Brain BehavImmun, 2015, 48: 258-264.

[66] Balanzá Martínez V. Nutritional supplements in psychotic disorders [J]. Actas Esp De Psiquiatr, 2017, 45: 16-25.

[67] Burokas A, Arboleya S, Moloney R D, et al. Targeting the microbiota-gut-brain axis: prebiotics have anxiolytic and antidepressant-like effects and reverse the impact of chronic stress in mice [J]. Biol Psychiatry, 2017, 82: 472-487.

[68] Dinan T G, Cryan J F. The microbiome-gut-brain axis in health and disease [J]. Gastroenterol Clin N Am, 2017, 46: 77-89.

[69] Schmidt K, Cowen P J, Harmer C J, et al. Prebiotic intake reduces the waking cortisol response and alters emotional bias in healthy volunteers [J]. Psychopharmacology, 2015, 232: 1793-1801.

[70] Savignac H M, Couch Y, Stratford M, et al. Prebiotic administration normalizes lipopolysaccharide (LPS)-induced anxiety and cortical 5-HT2A receptor and IL1-βlevels in male mice [J]. Brain BehavImmun, 2016, 52: 120-131.

[71] Salminen S, Collado M C, Endo A, et al. The international Scientific Association of Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of postbiotics [J]. Nat Rev Gastroenterol Hepatol, 2021, 18: 649-667.

[72] Taverniti V, Guglielmetti S. The immunomodulatory properties of probiotic microorganisms beyond their viability (ghost probiotics: proposal of paraprobiotic concept) [J]. Genes Nutr, 2011, 6: 261-274.

[73] Maehata H, Kobayashi Y, Mitsuyama E, et al. Heat-killed *lactobacillus helveticus strain* MCC1848 confers resilience to anxiety or depression-like symptoms caused by subchronic social defeat stress in mice [J]. Biosci Biotechnol Biochem, 2019, 83: 1239-1247.

[74] Kambe J, Watcharin S, MakiokaItaya Y, et al. Heat-killed enterococcus fecalis (EC-12) supplement alters the expression of neurotransmitter receptor genes in the prefrontal cortex and alleviates anxiety-like behavior in mice [J]. Neurosci Lett, 2020, 720: 134753.

[75] Murata M, Kondo J, Iwabuchi N, et al. Effects of paraprobiotic *Lactobacillus paracasei* MCC1849 supplementation on symptoms of the common cold and mood states in healthy adults [J]. Benef Microbes, 2018, 9: 855-864.

[76] Nishida K, Sawada D, Kuwano Y, et al. Health benefits of *lactobacillus gasseri* CP2305 tablets in young adults exposed to chronic stress: A randomized, double-blind, placebo-controlled study [J]. Nutrients, 2019, 11: 1859.

[77] Markowiak P, ´Sli˙zewska K. Effects of probiotics, prebiotics, and synbiotics on human health [J]. Nutrients, 2017, 9: 1021.

[78] Kleniewska P, Pawliczak R. Influence of synbiotics on selected oxidative stress parameters [J]. Oxidative Med Cell Longev, 2017, 15: e9315375.

[79] Schröder J, Dören M, Schneider B, et al. Are the antioxidative effects of 17β-Estradiol modified by concomitant administration of a progestin? [J]. Maturitas, 1996, 25: 133-139.

[80] Haghighat N, Rajabi S, Mohammadshahi M. Effect of

synbiotic and probiotic supplementation on serum brain-derived neurotrophic factor level, depression and anxiety symptoms in hemodialysis patients: A randomized, double-blinded, clinical trial [J]. Nutr Neurosci, 2021, 24: 490-499.

[81] Cheung S G, Goldenthal A R, Uhlemann A C, et al. Systematic review of gut microbiota and major depression [J]. Front Psychiatry, 2019, 10: 34.

[82] PintoSanchez M I, Hall G B, Ghajar K, et al. Probiotic *Bifidobacterium longum* NCC3001 reduces depression scores and alters brain activity: A pilot study in patients with irritable bowel syndrome [J]. Gastroenterology, 2017, 153: 448-459.

[83] Messaoudi M, Lalonde R, Violle N, et al. Assessment of psychotropic-like properties of a probiotic formulation (*Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175) in rats and human subjects [J]. Br J Nutr, 2011, 105: 755-764.

[84] Dinan T G, Cryan J F. Brain-gut-microbiota axis and mental health [J]. PsychosomMed, 2017, 79: 920-926.

[85] Desbonnet L, Garrett L, Clarke G, et al. The probiotic bifidobacteria infantis: an assessment of potential antidepressant properties in the rat [J]. J Psychiatr Res, 2008, 43: 164-174.

[86] Desbonnet L, Garrett L, Clarke G, et al. Effects of the probiotic bifidobacterium infantis in the maternal separation model of depression [J]. Neuroscience, 2010, 170: 1179-1188.

[87] Nakaita Y, Kaneda H, Shigyo T. Heat-killed *Lactobacillus brevis* SBC8803 induces serotonin release from intestinal cells [J]. Food Nutr Sci, 2013, 4: 767-771.

[88] Liu W H, Chuang H L, Huang Y T, et al. Alteration of behavior and monoamine levels attributable to *Lactobacillus plantarum* PS128 in germ-free mice [J]. Behav Brain Res, 2016, 298: 202-209.

[89] Bravo J A, Forsythe P, Chew M V, et al. Ingestion of lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve [J]. Proc Natl Acad Sci USA, 2011, 108: 16050-16055.

[90] Cryan J F, Dinan T G. Mind-altering microorganisms: The impact of the gut microbiota on brain and behaviour [J]. Nat Rev Neurosci, 2012, 13: 701-712.

[91] Holzer P, Farzi A. Neuropeptides and the microbiota-gut-brain axis [J]. Adv Exp Med Biol, 2014, 817: 195-219.

[92] Benton D, Williams C, Brown A. Impact of consuming a milk drink containing a probiotic on mood and cognition [J]. Eur J Clin Nutr, 2007, 61: 355-361.

[93] Takada M, Nishida K, KataokaKato A, et al. Probiotic lactobacillus casei strain shirota relieves stress-associated symptoms by modulating the gut-brain interaction in human and animal models [J]. Neurogastroenterol Motil, 2016, 28: 1027-1036.

[94] 刘志强,邹永周,何敏,等.绿茶多酚改善社会挫败模型小鼠的抑郁行为研究[J].重庆医学,2021,50(5):741-745.

[95] Jiang H, Wang Z, Wang Y, et al. Antidepressant-like effects of curcumin in chronic mild stress of rats: involvement of its anti-inflammatory action [J]. Prog Neuro-Psychopharmacol Biol Psychiatry, 2013, 47: 33-39.

[96] Wang Z, Zhang Q, Yuan L, et al. The effects of curcumin on depressive-like behavior in mice after lipopolysaccharide administration [J]. Behav Brain Res, 2014, 274: 282-290.

[97] Rozan P, Hidalgo S, Nejdi A, et al. Preventive antioxidant effects of cocoa polyphenolic extract on free radical production and cognitive performances after heat exposure in wistar rats [J]. J Food Sci, 2007, 72: S203-S206.

[98] Spohr L, Soares M S P, Oliveira P S, et al. Combined actions of blueberry extract and lithium on neurochemical changes observed in an experimental model of mania: Exploiting possible synergistic effects [J]. Metab Brain Dis, 2019, 34: 605-619.

[99] Grzelczyk J, Budryn G, PeñaGarcía J, et al. Evaluation of the inhibition of monoamine oxidase a by bioactive coffee compounds protecting serotonin degradation [J]. Food Chem, 2021, 348: 129108.

[100] Sandhu K V, Sherwin E, Schellekens H, et al. Feeding the microbiota-gut-brain axis: Diet, microbiomeand neuropsychiatry [J]. Transl Res, 2017, 179: 223-244.

[101] Bhat A, Mahalakshmi A M, Ray B, et al. Benefits of curcumin in brain disorders [J]. Bio Factors, 2019, 45: 666-689.

[102] Sharma R, Sharma A, Kumari A, et al. Consumption of green tea epigallocatechin-3-gallate enhances systemic immune response, antioxidative capacity and HPA axis functions in aged male swiss albino mice [J]. Biogerontology, 2017, 18: 367-382.

[103] Zhu W L, Shi H, Wei Y M, et al. Green tea polyphenols produce antidepressant-like effects in adult mice [J]. Pharmacol Res of J Ital Pharmacol Soc, 2011, 65: 74-80.

[104] Ge L, Liu L, Liu H, et al. Resveratrol abrogates lipopolysaccharide-induced depressive-like behavior,

neuroinflammatory responseand CREB/BDNF signaling in mice [J]. Eur JPharmacol, 2015, 768: 49-57.

[105] Pang C, Cao L, Wu F, et al. The effect of trans-resveratrol on post-stroke depression via regulation of hypothalamus-pituitary-adrenal axis [J]. Neuropharmacology, 2015, 97: 447-456.

[106] Zhao X, Yu C, Wang C, et al. Chronic resveratrol treatment exerts antihyperalgesic effect and corrects co-morbid depressive like behaviors in mice with mononeuropathy: Involvement of serotonergic system [J]. Neuropharmacology, 2014, 85: 131-141.

[107] 谷珊.跨文化交际中的中西饮食文化对比及翻译研究-《中西方饮食文化差异及翻译研究》评述[J].食品与机械,2021, 37(5):238-239.

[108] Fu S, Wang J, Xue W, et al. Anti-inflammatory effects of BHBA in both in vivo and in vitro Parkinson's disease models are mediated by GPR109A-dependent mechanisms [J]. J Neuroinflamm, 2015, 12(9): 25595674.

[109] Shimazu T, Hirschey M, Newman J, et al. Suppression of oxidative stress by *β*-hydroxybutyrate, an endogenous histone deacetylase inhibitor [J]. Science, 2013, 339: 211-214.

[110] Youm Y H, Nguyen K Y, Grant R W, et al. The ketone metabolite *β*-hydroxybutyrate blocks NLRP3 inflammasome-mediated inflammatory disease [J]. Nat Med, 2015, 21: 263-269.

[111] Qiao G, Lv T, Zhang M, et al. *β*-hydroxybutyrate (*β*-HB) exerts anti-inflammatory and antioxidant effects in lipopolysaccharide (LPS)-stimulated macrophages in Liza haematocheila [J]. Fish Shellfish Immunol, 2020, 107: 444-451.

[112] Noh H S, Hah Y S, Nilufar R, et al. Acetoacetate protects neuronal cells from oxidative glutamate toxicity [J]. J Neurosci Res, 2006, 83: 702-709.

[113] Maalouf M, Sullivan P G, Davis L, et al. Ketones inhibit mitochondrial production of reactive oxygen species production following glutamate excitotoxicity by increasing NADH oxidation [J]. Neuroscience, 2007, 145: 256-264.

[114] Hasan Olive M M, Lauritzen K H, Ali M, et al. A ketogenic diet improves mitochondrial biogenesis and bioenergetics via the PGC1*α*-SIRT3-UCP2 axis [J]. Neurochem Res, 2019, 44: 22-37.

[115] Zou X H, Sun L H, Yang W, et al. Potential role of insulin on the pathogenesis of depression [J]. Cell Prolif, 2020, 53(5): e12806.

[116] 毛高峰,李朝武,聂海岭,等.生酮饮食对抑郁模型幼鼠的抗抑郁作用及机制[J].广东医学,2016,37(6):820-823.

[117] 宋玉欣,龚志华,张娇,等.*L*-茶氨酸对高蛋白饮食诱导大鼠行为变化的干预作用[J].食品科学,2021,42(5):187-192.

[118] Kothari V, Luo Y, Tornabene T, et al. High fat diet induces brain insulin resistance and cognitive impairment in mice [J]. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease, 2017, 1863(2): 499-508.

[119] 秦海霞.素食对糖尿病的影响及机制探讨[J].现代食品, 2021,15:96-98.

[120] 田桂芹,唐佳琦,徐鹏飞,等.丁苯酞对慢性应激大鼠海马组织氧化应激及炎症因子的影响[J].中南药学,2017,15(4): 420-423.

[121] Slavich G M, Irwin M R, Hinshaw S P. From stress to inflammation and major depressive disorder: A social signal transduction theory of depression [J]. Psychological Bulletin, 2014, 140(3): 774-815.

[122] Aschbacher K, O Donovan A, WolkoWitz O M, et al. Good stress, bad stress and oxidative stress: Insights from anticipatory cortisol reactivity [J]. Psychoneuroendocrinology, 2013, 38(9): 1698-1708.

[123] Borody T J, Paramsothy S, Agrawal G. Fecal microbiota transplantation: indications, methods, evidence, and future directions [J]. Curr Gastroenterol Rep, 2013, 15(8): 337.

[124] Kelly J R, Borre Y, O' Brien C, et al. Transferring the blues: depression-associated gut microbiota induces neurobehavioural changes in the rat [J]. J Psychiatr Res, 2016, 82: 109-118.

[125] Chinna Meyyappan A, Forth E, Wallace C J K, et al. Effect of fecal microbiota transplant on symptoms of psychiatric disorders: A systematic review [J]. BMC Psychiatry, 2020, 20: 299.

[126] Collyer R, Clancy A, Borody T. Faecal microbiota transplantation alleviates symptoms of depression in individuals with irritable bowel syndrome: A case series [J]. Med Microecol, 2020, 6: 100029.

[127] Cai T, Shi X, Yuan L Z, et al. Fecal microbiota transplantation in an elderly patient with mental depression [J]. Int Psychogeriatr, 2019, 31: 1525-1526.

[128] Evrensel A, Ceylan M E. Fecal microbiota transplantation and its usage in neuropsychiatric disorders [J]. Clin Psychopharmacol Neurosci, 2016, 14(3): 231-237.