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Review 综 述

乳果糖调节肠道微生物并改善抑郁症状的研究进展

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摘　要：抑郁是一种常见的情绪障碍，对个体的情绪和认知功能产生显著的负面影响，多见于其他疾病共患病中。随着抑郁年轻化趋势加重，抑郁对我国精神健康事业产生严重影响。近年来，随着肠道菌群研究的深入，抑郁症状与肠道菌群的关系愈发引起重视，而乳果糖作为一种用于促进肠道健康且对认知功能和情绪存在一定的改善作用的药物，引起了人们对其在改善抑郁症状方面的临床应用的关注。本文综述了乳果糖在改善抑郁症状方面的一些临床研究成果，并概述了一些乳果糖改善抑郁症状可能的机制，对通过肠-脑轴改善抑郁症状提出了展望。

关键词：乳果糖；抑郁症状；肠道菌群；肠-脑轴

Research progress in the regulation of gut microbiota and mitigation of depressive symptoms by lactulose

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Abstract: Depression is a prevalent affective disorder exerting negative impacts on an individual’s emotional and cognitive functions and is commonly complicated with other diseases.

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As depression is affecting increasingly younger populations, it poses a serious challenge to the mental health initiatives in China. In recent years, the relationship between depressive symptoms and gut microbiota has garnered increasing attention, fueled by the deepening research on gut microbiota. Lactulose, a medication aimed at promoting gut health and known for its potential benefits on emotional and cognitive functions, has sparked interests regarding its clinical application in ameliorating depressive symptoms. This article reviews the clinical research findings on the efficacy of lactulose in alleviating depressive symptoms and outlines the potential mechanisms through which lactulose may mitigate these symptoms. Furthermore, this article offers a perspective on the mitigation of depressive symptoms through the gut-brain axis.

Keywords: lactulose; depressive symptoms; gut microbiota; gut-brain axis

抑郁作为一种常见的情绪障碍，在现代社会发病率逐年上升，在新型冠状病毒(corona virus disease 2019, COVID-19)大流行后更为显著[1-2]。同时，抑郁症状作为共患病在多种疾病中被观察到，并与疾病进程和药物使用密切相关[3]，因此引起了学界的广泛关注。在目前的研究中，认为抑郁症状的发生涉及多种因素，包括环境因素、遗传因素、大脑结构改变等[4-7]。近年来，随着肠道菌群研究的进一步深入，脑-肠轴理论的提出，使得越来越多的研究聚焦于肠道微生态与抑郁症状的相互影响[8-10]，如肠道中促炎细菌的富集和抗炎基因的衰竭[8,11-12]、短链脂肪酸和胆汁酸等代谢物水平变化[13-16]等得到了较为深入的研究。

乳果糖作为一种已被证实的能够改善肠道微生态的药物[12,17-19]，其在改善抑郁症状方面的作用受到广泛关注。一项针对便秘患者的临床队列研究发现，与其他改善便秘的药物相比，乳果糖干预在改善便秘的同时，更为显著地改善了患者的抑郁症状[20]，揭示了乳果糖干预在改善抑郁症状中的潜在作用。尽管乳果糖改善抑郁症状的机制尚不清楚，但本综述对现有机制进行了总结，以期为后续研究提供参考。

首先，短链脂肪酸等关键循环代谢物在大脑功能调节中占据重要地位，已有研究揭示其通过影响小胶质细胞发育进而影响大脑功能[21-22]。在乳果糖干预后，与短链脂肪酸生成相关的细菌显著增多[23]，同时观察到胆汁酸、N-乙酰神经氨酸和维生素 D 等代谢物水平的变化[12,18,24-26]。其次，神经炎症在抑郁症状的研究中受到广泛关注[27-29]，而且与肠道微生态密切相关[30-31]。乳果糖作为常用的肠道微生态调节剂，能够增加抗炎和促认知功能的肠道菌群丰度[12]，从而可能通过调节机体炎症水平对早期抑郁进行干预。此外，肠道细菌产生的神经递质和神经营养因子对抑郁等神经性疾病具有重要影响[32-35]。乳果糖干预可改变神经递质水平，如降低 γ-氨基丁酸(γ-aminobutyric acid, GABA)水平[36]，这可能与改善抑郁症状相关。鉴于细胞自噬与抗抑郁作用的关联[37]，乳果糖可能通过减少神经炎症并提升自噬相关通路水平，为抗抑郁治疗提供新的策略[38]。

在目前的临床实践中，粪菌移植(fecal microbiota transplantation, FMT)治疗抑郁症患者已取得一定进展，但仍存在疗效维持时间较短等缺陷[39-40]。目前有研究表明益生元或膳食纤维等有利于维持肠道微生态的稳定[15]。乳果糖作为常见的能够改善肠道微生态的益生元，在联合粪菌移植方面具有广阔的研究前景。

本综述基于肠-脑轴(gut-brain axis)与抑郁

症状相关性的基础讨论乳果糖改变肠道菌群和代谢途径来治疗抑郁症状的进展，以期为乳果糖在改善抑郁症状的研究提供参考。

1 抑郁症状与肠道菌群的关系

1.1 抑郁的发生机制简述

抑郁是一种常见的情绪障碍，其常见的症状有疲劳和缺乏能量[41]、悲观或无法集中注意力[42]、食欲或体重发生显著变化[43]和产生睡眠问题[44]等。在目前的研究中，抑郁症状在多种疾病中被观察到，而且与疾病的进程和药物使用密切相关[3]。根据美国国家精神卫生研究所(National Institute of Mental Health, NIMH)的数据，2021 年美国成年人中至少有一次大型抑郁发作的人数估计为 2 100 万，占全部成年人口的 8.3%[1]。研究指出，COVID-19 的大流行加重了全球抑郁的患病率[2]。

抑郁是一种复杂的情绪障碍，可能涉及多种因素。遗传学上有研究发现，个体出现抑郁症状的风险受基因影响[4]，并已发现一些与之相关的基因，如核因子 κB (nuclear factor kappa-B, NF-κB)、cAMP 反应元件结合蛋白(cyclic-AMP response binding protein, CREB)和糖皮质激素受体(glucocorticoid receptor, GR)基因等[5]。此外，环境因素，包括压力事件，如失去亲人、工作压力等，均可增加出现抑郁症状的风险[6]。也有研究发现，抑郁症患者的大脑结构可能与正常人存在差异，如情绪反应区的海马体体积越小，对悲伤面孔的反应越大，可以预测扫描时抑郁症状的增加，而杏仁核体积越大，脑岛体积越小和情绪反应区反应越大则可以预测情绪调节技能的下降[7]。

1.2 抑郁症状与肠道菌群

1.2.1 肠道菌群组成改变

近年来，随着肠道菌群研究的进一步深入，抑郁症状与肠道菌群组成的关系愈发引起重视。研究表明，抑郁症患者中菌群多样性与正常人存在差异，如在 β 多样性中，抑郁状态下的肠道微生物与对照组存在明显差异[8]，而且在使用抗生素后导致的菌群多样性下降增加了出现抑郁症状的风险[9]；这些差异体现在抑郁症状的炎症假说中[10]，即促炎细菌的富集和抗炎细菌的耗竭，如脱硫弧菌(*Desulfovibrio*)和埃希氏菌/志贺氏菌(*Escherichia*/*Shigella*)的富集、双歧杆菌(*Bifidobacterium*)和粪杆菌(*Faecalibacterium*)的耗竭[8,11]。此外，乳果糖干预也被证实可以使得轻度肝性脑病(mild hepatic encephalopathy, MHE)患者肠道中抗炎相关菌群的相对丰度增加[12]。更为重要的是，Kelly 等和 Zheng 等[45-46]在啮齿动物中进行粪菌移植后发现肠道微生态失调先于抑郁症发生。

同时，抑郁症状存在的时间[47-48]和不同样本的地域差异[49]也均在肠道菌群组成差异上有所体现，进一步揭示了肠道菌群与抑郁症状之间的密切关系。除上述提及的肠道细菌之外，肠道病毒组[50-51]和肠道真菌[52]的研究也逐渐发展，肠道微生态在抑郁症状的产生和发展中愈发引起重视。

1.2.2 肠道菌群代谢物的改变

肠道菌群代谢物改变是肠道菌群组成改变影响抑郁症状的重要途径。目前研究发现，抑郁症状严重程度与胆汁酸水平成反比[13]，而与氧化三甲胺水平则成正比[53]。同时，在抑郁患者中发现了短链脂肪酸(short chain fatty acid, SCFAs)，尤其是丁酸的耗竭[14-16]，在补充丁酸盐后，抑郁症状得到改善[54]，研究证明，使用乳果糖治疗使得肠道菌群衍生的 SCFAs 增多[55]。除此之外，脂多糖、乳酸盐和维生素等也被发现与抑郁症状相关[55-57]，可见代谢物水平在抑郁症状的发生机制中发挥着重要作用。

1.2.3 肠道菌群和代谢物改变通过肠-脑轴影响抑郁症状

目前针对肠道菌群与神经性疾病的关系，提出了肠-脑轴的概念[58]。肠道菌群和代谢物通过破坏肠道上皮，使得肠道屏障功能受损和局部炎症发生[59]，而炎症因子透过受损的肠道屏障引起全身炎症[60]，继而影响抑郁症状。同时肠神经系统也被认为在肠-脑轴中发挥重要作用，肠道中的微生物信号通过迷走神经途径进而对大脑产生影响[61]。此外，部分可以通过血脑屏障的代谢物，如革兰氏阴性菌产生的脂多糖，透过血脑屏障引起神经炎症，进而加重抑郁症状[55,60]。

综上，肠道菌群与抑郁症状的发生密切相关。本综述将基于此，探索肠-脑轴介导的代谢因素对抑郁症状的影响[62-63]，并综述乳果糖改变肠道菌群和代谢途径来治疗抑郁症状的进展。

2 乳果糖通过肠道微生态影响抑郁症状

乳果糖是一种合成双糖，包含果糖和半乳糖[64]。作为一种不被吸收的双糖，乳果糖已被广泛应用于肝性脑病的治疗。肝性脑病(hepatic encephalopathy, HE)是一种与神经系统并发症相关的脑功能障碍，其早期患者常伴有抑郁症状和情绪障碍，高氨血症、促炎细胞因子和特定神经递质的积累等被认为参与 HE 发展的因素[65]，并且其发生与肠道微生态失调有密切联系[66]。Yang 等[67]研究探讨了乳果糖促进神经可塑性，改善早期肝性脑病的认知功能，为乳果糖治疗抑郁这一神经系统性疾病提供了理论基础。Hudson 等的综述文章回顾了乳果糖和/或利福昔明在长期管理肝性脑病中的应用，提到了乳果糖对认知功能和情绪改善的潜在作用，为改善抑郁症状提供了一定的基础[68]。

据此不难推测乳果糖具有影响肠道微生态来改善抑郁症状的作用。具体而言，目前较为清晰的机制是乳果糖在肠-脑轴的介导下改善抑郁症状，其干预既能使肠道微生物衍生的短链脂肪酸、神经营养因子以及神经元分泌的神经递质等有益产物增多，又能下调炎症反应及氧化应激水平(图 1)。

2.1 乳果糖治疗便秘同时改善抑郁症状

国内一项最新的队列研究表明，便秘患者更容易患有抑郁症状[69]。传统上通常用乳果糖改善患者的便秘症状[70]，而便秘患者常伴有抑郁焦虑等症状[71]。通过综合大量相关研究发现，乳果糖具有改善抑郁症状的作用，这一发现为临床实践中关注及治疗便秘患者的心理健康提供了重要依据。乳果糖干预的机制在于其能发挥益生元作用，加强肠道屏障、加速肠道蠕动，抑制炎症反应，并改善肠道中的代谢[72]。具体而言，乳酸杆菌对慢性功能性便秘患者的积极影响被证实[73]，其在缓解压力诱导的焦虑和抑郁方面的作用也被揭示[74]，而乳果糖作为益生元，其促进乳酸杆菌主导的微生物群落形成的特性也得到了验证[75]。因此，乳果糖疗法可能通过促进肠道内益生菌定殖，在调节肠道微生态的同时对抑郁情绪产生积极影响，间接进行抑郁进程的早期干预，可以作为一种神经(退行)性疾病的试验性治疗药物。马后莲等通过乳果糖与莫沙必利治疗老年患者慢性功能性便秘及伴随症状的前瞻性随机对照研究，验证了乳果糖在改善便秘的同时降低便秘相关的焦虑、抑郁评分[20]。潘姣等自拟缩泉润肠汤治疗阴虚肠燥型慢性便秘的临床研究中用到乳果糖口服液作为治疗慢性功能性便秘患者的干预对照组，与服用前相较，患者症状得到了显著改善[76-77]。在帕金森患者中，便秘和抑郁是常见的共患病，大量研究表明[78-79]在用乳果糖改善帕金森患者

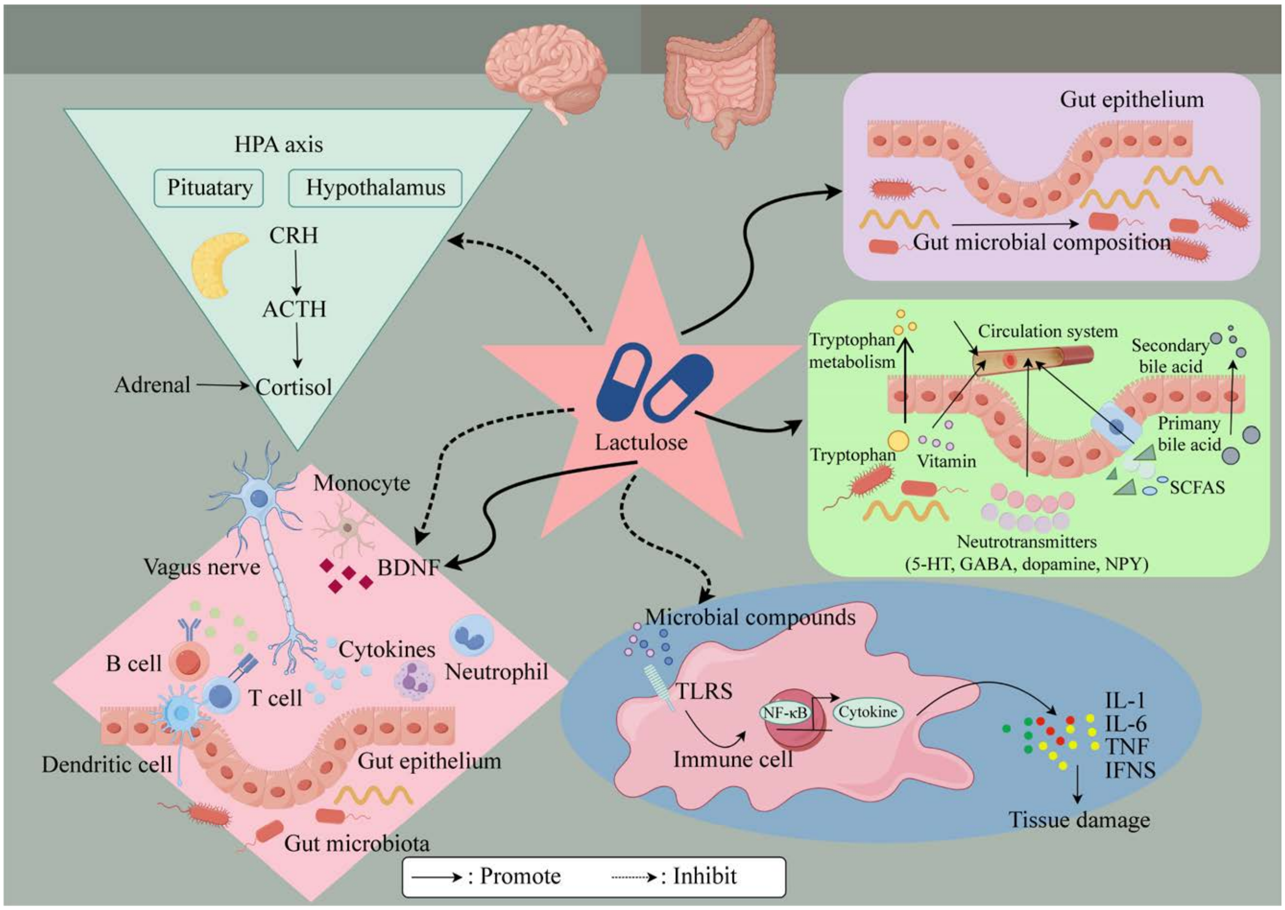

图 1　乳果糖作用于肠-脑轴从而影响抑郁的发生(本图由 Figdraw 绘制)

Figure 1　Lactulose acts on the brain gut axis and affects the occurrence of depression (drawn by Figdraw).

的便秘症状时发现同时改善了抑郁症状，这一发现不仅拓宽了乳果糖的临床应用范围，也为帕金森病患者提供了更为全面的治疗方案。

以上案例均表明，尽管目前关于乳果糖在改善抑郁的临床应用的研究仍然有限，但已有一些工作证实了乳果糖对认知功能和情绪改善的潜在作用。乳果糖作为一种传统的治疗便秘的药物，其潜力远不止于此。随着研究的深入，有望发现更多关于乳果糖在治疗抑郁症状方面的新应用。

2.2　短链脂肪酸和循环代谢物

在患有抑郁症状的群体中，由于肠道菌群的种类和数目不同[8], 短链脂肪酸和循环代谢物水平存在显著差异[14-16]，并在抑郁症状的发生和发展中起关键作用[62-63]，因此肠道菌群代谢物的检测和干预可以初步对抑郁患者进行诊断和治疗。

这些短链脂肪酸通过神经、化学及免疫作用，并以肠-脑轴为中介调节肠道与大脑功能的相互作用[21]。首先，SCFAs 被证实有助于调节下丘脑中神经递质如谷氨酸、谷氨酰胺等的合成[80]，进而调节迷走神经信号传导。另外，微生物群-肠道-免疫-神经胶质细胞轴被推测在抑郁症状中起作用[81]。具体而言，小胶质细胞的成熟依赖于 SCFAs 的持续输入，肠道微生物损耗会导致小胶质细胞不成熟和功能障碍[22]，从

而可能加剧抑郁症状。最后，SCFAs 可以通过血脑屏障直接向神经细胞提供能量[82]并充当信号分子[83]，也可以作为肠上皮细胞的重要能量来源[84]，还可以增强肠道屏障功能、维持血脑屏障完整性、减少海马细胞凋亡和调节免疫稳态[85-86]，这些功能共同维护了肠道与大脑之间的平衡状态。

乳果糖治疗可能使肠道菌群衍生的 SCFAs 增多，改善抑郁症状。研究表明，乳果糖可以逆转 AOM/DSS 处理诱导的毛螺菌科(*Lachnospiraceae*)丰度降低[23]，而毛螺菌科是肠道微生物群的核心，其成员是短链脂肪酸的主要生产者。短链脂肪酸不仅影响肠道健康，还可能通过肠-脑轴影响大脑的功能和情绪状态。因此，毛螺菌科通过产生短链脂肪酸可能对抑郁症状有缓解作用，这提示了乳果糖逆转的毛螺菌科丰度下调在抑郁治疗中有潜在积极作用。值得注意的是，在一项鉴定重度抑郁症(major depressive disorder, MDD)患者的性别特异性肠道微生物群研究中，不同性别的 MDD 患者减少的肠道菌群均主要归入毛螺菌科[87]，进一步说明了乳果糖诱导毛螺菌科丰度上调这一现象揭示了乳果糖治疗抑郁症状的潜力。Wang 等[18]采用气相色谱-质谱联用(gas chromatography-mass spectrometry, GC-MS)检测体内 SCFAs 含量，发现乳果糖干预后的短链脂肪酸水平显著升高并伴有毛螺菌属相对丰度增加，这一结果证实了上述观点。

除了衍生短链脂肪酸，肠道微生物还可以调节循环代谢物，包括氨基酸、胆汁酸和维生素等。肝性脑病的患者早期可能伴有抑郁症状及认知功能减退，早有研究表明，乳果糖能够使有毒的含氮产物如血氨和有机酸产物含量显著下降，降低肝性脑病相应并发症的发生且不具有一般药物的肝毒性[88]，是肝性脑病的一线治疗药物[89-90]，提示了乳果糖改善抑郁症状的潜力。一项前瞻性队列研究也显示，乳果糖疗法可以在改善慢性肝病时改善患者的认知障碍与睡眠障碍[91]，进一步表明乳果糖可能参与抑郁症状的改善。另外，一些胆汁酸可以通过血脑屏障，作用于中央法尼醇 X 受体(farnesoid X receptor, FXRFXR)和 G 蛋白胆汁酸激活受体 1 (G protein bile acid activates receptor 1, GPBAR-1)[25]，进而加重抑郁症状的风险，而通过构建急性肝损伤大鼠模型，研究人员证实乳果糖干预可能通过调节肠道菌群，降低甘氨鹅脱氧胆酸，进而改善肝脏及肠道病情[92]。以上证据均表明乳果糖有助于维持神经细胞的正常功能，降低抑郁发生的风险。除此之外，维生素也参与宿主微生物群的串扰并有利于抑郁症状的治疗。人类依靠肠道微生物群代谢来产生维生素[93]，在人体中(包括大脑)的多种生理过程中发挥着作用[94-95]。在中枢神经系统中，维生素在从能量稳态扩展到神经递质的产生中都发挥着作用，维生素缺乏会对神经功能产生显著的负面影响[96]。例如，维生素 D 具有神经调节、抗炎和抗氧化特性[97]，通过将血清素水平保持在正常水平来有效预防抑郁症状[98]；叶酸和维生素 B_{12} 是一碳代谢的主要决定因素，其中形成的 S-腺苷甲硫氨酸(S-adenosylmethionine, SAMe)可以提供对神经功能至关重要的甲基[99]。值得注意的是，虽然目前尚无研究直接对乳果糖干预后的维生素水平做出评定，但乳果糖促进益生菌定殖[12]及益生菌促进肠道微生物产生维生素的作用[26]均已被证实。

综上所述，肠道微生物衍生的短链脂肪酸和循环代谢产物可以充当肠道微生物信使参与肠-脑轴的信息传递，可能是治疗抑郁症状的有效干预措施。未来的研究可结合乳果糖对肠道微生物和循环代谢物的具体作用机制，进一步探讨乳果糖在治疗抑郁中的临床效果和安全性。

2.3 炎症因子和氧化应激

抑郁经常作为一种共发症状，大量研究通过Meta分析证实其与炎症生物标志物的存在有关[27-29]。与健康个体相比，抑郁患者在肠道菌群的相对丰度方面表现出显著变化，其中促炎细菌的增加和抗炎细菌的减少能较大程度地影响免疫反应和大脑功能(肠-脑轴)[10]。肠道微生态受损时，外周炎症因子可以直接穿过血脑屏障激活小胶质细胞，也可以通过炎症因子的迁移激活下丘脑-垂体-肾上腺(hypothalamic-pituitary-adrenal, HPA)轴从而诱发抑郁症状[100-102]。另外，抑郁患者的肠道菌群失调还会引起血浆脂多糖(lipopolysaccharide, LPS)的升高[103]。LPS作为常见的内毒素，可诱导多种促炎细胞因子释放，从而引发炎症，诱导抑郁发生[104]。

一项临床研究发现[105]，肠易激综合征(irritable bowel syndrome, IBS)症状与心理障碍密切相关，在高症状患者中特定炎症因子升高。在抑郁小鼠的大脑中也观察到炎症因子，特别是肿瘤坏死因子-α (tumor necrosis factor-α, TNF-α)、白细胞介素-1β (interleukin-1β, IL-1β)、IL-6、IL8等水平上调以及星形胶质细胞和小胶质细胞的增加，这些因素可以激活NF-κB信号传导并诱发抑郁行为[30-31]。相反，IL-6缺陷的小鼠对抑郁样症状的发展产生了抵抗力[107-108]，表明抑制这些炎症因子可能有助于预防或治疗抑郁症状。

乳果糖干预可以减少炎症因子的产生，有利于抑郁症状的治疗。乳果糖治疗后的MHE患者肠道中与抗炎和良好认知功能相关的特定分类菌群的相对丰度增加[12]。与之相反，在Wang等[18]实验中，乳果糖抑制可使炎性细胞因子上调，显著提高TNF-α、IL-6和TGF-β1的转录水平表达。乳果糖通过抑制这些炎症因子可能抑制小胶质细胞形态转化，通过TGF-β/Smad等信号转导通路调节应激反应，进而发挥神经保护作用[109]。基于上述细胞因子的外周血液循环水平被证实具有潜在的预测抑郁症状发展的临床价值，我们进一步认为乳果糖干预疗法有助于早期的抑郁干预和治疗。

除此之外，氧化应激也与神经功能障碍和情绪困扰密切相关[110]。目前，越来越多证据表明肠道菌群可与HPA轴相互作用，即通过内分泌途径作用于肠-脑轴，调节机体对外界环境的应激反应，进而影响包括抑郁在内的精神性疾病[111-112]。一项系统评价表明，运动员的抑郁行为增加与肠道微生物群的内分泌作用影响了HPA轴有关[106]。因此，基于乳果糖对肠道微生物的调节作用，乳果糖治疗可能通过肠-脑轴对HPA轴功能产生影响进而干预抑郁症状。Zheng等[113]发现乳果糖可以防止镰菌真菌毒素引起的氧化损伤，直接揭示了乳果糖减少氧化应激反应的潜力。因此推测，乳果糖干预可能同其他益生菌相似，能够使体内氧化应激减弱和抗氧化防御系统增强，如还原性物质谷胱甘肽(glutathione, GSH)的水平和过氧化氢酶活性升高[114-116]等，但具体机制仍需大量实验进一步探究。

综上所述，肠道菌群变化引起的炎症和一些代谢性变化疾病能够作为抑郁患者的标志性疾病。尽管该反应不具有特异性，但通过乳果糖干预相应的炎症反应对患者而言有着积极作用。

2.4 神经递质和脑神经营养因子

神经递质和神经营养因子对抑郁症状与肠道菌群的串扰很重要，在调节肠-脑轴中起重要作用[117]。肠道细菌所分泌的各种神经递质和神经营养因子可以通过神经作用影响脑，进行由肠道至脑的信息传递。神经细胞又反过来通过迷走神经改变神经递质和其他细胞因子水平对中枢和外周神经系统进行神经调节，维持稳定的双向肠-脑轴信号传导[21]。

研究表明[32-35]，肠道细菌可产生多种神经递质和神经营养因子，这些物质通过血液循环作用于脑，包括脑源性神经营养因子(brain derived neurotrophic factor, BDNF)、5-羟色胺(5-hydroxytryptamine, 5-HT)、γ-氨基丁酸(gamma-aminobutyric acid, GABA)、色氨酸和神经肽等，最终引起个体应激反应和认知水平的改变，进而影响抑郁等神经性疾病的发展。

色氨酸作为一种必需氨基酸，可产生具有既定情绪调节特性的神经活性分子，包括血清素、犬尿氨酸和吲哚，对肠道微生物群和肠-脑轴之间的相互作用有着深远影响[118]。膳食中摄入色氨酸主要通过调节中枢神经系统的血清素水平影响抑郁症状的发展，而色氨酸的耗竭则会导致抑郁症状的加重[119]。2 项动物实验也均发现乳果糖饮食使色氨酸代谢水平显著增高[72,120]，在乳果糖发酵实验中色氨酸代谢物水平也显著上调[121]，直接表明了乳果糖的治疗潜力。值得注意的是，“抑郁症的单胺理论”提出，抑郁的生物学机制之一是单胺水平的缺乏，即 5-HT、去甲肾上腺素和多巴胺的缺乏。目前研究显示，许多抗抑郁药物如单胺氧化酶抑制剂和三环类抗抑郁药虽然可以通过增强 5-HT 和去甲肾上腺素活性来改善抑郁症状，但其增加单胺水平的作用几乎是瞬间的，而抗抑郁药治疗的临床效果通常需要数周才能观察到[122]。乳果糖干预诱导的益生菌定殖增加被证明可以合成单胺类物质，其作为益生元有着较小的副作用且无成瘾性[123-125]，因此认为乳果糖可以显著地改善目前已有的单胺靶向药物的治疗局限性，其对肠道微生物群的调节可能成为抑郁的一种新兴治疗方式，有利于为抗抑郁药物的研发和改进提供方向。

另外，徐婧等[125]发现伊托必利联合乳果糖可以显著提高 5-HT 水平和更好改善便秘症状，乳果糖治疗的健康小鼠全身血清 GABA 水平也显著低于健康对照组[36]，基于 GABA 作为一种重要的抑制性神经递质在中枢神经系统中发挥抑制作用，这一现象可能赋予了对抑郁样状态的保护[126]。除了上述物质，神经肽 Y (neuropeptide Y, NPY)表达异常也是抑郁症状的重要致病机制[127-128]。肠脑肽(如甘丙肽、胆囊收缩素等)作为神经肽的一种，主要由内分泌系统产生并在调节抑郁症状方面有重要作用；一些神经肽作为信号分子从神经元中释放出来[129]，可以影响兴奋细胞上的神经递质或调节剂，通过细胞信号传导实现脑对肠道的调节[130]。Zhou 等[131]研究发现与观察组相比，对照组使用乳果糖治疗可以使 NPY 水平上升并降低焦虑、健康担忧及社会反应得分，表明乳果糖可以有效干预抑郁症状。

除神经递质以外，神经营养因子，尤其是 BDNF，广泛分布于中枢和周围神经系统，由神经所支配的组织、星形胶质细胞或者神经元合成[132]，与神经元的生长、发育和功能完整性以及抑郁症状的发生发展密切相关[127,132-134]。深入探究 BDNF 与抑郁之间的关联发现，临床证据明确指出了改变 BDNF 水平对应激诱导的抑郁病理有着显著的影响[135]，这为理解抑郁的发病机制提供了新的视角，同时也为抑郁的治疗提供了新的潜在靶点。在动物模型的实验中，研究人员通过将 BDNF 直接输注到海马体或中脑中，成功观察到了持久的抗抑郁样作用[136]，这进一步验证了 BDNF 在抗抑郁治疗中的潜力。最近一项随机双盲实验也表明[137]，益生菌干预显著增加血清 BDNF 水平，促进健康老年人的心理健康，证实了益生元作用对抑郁症状的改善。然而，尽管已经对 BDNF 有了较为深入的了解，但目前对于乳果糖这种常用的治疗药物是否能够对神经营养因子产生调节作用，仍缺乏足够的研究和了解。因此，为了更全面地理

解乳果糖在治疗抑郁等神经系统疾病中的作用机制，仍需要进行更为深入和系统的研究。

2.5 细胞自噬

最近，细胞自噬与抗抑郁作用之间的关联已被报道，提出自噬在抑郁症状的发生发展中至关重要。细胞自噬作为支持细胞在应激下存活的关键机制，在神经元的存活和突触可塑性中扮演着重要角色[37]。通过维持神经元的功能、调节神经递质和神经肽的水平及参与神经再生和突触可塑性的调节，自噬被认为可以辅助抑郁的治疗[138]。研究人员利用小鼠模型和体外实验确定了氟西汀作为一种典型的抗抑郁药物，其自噬原作用与抑郁症状患者中对星形胶质细胞保护之间有显著的相关性，确定了氟西汀以 p53 依赖性机制促进星形胶质细胞自噬从而有效减轻抑郁症状，肯定了自噬对于抑郁的改善作用[139]。

综合已有文献，推测乳果糖可能可以作为一种抗抑郁药，触发自噬以对应激状况做出反应。近几年的研究显示，乳果糖改善抑郁症状的机制主要涉及 2 个方面：自噬和抗炎。首先，从病理学分析来看，乳果糖能够下调炎症因子水平，减少神经炎症并增加自噬通路的水平，这表明其通过抗炎和自噬可以实现神经保护作用。Lee 等[140]等通过检查阿尔茨海默病(Alzheimer’s disease, AD)小鼠海马体中巨自噬标志物 LC3 和 p62 以及伴侣介导的自噬(chaperone-mediated autophagy, CMA)标记物 Hsc70 和 Lamp-2a 的水平证实，乳果糖干预使 LC3 II 升高且 P62 同时降低，表明自噬流通畅；另外，免疫荧光分析显示乳果糖可以逆转 Aβ 处理导致的 Lamp-2a 降低和显著增加 Hsc70 水平，表明其在 CMA 中的促进作用，而自噬作用的促进最终导致 AD 小鼠认知障碍的改善。研究表明抑郁和认知障碍可能共享一些神经生物学机制，抑郁患者往往表现出动机下降和认知控制障碍，通过增强动机和认知控制，可能有助于同时改善抑郁和认知障碍[141]。因此，乳果糖改善认知障碍的同时可能对改善抑郁症状有着极大的促进作用。除此之外，研究发现褪黑激素治疗抑郁小鼠依赖于逆转抑郁时的 FOXO3a 水平下调和 p-FOXO3a 水平升高[142]。虽然仍未有实验探究乳果糖与 FOXO3a 的直接关系，但两歧双歧杆菌(*Bifidobacterium bifidum*)和副干酪乳杆菌(*Lactobacillus paracasei*)干预被证实可以激活 FOXO3a 信号通路[38]，基于乳果糖诱导双歧杆菌等有益菌定殖增加的作用，推测乳果糖干预有利于通过上调 FOXO3a 信号通路，这可以为深入研究乳果糖治疗抑郁的分子作用机制提供方向。

总的来说，这些研究结果共同指向了乳果糖在改善抑郁方面的潜在机制，即通过促进自噬来发挥作用，提供了一种根据星形胶质细胞自噬治疗抑郁症状的新方法，并为除调节神经递质之外的抗抑郁药物如乳果糖等的利用，提供了一个有前途的分子靶点。

然而，神经炎症、自噬和抑郁症状之间的机制相互作用在很大程度上仍然存在争议。一项最新研究发现慢性皮质酮可诱导小鼠海马齿状回中过度活跃的神经元自噬，并导致神经元中 BDNF 的过度溶酶体降解，最终诱导抑郁样行为[143]。因此，通过乳果糖温和的益生元作用以调节细胞自噬活性，维持 BDNF 的正常水平，可能是治疗抑郁的有效策略。

3 粪菌移植联合乳果糖在改善抑郁症状中的潜在应用

粪菌移植是一种将健康供体的肠道微生物移植到患者肠道，直接改变受者肠道微生物群，使其组成正常化，从而获得治疗效果的方法。陈容平等[144]基于将 FMT 应用于干预肥胖糖尿

病形成了专家共识。肠道微生物组与中枢神经系统之间存在相互作用，特别是通过微生物-肠-脑轴的通信途径。张艺等[62]综述了粪菌移植通过微生物-肠-脑轴改善抑郁症的研究进展，提及肠道微生物组与抑郁症之间存在关联，并且抑郁症患者的肠道微生物组与健康人存在差异。粪菌移植的应用已经为多种肠道疾病(如肠易激综合征[145]、溃疡性肠炎[146])或非肠道疾病(如抑郁症)的治疗或改善提供了新的治疗方向。Guo 等[147]的随机对照实验和 Doll 等[148]的案例报告均表明，粪菌移植可调整肠道微生物群，改善胃肠道和抑郁症状。通过粪菌移植治疗，有益菌可以取代异常菌，细菌多样性上调，肠道微生物的组成丰度得到改善，肠道菌群平衡重新建立，胃肠道症状和抑郁症状得到改善。

目前粪菌移植治疗抑郁症状患者已取得一定的进展，但仍存在维持时间较短的缺陷[39-40]，因为一段时间后一些有害菌群会重新达到较高的丰度，有益菌群丰度的变化趋势则相反，使得菌群移植的效果减弱。目前解决这种缺陷的办法主要为移植后患者口服益生元或膳食纤维等维持肠道微生态的稳定[149]。乳果糖是一种不可吸收的合成双糖[64]，也是一种益生元。研究表明，乳果糖可以通过调整肠道微生物群结构[23]、调节 SCFAs[18]等肠道菌群代谢产物含量和改善肠道屏障[150]等途径改善抑郁症状。这些研究和报告提示粪菌移植联合乳果糖对于抑郁症状的疗效值得进一步追踪，并且对于探索和确定粪菌移植在抑郁症治疗中的潜力具有重要意义。

虽然乳果糖作为益生元可能在抑郁症状的治疗及改善粪菌移植的疗效中起作用，而且在临床实验中报告显示研究对象对乳果糖无不良反应或症状较轻[151,70]，表明其安全性是可靠的。目前记录较多的用于抑郁症治疗的益生元是低聚果糖和低聚半乳糖，而将乳果糖用于抑郁症治疗或抑郁症状的改善的临床研究较少，因此，在联合粪菌移植方面，乳果糖相对于其他益生元的优势或不足仍需要进一步地探索。同时，由于乳果糖改善抑郁症状的具体分子机制尚未明晰，以及针对粪菌移植用于治疗抑郁症的研究数量有限，其长期的安全性和疗效有待进一步评估，因此乳果糖联合粪菌移植的治疗方法仍需要更多的临床试验。

4 总结与展望

抑郁症状患者的肠道菌群多样性与正常人存在差异，肠道菌群代谢物的改变也影响抑郁症状的发生和发展。然而乳果糖作为一种调节肠道健康的合成双糖，其在改善抑郁症状方面的潜在作用引起了研究者的广泛关注。

乳果糖通过调节肠道微生态和菌群代谢产物，影响肠-脑轴功能，可能对改善抑郁症状有潜在作用。乳果糖可以平衡肠道微生物，增加有益菌、减少有害菌，从而积极影响抑郁症状。此外，乳果糖可能通过调节炎症因子和氧化应激水平等方式改善抑郁症状。

近年来，细胞自噬在抑郁症发生发展中的作用逐渐被揭示，乳果糖对细胞自噬的潜在调控作用可能成为未来研究的新方向。

尽管目前关于乳果糖调节肠道菌群以改善抑郁症状的研究已取得初步成果，但尚需更多严谨的动物实验和临床试验来验证其作用机制和疗效。粪菌移植(FMT)作为一种直接干预肠道微生物群的治疗方法，与乳果糖的联合应用可能成为抑郁症状的辅助治疗手段。进一步的研究可以深入探讨乳果糖对肠道菌群-肠-脑轴信号传导路径的具体影响，以及粪菌移植联合乳果糖在抑郁症状治疗中的协同效应，以期为抑郁症状的临床治疗提供更为精准和个性化的干预措施。

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