(lactulose/mannitol ratio, LMR)。利用这些肠道通透性标志物,研究者们也在抑郁症患者中看到了肠道通透性改变。既往研究证明,I-FABP[9-11]、LBP[9-10]、zonulin[12]、肠道革兰阴性菌的免疫球蛋白IgM和IgA[13-14]在抑郁症患者体内明显高于健康对照者;而在LMR[15]的相关研究中,研究者则未发现抑郁症患者与健康对照者间的显著差距。抑郁症患者肠道通透性的临床研究详细信息均展示在表1中。

3 抑郁症与肠道通透性的相互作用机制

中枢神经系统的行为、情绪和认知,与胃肠道的功能及微生态通过"微生物群-肠-脑"轴这一途径相互联系。肠道屏障是肠道与中枢神经系统建立联系的门户。如前文所述,在抑郁症患者中观察到了肠道通透性的增高,而其升高的机制可主要归纳为3种:炎症反应机制、迷走神经调节机制和应激机制(图1)。

表 1 抑郁症患者肠道通透性临床研究概况

Table 1 Overview of clinical studies on intestinal permeability in MDD patients

Intestinal permeability biomarker	Reference	Experimental group	Control group	Test sample	Test method	Results
Zonulin	ALVAREZ-MON, 2019[9]	MDD (n=22)	HC (n=14)	Serum	ELISA	No significant difference
	ALVAREZ-MON, 2021[10]	MDD (n=30)	HC (n=20)	Serum	ELISA	No significant difference
	OHLSSON, 2019[11]	MDD (n=13)	HC (n=17)	Plasma	ELISA	No significant difference
	WU, 2023[12]	MDD (n=50)	HC (n=40)	Plasma	ELISA	Higher in MDD
Intestinal fatty acid-binding protein (I-FABP)	ALVAREZ-MON, 2019[9]	MDD (n=22)	HC (n=14)	Serum	ELISA	Higher in MDD
	ALVAREZ-MON, 2021[10]	MDD (n=30)	HC (n=20)	Serum	ELISA	Higher in MDD
	OHLSSON, 2019[11]	MDD (n=13)	HC (n=17)	Plasma	ELISA	No significant difference
Lipopolysaccharide-binding protein (LBP)	ALVAREZ-MON, 2019[9]	MDD (n=22)	HC (n=14)	Serum	ELISA	Higher in MDD
	ALVAREZ-MON, 2021[10]	MDD (n=30)	HC (n=20)	Serum	ELISA	Higher in MDD
IgM and IgA against gram-negative enterobacteria	MAES, 2008[13]	MDD (n=28)	HC (n=23)	Serum	ELISA	Higher in MDD
	MAES, 2012[14]	Depression (n= 112)	HC (n=28)	Serum	ELISA	Higher in depressive disorder
Lactulose/Mannitol ratio (LMR)	CALARGE, 2019[15]	MDD (n=16)	HC (n=14)	Urine	Liquid chromatographic analysis	No significant difference

MDD: major depressive disorder; HC: healthy control; ELISA: enzyme-linked immunosorbent assay; LAL: limulus amebocyte lysate.

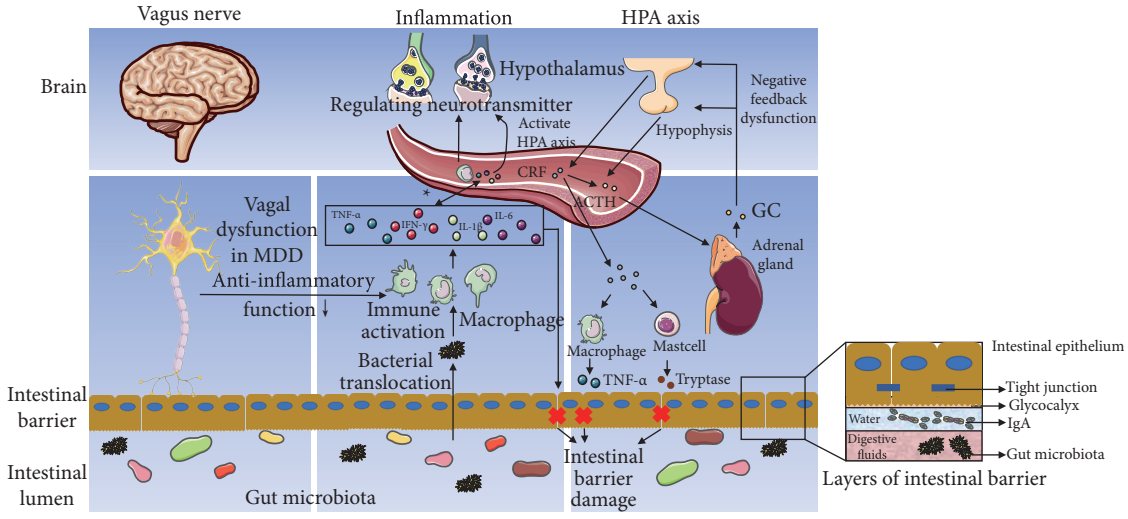

图 1 抑郁症与肠道通透性相互作用机制

Fig 1 The interaction mechanism between major depressive disorder and intestinal permeability

HPA: hypothalamic-pituitary-adrenal; CRF: corticotropin releasing factor; ACTH: adrenocorticotropic hormone; GC: glucocorticoid; IFN-γ: interferon-γ; IL-1β: interleukin-1β; IL-6: interleukin-6; TNF-α: tumor necrosis factor-α. * The bidirectional arrow indicates that the low-grade inflammation of the whole body in patients with depressive disorder may come from the intestinal tract, or may be caused by other factors acting on intestinal barrier. We created the figure by using images provided by Servier Medical Art (http://smart.servier.com). Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/).

3.1　炎症反应机制

抑郁症被视为一种炎症性疾病。现在有大量数据表明, 抑郁症与慢性低度炎症反应、细胞免疫的激活和代偿性抗炎反射系统的激活有关[16-17]。

肠道通透性增加是抑郁症炎症的可能源头之一。抑郁症炎症产生源头可能是应激、饮食、肥胖等因素, 肠道通透性增加、肠道微生物易位也是可能的源头之一[18]。肠道通透性增加会引起肠道微生物及其代谢产物进入血液, 从而激活免疫系统, 活化各种免疫细胞, 导致促炎细胞因子分泌增加, 如肠道细菌的内毒素脂多糖通过CD14激活toll样受体(toll-like receptor, TLR)最终活化单核细胞, 分泌白细胞介素-6(interleukin-6, IL-6)、白细胞介素-2(interleukin-2, IL-2)等促炎症细胞因子[19-20], 造成全身轻度炎症[21]。在脑部, 这些炎症因子通过对神经递质的合成、代谢、再摄取、受体表达等途径产生影响, 造成抑郁症状的出现[22-25]。

肠道既可能是抑郁症患者全身低度炎症的源头, 也是炎症反应的靶点, 即患者体内的炎症也能引起肠道屏障结构的破坏。抑郁症患者与健康对照相比, 血清内各种炎症因子含量更高, 包括干扰素γ(interferon-γ, IFN-γ)、白细胞介素-1β(interleukin-1β, IL-1β)、IL-6和肿瘤坏死因子-α(tumor necrosis factor-α, TNF-α)等[26], 上述炎症因子都对肠道通透性有一定影响。TNF-α能诱导Caco-2细胞模型紧密连接通透性增加, 这一过程与肌球蛋白轻链激酶(myosin light chain kinase, MLCK)表达增加有关, MLCK表达增加会引起肌球蛋白轻链(myosin light chain, MLC)磷酸化增加, 导致紧密连接蛋白分布改变和屏障功能损伤[27]。IFN-γ和IL-1β也可能通过MLCK-MLC通路诱导紧密连接结构损害[28-29], IFN-γ还可诱导上皮细胞胞饮作用内吞分解紧密连接蛋白[30]。IL-6升高后结肠上皮细胞中紧密连接蛋白下调, 可能机制的是IL-6 增加了紧密连接基因启动子处的组蛋白H3K9甲基化[31]。

3.2　迷走神经调节机制

抑郁症患者的迷走神经功能存在一定障碍。有研究表明, 抑郁症患者表现出副交感神经反应性降低[32-33]。这说明抑郁症患者的副交感神经系统功能受到抑制, 这一改变也会影响肠道通透性。有动物实验表明, 刺激迷走神经对肠道屏障有改善作用[34]。抑郁症患者迷走神经障碍会影响肠道紧密连接蛋白的表达。迷走神经可通过其抗炎作用, 降低炎症水平, 改善细胞间紧密连接蛋白的表达。有研究表明[35], 抑郁样行为小鼠模型的迷走神经抑制促炎巨噬细胞作用减弱, 肠道的炎症易感性增加, 其肠道通透性增加。这一作用是通过抑制迷走神经胆碱能抗炎通路(cholinergic anti-inflammatory pathway, CAP)实现的。此通路中, 传出迷走神经与肠神经相互作用, 肠神经释放的乙酰胆碱与巨噬细胞的α7型烟碱型乙酰胆碱受体结合, 抑制肠道肌层的巨噬细胞释放TNF-α, 从而引起紧密连接蛋白分布改变和屏障功能损伤[36-38]。

暂未发现直接证据表明肠道通透性改变可通过迷走神经通路引起抑郁症。肠道菌群产生的神经递质可通过传入迷走神经向中枢发出信号[39], 但这与肠道屏障的直接关系较弱。

3.3　应激机制

大多数抑郁症患者的应激系统异常, 下丘脑-垂体-肾上腺(hypothalamic–pituitary–adrenal, HPA)轴处于紊乱状态。超过40% ~ 60%的抑郁症患者会出现高皮质醇血症[40]或HPA系统的其他紊乱, 如昼夜节律改变[41]等。当HPA轴功能异常, HPA轴慢性过度活跃导致出现糖皮质激素抵抗时, 糖皮质激素的抗炎作用以及对HPA轴的负反馈调节作用减弱[42], 从而导致体内炎症无法受到抑制, 促肾上腺皮质激素释放因子(corticotropin releasing factor, CRF)分泌异常增多[43-45]。

应激系统异常对肠道屏障有损害作用。母婴分离大鼠模型是一种常用的抑郁症动物模型, 有研究表明这种大鼠模型存在HPA轴紊乱, 成年后体内CRF反应性, 这导致了肠上皮细胞旁通道通透性升高[46]。在动物回肠模型中发现, CRF可以诱导肥大细胞释放TNF-α和蛋白酶[47]。TNF-α可以通过增加MLCK-MLC途径增加肠道通透性[48]; 肥大细胞释放的类胰蛋白酶可调节结肠细胞紧密连接旁F-肌动蛋白的重组, 导致肠道通透性增加[49]。

肠道通透性升高可以导致HPA轴激活, 对抑郁症的发生有潜在影响。肠道通透性增高引起肠道细菌易位, 肠道细菌的内毒素及肽聚糖可激活HPA轴[50-51]。同时, 肠道细菌易位引起的炎症反应会导致各种炎症因子IL-1β、IL-6和TNF-α升高, 激活HPA轴[52-53]。HPA轴激活后, 糖皮质激素水平升高, 它能激活色氨酸2,3-双加氧酶, 降低色氨酸水平, 从而抑制中枢神经系统血清素的合成[54]。

4　抗抑郁症药物与肠道通透性改善药物

目前, 多种抗抑郁药物已被允许用于脑-肠互动障碍疾病(disorders of gut–brain interaction, DGBI), 如肠易激综合征[55], 在炎症性肠病中也有抗抑郁药物减轻局部炎症及微观损伤、改善疾病活动指数的证据[56-57], 但目前针对抗抑郁药物改善肠道通透性的直接证据仍然缺乏, 但抗抑郁药物在消除炎症免疫反应、改善迷走神经功能、促进应激系统稳定方面的作用或许能够改善肠道通透

[16] MAES M. Evidence for an immune response in major depression: a review and hypothesis. Prog Neuropsychopharmacol Biol Psychiatry, 1995, 19(1): 11–38. doi: 10.1016/0278-5846(94)00101-m.

[17] MAES M, BERK M, GOEHLER L, *et al*. Depression and sickness behavior are janus-faced responses to shared inflammatory pathways. BMC Med, 2012, 10: 66. doi: 10.1186/1741-7015-10-66.

[18] BERK M, WILLIAMS L J, JACKA F N, *et al*. So depression is an inflammatory disease, but where does the inflammation come from? BMC Med, 2013, 11: 200. doi: 10.1186/1741-7015-11-200.

[19] STEHLE J R, Jr, LENG X, KITZMAN D W, *et al*. Lipopolysaccharide-binding protein, a surrogate marker of microbial translocation, is associated with physical function in healthy older adults. J Gerontol A Biol Sci Med Sci, 2012, 67(11): 1212–1218. doi: 10.1093/gerona/gls178.

[20] MUTA T, TAKESHIGE K. Essential roles of CD14 and lipopolysaccharide-binding protein for activation of toll-like receptor (TLR)2 as well as tlr4 reconstitution of TLR2- and TLR4-activation by distinguishable ligands in lps preparations. Eur J Biochem, 2001, 268(16): 4580–4589. doi: 10.1046/j.1432-1327.2001.02385.x.

[21] JAYASHREE B, BIBIN Y S, PRABHU D, *et al*. Increased circulatory levels of lipopolysaccharide (LPS) and zonulin signify novel biomarkers of proinflammation in patients with type 2 diabetes. Mol Cell Biochem, 2014, 388(1/2): 203–210. doi: 10.1007/s11010-013-1911-4.

[22] TILLEUX S, HERMANS E. Neuroinflammation and regulation of glial glutamate uptake in neurological disorders. J Neurosci Res, 2007, 85(10): 2059–2070. doi: 10.1002/jnr.21325.

[23] SATO T, SUZUKI E, YOKOYAMA M, *et al*. Chronic intraperitoneal injection of interferon-alpha reduces serotonin levels in various regions of rat brain, but does not change levels of serotonin transporter mrna, nitrite or nitrate. Psychiatry Clin Neurosci, 2006, 60(4): 499–506. doi: 10.1111/j.1440-1819.2006.01538.x.

[24] CAPURON L, SCHROECKSNADEL S, FÉART C, *et al*. Chronic low-grade inflammation in elderly persons is associated with altered tryptophan and tyrosine metabolism: role in neuropsychiatric symptoms. Biol Psychiatry, 2011, 70(2): 175–182. doi: 10.1016/j.biopsych.2010.12.006.

[25] TSAO C W, LIN Y S, CHENG J T, *et al*. Interferon-alpha-induced serotonin uptake in jurkat T cells via mitogen-activated protein kinase and transcriptional regulation of the serotonin transporter. J Psychopharmacol, 2008, 22(7): 753–760. doi: 10.1177/0269881107082951.

[26] LAN X, ZHOU Y, WU F, *et al*. The relationship between plasma cytokine levels and antidepressant response in patients with first-episode major depressive disorder. J Affect Disord, 2021, 287: 327–333. doi: 10.1016/j.jad.2021.03.036.

[27] CHEN S W, ZHU J, ZUO S, *et al*. Protective effect of hydrogen sulfide on TNF-α and IFN-γ-induced injury of intestinal epithelial barrier function in caco-2 monolayers. Inflamm Res, 2015, 64(10): 789–797. doi: 10.1007/s00011-015-0862-5.

[28] GUO S, CHEN S, MA J, *et al*. *Escherichia coli* nissle 1917 protects intestinal barrier function by inhibiting nf-κb-mediated activation of the mlck-p-mlc signaling pathway. Mediators Inflamm, 2019, 2019: 5796491. doi: 10.1155/2019/5796491.

[29] Al-SADI R, YE D, DOKLADNY K, *et al*. Mechanism of IL-1beta-induced increase in intestinal epithelial tight junction permeability. J Immunol, 2008, 180(8): 5653–5661. doi: 10.4049/jimmunol.180.8.5653.

[30] BRUEWER M, UTECH M, IVANOV A I, *et al*. Interferon-gamma induces internalization of epithelial tight junction proteins via a macropinocytosis-like process. Faseb J, 2005, 19(8): 923–933. doi: 10.1096/fj.04-3260com.

[31] WILEY J W, ZONG Y, ZHENG G, *et al*. Histone h3k9 methylation regulates chronic stress and IL-6-induced colon epithelial permeability and visceral pain. Neurogastroenterol Motil, 2020, 32(12): e13941. doi: 10.1111/nmo.13941.

[32] GUINJOAN S M, BERNABÓ J L, CARDINALI D P. Cardiovascular tests of autonomic function and sympathetic skin responses in patients with major depression. J Neurol Neurosurg Psychiatry, 1995, 59(3): 299–302. doi: 10.1136/jnnp.59.3.299.

[33] WANG Y, ZHAO X, O'NEIL A, *et al*. Altered cardiac autonomic nervous function in depression. BMC Psychiatry, 2013, 13: 187. doi: 10.1186/1471-244X-13-187.

[34] COSTANTINI T W, BANSAL V, PETERSON C Y, *et al*. Efferent vagal nerve stimulation attenuates gut barrier injury after burn: modulation of intestinal occludin expression. J Trauma, 2010, 68(6): 1349–1354; discussion 1354-1356. doi: 10.1097/TA.0b013e3181dccea0.

[35] GHIA J E, BLENNERHASSETT P, COLLINS S M. Impaired parasympathetic function increases susceptibility to inflammatory bowel disease in a mouse model of depression. J Clin Invest, 2008, 118(6): 2209–2218. doi: 10.1172/JCI32849.

[36] BOROVIKOVA L V, IVANOVA S, ZHANG M, *et al*. Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. Nature, 2000, 405(6785): 458–462. doi: 10.1038/35013070.

[37] CAILOTTO C, GOMEZ-PINILLA P J, COSTES L M, *et al*. Neuro-anatomical evidence indicating indirect modulation of macrophages by vagal efferents in the intestine but not in the spleen. PLoS One, 2014, 9(1): e87785. doi: 10.1371/journal.pone.0087785.

[38] MATTEOLI G, GOMEZ-PINILLA P J, NEMETHOVA A, *et al*. A distinct vagal anti-inflammatory pathway modulates intestinal muscularis resident macrophages independent of the spleen. Gut, 2014, 63(6): 938–948. doi: 10.1136/gutjnl-2013-304676.

[39] PARASHAR A, UDAYABANU M. Gut microbiota regulates key modulators of social behavior. Eur Neuropsychopharmacol, 2016, 26(1): 78–91. doi: 10.1016/j.euroneuro.2015.11.002.

[40] MURPHY B E. Steroids and depression. J Steroid Biochem Mol Biol, 1991, 38(5): 537–559. doi: 10.1016/0960-0760(91)90312-s.

[41] DEUSCHLE M, GOTTHARDT U, SCHWEIGER U, *et al*. With aging in humans the activity of the hypothalamus-pituitary-adrenal system increases and its diurnal amplitude flattens. Life Sci, 1997, 61(22): 2239–2246. doi: 10.1016/s0024-3205(97)00926-0.

[42] SLAVICH G M, IRWIN M R. From stress to inflammation and major

depressive disorder: a social signal transduction theory of depression. Psychol Bull, 2014, 140(3): 774–815. doi: 10.1037/a0035302.

[43] HARTLINE K M, OWENS M J, NEMEROFF C B. Postmortem and cerebrospinal fluid studies of corticotropin-releasing factor in humans. Ann N Y Acad Sci, 1996, 780: 96–105. doi: 10.1111/j.1749-6632.1996.tb15114.x.

[44] BANKI C M, BISSETTE G, ARATO M, *et al*. Csf corticotropin-releasing factor-like immunoreactivity in depression and schizophrenia. Am J Psychiatry, 1987, 144(7): 873–877. doi: 10.1176/ajp.144.7.873.

[45] SIMKIN D R. Microbiome and mental health, specifically as it relates to adolescents. Curr Psychiatry Rep, 2019, 21(9): 93. doi: 10.1007/s11920-019-1075-3.

[46] BARREAU F, CARTIER C, LEVEQUE M, *et al*. Pathways involved in gut mucosal barrier dysfunction induced in adult rats by maternal deprivation: corticotrophin-releasing factor and nerve growth factor interplay. J Physiol, 2007, 580(Pt 1): 347–356. doi: 10.1113/jphysiol.2006.120907.

[47] OVERMAN E L, RIVIER J E, MOESER A J. Crf induces intestinal epithelial barrier injury via the release of mast cell proteases and TNF-α. PLoS One, 2012, 7(6): e39935. doi: 10.1371/journal.pone.0039935.

[48] MA T Y, IWAMOTO G K, HOA N T, *et al*. Tnf-alpha-induced increase in intestinal epithelial tight junction permeability requires NF-kappa B activation. Am J Physiol Gastrointest Liver Physiol, 2004, 286(3): G367–G376. doi: 10.1152/ajpgi.00173.2003.

[49] GEBHARDT T, GERHARD R, BEDOUI S, *et al*. Beta2-adrenoceptor-mediated suppression of human intestinal mast cell functions is caused by disruption of filamentous actin dynamics. Eur J Immunol, 2005, 35(4): 1124–1132. doi: 10.1002/eji.200425869.

[50] VAKHARIA K, HINSON J P. Lipopolysaccharide directly stimulates cortisol secretion by human adrenal cells by a cyclooxygenase-dependent mechanism. Endocrinology, 2005, 146(3): 1398–1402. doi: 10.1210/en.2004-0882.

[51] ARENTSEN T, QIAN Y, GKOTZIS S, *et al*. The bacterial peptidoglycan-sensing molecule Pglyrp2 modulates brain development and behavior. Mol Psychiatry, 2017, 22(2): 257–266. doi: 10.1038/mp.2016.182.

[52] BANKS W A. Blood-brain barrier transport of cytokines: a mechanism for neuropathology. Curr Pharm Des, 2005, 11(8): 973–984. doi: 10.2174/1381612053381684.

[53] TURNBULL A V, RIVIER C. Regulation of the HPA axis by cytokines. Brain Behav Immun, 1995, 9(4): 253–275. doi: 10.1006/brbi.1995.1026.

[54] De JONG R A, NIJMAN H W, BOEZEN H M, *et al*. Serum tryptophan and kynurenine concentrations as parameters for indoleamine 2, 3-dioxygenase activity in patients with endometrial, ovarian, and vulvar cancer. Int J Gynecol Cancer, 2011, 21(7): 1320–1327. doi: 10.1097/IGC.0b013e31822017fb.

[55] MIKOCKA-WALUS A, FORD A C, DROSSMAN D A. Antidepressants in inflammatory bowel disease. Nat Rev Gastroenterol Hepatol, 2020, 17(3): 184–192. doi: 10.1038/s41575-019-0259-y.

[56] VARGHESE A K, VERDÚ E F, BERCIK P, *et al*. Antidepressants attenuate increased susceptibility to colitis in a murine model of depression. Gastroenterology, 2006, 130(6): 1743–1753. doi: 10.1053/j.gastro.2006.02.007.

[57] DAGHAGHZADEH H, NAJI F, AFSHAR H, *et al*. Efficacy of duloxetine add on in treatment of inflammatory bowel disease patients: a double-blind controlled study. J Res Med Sci, 2015, 20(6): 595–601. doi: 10.4103/1735-1995.165969.

[58] WANG L, WANG R, LIU L, *et al*. Effects of ssris on peripheral inflammatory markers in patients with major depressive disorder: a systematic review and meta-analysis. Brain Behav Immun, 2019, 79: 24–38. doi: 10.1016/j.bbi.2019.02.021.

[59] HEUSER I J, SCHWEIGER U, GOTTHARDT U, *et al*. Pituitary-adrenal-system regulation and psychopathology during amitriptyline treatment in elderly depressed patients and normal comparison subjects. Am J Psychiatry, 1996, 153(1): 93–99. doi: 10.1176/ajp.153.1.93.

[60] De BELLIS M D, GOLD P W, GERACIOTI T J, *et al*. Association of fluoxetine treatment with reductions in csf concentrations of corticotropin-releasing hormone and arginine vasopressin in patients with major depression. Am J Psychiatry, 1993, 150(4): 656–657. doi: 10.1176/ajp.150.4.656.

[61] ISING M, KÜNZEL H E, BINDER E B, *et al*. The combined dexamethasone/CRH test as a potential surrogate marker in depression. Prog Neuropsychopharmacol Biol Psychiatry, 2005, 29(6): 1085–1093. doi: 10.1016/j.pnpbp.2005.03.014.

[62] LIANG S, WANG T, HU X, *et al*. Administration of lactobacillus helveticus ns8 improves behavioral, cognitive, and biochemical aberrations caused by chronic restraint stress. Neuroscience, 2015, 310: 561–577. doi: 10.1016/j.neuroscience.2015.09.033.

[63] KAZEMI A, NOORBALA A A, AZAM K, *et al*. Effect of probiotic and prebiotic vs placebo on psychological outcomes in patients with major depressive disorder: a randomized clinical trial. Clin Nutr, 2019, 38(2): 522–528. doi: 10.1016/j.clnu.2018.04.010.

[64] CRISTOFORI F, DARGENIO V N, DARGENIO C, *et al*. Anti-inflammatory and immunomodulatory effects of probiotics in gut inflammation: a door to the body. Front Immunol, 2021, 12: 578386. doi: 10.3389/fimmu.2021.578386.

[65] ARSENEAULT-BRÉARD J, RONDEAU I, GILBERT K, *et al*. Combination of lactobacillus helveticus r0052 and bifidobacterium longum r0175 reduces post-myocardial infarction depression symptoms and restores intestinal permeability in a rat model. Br J Nutr, 2012, 107(12): 1793–1799. doi: 10.1017/S0007114511005137.

(2023 – 01 – 04收稿, 2023 – 02 – 28修回)

编辑 汤 洁