·综　述·

基于抑郁症病理机制探讨芦丁抗抑郁作用

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摘要：芦丁是一种广泛存在于芸香、槐角、红旱莲等植物中的黄酮醇苷类成分，具有抗氧化、抗菌、抗炎、保护心脑血管等药理作用。目前研究已证明，芦丁可通过血脑屏障，作用于大脑改善认知障碍，对氧化应激、脑缺血所致的神经损伤发挥保护作用。抑郁症是一类精神障碍类疾病，主要症状为情绪低落、思维迟缓、认知功能受损等，严重影响着人类健康和生命安全。通过查阅中国知网、PubMed 等数据库，本文将基于抑郁症的病理机制，从芦丁调控单胺类神经递质与脑源性神经营养因子水平，改善下丘脑-垂体-肾上腺轴功能，影响谷氨酸能、GABA 能、胆碱能系统与肠道微生物群、炎症等方面进行文献梳理，探讨其潜在抗抑郁作用的研究进展，为深入研究芦丁治疗抑郁症提供思路与理论基础。

关键词：芦丁；抑郁症；病理机制；研究进展

中图分类号：R285.5　　**文献标志码：**A　　**文章编号：**1007-7693(2022)14-1895-06

DOI: 10.13748/j.cnki.issn1007-7693.2022.14.017

引用本文：王香君，夏小雯，马明钰，等. 基于抑郁症病理机制探讨芦丁抗抑郁作用[J]. 中国现代应用药学，2022，39(14): 1895-1900.

Study on Antidepressant Effect of Rutin Based on Pathological Mechanism of Depression

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ABSTRACT: Rutin is a flavonol glycoside widely found in plants such as ruta, *Sophora japonica*, and red dry lotus. It has antioxidant, antibacterial, anti-inflammatory, cardio-cerebrovascular protection and other pharmacological effects. At present, studies have proved that rutin can act on the brain through the blood-brain barrier, improve cognitive impairment, and play a protective role against nerve injury caused by oxidative stress and cerebral ischemia. Depression is a kind of mental disorder. Its main symptoms are depression, slow thinking and impaired cognitive function, which seriously affect human health and life safety. By consulting databases such as CNKI and PubMed, based on the pathological mechanism of depression, this paper combs the literature from the aspects of rutin regulating the levels of monoamine neurotransmitters and brain-derived neurotrophic factors, improving the function of hypothalamic pituitary adrenal axis, affecting glutamatergic, GABAergic, cholinergic system and intestinal microbiota, inflammation and so on, explores the research progress of potential antidepressant effect of rutin, provides ideas and theoretical basis for in-depth study of rutin in the treatment of depression.

KEYWORDS: rutin; depression; pathological mechanism; research progress

芦丁是一种存在于多种植物(贯叶连翘、金丝桃、荞麦、槐米等)中的天然黄酮醇型多酚，由黄酮醇槲皮素和二糖芸香糖组成[1]。1842 年因首次从芸香(*Ruta graveolens* L.)中提取出[2]，故又名芸香苷，也被称为维生素 P、紫槲皮苷、路丁、络通、紫皮苷等。芦丁为浅黄色或淡绿色针状结晶，分子式为 $C_{27}H_{30}O_{16}$，分子量为 610.51，熔点 176~178 ℃，能溶于吡啶、甲酰、碱液，微溶于乙醇、丙酮和乙酸乙酯，几乎不溶于氯仿、醚、苯、二硫化碳和石油醚[3]。因水溶性差(室温下约为 0.125 $g\cdot L^{-1}$)、生物利用度低，极大地限制了芦丁的使用。因此，芦丁常被加工成钠盐[4]、纳米乳剂[5]等以提高其生物利用度。目前研究发现，芦丁作用于中枢神经系统具有预防神经炎症[6]、促

基金项目：“重大新药创制”国家科技重大专项(2017ZX09301064)；山东省自然科学基金面上项目(ZR2020MH341)；山东省中医药科技项目(2021M121)；济南市“高校 20 条”资助项目(2020GXRC002)

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进神经嵴细胞存活[7]、镇静[8]、抗惊厥[9]、抗抑郁[10]等作用；作用于内分泌系统可以治疗糖尿病[11]、高胆固醇血症[12]，促进甲状腺摄取[13]；作用于心血管系统可以治疗高血压[14]、血液凝固[15]；此外，芦丁还具有利尿、平喘、镇痛、抗肿瘤等药理作用[16]。

抑郁症的临床特征为心境低落、思维迟缓、意志活动减退、认知功能损害，甚至悲观厌世，有自杀行为，严重影响工作、学习、生活和社交[17]。早在 2008 年，世界卫生组织就将其列为全球第三大疾病，并预测到 2030 年，该疾病将排名第一。据全球卫生数据交换平台(GHDx)2019 年的数据显示，全世界约有 2.8 亿人患抑郁症，其中中国的抑郁症患者人数>5 000 万，成人占比约 4.38%[18]，且人数逐年攀升。抑郁症的发生为多种因素协同作用的结果，具体病因尚不明确，目前较为公认的发病假说包括单胺神经递质假说、下丘脑-垂体-肾上腺轴功能异常假说、脑源性神经营养因子假说、肠道菌群假说及 GABA 能假说等[19-20]。关于抑郁症的治疗，目前有中医治疗、西药治疗、物理疗法(如经颅磁刺激及电休克治疗)、心理疗法等，但分别具有起效缓慢、不良反应大、易复发等缺点。因此，从天然植物中开发快速、有效、不良反应小的新型抗抑郁药物成为治疗此类疾病的重点。芦丁可通过血脑屏障[21-22]，通过调控体内单胺类神经递质与脑源性神经营养因子水平，改善下丘脑-垂体-肾上腺轴功能，影响谷氨酸能、GABA 能、胆碱能神经系统等发挥神经保护作用。且芦丁作为一种新型药物，安全、高效、成本低，具有显著的生物活性，在医疗领域具有广泛的应用前景[23]。本文将基于抑郁症病理机制，探讨芦丁抗抑郁的研究进展。

1 芦丁抗抑郁作用探讨

1.1 芦丁调控体内单胺类神经递质水平

1.1.1 芦丁对单胺类神经递质含量的影响 单胺类神经递质主要包括去甲肾上腺素(norepinephrine，NE)、多巴胺(dopamine，DA)和 5-羟色胺(5-hydroxy tryptamine，5-HT)。5-HT、NE、DA 与情绪调控、学习记忆、自主反射、奖赏和生活兴趣等密切相关[24]，其含量的减少或其受体数量和敏感性的改变都将导致抑郁症的发生[25]。Zhang 等[26]使用三甲基锡(trimethyltin，TMT)诱导空间记忆损伤小鼠模型，Morris 水迷宫实验显示，芦丁预处理能有效改善 TMT 诱导的空间学习记忆障碍，且通过小鼠海马中 DA 及其代谢产物高香草酸的含量测定，发现芦丁预处理部分逆转了 TMT 引起的 DA 和高香草酸含量改变。这提示芦丁可通过影响多巴胺系统发挥学习记忆保护作用。Du 等[27]发现芦丁是水醇香茅提取物中的主要抗抑郁成分，可能通过提高中枢神经系统 5-HT 和 DA 水平发挥药理作用。Machado 等[28]也发现芦丁可显著缩短悬尾实验中小鼠摇摆不动时间，使用 5-HT/NE 合成抑制剂对氯苯丙氨酸、酪氨酸羟化酶抑制剂显著逆转了芦丁在悬尾实验中的抗抑郁作用，提示芦丁可通过提高突触间隙中 5-HT、NE、DA 含量发挥抗抑郁作用。

1.1.2 芦丁对单胺氧化酶的抑制作用 单胺氧化酶(monoamine oxidase，MAO)是一种广泛存在于神经元、神经胶质细胞线粒体外膜的酶，含有共价结合的黄素腺嘌呤二核苷酸，参与单胺类神经递质的氧化脱氨过程，其过度表达会加快 5-HT、NE 和 DA 的代谢[29]。早期临床使用的 MAO 抑制剂如苯乙肼、强内心百乐明，由于其肝脏毒性及高血压危害，严重限制了该类药物的发展，新一代可逆的 MAO 抑制剂吗氯贝胺可选择性作用于 MAO-A 达到抗抑郁作用[30]。Oboh 等[31]使用氯化镉连续灌胃 14 d 诱导 Wistar 大鼠认知功能障碍，芦丁可显著逆转镉引起的大鼠皮质和海马中的 MAO 活性升高。Mazumder 等[32]利用计算机辅助药物设计研究 40 种天然小分子物质抑制 MAO-B 的效率，结果发现芦丁显示出最高的 MolDock 得分(比司来吉兰高 2.15 倍)，提示芦丁可能是 MAO-B 的最有效抑制剂。Ahmed 等[33]通过纳米银诱导的神经毒性大鼠模型也证明了芦丁可以有效抑制 MAO-A、MAO-B 的 mRNA 表达并减轻神经毒性。由上述研究推论，芦丁可能通过抑制体内 MAO 发挥抗抑郁作用。

1.2 芦丁改善下丘脑-垂体-肾上腺轴功能亢进

下丘脑-垂体-肾上腺(HPA)轴与多种情绪和认知障碍有关。重度抑郁症患者 HPA 轴过度活动，患者发病与皮质醇含量升高及盐皮质激素受体、糖皮质激素受体活性降低密切相关[34]。机体内皮质醇含量过多时会刺激下丘脑萎缩进而引发焦虑、紧张情绪。Schloms 等[35]发现，芦丁可显著降低肾上腺 H295R 细胞中的皮质醇水平。此外，芦丁可有效阻止抑郁小鼠模型血浆中促肾上腺皮质

激素和血清中皮质醇含量变化，且在旷场实验、强迫游泳实验及蔗糖偏好实验中显示抗抑郁作用[36]。地塞米松是一种人工合成的糖皮质激素，其给药导致海马 CA3 层神经元死亡，进而引起学习和记忆障碍。通过水迷宫试验发现，与地塞米松组相比，芦丁预处理组逃逸潜伏期显著降低，芦丁预处理可有效改变地塞米松导致的 CA3 区形态学损伤[37]。此研究提示，芦丁可能通过影响体内糖皮质激素水平调节 HPA 轴活动，进而参与神经保护，发挥抗抑郁作用。

1.3 芦丁影响体内脑源性神经营养因子(brain-derived neurotrophic factor，BDNF)水平

BDNF 与体内神经发生、神经元成熟、存活和突触可塑性有关[38]。BDNF 与其受体原肌球蛋白受体激酶 B(TrkB)结合激活下游信号通路，包括磷脂酰肌醇 3-激酶(PI3K)/Akt 和丝裂原活化蛋白激酶(MAPK)，发挥其促生长作用[39]。有研究报道，在抑郁症患者、动物模型的海马中均发现 BDNF 水平的下降[40-41]。Liu 等[42]发现，芦丁能增强大鼠海马和皮层中 ERα、ERβ、BDNF、神经生长因子(NGF)、原肌球蛋白受体激酶 A (TrkA)、TrkB 和磷酸环磷酸腺苷反应元件结合蛋白(p-CREB)的水平，并且改善去卵巢大鼠脑缺血/再灌注损伤。Ko 等[43]发现，胡枝子通过调节海马区 BDNF 信号通路(包括 Akt、ERK 和 CREB)改善 $A\beta_{25-35}$ 诱导的记忆损伤，而对其粗提物进行定量分析发现芦丁是胡枝子中含量较高的化合物，提示芦丁可能作为胡枝子的主要成分在上调海马 BDNF 信号通路过程中参与记忆保护作用。

1.4 芦丁对谷氨酸能、GABA 能、胆碱能神经的影响

1.4.1 芦丁对谷氨酸能神经的影响　谷氨酸是大脑中主要的兴奋性神经递质，与其受体 NMDAR、mGluR 等共同参与机体的学习记忆、神经信号传导及突触可塑性[44]。Ferreira 等[45]发现，芦丁对谷氨酸诱导的脑组织毒性具有保护作用，与其提高脑中谷氨酸-天冬氨酸转运体 mRNA 水平、提高谷氨酰胺合成酶活性、增加大脑皮层对谷氨酸摄取有关。Anjomshoa 等[46]发现，在母子隔离应激小鼠模型中，芦丁可显著降低抑郁小鼠在 FST 中的悬浮不动时间，降低海马 NMDA 受体 2A(N-methyl-D-aspartic acid receptor 2A，NR2A)、NMDA 受体 2B(N-methyl-D-aspartic acid receptor 2B，NR2B)亚基的表达，增加海马 CA3 区直径，降低海马锥体神经元的百分比，提示芦丁可能通过谷氨酸能系统中的 NMDA 受体发挥抗抑郁作用。

1.4.2 芦丁对 GABA 能神经的影响　GABA 是一种抑制性神经递质，其与兴奋性神经传递的平衡对大脑发挥正常功能至关重要[47]。研究发现，抑郁症患者血浆、脑脊液和脑组织样本中 GABA 含量降低[48]，GABAR 功能存在缺陷[49]，GABA 合成酶 GAD67 表达下调[50]。针对抑郁症中 GABA 缺乏，目前已有可以增强 $GABA_AR$ γ2 亚基功能的苯二氮䓬类药物，作用于 $GABA_A$ 受体的四氢孕酮制剂等[51]。Yaşar 等[52]研究发现，芦丁是金丝桃提取物中的主要酚类化合物，使用此提取物给药显示出明显的抗抑郁、抗焦虑作用，而苯二氮䓬类拮抗剂氟马西尼可拮抗此现象。由此推测，芦丁可能作用于 GABA 苯二氮䓬位点发挥抗抑郁作用。在精神分裂小鼠实验[53]中发现，芦丁通过上调纹状体、前额叶皮质中 GAD67 表达，防治氯胺酮引起的空间学习记忆障碍，提高其社交能力。且任娜[54]发现，与铝染毒组相比，芦丁高剂量组(200 $mg \cdot kg^{-1}$)大鼠脑组织中的 GABA 含量显著升高。因此，结合上述研究推测，芦丁可通过影响 GABA 能系统发挥抗抑郁作用。

1.4.3 芦丁对胆碱能神经的影响　中枢乙酰胆碱水平降低或乙酰胆碱酯酶 AchE 表达与活性升高均会引发抑郁[55]。Ishola 等[56]发现，在不影响自发活动的情况下，芦丁预处理可有效阻止东莨菪碱诱导的小鼠学习和空间记忆障碍，显著降低小鼠前额叶皮质和海马乙酰胆碱酯酶活性[56]。Qu 等[57]发现，芦丁可显著改善慢性脑灌注不足引起的中枢胆碱功能障碍，提高 Ach 水平并降低 AchE 活性，治疗空间学习和工作记忆缺陷。Oshodi 等[53]也发现，芦丁通过抑制小鼠纹状体、前额叶皮质和海马中的 AchE 活性，减轻氯胺酮诱导的空间工作记忆障碍及社会交往缺陷。

1.5 芦丁调控肠道微生物群与炎症机制

肠道作为机体重要的消化吸收器官，具有丰富的神经系统和肠道微生物群。由细菌、真菌、病毒和原生生物组成的肠道微生物群可通过微生物-肠-脑轴调控机体的神经传导、免疫功能和信号传递[58]。已有研究证明，抑郁症与肠道微生物群的丰富性和多样性改变有关，对比抑郁症患者与健康人肠道微生物群，发现拟杆菌门、厚壁菌门、

变形菌门和放线菌门内不同属丰富度的显著变化[59]。Peng 等[60]发现，芦丁可降低高脂饮食大鼠肠道中的普雷沃氏菌科、脱硫弧菌科、阿克曼菌科等的丰度至正常水平，在一定程度上维持肠道微生物群的平衡。Power 等[61]也通过葡聚糖硫酸钠(dextran sodium sulfate，DSS)诱导的小鼠结肠炎模型证明，芦丁可缓解 DSS 引发的微生物群失调，并减轻结肠损伤。

此外，处在长期应激环境中，交感神经系统和 HPA 轴亢进会引发外周炎症，机体免疫系统虽能快速应答，但最终会导致免疫功能下降，炎性细胞因子损坏中枢神经系统，引起抑郁症。研究表明，抑郁障碍与中枢外周促炎细胞因子如肿瘤坏死因子 α(TNF-α)、白细胞介素(ILs)等的含量升高及神经胶质细胞中 P2X7 受体、TLR4、NLRP3 炎性小体的激活有关[62]。研究发现，芦丁可显著抑制 IL-6[63]、TNF-α 及 IL-1β[64] mRNA 表达，降低 NLRP3 蛋白表达水平[65]。Tian 等[66]也发现，芦丁通过降低 TLR4、MyD88、TRAF6 的基因及蛋白表达水平，上调 NF-κB 抑制蛋白(IκB)基因表达并抑制其磷酸化调控 TLR4-MyD88-TRAF6-NF-κB 通路发挥抗炎作用。上述研究提示，芦丁可能通过调控肠道菌群与促炎细胞因子缓解抑郁障碍。

1.6 其他

线粒体通过调节 Ca^{2+}、活性氧(reactive oxygen species，ROS)水平和细胞凋亡维持细胞稳定性。研究发现，抑郁症患者多出现 ROS 水平升高与钙稳态失调引起的线粒体功能障碍[67]。Li 等[68]发现，芦丁可有效降低大鼠耗氧率，增强 Na^{+}/K^{+}-ATP 酶和 Ca^{2+}-ATP 酶活性以改善线粒体障碍。Wang 等[65]等也发现芦丁可呈剂量依赖性地抑制 ROS 表达，并抑制 ROS 敏感的 NLRP3 炎性小体及其下游蛋白的表达。Arowoogun 等[69]发现铜诱导的大鼠脑中丙二醛、NO 水平提高，超氧化物歧化酶和过氧化氢酶活性降低，神经元发生退化。而芦丁给药可改善神经损伤，调控上述生物标志物水平，通过抗氧化和抗炎途径参与神经保护，提示芦丁可通过防止线粒体功能障碍和抑制氧化应激发挥抗抑郁作用。

2 结论与展望

综合上述研究结果推测，芦丁可通过上调体内 5-HT、DA、NE 等单胺类神经递质及 BDNF 水平，抑制 MAO 表达与 HPA 轴功能，影响谷氨酸能、GABA 能、胆碱能神经系统，改善学习记忆与认知障碍，促进神经保护等发挥抗抑郁作用。虽然目前少有芦丁通过影响肠道微生物群与促炎细胞因子发挥抗抑郁作用的直接研究，但肠道微生物群、细胞因子均可调控神经活性物质如 5-HT、GABA 水平与 HPA 轴等进而影响大脑神经状态。有文献提示，一些免疫性疾病如系统性红斑狼疮会引起抑郁障碍[70]，促炎细胞因子可能是情感障碍类疾病的基础，因此，对既可以抗炎又可以保护神经系统的芦丁展开研究非常重要。

国内外研究已证明了芦丁治疗抑郁症的巨大潜力，但目前大多研究集中在基本药理药效，其深入机制尚待进一步确认。另外上述文献实验研究结果是基于啮齿类疾病动物模型，虽然其与人类有相似性，但仍然存在种属差别，结果可能存在假阳性或者假阴性。且芦丁本身生物利用度低，虽已开发出钠盐、纳米乳剂等剂型，但缺少体内外研究及安全性/毒性评估，极大地限制了它的应用。后期应深入研究芦丁抗抑郁的作用机制，确定主要靶点，其次结合多学科开发新型递药系统，提高芦丁生物利用度，为开发新药、临床治疗抑郁症提供最佳选择。

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收稿日期：2021-11-25
(本文责编：蔡珊珊)