黄酮类化合物抗抑郁作用研究进展

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摘要 抑郁症是现代社会最常见的一种心理疾病，严重影响身心健康。当前，治疗抑郁症的药物长期使用可能导致多种不良反应，迫切需要寻找新的途径来改善抑郁症状，减少副作用。黄酮类化合物普遍存在于植物中，对人体健康具有积极影响，已有多项研究证实其具有显著的抗抑郁作用。本文从神经递质、神经营养、炎症反应、氧化应激、下丘脑-垂体-肾上腺轴、微生物-肠道-大脑轴 6 个方面综述抑郁症的形成机制。针对发病途径阐明黄酮类化合物改善认知和情绪，发挥抗抑郁作用的主要成分及作用机制，为膳食预防、改善抑郁症相关功能食品的开发提供理论依据。

关键词 黄酮类化合物；抑郁症；机制
文章编号 1009-7848(2024)12-0464-15 **DOI**：10.16429/j.1009-7848.2024.12.041

抑郁症是一种常见的精神疾病，表现为长期情绪低落、烦躁、注意力下降等，是社会、心理和生物因素综合作用的结果。据估计全球有 5%的成年人患有抑郁症，且女性中的发病率比男性高 50%左右[1]。在世界范围，超过 10%的孕妇和刚分娩的妇女患有抑郁症[2]，是导致自杀的重要诱因。世界卫生组织曾多次探讨精神卫生议题，并于 2019 年批准将《全面心理健康行动计划》延长至 2030 年，以推动和改善全球精神卫生状况。治疗抑郁症的方法包括心理治疗和药物治疗或两者相结合。临床上常用的抗抑郁药物有多种类型，如单胺氧化酶抑制剂、选择性 5-羟色胺再摄取抑制剂等，它们通过影响大脑中的神经递质来改善个体情绪和行为。然而这些抗抑郁药物长期使用可能会产生一系列副作用，如头痛、恶心、便秘和性功能障碍等[3]。越来越多的研究表明植物中的多种天然有机化合物，如多酚[4]、多糖[5]、生物碱[6]、植物激素[7]等能缓解抑郁症状的同时减少副作用，对于抑郁患者生活质量的提升具有十分重要的意义。

收稿日期：2023-12-11
基金项目：湖南省农业科技创新资金项目(2022CX02)；长沙市自然科学基金项目(kq2202334)；湖南省创新平台与人才计划项目(2019TP2066)
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黄酮类化合物是一类多酚类次生代谢产物，广泛存在于植物和饮食中，具有调节激素水平[8]、抗炎[9]、抗氧化[10]、抑制肿瘤[11]等多种生物活性，与人体健康密切相关。多项动物实验揭示黄酮类化合物可以降低神经元损伤，减少神经炎症发生，以及提高认知和记忆力[12-13]，对大脑产生深刻影响，具有改善精神类疾病的作用[14]。黄酮类化合物能穿过血脑屏障，与多种神经传递系统相互作用，从而激活大脑中的信号通路，参与抑郁症的生理病理[15]。本文从抑郁症的发病机制角度出发，阐述抑郁症的形成及临床治疗措施研究进展，论述黄酮类化合物的抗抑郁作用，为抑郁症的改善与黄酮类化合物对人类健康的促进作用提供理论支撑。

1 抑郁症的发病机制

虽然抑郁症的确切病因和病理生理仍不明确，但现代抑郁症发展的理论认为抑郁症的发生主要涉及 6 个方面：神经递质通路失衡、脑功能障碍(神经发生、神经元可塑性改变和脑源性神经营养因子代谢紊乱)、炎症反应、氧化和氮化应激增加、下丘脑-垂体-肾上腺轴和微生物-肠道-大脑轴功能障碍[16-18]。

1.1 神经递质说

单胺类递质作为情绪的神经基础假说于 20

世纪 50 年代首次提出[19],认为抑郁症的主要生化原因是单胺类神经递质代谢紊乱,涉及 5-羟色胺(5-Hydroxytryptamine, 5-HT)、去甲肾上腺素(Norepinephrine,NE)和多巴胺(Dopamine,DA)信号传导[20-21],这些神经递质在调节抗抑郁药物诱导的行为活动中起着重要作用。5-HT 又名血清素,主要由肠嗜铬细胞合成[22],能产生愉悦情绪,5-HT 的合成、释放、转运和再摄取的紊乱会导致抑郁症[23]。NE 系统是重要的弥散性神经递质系统,能调节个体的动机、专注力等[24],反复的情绪刺激促进大脑中 NE 的释放, 它在一定程度上导致了焦虑和相关的重度抑郁症[25]。DA 与快乐、兴奋等情绪相关,DA 系统功能缺陷可导致海马突触可塑性受损,从而导致认知功能受损[26]。抑郁症最主要的特征是缺乏快乐的情绪, 这与神经递质通路失衡密切相关。单胺类神经递质是调节人体情绪的主要神经基础, 也是目前临床应用的不同类型抗抑郁药的基本机制, 一些药物通过抑制 5-HT 的摄取而发挥作用[27],从而改善情绪,如丙咪嗪、氟西汀等。

1.2　神经营养假说

神经营养假说认为,神经元连接越多,代表其周围神经营养因子的浓度就越高, 因此存活的机会就越大[28]。脑源性神经营养因子(Brain-derived neurotrophic factor, BDNF)是神经营养家族中重要的一员,对神经元集群的增长、发育、存活及突触的可塑性起重要作用,BDNF 的不足和代谢紊乱是导致抑郁症发病的重要因素。BDNF 在抑郁症发病机制中的功能是异质的, 取决于大脑区域和单个回路。BDNF 的抗抑郁作用机制与原肌球蛋白受体激酶 B (Tropomyosin receptor kinase B, TrkB) 受体激活、*N*-甲基-*D*-天冬氨酸受体途径、诱导增加抗氧化酶的表达水平有关[29]。BDNF 表达水平变化及其受体所介导的信号通路为明确抑郁症的机制提供了较好的解释。有研究表明,抑郁症患者边缘系统部分脑区 BDNF 水平明显低于正常人[30],且在动物实验中,慢性应激和促抑郁条件会导致海马部位 BDNF 表达减少、神经元凋亡增加和再生能力降低, 脑内其它部位的 BDNF 表达也减少[31]。由此可见,在神经营养假说来讲,BDNF 表达减少与抑郁症的发生有着密切的关联,这也解释了抑郁症与神经元发生之间的关系。有报道沃替西汀(一种 5-HT 转运体抑制剂)治疗在 4 周内服用 5~15 mg 可增加重度抑郁症患者血浆 BDNF 水平[32]。

1.3　神经炎症反应

抑郁情绪可引发一系列免疫炎症反应通路的激活, 而炎症反应导致的神经元损伤是抑郁症发病的重要因素之一,特征包括炎症介质的产生,小胶质细胞和星形胶质细胞的激活, 以及先天免疫细胞和适应性免疫细胞在炎症部位的聚集[33]。一方面, 炎症因子过度分泌会对相关神经产生毒性作用,进而影响神经元表达,降低神经的兴奋性,研究表明血清中的促炎细胞因子水平与与抑郁症的病理生理密切相关[34-35]。应激源通过激活关键炎症通路,如调节核因子 κB(Nuclear factor kappa-B,NF-κB)通路,从而促进血液和大脑中促炎细胞因子表达水平增加[36-37],如白细胞介素-1β (Interleukin-1β, IL-1β)、肿瘤坏死因子 α(Tumor necrosis factor α, TNF-α)和白细胞介素-6 (Interleukin-6, IL-6)等。对健康个体的研究结果也证实,炎症性细胞因子,特别是 TNF-α 和 IL-6,可诱导抑郁情绪、焦虑和记忆和注意力受损。另一方面, 炎症介质能够穿过血脑屏障并激活小胶质细胞,小胶质细胞是神经元功能发挥的关键介质,为神经元提供营养支持和修复的作用。在炎症和应激条件下, 活化后的小胶质细胞逐渐从向神经元功能障碍转变,抑制神经发生[38-39]。此外,与炎症相关的另一种细胞是星形胶质细胞, 星形胶质细胞与突触末梢保持密切联系, 并改变神经元的兴奋性、代谢和神经传递,它一旦被激活,就会发生形态变化, 成为能够分泌促炎细胞因子的肥大细胞[40]。因此,通过探究应激触发的炎症信号与相关的神经元功能、可塑性和行为改变可为抑郁症治疗提供新的思路, 目前有研究已确定小胶质细胞是神经元功能的关键介质, 并发现了靶向治疗重度抑郁症的途径[41]。

1.4　氧化应激

氧化应激通过自由基、非自由基分子、活性氧(Reactive oxygen species, ROS)和活性氮在抑郁症的病理生理中发挥重要作用。大脑更容易受到氧化应激的影响, 因为它的耗氧量、脂质含量更

高,而抗氧化防御能力更弱[42]。 ROS 生成的增加和抗氧化防御的衰竭是导致大脑结构改变的重要原因[43],ROS 会使氧化还原系统相关基因表达发生改变,如超氧化物歧化酶 (Superoxide dismutase, SOD) 、过氧化氢酶(Hydrogen peroxidase, CAT) 等的失衡。慢性不可预知性应激(Chronic unpredictable mild stress, CUMS) 抑郁小鼠模型的体内研究结果表明, 抑郁症的形成与大脑中单胺氧化酶(Monoamine oxidase, MAO)和脂质过氧化终产物丙二醛(Malondialdehyde, MDA)水平升高以及谷胱甘肽水平降低、谷胱甘肽还原酶和谷胱甘肽过氧化物酶 (Glutathione peroxidase, GSH-PX)活性的降低密切相关[44-45]。值得注意的是, 氧化损伤过程中释放或暴露的特定分子可能引发大脑中的先天免疫反应并引发神经炎症[43],脑部氧化应激和神经炎症过程均是抑郁症发展的潜在因素。然而,据报道部分抗抑郁药物会诱导氧化应激 [46-47], 因此寻找天然类化合物替代对抑郁症的改善具有重要生理意义。

1.5 下丘脑-垂体-肾上腺轴功能障碍

下丘脑-垂体-肾上腺 (The hypothalamic-pituitary-adrenal, HPA) 轴是控制和调节应激反应的主要神经-内分泌系统, 可能涉及多种机制,包括免疫、内分泌和神经通路。研究发现,抑郁症患者中很大一部分表现出 HPA 轴的过度激活,皮质醇、促肾上腺皮质激素 (Adrenocorticotropic hormone, ACTH) 和促肾上腺皮质激素释放激素(Corticotropin releasing hormone, CRH)的水平升高[48-49],这些激素调节许多过程,如发育、代谢、行为和免疫功能等。HPA 轴由下丘脑室旁核、垂体额叶和肾上腺皮质组成, 始于下丘脑的神经分泌细胞,释放 CRH。CRH 刺激垂体前叶 ACTH 的释放,而 ACTH 被释放到血液中到达肾上腺皮质, 在那里它刺激糖皮质激素的合成和释放, 主要是皮质醇,皮质醇能够通过调节 HPA 轴活性的负反馈机制调节自身的合成和释放[50-51],在慢性应激期间,这些负反馈回路可能会被消除,导致 HPA 轴持续被激活[52],表现为 HPA 轴功能障碍。尽管有很强的临床前和临床数据阐明了应激相关精神障碍(如重度抑郁症)中 HPA 轴的失调,但目前尚未批准任何靶向 HPA 轴的药物治疗抑郁症[53]。

1.6 微生物-肠道-大脑轴功能障碍

微生物-肠道-大脑 (Microbiota-gut-brain, MGB)轴是一个综合的生理的概念,包括传入和传出神经、内分泌和免疫中枢神经系统和胃肠道系统之间的信号。研究表明,肠道菌群组成与宿主生理调节的变化相关, 胃肠道中的细菌, 包括共生菌、益生菌和致病菌的改变会影响大脑的功能。抑郁症患者体内肠道菌群 β-多样性存在显著差异,致病菌属(如脱硫弧菌和埃希氏杆菌属/志贺氏杆菌)呈现增加趋势,以及有益细菌属(如双歧杆菌和粪杆菌)呈减少趋势[54]。MGB 轴通过免疫系统激活(如炎症细胞因子和趋化因子)、神经递质产生(如 5-HT)及其代谢物(如短链脂肪酸和关键膳食氨基酸)发挥作用[55]。肠道菌群能够通过产生代谢物刺激中枢神经系统和肠道来影响身体神经递质水平[56-57]。例如,短链脂肪酸(Short-chain fatty acids, SCFAs)是肠道菌群的主要代谢产物,可能通过穿过血脑屏障直接影响大脑, 导致血脑屏障完整性、神经传递、BDNF 和 5-HT 生物合成的改变[58-59]。此外,肠道菌群还能产生一系列其它的神经活性和免疫调节化合物,包括 DA[60],γ-氨基丁酸(γ-Aminobutyric acid, GABA)[61],组胺[62]和乙酰胆碱[63]等,它们可以通过不同的途径影响中枢神经系统,包括免疫系统、肠脑神经系统和全身循环[64],因此肠道菌群可以影响情绪中枢神经系统的活动。利用肠道菌群和 MGB 轴的作用机制可以在预防和缓解抑郁症中发挥重要作用, 针对抑郁症患者肠道菌群发生的特征变化,采用益生菌、益生元干预治疗显示出较好的结果[65-66]。

2 黄酮类化合物对抑郁症的改善作用及其机制

黄酮类化合物对抑郁症有显著的改善作用,多项研究评估了黄酮类化合物抗抑郁的潜力。Sawan 等[67]对 2 788 名参与者的 36 项临床试验进行了系统分析, 结果显示黄酮类化合物对抑郁症状的影响具有统计学意义, 表明摄入更多的黄酮类化合物可能会改善抑郁症症状;Chang 等[68]评估了为期 10 年共 10 752 例抑郁症病例患者的膳食黄酮类化合物摄入量与抑郁风险的相关性及程度, 结果显示摄入富含黄酮类化合物的食物与抑

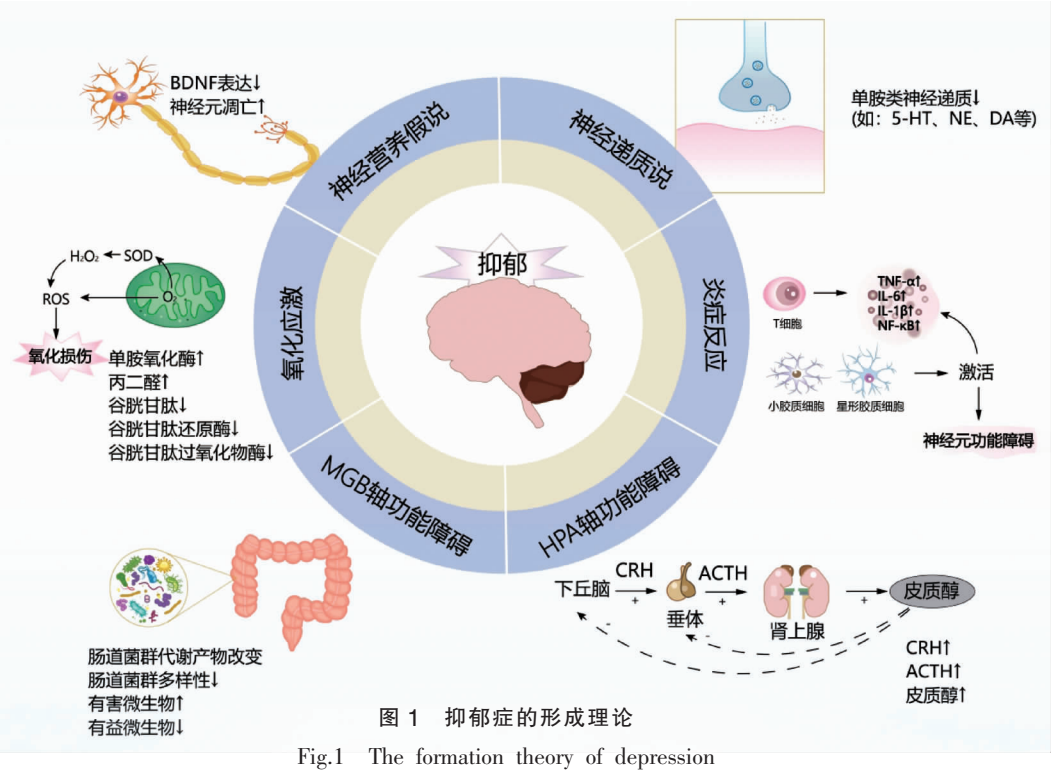

图 1　抑郁症的形成理论

Fig.1　The formation theory of depression

郁风险显著降低有关，尤其是在老年女性的分析中，除黄烷-3-醇外，所有黄酮类化合物亚类的摄入增加与抑郁风险显著降低相关，且黄酮类和原花青素显示出最强的相关性。含有多个羟基结构的黄酮类化合物大多被报道具有抗抑郁性能[69]，如芹菜素(4′,5,7 -三羟基黄酮)、槲皮素(3,3′,4′,5,7 -五羟基黄酮)、漆黄素(3,3′,4′,7 -四羟基黄酮)和木犀草素(3′,4′,5,7 -四羟基黄酮)，对这 4 种黄酮类化合物进行构效关系的研究表明：A 环上第 5 或第 7 位存在羟基是具有抗抑郁作用的黄酮类化合物的共同特征；另一个结构特征是 C-糖苷的存在，如淫羊藿苷、芦丁和牡荆素。

黄酮类化合物有广泛的抗抑郁作用，表 1 列举了黄酮类化合物发挥抗抑郁作用的成分及其机制，为预防和改善抑郁症和相关功能食品的开发提供理论依据。

2.1　提高大脑中的神经递质水平

黄酮类化合物能够穿过血脑屏障到达中枢神经系统[108]，与神经元受体和激酶信号通路相互作用，对神经元激活、通信和调节脑突触可塑性有重要意义[109]，其发挥抗抑郁作用的机制主要是提高神经递质(包括 5-HT、NE 和 DA)水平、抑制 MAO 活性。

Wang 等[110]综述了黄酮类化合物对 GABA、5-HT、DA 等神经递质的调节作用，阐明了其与抑郁情绪的改善具有极强的相关性。Rodríguez-Landa 等[111]综述了白杨素的抗抑郁作用，其发挥抗抑郁作用的机制是通过与特定的神经递质系统相互作用，包括神经递质系统(5-HT、NE 和 DA)、神经营养因子（如 BDNF 和神经生长因子）的激活[112]。Chen 等[113]综述了槲皮素抗抑郁作用研究进展，表明槲皮素不仅能直接提高 5-HT 的水平和降低其代谢产物的水平，还可以抑制 MAO 对 5-HT 的代谢，从而防止体内 5-HT 水平的下降，即通过调节单胺能神经系统的功能来发挥抗抑郁作用。Swati 等[114]研究了番石榴叶黄酮提取物的抗抑郁活性及其对神经递质系统的影响，结果表明，该提取物通过降低海马、大脑皮层、小脑和大脑干区域的 5-HT、NE 和 DA 的水平，改善抑郁症状。Fang 等[105]研究探讨了紫色花椰菜的花青素对 CUMS 小鼠抑郁模型的影响及其机制，结果显示给药小鼠抑郁行为发生明显改变，其作用机制归因于通过抑制 MAO 活性从而增加单胺类神经递质含量，增加海马 BDNF 的表达。

表1 黄酮类化合物发挥抗抑郁作用的成分及其机制

Table 1 The components and mechanisms of flavonoids exerting antidepressant effects

分类	代表物质	来源	发挥抗抑郁作用机制	试验模型	参考文献
黄酮类	芹菜素	柑橘	提高了5-HT水平，同时调节HPA轴活性和单胺类神经递质水平;恢复细胞抗氧化水平,改善神经炎症	慢性轻度应激(CMS)小鼠模型;链脲佐菌素介导	[70], [71]
	木犀草素	金银花、菊花等	显著增加了抑郁小鼠海马和前额叶皮层的神经递质 (5-HT和NE)的含量,改善神经炎症和突触可塑性损伤	噪声诱导的小鼠模型	[72]
	白杨素(5,7-二羟基黄酮)	蜂蜜、蜂胶等	提高了5-HT水平、对HPA轴的调节作用、改善神经炎症;抑制皮质和海马小胶质细胞活化	CUMS小鼠模型;CMS小鼠模型	[73], [74]
	黄芩苷	黄芩	上调部分糖酵解和三羧酸循环相关酶编码基因的表达，改善线粒体功能,提高脑内ATP水平,恢复HPA轴功能	CUMS小鼠模型;慢性皮质酮(Corticosterone，CORT)诱导小鼠	[75], [76]
黄酮醇类	槲皮素	广泛分布于植物中	减少氧化应激、抑制炎症和调节多种神经递质(NE、DA和5-HT)	CUMS大鼠模型	[77]
	芦丁	黄花菜	降低脱硫弧菌属产生的脂多糖水平,从而降低抑郁小鼠肠道、血液和大脑中炎症因子的含量	CUMS小鼠模型	[78]
	杨梅素	杨梅树皮和树叶	增加BDNF的表达、提高应激小鼠海马谷胱甘肽过氧化物的活性	CMS小鼠模型	[79], [80]
	桑色素(2′,3,4′,5,7-五羟基黄酮)	番石榴、洋葱等	提高大脑皮层和海马体神经递质水平，提高还原型谷胱甘肽水平和降低MDA水平,显著降低神经炎症标记物	CUMS大鼠模型	[81]
	异鼠李素、槲皮素、山柰酚	沙棘	缓解神经营养因子、神经递质和应激相关激素的紊乱水平,抑制肠道和大脑的炎症因子表达和保护肠道环境，改变肠道菌群多样性	CUMS小鼠模型	[82]
	3,3′,4′,7-四羟基黄酮	草莓	抗炎和神经保护作用	CMS小鼠模型	[83]
	水飞蓟素	水飞蓟	减轻单胺能、神经发生(提高5-HT、NE和BDNF水平)、减轻炎性细胞因子系统和氧化应激	CUMS小鼠模型	[84]

（续表 1）

分类	代表物质	来源	发挥抗抑郁作用机制	试验模型	参考文献
黄烷醇类	儿茶素	绿茶	减轻氧化应激；对 HPA 轴的调节作用	CUMS 大鼠模型；CORT 诱导大鼠	[85], [86]
	表儿茶素	可可	调节犬尿氨酸氨基转移酶水平	CMS 小鼠模型	[87]
	茶黄素	红茶	抑制小胶质细胞中促炎细胞因子的产生、减轻大脑炎症而发挥神经保护作用	LPS 诱导小鼠模型	[88]
	表没食子儿茶素没食子酸酯	绿茶叶	恢复 HPA 活性，改善 GABA 的传递；提高海马的 5-HT 水平和神经保护；对全身 IL-1β 的抑制作用、海马中 BDNF mRNA 水平的增加	CUMS 小鼠模型	[89], [90]
黄烷酮类	柚皮素	柑橘	可增加海马 5-HT、NE 和糖皮质激素受体水平，并降低血清 CORT 水平；调节氧化炎症损伤和核因子(NF)-κB/BDNF 表达	CUMS 小鼠模型；缺氧应激诱导的小鼠	[91]-[93]
	橙皮苷	柑橘皮	抑制小胶质细胞活化和炎症；减弱 HMGB1 / RAGE /NF-κB 信号通路和 BDNF / TrkB 通路来降低炎性细胞因子水平；提高 BDNF 水平和减少氧化应激生物标志物	CUMS 大鼠模型；利血平诱导的雄性大鼠	[94]-[96]
	松属素(5,7-二羟基黄烷酮)	蜂蜜、蜂胶	改善神经炎症和细胞凋亡、抑制海马中的小胶质细胞活化	CUMS 小鼠模型	[97], [98]
	圣草酚	花生壳提取物	对神经递质、神经营养因子、应激激素、炎症因子和肠道菌群的全面调节	CUMS 小鼠模型	[99]
异黄酮类	大豆异黄酮	大豆	重塑肠道微生物群的结构、增加单胺类神经递质水平；抑制神经炎症、介导色氨酸代谢和促进突触可塑性	CUMS 大鼠模型	[100], [101]
	染料木素	大豆	显著增高单胺水平和 BDNF 表达，降低血清皮质醇水平；抑制 MAO 活性	CMS 大鼠模型	[102], [103]
	葛根素	葛根	调节肠道菌群组成、调节肠道免疫，缓解肠道炎症，保护肠道黏膜	CUMS 大鼠模型	[104]
花色素类	花青素	紫色花椰菜、黑米	抑制 MAO 活性而增加单胺类神经递质含量，增加海马 BDNF 的表达；调节肠道菌群稳态	CUMS 小鼠模型	[105], [106]
	矢车菊素	黑米、黑豆	减少海马炎症、改善神经营养功能和减轻谷氨酸诱导的兴奋毒性	LPS 诱导小鼠模型	[107]

2.2 改善神经炎症

天然黄酮类化合物具有下调促炎因子的表达、加速抗炎因子的分泌、抑制星形胶质细胞增生、抑制小胶质细胞的活化和极化等利于改善炎症作用[33]。在抑郁症中主要机制包括 NF-κB 通路、toll 样受体通路、丝裂原活化蛋白激酶通路、核因子红细胞 2 相关因子 2 (Nuclear factor erythroid 2-related factor 2, Nrf2)途径、TrkB、诱导型一氧化氮合酶 (Inducible nitric oxide synthase, iNOS)、环氧合酶 2 (Cyclooxygenase 2, COX2)和 NOD 样受体蛋白 3 (NOD-like receptor thermal protein domain associated protein 3, NLRP3)炎性体等相关炎症表达改善神经炎症[71,74,115-116]。

Xie 等[95]研究表明 CUMS 大鼠口服 100 mg/kg/d 的橙皮苷具有抗抑郁作用, 能显著降低 CMS 诱导大鼠大脑前额叶皮层和小胶质细胞中 NLRP3 炎性体的表达活化, 有效降低了活化的小胶质细胞的数量和促炎细胞因子 (IL-1β、TNF-α、IL-6)水平。Wang 等[97]研究了每日 10 mg/kg 松属素,连续灌胃 3 周能够有效改善 CUMS 小鼠神经炎症和细胞凋亡来减轻其抑郁行为, 其机制是松属素能抑制 CUMS 小鼠海马细胞凋亡, 调节炎症因子表达(抑制 TNF-α 和 IL-1β,增加 TGF-β 和 IL-10), 且通过激活 Nrf2/HO-1 信号通路,抑制 NF-κB 的磷酸化。Li 等[74]研究了腹腔注射 20 mg/kg 的白杨素持续 28 d 的 CUMS 小鼠,结果表明白杨素靶向抑制 Fyn 可减轻 CUMS 诱导的神经炎症和抑郁样行为, 其机制是抑制 NF-κB 途径介导的 iNOS、COX2 和 NLRP3 炎症小体的表达从而靶向抑制 Fyn,首次揭示了 Fyn 是白杨素抗神经炎症和神经炎症相关抑郁的直接靶点。Soroush 等[71]研究了芹菜素对链脲佐菌素介导的抑郁症的影响, 结果表明,20 mg/kg 的芹菜素对试验动物无毒性且可以调节抑郁动物的行为功能障碍、炎症标志物和恢复细胞抗氧化水平, 是治疗抑郁症的一种合适的候选药物。

2.3 降低氧化应激

黄酮类化合物作为天然抗氧化剂, 具有降低神经系统氧化应激的潜力, 能够调节抑郁症的脑部氧化应激状态, 减少与氧化应激相关的认知能力下降而表现出抗抑郁活性。Lucian 等[117]对黄酮类化合物的抗抑郁活性及其与氧化应激关系进行了综述, 其中发挥抗抑郁作用的黄酮类化合物包括橙皮苷、白杨素、柚皮素、落新妇苷、淫羊藿苷、7,8-二羟基黄酮、金丝桃苷、黄芩苷、3,5,6,7,8,3′,4′-七甲氧基黄酮等。Thakare 等[84]研究表明对 CUMS 小鼠持续给药 21 d 水飞蓟素(100 mg/kg 和 200 mg/kg)有效地抑制了脂质过氧化过程,减少了 MDA 的形成, 提高了海马和大脑皮层中 SOD 和 CAT 的活性,通过中和或清除过量自由基的形成, 恢复大脑皮层和海马的抗氧化防御系统。Ortmann 等[118]研究了给予慢性应激(Chronic mild stress, CMS)诱导大鼠银伞树叶黄酮提取物(主要成分为异红草素)50 mg/kg 持续 42 d,能显著改善应激大鼠的抑郁行为,并逆转了 CMS 大鼠脑内过氧化物酶活性增加的情况, 表明该黄酮提取物对应激和抑郁相关的氧化损伤具有显著的保护作用。Ma 等[79]研究表明给药杨梅素 50 mg/kg 持续 21 d 能显著改善小鼠的抑郁行为, 提高了应激小鼠海马 GSP-PX 活性, 其抗抑郁机制可能归因于杨梅素介导的海马抗氧化应激。

2.4 调控 HPA 轴

黄酮类化合物能有效改善应激诱导的 HPA 轴功能障碍,调控与 HPA 轴相关的激素,从而改善抑郁行为。Zhang 等[76]研究了黄芩苷对 CORT 诱导的抑郁小鼠的抗抑郁作用, 发现黄芩苷能显著减轻 CORT 诱导的抑郁症状, 其机制体现在黄芩苷可以降低海马糖皮质激素受体(Glucocorticoid receptor, GR)中 pSer203 和 pSer211 的水平,逆转了异常的 GR 核易位,恢复 HPA 轴的负反馈。Liu 等[119]研究表明天然黄酮类化合物羟基红花黄色素 A 能够有效抑制 CUMS 大鼠的 ACTH、CRH 和 CORT 水平升高, 表明羟基红花黄色素 A 显著改善抑郁大鼠 HPA 轴的持续激活, 可能通过调控 HPA 轴来改善抑郁行为。Kawabata 等[120]研究表明槲皮素可显著抑制束缚水浸应激诱导大鼠血浆 CORT 和 ACTH 水平升高以及下丘脑区促肾上腺皮质激素释放因子 mRNA 的表达,从而减弱 HPA 轴的激活。Bongjun 等[121]研究表明在 20 mg/kg 的剂量下可以减轻大鼠的抑郁行为, 降低血浆 ACTH 和 CORT 水平的升高, 使大鼠海马和前额皮质的 5-HT 和 NE 水平正常化。

2.5 改善 MGB 轴障碍

黄酮类化合物通过调节肠道菌群产生代谢物来影响中枢神经的发育和免疫屏障[122],SCFAs 和次级胆汁酸(如去氧胆酸,由腔内细菌作用于分泌的初级胆汁酸产生) 已被证明会影响肠道 5-HT 的产生[123],它们可以穿过血脑屏障,调节大脑发育和行为[124]。此外,黄酮类化合物还可以通过调节肠道中与炎症相关的细胞和肠道菌群的组成, 具有明显的抗炎特性[125]。虽然关于 MGB 轴的研究还处于相对初级阶段, 具体作用途径机制尚未被完全阐明, 但黄酮类化合物对肠道菌群的调节确实显示出抗抑郁作用。

黄酮类化合物可通过调节肠道菌群的种类和丰度改善抑郁症, Song 等[126]探讨了葛根素的抗抑郁作用与肠道菌群的变化关系, 发现葛根素(100 mg/kg) 治疗可减轻 CUMS 诱导的小鼠抑郁样行为, 在该研究中, 慢性应激导致病理性微生物菌群,其主要特征在于病原细菌(变形杆菌属、柔螺菌属、脱硫弧菌属)的丰度增加和有益细菌(厚壁菌属、芽孢杆菌属、乳杆菌属)的丰度降低,而葛根素治疗逆转了这些变化, 证明葛根素对抑郁小鼠的肠道菌群调控有积极意义。Liu 等[78]对黄花菜水提物和芦丁的抗抑郁活性进行了研究, 结果表明芦丁具有显著的抗抑郁活性, 是主要活性成分之一, 且两者均增加了抑郁小鼠肠道菌群的多样性和丰富度, 调节了拟杆菌属和脱硫弧菌属等特定肠道微生物。Wang 等[101]以 CUMS 诱导的抑郁大鼠为模型, 研究大豆异黄酮减轻抑郁行为中的作用机制, 结果显示特定剂量的大豆异黄酮能显著调节肠道菌群的组成和增加单胺类神经递质水平,主要表现为抑郁小鼠体内厚壁菌门与拟杆菌门的比例恢复正常、丹毒科和双歧杆菌科的相对丰度降低。也就是说,大豆异黄酮可能通过重塑肠道菌群的结构来影响 CUMS 大鼠的单胺类神经递质,从而改善抑郁行为。

3 结语

近年来, 抑郁症由于其极高的自杀率越来越受到人们的关注, 目前使用的大部分药物都存在嗜睡、过度镇静;胃肠道症状,如恶心、腹泻;代谢问题,如容易肥胖,便秘等副作用。因此,寻找天然安全的活性成分替代传统药物预防和改善抑郁症将成为营养与健康研究的热点。存在于植物中的多种天然黄酮类化合物与人体各项生理健康息息相关,并且能从日常膳食中直接摄取。国内外许多研究表明黄酮类化合物具有良好的抗抑郁效果,其具体机制可以从以上 5 个方面解释。因此,黄酮类化合物作为一种安全、有效的替代天然物质,可纳入未来的抑郁症干预计划, 形成有效预防与改善抑郁症的膳食策略。然而,值得注意的是目前许多研究仅停留在动物实验层面, 这也为后续临床研究替代治疗提出了新的挑战。相信随着研究的不断深入,未来可从抑郁症的不同发病机制出发,针对性地提出营养和膳食策略, 助力推动人类精神健康发展。

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Research Progress on the Antidepressant Effects of Flavonoids

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Abstract Depression is one of the most common psychological disorder in modern society, which seriously affecting both mental and physical health. Currently, long term use of medications for treating depression could result in various adverse reactions. Therefore, there is an urgent need to find new approaches to improve depression symptoms while minimizing side effects. Dietary flavonoids are commonly present in plants and have a positive impact on human health. Several studies have confirmed their significant antidepressant effects. This article provides an overview of the mechanisms underlying depression from six aspects: neurotransmitters theory, neurotrophic theory, neuroinflammatory, oxidative stress, hypothalamic-pituitary-adrenal axis, and the microbiota-gut-brain axis. It elaborates on the formation mechanisms of depression and elucidates how flavonoids can improve cognition and emotions, acting as the main components for alleviating depressive symptoms. This paper serves as a theoretical basis for the development of dietary prevention, as well as the improvement of depression and related functional foods.

Keywords flavonoids; depression; mechanism