围绝经期抑郁症发病机制及中医药防治研究进展

朱丽君，徐莲薇，李克倩，李盛楠*
（上海中医药大学 附属龙华医院，上海 200032）

［摘要］ 围绝经期抑郁症（PMD）是女性在进入绝经期前后易发生的一种精神障碍类疾病，因其高发病率、低普及率、低诊断率、反复发作等特点，已经成为对围绝经期女性健康造成重大威胁的重要公共卫生问题。PMD发病机制复杂，主要涉及下丘脑-垂体-卵巢（HPO）轴老化导致的生殖激素异常波动、炎症及级联反应、氧化应激等方面。目前针对PMD的治疗尚无特异性的药理干预措施，而中医药作为祖国医学的瑰宝，融汇数千年传统中医经验与智慧，在防治PMD方面具有整体调节、多靶向、不良反应小等优势。近年来中药活性成分、中药提取物、复方通过多组分、多方向干预PMD的相关研究越来越多，且取得了一定进展。大量研究表明，中医药防治PMD的潜在机制包括抗炎、抗氧化、调节单胺神经递质等，主要涉及NOD样热蛋白结构域相关蛋白3（NLRP3）炎性小体、核因子E_2相关因子2（Nrf2）/血红素加氧酶-1（HO-1）、脑源性神经营养因子（BDNF）/酪氨酸激酶受体B（TrkB）等信号通路的调控。该文通过整理总结中医药治疗PMD的临床及基础研究，明析其致病机制和治疗靶向，以期为中医药治疗PMD提供基础理论支持和新的策略及借鉴。

［关键词］ 围绝经期抑郁症；发病机制；中药活性成分；中药提取物；中药复方；研究进展
［中图分类号］ R2-0；R33；G353.11；R271.1 ［文献标识码］ A ［文章编号］ 1005-9903（2024）21-0252-10
［doi］ 10.13422/j.cnki.syfjx.20240443 ［增强出版附件］ 内容详见http://www.syfjxzz.com或http://cnki.net
［网络出版地址］ https://link.cnki.net/urlid/11.3495.R.20240409.1529.003
［网络出版日期］ 2024-04-10 20:11:00

Pathogenesis of Perimenopausal Depression and Prevention and Treatment by Traditional Chinese Medicine: A Review

ZHU Lijun, XU Lianwei, LI Kething, LI Shengnan*
（*Longhua Hospital*, *Shanghai University of Traditional Chinese Medicine*, *Shanghai* 200032, *China*）

［**Abstract**］ PPerimenopausal depression (PMD) is a mental disorder that occurs in women before and after menopause. It has become a major public health problem posing a threat to the health of perimenopausal women due to its high incidence, low prevalence, low diagnostic rate, and recurrent episodes. The pathogenesis of PMD is complex and mainly involves the aging of the hypothalamic-pituitary-ovarian (HPO) axis, which leads to abnormal fluctuations in reproductive hormones, inflammation and cascade reactions, and oxidative stress. Currently, there are no specific pharmacological interventions for PMD. Traditional Chinese medicine (TCM), as a treasure of motherland medicine, integrates thousands of years of TCM experience and wisdom and has the advantages of holistic regulation, low toxicity, and mild adverse reactions in the prevention and treatment of PMD. In recent years, more and more studies have been conducted on the active ingredients, extracts, and compound formulas of TCM for treating PMD via multi-components and multi-directions, achieving fruitful results. A large number of studies have shown that TCM treats PMD by reducing inflammation, inhibiting oxidation, and modulating monoamine neurotransmitter levels, which mainly involve NOD-like receptor thermal protein domain-associated protein 3 (NLRP3) inflammasome, nuclear factor

［收稿日期］ 2024-02-04
［基金项目］ 国家自然科学基金项目（82205161）；上海中医药大学附属龙华医院“龙医学者”临床科技创新培育计划项目（KY22034）
［第一作者］ 朱丽君，在读硕士，从事中医药诊治妇科内分泌及不孕症研究，E-mail：zlj19980124@163.com
［通信作者］ *李盛楠，博士，主治医生，从事中医药防治生殖内分泌疾病研究，E-mail：lisncq@163.com

E_2-related factor 2 (Nrf2)/hemeoxygenase-1 (HO-1), brain-derived neurotrophic factor (BDNF)/tyrosine kinase receptor B (TrkB) and other signaling pathways. This article reviews the clinical and basic studies about TCM treatment of PMD to analyzes the pathogenesis of PMD and the therapeutic targets of TCM, aiming to provide basic theoretical support and new approaches for the TCM treatment of PMD.

[**Keywords**] perimenopausal depression; pathogenesis; active ingredients of traditional Chinese medicine (TCM); extracts of TCM; compound formula of TCM; research progress

围绝经期是指女性月经周期变异发生(±7 d)或出现绝经有关的内分泌、生物学和临床特征起直至末次月经后1年的一段时期,包括绝经过渡期及绝经后的早期阶段[1-2]。在此时期女性机体出现生殖系统的过渡,即卵母细胞逐渐丢失、对性腺类固醇反馈的反应能力改变、激素波动剧烈和月经模式不规则,并伴随着神经系统症状的变异性增加[3]。大量研究表明围绝经期是女性发生抑郁症的易感窗口,与绝经前女性相比,围绝经期女性抑郁症状的发生率明显升高[4-5]。围绝经期抑郁症(PMD)是发生在围绝经期复杂而常见的精神障碍性疾病,包括长期抑郁情绪、精力不足、注意分散甚至产生自杀倾向等情感症状,以及血管舒缩症状、睡眠障碍、关节痛等围绝经期常见的躯体不适[6]。多项大型队列研究显示,45%~68%的围绝经期女性会出现抑郁障碍,其中新发重性抑郁和轻度抑郁的发生率很高,分别为17%和16%,严重危害女性的身心健康[7-8]。

本病的发病机制复杂,目前临床上尚无特异性疗法。PMD与抑郁症的主要区别在于生殖激素波动幅度较大。故现代医学多采用雌激素替代疗法、口服抗抑郁类药物或二者联合使用,虽对治疗PMD有确切疗效,但长期服用会增加罹患乳腺癌、子宫内膜癌、心血管疾病等风险,影响患者的生活质量、降低患者对药物依从性[9]。近年来多项随机临床荟萃分析显示,中医药能够有效干预PMD[10]。中医药在身心一体观和辨证论治的思想指导下,以多组分、多环节、多靶向、不良反应小等优势在防治PMD方面发挥着重要作用。本文通过梳理近年相关研究,总结PMD致病机制,并同时对中药及有效成分防治PMD的作用机制的最新研究作简要综述,以期寻求安全、有效的PMD临床诊疗方案,为基础和临床深入研究提供参考和借鉴。

1 PMD的发病机制

女性在围绝经期出现负面情绪和抑郁症状的风险增加,可能是由一系列生物化学-社会心理危险因素共同造成[11]。围绝经期是女性在神经生化和内分泌水平上剧烈变动的一个时期,可累及多种组织和器官系统,尤其是情绪调控系统,导致女性对社会心理压力的敏感性和逆境中出现抑郁情绪的脆弱性增加[12-13]。而在此时期长期慢性压力及重大应激性生活事件会引起神经内分泌紊乱、情绪调控系统失衡,加快抑郁症的发生发展[14]。虽然女性易患此类疾病的病理机制尚未完全清楚,但已有研究表明,女性在围绝经期由于机体内环境的变化会造成生物易损性,其与生活压力相互作用易触发抑郁症发生的潜在机制[15],包括激素波动异常、下丘脑-垂体-肾上腺(HPA)轴紊乱、炎症及级联放大反应、单胺类神经递质缺乏、氧化应激、自噬、肠道菌群失调和肠黏膜屏障受损等,现从这些方面对PMD的致病机制进行总结,见增强出版附加材料。

1.1 激素波动异常 下丘脑-垂体-卵巢(HPO)轴是由下丘脑、垂体和卵巢三者紧密结合相互作用组成的神经内分泌系统,主要通过调节下丘脑促性腺激素释放激素(GnRH)神经元网络、垂体促性腺激素分泌、卵巢卵泡生长及类固醇激素的生成影响生殖和神经功能[16-17]。在围绝经期,女性易出现抑郁症状的本质是HPO轴的老化,即卵巢逐渐衰竭,卵泡数量下降、卵母细胞质量减退,导致性激素波动剧烈,对下丘脑、垂体的负反馈作用削弱,使整个神经内分泌系统呈现紊乱状态,从而增加PMD发生的风险[18]。目前研究已证实,围绝经期生殖激素动态的不稳定性和不可预测性与抑郁症状发生存在相关性[19]。以下将从生殖激素对PMD致病机制的作用展开探讨。

1.1.1 雌激素 雌激素是主要由卵巢分泌的一种类固醇激素,包括雌酮、雌二醇(E_2)等,具有神经保护和调节作用[20]。雌激素主要通过结合和激活雌激素受体发挥作用。在围绝经期,女性机体内环境发生复杂变化,雌激素受体网络与生物能量系统脱节,导致多个雌激素调节系统(包括睡眠、昼夜节律和感觉处理等)紊乱,从而出现失眠、抑郁等神经系统症状[3]。GORDON等[13]研究表明E_2剧烈波动会引发围绝经期女性抑郁情绪,而经皮E_2疗法可以有效防治围绝经期女性抑郁症状[21]。以上研究提示

雌激素与PMD的发生密切相关。多项动物实验研究揭示，雌激素与受体结合后，可以通过调节单胺能神经递质[22]、缓解HPA轴功能亢进[23]、激活脑源性神经营养因子（BDNF）/瞬时受体电位通道6（TRPC6）信号通路[24]及NOD样受体（NLR）信号通路[25]等途径对PMD模型大鼠发挥神经保护作用，有助于改善抑郁症状。然而，SCHMIDT等[26]研究发现在停用E_2后，既往PMD女性会出现抑郁症状复发甚至加重的情况。因此，通过调控雌激素水平改善PMD是一种有效的干预措施，同时需要警惕雌激素戒断可能引起PMD复发或加重潜在风险。

1.1.2 孕激素 围绝经期除E_2的大幅波动外，类固醇激素的变化还包括孕激素（主要为黄体酮）减少[27]。孕激素及其代谢物在围绝经期女性的情感调节中发挥重要作用，包括抗抑郁、抗应激、抗焦虑和镇静作用[28]。SÜSS等[29]研究表明，在围绝经期孕激素水平较高女性的生活满意度更高，压力易感性较低，抑郁症状较轻；另外SOVIJIT等[30]研究发现对去卵巢（OVX）小鼠补充黄体酮后可减轻其抑郁和焦虑症状，说明提高孕激素水平对防治PMD有重要意义。孕激素主要通过激活其受体[31]、代谢转化为神经活性类固醇[γ-氨基丁酸（GABA）能神经甾体][15]、调节胆碱类及单胺类神经递质[32]等途径参与神经保护和再生机制，调控大脑中情绪神经环路以发挥抗抑郁作用。目前单独使用雌激素治疗PMD会增加子宫内膜癌的发生风险。相比之下，黄体酮可以对抗雌激素，保护子宫内膜，与雌激素联合使用时可减轻雌激素不良反应，且能有效防治围绝经期和绝经后早期抑郁症状[33-34]。因此，适度提高孕激素水平可能是改善PMD症状的有效途径，而雌激素与之联合使用可能更为安全可行。

1.1.3 促性腺激素 卵泡刺激素（FSH）和黄体生成素（LH）是垂体前叶响应下丘脑释放的GnRH而分泌的两种重要的促性腺激素，由雌、孕激素的负反馈机制调节。在女性特定的生殖周期，促性腺激素对情绪和行为有重要影响，例如经前、孕中、产后和围绝经期[35]。临床资料显示，FSH水平的升高可能与围绝经期女性的负性情绪相关[36]。RYAN等[37]研究发现FSH水平的降低有助于减轻围绝经期抑郁的症状并降低发病风险，进一步证实了FSH升高可能会诱发围绝经期女性抑郁情绪。值得注意的是，FSH水平的降低同样也可能导致相似的效应[38]。例如，BI等[39]研究发现卵泡刺激素受体（FSHR）的失活可能引发PMD模型大鼠抑郁样行为。此外，PMD模型大鼠的血清中LH水平显示异常升高，而通过针刺或药物治疗降低LH水平、缓解HPO轴功能障碍，可以有效缓解大鼠的抑郁症状[40-41]。因此，积极调控LH和FSH水平，维持HPO轴稳态对防治PMD有重要意义。

1.2 HPA轴功能障碍 近年来，与应激相关的神经内分泌系统紊乱成为抑郁症发病机制的研究热点，特别是HPA轴[42]。HPA轴的平衡主要通过调节糖皮质激素（GC，人体内主要是皮质醇）的水平来实现[43]。研究表明，在围绝经期女性体内皮质醇随年龄增加呈逐渐升高的趋势[44]。同时，围绝经期女性长期受慢性压力或应激性生活事件的影响，HPA轴过度激活，也会导致GC分泌增加[34-45]。高浓度的GC集聚，使糖皮质激素受体敏感性下降，对下丘脑和垂体前叶负反馈调节异常，导致HPA轴持续超活化，具体表现为GC、促肾上腺皮质激素释放激素（CRH/CRF）、促肾上腺皮质激素（ACTH）等长时间处于高水平状态，使女性罹患PMD风险增加[46-47]。

此外，GORDON等[15]研究发现围绝经期间卵巢激素波动可能导致HPA轴失调，从而增加围绝经期女性对社会压力敏感性，致使PMD发生率升高。该研究指出，在围绝经期，女性体内黄体酮降低，其衍生的神经甾体别孕烷醇酮（ALLO）随之下降，导致ALLO与$GABA_A$受体结合减少，使Cl-离子通道开放不完全，进而降低抑制性神经递质GABA能传递，引发应激反应中HPA轴的过度激活，最终增加围绝经期女性抑郁情绪易感性。ESKOLA等[48]研究发现女性抑郁症状和胰岛素抵抗相关性的转变源于围绝经期激素波动引发的HPA轴失衡，为上述研究提供了有力证据。因此，调节HPA轴功能障碍可能是缓解PMD的一个有效靶向。

1.3 炎症及级联放大反应 炎症反应是机体应对外界刺激的一种非特异性免疫反应，与PMD发生发展密切相关。有研究发现，在PMD患者的血液中，炎症因子如C反应蛋白（CRP）、肿瘤坏死因子-α（TNF-α）、白细胞介素-6（IL-6）水平异常升高[49]。这种高炎状态可能会导致神经元受损和神经递质紊乱，使大脑中情绪调节相关区域出现结构功能障碍，如前皮质扣带回、海马等，引发抑郁症状[50]。

在炎症反应中，NLR样受体在识别慢性不可预知性温和应激（CUMS）或OVX等刺激产生的相关模式分子后，可通过自身寡聚化组装形成NOD样受体蛋白3（NLRP3）炎性小体，导致胱天蛋白酶-1前体（pro-Caspase-1）剪切活化成Caspase-1，以促进炎

症细胞因子IL-1β和IL-18的成熟和释放，从而引起巨噬细胞（如小胶质细胞）和神经炎症细胞（如星形胶质细胞）在中枢神经系统损伤部位的集聚，进一步释放促炎因子IL-6、IL-8和TNF-α等，引起一系列炎症级联放大反应，进而诱发PMD[25]。核转录因子-κB（NF-κB）是一种在炎症调节中起关键作用的蛋白复合物。有报道称，通过抑制NF-κB和NF-κB抑制蛋白α（IκBα）的磷酸化可以降低RelA（p65）的表达、下调促炎细胞因子和神经毒性介质的转录调控，维持小胶质细胞M1（促炎激活）和M2（抗炎激活）表型之间转换的稳态平衡，从而减轻PMD[51]。因此，控制炎症反应对改善PMD有重要意义。

1.4 单胺类神经递质缺乏 脑内与PMD发生有关的单胺类神经递质主要包括去甲肾上腺素（NE）、多巴胺（DA）和5-羟色胺（5-HT）。研究表明，围绝经期女性体内5-HT明显减少，可增加抑郁和潮热等症状严重程度[52]。动物实验进一步发现，可通过逆转单胺神经递质NE、DA、5-HT水平缓解PMD模型小鼠的抑郁症状[53]。单胺氧化酶-A（MAO-A）是一种重要的脑酶，主要参与单胺类神经递质的代谢，并产生氧化应激，影响神经元凋亡[54]。REKKAS等[55]研究表明围绝经期和绝经后女性的抑郁情绪与MAO-A呈正相关，提示单胺类神经递质代谢异常可影响围绝经期女性情绪。ABD-RABO等[56]研究发现下调MAO-A，增加血清素水平，可改善OVX大鼠的抑郁症状。因此，增加单胺类神经递质水平可能是减缓PMD的有效治疗方向。

1.5 氧化应激 氧化应激是机体内环境氧化还原失衡的状态，当氧自由基的产生超过抗氧化防御系统的清除能力时，会引发大量的蛋白质氧化和脂质过氧化，导致脑神经组织的线粒体损伤和功能障碍，出现神经元功能失调和信号传导异常，进而诱发PMD[57]。据报道，通过激活G蛋白偶联雌激素受体（GPER）介导蛋白激酶A（PKA）信号通路，可以提高转运蛋白18 kDa（TSPO）的磷酸化水平，从而恢复OVX大鼠的线粒体功能和氧化还原稳态，发挥抗抑郁的作用[58]。另有报道称可通过激活核因子E_2相关因子2（Nrf2）/血红素加氧酶-1（HO-1）信号通路以启动下游抗氧化防御系统，抑制氧化应激和炎症反应，进而发挥神经保护作用，缓解OVX小鼠的抑郁症状[59]。因此，抗氧化可能是治疗PMD的一个有效方向。

1.6 自噬失调 自噬作为机体内促进细胞活力和消除有害物质的关键调节机制，能够在多种应激条件下被激活以发挥生理作用[60]。而自噬抑制或过度激活均会引起神经元损伤，可参与PMD的发生发展。ZAKI等[61]研究发现PMD模型大鼠海马中自噬蛋白表达异常，Beclin-1水平降低、自噬相关蛋白1轻链3（LC3）Ⅱ/LC3Ⅰ明显下降、p62表达增加，使胞内外错误折叠蛋白和受损细胞器堆积，导致神经元供能不足，出现功能障碍甚至死亡；而PDE4抑制剂通过激活腺苷酸活化蛋白激酶（AMPK）/哺乳动物雷帕霉素靶蛋白（mTOR）/unc-51样激酶1（ULK1）信号通路促进自噬以发挥神经保护作用，进而改善抑郁样行为。另有报道称可以通过激活磷脂酰肌醇3-激酶（PI3K）/蛋白激酶B（Akt）/mTOR/细胞外调节蛋白激酶（ERK）信号通路以上调自噬，促进神经发生，进而缓解PMD[62]。以上研究提示PMD可以通过上调自噬而缓解。然而，JIN等[63]研究发现自噬一旦过度激活，超过自身的代偿范围会降低神经元的存活率，促进神经元凋亡，导致抑郁样症状；可以通过激活BDNF/mTORC1信号通路抑制自噬过度激活，有效缓解OVX大鼠的抑郁症状。因此，调控自噬相关通路可能是PMD的潜在治疗靶点。

1.7 肠菌失调和肠黏膜屏障受损 肠道是阻碍肠内细菌及毒素发生易位的先天性屏障，对维持人体内环境稳态具有重要意义[64]。肠道以肠道菌群为调节因子通过神经、内分泌和免疫途径与大脑形成双向通信网络，即微生物群-肠-脑轴[65]。据报道，伴有抑郁症状的OVX大鼠的肠道菌群发生紊乱，其中*Lactobacillus*和*Akkermansia*丰度减少，而Firmicutes/*Bacteroides*显著增加[66]。这种变化会破坏肠道微环境稳态，损伤肠黏膜屏障，致使肠内细菌和毒素易位到体循环和大脑，引发炎症反应，进而破坏血脑屏障，导致肠脑轴失衡，最终形成PMD。而补充或促进乳杆菌可以改善肠道菌群结构组成，提高紧密连接蛋白水平，修复肠道渗漏，并通过抑制IDO反应，恢复犬尿氨酸代谢，减轻炎症反应等途径缓解PMD[30,66]。此外，HUANG等[67]研究发现补充*Prevotella histicola*也可以调节OVX小鼠紊乱的肠道菌群，恢复肠黏膜屏障的功能，并通过阻断Toll样受体（TLR）4/c-Jun氨基末端激酶（JNK）丝裂原活化蛋白激酶（MAPK）信号通路抑制炎症反应，上调BDNF的表达以促进海马神经发生，从而减轻抑郁症状。因此，靶向脑肠轴治疗PMD为未来临床研究提供了新思路。

1.8 其他 此外，还包括BDNF含量减少、一氧化

氮(NO)产生增多、线粒体结构和功能障碍、神经元过度凋亡、MicroRNA表达异常、谷氨酸水平降低、GABA能系统过度活跃、突触可塑性受损等,与上述各种发病机制之间形成多途径相互交织协作,可导致PMD并加快其发展进程。

2 中药及其有效成分防治PMD的研究进展

PMD属于中医学“脏躁”“郁证”“经断前后诸症”等范畴。围绝经期女性天癸将竭,肾气渐衰,冲任虚损,气血阴阳失调,脏腑功能紊乱,而致情志失调,易发抑郁症。本病以肾为本,与肝密切相关,可涉及心、脾、胃等脏腑;目前多认为其病机为肾虚肝郁,在治则治法以补肾填精,理气疏肝为主[68]。目前已有大量研究表明,中药及其有效成分可以通过多靶向、多途径有效防治PMD。

2.1 中药活性成分 近年来,研究发现对PMD具有调控作用的中药活性成分主要包括黄酮类、酚类、糖与苷类、苯丙素类及生物碱等化合物。淫羊藿苷作为小檗科植物淫羊藿的主要活性成分,具有抗炎、调节神经递质等多种药理作用。研究表明淫羊藿苷对中枢神经系统疾病具有保护作用,可以通过调控PI3K/Akt信号通路,提高脑组织单胺神经递质5-HT、DA和NA的表达水平,促进抗炎因子IL-2的分泌,增强免疫以改善PMD症状[69]。黄芪甲苷是从传统中药黄芪中提取出来的四环三萜皂苷类化合物,能够通过激活海马白细胞介素-4受体(IL-4R)/JAK激酶1(JAK1)信号转导/转录激活蛋白6(STAT6)信号通路促进小胶质细胞的M2型极化,抑制促炎因子TNF-α、IL-1β和IL-6等分泌,发挥抗炎及神经再生修复的作用,有效缓解PMD[70]。苔黑酚葡萄糖苷(OG)是从仙茅中分离出来的一种具有抗抑郁作用的生物活性成分[71]。LI等[72]研究发现,OG能调节PMD模型小鼠的激素异常波动,缓解HPO轴功能紊乱,并逆转HPA轴功能亢进。同时,OG还能够激活BDNF/酪氨酸激酶受体B(TrkB)/环磷腺苷效应元件结合蛋白(CREB)信号通路,增强突触可塑性,促进海马神经发生,减轻PMD[72]。其他治疗PMD的中药有效成分还包括葛根素、白杨素、枸杞多糖、小檗碱等,相关信息见增强出版附加材料[73-89]。

2.2 中药提取物 现代药理研究发现防治PMD的中药提取物具有诸多药理作用,包括抗炎、调节单胺神经递质、抑制氧化应激等。如熟地黄提取物和百合球茎水提取物能够激活雌激素受体β(Erβ),调节脑神经递质和神经营养因子水平,发挥神经保护作用,从而缓解PMD;牛蒡根提取物可以通过激活ERK/CREB/BDNF通路,提高海马中的神经型一氧化氮合酶(nNOS)水平,改善OVX小鼠抑郁行为;此外,藏红花、银杏叶、牛蒡根、青蒿等中药提取物均可发挥神经保护作用治疗PMD,相关信息见增强出版附加材料[90-95]。

2.3 中药复方 中药复方作为中医药配伍理论指导下中医临床用药的主要形式,基于中药复方分子层面的研究直观剖析其有效防治PMD内在机制。加味百合地黄汤是以张仲景《金匮要略》百合地黄汤为基础方,加味郁金、白芍、麦冬、夜交藤、茯神、苏叶等药物而成,具有补益气血、调和阴阳、活血安神之功效[96]。研究表明加味百合地黄汤能够通过调节基质细胞衍生因子-1(SDF-1)/趋化因子受体-4(CXCR4)信号通路,抑制小胶质细胞的过度激活,调节促炎/抗炎因子的分泌水平,改善下丘脑神经炎性损伤,促进神经元的自我修复,缓解PMD[96]。小柴胡汤由柴胡、黄芩、人参、半夏、甘草、生姜、大枣组成,具有和解少阳、理气疏肝之效。ZHANG等[97]研究发现小柴胡汤可通过调节HPO/HPA轴功能障碍,提高前额叶皮层和下丘脑中ERβ和色氨酸羟化酶2(TPH2)表达,增加脑组织单胺类递质含量发挥抗围绝经期抑郁的作用。此外,桃红四物汤[98]、滋肾疏肝方[99]及舒肝颗粒[100]、胶泰丸[101]等亦可通过调节HPO/HPA轴功能障碍,增加单胺递质含量、抗炎等作用机制干预PMD。

3 总结与展望

女性进入围绝经期后,由于卵巢功能逐渐下降,机体内环境稳态失衡,会出现多种生理或病理性的变化。同时,社会经济压力的加剧,使其处于极度敏感的状态。因此,围绝经期女性在社会、心理和生理等多因素的交互影响下更易罹患抑郁症。PMD的风险因素较多,发病机制复杂,主要涉及HPO轴老化导致的激素波动异常、HPA轴功能障碍、炎症及级联反应、单胺类神经递质缺乏、氧化应激、自噬失调、菌群失调和肠屏障受损等诸多方面。因PMD发病机制未能被完全精准阐明,目前现代医学对其尚无特异性的药理干预措施,在临床治疗上存在一定的困难和挑战。而传统中药在治疗情绪障碍方面有较大的优势,具有整体性、平衡性、持久性的特点。研究发现,中药活性成分、中药提取物及复方可通过调控NF-κB、IL-4R/JAK1/STAT6、BDNF/TrkB及NLRP3炎性小体等信号通路以发挥抗炎、减轻氧化应激、增强突触可塑性、调节HPO及

HPA轴等多种作用改善PMD，且因其多靶向、不良反应小等特点，已经成为临床及基础研究的重要内容。

众多研究报道显示，中医药能有效干预PMD，但其临床与基础研究尚不充分，存在一些问题亟需进一步研究：(1)中医药治疗PMD尚未有规范的专家共识和指南，多数基于围绝经期综合征有关临床诊疗方案实施诊治，亟需公认安全有效的治疗方案，可以通过深入挖掘经典古籍、整合名老中医经验医案，并结合心理学干预手段等规范PMD辨证分型，充分发挥中医药防治PMD的优势。(2)现阶段基础研究多采用OVX或OVX+CUMS等单纯疾病模型，缺乏中医特色病证结合的动物模型，未来研究可基于中医辨证论治和临床实践构建方药功效相关的病证结合动物模型，开展中医药特色基础创新研究。(3)中药及复方作用机制的研究中涉及到的信号通路缺乏多元化、分子靶点较为单一，且各通路之间的交叉互作机制尚不明确，未来可以利用单细胞测序技术、联合空间转录组学、免疫分析、生物信息学和分子对接等新兴技术与传统方法学相结合，拓展中医药在该领域的研究维度。(4)目前研究多集中于动物实验，不仅缺乏体外细胞模型的构建及有效分子验证，临床循证医学研究证据也不足，未来可以在联合动物实验的基础上，积极探索特征性的体外细胞实验，并开展长期、多中心、规范化、大规模的临床试验，丰富验证角度，为中医药治疗PMD的临床应用提供更为可靠的证据。基于此，诸位医家在未来应充分发挥中医药在防治PMD中的独特优势，将中医基础理论与现代医学机制紧密结合，深入挖掘中医药相关分子作用机制，以期为中医药防治PMD提供深度理论支持，积极提高围绝经期抑郁患者的诊疗质量。

[参考文献]

[1] WILLI J, EHLERT U. Assessment of perimenopausal depression: A review[J]. J Affect Disord, 2019, 249: 216-222.
[2] VOEDISCH A J, DUNSMOOR-SU R, KASIRSKY J. Menopause: A global perspective and clinical guide for practice[J]. Clin Obstet Gynecol, 2021, 64(3): 528-554.
[3] BRINTON R D, YAO J, YIN F, et al. Perimenopause as a neurological transition state[J]. Nat Rev Endocrinol, 2015, 11(7): 393-405.
[4] MULHALL S, ANDEL R, ANSTEY K J. Variation in symptoms of depression and anxiety in midlife women by menopausal status[J]. Maturitas, 2018, 108: 7-12.
[5] DE KRUIF M, SPIJKER A T, MOLENDIJK M L. Depression during the perimenopause: A Meta-analysis[J]. J Affect Disord, 2016, 206: 174-180.
[6] WILLI J, EHLERT U. Symptoms assessed in studies on perimenopausal depression: A narrative review[J]. Sex Reprod Healthc, 2020, 26: 100559.
[7] VIVIAN-TAYLOR J, HICKEY M. Menopause and depression: Is there a link?[J]. Maturitas, 2014, 79(2): 142-146.
[8] MAKI P M, KORNSTEIN S G, JOFFE H, et al. Guidelines for the evaluation and treatment of perimenopausal depression: Summary and recommendations[J]. J Womens Health (Larchmt), 2019, 28(2): 117-134.
[9] SHUFELT C L, MANSON J E. Menopausal hormone therapy and cardiovascular disease: The role of formulation, dose, and route of delivery[J]. J Clin Endocrinol Metab, 2021, 106(5): 1245-1254.
[10] CAO X J, HUANG X C, WANG X. Effectiveness of Chinese herbal medicine granules and traditional Chinese medicine-based psychotherapy for perimenopausal depression in Chinese women: A randomized controlled trial[J]. Menopause, 2019, 26(10): 1193-1203.
[11] ALBLOOSHI S, TAYLOR M, GILL N. Does menopause elevate the risk for developing depression and anxiety? Results from a systematic review[J]. Australas Psychiatry, 2023, 31(2): 165-173.
[12] NEWHOUSE P, ALBERT K. Estrogen, stress, and depression: A neurocognitive model[J]. JAMA Psychiatry, 2015, 72(7): 727-729.
[13] GORDON J L, SANDER B. The role of estradiol fluctuation in the pathophysiology of perimenopausal depression: A hypothesis paper[J]. Psychoneuroendocrinology, 2021, 133: 105418.
[14] XU Q, JIANG M, GU S, et al. Metabolomics changes in brain-gut axis after unpredictable chronic mild stress[J]. Psychopharmacology (Berl), 2022, 239(3): 729-743.
[15] GORDON J L, GIRDLER S S, MELTZER-BRODY S E, et al. Ovarian hormone fluctuation, neurosteroids, and HPA axis dysregulation in perimenopausal depression: A novel heuristic model[J]. Am J Psychiatry, 2015, 172(3): 227-236.
[16] ESTIENNE A, BONGRANI A, RAMÉ C, et al. Energy sensors and reproductive hypothalamo-pituitary

ovarian axis (HPO) in female mammals: Role of mTOR (mammalian target of rapamycin), AMPK (AMP-activated protein kinase) and SIRT1 (Sirtuin 1) [J]. Mol Cell Endocrinol, 2021, 521: 111113.

[17] CHEN X, XIAO Z, CAI Y, et al. Hypothalamic mechanisms of obesity-associated disturbance of hypothalamic-pituitary-ovarian axis [J]. Trends Endocrinol Metab, 2022, 33(3): 206-217.

[18] ALLSHOUSE A, PAVLOVIC J, SANTORO N. Menstrual cycle hormone changes associated with reproductive aging and how they may relate to symptoms[J]. Obstet Gynecol Clin North Am, 2018, 45(4): 613-628.

[19] WILLIAMS K. Perimenopausal depression: Review of recent findings and implications for future research[J]. Curr Opin Obstet Gynecol, 2023, 35(2): 150-153.

[20] DUBOL M, EPPERSON C N, SACHER J, et al. Neuroimaging the menstrual cycle: A multimodal systematic review [J]. Front Neuroendocrinol, 2021, 60: 100878.

[21] SCHMIDT P J, WEI S M, MARTINEZ P E, et al. The short-term effects of estradiol, raloxifene, and a phytoestrogen in women with perimenopausal depression[J]. Menopause, 2021, 28(4): 369-383.

[22] MIAO M, YAN X, GUO L, et al. Effect of Cynomorium total flavone on depression model of perimenopausal rat[J]. Saudi J Biol Sci, 2017, 24(1): 139-148.

[23] LI J, HE P, ZHANG J, et al. Orcinol glucoside improves the depressive-like behaviors of perimenopausal depression mice through modulating activity of hypothalamic-pituitary-adrenal/ovary axis and activating BDNF-TrkB-CREB signaling pathway [J]. Phytother Res, 2021, 35(10): 5795-5807.

[24] SONG Q, HUANG W, YE W, et al. Neuroprotective effects of estrogen through BDNF-transient receptor potential channels 6 signaling pathway in the hippocampus in a rat model of perimenopausal depression [J]. Front Aging Neurosci, 2022, 14: 869274.

[25] XU Y, SHENG H, BAO Q, et al. NLRP3 inflammasome activation mediates estrogen deficiency-induced depression- and anxiety-like behavior and hippocampal inflammation in mice [J]. Brain Behav Immun, 2016, 56: 175-186.

[26] SCHMIDT P J, BEN DOR R, MARTINEZ P E, et al. Effects of estradiol withdrawal on mood in women with past perimenopausal depression: A randomized clinical trial [J]. JAMA Psychiatry, 2015, 72(7): 714-726.

[27] JOFFE H, DE WIT A, COBORN J, et al. Impact of estradiol variability and progesterone on mood in perimenopausal women with depressive symptoms[J]. J Clin Endocrinol Metab, 2020, 105(3): e642-e650.

[28] STEFANIAK M, DMOCH-GAJZLERSKA E, JANKOWSKA K, et al. Progesterone and its metabolites play a beneficial role in affect regulation in the female brain[J]. Pharmaceuticals (Basel), 2023, 16(4): 520.

[29] SÜSS H, WILLI J, GRUB J, et al. Estradiol and progesterone as resilience markers? Findings from the swiss perimenopause study [J]. Psychoneuroendocrinology, 2021, 127: 105177.

[30] SOVIJIT W N, SOVIJIT W E, PU S, et al. Ovarian progesterone suppresses depression and anxiety-like behaviors by increasing the Lactobacillus population of gut microbiota in ovariectomized mice [J]. Neurosci Res, 2021, 168: 76-82.

[31] DUBOL M, EPPERSON C N, LANZENBERGER R, et al. Neuroimaging premenstrual dysphoric disorder: A systematic and critical review [J]. Front Neuroendocrinol, 2020, 57: 100838.

[32] SUNDSTRÖM-POROMAA I, COMASCO E, SUMNER R, et al. Progesterone-Friend or foe?[J]. Front Neuroendocrinol, 2020, 59: 100856.

[33] 陈蓉.《中国绝经管理与绝经激素治疗指南 2023 版》解读[J]. 协和医学杂志, 2023, 14(3): 514-519.

[34] GORDON J L, RUBINOW D R, EISENLOHR-MOUL T A, et al. Efficacy of transdermal estradiol and micronized progesterone in the prevention of depressive symptoms in the menopause transition: A randomized clinical trial[J]. JAMA Psychiatry, 2018, 75(2): 149-157.

[35] PADDA J, KHALID K, HITAWALA G, et al. Depression and its effect on the menstrual cycle[J]. Cureus, 2021, 13(7): e16532.

[36] BERENT-SPILLSON A, MARSH C, PERSAD C, et al. Metabolic and hormone influences on emotion processing during menopause [J]. Psychoneuroendocrinology, 2017, 76: 218-225.

[37] RYAN J, BURGER H G, SZOEKE C, et al. A prospective study of the association between endogenous hormones and depressive symptoms in postmenopausal women[J]. Menopause, 2009, 16(3): 509-517.

[38] BRAMBILLA F, MAGGIONI M, FERRARI E, et al.

Tonic and dynamic gonadotropin secretion in depressive and normothymic phases of affective disorders[J]. Psychiatry Res, 1990, 32(3): 229-239.

[39] BI W K, SHAO S S, LI Z W, et al. FSHR ablation induces depression-like behaviors[J]. Acta Pharmacol Sin, 2020, 41(8): 1033-1040.

[40] GU S, JING L, LI Y, et al. Stress induced hormone and neuromodulator changes in menopausal depressive rats [J]. Front Psychiatry, 2018, 9: 253.

[41] ZHAO F Y, FU Q Q, SPENCER S J, et al. Acupuncture: A promising approach for comorbid depression and insomnia in perimenopause[J]. Nat Sci Sleep, 2021, 13: 1823-1863.

[42] KAMRAN M, BIBI F, UR REHMAN A, et al. Major depressive disorder: Existing hypotheses about pathophysiological mechanisms and new genetic findings[J]. Genes (Basel), 2022, 13(4): 646.

[43] KALAFATAKIS K, RUSSELL G M, FERGUSON S G, et al. Glucocorticoid ultradian rhythmicity differentially regulates mood and resting state networks in the human brain: A randomised controlled clinical trial [J]. Psychoneuroendocrinology, 2021, 124: 105096.

[44] 周丹妮, 卫若楠, 康梦娇, 等. 围绝经期综合征动物模型研究进展[J]. 中国实验方剂学杂志, 2021, 27(18): 243-250.

[45] HANTSOO L, JAGODNIK K M, NOVICK A M, et al. The role of the hypothalamic-pituitary-adrenal axis in depression across the female reproductive lifecycle: Current knowledge and future directions [J]. Front Endocrinol (Lausanne), 2023, 14: 1295261.

[46] HERMAN J P, MCKLVEEN J M, GHOSAL S, et al. Regulation of the hypothalamic-pituitary-adrenocortical stress response [J]. Compr Physiol, 2016, 6(2): 603-621.

[47] 刘晓钰, 钱欣, 韩玉苹, 等. 下丘脑-垂体-肾上腺轴和性腺轴在围绝经期抑郁症中的作用(综述)[J]. 中国健康心理学杂志, 2024, 32(2): 161-167.

[48] ESKOLA P J, JOKELAINEN J, JÄRVELIN M R, et al. Depression and insulin resistance: Additional support for the novel heuristic model in perimenopausal depression[J]. Am J Psychiatry, 2015, 172(8): 796-797.

[49] GUO L, REN L, ZHANG C. Relationship between depression and inflammatory factors and brain-derived neurotrophic factor in patients with perimenopause syndrome [J]. Exp Ther Med, 2018, 15(5): 4436-4440.

[50] BEUREL E, TOUPS M, NEMEROFF C B. The bidirectional relationship of depression and inflammation: Double trouble [J]. Neuron, 2020, 107(2): 234-256.

[51] WU B, SONG Q, ZHANG Y, et al. Antidepressant activity of ω-3 polyunsaturated fatty acids in ovariectomized rats: Role of neuroinflammation and microglial polarization[J]. Lipids Health Dis, 2020, 19(1): 4.

[52] SCHNEIDER-MATYKA D, GROCHANS E, LUBKOWSKA A, et al. The effect of tryptophan and serotonin levels on the severity of depressive and climacteric symptoms in perimenopausal women [J]. Eur Rev Med Pharmacol Sci, 2021, 25(9): 3425-3431.

[53] MIAO M, TIAN S, GUO L, et al. The effect of curculigoside on mouse model of perimenopausal depression [J]. Saudi J Biol Sci, 2017, 24(8): 1894-1902.

[54] BHAWNA, KUMAR A, BHATIA M, et al. Monoamine oxidase inhibitors: A concise review with special emphasis on structure activity relationship studies[J]. Eur J Med Chem, 2022, 242: 114655.

[55] REKKAS P V, WILSON A A, LEE V W, et al. Greater monoamine oxidase a binding in perimenopausal age as measured with carbon 11-labeled harmine positron emission tomography[J]. JAMA Psychiatry, 2014, 71(8): 873-879.

[56] ABD-RABO M M, GEORGY G S, SAIED N M, et al. Involvement of the serotonergic system and neuroplasticity in the antidepressant effect of curcumin in ovariectomized rats: Comparison with oestradiol and fluoxetine [J]. Phytother Res, 2019, 33(2): 387-396.

[57] BHATT S, NAGAPPA A N, PATIL C R. Role of oxidative stress in depression[J]. Drug Discov Today, 2020, 25(7): 1270-1276.

[58] WANG J, LI H Y, SHEN S Y, et al. The antidepressant and anxiolytic effect of GPER on translocator protein (TSPO) via protein kinase a (PKA) signaling in menopausal female rats [J]. J Steroid Biochem Mol Biol, 2021, 207: 105807.

[59] SAMY D M, MOSTAFA D K, SALEH S R, et al. Carnosic acid mitigates depression-like behavior in ovariectomized mice via activation of Nrf2/HO-1 pathway[J]. Mol Neurobiol, 2023, 60(2): 610-628.

[60] NGUYEN D T, WRIGHT E P, DEDDING C, et al. Low self-esteem and its association with anxiety, depression, and suicidal ideation in vietnamese secondary school students: A cross-sectional study[J].

Front Psychiatry, 2019, 10: 698.

[61] ZAKI E S, SAYED R H, SAAD M A, et al. Roflumilast ameliorates ovariectomy-induced depressive-like behavior in rats via activation of AMPK/mTOR/ULK1-dependent autophagy pathway [J]. Life Sci, 2023, 327: 121806.

[62] AMIN N, XIE S, TAN X, et al. Optimized integration of fluoxetine and 7, 8-dihydroxyflavone as an efficient therapy for reversing depressive-like behavior in mice during the perimenopausal period [J]. Prog Neuropsychopharmacol Biol Psychiatry, 2020, 101: 109939.

[63] JIN Y, PANG H, ZHAO L, et al. Ginseng total saponins and Fuzi total alkaloids exert antidepressant-like effects in ovariectomized mice through BDNF-mTORC1, autophagy and peripheral metabolic pathways[J]. Phytomedicine, 2022, 107: 154425.

[64] LIU L, WANG H, CHEN X, et al. Gut microbiota and its metabolites in depression: From pathogenesis to treatment[J]. EBioMedicine, 2023, 90: 104527.

[65] QUIGLEY E. Microbiota-brain-gut axis and neurodegenerative diseases[J]. Curr Neurol Neurosci Rep, 2017, 17(12): 94.

[66] LIM E Y, SONG E J, KIM J G, et al. Lactobacillus intestinalis YT2 restores the gut microbiota and improves menopausal symptoms in ovariectomized rats [J]. Benef Microbes, 2021, 12(5): 503-516.

[67] HUANG F, LIU X, XU S, et al. Prevotella histicola mitigated estrogen deficiency-induced depression via gut microbiota-dependent modulation of inflammation in ovariectomized mice[J]. Front Nutrit, 2022, doi: 10. 3389/fnut. 2021. 805465.

[68] 司夏樱,岳秀宁,王昕,等. 舒肝解郁胶囊联合重复经颅磁刺激治疗对围绝经期抑郁神经内分泌功能的影响[J]. 中国实验方剂学杂志,2019,25(1):163-168.

[69] CAO L H, QIAO J Y, HUANG H Y, et al. PI3K-Akt signaling activation and icariin: The potential effects on the perimenopausal depression-like rat model[J]. Molecules, 2019, 24(20): 3700.

[70] YAO G, BAI Z, NIU J, et al. Astragalin attenuates depression-like behaviors and memory deficits and promotes M2 microglia polarization by regulating IL-4R/JAK1/STAT6 signaling pathway in a murine model of perimenopausal depression [J]. Psychopharmacology, 2022, 239(8): 2421-2443.

[71] CHEN B, LIU X, WANG Y, et al. Production of the antidepressant orcinol glucoside *in Yarrowia lipolytica* with yields over 6,400-fold higher than plant extraction [J]. PLoS Biol, 2023, 21(6): e3002131.

[72] LI J, HE P, ZHANG J, et al. Orcinol glucoside improves the depressive-like behaviors of perimenopausal depression mice through modulating activity of hypothalamic-pituitary-adrenal/ovary axis and activating BDNF-TrkB-CREB signaling pathway [J]. Phytother Res, 2021, 35(10): 5795-5807.

[73] 王睿,刘吉成,罗春娟,等. 葛根素对围绝经期抑郁症模型小鼠的神经保护作用及机制研究[J]. 神经解剖学杂志,2017,33(2):190-196.

[74] 王睿,刘吉成,罗春娟,等. 葛根素对围绝经期抑郁症模型小鼠神经元凋亡的影响及机制研究[J]. 医学研究杂志,2017,46(8):121-125.

[75] CAO L H, QIAO J Y, HUANG H Y, et al. PI3K-Akt signaling activation and icariin: The potential effects on the perimenopausal depression-like rat model[J]. Molecules, 2019, 24(20): 3700.

[76] 杨琴,任昊阳,朱寒雨,等. 白杨素通过抑制NLRP3炎性小体信号通路对围绝经期抑郁症模型大鼠产生保护作用[J]. 中国药理学通报,2020,36(7):1006-1011.

[77] ZHANG Z, CHEN Y, XIANG L, et al. Effect of curcumin on the diversity of gut microbiota in ovariectomized rats[J]. Nutrients, 2017, 9(10): 1146.

[78] LI J, HE P, ZHANG J, et al. Orcinol glucoside improves the depressive-like behaviors of perimenopausal depression mice through modulating activity of hypothalamic-pituitary-adrenal/ovary axis and activating BDNF-TrkB-CREB signaling pathway [J]. Phytother Res, 2021, 35(10): 5795-5807.

[79] LIU T, MA Y, ZHANG R, et al. Resveratrol ameliorates estrogen deficiency-induced depression- and anxiety-like behaviors and hippocampal inflammation in mice [J]. Psychopharmacology (Berl), 2019, 236(4): 1385-1399.

[80] 倪佳颖, 姚丽华, 张荣荣. 白藜芦醇对围绝经期抑郁症模型大鼠血清性激素水平及雌激素受体蛋白表达的影响[J]. 中国临床药理学杂志, 2019, 35(17): 1905-1908.

[81] CHEN X Q, CHEN S J, LIANG W N, et al. Saikosaponin A attenuates perimenopausal depression-like symptoms by chronic unpredictable mild stress [J]. Neurosci Lett, 2018, 662: 283-289.

[82] HAO K, GONG P, SUN S Q, et al. Beneficial estrogen-like effects of ginsenoside Rb_1, an active component of *Panax ginseng*, on neural 5-HT disposition and behavioral tasks in ovariectomized mice [J]. Eur J Pharmacol, 2011, 659(1): 15-25.

[83] SOYTÜRK H, BOZAT B G, PEHLIVAN KARAKAS F, et al. Neuroprotective effects of goji berry (*Lycium barbarum* L.) polysaccharides on depression-like behavior in ovariectomized rats: behavioral and biochemical evidence[J]. Croat Med J, 2023, 64(4): 231-242.

[84] ZHANG Q-P, CHENG J, LIU Q, et al. Dendrobium officinale polysaccharides alleviate depression-like symptoms via regulating gut microbiota-neuroinflammation in perimenopausal mice [J]. J Funct Foods, 2022, 88: 104912.

[85] ZHOU X D, ZHENG Y, SHARMA R, et al. Total polysaccharides of lily bulb ameliorate menopause-like behavior in ovariectomized mice: Multiple mechanisms distinct from estrogen therapy [J]. Oxid Med Cell Longev, 2019, 2019: 6869350.

[86] ADU-NTI F, GAO X, WU J M, et al. Osthole ameliorates estrogen deficiency-induced cognitive impairment in female mice[J]. Front Pharmacol, 2021, 12: 641909.

[87] 徐红丹, 张博, 李薇, 等. 五味子乙素对长期OVX小鼠抑郁样行为的治疗作用及机制研究[J]. 现代中药研究与实践, 2019, 33(2): 17-20.

[88] FAN J, LI B, GE T, et al. Berberine produces antidepressant-like effects in ovariectomized mice[J]. Sci Rep, 2017, 7(1): 1310.

[89] HARAMIPOUR P, ASGHARI A, HASSANPOUR S, et al. Anti-depressant effect of betaine mediates via nitrergic and serotoninergic systems in ovariectomized mice[J]. Arch Razi Inst, 2021, 76(5): 1404-1417.

[90] LOPRESTI A L, SMITH S J. The effects of a saffron extract (affron®) on menopausal symptoms in women during perimenopause: A randomised, double-blind, placebo-controlled study[J]. J Menopausal Med, 2021, 27(2): 66-78.

[91] ZHOU X D, SHI D D, ZHANG Z J. Ameliorative effects of Radix rehmanniae extract on the anxiety-and depression-like symptoms in ovariectomized mice: A behavioral and molecular study [J]. Phytomedicine, 2019, 63: 153012.

[92] ZHOU X D, SHI D D, WANG H N, et al. Aqueous extract of lily bulb ameliorates menopause-like behavior in ovariectomized mice with novel brain-uterus mechanisms distinct from estrogen therapy[J]. Biomed Pharmacother, 2019, 117: 109114.

[93] BANIN R M, MACHADO M, DE ANDRADE I S, et al. *Ginkgo biloba* extract (GbE) attenuates obesity and anxious/depressive-like behaviours induced by ovariectomy[J]. Sci Rep, 2021, 11(1): 44.

[94] LIM D W, KIM M, YOON M, et al. 1, 3-dicaffeoylquinic acid as an active compound of arctium lappa root extract ameliorates depressive-like behavior by regulating hippocampal nitric oxide synthesis in ovariectomized mice[J]. Antioxidants (Basel), 2021, 10(8): 1281.

[95] KIM D Y, SON S R, KIM J Y, et al. Effects of *Artemisia annua* L. on postmenopausal syndrome in ovariectomized mice [J]. J Ethnopharmacol, 2023, 317: 116800.

[96] 刘洋, 李翎熙, 周密, 等. 加味百合地黄汤通过调控SDF-1/CXCR4轴对围绝经期抑郁症大鼠下丘脑炎性损伤的改善作用[J]. 中成药, 2024, 46(1): 250-255.

[97] ZHANG K, WANG Z, PAN X, et al. Antidepressant-like effects of Xiaochaihutang in perimenopausal mice [J]. J Ethnopharmacol, 2020, 248: 112318.

[98] 张欣, 邓琳琳, 王爱梅, 等. 桃红四物汤对围绝经期抑郁症模型大鼠HPA轴及神经元活性的影响[J]. 中药药理与临床, 2022, 38(2): 27-32.

[99] 邓艳华, 陈璐佳, 刘宏飞, 等. 滋肾疏肝方对围绝经期抑郁模型小鼠的作用及机制研究[J]. 中华中医药学刊, 2024, 42(4): 54-60, 276.

[100] 王贵贤, 常麦会, 李庆丽, 等. 舒肝颗粒治疗围绝经期肝郁气滞型抑郁症的疗效观察[J]. 中国实验方剂学杂志, 2019, 25(6): 114-119.

[101] XIANG L, FENG Y, HU Q, et al. Jiao-Tai-Wan ameliorates depressive-like behavior through the AR pathway in ovariectomized mice after unpredictable chronic stress[J]. Biomed Res Int, 2020, doi: 10. 1155/2020/1507561.

[责任编辑 孙丛丛]