经方及其共有黄酮类成分抗抑郁机制研究进展

郝闻致[1], 王　璐[1], 黄俊卿[1*], 陈家旭[1,2*]

(1. 暨南大学, 广州市中医方证重点实验室, 广东 广州 510632;　2. 北京中医药大学中医学院, 北京 100029)

摘要: 抑郁症是以长久的情绪低落, 伴有认知、睡眠与社交障碍的精神疾病。抑郁症在中医属"郁证"、"脏躁"、"癫狂"等范畴, 以肝郁脾虚为主要证型, 以疏肝解郁、养血健脾为主要治则。逍遥散、四逆散、柴胡疏肝散等是中医临床治疗抑郁症的经方。临床与基础研究表明, 经方共有的黄酮类成分具有抗炎、抗氧化、神经保护等药理作用, 能从不同作用途径预防和抑制抑郁症的发生发展。基于此, 本综述围绕抑郁症的发病机制, 总结和讨论了抗抑郁经方及其共有黄酮类成分的抗抑郁作用及机制, 以期为抑郁症的防治提供思路。

关键词: 抑郁症; 黄酮类成分; 神经递质; 氧化应激; 神经炎症

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Research progress on the pharmacodynamic mechanism of antidepressant compound prescriptions and its flavonoids active ingredients

HAO Wen-zhi[1], WANG Lu[1], HUANG Jun-qing[1*], CHEN Jia-xu[1,2*]

(*1. Guangzhou Key Laboratory of Formula-Pattern of Traditional Chinese Medicine, Jinan University, Guangzhou 510632, China;　2. School of Traditional Chinese Medicine, Beijing University of Chinese Medicine, Beijing 100029, China*)

Abstract: Depression is a psychiatric disease characterized by long-lasting low mood, accompanied by symptoms such as cognitive, sleep and social disturbances. In the theory of traditional Chinese medicine, depression is included in the categories of "depression syndrome" and "madness", and the main syndrome type is liver stagnation and spleen deficiency. Xiaoyao san, Sini san and Chaihushugan san are commonly used prescriptions for clinical treatment of depression, and flavonoids are the common active ingredients. Clinical and basic studies have shown that the flavonoids derived from antidepressant compound prescription have pharmacological effects such as anti-inflammatory, antioxidant, neuroprotective, and intestinal flora regulation which could prevent the occurrence and development of depression from different pathways. Based on this, this review focuses on the pathogenesis of depression, summarizes the common flavonoids in antidepressant prescriptions, and summarizes their regulatory mechanisms and effects in order to provide ideas for the prevention and treatment of depression.

Key words: depression; flavonoid; neurotransmitter; oxidative stress; neuroinflammation

抑郁症属于常见的神经精神疾病, 以持续的心境低落及认知、睡眠、社交障碍等为主要临床症状。"血脉和利, 精神乃居", 抑郁症也是老年患者心脑血管疾病的重要并发症之一, 已成为全球致残的主要原因[1-3]。目前研究表明, 抑郁症的发病机制多样, 主要包括肠道微生态破坏、神经递质异常、下丘脑–垂体–肾上腺(hypothalamic-pituitary-adrenal, HPA) 轴紊乱及神经炎

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*通讯作者 Tel: 86-25-85221323,
E-mail: jqhuang@jnu.edu.cn; chenjiaxu@hotmail.com

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症等[4]。疾病的临床治疗以选择性五羟色胺 (serotonin, 5-HT) 再摄取抑制剂 (舍曲林、帕罗西汀、氟西汀、氟伏沙明、西酞普兰) 为主, 存在起效时间长、药物依赖性强、肝肾损伤及心血管损伤等不良反应[5]。因此, 进一步探究及开发更加安全有效的抑郁症防治药物是亟需解决的问题。

中医药防治抑郁症是目前抑郁症研究的重要内容[6,7]。在中医理论中, 抑郁症属"郁证"、"脏躁"、"癫狂"等范畴, 以肝郁脾虚、肝郁气滞等为主要证型, 以疏肝解郁、养血健脾为主要治则[8-10]。依据中医方证相应的治则治法, 抑郁症的临床治疗多以逍遥散、四逆散、柴胡疏肝散、小柴胡汤等抗抑郁经方为主[11]。研究表明, 黄酮类成分是抗抑郁经方共有的有效成分之一 (图 1), 具有显著的抗炎、抗氧化、神经保护等药理作用, 可从不同途径阻断、预防抑郁症的发生发展, 对于抑郁症的防治具有积极意义[12,13]。基于此, 本综述总结和讨论了抗抑郁经方及其共有黄酮类成分的抗抑郁作用及机制, 以期为抑郁症的防治研究提供思路。

1　抑郁症发病机制研究

多种机制参与抑郁症发生发展的病理过程, 其中以神经递质假说、神经可塑性与神经营养因子假说、免疫与细胞因子假说、HPA 轴功能紊乱假说、肠道菌群失衡假说与氧化应激假说等为当前主要探索的机制, 且彼此密切联系 (图 2)。神经递质 (单胺类神经递质、氨基酸类神经递质、肽类神经递质) 被认为在抑郁症等人体精神疾病的发病过程中起到关键作用。抑郁患者大脑中 5-HT、多巴胺 (dopamine, DA) 水平减少, 而靶向神经递质的药物治疗则可改善抑郁症患者的临床症状, 提示神经递质紊乱在抑郁症发病过程中的重要作用[14]。作为中枢神经系统中重要的神经营养因子, 脑源性神经营养因子 (brain-derived neurotrophic factor, BDNF) 对神经元的成熟分化起到关键作用, 介导神经可塑性的调节及神经新生的维持。研究表明[15], BDNF 减少会导致大脑边缘结构系统海马、前额叶皮层 (prefrontal cortex, PFC) 及杏仁核等区域的神经元萎缩, 影响神经可塑性, 降低神经发生从而诱发抑郁症。抗抑郁药物治疗可增加 BDNF 表达水平, 恢复神经可塑性并促进神经发生。细胞凋亡与神经免疫失衡也是介导抑郁症发生发展的重要机制。海马区的神经元凋亡及中枢促炎性细胞因子白细胞介素 (interleukin, IL)-1β、IL-6、肿瘤坏死因子-α (tumor necrosis factor-α, TNF-α) 的高表达与抑郁症的严重程度呈正相关[16]。抑郁症患者脑脊液中炎症介质及其受体的表达显著增加[17]。基础研究也证实多种抑郁动物模型存在中枢促炎因子 IL-1β、IL-6、TNF-α 表达水平的升高及炎症通路的激活[18-20]。HPA 轴是由下丘脑、垂体、肾上腺及下游相应靶器官构成的人体神经内分泌免疫网络调节枢纽, 具有维持内环境稳态的重要作用。HPA 轴功能亢进是抑郁症患者常见神经生物学异常表现, 特别是促肾上腺皮质激素释放激素 (adreno-cortico-tropic-hormone, ACTH) 和促皮质素释放激素 (corticotropin releasing hormone, CRH) 过度分泌及糖皮质激素 (glucocorticoid, GC) 与糖皮质激素受体 (glucocorticoid receptor, GR) 的高表达会介导神经元的退行性病变, 诱导抑郁症患者出现认知障碍与失落情绪[21]。最新研究还揭示了肠道菌群紊乱在抑郁症发病过程中的重要作用[22]。

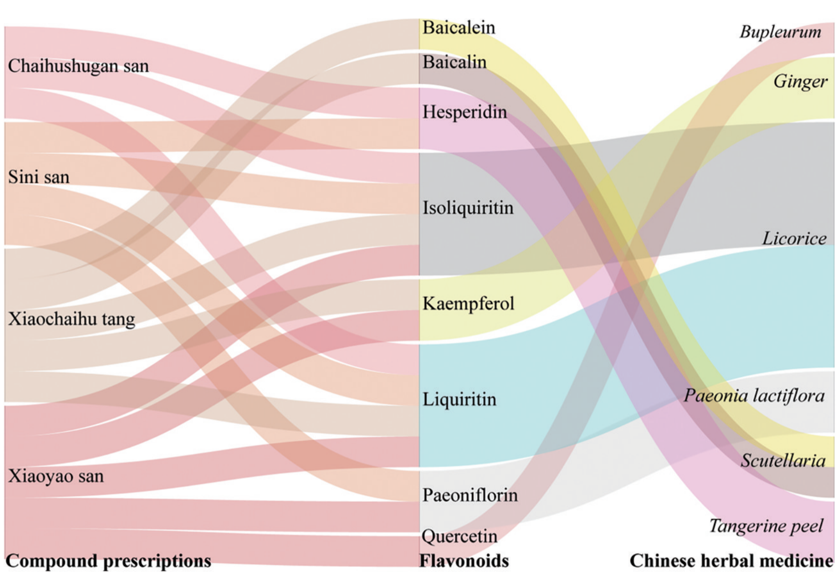


Figure 1　Flavonoids active ingredients in antidepressant compound prescriptions. The compound prescriptions are composed of some of the same traditional Chinese herbal medicines, and there are shared flavonoids

相较于健康人而言, 抑郁症患者的肠道菌群存在明显组成与结构的紊乱, 接受抑郁患者粪菌定植的无菌小鼠也存在明显的抑郁样行为, 揭示了肠道菌群与抑郁症发病之间的密切联系[23,24]。氧化应激也是与抑郁症患者病程、症状等临床表现具有重要联系的机制, 高水平的活性氧 (reactive oxygen species, ROS) 易诱导神经元损伤。研究也表明抑制ROS与丙二醛 (malondialdehyde, MDA) 及提升抗氧化酶超氧化物歧化酶 (super oxide dismutase, SOD)、过氧化氢酶 (catalase, CAT) 可改善抑郁症状[25,26]。

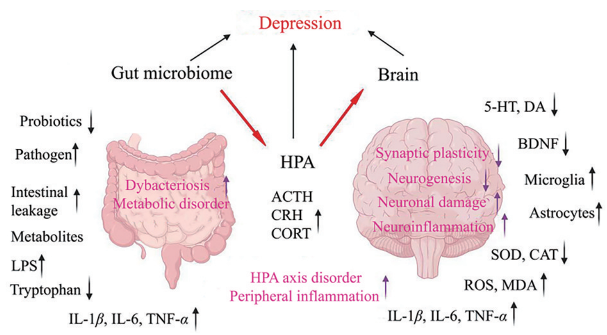


Figure 2 The main pathogenesis of depression. Neurotransmitters, neuroplasticity and neurotrophic factors, neuroinflammation, hypothalamic-pituitary-adrenal (HPA) axis dysfunction, gut microbiota imbalance and oxidative stress are considered to be the main mechanisms mediating the occurrence and development of depression and are closely related to each other. IL: Interleukin; TNF-α: Tumor necrosis factor-α; LPS: Lipopolysaccharide; ACTH: Adreno-cortico-tropic-hormone; CRH: Corticotropin releasing hormone; CORT: Cortisol; 5-HT: Serotonin; DA: Dopamine; BDNF: Brain-derived neurotrophic factor; SOD: Super oxide dismutase; CAT: Catalase; ROS: Reactive oxygen species; MDA: Malondialdehyde

2 抗抑郁经方及其作用机制

2.1 逍遥散

逍遥散出自宋朝《太平惠民和剂局方》, 由当归、茯苓、白芍、白术、柴胡、甘草、薄荷、生姜组成, 功用为疏肝解郁、养血健脾, 是临床治疗抑郁症的经方, 对广泛的轻中度抑郁症、产后抑郁症等具有良好的治疗作用[27]。鉴于复方构成的多成分特性, 其抗抑郁机制也呈现多系统多层次的特性。近年来的研究表明, 逍遥散及其活性成分主要通过抑制神经炎症、促进神经新生、调节肠道微生态等途径发挥抗抑郁作用[28-35]。PFC被认为是大脑的命令与控制中心, 与短期记忆、认知、情绪与注意力相关联。重度抑郁症患者存在功能性和结构性PFC的异常, 特别是前额叶-纹状体、前额叶-边缘与皮质-皮质的连接障碍与快感缺乏、负面情绪与绝望等抑郁症表型密切相关。研究表明, 逍遥散可通过抑制PFC中miR-200a/b-3p/核受体亚家族3C糖皮质激素受体基因 (nuclear receptor subfamily 3, group C, member 1; NR3C1) 通路的激活发挥抗神经元凋亡与改善抑郁、焦虑的作用, 且芍药苷是通路抑制的主要活性成分[28]。同时, 逍遥散还可通过星形细胞兴奋性氨基酸转运蛋白减轻谷氨酸诱导的PFC神经元损伤[29]。海马区的神经元损伤与抑郁关系密切, 抑郁症患者存在海马区神经元损伤及海马体积萎缩等表型。研究表明, 逍遥散可通过抑制神经损伤, 促进神经发生改善抑郁症状[30-32]。基于磁共振成像表明逍遥散可增加海马齿状回神经发生, 恢复海马神经元可塑性[30]。此外, 逍遥散还可降低海马谷氨酸水平, 调节磷脂酰肌醇3激酶 (phosphatidylinositol 3-kinase, PI3K)/蛋白激酶B (protein kinase B, AKT) 通路抑制兴奋性神经毒性引起的海马神经元丢失, 降低IL-1β、IL-6、TNF-α水平, 提升5-HT表达, 发挥抗抑郁作用[31-33]。肠道微生态的紊乱与抑郁症发生发展密切相关, 也是复方药效功能发挥的重要靶点。研究表明, 逍遥散可通过改善肠道菌群的组成与结构 (提升肠道有益菌比例, 降低抑郁相关条件致病菌丰度)、恢复菌群代谢紊乱、强化肠道屏障来抑制IL-1β、IL-6、TNF-α等促炎因子在结肠的表达并阻断其向外周与中枢迁移[34-36]。

2.2 四逆散

四逆散出自《伤寒论•辨少阳病脉证病治》, 由炙甘草、枳实、柴胡、芍药组成, 功效为透邪解郁、疏肝理脾, 是治疗肝郁气滞型抑郁症的经方, 临床上多治疗功能性消化不良伴抑郁、产后抑郁、脑卒中后抑郁等不同类型的抑郁症[37]。四逆散的抗抑郁机制以增加神经递质、调节突触可塑性、抑制神经炎症为主。研究表明, 四逆散可激活海马区BDNF/蛋白激酶A (protein kinase A, PKA)/cAMP反应元件结合蛋白 (cAMP-response element binding protein, CREB) 通路从而上调BDNF与5-HT的表达, 以及降低海马中促炎因子IL-1β、IL-6和TNF-α的水平[38]。网络药理学研究则表明四逆散潜在的抗抑郁机制涉及多巴胺能突触和苯丙胺成瘾信号通路的抑制, 且芍药苷、橙皮苷等黄酮类成分是主要药效活性成分[39]。含药血清研究表明四逆散可通过PI3K/AKT/雷帕霉素靶蛋白 (mechanistic target of rapamycin, mTOR) 通路保护原代海马神经元免受皮质酮诱导的神经毒性[40]。此外, 四逆散被证实可显著上调成年应激大鼠海马和PFC钙通道蛋白和突触表达从而调节神经可塑性发挥抗抑郁作用[41]。

2.3 柴胡疏肝散

柴胡疏肝散出自《景岳全书》, 由四逆散化裁而成, 由柴胡、香附、枳壳、陈皮、白芍、川芎、炙甘草构成, 是

治疗肝郁气滞型抑郁症的经方。研究表明, 柴胡疏肝散可通过上调海马区神经递质水平、恢复神经可塑性、抑制神经炎症、调节HPA轴紊乱与改善肠道菌群等途径发挥抗抑郁作用。在高脂诱导的小鼠伴抑郁模型中, 柴胡疏肝散可下调血浆和海马中促炎因子TNF-α、IL-1β和IL-6的水平, 增加海马区BDNF蛋白与基因的表达来改善抑郁样症状[42]。在慢性温和应激 (chronic unpredictable mild stress, CUMS) 抑郁模型大鼠中, 柴胡疏肝散可提升海马5-HT水平[43]。HPA轴与肠道菌群密切相关, 同时也是柴胡疏肝散抗抑郁的重要机制。研究表明, 柴胡疏肝散可通过调节肠道菌群紊乱来抑制抑郁小鼠海马与结肠中核因子κB (nuclear factor kappa-B, NF-κB) 活化及促炎因子IL-6的表达, 同时降低血液中的皮质酮 (cortisol, CORT) 水平并提升BDNF在海马中的表达[44]。此外, 柴胡疏肝散的抗抑郁作用随着抗生素的干扰显著减弱, 提示肠道菌群是介导柴胡疏肝散抗抑郁作用的关键因素[45]。

2.4 小柴胡汤

小柴胡汤出自《伤寒论》, 由柴胡、黄芩、人参、半夏、甘草、生姜、大枣组成, 是主治伤寒少阳证的经方, 临床也被用于治疗抑郁症[46]。小柴胡汤的抗抑郁作用机制以重塑HPA轴负反馈, 增加神经递质表达, 促进神经新生为主。研究表明, 在卵巢切除联合慢性不可预知轻度应激构建的围绝经期抑郁模型小鼠中, 小柴胡汤可降低CORT、ACTH和CRH表达, 提升PFC中5-HT与色氨酸羟化酶2 (tryptophan hydroxylase 2, TPH2) 表达水平[46]。此外, 在社会隔离抑郁模型小鼠中, 小柴胡汤被证实可抑制血清素转运体与单胺神经递质降解酶的表达来提升5-HT水平与BDNF表达及神经新生[47]。在慢性CORT诱导的抑郁小鼠模型中, 小柴胡汤可重塑HPA轴负反馈回路的完整性, 促进海马神经新生[48]。

2.5 越鞠丸

越鞠丸出自《丹溪心法》, 由苍术、香附、川芎、神曲、栀子五味药组成,复方配伍以“五药化六郁”为特色, 是治疗郁证的经方, 具有快速抗抑郁的功效[49]。越鞠丸抗抑郁的机制以增加海马区BDNF表达与抑制炎性细胞因子为主。研究表明, 越鞠丸可上调海马垂体腺苷酸环化酶激活多肽 (pituitary adenylate cyclase activating polypeptide, PACAP) 的表达, 抑制钙/钙调素蛋白依赖的蛋白激酶II磷酸化并增强mTOR/4EBP1/P70S6k/BDNF信号来提升海马BDNF表达发挥抗抑郁作用, 且栀子苷和山栀苷甲酯是主要的药效贡献成分[50]。此外, 在脂多糖 (lipopolysaccharide, LPS) 的抑郁模型小鼠中, 越鞠丸可提高海马中BDNF、酪氨酸激酶受体B (tyrosine kinase receptor B, TrkB) 表达及降低外周血清中炎症因子含量来产生抗抑郁作用[51]。

3 抗抑郁经方共有黄酮类成分及其作用机制

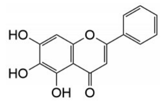
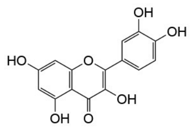
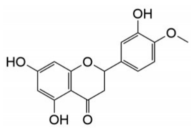
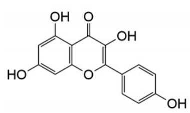
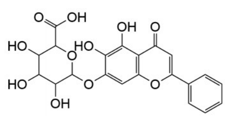
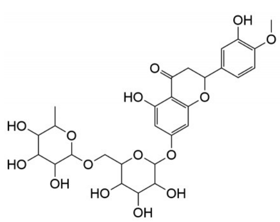
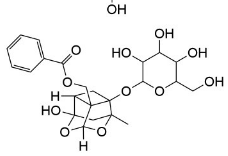
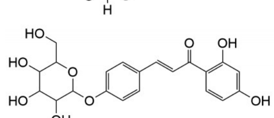
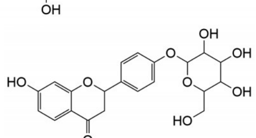
黄酮类化合物是以2-苯基色原酮为骨架衍生的一类化合物的总称。研究表明, 黄酮类成分是复方中普遍存在的活性成分, 其中以黄芩素、槲皮素、橙皮素、山柰酚为代表的黄酮苷元以及芍药苷、甘草苷、黄芩苷、异甘草苷、橙皮苷等黄酮苷被证实是抗抑郁经方的共有活性成分, 具有抗抑郁的疗效 (表1[52-111])。

3.1 黄酮苷元

3.1.1 黄芩素 黄芩素是来源于黄芩的主要活性成分之一, 是小柴胡汤等抗抑郁经方的共有黄酮类物质[52,53]。研究表明, 黄芩素可通过调节神经免疫、抑制促炎因子释放、调控HPA轴、增加神经递质、减少细胞凋亡等不同机制途径阻断抑郁症的发生发展, 发挥抗抑郁作用[54-59]。在LPS诱导的抑郁小鼠模型中及痴呆伴抑郁小鼠模型中, 黄芩素被证实可降低PFC促炎细胞因子IL-1β、IL-6、TNF-α表达与抑制海马中NF-κB炎症通路的激活来减少抑郁样行为[55,56]。此外, 黄芩素还可通过调控HPA轴影响中枢神经递质及BDNF的释放。在反复束缚压力之前进行黄芩素的预防性给药可改善HPA轴紊乱, 增加海马中DA及BDNF的表达[57]。类似地, 在鱼藤酮诱导的小鼠模型中, 黄芩素在显著减轻抑郁样行为的同时, 减少了突触核蛋白的聚集, 维持了小鼠突触可塑性并上调BDNF表达[58]。对于细胞凋亡的抑制也是黄芩素抗抑郁的重要机制。基于纳米载体的黄芩素递送显示, 其可显著抑制下丘脑的细胞凋亡并减少乳酸脱氢酶的释放从而改善嗅球切除大鼠的抑郁样行为[59]。

3.1.2 槲皮素 槲皮素是来源于柴胡的黄酮醇类物质, 是逍遥散、四逆散、柴胡疏肝散共有的黄酮类成分, 具有抗炎、抗氧化特性[60,61]。研究表明, 槲皮素可通过降低炎性因子、改善氧化应激、调节HPA轴、调节神经突触可塑性等多种途径改善包括抑郁症在内的神经系统疾病[62-68]。中枢炎性因子的升高是抑郁症患者的重要表现。通过降低大脑中包括IL-6、TNF-α和IL-1β在内的神经炎症介质的水平, 槲皮素可有效预防CUMS和LPS诱导的小鼠抑郁样行为[62,63]。通过降低PFC和海马中IL-6、TNF-α和半胱氨酸蛋白酶3 (cysteine aspartate specific protease 3, caspase-3) 的水平, 槲皮素可治疗嗅球切除大鼠的抑郁样行为[64]。氧化应激参与了抑郁症的病理过程, 抑郁症发作患者存在MDA升高及SOD、CAT的降低[65]。槲皮素对于氧化应激有显著抑制作用, 研究表明, 槲皮素注射治疗可缓解大鼠抑郁样行为, 上调脑内SOD、CAT及下调MDA表达量, 抑制氧化应激[66,67]。此外, 槲皮素还被证实可通过调节HPA轴紊

Table 1 The flavonoids active ingredients of compound prescriptions and its antidepressant mechanism. NF-κB: Nuclear factor kappa-B; CRF: Corticotropin releasing factor; Nrf2: Nuclear factor erythroid-2-related factor 2; ARE: Antioxidant response element; GST: Glutathione *S*-transferase; NE: Norepinephrine; NLRP3: NOD-like receptor thermal protein domain associated protein 3; ERK: Extracellular regulated protein kinases; CREB: cAMP-response element binding protein; ASC: Apoptosis-associated speck-like protein containing a caspase-recruitment domain

Active ingredient	Structure	Source	Effect and mechanism	Ref.
Baicalein		*Scutellaria baicalensis*	Reduced the IL-1β, IL-6, TNF-α in the prefrontal cortex and inhibited the NF-κB in the hippocampus; increased the expression of DA and BDNF in the hippocampus	[52−59]
Quercetin		*Radix Bupleuri*	Reduced the levels of IL-6, IL-1β and TNF-α in the prefrontal cortex and hippocampus; up-regulated SOD, CAT and down-regulated the expression of MDA in the brain; inhibited the expression of CRF mRNA	[60−68]
Hesperetin		*Citri reticulatae Pericarpium*; *Fructus aurantii*	Increased the expression level of Nrf2 by activating the Nrf2/ARE pathway; up-regulated the levels of SOD and CAT in the hippocampus and reduce the expression of MDA; up-regulated the level of hippocampal BDNF	[69−72]
Kaempferol		*Ginger*	Reduced levels of GST and MDA in the prefrontal cortex, inhibited IL-1β and TNF-α; significantly increased the levels of NE, DA and 5-HT in the hippocampus and prefrontal cortex	[73−77]
Baicalin		*Scutellaria baicalensis*	Reduced levels of IL-1β, IL-6 and TNF-α in the hippocampus; inhibit the production of NLRP3 and proinflammatory cytokines IL-1β and IL-6 in the prefrontal cortex; regulating the activation of hippocampal BDNF/ERK/CREB signaling pathway	[78−83]
Hesperidin		*Citri reticulatae Pericarpium*; *Fructus aurantii*	Reduced microglia-induced neuroinflammation and inhibited NLRP3 inflammasome activation in prefrontal cortex; inhibited the level of serum CORT and the expression of CRF mRNA in the hypothalamus	[84−92]
Paeoinflorin		*Chinese herbaceous peony*	Inhibited expression of NF-κB inflammatory pathway in hippocampus and regulate ERK/CREB pathway; significantly decreased the levels of CORT, ACTH, CRH and glutamate in the hippocampus	[93−102]
Isoliquiritin		*Licorice*	Significantly increased 5-HT levels in the hippocampus; increased SOD and CAT level, decreased ROS and MDA	[103−106]
Liquiritin		*Licorice*	Reduced the IL-18 and IL-1β in the hippocampus, down-regulated the expressions of NLRP3 and inflammasome-related proteins caspase-1 and ASC in the hippocampus; increased levels of 5-HT in the hypothalamus	[107−111]

乱发挥抗抑郁作用。研究表明, 槲皮素能通过显著抑制促肾上腺皮质激素释放因子 (corticotropin releasing factor, CRF) mRNA的表达而抑制HPA轴机能亢进, 治疗抑郁样行为[68]。

3.1.3 橙皮素 橙皮素来源于陈皮、枳壳等, 是柴胡疏肝散、四逆散的共有活性成分之一, 被证明具有抗炎特性, 在预防和治疗神经、心血管和胃肠道疾病方面发挥积极作用[69,70]。最新的基础研究揭示了橙皮素调节抑郁症病理生理的多种神经生物学机制, 这些机制主要与氧化应激及神经营养有关[71,72]。研究表明, 橙皮素可通过激活氧化应激的经典核因子E2相关因子2 (nuclear factor erythroid-2-related factor 2, Nrf2)/抗氧化

反应因子原件 (antioxidant response element, ARE) 通路, 增加Nrf2表达水平来减轻大脑神经元损伤从而改善糖尿病大鼠的抑郁样行为与焦虑样行为。此外, 橙皮素还可上调海马中的SOD、CAT的水平及降低MDA的表达来抑制中枢氧化应激[71,72]。对于BDNF的调控也是介导橙皮素抗抑郁作用的机制之一。研究表明, 橙皮素可上调抑郁模型大鼠中海马BDNF的水平来改善在强迫游泳及糖水偏好实验中的抑郁样症状[71]。

3.1.4 山柰酚 山柰酚来自于中药生姜, 是逍遥散、柴胡疏肝散等抗抑郁经方的共有活性成分[73]。研究表明, 山柰酚可通过提升海马神经营养因子水平、抑制细胞过度自噬、减少氧化应激损伤、抑制神经炎症等途径发挥抗抑郁作用[74-77]。Liang等[74]研究表明山柰酚治疗可显著提高CUMS抑郁模型大鼠海马区BDNF水平的表达, 提升大鼠糖水偏好。Zhang等[75]则发现山柰酚给药可显著提升大鼠血清SOD和还原型谷胱甘肽 (glutathione, GSH) 浓度, 降低MDA、IL-1β和TNF-α浓度, 表明山柰酚可通过抑制自噬和氧化应激减轻CUMS抑郁症模型大鼠海马神经元的损伤。此外, 研究者在社会击败抑郁模型小鼠中也证实山柰酚可降低PFC中MDA等氧化应激标志物的水平, 抑制IL-1β和TNF-α浓度, 上调前额叶皮层的AKT/β-连环蛋白级联活性来增强抗氧化能力和抗炎作用从而发挥抗抑郁作用[76]。对于神经递质的调节也是山柰酚抗抑郁的作用靶点之一。研究表明, 山柰酚可显著提升抑郁大鼠海马及前额叶皮质部位DA、5-HT递质水平并发挥抗抑郁作用[77]。

3.2 黄酮苷

3.2.1 黄芩苷 黄芩苷是黄芩的主要有效成分之一, 主要存在于小柴胡汤等方剂中[78]。新出现的数据表明[79-83], 黄芩苷具有抑制关键促炎介质和信号通路表达、增加脑源性神经营养因子、调控氧化应激、抑制细胞凋亡及神经保护的能力, 是一种很有前景的抑郁症潜在疗法。研究表明, 黄芩苷可显著改善慢性应激引起的抑郁样症状, 降低海马中IL-1β、IL-6和TNF-α的水平。此外, 黄芩苷的应用可显著增加PI3K、AKT和叉头框转录因子1 (forkhead box1, FoxO1) 的磷酸化, 改善了神经炎症[79]。此外, 抑制PFC中NOD样受体3 (NOD-like receptor thermal protein domain associated protein 3, NLRP3) 和促炎细胞因子IL-1β和IL-6的产生, 抑制增殖物激活受体-γ共激活因子-1α (PGC-1α)/NF-κB通路, 以及负调控海马和下丘脑中IL-1β、IL-6和TNF-α的表达也是黄芩苷缓解抑郁症神经炎症的关键机制[80,81]。BDNF可激活细胞外调节蛋白激酶 (extracellular regulated protein kinases, ERK)/CREB级联反应, 在抗抑郁作用中发挥重要作用[73]。研究表明, 黄芩苷可通过调控海马BDNF/ERK/CREB信号通路的激活来改善抑郁小鼠的抑郁样行为及认知障碍[82]。细胞凋亡被认为与包括重度抑郁症在内的神经系统疾病有关[83]。在一项基于嗅球切除术抑郁大鼠模型的研究中, 黄芩苷治疗显著改善了大鼠的抑郁样行为并调节了SOD、CAT和MDA的活性, 阻止了凋亡蛋白酶激活因子-1的表达, 有效抑制了半胱天冬酶介导的凋亡信号级联反应, 逆转了模型鼠存在的氧化应激增加、突触素表达减少和海马细胞凋亡, 提示其对于氧化应激与细胞凋亡的调控是介导抗抑郁药效的重要机制[83]。

3.2.2 橙皮苷 橙皮苷来源于陈皮、枳壳, 是柴胡疏肝散、四逆散的共有活性成分之一, 属于黄烷酮糖苷亚组[84,85]。研究表明, 橙皮苷可通过降低参与抑郁症发病机制的炎症介质和信号通路、抑制海马神经细胞凋亡、调控HPA轴发挥抗抑郁作用[86-92]。在CUMS诱导的抑郁大鼠模型中, 研究者发现橙皮苷可通过减少小胶质细胞诱导的神经炎症和抑制前额皮层中的NLRP3炎症小体激活来缓解抑郁样行为症状[56]。此外, 橙皮苷还可通过NF-κB通路调节高迁移率族蛋白1的表达和炎性细胞因子 (IL-1β、IL-6和TNF-α) 的释放[87-90]。Chen等[91]研究还表明橙皮苷可通过减少神经细胞凋亡和调控GR及*N*-甲基-*D*-天冬氨酸受体表达发挥抗抑郁的作用。对于HPA轴的调控也是橙皮苷抗抑郁的重要机制。研究表明在显著改善抑郁行为症状的同时, 橙皮苷可逆转抑郁大鼠过高的CORT水平和肾上腺指数, 并能抑制CUMS大鼠下丘脑CRF mRNA表达、上调室旁核GR蛋白表达, 表明橙皮苷的抗抑郁作用机制可能与调节HPA轴的功能有关[92]。

3.2.3 芍药苷 芍药苷是逍遥散与四逆散共有的重要活性成分, 同时也是逍遥散复方的质控标准[93]。研究表明芍药苷具有抗炎、神经保护和免疫调节作用, 可能是其改善抑郁样行为的可能机制[94-102]。研究表明, 芍药苷可上调大脑中ERK1/2信号通路相关蛋白的表达水平, 改善慢性约束应激模型小鼠的抑郁样行为[96]。同时, 芍药苷还可抑制海马区NF-κB炎性通路蛋白表达并调节ERK/CREB通路改善神经元损伤[97,98]。对于HPA轴功能的调控及氧化应激的抑制也是芍药苷抗抑郁药效发挥的重要机制。研究表明芍药苷可显著降低抑郁大鼠血清中的CORT、ACTH、CRH和海马中谷氨酸的水平, 并显著增加了海马GR核易位[99]。此外, 体外细胞实验结果还证实芍药苷可抑制活性氧的产生, 从而抑制细胞凋亡发挥神经保护作用[99]。对于microRNA的干预也是芍药苷抗细胞凋亡的机制之一[100]。Hou[100]的研究表明, 芍药苷可上调miR-29b mRNA表达水平, 抑制海马区的细胞自发性凋亡, 发挥抗抑郁作

用。大脑皮层神经元的发育与抑郁症的发病联系密切。体外研究表明芍药苷可增加胎鼠大脑皮层的神经细胞，降低神经元的死亡率，具有显著的神经保护作用[101]。此外，对于血清BDNF水平及海马组织BDNF水平的上调也可表明芍药苷的神经营养保护作用[102]。

3.2.4 异甘草苷 异甘草苷来自于中药甘草，是逍遥散、柴胡疏肝散、小柴胡汤等抗抑郁经方共有的重要活性成分[103]。研究表明异甘草苷具有抗炎、抗凋亡、神经保护和免疫调节作用，可能是其改善抑郁样行为的可能机制[104-106]。研究表明，异甘草苷可上调海马中神经元蛋白水平，改善神经元的存活和形态，并减少与细胞焦亡相关的神经元细胞死亡[104]。同时，异甘草苷可降低LPS及CUMS抑郁模型海马中p-NF-κB和NLRP3的蛋白质水平，抑制中枢IL-1β、IL-6和TNF-α等促炎因子的表达从而调节抑郁样行为[104]。对于神经递质及氧化应激的调控也是异甘草苷抗抑郁与抗焦虑的重要机制之一。研究表明，异甘草苷治疗可显著提升抑郁小鼠的单胺水平，尤其是5-HT，并且降低氧化酶活性[105]。此外，在模拟抑郁症发病的皮质醇损伤细胞模型中，异甘草苷也被发现增加了SOD和CAT的活性，降低了ROS和MDA的含量，表明其良好的抗氧化应激作用[106]。

3.2.5 甘草苷 与异甘草苷相似，甘草苷也是来自于中药甘草，属于逍遥散、柴胡疏肝散、小柴胡汤、半夏厚朴汤等抗抑郁经方共有的重要活性成分[103]。研究表明甘草苷具有抗神经炎症和抗氧化应激的作用，可能是其改善抑郁样行为的可能机制[107-111]。在抑郁大脑的脑组织中，研究者通过色谱–四极串联质谱法测定了与炎症相关的脂质，并发现甘草苷可促进抗炎脂质合成，提示甘草苷潜在的抗神经炎症作用[107]。在行为绝望和CUMS抑郁模型中，研究者发现甘草苷可通过增加海马SOD活性，降低MDA水平改善小鼠的抑郁样行为。甘草苷还可降低小鼠海马区细胞炎性因子IL-18和IL-1β，下调海马区NLRP3炎性小体表达，提示其对于神经炎症的抑制作用[108]。此外，研究人员发现甘草苷可抑制由LPS引起的海马区小胶质细胞活化，降低IL-1β、IL-6和TNF-α等促炎因子表达，增加海马中树突棘的密度[109]。对于神经递质的调节也是甘草苷的重要药理机制。研究表明，甘草苷可提升下丘脑中5-HT和去甲肾上腺素的含量[110]。基于超高效液相色谱–串联质谱的研究也表明甘草苷治疗抑郁大鼠的机制与神经递质的前体色氨酸生物合成及酪氨酸代谢相关，提示甘草苷潜在的神经递质调节作用[111]。

4 总结与展望

随着对于抑郁症发病机制研究的深入，作为一种机制复杂的精神疾病，靶向神经递质的治疗已无法满足对于炎症反应、氧化应激及肠道菌群紊乱等多种抑郁症致病因素的调控，因此对于某些抑郁症患者的临床疗效有限。基于此，从多种靶点途径对于抑郁症进行干预治疗的策略可能是未来抑郁症治疗发展的方向。

以逍遥散、四逆散、柴胡疏肝散、越鞠丸为代表的抗抑郁经方是中医治疗抑郁症的重要方法，黄酮类物质则是其共有的活性成分之一。通过对于神经递质、

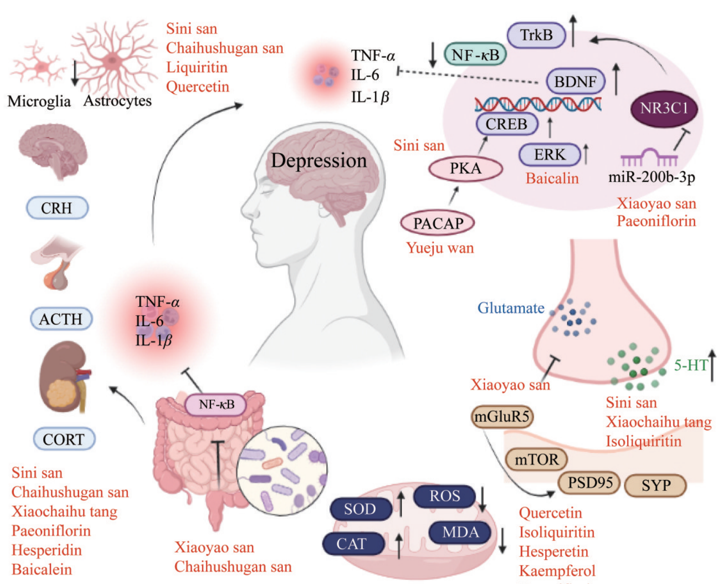


Figure 3 The pharmacodynamic mechanism of antidepressant compound prescriptions and its flavonoids active ingredients. NR3C1: Nuclear receptor subfamily 3, group C, member 1; TrkB: Tyrosine kinase receptor B; PKA: Protein kinase A; PACAP: Pituitary adenylate cyclase activating polypeptide; mGluR5: Metabotropic glutamate receptor 5; mTOR: Mechanistic target of rapamycin; PSD95: Postsynaptic protein-95; SYP: Synaptophysin

神经炎症、氧化应激、HPA轴、肠道菌群等多种途径的调控, 复方及其黄酮类成分可以协同调控多个途径发挥抗抑郁作用。具体而言, 复方及其黄酮类可增加大脑中的5-HT、DA等神经递质和BDNF的含量, 降低中枢系统促炎因子的水平与小胶质细胞与星形胶质细胞的异常激活, 抑制神经系统的氧化应激, 调控HPA轴, 恢复肠道菌群的组成与结构及紊乱的微生物代谢产物, 多靶点多层次来预防与治疗抑郁症 (图3)。基于此, 基于经方中黄酮类成分的抗抑郁药物开发是具有潜力的方向。

事实上, 对于抗抑郁经方黄酮类成分的作用机制研究也存在局限性。首先是缺乏多中心、大样本的临床研究, 目前进行的一些研究纳入的病例数较少。其次, 对于药物的抗抑郁作用研究大多还仅仅从分子生物学层面以基因蛋白研究为主, 仍需引入蛋白组学代谢组学及单细胞测序等多组学技术进行深入的研究, 从而明确其抗抑郁的机制。此外, 对于中药活性成分的体内代谢研究及代谢情况与其抗抑郁功效之间的相关性的研究较少, 特别是对于药物突破血脑屏障, 提升生物利用度方面研究较为局限, 对于明确其给药方式, 了解其起效时间及维持时间仍存在挑战。

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References

[1] Hao WZ, Li XJ, Zhang PW, et al. A review of antibiotics, depression, and the gut microbiome [J]. Psychiatry Res, 2020, 284: 112691.

[2] Wang QG, Ding SY, Wang Q, et al. Treatment of cardiovascular and cerebrovascular diseases complicated with depression from perspective of "smooth blood flow leading to normal mind" [J]. Chin Arch Tradit Chin Med (中华中医药学刊), 2021, 39: 109-111.

[3] Cao QY. Research progress on the relationship between the pathogenesis of depression in old age and stroke [J]. Pract Geriatr (实用老年医学), 2013, 27: 538-542.

[4] Hao WZ, Chen Q, Wang L, et al. Emerging roles of long non-coding RNA in depression [J]. Prog Neuropsychopharmacol Biol Psychiatry, 2022, 115: 110515.

[5] Gan H, Lei Y, Yuan N, et al. Circular RNAs in depression: biogenesis, function, expression, and therapeutic potential [J]. Biomed Pharmacother, 2021, 137: 111244.

[6] Da XL, Hao WZ, Li XJ. Summary of seasonal characteristics and pathogenesis of depression with liver stagnation and spleen deficiency [J]. Global Tradit Chin Med (环球中医药), 2021, 14: 879-882.

[7] Da XL, Li XJ, Qiu WQ, et al. Animal models of depression and progress in prevention and treatment of Chinese medicine prescription [J]. Chin J Basic Med Tradit Chin Med (中国中医基础医学杂志), 2020, 26: 1582-1586.

[8] Zhang MY, Xu EP, Shang LZ, et al. Research progress on TCM syndrome differentiation and classification of depression [J]. Mod Tradit Chin Med Mater Med-World Sci Technol (世界科学技术-中医药现代化), 2021, 23: 4251-4258.

[9] He N, Lv HB. Treatment of depression combined with coronary heart disease by detoxifying the liver and relieving depression, activating blood circulation and removing blood stasis [J]. Mod J Integr Tradit Chin West Med (现代中西医结合杂志), 2020, 29: 3600-3603.

[10] Zhang LY, Jiang J, He M, et al. Research progress on pharmacology of traditional Chinese medicine against depression [J]. Chin J Exp Tradit Med Form (中国实验方剂学杂志), 2017, 23: 224-234.

[11] Xu XJ, Li TY, Fan WD, et al. Research survey of traditional Chinese medicine compound therapy for depression [J]. Med Recapit (医学综述), 2021, 27: 3687-3693.

[12] Wang Z, Lam KL, Hu J, et al. Chlorogenic acid alleviates obesity and modulates gut microbiota in high-fat-fed mice [J]. Food Sci Nutr, 2019, 7: 579-588.

[13] Vissiennon C, Nieber K, Kelber O, et al. Route of administration determines the anxiolytic activity of the flavonols kaempferol, quercetin and myricetin - are they prodrugs? [J]. J Nutr Biochem, 2012, 23: 733-740.

[14] Bhattacharyya S, Ahmed AT, Arnold M, et al. Metabolomic signature of exposure and response to citalopram/escitalopram in depressed outpatients [J]. Transl Psychiatry, 2019, 9: 173.

[15] Hao WZ. Study on the Regulatory Effect of Xiaoyaosan on the Abnormal Behaviors of Mice with Intestinal Flora Disorder Based on the NLRP3-ASC-CASPASE-1 Signal of Colon (基于结肠NLRP3-ASC-CASPASE-1炎性信号探究逍遥散对肠道菌群失调小鼠行为异常的调节作用) [D]. Guangzhou: Jinan University, 2020.

[16] Neupane SP, Virtej A, Myhren LE, et al. Biomarkers common for inflammatory periodontal disease and depression: a systematic review [J]. Brain Behav Immun Health, 2022, 21: 100450.

[17] Sakamoto S, Zhu X, Hasegawa Y, et al. Inflamed brain: targeting immune changes and inflammation for treatment of depression [J]. Psychiatry Clin Neurosci, 2021, 75: 304-311.

[18] Li K, Yan L, Zhang Y, et al. Seahorse treatment improves depression-like behavior in mice exposed to CUMS through reducing inflammation/oxidants and restoring neurotransmitter and neurotrophin function [J]. J Ethnopharmacol, 2020, 250: 112487.

[19] Cao P, Chen C, Liu A, et al. Early-life inflammation promotes depressive symptoms in adolescence *via* microglial engulfment

of dendritic spines [J]. Neuron, 2021, 109: 2573-2589.

[20] 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.

[21] Gao ZH, Jin WD. Research progress on the relationship between antidepressant drugs and HPA axis function in depression [J]. Her Med (医药导报), 2017, 36: 659-664.

[22] Carlessi AS, Borba LA, Zugno AI, et al. Gut microbiota-brain axis in depression: the role of neuroinflammation [J]. Eur J Neurosci, 2021, 53: 222-235.

[23] Lee SM, Dong TS, Krause-Sorio B, et al. The intestinal microbiota as a predictor for antidepressant treatment outcome in geriatric depression: a prospective pilot study [J]. Int Psychogeriatr, 2022, 34: 33-45.

[24] Zheng P, Zeng B, Zhou C, et al. Gut microbiome remodeling induces depressive-like behaviors through a pathway mediated by the host's metabolism [J]. Mol Psychiatry, 2016, 21: 786-796.

[25] Vaváková M, Ďuračková Z, Trebatická J. Markers of oxidative stress and neuroprogression in depression disorder [J]. Oxid Med Cell Longev, 2015, 2015: 898393.

[26] Lindqvist D, Dhabhar FS, James SJ, et al. Oxidative stress, inflammation and treatment response in major depression [J]. Psychoneuroendocrinology, 2017, 76: 197-205.

[27] Liang Y, Zhao H, Yue LF, et al. Clinical and experimental research progress of Xiaoyao powder for depression [J]. J New Chin Med (新中医), 2017, 49: 142-145.

[28] Yuan N, Li X, Tang K, et al. Xiaoyaosan inhibits neuronal apoptosis by regulating the miR-200/NR3C1 signaling in the prefrontal cortex of chronically stressed rats [J]. Phytomedicine, 2022, 103: 154239.

[29] Liu Y, Ding XF, Wang XX, et al. Xiaoyaosan exerts antidepressant-like effects by regulating the functions of astrocytes and EAATs in the prefrontal cortex of mice [J]. BMC Complement Altern Med, 2019, 19: 215.

[30] Gao L, Huang P, Dong Z, et al. Modified Xiaoyaosan (MXYS) exerts anti-depressive effects by rectifying the brain blood oxygen level-dependent fMRI signals and improving hippocampal neurogenesis in mice [J]. Front Pharmacol, 2018, 9: 1098.

[31] Zhou XM, Liu CY, Liu YY, et al. Xiaoyaosan alleviates hippocampal glutamate-induced toxicity in the CUMS rats *via* NR2B and PI3K/Akt signaling pathway [J]. Front Pharmacol, 2021, 12: 586788.

[32] Wan XM, Zhou R, Huang XT, et al. Effect of Xiaoyao powder on IL-6 and TNF-α in hippocampus of depression rats with chronic unpredictable mild stress [J]. J Liaoning Univ Tradit Chin Med (辽宁中医药大学学报), 2020, 22: 47-51.

[33] Zhou XM, Yin YJ, Chang Z, et al. Regulation effect of Xiaoyao powder on PI3K/AKT signaling pathway in hippocampal CA1 region of CUMS rats [J]. Acta Chin Med Pharmacol (中医药学报), 2022, 50: 12-17.

[34] Hao W, Wu J, Yuan N, et al. Xiaoyaosan improves antibiotic-induced depressive-like and anxiety-like behavior in mice through modulating the gut microbiota and regulating the NLRP3 inflammasome in the colon [J]. Front Pharmacol, 2021, 12: 619103.

[35] Feng Y, Meng M, Feng J, et al. Antidepressant-like effects of the petroleum ether fraction of Xiaoyaosan in the CUMS rat model of depression [J]. Acta Pharm Sin (药学学报), 2020, 55: 305-314.

[36] Lv M. Comparative Researches on the Antidepressant Effects of Xiaoyaosan and Its Efficacy Groups Based on Gut Microbiota and Fecal Metabolomics (基于肠道菌群和粪便代谢组学的逍遥散及其功效药队抗抑郁作用比较研究) [D]. Taiyuan: Shanxi University, 2021.

[37] Shao L, Zhou CY, Mao MD, et al. Research progress of Sini powder in treatment of depression [J]. Acta Chin Med (中医学报), 2022, 37: 1198-1203.

[38] Cao K, Shen C, Yuan Y, et al. SiNiSan ameliorates the depression-like behavior of rats that experienced maternal separation through 5-HT1A receptor/CREB/BDNF pathway [J]. Front Psychiatry, 2019, 10: 160.

[39] Li B, Rui J, Ding X, et al. Deciphering the multicomponent synergy mechanisms of SiNiSan prescription on irritable bowel syndrome using a bioinformatics/network topology based strategy [J]. Phytomedicine, 2019, 63: 152982.

[40] Zhang M, Zhang Y, Sun H, et al. Sinisan protects primary hippocampal neurons against corticosterone by inhibiting autophagy *via* the PI3K/Akt/mTOR pathway [J]. Front Psychiatry, 2021, 12: 627056.

[41] Shen C, Cao K, Cui S, et al. SiNiSan ameliorates depression-like behavior in rats by enhancing synaptic plasticity *via* the CaSR-PKC-ERK signaling pathway [J]. Biomed Pharmacother, 2020, 124: 109787.

[42] Li L, Yu AL, Wang ZL, et al. Chaihu-Shugan-San and absorbed meranzin hydrate induce anti-atherosclerosis and behavioral improvements in high-fat diet *ApoE*$^{-/-}$ mice *via* anti-inflammatory and BDNF-TrkB pathway [J]. Biomed Pharmacother, 2019, 115: 108893.

[43] Chen Q, Li C, Tao E, et al. Exploration of a brain-liver-communication-related mechanism involved in the experimental perimenopausal depression rat model using Chaihu-Shugan-San [J]. Neurochem Res, 2022, 47: 1354-1368.

[44] Han SK, Kim JK, Park HS, et al. Chaihu-Shugan-San (Shihosogansan) alleviates restraint stress-generated anxiety and depression in mice by regulating NF-κB-mediated BDNF expression through the modulation of gut microbiota [J]. Chin Med, 2021, 16: 77.

[45] Yu M, Jia HM, Zhang T, et al. Gut microbiota is the key to the antidepressant effect of Chaihu-Shu-Gan-San [J]. Metabolites,

2020, 10: 63.
[46] Zhang K, Wang Z, Pan X, et al. Antidepressant-like effects of Xiaochaihutang in perimenopausal mice [J]. J Ethnopharmacol, 2020, 248: 112318.
[47] Ma J, Wang F, Yang J, et al. Xiaochaihutang attenuates depressive/anxiety-like behaviors of social isolation-reared mice by regulating monoaminergic system, neurogenesis and BDNF expression [J]. J Ethnopharmacol, 2017, 208: 94-104.
[48] Zhang K, Yang J, Wang F, et al. Antidepressant-like effects of Xiaochaihutang in a neuroendocrine mouse model of anxiety/depression [J]. J Ethnopharmacol, 2016, 194: 674-683.
[49] Zhou ZL, Zhang YX, Chen G. Research progress on Yueju pill in the treatment of depression and associated traditional Chinese medicine connotation [J]. Mod Tradit Chin Med Mater Med-World Sci Technol (世界科学技术-中医药现代化), 2018, 20: 875-879.
[50] Zhang H, Sun Y, Yau SY, et al. Synergistic effects of two naturally occurring iridoids in eliciting a rapid antidepressant action by up-regulating hippocampal PACAP signalling [J]. Br J Pharmacol, 2022, 179: 4078-4091.
[51] Nie CY, Wang JH, Zhang HL, et al. Study on mechanism of the antidepressant-like effect of Yueju pill in LPS-induced mice [J]. Lishizhen Med Mater Med Res (时珍国医国药), 2020, 31: 774-778.
[52] Wang YS, Shen CY, Jiang JG. Antidepressant active ingredients from herbs and nutraceuticals used in TCM: pharmacological mechanisms and prospects for drug discovery [J]. Pharmacol Res, 2019, 150: 104520.
[53] Zhao F. Study on the Compatibility of Radix Scutellariae in the Prescription of Treating Depression and Its Mechanism of Antidepressant Action (黄芩在治疗抑郁症方剂中的配伍应用及其抗抑郁机制研究) [D]. Nanjing: Nanjing University of Chinese Medicine, 2020.
[54] Liu JF, Su G, Gao J, et al. Research advances on the neuroprotective effect of baicalein [J]. Chin J Clin Pharmacol (中国临床药理学杂志), 2019, 35: 2773-2776.
[55] Liu HT, Lin YN, Tsai MC, et al. Baicalein exerts therapeutic effects against endotoxin-induced depression-like behavior in mice by decreasing inflammatory cytokines and increasing brain-derived neurotrophic factor levels [J]. Antioxidants (Basel), 2022, 11: 947.
[56] Gao L, Li J, Zhou Y, et al. Effects of baicalein on cortical proinflammatory cytokines and the intestinal microbiome in senescence accelerated mouse prone 8 [J]. ACS Chem Neurosci, 2018, 9: 1714-1724.
[57] Lee B, Sur B, Park J, et al. Chronic administration of baicalein decreases depression-like behavior induced by repeated restraint stress in rats [J]. Korean J Physiol Pharmacol, 2013, 17: 393-403.
[58] Zhao X, Kong D, Zhou Q, et al. Baicalein alleviates depression-like behavior in rotenone-induced Parkinson's disease model in mice through activating the BDNF/TrkB/CREB pathway [J]. Biomed Pharmacother, 2021, 140: 111556.
[59] Chen B, Luo M, Liang J, et al. Surface modification of PGP for a neutrophil-nanoparticle co-vehicle to enhance the anti-depressant effect of baicalein [J]. Acta Pharm Sin B, 2018, 8: 64-73.
[60] Ma YX, Liu Q, Wu YK, et al. Content determination of quercetin and isorhamnetin in the Dianchaihu by HPLC [J]. J Kunming Univ (昆明学院学报), 2019, 41: 88-92, 98.
[61] Wang W, Lin P, Ma L, et al. Separation and determination of flavonoids in three traditional Chinese medicines by capillary electrophoresis with amperometric detection [J]. J Sep Sci, 2016, 39: 1357-1362.
[62] Fang K, Li HR, Chen XX, et al. Corrigendum: quercetin alleviates lps-induced depression-like behavior in rats *via* regulating BDNF-related imbalance of copine 6 and TREM1/2 in the hippocampus and PFC [J]. Front Pharmacol, 2020, 11: 518.
[63] Mehta V, Parashar A, Udayabanu M. Quercetin prevents chronic unpredictable stress induced behavioral dysfunction in mice by alleviating hippocampal oxidative and inflammatory stress [J]. Physiol Behav, 2017, 171: 69-78.
[64] Rinwa P, Kumar A. Quercetin suppress microglial neuroinflammatory response and induce antidepressent-like effect in olfactory bulbectomized rats [J]. Neuroscience, 2013, 255: 86-98.
[65] Tsai MC, Huang TL. Increased activities of both superoxide dismutase and catalase were indicators of acute depressive episodes in patients with major depressive disorder [J]. Psychiatry Res, 2016, 235: 38-42.
[66] Şahin TD, Gocmez SS, Duruksu G, et al. Resveratrol and quercetin attenuate depressive-like behavior and restore impaired contractility of vas deferens in chronic stress-exposed rats: involvement of oxidative stress and inflammation [J]. Naunyn Schmiedebergs Arch Pharmacol, 2020, 393: 761-775.
[67] Khan K, Najmi AK, Akhtar M. A natural phenolic compound quercetin showed the usefulness by targeting inflammatory, oxidative stress markers and augment 5-HT levels in one of the animal models of depression in mice [J]. Drug Res (Stuttg), 2019, 69: 392-400.
[68] Kawabata K, Kawai Y, Terao J. Suppressive effect of quercetin on acute stress-induced hypothalamic-pituitary-adrenal axis response in Wistar rats [J]. J Nutr Biochem, 2010, 21: 374-380.
[69] Liu Y, Wang W, Chen Y, et al. Simultaneous quantification of nine components in the plasma of depressed rats after oral administration of Chaihu-Shugan-San by ultra-performance liquid chromatography/quadrupole-time-of-flight mass spectrometry and its application to pharmacokinetic studies [J]. J Pharm Biomed Anal, 2020, 186: 113310.
[70] Liu L, Shu Y, Jian D, et al. Identication of the metabolites of Sinisan extract in rat plasma, urine, feces and bile after intragastric administration [J]. Acta Pharm Sin (药学学报), 2011, 46: 1374-1379.

[71] Alizadeh Makvandi A, Khalili M, Roghani M, et al. Hesperetin ameliorates electroconvulsive therapy-induced memory impairment through regulation of hippocampal BDNF and oxidative stress in a rat model of depression [J]. J Chem Neuroanat, 2021, 117: 102001.
[72] Zhu X, Zhang YM, Zhang MY, et al. Hesperetin ameliorates diabetes-associated anxiety and depression-like behaviors in rats *via* activating Nrf2/ARE pathway [J]. Metab Brain Dis, 2021, 36: 1969-1983.
[73] Zhang S, Lu Y, Chen W, et al. Network pharmacology and experimental evidence: PI3K/AKT signaling pathway is involved in the antidepressive roles of Chaihu Shugan San [J]. Drug Des Devel Ther, 2021, 15: 3425-3441.
[74] Liang YD, Tan YG, Zhang S, et al. Effect and mechanism of kaempferol on depression-like behavior in elderly rats with chronic stress depression [J]. Chin J Clin Pharmacol (中国临床药理学杂志), 2020, 36: 4028-4030.
[75] Zhang S, Zhang Y, Li B, et al. Protective effects of kaempferol on autophagy-and oxidative stress-mediated injury of hippocampal neuron in CUMS-induced depression model rats [J]. Chin J Immunol (中国免疫学杂志), 2019, 35: 146-150, 155.
[76] Gao W, Wang W, Peng Y, et al. Antidepressive effects of kaempferol mediated by reduction of oxidative stress, proinflammatory cytokines and up-regulation of AKT/β -catenin cascade [J]. Metab Brain Dis, 2019, 34: 485-494.
[77] Wang J, Xie J, Chen YM, et al. Antidepressant effect of kaempferol on rat complex model of depression and breast cancer [J]. Chin J Mod Appl Pharm (中国现代应用药学), 2016, 33: 277-280.
[78] Huang T, Liu Y, Zhang C. Pharmacokinetics and bioavailability enhancement of baicalin: a review [J]. Eur J Drug Metab Pharmacokinet, 2019, 44: 159-168.
[79] Liu X, Liu C. Baicalin ameliorates chronic unpredictable mild stress-induced depressive behavior: involving the inhibition of NLRP3 inflammasome activation in rat prefrontal cortex [J]. Int Immunopharmacol, 2017, 48: 30-34.
[80] Guo LT, Wang SQ, Su J, et al. Baicalin ameliorates neuroinflammation-induced depressive-like behavior through inhibition of toll-like receptor 4 expression *via* the PI3K/AKT/FoxO1 pathway [J]. J Neuroinflammation, 2019, 16: 95.
[81] Yu H, Zhang F, Guan X. Baicalin reverse depressive-like behaviors through regulation SIRT1-NF-κB signaling pathway in olfactory bulbectomized rats [J]. Phytother Res, 2019, 33: 1480-1489.
[82] Jia Z, Yang J, Cao Z, et al. Baicalin ameliorates chronic unpredictable mild stress-induced depression through the BDNF/ERK/CREB signaling pathway [J]. Behav Brain Res, 2021, 414: 113463.
[83] Yu HY, Yin ZJ, Yang SJ, et al. Baicalin reverses depressive-like behaviours and regulates apoptotic signalling induced by olfactory bulbectomy [J]. Phytother Res, 2016, 30: 469-475.
[84] Parhiz H, Roohbakhsh A, Soltani F, et al. Antioxidant and anti-inflammatory properties of the citrus flavonoids hesperidin and hesperetin: an updated review of their molecular mechanisms and experimental models [J]. Phytother Res, 2015, 29: 323-331.
[85] Li F, Zhang K, Yu M, et al. Antidepressant-like effect and phytochemical profile of supercritical CO_2 extract from *Citri reticulatae pericarpium* [J]. Pharmazie, 2021, 76: 249-255.
[86] Xie L, Gu Z, Liu H, et al. The anti-depressive effects of hesperidin and the relative mechanisms based on the NLRP3 inflammatory signaling pathway [J]. Front Pharmacol, 2020, 11: 1251.
[87] Fu H, Liu L, Tong Y, et al. The antidepressant effects of hesperidin on chronic unpredictable mild stress-induced mice [J]. Eur J Pharmacol, 2019, 853: 236-246.
[88] Kosari-Nasab M, Shokouhi G, Ghorbanihaghjo A, et al. Hesperidin attenuates depression-related symptoms in mice with mild traumatic brain injury [J]. Life Sci, 2018, 213: 198-205.
[89] Li M, Shao H, Zhang X, et al. Hesperidin alleviates lipopolysaccharide-induced neuroinflammation in mice by promoting the miRNA-132 pathway [J]. Inflammation, 2016, 39: 1681-1689.
[90] Kwatra M, Ahmed S, Gawali B, et al. Hesperidin alleviates chronic restraint stress and lipopolysaccharide-induced hippocampus and frontal cortex damage in mice: role of TLR4/NF-κB, p38 MAPK/JNK, Nrf2/ARE signaling [J]. Neurochem Int, 2020, 140: 104835.
[91] Chen X, Cao H, Hu L. Effects of hesperidin on apoptosis of hippocampal neurons, GR and NR2B in depression rats [J]. China Pharm (中国药师), 2020, 23: 2118-2122.
[92] Cai L, Li R, Wu QQ, et al. Effect of hesperidin on behavior and HPA axis of rat model of chronic stress-induced depression [J]. China J Chin Mater Med (中国中药杂志), 2013, 38: 229-233.
[93] Yuan N, Gong L, Tang K, et al. An integrated pharmacology-based analysis for antidepressant mechanism of Chinese herbal formula Xiao-Yao-San [J]. Front Pharmacol, 2020, 11: 284.
[94] Zhang L, Wei W. Anti-inflammatory and immunoregulatory effects of paeoniflorin and total glucosides of paeony [J]. Pharmacol Ther, 2020, 207: 107452.
[95] She Y, Shao L, Zhang Y, et al. Neuroprotective effect of glycosides in Buyang Huanwu Decoction on pyroptosis following cerebral ischemia-reperfusion injury in rats [J]. J Ethnopharmacol, 2019, 242: 112051.
[96] Tang M, Chen M, Li Q. Paeoniflorin ameliorates chronic stress-induced depression-like behavior in mice model by affecting ERK1/2 pathway [J]. Bioengineered, 2021, 12: 11329-11341.
[97] Bai H, Chen S, Yuan T, et al. Paeoniflorin ameliorates neuropathic pain-induced depression-like behaviors in mice by inhibiting hippocampal neuroinflammation activated *via* TLR4/NF- κB pathway [J]. Korean J Physiol Pharmacol, 2021, 25: 217-225.

[98] Zhong X, Li G, Qiu F, et al. Paeoniflorin ameliorates chronic stress-induced depression-like behaviors and neuronal damages in rats *via* activation of the ERK-CREB pathway [J]. Front Psychiatry, 2019, 9: 772.

[99] Li YC. Paeoniflorin Ameliorates Depressive-like Behavior in Prenatally Stressed Offspring through the HPA Axis and GR (芍药苷通过HPA轴和GR改善产前应激子代抑郁样行为的作用研究) [D]. Chongqing: Northwest University, 2021.

[100] Hou JY. Exploring the Mechanism of Antidepressant Effect of Xiaoyaosan and Paeoniflorin Based on miR-29b Inhibition of Hippocampal Neuron Apoptosis (基于miR-29b抑制海马神经元凋亡探究逍遥散及芍药苷抗抑郁作用机制) [D]. Beijing: Beijing University of Chinese Medicine, 2021.

[101] Wu YM. The Effects of Paeoniflorin on Viability and Survival of Cortical Neurons *in vitro* (芍药甙促小鼠皮层神经元活性及存活的体外研究) [D]. Xi'an: Air Force Medical University, 2002.

[102] Xue M, Mu DZ, Huang X, et al. Effect of Paeoniflorin on Hippocamp Tissue Pathomorphology and BDNF Level of Forced Swimming Rats Model [J]. J Nanjing Univ Tradit Chin Med (南京中医药大学学报), 2016, 32: 439-441.

[103] Shen QN, Chen LH, Huang ZY, et al. Effects of different softening methods on quality of Glycyrrhizae Radix et Rhizoma [J]. Chin Tradit Herb Drugs (中草药), 2020, 51: 76-83.

[104] Li Y, Song W, Tong Y, et al. Isoliquiritin ameliorates depression by suppressing NLRP3-mediated pyroptosis *via* miRNA-27a/SYK/NF-κB axis [J]. J Neuroinflammation, 2021, 18: 1.

[105] Yu C, Zhang Y, Gao KX, et al. Serotonergically dependent anti-hyperalgesic and antiallodynic effects of isoliquiritin in a mouse model of neuropathic pain [J]. Eur J Pharmacol, 2020, 881: 173184.

[106] Zhou YZ, Li X, Gong WX, et al. Protective effect of isoliquiritin against corticosterone-induced neurotoxicity in PC12 cells [J]. Food Funct, 2017, 8: 1235-1244.

[107] Jin W, Yang J, Liu D, et al. Determination of inflammation-related lipids in depressive rats by on-line supercritical fluid extraction-supercritical fluid chromatography-tandem mass spectrometry [J]. J Pharm Biomed Anal, 2021, 203: 114210.

[108] Liu C, Yuan D, Zhang C, et al. Liquiritin alleviates depression-like behavior in CUMS mice by inhibiting oxidative stress and NLRP3 inflammasome in hippocampus [J]. Evid Based Complement Alternat Med, 2022, 2022: 7558825.

[109] Chen M, Zhang QP, Zhu JX, et al. Involvement of FGF-2 modulation in the antidepressant-like effects of liquiritin in mice [J]. Eur J Pharmacol, 2020, 881: 173297.

[110] Lan XY, Yu H, Chen QJ, et al. Effect of liquiritin on neuroendocrine-immune network in menopausal rat model [J]. Phytother Res, 2020, 34: 2665-2674.

[111] Yang J, Jin W, Liu D, et al. Enhanced pseudotargeted analysis using a segment data dependent acquisition strategy by liquid chromatography-tandem mass spectrometry for a metabolomics study of liquiritin in the treatment of depression [J]. J Sep Sci, 2020, 43: 2088-2096.