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中医药治疗乳腺癌相关抑郁发展的机制研究进展

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【摘要】 乳腺癌诊断与治疗过程中出现以抑郁为主的病理性情绪变化,临床上称之为乳腺癌相关抑郁。大量的流行病学和临床研究已证实乳腺癌相关抑郁病情复杂且治疗难度大、预后差。现有临床治法大多是乳腺癌术后化疗服用抗抑郁药物,将乳腺癌和抑郁症作为两个独立的疾病进行治疗,存在效率低、不良反应强等诸多缺陷。而中医药凭借其多成分同时调控多通路、多靶点显著优势,在防治乳腺癌相关抑郁的方面具有独特价值。本文主要是从神经系统紊乱、炎症免疫反应、肠道菌群失调等方面对乳腺癌相关抑郁机制,以及中医药的治疗机制进行综述,以期对中医药治疗乳腺癌相关抑郁临床应用和研究提供一定的参考。

【关键词】 乳腺癌相关抑郁;发病机制;中医药治疗;综述
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Research progress on the use of Traditional Chinese Medicines to treat breast cancer-related depression and associated diseases

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【**Abstract**】 Pathological mood changes, mainly depression, occurring during the diagnosis and treatment of breast cancer are referred to as breast cancer-related depression (BCRD). Numerous epidemiological and clinical studies have confirmed that BCRD is a complex condition that is difficult to treat and has a poor prognosis. Most existing clinical treatments involve the use of postoperative chemotherapy for breast cancer, and antidepressant drugs, which treat breast cancer and depression as two independent diseases and have various disadvantages such as low efficiency and strong adverse reactions. Traditional Chinese Medicine (TCM) has a unique value in the prevention and treatment of BCRD via its ability to regulate multiple pathways and targets using multiple components at the same time. In this paper, we review the mechanism of BRCD and the therapeutic mechanisms of TCM from the aspects of neurological disorders, inflammatory immune response, and intestinal flora disorders, with a view to providing references for the clinical application and research of TCM in the treatment of BCRD.

【**Keywords**】 breast cancer-related depression; pathogenesis; Chinese medicine treatment; review
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乳腺癌是导致全球女性癌症致死的首要原因,2022 年乳腺癌全球发病率仅次于肺癌,占所有新发癌症病例的 11.6%[1]。抑郁症是一种以持久心境低落为主要特征的精神疾病,居全球患者自杀的 20 个主要原因之首。2015 年专家共识提出了“肿瘤相关抑郁”的概念,即在肿瘤诊断与治疗过程中出现以抑郁为主的病理性情绪变化[2]。严重的焦虑、抑郁等情志刺激能促进乳腺癌的发展、转移[3],而乳腺癌的确诊、手术后形体缺陷、后续射频和化疗等长期治疗可使患者长期承受巨大的心理压力,导致乳腺癌患者抑郁症患病率远高于普通人群,是最常见的并发症。在针对 47 424 名乳腺癌患者的荟萃分析中,研究显示乳腺癌患者的抑郁症发病率为 32.2%,远高于其他癌症中抑郁症的患病率[4]。对 282 203 例乳腺癌患者的研究分析中发现,抑郁与乳腺癌患者的复发率和全因死亡率增加有关。抑郁症使乳腺癌患者的死亡风险增加 30%[5]。因此深入研究乳腺癌相关抑郁(breast cancer related depression,BCRD)发生发展机制已成为乳腺癌防治工作的重中之重。

目前主流观点认为 BCRD 的发病机制与神经-免疫-肠道调节功能紊乱密切相关,是多通路多靶点紊乱相互作用的结果,但是其深层的生物学调控机制还有待进一步揭示。临床上对 BCRD 的治疗多采用手术、放化疗与抗抑郁药联合。但在治疗中存在临床症状改善缓慢、易复发及副作用多等缺陷。而中医在治疗 BCRD 上有得天独厚的优势,其多成分、多通路、多靶点的治疗特点正好契合了 BCRD 发病机制复杂的本质。同时,中医理论体系的整体观念和辨证论治指导下,中医药更加注重癌症患者的个性化治疗,在疾病动态进程中把握机体的阴阳平衡,与现代医学精准理疗理念相合。大量的临床研究以及体内外实验也验证了中医药在乳腺癌相关抑郁治疗中的显著疗效。

1 乳腺癌相关抑郁发病机制

随着乳腺癌和抑郁症此两种疾病之间的密切关系被越来越多的研究所揭示,关于 BCRD 的发生机制也进行了大量研究,研究发现 BCRD 的发病涉及机体神经-免疫-肠道在内的多系统功能障碍[6]。乳腺癌可增加抑郁的易感性,导致疾病预后不良。临床研究报道,乳腺癌化疗、激素治疗和靶向治疗后可使乳腺癌患者抑郁患病率增加[7],如有荟萃分析显示 5-氟尿嘧啶、表柔比星、环磷酰胺、阿霉素和紫杉烷引起不同程度的认知障碍[8],紫杉烷可显著增加乳腺癌患者抑郁症的患病率[9]。

1.1 神经系统紊乱

癌症患者可能通过其下丘脑-垂体-肾上腺皮质轴(hypothalamic-pituitary-adrenal axis,HPA axis)和单胺神经系统的信号传递引起了包括抑郁在内的神经症候群症状[10]。乳腺癌患者抑郁症状之间的显著性差异可能由神经内分泌系统激活 HPA 轴和五羟色胺(5-hydroxy tryptamine,5-HT)、多巴胺(dopamine,DA)、去甲肾上腺素(noradrenaline,NE)等单胺类递质紊乱导致[11]。Seok 等[12]研究结果发现,乳腺癌患者抑郁症状的诊断与 HPA 轴的过度活跃显著相关。体内实验研究显示,BCRD 大鼠海马出现明显病理改变,血浆中 HPA 轴相关指标促肾上腺皮质激素释放激素(corticotropin releasing hormone, CRH)、促肾上腺皮质激素(adrenocorticotropic hormone, ACTH)、皮质酮(corticosterone,CORT)的水平明显升高[13],该研究结果也在小鼠体内得到了进一步验证[14-15]。以上研究表明,BCRD 的发生与乳腺癌患者和动物机体内 HPA 轴过度激活以及神经的递质分泌紊乱有关。

1.2 免疫功能障碍

机体免疫功能障碍是乳腺癌和抑郁症的共同致病机制。实验研究观察到,乳腺癌荷瘤小鼠血液中炎症因子如白细胞介素-1β(interleukin-1β,IL-1β)、白细胞介素-6(interleukin-6,IL-6)和肿瘤坏死因子 α(tumor necrosis factor-α,TNF-α)升高,且此类炎症因子水平的升高可能与乳腺癌荷瘤小鼠的抑郁行为呈正相关[16]。同时在临床研究中也观察到,BCRD 患者血清中的 IL-6、TNF-α 的水平显著升高,而 IL-1β、TNF-α、IL-6 的水平与患者抑郁程度成正比[17]。自然杀伤细胞(natural killer cell,NK)在机体免疫监控中发挥着重要作用,对早期的未经治疗的乳腺癌患者有积极的抗肿瘤作用,可被化疗激活并抑制乳腺癌转移[18]。NK 细胞、T 淋巴细胞($CD4^+$、$CD8^+$)的表达在晚期乳腺癌体内显著下降[19],而抑郁症患者体内 NK 细胞活性也显著降低[20]。体内研究也进一步证实,在接受慢性不可预知刺激的乳腺癌小鼠,其肿瘤、血液以及脾样本中,其 T 细胞和 NK 细胞的百分比均显著降低,髓源性抑制细胞(myeloid-derived suppressor cells,MDSCs)、肿瘤相关巨噬细胞(tumour-associated macrophages,

TAMs)比例上调[21-22]。

临床研究表明,情绪障碍的乳腺癌患者血液中 NK 细胞活性显著减弱[23]。乳腺癌术后化疗患者抑郁的发生与 NK 细胞、$CD3^+$、$CD4^+$、$CD4^+/CD8^+$的表达呈负相关[24]。中度以上精神心理压力可以使乳腺癌组织中的 TAMs 和 MDSCs 明显增多[25]。荟萃分析结果显示乳腺癌术后抑郁患者体内 T 细胞亚群($CD3^+$、$CD4^+$、$CD4^+/CD8^+$)显著下降[26]。此一系列研究均表明乳腺癌引起的机体免疫系统紊乱也是患者出现抑郁症状的重要病理机制。

1.3 肠道菌群失调

乳腺癌可以下调机体肠道菌群中有益菌丰度,上调有害菌丰度,而此种改变与抑郁情绪密切相关。临床报道显示,乳腺癌患者抑郁症状与肠道菌群多样性下降及菌群组成紊乱有关。与非抑郁症乳腺癌患者相比,BCRD 患者肠道变形菌相对丰度增加,厚壁菌丰度降低,这表明变形菌的过度表达和较低的厚壁菌丰度可能与 BCRD 患者抑郁情绪有关[27]。乳腺癌荷瘤小鼠肠道菌群多样性发生显著变化,厚壁菌门/拟杆菌门的比值明显升高,而此种改变与小鼠的行为学改变有显著的相关性,厚壁菌门的相对丰度与旷场实验中心区域移动距离、糖水偏爱指数、高架十字迷宫开放臂的时间和进入开放臂次数呈负相关,而拟杆菌门的相对丰度与中心区域移动距离呈显著正相关[28]。以上研究均表明乳腺癌引起的肠道菌群紊乱也是患者出现抑郁症状的重要病理机制。

2 中医药对乳腺癌相关抑郁的调节作用

乳腺癌相关抑郁,归属于中医“郁证”范畴[29],其中最常见的病位证候要素为肝,其次是心、脾、肾,基本病机是情志失调,气机不畅。《傅青主女科》曰“乳头属足厥阴肝经,乳房属足阳明胃经”,肝胃二经与乳腺癌形成尤为相关。《外科正宗》中,陈实功提出乳腺癌的发病与长期忧郁伤肝,思虑伤脾,情志难抒,致使经络不通,气机郁滞有关。乳腺癌患者也常因情绪因素、手术放化疗的副作用以及长期服用药物导致体内雌激素水平降低等原因出现抑郁症状。因此 BCRD 的发生必然存在肝郁这一核心病机,与肝主疏泄、调畅情志功能关系最为密切。大量研究结果表明,疏肝解郁和疏肝健脾类中药能有效改善 BCRD 患者的身心症状[30]。探索 BCRD 发生发展之间的相关性以及中医药对于疾病发展的保护机制,可以为其防治及中医药的临床运用提供实验依据和新思路。

2.1 中药对乳腺癌相关抑郁神经内分泌系统紊乱的调节作用

2.1.1 调节 HPA 轴

HPA 轴是神经内分泌反馈调节系统的重要组成部分,由下丘脑室旁核、垂体前叶、肾上腺皮质构成。应激条件下,室旁核分泌 CRH 作用于垂体前叶,从而促进 ACTH 的释放。肾上腺皮质在 ACTH 的作用下合成糖皮质激素如 CORT 等应激激素,这些激素通过体循环到达靶器官,引起生理反应[31]。癌症可诱导下丘脑等处的炎症细胞因子长期激活,导致 HPA 轴功能亢进,糖皮质激素分泌过多,降低糖皮质激素受体的敏感性,破坏 HPA 轴的负反馈调节,导致海马区神经元障碍,从而诱发癌症相关抑郁[32]。中医药对 BCRD 有积极的干预作用。例如在乳腺癌癌前病变及慢性轻度不可应激大鼠模型中,中药复方金贝乳康片可通过降低 CORT 的表达,明显抑制大鼠肿瘤发病率,组织病理学观察结果显示,金贝乳康片组大鼠的癌前病变乳腺组织向一般增生转化[33]。柴胡疏肝散同样可抑制肝郁证乳腺癌荷瘤大鼠 HPA 轴功能的的亢进,降低 HPA 轴相关指标(CRH、ACTH、CORT)的表达,升高小鼠糖水偏嗜度,改善其抑郁样行为[34]。逍遥抗癌解郁方可显著抑制 HPA 轴的激活和肾上功能亢进,缓解 BCRD 小鼠抑郁样指征[35]。

2.1.2 调节单胺类神经递质

单胺类神经递质是包括 5-HT、DA、NE 在内的一类小分子生物胺,在人体外周及中枢系统中表达,可参与调控包括情绪在内的一系列重要的生理活动[36]。肿瘤通过分泌炎症因子调节 5-HT 合成吲哚氨 2,3 双加氧酶(indoleamine-2,3-dioxygenase,IDO),同时将色氨酸(tryptophan,Trp)转化为犬尿氨酸(kynurenine,KYN),KYN 可调节小胶质细胞的氧化应激及星形胶质细胞凋亡等反应,从而诱发机体的抑郁样行为[37-38]。BCRD 患者血浆中 Trp 的水平显著低于单纯乳腺癌患者[28],而 KYN/Trp 比例与抑郁严重程度呈正相关[39]。乳腺癌患者体内 KYN 的高表达能预测抑郁焦虑症状[40]。

DA 可在多巴胺-β-羟化酶的作用下转化生成 NE,BCRD 小鼠体内 DA、NE 的含量显著降低[41]。临床研究发现逍遥散加味可显著提高乳腺癌术后患者血清中 5-HT、NE、DA 的含量,降低抑郁量表评

分,减轻患者抑郁情绪[42]。逍遥抗癌解郁方可显著提升应激乳腺癌荷瘤模型小鼠血清中单胺类神经递质 NE、DA 和 5-HT 的表达水平,同时糖水实验、旷场实验、新奇摄食等行为学实验结果显示,小鼠抑郁样行为得到明显改善[43]。

2.2 中药对乳腺癌相关抑郁炎症免疫反应的调节作用

2.2.1 调节炎症因子

肿瘤相关抗原刺激免疫系统释放的一系列炎症细胞因子是导致乳腺癌患者抑郁的重要原因[44]。其中促炎因子的分泌可多通路作用于中枢神经系统,使小胶质细胞激活,神经元数量减少、可塑性降低,以及神经内分泌功能紊乱等,从而影响认知功能,导致抑郁发生[45]。研究显示,中药复方扶正解郁方可降低 BCRD 小鼠外周血中炎症相关因子 IL-6 的水平,改善肿瘤微环境[46]。临床观察显示,三黄煎剂能降低激素受体阳性乳腺癌以及三阴乳腺癌患者血清中促炎因子 IL-6、TNF-α 的含量,降低血清中氧化应激相关指标,缓解患者抑郁情绪和相关的应激症状[47-49]。桑毅婷[50]采用疏肝健脾方治疗乳腺癌肝郁脾虚证患者,结果显示,患者肝郁脾虚症状明显改善,抑郁、焦虑量表评分显著降低,TNF-α、IL-8 的水平抑制,免疫功能提高。

2.2.2 调节肿瘤浸润性淋巴细胞

MDSCs 是一群在肿瘤等病理条件下被激活和动员的、具有 T 细胞抑制功能的、骨髓来源的未成熟细胞。肿瘤细胞通常可影响祖细胞的分化过程,最终致使 MDSCs 积累,降低肿瘤免疫治疗的疗效。在中度抑郁症患者体内,MDSCs 可通过产生活性氧来抑制 T 细胞免疫,也可通过精氨酸酶抑制 T 细胞增殖[51]。研究显示,扶正解郁方能抑制乳腺癌合并抑郁障碍小鼠脾细胞中 MDSCs 增殖,减缓 $CD8^+$T 细胞凋亡缓解[46]。中药复方疏肝健脾方可以通过下调 MDSCs、TAMs 细胞比例、降低 T 淋巴细胞凋亡来抑制肿瘤细胞活性,改善乳腺癌荷瘤小鼠的抑郁状态[52]。在乳腺癌患者治疗的临床研究中,柴氏逍遥散、甘麦大枣汤与逍遥散加减合方、调补肝肾消积疗法、可分别上调 NK 和 T 淋巴细胞亚群($CD3^+$水平、$CD4^+$水平、$CD4^+/CD8^+$比值)的细胞比例,明显改善细胞免疫功能,有效缓解患者抑郁焦虑相关症状,明显降低乳腺癌患者的应激症状[53-55]。CXC 趋化因子配体 1(C-X-C motif chemokine ligand 1,CXCL1)具有促进 MDSCs 增殖、迁移和抗 $CD8^+$T 细胞的功能[22]。BCRD 患者和动物体内的 CXCL1 显著上升[56],研究显示消癖颗粒可改善三阴乳腺癌巩固期患者的抑郁状态,降低其血清中 CXCL1 浓度[57]。以上研究表明,MDSCs 与 BCRD 患者肿瘤症状恶化和抑郁情绪有关,但是 MDSCs 是否是抑郁促乳腺癌进展的关键机制还需要更多的证据来证明(见表 1)。

2.3 中药对乳腺癌相关抑郁肠道菌群的调节作用

BCRD 的发病与肠道菌群组成的改变继而影响脑神经递质有关。肠道菌群中的益生菌有治疗和预防抑郁症的作用,如双歧杆菌其抗抑郁的机制可能与抗炎、调整 Trp 代谢、促进 5-HT、抑制 HPA 轴的激活有关[58]。研究显示,乳腺癌能影响肠道菌群多样性及结构组成,并通过 Trp/5-HT 途径影响小鼠神经递质的分泌从而影响小鼠抑郁样行为[28]。研究显示,中药复方柴氏逍遥散可降低厚壁菌门/拟杆菌比例,改变肠道菌群结构,提升脑神经递质水平,从而改善海马区的神经细胞排列,增加神经元数目,使脑结构趋于正常,使 BCRD 小鼠的抑郁行为得到改善,同时促进 Trp 流入脑,改变血浆氨基酸代谢再分布,从而改变肿瘤能量供给,缩小肿瘤体积,放缓肿瘤生长速度[59](见表 1)。

3 展望

综上可知,BCRD 的发病与机体神经-免疫-肠道等多系统功能障碍有关,其发病机制复杂,是多靶点同时综合作用的结果。荟萃分析显示,与常规治疗的患者相比,中药联合西医常规治疗的 BCRD 患者具有显著性更好的临床疗效且不良反应发生率远低于单纯的西医常规治疗[26],究其深层原因可能是因为中药治疗疾病往往是多种成分同时作用于多个靶点和多条通路综合治疗效果的反映。西药抗抑郁和肿瘤通常是成分明确,作用靶点较为单一。例如中药复方疏肝解郁中药通过神经内分泌系统和免疫功能,下调 CORT 水平,上调 NK 和 T 淋巴细胞亚群,有效缓解患者抑郁焦虑相关症状,明显降低乳腺癌患者的应激症状[54]。柴氏逍遥散可同时调节机体炎症免疫反应、肠道菌群,上调 NK 和 T 淋巴细胞亚群的细胞比例,下调厚壁菌门/拟杆菌比例,改变肠道菌群结构,提升脑神经递质水平,使脑结构趋于正常[53,59]。研究结果均一致说明中药能同时作用于多通路、多靶点,调动机体的多系统协同参与,对疾病进行综合调节,正好契合了乳腺

表 1 中药治疗乳腺癌相关抑郁治疗机制

Table 1 Mechanism of Traditional Chinese Medicine in treating breast cancer-related depression treatment

	干预对象 Subject of intervention	造模方式 Method of modeling	用药周期 Medication cycle	作用机制 Mechanism of action
金贝乳康片[33] Jinbei Rukang Table	SD 大鼠 Sprague Dawley (SD) rats	二甲基苯蒽(DMBA)联合 CUMS 及冷水刺激应激 7, 12-Dimethylbenz [a] anthracene (DMBA) combined with Chronic Unpredictable Mild Stress (CUMS) and cold water stimulation stress	每天 1 次,连续灌胃 1 个月 Once daily, administered by gavage for one month	降低大鼠血清中 CORT 的表达 Reduce the expression of CORT in rat serum
柴胡疏肝散[34] Chaihu Shugan Powder	Wistar 雌鼠 Wistar female rat	慢性束缚应激 Chronic restraint stress	每天 1 次,连续灌胃 14 天 Once daily, administered by gavage for 14 days	下调 HPA 轴相关指标(CRH、ACTH、CORT)提高 5-HT、DA、NE 的表达 Downregulate HPA axis markers (CRH, ACTH, CORT) and upregulate the expression of 5-HT, DA, NE
逍遥抗癌解郁方[35,43] Xiaoyao Kangai Jieyu Recipe	BALB/c 小鼠 BALB/c mice	腋下注射 4T1 炎性乳腺癌细胞联合腹腔注射皮质酮(CORT) Subcutaneous injection of 4T1 inflammatory breast cancer cells combined with intraperitoneal injection of corticosterone (CORT)	每天 1 次,连续灌胃 3 周 Once daily, administered by gavage for 3 weeks	下调 HPA 轴相关指标(CRH、ACTH、CORT)的表达;上调血清 5-HT、DA 和 NE 的表达 Downregulate the expression of HPA axis markers (CRH, ACTH, CORT); upregulate the expression of serum 5-HT, DA, and NE
逍遥散加味[42] Modified Xiaoyao Powder	乳腺癌术后患者 Postmastectomy breast cancer patient	/	每天 1 剂,早晚分 2 次服用,连服 6 周 One dose per day, divided into two administrations in the morning and evening, for 6 weeks	上调乳腺癌术后患者血清中 5-HT、NE、DA 的含量 Upregulate the levels of serotonin 5-HT, NE, DA in the serum of postoperative breast cancer patients
扶正解郁方[46] Chinese Medicine SFJP Formula	BALB/c 小鼠 BALB/c mice	CUMS 抑郁造模后腋下接种 4T1 细胞 Subcutaneous inoculation of 4T1 cells after Chronic Unpredictable Mild Stress (CUMS) depression model	每天 1 次,连续灌胃 2 周 Once daily, administered by gavage for 2 weeks	下调 MDSCs、IL-6、上调脾 $CD8^+$ Downregulate MDSCs, IL-6, upregulate $CD8^+$ T cells in the spleen
三黄煎剂[47-49] Sanhuang Decoction	乳腺癌患者 Breast cancer patient	/	每天 1 剂,早晚分 2 次服用,连服 6 月 One dose per day, divided into two administrations in the morning and evening, for 6 mouths	下调血清中促炎因子 IL-6、TNF-α 的含量,降低血清中氧化应激相关指标 Downregulate the levels of pro-inflammatory cytokines IL-6 and TNF-α in the serum, reduce the levels of oxidative stress-related indicators in the serum
疏肝健脾方[50] ShuGan Jianpi Recipe	乳腺癌术后患者 Postmastectomy breast cancer patient	/	每天 1 剂,早晚分 2 次服用,连服 8 周 One dose per day, divided into two administrations in the morning and evening, for 8 weeks	下调 TNF-α、IL-8 水平 Downregulate the levels of TNF-α, IL-8
疏肝健脾方[52] ShuGan Jianpi Recipe	BALB/c 小鼠 BALB/c mice	CUMS 抑郁造模后腋下接种 4T1 细胞 Subcutaneous inoculation of 4T1 cells after Chronic Unpredictable Mild Stress (CUMS) depression model	每天 1 次,连续灌胃 1 个月 Once daily, administered by gavage for one month	下调 MDSCs、TAMs 细胞比例、降低 T 淋巴细胞凋亡,下调 IL-6、IL-1β 的表达 Downregulate the proportion of MDSCs, TAMs, reduce T lymphocyte apoptosis, and downregulate the expression of IL-6 and IL-1β

续表1

	干预对象 Subject of intervention	造模方式 Method of modeling	用药周期 Medication cycle	作用机制 Mechanism of action
柴氏逍遥散[53] Chai's XiaoYaoSan	乳腺癌术后患者 Postmastectomy breast cancer patient	/	每天 1 剂,早晚分 2 次服用,连服 1 月 One dose per day, divided into two administrations in the morning and evening, for 1 mouth	上调 NK 和 T 淋巴细胞亚群(CD3$^+$水平、CD4$^+$水平、CD4$^+$/CD8$^+$比值)的细胞比例 Upregulate the proportion of NK cells and T lymphocyte subsets (CD3$^+$ level, CD4$^+$ level, CD4$^+$/CD8$^+$ ratio)
疏肝解郁中药[54] Shugan Jieyu medicine	乳腺癌术后患者 Postmastectomy breast cancer patient	/	每天 1 剂,连服 13 周 One dose per day, administered continuously for 13 weeks	上调 NK 和 T 淋巴细胞亚群(CD3$^+$水平、CD4$^+$水平、CD4$^+$/CD8$^+$比值)的细胞比例,下降 CORT 水平 Upregulate the proportion of NK cells and T lymphocyte subsets (including CD3$^+$ levels, CD4$^+$ levels, and the CD4$^+$/CD8$^+$ ratio), while downregulating CORT levels
调肝补肾消积疗法[55] Kidney Tonifying and Accumulation Eliminating	乳腺癌患者 Breast cancer patient	/	每天 2 袋,早晚分 2 次服用,连服 12 月 Two packets per day, administered twice daily in the morning and evening, for 12 months	上调 NK 和 T 淋巴细胞亚群(CD3$^+$水平、CD4$^+$水平、CD4$^+$/CD8$^+$比值)的细胞比例,上调免疫球蛋白 IgG、IgM、IgA Upregulate the proportions of NK cells and T lymphocyte subsets (CD3$^+$ levels, CD4$^+$ levels, CD4$^+$/CD8$^+$ ratios), and increase the levels of immunoglobulins IgG, IgM, and IgA
消癖颗粒[57] Xiaopi granules	乳腺癌患者 Breast cancer patient	/	每天 1 剂,连服 3 月 One dose per day, administered continuously for 3 mouths	下调血清中 CXCL1 浓度 Downregulate the concentration of CXCL1 in the serum
柴氏逍遥散[59] Chai's XiaoYaoSan	BALB/c 小鼠 BALB/c mice	CUMS 结合慢性束缚应激腋下接种 4T1 细胞 Subcutaneous inoculation of 4T1 cells following Chronic Unpredictable Mild Stress (CUMS) combined with chronic restraint stress	每天 1 次,连续灌胃 3 周 Once daily, administered by gavage for 3 weeks	下调厚壁菌门/拟杆菌比例,改变肠道菌群结构,提升脑神经递质水平,改善海马区的神经细胞排列,减少凋亡,增多神经元数目,脑结构趋于正常 Downregulate the ratio of *Firmicutes* to *Bacteroidetes*, alter the gut microbiota structure, elevate brain neurotransmitter levels, improve the arrangement of neuronal cells in the hippocampal region, reduce apoptosis, increase the number of neurons, and normalize brain structure

癌相关抑郁发病机制复杂的本质,可能为癌症相关抑郁症的治疗提供新的选择。

以上研究从多方面为 BCRD 的病理生理以及治疗之间的联系提供了证据,相关研究也取得了一定的进展,但中医药治疗 BCRD 的研究尚浅,关于中医药调节 BCRD 机制的研究仍然面对很大的挑战:一是关于中医药治疗 BCRD 的作用靶点和通路的研究并不充分,尤其是在中医药调节抑郁和乳腺癌两种症状之间的关联机制研究还有更多的深入空间。二是针对中医药治疗 BCRD,目前临床研究文献较少,对抑郁状态缺乏统一的标准,同时关于 BCRD 的诊断、造模、证候分型等,尚未建立全面、系统、权威的诊疗评价体系。需要大样本的临床流行病学调查来规范化辨证标准,为进一步探讨乳腺癌抑郁状态基本证候规律研究提供依据。三是既往关于 BCRD 的中医治疗机制研究重点多侧重于方剂对生

物效应的作用,忽略了中医“方证相关”辨证论治的规律。

所以以中医理论为指导,在大量临床研究的基础上,进一步深入探索 BCRD 中医病症的相关生物学基础以及中医药治疗机制仍是今后 BCRD 中医发病机制和治疗机制研究的主要方向。立足于中医理论基础上,依托现代研究手段,中西医结合,兼顾神经系统疾病的机制研究和生物信息学交叉学科等领域融合的研究趋势,加大中医药实验研究力度,充分发挥中医药优势,为治疗 BCRD 提供新策略。

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