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黄连解毒汤治疗神经系统疾病的研究进展

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[摘要] 黄连解毒汤出自名医王焘编著的《外台秘要》, 临床应用广泛, 有清热解毒、泻火除烦、安神定志之功效。神经系统疾病作为严重危害人类健康的重大疾病, 其防治始终是医学研究的难点与热点。大量临床证据表明, 黄连解毒汤对多种神经系统疾病具有明显治疗效果。针对该复方及其组成药物的实验研究已初步阐明其药理作用机制, 然而目前尚缺乏对临床应用与作用机制的系统性梳理。本文通过系统综述黄连解毒汤整方及各单味药在神经系统疾病治疗中的作用机制及临床应用现状, 旨在为该方的临床合理应用提供科学依据, 同时为其后续作用机制的深入研究提供理论参考。

[关键词] 黄连解毒汤; 神经系统疾病; 研究进展; 临床应用; 作用机制

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Research progress of Huanglian Jiedu Decoction in the treatment of neurological diseases

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View from specialist: It is creative, and of certain scientific and educational value.

[Abstract] Huanglian Jiedu Decoction is derived from “Wai Tai Mi Yao” compiled by the renowned doctor Wang Tao. It is widely used in clinical practice and has the effects of clearing heat and detoxifying, purging fire and relieving irritability, as well as calming the mind and stabilizing the will. Neurological diseases, as major diseases that seriously endanger human health, their prevention and treatment have always been the difficulties and hotspots in medical research. A large amount of clinical evidence indicates that Huanglian Jiedu Decoction has a significant therapeutic effect on a variety of neurological diseases. Experimental studies on this compound and its constituent drugs have initially clarified its pharmacological mechanism of action. However, at present, there is still a lack of a systematic review of its clinical application and mechanism of action. This article systematically reviews the mechanism of action and the current clinical application status of the entire formula of Huanglian Jiedu Decoction and each individual ingredient in the treatment of neurological diseases, aiming to provide a scientific basis for the rational clinical application of this formula and a theoretical reference for the in-depth study of its subsequent mechanism of action at the same time.

[Key words] Huanglian Jiedu Decoction; Neurological diseases; Research Progress; Clinical application; Mechanism of action

神经系统疾病 (neurodegenerative diseases, ND) 包括不同的中枢和周围神经系统疾病, 临床表现为认知功能减退、智力衰退, 并常伴随痴呆症

状^[1,2], 因其高发病率、不可逆性神经损伤及严重致残致死率, 已成为全球重大公共卫生问题^[3]。全球超三分之一的人口罹患 ND, 过去 30 年间, 该类疾病

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致死率明显上升近39%^[4],已成为全球健康的重大威胁,其社会负担和影响持续加重,且未来仍可能进一步攀升。中医将ND归为脑病范畴,其发病以七情内伤、饮食劳倦或禀赋不足为主,核心病机在于肝、肾、心、脾等脏腑功能失调,导致气血逆乱、津液代谢失常,继而产生痰浊、瘀血、风火等病理产物,上扰清窍、阻滞经脉,终致神机失用、髓亏筋痿。西医治疗虽具短期疗效,但存在治疗手段有限和长期用药安全性不足的缺陷。因此,亟需开发能有效促进神经修复的治疗新策略。

黄连解毒汤源于王焘《外台秘要·卷第一》引崔氏方,作为中医经典清热解毒方剂,由黄连、黄芩、黄柏、栀子四味药组成,组方精简而功效专一,四药协同,以苦寒之性直清热毒,通泻三焦火邪,使热退毒解而诸症自消,故在临床中应用广泛。黄连解毒汤通过抗炎、抗氧化及调节自噬等作用,靶向调控神经炎症、氧化应激和线粒体功能障碍等ND核心病理环节。其活性成分(如小檗碱、黄芩苷)还可改善血脑屏障通透性和肠脑轴功能,展现出多机制神经保护作用。本文归纳总结黄连解毒汤整方及单味成分在ND中的临床与实验研究进展,旨在为其进一步开发与应用提供科学依据,并为本方后续的机制研究提供思路。

1 黄连解毒汤治疗ND

1.1 阿尔兹海默症(Alzheimer's disease, AD)

在全球老龄化趋势下,痴呆症发病率不断上升,现已发展成为主要的致死病因之一^[5]。流行病学预测显示,1990~2019年全球痴呆症患者数量增长超一倍,达4 700万例(占全球人口0.7%),其中AD占比约80%;基于当前增速(约每20年翻番),预计2030年患者将突破8 000万,2050年可能达1.315亿例^[6,7]。中医学认为其由于七情内伤,久病不复,年迈体虚等致气血不足,肾精亏虚,痰瘀阻痹,渐使脑髓空虚脑髓失养所致。

何瑛琨等^[8]运用黄连解毒汤治疗AD,患者中医症状积分、血清炎症因子(IL-1 β 、TNF- α 、IL-6)及AD相关标志物(A β 1-42、Tau)水平明显降低;认知功能评估中,阿尔兹海默病认知功能量表(ADAS-Cog)评分降低,蒙特利尔认知评估量表(MoCA)评分升高,有效缓解患者神经炎症,改善认知功能。王俊力等^[9]基于“毒损脑络”理论,采用黄连解毒汤治疗中度AD患者,明显改善其综合临床指标(整体认知功能、总体印象、日常生活能力、精神行为症状)及中医证候,疗效优于盐酸多奈哌齐。李敏敏等^[10]发现,黄连解毒汤联合头穴丛刺针法可通过同

步调控AD患者大脑皮层功能及肠道微生态,抑制神经炎症、恢复肠脑轴功能,从而改善认知功能。临床研究显示^[11],黄连解毒汤联合丁苯酞及多奈哌齐的三联疗法可明显改善AD患者的认知功能及脑血管储备能力,具有协同增效作用。黄连解毒汤、复方苻蓉益智胶囊和多奈哌齐三联治疗方案可明显降低AD患者的中医证候评分,有效调节尿液AD7c神经元丝蛋白(AD7c-NTP)和炎症因子水平,展现出多靶点协同治疗优势^[12]。

1.2 缺血性脑卒中(ischemic stroke, IS)

IS又称缺血性中风,是因脑血管阻塞或血栓形成导致脑组织供血不足而引发的疾病,目前已成为中国死亡率最高的疾病类型^[13]。中国卒中现患率高居世界首位,据调查显示,2020年缺血性卒中发病率为413.3/10万,2021年脑梗死的患病率为2.30%,2020年我国农村、城市居民卒中死亡率分别为164.77/10万、135.18/10万^[14]。中医学认为,这种病症多由阴阳失调,气血逆乱所致。

黄连解毒汤在IS治疗中表现出明显疗效,可有效降低患者体内TNF- α 、IL-6等炎症因子水平,改善神经功能缺损评分,从而促进临床预后^[15]。安朋朋等^[16]发现在常规西医治疗基础上联用黄连解毒汤,可明显改善急性脑梗死患者的神经功能及伴随的胃肠功能障碍。黄连解毒汤可明显降低脑梗死患者血清超敏C反应蛋白(hs-CRP)水平,有效抑制神经炎症与免疫过度激活,减轻脑组织炎性损伤,促进神经功能恢复,并改善热毒炽盛证候^[17]。陈桂霞^[18]用黄连解毒汤加味治疗缺血性中风患者,与单纯常规西药治疗相比,黄连解毒汤能改善神经功能,且用药安全,临床效果明显。黄连解毒汤联用补阳还五汤结合电针辅助治疗脑梗死患者,可有效调节血脂代谢,改善神经功能、明显提升临床疗效^[19]。

1.3 帕金森病(Parkinson's disease, PD)

PD是一种常见的神经退行性疾病,临床常出现静止性震颤、肌强直、步态异常、行动迟缓等运动障碍。有研究者在2007年预估,到2030年,中国的PD患者数量可能攀升至500万例,或将占据全球PD患者总数的50%^[20]。中国PD患病率、死亡率高于全球平均水平^[21]。祖国医学将其归为“震颤”“强直”“颤病”“痉病”等范畴,中医认为PD病位在脑,与肝、脾、肾关系密切,肝肾阴虚为本,痰浊、瘀血、风火为标,致使阴阳失调、气血不冲、痰瘀阻络形成本虚标实之证。

张哲等^[22]发现,黄连解毒汤加味联用多巴丝肼片能够有效缓解PD认知功能障碍(PD-MCI)患者

症状,明显降低中医证候积分及临床症状量表(PSQI、HAMD、UPDRS)评分,提升认知与生活质量量表(MoCA、MMSE、PDQ-39)评分;通过抑制中枢神经炎症与氧化应激,改善认知、睡眠、抑郁并提高生活质量,同时减少多巴胺不良反应,临床应用价值显著。黄连解毒汤与西药联用可通过协同抗炎减轻PD-MCI患者神经炎症,发挥神经元保护作用,减少神经损伤,进而改善患者认知功能^[23]。

1.4 精神分裂症(schizophrenia)

精神分裂症是一种慢性精神疾病,主要表现为患者感知觉、思维、情感和意志不协调和行为失调等疾病特点^[24]。此疾病作为一种高致残性和高致死率精神障碍,全球患病率约1%^[25]。2020年流行病学数据显示,我国精神分裂症患者总数约为680万例^[26]。中医认为,精神分裂症归属于中医“癫狂”范畴,多因机体阴阳失调、七情内伤、痰气上扰、气血凝滞所致。

采用黄连解毒汤加味联用氯氮平对伴兴奋激越症状的精神分裂症患者进行中西医结合干预,可明显降低PANSS量表评分并减少不良反应^[27]。与单纯常规西药治疗相比,运用黄连解毒汤加味合并氯氮平治疗精神分裂症患者伴有兴奋激越症状,能更明显降低BPRS量表激越因子分,TESS量表评分更优,增效且减毒(减少西药用量及副反应)^[28]。

1.5 癫痫(epilepsy)

癫痫是由遗传、结构、代谢或免疫等多重机制引起的大脑神经网络异常超同步放电,导致反复性、发作性神经功能障碍^[29]。目前全球患病人数达7 000万,是导致发病和早期死亡的主要因素之一^[30]。中医称为“痫证”或“羊痫风”,常由风火触动,痰瘀内阻,蒙蔽轻窍致病。

黎兴键^[31]采用黄连解毒汤联合定痫丸治疗阳痫患者,可明显改善临床疗效,治疗组在国立医院癫痫严重程度量表(the national hospital seizure severity scale, NHS3)、改良 Barthel 指数(modified barthel index, MBI)、改良 Rankin 量表(modified rankin scale, MRS)、癫痫中医证素(symptoms factor, SF)得分等方面优于对照组,证实该中西医结合方案对控制发作期癫痫患者的症状具有明显优势。

2 黄连解毒汤治疗ND的作用机制

2.1 抗神经炎症

在中枢ND中,神经炎症既是病理改变的产物,又是促进疾病进展的主动因素^[32]。黄连解毒汤可明显抑制AD小鼠海马NLRP3炎性小体活性及小胶质细胞活化,减少A β 斑块沉积、下调tau蛋白磷

酸化,从而改善海马神经元损伤^[33]。黄连解毒汤含药脑脊液能降低BV2细胞促炎因子TNF- α 、IL-6、IL-1 β 含量,激活胆碱能抗炎通路中 α 7nAChR表达,改善A β ₁₋₄₂诱导BV2细胞炎症反应^[34]。黄连解毒汤通过抑制MAPK/NF- κ B通路减轻炎症介质的产生,明显改善了DNCB致敏小鼠AD样症状^[35]。此外,黄连解毒汤通过调控TREM2/Akt/GSK3 β 通路,下调IL-1 β 、IL-6 mRNA及CD86水平,上调抗炎因子IL-10、精氨酸酶1(arginase 1, Arg1)、关键磷酸化蛋白[p-PI3K(Y607)、p-Akt(T308)、p-GSK3 β (Ser9)]及 β -catenin表达,减少A β ₁₋₄₂沉积,发挥神经保护作用^[36]。

2.2 调节神经递质,保护神经元

神经递质作为神经元通讯的化学介质,在神经信息编码与传递过程中发挥核心作用,对机体生理稳态和行为适应性具有不可替代的调控功能^[37]。黄连解毒汤可能通过抑制星形胶质细胞活化以及ODC1介导的GABA生成,从而有效减少A β 沉积,改善AD小鼠学习记忆能力^[38]。黄连解毒汤可明显增加缺氧诱导因子-1 α (hypoxia-inducible factor-1 α , HIF-1 α)、促红细胞生成素(erythropoietin, EPO)、血管内皮生长因子(vascular endothelial growth factor, VEGF)表达水平,激活PI3K/Akt信号通路,抑制脑缺血诱导的神经元凋亡并促进神经元增殖^[39]。黄连解毒汤通过多靶点协同调节神经递质动态平衡、能量代谢、线粒体功能及氨基酸代谢稳态,明显减轻氧化应激和神经炎症,进而改善血脑屏障完整性和渗透压平衡,缓解脑卒中大鼠缺血/再灌注(I/R)损伤^[40]。黄连解毒汤的主要有效成分栀子苷、黄芩苷和黄芩素对神经元氧糖剥夺(oxygen-glucose deprivation, OGD)损伤有良好的保护作用,提高神经元存活率^[41]。

2.3 抗氧化应激

氧化应激的增强可能是多种神经退行性疾病共同的潜在致病因素^[42]。黄连解毒汤主要成分小檗碱、黄芩苷、栀子苷,可增强细胞抗氧化应激的能力,激活核因子E2相关因子2(Nrf2)信号通路,进而通过清除活性氧(ROS)减轻I/R诱导的氧化应激损伤^[43]。黄连解毒汤可增强AD小鼠抗氧化能力(\uparrow SOD、 \uparrow GSH-Px、 \downarrow MDA),并促进大脑皮层及海马区神经生长因子(NGF)、胰岛素样生长因子-1(insulin-like growth factor-1, IGF-1)表达,明显改善认知功能^[44]。黄连解毒汤通过调控MDA/SOD/GSH氧化应激指标,激活Nrf2/HO-1/NQO1通路,明显改善AD小鼠认知功能^[45]。

2.4 抑制细胞死亡

程序性细胞死亡(PCD)既是维持神经系统稳态的重要机制,也是脑损伤、神经退行性疾病和中枢神经系统肿瘤的共同病理特征,其异常调控可导致疾病恶性进展^[46]。黄连解毒汤通过明显升高Bcl-2/Bax水平、降低cleaved-/pro-Caspase-3水平并抑制GRP78/PERK/CHOP内质网应激通路,从而有效减轻A β 诱导的神经元凋亡^[47]。黄连解毒汤通过下调NF- κ B、TNF- α 、IL-1 β 、IL-18表达水平,抑制NLRP3/Caspase-1/GSDMD通路,改善神经炎症,抑制细胞焦亡,改善APP/PS1双转基因小鼠突触可塑性和学习记忆功能^[48]。黄连解毒汤靶向FBXL5/IRP2通路,调节VaD小鼠脑铁代谢,降低VMHvl区神经元铁沉积和氧化损伤,促进细胞内铁超载(热毒)的清除,保护髓鞘完整性,最终改善激越攻击症状^[49]。

2.5 调节自噬

自噬通过促进细胞存活和防止神经退行性病变发挥神经保护作用^[50,51]。黄连解毒汤可通过调控MAPK通路抑制mTORC1信号传导激活保护性自噬,从而明显减轻IS大鼠神经损伤^[52]。黄连解毒汤通过调控PINK1/Parkin介导的线粒体自噬通路,明显抑制百草枯(PQ)诱导的SH-SY5Y细胞凋亡^[53]。黄连解毒汤可降低自发性高血压病大鼠(spontaneous hypertension rat, SHR)的Akt、mTOR、Beclin-1、LC3-II蛋白表达水平,抑制Akt/mTOR及Beclin-1自噬信号通路,明显改善细胞凋亡率^[54]。

2.6 调节血管内皮的修复及再生,保护血脑屏障

脑微血管内皮细胞(brain microvascular endothelial cells, BMECs)作为血脑屏障(blood-brain barrier, BBB)的核心结构,在外周和中枢神经系统之间形成屏障,在神经稳态维持中发挥关键作用^[55]。黄连解毒汤及其主要活性成分(栀子苷、黄芩苷和小檗碱)能促进BMECs增殖,防止BMECs缺氧和复氧损伤^[56]。黄连解毒汤降低APP、HIF-1 α 、VEGF、VEGFA蛋白表达,增加BDNF蛋白表达,保持BBB的完整性,发挥对神经的保护作用,明显改善AD小鼠学习记忆能力^[57]。黄连解毒汤通过上调SHR大鼠主动脉miR-133a、eNOS、p-eNOS的表达,同时抑制Caveolin-1的表达,且给药剂量与作用水平呈正相关关系,从而修复血管内皮功能并发挥降压作用^[58]。

2.7 调节肠道菌群

微生物群-肠-脑轴不仅影响大脑认知和精神症状,还会诱发神经退行性疾病^[59]。黄连解毒汤治疗

明显增加PD小鼠肠道中梭状菌等的丰度,下调普雷沃氏菌、阿克曼菌的丰度,并通过调节粪便和纹状体中的色氨酸代谢通路,改善运动功能障碍^[60]。黄连解毒汤通过升高脑梗死合并肠损伤大鼠^[61]、脑出血急性期模型大鼠^[62]肠组织中干细胞因子(stem cell factor, SCF)/酪氨酸激酶受体(CD117, tyrosine kinase receptor kit, C-kit)mRNA及蛋白的表达水平,对肠黏膜产生保护性作用。黄连解毒汤水提物协同调控三大代谢(糖/氨基酸/脂肪酸),促进初级胆汁酸生成及梭菌属介导的次级胆汁酸转化,实现胆汁酸代谢网络正向调节^[63]。见图1。

3 黄连解毒汤各单味药相关活性成分及作用机制

3.1 黄连

黄连为毛茛科多年生草本植物黄连*Coptis chinensis* Franch.、三角叶黄连*Coptis deltoidea* C.Y. Cheng et Hsiao或云南黄连*Coptis teeta* Wall.的根茎,化学成分主要为生物碱类、木脂素类、黄酮类、有机酸类、挥发油类等。黄连治疗ND的有效成分包括小檗碱、黄连碱等。

小檗碱通过激活大脑中动脉闭塞(middle cerebral artery occlusion, MCAO)模型大鼠模型中的BDNF-TrkB-PI3K/Akt通路来抑制细胞凋亡发挥神经保护作用^[64];通过多靶点协同调控NLRP3炎性小体和TLR4/NF- κ B信号通路^[48,65]、调节肠道菌群-脑-肠轴功能^[66]、调节大脑生物胺(去甲肾上腺素、血清素和多巴胺)^[67]起抗抑郁药的作用;激活AMPK-NRF2-HO-1信号通路,明显抑制脊髓损伤大鼠模型中的神经元铁死亡进程^[68]。黄连碱通过抑制炎症介质(PGD₂、TNF- α)产生并减轻氧化应激,对大脑中动脉闭塞模型诱导的I/R发挥神经保护作用^[69];下调TNF- α 、IL-1 β 抑制炎症和氧化应激,调节花生四烯酸代谢(\uparrow PGA₂/PGJ₂/15d-PGJ₂),发挥神经保护作用并减轻脑缺血损伤^[70]。

综上,黄连活性成分通过调节肠道菌群微环境、抗炎、抗氧化、抑制细胞凋亡等方式调控神经免疫,维持神经内环境稳态。

3.2 黄芩

黄芩为唇形科多年生草本植物黄芩*Scutellaria baicalensis* Georgi的根,其主要化学成分有黄酮及其苷类、多糖类、有机酸类、挥发油类及微量元素等。黄芩中具有神经保护活性的主要药效成分为黄芩苷、汉黄芩苷、黄芩素、汉黄芩素等。

黄芩苷通过激活BDNF/TrkB下游的PI3K/AKT和MAPK/ERK信号通路,明显减轻神经元-星形胶质细胞共培养体系的氧糖剥夺/复氧(OGD/

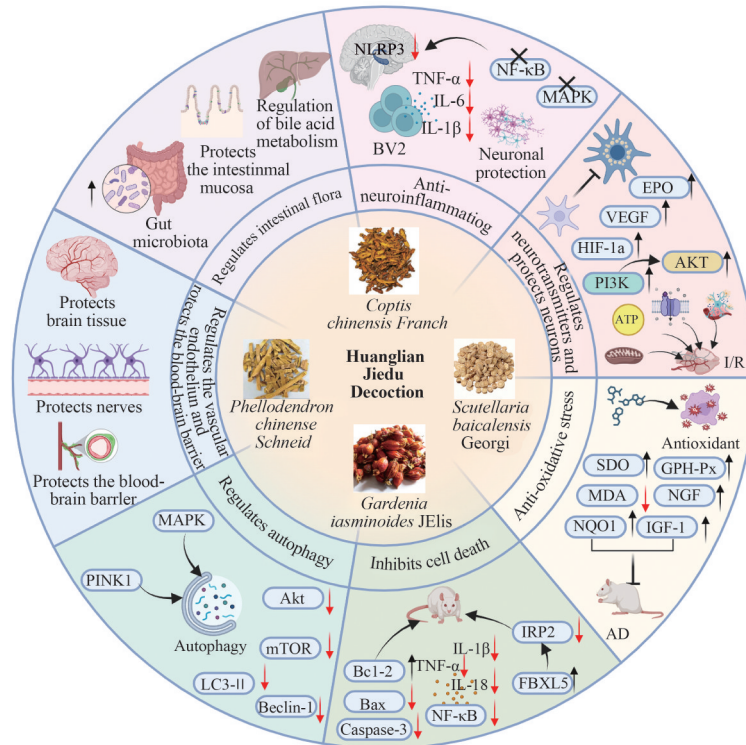


图1 黄连解毒汤治疗ND的作用机制

Fig 1 Mechanism of action of Huanglian Jiedu Decoction in treating ND

R) 损伤, 发挥抗氧化应激作用^[71]; 抑制琥珀酸脱氢酶(SDH)活性以减少ROS生成, 并增强谷氨酰胺合成酶(GS)蛋白稳定性, 以降低谷氨酸兴奋毒性, 最终减轻I/R神经元损伤^[72]。汉黄芩苷通过下调IL-1 β 、TNF- α 和IL-6水平, 抑制NF- κ B/I κ B和NLRP3/caspase-1/TLR4信号通路, 从而明显缓解脊髓损伤后的神经炎症反应^[73]。黄芩素通过调节氧化指标(\downarrow MDA/ROS、 \uparrow GSH)减轻氧化应激, 在SH-SY5Y细胞和PD小鼠模型中有效抑制MPP/MPTP神经毒性^[74]。汉黄芩素通过下调促炎因子(IL-1 β /TNF- α /IL-6)表达水平, 调控AMPK/SIRT1通路, 缓解VaD大鼠海马组织病理改变和神经炎症, 改善认知功能障碍^[75]。

综上, 黄芩活性成分通过抗氧化、抗炎, 抑制小胶质细胞活化, 调控关键信号通路, 抑制神经组织细胞凋亡, 进而促进神经修复与神经保护作用, 明显改善脑组织损伤并有效缓解认知功能与记忆障碍。

3.3 黄柏

黄柏为芸香科落叶乔木植物黄皮树 *Phellodendron chinense* Schneid. 或黄檗 *Phellodendron amurense* Rupr. 除去栓皮的树皮, 其化学成分以生物碱类、柠檬苦素类、酚酸类化合物为主, 同时含有萜类、苯丙素类及挥发性成分。黄柏治疗ND的有

效成分包括黄柏碱、木兰花碱、巴马汀等。

黄柏碱通过DRD1调控PI3K/Akt/mTOR信号通路, 发挥抗抑郁作用^[76]。木兰花碱通过特异性抑制JNK信号通路的异常激活, 明显改善AD特征性病理改变和认知缺陷^[77]。巴马汀通过调控AMPK/mTOR介导的自噬通路及调节肠道菌群平衡, 明显改善AD模型大鼠的认知功能损伤^[78]; 降低TNF- α 、iNOS、COX-2和NF- κ B免疫反应性, 减少神经炎症, 防止小胶质细胞和星形胶质细胞活化, 对IS小鼠神经元发挥保护作用^[79]; 抑制M1小胶质细胞极化并经由PDE4B/KLF4信号轴促进M2型抗炎极化, 从而建立神经保护性微环境并明显改善抑郁样行为表型^[80]。

综上, 黄柏有效成分通过调控相关通路, 调节免疫细胞活化, 调节神经递质、抗氧化等促进神经修复与保护作用。

3.4 栀子

栀子为茜草科常绿灌木栀子 *Gardenia jasminoides* Ellis 的成熟果实, 化学成分主要为萜类、有机酸类、黄酮类、多糖类、挥发油及其他类化合物等。栀子治疗ND的有效成分包括栀子苷、京尼平、西红花苷等。

栀子苷通过调控GSK3 β /STAT3/ROR γ T通路抑制Th17细胞分化, 从而减少内皮细胞损伤并

上调紧密连接蛋白表达减轻颅内动脉瘤的内皮损伤^[81];通过激活 Nrf2 信号通路减轻鱼藤酮(ROT)诱导的神经元氧化损伤,并抑制 mTOR 通路介导的神经元凋亡,从而发挥神经保护作用^[82];可通过阻断 BTK/JAK2/STAT1 信号通路减轻神经炎症反应、调控小胶质细胞极化状态、抑制 BDNF/TrkB 信号传导,从而对 LPS 诱导的抑郁小鼠发挥抗抑郁作用^[83]。京尼平可通过抑制 UCP2 蛋白表达,调控 ATP 水平及 NAD/NADH 平衡,进而激活 SIRT3,最终减轻 I/R 中的氧化应激反应和神经元凋亡^[84];可以有效地降低 A β 沉积和 Tau 蛋白磷酸化水平,

从而改善 AD 小鼠模型学习记忆和认知功能障碍。西红花苷调控 PI3K/AKT/mTOR 信号通路并上调 miRNA-7 和 miRNA-221 表达,在鱼藤酮诱导的帕金森病模型中发挥明显的神经保护效应^[85];还可通过激活 Nrf2/HO-1 通路^[86]及抑制内质网应激通路^[87],减轻氧化应激与神经炎症,缓解癫痫大鼠海马区神经损伤并改善其学习记忆功能。

综上,栀子有效成分通过抑制 A β 毒性损伤、抗氧化应激、减轻神经炎症,以及增强神经营养效应,从而发挥神经保护作用,维护神经元细胞功能。见表 1。

表 1 黄连解毒汤单味药主要活性成分及治疗神经系统疾病的作用机制

Tab 1 Main active components of the single herbs in Huanglian Jiedu Decoction and their mechanisms of action in treating nervous system diseases

中药名称	组成成分	药理作用机制	参考文献
黄连	小檗碱	激活 BDNF-TrkB-PI3K/Akt 信号通路,减少纹状体细胞凋亡	[64]
		调控 P2X7R-NLRP3 炎症信号通路,发挥抗抑郁样作用	[48,65]
		调节肠道菌群-脑-肠轴功能,发挥抗抑郁样作用	[66]
		调节大脑生物胺(去甲肾上腺素、血清素和多巴胺),起抗抑郁药的作用	[67]
黄连碱	下调 TNF- α 、IL-1 β ,上调 PGA2、PGJ2 和 15-deoxy-delta-12,14-PGJ2 表达,调节花生四烯酸代谢,减少神经炎症,发挥神经保护作用	激活 AMPK-Nrf2-HO-1 信号通路,抑制神经元铁死亡	[68]
		下调 PGD2 和 TNF- α ,减轻氧化应激	[69]
黄芩苷	下调 TNF- α 、IL-1 β ,上调 PGA2、PGJ2 和 15-deoxy-delta-12,14-PGJ2 表达,调节花生四烯酸代谢,减少神经炎症,发挥神经保护作用	激活 BDNF/TrkB 下游的 PI3K/AKT 和 MAPK/ERK 信号通路,发挥抗氧化应激作用	[71]
		抑制 SDH 活性、ROS 生成以防止 GS 降解,减轻神经元损伤	[72]
黄芩	汉黄芩素	下调 IL-1 β 、TNF- α 和 IL-6 水平,抑制 NF- κ B/I κ B 和 NLRP3/caspase-1/TLR4 信号通路,缓解神经炎症	[73]
		下调 MDA、ROS 水平,上调 GSH 水平,减轻氧化应激,抑制神经毒性	[74]
		调控 AMPK/SIRT1 通路,缓解神经炎症	[75]
		通过 DRD1 调控 PI3K/Akt/mTOR 信号通路,发挥抗抑郁作用	[76]
黄柏	木兰花碱	抑制 JNK 信号通路,改善认知缺陷	[77]
		调控 AMPK/mTOR 介导的自噬通路及调节肠道菌群平衡,改善认知功能损伤	[78]
栀子	巴马汀	下调 TNF- α 、iNOS、COX-2、NF κ B 表达,减少神经炎症,防止小胶质细胞和星形胶质细胞活化	[79]
		通过 PDE4B/KLF4 信号传导调节小胶质细胞极化,从而减轻抑郁样行为	[80]
		抑制 GSK3 β /STAT3/ROR γ T 通路,减少内皮细胞损伤	[81]
京尼平	西红花苷	激活 Nrf2 信号通路,抑制 mTOR 通路,减轻神经元氧化损伤和神经元死亡	[82]
		抑制 BTK/JAK2/STAT1、BDNF/TrkB 信号通路,减轻神经炎症反应、调控小胶质细胞极化状态	[83]
		下调 UCP2 表达,上调 NAD ⁺ /NADH、SIRT3、LDH、ATP,减轻氧化应激水平	[84]
		调控 PI3K/AKT/mTOR 信号通路,上调 miRNA-7、miRNA-221 表达,发挥神经保护效应	[85]
		抑制 Nrf2/HO-1 信号通路,减轻氧化应激损伤,降低神经炎症反应	[86]

4 讨论

黄连解毒汤作为经典清热解毒方剂,以“苦寒直折、泻火解毒”为根本,尤擅清三焦郁火、解脏腑热毒、宁心安神、平衡体内阴阳,于 ND 中彰显独特疗效。在 AD“痰热毒壅阻清窍”之证,本方可涤痰开窍、解毒醒神,改善健忘呆钝;对于 IS 恢复期

“痰热痹阻脑络”之候,既能清热解毒以消灼络之火,又可活血通络以启闭塞之窍,促进半身不遂康复。于 PD“肝风化火、筋脉失濡”之证,取其清肝泻火、解毒定颤之功,缓解肢体拘挛震颤。治疗精神分裂症“痰火扰心、神明失守”者,以泻心降火、涤痰开郁之法,平息躁狂谵妄;而对癫痫“痰热引动肝

风”之证,则藉清热豁痰、平肝熄风之效,遏制抽搐昏仆。随着病理因素的减轻,脑络无痰瘀,所阻得以畅通,气血得以输布,脑神得以涵养,神机得以正常运行,四肢得神机所统摄。药理学研究发现,黄连解毒汤及其四味药的活性成分可通过多成分(如小檗碱、黄芩苷、栀子苷等)、多靶点(NF- κ B/NLRP3、Nrf2/HO-1、BDNF/TrkB等)、多通路(抗炎、抗氧化、自噬调控等)协同作用,明显控制AD、PD、IS等神经退行性疾病的病理进程。故黄连解毒汤作为ND综合治疗的重要辅助手段,其单药应用或联合西医外治/手术/中医疗法表现出明显临床疗效,展现出广阔的协同治疗前景。

在文献梳理过程中,笔者注意到相关研究仍存在一些局限:首先,多数实验集中于动物模型,临床随机对照试验数据不足,尤其缺乏长期用药的安全性评估;其次,中枢ND的发病机制具有高度复杂性,涉及多通路交互作用,而当前中医药研究多聚焦于单一或有限病理环节的调控。未来研究需着力揭示不同信号通路的网络节点与协同机制,并深入阐明药物活性成分与疾病关键靶点的分子互作关系。最后,尽管黄连解毒汤在ND治疗中展现出多靶点调控优势,但其剂量-效应关系的精确解析及个体化用药方案的优化仍是当前研究的关键瓶颈。

综上所述,黄连解毒汤在神经退行性疾病治疗领域展现出巨大的潜力,未来研究需进一步阐明其对中枢ND的作用机制,借助先进的科研方法开展更全面、深入的实验与临床研究,为该药物的深度开发提供科学依据,并加强基础研究与临床实践的衔接,以提升疗效并推动精准应用,为中医药治疗ND提供更高级别的循证医学证据。

作者贡献度说明:

卢柠霞:参与论文撰写;高澳、杨津津、王业豪:收集相关文献;卢芳、刘树民参与论文指导并修改完善。

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