治疗炎症性肠病的中药药效物质及作用机制研究进展

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摘要: 炎症性肠病 (inflammatory bowel disease, IBD) 主要包括克罗恩病和溃疡性结肠炎, 是一种病因尚未完全明确的慢性肠道炎症性疾病。在全球范围内IBD的发病率持续上升, 其临床治疗面临诸多挑战, 包括不良反应、耐药性, 以及高昂的医疗成本等问题, 促使医学界积极寻找更加安全且高效的替代/补充疗法。在这一背景下, 中医药凭借整体观及辨证施治的理论优势, 发挥多成分、多靶点特性, 在调节机体免疫反应、发挥抗炎作用及修复受损肠道屏障等方面显示出了不可忽视的应用潜力。本文旨在综述近年来中药复方 (如乌梅丸、理中汤、四神丸等)、天然产物中的活性单体 (如厚朴酚、阿魏酸、绿原酸等) 在IBD治疗领域的应用进展, 并深入探讨其可能的作用机制, 以期为IBD治疗提供更多有效选择, 推动传统医学与现代科学的深度融合。

关键词: 炎症性肠病; 中药; 复方; 单体成分; 肠道屏障

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Research progress of the active substances and functional mechanism of traditional Chinese medicine in the treatment of inflammatory bowel disease

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Abstract: Inflammatory bowel disease (IBD), which mainly includes Crohn's disease and ulcerative colitis, is a chronic intestinal inflammatory disease whose etiology is not fully understood. As its global incidence increased, the clinical management of IBD still face multiple challenges, such as side effects, drug resistance, and high healthcare costs, prompting the medical community to actively search for safer and more effective alternative/complementary treatments. In this context, traditional Chinese medicine (TCM), with its holistic view and the theory of syndrome differentiation-based treatment, demonstrates significant potential in regulating immune responses, exerting anti-inflammatory effects, and repairing the damaged intestinal barrier through its multi-component and multi-target characteristics. Here we reviewed the recent progresses in the application of TCM formulae (e.g., Wumei pills, Lizhong decoction, Sishen pills, *etc*.) and active monomers (e.g., magnolol, ferulic acid, chlorogenic acid, *etc*.) in the treatment of IBD, as well as their possible mechanisms of action, in order to provide new therapeutic strategies for the clinical management of IBD and promote the integration between TCM and modern science.

Key words: inflammatory bowel disease; traditional Chinese medicine; TCM formula; monomer; intestinal barrier

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炎症性肠病 (inflammatory bowel disease, IBD) 是一组病因未明的慢性、复发性肠道炎症性疾病, 主要包括克罗恩病 (Crohn's disease, CD) 和溃疡性结肠炎 (ulcerative colitis, UC) 两种亚型。其中, CD 以透壁性炎症为特征, 可累及口腔至肛门的全消化道, 好发于回肠末端和结肠, 病变呈跳跃性分布, 常伴有瘘管、狭窄等并发症; UC 病变局限于结肠黏膜及黏膜下层, 呈连续性分布, 以反复发作的腹泻、黏液脓血便为主要表现[1]。

在 20 世纪, IBD 在北美、欧洲和大洋洲等地高发, 而 21 世纪以来, 随着新兴工业化国家的日益西方化和城市化, IBD 发病率在亚洲、拉丁美洲等各国也迅速上升, 逐渐演变成全球疾病[2]。近 20 年来, 传统高发地区如欧美国家的 IBD 患病率趋于稳定, 而发展中国家 IBD 发病率则呈现暴发式增长。临床上, 目前主要的治疗方案是采用氨基水杨酸类药物、糖皮质激素、免疫抑制剂和生物制剂等西药进行控制[3]。然而, 这几类药物均存在一定局限性, 如长期使用可能带来感染风险增加[4]、骨密度降低[5]、代谢紊乱[5]等不良反应; 部分患者对常规治疗反应不佳或产生耐药性[6]; 治疗成本高昂及患者依从性差[7]等。因此, 探索更安全、有效且经济的治疗方案成为 IBD 领域的重要临床需求。近年来, 大量临床及基础研究提示中药在调节机体免疫、抗炎及修复肠道黏膜屏障等方面疗效良好, 且兼具不良反应少、复发率低等优点[8]。本综述将详细探讨中药复方及单体在 IBD 治疗中的作用及分子机制, 以期推动 IBD 疾病的中西医结合治疗进程。

1　IBD 发病机制的中西医认识

1.1　现代医学理论中的 IBD 病因学说

IBD 病因尚未明确, 可能与遗传易感性、免疫失调、肠道菌群紊乱及环境因素等诸多因素均有关联[8]。遗传学研究显示, IBD 患者携带多个易感基因位点, 如核苷酸结合寡聚化结构域 2 (nucleotide-binding oligomerization domain 2, NOD2)、白细胞介素-23 受体 (interleukin-23 receptor, IL23R) 等[9,10], 这些基因参与固有免疫应答、自噬及上皮屏障修复, 约占疾病风险因素的 20%～30%[11]。在此基础上, 环境因素[12] (如西式饮食、吸烟、抗生素滥用等) 通过改变肠道菌群组成或代谢功能, 加剧肠道微生态失衡, 进而破坏肠黏膜屏障[13]。肠屏障功能受损导致细菌及抗原易位, 激活异常免疫反应[14]: ① 固有免疫: 巨噬细胞和树突状细胞通过 Toll 样受体 (Toll-like receptor, TLR)/核转录因子-κB (nuclear factor-κB, NF-κB) 通路过度激活, 大量释放促炎因子肿瘤坏死因子-α (tumor necrosis factor-α, TNF-α)、白细胞介素-6 (interleukin-6, IL-6) 等; ② 适应性免疫: 辅助性 T 细胞 1 (helper T cell 1, Th1)/Th17 过度活化, 分泌干扰素-γ (interferon-γ, IFN-γ) 与白细胞介素-17A (interleukin-17A, IL-17A) 等细胞因子, 可伴有调节性 T 细胞 (regulatory T cell, Treg) 功能缺陷, 共同驱动慢性炎症。此外, 肠上皮紧密连接蛋白 [如闭锁小带蛋白-1 (zonula occludens-1, ZO-1)] 与闭锁蛋白 (occludin) 表达下调[15]、黏液层分泌不足[16]及自噬障碍[17]等病理变化可进一步放大“肠漏”效应, 形成“遗传–环境–菌群–免疫”级联反应的恶性循环。

1.2　中医理论对 IBD 的病机描述

在中医理论中, IBD 可被归类为“肠澼”、“肠风”、“久痢”等疾病范畴, 该类疾病早在《黄帝内经》中便有记载[18]。中医认为, IBD 的发病与湿邪外侵、内伤饮食、情志失调及禀赋不足密切相关, 其核心病机可概括为脾虚湿盛为本, 湿热、瘀血、气滞为标, 病程中常虚实夹杂, 寒热交错。《证治汇补·痢疾》中提到:“饮食过多, 脾胃不运, 生冷失调, 湿热乃成, 痢下黄色, 或如鱼脑, 腹痛胀满, 不嗜饮食。”《景岳全书·泄泻》曰:“泄泻之本, 无不由于脾胃。”[19]脾主运化水湿, 脾胃当中又以脾为主, 脾病脾虚, 健运失职, 清气不升, 清浊不分, 湿性自生。同时, 湿性重浊, 阻遏气机; 湿邪久郁, 则化为热; 湿生津亏, 无以化血, 进而导致阴血亏虚, 血虚则滞[20]。湿热、瘀血、气滞并生, 以使肠络失和、气血壅滞, 发为本病。这些记载均与现代 IBD 病因与症状高度一致。

1.3　基于中医理论的 IBD 治则

中药治疗讲求辨证论治, 内外兼治。遵循辨证论治原则, UC 可被分为大肠湿热证、热毒炽盛证等 7 个证型, 根据证型、病程进展等不同, 可分型、分期论治, 采用清肠化湿、调气和血、补脾柔肝、祛湿止泻等法对症治疗[21]。CD 的中医病因病机以湿邪为核心, 本质为“脾胃虚弱为本, 痰湿热瘀毒互结为标”, 治疗强调辨证论治并结合分期、分段, 主要可采用运脾化湿、疏肝健脾等大法[22]。此外, 中医还强调内外兼治, 如中药灌肠可通过多靶点调控炎症免疫反应[23], 直接作用于病灶[24], 起效快, 临床疗效显著且复发率低; 另外, 针刺、艾灸及穴位贴敷等可通过刺激穴位, 疏通经络、调和气血、平衡脏腑功能, 在 IBD 治疗中展现出独特优势。笔者以“炎症性肠病/inflammatory bowel diseases”、“溃疡性结肠炎/ulcerative colitis”等为中英文关键词, 分别查阅 NCBI Pubmed、Web of Science 与 CNKI 等文献库, 对用于 IBD 治疗的几种常见的中药产物, 包括复方、单体、新制剂等进行综述, 为中药治疗 IBD 的临床应用提供一定的参考。

2 中药治疗IBD研究进展

现代研究证实, 中药治疗IBD可从抗炎、调节免疫、调节肠道微生态平衡、修复肠黏膜、抑制氧化应激等多个维度发挥综合效应 (图1)。

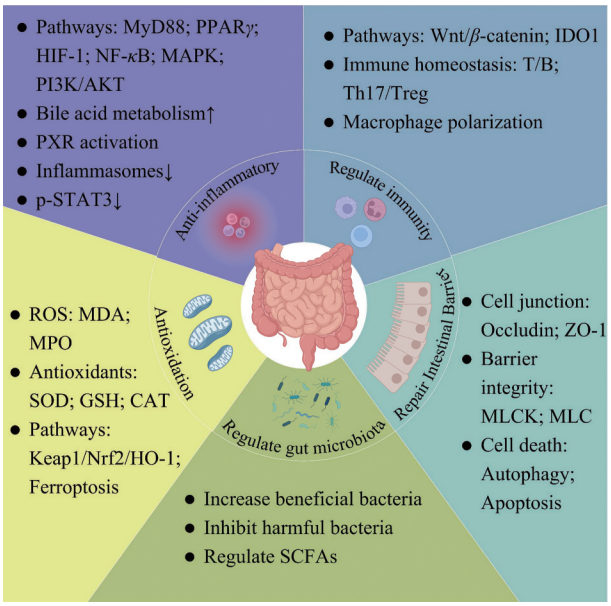


Figure 1 Summary of the mechanism of traditional Chinese medicine in treating IBD. IBD: Inflammatory bowel disease; MyD88: Myeloid differentiation primary response gene 88; PPAR-γ: Peroxisome proliferator-activated receptor γ; HIF-1: Hypoxia-inducible factor 1; NF-κB: Nuclear factor-κB; MAPK: Mitogen-activated protein kinase; PI3K: Phosphatidylinositol 3-kinase; AKT: Protein kinase B; MDA: Malondialdehyde; MPO: Myeloperoxidase; SOD: Superoxide dismutase; GSH: Glutathione; CAT: Catalase; Nrf2: Nuclear factor erythroid 2-related factor 2; HO-1: Heme oxygenase-1; Keap1: Kelch-like ECH-associated protein 1; IDO1: Indoleamine 2,3-dioxygenase 1; Th17: T helper 17 cell; Treg: Regulatory T cell; ZO-1: Zonula occludens-1; MLCK: Myosin light chain kinase; MLC: Myosin light chain. Created in https://BioRender.com

2.1 中药复方研究

2.1.1 乌梅丸

《伤寒论》中记载“蛔厥者, 乌梅丸主之, 又主久利”, 其原方由乌梅、当归、细辛、附子、黄柏、花椒、桂枝、人参、黄连和干姜等10味药组成[25]。清代著名医家柯韵伯亦云,“仲景制乌梅丸方, 寒热并用, 攻补兼施, 通理气血, 调和三焦, 为平治厥阴之主方”[26]。乌梅丸温肾暖脾, 清热和中, 在UC、肠易激综合征等临床治疗中疗效显著, 主要应用于IBD寒热错杂证的治疗[27-30]。

现代研究表明, 乌梅丸可通过多种机制发挥作用, 包括抗氧化[31]、抗炎[32]、免疫调控[33]、屏障修复[34]、菌群调节[35]等。其治疗作用源于其复方配伍的多成分协同效应。首先, 方中君药乌梅富含有机酸和多酚类成分, 系统药理学研究显示乌梅可通过调节TNF-α、IL-8、IL-17与IL-4等水平调节免疫功能[36], 并通过调节肠道菌群改善肠道炎症[37]; 其次, 黄连中的主要活性成分小檗碱可在肠道菌群氧化作用下产生氧化小檗碱, 该代谢物能够通过抑制Kelch样环氧氯丙烷相关蛋白1 (Kelch-like ECH-associated protein 1, Keap1)/核转录因子E2相关因子2 (nuclear factor erythroid 2-related factor 2, Nrf2)/NF-κB信号通路抑制炎症与氧化应激[38], 同时小檗碱可调节肠道菌群与Th17/Treg平衡, 修复肠道屏障, 恢复肠道免疫稳态[39]。此外, 黄柏所含的黄柏碱能通过调节5'-腺苷酸活化蛋白激酶 (5'-adenosine monophosphate-activated protein kinase, AMPK)/哺乳动物雷帕霉素靶蛋白 (mammalian target of rapamycin, mTOR) 通路促进自噬[40], 而花椒的挥发油成分则通过显著下调TNF-α、IL-6和IL-1β等促炎因子水平, 上调IL-10等抗炎因子表达等机制来改善炎症[41]。这些活性成分通过抗炎、免疫调节、自噬激活等多途径协同作用, 共同构成了乌梅丸治疗UC的药效学基础。

2.1.2 黄芩汤

黄芩汤出自《伤寒论》, 被称为“万世治痢之祖剂”[42], 其原方由黄芩、芍药、甘草、大枣4味药组成, 具有“清热止痢, 和中止痛”之功, 常用于治疗湿热下痢, 即脾胃湿热内蕴所致的痢疾。黄芩汤广泛用于UC活动期大肠湿热证的治疗, 临床研究表明其可显著改善腹痛、腹泻及黏液脓血便等症状[43]。

现代研究表明, 黄芩汤可通过抗炎抗氧化[44]、免疫调控[45]、改善肠道菌群[46]、抑制细胞焦亡[47]等多种机制发挥作用。如Wu等[47]通过葡聚糖硫酸钠 (dextran sulfate sodium, DSS) 诱导的UC小鼠模型发现, 黄芩汤可通过调控氧化应激及铁死亡相关通路, 抑制长链脂酰辅酶A合成酶4 [acyl-coenzyme A (CoA) synthetase long-chain family member 4, ACSL4] 表达, 上调谷胱甘肽过氧化物酶4 (glutathione peroxidase 4, GPX4)、铁蛋白重链1 (ferritin heavy polypeptide 1, FTH1) 及胱氨酸/谷氨酸逆向转运蛋白溶质载体家族7成员11 (solute carrier family 7 member 11, SLC7A11) 的表达, 从而抑制细胞焦亡, 达到治疗效果。其方中含多种具有良好抗炎效果的抗炎物质, 如主方黄芩的主要活性成分黄芩苷具有显著的免疫调节[48]与抗氧化作用[49], Zhang等[50]将其与镁离子结合, 在提升其水溶性的同时增强其疗效, 该团队通过DSS处理的UC小鼠模型发现, DSS可导致胆汁酸调节失衡, 使用黄芩苷镁处理

可改善胆汁酸代谢紊乱, 提高鹅去氧胆酸、熊去氧胆酸等次级胆汁酸水平, 降低α-鼠胆酸与β-鼠胆酸水平, 并由此激活G蛋白偶联胆汁酸受体1和法尼醇X受体(farnesoid X receptor, FXR), 进而抑制结肠黏膜中促炎因子的产生, 减轻肠道炎症。其次, 芍药中的芍药苷可抑制3型天然淋巴细胞中死亡受体3 (death recptor 3, DR3) 信号通路, 减少DR3及其下游蛋白如IL-17A表达, 降低p38和p65蛋白磷酸化水平, 并调节炎症介质分泌, 改善紧密连接蛋白表达, 进而发挥对肠道屏障的保护作用[51]。另外, Wang等[52]发现, 在偶氮甲烷/DSS诱导的UC相关结肠癌小鼠结肠组织中, 表皮生长因子结构域7 (epidermal growth factor-like domain multiple 7, EGFL7) 呈高表达状态, 而芍药苷可有效降低结肠癌细胞中EGFL7的表达, 减少炎症细胞在结肠组织的浸润, 修复肠道黏膜屏障。此外, 甘草所含的甘草酸具有抗氧化和黏膜保护作用[53], 而大枣富含的多糖成分则能促进肠道有益菌增殖[54]。这些活性成分通过抗炎、免疫调节、抗氧化、菌群调控等多靶点协同作用, 共同构成了黄芩汤治疗UC的药效物质基础。

2.1.3　理中汤

理中汤也出自《伤寒论》, 由人参、干姜、白术、炙甘草4味药组成, 主治“脾胃虚寒、腹痛泄泻”。明代医家张景岳在《景岳全书》中称其“温中散寒、健脾益气”, 适用于脾胃虚寒所致的慢性腹泻。理中汤广泛用于IBD缓解期脾胃虚寒证的治疗, 临床研究表明其可显著改善腹痛、腹泻及溃疡等症状[55]。

研究表明, 理中汤可通过调节mTOR/磷酸化核糖体蛋白S6激酶1 (phosphorylated ribosomal protein S6 kinase 1, p-S6K1) [56]、纤维肉瘤 (rapidly accelerated fibrosarcoma, Raf)/丝裂原活化蛋白激酶激酶 (mitogen-activated protein kinase kinase, MAPKK, or MEK)/细胞外信号调节激酶 (extracellular signal-regulated kinase, ERK) [57]、Keap1/Nrf2/抗氧化反应元件 (antioxidant response element, ARE)[58]等信号通路, 减轻肠黏膜炎症反应, 改善氧化应激。其方中人参、干姜、白术等都具有较好的抗炎效果。如人参的主要活性成分人参皂苷可从抗炎、抗氧化、免疫调节等多方面对IBD起到治疗作用。干姜中的6-姜酚可通过降低铁负荷和脂质过氧化来抑制铁死亡[59], 同时抑制NF-κB核转位, 下调NF-κB信号通路, 从而发挥抗溃疡作用[60]。白术所含的白术内酯III可通过抑制NF-κB介导的肌球蛋白轻链激酶 (myosin light chain kinase, MLCK)-磷酸化肌球蛋白轻链 (phosphorylated myosin light chain, pMLC) 信号通路来增强肠上皮屏障功能[61]; 同时通过激活AMPK/沉默信息调节因子1 (silent information regulator 1, SIRT1)/过氧化物酶体增殖物激活受体γ辅激活因子-1α (peroxisome proliferator-activated receptor gamma coactivator-1α, PGC-1α) 通路改善线粒体功能, 预防UC[62]。这些活性成分通过多靶点、多通路的协同作用, 从抗氧化、抗炎、免疫调节、屏障修复等多个方面共同阐释了理中汤“温中散寒、健脾益气”的传统功效。

2.1.4　白头翁汤

白头翁汤出自《伤寒论》, 原方由白头翁、黄柏、黄连、秦皮4味药组成, 主治“热痢下重”, 即湿热下注所致的痢疾。清代医家吴鞠通在《温病条辨》中进一步阐述其“清热解毒、凉血止痢”之功, 适用于治疗湿热蕴结肠道、灼伤血络所致的黏液脓血便[63]。白头翁汤广泛用于UC活动期的治疗, 主治IBD热毒炽盛证[30], 临床研究表明其可显著改善腹痛、腹泻及黏液脓血便症状[64]。

现代研究显示, 白头翁汤可通过抗炎抗氧化[65,66]、修复肠道平整[67]、改善免疫功能[68]、改善肠道菌群失调[69]等机制发挥作用。现代药理学研究表明, 方中君药白头翁的主要活性成分白头翁皂苷具有显著的抗炎作用, 可通过激活G蛋白偶联受体43-NOD样受体热蛋白结构域相关蛋白3 (NOD-like receptor pyrin domain containing 3, NLRP3) 信号通路降低IL-6、TNF-α等促炎因子表达[70], 同时能够调节肠道菌群的组成和多样性, 改善肠道微生态环境[71]。黄柏所含的小檗碱已被证明具有良好的抗氧化[39]、免疫调节功能[38]。黄连的主要成分黄连碱能够增强肠道屏障功能, 保护肠黏膜完整性[72]。而秦皮的主要成分秦皮甲素则通过抑制TLR4/NF-κB和丝裂原活化蛋白激酶 (mitogen-activated protein kinase, MAPK) 信号通路的活化, 调节氧化应激和炎症反应, 从而改善UC症状[73]。这些活性成分通过抗炎、免疫调节、屏障保护和氧化应激调节等多靶点协同作用, 体现了中药复方“多成分–多靶点–多通路”的整体调节特点。

2.1.5　葛根芩连汤

葛根芩连汤源自《伤寒论》, 由葛根、黄芩、黄连、甘草4味药配伍而成,“主治协热下利”, 适用于太阳表邪内陷引发的邪热下利症。《广瘟疫论》指出该方还可用于治疗感染疫病后“烦、渴、谵妄悉具而便脓血者”。

现代研究表明, 葛根芩连汤可通过调节氧化应激、抑制炎症反应、调节肠黏膜菌群平衡等多种途径, 发挥保护肠道屏障、改善肠炎的作用[74]。如在DSS诱导的小鼠结肠炎模型中, Wang等[75]发现葛根芩连汤可降低铁负荷, 下调丙二醛 (malondialdehyde, MDA) 水平, 并调节GPX4、SLC7A11、ACSL4等铁死亡相关蛋白表

达, 通过抑制铁死亡改善上皮屏障功能障碍, 抑制结肠损伤。葛根芩连汤亦可通过激活过氧化物酶体增殖物激活受体 γ (peroxisome proliferator-activated receptor γ, PPAR-γ) 信号, 降低管腔中的硝酸盐水平, 从而防止潜在致病性大肠杆菌的菌群失调扩张, 改善UC[76]。

除方中各味药可发生抗炎作用外, 研究发现中药配方煎煮后产生的大分子物质在IBD的治疗中也发挥着重要作用。在通过中脑动脉闭塞手术诱导的大鼠肠道屏障损伤模型研究中, Lian等[77]将中药葛根经热提得到的大分子葛根淀粉 (PLR-RS) 对大鼠进行给药, 发现其可上调结肠紧密连接蛋白表达, 有效改善结肠病理损伤, 修复肠道屏障完整性。同时, PLR-RS还能通过调节菌群代谢, 显著提高盲肠内容物中的褪黑素水平。褪黑素水平的提高又可富集有益菌, 形成正向共现模式, 实现对肠道屏障的修复。

2.1.6 其他方剂

中医治疗IBD的经典方剂还包括参苓白术散、芍药汤、四神丸等, 可根据IBD患者不同中医临床证型灵活运用。如参苓白术散 (出自《太平惠民和剂局方》)[78], 由人参、茯苓、白术、山药、白扁豆、莲子、薏苡仁、砂仁、桔梗、甘草10味药组成, 具有益气健脾、渗湿止泻的作用, 被广泛用于IBD脾虚湿蕴证的治疗[30,79]; 芍药汤 (出自《黄帝内经·素问·病机气宜保命集》), 由黄连、黄芩、大黄、白芍、当归、木香、槟榔、肉桂、甘草9味药构成[80], 因其具有清热利湿、调气活血功效, 后世医家皆推此方为治疗湿热泄痢之主方, 主要用于IBD大肠湿热证的治疗[30]; 四神丸 (出自《证治准绳》), 由补骨脂、肉豆蔻、五味子、吴茱萸4味药组成, 主治“脾肾阳虚、五更泄泻”[81], 常用于IBD缓解期脾肾阳虚证的治疗, 可显著改善腹泻、腹痛及乏力症状, 复发率低[82]。现代药理学研究提示, 上述方剂作用与调节肠壁通透性、调节炎症信号通路、调节免疫功能、调节肠道菌群平衡等多种机制相关[35,83-85]。

2.2 中药单体成分研究

中药单体成分是中药发挥药效的重要物质基础, 其成分明确、作用机制相对清晰。大量研究表明, 多种中药单体成分可通过调节炎症水平、改善免疫功能、抑制氧化应激、修复黏膜屏障、调节肠道菌群等多种途径, 发挥对IBD的治疗作用。

2.2.1 苯丙素类

苯丙素类化合物是天然存在的一类酚类活性物质, 多具有苯酚结构, 主要包括苯丙酸类、香豆素类与木脂素类等[86]。研究表明, 苯丙素类化合物可通过抑制炎症因子产生, 发挥抗炎作用[87], 在IBD治疗中发挥重要作用。

2.2.1.1 厚朴酚

厚朴酚为厚朴的主要活性成分, 具有消炎、镇痛、抗菌等多种药理作用[88]。研究表明, 厚朴酚可抑制TNF-α的表达, 通过对NF-κB和PPAR-γ途径的调节, 有效调控IL-1β和IL-12等促炎因子水平[89]。Shen等[89]在DSS诱导的小鼠结肠炎模型中发现, 厚朴酚可增强结肠组织中紧密连接蛋白ZO-1和occludin的表达, 显著改善小鼠体重减轻和结肠长度缩短等症状, 降低疾病活动指数, 缓解结肠病理损害。厚朴酚还可抑制肠毒素过表达所诱导的诱导型一氧化氮合酶 (inducible nitric oxide synthase, iNOS)、一氧化氮 (nitric oxide, NO)、二胺氧化酶 (diamine oxidase, DAO)、环氧化酶-2 (cyclooxygenase-2, COX-2)、TNF等物质的产生或活性, 对抗肠道氧化应激性炎症反应, 保护肠黏膜[90]。此外, 一项基于脂多糖 (lipopolysaccharide, LPS) 诱导的败血症大鼠模型的研究提示, 厚朴酚还可作为钙离子通道阻滞剂, 降低肠上皮细胞内游离钙离子浓度, 抑制肠道过度运动和肠分泌, 产生抗腹泻效应[91]。

2.2.1.2 阿魏酸

阿魏酸广泛存在于多种药材, 具有良好抗炎作用, 可显著降低各种炎症因子产生[92]。研究表明, 阿魏酸可能通过阻断硫氧还蛋白相互作用蛋白 (thioredoxin interacting protein, TXNIP)/NLRP3信号途径, 下调IL-6、IL-12等炎症因子水平, 并减少细胞凋亡相关蛋白半胱天冬酶 (cysteine aspartate specific protease, caspase)-1和caspase-3的表达, 从而抑制人肠道微血管内皮细胞凋亡, 并减轻UC大鼠肠道损伤[93]。在结肠炎发生过程中, 细胞会由于DSS刺激而产生大量活性氧 (reactive oxygen species, ROS), 引发氧化应激并导致DNA损伤, 损伤DNA可通过环鸟苷酸−腺苷酸合成酶 (cyclic GMP-AMP synthase, cGAS)-干扰素基因刺激因子 (stimulator of interferon genes, STING) 通路引发一系列反应, 导致促炎因子大量生成, 加剧炎症。Xiao等[94]通过构建一种果胶负载阿魏酸 (PC-FA) 纳米颗粒, 减少DNA损伤并显著下调cGAS、STING表达, 减少促炎因子分泌的同时调节免疫失衡, 可有效缓解炎症。此外, 阿魏酸还可通过调节结肠组织中抗氧化因子, 如超氧化物歧化酶 (superoxide dismutase, SOD)、过氧化氢酶 (catalase, CAT) 等水平, 减轻氧化应激[95]。Shen等[96]还报道, 产阿魏酸酯酶的细菌 (FAEb) 对DSS诱导IBD小鼠模型中厚壁菌门数目有显著下调作用, 同时可增加阿克曼菌与普通拟杆菌的相对丰度, 提示阿魏酸的肠道微生态调节功能。

2.2.1.3 绿原酸

绿原酸可见于金银花等多种药材, 具有抗菌、免疫调节和抗肿瘤等多方面药理作用[97]。通过使用断奶仔猪模型, Chen等[98]报道, 在基础日粮

中添加 1 000 mg·kg^{-1}绿原酸, 可有效减少正常断奶仔猪小肠肥大细胞数量, 增加密蛋白-1 (claudin-1) 表达, 下调多种炎症因子水平, 其机制可能与 TLR4/NF-κB 信号通路以及激活 Nrf2/血红素加氧酶-1 (heme oxygenase-1, HO-1) 信号通路有关。该课题组进一步发现, 绿原酸可减轻氧化应激诱导肠道炎症仔猪模型中肠道损伤, 并在体外模型中协同调控磷脂酰肌醇 3-激酶 (phosphatidylinositol 3-kinase, PI3K)/蛋白激酶 B (protein kinase B, AKT) 与 NF-κB 抑制剂α (inhibitor of nuclear factor-κBα, IκBα)/NF-κB 信号通路[99]。另外, Zeng 等[100]研究发现, 在 LPS/腺苷三磷酸 (adenosine triphosphate, ATP) 刺激的 RAW264.7 细胞以及 DSS 诱导的结肠炎小鼠结肠组织中, 微小 RNA-155 (microRNA 155, miR-155) 过表达可激活 NF-κB 炎症信号通路并调节免疫细胞分化发育, 形成慢性炎症状态, 而给予绿原酸可使 miR-155 的表达剂量依赖性降低, 改善炎症。此外, 绿原酸还能通过减轻氧化应激损伤[101]、减少细胞凋亡等途径保护肠道上皮细胞[102], 减轻炎症水平。

2.2.2　醌类

醌类化合物广泛存在于各类植物中, 是大黄、虎杖、何首乌等植物中的主要有效成分, 属于天然活性化合物。根据结构不同, 可以分为苯醌、萘醌、菲醌和蒽醌 4 种。大量研究提示, 醌类化合物通过抑制炎症信号通路、抗氧化、调节肠道菌群和保护肠道屏障功能等多种机制, 在 IBD 治疗中发挥作用。

2.2.2.1　大黄素　大黄素为多种蓼科植物如唐古特大黄中提取的蒽醌类化合物, 为传统中药成分, 具有抗炎、抗肾间质纤维化等功效[103]。大黄素可通过激活 UC 小鼠的 PPAR-γ 信号通路, 调节花生四烯酸代谢、类固醇激素生物合成、氧化磷酸化、甘油磷脂代谢、嘧啶与嘌呤代谢等生物过程, 减少炎症介质产生, 并促进线粒体β-氧化, 在结肠上皮细胞中创造缺氧环境, 抑制兼性厌氧菌生长。作为 PPAR-γ 激动剂, 大黄素可抑制 iNOS 和 NF-κB p65 的表达, 降低炎症因子水平, 同时减少中性粒细胞浸润[104]。iNOS 的表达下调亦可减少 NO 介导的氧化应激, 保护肠道黏膜细胞[105]。同时, 大黄素能够增加肠道中有益菌的相对丰度, 有助于物种丰富度的恢复, 调节肠道菌群[104]。大黄素还可通过加强肠黏膜上皮之间的紧密连接, 修复胃肠道黏膜损伤[106]等方式改善肠道炎症。

2.2.2.2　大黄酸　大黄酸为药用大黄等植物中提取出的天然活性物质, 具有抗炎、抗氧化、调节肠道菌群等作用。大黄酸可以促进巨噬细胞从 M1 型 (经典激活型巨噬细胞, classically activated macrophages) 促炎型向 M2 型 (替代激活型巨噬细胞, alternatively activated macrophages) 抑炎型极化、抑制趋化因子介导的巨噬细胞向肠炎部位的迁移, 纠正促炎与抗炎介质失衡; 在 DSS 诱导的小鼠结肠炎模型中, Zhou 等[107]还发现大黄酸可通过抑制相关蛋白磷酸化, 抑制 NLRP3 炎性小体的激活, 降低 IL-1β 等炎症因子分泌, 减轻炎症反应; 大黄酸亦可通过调节 NF-κB 通路, 抑制 MLCK 的表达及磷酸化, 抑制 ZO-1 的重排和转录, 保护肠上皮细胞屏障[108]; 在 DSS 诱导的结肠炎小鼠模型中, Wu 等[109]发现大黄酸可能通过调节肠道微生物群来间接影响嘌呤代谢, 大黄酸处理可增加乳酸杆菌水平, 后者发酵产物能够减少尿酸产生, 纠正嘌呤代谢异常, 从而对炎症发展起到抑制作用。

2.2.2.3　百里醌　百里醌为从黑种草种子中提取的活性物质, 具有抗氧化、抗炎和抗肿瘤等作用。Madani 等[110]在 5-氟尿嘧啶处理得到的肠黏膜炎小鼠模型中发现, 百里醌可以通过抑制 NF-κB 和缺氧诱导因子-1 (hypoxia inducible factor-1, HIF-1) 信号通路, 减少 TNF-α、IL-1β、IL-6 等炎症因子的产生, 而 Venkataraman 等[111]则发现其对 NF-κB 的抑制来源于其对 PPAR-γ 转录因子的激活。同时, 百里醌亦能通过调节抗氧化因子水平、上调紧密连接蛋白数目等方式, 增强肠道黏膜完整性, 保护肠道屏障功能[110]。此外, 有研究发现, 百里醌和蜂胶脂质体制剂联合治疗醋酸诱导的 UC 具有比游离百里醌更高的有效性, 其机制除上述外, 还包含降低 caspase-3 免疫阳性面积百分比, 调节细胞凋亡等[112]。

2.2.2.4　丹参酮 IIA　丹参酮 IIA 是从丹参中提取的脂溶性成分, 具有抗炎、抗氧化、抗血小板聚集等多种药理作用。Zhu 等[113]运用代谢组学技术, 以 6～8 周龄雄性 C57BL/6J 小鼠结肠组织为样本, 研究丹参酮 IIA 对 UC 作用, 发现丹参酮 IIA 处理可以改变牛磺酸和亚牛磺酸代谢、甘氨酸−丝氨酸−苏氨酸代谢、花生四烯酸代谢及丙氨酸−天冬氨酸−谷氨酸代谢等代谢通路, 显著改善疾病活动指数评分和结肠组织病理损伤, 此外, Wang 等[114]报道丹参酮 IIA 还可有效抑制肠上皮细胞系 No.6 (intestinal epithelioid cell line No.6, IEC-6) 中铁死亡。铁死亡[115]是一种由铁、ROS 和细胞膜脂质过氧化共同驱动的受控细胞死亡形式, 可参与 IBD 的发病机制: UC 与 CD 均能导致肠道上皮细胞中 GPX4 活性降低和脂质过氧化增加, 而 GPX4 是 GPX 家族中唯一能够清除嵌入细胞膜的脂质过氧化物的成员。丹参酮 IIA 则可通过上调 GPX4、SLC7A11 和 miR-17-92 等铁死亡早期响应基因, 显著保护 RAS 选择性致死因子 3 (RAS-selective lethal 3, RSL3) 诱导的 IEC-6 细胞铁

死亡, 发挥对IBD的治疗作用[114]。此外, 丹参酮IIA还可能通过下调炎症因子水平[116]、修复肠道黏膜屏障[117]、抗氧化[118]等途径, 抑制肠道炎症, 减轻肠道损伤。

2.2.3 黄酮类

黄酮类化合物是自然界中天然存在的羟基多酚类化合物, 具有显著的自由基清除能力, 抗氧化能力强[119], 可调节肠道微生态平衡、增强免疫。除黄芩苷(见2.1.2)外, 本类化合物中还有若干单体在IBD治疗中表现出了极大的潜力。

2.2.3.1 葛根素 葛根素为药食同源药材葛根的主要成分之一, 对发烧、炎症、高脂血症等诱导的疾病和氧化损伤均能起到保护作用[120]。Tao等[121]在DSS诱导的结肠炎小鼠模型与LPS诱导的M1巨噬细胞炎症模型上研究发现, 葛根素可逆转促炎基因(如iNOS、IL-6)和抗炎基因[如精氨酸酶1 (arginase-1, Arg-1)]表达变化, 激活mTOR复合体1信号基因和未折叠蛋白反应相关基因, 上调主要组织相容性复合体(major histocompatibility complex, MHC) I和MHC II类基因表达, 并促使巨噬细胞向M2状态极化, 有效抑制由嗜黏蛋白阿克曼菌(*Akkermansia muciniphila*, Amuc)分泌的Amuc-2172蛋白诱导的巨噬细胞M1样极化, 从而改善肠炎。此外, 通过调节基因表达, 葛根素还能促使杯状细胞增多, 从而上调黏蛋白2 (mucin2, Muc2)分泌水平, 增强结肠黏液屏障, 阻挡细菌及其代谢产物对肠上皮的侵蚀, 在增加分泌的同时还抑制黏蛋白利用型细菌的过度增殖, 减少黏蛋白的过度消耗, 维持黏液层功能[122]。除基因调控外, 葛根素还可通过调节TNF、HIF-1、IL-17、PI3K-AKT、Nrf2/Keap1等信号通路, 降低炎症水平与氧化应激, 多途径干预IBD治疗[123,124]; 除此之外, Zhong等[125]报道葛根素还能够通过促进肠共生菌生长, 逆转肠道上皮细胞紧密连接蛋白的表达下调, 保护肠道屏障。

2.2.3.2 柚皮苷 柚皮苷是从葡萄和柑橘类等水果中提取的黄酮类化合物, 为葡萄糖、鼠李糖和柚配质组成的复合体, 具有抗过敏和抗炎等功效。研究表明, 柚皮苷为PPAR-γ激动剂, 可通过PPAR-γ的激活抑制NF-κB的活化, 从而抑制一系列炎症反应[126]。在2,4,6-三硝基苯磺酸(2,4,6-trinitrobenzenesulfonic acid, TNBS)诱导的UC小鼠模型中, 柚皮苷可显著提高SOD、谷胱甘肽(glutathione, GSH)和CAT水平, 降低MDA和髓过氧化物酶水平, 增强结肠组织的抗氧化能力, 减轻炎症[127]; 在保护肠道屏障方面, 柚皮苷能下调iNOS和COX-2的表达, 上调ZO-1和occludin的表达, 维护肠道上皮屏障功能; 柚皮苷亦能恢复小鼠肠道厚壁菌门/拟杆菌门的比例, 降低变形菌门数量, 调节肠道菌群, 对IBD治疗产生作用[128]。

2.2.4 萜类

萜类化合物是一类由异戊二烯单元组成的天然有机化合物, 根据异戊二烯单元的个数, 可分为单萜、倍半萜、二萜、三萜等。研究表明, 萜类化合物可以通过抑制炎症介质的产生与释放、调节炎症信号通路、抗氧化应激等途径产生抗炎作用[129], 除芍药苷(见2.1.2)外, 齐墩果酸、穿心莲内酯等单体也在IBD治疗具有潜在作用。

2.2.4.1 齐墩果酸 齐墩果酸是女贞子的主要活性成分, 为五环三萜类化合物, 在抗炎、抗氧化等方面具有显著作用[130]。Hu等[131]基于小鼠初始分化簇4 (cluster of differentiation 4, CD4)阳性T细胞体外分化实验与TNBS诱导的小鼠结肠炎模型研究提示, 齐墩果酸可以直接与激活状态的含Src同源2结构域的蛋白酪氨酸磷酸酶2 (Src homology 2 domain-containing protein tyrosine phosphatase 2, SHP2)结合, 后者是细胞信号通路调节与炎症反应中的重要蛋白。齐墩果酸通过稳定其开放构象, 维持SHP2活性; 同时齐墩果酸还可使信号转导及转录激活因子3 (signal transducer and activator of transcription 3, STAT3)去磷酸化, 阻断STAT3信号通路, 抑制Th17细胞分化, 减少IL-17等促炎细胞因子分泌, 减轻炎症反应。齐墩果酸亦可以抑制NF-κB、MAPK通路的激活, 减少促炎细胞因子如TNF-α、IL-1β、IL-6的产生[132]。部分齐墩果酸衍生物可抑制iNOS和COX-2等酶的活性, 减少炎症介质的生成, 产生抗炎效果[133]。此外, Zhang等[134]制备齐墩果酸纳米颗粒(OA NPs), 证明其可降低LPS刺激的RAW264.7细胞的线粒体膜电位, 避免细胞氧化损伤, 同时OA NPs可通过增强渗透和滞留(enhanced permeability and retention, EPR)效应, 有效靶向结肠炎症区域, 在IBD治疗中具有良好潜力。

2.2.4.2 穿心莲内酯 穿心莲内酯是穿心莲主要有效成分, 为二萜内酯类化合物, 具有抗炎、免疫调节、改善肠道菌群等药理作用[135]。Kim等[136]基于LPS诱导的巨噬细胞炎症模型与DSS诱导的小鼠结肠炎模型研究发现, 穿心莲内酯可通过激活巨噬细胞中的AMPK通路, 抑制NF-κB、MAPK及其上游信号通路, 下调促炎细胞因子水平, 减轻LPS诱导的炎症反应, 在体内则可以相同途径, 改善小鼠急性结肠炎症状, 发挥治疗作用。UC患者常出现免疫失常, IL-23/IL-17轴对UC的发病可能有重要影响, 而穿心莲内酯可下调IL-23/IL-17轴, 抑制IL-17、TNF-α等促炎细胞因子水平, 同时有效促进结肠炎小鼠的结肠黏膜修复[137]。另外, Guan

等[138]发现, 当肠道屏障受损时, LPS会进入肝脏激活TLR4/髓样分化初级反应基因88 (myeloid differentiation primary response gene 88, MyD88)/NF-κB信号通路, 引发肝脏炎症, 而肝损产生的促炎细胞因子又会加重结肠炎。穿心莲内酯可通过下调肝脏中TLR4与MyD88表达, 减轻肝脏炎症和对肠道炎症的加剧作用, 间接治疗结肠炎。除此之外, 穿心莲内酯亦可通过增加有益菌如厚壁菌门水平, 抑制部分有害菌生长[139], 激活Nrf2/HO-1信号通路, 抑制氧化应激[140]等途径, 促进肠道健康, 增强肠道屏障。

2.2.5　生物碱类

生物碱是一类含氮有机化合物, 广泛存在于植物、微生物中。根据结构不同, 可分为吲哚类、喹啉类、吡咯类、托品类与异喹啉类。研究提示生物碱可能从抗炎、免疫调节、抗氧化、改善肠道屏障等多方面对IBD发挥治疗作用。

2.2.5.1　小檗碱　小檗碱是黄连中含量最高的生物碱, 为异喹啉类, 具有抗炎、抗氧化、抗菌等多种药理活性, 在IBD的治疗方面已有较多研究[141]。除抗氧化与免疫调节等机制外, 小檗碱还可通过多种途径对IBD产生治疗作用。硒蛋白S (selenoprotein S, SelS)是一类硒蛋白, 硒是一种机体必需的微量元素, 硒的缺乏会导致肠道功能受损。Qian等[142]报道小檗碱可显著上调DSS诱导后人正常结肠上皮细胞中SelS mRNA和蛋白的表达, 减少肠道疾病发生率。小檗碱亦可通过抑制TNBS诱导的结肠炎小鼠iNOS、COX-2等的mRNA表达, 抑制NF-κB和TLR-4的激活, 改善肠炎[143]; 同时, 小檗碱可抑制NLRP3、凋亡相关斑点样蛋白 (apoptosis-associated speck-like protein containing a CARD, ASC)和剪切型半胱天冬酶-1 (cleaved caspase-1)等炎症小体相关蛋白的表达, 显著降低多种促炎细胞因子如TNF-α、IL-6的水平, 减轻炎症[144]; 此外, 一项基于DSS诱导的结肠炎大鼠模型与人结直肠腺癌细胞(Caco-2细胞)单层模型的研究还发现, 小檗碱可以改善结肠炎引起的肠道菌群异常紊乱, 调控肠道菌关联色氨酸代谢产物的合成表达, 进一步激活芳香烃受体, 修复肠屏障损伤[145]。不仅如此, 小檗碱还可通过调控肠道神经胶质细胞–上皮细胞–免疫细胞相互作用, 明显改善小鼠结肠病理性损伤, 维持其黏膜屏障功能[146]。

2.2.5.2　苦参碱　苦参碱是从豆科植物苦参中所提取的生物碱, 属于喹嗪啶类。据研究, 苦参碱具有抗炎和免疫抑制作用, 对UC具有广泛的治疗作用[147]。网络药理学分析提示, 苦参碱约有28个治疗IBD的潜在靶点, 包括CHRNA7、DRD1、CHRNA4、SLC6A3、GRM5等, 这些靶点可能与神经活性配体–受体相互作用、胆碱能突触等通路相关, 并可对炎症因子、免疫反应等产生调节作用[148]。Sun等[149]研究表明, 苦参碱可通过抑制核小体高迁移率族蛋白B1 (nucleosomal high mobility group box-1, HMGB1)/NLRP3/caspase-1信号通路相关蛋白和基因表达, 减少促炎细胞因子的产生和释放。同时, 苦参碱具有强效的抗氧化作用, 可降低IL-6表达、抑制STAT3磷酸化与炎症因子分泌并提升抗氧化酶活性, 从而减轻炎症、抑制氧化应激反应[150]。DSS诱导的结肠炎小鼠模型研究提示, 苦参碱可增加$CD4^+$叉头框转录因子P3 (forkhead box P3, Foxp3)$^+$/$CD4^+$IL-$17A^+$细胞的比值, 调节Treg/Th17细胞平衡, 抑制炎症反应; 苦参碱亦可通过调节结肠组织中紧密连接蛋白表达、增加微生物群落多样性, 增加有益菌属相对丰度等途径, 保护肠道屏障, 改善炎症[151]。

2.2.5.3　氧化苦参碱　氧化苦参碱是从豆科槐属植物苦豆子中提取的生物碱, 具有抗炎、抗缺氧、免疫调节等作用。研究表明, 氧化苦参碱可通过调控PI3K/AKT通路, 下调Th17和Th13的分化, 从而抑制炎症因子的过度分泌与细胞凋亡[152]; 氧化苦参碱还可调节视黄醇相关孤儿受体γt (retinoic acid receptor-related orphan receptor γt, RORγt)和FOXP3的表达, 进一步维持Th17/Treg细胞平衡, 减轻炎症[153]; 在UC发展过程中, 铁死亡与炎症会相互促进, 氧化苦参碱可作用于IL-1β、IL-6、一氧化氮合酶2 (nitric oxide synthase 2, NOS2)等与铁死亡和炎症相关的关键基因和蛋白, 提升GSH水平并改善细胞线粒体损伤, 从而减轻铁死亡对细胞超微结构的损伤, 阻断炎症和铁死亡的相互促进作用[154]。除GSH外, 氧化苦参碱还可降低DSS诱导的结肠炎小鼠体内MDA和NO水平, 提高SOD等抗氧化物活性[155], 同时氧化苦参碱还可增强UC小鼠结肠黏膜细胞自噬, 降低病灶ROS水平[153], 进一步减轻氧化应激损伤; 除此之外, 氧化苦参碱还可抑制结肠黏膜中NOD2蛋白过度表达, 降低TNF-α分泌, 减轻结肠黏膜炎症, 保护肠黏膜[156]。

2.2.5.4　胡椒碱　胡椒碱是胡椒中的主要成分, 具有温中散寒、开胃下气等功效, 多用于治疗胃寒呕吐、腹痛泄泻、癫痫痰多等。研究表明, 胡椒碱为孕烷X受体 (pregnane X receptor, PXR)激动剂, 可诱导细胞色素P450 3A4酶 (cytochrome P450 3A4, CYP3A4)表达, 并通过抑制NF-κB介导的促炎反应, 减轻炎症水平, 改善结肠损伤[157]; 胡椒碱也可降低由游离脂肪酸诱导的TLR4介导的炎症反应, 减少TNF-α、IL-1β等炎症介质的释放[158]; 通过调节B细胞抑制因子-α (B lymphocyte stimulator factor-α, BLyS-α)/NF-κB信号通路, 胡椒碱亦可抑制TNF-α、COX-2、iNOS、caspase-1

等的过表达, 从而改善紧密连接蛋白如 claudin-1、occludin 和 ZO-1 的表达, 修复肠道屏障[159]。总体来说, 胡椒碱可有效减轻结肠炎的病理和组织学变化, 防止结肠长度缩短, 减轻水肿、出血和细胞浸润等现象, 改善 IBD[160]。

2.2.6 多糖类

多糖类物质是 10 个以上单糖分子通过糖苷键连接而成的长链聚合物, 为天然产物的主要成分之一。研究表明, 多糖类成分主要在大肠中消化吸收, 可通过抗氧化、抗炎、维持肠内稳态等机制对 IBD 产生治疗效果[161]。

2.2.6.1 黄芪多糖 黄芪多糖为黄芪的有效成分之一, 有研究证实其具有调节免疫、调节肠道微生态与促进黏膜修复等作用[162]。Shen 等[163]研究发现, 黄芪多糖可通过促进磷脂酶 C-β2 表达, 抑制 NLRP3、cleaved caspase-1 和 gasdermin D 的 N 端结构域表达等途径, 阻断细胞焦亡, 从而修复受损上皮组织。在 DSS 诱导的 UC 小鼠模型和 RSL3 刺激的 Caco-2 细胞中, 黄芪多糖可通过调控 Nrf2/HO-1 信号通路、调节 PTGS2、FTH1 和 FTL 等铁死亡相关基因, 抑制铁死亡, 保护肠道细胞[164]。另外, Deng 等[165]发现, 黄芪多糖可通过恢复线粒体代谢来维持记忆 B 细胞 (memory B cells, MBCs) 激活, 恢复 MBCs 亚群平衡, 进而维持体液免疫稳态, 缓解结肠炎损伤。通过调节 TLR4/NF-κB、Janus 激酶 2 (Janus kinase 2, JAK2)/STAT3 等信号通路, 调控 RORγt、Foxp3 等转录因子水平, 黄芪多糖亦可改善炎症因子的过度分泌, 调节 Th17/Treg 数量平衡, 维持免疫稳态[166]。Huo 等[167]将黄芪多糖进行超滤得到分子质量小于 10 kDa 的多糖组分, 并发现该组分可显著降低血清和结肠组织中炎症因子水平, 还可促进有益微生物生长、抑制潜在病原体增殖, 增加短链脂肪酸水平, 改善肠道菌群失调。Zhang 等[168]也报道黄芪多糖可增加拟杆菌门与双歧杆菌相对丰度, 降低厚壁菌门相对丰度, 增强小鼠免疫功能; 黄芪多糖还可升高 UC 大鼠结肠中的表皮生长因子含量, 降低转化生长因子-β 含量, 上调 occludin、ZO-1 蛋白表达水平, 促进肠道黏膜修复[169]。

2.2.6.2 枸杞多糖 枸杞多糖为枸杞子中提取的天然活性大分子, 可用于治疗肠道损伤[170]。通过 16S rRNA 测序发现, 枸杞多糖可有效恢复 UC 小鼠肠道微生物多样性, *Dubosiella*、*Lactobacillus* 等有益菌相对丰度与石胆酸、脱氧胆酸等胆汁酸水平呈正相关, 石胆酸与脱氧胆酸则可激活 G 蛋白偶联受体 5, 促进肠道上皮受损后的再生过程, 增强肠道屏障功能[171]。此外, Wang 等[172]研究表明枸杞多糖可作用于 STAT1 和 STAT6 信号通路, 通过抑制 STAT1 磷酸化, 阻碍 M1 型巨噬细胞形成并降低 iNOS 水平, 同时通过促进 STAT6 磷酸化, 推动 M2 型巨噬细胞分化并增加其标记蛋白 Arg-1 的水平, 从而减轻炎症。枸杞多糖还可抑制 TNF-α 诱导的 p-IκBα 与 NF-κB p65 的激活, 减少炎症因子释放, 并抑制暴露于促炎细胞因子的 Caco-2 细胞中 MLCK 蛋白表达的上调和 MLC 的磷酸化, 改善肠道屏障功能障碍[173]。枸杞多糖亦能降低血清 IL-6 和血清脂质过氧化标志物 MDA 水平, 升高血清 CAT 活性, 改善氧化应激[174]。

2.2.6.3 马齿苋多糖 马齿苋多糖为中药马齿苋的有效成分之一, 研究提示其可调节肠道菌群, 对 UC 有一定的治疗效果[175]。Ning 等[176]研究表明, 马齿苋多糖在改善肠道屏障、调节肠道内环境稳态的同时, 可维持肠道内视黄醇和短链脂肪酸水平, 促进结肠中 B 细胞的增殖和分化, 并增加免疫球蛋白 A 的表达, 进而通过免疫调节而改善肠炎。马齿苋多糖还可下调 IL-6-JAK-STAT3 信号通路中的信号传递系统, 抑制 IL-6 的释放及其与受体结合, 并明显下调 STAT3 表达, 阻断 IL-6 释放产生的后续效应[177]; 马齿苋多糖由甘露糖、鼠李糖、葡萄糖醛酸等 7 种单糖组成, 分子对接显示其可与 TLR4、IL-1β、STAT3 等 10 个 UC 相关靶点对接, 多靶点治疗 UC。如马齿苋多糖可能通过结合 TLR4 并抑制其激活, 减少下游 MyD88 和 NF-κB 等关键蛋白的激活, 降低炎症介质和细胞因子释放, 减轻炎症反应[178]。此外, Dai 等[175]报道马齿苋多糖可增加肠道黏膜中分泌型免疫球蛋白 A 含量, 增强肠道防御功能。Feng 等[179]发现马齿苋多糖还具有益生元特性, 可促进乳酸菌、双歧杆菌等有益菌生长, 抑制致病菌如志贺氏菌的植入, 通过调节肠道微生物群发挥抗炎和免疫调节功能[180]。

2.2.6.4 白术多糖 白术可用于治疗脾虚食少、腹胀泄泻, 白术多糖为其主要有效成分之一。Yang 等[181]基于超高效液相色谱−四极杆飞行时间质谱联用技术对 UC 小鼠血清样本进行代谢组学分析, 发现白术多糖可通过调节 α-亚麻酸代谢等通路, 改善小鼠代谢紊乱, 治疗 IBD; 同时, 白术多糖可能通过下调 Wnt/β-catenin 信号通路蛋白, 调节 Th17/Treg 平衡, 降低 TNF-α、IL-6、IL-1β 等促炎因子水平, 修复受损肠道黏膜[182]。在调节肠道微生物方面, 白术多糖可增加丁酸菌和乳杆菌相对丰度, 减少细小杆菌、疣状芽胞杆菌等相对丰度, 对 UC 产生治疗效果[183]。

2.2.7 皂苷类

皂苷是一类由皂苷元和糖、糖醛酸或其他有机酸组成的苷类化合物, 是人参、黄芪等植物中的主要成

分。研究表明, 皂苷有强大的抗炎作用, 可诱导免疫稳态, 对IBD、肠易激综合征等都有较好治疗效果[184]。

2.2.7.1　人参皂苷　人参为一类常见的中药, 可大补元气。人参皂苷是人参的主要活性成分之一, 为一大类成分, 在增强免疫、抗炎、抗氧化等方面都有广泛疗效[185]。Tang等[186]研究表明, 人参皂苷Rc可激活FXR信号通路, 其下游的SHP可直接阻止NF-κB募集, 从而抑制IL-1β、TNF-α等炎症因子表达, 减轻炎症。Zhong等[187]发现人参皂苷Rg1在调节Th1/Th2/Th17细胞平衡的同时, 可促进肥胖小鼠结肠炎模型中初始T细胞及其CD4/CD8亚群分化, 减少记忆T细胞及其亚群分化, 重塑记忆T细胞稳态, 通过免疫调节抑制炎症反应。此外, 在DSS诱导的小鼠模型中, miR-125a-5p被发现表达降低, 而人参皂苷Rh2可使其表达回升。miR-125a-5p可靶向结合特异性蛋白1 (specific protein 1, SP1), 抑制SP1表达, 进而抑制铁死亡, 从而缓解炎症[188]。另有一些人参皂苷如Rb1可通过调节细胞外信号调节激酶、调控Rho家族小GTP酶信号通路, 促进微血管修复等途径, 修复肠道黏膜损伤[189]。人参皂苷可通过调节多条炎症相关信号通路, 如NF-κB、p38 MAPK、ERK/MEK等, 调节相关炎症信号传递, 改善炎症水平[190]。在调节肠道微生态方面, 人参皂苷还能增加益生菌相对丰度, 调节厚壁菌门/拟杆菌门比例, 促进肠道健康[189]。Liu等[191]还发现人参皂苷主要代谢产物人参皂苷化合物K可增加肠道乳酸杆菌和阿克曼菌数量, 显著提高源自乳酸杆菌的色氨酸代谢物浓度, 激活AhR-CYP1A1通路, 上调IL-22表达并调节炎症与免疫反应。此外, 人参皂苷亦能通过抗氧化应激等方式减轻肠道组织损伤[192]。

2.2.7.2　三七皂苷　三七皂苷是三七的主要活性成分。研究表明, 三七皂苷可显著降低DSS诱导的结肠炎小鼠中IκB激酶 (IκB kinase, IKK) α/β、IκBα和p65的磷酸化水平, 阻碍NF-κB信号通路的激活, 减少炎症相关基因转录, 同时可通过调节MAPK信号通路, 下调COX-2和iNOS的表达, 抑制炎症反应[193]。三七皂苷亦可通过抑制STAT1/吲哚胺2,3-双加氧酶1 (indoleamine 2,3-dioxygenase 1, IDO1)通路, 减少Treg细胞的分化, 同时减少巨噬细胞的积累, 重塑免疫微环境并减少IL-1β等促炎细胞因子的分泌[194]。Zhang等[195]发现三七皂苷中主要成分之一三七皂苷R1可激活PXR, 上调外源性物质代谢关键基因CYP3A11、UGT1A1、MDR1a等表达水平, 进而维持肠道上皮屏障完整性。Yu等[196]报道结果显示三七皂苷R1亦可通过激活Wnt/β-catenin信号通路, 恢复被DSS下调的隐窝增殖和干细胞相关基因的mRNA水平, 如细胞周期蛋白D1 (cyclin D1)、富含亮氨酸重复序列的G蛋白偶联受体5 (leucine-rich repeat-containing G-protein coupled receptor 5, Lgr5)等, 从而促进Lgr5干细胞再生和肠道重建, 缓解DSS诱导的小鼠结肠炎。三七皂苷还可以通过调节肠道菌群, 增加有益菌数量, 减少有害菌, 维持肠道微生态[197]。粪菌移植显示, 经三七皂苷重塑的肠道菌群对胆汁酸代谢具有调节作用, 可上调牛磺胆酸和牛磺鹅脱氧胆酸的相对含量, 从而减轻IBD[198]。

2.2.8　多酚类

多酚类化合物是一类天然的植物次生代谢产物, 根据化学结构不同可分为酚酸类、黄酮类、二苯乙烯类与木脂素类。多酚类化合物具有广泛的生物活性, 如抗氧化、抗菌、抗炎等, 在IBD的治疗中已有较多研究[199]。

2.2.8.1　姜黄素　姜黄素是姜黄、郁金等植物中的主要活性成分, 具有改善免疫功能、抗炎、抗氧化等多种药理作用。研究表明, 姜黄素可以通过改变Th1与Th2、Th17与Treg之间的细胞平衡, 下调IL-1、IL-17、TNF-α和IFN-γ等促炎性因子水平, 并上调抗炎因子IL-2水平, 通过免疫调节产生抗炎作用[200]; 在调节信号通路方面, 姜黄素可使AKT、PI3K与IKK等多种激酶失活, 进而抑制NF-κB的产生, 阻断NF-κB通路, 最终抑制IL-6的表达并降低C反应蛋白水平; 姜黄素亦可通过抑制包括NF-κB、TLR4和MAPKs在内的多种炎症级联反应, 下调促炎因子水平, 对IBD具有潜在治疗效果[201]; 在抗氧化方面, 姜黄素可通过调节Keap1-Nrf2途径, 改善空肠抗氧化能力, 缓解空肠氧化应激; 同时姜黄素还可通过升高B淋巴细胞瘤-2基因 (B-cell lymphoma-2, Bcl2)家族中抗凋亡蛋白水平、调控细胞自噬、抑制TLR信号通路传导等途径, 改善肠道黏膜屏障功能[202]。

2.2.8.2　白藜芦醇　白藜芦醇属于非黄酮类多酚化合物, 广泛存在于藜芦、虎杖、决明等植物中。研究表明, 白藜芦醇可通过调节肠道微生物群–巨噬细胞–精氨酸代谢轴来改善IBD, 一方面, 白藜芦醇可使结肠炎小鼠中失调的微生物群相关功能恢复正常, 减少因结肠炎引起的功能紊乱; 另一方面, 白藜芦醇还可增加巨噬细胞中SLC6A8表达, 影响精氨酸代谢并上调Arg1基因水平, 减少iNOS产生, 从而减少促炎因子释放。具体而言, 白藜芦醇可逆转拟杆菌门、变形菌门和厚壁菌门等分布, 减少潜在致病菌属, 增加有益菌属, 维持肠道微生态稳态[203]。此外, 白藜芦醇及其衍生物对细胞周期具有调控作用, 可使细胞周期阻滞在不同阶段, 并能降低细胞周期关键蛋白cyclin D1和cyclin A的表达, 限制细胞周期进展, 对减轻IBD相关的肠道细胞异常增殖具有重要意义[204]。白藜芦醇亦可作为烟酰胺

腺嘌呤二核苷酸 (nicotinamide adenine dinucleotide, NAD) 依赖的SIRT1激活剂, 显著提升脾脏和胸腺等免疫器官中SIRT1的表达水平, 从而抑制NF-κB, 阻断NLRP3炎性小体表达[205]。Zhang等[206]研究发现白藜芦醇还可通过抑制STAT3的O-GlcNAcylation修饰, 抑制JAK2/STAT3通路激活, 减少COX-2等蛋白表达, 缓解炎症损伤。Li[207]还报道, 白藜芦醇可下调claudin-2表达, 增加热休克蛋白、Muc2和紧密连接蛋白基因的转录水平, 提高肠道屏障完整性。

2.2.8.3 茶多酚 茶多酚为茶叶中提取的多酚类化合物, 具有抗炎、抗氧化、调节肠道菌群等多种药理活性。据研究, 茶多酚可抑制NF-κB抑制蛋白降解, 降低NF-κB活性, 从而降低结肠炎大鼠血清中IL-1β、TNF-α等促炎因子水平, 并增高IL-4、IL-10等抑炎因子水平[208]。同时, 茶多酚可诱导内源性抗氧化防御系统, 激活Nrf2, 上调抗氧化酶的基因表达, 降低ROS/活性氮 (reactive nitrogen species, RNS) 水平, 改善肠道氧化应激[209]。茶多酚亦可促进肠道微生物产生短链脂肪酸, 维持肠道上皮黏膜免疫系统稳定, 提升有益菌相对丰度, 改善肠道微环境, 发挥抗炎作用[210]。

3 中药治疗IBD的挑战与展望

尽管近年来在中药治疗IBD研究领域已取得上述诸多进展, 但仍存在许多挑战亟待解决。首先, 中药复方治疗IBD理论基础深厚, 临床疗效确凿, 并可根据患者的不同临床表现分型辨证施治, 优势明显。但因其化学体系庞杂, 多通过炎症、免疫、菌群、肠道屏障等多途径发挥作用, 其药效物质基础仍不明晰, 尚需深入研究。其次, 既往中药复方或化合物治疗IBD相关机制研究中, 多围绕对炎症因子水平与氧化应激水平的非特异性调控进行描述[211]。然而, 随着IBD相关科研手段的不断进步与研究视角的拓展, 近年来该领域高水平研究已逐渐深入到肠道菌群稳态、巨噬细胞信号通路、细胞自噬[212]等多个维度。如胆汁酸代谢稳态[213]、肠脑轴调控[214]、线粒体功能和铁死亡[215]等新型研究方向, 都为中药治疗IBD相关机制的深入研究提供了新思路。再则, 中药治疗IBD的高质量临床研究数据仍较为缺乏, 制约其推广应用, 亟需开展多中心、大样本的临床试验, 为中药或中西医结合治疗IBD提供更高水平的循证医学证据。

中医药治疗在IBD临床应用中的局限性主要体现在以下3个方面。首先, 在辨证论治方面, 目前中医学者对IBD病因病机的认识尚未完全统一, 临床辨证分型标准仍存在一定差异, 导致诊疗过程的主观性较强, 亟需建立更加规范、统一的辨证标准及各病程阶段的核心病机判定体系[216]; 其次, 在用药安全性方面, 中药毒性成分、炮制工艺不规范[217]、药材质量波动及患者个体差异等因素均可能引发不良反应[218], 尤其值得注意的是, 部分中药注射剂在临床不当使用时可能出现发热、过敏等不良反应[219]; 最后, 在疗效评价方面存在双重挑战: 一方面, 传统用药剂量标准缺乏现代循证医学依据, 临床常见剂量不足导致疗效受限[220]; 另一方面, 现有中医药疗效评价多侧重于活动期症状缓解和维持治疗, 尚未建立整合临床症状、中医证候、内镜表现、病理学改变及生活质量评估等多维度的综合疗效评价体系[221], 这在一定程度上限制了中医药在IBD器质性病变治疗中的精准应用。

中药是我国优秀传统资源, 具有多成分、多靶点作用特点, 在IBD治疗领域中展现出巨大潜力。随着研究的不断深入, 未来有望发现更多高效、安全的中药方剂或单体成分。在此基础上, 应通过深入挖掘中药复方药效物质基础、阐明其作用机制, 进一步阐明中药治疗IBD的科学内涵; 开展大规模、多中心的临床研究, 为中药治疗IBD提供更坚实的循证医学证据; 优化药物剂型和给药途径, 提高中药治疗IBD疗效, 增强患者依从性。这不仅将造福IBD患者群体, 也有助于推动中医药在国际医学舞台上的发展, 为中医药现代化发展注入强大动力, 开启中医药治疗疑难病症的新篇章。

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利益冲突: 本文所有作者声明不存在利益冲突关系。

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