中药调控NLRP3炎症小体活性治疗痛风性关节炎的研究进展

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摘要: 痛风性关节炎是一种由尿酸盐结晶沉积引发的炎性关节病, NOD (nucleotide binding oligomerization domain) 样受体家族3 (NOD-like receptor protein 3, NLRP3) 炎症小体的过度活化是驱动其急性炎症反应的核心环节。尽管针对NLRP3炎症小体的相关药物已进入临床试验阶段, 但其临床应用仍受限于不良反应与未知的长期风险。在此背景下, 中药凭借其多成分、多靶点的协同调控特点, 为痛风防治提供了新策略。研究表明, 中药在缓解关节急性炎症、降低血尿酸水平及预防复发等方面展现出多维度疗效, 凸显其在系统干预方面的潜力。本综述系统归纳了中药活性成分及复方调控NLRP3炎症小体活化通路的关键环节——抑制上游启动信号、阻断激活信号转导、直接干预炎症小体组装及增强自噬清除功能等, 从而抑制IL-1β等关键炎症因子释放的作用机制, 旨在为中药调控NLRP3治疗痛风性关节炎的深入研究与临床应用提供理论依据与方向参考。

关键词: 痛风性关节炎; NLRP3炎症小体; 中药; 活性成分; 信号通路

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Research progress on the regulation of NLRP3 inflammasome activity by traditional Chinese medicine for the treatment of gouty arthritis

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Abstract: Gouty arthritis is an inflammatory joint disease triggered by urate crystal deposition, with nucleotide binding oligomerization domain (NOD)-like receptor protein 3 (NLRP3) inflammasome overactivation serving as the core driver of its acute inflammatory response. Although NLRP3-targeting drugs have advanced to clinical trials, their clinical application remains limited by adverse effects and uncertain long-term risks. In this context, traditional Chinese medicine (TCM), with its multi-component, multi-target, and synergistic regulatory properties, offers novel strategies for the prevention and treatment of gout. Studies have shown that TCM exerts multidimensional therapeutic effects, including alleviation of acute joint inflammation, reduction of serum uric acid levels, and prevention of disease recurrence, underscoring its potential for systemic intervention. This review systematically summarizes the mechanisms by which active components and formulations of TCM modulate key aspects of NLRP3 inflammasome activation pathways. These include inhibition of upstream initiation signals, blockade of activation signal transduction, direct interference with inflammasome assembly, and enhancement of autophagic clearance, collectively leading to suppressed release of key inflammatory mediators such as IL-1β. This review aims to provide theoretical foundations and directional insights for further research and clinical application

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of TCM regulating NLRP3 in gouty arthritis treatment.

Key words: gouty arthritis; NLRP3 inflammasome; traditional Chinese medicine; active component; signaling pathway

痛风性关节炎是一种常见炎症性关节炎。据全球疾病负担 (Global Burden of Disease, GBD) 研究数据统计[1], 2020年全球痛风患病人数约5 580万人, 较1990年相比增加150.6%, 年龄标化患病率上升22.5%, 达到659.3/10万人。值得注意的是, 我国痛风患病人群呈显著年轻化趋势, 2023版《痛风诊疗规范》数据指出, 我国青年男性高尿酸血症患病率高达32%。除关节损伤外, 痛风常合并肾脏病变、高血压、高血脂、心血管疾病等[2,3]对各年龄段人群的健康带来的影响不容小觑。

痛风被广泛视为一种自身炎症性疾病, 其发作与沉积在关节和法氏囊组织中的单钠尿酸盐 (monosodium urate, MSU) 晶体[4]沉积密切相关。MSU晶体被巨噬细胞等固有免疫细胞识别, 随后通过激活NOD (nucleotide binding oligomerization domain) 样受体家族3 (NOD-like receptor protein 3, NLRP3) 炎症小体为核心的多条炎症相关信号通路[5]引发炎症。近年来, 针对NLRP3炎症小体的治疗策略展现出良好前景: 如OLT1177能够直接结合NLRP3蛋白并抑制腺嘌呤核苷三磷酸 (adenosine triphosphate, ATP) 酶活性[6], 已进入急性痛风的III期临床试验; 曲尼司特可以结合NLRP3的NACHT (nucleoside triphosphatase domain) 结构域, 干扰内源性NLRP3-ASC (apoptosis-associated speck-like protein containing a caspase-recruitment domain) 以及NLRP3-NLRP3相互作用[7], 目前曲尼司特联合降尿酸药物治疗痛风、高尿酸血症和类风湿性关节炎的几个II期临床试验已经完成; 中药活性成分冬凌草素衍生物HAO472已进入I期临床试验。以上进展表明, 调控NLRP3炎症小体活性是治疗痛风的有效策略。

中医将痛风归为"痹症, 热痹, 白虎历节风"等范畴, 治疗主要以清热解毒、祛湿通络为主。长期的临床应用表明, 传统中药对痛风的治疗不仅不良反应小且少, 还在炎症发作期改善症状、影响炎症进展方面有一定优势。近年来研究发现, 多种中药复方及有效成分能够干预NLRP3炎症小体活化, 为痛风防治提供了丰富的药物候选资源。本文将系统梳理中药调控NLRP3炎症小体活性治疗痛风的研究进展, 以期为相关药物开发与临床应用提供参考。

1 NLRP3炎症小体的调控在痛风中的作用

1.1 NLRP3炎症小体的结构与组装

NLRP3炎症小体是由NLRP3受体蛋白、接头蛋白ASC和效应蛋白半胱天冬氨酸蛋白水解酶1前体 (pro-cysteinyl aspartate specific proteinase 1, pro-caspase-1) 构成的多蛋白复合物。NLRP3蛋白由C端富含亮氨酸重复序列结构域 (leucine-rich repeat, LRR)、中间的NACHT结构域和N端pyrin结构域 (pyrin domain, PYD) 组成。在检测到危险信号后, NLRP3通过LRR结构域发生寡聚化, 并借PYD与ASC的PYD相互作用; 随后ASC通过其caspase-1招募结构域 (caspase recruitment domain, CARD) 招募pro-caspase-1[8], 最终激活caspase-1。活化的caspase-1可介导促炎细胞因子白介素-1β (interleukin-1β, IL-1β) 和白介素-18 (interleukin-18, IL-18) 的成熟和分泌, 并在一定条件下诱导细胞焦亡[9,10]。

NLRP3炎症小体的经典激活通常依赖双重信号。第一个信号 (启动信号) 由多种内源性或外源性分子通过激活Toll样受体 (toll like receptor, TLR) 等模式识别受体, 进而激活细胞内有丝分裂原激活蛋白激酶 (mitogen-activated protein kinase, MAPK) 和核转录因子-κB (nuclear factor kappa B, NF-κB) 信号, 促进NLRP3蛋白、pro-IL-1β和pro-IL-18的转录和表达。第二信号 (激活信号) 多由ATP和线粒体活性氧 (reactive oxygen species, ROS) 等外源性细胞损伤信号触发, 诱导NLRP3炎症小体组装并激活caspase-1, 进而剪切IL-1β和IL-18前体[9], 促进炎症细胞因子释放[11]和细胞焦亡[12]。此外, 还存在非经典NLRP3炎症小体激活途径, 如在革兰阴性菌感染中, caspase-11可被直接激活, 进一步诱导caspase-1活化导致细胞死亡[13]。

1.2 NLRP3炎症小体与痛风

尿酸作为内源性危险信号, 可从受损细胞释放, 激活T细胞免疫并推动炎症级联反应[14]。在分子层面, 被巨噬细胞吞噬的MSU晶体可激活NLRP3炎症小体, 通过caspase-1依赖性途径促使IL-1β前体成熟并释放[9]。值得注意的是, 单独MSU晶体并不足以诱发强烈的IL-1β表达, 通常需要脂多糖 (lipopolysaccharide, LPS) 协同TLRs预先启动炎症反应[15]。研究表明, 敲除TLR2或TLR4基因可抑制MSU诱导的IL-1β产生及中性粒细胞聚集[16], 但髓样分化因子88 (myeloid differentiation primary response 88, MyD-88) 依赖的IL-1受体信号仍可维持急性炎症反应[17], 提示痛风炎症调控网络的复杂性。

痛风发病的核心在于单核吞噬细胞系统的激活和IL-1β的释放[18]。NLRP3炎症小体活化所产生的IL-1β可诱导CXC趋化因子配体8 (C-X-C motif chemokine ligand 8, CXCL8) 和单核细胞趋化蛋白-1 (monocyte chemotactic protein 1, MCP-1) 等趋化因子表达, 引起局部血管扩张, 并招募单核细胞、巨噬细胞和中性粒细胞等向关节部位聚集, 形成自我放大的炎症级联反应[19]。体外研究证实, MSU诱导的IL-1β释放严格依赖NLRP3炎症小体的激活[20]。在动物模型中, NLRP3缺失可显著缓解MSU诱发的关节炎症[9], 且IL-1R缺陷小鼠及IL-1抑制剂处理的野生型小鼠同样显示出明显的炎症抑制[17]。综上所述, NLRP3-caspase-1-IL-1β轴已被确立为痛风性关节炎的核心致病通路及重要治疗靶标 (图1)。

2 痛风性关节炎的临床药物治疗现状

目前, 痛风性关节炎的临床治疗策略主要分为抗炎镇痛和降低尿酸两大类, 旨在快速缓解相关症状并长期控制疾病根源。急性期治疗一线药物包括秋水仙碱、非甾体抗炎药 (nonsteroidal anti-inflammatory drugs, NSAIDs) 和糖皮质激素。这些药物能够通过非特异性抑制炎症通路来缓解红肿热痛, 达到控制急性发作症状的效果。然而, 其作用机制多针对炎症通路的中下游, 属于广谱抗炎, 靶向性较弱。更突出的问题在于其安全性: 秋水仙碱治疗窗窄, 易引起严重的胃肠道反应甚至骨髓抑制[21]; NSAIDs长期使用与胃肠道溃疡、心血管、肾脏损伤等风险增加相关[22,23]; 而糖皮质激素则可能引起骨质疏松、高血糖、胰岛素抵抗、脂肪沉积异常、高血压和肌肉萎缩等多种不良反应[24]。因此, 传统抗炎药在“治标”的同时, 其长期或反复使用的安全性与靶向性不足, 构成了主要的临床局限。

对于痛风的长期管理, 临床常用降尿酸药物, 包括黄嘌呤氧化酶抑制剂别嘌醇、非布司他, 以及促尿酸排泄药苯溴马隆等。这类药物能有效控制血尿酸水平, 从源头上减少晶体沉积。然而, 这些药物对已沉积晶体触发的持续炎症或急性发作的“炎症启动”环节无直接作用, 在治疗初期由于血尿酸的快速波动和晶体溶解, 反而会诱发或加剧急性炎症发作[25]。因此, 单纯的降尿酸治疗无法覆盖疾病的全部病理过程, 特别是在炎症启动和急性发作期, 需要联用独立的抗炎策略。

近年来, 随着病理机制的深入解析, 新兴靶向疗法为痛风治疗带来了新方向。以IL-1受体拮抗剂 (如阿那白滞素、卡那单抗等) 为代表的生物制剂, 能够精准阻断NLRP3炎症小体的关键下游效应因子IL-1β, 对难治性痛风疗效显著, 从临床层面确证了NLRP3/IL-1β轴在痛风炎症中的枢纽地位。尽管如此, 该疗法仍存在局限: 生物制剂价格昂贵、需注射给药并可能增加感

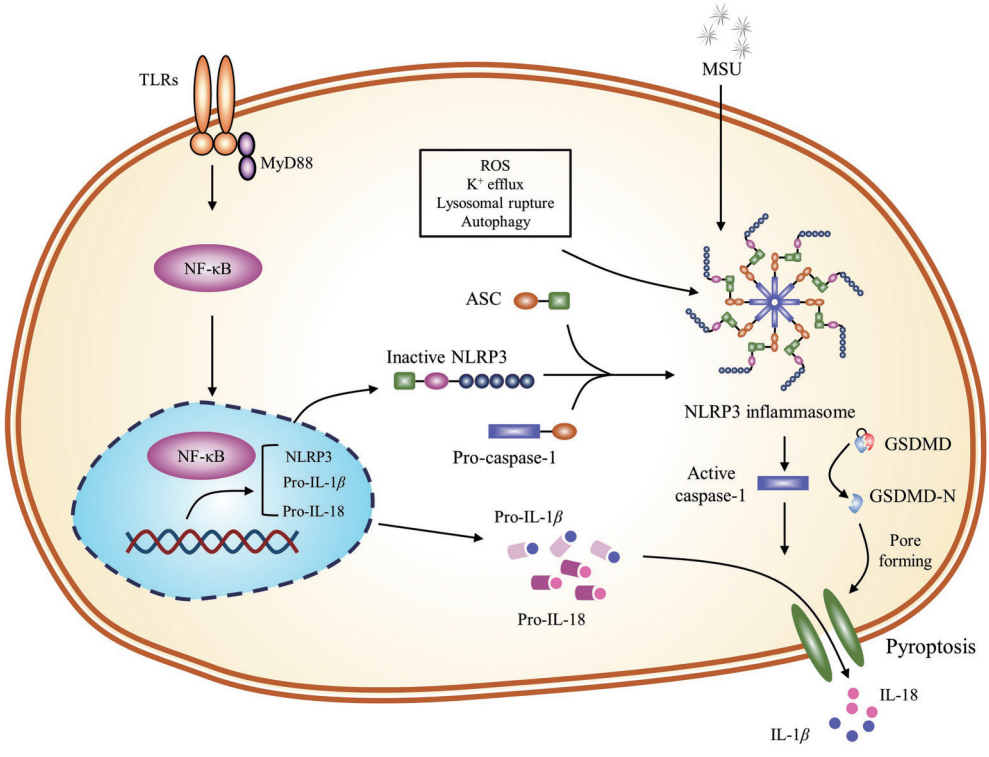


Figure 1 MSU crystals activated the NLRP3 inflammasome through a multi-step process. MSU: Monosodium urate; NLRP3: NOD-like receptor protein 3; TLRs: Toll-like receptors; MyD88: Myeloid differentiation primary response 88; NF-κB: Nuclear factor-κB; ROS: Reactive oxygen species; ASC: Apoptosis-associated speck-like protein containing a caspase recruitment domain; GSDMD: Gasdermin D

染风险, 限制了其普及; 而高度特异性的NLRP3抑制剂作为新靶点药物, 其长期用药的安全性、对复杂免疫网络的潜在影响以及最终的临床获益风险比, 仍有待大规模临床试验的全面验证。

因此, 探寻能够直接、安全且经济地干预上游NLRP3炎症小体活化的新型策略, 成为补充现有方案的重要方向。这也为中药及其活性成分的研究提供了明确的科学切入点——即探讨其能否通过多成分、多靶点的方式调节这一关键通路, 为痛风性关节炎的炎症控制提供新的可能。

3 中药有效成分调控NLRP3炎症小体干预痛风

中药防治痛风历史悠久, 疗效确切, 其现代药理研究正不断深入。在明确NLRP3炎症小体作为痛风炎症核心枢纽的地位后, 探究中药如何干预该通路, 成为阐释其作用机制的重要突破口。相较于成分复杂的中药复方, 从单味药的有效成分入手, 能够更清晰、直接地揭示中药与NLRP3炎症小体相互作用的具体环节与分子靶点。本章节将系统梳理具有抗痛风作用的中药成分, 并重点围绕其核心有效成分靶向NLRP3炎症小体的分子机制研究进展进行归纳与阐述, 旨在为痛风治疗提供源自中药的先导化合物, 为后续中药复方的机制研究和创新药物研发奠定理论基础。

3.1 抑制NLRP3炎症小体的启动信号

NLRP3炎症小体的启动信号不仅上调了NLRP3、pro-IL-1β等成分的转录表达, 为炎症小体的组装提供了必要的物质基础, 更使细胞处于一种“预激活”的敏感状态, 对后续的激活信号产生剧烈应答。因此, 靶向抑制NF-κB介导的启动信号, 是从上游阻断NLRP3炎症小体活化、控制痛风炎症的理性策略。近年研究揭示, 多种天然活性成分正是通过精准干预这一启动环节, 发挥显著的抗痛风效应。

黄酮类化合物因其广泛的来源与多样的生物活性, 已成为痛风治疗药物研究的热点之一。研究表明, 表儿茶素能够显著抑制痛风小鼠关节组织中p65蛋白的磷酸化和核转位, 从而阻断NF-κB活性, 减弱NLRP3炎性小体活化并抑制下游肿瘤坏死因子-α (tumor necrosis factor-alpha, TNF-α)、IL-6等炎症因子分泌, 最终减轻关节肿胀和炎性浸润[26]。类似地, 新异落新妇苷也被证实能够剂量依赖地抑制IκB激酶α/β (IκB kinase, IKKα/β) 的激活, 调节IκB的磷酸化, 进而抑制p65蛋白在细胞质与细胞核之间的异常转位, 从源头上削弱NLRP3炎症小体组装必需的预备信号[27]。部分黄酮类成分的作用靶点更为上游, 如从短穗兔耳草分离得到的木犀草素、木犀草苷和芹菜素, 它们能抑制滑膜组织中TLR4/MyD88/NF-κB信号轴激活, 并降低NLRP3炎症小体的水平, 但对TLR2水平无显著影响[28], 提示其作用具有一定的选择性。此外, 部分黄酮成分还能通过缓解氧化应激来协同增强其抗炎功效。如桑色素除抑制NLRP3炎症小体和NF-κB信号通路激活外, 还能够抑制MCP-1、环氧合酶-2 (cyclooxygenase-2, COX-2)、诱导型一氧化氮合酶 (inducible nitric oxide synthase, iNOS), 并上调次黄嘌呤磷酸核糖基转移酶 (hypoxanthine phosphoribosyltransferase, HPRT) 的mRNA表达[29]; 淫羊藿苷在减轻关节肿胀、抑制NF-κB/NLRP3信号通路过度激活的同时, 还能提升超氧化物歧化酶 (superoxide dismutase, SOD)、谷胱甘肽过氧化物酶 (glutathione peroxidase, GPx)、谷胱甘肽 (glutathione, GSH) 等抗氧化酶活性[30]; 槲皮素则可通过调控NLRP3/NF-κB信号通路, 抑制高尿酸血症和痛风小鼠肾组织氧化应激, 从而达到缓解痛风性关节炎的效果[31]。

除黄酮类外, 其他类型的天然产物也在干预NLRP3炎症小体启动信号并作用于多重靶点发挥抗痛风药效方面有所报道。酚类成分丹皮酚不仅能够抑制NF-κB信号通路的活化, 还能同时抑制MAPK信号通路中磷酸化c-Jun氨基末端激酶 (phosphorylated c-Jun N-terminal kinase, p-JNK)、磷酸化细胞外信号调节激酶 (phosphorylated extracellular signal-regulated kinase, p-ERK) 和磷酸化p38丝裂原活化蛋白激酶 (phosphorylated p38 mitogen-activated protein kinase, p-p38) 的水平, 多维度减弱NLRP3炎症小体的启动信号, 更好地抑制了NLRP3炎症小体的活化及后续相关炎症因子的释放[32]。生物碱类成分巴马汀则展现出更综合的调控网络: 除显著抑制NF-κB信号通路以阻断启动信号外, 巴马汀还能提高SOD和GSH水平, 降低丙二醛 (malondialdehyde, MDA) 水平, 并激活核因子E2相关因子2/血红素加氧酶-1 (nuclear factor erythroid 2-related factor 2/heme oxygenase-1, Nrf2/HO-1) 抗氧化通路, 缓解组织氧化损伤[33]。另有研究报道, 巴马汀还可以通过抑制焦亡相关蛋白及中性粒细胞胞外陷阱 (neutrophil extracellular trap, NETs) 形成相关蛋白的表达, 上调基质金属蛋白酶-3 (matrix metalloproteinase-3, MMP-3), 从而减轻MSU诱导的痛风性关节炎炎症反应, 并对关节软骨具有保护作用[34]。

综上所述, 这些天然活性成分虽结构各异, 但均能通过直接或间接的方式, 有效抑制由NF-κB主导的NLRP3炎症小体“启动信号”, 部分化合物还协同调节氧化应激及免疫细胞死亡等旁路进程, 共同构成了一个多靶点的协同调控网络, 为开发基于天然产物的痛风炎症调控剂奠定了坚实的药理学基础。

3.2 直接抑制NLRP3炎症小体的组装与激活

在痛风性关节炎中, NLRP3炎症小体的组装与激活是导致IL-1β等核心炎症因子释放的最终步骤。MSU晶体作为“激活信号”, 触发NLRP3、ASC和caspase-1形成复合体, 进而切割并活化IL-1β, 驱动炎症级联反应。因此, 直接抑制该炎症小体的组装或功能, 是从下游阻断痛风炎症的关键策略。近年研究发现, 多种天然产物不仅调控上游信号, 更能直接作用于NLRP3炎症小体本身, 干扰其寡聚化或抑制caspase-1活性, 从而发挥快速、直接的抗炎作用。

3.2.1 靶向NACHT结构域 NACHT结构域是NLRP3 ATP酶活性的活性中心, 它不仅能通过水解ATP为炎症小体组装提供能量, 更是介导NLRP3自身寡聚化以及与衔接蛋白NEK7结合的结构基础[35]。当细胞接收到激活信号后, 驱动多个NLRP3单体聚集, 进而招募ASC和pro-caspase-1, 完成炎症小体的组装。因此, NACHT结构域也是研发特异性抑制剂的重要靶点。目前, 多个已被鉴定的天然产物可通过直接结合或共价修饰NACHT结构域中的关键氨基酸位点, 有效阻断这一过程。

在一项针对150种天然化合物的筛选中, 土木香内酯显示出对巨噬细胞IL-1β分泌最强的抑制活性。机制研究表明, 它能够直接结合于NLRP3 NACHT结构域的精氨酸335位点, 从而竞争性地阻断了NLRP3与NEK7的相互作用, 抑制炎症小体组装。在MSU诱导的小鼠痛风模型中, 该化合物能显著缓解关节炎症[36]。作为类似的倍半萜内酯, 云木香中的主要成分木香烃内酯可与NLRP3的NACHT结构域中半胱氨酸598位点发生共价结合, 改变了ATP酶活性并抑制NLRP3炎症小体的组装, 最终抑制其活化, 并在动物模型中验证其抗痛风效果[37]。冬凌草甲素同样可作为NLRP3炎症小体的特异性共价抑制剂: 它能够通过与NLRP3蛋白NACHT结构域中的半胱氨酸279形成共价键, 阻断NLRP3与NEK7的相互作用, 从而抑制其组装与活化。重要的是, 在腹膜炎、痛风性关节炎和2型糖尿病小鼠模型中, 冬凌草甲素均展现出预防和治疗双重功效[38]。而旋覆花内酯能直接作用于NACHT结构域内的精氨酸335与甘氨酸271两个位点干扰NLRP3与NEK7的结合, 从而抑制NLRP3炎症小体的活化。值得注意的是, 该抑制作用并不依赖于NLRP3的ATP酶活性, 提示其具有独特的作用机制, 因而被认为是开发新型NLRP3抑制剂的重要先导化合物。在MSU诱导的痛风性关节炎小鼠模型中, 腹腔注射旋覆花内酯显著减轻了NLRP3介导的炎症反应, 该治疗效果在NLRP3基因敲除小鼠中完全消失, 进一步佐证其靶向特异性[39]。

3.2.2 干扰ASC寡聚化 衔接蛋白ASC在接收上游信号后, 通过CARD结构域招募pro-caspase-1, 进一步通过分子间同型相互作用形成被称为“ASC斑点”的大型寡聚化蛋白聚合物。该斑点的形成能够放大上游信号, 并为pro-caspase-1的自剪切构建了一个高效的平台, 从而驱动大量IL-1β等炎症因子的成熟与释放[40]。因此, 抑制ASC的寡聚化是阻断炎症小体信号级联、控制过度炎症反应的重要策略。

部分天然产物可通过直接干扰衔接蛋白ASC的寡聚化, 有效抑制NLRP3炎症小体的组装与激活。如咖啡酸苯乙酯被证实可直接靶向ASC蛋白。表面等离子共振及免疫共沉淀实验证实, 咖啡酸苯乙酯能够结合于ASC蛋白PYD结构域的谷氨酸13与赖氨酸24位点。该结合作用可阻断MSU晶体诱导的NLRP3与ASC之间的相互作用, 进而抑制caspase-1的活化及IL-1β的成熟与释放[41]。与之类似, 白藜芦醇通过脾酪氨酸激酶 (spleen tyrosine kinase, Syk) 和p38丝裂原活化蛋白激酶 (p38 mitogen-activated protein kinase, p38)通路抑制pro-IL-1β合成的同时, 还能直接影响ASC蛋白的寡聚化从而抑制NLRP3炎症小体组装与活化[42]。和厚朴新酚则在抑制ASC斑点的形成的基础上, 同时还能减弱caspase-1蛋白的活性以及线粒体ROS的生成, 对NLRP3和黑色素瘤缺失因子2 (absent in melanoma 2, AIM2)炎症小体均发挥抑制作用[43]。

3.2.3 抑制caspase-1活性 除了上述作用于上游信号及组装环节的天然产物外, 部分化合物还可直接靶向NLRP3炎症小体的下游关键执行蛋白——caspase-1, 从而阻断炎症信号的最终释放。Caspase-1的活化是NLRP3炎症小体激活的标志性事件, 其通过切割pro-IL-1β和pro-IL-18产生具有强烈致炎活性的成熟细胞因子[9]。因此, 直接抑制caspase-1的活性, 成为干预NLRP3炎症小体通路下游的有效策略之一。

黄连碱被证实能以优势构象结合于caspase-1活性位点, 在多种激动剂导致的NLRP3炎症小体活化过程中, 有效阻断caspase-1的自剪切与活化, 进而显著抑制成熟IL-1β的分泌。在MSU诱导的痛风小鼠模型中, 黄连碱可明显缓解足部水肿, 其抗炎作用与抑制caspase-1介导的炎症小体活化密切相关[44]。小白菊内酯是一种分离自小白菊的植物倍半萜内酯, 临床上广泛用于治疗多种炎症性疾病, 包括发烧、偏头痛、关节炎、银屑病和动脉粥样硬化等[45]。研究发现, 小白菊内酯可通过直接抑制caspase-1的蛋白酶活性, 抑制多种炎症小体的活性; 同时它还能干扰NLRP3的ATP酶活性, 这表明该化合物对炎症小体活性的抑制作用可能

源于对NLRP3的ATP酶活性影响, 提示小白菊内酯作为治疗痛风性关节炎药物的开发潜力[46]。

3.3 调控线粒体功能与活性氧信号

线粒体功能障碍及其产生的ROS是激活NLRP3炎症小体的关键上游信号。受损线粒体释放的ROS及线粒体DNA等损伤相关分子模式 (damage-associated molecular patterns, DAMPs) 可直接氧化修饰NLRP3蛋白促进其寡聚化, 并通过稳定硫氧还蛋白相互作用蛋白 (thioredoxin-interacting protein, TXNIP) 使其与NLRP3结合, 正向调控小体组装[47]。因此, 线粒体ROS不仅是细胞应激标志, 更是直接触发炎症小体活化的信使。增强线粒体自噬以清除受损线粒体, 则可负向调节这一过程。

一些天然产物通过调节线粒体功能、抑制氧化应激及激活内源性抗氧化通路, 干预NLRP3炎症小体的活化。柯里拉京可抑制ROS产生, 并阻断TXNIP与NLRP3的相互作用, 在动物模型中有效缓解关节肿胀及炎症细胞浸润[48]。吴茱萸在提升血清SOD活性, 降低ROS、MDA等氧化应激指标的同时, 能够下调TXNIP、NLRP3、ASC及caspase-1等蛋白表达[49]。没食子酸则通过双重机制发挥作用: 一方面激活Nrf2抗氧化通路以减少线粒体ROS生成; 另一方面直接干扰NLRP3与NEK7的相互作用及ASC寡聚化, 且其作用可被Nrf2抑制剂逆转[50-52]。小檗碱展现出多靶点调控特点, 能同时下调Kelch样ECH关联蛋白1 (Kelch-like associated protein 1, Keap1)、上调Nrf2及其下游抗氧化酶 [如HO-1、NAD(P)H:醌氧化还原酶1 (NAD(P)H: quinone oxidoreductase 1, NQO1)] 的表达, 从而激活内源性抗氧化防御系统[53]。丹参酮是从传统活血化瘀中药丹参中提取的一类二萜醌类化合物, 具有明确的抗炎活性[54]。研究显示, 在多种丹参酮衍生物中, 丹参酮IIA、异隐丹参酮及二氢丹参酮I等成分能显著抑制NLRP3炎症小体的活化。其作用机制与改善线粒体功能密切相关: 这些化合物可调节线粒体膜电位、维持线粒体复合物活性、促进ATP与NADH生成, 并抑制ROS的产生[55]。

3.4 其他具有NLRP3抑制活性的天然产物

除了前述通过直接靶向NLRP3蛋白、干扰ASC寡集化、抑制caspase-1活性及调控线粒体与活性氧等明确机制的天然产物外, 尚有其他多种植物活性成分也被证实可有效抑制NLRP3炎症小体, 进而缓解痛风性关节炎。这些成分虽在具体作用节点上各有侧重, 但均共同指向对NLRP3炎症小体通路的整体调控, 进一步丰富了天然产物抗痛风的物质基础与作用谱系。如二氢槲皮素在痛风模型中展现出优良的治疗潜力, 能够显著减轻足部肿胀和炎症因子浸润。机制探究表明, 二氢槲皮素可促进细胞自噬和吞噬过程, 进而影响NLRP3炎症小体的活化, 从而发挥缓解痛风的作用[56]。姜黄素能有效缓解急性痛风关节肿胀, 其核心机制在于直接抑制NLRP3炎症小体的激活与下游IL-1β等炎症因子的释放。此外, 它还能通过抑制黄嘌呤氧化酶 (xanthine oxidase, XOD) 活性及上调肾脏ATP结合盒转运蛋白亚家族G成员2 (ATP-binding cassette sub-family G member 2, ABCG2) 表达来降低尿酸水平, 从源头减少MSU这一NLRP3的关键激活物, 从而间接强化其抗炎作用[57,58]。

综上所述, 调控NLRP3炎症小体是中药有效成分干预痛风的关键机制之一。基于前文论述, 现将主要活性成分及其作用机制归纳整理, 汇总于表1[26-34,36-39,41-46,48-58]。

4 中药复方多靶点协同调控NLRP3炎症小体治疗痛风

如前所述, 诸多中药活性成分能够通过干预NLRP3炎症小体的活化, 有效缓解痛风性关节炎。与单一成分针对特定靶点的作用模式不同, 中药复方秉承“君臣佐使”的组方原则, 通过多组分、多靶点、多通路的协同整合, 发挥其整体调节的治疗优势。在痛风性关节炎的治疗中, 中药复方构建了能够同步干预“尿酸代谢–炎症暴发–组织损伤”网络的协同治疗系统, 而NLRP3炎症小体正是该网络中的核心枢纽。下文将通过分析代表性复方, 依据核心作用机制与调控层次, 将复方归纳为以下3类, 旨在系统揭示中药复方多维度调控NLRP3炎症小体的科学内涵。

4.1 代谢–炎症双重调控

在代谢–炎症双重调控类复方中, 中药不仅直接抑制NLRP3炎症小体介导的相关炎症反应, 更注重调控高尿酸血症这一诱因, 体现了中医药“标本兼治”的治疗策略。四妙散是该类复方的典范。其抗痛风疗效源于“君臣佐使”配伍下各味药构成的协同治疗网络, 系统干预“代谢–炎症”病理过程: 一方面通过抑制NLRP3炎症小体活化, 减少IL-1β等多种炎症因子的释放; 另一方面通过下调肾尿酸转运蛋白表达, 增强抗氧化酶活性, 抑制并降低尿酸 (uric acid, UA) 及肝脏XOD水平[59,60], 从源头减少了MSU的形成与沉积, 而MSU正是激活NLRP3的关键内源性危险信号, 从而实现从上游消除炎症触发因素的目的。在此模式基础上, 临床上衍生方进一步拓展其治疗维度, 如清热化浊降酸方在继承四妙散清热利湿基础上强化了降尿酸与抗炎的双重作用。动物实验证实, 该方不仅有效降低尿酸水平, 还显著抑制滑膜组织中NLRP3炎症小体相关基因的表达, 且未发现明显不良反应[61]。祛湿解毒

Table 1 Regulatory effects of traditional Chinese medicine (TCM) active compounds on the NLRP3 inflammasome in gouty arthritis

Action stage	Component	Key target & pathway
Inhibiting priming signal	Epicatechin	Inhibits p65 phosphorylation and nuclear translocation, blocks NF-κB activity[26]
	Neoastilbin	Inhibits IKKα/β activation, modulates IκB phosphorylation, prevents abnormal p65 translocation[27]
	Luteolin/luteoloside/ apigenin	Inhibits TLR4/MyD88/NF-κB signaling axis activation, selectively reduces NLRP3 levels[28]
	Morin	Inhibits NF-κB/NLRP3 pathway, downregulates COX-2, iNOS, MCP-1, upregulates HPRT expression[29]
	Icariin	Inhibits NF-κB/NLRP3 pathway, elevates activities of antioxidant enzymes (SOD, GPx, GSH)[30]
	Quercetin	Modulates NLRP3/NF-κB signaling pathway, inhibits renal oxidative stress[31]
	Paeonol	Inhibits activation of NF-κB and MAPK pathways[32]
	Palmatine	Inhibits NF-κB pathway; activates Nrf2/HO-1 antioxidant pathway; inhibits pyroptosis and NETosis[33,34]
Targeting NACHT domain	Alantolactone	Directly binds NLRP3 NACHT domain (Arg335), competitively blocks NLRP3-NEK7 interaction[36]
	Costunolide	Covalently binds NLRP3 NACHT domain (Cys598), alters ATPase activity[37]
	Oridonin	Covalently binds NLRP3 NACHT domain (Cys279), blocks NLRP3-NEK7 interaction[38]
	Inulanolide	Acts on NACHT domain (Arg335, Gly271) to interfere with NLRP3-NEK7 binding (ATPase-independent)[39]
Interfering with ASC oligomerization	Caffeic acid phenethyl ester	Binds ASC protein PYD domain, blocks NLRP3-ASC interaction[41]
	Resveratrol	Inhibits ASC oligomerization; also inhibits pro-IL-1β synthesis (*via* Syk/p38 pathway)[42]
	Obovatol	Inhibits ASC speck formation, attenuates caspase-1 activity and mitochondrial ROS[43]
Inhibiting caspase-1 activity	Coptisine	Binds caspase-1 active site in a dominant conformation, blocks its autoprocessing and activation[44]
	Parthenolide	Directly inhibits caspase-1 protease activity and interferes with NLRP3 ATPase activity[45,46]
Regulating mitochondrial function & ROS signaling	Corilagin	Inhibits ROS production, blocks TXNIP-NLRP3 interaction[48]
	Evodiamine	Reduces ROS and MDA, increases SOD, downregulates TXNIP, NLRP3, and related protein expression[49]
	Gallic acid	Activates Nrf2 pathway to reduce ROS; directly interferes with NLRP3-NEK7 binding and ASC oligomerization[50-52]
	Berberine	Activates Keap1/Nrf2 antioxidant pathway; concurrently inhibits TLR4/NF-κB pathway[53]
	Tanshinone IIA/ isocryptotanshinone/ dihydrotanshinone I	Modulates mitochondrial membrane potential, complex activity, and inhibits ROS production[54,55]
Other multi-pathway regulation	Taxifolin	Promotes cellular autophagy and efferocytosis, thereby affecting NLRP3 activation[56]
	Curcumin	Inhibits XOD and upregulates renal ABCG2 to lower uric acid; inhibits NLRP3 *via* antioxidant effects and disruption of NEK7-NLRP3 complex[57,58]

汤能够显著缓解痛风患者关节肿胀、发热和剧烈疼痛, 并有助于降低尿酸、血脂水平和关节中MSU沉积, 延缓骶髂关节骨破坏[62]。网络药理学与转录组学分析提示, 其活性成分可直接与S100钙结合蛋白A8/A9复合物 (S100 calcium-binding protein A8/A9 complex, S100A8/A9) 结合, 从而抑制S100A8/A9-NLRP3-IL-1β信号轴, 对MSU诱导的痛风发挥治疗作用[63]。另一衍生方化浊散结除痹汤在临床上改善血尿酸、肌酐和血沉水平[64]的同时, 方中马鞭草苷、柠檬苦素和槲皮苷等活性成分可通过磷脂酰肌醇3-激酶/蛋白激酶B (phosphoinositide 3-kinase/protein kinase B, PI3K/AKT) 信号通路抑制NLRP3炎症小体、COX-2及iNOS表达, 并下调细胞凋亡通路, 从而缓解痛风导致的关节肿胀与病理损伤[65]。

4.2 经典炎症通路的协同抑制

在经典炎症通路协同抑制策略中, 中药复方通过同时干预NLRP3炎症小体及其上游信号网络, 实现对炎症级联反应的系统阻断。如桂枝芍药知母汤出自《金匮要略》, 由桂枝、芍药、知母、麻黄、防风、白术、附子、甘草与生姜等九味药材组成, 历来用于中医“痹证”治疗。Meta分析显示, 其在痛风综合疗效及改善UA、红细胞沉降率 (erythrocyte sedimentation rate, ESR)、C反应蛋白 (C-reactive protein, CRP) 及IL-6等方面优于常规西药[66]。机制上, 该方能同步抑制NF-κB通路关键蛋白 (p-p65、p-IKKβ、核p65及p-MAPKs) 活化和NLRP3炎症小体组装 (减弱ASC与pro-caspase-1相互

作用), 实现对炎症的双重抑制[67]。三石汤则通过同时抑制P2X7R/PKR[68]和BRD4/NF-κB这两条上游信号通路, 有效抑制氧化应激、NLRP3炎症小体的组装和细胞焦亡等下游环节, 从而缓解痛风性关节炎的炎症反应[69]。

4.3 免疫微环境与系统调节

在免疫微环境与系统调节层面, 部分中药复方的作用不仅在于抑制炎症小体激活, 更展现出通过多维度重塑免疫稳态、清除内源性损伤信号及调节系统内环境来实现整合干预的独特性。研究显示, 祛浊化淤方可抑制巨噬细胞M1极化及NLRP3/IL-1β通路活化对痛风性关节炎发挥治疗作用。研究进一步提示, 该方还能调控NF-κB/HIF-1信号通路及NETs形成, 多维度重塑局部免疫微环境[70]。与之类似, 国医大师朱良春临床经验方“痛风汤”在抑制NLRP3炎症小体激活的同时, 也能显著减少NETs生成[71]。出自孙思邈《备急千金要方》的独活寄生汤不仅能降低痛风小鼠的尿酸和CRP水平, 还能调控PINK1/Parkin信号通路介导的线粒体自噬, 从源头上减少NLRP3炎症小体活化的危险信号[72]。加味白虎汤的研究则揭示了系统调节的新视角, 该方不仅能缓解急性痛风性关节炎相关症状, 更能够逆转急性痛风引起的肠道菌群紊乱, 恢复毛螺菌科、Muribaculaceae、双歧杆菌科、乳酸菌科等菌群相对丰度, 并改善与氨基酸代谢和环境感知相关的微生物功能, 并同步抑制关节局部NLRP3炎症信号, 提示其部分疗效源于对“肠道菌群–免疫系统”轴的调节[73]。

基于上述分类, 代表性复方均以NLRP3炎症小体为核心枢纽, 通过多组分协同干预其活化环节。现将各类复方的组成、调控机制等汇总如下 (表2)[59-73]。

Table 2 Mechanisms of TCM formulations in treating gouty arthritis *via* modulation of the NLRP3 inflammasome

Mechanism category	Formula name	Composition	Integrated regulatory mechanism & key pathway
Dual regulation of metabolism & inflammation	Simiao powder	Atractylodis Rhizoma, Phellodendri Chinensis Cortex, Cyathulae Radix, Coicis Semen	Downregulates renal urate transporter expression, enhances antioxidant enzyme activity, inhibits NLRP3 inflammasome activation, reduces uric acid and hepatic XOD levels[59,60]
	Qingre Huazhuo Jiangsuan Decoction	Poria, Coicis Semen, Clematidis Radix et Rhizoma, Polygoni Cuspidati Rhizoma et Radix, Perillae Folium	Lowers uric acid levels and suppresses the expression of genes related to the NLRP3 inflammasome[61]
	Qushi Xiezhuo formula	Phellodendri Chinensis Cortex, Atractylodis Rhizoma, Coicis Semen, Smilacis Glabrae Rhizoma, Poria, Dioscoreae Hypoglaucae Rhizoma, Alismatis Rhizoma, Imperatae Rhizoma, Stigma Maydis, Crataegi Fructus, Achyranthis Bidentatae Radix	Alleviates joint swelling and pain, reduces blood lipids and MSU crystal deposition in joints; inhibits the S100A 8/A9-NLRP3-IL-1β signaling axis[62,63]
	Huazhuo Sanjie Chubi Decoction	Atractylodis Rhizoma, Smilacis Chinae Rhizoma, Phellodendri Chinensis Cortex, Coicis Semen, Dioscoreae Rhizoma, Chrysanthemi Flos, Ranunculi Ternati Radix, Verbenae Herba, Achyranthis Bidentatae Radix	Reduces serum uric acid, creatinine, and ESR; inhibits the PI3K-AKT signaling pathway; suppresses NLRP3 inflammasome activation, and decreases COX-2 and iNOS expression[64,65]
Synergistic inhibition of classic inflammatory pathways	Guizhi Shaoyao Zhimu Decoction	Cinnamomi Ramulus, Paeoniae Radix Alba, Anemarrhenae Rhizoma, Ephedrae Herba, Saposhnikoviae Radix, Atractylodis Macrocephalae Rhizoma, Aconiti Lateralis Radix Praeparata, Glycyrrhizae Radix et Rhizoma, Zingiberis Rhizoma Recens	Simultaneously inhibits NF-κB pathway activation and NLRP3 inflammasome assembly[66,67]
	Sanshi Decoction	Talcum, Gypsum Fibrosum, Calcitum, Armeniacae Semen Amarum, Bambusae Caulis in Taeniam, Tetrapanacis Medulla, Lonicerae Japonicae Flos, "Jinzhi" (historical preparation)	Concurrently inhibits P2X7R/ PKR and BRD4/ NF-κB pathways, thereby suppressing oxidative stress, NLRP3 assembly, and pyroptosis[68,69]
Immune microenvironment & systemic regulation	QuZhuoHuaYu Decoction	Smilacis Glabrae Rhizoma, Dioscoreae Hypoglaucae Rhizoma, Gentianae Macrophyllae Radix, Paeoniae Radix Alba, Achyranthis Bidentatae Radix, Corni Fructus, Cremastrae Pseudobulbus	Inhibits M1 macrophage polarization and activation of the NLRP3/IL-1β pathway; modulates NF-κB and HIF-1 signaling pathways and NETs formation[70]
	Tongfeng Tang Decocotion	Smilacis Glabrae Rhizoma, Dioscoreae Hypoglaucae Rhizoma, Bombyx Batryticatus, Coicis Semen, Clematidis Radix et Rhizoma, Plantaginis Semen, Paeoniae Radix Rubra, Paeoniae Radix Alba, Sinapis Semen, Pinelliae Rhizoma Praeparatum, Bombyx Batryticatus	Inhibits NLRP3 inflammasome activation while significantly reducing the generation of NETs[71]

Continued

Mechanism category	Formula name	Composition	Integrated regulatory mechanism & key pathway
	Duhuo Jisheng Decoction	Angelicae Pubescentis Radix, Taxilli Herba, Eucommiae Cortex, Achyranthis Bidentatae Radix, Asari Radix et Rhizoma, Gentianae Macrophyllae Radix, Poria, Cinnamomi Ramulus, Saposhnikoviae Radix, Chuanxiong Rhizoma, Ginseng Radix et Rhizoma, Glycyrrhizae Radix et Rhizoma, Angelicae Sinensis Radix, Paeoniae Radix Alba, Rehmanniae Radix	Activates PINK1/Parkin-mediated mitophagy to clear endogenous danger signals that activate NLRP3[72]
	Modified Baihu Decoction	Gypsum Fibrosum, Anemarrhenae Rhizoma, Glycyrrhizae Radix et Rhizoma, Oryzae Semen, Achyranthis Bidentatae Radix, Lonicerae Japonicae Flos	Alleviates joint symptoms and inhibits local NLRP3 signaling; reverses gut microbiota dysbiosis, restoring the abundance of Lachnospiraceae, Muribaculaceae, Bifidobacteriaceae, Lactobacillaceae, *etc*[73]

5 总结与展望

中药在防治痛风的长期临床实践中积累了丰富的经验, 其在缓解急性期症状、降低血尿酸及减少复发方面显示出良好疗效。现有证据表明, 中药在该领域展现出巨大的潜力, 其作用机制复杂且多层次, 为痛风的防治提供了独特的视角和丰富的药物资源。

目前对中药活性成分的研究已从整体动物模型深入到细胞分子水平, 初步揭示了中药成分干预NLRP3炎症小体活化的具体环节, 包括抑制上游启动信号、干扰NLRP3的激活信号、直接作用于NLRP3蛋白本身以影响其寡聚化或与ASC的相互作用、促进自噬等。与化学合成药物通常作用于单一靶点不同, 中药尤其是复方的核心优势在于其系统调控能力, 能够同时对炎症网络多个环节进行干预, 这一特点更契合痛风这种多因素、复杂性的疾病, 有助于减少耐药性并提高疗效。然而, “多成分、多靶点”的属性既是中药的优势也是研究的难点。中药复方及单味药化学成分复杂, 其疗效往往是多种成分协同作用的结果, 目前难以明确界定哪些化合物群构成其核心功效体系, 以及这些成分在体内的相互作用。此外, 中药成分在体内的动态过程研究仍较为薄弱, 尚不清楚哪些成分能被吸收入血、如何分布到靶器官、在肝脏等代谢器官中如何转化, 以及其最终排泄途径如何。这种“黑箱”状态, 使得研究者无法将体外实验观察到的活性与体内的真实药效直接关联。当前机制研究仍遵循“单一成分−单一靶点”的验证范式, 虽能初步锁定如抑制NLRP3寡聚化或促进自噬等环节, 却难以完整阐释复方整体调节炎症网络的药理内涵。因此, 突破现有研究范式至关重要。

未来的研究突破有赖于研究方法的革新与多技术整合。应重视中医证候的现代生物学阐释, 将“湿热痹阻”“痰瘀互结”等痛风常见证候与NLRP3炎症小体激活特征及其上游代谢信号进行关联研究, 从系统层面建立“证候−生物学标志−炎症网络”的对应关系, 为精准干预提供依据。在此基础上, 可基于系统生物学策略解析中药的有效成分群, 结合代谢组学与生物活性导向分离技术, 从整体鉴定能够调控NLRP3炎症小体激活的关键节点的化合物组合, 而非孤立寻找单一活性成分。在机制层面, 可借助基因编辑 (CRISPR/Cas9)、蛋白质组学、分子对接模拟等技术, 进一步明确中药活性成分与NLRP3炎症小体及其调控蛋白之间的直接相互作用靶点。此外, 利用药物代谢组学与质谱成像等技术, 能够追踪中药口服后在体内的动态过程, 明确前期入血成分及代谢产物在组织中的靶向分布, 进而建立药代动力学与药效学的动态关联模型, 从而阐明真正的体内药效物质基础。进一步整合网络药理学、代谢组学与高通量筛选相结合的策略, 构建“成分−靶点−通路−疾病”的多维网络, 有助于系统阐释中药科学内涵及其对NLRP3炎症网络的整体调控作用。

综上所述, 干预NLRP3炎症小体活性为中药治疗痛风开辟了一条具有前景的研究路径。通过现代科学技术深度挖掘其作用机制, 克服现有研究的局限性, 并积极推动临床转化, 进一步促进具有自主知识产权的抗痛风中药新药的研发, 为中医药的现代化和国际化注入新的活力。

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