生物碱对免疫系统的调节作用及其机制研究进展

张书荣, 白祎名, 颜彩琴, 陈毅恒, 王 喆, 刘艾林*

(中国医学科学院 北京协和医学院, 药物研究所, 北京 100050)

摘要: 生物碱作为天然产物中的重要活性成分, 具有来源广泛、结构多样、多靶点、多层级的作用特点, 有较强的免疫调节作用。尽管已有大量文献探讨生物碱的药理效应及机制, 但针对其免疫调节活性及作用机制的系统性梳理仍有待完善, 尤其缺乏对近年最新研究进展的整合分析。因此, 本文整理了近年来关于生物碱在免疫调节领域的研究成果, 综述了生物碱对免疫系统的调节作用, 并进一步总结了其对免疫系统作用的主要分子机制, 同时也对生物碱在免疫相关疾病治疗中的应用进行了梳理, 以期为生物碱的后续机制研究及相关药物开发提供参考。

关键词: 生物碱; 天然产物; 免疫调节; 作用机制; 研究进展

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Research progress on the regulatory effects of alkaloids on the immune system and its mechanisms

ZHANG Shu-rong, BAI Yi-ming, YAN Cai-qin, CHEN Yi-heng, WANG Zhe, LIU Ai-lin*

(*Institute of Materia Medica, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100050, China*)

Abstract: As significant bioactive constituents within natural products, alkaloids exhibit characteristics of extensive sources, diverse structures, multi-targeted and multi-level actions, and possess potent immunomodulatory effects. Although numerous studies have explored the pharmacological effects and mechanisms of alkaloids, a systematic review of their immunomodulatory activities and underlying mechanisms remains to be systematically reviewed, particularly an integrative analysis of the most recent research advances. Therefore, this paper collates recent research findings on alkaloids within the field of immunoregulation. It reviews the modulatory effects of alkaloids on the immune system, summarises the principal molecular mechanisms underlying their actions, and outlines their applications in the treatment of immune-related diseases. This review aims to provide a reference for subsequent mechanistic studies and the development of related pharmaceuticals.

Key words: alkaloid; natural product; immune regulation; mechanism of action; research progress

免疫系统是机体执行免疫应答及免疫功能的重要系统, 由免疫器官、免疫细胞和免疫分子组成, 其核心功能在于识别并清除外来病原体, 监视并清除体内异常细胞, 同时维持对自身组织的耐受[1]。免疫系统的核心在于维持精确的平衡, 一旦其调节机制失衡, 就会导致多种疾病。免疫缺陷会导致机体防御能力和免疫监视功能下降, 常常出现免疫失调, 导致感染和恶性肿瘤风险增加; 而免疫反应过度会导致身体攻击并损伤自身组织, 导致过敏、自身免疫病和各类炎症性疾病, 如哮喘、类风湿关节炎 (rheumatoid arthritis, RA)、系统性红斑狼疮、动脉粥样硬化等[2,3]。

免疫调节剂在免疫治疗中发挥着重要作用。目前临床上多使用免疫抑制药物、免疫调节类固醇、疫苗和抗生素来增强免疫功能或抑制病理性免疫反应。然

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*通讯作者 Tel: 86-10-63165184, E-mail: liuailin@imm.ac.cn
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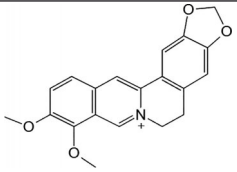
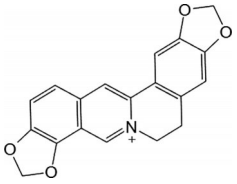
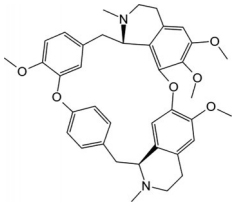
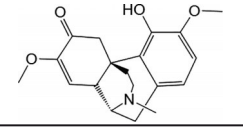
而, 这些化合物的使用也可能具有一定的不良反应, 如药物相互作用和耐药性、疫苗接种后不良事件, 或因抗生素过度使用而产生的抗生素耐药性[4]。而天然产物及其衍生物来源广泛、结构多样、生物活性多样, 能够通过多靶点、多通路的方式协同调节免疫网络, 相较于传统化学药物, 具有较低的毒性和更好的安全性, 作为免疫调节剂可能更具有优势。生物碱作为天然产物中的重要组成部分, 以其复杂的结构与广泛的生物学效应受到药理学和免疫学研究的持续关注。大量研究表明, 天然生物碱不仅具有抗病毒[5]、抗氧化[6]、抗菌[7]、镇痛[8]、降血压[9]等多种生物学活性, 还具有显著的免疫调节活性, 在炎症性疾病、肿瘤及自身免疫性疾病等多种病理状态中展现出潜在应用价值[9-12]。本文综述了近年来生物碱对先天免疫系统与适应性免疫系统的影响, 深入探讨了其免疫调节的分子机制, 并对生物碱在免疫相关疾病治疗中的应用进行了梳理, 以期为免疫调节剂的后续研究和开发奠定基础。

1 生物碱概述

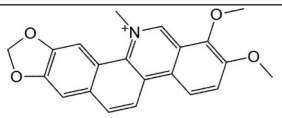
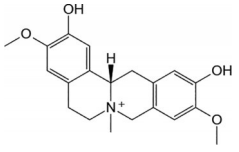
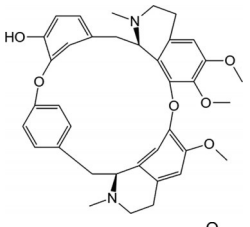
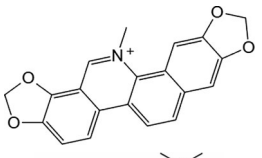
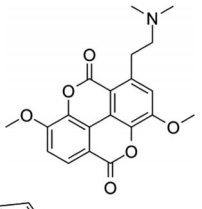
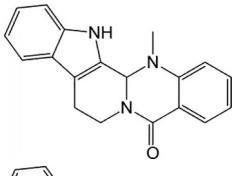
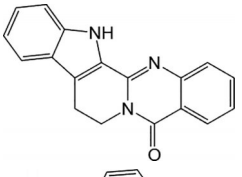
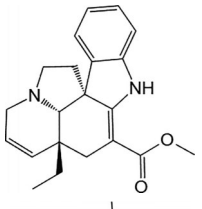
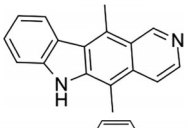
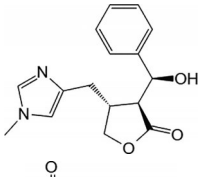
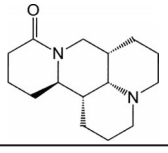
生物碱通常指一大类广泛存在于生物界的含氮的碱性有机化合物, 通常具有复杂的环状结构和显著的生物活性。从化学结构上看, 大多数生物碱分子中含有至少一个以胺态或季铵态存在的氮原子, 多嵌入吲哚、吡啶、喹啉、异喹啉等芳香杂环骨架中, 表现出一定的碱性和较高的结构复杂性[13]。生物碱最早主要从植物中分离获得, 如毛茛科、罂粟科、豆科、茄科和防己科等植物均富含各类典型生物碱[14-18]。随着分离与结构鉴定技术的发展, 人们逐渐在微生物和海洋生物中也发现了大量新型生物碱结构, 使得这一类天然产物不断拓展[19,20]。

生物碱类化合物通常以氨基酸为生物合成前体, 经由酶促反应构建形成结构复杂的含氮多环或稠环骨架, 从而呈现出显著的化学结构多样性[21]。氮杂环不仅影响了分子的电子分布、离子化特性及三维构象, 还为其与多种生物大分子靶点之间形成相互作用提供了关键的结构基础, 因此生物碱广泛的生物活性在很大程度上归因于其独特的结构特征, 对不同位点进行修饰能够进一步揭示其构效关系或优化化合物活性。有研究表明, 对异喹啉生物碱进行结构–活性关系分析发现, C8 与 C13 位的烷基化能够增强细胞毒性, 是抗肿瘤的关键修饰位点, 而在 C9/C10 位的修饰有助于提升抗炎效果[22]。小檗碱的多环骨架在其抗菌活性中发挥关键作用, 促进 DNA 靶向和膜穿透, 其 A 环上的亚甲二氧基、B 环、C 环和 D 环与抗癌、抗菌和抗病毒特性相关。小檗碱中的铵盐 N 原子能够与各种生物靶点相互作用, 从而在其抗糖尿病作用中发挥关键作用[23]。也有研究表明, atisine 型 C20 二萜生物碱的 C-6 位 R1、C-11 位 R2、C-15 位 R3 等取代基与抑制肿瘤细胞生长有关, C19-型二萜生物碱的抗炎活性可能与 C-8 位乙酰氧基有密切的关系[24,25]。这种结构–功能的多样性和可塑性使生物碱被认为是挖掘免疫调节先导化合物的重要天然分子库。文章中出现的单分子生物碱的分类与结构如表 1 所示。

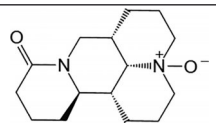
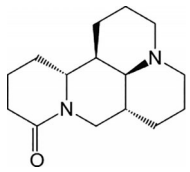
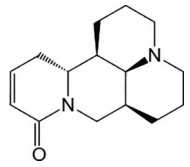
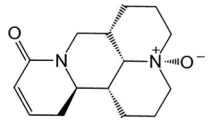
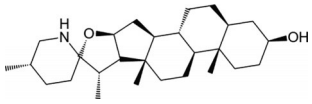
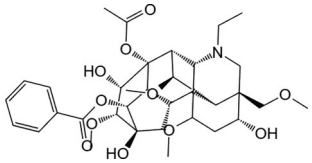
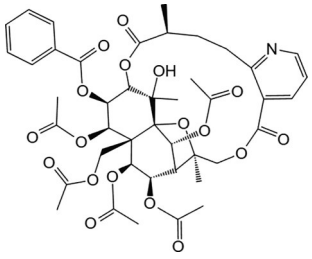
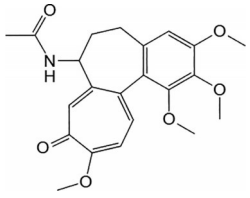
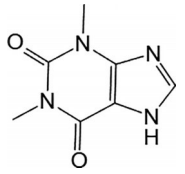
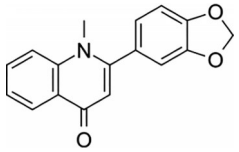
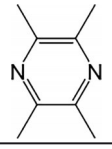
Table 1 The classification and structure of single-molecule alkaloids in the article

Classification	Structural characteristics	Example	CAS	Structure
Isoquinoline alkaloids	Characterized by an isoquinoline moiety serving as the core structural scaffold	Berberine	2086-83-1	
		Coptisine	3486-66-6	
		Tetrandrine	518-34-3	
		Sinomenine	115-53-7	

Continued

Classification	Structural characteristics	Example	CAS	Structure
		Chelerythrine	34316-15-9	
		Phellodendrine	6873-13-8	
		Berbamine	478-61-5	
		Sanguinarine	2447-54-3	
		Taspine	602-07-3	
Indole alkaloids	Characterized by the presence of an indole ring system as the fundamental skeleton	Evodiamine	518-17-2	
		Rutaecarpine	84-26-4	
		Tabersonine	4429-63-4	
		Ellipticine	519-23-3	
Imidazole alkaloids	Possess an imidazole ring as the principal structural framework	Epiisopiloturine	69460-80-6	
Quinolizidine alkaloids	Feature a fused bicyclic quinolizidine skeleton formed by two piperidine rings sharing a common nitrogen atom	Matrine	519-02-8	

Continued

Classification	Structural characteristics	Example	CAS	Structure
		Oxymatrine	16837-52-8	
		Sophoridine	6882-68-4	
		Sophocarpine	6483-15-4	
		Oxysophocarpine	26904-64-3	
Steroidal alkaloids	Based on the cyclopentanoperhydrophenanthrene steroid nucleus as the parent structure	Tomatidine	77-59-8	
Terpenoid alkaloids	Contain isoprenederived structural units and incorporate nitrogen atoms within the terpenoid framework	Aconitine	302-27-2	
		Wilforine	11088-09-8	
Organic amine alkaloids	Comprise nitrogen atoms in the form of non-cyclic free amino groups rather than heterocyclic ring systems	Colchicine	64-86-8	
Purine alkaloids	Contain a purine nucleus or structurally related purine-derived motifs	Theophylline	58-55-9	
Quinolone alkaloids	Characterised by a 4-quinolone as its basic skeleton	Graveoline	485-61-0	
Other alkaloids	Alkaloids that cannot be assigned to the aforementioned structural categories	Ligustrazine	1124-11-4	

2 生物碱对免疫系统的调节作用

大量研究表明, 生物碱不仅可直接作用于病原体或肿瘤细胞, 还可通过多靶点调控免疫系统的组成细胞和信号通路, 在炎症性疾病、肿瘤及自身免疫性疾病等多种病理状态中发挥复杂的免疫调节作用[26,27]。从免疫学角度看, 这种调节作用贯穿先天免疫与适应性免疫。一方面, 通过影响先天免疫改变机体对病原体的初始响应; 另一方面, 通过影响适应性免疫最终决定免疫应答的强度与方向。不同生物碱对免疫应答过程影响的异同如表2所示。

2.1 对先天免疫系统的影响

先天免疫是机体抵御病原体侵袭的第一道防线, 能够广泛识别并清除多种病原体, 由多种物理屏障、免疫细胞和免疫活性物质组成, 其特点是反应迅速、作用广泛。巨噬细胞、中性粒细胞、自然杀伤细胞 (natural killer cells, NKs) 和树突状细胞 (dendritic cells, DCs) 是该免疫类型的关键效应细胞。越来越多的研究表明, 天然生物碱能够通过改善物理屏障、调控免疫细胞的活化状态和效应功能以及免疫活性物质的释放, 从而在多种病理过程中发挥重要的免疫调节作用。

2.1.1 对物理屏障的影响 物理屏障是机体防御最基础的防线, 其核心任务是通过物理和化学方式, 阻止病原体和有害物质进入体内。物理屏障的完整性在分子水平上依赖于上皮细胞之间形成的复杂连接结构, 其中紧密连接及其相关蛋白起着决定性作用。有研究表明, 部分生物碱能够改善物理屏障从而在免疫反应中发挥作用。小檗碱是一种异喹啉生物碱, 近年来, 因其多样的药理作用而受到广泛关注。小檗碱能显著抑制葡聚糖硫酸钠 (dextran sulfate sodium salt, DSS) 诱导的结肠炎模型中紧密连接蛋白的下调, 从而降低肠道通透性, 改善肠道屏障功能。显微结构观察也证实, 小檗碱能够维持肠道微绒毛结构和紧密连接的完整性[28,29]。此外, 小檗碱还能改善人类视网膜色素上皮细胞、内皮细胞及Caco-2结直肠腺癌细胞中的屏障功能[30-32]。

2.1.2 对巨噬细胞的影响 巨噬细胞是先天免疫系统中的关键效应细胞, 不仅能吞噬、消化和清除大颗粒抗原, 发挥抗感染作用, 还能吞噬并清除衰老、死亡或转化的细胞, 从而维持免疫稳态。此外, 巨噬细胞作为抗原呈递细胞 (antigen-presenting cell, APC), 可以通过向$CD4^+$ T细胞呈递抗原pMHC类复合物来摄取、处理和呈现抗原[33]。其功能具有高度的多样性和可塑性, 能够根据微环境信号极化为不同的功能表型, 即M1型巨噬细胞和M2型巨噬细胞, 从而在炎症、免疫应答、组织稳态和修复中发挥关键的调节作用[34,35]。

生物碱可通过抑制关键炎症信号通路, 调节巨噬细胞的极化状态, 抑制肿瘤坏死因子-α (tumour necrosis factor-α, TNF-α)、白细胞介素-1β (interleukin-1 β, IL-1β)、IL-6等促炎因子的表达, 促进IL-10、转化生长因子-β (transforming growth factor β, TGF-β) 等抗炎因子表达, 发挥免疫调节作用。研究发现, 小檗碱能够抑制NF-κB信号通路, 降低促炎细胞因子IL-1β、IL-6、干扰素γ (interferon-γ, IFN-γ) 和TNF-α的表达, 促进抗炎细胞因子IL-10和TGF-β表达, 从而改善肠易激综合征大鼠的终末回肠组织炎症[36]。小檗碱还能够直接结合和激活SIRT3, 抑制NF-κB通路, 抑制巨噬细胞浸润和异常细胞外基质沉积, 调节M1与M2巨噬细胞的比例, 缓解脂肪组织的炎症和纤维化[37]。Mao等[38]建立脂多糖 (lipopolysaccharide, LPS) 诱导的肠道屏障损伤模型, 发现苦参碱能抑制M1巨噬细胞极化, 并促进M2巨噬细胞极化, 减少了促炎细胞因子IL-6、IL-1β、TNF-α和促炎介质一氧化氮的产生, 同时增加抗炎细胞因子

Table 2 Comparative analysis of how different alkaloids influence the immune response process. + indicates promotion; - indicates inhibition

Alkaloids	Innate immune process					Adaptive immune process	
	Physical barrier function	Macrophage	Neutrophil	Dendritic cell	Innate lymphoid cell	T lymphocyte	B lymphocyte
Berberine	+	-		-	+	-	±
Matrine		-		+		-	
Rutaecarpine			-				
Colchicine			-				
Phellodendrine			-				
Oxysophocarpine			-				
Sanguinarine		-	-				
Sophoridine		+					
SMU-Y6		-	-				
Total alkaloids of *Fritillaria cirrhosa* D.		-					
Total alkaloids of *Alstonia scholaris* (L.) R. Br.					-		
Total alkaloids of *Sophora alopecuroides* L.						-	-

IL-10的含量。此外, 苦参碱还抑制了NF-κB p65亚基的核易位, 并通过抑制TLR4/NF-κB/MAPK通路的激活发挥抗炎作用。Wang等[39]发现川贝母总生物碱能够降低肺组织中的IL-1β、TNF-α和IL-4水平, 缓解气道炎症。此外, 川贝母总生物碱还显著降低了与M2巨噬细胞密切相关的Arg1和CD206水平, 并下调了p-STAT3和p-JAK2的表达。表明川贝母总生物碱可能是通过调控JAK2/STAT3通路来抑制M2巨噬细胞极化, 从而缓解过敏性哮喘小鼠的气道重塑和炎症。Taspine衍生物SMU-Y6属于异喹啉类生物碱, 能够通过拮抗TLR2通路调控巨噬细胞极化, 减少细胞因子产生及中性粒细胞浸润, 并缓解急性足跖水肿和结肠炎小鼠的局部炎症[40]。

2.1.3 对中性粒细胞的影响 中性粒细胞是白细胞中最主要、数量最多的一种, 是最早被动员至炎症或感染部位的细胞之一, 通过吞噬、脱颗粒、产生活性氧(reactive oxygen species, ROS)以及形成中性粒细胞胞外诱捕网(neutrophil extracellular traps, NETs)等方式参与病原清除与炎症反应[41]。

生物碱对中性粒细胞的调节主要涉及趋化迁移、效应分子释放与NETs形成等方面。在急性胰腺炎、急性肝损伤及急性肺损伤等高炎症状态中, 部分生物碱可抑制中性粒细胞过度聚集和相关炎症通路, 降低弹性蛋白酶、髓过氧化物酶等组织损伤因子的释放, 并减弱ROS过量产生, 从而抑制炎症, 减轻损伤和实质器官坏死[42-45]。吴茱萸次碱通过抑制MAPK和NF-κB信号通路, 降低急性胰腺炎大鼠炎症标志物(IL-1β、IL-6、TNF-α)、组织氧化应激以及中性粒细胞浸润水平, 减轻组织损伤和急性胰腺炎, 并且恢复了模型大鼠胰腺抗氧化能力[42,43]。秋水仙碱的抗炎特性可能对急性心肌梗死后的生存率、心脏功能和心脏重塑产生积极影响。秋水仙碱抑制了急性心肌梗死后NETs的形成和炎症, 这种抑制作用被归因于NOX2/ROS和Ca^{2+}流入中性粒细胞的减少[44]。黄柏碱通过靶向p38 MAPK-$p47^{phox}$通路, 抑制NETs形成和ROS的产生, 并且使中性粒细胞浸润减少, 从而减轻急性胰腺炎中的胰腺损伤和炎症反应[45]。从苦参中提取得到的氧化槐果碱能通过调控KIT/PI3K信号通路, 减少炎症性细胞因子的产生、中性粒细胞聚集和肺上皮细胞凋亡, 从而改善急性肺损伤[46]。血根碱是一种具有强效抗炎和抗菌特性的生物碱。在真菌性角膜炎模型中, 血根碱通过抑制真菌生长、破坏菌丝形态, 减少中性粒细胞和巨噬细胞的浸润以及抑制炎症介质IL-1β、IL-6和C-C基序趋化因子配体2的表达, 从而发挥抗真菌、抗炎作用[47]。

2.1.4 对DCs的影响 DCs是APCs, 对于启动和调控T细胞对外来及自身抗原的反应至关重要。DCs分为常规DCs (conventional dendritic cells, cDCs)、浆细胞样DCs和单核细胞衍生的DCs, 其中cDCs又分为cDC1和cDC2, 这些不同的亚群具有不同的功能[48]。

已有研究表明, 生物碱能够调节DCs的成熟、抗原呈递及细胞因子分泌谱。在自身免疫性疾病和炎症模型中, 部分生物碱被发现可抑制DCs成熟, 表现为下调CD80、CD86等共刺激分子的表达, 减少IL-6、IL-23等促Th1/Th17分化细胞因子的分泌, 从而缓解病理性免疫应答[49,50]。在DSS诱导性结肠炎模型中, 小檗碱抑制DCs分泌IL-6, 进而抑制Th17细胞分化, 从而缓解结肠炎[49]。Yang等[50]在对小柳原田病综合征患者和小鼠模型研究中发现, 小檗碱能够下调共刺激分子CD40、CD80和CD86的表达, 抑制CDs分泌的IL-6、IL-1β和IL-23, 从而下调Th17反应, 改善炎症。也有研究表明小檗碱能选择性诱导DCs (尤其是成熟DCs)凋亡, 减少体内成熟DCs的数量, 从而间接减少对T细胞的启动刺激, 这可能是其发挥免疫抑制和抗自身免疫病作用的机制之一[51,52]。此外, 不同生物碱通过不同的分子机制, 对DCs的存活和功能产生不同的调控作用, 部分生物碱能够上调DCs中MHC-II、CD80和CD86等的表达, 促进炎症性细胞因子的分泌, 增强免疫功能。有研究表明, 苦参碱通过调控Toll样受体(Toll like receptors, TLRs)信号转导通路, 显著提高了TLR7、TLR8、髓样分化因子88 (myeioid differentiation factor 88, MyD88)、肿瘤坏死因子受体相关因子6和IκB激酶(IκB kinase, IKK)的mRNA表达水平, 增强了TLR7和TLR8的蛋白表达, 并上调了IL-12、IL-6和TNF-α的水平, 同时增强了DCs中MHC-II、CD54、CD80和CD86的表达, 从而增强免疫功能, 发挥显著的抗肿瘤活性[53]。

2.1.5 对先天性淋巴细胞的影响 先天性淋巴细胞(innate lymphoid cells, ILCs)是一类属于淋巴系但不具备经典抗原受体的先天免疫淋巴细胞, 是固有免疫系统的重要组成部分。其激活不依赖于抗原呈递, 而是能直接被应激信号、微生物化合物及细胞因子等激活并扩增, 这使其在调控炎症及免疫反应的过程中具有高度的反应性[54]。根据ILCs的功能将其分为三种, 第一种ILC以产生IFN-γ为特征, 包括NKs、1型先天性淋巴细胞; 第二种ILC能产生Th2细胞相关的细胞因子IL-5和IL-13, 包括2型先天性淋巴细胞; 第三种ILC可产生与Th17细胞相关的细胞因子IL-17和IL-22, 包括3型先天性淋巴细胞和淋巴组织诱导细胞[55]。ILCs受到环境刺激调控后, 可迅速释放细胞因子和其他介质来促进免疫反应, 桥接先天免疫与适应性免疫[56]。

ILCs通常存在于淋巴组织和外周器官, 尤其是皮肤、肝脏、小肠和肺部, 它们在炎症激活、组织重塑以及影响适应性免疫反应中发挥着关键作用。有研究表明, 绒毛细胞通过苦味受体感知小檗碱, 进而分泌IL-25刺激II型免疫反应, 调控ILC2和Th2免疫细胞, 最终促进绒毛细胞再生, 维持肠道屏障完整性及Th1/Th2/Th17细胞的稳态平衡, 改善DSS诱导的结肠炎[57]。糖胶树总生物碱能够抑制嗜酸性粒细胞的产生和嗜酸性粒细胞的招募, 调节Th1、Th2及Th17细胞因子水平, 减少ILC2数量, 并抑制肥大细胞活化及白三烯释放, 从而发挥对小鼠卵清蛋白诱导哮喘的预防与治疗作用[58]。

2.2 对适应性免疫系统的影响

适应性免疫是机体在接触特定抗原后, 通过淋巴细胞产生的高度特异性、具有记忆性的防御反应。它与先天免疫协同工作, 共同构成完整的免疫防御体系。适应性免疫主要由T淋巴细胞和B淋巴细胞介导, 其亚群平衡及活化状态是维持免疫稳态的重要基础。

2.2.1 对T淋巴细胞的影响 T淋巴细胞包含多种亚型, 主要为$CD4^+$ T细胞和$CD8^+$ T细胞。Th细胞属于$CD4^+$ T细胞的一个功能亚群, 可进一步分为Th1、Th2、Th17以及调节性T细胞 (regulatory T cells, Tregs), 这些细胞通过分泌各种细胞因子来激活和调节其他免疫细胞的功能, 包括辅助B细胞产生抗体、激活巨噬细胞以及帮助$CD8^+$ T细胞的有效分化与功能维持等[59,60]。而$CD8^+$ T细胞是通过直接杀伤被病原体感染或发生癌变的靶细胞, 从而发挥免疫作用。研究显示, 生物碱在多种疾病模型中均可调节T细胞的功能, 从而发挥免疫调节作用。如小檗碱通过调控PTEN介导的Akt/mTOR及其他信号通路, 抑制T细胞的活化、增殖及细胞因子分泌, 显著缓解T细胞引起的肺损伤[61]。苦参碱能够降低RA大鼠中Th1细胞因子IFN-γ、TNF-α、IL-1β水平, 调节Th1和Th2细胞因子的失衡, 同时通过抑制T细胞中的NF-κB信号, 增加了Th2细胞因子IL-4和IL-10的水平, 从而改善自身免疫性关节炎[62]。苦豆子总生物碱可以显著减轻关节肿胀, 降低胶原蛋白诱发关节炎小鼠脾脏滤泡辅助T细胞与B淋巴细胞的数量, 并显著降低其足踝关节中TLR2、TLR9、p-NF-κB p65、CXC趋化因子受体5、B细胞淋巴瘤6蛋白和诱导性共刺激分子的表达, 从而改善RA[63]。

2.2.2 对B淋巴细胞的影响 B淋巴细胞识别不同的抗原后, 随后被激活、增殖, 分化为产生抗体的B细胞和记忆B细胞[64]。B淋巴细胞通过产生各种类型的抗体介导体液免疫, 从而中和病原体、标记目标以供其他免疫细胞清除, 并形成长期免疫记忆, 在宿主免疫反应中发挥关键作用, 同时也参与多种炎症性、自身免疫性和肿瘤性疾病的发病机制[65]。有研究表明, 小檗碱对B淋巴细胞具有显著的双向免疫调节作用。在过敏、自身免疫性疾病等病理状态下, 它主要通过抑制NF-κB、MAPK、JAK/STAT及PI3K等关键信号通路, 有效抑制B细胞的异常活化与增殖, 进而影响过敏原特异性抗体 (IgE) 和自身反应性抗体 (IgG和IgA) 的生成。相反, 在感染模型中, 小檗碱能显著增强B细胞的抗体生成能力, 增强体液免疫, 促进IgM、IgA和IgG的生成。此外, 小檗碱及其衍生物对B细胞淋巴瘤/白血病展现出明确的抗肿瘤活性, 其机制涉及诱导DNA损伤、细胞周期阻滞、ROS积累、线粒体功能障碍和细胞凋亡, 并与调控c-Myc/CD47轴、ROS/JNK通路及CDK4/6、Bcl-2等分子表达相关[66]。生物碱对免疫细胞的影响如图1所示。

3 生物碱调节免疫系统的分子机制

3.1 NF-κB信号通路

NF-κB是在几乎所有细胞中表达的转录因子家

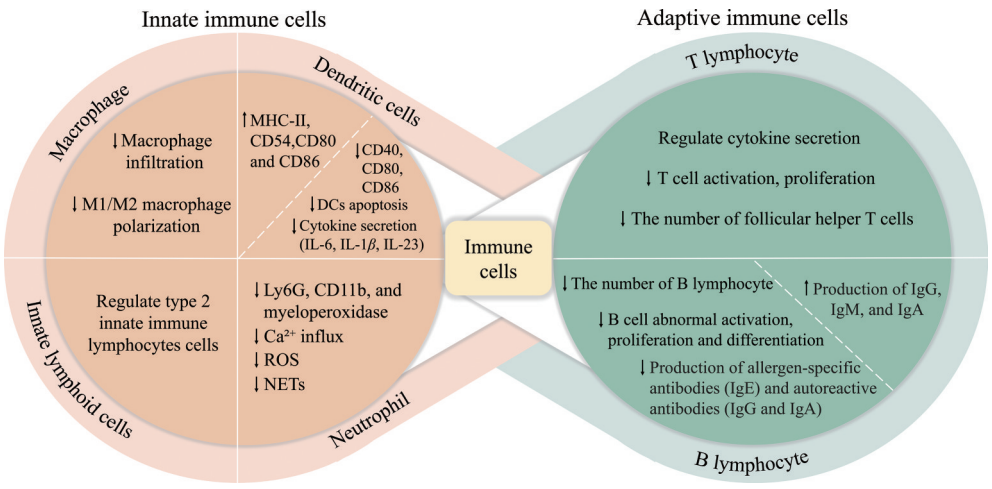


Figure 1 The effects of alkaloids on immune cells

族, 由5个成员RelA (p65)、RelB、c-Rel、NF-κB1 (p105)和NF-κB2 (p100)组成, 可形成多种二聚体以调控广泛的基因表达。在静息状态下, NF-κB二聚体与IκB抑制蛋白结合并滞留于胞质内。经典激活途径由TNFR、IL-1R、TLRs、B细胞受体和T细胞受体触发, 促使IKK复合体 (IKKα、IKKβ、NEMO) 磷酸化IκBα, 引导其泛素化降解, 使NF-κB释放并进入细胞核启动基因表达。非经典激活途径则由BAFFR、CD40、RANK等受体激活CD40或淋巴毒素β受体, 激活NIK-IKKα轴, 促进p100的部分降解生成p52/RelB复合体, 从而进一步激活NF-κB信号通路。此外, NF-κB还可由DNA损伤、酪蛋白激酶2或受体酪氨酸激酶等刺激激活。NF-κB信号终止主要依赖NF-κB诱导自身抑制蛋白IκBα的再合成, 以及去泛素化酶A20、CYLD赖氨酸63去泛素化酶的负反馈调控[67]。整体而言, NF-κB信号通路通过多重激活模式、高度的蛋白互作网络以及精细的反馈回路, 实现对炎症、免疫反应、细胞生存与转录程序的系统性调控。

NF-κB信号通路作为免疫与炎症反应中最核心的转录枢纽之一, 在机体抵御病原体、维持免疫稳态及应对组织损伤的过程中发挥不可替代的调控作用。经典NF-κB通路通过整合炎症因子、TLRs及细胞应激等多源信号, 迅速诱导IL-1β、TNF-α等炎症介质的表达, 从而驱动先天免疫反应并启动炎症级联[68]。同时, NF-κB通过控制生发中心B细胞维持、终末分化及适应性免疫建构, 调控髓系细胞的产生、功能和代谢, 从而构建免疫系统的关键调节层。此外, NF-κB也是连接代谢应激与免疫反应的核心节点, 在能量供应不足、营养过剩或氧化应激等条件下感知代谢失衡, 并通过重编程免疫细胞代谢, 促进炎症反应的维持或慢性化。并且, NF-κB在炎症小体启动阶段也发挥着重要作用, 又进一步将代谢信号与炎症放大机制联系在一起。因此, NF-κB不仅是免疫与炎症网络的中心调控开关, 也参与多种免疫学生物学过程, 如感染性疾病、慢性炎症、自身免疫病与肿瘤免疫等[69]。

通过调控NF-κB信号通路, 生物碱可能在多种免疫性疾病中发挥作用。小檗碱作为一种强效的天然药用成分, 能够通过多种途径有效调节炎症反应, 广泛应用于治疗多种炎症性疾病。小檗碱能够通过抑制IκBα降解、抑制IKK活性、抑制p65/p50复合物形成以及抑制核转录因子活性, 从而多层面抑制NF-κB的激活, 最终共同导致炎症性细胞因子如IL-1β、IL-6、TNF-α的表达显著下降[70]。也有研究表明, 小檗碱能够抑制NF-κB的表达, 并进一步抑制下游基因NOD样受体热蛋白结构域相关蛋白3 (NOD-like receptor thermal protein domain associated protein 3, NLRP3), 从而减少LPS诱导的促炎因子IL-1β和IL-18的产生和积累。其作用依赖于完整的NF-κB/NLRP3信号轴, 并能直接与NLRP3蛋白结合[71]。Niu等[62]建立了RA大鼠模型, 发现苦参碱治疗显著减轻了RA的炎症和严重程度。机制上, 苦参碱可能通过抑制T细胞中的NF-κB信号通路, 降低Th1细胞因子IFN-γ、TNF-α和IL-1β水平, 同时提高Th2细胞因子IL-4和IL-10的水平, 从而调节RA大鼠中Th1和Th2细胞因子的失衡。从小叶毛果中提取的生物碱表异毛果碱能显著抑制LPS诱导的TLR4受体表达上调和NF-κB关键亚基p65的磷酸化, 从而阻断该转录因子核转位及其下游促炎基因的转录, 显著降低小胶质细胞中促炎因子IL-1β、IL-6、TNF-α的产生, 从而发挥抗神经炎症作用。同时, 表异毛果碱也抑制了MAPK信号通路中细胞外信号调节激酶(extracellular signal-regulated kinase, ERK)、c-Jun氨基末端激酶 (c-Jun N-terminal kinase, JNK) 的活化, 协同减弱炎症应答[72]。TLR作为NF-κB通路的上游启动受体, 参与多种免疫反应如炎症、感染、肿瘤等, 因此TLR抑制剂的开发具有重要意义。Yang等[40]发现新型阿朴啡类生物碱衍生物SMU-Y6, 该衍生物作为TLR2抑制剂, 能够有效抑制TLR2, 阻碍TLR2/MyD88复合物的形成, 并阻断下游NF-κB和MAPK信号通路, 从而抑制炎症性细胞因子的释放, 在体内表现出优异的抗炎效果。Cen等[73]发现新型TLR3抑制剂玫瑰树碱衍生物SMU-CX24, 该化合物具有高效性、水溶性、特异性, 能够抑制TLR3诱导的NF-κB、MAPK和IFN信号通路及炎症反应, 从而缓解并预防动脉粥样硬化。而另一种玫瑰树碱衍生物SMU-14a能够调节与TLR3激活相关的IRF3、NF-κB及MAPK通路中的关键蛋白水平, 抑制炎症通路的活化, 从而缓解急性肝炎[74]。不同生物碱通过NF-κB信号通路调节免疫的机制如图2所示。

3.2 JAK-STAT信号通路

JAK-STAT通路是细胞从细胞外受体将细胞因子信号快速传递至细胞核的关键机制, 广泛参与多类免疫和炎症相关基因的表达调控。该通路由4种JAK (JAK1、JAK2、JAK3、Tyk2) 和7种STAT (STAT1～4、STAT5a/b、STAT6) 组成。目前, JAK-STAT通路主要有两种激活方法: 经典途径与非经典途径。经典通路中, 细胞因子与其I/II型受体结合后, 使受体二聚化并激活关联的JAK, 引发受体酪氨酸位点磷酸化, 随后招募STAT并使其形成二聚体并入核, JAK-STAT通路被激活, 调控多种免疫基因的转录。除了经典途径激活外, JAK/STAT还参与了更复杂的非经典途径激活。

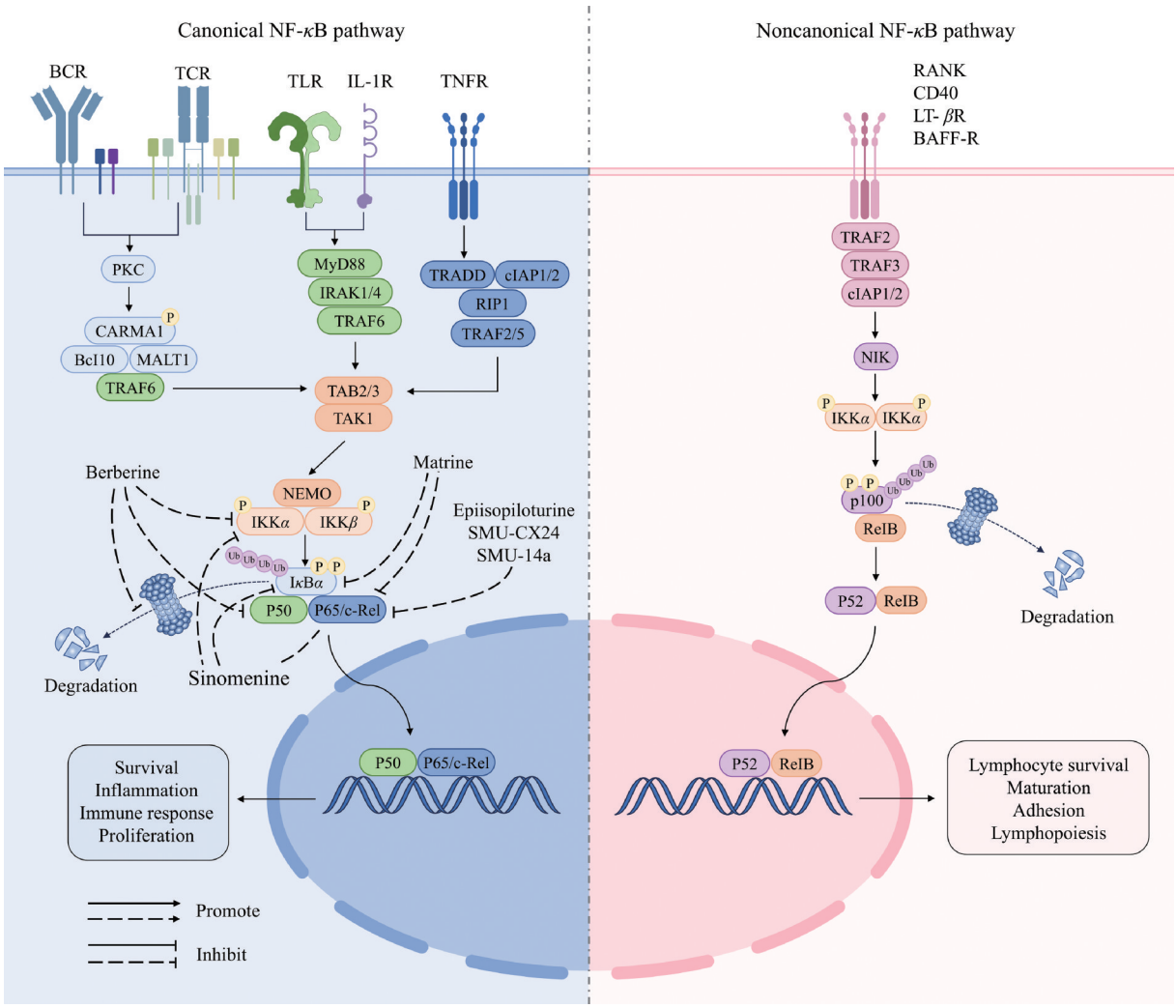


Figure 2 Alkaloids modulate immunity through the NF-κB signaling pathway

与经典途径模式不同, 非经典途径的核心特征是STAT在未被磷酸化的情况下依然能调控基因表达, 多种STAT3靶基因可以响应未磷酸化的STAT3表达[75]。并且该通路具备严格的负调控机制, 包括细胞因子信号抑制因子、活化STAT蛋白抑制因子和蛋白酪氨酸磷酸酶, 共同确保细胞因子信号不过度激活[76]。在免疫系统中, JAK-STAT是连接先天与适应性免疫反应的关键枢纽, 其异常激活可导致多种免疫疾病, 如系统性红斑狼疮、特应性皮炎及RA等, 是免疫调控网络中不可替代的核心枢纽, 目前已成为重要的免疫调节药物靶点。

目前大量研究表明, 生物碱能够通过调节JAK-STAT通路治疗多种炎症性疾病。小檗碱在炎症方面表现出显著疗效, 其能够通过多种机制推动JAK-STAT的激活和信号传导, 一方面小檗碱能够直接触发JAK/STAT1通路, 提升STAT1表达和磷酸化; 另一方面, 小檗碱还能够抑制蛋白酪氨酸磷酸酶活性, 增强JAK/STAT1信号通路, 从而加强IFN-γ与细胞表面受体的结合, 增强细胞的免疫功能[70]。乌头总生物碱具有“多成分”和“多靶点”特性, 参与调控多种信号通路, NF-κB和JAK/STAT是其发挥抗类风湿效果的重要调控通路。乌头总生物碱通过抑制NF-κB信号通路的磷酸化过程以及p-p65的核内易位, 并且调控JAK/STAT信号通路的激活, 从而影响IL-1β和IL-6水平, 发挥抗炎作用[77]。植物中分离出来的吲哚生物碱水甘草碱可缓解小鼠中LPS引起的急性肺损伤和炎症浸润, 并抑制肺组织中JAK1/STAT3信号通路的激活, 而JAK1抑制剂的使用增强了水甘草碱的治疗效果。因此, 水甘草碱缓解急性肺损伤的潜在机制被认为与JAK1/STAT3通路介导的炎症和凋亡相关[78]。此外, 部分生物碱也能够通过JAK-STAT通路干预肿瘤的发生发展。如吴茱萸碱通过下调磷酸葡萄糖异构酶抑制JAK2/STAT3通路, 抑制HCT-116人类结直肠癌细胞的迁移, 调节p53信号通路的活性, 从而诱导细胞凋亡并

下调基质金属蛋白酶3 (matrix metalloproteinases-3, MMP-3) 表达[79]。苦参碱可以通过抑制JAK2/STAT3信号来诱发胆管癌细胞的线粒体凋亡[80]。不同生物碱通过JAK-STAT信号通路调节免疫的机制如图3所示。

3.3 MAPK信号通路

MAPK信号通路是一种高度保守的激酶级联反应系统, 在哺乳动物免疫应答的多个阶段都发挥着核心作用。该通路主要由3个亚家族构成, 即ERK、JNK和p38 MAPK[81]。它们通过三级激酶级联 (MAP3K-MAP2K-MAPK) 被上游信号激活, 进一步磷酸化下游转录因子、细胞骨架蛋白、酶等效应分子等, 从而影响免疫细胞的活化、分化、细胞因子产生及炎症反应强度[82]。

生物碱可通过调节ERK、JNK、p38等不同分支, 在炎症性疾病和肿瘤免疫中发挥多样化的调节功能, 但这一调节作用非单向抑制, 而是取决于生物碱的种类、细胞类型和病理背景的复杂调控。一方面, 生物碱能够抑制MAPK通路以发挥抗炎作用。如小檗碱不仅能够作用于上述的NF-κB通路和JAK-STAT通路, 还能够抑制丝裂原活化的ERK活性以及其他MAPKs, 降低ERK、JNK和p38等MAPK的激活程度, 从而降低单核细胞趋化蛋白1和巨噬细胞炎症蛋白-1α等趋化因子与炎症细胞因子水平[70]。另一方面, 生物碱能够激活p-ERK、p-p38等, 在肿瘤免疫中发挥调节作用。如槐定碱在非小细胞肺癌模型中可上调p-ERK、p-JNK和p-p38的表达, 激活MAPKs信号通路, 促进促炎细胞因子和M1表面标记CD86的表达增加[83]。不同生物碱通过MAPK信号通路调节免疫的机制如图4所示。

3.4 PI3K/Akt/mTOR信号通路

PI3K/Akt/mTOR信号通路在广泛的细胞活动中起着核心作用, 尤其是在细胞生长、增殖、存活和分化方面。大量研究表明, mTOR作为PI3K/Akt轴的下游关键效应分子, 通过整合抗原受体信号、共刺激分子、细胞因子以及营养与能量状态, 精细调控免疫细胞的激活、分化与效应功能。在B细胞或T细胞中, mTOR在PI3K-Akt信号传导下游被激活, 使淋巴细胞进入细胞周期并增殖; 而在先天免疫细胞中, mTOR则提供启动信号, 支持促炎细胞因子的快速分泌和吞噬能力, 并调节巨噬细胞和DCs的代谢状态及免疫效应强度[84]。总体而言, PI3K/Akt/mTOR通路将免疫信号与细胞代谢联系起来, 在维持免疫稳态、调控炎症反应及免疫相关疾病发生发展中发挥重要作用。

PI3K/Akt/mTOR通路对免疫细胞代谢的调控使其成为天然活性成分发挥免疫调节作用的重要分子靶点。生物碱通过干预PI3K/Akt/mTOR信号转导, 影响免疫细胞的增殖分化、炎症因子的分泌及细胞凋亡等, 从而改善多种免疫性疾病。细胞因子释放综合征 (cytokine release syndrome, CRS) 是嵌合抗原受体T细胞 (chimeric antigen receptor T-cell, CAR-T) 治疗后严重的并发症, 其发生机制源于巨噬细胞过度释放细胞

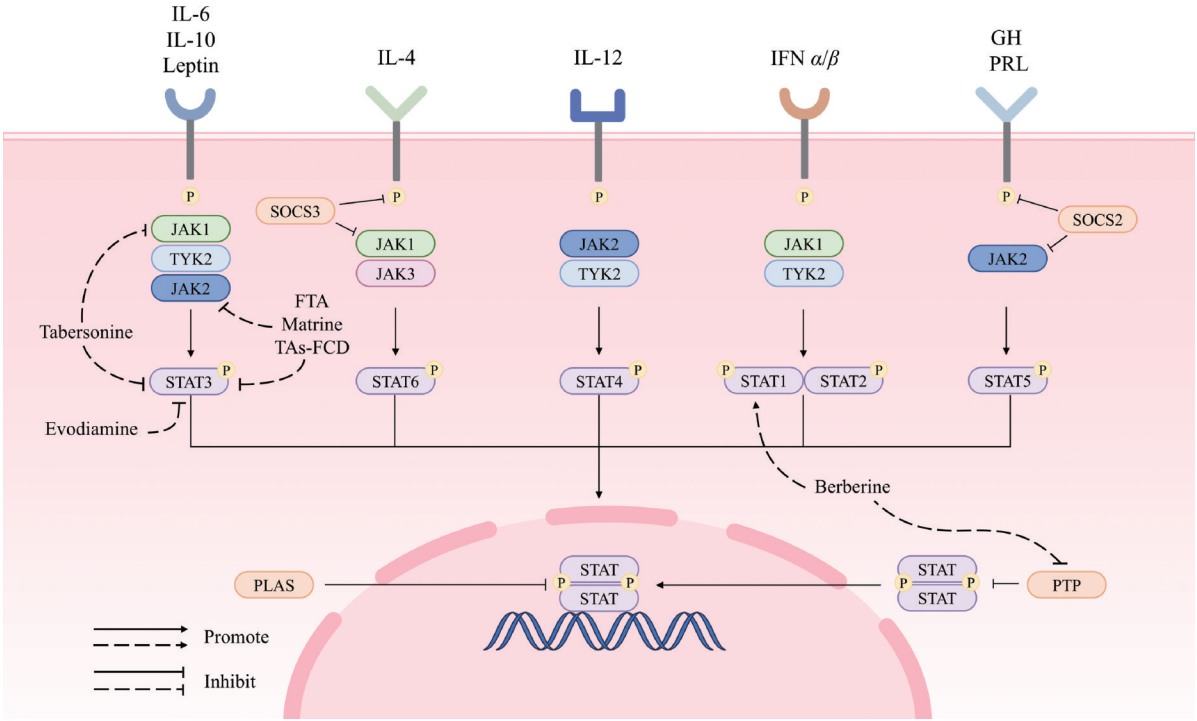


Figure 3 Alkaloids modulate immunity through the JAK/STAT signaling pathway. TAs-FCD: Total alkaloids of *Fritillaria cirrhosa* D. Don; FTA: Fuzi total alkaloids

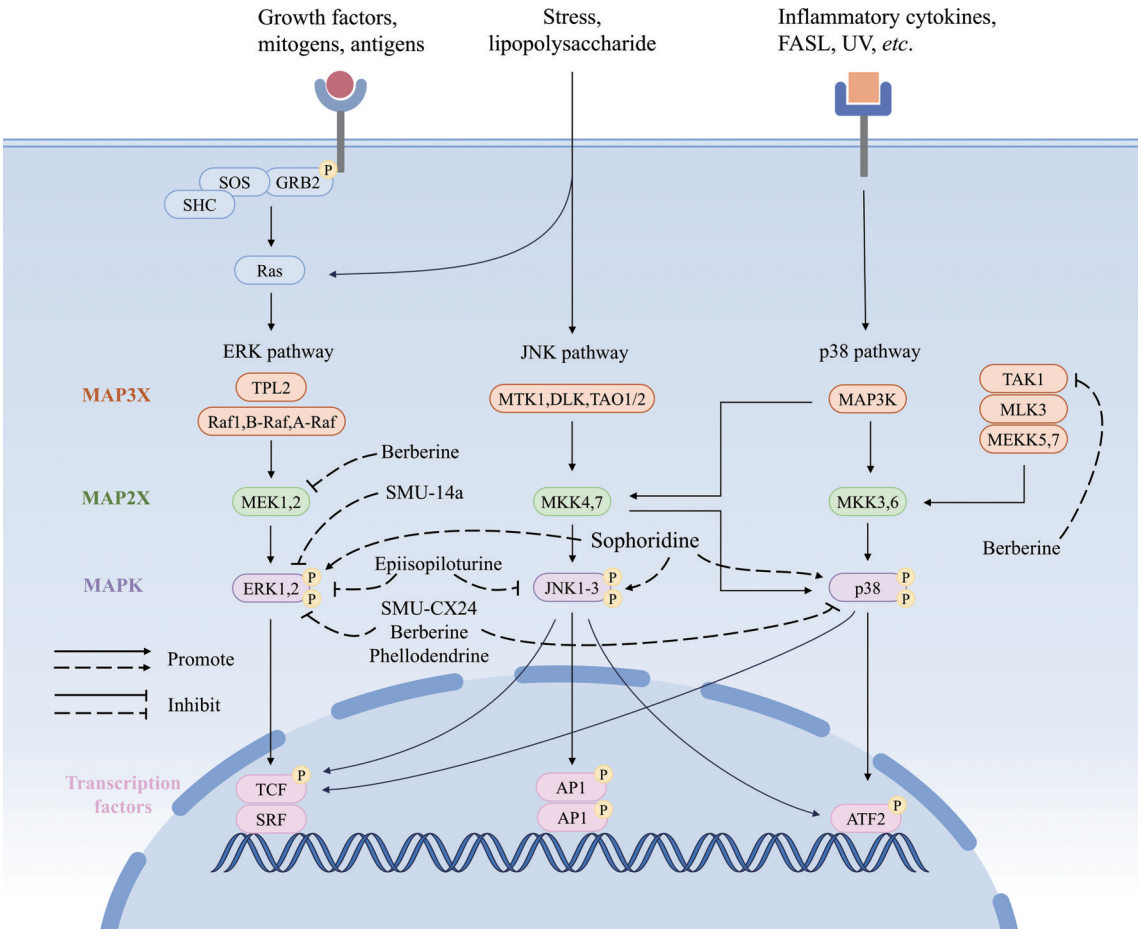


Figure 4 Alkaloids modulate immunity through the MAPK signaling pathway

因子。汉防己甲素能够抑制在CRS期间巨噬细胞中失调的Akt/mTOR信号通路来增强自噬, 有效降低小鼠血清中IL-6及人源IFN-γ浓度, 同时维持CAR-T细胞的治疗效果[85]。Chen等[86]建立溃疡性结肠炎小鼠模型, 发现氧化苦参碱能够通过PI3K/Akt通路发挥抗炎、促凋亡作用, 并下调Th1和Th17细胞分化, 从而显著改善溃疡性结肠炎。也有研究表明, 青藤碱能够通过抑制PI3K/Akt和NF-κB信号通路的激活, 恢复Th17和Tregs之间的平衡, 从而缓解自身免疫性葡萄膜炎的炎症[87]。小檗碱眼药水通过抑制PI3K/Akt/NF-κB和MAPK通路, 减少结膜中的炎症因子和$CD4^+$ T细胞的浸润, 并抑制凋亡、降低MMP-3和MMP-9水平, 从而治疗干眼症[88]。苦参碱能够抑制A549和95D肺癌细胞的增殖, 并通过PI3K/Akt/mTOR信号通路以剂量和时间依赖的方式促进肺癌细胞凋亡, 以及抑制凋亡蛋白家族蛋白表达的下调, 发挥抗癌效果[89]。茶碱能够上调环磷酸腺苷, 激活PKA和PKB, 从而抑制mTOR, 减轻炎症并阻断病毒复制, 这可能是茶碱有助于治疗SARS-CoV-2病理生理学的潜在作用机制[90]。不同生物碱通过PI3K/Akt/mTOR信号通路调节免疫的机制如图5所示。

3.5 其他信号通路

除了上述信号通路, 生物碱还能够通过其他信号通路发挥免疫调节作用。如小檗碱、白屈菜红碱、青藤碱等生物碱类活性成分可调控AMPK/mTORC1、AMPK/NF-κB、AMPK/mTOR等信号通路, 通过调控细胞凋亡、调控细胞自噬、改善免疫微环境、改善炎症反应等途径来发挥抗RA的作用[91]。Epiisopiloturine通过调节Wnt/β-catenin信号通路对哮喘相关的病理变化、炎症和气道重塑均有一定的治疗作用[92]。马齿苋生物碱通过调控TLR4/MyD88/NF-κB信号通路, 可减轻DSS诱导溃疡性结肠炎小鼠的肠道炎症损伤[93]。吴茱萸碱通过下调HMGB1/NF-κB/TLR-4通路, 减少肺组织中的气道炎症和重塑, 从而治疗哮喘[94]。

4 生物碱在免疫相关疾病治疗中的应用

随着对生物碱的深入研究, 众多生物碱被证实能够通过调节免疫细胞功能、细胞因子水平及干预信号通路等机制, 在自身免疫性疾病、炎症性疾病及哮喘等疾病的治疗中展现出重要潜力。生物碱在免疫相关疾病中的治疗作用如表3[39,42,62,63,70,74,86,93-115]所示。

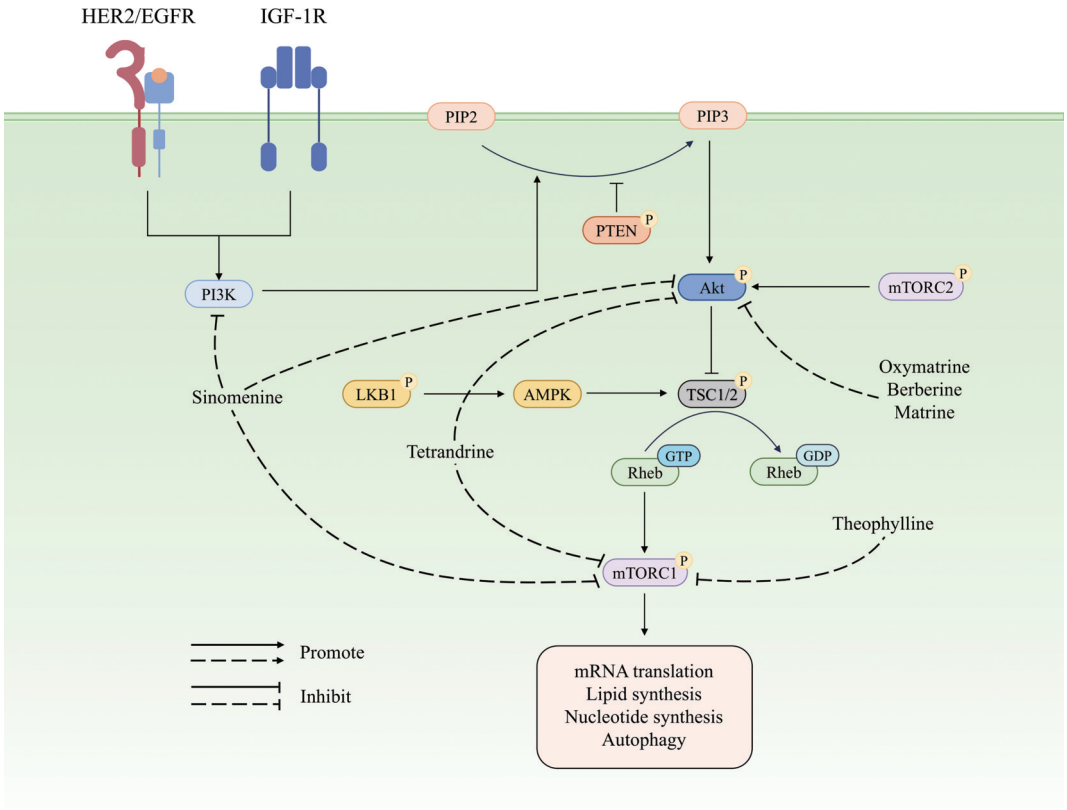


Figure 5 Alkaloids modulate immunity through the PI3K/Akt/mTOR signaling pathway

Table 3 The therapeutic effects of alkaloids in immune-related diseases. SLE: Systemic lupus erythematosus; RA: Rheumatoid arthritis

Disease	Alkaloid	Therapeutic mechanism	Reference
SLE	Berbamine	Downregulates autoantibody levels and alleviates vascular inflammation	[95]
	Sophocarpine	Inhibits NF-κB activation in renal tissue and reduces the expression of proteins constituting the NLRP3 inflammasome	[96]
	Aconitine	Decreases plasma leukocyte counts and anti-double-stranded DNA antibody levels, significantly improves renal histopathological damage, and reduces IgG deposition in glomeruli	[97]
	Coptisine	Suppresses the NF-κB signaling pathway and downstream signaling molecules, reduces autoantibody and serum inflammatory marker levels, attenuates renal inflammation, and improves renal function	[98]
	Berberine	Modulates immune cell activity, suppresses immune activation and autoantibody production, and prevents or alleviates severe SLE-associated complications through inhibition of platelet aggregation and antioxidant effects	[70]
RA	Wilforine	Reduces IL-6, IL-1β, TNF-α levels and MMP-3 expression; ameliorates RA by inhibiting activation of the Wnt/β-catenin signaling pathway and downregulating Wnt11, β-catenin, CCND1, GSK-3β, and c-Myc expression	[99]
	Total alkaloids of *Strychnos nux-vomica* L.	Inhibits the PI3K/Akt/mTOR signaling pathway, reduces IL-1β, IL-6, TNF-α, and RANKL expression, alleviates inflammation, and improves symptoms in RA rat models	[100]
	Sinomenine	Regulates the balance between Treg and Th17 cells in mesenteric lymph nodes and promotes lymphocyte migration to joints; blocks T-cell co-stimulation by inhibiting DCs CD80 and CD86 mRNA expression	[101,102]
	Berberine	Suppresses NF-κB signaling activation, reduces the production and release of pro-inflammatory cytokines IL-6, TNF-α, IL-1β, and downregulates macrophage-mediated inflammatory responses	[70,103]
	Aconitum alkaloid	Reduces TNF-α and COX-2 protein expression, and inhibits inflammation in RAW264.7 macrophages *in vitro via* signalling pathways including NF-κB and JAK1	[104]
	Total alkaloids of *Sophora alopecuroides* L.	Inhibits the TLRs/NF-κB pathway, downregulates the number and function of Tfh cells, suppresses germinal center B cells, reduces autoantibody production, and alleviates immune-pathological processes in collagen-induced arthritis models	[63]
	Matrine	Inhibits NF-κB signaling in T cells and regulates the imbalance of Th1/Th2 cytokines	[62]

Continued

Disease	Alkaloid	Therapeutic mechanism	Reference
Ulcerative colitis	Berberine	Enhances intestinal barrier function and inhibits the NF-κB pathway, thereby suppressing inflammatory cell infiltration and activation and alleviating local tissue inflammation	[70]
	Oxymatrine	Downregulates Th1 and Th17 differentiation and exerts anti-inflammatory and pro-apoptotic effects *via* the PI3K/Akt signaling pathway	[86]
	Total alkaloids of *Aconitum carmichaelii* Debx.	Inhibits the NLRP3 inflammasome and reduces levels of pro-inflammatory cytokines such as IL-1β and IL-6, exerting anti-inflammatory effects	[105]
	Alkaloids of *Portulaca oleracea* L.	Acts on the TLR4/MyD88/NF-κB signaling pathway to alleviate intestinal inflammatory injury and reduce serum TNF-α and IL-1β levels as well as histopathological damage	[93]
Acute pancreatitis	Rutaecarpine	Inhibits the MAPK/NF-κB signaling pathway, alleviates histopathological alterations, decreases IL-6 and TNF-α levels, increases IL-10 levels, and improves inflammatory responses in acute pancreatitis	[42]
	Oxymatrine	Alleviates intestinal injury by regulating Th1/Th17 cytokines and the MAPK/NF-κB signaling pathway	[106]
	Ligustrazine	Downregulates TNF-α, IL-1β, and IL-6 levels, inhibits the p38 and ERK MAPK pathways, and accelerates acinar cell apoptosis	[107]
	Berberine	Inhibits JNK signaling activation, downregulates iNOS, TNF-α, IL-1, IL-6, and JNK protein expression, and reduces pancreatic injury	[108]
	Colchicine	Inhibits the TNF-α/TNF-R1 signaling pathway, alleviates inflammation and oxidative stress, and improves microcirculation	[109]
	Tetrandrine	Inhibits NF-κB activity, reduces production of pro-inflammatory cytokines TNF-α and IL-6, and alleviates inflammation and pancreatic pathological damage	[110]
Acute hepatitis	SMU-14a	Inhibits the NF-κB, MAPK, and IRF3 signaling pathways, reduces IL-6 level, decreases serum levels of alanine aminotransferase and aspartate aminotransferase, exerting anti-inflammatory and hepatoprotective effects	[74]
	Graveoline	Inhibits TNF-α inflammasomes, activates IL-4 and IL-10, and suppresses the JAK1/STAT3 signalling pathway to alleviate inflammation and exert hepatoprotective effects	[111]
Hepatitis B	Berberine	Inhibits hepatitis B virus replication, reduces viral load, enhances immune responses, decreases oxidative stress and apoptosis, and protects host tissues	[70]
	Matrine	Competitively inhibits hepatitis B virus DNA polymerase, thereby suppressing viral DNA replication	[112]
Asthma	Total alkaloids of *Fritillaria cirrhosa* D.	Regulates the JAK2/STAT3 pathway to inhibit M2 macrophage polarization, alleviating airway remodeling and inflammation in allergic asthma models	[39]
	Matrine	Suppresses Th2 cytokines and eosinophil-attracting chemokines, thereby reducing eosinophil infiltration, airway hyperresponsiveness, and airway inflammation	[62]
	Tomatidine	Blocks Th2 cell activity, significantly inhibits mucus production, airway inflammation, acute airway hyperresponsiveness, and eosinophil infiltration, improving asthma symptoms in mice	[113]
	Ligustrazine	Rebalances cytokine profiles and related transcription factors T-bet/GATA-3 and Foxp3/RORγt, correcting Th1/Th2 and Treg/Th17 imbalance and improving asthma-associated pulmonary inflammation	[114]
	Tetrandrine	Inhibits the HMGB1/TLR4/NF-κB signaling pathway, reduces TNF-α, IL-6, and IL-1β levels, and attenuates airway remodeling	[115]
	Evodiamine	Suppresses the HMGB1/NF-κB/TLR4 pathway, decreases IL-4, IL-9, IL-13, and IgE levels, increases IFN-γ levels, and reduces airway inflammation and remodeling	[94]

5 结语与展望

生物碱作为天然产物中的重要活性成分, 具有来源广泛、结构多样、多靶点、多层级的特点, 在免疫调节方面具有很大潜力。本文综述了生物碱对先天免疫系统和适应性免疫系统的影响, 并进一步总结了其对免疫系统作用的主要分子机制, 同时也对生物碱在免疫相关疾病治疗中的应用进行了梳理, 以期为生物碱的后续机制研究及相关药物开发提供参考。目前针对生物碱对巨噬细胞、中性粒细胞、DCs及T淋巴细胞的调节作用已取得较为丰富的进展, 但对于ILCs等其他先天免疫细胞以及B淋巴细胞的调节作用的研究仍存在显著的局限性。除上述研究较为广泛的先天免疫细胞外, 先天免疫系统中还存在ILCs、自然杀伤T细胞、黏膜相关恒定T细胞、$\gamma\delta$T细胞等免疫细胞, 这些细胞在免疫调节和稳态维持中也发挥着关键作用。但目前针对生物碱调控ILCs等其他先天免疫细胞的研究仍处

于起步阶段, 未来研究应着力于结合高通量筛选、组学技术及体内外功能验证模型, 系统解析生物碱类化合物与这些免疫细胞相互作用的分子机制。同时, 未来研究也应基于天然产物的结构多样性, 对生物碱类化合物进行结构优化, 以期发现能够调节这些细胞功能的新型先导化合物, 为开发针对自身免疫病、感染及肿瘤等疾病提供新的思路和候选分子。B淋巴细胞不仅是产生和介导体液免疫的关键细胞, 更是连接先天免疫与适应性免疫的枢纽, 是机体免疫调节的重要环节。但当前研究多聚焦于B细胞增殖、凋亡或免疫球蛋白总量变化, 而对记忆B细胞形成、B-T细胞相互作用及免疫代谢等关键过程并未开展深入研究。未来研究应聚焦于生物碱对B细胞发育、分化、抗体生成等功能性作用的影响, 并深入挖掘其调节B细胞免疫反应的分子机制及作用通路。并且, 对于生物碱免疫调控的分子机制研究正从零散的单靶点分析向以NF-κB、JAK-STAT等关键枢纽为核心、多通路交互的系统性研究转变。未来, 可以通过系统生物学的方法, 利用转录组、蛋白质组、代谢组等多组学技术, 构建生物碱作用下信号通路、免疫细胞与组织的响应网络, 进一步深入挖掘其中的分子机制, 全面解析其多靶点作用网络。

此外, 生物碱多靶点、多层级的免疫调节作用也使得其免疫效应常呈环境依赖性和不可预测性, 如在炎症性疾病或自身免疫疾病模型中, 生物碱往往通过抑制过度激活的免疫反应而发挥保护作用, 而在感染或肿瘤模型中, 某些生物碱则表现出增强免疫应答的作用, 由此可推测部分生物碱具有双向调节作用, 可作用于免疫组织与器官、免疫细胞及免疫分子, 在多层次上对机体免疫功能实施双向调控, 促进免疫系统各组成成分之间的相互作用与协同调节, 从而实现对机体免疫功能的系统性和精准性调控。目前, 生物碱的双向调节作用受到广泛关注, 但其多靶点、多层级的调节作用也增加了机制阐明与临床转化难度。未来研究应聚焦于细胞、组织、微环境特异性等研究, 系统性地探究其在肿瘤、慢性炎症等不同环境中起效的细胞与分子条件, 深入挖掘生物碱的免疫调节机制。

总之, 生物碱在免疫调节中发挥着重要作用, 后续应更加深入、全面地研究其作用机制及其在不同生理或病理环境中起效的细胞与分子条件, 为未来免疫调节剂的开发和相关疾病的治疗提供理论依据。

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References

[1] Fernandez MM, Motrich RD, Ostrowski M, et al. Editorial: Immune system disorders: From molecular mechanisms to clinical implications [J]. Front Immunol, 2024, 15: 1498830.

[2] Laiba A, Ibrahim J, Abbas BSN, et al. Immunosuppressive effects of natural α,β-unsaturated carbonyl-based compounds, and their analogs and derivatives, on immune cells: A review [J]. Front Pharmacol, 2017, 8: 22.

[3] Min Q, Walter JE, Schroeder HW, et al. Editorial: Mechanisms of dysregulated antibody responses in inborn errors of immunity [J]. Front Immunol, 2023, 14: 1335217.

[4] Tieu S, Charchoglyan A, Wagter-Lesperance L, et al. Immunoceuticals: Harnessing their immunomodulatory potential to promote health and wellness [J]. Nutrients, 2022, 14: 4075.

[5] Moradi MT, Karimi A, Rafieian-Kopaei M, et al. *In vitro* antiviral effects of *Peganum harmala* seed extract and its total alkaloids against influenza virus [J]. Microb Pathog, 2017, 110: 42-49.

[6] Zhang Y, Wen J, Liu D, et al. Demethylenetetrahydroberberine alleviates nonalcoholic fatty liver disease by inhibiting the NLRP3 inflammasome and oxidative stress in mice [J]. Life Sci, 2021, 281: 119778.

[7] Yuan HL, Liu L. Optimization of extraction process and antibacterial activity of total alkaloids from *Glaucium fimbriiligerum* [J]. Chem Res Appl (化学研究与应用), 2025, 37: 3327-3334.

[8] Hashemzaei M, Rezaee R. A review on pain-relieving activity of berberine [J]. Phytother Res, 2021, 35: 2846-2853.

[9] Zhang SB, Liu XM, Wei N, et al. Quality control status and predictive analysis of quality marker for Gouteng (*Uncaria rhynchophylla*) [J/OL]. Chin Arch Tradit Chin Med (中华中医药学刊), 2025. https://link. cnki. net/urlid/21.1546. R. 20251106. 0936.002.

[10] Lin Y, Zheng F, Xiong BJ, et al. Koumine alleviates rheumatoid arthritis by regulating macrophage polarization [J]. J Ethnopharmacol, 2023, 311: 116474.

[11] Anwar MM, Albanese C, Hamdy NM, et al. Rise of the natural red pigment 'prodigiosin' as an immunomodulator in cancer [J]. Cancer Cell Int, 2022, 22: 419.

[12] Alqathama A. Natural products as promising modulators of breast cancer immunotherapy [J]. Front Immunol, 2024, 15: 1410300.

[13] Ma X, Cao N, Zhang C, et al. Cytotoxic carbazole alkaloid derivatives from the leaves and stems of *Murraya microphylla* [J]. Fitoterapia, 2018, 127: 334-340.

[14] Dou PC, Chang S, Song RP, et al. Research status of PI3K/Akt signaling pathway in precancerous lesion of gastric cancer and traditional Chinese medicine intervention [J]. Chin J Clin Pharmacol (中国临床药理学杂志), 2025, 41: 2679-2684.

[15] Wang H, Ding JL, Sun GJ, et al. Intervention of signaling pathways related to ulcerative colitis with traditional Chinese medicine: A review [J]. Chin J Exp Tradit Med Formulae (中国实验方剂学杂志), 2026, 32: 331-340.

[16] Wang ZY, Liu TJ, Wang H, et al. Exploring the mechanism of traditional Chinese medicine in treating ulcerative colitis based on the SIRT signaling pathway [J]. Chin J Mod Appl Pharm (中国现代应用药学), 2026, 43: 329-339.

[17] Deng SL, Zhu F, Zhang H, et al. Determination of scopolamine, racanisodamine and atropine in biological samples by liquid chromatography-tandem mass spectrometry [J]. J Instrum Anal (分析测试学报), 2026, 45: 150-156.

[18] Zhou ZW, Cai J, Zheng L, et al. Mechanism of dauricine in reducing ischemia-reperfusion acute kidney injury [J]. J Pract Med (实用医学杂志), 2025, 41: 2336-2341.

[19] Yin Q, Liu X, Zhang Z, et al. Chemistry and bioactivities of alkaloids isolated from marine fungi (covering 2016-2022) [J]. Fitoterapia, 2023, 164: 105377.

[20] Shi J, Yu M, Chen W, et al. Recent discovery of nitrogen heterocycles from marine-derived *Aspergillus* species [J]. Mar Drugs, 2024, 22: 321.

[21] Lichman BR. The scaffold-forming steps of plant alkaloid biosynthesis [J]. Nat Prod Rep, 2021, 38: 103-129.

[22] Yang X, Bu T, Ma Y, et al. An updated review of isoquinoline alkaloids: Biological activity and mode of action, structural modifications, and agricultural applications [J]. Ind Crop Prod, 2025, 234: 121591.

[23] Jiang W, Zhang W, Jing C, et al. Plant protoberberine alkaloids: Structural diversity, biosynthesis, synthesis, biological activity, structure-activity relationships and clinical applications of berberine [J]. Phytochemistry, 2026, 242: 114690.

[24] Li RY, Feng F, Liu JH. Advance in studies on structure-activity relationships of C20-diterpenoid alkaloids [J]. Strait Pharm J (海峡药学), 2013, 25: 1-4.

[25] Cai CQ, Yang CH, Liang JY, et al. Advance in studies on structure-activity relationships of diterpenoid alkaloids in genus *Aconitum* [J]. Strait Pharm J (海峡药学), 2013, 25: 1-5.

[26] Zhu RL, Zhi YK, Yi L, et al. Sinomenine regulates CD14/TLR4, JAK2/STAT3 pathway and calcium signal *via* α7nAChR to inhibit inflammation in LPS-stimulated macrophages [J]. Immunopharmacol Immunotoxicol, 2019, 41: 172-177.

[27] Thawabteh A, Juma S, Bader M, et al. The biological activity of natural alkaloids against herbivores, cancerous cells and pathogens [J]. Toxins (Basel), 2019, 11: 656.

[28] Zhang LC, Wang Y, Tong LC, et al. Berberine alleviates dextran sodium sulfate-induced colitis by improving intestinal barrier function and reducing inflammation and oxidative stress [J]. Exp Ther Med, 2017, 13: 3374-3382.

[29] Li H, Feng C, Fan C, et al. Intervention of oncostatin M-driven mucosal inflammation by berberine exerts therapeutic property in chronic ulcerative colitis [J]. Cell Death Dis, 2020, 11: 271.

[30] Cui HS, Hayasaka S, Zhang XY, et al. Effect of berberine on barrier function in a human retinal pigment epithelial cell line [J]. Jpn J Ophthalmol, 2007, 51: 64-67.

[31] Zhang DM, Liu HY, Xie L, et al. Effect of baicalin and berberine on transport of nimodipine on primary-cultured, rat brain microvascular endothelial cells [J]. Acta Pharmacol Sin, 2007, 28: 573-578.

[32] Cao M, Wang P, Sun C, et al. Amelioration of IFN-γ and TNF-α-induced intestinal epithelial barrier dysfunction by berberine *via* suppression of MLCK-MLC phosphorylation signaling pathway [J]. PLoS One, 2013, 8: e61944.

[33] Chaintreuil P, Kerreneur E, Bourgoin M, et al. The generation, activation, and polarization of monocyte-derived macrophages in human malignancies [J]. Front Immunol, 2023, 14: 1178337.

[34] Sica A, Mantovani A. Macrophage plasticity and polarization: *In vivo* veritas [J]. J Clin Invest, 2012, 122: 787-795.

[35] Zhang C, Yang M, Ericsson AC. Function of macrophages in disease: Current understanding on molecular mechanisms [J]. Front Immunol, 2021, 12: 620510.

[36] Yu ZC, Cen YX, Wu BH, et al. Berberine prevents stress-induced gut inflammation and visceral hypersensitivity and reduces intestinal motility in rats [J]. World J Gastroenterol, 2019, 25: 3956-3971.

[37] Li D, Yang C, Zhu JZ, et al. Berberine remodels adipose tissue to attenuate metabolic disorders by activating sirtuin 3 [J]. Acta Pharmacol Sin, 2022, 43: 1285-1298.

[38] Mao N, Yu Y, Lu X, et al. Preventive effects of matrine on LPS-induced inflammation in RAW 264.7 cells and intestinal damage in mice through the TLR4/NF-κB/MAPK pathway [J]. Int Immunopharmacol, 2024, 143: 113432.

[39] Wang Y, Peng M, Yang X, et al. Total alkaloids in *Fritillaria cirrhosa* D. Don alleviate OVA-induced allergic asthma by inhibiting M2 macrophage polarization [J]. J Ethnopharmacol, 2025, 337: 118935.

[40] Yang J, Pan Y, Zeng X, et al. Discovery of novel aporphine alkaloid derivative as potent TLR2 antagonist reversing macrophage polarization and neutrophil infiltration against acute inflammation [J]. Acta Pharm Sin B, 2023, 13: 3782-3801.

[41] Rosales C. Neutrophils at the crossroads of innate and adaptive immunity [J]. J Leukoc Biol, 2020, 108: 377-396.

[42] Huang H, Wang M, Guo Z, et al. Rutaecarpine alleviates acute pancreatitis in mice and AR42J cells by suppressing the MAPK and NF-κB signaling pathways *via* calcitonin gene-related peptide [J]. Phytother Res, 2021, 35: 6472-6485.

[43] Jia Y, Shi YX, Gu H, et al. Rutaecarpine targets F-box and WD repeat domain containing 11 to inhibit inflammatory infiltration and alleviate acute pancreatitis [J]. World J Gastroenterol, 2025, 31: 109486.

[44] Li YW, Chen SX, Yang Y, et al. Colchicine inhibits NETs and

alleviates cardiac remodeling after acute myocardial infarction [J]. Cardiovasc Drugs Ther, 2024, 38: 31-41.

[45] Zhang J, Li P, Xu X, et al. Phellodendrine alleviates acute pancreatitis by inhibiting p38 MAPK-p47^{phox} pathway-mediated neutrophil extracellular traps formation and ROS production [J]. Int Immunopharmacol, 2025, 167: 115658.

[46] Qiao Z, Long K, Ding K, et al. Oxysophocarpine inhibits apoptosis of lung epithelial cells to alleviate acute lung injury *via* KIT/PI3K signaling pathway [J]. Drug Des Devel Ther, 2025, 19: 8657-8674.

[47] Luan J, Lu Y, Wang Q, et al. Sanguinarine attenuates *Aspergillus fumigatus* keratitis by exerting antifungal and anti-inflammatory effects [J]. Exp Eye Res, 2026, 262: 110744.

[48] Badillo O, Helfridsson L, Niemi J, et al. Exploring dendritic cell subtypes in cancer immunotherapy: Unraveling the role of mature regulatory dendritic cells [J]. Ups J Med Sci, 2024, 129: e10627.

[49] Zheng C, Wang Y, Xu Y, et al. Berberine inhibits dendritic cells differentiation in DSS-induced colitis by promoting *Bacteroides fragilis* [J]. Int Immunopharmacol, 2021, 101: 108329.

[50] Yang Y, Qi J, Wang Q, et al. Berberine suppresses Th17 and dendritic cell responses [J]. Invest Ophthalmol Vis Sci, 2013, 54: 2516-2522.

[51] Gutcher I, Becher B. APC-derived cytokines and T cell polarization in autoimmune inflammation [J]. J Clin Invest, 2007, 117: 1119-1127.

[52] Hu Z, Jiao Q, Ding J, et al. Berberine induces dendritic cell apoptosis and has therapeutic potential for rheumatoid arthritis [J]. Arthritis Rheum, 2011, 63: 949-959.

[53] Wang JK, Zhao BS, Wang M, et al. Anti-tumor and phenotypic regulation effect of matrine on dendritic cells through regulating TLRs pathway [J]. Chin J Integr Med, 2021, 27: 520-526.

[54] Shen XC, Zhang L. Research progress on the role and mechanism of innate lymphoid cells in inflammatory bowel disease [J]. Zhejiang Med J (浙江医学), 2025, 47: 2224-2230.

[55] Spits H, Artis D, Colonna M, et al. Innate lymphoid cells--a proposal for uniform nomenclature [J]. Nat Rev Immunol, 2013, 13: 145-149.

[56] Kortekaas Krohn I, Shikhagaie MM, Golebski K, et al. Emerging roles of innate lymphoid cells in inflammatory diseases: Clinical implications [J]. Allergy, 2018, 73: 837-850.

[57] Yang Y, Li W, Sun K, et al. Berberine ameliorates dextran sulfate sodium-induced colitis through tuft cells and bitter taste signaling [J]. BMC Biol, 2024, 22: 280.

[58] Tong X, Zhao Y, Fu R, et al. Effects of total alkaloids from *Alstonia scholaris* (L.) R. Br. on ovalbumin-induced asthma mice [J]. J Ethnopharmacol, 2024, 318: 116887.

[59] Zander R, Schauder D, Xin G, et al. CD4$^+$ T cell help is required for the formation of a cytolytic CD8$^+$ T cell subset that protects against chronic infection and cancer [J]. Immunity, 2019, 51: 1028-1042.e4.

[60] Rotteveel FT, Kokkelink I, van Lier RA, et al. Clonal analysis of functionally distinct human CD4$^+$ T cell subsets [J]. J Exp Med, 1988, 168: 1659-1673.

[61] Ma Z, Zhou Y, Gu F, et al. Berberine alleviates T cell-driven lung inflammation by inhibiting cytokine secretion and regulating pulmonary microbiota [J]. Biochem Biophys Res Commun, 2025, 778: 152390.

[62] Niu Y, Dong Q, Li R. Matrine regulates Th1/Th2 cytokine responses in rheumatoid arthritis by attenuating the NF-κB signaling [J]. Cell Biol Int, 2017, 41: 611-621.

[63] Cao G, Yue X, Chi S, et al. Total alkaloids of *Sophora alopecuroides* Linn. attenuates rheumatoid arthritis through regulating follicular helper T cells [J]. J Inflamm Res, 2024, 17: 3587-3602.

[64] Eibel H, Kraus H, Sic H, et al. B cell biology: An overview [J]. Curr Allergy Asthma Rep, 2014, 14: 434.

[65] Raza IGA, Clarke AJ. B cell metabolism and autophagy in autoimmunity [J]. Front Immunol, 2021, 12: 681105.

[66] Mohammadian Haftcheshmeh S, Musavi M, Lotfi S, et al. Berberine as a natural immunomodulator of B lymphocytes [J]. Inflammopharmacology, 2025, 33: 4191-4204.

[67] Zhang T, Ma C, Zhang Z, et al. NF-κB signaling in inflammation and cancer [J]. MedComm, 2021, 2: 618-653.

[68] Begalli F, Bennett J, Capece D, et al. Unlocking the NF-κB conundrum: Embracing complexity to achieve specificity [J]. Biomedicines, 2017, 5: 50.

[69] Capece D, Verzella D, Flati I, et al. NF- κB: Blending metabolism, immunity, and inflammation [J]. Trends Immunol, 2022, 43: 757-775.

[70] Wang K, Yin J, Chen J, et al. Inhibition of inflammation by berberine: Molecular mechanism and network pharmacology analysis [J]. Phytomedicine, 2024, 128: 155258.

[71] Chen J, Huang Y, Bian X, et al. Berberine ameliorates inflammation in acute lung injury *via* NF-κB/NLRP3 signaling pathway [J]. Front Nutr, 2022, 9: 851255.

[72] De Sousa JAC, Azul FVCS, De Araújo AB, et al. Epiisopiloturine, an alkaloid from *Pilocarpus microphyllus*, attenuates LPS-induced neuroinflammation by interfering in the TLR4/NF-κB-MAPK signaling pathway in microglial cells [J]. Oxid Med Cell Longev, 2023, 2023: 4752502.

[73] Cen X, Wang B, Liang Y, et al. Small molecule SMU-CX24 targeting Toll-like receptor 3 counteracts inflammation: A novel approach to atherosclerosis therapy [J]. Acta Pharm Sin B, 2022, 12: 3667-3681.

[74] Cao Z, Liu M, Yang M, et al. Ellipticine derivatives as Toll-like receptor 3 inhibitor for treating acute hepatitis [J]. Eur J Med Chem, 2025, 294: 117762.

[75] Sun H, Ma D, Cheng Y, et al. The JAK-STAT signaling pathway in epilepsy [J]. Curr Neuropharmacol, 2023, 21: 2049-2069.

[76] Hu X, Li J, Fu M, et al. The JAK/STAT signaling pathway: From bench to clinic [J]. Signal Transduct Target Ther, 2021, 6: 402.

[77] Wu Y, Liu Y, Zhang L, et al. *Aconiti lateralis* radix praeparata total alkaloids exert anti-RA effects by regulating NF-*κ*B and JAK/STAT signaling pathways and promoting apoptosis [J]. Front Pharmacol, 2022, 13: 980229.

[78] Ji M, Chen M, Zhang N. Tabersonine inhibits inflammation and apoptosis through the JAK1/STAT3 signaling pathway to alleviate LPS-induced acute lung injury [J]. Sci Rep, 2025, 15: 32764.

[79] Zhao LC, Li J, Liao K, et al. Evodiamine induces apoptosis and inhibits migration of HCT-116 human colorectal cancer cells [J]. Int J Mol Sci, 2015, 16: 27411-27421.

[80] Yang N, Han F, Cui H, et al. Matrine suppresses proliferation and induces apoptosis in human cholangiocarcinoma cells through suppression of JAK2/STAT3 signaling [J]. Pharmacol Rep, 2015, 67: 388-393.

[81] Qin Z, Xie L, Li W, et al. New insights into mechanisms traditional Chinese medicine for allergic rhinitis by regulating inflammatory and oxidative stress pathways [J]. J Asthma Allergy, 2024, 17: 97-112.

[82] Huang G, Shi LZ, Chi H. Regulation of JNK and p38 MAPK in the immune system: Signal integration, propagation and termination [J]. Cytokine, 2009, 48: 161-169.

[83] Zhao B, Hui X, Zeng H, et al. Sophoridine inhibits the tumour growth of non-small lung cancer by inducing macrophages M1 polarisation *via* MAPK-mediated inflammatory pathway [J]. Front Oncol, 2021, 11: 634851.

[84] Patel CH, Powell JD. More TOR: The expanding role of mTOR in regulating immune responses [J]. Immunity, 2025, 58: 1629-1645.

[85] Wang Y, Ding L, Wang Y, et al. Tetrandrine alleviates macrophage activation syndrome after CAR-T cell therapy [J]. Phytomedicine, 2025, 139: 156483.

[86] Chen Q, Duan X, Fan H, et al. Oxymatrine protects against DSS-induced colitis *via* inhibiting the PI3K/Akt signaling pathway [J]. Int Immunopharmacol, 2017, 53: 149-157.

[87] Gao Q, Peng J, Xiong M, et al. Sinomenine alleviates experimental autoimmune uveitis in rats: Possible involvement of PI3K/Akt and NF-*κ*B signaling pathways [J]. Eur J Pharmacol, 2025, 996: 177571.

[88] Han Y, Guo S, Li Y, et al. Berberine ameliorate inflammation and apoptosis *via* modulating PI3K/Akt/NF*κ*B and MAPK pathway on dry eye [J]. Phytomedicine, 2023, 121: 155081.

[89] Niu H, Zhang Y, Wu B, et al. Matrine induces the apoptosis of lung cancer cells through downregulation of inhibitor of apoptosis proteins and the Akt signaling pathway [J]. Oncol Rep, 2014, 32: 1087-1093.

[90] Montaño LM, Sommer B, Gomez-Verjan JC, et al. Theophylline: Old drug in a new light, application in COVID-19 through computational studies [J]. Int J Mol Sci, 2022, 23: 4167.

[91] Wang CZ, Li SW, Du MM, et al. Research progress on regulation of AMPK signaling pathway by traditional Chinese medicine in treatment of rheumatoid arthritis [J]. Drug Eval Res (药物评价研究), 2025, 48: 2989-3002.

[92] Jiao HY, Liu Y, Xue X, et al. Isosteroidal alkaloids from *Fritillariae pallidiflorae* Bulbus inhibit airway inflammation and remodeling by modulating Wnt/*β*-catenin signal pathway in asthma rats [J]. Mod Tradit Chin Med Mater Med-World Sci Technol (世界科学技术−中医药现代化), 2020, 22: 1871-1876.

[93] Zheng JH, Song YY, Zhang TC, et al. Effect and mechanism of alkaloids from portulacae herba on ulcerative colitis in mice based on TLR4/MyD88/NF-*κ*B signaling pathway [J]. China J Chin Mater Med (中国中药杂志), 2025, 50: 874-881.

[94] Wang Q, Cui Y, Wu X, et al. Evodiamine protects against airway remodelling and inflammation in asthmatic rats by modulating the HMGB1/NF-*κ*B/TLR-4 signalling pathway [J]. Pharm Biol, 2021, 59: 192-199.

[95] Wang HL, Zhan JP, Miao XY, et al. The immunomodulatory effect of berbamine on mice with systemic lupus erythematosus [J]. Acta Physiol Sin (生理学报), 2025, 77: 432-440.

[96] Li X, Wang M, Hong H, et al. Sophocarpine attenuates murine lupus nephritis *via* inhibiting NLRP3 inflammasome and NF-*κ*B activation [J]. Immunol Res, 2018, 66: 521-527.

[97] Li X, Gu L, Yang L, et al. Aconitine: A potential novel treatment for systemic lupus erythematosus [J]. J Pharmacol Sci, 2017, 133: 115-121.

[98] Yan Y, Zhang Z, Chen Y, et al. Coptisine alleviates pristane-induced lupus-like disease and associated kidney and cardiovascular complications in mice [J]. Front Pharmacol, 2020, 11: 929.

[99] Huang Y, Peng Y, Li H, et al. Wilforine inhibits rheumatoid arthritis pathology through the Wnt11/*β*-catenin signaling pathway axis [J]. Arthritis Res Ther, 2023, 25: 243.

[100] Sun DF, Niu ZZ, Zhang SY, et al. Effect and mechanism of total alkaloids from *Strychnos nux-vomica* on rheumatoid arthritis rats based on PI3K/Akt/mTOR pathway [J]. Mod Chin Med (中国现代中药), 2023, 25: 2521-2527.

[101] Tong B, Yu J, Wang T, et al. Sinomenine suppresses collagen-induced arthritis by reciprocal modulation of regulatory T cells and Th17 cells in gut-associated lymphoid tissues [J]. Mol Immunol, 2015, 65: 94-103.

[102] Yu KQ, Zhao Y, Li J. Effect of sinomenine on the expression of CD80 mRNA and CD86 mRNA in dendritic cells in rheumatoid arthritis [J]. China Pharm (中国药房), 2006, 17: 331-333.

[103] Jeong HW, Hsu KC, Lee JW, et al. Berberine suppresses proinflammatory responses through AMPK activation in macrophages [J]. Am J Physiol Endocrinol Metab, 2009, 296: E955-E964.

[104] Liu TT, Xiao ZB, Chen Q, et al. Systematic study on molecular mechanism of aconitum alkaloid in treatment of rheumatoid

arthritis [J]. Chin J Exp Tradit Med Formulae (中国实验方剂学杂志), 2021, 27: 171-181.

[105] Jin C, Yu SX, Zhao F, et al. Anti-ulcerative colitis effects and the mechanisms of total alkaloids extracted from processed *Aconitum carmichaelii* Debx [J]. Chin Pharm J (中国药学杂志), 2024, 59: 1573-1580.

[106] Zhang Z, Liu Q, Zang H, et al. Oxymatrine protects against *L*-arginine-induced acute pancreatitis and intestine injury involving Th1/Th17 cytokines and MAPK/NF-*κ*B signaling [J]. Pharm Biol, 2019, 57: 595-603.

[107] Chen J, Chen J, Wang X, et al. Ligustrazine alleviates acute pancreatitis by accelerating acinar cell apoptosis at early phase *via* the suppression of p38 and Erk MAPK pathways [J]. Biomed Pharmacother, 2016, 82: 1-7.

[108] Choi SB, Bae GS, Jo IJ, et al. Berberine inhibits inflammatory mediators and attenuates acute pancreatitis through deactivation of JNK signaling pathways [J]. Mol Immunol, 2016, 74: 27-38.

[109] Hu YL, Feng C, Liu KQ, et al. Effects of colchicine on acute pancreatitis in rat models and the underlying mechanisms [J]. China J Mod Med (中国现代医学杂志), 2023, 33: 6-10.

[110] Zhang H, Li YY, Wu XZ. Effect of tetrandrine on LPS-induced NF-kappaB activation in isolated pancreatic acinar cells of rat [J]. World J Gastroenterol, 2006, 12: 4232-4236.

[111] He J, Feng X, Liu Y, et al. Graveoline attenuates *D*-GalN/LPS-induced acute liver injury *via* inhibition of JAK1/STAT3 signaling pathway [J]. Biomed Pharmacother, 2024, 177: 117163.

[112] Ma XN, Yang SQ, Zhang JC, et al. Research progress on pharmacological action of Kushen (Sophorae Flavescentis Radix) [J]. J Liaoning Univ Tradit Chin Med (辽宁中医药大学学报), 2023, 25: 152-156.

[113] Kuo CY, Huang WC, Liou CJ, et al. Tomatidine attenuates airway hyperresponsiveness and inflammation by suppressing Th2 cytokines in a mouse model of asthma [J]. Mediators Inflamm, 2017, 2017: 5261803.

[114] Ji NF, Xie YC, Zhang MS, et al. Ligustrazine corrects Th1/Th2 and Treg/Th17 imbalance in a mouse asthma model [J]. Int Immunopharmacol, 2014, 21: 76-81.

[115] Wang SC, Li Q, Cai XY, et al. Effect and mechanism of tetrandrine on airway remodeling in bronchial asthma mice [J]. Tianjin Med J (天津医药), 2023, 51: 943-948.