雷公藤甲素纳米载药系统及其抗类风湿性关节炎作用机制研究进展

安凯丽[1], 李扬博[2], 张 茹[3], 杨 卉[1*]

(1. 中国中医科学院广安门医院免疫学研究室, 北京 100053; 2. 广州中医药大学第三临床医学院, 广东 广州 510006; 3. 石河子大学第一附属医院, 新疆 石河子 832008)

摘要: 雷公藤甲素 (triptolide, TP) 是一种来源于雷公藤的活性成分, 具有显著的抗类风湿性关节炎 (rheumatoid arthritis, RA) 作用。研究表明, TP通过抑制多种炎症因子 (如TNF-α、IL-1β、IL-6等) 的表达, 发挥强效的抗炎和抗氧化作用。在免疫调节方面, TP可以通过调节T细胞和中性粒细胞等免疫细胞的活性, 抑制炎症进展并减少组织损伤。此外, TP还能够通过调节NF-κB、JAK/STAT和MAPK等多条信号通路, 抑制RA中关节滑膜细胞的增殖与侵袭, 减轻关节损伤。然而, 雷公藤甲素也存在水溶性低、有毒性等缺点, 这些问题亟待解决。近年来, 随着纳米技术的发展, TP纳米载药系统的研究逐渐兴起。聚合物纳米粒、外泌体、无机纳米载药系统等新型纳米载体的开发, 大大改善了雷公藤甲素的治疗效果。例如, 对包裹雷公藤甲素的纳米材料表面进行修饰, 可以增强其在RA炎症部位的靶向释放能力, 实现精准递送。同时, 纳米载药系统还能够延长TP的体内循环时间, 减少毒性反应, 有效改善RA的治疗效果。综上所述, TP及其纳米载药系统在RA治疗中的应用前景广阔, 未来研究应继续探索其机制和临床应用, 为类风湿性关节炎的治疗提供新的思路。

关键词: 雷公藤甲素; 类风湿性关节炎; 纳米载药系统; 作用机制; 信号通路; 靶向递送

中图分类号: R943 **文献标识码**: A **文章编号**: 0513-4870(2025)09-2740-12

Triptolide in rheumatoid arthritis therapy: mechanistic breakthroughs and nano drug delivery advancements

AN Kai-li[1], LI Yang-bo[2], ZHANG Ru[3], YANG Hui[1*]

(*1. Immunology Laboratory of Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing 100053, China; 2. The Third Clinical Medical College of Guangzhou University of Chinese Medicine, Guangzhou 510006, China; 3. The First Affiliated Hospital of Shihezi University, Shihezi 832008, China*)

Abstract: *Tripterygium wilfordii* Hook F (TWHF), specifically triptolide (TP), is an active compound derived from the plant with significant anti-rheumatoid arthritis (RA) effects. Studies show that TP exerts potent anti-inflammatory and antioxidant properties by inhibiting the expression of several inflammatory cytokines, such as TNF-α, IL-1β, and IL-6. In terms of immune regulation, TP modulates the activity of immune cells like T cells and neutrophils, reducing inflammation and tissue damage. Additionally, TP can regulate multiple signaling pathways, including NF-κB, JAK/STAT, and MAPK, to suppress the proliferation and invasion of synovial cells in RA, thereby mitigating joint damage. With the advancement of nanotechnology, the development of TP-based nanomedicine has gained attention in recent years. Innovative nanocarriers, such as polymer nanoparticles, exosomes, and inorganic nanoparticle drug delivery systems, have significantly improved TP's bioavailability and targeting capabilities while reducing its toxicity. By modifying the surface of these nanomaterials, their ability to target and release TP at inflammation sites is enhanced, leading to more precise drug delivery. Moreover, nanomedicines extend TP's

收稿日期: 2025-05-16; 修回日期: 2025-06-27.

基金项目: 中国中医科学院创新工程重大攻关项目 (CI2021A04306); 北京市自然科学基金面上项目 (7222315).

*通讯作者 E-mail: yanghui1517@163.com

DOI: 10.16438/j.0513-4870.2025-0559

circulation time in the body and reduce early-stage toxicity, thus improving the therapeutic outcomes for RA. In conclusion, TP and its nanomedicine formulations show great promise in RA treatment. Future research should continue to explore their mechanisms and clinical applications, offering new perspectives for the treatment of rheumatoid arthritis.

Key words: triptolide; rheumatoid arthritis; nano drug delivery system; mechanism; signaling pathway; targeted delivery

类风湿性关节炎 (rheumatoid arthritis, RA) 是一种慢性、系统性的自身免疫性疾病, 主要累及关节滑膜, 导致关节的炎症、疼痛及破坏。尽管现有的治疗手段 (如非甾体抗炎药、糖皮质激素及生物制剂等) 能够缓解症状并减缓病情进展, 但仍无法彻底治愈RA, 且长期使用这些药物常伴随严重的不良反应[1]。因此, 开发安全且有效的新型治疗手段显得尤为迫切。在此背景下, 雷公藤甲素 (triptolide, TP) 作为一种从中药雷公藤 (*Tripterygium wilfordii* Hook F, TWHF) 中提取的天然化合物, 凭借其显著的抗肿瘤、免疫抑制及抗风湿作用, 逐渐引起了科研界的广泛关注[2]。雷公藤甲素的多重生物学活性已经被广泛研究, 尤其在类风湿性关节炎的治疗中表现出显著的疗效[3]。大量研究表明, TP能够通过多条信号通路调控类风湿性关节炎的发病机制, 包括抑制炎症因子的产生、调节免疫反应以及抑制滑膜细胞的增殖和侵袭等[4]。此外, TP还能够通过调控氧化应激和自噬等细胞过程, 进一步缓解类风湿性关节炎的症状[5]。然而, 尽管雷公藤甲素具有良好的治疗潜力, 但其在实际应用中仍面临一些挑战。首先, TP的水溶性差且在体内的生物利用度低, 导致其治疗效果受到限制[6]; 其次, TP具有较强的毒性, 尤其对肝脏、肾脏和生殖系统有明显的不良作用[7]。因此, 如何提高TP的治疗效果并减少其毒副作用成为了一个亟待解决的问题。

近年来, 随着纳米技术的快速发展, 纳米载药系统逐渐成为解决上述问题的重要手段。通过将TP加载到各种纳米载体中, 可以显著提高其溶解性和生物利用度, 同时减少药物在体内的非特异性分布, 从而降低其毒副作用[8]。纳米技术不仅能够实现药物的靶向递送, 还可以通过调控药物的释放速率, 延长药物的体内循环时间, 进一步增强TP的治疗效果[9]。例如, 聚合物纳米粒、外泌体、无机纳米载体等多种纳米递送系统已经被用于TWHF的递送研究, 显示出良好的前景。通过这些载体, TP的体内分布和药代动力学特性得到了极大改善, 显著提高了其治疗效果并减少了毒副作用[10]。雷公藤甲素及其纳米载药系统在类风湿性关节炎的治疗中展现出了巨大的潜力, 具有抗炎、免疫调节及抗氧化等多重作用, 为提高TP的治疗效果、降低毒副作用提供了新的策略。未来的研究应进一步探索TP纳米载药系统在临床应用中的安全性和有效性, 并继续开发更高效的纳米载药系统, 以期为类风湿性关节炎的治疗带来新的突破。本综述不仅为RA的靶向治疗提供新思路, 也为其他自身免疫性疾病的纳米药物研发提供技术参考, 具有重要的理论价值与应用前景。

1 雷公藤抗RA作用机制

1.1 炎症与氧化应激

在RA的发病机制中, 炎症细胞因子如TNF-α、IL-1β和IL-6等发挥着关键作用, 可诱导滑膜组织的炎症反应[6] (图1)。而研究发现, 雷公藤甲素能够有效抑制这些炎症细胞因子的产生, 有效缓解RA病变关节的炎症[5]。此外, 核因子-κB (nuclear factor kappa-B, NF-κB) 是调控炎症反应的关键转录因子, 其下游的靶标促炎细胞因子TNF-α等介导炎症反应[11]。TP、雷公藤红素 (celastrol, CEL) 和雷公藤内酯甲等可以通过抑制p56亚基, 下调TNF和IFN等炎症因子的表达来发挥抗炎作用[4]。RA患者活性氧 (reactive oxygen species, ROS) 产生、脂质过氧化、蛋白质氧化和DNA损伤增加, 导致抗氧化防御系统的活性降低, 最终导致氧化应激[12]。氧化应激可促进炎性细胞因子的产生, 导致RA中炎症的产生。在抗氧化方面, 雷公藤多苷可以上调超氧化物歧化酶和谷胱甘肽过氧化物酶的水平, 从而诱导ROS和活性氮物质的清除, 减少氧化应激和炎症[13]。此外, 雷公藤通过抑制核苷酸结合寡聚化结构域 (nucleotide-binding oligomerization domain, NOD) 样受体热蛋白结构域相关蛋白3 (NOD-like receptor family pyrin domain containing 3, NLRP3) 炎性小体的激活, 进而抑制IL-1β和IL-18的释放[14]。而进一步的研究表明, CEL可以通过抑制ROS-NF-κB-NLRP3轴来调节炎症与氧化应激, 缓解RA症状[15]。

1.2 免疫调节

RA作为一种常见的自身免疫性疾病, 涉及多种免疫细胞和分子的异常活动[16]。在先天性免疫中, TP可以抑制活化的中性粒细胞中细胞因子和趋化因子的表达和分泌[17]。此外, RA患者关节中存在的胞外瓜氨酸

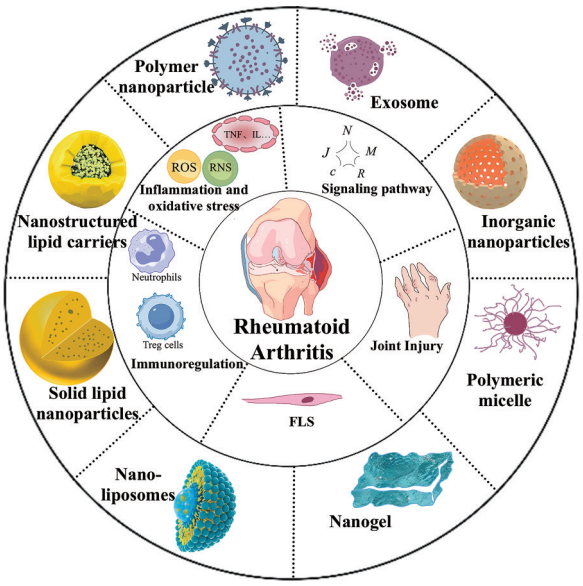


Figure 1 Triptolide nano drug delivery system and its mechanism of anti-rheumatoid arthritis. FLS: Fibroblast-like synoviocytes; ROS: Reactive oxygen species; RNS: Reactive nitrogen species; TNF: Tumor necrosis factor; IL: Interleukin

自身抗原主要来源于中性粒细胞胞外陷阱 (neutrophil extracellular traps, NETs) 升高[18]。中性粒细胞作为先天免疫系统的重要组成部分, 可以分泌细胞因子和释放NETs, 在协调RA的进展中发挥积极作用[19]。Huang等[20]发现, TP通过诱导中性粒细胞凋亡和减少中性粒细胞浸润, 以及抑制中性粒细胞自噬和NETs形成来改善佐剂性关节炎 (adjuvant-induced arthritis, AIA) 小鼠的关节炎。此外, 适应性免疫在RA的发病机制中起着核心作用。调节性T细胞 (Treg细胞) 在自身免疫性疾病中很常见, 表观遗传稳定性不稳定。当受到各种细胞因子的刺激时, Treg细胞可能转化为致病性Th17细胞, 而信号转导和转录激活因子3 (signal transducer and activator of transcription 3, STAT3) 是参与Th17发育的信号分子中细胞因子激活的关键调节因子[21]。Wang等[22]发现, TP通过下调IL-6诱导的信号转导和STAT3磷酸化来抑制Th17分化和IL-17表达。Xu等[23]发现, Treg细胞可以减少破骨细胞分化和骨吸收, 而TP治疗可以通过增加IL-10和转化生长因子-β1 (TGF-β1) 的分泌来增强Treg细胞的抑制作用。

1.3 成纤维样滑膜细胞的异常增殖

成纤维样滑膜细胞 (fibroblast-like synoviocytes, FLS) 作为关节滑膜中的主要细胞类型, 在RA的病理过程中, 表现出异常的增殖和活化[24]。关节的慢性炎症导致FLS的异常增殖, 从而导致DNA甲基化、组蛋白修饰异常, 激活致病基因 (如基质降解酶、趋化因子), 使其获得表观遗传印记, 即使炎症消退仍持续活化; 而FLS的持续活化, 导致黏附分子和基质降解酶过度表达, 使其突破基底膜侵入软骨和骨[25]。Piao等[26]观察到, TP显著抑制了FLS的侵袭和迁移, 并降低了基质降解酶的活化, 从而缓解了胶原诱导的关节炎 (collagen-induced arthritis, CIA) 大鼠模型的关节炎症状和骨破坏。Xie等[27]证明, TP通过抑制自噬, 从而抑制滑膜细胞流动性并维持氧化还原平衡。

1.4 关节损伤

RA关节损伤的表现多样, 如关节畸形、肿痛和晨僵等。雷公藤可以显著降低血管通透性和血管生成, 缓解大鼠的爪肿胀[28]。此外, TP可以抑制巨噬细胞释放趋化因子, 从而减少对滑膜细胞和软骨细胞的影响, 抑制滑膜细胞的异常增殖[29]。另外, 炎症性关节的骨破坏是由破骨细胞的激活引起的, 破骨细胞具有骨吸收功能, 可分泌盐酸溶解骨矿物质, 并释放蛋白酶 (如组织蛋白酶K) 降解骨基质胶原。RA患者破骨细胞吸收骨的速度远超成骨细胞修复能力, 这将导致进行性关节变形。RA患者关节的骨−软骨交界处 (常被称为“血管翳−骨界面”) 存在大量活化破骨细胞, 形成骨侵蚀灶, 表现为虫噬样缺损[30]。Liu等[31]发现, TP处理显著减少了破骨细胞数量, 抑制了骨破坏区域的破骨细胞形成, 且具有剂量依赖性趋势。

1.5 相关信号通路的调节

TP可通过NF-κB、JAK/STAT、MAPK、cGAS-STING及RANKL/RANK/OPG等多条信号通路调节RA病变关节, 本文列举了以下具有代表性的信号通路, 并阐述其作用机制 (图2)。

1.5.1 NF-κB NF-κB是RA炎症、增生和关节破坏的关键调节因子, 其异常活化与RA中的滑膜炎症增生及其对关节局部组织的侵蚀密切相关[32]。NF-κB含有调节炎症和免疫反应的Rel结构域蛋白, 这些蛋白被一组抑制蛋白 (如IκBα) 保留在细胞质中。随着NF-κB激活, IκBα磷酸化后被蛋白酶体泛素化并破坏。这个过程将NF-κB释放到细胞核中, 从而激活与RA相关的基因, 影响着RA的发病过程[33]。TP可以阻止NF-κB从细胞质转移到细胞核, 抑制NF-κB与DNA的结合, 从而减少炎症因子的基因转录和蛋白表达。这种抑制作用有助于减轻RA患者的关节炎症和疼痛, 减缓疾病进展[34]。此外, Song等[35]基于网络药理学和分子对接, 预测了TP治疗RA的候选蛋白靶点。他们发现TP可以抑制炎症细胞因子通路, 如NF-κB、RANKL/RANK/OPG及血管内皮生长因子 (vascular endothelial growth factor, VEGF) 等。这些重叠的通路涉及Th1和Th2细胞、巨噬细胞、成纤维细胞和内皮细胞的激活, 在类风湿关节炎中发挥着重要的作用。

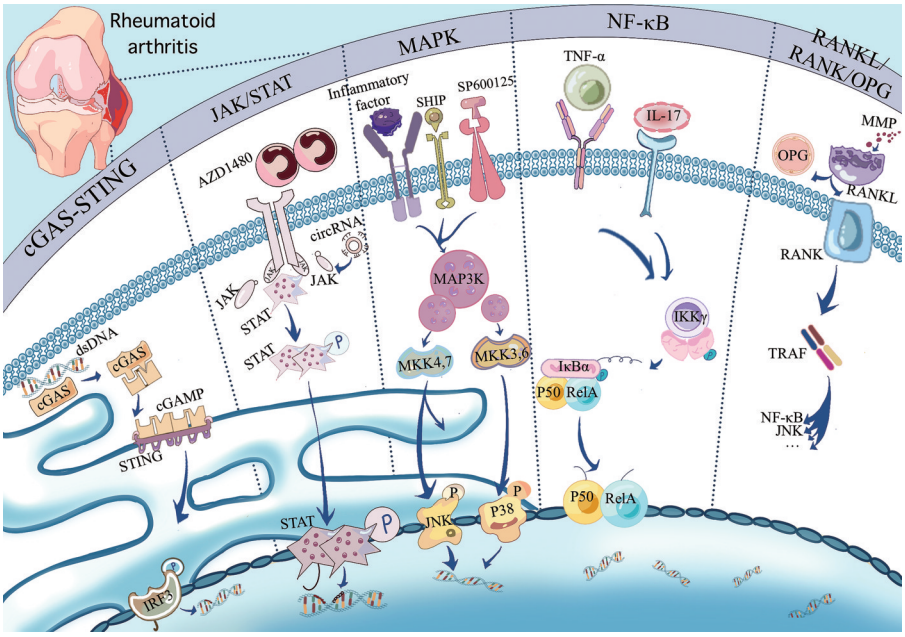


Figure 2 Five signaling pathways regulated by triptolide (TP) in rheumatoid arthritis (RA) diseased joints. dsDNA: Double-stranded DNA; cGAS: Cyclic GMP-AMP synthase; STING: Stimulator of interferon genes; cGAMP: Cyclic GMP-AMP; IRF3 : Interferon regulatory factor 3; JAK: Janus kinase; STAT: Signal transducer and activator of transcription; circRNA: Circular RNA; IKK*γ*: Inhibitor of nuclear factor kappa-B kinase subunit gamma; I*κ*B*α*: Inhibitor of kappa light polypeptide gene enhancer in B-cells; p50: Nuclear factor kappa B subunit 1; RelA: V-rel avian reticuloendotheliosis viral oncogene homolog A; RANKL: Receptor activator of nuclear factor kappa-B ligand; RANK: Receptor activator of nuclear factor kappa-B; OPG: Osteoprotegerin; MMP: Matrix metalloproteinase; TRAF: TNF receptor-associated factor; JNK: C-Jun N-terminal kinase

Xiao 等[36]发现 RA 大鼠口服 TP 可降低软骨细胞因子 TNF-*α*、IL-6、COX-2 等的水平, 而这些细胞因子的炎症作用依赖于 NF-*κ*B 信号通路。此外, IL-17A 通过与 IL-17RA 受体复合物结合, 募集信号接头 Act1, 激活 IKK 复合物, 并诱导 NF-*κ*B 信号通路。Zhang 等[32]发现 TP 和姜黄素可以通过 IL-17/NF-*κ*B 信号通路, 对细胞增殖和凋亡产生协同作用。

1.5.2 JAK/STAT JAK/STAT 信号在调节免疫和炎症反应中起着重要作用, 其可分为 3 个组成部分: 受体相关酪氨酸激酶、JAK 酪氨酸激酶和 STAT 转录因子。JAK 激酶通过受体结合激活 JAK, 导致 STAT 磷酸化。STAT3 表达升高会抑制程序性细胞死亡诱导的抗凋亡分子的表达, 阻断 RA-FLS 的凋亡, 导致 RA 滑膜增厚[37]。circRNAs 是一类新型的 RNA, Wang 等[38]通过高通量测序及 GO 分析研究, 认为 circRNA 0003353 是参与 RA 炎症反应的关键。通过实验观察发现, TP 可通过 circRNA 0003353 抑制 p-JAK2、p-STAT3 表达, 降低 p-JAK2/JAK2、p-STAT3/STAT3 比值。此外, Lin 等[39]利用 JAK2 抑制剂/STAT3 激活阻滞剂 AZD1480 治疗 FLS。实验结果显示, AZD1480 会抑制 p-JAK2、JAK2、p-STAT3 和 STAT3 的表达水平以及 FLS 的增殖。这表明 TP 可以通过抑制 JAK2/STAT3 信号通路, 抑制炎性细胞因子表达和 FLS 增殖。

1.5.3 MAPK 丝裂原活化蛋白激酶信号通路 (mitogen-activated protein kinase, MAPK) 在调节 RA 进行性关节破坏中起关键作用, 其包括多个分支, 如 p38 MAPK、JNK 和 ERK 等。p38 MAPK 主要由胞外应激因子调节, 可以调节滑膜侵袭和炎症细胞因子分泌; JNK 通路及其下游蛋白可以调节 RA FLSs 的侵袭和胶原酶的生成, 影响 RA 骨侵蚀的发展[40]。Wan 等[41]采用随机游走模型和网络药理学方法, 探讨了 TWHF 在 RA 中的分子靶点和作用机制, 并进行临床观察和关节炎动物模型实验。结果证实 TP 可下调巨噬细胞 M1 分泌因子的表达, 抑制 p38 MAPK 等炎症信号通路的过度激活, 从而改善 RA 关节炎症, 固定免疫失衡。Wang 等[42]研究发现, TP 刺激诱导 SHIP 负调节因子相关磷酸化的增强, 而 SHIP 通过催化或非催化激活来调节 MAPK 通路中 P38 磷酸化。Yang 等[40]观察了 TP 对 RA FLSs 侵袭行为的影响, 发现 JNK 特异性抑制剂 SP600125 可以减少 RA FLSs 的迁移和侵袭, 并且证明 TP 阻断了 JNK MAPK 的激活, 阻止了 JNK 通路的磷酸化。

1.5.4 cGAS-STING 环 GMP-AMP 合成酶刺激干扰素基因信号通路 (the cyclic GMP-AMP synthase

stimulates the interferon gene, cGAS-STING) 是一种DNA感应机制, 负责识别和响应细胞内基因组、线粒体和微生物来源的双链DNA (double-stranded DNA, dsDNA)。在RA中, 细胞损伤、感染或自身免疫反应等导致DNA从细胞核泄漏到细胞质, 激活了cGAS-STING通路[43]。进而, cGAS-STING信号通路通过引起I型IFN反应, 加速抗瓜氨酸化蛋白抗体的形成、促进M1型巨噬细胞极化以及成纤维细胞样滑膜细胞增殖, 从而参与RA的发生和发展[44]。Xu等[45]发现, TP可以抑制FLS细胞炎症因子释放, 并且显著降低FLS细胞中cGAS和STING蛋白表达水平, 其作用机制与阻断cGAS-STING信号通路有关。此外, Xu等[46]开发了能够抑制cGAS-STING通路的M1巨噬细胞靶向胶束FDL@TP。在M1巨噬细胞中, 释放的TP具有抗炎和免疫抑制剂的作用, 可明显下调cGAS和STING蛋白的表达, 从而降低TNF-α、IL-1β和IL-6的分泌。

1.5.5 RANKL/RANK/OPG 炎症性关节的骨破坏是RA最典型的特征, 这是由破骨细胞的激活引起的[47]。而破骨细胞主要位于滑膜炎症组织, 是骨吸收的主要细胞。破骨细胞介导的骨吸收受核因子-κB (receptor activator of nuclear factor kappa-B, RANK)、配体受体激活剂 (receptor activator of nuclear factor kappa-B ligand, RANKL) 和骨保护素 (osteoprotegerin, OPG) 的调节[48]。RANKL与RANK结合时, 可刺激破骨细胞形成和分化, OPG可通过与RANKL竞争RANK来阻止骨吸收, 以此确保骨形成与骨吸收之间的动态平衡。Liu等[31]发现, TP显著下调了CIA小鼠RANKL和RANK的表达, 并上调了OPG的表达, 从而抑制了骨破坏区域的破骨细胞形成。此外, 基质金属蛋白酶 (matrix metalloproteinase, MMP) 是参与软骨细胞外基质侵袭和降解的主要蛋白酶, 在RA患者的滑液中显著过表达。在MMP的执行下, RANKL蛋白水解生成sRANKL, 而sRANKL主要通过促进破骨细胞的生成和激活来影响骨吸收, 影响RA关节炎症和滑膜增生等病理过程[49,50]。Lin等[51]证明, TP通过降低FLS和巨噬细胞中IL-1、IL-6和前列腺素E2等的表达水平, 抑制炎症关节中MMPs的表达, 从而抑制破骨细胞的生成。

2 雷公藤纳米载药系统

2.1 聚合物纳米粒

聚合物纳米粒 (polymer nanoparticle, PNP) 是指由天然或合成的聚合物材料制备的纳米级颗粒, 具有靶向性高、药物载量高和稳定性好等特点[52]。在进入体内时, 为了避免会被网状内皮系统和吞噬细胞识别清除, 同时进一步提高药物递送的精准性和时效性, 常常需要对PNP进行功能化改造, 常见的改造策略有表面修饰、核−壳结构设计和刺激响应性设计[53]。其中, 表面修饰 (如PEG隐形修饰、靶向配体共价嫁接) 可优化药代动力学; 核−壳结构设计则通过两亲性自组装实现疏水药物增溶与缓释; 而刺激响应性PNP可以对不同外界刺激 (如pH值、温度、ROS和光等) 做出相应的响应, 从而实现聚合物纳米粒的控释作用[54]。

2.1.1 经表面修饰的PNP PNP常应用广泛的天然或合成的聚合物材料进行表面修饰, 如壳聚糖、聚乳酸 (polylactic acid, PLA) 和白蛋白等。Zhang等[55]通过将雷公藤甲素与羧甲基壳聚糖 (carboxymethyl chitosan, CMCS) 偶联, 制备了TP递送的新平台 (TP-CMCS)。CMCS是一种化学改性的壳聚糖, 带弱负电荷的链, 可以避免不良的细胞毒性, 并阻止巨噬细胞和网状内皮系统对TP的摄取。其可降解性、生物相容性、低毒性和成本合理的特点, 大大地缓解TP诱导的细胞抑制和细胞凋亡, 抑制滑膜炎及骨组织侵蚀。此外, PLA具有良好的生物相容性和可生物降解性, 被美国食品药品监督管理局 (Food and Drug Administration, FDA) 批准用于临床, 是制备聚合物纳米载药系统的重要材料。Liu等[56]设计了一种负载TP的PLA纳米颗粒 (TP-PLA-NPs), 用于灌胃治疗佐剂性关节炎大鼠的抗炎作用。结果表明, TP-PLA-NPs对佐剂性关节炎有明显的抗炎作用; 并且随着给药时间的延长, TP在PLA纳米颗粒中的体外释放曲线显示出双相释放模式, 即最初的爆发性释放和随后的缓慢释放。

2.1.2 核−壳结构PNP 聚γ-谷氨酸 (poly-γ-glutamic acid, γ-PGA) 是一种具有高度亲水性的多肽聚合物, 具有良好的生物相容性和可生物降解性, 能够在体内被完全降解为氨基酸, 减少了对组织的刺激和潜在毒性[57]。由于γ-PGA的亲水性和高分子质量, 它能够在纳米颗粒表面形成一层保护壳, 进而内包疏水性的壳。以此形成的核−壳结构, 大大提高了纳米材料的药物包封效率。Zhang等[58]采用γ-PGA接枝天冬氨酸二叔丁基盐酸, 设计了一种新型的负载TP纳米颗粒 (poly-γ-glutamic acid-grafted di-*tert*-butyl *L*-aspartate hydrochloride with TP, PAT)。天冬氨酸二叔丁基盐酸与PGA通过酰胺化反应形成了具有疏水性侧链的PGA共聚物, 这种疏水结构结合使亲水性的PGA能够包裹疏水性的TP, 展现出优异的控释性能, 能够在体内缓慢释放TP, 减少早期毒性反应, 同时有效缓解了软骨侵蚀和骨质破坏等炎症关节症状。此外, Zhang等[59]设计了一种以γ-PGA接枝的苯丙氨酸乙酯共聚物 (*L*-phenylalanine ethylester, *L*-PAE) 负载TP的纳米药物载体 [γ-PGA-*L*-PAE-TP (PPT)]。*L*-PAE作为疏水性部分,

与PGA的亲水性部分结合形成两亲性纳米颗粒, 用于包裹疏水性药物如TP, 也表现出可控的药物释放行为。并且, PPT显著降低了TP引起的细胞毒性和氧化应激反应, 具有良好生物相容性、缓释特性和pH响应性。

2.1.3 刺激响应性PNP 刺激响应性PNP能够在炎症部位的特定环境下释放药物, 实现精准的药物释放[60]。RA患者的炎症关节pH值约为6.0, 这个酸性微环境, 适合开发顺应从血液循环到局部炎症关节组织的pH梯度的纳米药物。Li等[61]研究设计了一种基于透明质酸 (hyaluronic acid, HA) 和季铵化聚β-氨基酯的pH敏感纳米多电解质复合材料, 用于靶向巨噬细胞并递送雷公藤甲素。该复合物利用pH刺激引发药物在酸性环境中的释放, 促进溶酶体逃逸, 增强细胞内化和抗炎效果。该系统不仅延长了药物的体内循环时间, 还显著缓解了实验性关节炎模型中的炎症反应和软骨损伤, 同时减少了雷公藤甲素的系统性不良反应。Liu等[62]设计了一种将TP封装在星形两亲嵌段共聚物中的纳米材料 (polyhedral oligomeric silsesquioxane-polycaprolactone-pH-responsive poly methylaminoethyl methacrylate, POSS-PCL-b-PDMAEMA), 该材料在弱酸性环境下能够触发药物释放, 靶向RA炎症关节, 具有显著的抗炎和软骨保护效果, 并有效延长了药物在体内的循环时间。Li等[63]利用半乳糖 (galactose, GDR) 设计了一种纳米颗粒 (GDR-triptolide, GDR-TPT)。GDR-TPT以巨噬细胞为靶点, 通过pH敏感腙键将全反式视黄醛缀合成葡聚糖骨架。然后将葡聚糖骨架与GDR接枝, 并将TP包封其中。通过GDR与巨噬细胞特异性受体结合, 主动靶向炎症部位, 并在酸性环境下释放药物, 实现药物的靶向递送。GDR-TPT能够有效减少炎症部位的T细胞和巨噬细胞浸润, 抑制炎症因子TNF-α、IL-6和IL-1β的表达。此外, 温度响应性纳米材料也常用于聚合物纳米材料中, 可以在特定温度下发生的可逆相转变或形态变化。Li等[64]设计了新型的一种具有抗炎、软骨保护、光热化疗和体内成像特性的温度响应性纳米材料 (TP-*DL*-lactic-*co*-glycolic acid-Au@arginine-glycine-aspartic acid/hyaluronic acid, TP-PLGA-Au@RGD/HA)。其中, HA用于模拟软骨的药物释放特性, 近红外共振作用下的金纳米颗粒产生局部热量, 促进TP从纳米颗粒中释放。TP-PLGA-Au@RGD/HA可有效改善胶原性关节炎小鼠的炎症症状, 并通过抑制雷帕霉素哺乳动物靶蛋白 (mammalian target of rapamycin, mTOR) 及其底物p70S6K1的磷酸化, 显著降低RA成纤维样滑膜细胞的迁移和侵袭能力。

2.2 外泌体

合成纳米颗粒的高费用和复杂的制造过程导致纳米材料价格过高, 阻碍了其广泛用于临床。外泌体 (exosome, EXO) 是由细胞天然分泌到细胞外环境的膜结合小泡, 具有跨越生物屏障的能力和很高的生物相容性[65]。将药物直接装载到EXO中制成纳米材料, 可以降低制备成本, 并且大大提高药物的稳定性和靶向性[66]。Jiang等[67]从人RA成纤维细胞 (human RA fibroblasts, hRAF) 中分离外泌体 (hRAF-Exo), 并将其装载TP以生成工程外泌体 (hRAF-Exo@TP)。实验结果证实, hRAF-Exo@TP对RA病变部位表现出显著的选择性, 并且对人RA成纤维细胞的增殖活性有抑制作用。此外, 树突状细胞 (dendritic cell, DC) 来源的外泌体 (DC-derived exosomes, DEX) 在体内也可以选择性进入DC。Rao等[68]设计了一种用DEX封装TP的外泌体材料 (dendritic cell-derived exosomes-TP, DEXTP)。结果表明, DEXTP在体内能有效地将TP携带至DC, 减轻结肠炎和RA小鼠的局部炎症和损伤, 并且无明显毒性。此外, DEXTP还可以抑制DC活化, 诱导DC凋亡, 进而诱导T细胞免疫抑制。

2.3 无机纳米载药系统

无机纳米载药系统 (inorganic nano-drug delivery system, NDDS) 是一种利用无机纳米材料作为载体来递送药物的纳米给药系统, 具有毒性低、可功能化修饰以及粒径可控等特点。其中介孔二氧化硅 (mesoporous silica, MSN) 纳米粒子作为一种无机氧化物纳米材料, 具有较大的比表面积和可调节的孔径等优点, 且表面易于被多肽或其他官能团修饰[69]。这使得MSN能够有效地负载多种药物, 并且在体内环境中有更多靶向性可能。Wu等[70]设计了一种关节内介孔二氧化硅纳米系统 (MSN-TP@polydopamine-glucosamine, MSN-TP@PDA-GlcN)。将TP包封在介孔二氧化硅纳米颗粒中, 在其上包覆pH敏感的聚多巴胺 (polydopamine, PDA), 并在PDA上接枝天然产物葡萄糖胺 (glucosamine, GlcN)。该纳米系统延长了TP的停留时间, 降低了C_{max}值, 提高了TP的相对生物利用度。MSN-TP@PDA-GlcN在体外和体内均有良好的抗炎作用, 可以有效修复关节损伤, 并且不产生组织毒性。Zhang等[71]设计了一种 (MSNs@cell membrane penetrating peptide@miR-30-5p, MSNs@CADY@miR-30-5p) 抑制剂与MSNs@PCM@TP联合使用的纳米材料。他们将miR-30-5p抑制剂装载到细胞膜穿透肽修饰的介孔二氧化硅纳米颗粒中, 提高了miR-30-5p抑制剂的细胞内化性能; 并将TP装载到1-十四醇和药物的相变材料 (phase-change material, PCM) 填充的MSN中, 制备出MSNs@PCM@TP。其中PCMs是一种具有较大潜热的材料, 因此该MSN可由近红外激光与热化学联合触发。在808 nm

激光照射下, MSNs@CADY@miR-30-5p抑制剂与MSNs@PCM@TP的联合使用可以抑制过度活跃的免疫系统, 维持滑膜成纤维细胞的生理平衡, 显著提高了RA的治疗效果。

2.4 聚合物胶束

聚合物胶束 (polymeric micelle, PM) 是另一种聚合物纳米载药系统, 通常为水溶性嵌段共聚物或接枝共聚物。它具有亲水性的外壳和疏水性的内核, 能够在水中溶解后自发形成胶束, 可以对药物进行很好的增溶和包覆[72]。Xu等[46]开发了一种能够抑制cGAS-STING通路的M1巨噬细胞靶向胶束FDL@TP。将叶酸 (folic acid, FA) 和月桂酸 (lauric acid, LA) 在右旋糖酐上进行修饰, 得到两亲性聚合物 (folic acid and lauric acid modified on dextran, FDL)。随后将TP包封于FDL内, 形成FDL@TP纳米胶束。FDL@TP可以靶向关节, 增强M1巨噬细胞中过表达叶酸受体-b对TP的细胞摄取, 同时减少TP对正常组织的不良反应。在M1巨噬细胞中, 释放的TP具有抗炎和免疫抑制剂的作用, 可以明显下调cGAS和STING蛋白的表达, 从而降低TNF-α、IL-1β和IL-6的分泌。维生素C又称抗坏血酸, 可以通过维持羟基氧化酶的抗氧化活性, 减少活性氧和组织氧化损伤。Li等[73]设计了一种维生素C衍生物l-抗坏血酸棕榈酸酯 (ascorbyl palmitate, VP) 为负载TP的纳米胶束 (TP-VP nano particles, TP-VP NPs)。TP-VP NPs能有效下调IL-1β、IL-6和TNF-α水平, 抑制滑膜炎和骨组织糜烂, 减轻CIA小鼠足部肿胀变形。与TP相比, TP-VP NPs能有效抑制肝脏氧化应激, 显著减轻雷公藤甲素对肝脏、肾脏和睾丸的毒性损伤。

2.5 纳米凝胶

TP不溶于水, 且对人体各个系统有严重毒性, 因此在临床上并未被广泛应用。经皮给药系统 (transdermal drug delivery system, TDDS) 是一种有吸引力的给药途径[74]。TDDS的作用包括预防首过代谢、消除胃肠道刺激、给药频率低和药物作用的快速终止等, 可以有效避免TP的毒性和不良反应。Wang等[75]开发了一种负载TP的双动态交联海藻酸钠水凝胶 (sodium alginate-3-aminophenylboronic acid-tea polyphenols@TP, SPT@TP), 能够积极响应和清除RA微环境中过量的ROS。并且水凝胶在硼酸酯断裂后, 可以立即形成大量分子间氢键, 进而进行结构修复。因此ROS调节过程不会引发TP的突然释放, 这大大降低了TP产生毒性的风险。RA病变关节附近穿行着多条经络, 刺激相关腧穴可以对炎症关节起到近治作用。Ren等[76]构建了一种以人类血清蛋白 (human serum protein, HSA) 作为纳米载体, 包裹和递送TP和2-氯-*N*(6)-环戊基腺苷 (cyclopentyladenosine, CCPA) 纳米复合水凝胶 (TP@HSA NPs)。该给药系统靶向给药抗炎药物和模拟针灸镇痛的穴位, 用于刺激特定的穴位。结果证明, TP@HSA NPs-ccpagel能明显增强穴位处的镇痛效果, 并且对炎症、骨侵蚀和全身毒性的降低有良好效果。Xu等[77]开发了一种新型的载TP水凝胶 (TP-hydrogel-thickened microemulsion, TP-MTH), 在微乳的基础上加入水凝胶增稠剂, 既具有微乳的提高皮肤渗透性等优点, 又利用了水凝胶的增稠效果来提高药物的稳定性和局部滞留能力。结果表明, TP-MTH可以在局部皮肤中保持较高的药物浓度, 并且表现出很低的组织毒性, 仅在动物皮肤上观察到轻微的可逆性皮肤刺激迹象。

2.6 纳米脂质体

纳米脂质体 (nano-liposomes, NL) 是由类脂质 (如磷脂) 形成的囊泡结构, 内部的水相核心用作包裹药物, 外层是磷脂双层膜。NL结构同样具有可修饰性, 可以开发为具有不同特殊性能的纳米材料。巨噬细胞在RA发病过程中发挥重要作用, 活化的RA滑膜巨噬细胞表面高表达叶酸受体β (folate receptor β, FR-β)。Guo等[78]构建了一种靶向FR-β的叶酸修饰的TP脂质体 (folate-TP-liposomes, FA-TP-Lips), 从而安全有效地治疗RA。结果表明, FA-TP-Lips具有明显的软骨保护和抗炎作用, 同时可以有效抑制破骨细胞的生成。此外, 脂质体可以延长TP在体内的循环, 且与游离TP组相比毒性更低。同样, Zhou等[79]也设计出了一种用于包封TP的叶酸修饰的纳米脂质体 (FALips/TP)。FALips/TP靶向M1巨噬细胞和从M1到M2亚型的再极化巨噬细胞, 在AIA大鼠中表现出显著提高的治疗效果和低毒性。体内实验结果表明, FA-Lips在AIA大鼠模型的炎症足部表现出明显的选择性积累, 可以通过巨噬细胞复极化实现对RA的炎症靶向治疗。

2.7 固体脂质纳米颗粒

固体脂质纳米颗粒 (solid lipid nanoparticles, SLN) 是由固态的脂质制备的纳米载药系统, 具有体积小、表面积大、载药量高和界面相相互作用等特性。药物被包裹在固体脂质基质中, 常温条件下稳定性较好。Li等[80]设计了一种在超声引导下关节内注射的包载TP的SLN (TP-SLN), 用于治疗AIA兔模型关节炎。由于关节腔内的药物代谢非常迅速, 直接注射到关节腔内的TP会被迅速清除, 而SLN可以选择性吸附在炎性滑膜细胞上, 增加药物滞留时间, 有效缓解了AIA兔关节的滑膜炎症和骨侵蚀。此外, 有人认为雷公藤的安全性和有效性不能被任何单独的成分完全模仿, 因为雷公藤的整体活性是基于所有有效成分的。因此, Xue等[81]研发了一种负载TWHF的固体脂质纳米

颗粒 (TWHF-SLN)。研究结果表明, TWHF-SLN 未引起大鼠精子活力、血清睾酮水平、睾丸超微结构可视化和生殖能力的改变, 对 TWHF 引起的雄性生殖毒性和肝毒性具有保护作用, 同时增强了 TWHF 的抗炎活性。

2.8 纳米结构脂质载体

纳米结构脂质载体 (nanostructured lipid carriers, NLC) 是在 SLN 基础上进一步发展的脂质纳米材料, 由固体脂质和液体脂质混合制备而成。与 SLN 不同, NLC 不规则和非均质的核心结构, 使其比 SLN 具有更高的载药量和更灵活的释放特性, 能够通过调整液态脂质比例来调节药物的释放速率。Liu 等[82]设计了一种 TP 磷脂复合物纳米载药系统 (TP-phospholipid complex, TPCX), 通过透皮给药治疗 RA 大鼠病变关节。TPCX 属于脂质纳米载药系统的一种类型, 有效增加了雷公藤甲素的亲水性, 有利于其经皮吸收, 从而增强其对 RA 大鼠的治疗作用。实验结果表明, TPCX 通过下调 TNF-α、IL-1β、IL-6 水平抑制炎症反应, 减轻足跖肿胀, 减缓关节炎进展, 具有良好的抗关节炎作用。Gu 等[83]开发了一种 TP 负载的纳米结构脂质载体 (TP-NLCs), 通过 TDDS 治疗 RA。结果表明, TP-NLCs 可以避免肝脏第一反应和胃肠道反应的不良反应, 同时改善 TNF-α、IL-1β 和 IL-6 水平, 明显减轻膝关节水肿, 具有抑制 RA 炎症的作用。

综上所述, 近年来, 雷公藤纳米载药系统在 RA 疾病靶向方面进行了大量的研究, 在提高药物在 RA 靶向和疗效方面具有显著的优势 (图 1, 表 1)。

Table 1 Triptolide related nano-drug delivery system. CMCS: Carboxymethyl; PLA: Polylactic acid; NPs: Nano particles; SESD: Spontaneous emulsion solvent diffusion; PAT: Poly-γ-glutamic acid-grafted di-*tert*-butyl *L*-aspartate hydrochloride with triptolide; PGA: Poly-γ-glutamic acid; PAE: Phenylalanine ethylester; PNPs: Polymer nanoparticles; POSS: Polyhedral oligomeric silsesquioxane; PCL: Polycaprolactone; PDMAEMA: pH-responsive poly methylaminoethyl methacrylate; GDR: Galactose; PLGA: Poly(lactic-*co*-glycolic acid); RGD: Arginine-glycine-aspartic acid; HA: Hyaluronic acid; NIR: Near infrared spectrum; RAF: Fibroblasts; DEXTP: Dendritic cell-derived exosomes-triptolide; DCs: Dendritic cells; MSN: Mesoporous silica; PDA: Polydopamine; MSNs: Mesoporous silicas; CADY: Cell membrane penetrating peptide; PCM: Phase-change material; FDL: Folic acid and lauric acid were modified on dextran; VP: Ascorbyl palmitate; SPT: Sodium alginate-3-aminophenylboronic acid-tea polyphenols; HSA: Human serum protein; CCPA: Cyclopentyladenosine; MTH: Hydrogel-thickened microemulsion; FA: Folate; FALips: FA-liposomes; SLN: Solid lipid nanoparticles; TWHF: *Tripterygium wilfordii* Hook F; TPCX: Triptolide phospholipid complex; NLCs: Nanostructured lipid carriers

Category	Nanoparticle	Main preparation technique	Administration route	Advantage	Ref.
Polymer nanoparticle	TP-CMCS	Chemical conjugation	Intravenous	TP-CMCS have better biocompatibility and degradability, while reducing the immunogenicity and potential toxicity of TP	[55]
	TP-PLA-NPs	Modified-SESD	Intragastric	TP-PLA-NPs showed a significant anti-inflammatory effect, and the anti-inflammatory effect was gradually enhanced with prolonged administration, exceeding the equivalent dose of free TP	[56]
	PAT	Self-assembly	Intravenous	PAT has a small average diameter, high drug encapsulation efficiency and drug loading, which can continuously accumulate in the inflamed joints	[58]
	γ-PGA-l-PAE-TP	Self-assembly	Intravenous	γ-PGA-l-PAE-TP enhances TP permeation and retention effects, which has controlled release properties	[59]
	TP/PNPs	Nanoprecipitation	Intravenous	TP/PNPs are able to release drugs responsively in the weakly acidic environment of inflamed joints	[61]
	POSS-PCL-b-PDMAEMA	Nanoprecipitation method	Intravenous	Passive targeting of drugs in inflamed joints is improved by enhanced permeation and retention effects and pH-triggered drug release	[62]
	GDR-TPT	Chemical conjugation and physical self-assembly binding	Intravenous	GDR-TPT prevents drug leakage in neutral or weakly acidic environments, whereas rapid drug release occurs in acidic endosomes/lysosomes in inflammatory environments	[63]
	TP-PLGA-Au@RGD/HA	Physical adsorption and chemical crosslinking	Intra-articular injection	TP-PLGA-Au@RGD/HA realizes NIR-triggered controlled release drug release through the photothermal conversion function of AuNPs to achieve photothermo-chemotherapy combination therapy	[64]
Exosome	hRAF-Exo@TP	Electroporation	Intra-articular injection	As a kind of natural extracellular vesicles, exosomes have good biocompatibility and low immunogenicity, which helps to reduce the toxicity of drugs	[67]

Continued

Category	Nanoparticle	Main preparation technique	Administration route	Advantage	Ref.
	DEXTP	Co-incubation	Intravenous	DEXTP can specifically target DCs, alter the function of DCs or induce apoptosis of DCs, further change the differentiation and distribution of T cells	[68]
Inorganic nano-drug delivery system	MSN-TP@PDA-GlcN	Templet	Intra-articular injection	MSN-TP@PDA-GlcN exhibits sustained drug release behavior in acidic environments, such as inflamed joints	[70]
	MSNs@CADY @miR-30-5p; MSNs@PCM@TP	Solvent thermal method	Intra-articular injection; s.c. (808 nm laser irradiation)	By combining near-infrared laser-responsive PCM and TP, it enables precise control of drug release, improving efficacy while reducing systemic toxicity	[71]
Polymeric micelle	FDL@TP	Self-assembly method	Intravenous	Active targeting of FDL@TP to RA joints enhances micelle accumulation at sites of inflammation through folate receptor-mediated cellular uptake. It is pH sensitive and can release drugs in the acidic microenvironment of RA joints	[46]
	TP-VP NPs	Solvent evaporation-ultrasonic dispersion	Intravenous	TP-VP NPs showed good physical stability and suitable particle size. The water solubility of TP was improved and the toxicity of TP *in vivo* was reduced	[73]
Nanogel	SPT@TP	Chemical synthesis, physical mixing and cross-linking	Intra-articular injection	The dual dynamic cross-linking network of hydrogel allows it to quickly recombine after being damaged by external stimuli and prolong the release time of TP	[75]
	TP@HSA NPs-CCPA	Self-assembly method: stirring and solvent evaporation	Specific acupoint injection	It combines nanoparticles and hydrogels to mimic the effect of acupuncture. Through acupoint administration, it achieves sustained and controlled drug release	[76]
	TP-MTH	Microemulsion method	Transdermal drug delivery	As an accelerator of transdermal absorption, the microemulsification system increases the transdermal rate of the drug	[77]
Nano-liposomes	FA-TP-Lips	Thin-film hydration	Intravenous	FA-TP-Lips exhibited significant chondroprotective and anti-inflammatory effects by reducing the cytotoxicity and prolonging the circulation time of TP *in vivo*	[78]
	FALips/TP	Thin-film hydration method	Intravenous	By targeting and repolarizing M1 macrophages from the M1 to M2 subtype, it has shown substantial therapeutic efficacy and low toxicity	[79]
Solid lipid nanoparticles	TP-SLN	Microemulsion method	Intra-articular injection	TP-SLN is ultrasound-guided, which can ensure that the drug is injected precisely into the joint cavity, and it remains in the joint cavity for a longer time	[80]
	TWHF-SLN	Emulsification technique	Intragastric	TWHF-SLN has high encapsulation efficiency and TP loading, and improves the solubility and bioavailability of the drug	[81]
Nanostructured lipid carriers	TPCX	Thin-film hydration method	Transdermal drug delivery	Transdermal administration of TPCX can avoid gastrointestinal irritation and toxicity that may be caused by oral or injection routes, and achieve targeted therapy for rheumatoid arthritis	[82]
	TP-NLCs	Emulsification technique	Transdermal drug delivery	TP-NLCs can effectively penetrate the skin, and improve the encapsulation efficiency and drug loading of TP, and can continuously release drug	[83]

3 总结与展望

TP及其纳米载药系统在RA治疗领域展现出突破性治疗潜力。作为天然二萜类化合物, TP通过多靶点作用机制调控NF-κB、MAPK和JAK-STAT等关键信号通路, 抑制促炎因子释放并调节Th17/Treg细胞平衡, 从而有效阻断滑膜炎症级联反应, 促进关节组织修复和免疫稳态重建。近年研发的纳米递药系统通过改善其难溶特性和优化药代动力学行为, 使其生物利用度取得巨大提升, 同时实现滑膜巨噬细胞靶向和病理微环境响应性释药。本综述系统整合TP对RA的炎症抑制、免疫调节及自噬激活等多重作用机制, 提出“多靶点协同治疗”策略, 突破现有单一通路靶向药物的局限性, 为RA的靶向治疗提供新思路。但需注意到, 现有研究在跨物种转化、批次稳定性及长期毒理评价方面仍存瓶颈。后续研究应整合单细胞测序和类器官模型, 系统阐明纳米载药系统的胞内转运机制, 并加

速实现从基础研究到临床转化的突破, 为自身免疫疾病精准治疗提供创新解决方案。

作者贡献: 安凯丽、李扬博负责文章资料收集与初稿撰写; 安凯丽、杨卉和张茹负责文章的选题建议与修改; 杨卉为该文章的负责人。所有作者阅读并认可终稿。

利益冲突: 本文所有作者声明不存在利益冲突关系。

References

[1] Wang XW, Ni TY, Miao JR, et al. The role and mechanism of triptolide, a potential new DMARD, in the treatment of rheumatoid arthritis [J]. Ageing Res Rev, 2025, 104: 102643.

[2] Bao SW, Yi M, Xiang B, et al. Antitumor mechanisms and future clinical applications of the natural product triptolide [J]. Cancer Cell Int, 2024, 24: 150.

[3] Zhang X, Xia J, Jiang Y, et al. 2023 international consensus guidance for the use of *Tripterygium wilfordii* Hook F in the treatment of active rheumatoid arthritis [J]. J Autoimmun, 2024, 142: 103148.

[4] Song J, He GN, Dai L. A comprehensive review on celastrol, triptolide and triptonide: insights on their pharmacological activity, toxicity, combination therapy, new dosage form and novel drug delivery routes [J]. Biomed Pharmacother, 2023, 162: 114705.

[5] Zhong XF, Deng XY, Yang YQ, et al. Immuno-engineered macrophage membrane-coated nanodrug to restore immune balance for rheumatoid arthritis treatment [J]. Acta Biomater, 2025, 197: 374-385.

[6] Liu XL, Wang ZG, Qian H, et al. Natural medicines of targeted rheumatoid arthritis and its action mechanism [J]. Front Immunol, 2022, 13: 945129.

[7] Fang JY, Liu MX, Huang ZH, et al. Efficacy and safety of TCMs with anti-inflammatory effect in patients with rheumatoid arthritis: a network meta-analysis [J]. Front Immunol, 2023, 14: 1114930.

[8] Sun R, Dai JY, Ling MJ, et al. Delivery of triptolide: a combination of traditional Chinese medicine and nanomedicine [J]. J Nanobiotechnology, 2022, 20: 194.

[9] Ren Q, Li MM, Deng Y, et al. Triptolide delivery: nanotechnology-based carrier systems to enhance efficacy and limit toxicity [J]. Pharmacol Res, 2021, 165: 105377.

[10] Jing ZQ, Wang X, Yan TY, et al. Construction of folate receptors and mitochondria targeting celastrol-loaded PAMAM nano-drug delivery system and its *in vitro* anti-inflammatory effect [J]. Acta Pharm Sin (药学学报), 2023, 58: 550-559.

[11] Lawrence T. The nuclear factor NF-kappaB pathway in inflammation [J]. Cold Spring Harb Perspect Biol, 2009, 1: a001651.

[12] Jiang SY, Wan F, Lian H, et al. Friend or foe? The dual role of triptolide in the liver, kidney, and heart [J]. Biomed Pharmacother, 2023, 161: 114470.

[13] Lv MY, Liang QL, Luo ZY, et al. UPLC-LTQ-orbitrap-based cell metabolomics and network pharmacology analysis to reveal the potential antiarthritic effects of pristimerin: *in vitro*, *in silico* and *in vivo* study [J]. Metabolites, 2022, 12: 839.

[14] Kianmehr M, Behdadfard M, Hedayati-Moghdam M, et al. Effects of herbs and derived natural products on lipopolysaccharide-induced toxicity: a literature review [J]. Oxid Med Cell Longev, 2023, 2023: 7675183.

[15] Jing M, Yang JJ, Zhang LR, et al. Celastrol inhibits rheumatoid arthritis through the ROS-NF-κB-NLRP3 inflammasome axis [J]. Int Immunopharmacol, 2021, 98: 107879.

[16] Song CY, Xu YG, Lu YQ. Use of *Tripterygium wilfordii* Hook F for immune-mediated inflammatory diseases: progress and future prospects [J]. J Zhejiang Univ Sci B, 2020, 21: 280-290.

[17] Blomberg NJ, Kristyanto H, Verstappen M, et al. Autoreactive B cells in extremes of rheumatoid arthritis disease phenotypes [J]. Ann Rheum Dis, 2025. DOI: 10.1016/j.ard.2025.05.006.

[18] Sur Chowdhury C, Giaglis S, Walker UA, et al. Enhanced neutrophil extracellular trap generation in rheumatoid arthritis: analysis of underlying signal transduction pathways and potential diagnostic utility [J]. Arthritis Res Ther, 2014, 16: R122.

[19] Siebert S, Tsoukas A, Robertson J, et al. Cytokines as therapeutic targets in rheumatoid arthritis and other inflammatory diseases [J]. Pharmacol Rev, 2015, 67: 280-309.

[20] Huang GR, Yuan K, Zhu QQ, et al. Triptolide inhibits the inflammatory activities of neutrophils to ameliorate chronic arthritis [J]. Mol Immunol, 2018, 101: 210-220.

[21] Jung SM, Kim KW, Yang CW, et al. Cytokine-mediated bone destruction in rheumatoid arthritis [J]. J Immunol Res, 2014, 2014: 263625.

[22] Wang Y, Jia L, Wu CY. Triptolide inhibits the differentiation of Th17 cells and suppresses collagen-induced arthritis [J]. Scand J Immunol, 2008, 68: 383-390.

[23] Xu HH, Zhao HY, Lu C, et al. Triptolide inhibits osteoclast differentiation and bone resorption *in vitro via* enhancing the production of IL-10 and TGF-β1 by regulatory T cells [J]. Mediators Inflamm, 2016, 2016: 8048170.

[24] Nygaard G, Firestein GS. Restoring synovial homeostasis in rheumatoid arthritis by targeting fibroblast-like synoviocytes [J]. Nat Rev Rheumatol, 2020, 16: 316-333.

[25] Han CC, Jiang LP, Wang WK, et al. GRK2 activates TRAF2-NF-κB signalling to promote hyperproliferation of fibroblast-like synoviocytes in rheumatoid arthritis [J]. Acta Pharm Sin B, 2025, 15: 1956-1973.

[26] Piao XM, Zhou JR, Xue L. Triptolide decreases rheumatoid arthritis fibroblast-like synoviocyte proliferation, invasion, inflammation and presents a therapeutic effect in collagen-induced arthritis rats *via* inactivating lncRNA RP11-83J16.1 mediated URI1 and β-catenin signaling [J/OL]. Int Immunopharmacol, 2021, 99: 108010.

[27] Xie CM, Jiang J, Liu JP, et al. Triptolide suppresses human

synoviocyte MH7A cells mobility and maintains redox balance by inhibiting autophagy [J]. Biomed Pharmacother, 2019, 115: 108911.

[28] Ashrafizadeh M, Paskeh MDA, Mirzaei S, et al. Targeting autophagy in prostate cancer: preclinical and clinical evidence for therapeutic response [J]. J Exp Clin Cancer Res, 2022, 41: 105.

[29] Yang BQ, Ma D, Zhao XX, et al. Effect of anti-rheumatic drugs on cardiovascular disease events in rheumatoid arthritis [J]. Front Cardiovasc Med, 2021, 8: 812631.

[30] Ho TY, Santora K, Chen JC, et al. Effects of relaxin and estrogens on bone remodeling markers, receptor activator of NF-*κ*B ligand (RANKL) and osteoprotegerin (OPG), in rat adjuvant-induced arthritis [J]. Bone, 2011, 48: 1346-1353.

[31] Liu CF, Zhang YQ, Kong XX, et al. Triptolide prevents bone destruction in the collagen-induced arthritis model of rheumatoid arthritis by targeting RANKL/RANK/OPG signal pathway [J]. Evid Based Complement Alternat Med, 2013, 2013: 626038.

[32] Zhang CF, Weng YY, Wang HB, et al. A synergistic effect of triptolide and curcumin on rheumatoid arthritis by improving cell proliferation and inducing cell apoptosis *via* inhibition of the IL-17/NF-*κ*B signaling pathway [J]. Int Immunopharmacol, 2024, 142: 112953.

[33] Song XQ, Zhang Y, Dai EQ. Therapeutic targets of thunder god vine (*Tripterygium wilfordii* Hook) in rheumatoid arthritis (review) [J]. Mol Med Rep, 2020, 21: 2303-2310.

[34] Lu Y, Wang WJ, Leng JH, et al. Inhibitory effect of triptolide on interleukin-18 and its receptor in rheumatoid arthritis synovial fibroblasts [J]. Inflamm Res, 2008, 57: 260-265.

[35] Song XQ, Zhang Y, Dai EQ, et al. Prediction of triptolide targets in rheumatoid arthritis using network pharmacology and molecular docking [J]. Int Immunopharmacol, 2020, 80: 106179.

[36] Xiao C, Zhou J, He YH, et al. Effects of triptolide from Radix *Tripterygium wilfordii* (Leigongteng) on cartilage cytokines and transcription factor NF-*κ*B: a study on induced arthritis in rats [J]. Chin Med, 2009, 4: 13.

[37] Tong YT, Li XY, Deng QC, et al. Advances of the small molecule drugs regulating fibroblast-like synovial proliferation for rheumatoid arthritis [J]. Front Pharmacol, 2023, 14: 1230293.

[38] Wang J, Liu J, Wen J, et al. Triptolide inhibits inflammatory response and migration of fibroblast like synovial cells in rheumatoid arthritis through the circRNA 0003353/JAK2/STAT3 signaling pathway [J]. J South Med Univ (南方医科大学学报), 2022, 42: 367-374.

[39] Lin JJ, Tao K, Gao N, et al. Triptolide inhibits expression of inflammatory cytokines and proliferation of fibroblast-like synoviocytes induced by IL-6/sIL-6R-mediated JAK2/STAT3 signaling pathway [J]. Curr Med Sci, 2021, 41: 133-139.

[40] Yang YL, Ye YJ, Qiu Q, et al. Triptolide inhibits the migration and invasion of rheumatoid fibroblast-like synoviocytes by blocking the activation of the JNK MAPK pathway [J]. Int Immunopharmacol, 2016, 41: 8-16.

[41] Wan L, Liu J, Huang CB, et al. A novel pharmaceutical preparation of *Tripterygium wilfordii* Hook. F. regulates macrophage polarization to alleviate inflammation in rheumatoid arthritis [J]. J Pharm Pharmacol, 2023, 75: 1442-1457.

[42] Wang N, Min XY, Ma N, et al. The negative impact of triptolide on the immune function of human natural killer cells [J]. Pharmaceuticals (Basel), 2023, 16: 458.

[43] Yang XC, Zhao LL, Pang YQ. cGAS-STING pathway in pathogenesis and treatment of osteoarthritis and rheumatoid arthritis [J]. Front Immunol, 2024, 15: 1384372.

[44] Hu Y, Chen BJ, Yang F, et al. Emerging role of the cGAS-STING signaling pathway in autoimmune diseases: biologic function, mechanisms and clinical prospection [J]. Autoimmun Rev, 2022, 21: 103155.

[45] Xu AL, Long YJ, Wang X, et al. Effects of triptolide on cGAS-STING signaling pathway in synovial fibroblasts from patients with rheumatoid arthritis [J]. China J Tradit Chin Med Pharm (中华中医药杂志), 2022, 37: 1087-1090.

[46] Xu AL, Yang RX, Zhang MF, et al. Macrophage targeted triptolide micelles capable of cGAS-STING pathway inhibition for rheumatoid arthritis treatmen [J]. J Drug Target, 2022, 30: 961-972.

[47] Gravallese EM. Bone destruction in arthritis [J]. Ann Rheum Dis, 2002, 61 Suppl 2: ii84-ii86.

[48] Li P, Wang L, Wang W. Effects of methopterin on osteoclasts and study of its mechanism of action [J]. Acta Pharm Sin (药学学报), 2008, 43: 1025-1031.

[49] Yu T, Liu X, Jiang M, et al. Cucumber seed polypeptides regulate RANKL-induced osteoclastogenesis through OPG/RANKL/RANK and NF-*κ*B [J]. In Vitro Cell Dev Biol Anim, 2024, 60: 54-66.

[50] Sabry M, Mostafa S, Kamar S, et al. The cross-talk between matrix metalloproteinase-9, RANKL/OPG system and cardiovascular risk factors in ovariectomized rat model of postmenopausal osteoporosis [J]. PLoS One, 2021, 16: e0258254.

[51] Lin N, Liu CF, Xiao C, et al. Triptolide, a diterpenoid triepoxide, suppresses inflammation and cartilage destruction in collagen-induced arthritis mice [J]. Biochem Pharmacol, 2007, 73: 136-146.

[52] Farjadian F, Ghasemi A, Gohari O, et al. Nanopharmaceuticals and nanomedicines currently on the market: challenges and opportunities [J]. Nanomedicine (Lond), 2019, 14: 93-126.

[53] Cui YQ, Lei FB, Zhang LQ. Advances in bioanalysis methods and pharmacokinetics of polymer nanopharmaceuticals [J]. Acta Pharm Sin (药学学报), 2023, 58: 844-851.

[54] Zhang SX, Zhang MM, Li XY, et al. Nano-based co-delivery system for treatment of rheumatoid arthritis [J]. Molecules, 2022, 27: 5973.

[55] Zhang L, Yan M, Chen K, et al. Novel carboxylated chitosan-

based triptolide conjugate for the treatment of rheumatoid arthritis [J]. Pharmaceutics, 2020, 12: 202.

[56] Liu MX, Dong J, Yang YJ, et al. Anti-inflammatory effects of triptolide loaded poly(*D*,*L*-lactic acid) nanoparticles on adjuvant-induced arthritis in rats [J]. J Ethnopharmacol, 2005, 97: 219-225.

[57] Halmschlag B, Steurer X, Putri SP, et al. Tailor-made poly-*γ*-glutamic acid production [J]. Metab Eng, 2019, 55: 239-248.

[58] Zhang L, Chang JL, Zhao YJ, et al. Fabrication of a triptolide-loaded and poly-*γ*-glutamic acid-based amphiphilic nanoparticle for the treatment of rheumatoid arthritis [J]. Int J Nanomedicine, 2018, 13: 2051-2064.

[59] Zhang L, Wang TT, Li Q, et al. Fabrication of novel vesicles of triptolide for antirheumatoid activity with reduced toxicity *in vitro* and *in vivo* [J]. Int J Nanomedicine, 2016, 11: 2663-2673.

[60] de Vries RR, Huizinga TW, Toes RE. Redefining the HLA and RA association: to be or not to be anti-CCP positive [J]. J Autoimmun, 2005, 25 Suppl: 21-25.

[61] Li JX, Zhang MJ, Shi JF, et al. pH-sensitive nano-polyelectrolyte complexes with arthritic macrophage-targeting delivery of triptolide [J]. Int J Pharm, 2023, 632: 122572.

[62] Liu Y, Jin JQ, Xu H, et al. Construction of a pH-responsive, ultralow-dose triptolide nanomedicine for safe rheumatoid arthritis therapy [J]. Acta Biomater, 2021, 121: 541-553.

[63] Li P, Yang XY, Yang Y, et al. Synergistic effect of all-*trans*-retinal and triptolide encapsulated in an inflammation-targeted nanoparticle on collagen-induced arthritis in mice [J]. J Control Release, 2020, 319: 87-103.

[64] Li CX, Liu R, Song YR, et al. Hyaluronic acid hydrogels hybridized with Au-triptolide nanoparticles for intraarticular targeted multi-therapy of rheumatoid arthritis [J]. Front Pharmacol, 2022, 13: 849101.

[65] Zhang YF, Zhang Q, Li CH, et al. Advances in cell membrane-based biomimetic nanodelivery systems for natural products [J]. Drug Deliv, 2024, 31: 2361169.

[66] Song H, Liu B, Dong B, et al. Exosome-based delivery of natural products in cancer therapy [J]. Front Cell Dev Biol, 2021, 9: 650426.

[67] Jiang XH, Shi LL, Feng H, et al. Engineered exosomes loaded with triptolide: an innovative approach to enhance therapeutic efficacy in rheumatoid arthritis [J]. Int Immunopharmacol, 2024, 129: 111677.

[68] Rao Q, Ma GC, Li M, et al. Targeted delivery of triptolide by dendritic cell-derived exosomes for colitis and rheumatoid arthritis therapy in murine models [J]. Antimicrob Agents Chemother, 2023, 180: 330-346.

[69] Dong JH, Ma Y, Li R, et al. Smart MSN-drug-delivery system for tumor cell targeting and tumor microenvironment release [J]. ACS Appl Mater Interfaces, 2021, 13: 42522-42532.

[70] Wu YZ, Chen WY, Zeng Y, et al. Inflammation-responsive mesoporous silica nanoparticles with synergistic anti-inflammatory and joint protection effects for rheumatoid arthritis treatment [J]. Pharm Res, 2024, 41: 1493-1505.

[71] Zhang XN, Zhang X, Wang XP, et al. Efficient delivery of triptolide plus a miR-30-5p inhibitor through the use of near infrared laser responsive or CADY modified MSNs for efficacy in rheumatoid arthritis therapeutics [J]. Front Bioeng Biotechnol, 2020, 8: 170.

[72] Hwang D, Ramsey JD, Kabanov AV. Polymeric micelles for the delivery of poorly soluble drugs: from nanoformulation to clinical approval [J]. Adv Drug Deliv Rev, 2020, 156: 80-118.

[73] Li M, Wang GQ, Yan YY, et al. Triptolide and *L*-ascorbate palmitate co-loaded micelles for combination therapy of rheumatoid arthritis and side effect attenuation [J]. Drug Deliv, 2022, 29: 2751-2758.

[74] Phatale V, Vaiphei KK, Jha S, et al. Overcoming skin barriers through advanced transdermal drug delivery approaches [J]. J Control Release, 2022, 351: 361-380.

[75] Wang TY, Huang C, Fang ZY, et al. A dual dynamically cross-linked hydrogel promotes rheumatoid arthritis repair through ROS initiative regulation and microenvironment modulation-independent triptolide release [J]. Mater Today Bio, 2024, 26: 101042.

[76] Ren SJ, Liu H, Wang XT, et al. Acupoint nanocomposite hydrogel for simulation of acupuncture and targeted delivery of triptolide against rheumatoid arthritis [J]. J Nanobiotechnology, 2021, 19: 409.

[77] Xu LY, Pan JY, Chen QY, et al. *In vivo* evaluation of the safety of triptolide-loaded hydrogel-thickened microemulsion [J]. Food Chem Toxicol, 2008, 46: 3792-3799.

[78] Guo RB, Zhang XY, Yan DK, et al. Folate-modified triptolide liposomes target activated macrophages for safe rheumatoid arthritis therapy [J]. Biomater Sci, 2022, 10: 499-513.

[79] Zhou X, Huang DD, Wang RK, et al. Targeted therapy of rheumatoid arthritis *via* macrophage repolarization [J]. Drug Deliv, 2021, 28: 2447-2459.

[80] Li SL, Su LY, Lv GR, et al. Ultrasound guided intra-articular injection of triptolide-loaded solid lipid nanoparticle for treatment of antigen-induced arthritis in rabbits [J]. Front Pharmacol, 2022, 13: 824015.

[81] Xue M, Jiang ZZ, Wu T, et al. Anti-inflammatory effects and hepatotoxicity of *Tripterygium*-loaded solid lipid nanoparticles on adjuvant-induced arthritis in rats [J]. Phytomedicine, 2012, 19: 998-1006.

[82] Liu XY, Pei WJ, Wu YZ, et al. Transdermal delivery of triptolide-phospholipid complex to treat rheumatoid arthritis [J]. Drug Deliv, 2021, 28: 2127-2136.

[83] Gu YW, Tang XM, Yang M, et al. Transdermal drug delivery of triptolide-loaded nanostructured lipid carriers: preparation, pharmacokinetic, and evaluation for rheumatoid arthritis [J]. Int J Pharm, 2019, 554: 235-244.