雷公藤甲素治疗肾脏疾病的研究进展

卢梦丹[1,2], 万 凤[1*]

(1. 浙江中医药大学附属杭州市中医院, 浙江 杭州 310007; 2. 浙江中医药大学生命科学学院, 浙江 杭州 310053)

摘要: 雷公藤甲素作为中药雷公藤的关键活性成分, 在肾脏疾病治疗领域展现出重要潜力。本文系统综述了其用于肾脏疾病治疗的研究进展, 涵盖化学特性、药理与毒理机制及靶向递药策略。在药理机制方面, 雷公藤甲素主要通过保护足细胞、抑制炎症及抗纤维化等多途径发挥肾脏保护作用。然而, 其显著的毒性是临床应用的关键限制因素, 涉及复杂的代谢途径、信号通路及细胞过程。为提升疗效并降低毒性, 研究者已开发多种靶向肾脏递送系统, 如基于偶联技术的递送系统、纳米颗粒、聚合物胶束、脂质体修饰及其衍生物策略等。尽管当前研究已取得积极进展, 但为确保临床安全应用, 仍需深入阐明其药理与毒理机制, 并对现有增效减毒策略进行长期毒理学评估。这些工作将有助于科学评估雷公藤甲素的临床应用前景, 为其在肾脏疾病治疗中的转化应用奠定基础。

关键词: 雷公藤甲素; 药理; 毒理; 靶向递药; 肾脏疾病

中图分类号: R285 **文献标识码**: A **文章编号**: 0513-4870(2026)05-1532-10

Research progress on the treatment of kidney disease with triptolide

LU Meng-dan[1,2], WAN Feng[1*]

(*1. Hangzhou TCM Hospital Affiliated to Zhejiang Chinese Medical University, Hangzhou 310007, China; 2. College of Life Sciences, Zhejiang Chinese Medical University, Hangzhou 310053, China*)

Abstract: Triptolide, as a key active ingredient in the traditional Chinese medicine *Tripterygium wilfordii*, has shown significant potential in the treatment of kidney diseases. This article systematically reviews the research progress of its application in the treatment of kidney diseases, covering chemical properties, pharmacological and toxicological mechanisms, and targeted drug delivery strategies. In terms of pharmacological mechanisms, triptolide mainly exerts renal protection through multiple pathways such as protecting podocytes, inhibiting inflammation, and anti fibrosis. However, its significant toxicity is a key limiting factor for clinical applications, involving complex metabolic pathways, signaling pathways, and cellular processes. To enhance therapeutic efficacy and reduce toxicity, researchers have developed various targeted kidney delivery systems, such as delivery systems based on coupling technology, nanoparticles, polymer micelles, liposome modification, and derivative strategies. Although positive progress has been made in current research, in order to ensure safe clinical application, it is still necessary to further elucidate its pharmacological and toxicological mechanisms, and conduct long-term toxicological evaluations of existing strategies for enhancing efficacy and reducing toxicity. These works will contribute to the scientific evaluation of the clinical application prospects of triptolide and lay the foundation for its translational application in the treatment of kidney diseases.

Key words: triptolide; pharmacology; toxicology; targeted drug delivery; kidney disease

肾脏疾病是重大公共卫生问题, 严重影响患者生活质量并导致高死亡率。近年来, 伴随人口老龄化进程加速和代谢性疾病患病率攀升, 肾脏疾病发病率持续上升, 给全球公共卫生体系带来沉重负担。

雷公藤甲素作为中药雷公藤的主要活性成分, 凭借

收稿日期: 2025-08-11; 修回日期: 2026-01-04.

基金项目: 浙江省医药卫生计划项目 (2024KY1375); 国家自然科学基金青年基金资助项目 (81803911); 杭州市医学重点学科建设项目 (2025HZGF12).

*通讯作者 Tel: 18806505466, E-mail: wfthebest@163.com

DOI: 10.16438/j.0513-4870.2025-0940

其显著的抗炎、抗纤维化及免疫抑制等药理活性, 在肾脏疾病治疗中展现出重要治疗潜力。然而, 其临床应用受到显著肝肾毒性及低水溶性等因素的限制。本综述旨在系统总结雷公藤甲素在肾脏疾病治疗中的研究进展, 涵盖其化学特性、药理机制、毒性机制及靶向肾脏递药策略。通过对现有研究的深入分析与整合, 旨在为临床医生制定肾脏疾病治疗方案提供科学依据和参考。

1 雷公藤甲素的化学特性

雷公藤甲素是从卫矛科植物雷公藤的根、叶、花及果实中提取的一种环氧二萜内酯类化合物 (图1), 分子式为$C_{20}H_{24}O_6$, 相对分子质量为360.401。其分子结构中含有3个环氧基团和1个α,β-不饱和五元内酯环, 这使其具有显著的生物活性, 如抗炎、免疫抑制和抗肿瘤作用。然而, 这种特殊的分子结构也带来了化学稳定性问题: 环氧基团对酸、碱、热等条件极为敏感, 容易发生开环反应, 导致结构破坏; α,β-不饱和内酯环则容易发生加成反应或水解反应, 尤其在碱性或高温条件下更易失活。因此, 在提取或制剂过程中, 雷公藤甲素可能与某些有机溶剂或辅料发生反应, 形成副产物, 从而影响其纯度和药效。由此可见, 雷公藤甲素的化学稳定性差及杂质易形成, 导致其纯度难以控制, 这给其提取和分离过程带来了诸多挑战, 并增加了操作难度。

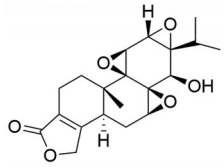


Figure 1 Structure of triptolide

雷公藤甲素分子的每一个结构都对分子的整体活性有独特贡献。C-12的开环使其免疫抑制活性丧失, 但对其抗炎活性影响有限[1]。五元不饱和内酯环 (D环) 对其强大的抗癌活性至关重要, 而C18羰基可能对雷公藤甲素与启动其细胞毒性作用的靶分子之间的相互作用产生重要影响[2]。12,13-环氧化物对雷公藤甲素的生物活性尤为重要, 它有助于其与XPB蛋白上的半胱氨酸残基相互作用, 从而使雷公藤甲素与转录因子TFIIH的亚基XPB共价结合, 并抑制其DNA依赖性ATP酶活性, 进而抑制RNA聚合酶II介导的转录及可能的核苷酸切除修复[3]。这些相互作用对雷公藤甲素的作用机制至关重要。其中7,8-环氧化物更是不可或缺, 该位点的开环修饰显著降低了其生物学功效, 凸显了其在维持分子生物活性方面的关键作用[4]。因此, 保持这些结构特征的完整性对于维持药物的生物活性至关重要。

2 雷公藤甲素治疗肾脏疾病的药理机制

细胞实验、动物实验及多项临床队列研究均证实, 雷公藤甲素在IgA肾病 (IgA nephropathy, IgAN)、膜性肾病、狼疮性肾炎、糖尿病肾病 (diabetic nephropathy, DN) 及多柔比星诱导或5/6肾切除等多种急慢性肾损伤模型中, 能够显著降低蛋白尿水平, 延缓血肌酐升高及肾小球滤过率的下降。其作用机制主要通过保护足细胞、抑制肾纤维化及发挥抗炎作用来实现, 且这些机制通过“多靶点–多通路”的协同效应共同发挥作用 (图2)。

2.1 保护足细胞损伤

2.1.1 体外细胞模型 在TGF-β1诱导的足细胞损伤模型中, 雷公藤甲素可保护足细胞免受细胞骨架损伤和凋亡, 阻止p38 MAPK、NF-κB p65及钙调磷酸酶/NFATC3信号激活, 同时能阻止Smad2/3磷酸化, 恢复miR-30表达[5]。在高糖诱导的足细胞损伤模型中, 雷公藤甲素干预恢复nephrin和ZO-1的蛋白表达水平, 抑制胶原蛋白I和FN的蛋白表达水平, 改善足细胞上皮–间充质转化 (epithelial-mesenchymal transition, EMT), 此外通过下调NLRP3和ASC的蛋白表达水平, 抑制NLRP3炎症小体激活, 进而减少下游效应分子Caspase-1、IL-1β和IL-18的蛋白表达水平, 阻断炎症级联反应, 减轻足细胞的炎症损伤程度[6]。在高糖诱导的足细胞损伤模型中, 低剂量雷公藤甲素 (3 μg·L^{-1}) 可显著恢复nephrin和podocin的蛋白表达水平, 抑制desmin、collagen I和snail在足细胞中的蛋白表达, 进一步改善足细胞EMT状态, 并且能够显著降低足细胞中Wnt3α和β-catenin的表达水平, 从而抑制Wnt3α/β-catenin信号通路的过度激活[7]。在C5b-9介导的足细胞损伤模型中, 雷公藤甲素可使NADPH氧化酶失活, 抑制活性氧 (reactive oxygen species, ROS) 的生成以及p38 MAPK, 并恢复RhoA信号活性[8]。在嘌呤霉素诱导的足细胞损伤模型中, 雷公藤甲素预处理能够防止肌动蛋白细胞骨架和微丝相关蛋白synaptopodin的破坏, 同时保护了nephrin和podocin的表达, 其机制也与抑制ROS的生成和p38 MAPK的激活, 恢复RhoA信号活性相关[9]。此外, 本课题组在嘌呤霉素诱导的足细胞损伤模型中发现雷公藤甲素可上调去甲基化酶TET2, 增加紧密连接蛋白ZO-1启动子的羟甲基化水平, 降低足细胞通透性[10]; 在TGF-β1诱导的足细胞损伤模型中, 还可通过调控TET2介导的足细胞标记分子如nephrin和NEPH1启动子的去甲基化, 逆转足细胞的EMT过程[11]。

2.1.2 斑马鱼模型 在斑马鱼模型中, 雷公藤甲素能有效缓解甲硝唑诱导的水肿、蛋白尿及足突融合症状,

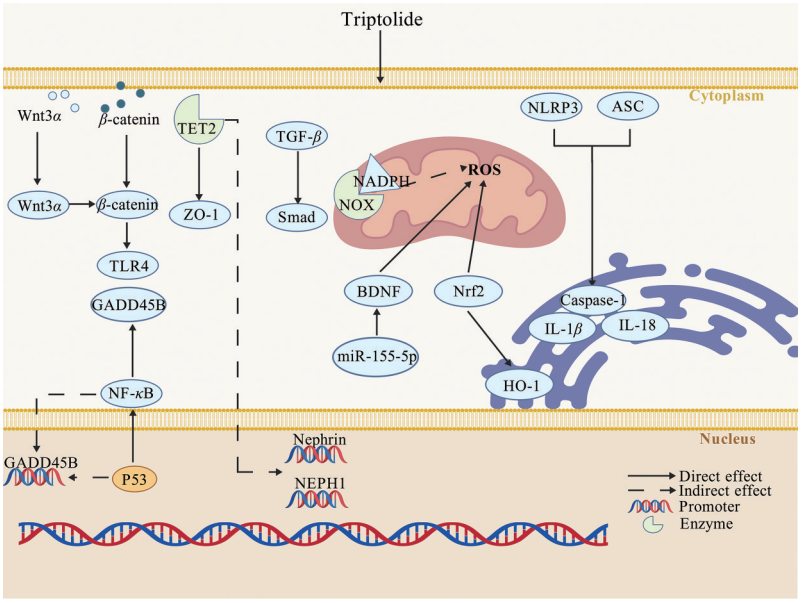


Figure 2 Summary of the pharmacological mechanisms of triptolide in protecting podocytes. NOX: NADPH oxidase; TET2: Tet methylcytosine dioxygenase 2; P53: Tumor protein p53; ROS: Reactive oxygen species; BDNF: Brain-derived neurotrophic factor; Nrf2: Nuclear factor erythroid 2-related factor 2; HO-1: Heme oxygenase-1; IL-1*β*: Interleukin-1 *β*; IL-18: Interleukin-18; TGF-*β*: Transforming growth factor-*β*; Smad: Small mothers against decapentaplegic; NF-*κ*B: Nuclear factor kappa-light-chain-enhancer of activated B cells; GADD45B: Growth arrest and DNA-damage-inducible beta; TLR4: Toll-like receptor 4; Wnt3*α*: Wingless-type MMTV integration site family, member 3A; ZO-1: Zonula occludens-1; NEPH1: Kirre like nephrin family adhesion molecule 1; ASC: Apoptosis associated speck-like protein containing a CARD; NLRP3: NOD-like receptor protein 3

主要通过抑制NF-*κ*B信号通路激活及NF-*κ*B与GADD45B启动子的结合, 进而抑制足细胞凋亡, 在斑马鱼足细胞中特异性过表达GADD45B则会消除雷公藤甲素的保护作用[12]。随后, 该课题组又发现雷公藤甲素还可抑制斑马鱼足细胞p53和GADD45B的表达, 干预或通过Morpholino抑制p53和GADD45B能缓解甲硝唑诱导的斑马鱼水肿, 同样, 在足细胞中过表达GADD45B则阻断了雷公藤甲素和抑制p53对足细胞的保护作用。进一步研究表明, 雷公藤甲素可抑制p53与GADD45B启动子的结合, 进而影响GADD45B的转录, 推测p53可能通过NF-*κ*B信号通路间接调控GADD45B的表达[13]。

2.1.3 大小鼠模型 在不同的大小鼠肾病模型中, 雷公藤甲素也发挥着保护足细胞的作用。雷公藤甲素有效降低嘌呤霉素诱导的肾病大鼠的蛋白尿, 其减少蛋白尿的效果与足突融合的改善、足细胞损伤标志物结蛋白的减少以及nephrin和podocin表达和分布的恢复相关[9]。在被动Heymann肾炎的大鼠模型中, 雷公藤甲素可显著降低蛋白尿、循环中大鼠抗兔IgG抗体滴度及肾小球C5b-9沉积, 降低足细胞损伤标志物蛋白表达, 逆转足突融合现象[8]。在高脂饮食联合链脲佐菌素诱导的DN小鼠模型中, Lv等[14]发现雷公藤甲素能够显著改善模型小鼠的肾功能和肾脏病理损伤, 其机制主要是通过激活Nrf2/HO-1信号通路降低氧化应激水平和ROS水平, 同时通过抑制NLRP3炎性体通路来减弱焦亡; 而Gao等[15]发现雷公藤甲素能够降低模型小鼠的空腹血糖和24 h尿微量白蛋白水平, 减轻病理损伤和足细胞损伤, 上调nephrin水平并下调miR-155-5p水平。进一步的实验表明雷公藤甲素通过抑制miR-155-5p上调BDNF, 从而抑制氧化应激和炎症损伤, 缓解足细胞损伤。在糖尿病小鼠 (*db*/*db*) 模型中, 雷公藤甲素治疗能够减轻肾脏结构损伤和功能异常, 增加nephrin、podocin和E-钙黏蛋白的表达, 同时降低*α*-SMA的表达。进一步研究发现, 雷公藤甲素可能通过抑制kindlin-2活性和下调TGF-*β*/Smad信号通路中的p-Smad3来抑制足细胞EMT, 从而在DN中保护足细胞[16]。此外, 雷公藤甲素还通过上调Nrf2抑制*db*/*db*小鼠的铁死亡, 稳定肾小球足细胞细胞骨架, 减少蛋白尿[17]。经雷公藤甲素处理的*db*/*db*糖尿病小鼠蛋白尿明显减轻, 肾小球肥大和足细胞损伤得到缓解, 同时肾脏炎症和氧化应激减轻, 高脂血症和肥胖状况也得到了改善[18]。

2.2 抑制纤维化作用

雷公藤甲素在肾脏疾病中抑制纤维化作用的药理机制 (图3) 已受到广泛关注, 并已有诸多研究探讨。雷

公藤甲素在TGF-β1诱导的肾小球系膜细胞模型及慢性血清病诱导的肾小球肾炎大鼠模型中, 通过上调Ski蛋白表达, 影响TGF-β1/Smad3信号通路, 从而减轻纤维化程度[19]。在血管紧张素-II刺激的人肾小管上皮细胞中, 雷公藤甲素显著下调血栓蛋白-1和转化生长因子β1的表达[20]。雷公藤甲素还能显著降低DN大鼠的白蛋白尿, 改善肾小球硬化, 抑制细胞外基质蛋白积累, 其机制与上调miR-137抑制Notch1通路激活相关[21]。在单侧肾切除联合盐皮质激素醋酸去氧皮质酮 (deoxycorticosterone acetate, DOCA) 构建的小鼠模型中, 雷公藤甲素减轻了DOCA-salt处理小鼠尿白蛋白和8-异前列烷排泄的增加, 以及肾小球硬化和肾小管间质损伤及纤维化。雷公藤甲素主要通过miR-141-3p/PTEN/Akt/mTOR通路恢复自噬, 缓解高脂饮食联合链脲佐菌素诱导的DN大鼠和高糖培养的人系膜细胞中的纤维化[22]。在IgAN小鼠模型和IgA1诱导的人系膜细胞模型中, 雷公藤甲素可通过CARD9/p38 MAPK通路促进系膜细胞自噬和抑制IgAN中系膜细胞的增殖[23]。雷公藤甲素能抑制糖尿病大鼠肾组织RANTES的过度表达, 改善肾小球硬化及肾间质纤维化[24]。雷公藤甲素改善高脂饮食/链脲佐菌素诱导的糖尿病大鼠的白蛋白尿症状, 抑制肾小球硬化, 其机制可能与抑制PDK1/Akt/mTOR通路有关[25]。雷公藤甲素还通过下调miR-188-5p, 影响miR-188-5p与PTEN之间的相互作用, 减弱PI3K/AKT通路的激活, 改善肾脏EMT[26]。

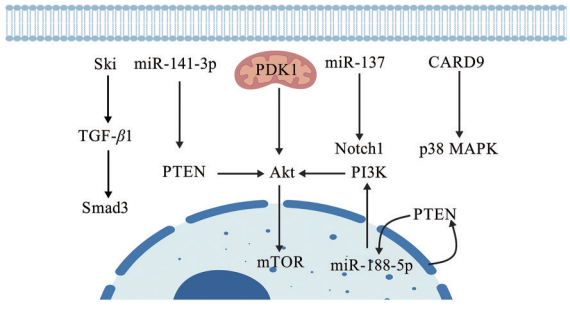


Figure 3 Summary of the signaling pathways involved in the anti-fibrotic effect of triptolide. Ski: Sloan-kettering Institute proto-oncogene; PTEN: Phosphatase and tensin homolog; Akt: AKR mouse strain thymoma proto-oncogene; mTOR: Mechanistic target of rapamycin; PDK1: 3-Phosphoinositide-dependent protein kinase 1; PI3K: Phosphoinositide 3-kinase; CARD9: Caspase recruitment domain-containing protein 9; p38 MAPK: p38 mitogen-activated protein kinase

2.3 抗炎作用

在抗炎方面, 雷公藤甲素处理以剂量依赖性方式抑制了DOCA-salt诱导的间质单核细胞/巨噬细胞浸润, 降低肾脏促炎细胞因子/趋化因子和黏附分子水平, 并抑制肾脏NF-κB活化[27]。雷公藤甲素通过调节Th1/Th2细胞平衡及减少巨噬细胞浸润和肾脏相关炎症因子的表达来改善糖尿病肾病[28]。在高脂高糖喂养联合链脲佐菌素注射的大鼠模型中, 雷公藤甲素降低血清炎症因子TNF-α、IL-6、IL-1β水平, 减少肾脏TGF-β1、Smad3、α-SMA、波形蛋白表达, 增加Smad7表达, 从而减轻肾脏损伤[29]。雷公藤甲素治疗显著减轻了膜性肾小球肾炎大鼠的病理肾脏损伤, 抑制炎症细胞因子水平, 降低丙二醛 (malondialdehyde, MDA) 水平, 同时增强超氧化物歧化酶 (superoxide dismutase, SOD) 活性, 阻断IκBα的降解, 并抑制核因子NF-κB p65水平[30]。在临床试验中, 雷公藤甲素可抑制DN患者的炎症反应, 降低尿MCP-1水平, 改善肾功能[31]。采用口服和静脉注射牛血清白蛋白诱导的IgAN大鼠模型中, 雷公藤甲素灌胃治疗17周后, 显著改善了IgAN大鼠肾功能, 抑制系膜细胞增生、系膜区扩张和IgA的沉积, 降低了血清中IL-1β和IL-18水平, 可能通过下调NLRP3和TLR4表达发挥抗炎作用[32]。

2.4 其他机制

此外, 雷公藤甲素还具有其他机制。如来自IgAN患者的扁桃体单个核细胞处于由Bcl-2家族蛋白介导的凋亡抑制状态, 而雷公藤甲素治疗可能逆转这种状态[33]。雷公藤甲素还能抑制促炎因子诱导的肾小管上皮细胞II类MHC、B7-1和B7-2共刺激因子的过表达[34], 抑制TNF-α诱导的人近曲小管上皮细胞中C3、B7h和CD40的表达[35], 在非细胞毒性浓度下, 下调TNF-α刺激的肾小管上皮细胞上B7-H1的表达, 该效应依赖于转录因子NF-κB[36]。

3 雷公藤甲素的肾毒性及其作用机制

3.1 肾毒性表现

随着雷公藤甲素的广泛应用, 其临床安全性问题备受关注, 尤其是肾毒性限制了其应用并受到广泛关注。雷公藤甲素导致肾结构和功能严重受损, 表现为肾小管损伤及短时间内血清肌酐和尿素氮浓度显著增加。但使用抗氧化剂维生素C预处理可显著改善雷公藤甲素引起的肾SOD和谷胱甘肽过氧化物酶 (glutathione peroxidase, GSH-Px) 活性降低, 使肾MDA含量明显恢复正常, 并减轻肾小管和肾功能的损伤[37]。对Wistar大鼠进行为期28天的雷公藤甲素灌胃处理, 病理结果显示雷公藤甲素的肾毒性主要表现为近端小管上皮细胞相互脱离, 血尿素氮水平显著升高, 闭合小环蛋白1的定位发生显著改变, 且经处理后大鼠近端小管对异硫氰酸荧光素标记的右旋糖酐的摄取量明显降低。相应的体外实验显示雷公藤甲素导致了体外NRK-52E细胞紧密连接复合体的改变, 进而使得细胞旁路通透

性发生改变[38]。虽然在体内实验中, 长期高剂量雷公藤甲素处理未导致小鼠出现足细胞损伤、关键基因下调和蛋白尿, 且对体外分离的肾小球足细胞也无毒性。然而, 在永生化的健康足细胞中, 仅 10 μg·L^{-1} 的雷公藤甲素就足以激活 p38 MAPK、p53 和 BAX 的促凋亡信号, 诱导足细胞凋亡, 更高浓度的雷公藤甲素会进一步加剧 p38、p53 和 BAX 的激活及凋亡过程。此外, 雷公藤甲素严重下调了对足细胞结构和功能至关重要的基因[39]。

3.2 基于组学的肾毒性机制

整合基于 iTRAQ 的 2D-LC-MS/MS 蛋白质组学和靶向脂肪酸分析研究, 发现与雷公藤甲素毒性相关的差异表达蛋白质和脂肪酸均参与了细胞脂解作用、过氧化物酶体脂肪酸 β-氧化等途径, 且参与脂肪酸代谢的细胞色素 P450 蛋白家族成员中的 YP2E1 与雷公藤甲素的毒性紧密相连[40]。结合蛋白质组学和代谢组学方法, Xie 等[41]鉴定出与雷公藤甲素诱导的肾毒性相关的蛋白质和小分子代谢物。高分辨率代谢组学数据显示, 包括次黄嘌呤、磷脂酰胆碱 [phosphatidylcholine, PC (22∶0/18∶4)]、鞘氨醇、苯丙氨酸等在内的 9 种代谢物水平发生显著变化。富集分析表明, 涉及的代谢途径包括嘌呤和嘧啶代谢、甘油和磷脂代谢、鞘脂代谢及氨基酸代谢。Huang 等[42]结合网络药理学和靶向代谢组学的方法, 发现了与雷公藤甲素肾毒性相关的 6 种生物标志物: 二氢乳清酸、胸苷、2′-脱氧鸟苷、尿酸、腺苷和黄嘌呤。同时, Toll 样受体信号通路的激活可促进下游蛋白 NF-κB 的磷酸化, 进而引发炎症反应, 最终导致肾毒性。Wu 等[43]在单细胞水平上全面分析了雷公藤甲素肾毒性相关的转录组特征和细胞组成, 发现雷公藤甲素暴露后, 肾单位上皮细胞表现出异质性反应。雷公藤甲素通过激活内皮细胞免疫和损伤成纤维细胞来破坏血管功能, 同时触发针对 Macro_C1 细胞的骨桥蛋白 SPP1 信号通路, 导致免疫细胞严重受损及促炎性 Macro_C1 细胞的激活, 从而加剧肾脏毒性。此外, 在雷公藤甲素引起的迟发型超敏反应 Balb/c 小鼠中, 高剂量的雷公藤甲素可引起严重的肝肾损伤。深入分析发现, 雷公藤甲素主要影响参与鞘脂代谢的酶, 导致神经酰胺 (ceramides, Cers)、鞘磷脂和鞘氨醇的水平升高, 而二氢神经酰胺和己糖神经酰胺下调。肝脏中的 CerS2、CerS4、CerS5 和 CerS6 及肾脏中的 Cerk 等几种酶可能是雷公藤甲素引起毒性作用的罪魁祸首[44]。

3.3 其他机制

雷公藤甲素还能破坏抗氧化系统, 引发氧化应激, 而氧化应激又会进一步加重雷公藤甲素诱导的急性肾毒性。Yan 等[33]发现单次腹腔注射大剂量雷公藤甲素可导致大鼠严重的氧化应激。具体表现为肾组织 SOD 和 GSH-Px 活性显著降低, MDA 含量显著升高。有研究发现, 雷公藤甲素肾毒性的潜在机制可能是由于过量消耗黄嘌呤和尿酸, 导致体内氧化应激释放大量 ROS[38]。利用雷公藤甲素在 BALB/c 小鼠和人类肾小管上皮细胞中建立肾损伤模型, 研究发现雷公藤甲素促进 STING、TBK1 和 IRF3 的磷酸化水平增强, 并上调了 IFN-β 的表达。由于 IFN-β 是 cGAS-STING 信号通路的产物, 而 STING 抑制剂 C176 对雷公藤甲素引起的肾细胞损伤具有保护作用, 这表明 cGAS-STING 信号通路参与了雷公藤甲素诱导的肾毒性[45]。

综上所述, 雷公藤甲素的毒性机制复杂多样, 涉及多个代谢途径、信号通路和细胞过程。深入理解这些机制有助于发现新的治疗靶点和诊断标志物, 为开发更安全有效的雷公藤甲素治疗策略提供科学依据。

4 靶向肾脏的雷公藤甲素递送系统

雷公藤甲素的口服吸收率较差, 血浆半衰期短。游离的雷公藤甲素全身分布广, 肝、睾丸、骨髓药物浓度高, 通过靶向设计可以减少其他器官暴露, 实现肾外器官低分布, 降低毒性。采用纳米粒、脂质体或白蛋白纳米粒等介质包载后, 雷公藤甲素在水中溶解度提高, 且避免了水解与氧化, 提高了治疗效果。靶向肾脏的雷公藤甲素递送系统可以很好地解决其水溶性差、稳定性差、肾组织选择性低和毒性大等问题, 以此来克服雷公藤甲素在临床上所面临的治疗局限性。

4.1 基于偶联技术的靶向递送系统

鉴于溶菌酶对肾脏近端小管细胞有特异性蓄积能力, 可在血浆中稳定存在、在溶酶体环境中快速释放药物, Zheng 等[46]通过化学偶联技术开发了雷公藤甲素−溶菌酶偶联物 (triptolide-lysozyme conjugate, TP-LZM), 可有效抑制脂多糖 (lipopolysaccharide, LPS) 诱导的炎症反应, 且对正常肾细胞毒性低于游离雷公藤甲素。在此基础上, 该研究团队[47]又合成了一种 14-琥珀酰雷公藤甲素溶菌酶 (14-succinyl triptolide-lysozyme conjugate, TPS-LZM) 偶联物, 可提高雷公藤甲素靶向递送至近曲小管上皮细胞的效率, 在极低浓度下即可显著逆转肾缺血再灌注 (ischemia/reperfusion, I/R) 损伤动物模型的疾病进展, 且比游离雷公藤甲素的肝毒性低, 对免疫和生殖系统也无不良影响。Zhou 等[48]通过氨基甲酸酯键将雷公藤甲素与 2-葡萄糖胺偶联生成雷公藤甲素−葡萄糖胺偶联物 (triptolide-glucosamine conjugate, TPG)。在 I/R 损伤小鼠和大鼠中, TPG 更有效地改善了肾脏损伤的发展进程, 且较单独的雷公藤甲素具有更低的肝脏、雄性生殖系统和免疫系统毒性。该研究团队[49]进一步的研究表明 TPG 通过巨蛋白受体相互作用靶向递送近曲小管。在 I/R 处理的大鼠中, 与雷公

藤甲素单独给药相比, TPG给药使肾脏中促炎细胞因子如TNF-α、IL-6、IL-1、TGF-β和趋化细胞因子MCP-1水平下降得更为显著, 且更显著地抑制了肾脏中氧化应激和细胞内黏附分子水平的升高。GSHPD是由谷胱甘肽修饰的聚酰胺–胺树枝状聚合物构成的, 并且与雷公藤甲素相连。在儿童肾病综合征患者中, GSHPD能够被运输到肾小球。在肾小球中, 过量表达的γ-谷氨酰转肽酶会激活谷胱甘肽的γ-谷氨酰转移反应。这一反应产生的阳离子偶联物会迅速经历胞吞作用和胞吐作用, 从而增强了其在肾脏的积累及细胞内吞。活性雷公藤甲素会通过细胞内酶的水解作用逐渐释放, 使得治疗效果得以持续, 进而显著改善肾的生理功能[50]。

4.2 纳米颗粒递送系统

纳米颗粒给药系统作为一种前沿的药物递送技术, 近年来在药物递送领域取得了显著进展, 展现出巨大的应用潜力。其核心原理是利用纳米颗粒的独特物理化学性质, 如小尺寸、高比表面积和可修饰性, 将药物包裹或结合在纳米颗粒内部或表面, 从而实现药物的高效递送。基于人血清白蛋白肽片段PF-A299-585的肾脏靶向递送系统, Yuan等[51]合成了雷公藤甲素纳米药物(TPS-PF-A299-585), 该纳米药物在保留雷公藤甲素抗炎活性的同时显著降低了游离药物的细胞毒性, 可有效富集于肾脏, 通过靶向递送显著减轻了膜性肾病大鼠的肾脏炎症和病理损伤。Xue等[52]开发了雷公藤甲素–固体脂质纳米粒 (TP-SLN)。毒代动力学结果显示, 与游离雷公藤甲素相比, 其曲线下面积显著增加, 达峰时间和平均滞留时间显著延长, 最大血药浓度显著降低, 表明纳米制剂促进了雷公藤甲素的吸收并具有缓释特性, 是增强疗效的重要机制。组织分布结果表明, TP-SLN组中肺和脾脏中的雷公藤甲素浓度有增加趋势, 而血浆、肝脏、肾脏和睾丸中的雷公藤甲素浓度则有降低趋势, 在多个时间点, TP-SLN组睾丸组织中的雷公藤甲素浓度低于游离雷公藤甲素组。Huang等[53]开发了叶酸修饰的纳米颗粒 (folate-modified pluronic F127/P123 nanoparticles, FPNPs), 可通过叶酸受体介导的内吞作用增强细胞摄取, 显著提高肾脏选择性并延长药物滞留时间, 降低急性肾小管损伤指数、改善肾功能指标, 同时显著减轻肝、肾和生殖系统毒性。Deng等[54]通过纳米沉淀法制备了具有良好细胞相容性的包载雷公藤甲素的中尺度纳米粒 (TP-MNPs), 具有单分散性、粒径均一性、肾脏靶向性优异和药物滞留时间长的特性。极低剂量的TP-MNPs可显著降低I/R小鼠的血清肌酐、尿素氮、抑制补体激活及ERK信号通路活化, 且小鼠的转氨酶水平降低、肝脏、生殖毒性和免疫毒性均显著降低, 如丙氨酸氨基转移酶和天门冬氨酸氨基转移酶水平更低, $CD4^+/CD8^+$比值更高。Liu等[55]采用聚乳酸(polylactic acid, PLA) 纳米颗粒作为雷公藤甲素的载体进行包裹。与相同剂量的游离雷公藤甲素相比, 载药PLA纳米颗粒可减轻雷公藤甲素的肾毒性。长期应用时, 剂量越高 (0.6 $mg\cdot kg^{-1}$), 这种趋势越明显。Guo等[56]设计了一种级联靶向纳米化系统TL-N@TP, 集成了三苯基膦和溶菌酶功能化的PEG-PLGA共聚物, 用于肾脏特异性递送。该纳米平台能够靶向受损肾脏并定位在急性肾损伤 (acute kidney injury, AKI) 小鼠的肾小管细胞中, 并显示出抗氧化、抗炎和抗凋亡作用, 有效地改善了肾功能。仿生高密度脂蛋白 (biom imetic high-density lipoprotein, bHDL) 脂质纳米颗粒通过肾损伤分子-1介导的内化对受损伤的肾小管上皮细胞具有优异的靶向能力。因此, 将雷公藤甲素与尼达尼布共加载到bHDL纳米颗粒上, 靶向递送并使疗效相互增强, 在不同慢性肾脏病小鼠模型中有效减少肾损伤, 缓解肾纤维化。bHDL载体还具有较高的可制造性、良好的安全性, 并充分降低了雷公藤甲素的毒性[57]。

4.3 基于聚合物胶束系统的递送系统

胶束体系统是利用两亲性聚合物在水中自组装形成的纳米级胶束结构, 将药物包裹在胶束的疏水核心中, 从而实现药物的高效递送和靶向释放。Xu等[58]开发了一种新型含雷公藤甲素聚合物胶束体系统 (TP-PM), 可显著提高睾丸的酸性磷酸酶活性, 降低血清中的MDA水平。Yin等[59]通过薄膜水化法制备含载雷公藤甲素的叶酸修饰混合普朗尼克胶束 (FA-F-127/F-68-TPL), 体外对肝癌细胞毒性显著增强, 体内抑瘤效果优于游离药物, 且可通过肾脏高效排泄, 避免药物在长时间循环中释放并减少对正常组织的潜在损伤, 安全性良好。

4.4 基于脂质体修饰技术的递送系统

脂质体是一种由磷脂双分子层构成的纳米级囊泡, 能够包裹药物并将其递送至目标部位。Yuan等[60]首次将雷公藤甲素装载到3,5-双十五烷氧基苯盐酸盐(TRX-20) 修饰脂质体 (TRX-LP), 并进一步用PEG5000修饰 (PEG-TRX-TP-LP), 以延长其在血液中的循环时间并增强雷公藤甲素介导的免疫抑制作用。由于其与系膜细胞的特异性结合, 与同剂量游离的雷公藤甲素相比, PEG-TRX-TP-LP在体外可有效抑制LPS刺激的系膜细胞释放NO和TNF-α, 显示出更好的抗炎作用, 体内PEG-TRX-TP-LP有效减轻了膜性肾病大鼠的症状, 并改善了包括蛋白尿、血清胆固醇和白蛋白在内的生化指标, 且全身毒性显著降低。

4.5 开发衍生物

除了上述纳米给药等方法, Qi等[61]以2-葡萄糖胺作为糖基供体, 雷公藤甲素作为受体, 生成了一种不可水解

的雷公藤甲素衍生物−雷公藤甲素氨基糖苷 (triptolide aminoglycoside, TPAG)。与雷公藤甲素相比, TPAG 显示出 6.94 倍的肾脏暴露量和 13.96 倍的肾脏平均滞留时间。此外, TPAG 对 I/R 大鼠显示出更好的保护作用。与雷公藤甲素的多器官毒性相比, TPAG 对肾脏和生殖系统的毒性最小, 并显著降低了对肝脏和免疫系统的毒性。Kim 等[62]开发了一种水溶性雷公藤甲素衍生物 14-琥珀酰雷公内酯钠盐 (PG490-88), 可显著降低顺铂诱导的 AKI 小鼠模型的血尿素氮、血肌酐和肾小管坏死程度, 机制可能与降低 p-ERK 通路相关。雷公藤甲素靶向肾脏递送系统总结见表 1[46-48,50-62]。

总之, 这些肾脏靶向递送系统的研究为降低雷公藤甲素的毒性、提高其疗效提供了多种方法和思路, 展示了良好的应用前景。

Table 1 A renal-targeted triptolide drug delivery system. TP-LZM: Triptolide-lysozyme conjugate; TPS-LZM: 14-Succinyl triptolide-lysozyme conjugate; TPG: Triptolide-glucosamine conjugate; GSHPD: GSH-modified PAMAM-TP conjugate; TPS-PF-A299-585: 14-Succinyl triptolide-PF-A299-585 conjugate; TP-SLN: Triptolide-loaded solid lipid nanoparticles; FPNPs: Folate-modified pluronic F127/P123 nanoparticles; TP-MNPs: Triptolide-loaded magnetic nanoparticles; PLA: Polylactic acid; TL-N@TP: Triptolide-loaded TPP-LZM-anchored nanocarrier @ TP (or TP derivative); TP/BIBF-bHDL: Triptolide- and nintedanib-*co*-loaded biomimetic high-density lipoprotein nanoparticles; TP-PM: Triptolide-loaded polymeric micelles; FA-F-127/F-68-TPL: Folic-acid-decorated pluronic F-127/F-68 mixed micelles loaded with triptolide; PEG-TRX-TP-LP: PEGylated TRX-20-modified triptolide-loaded liposomes; TPAG: Triptolide aminoglycoside; PG490-88: 14-(Succinoyl-glucosaminyl) triptolide; PF: Peptide fragment; PEG: Polyethylene glycol; PLGA: Poly [lactic-*co*-glycolic acid]; BIBF: Nintedanib; FA: Folic acid; TRX: Triproline-modified and X-shaped structure

Type	Drug delivery system name	Route of administration	Preparation method	Advantage	Ref.
Conjugation technology	TP-LZM	Parenteral administration	Developed *via* chemical conjugation technology	Suppresses inflammatory responses while exhibiting low cytotoxicity toward normal renal cells	[46]
	TPS-LZM	Parenteral administration	14-Succinyl triptolide was conjugated with lysozyme to generate the conjugate	Enhanced targeting delivery efficiency; intervenes in I/R animal models at ultra-low concentrations, with minimal hepatotoxicity and no adverse effects on the immune or reproductive systems	[47]
	TPG	Parenteral administration	Triptolide was conjugated with 2-glucosamine *via* a carbamate bond to generate the conjugate	Effectively ameliorates renal injury and suppresses oxidative stress, while exhibiting significantly lower toxicity toward the liver, male reproductive system, and immune system	[48, 49]
	GSHPD	Parenteral administration	Composed of generation 5 polyamidoamine dendrimer chemically conjugated with triptolide prodrug and glutathione	Enhances renal accumulation and intracellular uptake, provides sustained therapeutic efficacy, and markedly restores renal physiological function	[50]
Nanoparticle-based drug delivery	TPS-PF-A299-585	Parenteral administration	Synthesis of a targeted delivery system based on the human serum albumin peptide fragment PF-A299-585	Enhanced anti-inflammatory activity, reduced cytotoxicity, and preferential accumulation in the kidney	[51]
	TP-SLN	Oral administration	Triptolide was incorporated into solid lipid nanoparticles to produce the triptolide-SLN formulation	Features sustained-release properties, promotes absorption to enhance therapeutic efficacy, and maintains low concentrations in non-renal tissues	[52]
	FPNPs	Parenteral administration	Folate-modified nanoparticles	Improved kidney selectivity, prolonged drug residence time, reduced acute tubular damage index, and diminished toxicity to the kidney, liver, and reproductive system	[53]
	TP-MNPs	Parenteral administration	Mesoscale nanoparticles loaded with triptolide were prepared *via* nanoprecipitation	Monodisperse with uniform particle size, excellent kidney targeting, prolonged drug retention, and reduced hepatic, reproductive, and immunologic toxicity	[54]
	PLA	Oral administration	Using polylactic acid nanoparticles as the carrier	Reduces nephrotoxicity	[55]
	TL-N@TP	Parenteral administration	A cascade-targeting nanosystem integrating triphenylphosphonium- and lysozyme-functionalized PEG-PLGA copolymers	Attenuates oxidative stress and inflammation, effectively restoring renal function	[56]

Continued

Type	Drug delivery system name	Route of administration	Preparation method	Advantage	Ref.
	TP/BIBF-bHDL	Parenteral administration	The anti-inflammatory agent triptolide and the antifibrotic agent BIBF were co-encapsulated into bHDL to obtain co-loaded nanoparticles	Attenuates renal injury, ameliorates renal fibrosis, and markedly diminishes overall toxicity	[57]
Micelle-based system	TP-PM	Parenteral administration	Triptolide-loaded polymeric micelle system	Increases acid phosphatase activity and reduces serum MDA levels	[58]
	FA-F-127/F-68-TPL	Parenteral administration	Folate-decorated mixed Pluronic micelles loaded with triptolide were prepared by the thin-film hydration method	Superior tumor-suppressive efficacy, high renal excretion without premature drug release, and an excellent safety profile	[59]
Liposome surface modification technology	PEG-TRX-TP-LP	Parenteral administration	Triptolide was loaded into 3,5-dipentadecyloxybenzene hydrochloride-modified liposomes and subsequently PEGylated with PEG5000	Prolonged blood-circulation time, intensified immunosuppressive action, potent anti-inflammatory effects, and markedly reduced systemic toxicity	[60]
Derivative	TPAG	Parenteral administration	Using 2-glucosamine as the glycosyl donor and triptolide as the glycosyl acceptor, the triptolide aminoglycoside derivative was synthesized	Increased kidney exposure and prolonged mean residence time in renal tissue, with a significant reduction in toxicity	[61]
	PG490-88	Parenteral administration	Water-soluble triptolide derivative: 14-succinyl triptolide sodium salt	Significantly reduces blood urea nitrogen, serum creatinine, and the extent of renal tubular necrosis	[62]

5 总结与展望

雷公藤甲素作为雷公藤中极为关键的活性成分之一, 其多靶点、强效的抗炎、抗纤维化及足细胞保护潜力已被大量实验证实, 为DN和IgAN等难治性肾脏疾病提供了治疗思路。然而, 其临床转化仍受两大瓶颈限制, 显著的肝肾毒性与低水溶性的缺陷及缺乏对肾脏病灶的精准富集而导致治疗窗狭窄。现阶段, 相关研究主要集中在开发高效的肾脏靶向递送系统方面, 以此来克服雷公藤甲素所面临的局限性。这些药物递送方法有效地增强了雷公藤甲素的肾脏靶向性, 进而提升了治疗效果, 显著降低雷公藤甲素在全身的暴露量及对非靶器官的毒性影响。

在未来, 要进一步探究雷公藤甲素发挥肾脏保护作用及诱导产生毒性反应的精确分子机制, 重点关注其在特定肾脏细胞类型, 如足细胞、系膜细胞、肾小管上皮细胞等的具体作用及对相关信号网络的调控作用。不断改进现有递送系统的靶向效率、载药量、稳定性及生物相容性等性能指标, 同时积极探索新型的智能响应型 (例如pH响应、ROS响应等) 和具备多功能协同作用的递送平台。

总的来说, 雷公藤甲素在肾脏疾病治疗领域展现出极为广阔的前景。只要持续不断地开展深入的机制研究, 着力开发创新的递送技术, 并且严谨地推进临床转化工作, 雷公藤甲素就很有希望突破现有的瓶颈制约, 最终成为一种具有重大临床价值的肾脏疾病治疗药物。

作者贡献: 卢梦丹负责综述的撰写及修改; 万凤负责论文的指导与审阅。

利益冲突: 本文所有作者声明不存在利益冲突关系。

References

[1] Yu DQ, Zhang DM, Wang HB, et al. Structure modification of triptolide, a diterpenoid from *Tripterygium wilfordii* [J]. Acta Pharm Sin (药学学报), 1992, 27: 830-836.

[2] Zhou B, Li XM, Tang HY, et al. Total synthesis of novel D-ring-modified triptolide analogues: Structure-cytotoxic activity relationship studies on the D-ring of triptolide [J]. Org Biomol Chem, 2011, 9: 3176-3179.

[3] Titov DV, Gilman B, He QL, et al. XPB, a subunit of TFIIH, is a target of the natural product triptolide [J]. Nat Chem Biol, 2011, 7: 182-188.

[4] Zhou ZL, Yang YX, Ding J, et al. Triptolide: Structural modifications, structure-activity relationships, bioactivities, clinical development and mechanisms [J]. Nat Prod Rep, 2012, 29: 457-475.

[5] Yang QQ, Sun MJ, Chen Y, et al. Triptolide protects podocytes from TGF-β-induced injury by preventing miR-30 downregulation [J]. Am J Transl Res, 2017, 9: 5150-5159.

[6] Wu W, Liu BH, Wan YG, et al. Triptolide inhibits NLRP3 inflammasome activation and ameliorates podocyte epithelial-mesenchymal transition induced by high glucose [J]. China J Chin Mater Med (中国中药杂志), 2019, 44: 5457-5464.

[7] Shi G, Wu W, Wan YG, et al. Low dose of triptolide ameliorates podocyte epithelial-mesenchymal transition induced by high dose of *D*-glucose *via* inhibiting Wnt3α/β-catenin signaling pathway activation [J]. China J Chin Mater Med (中国中药杂志), 2018, 43: 139-146.

[8] Chen ZH, Qin WS, Zeng CH, et al. Triptolide reduces proteinuria

in experimental membranous nephropathy and protects against C5b-9-induced podocyte injury *in vitro* [J]. Kidney Int, 2010, 77: 974-988.

[9] Zheng CX, Chen ZH, Zeng CH, et al. Triptolide protects podocytes from puromycin aminonucleoside induced injury *in vivo* and *in vitro* [J]. Kidney Int, 2008, 74: 596-612.

[10] Tang YW, Jiang MY, Cao JW, et al. Triptolide decreases podocytes permeability by regulating TET2-mediated hydroxymethylation of ZO-1 [J]. Exp Biol Med (Maywood), 2024, 249: 10051.

[11] Wan F, Tang YW, Tang XL, et al. TET2 mediated demethylation is involved in the protective effect of triptolide on podocytes [J]. Am J Transl Res, 2021, 13: 1233-1244.

[12] Wang L, Zhang LW, Hou Q, et al. Triptolide attenuates proteinuria and podocyte apoptosis *via* inhibition of NF-κB/GADD45B [J]. Sci Rep, 2018, 8: 10843.

[13] Zhai XW, Wang L, Xu C, et al. Triptolide preserves glomerular barrier function *via* the inhibition of p53-mediated increase of GADD45B [J]. Arch Biochem Biophys, 2019, 671: 210-217.

[14] Lv CL, Cheng TY, Zhang BB, et al. Triptolide protects against podocyte injury in diabetic nephropathy by activating the Nrf2/HO-1 pathway and inhibiting the NLRP3 inflammasome pathway [J]. Ren Fail, 2023, 45: 2165103.

[15] Gao J, Liang Z, Zhao F, et al. Triptolide inhibits oxidative stress and inflammation *via* the microRNA-155-5p/brain-derived neurotrophic factor to reduce podocyte injury in mice with diabetic nephropathy [J]. Bioengineered, 2022, 13: 12275-12288.

[16] Ren LY, Wan RR, Chen Z, et al. Triptolide alleviates podocyte epithelial-mesenchymal transition *via* Kindlin-2 and EMT-related TGF-β/Smad signaling pathway in diabetic kidney disease [J]. Appl Biochem Biotechnol, 2022, 194: 1000-1012.

[17] Wang HQ, Wu HX, Shi WQ, et al. Triptolide attenuates renal slit diagram to tight junction transition in diabetic kidney disease by regulating Nrf2-ferroptosis pathway [J]. Am J Chin Med, 2024, 52: 2161-2185.

[18] Gao Q, Shen WW, Qin WS, et al. Treatment of *db*/*db* diabetic mice with triptolide: A novel therapy for diabetic nephropathy [J]. Nephrol Dial Transplant, 2010, 25: 3539-3547.

[19] Cao YJ, Huang XZ, Fan YP, et al. Protective effect of triptolide against glomerular mesangial cell proliferation and glomerular fibrosis in rats involves the TGF-β1/Smad signaling pathway [J]. Evid Based Complement Alternat Med, 2015, 2015: 814089.

[20] Zeng R, Duan L, Sun LN, et al. Effect of triptolide on expression of thrombospondin-1 and transforming growth factor-β1 in renal tubular cells [J]. Ren Fail, 2015, 37: 1039-1043.

[21] Han F, Wang SS, Chang YP, et al. Triptolide prevents extracellular matrix accumulation in experimental diabetic kidney disease by targeting microRNA-137/Notch1 pathway [J]. J Cell Physiol, 2018, 233: 2225-2237.

[22] Li XY, Wang SS, Han Z, et al. Triptolide restores autophagy to alleviate diabetic renal fibrosis through the miR-141-3p/PTEN/Akt/mTOR pathway [J]. Mol Ther Nucleic Acids, 2017, 9: 48-56.

[23] Zhao L, Lan ZX, Peng L, et al. Triptolide promotes autophagy to inhibit mesangial cell proliferation in IgA nephropathy *via* the CARD9/p38 MAPK pathway [J]. Cell Prolif, 2022, 55: e13278.

[24] Zhu JJ, Wang BF, Hong YZ, et al. Effect of triptolide on the expression of RANTES in the renal tissue of diabetic nephropathy rats [J]. Chin J Integr Tradit West Med (中国中西医结合杂志), 2014, 34: 1231-1237.

[25] Han F, Xue M, Chang YP, et al. Triptolide suppresses glomerular mesangial cell proliferation in diabetic nephropathy is associated with inhibition of PDK1/Akt/mTOR pathway [J]. Int J Biol Sci, 2017, 13: 1266-1275.

[26] Xue M, Cheng Y, Han F, et al. Triptolide attenuates renal tubular epithelial-mesenchymal transition *via* the miR-188-5p-mediated PI3K/AKT pathway in diabetic kidney disease [J]. Int J Biol Sci, 2018, 14: 1545-1557.

[27] Zhang J, Zhu MJ, Zhang SY, et al. Triptolide attenuates renal damage by limiting inflammatory responses in DOCA-salt hypertension [J]. Int Immunopharmacol, 2020, 89: 107035.

[28] Guo H, Pan C, Chang B, et al. Triptolide improves diabetic nephropathy by regulating Th cell balance and macrophage infiltration in rat models of diabetic nephropathy [J]. Exp Clin Endocrinol Diabetes, 2016, 124: 389-398.

[29] Pang RY, Gu DH. Triptolide improves renal injury in diabetic nephropathy rats through TGF-β1/Smads signal pathway [J]. Endocr Metab Immune Disord Drug Targets, 2021, 21: 1905-1911.

[30] Zhou Y, Hong Y, Huang HH. Triptolide attenuates inflammatory response in membranous glomerulo-nephritis rat *via* downregulation of NF-κB signaling pathway [J]. Kidney Blood Press Res, 2016, 41: 901-910.

[31] Song HX, Gong J, Chen W. Effect of triptolide on urinary monocyte chemottractant protein-1 in patients with diabetic nephropathy [J]. Chin J Integr Tradit West Med (中国中西医结合杂志), 2005, 25: 416-418.

[32] He LY, Peng XF, Liu GY, et al. Anti-inflammatory effects of triptolide on IgA nephropathy in rats [J]. Immunopharmacol Immunotoxicol, 2015, 37: 421-427.

[33] Yan WZ, Peng YM, Liu C, et al. Efficacy of triptolide on the apoptosis of tonsillar mononuclear cells from patients with IgA nephropathy [J]. Ren Fail, 2016, 38: 109-116.

[34] Li H, Liu ZH, Dai CS, et al. Triptolide inhibits proinflammatory factor-induced over-expression of class II MHC and B7 molecules in renal tubular epithelial cells [J]. Acta Pharmacol Sin, 2002, 23: 775-781.

[35] Hong YZ, Zhou WD, Li K, et al. Triptolide is a potent suppressant of C3, CD40 and B7h expression in activated human proximal tubular epithelial cells [J]. Kidney Int, 2002, 62: 1291-1300.

[36] Chen YW, Zhang JB, Li JY, et al. Triptolide inhibits B7-H1

expression on proinflammatory factor activated renal tubular epithelial cells by decreasing NF-κB transcription [J]. Mol Immunol, 2006, 43: 1088-1098.

[37] Yang F, Ren L, Zhuo L, et al. Involvement of oxidative stress in the mechanism of triptolide-induced acute nephrotoxicity in rats [J]. Exp Toxicol Pathol, 2012, 64: 905-911.

[38] Sun LX, Li H, Huang X, et al. Triptolide alters barrier function in renal proximal tubular cells in rats [J]. Toxicol Lett, 2013, 223: 96-102.

[39] Sun MJ, Song H, Ye YT, et al. Differential toxicities of triptolide to immortalized podocytes and the podocytes *in vivo* [J]. Biomed Pharmacother, 2019, 109: 2375-2386.

[40] Li ML, Hu T, Tie C, et al. Quantitative proteomics and targeted fatty acids analysis reveal the damage of triptolide in liver and kidney [J]. Proteomics, 2017, 17: 22.

[41] Xie LJ, Zhao YW, Duan JY, et al. Integrated proteomics and metabolomics reveal the mechanism of nephrotoxicity induced by triptolide [J]. Chem Res Toxicol, 2020, 33: 1897-1906.

[42] Huang W, Liu CX, Xie LJ, et al. Integrated network pharmacology and targeted metabolomics to reveal the mechanism of nephrotoxicity of triptolide [J]. Toxicol Res (Camb), 2019, 8: 850-861.

[43] Wu JP, Guo JN, Xia SY, et al. A single-cell transcriptome profiling of triptolide-induced nephrotoxicity in mice [J]. Adv Biol (Weinh), 2024, 8: e2400120.

[44] Qu L, Qu F, Jia ZX, et al. Integrated targeted sphingolipidomics and transcriptomics reveal abnormal sphingolipid metabolism as a novel mechanism of the hepatotoxicity and nephrotoxicity of triptolide [J]. J Ethnopharmacol, 2015, 170: 28-38.

[45] Lu J, Zhang Y, Dong HY, et al. New mechanism of nephrotoxicity of triptolide: Oxidative stress promotes cGAS-STING signaling pathway [J]. Free Radic Biol Med, 2022, 188: 26-34.

[46] Zheng Q, Gong T, Sun X, et al. Synthesis, characterization and *in vitro* evaluation of triptolide-lysozyme conjugate for renal targeting delivery of triptolide [J]. Arch Pharm Res, 2006, 29: 1164-1170.

[47] Zhang ZR, Zheng Q, Han J, et al. The targeting of 14-succinate triptolide-lysozyme conjugate to proximal renal tubular epithelial cells [J]. Biomaterials, 2009, 30: 1372-1381.

[48] Zhou P, Sun X, Gong T, et al. Conjugating glucosamine to triptolide to enhance its protective effect against renal ischemia-reperfusion injury and reduce its toxicity [J]. J Drug Target, 2014, 22: 200-210.

[49] Fu Y, Lin Q, Gong T, et al. Renal-targeting triptolide-glucosamine conjugate exhibits lower toxicity and superior efficacy in attenuation of ischemia/reperfusion renal injury in rats [J]. Acta Pharmacol Sin, 2016, 37: 1467-1480.

[50] Chen DF, Xu JJ, Lv S, et al. Enzyme-activatable kidney-targeted dendrimer-drug conjugate for efficient childhood nephrotic syndrome therapy [J]. Theranostics, 2024, 14: 6991-7006.

[51] Yuan ZX, Wu XJ, Mo J, et al. Renal targeted delivery of triptolide by conjugation to the fragment peptide of human serum albumin [J]. Eur J Pharm Biopharm, 2015, 94: 363-371.

[52] Xue M, Zhao Y, Li XJ, et al. Comparison of toxicokinetic and tissue distribution of triptolide-loaded solid lipid nanoparticles *vs* free triptolide in rats [J]. Eur J Pharm Sci, 2012, 47: 713-717.

[53] Huang CL, Zeng T, Li JW, et al. Folate receptor-mediated renal-targeting nanoplatform for the specific delivery of triptolide to treat renal ischemia/reperfusion injury [J]. ACS Biomater Sci Eng, 2019, 5: 2877-2886.

[54] Deng XL, Zeng T, Li JW, et al. Kidney-targeted triptolide-encapsulated mesoscale nanoparticles for high-efficiency treatment of kidney injury [J]. Biomater Sci, 2019, 7: 5312-5323.

[55] Liu MX, Dong J, Yang YJ, et al. Effect of poly(*D*,*L*-lactic acid) nanoparticles as triptolide carrier on abating rats renal toxicity by NMR-based metabolic analysis [J]. J Nanosci Nanotechnol, 2008, 8: 3493-3499.

[56] Guo QQ, Lu X, Zhang YQ, et al. A nanoplatform targeting cascade pathways for enhanced triptolide delivery in acute kidney injury therapy [J]. Adv Healthc Mater, 2025, 14: e2500595.

[57] He SS, Li X, He YY, et al. High-density lipoprotein nanoparticles spontaneously target to damaged renal tubules and alleviate renal fibrosis by remodeling the fibrotic niches [J]. Nat Commun, 2025, 16: 1061.

[58] Xu LY, Qiu YS, Xu HB, et al. Acute and subacute toxicity studies on triptolide and triptolide-loaded polymeric micelles following intravenous administration in rodents [J]. Food Chem Toxicol, 2013, 57: 371-379.

[59] Yin MZ, Zhang XY, Zhang TG, et al. Folic acid-trgeted mixed pluronic micelles for delivery of triptolide [J]. Polymers (Basel), 2024, 16: 24.

[60] Yuan ZX, Jia L, Lim LY, et al. Renal-targeted delivery of triptolide by entrapment in pegylated TRX-20-modified liposomes [J]. Int J Nanomedicine, 2017, 12: 5673-5686.

[61] Qi BW, Wang XY, Zhou YY, et al. A renal-targeted triptolide aminoglycoside (TPAG) conjugate for lowering systemic toxicities of triptolide [J]. Fitoterapia, 2015, 103: 242-251.

[62] Kim HJ, Ravichandran K, Ozkok A, et al. The water-soluble triptolide derivative PG490-88 protects against cisplatin-induced acute kidney injury [J]. J Pharmacol Exp Ther, 2014, 349: 518-525.