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雷公藤红素改善自身免疫性疾病的研究进展

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摘　要

雷公藤是卫矛科雷公藤属木质藤本植物，其根部可入药，用于治疗风湿免疫性疾病，具有悠久的使用历史。雷公藤红素为雷公藤的主要活性成分之一，经由多靶点、多信号通路发挥免疫抑制效应，对自身免疫性疾病具有良好的改善作用。近年来，雷公藤红素因其潜在的药用价值引起广泛关注。本文总结雷公藤红素改善自身免疫性疾病的药理活性和机制，为其进一步研究开发提供参考。

关键词

雷公藤红素，类风湿性关节炎，银屑病，自身免疫性肝炎

Research Progress on Improving Autoimmune Diseases with Celastrol

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Abstract

Celastrol is a woody vine of the family Celastraceae, belonging to the genus *Tripterygium*. Its roots can be used as medicine to treat rheumatic and immune diseases, and it has a long history of use. Celastrol is one of the main active components of *Tripterygium wilfordii*, which exerts immunosuppressive effects through multiple targets and signaling pathways, and has a good improvement effect on autoimmune diseases. In recent years, celastrol has attracted widespread attention due to its potential medicinal value. This article summarizes the pharmacological activity and mechanism of celastrol in improving autoimmune diseases, providing reference for its further research and development.

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Keywords

Celastrol, Rheumatoid Arthritis, Psoriasis, Autoimmune Hepatitis

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1. 引言

雷公藤(*Tripterygium wilfordii* Hook. f.)属于藤本植物，最早记载于 16 世纪的《本草纲目》中，是一种使用历史悠久的中药材，目前已从中分离出约有 70 多种化学成分，包括二萜类、三萜类化合物和生物碱等[1]。雷公藤红素是从雷公藤根部提取得到的一种醌甲基化的五环三萜类化合物，是雷公藤中药用活性最高的成分之一，具有抗肿瘤、抗炎、抑制免疫和抗肥胖等生物活性[2]。含有雷公藤红素的药物现已被广泛应用于类风湿性关节炎、炎症性肠炎、肾病疾病、系统性红斑狼疮和银屑病等疾病[2] [3]。雷公藤多苷片是由国家药品监督管理局批准的用于治疗类风湿性关节炎的药物，雷公藤红素为其主要有效成分。

自身免疫性疾病是一组具有不同临床表现的异质性疾病，可分为系统性疾病和器官特异性疾病。自身免疫性疾病的常见病因是免疫耐受的破坏和自身抗体的产生，其攻击体内的特定组织和器官，自身免疫性疾病的发病机制十分复杂，环境、遗传、感染甚至心理因素共同作用将导致先天或适应性免疫反应[4]。自身免疫性疾病包括类风湿性关节炎、银屑病、自身免疫性肝炎、多发性硬化、系统性红斑狼疮和溃疡性结肠炎等。

本文总结雷公藤红素对各种自身免疫性疾病的改善作用与潜在机制，为其开发与利用提供了理论支持。

2. 雷公藤红素的药理作用

2.1. 抗肿瘤作用

雷公藤红素对乳腺癌、视网膜母细胞瘤、肺癌、胃癌和黑色素瘤等均具有广泛的抗肿瘤活性。雷公藤红素可以通过多种药理学机制抗肿瘤，包括抑制热休克蛋白 90 [5]、抑制血管的生成[6]、诱导肿瘤细胞自噬和凋亡[7]、阻止 DNA 损伤修复[8]和抑制肿瘤相关转录因子激活[9]等。

2.2. 抗炎作用

炎症性疾病导致显著的发病率和死亡率，传统药物和天然产品有望被开发成这些疾病的新疗法。目前已在炎症性疾病的各种细胞和小鼠模型中研究了雷公藤红素的抗炎作用，如肝纤维化、过敏性哮喘、骨关节炎、类风湿性关节炎、皮肤炎症、溃疡性结肠炎和脂多糖诱导的炎症等[10]。

2.3. 免疫抑制

雷公藤红素具有良好的免疫抑制作用，其可以降低关节炎动物关节中 $CD4^+$ T 和 $CD8^+$ T 细胞的数量、降低自身免疫性脑脊髓炎大鼠的 $CD3^+$ T 淋巴细胞数目。此外，雷公藤红素还可通过下调糖酵解抑制 Th17 细胞的形成，并通过促进脂肪酸氧化诱导 Treg 细胞的形成从而降低 Th17/Treg 细胞的平衡，以发挥免疫抑制作用[11]。

2.4. 抗糖尿病

II型糖尿病和肥胖被认为是全球公共卫生面临的两大挑战。雷公藤红素可作为蛋白酶体抑制剂，具有降低胰岛素抵抗和增强 β 细胞功能的作用[12]。雷公藤红素还可通过抑制脂肪组织中的 NF-κB 活化[13]、抗氧化应激[14]、通过 PI3K/Akt 途径增加葡萄糖摄取和改善线粒体功能[15]等途径抵抗II型糖尿病。

2.5. 抗病毒

雷公藤红素还具有抗病毒特性。雷公藤红素对一种病毒反式激活因子 Tat 表现出抑制作用，从而抑制艾滋病毒转录和复制[16]。雷公藤红素还对严重急性呼吸综合征(SARS)具有改善作用[17]。雷公藤红素还可通过诱导 IFN-α 的表达以及下游 JAK-STAT 信号的激活抑制登革热病毒的复制[18]。

3. 雷公藤红素对自身免疫性疾病中的改善作用与机制

3.1. 类风湿性关节炎

类风湿性关节炎(rheumatoid arthritis, RA)是一种慢性系统性自身免疫性疾病，其会造成骨损伤等[19]。雷公藤红素可以通过灌胃[20]或腹腔注射[21]给药改善佐剂性关节炎大鼠 RA 症状，通过静脉注射[22]、灌胃[23] [24]以及腹腔注射[25]给药延缓胶原诱导的小鼠及大鼠关节炎，还可通过腹腔注射给药改善前交叉韧带横断关节炎大鼠疾病症状[26] [27]。

目前关于雷公藤红素改善类风湿关节炎的作用机制也有大量研究。NLRP3 炎症小体活化在类风湿性关节炎的发病机制中有着重要的作用，雷公藤红素抑制 ROS-NF-κB 轴，这在 NLRP3 炎症小体活化过程中起到重要的作用，从而缓解大鼠关节肿胀，减少炎性细胞的浸润和滑膜增生[20]。雷公藤红素通过抑制 Ca^{2+}/钙调蛋白依赖性激酶激酶-β-AMP-活化蛋白激酶-mTOR 通路减轻佐剂性关节炎大鼠关节组织炎症[21]。雷公藤红素可通过抑制 TLR2 表达，下调滑膜 HMGB1 水平，减少滑膜增生和炎症细胞浸润，抑制炎症细胞因子 TNF-α、IL-6、IL-1β 的释放，进而缓解小鼠关节炎症状[24]。研究发现，雷公藤红素通过抑制 TNF-α 诱导的滑膜成纤维细胞的增殖和 PI3K/AKT/mTOR 信号通路减轻小鼠足跖肿胀程度[23]。含铜代谢 MURR1 结构域(COMMD)蛋白家族由从原生动物到人类存在的 10 种高度保守的蛋白组成，该蛋白参与小鼠 RA 进展，并表明雷公藤红素可以干扰 COMMD3 和 COMMD8 互作，抑制 COMMD3/8 复合物形成，进而抑制小鼠滑膜 B 细胞浸润，发挥免疫抑制作用，缓解小鼠关节炎红肿等疾病症状[25]。此外，基于活性氧敏感聚合物的雷公藤红素聚合物胶束可以提高雷公藤红素的给药效率，其经由 NF-κB 和 Notch1 途径抑制巨噬细胞向促炎性 M1 表型的极化，从而改善小鼠关节炎症状[22]。

3.2. 银屑病

银屑病是一种炎症性慢性皮肤病。雷公藤红素灌胃给药可以改善咪喹莫特(imiquimod, IMO)诱导的银屑病模型小鼠症状[28] [29]。雷公藤红素凝胶涂抹于 IMO 诱导的银屑病小鼠皮肤表面可抑制小鼠表皮增厚等疾病症状[30]。

钙内流可能导致严重的免疫缺陷病，而参与钙内流的基因钙释放激活钙调节蛋白 1 (Orai1)和基质相互作用分子 1 (STIM1)被激活会造成银屑病模型小鼠细胞因子的产生和 Th17/Th1 细胞异常活化，雷公藤红素可以通过抑制钙内流、阻止 STIM1 的完全激活以及抑制 Orai1 的部分功能，改善皮肤增厚，减少皮损中炎性细胞浸润，从而缓解银屑病模型小鼠的症状[28]。雷公藤红素可以通过抑制 Th17/Th22 细胞异常活化，减少银屑病小鼠皮肤组织 IL-17A、IL-22 等炎性因子的产生，从而改善银屑病症状[31]。雷公藤红素还可以通过增强脂肪酸氧化促进 Treg 细胞分化，并且还可以通过下调糖酵解以抑制 Th17 细胞生成，这也为研究其改善银屑病的机制提供了思路[32]。此外，研究发现雷公藤红素给药导致银屑病模型小鼠体

内干扰素调节因子 1 (IRF1)表达下调，谷胱甘肽转移酶 3 (GSTM3)表达上调，该现象同时出现在人角质形成细胞中，表明雷公藤红素可通过调节 IRF1/GSTM3 通路改善银屑病[29]。朗格罕细胞是皮肤内最主要的抗原呈递细胞，在维持皮肤稳态中发挥关键作用，研究表明雷公藤红素可以抑制朗格罕细胞与 $\gamma\delta$T 细胞之间的相互作用，下调活化的 $\gamma\delta$T 细胞比例，抑制 IL-17 分泌，减轻银屑病样炎症[30]。雷公藤红素甘露糖修饰脂质体可通过抑制树突状细胞的激活改善小鼠银屑病症状[33]。

3.3. 自身免疫性肝炎

自身免疫性肝炎(autoimmune hepatitis, AIH)是一种炎症性慢性肝病[34]。雷公藤红素可通过灌胃给药缓解刀豆蛋白 A(ConA)诱导的自身免疫性肝炎模型小鼠肝损伤和肝脏炎性细胞浸润等症状[35] [36] [37]。

雷公藤红素可通过 PI3K/AKT 途径改善急性肝损伤和慢性自身免疫性肝炎模型小鼠肝脏炎症和肝纤维化[35]。雷公藤红素经由 IL-6/STAT3 信号通路可以抑制小鼠 Th17 细胞反应，从而减少肝脏中 IL-17 的分泌，显著减轻 ConA 诱导的肝损伤，还可以抑制肝细胞凋亡，从而在小鼠自身免疫性肝炎模型中发挥免疫调节作用[37]。自身免疫性肝炎模型小鼠的血浆代谢组学研究结果显示，雷公藤红素可使血浆胆汁酸代谢和脂肪酸代谢稳态恢复，上调肝脏衣康酸水平，激活肝损伤孕烷 X 受体 (PXR)和转录因子 EB (TFEB)介导的自噬，减轻自身免疫性肝炎小鼠的肝脏炎性细胞浸润和肝损伤[36]。

3.4. 其他自身免疫性疾病

系统性红斑狼疮(systemic lupus erythematosus, SLE)是一种慢性自身免疫性疾病，遗传和环境因素比如吸烟、药物、化学品、病毒感染和肠道微生物群等都可能导致系统性红斑狼疮[38]。狼疮性肾炎是继发于 SLE 的自身免疫性肾小球肾炎，雷公藤红素腹腔注射减轻狼疮性肾炎小鼠的肾功能障碍和肾损伤，抑制肾脏 $CD3^+$ T 细胞的浸润，下调肾组织中 IL-17A、IL-17F、IL-21 等促炎细胞因子的表达，上调狼疮性肾炎小鼠肾脏、脾脏和淋巴结 $CD4^+$ $Foxo3^+$ Treg 细胞比例，改善狼疮性肾炎小鼠疾病症状[39]。

多发性硬化(multiple sclerosis, MS)是一种免疫介导的中枢神经系统疾病。雷公藤红素经由 MAPK 途径，下调实验性脑脊髓炎模型小鼠的脾脏中 MAPK 下游编码血清/糖皮质激素调节激酶 1 基因的表达，抑制 Th17 细胞反应，增加 Treg 细胞比例，上调脑源性神经营养因子表达，改善髓鞘少突胶质细胞糖蛋白抗体诱导的实验性脑脊髓炎小鼠疾病症状[40]。

格林－巴利综合征(guillain-barre syndrome, GBS)是一种急性免疫介导的麻痹性神经系统疾病，灌胃给予雷公藤红素可通过抑制 TLR4/NF-κB/STAT3 信号通路下调实验性自身免疫神经炎模型大鼠的 Th1/Th17 细胞比例，下调 IFN-γ、TBX21、IL-18、RORγT、IL-17 和 IL-23 的水平，进而改善实验性自身免疫神经炎大鼠的疾病症状[41]。

溃疡性结肠炎是一种由许多因素引起的慢性炎症性肠病，其主要症状包括结肠炎症和微生物区生态失调。灌胃[42] [43]或腹腔注射[44]雷公藤红素均可改善葡聚糖硫酸钠(DSS)或 2,4,6-三硝基苯磺酸(TNBS)诱导的结肠炎小鼠的结肠缩短和便血等疾病症状。雷公藤红素通过阻断 NF-κB 信号激活抑制 HSP90 和 NLRP3 表达，还可通过增强 AMPK/mTOR 信号促进 NLRP3 降解，抑制 NLRP3 炎症小体活化改善大鼠结肠炎[44]。雷公藤红素－果胶－三甲基壳聚糖脂质体减轻雷公藤红素的毒性，该脂质体可以下调结肠促炎因子的水平，包括 IL-6、IL-1β 和 TNF-α 等，从而改善小鼠结肠炎[45]。

4. 总结与展望

本文总结了近年来雷公藤红素改善自身免疫性疾病的作用与机制研究进展，包括类风湿性关节炎、自身免疫性肝炎、银屑病、多发性硬化、系统性红斑狼疮、格林－巴利综合征和溃疡性结肠炎。

雷公藤红素对于自身免疫性疾病具有显著的改善作用，其作用的靶点呈现多样性，但其潜在机制仍

不完全清楚。雷公藤红素的生物利用度低，毒副作用强，而且治疗窗窄，这些都限制了其在临床上的应用。仍需设计并合成低毒的雷公藤红素衍生物或采用适宜的纳米载体或脂质载体解决其安全性以及溶解度等问题。因此亟待明确雷公藤红素改善自身免疫性疾病的具体作用机制、其衍生物的设计、改良型载体的设计等，为雷公藤红素的临床应用提供理论支撑。

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