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甘草查尔酮A的药理学作用

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摘　要

甘草查尔酮A (Licochalcone A, Lico A)是甘草中提取出的天然活性化合物，因具备强大的药理学作用而引起众多国内外研究者的关注，并被广泛用于治疗炎症相关性疾病。此外，还可以作为抗菌剂应用于医学领域。我们综述了现有研究成果及最新研究进展，总结了甘草查尔酮A在治疗领域的应用及其相关的分子机制，旨在为研究者们更深入地研究甘草查尔酮A提供参考。

关键词

甘草查尔酮A，药理学作用，治疗，分子机制

Pharmacological Effect of Licochalcone A

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Abstract

Licochalcone A (Lico A) is a naturally occurring active compound derived from licorice, which has garnered significant attention from researchers both domestically and internationally due to its potent pharmacological effects. It has been extensively utilized in the treatment of inflammation-related diseases, and also exhibits antibacterial properties in the medical field. In this review, we have examined existing research findings and recent advancements, summarized the application of Licochalcone A in therapeutic settings along with its associated molecular mechanisms. The

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aim is to provide researchers with a reference for further investigation into Licochalcone A.

Keywords

Licochalcone A, Pharmacological Effect, Treatment, Molecular Mechanism

1. 引言

甘草查尔酮 A，分子式 $C_{21}H_{22}O_4$，相对分子质量 338.4，是一种由甘草根中提取分离得到的反式查尔酮类化合物，被应用于食品着色剂和烟草行业等领域。其物理外观为黄色针状结晶，化学特征为 α，β-不饱和联苯酮[1]。在 Lico A 中，查尔酮骨架被两个酚羟基，一个甲氧基和一个类异戊二烯侧链取代，其中酚羟基可以作为自由基清除剂[2]。目前研究发现，Lico A 具有抗炎[3]-[7]、抗菌[8]-[11]、抗氧化[12]、抗寄生虫[13] [14]、抗病毒[15] [16]、抗增殖和抗肿瘤[17] [18]、骨保护[19] [20]、神经保护[21]、皮肤保护[22]以及血糖血脂调节[23] [24]等多种药理学作用。

2. 抗炎作用

2.1. Lico A 对急性炎症的影响

急性炎症的特征是损伤部位周围免疫细胞的快速聚集，具有持续时间短、局部水肿和白细胞迁移等特点[25]。Lico A 在多种小鼠急性炎症模型中抑制 NF-κB 信号，如 LPS 诱导的急性肺损伤[26] [27]、LPS 诱导的急性肾损伤[28]和 DSS 诱导的结肠炎[29]。在 LPS 诱导的急性肺损伤中，Lico A 抑制了 NF-κB 和 p38/ERK MAPK 信号通路，从而降低了炎症细胞数量、肺湿/干重比、蛋白渗漏和髓过氧化物酶活性[26] [27]；在 LPS 诱导的急性肾损伤中，Lico A 通过抑制 LPS 诱导的 NF-κB 活化，减少了促炎因子 TNF-α、IL-6 和 IL-1β 的产生，降低血清 BUN 和肌酐水平[28]；而且 Lico A 还通过抑制 NF-κB 和激活 Nrf2 信号通路，下调促炎因子和氧化应激，有效缓解 DSS 诱导的结肠炎[29]。此外，Lico A 通过抑制 H_2O_2、NO、IFN-γ、TNF-α 和 IL-17 的产生，以及调节 Th1 和 Th17 细胞的免疫应答改善了髓鞘少突胶质细胞糖蛋白肽诱导的小鼠脑脊髓炎的临床症状[30]。在较高剂量下，Lico A 还通过抑制 TLR4-MAPK-NF-κB 和 Txnip-NLRP3 信号通路[7]，减少促炎因子 TNF-α、IL-6 和 IL-1β 产生，进而减轻 LPS 诱导的小鼠急性肝损伤。体外研究发现，Lico A 在 5~20 μM 剂量范围内抑制 LPS 诱导的 RAW 264.7 巨噬细胞 NO、TNF-α、IL-1β、IL-6 和 PGE2 的产生[27] [31]。此外，Lico A 通过阻断 MAPK 和 AKT/NF-κB 信号，增加 ZO-1、occludin 和 claudin-3 的蛋白水平，对 LPS 诱导的小鼠乳腺上皮细胞发挥抗炎作用[4]，并且通过抑制 NF-κB 信号和 PGE2 分泌在 TNF-α 诱导急性肺损伤模型中抑制炎症反应[32]。

2.2. Lico A 对慢性炎症的影响

慢性炎症是一个缓慢的、长期的过程，而急性炎症往往由于炎症持续存在或损伤修复不良而发展为慢性炎症。Lico A 在 IL-1β 诱导的小鼠软骨细胞关节炎模型中发挥抗炎活性，其机制主要是抑制 NF-κB 和 IκBαn 的磷酸化，减少 PGE2 和 NO 的产生；并通过阻断 NF-κB 和 Wnt/β-catenin 信号通路下调 iNOS、COX-2、ADAMTS、MMP1、MMP3 和 MMP13 的表达[33]。在胶原抗体诱导的小鼠关节炎中，Lico A 通

过激活 Keap1-Nrf2 信号通路抑制促炎因子和抗氧化酶的上调，从而减轻炎症反应[12]。此外，Lico A 还改变了小鼠类风湿性关节炎滑膜成纤维细胞膜的形态、超微结构和硬度。

杨等人研究发现，Lico A 能通过抑制 IκBα 磷酸化和降解以及 p65 核转位和磷酸化，降低抗原诱导的小鼠足爪肿胀[34]。先前研究表明，在聚肌苷酸－聚胞苷酸诱导的 BEAS-2B 细胞和原代支气管上皮细胞中，Lico A 通过抑制 KK/NF-κB/TSLP 信号传导抑制了胸腺基质淋巴细胞生成素和其他促炎症介质(如 MCP-1，RANTES 和 IL-8)的表达，进而改善哮喘症状，减缓气道炎症的进展[35]。此外，Lico A 通过阻断 VEGFR2 和 ERK1/2 信号传导并下调 caveolin-1 的表达来抑制 VEGF 诱导的小鼠气道平滑肌细胞增殖[36]。楚和黄等人研究发现，Lico A 能够抑制 Ym-2，AMCase，Muc5ac，E-选择素，CCL11，CCR3 和辅助性 T 细胞 2 型细胞因子的表达，同时动态调节丙二醛，IgE，IgG 和谷胱甘肽的水平，从而逆转 OVA 诱导的过敏性哮喘小鼠气道炎症的进展[6] [37]。

3. 抗氧化作用

氧化应激是多种疾病的基础，抑制氧化应激可能是防止疾病发病或阻碍疾病的进展的有效策略。Nrf2 作为抗氧化传感器，是缓解氧化应激和炎症相关疾病所必需的关键转录因子[38]。在正常生理条件下，Nrf2 局限于细胞质，与 Keap1 结合。然而，当面临氧化应激时，胞质 Nrf2 会易位到细胞核中，与靶基因启动子区域中的抗氧化反应元件(ARE)结合，并导致抗氧化酶如血红素加氧酶-1(HO-1)、NAD(P)H 醌脱氢酶 1 (NQO1)和谷氨酸－半胱氨酸连接酶(GCL)的表达。这些酶在中和 ROS 和维持细胞氧化还原稳态方面发挥着至关重要的作用[39]。Lico A 在 L-02 细胞中显示出抗氧化特性，研究报道其能够在暴露于氧化应激的 RAW 264.7 细胞中激活 Nrf2 介导的抗氧化反应信号[40]。SIRT1 是与氧化应激相关的生理功能调节剂，并能够通过直接去乙酰化 Nrf2，增强其转录活性[41]。在大鼠原代皮质神经元中，Lico A 通过增强 SIRT1 的活性有效减轻了氧－葡萄糖剥夺/复氧诱导的 Nrf2 信号通路的抑制[42]。Chen 等人的研究证明[40]，Lico A 可以通过增加 SOD、CAT 和 GPx 等抗氧化酶的活性，剂量依赖性地降低 L-02 细胞中的细胞氧化应激。除此以外，Lico A 还通过有效清除自由基(包括超氧阴离子、羟基自由基和过氧化氢)表现出直接的抗氧化活性[43]；过渡金属(如铁和铜)是公认的产生高活性 ROS 的催化剂，Lico A 还具有螯合过渡金属的能力，而这种螯合作用有助于防止破坏性氧化物质的形成[44]。最近 Hasan 等人发现 Lico A 也对脂质过氧化具有抑制作用，而脂质过氧化是阻止细胞膜内氧化损伤的重要机制[45]。

4. 抗微生物作用

4.1. 抗细菌作用

天然化合物 Lico A 对广泛的革兰氏阳性细菌具有良好抗菌活性。已有研究发现，Lico A 能非常有效地控制耐甲氧西林金黄色葡萄球菌菌株，抑制其 α 毒素、肠毒素 A 和 B 的分泌，其最小抑菌浓度(MIC)范围为 18.4~47.0 μM [26] [46] [47]。在刘等人的一项研究中，Lico A 显著降低了急性肺损伤小鼠肺组织中的金黄色葡萄球菌负荷[26]。沈等人的转录组学分析显示，Lico A 显著影响金黄色葡萄球菌中编码自溶相关蛋白、细胞壁蛋白、致病因子、蛋白质合成和参与荚膜合成的酶的基因水平[48]。据报道，Lico A 能有效抑制猪链球菌的生长、生物被膜形成和溶血素分泌，研究者采用基因芯片技术发现 Lico A 可能通过氨基酸代谢控制复制起始和细胞分裂抑制猪链球菌的生长[49]。Feldman M 等人发现，Lico A 和 A 型蔓越莓原花青素的组合能在低浓度下抑制牙龈卟啉单胞菌生长、生物膜形成和胶原酶活性[50]。

4.2. 抗真菌作用

查尔酮是潜在的抗真菌剂，作用于真菌细胞中的多个靶标，如细胞壁、细胞膜[51]。Lico A 靶向对

真菌存活和感染的重要代谢途径。例如在红色毛癣菌共培养物中加入 Lico A 时，麦角甾醇合成相关的 ERG1、ERG6 和 ERG11 基因被抑制；此外，Lico A 抑制参与细胞壁合成的基因(DW681613, DW687269)，并通过抑制编码苹果酸合酶、柠檬酸合酶，尤其是乙醛酸循环的关键酶 ICL1 的基因来干扰乙醛酸循环[52]。有研究显示，Lico A 能与制霉菌素协同对白色念珠菌菌丝形成产生抑制作用[53]；进一步研究发现，Lico A 具有抑制白色念珠菌生物膜形成的能力和阻止白色念珠菌酵母向菌丝转化的能力，并且 Lico A 还能够显著降低白色念珠菌分泌的蛋白酶和磷脂酶的蛋白水解酶活性[53] [54]。口腔念珠菌病是影响口腔最常见的真菌感染之一[55]。体内实验显示 Lico A 的口腔局部治疗显著降低了小鼠口腔念珠菌病模型的真菌负荷[54]。

4.3. 抗病毒作用

A71 型肠道病毒(EV-A71)是手足口病的主要病原体之一，可引起严重的神经系统并发症。曹等人的实验结果表明 Lico A 在体内和体外均具有较强的抗 EV-A71 活性，其抗病毒作用主要是通过干扰病毒复制的早期步骤实现的[15]。最近的一项研究发现，Lico A 通过调控 IRES 的翻译抑制 D68 型肠道病毒(EV-D68)的复制，同时还抑制柯萨奇病毒 B3，但不显著抑制登革病毒 2 或人冠状病毒 229E 的复制[56]。此外，已有研究报道 Lico A 能够抑制丙型肝炎病毒，其与埃博拉病毒核蛋白的结合降低了蛋白质的热稳定性[16] [57]。

5. 抗肿瘤作用

Lico A 是一种有效的抗癌化合物，参与细胞凋亡和内质网应激。已有研究显示，Lico A 通过增加凋亡蛋白的表达、降低抗凋亡蛋白的表达，诱导 A549 肺癌细胞凋亡[58]。此外，Lico A 诱导 HepG2 细胞内质网应激，通过激活 VEGFR2 和 c-Met 受体 PLCγ1，并促进细胞内 Ca^{2+}从内质网释放，从而诱导细胞凋亡[59]。抑制增殖是 Lico A 抗癌作用的一个重要方面。大量研究表明，Lico A 在不同剂量下阻滞 G2/M 转换细胞周期，例如 Lico A 通过增加 Weel、P21、Cyclin D1 和 JNK1 的表达并降低 Survivin、Cyclin B1 和 CDK1 的表达来阻滞 HepG2 细胞的细胞周期[60]。Lico A 还通过与信号通路的相互作用直接抑制癌细胞的增殖。陈等人发现 Lico A 可通过直接抑制 HepG2 细胞中 p38/JNK/ERK 信号通路，抑制增殖并诱导细胞凋亡[40]。另外，癌细胞具有侵入和迁移到邻近组织并扩散到其他器官的能力。已有报道称 Lico A 通过抑制 MKK4/JNK 和 NF-κB 信号通路下调 uPA 在肝细胞癌中的表达，并抑制肝癌细胞的侵袭和迁移。

6. 在眼科疾病中的治疗作用

眼部疾病最常见的体征之一是眼部炎症，局部应用抗炎药物皮质类固醇可有效治疗眼表和眼前节炎症，但可能引起眼压升高和白内障形成[61]。在 Galindo-Camacho 等人的研究中，通过将 PLGA NPs 递送的 Lico A 的高抗炎活性与 B6 和 Tet-1 结合起来，在眼部使用原位形成凝胶，实现了眼部位点的特异性靶向[62]，对于使用 Lico A 治疗眼部炎症具有重要的临床意义，并为 CPPs 功能化的纳米颗粒提供了一种新的药物形式。脉络膜新生血管(CNV)是湿性年龄相关性黄斑变性(AMD)的标志，而 AMD 是世界范围内老年人不可逆性失明的主要原因[63]。CNV 起源于脉络膜，突破 Bruch 膜进入视网膜下或视网膜色素上皮下间隙，导致渗出、出血、视网膜水肿、色素上皮脱离和纤维瘢痕形成，严重损害中心视力[64]。目前，治疗 CNV 的首选方法是反复玻璃体腔注射抗血管内皮生长因子(VEGF)制剂。然而，抗 VEGF 治疗存在耐药、易复发等局限性[65]。最近研究发现，Lico A 对激光诱导的大鼠 CNV 有抑制作用，其机制可能与通过 PI3K/AKT 信号途径抑制内皮－间质转化相关[66]。

7. 展望

随着医疗界对天然药物需求的持续上升，国内外越来越多的研究者正将焦点转向对药用植物生物活性的探索。作为一种在自然界广泛分布的类黄酮化合物，Lico A 在抗炎、抗菌、抗氧化以及抗癌等多个领域展现出广阔的应用前景。目前对 Lico A 的研究主要集中在分子水平上的信号通路，探索 Lico A 靶向疾病相关的 DNA 和 RNA 片段是未来研究的重要方向。开展 Lico A 与其他药物或生物活性分子结合的临床研究很有价值。通过对 Lico A 结构进行适当改造以产生新的衍生物，或者将 Lico A 与 E3 (泛素连接酶)的连接子和配体精确连接以组装靶向嵌合体的蛋白水解物，可以发现具有优异治疗性能的 Lico A 衍生物。尽管 Lico A 的药效活性研究颇为丰富，大量研究成果仍停留在基础实验阶段。未来的研究工作需要突破传统应用的界限，开发出更为优化的药物制剂，这一过程需要更深入的科研探究和跨领域的协同合作。

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