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丹参酮IIA治疗脊髓损伤修复的可能机制

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摘　要

丹参酮IIA，也称为TanIIA，在生物体内代谢过程中扮演着多重角色，其产物能够影响多种生物化学反应。这些反应中，TanIIA有时作为辅酶参与，有时则可能促进或干扰这些反应过程，从而展现出多样的药理特性。尽管在脊髓损伤等神经系统疾病的治疗中，TanIIA已经显示出了一定的疗效，但其具体的作用机制尚未完全阐明。基于现有的研究成果，我们推测TanIIA可能通过多种药理途径，包括抗炎、抗氧化、抗细胞凋亡以及保护血管，来促进脊髓损伤后的神经细胞存活和修复。

关键词

丹参酮IIA，脊髓损伤，神经再生，机制

Possible Mechanisms of Tanshinone IIA in the Treatment of Spinal Cord Injury Repair

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Abstract

Tanshinone IIA, also known as TanIIA, plays multiple roles in the metabolic process of living organisms, and its products can affect a variety of biochemical reactions. In these reactions, TanIIA is sometimes involved as a coenzyme, and sometimes it may facilitate or interfere with these reaction processes, thus exhibiting diverse pharmacological properties. Although TanIIA has shown some efficacy in the treatment of neurological diseases such as spinal cord injury, its specific mechanism of action has not been fully elucidated. Based on the existing research results, we speculate

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that TanIIA may promote the survival and repair of nerve cells after spinal cord injury through multiple pharmacological pathways, including anti-inflammatory, antioxidant, anti-apoptosis, and vascular protection.

Keywords

Tanshinone IIA, Spinal Cord Injury, Nerve Regeneration, Mechanism

1. 引言

丹参，属于唇形科鼠尾草属的多年生草本植物，其根部富含丹参酮 IIA。该化合物呈樱红色针状结晶，分子量约为 294.34，不溶于水，但能溶于二甲基亚砜、乙醇等有机溶剂。为了从丹参中提取丹参酮 IIA，通常采用超临界二氧化碳萃取技术，该技术的关键参数包括 25 MPa 的萃取压力、40℃的温度、2 小时的提取时间和 1.0 mL/min 的乙醇流量，具体结构见图 1。

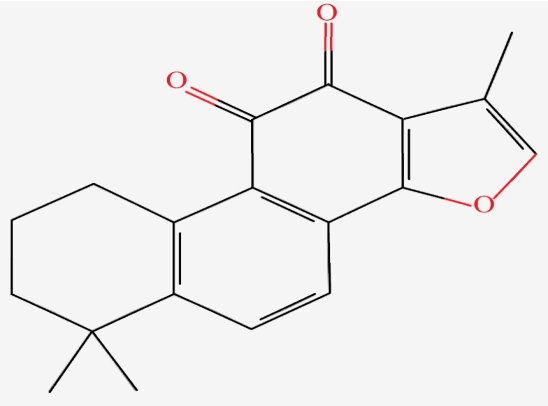

Figure 1. Molecular formula of tanshinone IIA
图 1. 丹参酮 IIA 的分子式

丹参酮IIA 是丹参中一个关键的化学成分，它在多个领域展现了显著的药理特性，包括对心血管疾病的治疗、肿瘤的抑制、炎症的缓解、器官纤维化的改善以及神经系统的保护[1]。根据现有文献的综合评估，丹参酮IIA 可能通过其抗炎、抗氧化和类似雌激素的生物活性来发挥其药理作用。因此，本研究的目标是深入研究丹参酮IIA 在抗炎和抗氧化方面的作用，以期为未来的相关研究提供科学依据和理论支持。

2. 抗炎作用

据研究显示，丹参酮 IIA 具备显著的抗炎能力，它能够调节多种炎症相关因子的生成，如 IL-6、IL-10、IL-1β 和 TNF-α，并抑制白细胞的激活[2]，研究表明，丹参酮 IIA 能够显著降低促炎因子如 IL-6、IL-1β 和 TNF-α 的表达，同时增加抗炎因子如 IL-10 的水平。这种调节作用帮助平衡炎症反应，减轻组织损伤，丹参酮 IIA 能够抑制白细胞的激活和迁移，减少其在炎症部位的积聚。这一机制有助于降低局部炎症反应和组织损伤，丹参酮 IIA 还具有抗氧化特性，可以清除自由基，减轻氧化应激对细胞的损伤。氧化应

激与炎症密切相关，因此其抗氧化作用也间接促进了抗炎效果。Huang 等人探讨了丹参酮 IIA 如何通过抑制炎症来缓解心脏功能障碍，发现提前使用丹参酮 IIA 可以显著改善心脏功能[3]。此外，丹参酮 IIA 还能抑制 LPS 诱导的 TNF-α 和 IL-1β 的增加，降低 NADPH 氧化酶的活性，并减少 ERK1/2 和 p38 MAPK 的磷酸化[4]。

在葡聚糖硫酸钠诱导的小鼠结肠炎模型中，[5]周艳等人观察到丹参酮 IIA 能够降低中性粒细胞的活性并减少炎症因子的水平，从而展现出抗炎特性。此外，丹参酮 IIA 还通过抑制髓过氧化物酶和去甲肾上腺素的活性，减轻了痛风性关节炎小鼠的踝关节肿胀[6]。

据研究显示，丹参酮 IIA 能够抑制 RAW264.7 细胞的增殖和磷脂酶 A2 的生成，同时促进这些细胞释放 IL-10，并减少 IL-6 的生成及其 mRNA 的表达[7]。此外，它还能够抑制 LPS 诱导的 EA.hy926 细胞中 TLR4 和 TNF-α mRNA 的表达，显示出其抗炎特性[8]。Tang 等人的研究还发现，丹参酮 IIA 有效抑制 VCAM-1 和 ICAM-1 的表达，并以剂量依赖方式减少 TNF-α 引起的 BMVECs 中性粒细胞粘附。它还显著降低 TNF-α 刺激下的活性氧和 MDA 生成，并阻止 NF-κB 活化，从而调控粘附分子的表达[9] [10]。

丹参酮 IIA 通过下调脑缺血再灌注大鼠脑内巨噬细胞迁移抑制因子(MIF)、TNF-α 和 IL-6 的水平，有助于减轻脑损伤并增强神经保护[11]。丹参酮 IIA 还能减轻辐射导致的初期炎症因子释放和 NF-κBp65 亚单位的核易位，其抗炎效果与阻遏 NF-κB 信号通路相关的炎症基因表达有关。，有助于减缓阿尔茨海默病的进展[12]。Jiang 等人的研究还表明，丹参酮 IIA 能降低 LPS 刺激的 RAW264.7 细胞产生的早期炎症因子，通过阻止 IκB-α 的磷酸化和抑制 NIK-IKK 及 MAPKs (p38、ERK1/2、JNK)途径的活化，防止 LPS 诱导的 IκB-α 降解和 NF-κB 激活，实现其抗炎作用[13]。此外，丹参酮 IIA 还能保护人类血脑屏障模型免受白细胞相关缺氧复氧损伤的影响[14]。

3. 抗氧化作用

在脊髓损伤后的病理过程中，氧化应激扮演着关键角色。研究指出，丹参酮IIA 具有显著的抗氧化效果[15]。丹参酮 IIA 能降低 ox-LDL 在血浆中的浓度，并减少超氧阴离子和 MDA 的形成[16] [17]。在高血压大鼠中，它通过抑制 NAD(P)H 氧化酶活性和减少活性氧的产生，改善心脏功能，发挥抗氧化作用[18] [19]。在 H_2O_2 诱导的 J774 巨噬细胞损伤和大脑中动脉闭塞大鼠脑缺血再灌注模型中，丹参酮 IIA 提升了谷胱甘肽过氧化物酶的活性[20]。

此外，丹参酮IIA 通过清除脂质自由基，阻断脂质过氧化的连锁反应，抑制 DNA 加合物的形成，从而降低细胞毒性，对 DNA 提供保护。同时，它还能提高脑缺氧区域谷胱甘肽过氧化物酶的活性，减少 MDA 的产生，有效缓解氧化应激[21]。

4. 抗自由基效能

丹参酮IIA 通过调节机体内的氧自由基代谢，降低自由基水平，有助于减轻大鼠局灶性脑缺血后 24 小时内脑组织的充血、水肿和缺血性损伤。[22]黑明燕等人的研究指出，丹参酮IIA 能在缺血缺氧损伤的早期阶段降低[Ca2+]的聚集。[23]叶龙彬等的研究显示，给予丹参酮IIA (剂量为 25 $mg \cdot kg^{-1}$)能够显著改善脑缺血大鼠的神经行为，减少脑梗死面积和脑含水量。此外，丹参酮IIA 还能对抗脑缺血－再灌注引起的超氧化物歧化酶(SOD)活性的下降和丙二醛(MDA)含量的增加，以及降低脑组织中的一氧化氮(NO)水平，显示出对大鼠局灶性脑缺血－再灌注损伤的保护作用，因此可能用于治疗脑血管疾病。

5. 抗细胞凋亡

丹参酮IIA 通过激活特定的细胞凋亡途径，能够抵御淀粉样 β 蛋白引发的神经元细胞毒性[24]。该化合物还能增强神经元的 ATP 酶和蛋白质二硫键异构酶的活性，促进能量代谢平衡和细胞内环境的稳定，

从而实现对神经元的保护与修复[25]。在脊髓缺血性损伤中，丹参酮IIA 还能促进 Bcl-2 的表达，通过抗凋亡机制减轻缺血再灌注引起的损伤[26]。

在脑缺血期间，星形胶质细胞的增殖和激活会引发周围组织形成胶质瘢痕，这会阻碍神经元轴突的正常生长。[27] Zhou 等人的研究发现，丹参酮IIA 能够抑制脑缺血引起的星形胶质细胞激活并减少胶质瘢痕的形成，从而为神经保护提供支持。[28]周丽等人的研究还表明，丹参酮 IIA 能够显著降低缺血再灌注大鼠模型脑组织中的 NF-κB 和 IκB 蛋白的表达水平，可能通过抑制 NF-κB 和 IκB 之间的正反馈循环，减少神经元损失，进而降低大脑的炎性反应。这些发现对于深入研究丹参酮 IIA 在脑保护方面的作用机制具有重要意义。

[29]张延辉等研究人员通过结扎兔腹主动脉的方法建立了脊髓缺血再灌注模型，并在不同时间点提取脊髓和静脉血样以检测谷氨酸含量。研究发现，丹参酮IIA 能够降低再灌注期间脊髓中的谷氨酸含量，从而对脊髓神经元提供保护。这可能归因于丹参酮 IIA 减少炎症因子 VCAM-1 的产生，改善血液流变学，进而减少脊髓组织的损伤。此外，近年来还发现丹参酮IIA 可以通过抑制胶质细胞的激活、减少炎性细胞因子的表达以及下调氧化应激等机制来缓解神经性疼痛[30]。

丹参酮IIA 因其独特的药理特性，在神经系统损害的修复领域得到了广泛的应用[31]。研究指出，丹参酮IIA 在体外实验中展现出通过降低细胞凋亡、改善组织缺氧状况并诱导细胞自噬，从而对放射性损伤产生神经保护效果[32]。在放射性脑损伤小鼠模型中，丹参酮IIA 通过抑制 ATP-P2X7R 信号通路的激活，有效减少了炎症和自由基的积累，改善了小鼠的空间记忆和学习能力，减轻了脑部水肿。另外，[33]研究表明，丹参酮IIA 在急性脊髓损伤小鼠中能够下调 RhoA 和 ROCKII 蛋白水平，抑制肌球蛋白轻链的磷酸化，进而促进神经细胞的修复和轴突再生。此外，丹参酮IIA 对于糖尿病引发的神经功能障碍、脊髓损伤后的运动功能损害以及惊厥等病症也展现出了一定的治疗效果[34] [35]。

6. 结论

综上所述，丹参酮IIA 展现出显著的抗氧化和抗炎等生物学活性，同时还具有血管保护和神经保护等多种药理作用，且长期使用副作用较小。近年来，大量科学研究表明，丹参酮IIA 具备许多其他药理效应，国内外学者在揭示其药理机制及疾病治疗策略方面亦取得了诸多进展。然而，这类研究主要集中在动物实验和体外细胞实验上，因此还需进一步的深入研究。基于丹参酮IIA 药理作用的最新进展，未来其有望成为治疗多种疾病的有效药物。为了进一步拓宽丹参及丹参酮IIA 的临床应用，迫切需要开展更多研究以揭示其潜在的药理作用和机制。

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