

白茅根提取物对多柔比星致心肌损伤的改善作用及分子机制[△]

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摘要 目的 探究白茅根(RI)提取物对多柔比星(DOX)致心肌损伤的改善作用及潜在分子机制。方法 借助网络药理学方法,筛选RI活性成分的预测核心靶点与心肌损伤相关靶点的交集靶点,并进行基因本体、京都基因和基因组数据库富集分析。基于网络药理学结果,以雄性C57BL/6J小鼠为对象,构建DOX诱导的心肌损伤小鼠模型,观察RI提取物[1 g/(kg·d)]对小鼠生存率、体重、心脏损伤的影响;以小鼠心肌细胞HL-1为对象,构建DOX诱导的心肌细胞损伤模型,观察不同质量浓度RI提取物(50、100、200 μg/mL)对线粒体膜电位、三磷酸腺苷(ATP)生成、活性氧(ROS)产生、细胞凋亡及相关靶蛋白表达的影响;并通过转染雌激素受体1(ESR1)小干扰RNA(siRNA)进行初步机制验证。**结果** 共筛选出交集靶点58个,富集于激素反应、缺氧反应等生物学过程,以及细胞凋亡、三羧酸循环和丙酮酸代谢等通路;同时,筛选出ESR1等关键靶蛋白。动物实验证实,DOX+RI组小鼠的生存率明显高于DOX组,体重下降速度较缓,心脏挛缩和炎症细胞浸润等病理改变均较DOX组有所改善。细胞实验证实,与DOX组比较,DOX+RI各质量浓度组细胞的线粒体膜电位,相对ATP水平,异柠檬酸脱氢酶3A(IDH3A)、琥珀酸脱氢酶A(SDHA)、过氧化物酶体增殖物激活受体γ共激活因子1α(PGC-1α)mRNA的表达,ESR1 mRNA及蛋白的表达均显著升高或上调,相对ROS水平和凋亡率均显著降低($P<0.05$);敲减ESR1后,RI提取物抗心肌细胞凋亡的作用被显著减弱($P<0.05$)。**结论** RI提取物可能通过激活ESR1信号通路、改善线粒体功能、抑制ROS过量生成和心肌细胞凋亡来缓解DOX诱导的心肌损伤。

关键词 白茅根;提取物;多柔比星;心肌损伤;线粒体功能;雌激素受体α;网络药理学

Ameliorative effects of Imperatae Rhizoma extract against doxorubicin-induced myocardial injury and its molecular mechanisms

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ABSTRACT **OBJECTIVE** To investigate the ameliorative effects of Imperatae Rhizoma (RI) extract against doxorubicin (DOX)-induced myocardial injury and its potential molecular mechanisms. **METHODS** Network pharmacology was employed to screen for target overlap between the predicted core targets of RI's active components and targets associated with myocardial injury, followed by gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses. Based on the network pharmacology results, a DOX-induced myocardial injury mouse model was established using male C57BL/6J mice to observe the effects of RI extract [1 g/(kg·d)] on the survival rate, body weight, and cardiac damage. A DOX-injured HL-1 cardiomyocyte model was established to assess the effects of different mass concentrations of RI extract (50, 100, 200 μg/mL) on mitochondrial membrane potential, adenosine triphosphate (ATP) production, reactive oxygen species (ROS) generation, apoptosis, and expression of the relevant target proteins. The mechanism was validated by transfecting with small interfering RNA of estrogen receptor 1 (ESR1). **RESULTS** A total of 58 overlapping targets were screened, which were enriched in biological processes such as hormone response and hypoxia response, as well as pathways including apoptosis, tricarboxylic acid cycle, and pyruvate metabolism. Key target proteins, such as ESR1, were also identified. Animal experiments confirmed that the survival rate of mice in the DOX+RI group was obviously higher than that in the DOX group, with a slower rate of weight loss and improved pathological changes, such as cardiac atrophy and inflammatory cell infiltration, compared to the DOX group. Cell experiments showed that, compared with the DOX group, the DOX+RI groups exhibited significantly increased or upregulated mitochondrial membrane potential, relative ATP

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