桑白皮汤对二手烟致肺纤维化小鼠的改善作用及机制研究Δ

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摘　要　目的　探讨桑白皮汤（SBP）对二手烟致肺纤维化（PF）小鼠的改善作用及潜在机制。**方法**　借助网络药理学方法，筛选SBP活性成分对应靶点与PF特异性靶点的共同靶点，进行蛋白-蛋白相互作用网络构建、京都基因和基因组数据库通路富集分析，并进行分子对接。基于上述结果，将雄性昆明小鼠分为正常对照组、模型对照组、SBP组（1.08 g/kg，以生药量计）、吡非尼酮组（阳性对照，90 mg/kg），每组8只。除正常对照组外，其余各组均采用香烟静式呼吸道染毒法（每天烟熏30 min×2次，持续20 d）构建二手烟致PF小鼠模型。各药物组小鼠于每天第2次烟熏结束后0.5 h时灌胃相应药液，正常对照组和模型对照组小鼠同步灌胃等体积水，每天1次，连续20 d。末次给药24 h后，观察小鼠肺组织病理改变，检测其肺组织中促炎因子、损伤标志物水平和相关通路蛋白表达情况。**结果**　筛选出共同靶点2 448个，其核心靶点包括蛋白激酶B1（AKT1）、肿瘤坏死因子α（TNF-α）、白细胞介素6（IL-6）等，富集于磷脂酰肌醇3激酶（PI3K）/AKT等信号通路；AKT1、PI3K、TNF-α、IL-6与活性成分chaksine的结合能分别为－11.0、－7.7、－9.0、－9.4 kcal/mol。与模型对照组比较，各药物组小鼠肺组织炎症细胞浸润、胶原沉积的病理改变均有所减轻；肺组织中Ⅲ型胶原蛋白的表达均显著下调；IL-6、TNF-α、组织金属蛋白酶抑制物1、肺表面活性物质相关蛋白D水平，肺纤维化阳性区域百分比和PI3K、AKT蛋白的磷酸化水平亦显著下调或降低（$P<0.05$）。**结论**　SBP改善二手烟致PF的作用，可能与调控AKT1等多个核心靶点、抑制PI3K/AKT信号通路，进而减轻肺部炎症及胶原沉积有关。

关键词　桑白皮汤；肺纤维化；二手烟；PI3K/AKT信号通路；网络药理学

Study on the improvement effects and mechanisms of Sangbaipi decoction in mice with second-hand smoke-induced pulmonary fibrosis

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ABSTRACT　OBJECTIVE To investigate the improvement effects and potential mechanisms of Sangbaipi decoction (SBP) on mice with second-hand smoke-induced pulmonary fibrosis (PF). **METHODS** Using network pharmacology methods, the common targets between the active components of SBP and PF-specific targets were screened, the protein-protein interaction network was constructed, the pathway enrichment analysis was performed using the Kyoto Encyclopedia of Genes and Genomes, and the molecular docking was conducted. Based on these results, the male Kunming mice were divided into a normal control group, a model control group, an SBP group (1.08 g/kg, calculated by crude drugs), and a pirfenidone group (positive control, 90 mg/kg), with eight mice in each group. Except for the normal control group, all other groups were exposed to second-hand smoke via the static respiratory tract smoking method (30 min of smoking twice daily for 20 consecutive days) to establish a mouse model of PF induced by second-hand smoke. Each drug group was administered the corresponding drug solution via gavage 0.5 h after the second daily smoke exposure; the normal control and model control groups were simultaneously administered an equal volume of water via gavage, once daily for 20 consecutive days. Twenty-four hours after the final administration, pathological changes in lung tissue were observed, and the levels of pro-inflammatory factors, injury markers, and the expression of proteins in related signaling pathways in lung tissue were detected. **RESULTS** A total of 2 448 common targets were identified, with core targets including protein kinase B1 (AKT1), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6), which were enriched in signaling pathways such as phosphoinositide 3-kinase (PI3K)/AKT. The binding energies of AKT1, PI3K, TNF-α, and IL-6 to the active compound chaksine were －11.0, －7.7, －9.0, and －9.4 kcal/mol, respectively. Compared with the model control group, pathological changes such as inflammatory cell infiltration and collagen deposition in lung tissue were alleviated in the administration groups. The expression of collagen Ⅲ in lung tissue was significantly downregulated, and the levels of IL-6, TNF-α, tissue inhibitor of metalloproteinase 1, and pulmonary surfactant-associated protein D, as well as the percentage of positive areas with pulmonary fibrosis and protein phosphorylation levels of PI3K and AKT, were all significantly downregulated or reduced ($P<0.05$). **CONCLUSIONS** The role of SBP in improving PF induced by second-hand smoke may be related to the regulation of multiple core targets, including AKT1, and the inhibition of the PI3K/AKT signaling pathway, thereby alleviating pulmonary inflammation and collagen deposition.

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