综述
Review

中药提取物干预矽肺纤维化的研究进展

杭文璐[1,2]，武琦[3]，赵莹[4]，周贤梅[1]

1. 南京中医药大学附属医院，江苏 南京 210023
2. 徐州医科大学第二附属医院呼吸与危重症医学科，江苏 徐州 221000
3. 徐州医科大学生理学教研室，江苏 徐州 221000
4. 徐州市中医院呼吸科，江苏 徐州 221000

摘要：

矽肺患者长期吸入结晶二氧化硅颗粒后，组织病理学出现矽结节及肺纤维化，难以逆转及恢复。矽肺的发病机制研究及治疗策略显著落后于医学进展及临床需求，导致该病仍是棘手的临床难题，中药提取物及复方制剂现已成为近年探索矽肺治疗策略的热点问题。本文阐述了矽肺致肺纤维化的主要病理过程，总结出转化生长因子 β1（TGF-β1）/Smad 信号通路、氧化应激反应、凋亡及自噬为最重要的致病机制，概述了不同中药提取物干预上述机制的研究进展、作用靶点及干预效果，为中药提取物抑制肺纤维化的理论与临床研究提供一定的科学依据。本文提出在今后的研究工作中可继续深入研究矽肺的发病、进展机制及药物治疗策略，并注重基础研究向临床实践转化，以期改变矽肺纤维化难以控制及逆转的临床现状。

关键词：矽肺；肺纤维化；中药提取物；治疗；干预

Research progress of traditional Chinese medicine extracts in intervention of fibrosis caused by silicosis

HANG Wenlu[1,2], WU Qi[3], ZHAO Ying[4], ZHOU Xianmei[1] (1. Affiliated Hospital of Nanjing University of Traditional Chinese Medicine, Nanjing, Jiangsu 210023, China; 2. Department of Respiratory and Critical Care Medicine, Second Affiliated Hospital of Xuzhou Medical University, Xuzhou, Jiangsu 221000, China; 3. Department of Physiology, Xuzhou Medical University, Xuzhou, Jiangsu 221000, China; 4. Department of Respiratory, Xuzhou City Hospital of Traditional Chinese Medicine, Xuzhou, Jiangsu 221000, China)

Abstract:

Silicotic nodules and pulmonary fibrosis are histopathological appearance in silicosis patients after long-term inhalation of crystalline silica particles, and are difficult to reverse and recover. Research on the pathogenesis and treatment strategies of silicosis has significantly lagged behind medical progress and clinical needs, resulting in the disease remaining a thorny clinical problem. Traditional Chinese medicine extracts or compound preparations have become a hot issue in exploring silicosis treatment strategies in recent years. This paper described the main pathological processes of pulmonary fibrosis caused by silicosis, followed by introducing its main pathogenesis mechanisms, including transforming growth factor-β1 (TGF-β1)/Smad signaling pathway, oxidative stress reaction, apoptosis, and autophagy. In addition, it briefly described the research progress, targets, and intervention effects of selected traditional Chinese medicine extracts, which provides a scientific basis for the theoretical and clinical research of traditional Chinese medicine extracts in inhibiting pulmonary fibrosis. To change the clinical status quo of silicosis fibrosis which is difficult to control and reverse, the paper proposed that we can further explore the pathogenesis and progression mechanisms of silicosis and drug treatment strategy, and focus on the transformation of basic research into clinical practice.

Keywords: silicosis; pulmonary fibrosis; traditional Chinese medicine; treatment; intervention

矽肺是长期吸入游离二氧化硅（SiO_2）含量较高的粉尘并在肺内潴留而引起的职业病，以肺部弥漫性纤维化为主要表现[1]。我国受矽尘影响严重，截至 2018 年底，共有职业性尘肺病 87 万余例，2019 年又新增 15 898 例[2]，此外，考虑到大量含硅材料的工业应用，估计全球数以千万计的工人直接暴露于这种矿物质中[3]。因此，探索矽肺发病机制及研究可延缓或阻断矽肺致肺纤维化进展

DOI 10.11836/JEOM21248

基金项目
国家自然科学基金面上项目（82074358）；徐州市卫生健康委科技项目（XWKYHT20200041）；徐州市科研技术项目 (KC18021)；徐州医科大学附属医院发展基金优秀人才基金项目（XYFY2020007）

作者简介
杭文璐（1988—），女，博士生，主治医师；
E-mail：609463244@qq.com

通信作者
周贤梅，E-mail：zhouxianmeijs@aliyun.com

伦理审批 不需要
利益冲突 无申报
收稿日期 2021-05-30
录用日期 2021-09-09

文章编号 2095-9982(2022)02-0229-07
中图分类号 R13
文献标志码 A

▸引用
杭文璐，武琦，赵莹，等. 中药提取物干预矽肺纤维化的研究进展 [J]. 环境与职业医学，2022，39（2）：229-235.

▸本文链接
www.jeom.org/article/cn/10.11836/JEOM21248

Funding
This study was funded.

Correspondence to
ZHOU Xianmei, E-mail: zhouxianmeijs@aliyun.com

Ethics approval Not required
Competing interests None declared
Received 2021-05-30
Accepted 2021-09-09

▸ To cite
HANG Wenlu, WU Qi, ZHAO Ying, et al. Research progress of traditional Chinese medicine extracts in intervention of fibrosis caused by silicosis[J]. Journal of Environmental and Occupational Medicine, 2022, 39(2): 229-235.

▸ Link to this article
www.jeom.org/article/en/10.11836/JEOM21248

的药物与措施具有重要的现实意义。

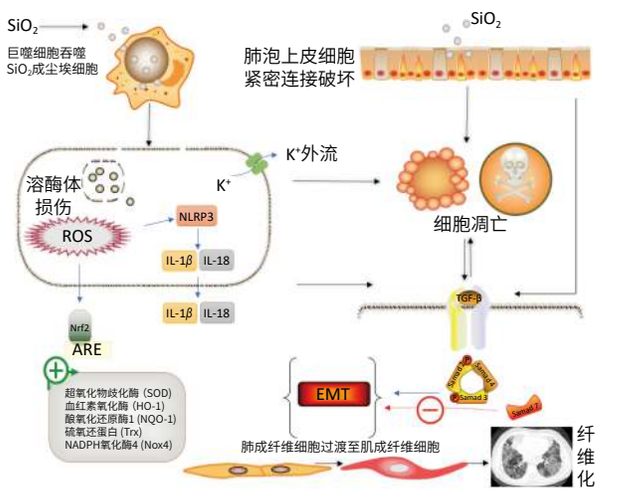
参与矽肺发生发展最重要的细胞是肺泡巨噬细胞(alveolar macrophage, AM)和肺泡上皮细胞(alveolar epithelial cell, AEC),此外,树突状细胞、肌成纤维细胞(主要由肺固有成纤维细胞和上皮细胞转化而成)聚集和细胞外基质沉积也发挥重要作用。SiO_2 颗粒吸入后,被 AM 吞噬成为尘埃细胞,此后 AM 可协同 AEC 释放大量活性氧(reactive oxygen species, ROS)参与氧化应激反应,通过溶酶体损伤[4]及钾外流[5]等途径激活核苷酸结合寡聚化结构域(nucleotide binding oligomerization domain, NOD)样受体家族 3(NOD-like receptors, NLRP3)炎性小体,激活释放炎症介质白细胞介素-1β(interleukin-1β, IL-1β)、白细胞介素-18(interleukin-18, IL-18)等细胞因子诱导上皮间充质转化(epithelial mesenchymal transition, EMT)[6],并参与含半胱氨酸的天冬氨酸蛋白水解酶依赖性细胞焦亡[7]。AM 可极化为 M1、M2 型,发挥促炎、促纤维化及抗原提呈作用,使肺成纤维细胞增殖及胶原合成与分泌增加,通过凋亡与自噬促进矽肺纤维化形成[8]。此外,AEC 在粉尘作用下也会破坏气道屏障,由紧密连接、缝隙连接、黏着连接、细胞半桥粒组成的细胞间连接复合体受损,促进上皮细胞衰老、凋亡,释放转化生长因子 β1(transforming growth factor-β1, TGF-β1)等促纤维化细胞因子,促使间充质细胞增生、分化,刺激成纤维细胞向肌纤维细胞转化[9]。在矽肺病变由肺泡炎转为纤维化的过程中,激活 TGF-β1/Smad(small mother against decapentaplegic)信号通路、氧化应激反应及自噬与凋亡是最重要的致病机制。SiO_2 致肺纤维化的主要机制见图 1。

目前尚无有效的药物逆转矽肺诱导的肺纤维化[10],同时,全肺灌洗、肺移植及干细胞治疗等非药物干预方式因收益与风险不确切也未成为矽肺的一线治疗策略[11],中药提取物抑制肺纤维化进程成为矽肺治疗性研究的一个方向。中草药粉防己提取物粉防己碱可抑制矽肺胶原蛋白合成和成纤维细胞增殖,现已进入尘肺治疗的专家共识[12]。本文将阐述矽肺致纤维化的主要发病机制,重点概述不同中草药提取物干预矽肺致纤维化发病进程作用机制的研究进展,为中药提取物抑制肺纤维化的理论与临床研究提供一定的科学依据。

1 激活 TGF-β1/Smad 信号通路

1.1 致病机制

AM 及 AEC 在 SiO_2 刺激下均会分泌 TGF-β1,通过 TGF-β1/Smad 信号通路,从细胞增殖、分化、迁移、免疫调节和细胞外基质转化方面广泛参与纤维化的发展过程[13–14]。信号传感器 Smad 蛋白家族能够被 TGF-β1 诱导细胞膜受体直接激活,使 Smad2 和 Smad3 磷酸化,与 Smad4 形成三聚体,易位至细胞核内与转录因子相互作用,形成转录复合物,诱导 EMT,出现上皮细胞标志性蛋白 E-钙黏蛋白(E-cadherin, E-cad)表达下降,肌成纤维细胞标志性蛋白 α 平滑肌肌动蛋白(α-smooth muscle actin, α-SMA)表达增加。该通路中,Smad2 和 Smad3 可促进 TGF-β1 介导纤维化[15],Smad7 发挥负反馈作用,阻断 TGF-β1 介导的矽肺纤维化进程[16]。



[注] SiO_2,二氧化硅;ROS,活性氧;Nrf2,核转录因子红系 2 相关因子 2;ARE,抗氧化反应构件;NLRP3,核苷酸结合寡聚化结构域样受体家族 3;IL-1β,白细胞介素-1β;IL-18,白细胞介素-18;TGF-β,转化生长因子-β;EMT,上皮间充质转化。

图 1 SiO_2 致纤维化的主要机制

Figure 1 The main mechanism of fibrosis induced by SiO_2

1.2 中药提取物干预 TGF-β1/Smad 信号通路的作用机理

研究发现,姜黄素固体分散剂[17]与虫草菌粉[18]均可降低矽肺模型肺组织 TGF-β1 的表达,产生抗纤维化作用。木犀草素[19–20]则能够通过抑制矽肺大鼠和染尘 AM 中 NLRP3 炎症小体的活化,进而抑制 IL-1β、IL-18 和 TGF-β1 表达,减轻炎症反应和纤维化;大黄素[21–23]也被发现可通过抑制矽肺小鼠 Smad3 和核因子 κB(nuclear factor-κB, NF-κB)磷酸化,增加 E-cad 水平,降低波形蛋白水平,同时还可通过靶向沉默信息调节因子 1 降低去乙酰化 Smad3 的水平,减轻胶原沉积,进而抑制纤维化进程。与这类中药提取物作用机制相似,美洲大蠊[24]、黄根多糖[25]也可降低 α-SMA 和 I 型胶原蛋白以及 TGF-β1、促炎因子肿瘤坏死因子 α(tumor

necrosis factor-α, TNF-α)及 IL-1β 的表达，抑制炎症反应和 EMT 的发展。另有研究发现，丹参酮 IIA[26–27] 可调控 EMT 和 TGF-β1/Smad 信号通路，并同黄芪甲苷[28–29] 类似，逆转矽肺大鼠 I 型胶原、纤维连接蛋白和 α-SMA 的过表达，干预 SiO_2 导致的肺纤维化。此外，薯蓣皂苷[30] 可改善 SiO_2 诱导的先天免疫应答(典型的巨噬细胞)、适应性免疫应答(淋巴细胞)和 Th 免疫应答，还能通过减少纤维细胞的募集，保护 AEC 免受损伤，减少成纤维细胞活化，发挥抑制纤维化作用。

除了单一中药提取物，中药复方制剂也可通过干预 TGF-β1/Smad 信号通路抑制矽肺致纤维化进程。大黄䗪虫丸[31] 由大黄、黄芩、甘草等 12 味药物组成，可呈剂量、时间依赖性调控 TGF-β1/Smad 通路抑制小鼠矽肺模型和 AM 的肺纤维化进程。益肺化纤方[32](含西洋参、三七、山萸肉等 8 种中药)和化纤中药颗粒[33](含金荞麦、防己、侧柏等 7 种中药)则均可抑制矽肺大鼠 TGF-β1 及 Smad3 等的表达，减少胶原沉积。此外，抗肺纤中药颗粒[34](含金荞麦、地榆、苍术等 12 种中药)还可升高肺组织 E-cad 表达，降低波形蛋白表达，抑制 SiO_2 诱导的 EMT。同时，临床研究也发现，含有黄芪、丹参等药物的参芪益肺汤[35]，可明显降低早期尘肺患者血清中的 TGF-β1 水平，改善患者的临床症状及肺功能。

2 氧化应激反应

2.1 致病机制

氧化应激在环境颗粒引起的疾病发生、发展中发挥关键作用[36]。核转录因子红系 2 相关因子 2(nuclear factor erythroid 2-related factor 2, Nrf2)是细胞氧化应激反应中的关键因子。稳态下，Nrf2 与 Kelch 样 ECH 关联蛋白 1(Kelch-like ECH-associated protein1, Keap-1)结合，Nrf2 会通过持续泛素化降解，防止其积累和激活[37]。SiO_2 暴露后，可导致丙二醛(malondialdehyde, MDA)和 ROS 的过量积累[38]，Keap-1 被灭活，Nrf2 被转位至细胞核中，直接与抗氧化反应构件(antioxidant response element, ARE)结合，诱导超氧化物歧化酶(superoxide dismutase, SOD)、血红素氧化酶、醌氧化还原酶 1、硫氧还蛋白等多种抗氧化基因的表达[39]。研究表明，还原型烟酰胺腺嘌呤二核苷酸氧化酶 4 可诱导 ROS 产生，并增强肌成纤维细胞对 TGF-β1 的激活，通过 TGF-β1/Smad3 通路介导氧化还原信号[40]，之后，TGF-β1 可增加 α-SMA 其他细胞外基质蛋白表达，进一步诱导细胞毒性、氧化应激和肺部炎症[41]。

2.2 中药提取物干预氧化应激反应的作用机理

研究发现，染尘巨噬细胞(Raw 264.7)能够诱导细胞内 ROS 的积累，使成纤维细胞存活率增加，而丹参酮磺酸钠[42] 可通过促进 AEC 中 Nrf2 的核易位，在矽肺早期抑制 ROS 的产生，同时还可通过上调体外肺成纤维细胞的 Nrf2 和硫氧还蛋白系统通路来增强抗氧化活性，在矽肺晚期发挥抗纤维化作用；另有研究发现，黄芪、黄芪多糖、黄芪总苷[43]、黄芩黄酮[44] 以及从白毫银针、白牡丹中获得的白茶提取物[45]，均可提高矽肺模型的 SOD 活性，减轻脂质过氧化损伤，发挥抗氧化和清除自由基的作用。白及多糖[46] 可提高矽肺大鼠血清 SOD 水平，降低 MDA 和一氧化氮含量，但并不能有效抑制肺纤维化；而药效组分主要为菲类、二氢菲类和苄类化合物的白及小分子[47] 除具有抗氧化活性，还能降低 NF-κB、IL-1β、TGF-β1、血小板衍生生长因子、TNF-α 含量，降低血清羟脯氨酸含量，延缓、改善肺组织纤维化；同时，进一步研究发现白及乙醇提取物[48] 二氢菲类化合物能够通过抑制 AM 的增殖和炎症因子的分泌，发挥潜在的矽肺治疗作用。萝卜硫素[49] 则可通过 Nrf2/ARE 通路使矽肺大鼠肺组织中 I 型、III 型胶原蛋白含量减少，降低 MDA 含量和 Keap-1 表达，增加 SOD、谷胱甘肽含量及 Nrf2、ARE 表达，减轻氧化应激反应。而地龙提取物[50] 则能通过激活 Nrf2 通路减弱硅诱导的氧化应激反应，进一步抑制上皮细胞线粒体凋亡及 EMT，干预矽肺纤维化。

此外，中药复方制剂同样可通过干预氧化应激反应的方式影响矽肺纤维化的进程，研究发现低剂量雾化吸入吸附排尘中草药制剂[51](由甘草、菊花、罗汉果、贝母等中草药提取液复合陈醋、蜂蜜等成分混合而成)，可降低 MDA 和 γ 干扰素的水平，改善矽肺大鼠肺纤维化和炎症。临床研究中，采用含黄芪、黄精等药物的尘肺经验方[52] 治疗尘肺合并慢性阻塞性肺疾病，可有效降低患者的 SOD、MDA、谷胱甘肽过氧化物酶及肺纤维化血清指标水平，延缓肺纤维化进展。

3 自噬与凋亡

3.1 致病机制

SiO_2 暴露可增强骨髓源性巨噬细胞的体外自噬活性和 AM 的体内自噬活性[53]。巨噬细胞吞噬 SiO_2 成为尘埃细胞后，会诱发氧化应激损伤，释放活性因子，还可通过受 *p53* 基因上调表达的凋亡调控蛋白 B 细胞淋巴瘤样因子-2(B-cell lymphoma-2, BCL2)绑定组件(BCL2-binding component 3, BBC3)和单核细胞趋化蛋白

-1 诱导蛋白 1（monocyte chemotactic protein-1-induced protein 1, MCPIP1）这两种促纤维生成因子诱导自噬导致 AM 凋亡[54–55]。凋亡的 AM 会再分泌大量炎症因子，引起炎症级联反应，随后，肺成纤维细胞增殖、激活和迁移，合成并分泌胶原，最终导致矽肺纤维化[56]。目前研究已发现 SiO_2 诱导的 AM 凋亡可通过线粒体介导的细胞内凋亡程序[57]、NF-κB 信号通路[58]、fas 介导的外源性途径[59]、*p53* 信号通路[60]、内质网应激[61] 等调控。

3.2 中药提取物干预自噬与凋亡的作用机理

研究发现大黄素除了能够通过干预 TGF-β1/Smad 信号通路来抑制矽肺纤维化进程，也可通过下调促凋亡蛋白-BCL2 关联 X 蛋白（BCL2 associated X protein, Bax）和上调抗凋亡蛋白 BCL2 来抑制硅诱导的细胞凋亡发挥抗纤维化作用[22]。薯蓣皂苷[62] 可促进 AM 自噬，增强矽尘损伤线粒体的清除，并减轻线粒体介导凋亡通路的激活，使 AM 抵抗矽尘所致的凋亡，减少细胞内过量的线粒体 ROS 产生，降低促炎促纤维化因子的分泌。SiO_2 通过丝裂原活化蛋白激酶和磷脂酰肌醇 3-激酶/蛋白激酶 B（phosphatidylinositol 3-kinase and protein kinase B, PI3K/Akt）通路诱导 AM 中高迁移率族蛋白 B1（high-mobility group box-1, HMGB1）的表达，进而通过 MCPIP1 通路诱导成纤维细胞激活，在此过程中，新藤黄酸[63] 可通过抑制 AM 来源的 HMGB1 和上调成纤维细胞中的 MCPIP1 来延缓 SiO_2 诱导的纤维化进程。此外，白术内酯 III[64] 可通过雷帕霉素受体蛋白（mammalian target of rapamycin, mTOR）依赖的方式抑制自噬，改善对 AM 自噬降解的阻断，减轻硅诱导的 AM 凋亡。

4 其他致病机制及相关中药提取物的作用机理

除上述研究外，尚有一些工作探索了中药提取物对矽肺纤维化影响的其他机制。有研究表明肺淋巴系统在清除肺内 SiO_2 过程中能够发挥重要作用，丹参酮 IIA 磺酸钠[65] 可以促进矽肺早期大鼠肺部淋巴管增生，改善淋巴循环，降低致纤维化因子的表达；通过检测染尘大鼠淋巴管内皮特异性标记物血管内皮生长因子受体-3（vascular endothelial growth factor receptor-3, VEGFR-3）和淋巴液中硅元素水平，发现银杏叶提取物[66] 能够通过促进淋巴循环，加快肺内 SiO_2 的排除；此外，人参皂甙 Rg1[67] 也被发现能够通过血管内皮生长因子-C（vascular endothelial growth factor-C, VEGFC）/VEGFR-3 信号增强 SiO_2 诱导的肺淋巴管生成和肺内 SiO_2 的淋巴运输，从而降低矽肺模型中的肺负荷。另有研究表明，干预 NF-κB 信号通路、细胞外信号调节蛋白激酶（extracellular-regulated kinase, ERK），影响肺部水液代谢也是中药提取物的主要干预机制。例如，姜黄素可通过抑制 NF-κB 信号通路，呈剂量-效应性阻断 SiO_2 诱导 AM 的 NLRP3 炎性小体活化，并降低矽肺大鼠肺组织中血小板衍生生长因子、磷酸化 ERK 1/2 及 mRNA 表达，还可通过调节水通道蛋白-1 保持细胞内外环境的稳态平衡，在矽肺发病中起到一定的保护作用[68–71]。

5 小结与展望

综上，目前已发现众多天然药物成分及中药复合制剂可分别通过干预矽肺 TGF-β1/Smad 信号通路、氧化应激机制、凋亡与自噬及影响肺内淋巴微循环等方面抑制矽肺纤维化；同时，各通路间也具有交互作用，像大黄素、丹参酮、姜黄素等多种中药提取物均可通过不同的干预机制发挥抗炎、抗纤维化作用。但已有研究多为动物实验，提取物的浓度和应用剂量也无统一标准，今后除应更深入地研究矽肺发病、进展机制外，剖析信号通路之间的相互关系及药物干预靶点，并注重基础研究向临床实践转化，也应成为中药提取物应用于临床治疗矽肺纤维化的重要研究方向。

参考文献

[1] YU X H, ZHAI R N, HUA B Y, et al. miR-let-7 d attenuates EMT by targeting HMGA2 in silica-induced pulmonary fibrosis[J]. RSC Adv, 2019, 9(34): 19355-19364.

[2] 规划发展与信息化司. 2019年我国卫生健康事业发展统计公报[EB/OL]. [2020-06-06]. http://www.nhc.gov.cn/guihuaxxs/s10748/202006/ebfe31f24cc145b198dd730603ec4442.shtml.
Department of Planning, Development and Information Technology. Statistical bulletin of the development of China's health work in 2019[EB/OL]. [2020-06-06]. http://www.nhc.gov.cn/guihuaxxs/s10748/202006/ebfe31f24cc145b198dd730603ec4442.shtml.

[3] LESO V, FONTANA L, ROMANO R, et al. Artificial stone associated silicosis: a systematic review[J]. Int J Environ Res Public Health, 2019, 16(4): 568.

[4] CAMPDEN R I, ZHANG Y. The role of lysosomal cysteine cathepsins in NLRP3 inflammasome activation[J]. Arch Biochem Biophys, 2019, 670: 32-42.

[5] LUNA-GOMES T, SANTANA P T, COUTINHO-SILVA R. Silica-induced inflammasome activation in macrophages: role of ATP and P2X7 receptor[J]. Immunobiology, 2015, 220(9): 1101-1106.

[6] LI X, YAN X, WANG Y, et al. NLRP3 inflammasome inhibition attenuates silica-induced epithelial to mesenchymal transition (EMT) in human bronchial epithelial cells[J]. Exp Cell Res, 2018, 362(2): 489-497.

[7] 杨旭, 单姗, 杜忠君. 细胞焦亡在呼吸系统疾病中的研究进展[J]. 中华劳动卫生职业病杂志, 2020, 38(11): 871-874.
YANG X, SHAN S, DU Z J. Research progress of pyroptosis in respiratory diseases[J]. Chin J Ind Hyg Occup Dis, 2020, 38(11): 871-874.

[8] 张元元, 薄存香, 张放. 肺泡巨噬细胞在矽肺发病机制中的研究进展[J]. 中国职业医学, 2020, 47(1): 109-113.
ZHANG Y Y, BO C X, ZHANG F. Research advances on alveolar macrophages in the pathogenesis of silicosis[J]. China Occup Med, 2020, 47(1): 109-113.

[9] 吴秋云, 徐甜甜, 刘易, 等. 肺泡上皮细胞在肺纤维化中的作用[J]. 中华劳动卫生职业病杂志, 2017, 35(7): 540-542.
WU Q Y, XU T T, LIU Y, et al. Role of alveolar epithelial cells in pulmonary fibrosis[J]. Chin J Ind Hyg Occup Dis, 2017, 35(7): 540-542.

[10] GUO J, YANG Z, JIA Q, et al. Pirfenidone inhibits epithelial-mesenchymal transition and pulmonary fibrosis in the rat silicosis model[J]. Toxicol Lett, 2019, 300: 59-66.

[11] 李巍铭, 彭莉君, 周敏, 等. 尘肺诊疗研究进展[J]. 职业卫生与病伤, 2019, 34(5): 261-266.
LI W M, PENG L J, ZHOU M, et al. Progress in the diagnosis and treatment of pneumoconiosis[J]. Occup Health Damage, 2019, 34(5): 261-266.

[12] 中华预防医学会劳动卫生与职业病分会职业性肺部疾病学组. 尘肺病治疗中国专家共识(2018年版)[J]. 环境与职业医学, 2018, 35(8): 677-689.
Occupational Lung Disease Group of Labor Hygiene and Occupational Diseases Branch of Chinese Preventive Medicine Association. Consensus of Chinese experts on pneumoconiosis treatment (2018)[J]. J Environ Occup Med, 2018, 35(8): 677-689.

[13] BELLAYE P S, SHIMBORI C, UPAGUPTA C, et al. Lysyl oxidase-like 1 protein deficiency protects mice from adenoviral transforming growth factor-β1-induced pulmonary fibrosis[J]. Am J Respir Cell Mol Biol, 2018, 58(4): 461-470.

[14] HU H H, CHEN D Q, WANG Y N, et al. New insights into TGF-β/Smad signaling in tissue fibrosis[J]. Chem Biol Interact, 2018, 292: 76-83.

[15] CHEN L, YANG T, LU D W, et al. Central role of dysregulation of TGF-β/Smad in CKD progression and potential targets of its treatment[J]. Biomed Pharmacother, 2018, 101: 670-681.

[16] WALTON K L, JOHNSON K E, HARRISON C A. Targeting TGF-β mediated SMAD signaling for the prevention of fibrosis[J]. Front Pharmacol, 2017, 8: 461.

[17] 韩刚, 翟冠钰, 范颖, 等. 姜黄素固体分散体对游离SiO_2染尘大鼠TNF-α、TGF-β1表达的影响[J]. 工业卫生与职业病, 2010, 36(5): 276-278.
HAN G, ZHAI G Y, FAN Y, et al. Effect of solid curcumin dispersion on expressions of TNF-α and TGF-β1 in silica exposed rats[J]. Ind Health Occup Dis, 2010, 36(5): 276-278.

[18] 刘乾中, 张伟, 崔宏福, 等. 虫草菌粉对兔矽肺纤维化早期干预作用[J]. 中华劳动卫生职业病杂志, 2014, 32(7): 530-532.
LIU Q Z, ZHANG W, CUI H F, et al. Study on effect of cordyceps sinensis on early-stage silicotic pulmonary fibrosis in rabbits[J]. Chin J Ind Hyg Occup Dis, 2014, 32(7): 530-532.

[19] 宋占帅, 张蓉, 张娟, 等. 抑制NLRP3炎症小体活化对二氧化硅粉尘致巨噬细胞炎性反应的影响[J]. 中华劳动卫生职业病杂志, 2020, 38(6): 406-409.
SONG Z S, ZHANG R, ZHANG J, et al. Inhibition of NLRP3 inflammasome activation on the inflammatory response of macrophage induced by silica dust[J]. Chin J Ind Hyg Occup Dis, 2020, 38(6): 406-409.

[20] 宋占帅. NLRP3/IL-1β/TGF-β1信号轴在矽肺纤维化发生发展中的作用及木犀草素的拮抗效应[D]. 济南: 山东中医药大学, 2019.
SONG Z S. Role of NLRP3/IL-1β/TGF-β1 signal axis in the development of silicosis pulmonary fibrosis and the antagonistic effect of luteolin[D]. Ji'nan: Shandong University of traditional Chinese Medicine, 2019.

[21] CUI Y, CHEN L J, HUANG T, et al. The pharmacology, toxicology and therapeutic potential of anthraquinone derivative emodin[J]. Chin J Nat Med, 2020, 18(6): 425-435.

[22] PANG X, SHAO L, NIE X, et al. Emodin attenuates silica-induced lung injury by inhibition of inflammation, apoptosis and epithelial-mesenchymal transition[J]. Int Immunopharmacol, 2021, 91: 107277.

[23] YANG T, WANG J, PANG Y, et al. Emodin suppresses silica-induced lung fibrosis by promoting Sirt1 signaling via direct contact[J]. Mol Med Rep, 2016, 14(5): 4643-4649.

[24] 张春妹, 杨永寿, 肖培云. 美洲大蠊活性组分对矽尘致大鼠肺纤维化的影响[J]. 环境与职业医学, 2018, 35(12): 1134-1138.
ZHANG C M, YANG Y S, XIAO P Y. Influence of active ingredients extracted from Periplaneta Americana on pulmonary fibrosis in silica-exposed rats[J]. J Environ Occup Med, 2018, 35(12): 1134-1138.

[25] 陆青兰, 黄世稳, 韦雪平, 等. 黄根多糖对大鼠矽肺纤维化的作用[J]. 中草药, 2020, 51(4): 1031-1036.
LU Q L, HUANG S W, WEI X P, et al. Anti-fibrosis effects of polysaccharide of Prismatomeris tetrandra on silicosis rats[J]. Chin Tradit Herb Drugs, 2020, 51(4): 1031-1036.

[26] FENG F, CHENG P, ZHANG H, et al. The protective role of tanshinone IIA in silicosis rat model via TGF-β1/Smad signaling suppression, NOX4 Inhibition and Nrf2/ARE signaling activation[J]. Drug Des Devel Ther, 2019, 13: 4275-4290.

[27] FENG F, CHENG P, XU S, et al. Tanshinone IIA attenuates silica-induced pulmonary fibrosis via Nrf2-mediated inhibition of EMT and TGF-β1/Smad signaling[J]. Chem-Biol Interact, 2020, 319: 109024.

[28] ZHANG J, WU C, GAO L, et al. Astragaloside IV derived from *Astragalus membranaceus*: a research review on the pharmacological effects[J]. Adv Pharmacol, 2020, 87: 89-112.

[29] LI N, FENG F, WU K, et al. Inhibitory effects of astragaloside IV on silica-induced pulmonary fibrosis via inactivating TGF-β1/Smad3 signaling[J]. Biomed Pharmacother, 2019, 119: 109387.

[30] LI C, LU Y, DU S, et al. Dioscin exerts protective effects against crystalline silica-induced pulmonary fibrosis in mice[J]. Theranostics, 2017, 7(17): 4255-4275.

[31] 吴丽娟. 大黄䗪虫丸基于TGF-β1/Smad信号通路抑制矽肺纤维化的作用机制研究[D]. 成都: 成都中医药大学, 2020.
WU L J. Mechanism of Dahuang Zhechong pills on silicosis fibrosis based on TGF-β1/Smad signaling pathway[D]. Chengdu: Chengdu University of TCM, 2020.

[32] 刘玉红. 益气养阴、化痰活血法调控TGF-β1/Smads信号通路阻遏矽肺纤维化的实验研究[D]. 泸州: 西南医科大学, 2019.
LIU Y H. Study on the regulation of TGF-β1/Smads signaling pathway repression and deuteration by Yiqi Yangyin, Huatan Huoxue method[D]. Luzhou: Southwest Medical University, 2019.

[33] 郭敬文. 自制中药和吡非尼酮对大鼠矽肺纤维化早期TGF-β1/Smad信号通路调节作用研究[D]. 济南: 济南大学, 2019.
GUO J W. Regulatory effect of self-made Traditional Chinese Medicine and pirfenidone on TGF-β1/Smad signaling pathway in rat early stage of silicosis[D]. Ji'nan: Ji'nan University, 2019.

[34] 郭敬文, 胡晨阳, 薄存香, 等. 抗肺纤中药颗粒抑制SiO_2诱导的大鼠肺组织上皮-间质转化[J]. 职业与健康, 2020, 36(17): 2329-2334.
GUO J W, HU C Y, BO C X, et al. Inhibition of anti-lung fibrosis traditional Chinese medicine particles on SiO_2–induced epithelial-mesenchymal transition in rat lung tissues[J]. Occup Health, 2020, 36(17): 2329-2334.

[35] 孙瑞玲, 李光杰, 闫瑢玓, 等. 参芪益肺汤对早期尘肺转化生长因子-β1的干预研究[J]. 中华中医药杂志, 2015, 30(12): 4516-4518.

SUN R L, LI G J, YAN R D, et al. Intervention study for Shenqi Yifei Decoction to TGF-beta 1 in the early pneumoconiosis[J]. China J Tradit Chin Med Pharm, 2015, 30(12): 4516-4518.

[36] YI S, ZHANG F, QU F, et al. Water-insoluble fraction of airborne particulate matter (PM_{10}) induces oxidative stress in human lung epithelial A549 cells[J]. Environ Toxicol, 2014, 29(2): 226-233.

[37] TONELLI C, CHIO I I C, TUVESON D A. Transcriptional regulation by Nrf2[J]. Antioxid Redox Signal, 2018, 29(17): 1727-1745.

[38] ZHANG X, JIA X, MEI L, et al. Global DNA methylation and PTEN hypermethylation alterations in lung tissues from human silicosis[J]. J Thorac Dis, 2016, 8(8): 2185-2195.

[39] KRAJKA-KUŹNIAK V, PALUSZCZAK J, BAER-DUBOWSKA W. The Nrf2-ARE signaling pathway: an update on its regulation and possible role in cancer prevention and treatment[J]. Pharmacol Rep, 2017, 69(3): 393-402.

[40] PENG L Y, AN L, SUN N Y, et al. *Salvia miltiorrhiza* restrains reactive oxygen species-associated pulmonary fibrosis via targeting Nrf2-Nox4 redox balance[J]. Am J Chin Med, 2019, 47(5): 1113-1131.

[41] AN L, PENG L Y, SUN N Y, et al. Tanshinone IIA activates nuclear factor-erythroid 2-related factor 2 to restrain pulmonary fibrosis *via* regulation of redox homeostasis and glutaminolysis[J]. Antioxid Redox Signal, 2019, 30(15): 1831-1848.

[42] ZHU Z, WANG Y, LIANG D, et al. Sodium tanshinone IIA sulfonate suppresses pulmonary fibroblast proliferation and activation induced by silica: role of the Nrf2/Trx pathway[J]. Toxicol Res, 2016, 5(1): 116-125.

[43] 陈丽, 颜春鲁, 赵翊, 等. 黄芪对矽肺大鼠肺组织胶原合成的影响[J]. 工业卫生与职业病, 2017, 43(5): 359-362.
CHEN L, YAN C L, ZHAO Y, et al. Effects of astragalus and astragalus extract on collagen synthesis in rat lungs exposed to silica[J]. Ind Health Occup Dis, 2017, 43(5): 359-362.

[44] 马文女, 谷江叶, 王迪, 等. 黄芩黄酮对矽肺小鼠脂质过氧化及纤维化损伤的影响[J]. 承德医学院学报, 2014, 31(5): 445-446.
MA W N, GU J Y, WANG D, et al. Effects of Baicalin on lipid peroxidation and fibrosis in silicosis mice[J]. J Chengde Med Coll, 2014, 31(5): 445-446.

[45] 朴秀美. 白茶提取物对纳米SiO_2诱导的大鼠纤维化抑制作用及机制[D]. 杭州: 浙江大学, 2019.
PIAO X M. The inhibition and mechanism of white tea extract on fibrosis in rats induced by silicon dioxide nanoparticles[D]. Hangzhou: Zhejiang University, 2019.

[46] 李浩宇, 史珍珍, 舒立峰, 等. 白及多糖抗矽肺大鼠肺纤维化活性研究[J]. 中药材, 2016, 39(7): 1639-1643.
LI H Y, SHI Z Z, SHU L F, et al. Research on the anti-pulmonary fibrosis effect of the *Bletilla striata* polysaccharide in rat silicosis model[J]. J Chin Med Mater, 2016, 39(7): 1639-1643.

[47] 邓延珍, 金丽霞, 高承贤, 等. 白及小分子组分抗矽肺大鼠肺纤维化活性研究[J]. 中药材, 2016, 39(11): 2618-2622.
DENG Y Z, JIN L X, GAO C X, et al. Research on the anti-pulmonary fibrosis effect of the small molecule components of *Bletilla striata* in rat silicosis model[J]. J Chin Med Mater, 2016, 39(11): 2618-2622.

[48] JIANG F, LI M, WANG H, et al. Coelonin, an anti-inflammation active component of *Bletilla striata* and its potential mechanism[J]. Int J Mol Sci, 2019, 20(18): 4422.

[49] 孙晓伟, 肖华, 宋学术, 等. 萝卜硫素通过Nrf2/ARE通路缓解矽肺模型大鼠肺组织纤维化及氧化应激的实验研究[J]. 临床和实验医学杂志, 2020, 19(6): 586-589.
SUN X W, XIAO H, SONG X S, et al. Effects of sulforaphane on pulmonary fibrosis and oxidative stress in silicosis model rats via Nrf2/ARE pathway[J]. J Clin Exp Med, 2020, 19(6): 586-589.

[50] 杨京津. 地龙提取物减弱矽尘诱导的小鼠肺纤维化机制研究[D]. 南京: 南京医科大学, 2016.
YANG J J. The protective effect and mechanism of earthworm extract on silica-induced pulmonary fibrosis[D]. Nanjing: Nanjing Medical University, 2016.

[51] 赵宏艳, 刘红, 潘静华, 等. 吸附排尘中草药制剂对矽肺大鼠干预作用[J]. 中国职业医学, 2020, 47(2): 190-195.
ZHAO H Y, LIU H, PAN J H, et al. Interventional effect of Chinese herbal preparation Xi Fu Pai Chen in rats with silicosis[J]. China Occup Med, 2020, 47(2): 190-195.

[52] 任文章, 刘冰. 中西医结合治疗对尘肺合并慢性阻塞性肺疾病患者肺纤维化、氧化应激及呼吸功能的影响[J]. 中国医药指南, 2020, 18(11): 6-9.
REN W Z, LIU B. Effect of integrated traditional Chinese and western medicine on pulmonary fibrosis, oxidative stress and respiratory function in patients with pneumoconiosis complicated with chronic obstructive pulmonary disease[J]. Guide China Med, 2020, 18(11): 6-9.

[53] JESSOP F, HAMILTON R F, RHODERICK J F, et al. Autophagy deficiency in macrophages enhances NLRP3 inflammasome activity and chronic lung disease following silica exposure[J]. Toxicol Appl Pharmacol, 2016, 309: 101-110.

[54] LIU H, CHENG Y, YANG J, et al. BBC3 in macrophages promoted pulmonary fibrosis development through inducing autophagy during silicosis[J]. Cell Death Dis, 2017, 8(3): e2657.

[55] LIU H, FANG S, WANG W, et al. Macrophage-derived MCPIP1 mediates silica-induced pulmonary fibrosis via autophagy[J]. Part Fibre Toxicol, 2016, 13(1): 55.

[56] QUAN B, ZHANG H, XUE R. miR-141 Alleviates LPS-Induced Inflammation Injury in WI-38 fibroblasts by up-regulation of NOX2[J]. Life Sci, 2019, 216: 271-278.

[57] THIBODEAU M, GIARDINA C, HUBBARD A K. Silica-induced caspase activation in mouse alveolar macrophages is dependent upon mitochondrial integrity and aspartic proteolysis[J]. Toxicol Sci, 2003, 76(1): 91-101.

[58] GOZAL E, ORTIZ L A, ZOU X, et al. Silica-induced apoptosis in murine macrophage: involvement of tumor necrosis factor-α and nuclear factor-κB activation[J]. Am J Respir Cell Mol Biol, 2002, 27(1): 91-98.

[59] YAO S Q, HE Q C, YUAN J X, et al. Role of Fas/FasL pathway-mediated alveolar macrophages releasing inflammatory cytokines in human silicosis[J]. Biomed Environ Sci, 2013, 26(11): 930-933.

[60] WANG L, BOWMAN L, LU Y, et al. Essential role of p53 in silica-induced apoptosis[J]. Am J Physiol Lung Cell Mol Physiol, 2005, 288(3): L488-L496.

[61] 陈慧萍, 周煜, 覃小峰, 等. 内质网应激调控二氧化硅诱导的RAW264.7细胞自噬及肿瘤坏死因子-α分泌[J]. 中华劳动卫生职业病杂志, 2020, 38(2): 91-95.
CHEN H P, ZHOU Y, QIN X F, et al. Endoplasmic reticulum stress regulates autophagy and tumor necrosis factor-α secretion of RAW264.7 cells induced by silica[J]. Chin J Ind Hyg Occup Dis, 2020, 38(2): 91-95.

[62] DU S, LI C, LU Y, et al. Dioscin alleviates crystalline silica-induced pulmonary inflammation and fibrosis through promoting alveolar macrophage autophagy[J]. Theranostics, 2019, 9(7): 1878-1892.

[63] ZHANG W, ZHANG M, WANG Z, et al. Neogambogic acid prevents silica-induced fibrosis via inhibition of high-mobility group box 1 and MCP-1-induced protein 1[J]. Toxicol Appl Pharmacol, 2016, 309: 129-140.

[64] CHEN S, TANG K, HU P, et al. Atractylenolide III alleviates the apoptosis

through inhibition of autophagy by the mTOR-dependent pathway in alveolar macrophages of human silicosis[J]. Mol Cell Biochem, 2021, 476(2): 809-818.

[65] 崔洁, 陈紫莺, 马景景, 等. 丹参酮IIA磺酸钠对大鼠矽肺早期的干预作用[J]. 环境与职业医学, 2019, 36(1): 79-83.
CUI J, CHEN ZY, MA JJ, et al. Intervention effect of sodium tanshinone IIA sulfonate on early-stage silicosis in rats[J]. J Environ Occup Med, 2019, 36(1): 79-83.

[66] 陈紫莺, 候晓敏, 崔洁, 等. 银杏叶提取物改善肺内淋巴转运对大鼠矽肺病程的影响[J]. 环境与职业医学, 2018, 35(4): 366-370.
CHEN ZY, HOU XM, CUI J, et al. Effects of promoting pulmonary lymphatic transportation by Ginkgo biloba extract on the pathogenesis of silicosis in rats[J]. J Environ Occup Med, 2018, 35(4): 366-370.

[67] YU J, MAO L, GUAN L, et al. Ginsenoside Rg1 enhances lymphatic transport of intrapulmonary silica *via* VEGF-C/VEGFR-3 signaling in silicotic rats[J]. Biochem Biophys Res Commun, 2016, 472(1): 182-188.

[68] SHEN F, FAN X, LIU B, et al. Downregulation of cyclin D1-CDK4 protein in human embryonic lung fibroblasts (HELF) induced by silica is mediated through the ERK and JNK pathway[J]. Cell Biol Int, 2008, 32(10): 1284-1292.

[69] 宋楠楠, 杜忠君, 贾强, 等. 姜黄素抑制游离二氧化硅诱导小鼠肺泡巨噬细胞NLRP3炎性小体活化机制[J]. 中国职业医学, 2020, 47(2): 121-128.
SONG NN, DU ZJ, JIA Q, et al. Mechanism of curcumin in inhibiting silica-induced NLRP3 inflammasome activation in mouse alveolar macrophages[J]. China Occup Med, 2020, 47(2): 121-128.

[70] 郝小惠, 李娟, 郭志义, 等. 姜黄素对矽肺大鼠肺组织PDGF及ERK1/2表达的影响[J]. 中国工业医学杂志, 2014, 27(3): 196-198.
HAO XH, LI J, GUO ZY, et al. Effect of curcumin on expression of PDGF and ERK1/2 in lung tissue of silicotic rats[J]. Chin J Ind Med, 2014, 27(3): 196-198.

[71] 郝小惠, 王宏丽, 刘和亮, 等. 姜黄素对矽肺大鼠肺组织水通道蛋白-1表达影响[J]. 中国职业医学, 2012, 39(6): 471-474.
HAO XH, WANG HL, LIU HL, et al. Effect of curcumin on expression of aquaporin-1 in lung tissue of silicotic rats[J]. China Occup Med, 2012, 39(6): 471-474.

(**英文编辑**: 汪源; **责任编辑**: 王晓宇)

(上接第 228 页)

[48] QAZI MR, NELSON BD, DEPIERRE JW, et al. 28-Day dietary exposure of mice to a low total dose (7 mg/kg) of perfluorooctanesulfonate (PFOS) alters neither the cellular compositions of the thymus and spleen nor humoral immune responses: does the route of administration play a pivotal role in PFOS-induced immunotoxicity?[J]. Toxicology, 2010, 267(1//2/3): 132-139.

[49] SAITO S, NAKASHIMA A, SHIMA T, et al. Review article: Th1/Th2/Th17 and regulatory T-cell paradigm in pregnancy[J]. Am J Reprod Immunol, 2010, 63(6): 601-610.

[50] ZHENG L, DONG GH, ZHANG YH, et al. Type 1 and Type 2 cytokines imbalance in adult male C57BL/6 mice following a 7-day oral exposure to perfluorooctanesulfonate (PFOS)[J]. J Immunotoxicol, 2011, 8(1): 30-38.

[51] DONG GH, LIU MM, WANG D, et al. Sub-chronic effect of perfluorooctanesulfonate (PFOS) on the balance of type 1 and type 2 cytokine in adult C57BL6 mice[J]. Arch Toxicol, 2011, 85(10): 1235-1244.

[52] MIDGETT K, PEDEN-ADAMS MM, GILKESON GS, et al. *In vitro* evaluation of the effects of perfluorooctanesulfonic acid (PFOS) and perfluorooctanoic acid (PFOA) on IL-2 production in human T-cells[J]. J Appl Toxicol, 2015, 35(5): 459-465.

[53] CASTAÑO-ORTIZ JM, JASPERS VL B, WAUGH CA. PFOS mediates immunomodulation in an avian cell line that can be mitigated via a virus infection[J]. BMC Vet Res, 2019, 15(1): 214.

[54] PALMER CN A, HSU MH, GRIFFIN KJ, et al. Peroxisome proliferator activated receptor-αexpression in human liver[J]. Mol Pharmacol, 1998, 53(1): 14-22.

[55] DEWITT JC, SHNYRA A, BADR MZ, et al. Immunotoxicity of perfluorooctanoic acid and perfluorooctane sulfonate and the role of peroxisome proliferator-activated receptor alpha[J]. Crit Rev Toxicol, 2009, 39(1): 76-94.

[56] TAKACS ML, ABBOTT BD. Activation of mouse and human peroxisome proliferator-activated receptors (α, β/δ, γ) by perfluorooctanoic acid and perfluorooctane sulfonate[J]. Toxicol Sci, 2007, 95(1): 108-117.

[57] ESCHER P, WAHLI W. Peroxisome proliferator-activated receptors: insight into multiple cellular functions[J]. Mutat Res, 2000, 448(2): 121-138.

[58] FANG X, ZHANG L, FENG Y, et al. Immunotoxic effects of perfluorononanoic acid on BALB/c mice[J]. Toxicol Sci, 2008, 105(2): 312-321.

[59] YANG J, WANG C, NIE X, et al. Perfluorooctane sulfonate mediates microglial activation and secretion of TNF-α through Ca^{2+}-dependent PKC-NF-κB signaling[J]. Int Immunopharmacol, 2015, 28(1): 52-60.

[60] CORSINI E, SANGIOVANNI E, AVOGADRO A, et al. In vitro characterization of the immunotoxic potential of several perfluorinated compounds (PFCs)[J]. Toxicol Appl Pharmacol, 2012, 258(2): 248-255.

[61] WANG C, YOULE RJ. The role of mitochondria in apoptosis[J]. Annu Rev Genet, 2009, 43: 95-118.

[62] MASHAYEKHI V, TEHRANI KH ME, HASHEMZAEI M, et al. Mechanistic approach for the toxic effects of perfluorooctanoic acid on isolated rat liver and brain mitochondria[J]. Hum Exp Toxicol, 2015, 34(10): 985-996.

[63] HU XZ, HU DC. Effects of perfluorooctanoate and perfluorooctane sulfonate exposure on hepatoma Hep G2 cells[J]. Arch Toxicol, 2009, 83(9): 851-861.

[64] LIU C, YU K, SHI X, et al. Induction of oxidative stress and apoptosis by PFOS and PFOA in primary cultured hepatocytes of freshwater tilapia (Oreochromis niloticus)[J]. Aquat Toxicol, 2007, 82(2): 135-143.

(**英文编辑**: 汪源; **责任编辑**: 王晓宇)