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Ameliorative Effect of Acetylshikonin on Cigarette Smoke Induced Lung Inflammation in Mice

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SUMMARY*. Cigarette smoke exposure is the major cause of chronic obstructive pulmonary disease (COPD), which is characterized by enhanced oxidative stress, inflammatory responses and tissue destruction. Acetylshikonin has been reported to exhibit anti-oxidative and anti-inflammatory effect. We hypothesized that acetylshikonin could protect against cigarette smoke induced acute lung injury via its anti-oxidative and anti-inflammatory properties. Acetylshikonin was given by tail vein injection to C57BL/6 mice daily 2 h before 4% cigarette smoke exposure for 1 h over five consecutive days. The lung tissues and bronchoalveolar lavage (BAL) fluid were collected and the tissue damage, inflammatory cytokines and anti-oxidative activity were analyzed. Meanwhile, the RAW264.7 cells were cultured in cigarette smoke treated medium and employed to study the mechanisms of action of acetylshikonin. Acetylshikonin could attenuate smoke-induced lung pathological changes, tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), interleukin-1β (IL-1β), and monocyte chemoattractant protein 1 (MCP-1) productions, and tissue damages caused by oxidative stress. Furthermore, acetylshikonin was found to enhance the expression of Nrf2 and Nur77-mediated COX-2 *in vivo* and *in vitro*. Our results indicated that acetylshikonin exhibited an ameliorative effect on smoke-induced acute lung injury and the possible mechanism was involved in increasing the expression of Nrf2 and Nur77-mediated COX-2.

RESUMEN. La exposición al humo del cigarrillo es la principal causa de la enfermedad pulmonar obstructiva crónica (EPOC), que se caracteriza por un aumento del estrés oxidativo, respuestas inflamatorias y destrucción de tejidos. Se ha informado que la acetilshikonina exhibe efectos antioxidantes y antiinflamatorios. Nuestra hipótesis es que la acetilshikonina podría proteger contra las lesiones pulmonares agudas inducidas por el humo del cigarrillo a través de sus propiedades antioxidantes y antiinflamatorias. La acetilshikonina se administró mediante inyección en la vena de la cola a ratones C57BL/6 diariamente 2 h antes del 4% de exposición al humo del cigarrillo durante 1 h durante cinco días consecutivos. Se recogieron los tejidos pulmonares y el fluido de lavado broncoalveolar (BAL) y se analizaron el daño tisular, las citoquinas inflamatorias y la actividad antioxidante. Mientras tanto, las células RAW264.7 se cultivaron en un medio tratado con humo de cigarrillo y se emplearon para estudiar los mecanismos de acción de la acetilshikonina. La acetilshikonina podría atenuar los cambios patológicos en el pulmón inducidos por el humo, el factor de necrosis tumoral α (TNF-α), la interleucina-6 (IL-6), la interleucina-1β (IL-1β) y las producciones de proteína quimioatrayente de monocitos 1 (MCP-1) y daños tisulares causados por estrés oxidativo. Además, se encontró que la acetilshikonina aumenta la expresión de Nrf2 y la COX-2 mediada por Nur77 *in vivo* e *in vitro*. Nuestros resultados indicaron que la acetilshikonina mostró un efecto de mejora en la lesión pulmonar aguda inducida por el humo y el posible mecanismo estuvo involucrado en el aumento de la expresión de Nrf2 y la COX-2 mediada por Nur77.

KEY WORDS: acetylshikonin, COPD, inflammation, oxidative stress, smoke inhalation,

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