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Anti-tuberculosis, Resistance Modulatory, Anti-pulmonary Fibrosis and Anti-silicosis Effects of Crinum Asiaticum Bulbs and Its Active Metabolite, Betulin

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Abstract : Drug-resistant tuberculosis, together with the associated comorbidities like pulmonary fibrosis and silicosis, has been one of the most serious global public health threats that requires immediate action to curb or mitigate it. This prolongs hospital stays, increases the cost of medication, and increases the death toll recorded annually. Crinum asiaticum bulb (CAE) and betulin (BET) are known for their biological and pharmacological effects. Pharmacological effects reported on CAE include antimicrobial, anti-inflammatory, anti-pyretic, anti-analgesic, and anti-cancer effects. Betulin has exhibited a multitude of powerful pharmacological properties ranging from antitumor, anti-inflammatory, anti-parasitic, anti-microbial, and anti-viral activities. This work sought to investigate the anti-tuberculosis and resistant modulatory effects and also assess their effects on mitigating pulmonary fibrosis and silicosis. In the anti-tuberculosis and resistant modulatory effects, both CAE and BET showed strong antimicrobial activities ($31.25 \leq MIC \leq 500$) µg/ml against the studied microorganisms and also produced significant anti-efflux pump and biofilm inhibitory effects ($\rho < 0.0001$) as well as exhibiting resistance modulatory and synergistic effects when combined with standard antibiotics. Crinum asiaticum bulbs extract and betulin were shown to possess anti-pulmonary fibrosis effects. There was an increased survival rate in the CAE and BET treatment groups compared to the BLM-induced group. There was a marked decrease in the levels of hydroxyproline and collagen I and III in the CAE and BET treatment groups compared to the BLM-treated group. The treatment groups of CAE and BET significantly downregulated the levels of pro-fibrotic and pro-inflammatory cytokine concentrations such as TGF-β1, MMP9, IL-6, IL-1β and TNF-alpha compared to an increase in the BLM-treated groups. The histological findings of the lungs suggested the curative effects of CAE and BET following BLM-induced pulmonary fibrosis in mice. The study showed improved lung functions with a wide focal area of viable alveolar spaces and few collagen fibers deposition on the lungs of the treatment groups. In the anti-silicosis and pulmonoprotective effects of CAE and BET, the levels of NF-κB, TNF-α, IL-1β, IL-6 and hydroxyproline, collagen types I and III were significantly reduced by CAE and BET ($\rho < 0.0001$). Both CAE and BET significantly ($\rho < 0.0001$) inhibited the levels of hydroxyproline, collagen I and III when compared with the negative control group. On BALF biomarkers such as macrophages, lymphocytes, monocytes, and neutrophils, CAE and BET were able to reduce their levels significantly ($\rho < 0.0001$). The CAE and BET were examined for anti-oxidant activity and shown to raise the levels of catalase (CAT) and superoxide dismutase (SOD) while lowering the level of malondialdehyde (MDA). There was an improvement in lung function when lung tissues were examined histologically. Crinum asiaticum bulbs extract and betulin were discovered to exhibit anti-tubercular and resistance-modulatory properties, as well as the capacity to minimize TB comorbidities such as pulmonary fibrosis and silicosis. In addition, CAE and BET may act as protective mechanisms, facilitating the preservation of the lung's physiological integrity. The outcomes of this study might pave the way for the development of leads for producing single medications for the management of drug-resistant tuberculosis and its accompanying comorbidities.

Keywords : fibrosis, crinum, tuberculosis, antiinflammation, drug resistant
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