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Title: Rikkunshito ameliorates bleomycin-induced lung injury in mice

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Body: Acute lung injury (ALI) is a critical illness syndrome consisting of acute respiratory failure with bilateral pulmonary infiltrates that is refractory to current therapies. ALI is characterized by injuries of the alveolar epithelial barrier, infiltrations of neutrophils into lung parenchyma, and induction of pro-inflammatory cytokines followed by devastating lung fibrosis. Rikkunshito (RKT), a traditional Japanese medicine, consists of several kind of flavonoids which have been shown to have anti-inflammatory effects. In addition, previous studies have reported that RKT increases plasma level of ghrelin, an acylated and orexygenic peptide, produced predominantly in the stomach. We investigated the pharmacological potential of RKT in the treatment of ALI by using a bleomycin (BLM)-induced lung injury model in mice. RKT or distilled water was given to mice orally and daily starting from the day of BLM administration. RKT-treated mice showed a definitively higher survival rate than distilled water-treated ones. They also had smaller reductions in body weight and food intake compared to the controls. Additionally, RKT-treated mice showed reduction of pulmonary epithelial permeability, neutrophil alveolar infiltration, and subsequent lung fibrosis. RKT administration resulted in increase of plasma levels of ghrelin in BLM-treated mice. However, RKT administration also exerted protective effects against BLM-induced ALI response on ghrelin-deficient mice in addition to ghrelin-competent mice. Our results indicate that RKT administration exerts a protective effects on BLM-induced lung injury in mice independently of the effects of ghrelin, and highlight RKT as a promising therapeutic strategy for the control of the ALI.