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Synergistic Effect and Different Toxicities of Adjuvant Components of Realgar-*Indigo naturalis* Formula

Huan-Hua Xu^{a,b}, Zeng-Chun Ma^{a,b}, Qiao-Li Shi^c, Shi-Han Yang^b, La Jiang^b, Xiang-Mei Chen^d, Yue Gao^{a,b*}

a. Guangdong Pharmaceutical University, Guangzhou 510006, China;

b. Institute of Radiation Medicine, Academy of Military Medical Sciences, Beijing 100850, China;

c. State Key Laboratory of Drug Metabolism, Hematological Pharmacology, Beijing Institute of Transfusion Medicine, Beijing 100850, China;

d. Department of Nephrology, Chinese PLA General Hospital, Chinese PLA Institute of Nephrology, State Key Laboratory of Kidney Diseases, National Clinical Research Center for Kidney Diseases, Beijing 100850, China.

Abstract

Objective Realgar-*Indigo naturalis* formula (RIF) is a well-known arsenic-containing preparation that is used to treat acute promyelocytic leukemia (APL) in China. In recent multicenter clinical trials, complete remission rates in APL patients have ranged from 96.08% to 100%. RIF has a satisfactory therapeutic effect, but its safety is a widespread concern, since the preparation contains arsenic, a wide-ranging and naturally occurring toxicant. In this study, in order to determine the toxic potential of RIF, acute toxicity and sub chronic toxicity assays were performed to evaluate the toxic potential of realgar and the adjuvant components of RIF in addition to realgar's synergy with these adjuvant components. **Methods** KM mice and Wistar rats were selected for these experiments. To evaluate acute toxicity, the toxic effects of a single dose of a gradient of concentrations of realgar were firstly determined. Then, the toxic effects of combinations of gradient doses of realgar and fixed doses of *I. naturalis* and *S. miltiorrhiza* were evaluated. **Results** The results showed that when realgar was used alone, the LD₅₀ was 2756.73 mg/kg (equivalent to 23.6 mg/kg As₂O₃). However, the LD₅₀ dropped to 936.90 mg/kg when realgar was used with *I. naturalis*. By contrast, the LD₅₀ increased to 7538.86 mg/kg when realgar was used with *S. miltiorrhiza*. Hence, *I. naturalis* strengthened the toxicity of realgar, whereas *S. miltiorrhiza* displayed the opposite effect. The sub chronic toxicity assessment results revealed a trend that was consistent with acute toxicity. Changes in the levels of different valence states of arsenic were also taken into account. The test results of the effects of *in vitro* combinations of realgar and adjuvant components on soluble arsenic dissolution showed that *I. naturalis* increased the level of soluble arsenic in realgar extracts and *I. naturalis* suspensions when the realgar/*I. naturalis* ratio was 2, 1.5, and 1.0. However, *S. miltiorrhiza* did not affect it. **Conclusion** Based on the collective experimental results presented

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