

Revealing the Effects of the Herbal Pair of Euphorbia kansui and Glycyrrhiza on Hepatocellular Carcinoma Ascites with Integrating Network Target Analysis and Experimental Validation

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Abstract :

Although the herbal pair of Euphorbia kansui (GS) and Glycyrrhiza (GC) is one of the so-called "eighteen antagonistic medicaments" in Chinese medicinal literature, it is prescribed in a classic Traditional Chinese Medicine (TCM) formula Gansui-Banxia-Tang for cancerous ascites, suggesting that GS and GC may exhibit synergistic or antagonistic effects in different combination designs. Here, we modeled the effects of GS/GC combination with a target interaction network and clarified the associations between the network topologies involving the drug targets and the drug combination effects. Moreover, the "edge-betweenness" values, which is defined as the frequency with which edges are placed on the shortest paths between all pairs of modules in network, were calculated, and the ADRB1-PIK3CG interaction exhibited the greatest edge-betweenness value, suggesting its crucial role in connecting the other edges in the network. Because ADRB1 and PIK3CG were putative targets of GS and GC, respectively, and both had functional interactions with AVPR2 approved as known therapeutic target for ascites, we proposed that the ADRB1-PIK3CG-AVPR2 signal axis might be involved in the effects of the GS-GC combination on ascites. This proposal was further experimentally validated in a H22 hepatocellular carcinoma (HCC) ascites model. Collectively, this systems-level investigation integrated drug target prediction and network analysis to reveal the combination principles of the herbal pair of GS and GC. Experimental validation in an in vivo system provided convincing evidence that different combination designs of GS and GC might result in synergistic or antagonistic effects on HCC ascites that might be partially related to their regulation of the ADRB1-PIK3CG-AVPR2 signal axis.

Key Word :

herb-herb combination; Euphorbia kansui; Glycyrrhiza; hepatocellular carcinoma ascites; network pharmacology

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