

Supplementary Material

Prediction of putative targets for GS and GC

We used Drug Similarity Search tool in Therapeutic Targets Database [1] (TTD, <http://xin.cz3.nus.edu.sg/group/cjttd/ttd.asp>, Version 4.3.02 release on Aug 25th 2011) to screen similar drugs of GS and GC through the structural similarity comparison. We only selected the drugs with high similar score (>0.85, similar ~ very similar) in the comparison with the structures of compositive compounds of GS and GC. The therapeutic targets of these similar drugs were also collected as putative targets of GS and GC. The performance of this prediction method has been evaluated in our previous study [2].

Definitions of the network topological features

For each node i in drug target network, topological features were calculated in four ways: (1) 'Degree': the number of links to node i ; (2) 'Node betweenness': the number of shortest paths between pairs of nodes which run through node i ; (3) 'Closeness': the sum of the distances of node i to all other nodes (the degree, node betweenness and closeness can be used to assess the topological importance of a node in a network, and the larger a node's degree, node betweenness, and closeness centrality, the more important that node is in the PPI network [3]); and (4) 'K coreness': a measure of the centrality of node i [4].

Additionally, we also used a Markov clustering algorithm to divide all nodes into different functional modules to assess the modularity of the network because proteins that are highly interconnected within a network are usually involved in the same biological modules or pathways.

For each edge in the interaction network of a major putative target, we calculated 'edge betweenness' to assess the importance of a specific interaction in the network. 'Edge betweenness' is defined as the frequency with an edge is placed on the shortest paths between all pairs of vertices in network and is calculated according to the formula below [5, 6]. The edges with the greatest betweenness values are most likely to lie between functional modules.

The edge betweenness for edge e is defined as

$$EB(e) = \sum_{vi \in V} \sum_{vj \in V \setminus \{vi\}} \frac{\sigma_{vij}(e)}{\sigma_{vij}} \dots\dots\dots f1$$

where σ_{vij} is defined as the number of shortest paths between nodes V_i and V_j in the network, and $\sigma_{vij}(e)$ is defined as the number of shortest paths between V_i and V_j .

References:

[1]. Zhu F, Shi Z, Qin C, et al. Therapeutic target database update 2012: a resource for facilitating target-oriented drug discovery. *Nucleic Acids Res.* 2012; 40: D1128- D1136.

[2]. Zhang Y, Wang D, Tan S, et al. A systems biology-based investigation into the pharmacological mechanisms of Wu Tou Tang acting on rheumatoid arthritis by integrating network analysis. *Evidence-Based Complementary and Alternative Medicine.* 2013; 2013: 548498.

[3]. Wuchty S, Almaas E. Evolutionary cores of domain co-occurrence networks. *BMC Evol Biol.* 2005; 5: 24

[4]. Zhang Y, Guo X, Xiong L, et al. Comprehensive analysis of microRNA-regulated protein interaction network reveals the tumor suppressive role of microRNA-149 in human hepatocellular carcinoma via targeting AKT-mTOR pathway. *Mol Cancer.* 2014; 13: 253.

[5]. Narayanan T, Gersten M, Subramaniam S, Grama A. Modularity detection in protein-protein interaction networks. *BMC Res Notes.* 2011; 4: 569.

[6]. Hashimoto TB, Nagasaki M, Kojima K, Miyano S. BFL: a node and edge betweenness based fast layout algorithm for large scale networks. *BMC Bioinformatics.* 2009; 10: 19.

Figure S1. Main chemical of *Euphorbia kansui* and *Glycyrrhiza* as determined by HPLC-MS.

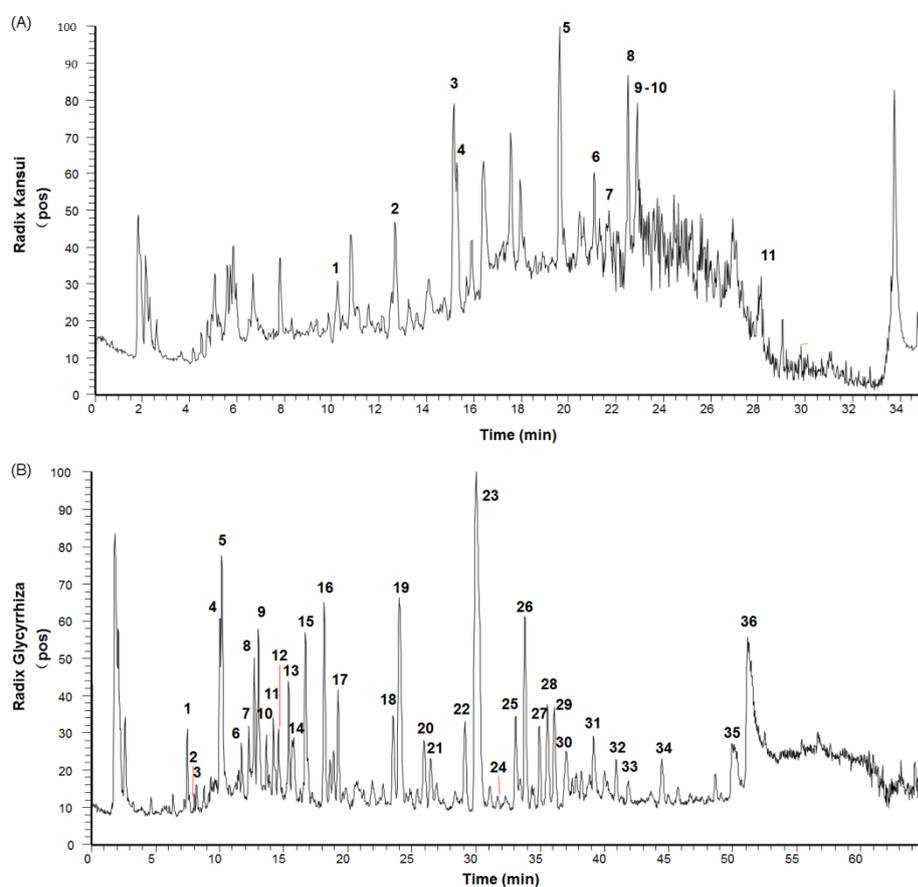


Figure S2. Expressions of the phosphorylated PI3K γ (p- PI3K γ , A) and p-AKT (B) proteins in the kidney tissues of the different groups as detected by western blot analysis. The data are represented as the means \pm the S.E. ^{*} and ^{***} P<0.05 and P<0.01, respectively, compared with the model group; [#] and ^{###} P<0.05 and P<0.01, respectively, compared with the GS group. Lanes 1-4 in the western blots denote the Model, GS, GS/GC_synergy and GS/GC_antagonism groups, respectively.

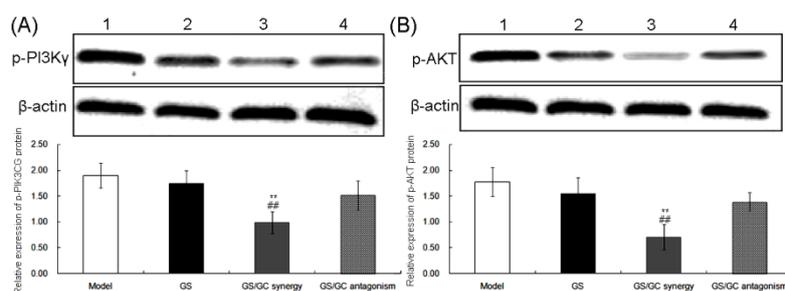


Table S1. Detailed information about the eight existing protein-protein interaction databases.

Table S2. Thirty-six and eleven chemical components were identified in *Euphorbia kansui* and *Glycyrrhiza*, respectively, as determined by HPLC-MS.

Table S3. U7²(7²) groups with different proportions and doses of *Euphorbia kansui* (GS)/ *Glycyrrhiza* (GC).

Table S4. Effects of *Euphorbia kansui* (GS)/*Glycyrrhiza* (GC) combinations with the different proportions and doses shown in Table S3 in the treatment of malignant ascites.

Table S5. Target genes detected by qRT-PCR and their primers.

Table S6. Detailed information on putative targets of *Euphorbia kansui* and *Glycyrrhiza*

Table S7. Detail information about the drug target PPI network based on the PPI information of the putative targets of GS and GC, known therapeutic targets for ascites and other human proteins.

Table S8. Detailed information on the interaction network of hubs screened from the drug target PPI network.

Table S9. Topological features of major putative targets.

Table S10. Edge-betweenness values of each interaction in the network of the major putative targets of *Euphorbia kansui* and *Glycyrrhiza*.

Table S11. Positive docking results for the compound-putative target interactions.