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Original Article

A new strategy for choosing "Q-markers" via network pharmacology, application to the quality control of a Chinese medical preparation

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ABSTRACT

Due to its chemical complexity, proper quality control for a Chinese medical preparation (CMP) has been a great challenge. Choosing the appropriate quality markers (Q-markers) for quality control of CMP is an important work. Best of all, the chosen Q-markers are the main chemical compounds from the herbals as well as the active constituents of this CMP. Only in this way the established quality control system can really achieve the purpose of controlling the quality of CMP and ensuring the safely and effectively use of CMP. To achieve the purpose, network pharmacology combined with the contents of chemical compounds in the CMP has been used in this research. We took an anti-arrhythmic CMP, Shenxian-Shengmai oral liquid (SSOL), as an example. Firstly, UPLC-QTOF-MS/MS method was used to analyze the main components of SSOL. A total of 64 compounds were unambiguously or tentatively identified and 32 of them were further validated by reference compounds. Secondly, the network was constructed based on the identified compounds to predict the effective compounds related to cardiac arrhythmias. Based on the existing database and the operation method of topology, a method of double network analysis (DNAA) was proposed, from which 10 important targets in the pathway of arrhythmia were screened out, and 26 compounds had good antiarrhythmic activity. Based on the prediction results of network pharmacology along with the contents of the compounds in this CMP, ten representative compounds were chosen as the Q-markers for the quality control of SSOL. We find that five of these ten compounds, including danshensu, rosmarinic acid,

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salvianolic acid A, epimedin A and icariin, have antiarrhythmic activity. Then, the UPLC-DAD method was established as the control method for SSOL.

1. Introduction

The characteristic of Chinese medical preparation (CMP), which contains most complicated chemical constituents, is embodied in the concept of multi-components and multi-targets [1]. Because of a large amount of natural metabolites in it, it is very difficult to control the quality of CMP. Currently, to ensure the safety and efficacy of CMP, fingerprinting combined with chemometrics and representative components determination are two common strategies [2]. To promote the healthy development of pharmaceutical industry and improve the quality standard system, core of national pharmacopoeia standards and product quality standards of CMP, the concept of quality marker (Q-marker), which is for the quality control for Chinese medicinal products, was proposed by Liu et al. [3,4]. Consequently, how to scientifically choose the appropriate Q-markers has been a great challenge for quality management.

Network pharmacology, which was first proposed by Hopkins [5,6], offers an ideal paradigm to deal with multi-target combination drugs and has recently been successfully adopted to investigate the formulae in traditional Chinese medicine (TCM) [7,8]. In our previous research, we have analyzed and predicted the active chemical constituents in Lianhua-Qingwen capsule [9,10] and Dangui-Jianzhong fomula [11] using the network analysis, and successfully validated the predicted results. Hence, the network analysis method was used to predict the active compounds to be the Q-markers in this work. In this case, we use the network pharmacology method combined with drug contents to select Q-markers, which is defined as the chemical constituents from the herb medicine or generated compounds during the processing preparation, to achieve control of the quality of CMP [12].

Finally, Shenxian-Shengmai oral liquid (SSOL) was used as a model to illustrate the confirmation process of Q-markers selection and application. SSOL is composed of 8 traditional Chinese herbs, including Gingseng Radix et Rhizoma Rubra (Hongshen), Epimedh Folium (Yinyanghuo), Psoralea Fructus (Buguzhi), Lych Fructus (Gouqi), Ephedrae Herba (Mahuang), Asari Radix et Rhizoma(Xixin), Salviae Miltiorrhizae Radix et Rhizoma(Danshen), Hirudo(Shuizhi), which has the efficacy of warming and invigorating heart and kidney, as well as promoting blood circulation to dissipate blood stasis. In this study, ultra performance liquid chromatography tandem quadrupole time-of-flight mass spectrometry (UPLC-QTOF-MS) [13–17] was used to analyze the major chemical constituents of SSOL. A total of 64 compounds were unambiguously or tentatively identified by comparing primary and secondary MS/MS spectral data with reference compounds or literature data and reference standards [13–22]. On the basis of qualitative analysis, the network pharmacology method was introduced to choose the Q-markers, 26 predicted effective ingredients were successfully identified. Based on the research results of qualitative analysis and network pharmacology, combined with the source of compounds which was contained in the medicinal materials, 10 representation compounds including danshensu, protocatechuic aldehyde, psoralenoside, isopsoralenoside, rosmarinic acid, salvianolic acid A, epimedin A_1, epimedin A, epimedin C and icariin were selected as the Q-markers of SSOL. The contents of the 10 compounds were determined by UPLC-DAD [22,23] method, which was accurate, sensitive and reliable and laid a good foundation for the quality control of SSOL.

2. Experimental

2.1. Chemicals and reagents

Epimedin A was purchased from Beijing LEYBOLD Cable Technology Co. Ltd. Standard compounds of citric acid, succinic acid, magnoflorine, rosmarinic acid, lithospermic acid, salvianolic acid C, p-hydroxybenzaldehyde, epimedin B and icariin, baohuoside I, ginsenoside Re, ginsenoside Rg_1, ginsenoside R_f, ginsenoside Rb_1, ginsenoside Rb_2, ginsenoside Rb_3, ginsenoside Ro, ginsenoside Rc and ginsenoside Rd were purchased from Shanghai Source Leaf Biotechnology Co. Ltd. Danshensu, protocatechuic acid, protocatechuic aldehyde, salvianolic acid B, salvianolic acid A, epimedin A_1, epimedin C and neobavaisoflavone were purchased from Nanjing Biological Engineering Co. Ltd. Psoralen glycosides, isopsoralen glycosides, psoralen and isopsoralen were obtained by our research team. The purity of each chemical was equal to or greater than 97%. SSOL was generously provided by Shandong Heze Buchang Pharma. All solvents, including methanol and acetonitrile with purity of 98% were of HPLC grade purchased from Sigma (U.S.A.), except formic acid which was purchased from Tedia (U.S.A.). Water was obtained from a Elix/RiO water purification system (Millipore, Bedford, MA, U.S.A.). All other reagents and chemicals were of analytical grade.

2.2. Preparation of standard and sample

2.2.1. The first group of standard and sample

Citric acid, succinic acid, danshensu, protocatechuic acid, protocatechuic aldehyde, magnoflorine, p-hydroxybenzaldehyde, psoralen and isopsoralen glycosides, rosmarinic acid, lithospermic acid, salvianolic acid B, salvianolic acid A, psoralen, isopsoralen, epimedin A_1, epimedin A, salvianolic acid C, epimedin B, epimedin C, icariin, baohuoside I,

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