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Research Paper

Traditional Chinese herbs as chemical resource library for drug discovery of anti-infective and anti-inflammatory

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ABSTRACT

Ethnopharmacological relevance: Infection is a major group of diseases which caused significant mortality and morbidity worldwide. Traditional Chinese herbs have been used to treat infective diseases for thousands years. The numerous clinical practices in disease therapy make it a large chemical resource library for drug discovery.

Materials and methods: In this study, we collected 1156 kinds of herbs and 22,172 traditional Chinese medicinal compounds (Tcmcs). The chemical informatics and network pharmacology were employed to analyze the anti-infective effects of herbs and Tcmcs. In order to evaluate the drug likeness of Tcmcs, the molecular descriptors of Tcmcs and FDA-approved drugs were calculated and the chemical space was constructed on the basis of principal component analysis in the eight descriptors. On purpose to estimate the effects of Tcmcs to the targets of FDA-approved anti-infective or anti-inflammatory drugs, the molecular docking was employed. After that, docking score weighted predictive models were used to predict the anti-infective or anti-inflammatory efficacy of herbs.

Results: The distribution of herbs in the phylogenetic tree showed that most herbs were distributed in family of Asteraceae, Fabaceae and Lamiaceae. Tcmcs were well coincide with drugs in chemical space, which indicated that most Tcmcs had good drug-likeness. The predictive models obtained good specificity and sensitivity with the AUC values above 0.8. At last, 389 kinds of herbs were obtained which were distributed in 100 families, by using the optimal cutoff values in ROC curves. These 389 herbs were widely used in China for treatment of infection and inflammation.

Conclusion: Traditional Chinese herbs have a considerable number of drug-like natural products and predicted activities to the targets of approved drugs, which would give us an opportunity to use these herbs as a chemical resource library for drug discovery of anti-infective and anti-inflammatory.

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1. Introduction

Infection is a group of major diseases which are induced by invasions of bacterial, fungal, viral, and parasitic pathogens. Infective diseases are a significant cause of mortality and morbidity worldwide which caused 10.5 million people death in 2011, according to the statistics of World Health Organization (World Health Organization, 2014). Currently, antibiotics are major drugs for treatment of infections. However, we are facing the challenge of bacterial resistances that were caused by the use and abuse of antibiotics (Cars et al., 2008). Before the discovery of antibiotics in the 1950s, the main method for treating those diseases was to find healing methods from herbs. Since the antibiotic resistances emerged, the use of antimicrobial and other drugs derived from medical plants has been increasingly receptive again (Cowan, 1999).

More than 12,000 species of medicinal plants were used in China according to the third national survey on Chinese material resources (The China Medicinal Materials Co., 1994). The herbs have been used for treatment of diseases more than four thousand years and some herbs are still widely used in traditional medicine (Mahady, 2005). For example, the flower of *Lonicera japonica*, the root of *Coptis chinensis* and the aerial part of *Artemisia annua* were used for anti-infection and anti-inflammatory (Woerdenbag et al., 1990; Schinella et al., 2002; Shang et al., 2011). Chinese modern medicines were created based on these herbs, such as *Reduning* injection, *Qinkailing* injection and *Shuanghuanglian* oral

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liquid, which were widely used in treatment of common cold and influenza (Wu et al., 2008; Zhang et al., 2013). In-depth phytochemical investigation from herbs afforded enormous natural products which gave us a natural chemical library for drug discovery. In last 30 years, about 50 percent new chemical entities of FDA-approved drugs were discovered from natural products or derivatives, especially in antibacterial filed (Newman and Cragg, 2012). Moreover it was believed that natural products would still provide an unlimited opportunity for new drug leads discovery (Cos et al., 2006).

Traditionally, the use of herbs for treatment of some diseases by traditional Chinese medicine (TCM) is based on "*Zheng*" (in Mandarin) which is similar with the symptoms of diseases (Li et al., 2007). Generally, each symptom of diseases may relate several bio-systems. Thus, we need effective tools to study the effects of herbs at systems level. Network pharmacology or molecular networks gave us such tools for drug discovery, which can be used for describing a comprehensive cellular and organism behavior at systems level (Hopkins, 2008). Researchers have used these tools to understand some basic TCM theories (Li et al., 2007; Zhao et al., 2010), predict the side effect of herbs (Xue et al., 2013), and evaluate the anti-platelet aggregation activity of natural products (Gu et al., 2013b). In this work, we used the network pharmacology method to study the effective compounds of anti-infective or anti-inflammatory traditional Chinese herbs in the context of interactions between compounds and disease-related targets.

2. Materials and methods

2.1. Data sets

The herbs were collected by the treatment of diseases, such as common cold (*Ganmao* in Mandarin), influenza (*Liugan* in Mandarin), malaria (*Nueji* in Mandarin), dysentery (*Liji* in Mandarin) and tuberculosis (*Jiehe* in Mandarin). The scientific names (Binomial nomenclature, without authors) of herbs were collected from *Zhonghua Bencao* (Zhonghua Bencao Compilation Committee, 1999) and were checked by two taxonomy databases: Global Biodiversity Information Facility (http://data.gbif.org) and The Plant List (The Plant List, 2013). Taxonomies of herbs were also downloaded from the two online databases. The structures of traditional Chinese medicinal compounds (Tcmcs) were obtained from the Universal Natural Products Database (UNPD) (Gu et al., 2013a), Chinese Natural Product Database (CNPD) (Shen et al., 2003) and Reaxys by the scientific names of herbs. The structures of approved drugs, drug targets and the drug–target interactions were obtained from DrugBank (Knox et al., 2011). Drugs used for antifungal, antiviral, antibacterial, anti-infective, anti-inflammatory or antimalarial were collected by the categories of drugs in DrugBank. The targets of these drugs were used to predict the anti-infective and anti-inflammatory effects of Tcmcs.

2.2. Phylogeny and herb-compounds network construction

In order to study the distribution of herbs at the family level, we used the family name of species to construct a phylogenetic tree by an iTOL tool (Letunic and Bork, 2007). The tree file was autogenerated in iTOL by the taxonomy IDs which were got from taxonomy database (http://www.ncbi.nlm.nih.gov/taxonomy) by using the scientific name of herb. The network of herbs to their compounds was constructed by Cytoscape 2.8.3 (Shannon et al., 2003) and analyzed by network analysis plugin.

2.3. Chemical space and drug-likeness analysis

The molecular descriptors of Tcmcs and approved drugs were calculated by Discovery Studio. Eight descriptors: AlogP, Molecular weight (MW), Molecular fractional polar surface area, number of hydrogen bond donors (NHBD), number of hydrogen bond acceptors (NHBA), number of rotatable bonds, Number of rings and Number of aromatic rings were selected to build the chemical space of Tcmcs and drugs which was performed by principal components analysis (Gu et al., 2013a). Lipinski's "rule of five" (Ro5) was employed to analyze the oral bioavailability of Tcmcs, where the oral bioavailability of small molecule drug may decrease if it violated these limits: MW $\leq$ 500 Da, AlogP $\leq$ 5, NHBD $\leq$ 5 and NHBA $\leq$ 10 (Lipinski, 2000).

2.4. The prediction of effective Tcmcs and herbs

In order to predict the efficacy of Tcmcs in anti-infection and anti-inflammatory, the targets of approved drug were used in virtual screening. First, the crystal or NMR structures of targets were downloaded from RCSB Protein Data Bank (http://www.rcsb.org/pdb/home/home.do). Second, the Discovery Studio was used to prepare protein targets by deletion of the hetero atoms and addition of hydrogen atoms. After that, the autodock 4.01 (Morris et al., 2009) in DOVIS 2.0 (Jiang et al., 2008) was employed to perform the molecular docking. For each docking, the binding site was set as a $40 \times 40 \times 40$ Å cube centered on the occupied space of the original ligand and the spacing of energy grid points was defined as 0.375 Å. At last, the docking scores above 0 were chose to further predication of actions about Tcmcs and targets. We used a docking scores weighted model to predict the coefficient of herb to a target (PCT_{herb}) and a disease (PCD_{herb}) which were calculated as follows:

$$PCT_{herb} = \sum_{i=1}^{n} Score_i \quad (1)$$

$$PCD_{herb} = \sum_{i=1}^{m} PCT_{herb(i)} \quad (2)$$

where $Score_i$ was the docking score of compound i to the target, n was the number of effective compounds contained in the herb, and m was the number of targets which were associated with the disease.

2.5. Prediction validation and herb-targets network construction

In order to validate the above predictions, the positive samples were constructed by known activities of herbs, which were gathered by literature mining in PubMed (http://www.ncbi.nlm.nih.gov/pubmed). In detail, we searched literatures in the abstract and title from PubMed by using the terms: "antibacterial", "anti-inflammatory", "antiviral", "antifungal", "antimalarial", "anti-infection" and "antimicrobial" combined with the scientific name of herbs. The activities of an herb, which were reported by two or more literatures, were defined as positive samples. The accuracy of predictions was estimated by receiver operating characteristic (ROC) curves, which were performed by ROCR package in R software (Sing et al., 2005). The optimal cutoff values of each predictive model were found from ROC curves.

3. Results and discussion

3.1. The distribution of herbs and Tcmcs

Their accumulated numerous experiences in treatment of diseases in thousands of years, and lots of herb resources have been explored from nature. In our investigation there were more

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