



Review

Network pharmacology-based prediction of the active ingredients and potential targets of Chinese herbal *Radix Curcumae* formula for application to cardiovascular disease

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ABSTRACT

Ethnopharmacology relevance: Cardiovascular and cerebrovascular diseases (CCVD), an abnormal function of the heart, brain or blood vessels, are the biggest cause of deaths worldwide. Traditional Chinese medicine (TCM) holds a great promise for preventing such diseases in an integrative and holistic way. However, its systems-level characterization of drug–target associations is still unknown. **Methods:** Here, we have constructed a computational approach by combining chemical predictors based on chemical structure, chemogenomics data linking compounds with pharmacological information, and a system biology functional data analysis and network reconstruction method.

Results: The pharmacological system generated 58 bioactive ingredients from the Chinese herbal *Radix Curcumae* formula, and predicted 32 potential targets related to the CCVD. The results indicates that *Radix Curcumae* share the most common targets with *Fructus Gardeniae* (15), while less common targets with *Moschus* and *Borneolum* (8 and 1, respectively). Further integrated network shows that *Radix Curcumae* represents the principal component for the prevention of CCVD, and other three medicines serve as adjuvant ones to assist the effects of the principal component, which together probably display synergistic actions. **Conclusions:** Our work successfully explains the mechanism of efficiency of *Radix Curcumae* formula for the prevention of CCVD, and meanwhile, predicts the potential targets of the Chinese medicines, which facilitates to elucidate the compatible mechanism of the complex prescription, i.e., “jun–chen–zuo–shi”, and provides basis for an alternative approach to investigate novel TCM formula on the network pharmacology level.

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1. Introduction

Cardiovascular and cerebrovascular diseases (CCVD), caused by high blood pressure, atherosclerosis, easy blood clotting, and heart enlargement, are the leading health problem all over the world claiming more than 17.3 million lives annually (<http://www.who.int/mediacentre/factsheets/fs317/en/index.html>). To reduce the risk of cardiovascular disease, millions of adults are treated by drug therapies which include blood pressure-lowering medications, such as diuretics, angiotensin-converting enzyme (ACE) inhibitors or beta blockers; blood-thinning medications (to reduce platelet aggregation); cholesterol-lowering medications, and/or anti-arrhythmic medications (Lawrence et al., 1992). These drugs have yielded desired responses while have also triggered serious side effects such as hot flush, fatigue, shortness of breath, headache and dizziness from some antihypertensive drugs (Toyoshima et al., 1997) and rhabdomyolysis and hepatic diseases from hypolipidemic drugs (Sgro and Escousse, 1991).

Different from the orthodox medicine focusing on a specific pathogenic process (Jiang, 2005), traditional Chinese medicine (TCM) has been recognized as a popular complementary and alternative medicine in western countries, emphasizing on individualized diagnosis and treatment of patients; maximizing the body's inherent healing ability; and treatment of the “whole” person by addressing their physical, mental, and spiritual attributes (Jonas, 1999; Xu, 2011). Presently, millions of patients around the world consume TCM, for examples, the TCM products from China have spent US\$7.6 billion for US and US\$2 billion for Europe in 2010, and that figure is rising at 10% per year (Cheung, 2011). For CCVD, herbal prevention has been to prevent the congestive heart failure, systolic hypertension, angina pectoris, atherosclerosis, cerebral insufficiency, venous insufficiency, and arrhythmia (Mashour et al., 1998). Moreover, several Chinese herbs have already been transformed into commercial products for treatment of CCVD, such as Compound Danshen Dripping Pills (Chinese name FufangDanshenDiwan) (Chu et al., 2011), ShexiangBaixin Pills (Chinese name ShexiangBaixin Wan) (Ye et al., 2004). This high rate of use translates into large out-of-pocket expenditures on TCM.

The consistency and quality control are the key issues for the application and development of TCM, since all herbal or animal medicines are mixtures of more than one active ingredient. However, the large number of TCM formulae (nearly 100,000) and the multiple active ingredients involved in each formula make it hard to distinguish the active ingredients and to identify the potential targets of the chemicals (Wang et al., 2008). During the past decade, TCM studies have followed a strategy of isolation/purification/structure identification, and pharmacological research for determining the principal bioactive components. Up to date, more than 30,000 chemicals have been isolated in hundreds of Chinese medicines, with more than 120,000 possessing pharmacological activities (http://www.tcm120.com/1w2k/tcm_species.asp). Nevertheless, this process is much resource-intensive and

time-consuming. Moreover, simple quantitative analysis of one or several active components in a herbal or an animal medicine does not endorse its quality and is difficult to identify the targets of the Chinese medicines, because multiple agents contained in each formula, at least in some formulas, could hit multiple targets and exert synergistic therapeutic efficacies (Anonymous, 1979; Anonymous, 2003). Thus, a comprehensive method which could reflect the variation of most constituents in the crude drugs, and more importantly, identify the targets of the drugs, is necessary.

Systems biology, such as network pharmacology, envisions an understanding of the function and behavior of a biological system. Its technological platforms, such as genomics, proteomics and metabolomics, provide holistic approaches to study the essence of TCM syndrome and the function of herbal compound recipe (Qiu, 2007). However, the analysis of TCM based on system biology concept is still in its infancy stage (Zhao et al., 2010), and few drug–target interaction network approaches have been specifically explored for TCM. These restrict the ability of network pharmacology approaches to probe new knowledge of bioactive compounds and potential targets for TCM from a proteome- or systems-level. In this scenario, we have developed an integrated model, which combines oral bioavailability (OB) prediction, multiple drug targets prediction and validation, network pharmacology techniques, to shed light on the mystery and effectiveness of TCM (Li et al., 2012).

In this work, we take *Radix Curcumae* formula, which consists of four Chinese medicines, i.e., *Radix Curcumae* (Yujin), *Fructus Gardeniae* (Zhizi), *Moschus* (Shexiang), and *Borneolum* (Bingpian), as an example. Actually, the relatively simple medicine has been widely applied to prevent CCVD (Xu et al., 2010). More recently, it has been demonstrated that this formula can directly act on the central nervous system through blood brain barrier (BBB) and reduce brain injury and enhance functional recovery after traumatic brain injury (TBI) and stroke in different clinical trials and animal models of injury (Xu et al., 2010). However, essential components in this formula have not been determined and the underlying mechanism of the formula remains poorly defined, thus hampering its “modernization” and “globalization”. Therefore, to predict the potential targets of *Radix Curcumae* formula and uncover the mechanisms of action of the active ingredients, we have applied our previously developed model (Li et al., 2012) to this formula, which offers an opportunity for deep understanding of the efficiency of *Radix Curcumae* formula for the prevention of CCVD.

2. Materials and methods

2.1. Chemical structures construction

All chemicals from these 4 medicines of *Radix Curcumae* formula were collected from (1) literature, (2) Chinese academy of sciences Chemistry Database (<http://www.organchem.csdb.cn>),

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