Molecular Docking-Based Study of Compatible Theory of TCM

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Abstract. In China, when people assembled appropriate drugs together in a group, they called the group prescription. Lots of prescriptions in TCM are prepared by compatible theory of TCM. Compatibility of TCM means to two or more different herbs are used together. Principal, assistant, complement and mediating guide is an important component of prescriptions compatible theory of TCM, but there exist some problems in its application: firstly, there have been some different views as to whether or not certain drug is principal drug; secondly, the concept of principal, assistant, complement and mediating guide is not accurate. In this paper, we proposed a new methodology based on molecular docking to classify drugs in the prescription into different kinds according to compatible theory of principal, assistant, complement and mediating guide.

1. Introduction

The compatible theory of principal, assistant, complement and mediating guide is from the perspective of multi-target application. It is highly summarized the principles of traditional Chinese medicine prescription and has great significance for the study and research of traditional Chinese medicine prescription and clinical therapy.

With the rapid development of system biology and computer technology, network pharmacology is developed. Traditional Chinese medicine (TCM) is consistent with the theory of network pharmacology in medical diagnosis and treatment, there are no fundamental diversities between the two methods. Performing research on Chinese medicine mechanism based on network pharmacology is very significant, but there are also some problems should be solved.

Principal drug in prescriptions plays a major role in drug treatment. It reflects the main direction of the prescription and ranks first in the prescription of the drug. It is an indispensable group in prescription drugs. Assistant drug is used to assist the principal drug to strengthen primary disease. There are three different kind drugs for complement, one kind is used for the treatment of secondary disease, the second kind pharmaceutical drug is used to eliminate or mitigate the potent drug toxicity induced by principal drug or assistant drug, and the third kind can play opposite and complementary role in the treatment for the primary disease. There are tow kind drugs in mediating guide drug, one can conduct the other drugs in the prescription to the pathological position, another plays the role of reconciling various drugs in prescription.
There are many researches on the compatibility theory of traditional Chinese medicine. TCM has a multi-target characteristic, and its mechanism is different while using different indexes to evaluate. Zhang Yuyan, Cai Yuquan and He Yu proposed structural equation model (SEM) [1], it could not only identify the individual path coefficient for each relationship, but also estimate the whole model fit to determine whether to revise the initial models. Song Xiaoli [2] believes the principal drug of Banxiaxiexin Decoction and its analogous is pinellia, she didn’t agree the viewpoint that principal drug of Gancaoxiexin Decoction is the licorice and principal drug of Shengjiangxiexin Decoction is ginger. In order to discuss the molecular microcosmic meaning of principle in TCM, Long Wei [3] classify the pharmacodynamic molecules in huanglian detoxiciting decoction by function. According to the standard build in the experiment, 12 molecules of principle component, 152 molecules of assistant component, 48 molecules of complement component, and 53 molecules of mediating guide component were found in 265 ingredient molecules in huanglian detoxiciting decoction.

According to molecular biology and maximal membership principle, fuzzy subset and membership functions were proposed by Liu Ming, Gao Yue and Xiao Rui. Using in vivo experiment on the effects of SiWu Decoction and its ingredients on mice with radiation-induced blood deficiency, it is concluded that DiHuang and DangGui belonged to the principal and assistant subset, BaiShao belonged to the contrary complement subset, ChuanXiong belonged to the mediating guide subset by maximal membership principle [4].

Principal, assistant, complement and mediating guide is an important component of prescriptions compatible theory of TCM, but there exist some problems in its application: firstly, there have been some different views as to whether or not certain drug is principal drug; secondly, the concept of principal, assistant, complement and mediating guide is not accurate. In this paper, we proposed a new methodology based on molecular docking to classify drugs in the prescription into different kinds according to compatible theory of principal, assistant, complement and mediating guide.

2. Materials and Methods

2.1. The application of molecular docking in pharmacology.
Molecular docking is a receptor structure-based approach. The ideal strategy for drug design is aimed at receptor and ligand, so receptor structure-based docking method is being widely used. Molecular docking can improve the efficiency of drug development, analyze the mechanism of the drugs, as well as reduce the cost. Molecular docking method has demonstrated an unparalleled advantage.

At present, many chemical composition in the TCM commonly used has been quite clear, but there is no or only a small amount of bioactivity data for most compounds. If adopting conventional method to systematically evaluate a variety of bioactivity compounds, it will be a difficult task. If there is a relatively accurate prediction of the bioactivity for the chemical composition, we can conduct targeted pharmacological experiments to verify predictions. Obviously, this will significantly improve the efficiency of bioactivity evaluation of the chemical composition, and it greatly shorten the process of finding the material basis of Chinese medicines. The use of molecular docking make the virtual screening become possible, it is very valuable in molecular docking-based study of compatible theory of principal, assistant, complement and mediating guide.

2.2. Methodology of molecular docking-based study of compatible theory.
If we want to analyze the compatibility of certain prescription, we should find out the diseases which the prescription can cure and identify the causative agent of the disease and all the corresponding targets. When the targets are identified, we should put them into different types in according to the function and the contribution to the treatment of diseases. In generally, the primary targets are responsible for the disease; the secondary targets are responsible for the complication. Molecular database should be constructed to perform the molecular docking experiment against targets; the compounds in the database are collected from the herbs in the TCM prescription.
Generally speaking, TCM cure disease is a multi-target effect. A Chinese herbal medicine contains many active drug molecules, and these drug molecules may act on a number of different targets. According to the docking results, herb in which there are some small molecules acting on the most main targets, you can think of it as principle drug; herb in which small molecules acting on the second target can be thought of as assistant drug; if small molecules in certain herb are mainly used for the treatment of secondary and primary disease or eliminate potent and toxic, the herb can be considered as complement; if small molecules in certain herb are mainly used to reconcile the role of drugs or induct other drugs reach the pathogenic location, the herb can be considered as mediating guide. The compatibility of principal, assistant, complement and mediating guide in TCM is based on single herb. Fig. 1 depicts the interaction mode between prescription and the targets.

3. Results and Discussion
As shown in Fig 2, we have identified the active constituents towards liver lipid-modulating targets and estimate probable multiple actions of FTZ [5] through docking-based virtual screening. The blue round rectangles represent targets, the ellipses represent the ligands from Rhizoma Coptidis, the diamond represents the ligand from Radix Notoginseng, the parallelogram represents the ligand from Fructus Ligustri Lucidi, the triangle represents the ligand from Cortex Eucommiae, and the hexagons represent the ligands from Radix Salvia Miltiorrhiza. The interactions between ligands and targets are elucidated by connecting edges. Red graph represents metabolites from FTZ. All ligands are marked by their compound Ids, targets are marked by corresponding target name. By our methodology, it is obviously that Rhizoma Coptidis is the principle drug, and Radix Salvia Miltiorrhiza is the assistant drug.
With the further development of life science research, people gradually become aware of that studying on a particular aspect of life can not explain all of the biomedical problems, so scientists proposed that we must study the interaction of cell structure, genes, proteins and their molecular interaction from a holistic perspective. It can provide new ideas for exploring the pathogenesis of human disease by the complete and exhaustive analysis of human tissue, organ function and metabolic state. The U.S. scientist Leory Hood is the first man proposed the concept of systems biology [6]. Biological systems have the characteristics of emergence, complexity, robustness and other features [7-9]. As a biological system, the human body consists of a number of subsystems, containing more than one individual and different level of interaction. The compatibility theory of principal, assistant, complement and mediating guide in TCM is consistent with the systems biology.

4. Conclusions
Chinese prescription is constituted with Chinese herbal medicine according to the principle of principal, assistant, complement and mediating guide. It follows the general philosophical principles. Compared with modern pharmacy view, Chinese compatibility theory is closely associated with the interaction of synergy, addition and antagonism. Under the guidance of the theory of TCM, the muti-component combination study provides much more specific material basis. The mechanism of component interaction and directly induce chemical reaction or influence other component’s characteristics of absorption, metabolism, pharmacodynamics and toxicity. From compatibility theory of TCM, we should distinguish which components have synergistic or additive effect, and which components can antagonist the side effect of other components. It is no doubt that muti-component combination points out the direction for the modernization and internationalization of Chinese medicine, and the molecular docking-based study of compatible theory have able to play an important role in distinguishing the principal, assistant, complement and mediating guide in TCM prescription.
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