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Systems pharmacology for traditional Chinese medicine with application to cardio-cerebrovascular diseases

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Abstract Identified as a treasure of natural herbal products, traditional Chinese medicine (TCM) has attracted extensive attention for their moderate treatment effect and lower side effect. Cardio-cerebrovascular diseases (CCVD) are a leading cause of death. TCM is used in China to prevent and treat CCVD. However, the complexity of TCM poses challenges in understanding the mechanisms of herbs at a systems-level, thus hampering the modernization and globalization of TCM. A novel model, termed traditional Chinese medicine systems pharmacology (TCMSP) analysis platform, which relies on the theory of systems pharmacology and integrates absorption, distribution, metabolism, excretion and toxicity (ADME/T) evaluation, target prediction and network/pathway analysis, was proposed to address these problems. Here, we review the development of systems pharmacology, the TCMSP approach and its applications in the investigations of CCVD and compare it with other methods. TCMSP assists in uncovering the mechanisms of action of herbal formulas used in treating CCVD. It can also be applied in ascertaining the different syndrome patterns of coronary artery disease, decoding the multi-scale mechanisms of herbs, and in understanding the mechanisms of herbal synergism.

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Introduction

Cardiovascular and cerebrovascular diseases (CCVD), including thrombosis, stroke, myocardial infarction, coronary heart disease, and high blood pressure, continue to pose a threat to human health. In 2008, approximately 17.3 million people died of cardiovascular diseases worldwide, of which an estimated 7.3 million deaths were due to coronary heart disease and 6.2 million deaths were due to stroke.[1] Given the high incidence and high mortality of CCVD, seeking feasible prevention and treatment strategies is highly imperative and critical to human health. Conventional drug therapies 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.[2] Although these drugs have played great therapeutic roles, most produce unwanted side effect, such as flushing, fatigue, shortness of breath, headache, dizziness from some antihypertensives,[3] as well as rhabdomyolysis and hepatic diseases from hypolipidemic agents.[4]

Traditional Chinese medicine (TCM) has attracted extensive attention for its ability to treat complex diseases due to its moderate treatment effect and lower side effect. There is growing recognition in the West that TCM, characterized by multiple compounds and multiple biological targets, is more effective than single drug remedies, especially for the treatment of complex chronic disorders such as schizophrenia, depression, diabetes, as well as cardiovascular diseases.[5] Despite the empirical efficacy and safety of TCM, there is still a lack of appropriate methods to explore the specific constituents in a particular herb when treating a disease and the biological factors that determine the herb's effectiveness.

Traditional pharmacology regards the cellular and tissue/organ-level systems as a black box, thus leading to a lack of mechanistic understanding of drug actions (pharmacodynamics) and the failure in clinical trials of most new drugs. Lack of drug mechanism understanding also means the inability to predict the adverse effects of drug, which has led to the withdrawal of or tight restrictions on the use of many drugs.[6] Systems pharmacology has emerged as a powerful tool to overcome these limitations by applying systems biology principles to the pharmacology field. It aims to reveal the dynamic interactions between drugs and the biological system as a whole, rather than individual constituents. Since there is some correlation between systems pharmacology and TCM, systems pharmacology strategies have been increasingly applied to explore the functional mechanism of TCM for the treatment of CCVD. This in turn has facilitated the discovery of novel effective drugs.[7]

In this review, we present an overview of systems pharmacology including its definition, characteristics, methods, and applications, as well as procedures to integrate it with current TCM research. Latest advances and application to CCVD are discussed to provide a new strategy to guide clinical studies, as well as to determine the risk of adverse drug effect for better treatment and control of complex diseases. Challenges and future directions in this field are also discussed.

Traditional Chinese medicine systems pharmacology (TCMSP) analysis platform

To fully understand drug pharmacodynamics, which in essence reveals how complex diseases emerge, a quantitative systems-level perspective is needed.[8] The field of systems pharmacology has made enormous progress in addressing drug action at the organ and organism levels. Systems pharmacology utilizes the concepts of systems biology to reveal pharmaceutical actions and guide drug discovery. Principal approaches for systems pharmacology include information integration of omics data sets, computer modeling, data analyses that focus on network analysis, and a direct experimental approach.

For centuries, herbal medicines have been used for health maintenance by every culture around the world. TCM is the only ethnomedicine with an unparalleled number of herbal formulas — nearly 50 000.[9] The diversity of components in each formula limits not only the extraction of the active ingredients of the herbs, but also the analyses of their pharmacologic mechanisms, and the identification of potential targets of the chemical constituents. To meet this challenge, a comprehensive systems-based approach that can simultaneously prioritize all active ingredients and their targets in the crude drug is needed.

Traditional Chinese medicine systems pharmacology (TCMSP) analysis platform is a set of novel and innovative approaches that has been proposed to develop a methodology for screening active herbal constituents, identifying drug targets, and investigating the relationship between active constituents and diseases.[10] Using this platform, a fundamental pharmacokinetics-pharmacodynamics theory for TCM can be constructed. The core of TCMSP is a series of integrated mathematical and computational models that are applied to efficiently explore the interactions among different elements (herbal compounds, drug targets, cells, tissues) and to reveal the functional mechanism of TCM theories. Its ultimate goal is to facilitate drug discovery and development as well as disease prevention and treatment.

Construction of the TCMSP framework begins with large-scale data mining from the literature and various databases to collect chemical, genomic and pharmacologic information on herbs and their corresponding constituents, followed by statistical analyses of the information (Fig. 1). To screen the promising active components, *in silico* models are established to predict the absorption, distribution, metabolism, excretion, and toxicity (ADME/T) properties of the chemicals. Then drug targeting, performed by applying an integrated model, is used to predict the multiple compound—protein interactions.[11] The interactions are then verified by other databases, the literature, and/or molecular dynamics simulations. Finally, the networks, including drug-target, drug-pathway, and drug-disease are generated and analyzed to form herb-disease-organism associations.[12]

ADME/T evaluations

ADME/T evaluations of drugs are critical procedures in drug discovery and development. The past years have witnessed advances in combinatorial chemistry and high throughput