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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

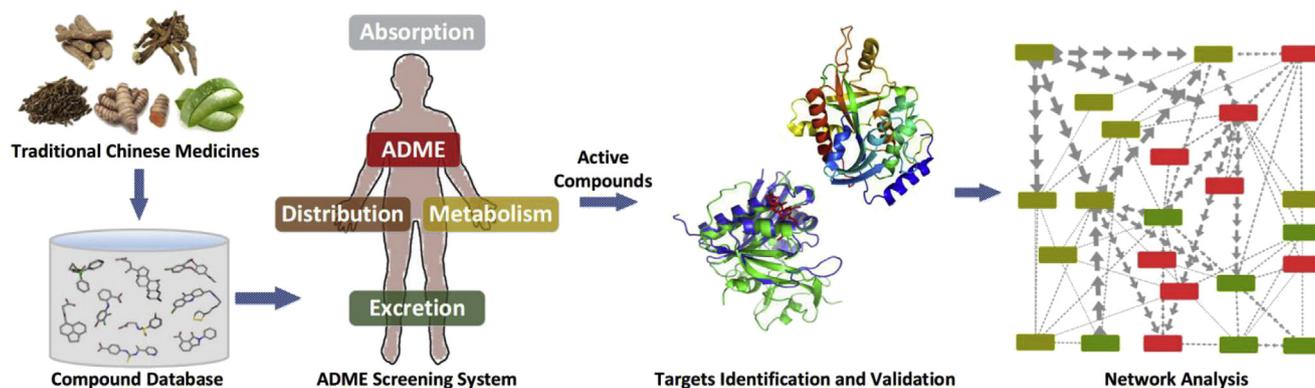


Figure 1 Construction of the TCMSF framework.

medicinal chemistry software, which can screen large numbers of compounds.¹³ A typical example is Chinese herbs, many of which contain up to 50 species and thousands of chemical compounds, but only a few compounds exhibit favorable ADME/T properties with potential biological effect.¹⁴ Hence, there is an urgent demand for ADME/T assessment of the effect or risks of these herbal ingredients on the human body. However, ADME/T screening and analysis of bioactive components remain challenging because conventional experimental approaches involving separation, purification, and structure elucidation must still be used to obtain ADME/T properties of drugs.^{7,15} These processes are time-consuming, laborious, and costly, and as such are limited in scope.

With the increase in computer processing power, *in silico* methods are being successfully applied to ADME/T prediction for drugs.^{16,17} *In silico* ADME/T prediction is composed of molecular modeling and data derived modeling (data modeling).^{18–20} Data modeling methods are used to efficaciously screen crucial compounds in herbs.^{21–24} One model is the human oral bioavailability (OB) prediction expert system,²⁵ which integrates P-glycoprotein (P-gp) and cytochrome P450s into the construction of QSAR modeling based on hundreds of structurally diverse drugs and drug-like molecules. OB is defined as the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action.²⁵ As a subcategory of absorption, OB is one of the most common pharmacokinetic parameters in drug screening cascades, since the main reason for stopping further development of drug candidates is often the low and highly variable bioavailability of potential drugs.²⁵ The blood brain barrier (BBB), which separates the brain and central nervous system (CNS) from the bloodstream, is also an important factor of concern in designing drug molecules. *In silico* prediction of a compound's ability to cross the BBB will contribute to the screening of efficient small molecules for treating brain diseases.^{26,27} Other important ADME-related properties, such as Caco-2 permeability and Lipinski's rule of five (MW, AlogP, TPSA, Hdon, Hacc), have also been applied to active compound screening of herbal medicines. Several *in silico* models have been developed for the enzyme kinetics of cytochrome P450 3A4 (CYP3A4)²⁸ and for predicting substrates and inhibitors of P-glycoprotein²⁹ as well as toxicity of drugs.

Target fishing

Target fishing is a useful tool to predict and validate drug targets and toxin targets and to detect drug-target interactions. However, even when the number of original herbal compounds has been significantly reduced, the work involved is still labor intensive due to the diversity of targets for each component and the fact that a single protein may correspond to multiple components.³⁰

To tackle this problem, *in silico* target fishing is an emerging technology^{31,32} for predicting the biological targets of compounds on the basis of chemical structure through the use of information from existing biologically annotated chemical databases. Though public databases have been established to store drug-target interactions, including DrugBank,³³ Matador,³⁴ STITCH,³⁵ and KEGG DRUG,³⁶ the interacting targets of the majority of small molecules remain unknown, especially targets for natural products extracted from Chinese herbs.

Currently, the most widely used target prediction methods are based on structure, ligand, and text-mining. Ligand-based methods (LBM) compare candidate ligands with known drugs of a target protein to find new compounds using statistical tools.³⁷ Performance of LBM relies on the number of known active molecules for a target. A drawback of LBM is that it has difficulty in identifying drugs with novel structural scaffolds that differ from the reference molecules. Structure-based methods, such as molecule docking, are constrained by available crystallographic structures of the target. Text mining, on the other hand, can uncover information that already exists in the literature but has been missed. But the inability to detect new biologic findings and the redundancy of the compound and gene names in the literature have hampered the efficiency of text mining approach.³⁸ In addition, a chemogenomics-guided target-ligand approach combines the ligand chemical space, target space and the currently known drug-target networks information to construct a complex forecast system, with purpose of predicting the ligands or targets for a given ligand or target without prior attempts to define a special set of similar receptors or ligands.³⁹ Previously, we have also constructed a systematic prediction model, which efficiently integrated chemical, genomic, and pharmacologic information on a large scale, supported by heterogeneous biologic data. This model has been successfully

applied to the prediction of the targets of active compounds in herbal medicines.¹¹

Network analysis

Advances in genomics, biochemistry, molecular and cell biology, and physiology have allowed initial glimpses of the complexity of human biology at the atomic/molecular, cellular and tissue, organ, and organismal levels. Network analysis is a useful approach for multi-scale understanding of the organization of interactions among the components of a system.⁶ Network analysis can be used to reveal the associations between topology structures and biological functions at each level and interactions between levels that come into being organ- and organismal-level functions. Understanding the specific functional connections between multi-scales of organization contributes to the interpretation of how drugs interact with molecular targets and how their initial effects at the cellular level produce therapeutic or adverse effects at the final organ and organismal levels.⁶

In this context, from a network perspective, network pharmacology aims to investigate drug intervention or effect to address the synergism of multicomponent drugs and to screen and develop highly efficient and low toxicity multi-target drugs.^{40,41} Network pharmacology is consistent with Chinese herbal medicines and has been successfully applied to discovering effective components and elucidating the pharmacologic mechanisms of herbs.⁴² Thus, it offers a new framework for drug discovery by attacking the pathology network at the systems level rather than by focusing on individual components. Limitations of this approach include the integrity and accuracy of existing data, as well as the insufficient experimental validations of the constructed model. Nevertheless, interesting findings have been reported, showing that through network analysis, topologic properties are bridged with functional features of herb-disease connections, thus elucidating therapies and serving as a guide for drug application.^{43,44}

Application of TCMSp to CCVD

CCVD is a series of disease caused by many factors, including genetic, physical/chemical, environmental, and psychological.⁷ In China, CCVD has been treated with herbs or herbal combinations for many years. Two such remedies are Compound Danshen Formula (CDF) and Radix Curcumae Formula (RCF). However, the underlying mechanisms of the herbs and formulas remain unknown. This has greatly hampered their modernization and globalization. These two formulas are comprised of multiple herbs and have great advantage over single agents, which may not be able to surmount the inherent characteristics of the disease system they are intended to treat. Studies using TCMSp have attempted to predict the potential targets of the herbs in the formulas and uncover the mechanisms of action of the active ingredients,^{7,14} so as to give novel possibility on how to treat CCVD. For example, Wang et al.⁴⁵ applied systems biology to understanding the pharmacologic synergy in CCVD herbal formulas and discovered potent drug/herb combinations that are individually

subtherapeutic. Zhou and Wang²⁴ used systems pharmacology to dissect the different TCM patterns of coronary artery disease (CAD) to explore combining Chinese herbs with pharmaceutical drugs to treat CCVD. Other studies have also attempted to decode the multi-level mechanisms of herbs for treatment and prevention of stroke.^{46,47} Thus, application of TCMSp to CCVD may provide new perspective on the management of CCVD (Fig. 2).

Chinese herbal formulas for CCVD treatment

Traditional Chinese herbal formulas (*fu fang*, or *fang ji*) have been used in China for millennia and are typically comprised of several herbs. Rather than an arbitrary combination of herbs, they are prescribed based on TCM theory, specifically the hierarchy principle of chief, deputy, assistant, and envoy (*jun, chen, zuo, shi*)^{48,49} and follow the rule of drug compatibility and combination. Several TCM formulas, such as CDF and RCF, have been extensively implemented in the treatment of CCVD with beneficial effects.

CDF is listed in the *Pharmacopoeia of the People's Republic of China (PPRC)*.⁵⁰ The formula is comprised primarily of three ingredients: salvia (*Salvia miltiorrhiza* Bge.), notoginseng root (*Panax notoginseng* (Burk.)), and borneol (*Borneolum*; crystallized resin and volatile oil of *Cinnamomum camphora* (L.) J. Presl), at a ratio of 450:141:8 (grams).⁵⁰ Clinical studies have shown desirable pharmacologic effect of CDF on CCVD, including dilating coronary vessels (which increases coronary flow rate) and activating superoxide dismutase.^{51–53} Studies have also shed light on the underlying molecular mechanisms of CDF. For example, a network pharmacology study of major active compounds of CDF found that tanshinone IIA, salvianolic acid B, protocatechuic aldehyde, danshensu, cryptotanshinone, notoginsenoside R₁, ginsenoside Rg₁, ginsenoside Rb₁, and borneol could modulate dozens of CCVD-associated genes that correspond to different diseases, which suggests new potential indications of CDF.⁵⁴ Zhang et al.⁵⁵ used metabolomics to investigate the therapeutic and synergistic effect of three major active ingredients (tanshinone IIA (T), salvianolic acid B (S) and ginsenoside Rb₁ (G)) of CDF in the rat model of myocardial ischemia (MI). Results suggested that TSG has nearly equal

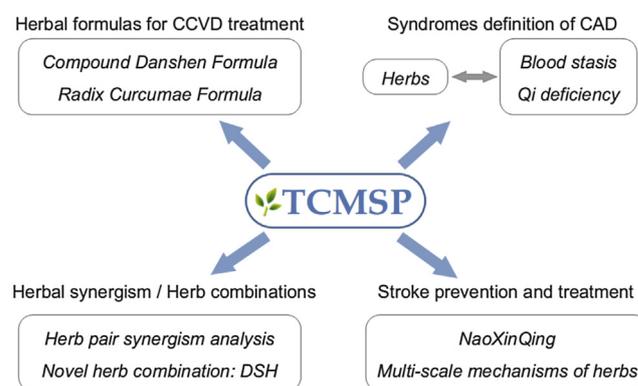


Figure 2 Application of TCMSp to CCVD mechanism and management.

therapeutic effect on MI as the formula itself, and has a more stable regulated action on several specific metabolites than a single compound alone.⁵⁵ Limitation of these studies is that they only focused on a portion of the active ingredients and were not able to provide a systems-level understanding of how the diverse chemical components in CDF contribute to the overall pharmacologic effect of the herbs on CCVD. Under a systems pharmacology framework, we performed a high-throughput *in silico* screening and obtained a group of compounds from CDF that possess desirable pharmacodynamic and pharmacologic characteristics. These compounds and corresponding protein targets were further used to search against biologic databases, such as compound-target associations, compound-pathway connections, and disease-target interactions for reconstructing biologically meaningful networks for CDF.¹⁴

RCF is another formula listed in *PPCR*.⁵⁰ It is comprised of four ingredients: curcuma tuber (*Curcuma longa* L.), cape jasmine fruit (*Gardenia jasminoides* Ellis), musk (*Moschus*; navel gland secretion of the musk deer), and borneol. RCF is another effective remedy that has been widely used in China to prevent CCVD.⁵⁶ Animal and human studies have demonstrated that RCF acts directly on the central nervous system through the blood brain barrier to reduce brain injury and enhance functional recovery after traumatic brain injury (TBI) and stroke. TCMSP analysis identified dozens of bioactive ingredients in RCF and potential targets related to CCVD.⁷ Results indicate that curcuma tuber shares the most common targets with cape jasmine fruit, and fewer common targets with musk and borneol. Further integrated networking shows that curcuma tuber is the principal component in the prevention of CCVD and the three other ingredients serve as adjuvants, synergistically assisting the effect of the principal component. These studies provide a clue for understanding the compatible mechanisms of complex prescriptions such as CDF and RCF and offer an alternative approach to investigate novel TCM formulas for CCVD treatment.

Exploration of syndrome definition of CAD

CAD is one of the most common CCVDs. CAD leads to sequelae such as myocardial infarction and heart failure and is the leading cause of mortality and disability worldwide.⁵⁷ Conventional therapies for CAD are pharmaceutical drugs, lifestyle changes, surgery, and other interventions. TCM, on the other hand, combats CAD with thousands of herbal prescriptions as well as other traditional modalities.⁵⁸

TCM is substantially different from the reductionism approach of Western medicine. TCM uses a holistic approach and focuses on the aggregate observation of signs and symptoms to describe the patient's body as a whole, using patterns or syndromes (*zheng*).²⁴ In TCM, CAD can be classified into different TCM syndromes: blood stasis, qi deficiency, phlegm-turbidity, cold coagulation, yin deficiency, and yang deficiency,⁵⁹ of which the three main syndromes are blood stasis, qi deficiency, and phlegm-turbidity.⁶⁰ Modern methods are being used to study CAD syndromes. Lu et al.⁶¹ applied SVM feature selection and

Bayesian network classifiers to proposing an *in silico* method to predict six syndromes of CAD, which may improve treatment.⁶¹ Shi et al.⁶² applied complex networking and chi-squared automatic interaction detector (CHAID) decision tree methodology to identify core TCM syndromes of CAD and established TCM syndrome identification modes of CAD based on biologic parameters. Wang et al.⁶³ analyzed two-dimensional electrophoresis results of blood samples of CAD patients and found 10 inflammatory factor proteins associated with blood stasis syndrome. They also proposed an unsupervised pattern-discovery algorithm to detect the significantly associated patterns, which resulted in the discovery of the association between CAD syndrome and proteome.

In our work, we analyzed the underlying mechanism of different CAD syndromes (mainly the blood stasis and qi deficiency syndromes), by using systems pharmacology to explore the complicated disease-syndrome correlation and established a diagnostic process at microcosmic level.²⁴ We found that herbs for eliminating blood stasis are capable of dilating blood vessels, improving microcirculation, reducing blood viscosity, and regulating blood lipids, while qi-enhancing herbs promote energy metabolism and anti-inflammation. These studies bring perspective to the integration of TCM and Western medicine and the combination of TCM with Western drugs to form an integrative/alternative medicine for the treatment of complex diseases such as CAD.

Herbal synergy and new herb combinations for treating CAD

Empirical use and clinical trials have shown that several herbs combined in a single formula are more efficacious than single herbs.⁶⁴ For instance, the pharmacologic effect of one herb as an ingredient of a single formula can be strengthened, extended, or its side effect suppressed by the other herbal ingredients. Thus, the therapeutic effect of multi-herb formulas likely arise from the synergistic actions of the combined herbal ingredients.⁶⁵ For example, it has been reported that saponins increase the absorption of corticosteroids and procyanidin B2 or hyperoside increases the solubility of hypericin.^{66,67} Several studies have focused on the underlying mechanisms of such multicomponent synergies associated with interacting targets, pathways, and diseases. In our work, we applied TCMSP to investigating the synergistic mechanisms of four widely used herbs for cardiovascular disease treatment: astragalus (*Astragalus membranaceus*), kudzu (*Puerariae lobata* (Willd.)), ophiopogon tuber (*Ophiopogon japonicus* (Thunb.) Ker-Gawl.), and salvia (*Salvia miltiorrhiza* Bge.).⁴⁵ Results found that the structural properties of molecules in the four herbs had substantial differences and the interactions of individual compounds in each herb with target proteins may be different, although the pharmacologic properties of the four herbs were quite similar in the treatment of CVD. The actions of different herb pairs may show mutual enhancement to exert a complementary synergistic effect in different modes.

Another study also applied systems pharmacology to the discovery of new herb/drug combinations. Relevant

pharmacologic information for CVD was collected and then CVD-associated target space was utilized to screen effective herbal molecules.⁶⁸ Biologic network analysis and experimental validation were then applied to discovering novel herb combinations. Experimental validation of one optimal herb combination *Dan Shan Hong* (DSH), which is comprised of salvia (*Salvia miltiorrhiza* Bge.), hawthorn fruit (*Crataegus pinnatifida* Bge.), and safflower (*Carthamus tinctorius* L.), showed that treatment with DSH improved myocardial function and mRNA expression levels of CVD-associated targets in the mouse model of myocardial infarction.⁶⁸ Research such as the aforementioned not only deepen the understanding of the pharmacologic synergy in herbal medicines, but also strengthen the foundation for the rational discovery of potent drug/herb combinations.

Multi-scale mechanisms of herbs in stroke treatment and prevention

Stroke, also referred to as cerebrovascular accident (CVA), is the second most common cause of cerebrovascular death worldwide⁶⁹ and can lead to irreversible neurologic damage or even death. Each year there are around 16 million persons who have first-ever strokes and 6.2 million deaths due to stroke.⁷⁰ Treatment and prevention with medication are not ideal due to diverse risk factors, such as old age, hypertension, previous stroke or transient ischemic attack, diabetes, hyperlipidemia, smoking, and atrial fibrillation.⁷¹ The gains in molecular neuroscience have resulted in life-saving therapies. Nevertheless, the demand for continued development of pharmacologic treatment of stroke remains urgent. For example, intravenous thrombolytic therapy with recombinant tissue plasminogen activator (rtPA) has been demonstrated to be an effective treatment for ischemic stroke. But its application is limited in that it can only be applied within 3–4.5 h of ischemic stroke onset, and it cannot benefit hemorrhagic stroke patients. Thus, rtPA therapy is limited to only 1%–2% of all stroke patients.⁷² Thus, there are still very few effective biomedical interventions available for the majority of stroke patients.

In China, however, a large number of herbs have been used to treat stroke. Representative herbs include salvia (*Salvia miltiorrhiza* Bge.), ginkgo leaf (*Ginkgo biloba* L.), ephedra (*Ephedra sinica* Stapf.), and lifeflower (*Erigeron breviscapus* (Vant.) Hand.–Mazz.). Some of these herbs or their related products have been shown to have desirable pharmacologic activities for stroke treatment, such as possession of neuroprotective effect, or the ability to dilate cerebrovascular vessels to improve brain microcirculation, inhibit platelet aggregation, as well as augment hypoxia tolerance of brain cells.^{73,74} Other studies have also been carried out to explore the molecular mechanisms of anti-stroke herbs. For example, Bei et al.⁴⁷ revealed the underlying mechanism of the TCM drug Nao Xin Qing (NXQ), an extraction from the leaves of Japanese persimmon (*Diospyros kaki* L. Dispyrosyl and Ebenaceae). NXQ was found to be capable of alleviating cell injury and apoptosis *in vitro* and improving redox imbalance in cells under exposure of H₂O₂. Sucher's work on 58 TCM herbs for stroke revealed

that by binding to different molecular targets the drugs exert functions in signaling pathways involved in N-methyl-D-aspartate (NMDA) receptor-mediated neuronal injury and death. In addition, the purification of those single chemical compounds from TCM interacting with these targets was also performed.⁷²

Recently, using a combined modified systems-pharmacology method with pathway analysis, we were able to dissect the multi-scale mechanisms of several anti-stroke herbal medicines to improve the management of cerebral stroke.⁴⁶ A list of medicinal herbs that exhibited notable correlations with stroke was obtained by large-scale text mining of the PubMed database. Results showed that anti-stroke herbal medicines could produce anti-inflammation, anti-oxidant, and anti-apoptosis effect against ischemic brain damage, and exert lipid-lowering, anti-diabetic, anti-thrombotic, and antiplatelet effect and simultaneously target several related pathways, thus exhibiting potential therapeutic benefits in stroke treatment and prevention.⁴⁶

Discussion and conclusions

Traditional Chinese herbs hold great promise for treating and preventing complex diseases in an integrative and holistic way. However, understanding the pharmacologic mechanisms of herbs at a systems-level remains a challenge. The new field of systems pharmacology, which focuses on the quantitative analysis of the dynamic interactions between drugs and a biological organism, has brought hope in meeting this challenge. Based on the theory of systems pharmacology, we proposed the concept of traditional Chinese medicine systems pharmacology, and constructed a novel model for the study of herbal drugs, their targets and effect, which not only involves the application of systems biology approaches, but also is integrated with pharmacokinetic and pharmacodynamic evaluations. Application of TCMS to CCVD research will help uncover the mechanisms of action of herbal formulas used to treat and prevent cardio-cerebrovascular diseases, and to exploring the syndrome types of coronary artery disease, as well as to understanding the mechanisms of herbal synergism.

In current drug discovery and drug development, network pharmacology is a cutting-edge field. Its studies emphasize the paradigm shift from "one target, one drug" to "network target, multicomponent therapeutics" highlighting a holistic thinking which is also shared by TCM.⁷⁵ Applying network pharmacology to Chinese herbal research may give impetus to the discovery of bioactive ingredients and endogenous/exogenous biomarkers, and in revealing mechanisms of action and exploring the scientific basis of numerous Chinese herbs and herbal formulas. However, network pharmacology falls short in its ability to investigate drug metabolism, pharmacokinetics, and toxicity of herbs. Systems pharmacology, integrating ADME/T evaluation and pathway/network analyses, makes up for network pharmacology's shortcomings.

When challenged by pressure to develop new drugs as rapidly as possible, conventional methods usually fail. This can be attributed partly to the lack of understanding of the

multi-scale mechanisms. TCMSP, on the other hand, has impacted the development and usage of herbal drugs. Thus, with the evolution of systems biology and medicine, the pace of drug development will gradually catch up with the explosion in scientific knowledge. In addition, continuous updating of the TCMSP analysis platform will raise the accuracy of the ADME/T virtual screening model, the compound-target interaction prediction model, and the integration of different levels of omics data and clinical information.

Looking to the future, TCMSP may also be applied to other complex diseases, such as rheumatoid arthritis, diabetes, and cancer. A strong research platform specializing in the pharmacologic mechanisms of the herbal medicines that treat these diseases, and combined application of systems pharmacology with modern scientific methods, such as the omics and informatics, will be a powerful tool to uncover the scientific value of Chinese herbal medicines, and to explore their application in new drug development. Such further investigations will undoubtedly facilitate the development, exploration, and exploitation of Chinese herbal medicine, as well as the modernization of TCM.

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