

Progress of Studies on Traditional Chinese Medicine Based on Complex Network Analysis

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Abstract

Traditional Chinese medicine (TCM) is a distinct medical system that deals with the life–health–disease–environment relationship using holistic, dynamic, and dialectical thinking. However, reductionism has often restricted the conventional studies on TCM, and these studies did not investigate the central concepts of TCM theory about the multiple relationships among life, health, disease, and environment. Complex network analysis describes a wide variety of complex systems in the real world, and it has the potential to bridge the gap between TCM and modern science owing to the holism of TCM theory. This article summarizes the current research involving TCM network analysis and highlights the computational tools and analysis methods involved in this research. Finally, to inspire a new approach, the article discussed the potential problems underlying the application of TCM network analysis.

Keywords: Complex network analysis, formula, mechanism, syndrome, traditional Chinese medicine

INTRODUCTION

Unlike allopathic Western medicine, traditional Chinese medicine (TCM) emphasizes managing the life–health–disease–environment relationship and regaining the balance of one's bodily functions, based on holistic, dynamic, and dialectical thinking. Thus, the holistic concepts of TCM coincide with the properties of a complex system in emergence, multidimensionality, nonlinearity, etc.^[1,2] However, the reductionism of Western medicine has restricted the experimental research on TCM to focusing on elucidating the chemical structures and bioactivities of single compounds, instead of tapping into the core concept of TCM, namely, the multiple relationships between different systems. Moreover, compared with the abundant achievements in the study of the chemical ingredients in Chinese materia medica (CMM),^[3,4] the modernization of TCM has developed slowly and been obstructed by the negligence of the theoretical system of TCM.

A complex network approach has been proposed to elucidate the wide variety of complex systems in physics, mathematics, economics, sociology, biology, and medical science.^[5] These complex systems in the real world are commonly characterized by scale-free degree distribution and small-world

effect rather than random graphs.^[5-7] Complex network approach has revealed some significant properties of real world including the global properties of natural and artificial systems, and the unifying principles on the basis of network architectures.^[8] Specifically speaking, complex network approach has been applied to various types of networks, such as social collaboration network,^[7] internet network,^[9] logistical network,^[10] epidemic spreading network,^[11] and energy-engineering network.^[12] More importantly, complex network approach shows promising application prospects in biology and medicine. Several pioneering interdisciplinary fields, such as systems biology, network biology, and network medicine, have explored the multiple correlations between biological systems, rather than single units, to

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unveil the complicated nature of life and disease from a systems view.^[13,14] Meanwhile, network pharmacology and system pharmacology both have integrated information from chemistry, pharmacology, informatics and biology, provided platforms to explore multiple interactions among genes, drugs, and diseases, and finally promoted the radical transformation of the drug development paradigm.^[15,16]

Owing to its complementarity with the holistic and complex character of TCM, complex network analysis is expected to bridge the gap between TCM and modern medicine.^[17] First, TCM network pharmacology stems from three initial research works as below. As a founder of TCM network pharmacology, Li originally proposed a hypothesis that there are potential associations between TCM Syndrome (ZHENG in mandarin) and molecular networks in 1999.^[18] On March 2006, biomolecular networks of cold/hot syndromes were first established, while intervention effects of hot/cold herbal formulae on hub nodes in the above biomolecular networks were demonstrated experimentally.^[19] In 2007, a milestone article proposed a new network-based TCM research paradigm, in which the relationships of formula-syndrome and of disease-syndrome can be clearly explicated by biological networks and synergistic actions within a herbal formula are regarded as a kind of network connections triggered by actions of multiple ingredients of a formula on targets.^[20] Afterward, the term “network pharmacology” was first introduced in a “news and views” article in *Nature Biotechnology* by Hopkins.^[21]

On the basis of above pioneering works, subsequent researchers have conducted studies on TCM network pharmacology, network toxicology, and network formulaology by integrating network approaches and TCM theory, and they have applied these approaches to explore the molecular mechanisms of CMMs or Chinese medicine formulas (CMFs), combinational roles, and TCM clinical principles.^[22-24] These studies have integrated methods from pioneering disciplines, such as network pharmacology, systems biology, bioinformatics, and cheminformatics, to explore the scientific significance of TCM from a systems perspective. The first part of this article outlined the general procedure of TCM network research. The second part introduced the computational approaches, data sources, and tools involved in the network-based research on TCM. The third part discussed network topological analysis. Finally, the fourth part discussed the current research status of TCM complex network analysis in the study of the biological mechanism of TCM syndrome, TCM therapeutic principles, combination role of CMMs, and molecular basis of CMMs/CMFs.

A DEVELOPMENT PROCESS OF THE NETWORK RESEARCH ON TRADITIONAL CHINESE MEDICINE

The progression of the TCM network research is as follows: (1) Various units, such as CMMs, molecules, cells, organs, and

diseases, are derived from databases, literature, experiments, and computational simulations; (2) these units are vertices which construct complex networks through the multiple correlations among them, and the complex network models are involved in the CMM combination network, compound/drug-target network, metabolism network, signaling pathway network, protein-protein interaction (PPI) network, drug-disease network, etc.; (3) the scientific significance of TCM is illustrated by integrating multiple disciplines, including bioinformatics, polypharmacology, and systems biology, on the basis of TCM theory; and (4) the computational results might be enhanced with further experimental validation. According to the holistic concept of CMM-compound-target-disease, the TCM complex network research has uncovered potential evidence, under the network topological structure, of a relationship between the structure and function of the network. Moreover, this promotes explanations of the scientific significance of TCM syndromes, principles of clinical therapy, combinational role of CMMs, and molecular basis of CMMs/CMFs.

METHODS AND TOOLS OF COMPLEX NETWORK ANALYSIS

For studies using TCM network analysis, it is possible to obtain comprehensive information from multiple sources, such as databases, experiments, literatures, and computational modeling. Furthermore, it is possible to visualize and analyze the network using network tools.

Databases

There are large-scale biological and chemical databases that can support TCM complex network analysis. These databases offer a wealth of information on various units as well as their interactions. Table 1 shows the classification of the resources as the following four categories in accordance with the type of information that these databases contain: (1) biological databases providing extensive information on biomolecules (PDB, UniProtKB), biomolecular interactions such as PPI (BioCarta, HPRD), gene ontology, and signaling pathways (KEGG, Reactome); (2) chemical or drug databases that provide useful cheminformatics and bioinformatics relating to chemical or drug substances, such as bioinformatics (ChemSpider), chemical structures, as well as physicochemical properties (ChemProt), comprehensive targets (DrugBank, ChEMBL, PubChem), bioactivities (STITCH), and drugs and diseases (TTD); (3) disease/phenotype databases on the phenotypes of human diseases and their related genes; and (4) TCM-related databases that provide comprehensive information on CMM (TCM database@Taiwan, CVDHD), CMFs (TCMID, NSTI), chemical ingredients, and relevant target proteins (HIT, TCMSP).

Text mining tools

The reliability of studying TCM from the perspective of complex network analysis depends on the accuracy and

Table 1: Databases for complex network analysis of traditional Chinese medicine

Type	Name	Application	Website	References
Biology database	BioCarta	PPIs and pathway analysis	http://www.biocarta.com/	[25]
	BioGRID	PPIs analysis	http://thebiogrid.org/	[26]
	GO	Gene functions and relationships	http://geneontology.org/	[27]
	HPRD	PPIs analysis	http://www.hprd.org/	[28]
	KEGG	PPIs and pathway analysis	http://www.kegg.jp/	[29]
	OPHID	PPIs analysis	http://ophid.utoronto.ca/ophidv2.204/	[30]
	PDB	Protein information	http://www.rcsb.org/pdb/	[31]
	PID	Pathway analysis	http://pid.nci.nih.gov/	[32]
	Pathguide	Pathway analysis	http://www.pathguide.org/	[33]
	Reactome	Pathway analysis	http://www.reactome.org/	[34]
	STRING	PPIs analysis	http://string-db.org/	[35]
Chemistry database	UniprotKB	Protein information	http://www.uniprot.org/help/uniprotkb	[36]
	ChEMBL	Cheminformatics	https://www.ebi.ac.uk/chembl/	[37]
	ChemProt	Cheminformatics	http://potentia.cbs.dtu.dk/ChemProt/ChemProt2/ChemProt-1.0/ChemProt-2.0	[38]
	ChemSpider	Cheminformatics	http://www.chemspider.com/	[39]
	CCD	Chemical ingredients	http://ccd.chemnetbase.com/tour/	
	DNP	Phytochemicals	http://dnp.chemnetbase.com/	
	Drugbank	Comprehensive analysis of drugs	http://www.drugbank.ca/	[40]
	PubChem	cheminformatics	https://pubchem.ncbi.nlm.nih.gov/	[41]
	Scifinder	Chemical ingredients	https://scifinder.cas.org/	
	STITCH	Chemical-protein interaction	http://stitch.embl.de/	[42]
	TTD	Drugs and targets retrievals	http://bidd.nus.edu.sg/group/TTD/ttd.asp	[43]
Disease database	DisgeNET	Disease-gene association	http://www.disgenet.org/	[44]
	HGMD	Disease phenotype	http://www.hgmd.cf.ac.uk/ac/index.php	[45]
	HPO	Disease phenotype	http://human-phenotype-ontology.github.io/	[46]
	OMIM	Disease-gene association	http://www.omim.org/	[47]
	PharmGKB	Disease-gene association	https://www.pharmgkb.org/index.jsp	[48]
	CTD	Disease-gene-chemicals association	http://ctdbase.org/	[49]
TCM database	Chemistry Database	Phytochemicals	http://www.organchem.csdb.cn/scdb/	
	CVDHD	Phytochemicals	http://pkuxxj.pku.edu.cn/CVDHD/	[50]
	HIT	Phytochemical-target interaction	http://lifecenter.sgst.cn/hit	[51]
	NSTI	TCM formulae	http://www.ncmi.cn/	
	TCM database@Taiwan	Phytochemical-target interaction	tcm.cmu.edu.tw	[52]
	TCMID	TCM formulae and phytochemicals	http://www.megabionet.org/tcmid/	[53]
	TCMGeneDIT	Comprehensive analysis of chemicals-targets-disease	http://tcm.lifescience.ntu.edu.tw/	[54]
	TCM-PTD	Phytochemicals retrievals	http://tcm.zju.edu.cn/ptd/	[55]
	TcmSP	Comprehensive analysis of chemicals-targets-disease	http://lsp.nwsuaf.edu.cn/tcmsp.php	[56]

TCM: Traditional Chinese medicine

availability of the data. As a sample from a single source that has limited scope and bias, it is beneficial to use multiple databases and various retrieval methods simultaneously to ensure the integrity and accuracy of the data and information. Besides databases, the scientific literature is another significant data source. One can obtain such data by using tools for text mining, such as Agilent literature search, Polysearch, and SciMiner.^[57-59] Otherwise, it is possible to explore and analyze the biomolecule-pathway-disease correlation using bioinformatics tools, such as Clugo and DAVID, to illustrate the biological signaling pathway and bioactive mechanism.^[57,60]

Computational simulation

Often, the interactions between chemical and biological substances are too finite to support certain research into TCM using network analysis that involves searching databases or conducting text mining. However, computational methods are extremely useful for predicting and simulating unexplored interactions from acknowledged information. The technologies for computational simulation can be divided into the following four categories as listed in Table 2: (1) computation modeling, such as a pharmacophore model and quantitative structure-activity relationships; (2) molecular docking; (3) similarity ensemble methods; and (4) machine

Table 2: Computational simulation technologies for traditional Chinese medicine complex network analysis

Type	Subtype	Description	References
Computation modeling	Pharmacophore model	A molecular feature is pertinent to bioactivity aligned in 3D structures, including hydrogen bonding, charge transfer, and electrostatic and hydrophobic interactions	[61]
	QSAR	A mathematical model or statistical method that builds relationship between molecular structures and biological properties	[62,63]
Molecular docking		Molecular recognition is achieved through the complementarity of molecular surface structures and energetics with, most commonly, associated minor conformational changes	[64,65]
Similarity ensemble methods		A quantitative measure of the degree of structural similarity between a pair of structural representations	[66]
Machine learning algorithm	KNN	A typical supervised classification algorithm based on closest training samples in the feature space	[67]
	BKD	A method scores test-set molecules by a function based on the ratio of the sums of its weighted hamming distances from the active and from the inactive molecules in the training-set	[68]
	SVM	A classification tool in which appropriate kernel functions are selected to map the data space into higher-dimensional hyperplane	[63,69]
	RF	An ensemble learning method for classification based on a multitude of trained decision trees	[69,70]
	Bayesian classification	A popular supervised classification method based on probabilistic decision rule	[71]

QSAR: Quantitative structure-activity relationships, KNN: K nearest neighbor algorithm, BKD: Binary kernel discrimination, SVM: Support vector machine, RF: Random forest, 3D: Three-dimensional

learning algorithm including binary kernel discrimination, support vector machine (SVM), random forest, Bayesian classification, etc.

Li *et al.* provided 14 algorithms (CIPHER, drugCIPHER, comCIPHER, CIPHER-HIT, DMIM, NADA, NIMS, SAF, LMMA, CSPN, sGSCA, ClustEx, GIFT, and DGPSubNet) and 2 platforms (HerbBioMap and dbNEI) for TCM network pharmacology based on the “network target” paradigm.^[22,72] The applications of these methods have further involved in the study of the activity of compounds in CMM or CMF, synergism of CMMs, the disease–syndrome–formulae relationship, and biological markers.^[72]

Network tools

The application of network tools is mainly for carrying out the visualization and topological analysis of a complex network. Network visualization tools are appropriate for mapping the indescribable relationships between connected units. Subsequently, using network analysis tools can uncover information hidden under the network topological structure. These two types of network tools are usually integrated using the same software. The major network tools involved in the study of TCM were initially developed for biological network analysis or social network analysis, such as Cytoscape, Pajek, Ucinet, Netdraw, NetMiner, Gephi, Guess, networkX, and so on.^[73–78] Besides this professional network software, network toolboxes of Matlab and R environment can be utilized in the network visualization and topological analysis.^[79,80]

NETWORK TOPOLOGICAL ANALYSIS

According to the graph theory and complex network approach, nodes in a complex network represent the units in the complex system, and edges indicate the relationships among them. The primary components of a complex network on which we focus are nodes, edges, and clusters. Then a network analysis can illustrate the inner correlation of the network function and topological structure. Subsequently, the analysis and application of the properties of the complex network, including heterogeneity, centrality, shortest path length, clustering coefficient, centralization, density, and degree distribution, can elucidate the topological structure. Network topological analysis plays an important role in understanding the network structure, discovering the hidden information, and predicting the function of the complex network.

Analysis of nodes

A node (or vertex) is an indispensable element of a complex network. To estimate the significance of nodes, centrality is a typical parameter for evaluating the status of nodes in the whole network. As Freeman formalized in 1978, degree, betweenness, and closeness are the three prime measurements of centrality, as shown in Table 3.^[81] The degree of a focal node is the number of its adjacencies in the network; betweenness is the sum of the number of shortest paths passing that focal node, and closeness is defined as the inverse sum of graph-theoretic distances from all other connected nodes.^[81,82] According to

Table 3: Three measurements of centrality in network

Type	Centrality		
	Degree	Closeness	Betweenness
Absolute type	$C_D(n_i) = d(n_i)$	$C_C = \left[\sum_{j=1}^n d(n_i, n_j) \right]^{-1}$	$C_B = \sum_{j < k} g_{jk}(n_i) / g_{jk}$
Relative type	$C_D(n_i) = \frac{d(n_i)}{N-1}$	$C_C = (n-1)C_C$	$C_B = C_B / [(n-1)(n-2)/2]$
Network centralization	$C_D = \frac{\sum_{i=1}^n (C_{D_{\max}} - C_{D_i})}{N-2}$	$C_C = \frac{\sum_{i=1}^n (C_{C_{\max}} - C_{C_i})}{(N-2)(N-1)} (2N-3)$	$C_B = \frac{\sum_{i=1}^n (C_{B_{\max}} - C_{B_i})}{N-1}$

the three different measures of centrality, higher degree or betweenness indicates more significance, whereas higher closeness means less significance. In TCM network analysis, many types of complex networks, such as a metabolic network or Chinese medicine (CM) combinational network, have shown identical properties, such as scale-free or power-law degree distribution. In such scale-free networks, small series of nodes with high degree, also called hubs, play a crucial role in discovering the key CMMs, screening active compounds, and predicting potential therapeutic targets.^[83-85] For instance, Kong *et al.* constructed a molecular network in the mechanism of thrombosis by combining platelet signaling, coagulation cascade, and natural clot dissolution systems, and further predicted potential therapeutic antithrombotic targets through a centrality analysis of the vertices.^[86]

Analysis of edges

As another essential element of a complex network, an edge (or arc) is a link between two different units as well as a path for information transmission within the network. The analysis of edges mainly concerns the weight and the shortest path. First, the capability or capacity of the association between a pair of adjacent nodes can be quantified as the weight of an edge.^[87] The weight of an edge indicates the strength of the link between two adjacent nodes to illustrate pairwise nodes.^[88] As an illustration, a pair of CMMs with high weight value in a formulae combination network might have high co-occurrence frequency and have a synergetic effect in clinical therapy.^[89,90] However, the shortest path plays a crucial role in the transmission and communication in a network.^[8] Closeness centrality and betweenness centrality are measured through the application of the shortest path. Meanwhile, the distance between any two indirectly connected nodes is defined as the number of edges along the shortest path between them.^[7,8] In the biological field, the shortest path is helpful for predicting the function of unknown genes from known genes and identifying functional modules of proteins in a PPI network.^[91]

Analysis of network community

A network community (or modularity, cluster, module) is a series of nodes with tight intra-community interactions and loose intercommunity correlations. That is, the nodes are

homogeneous in the same community and heterogeneous between communities. The available methods for detecting community structures are as follows: (1) participation graph clustering including a Kernighan–Lin algorithm,^[92] fast Newman algorithm,^[93] Guimera–Amaral algorithm,^[94] etc.; (2) clustering based on a heuristic algorithm, such as maximum flow community,^[17] hyperlink-induced topic search,^[20] Girvan–Newman,^[5] etc.; (3) hierarchical clustering including random walk similarity,^[95] clustering centrality,^[96] etc.; and (4) spatial clustering, such as K-mean.^[97] The homogeneity of a network community plays a crucial role in the topological analysis of biological networks aimed at identifying units with high similarity in function or structure.^[94,98,99] The studies on TCM network analysis have utilized network communities to uncover the core combinations of CMMs, chemical clusters with similar structures or bioactivities, and proteins with analogs functions.

APPLICATION OF A COMPLEX NETWORK IN THE STUDY OF TRADITIONAL CHINESE MEDICINE

The holistic thinking behind TCM about the associations among CM, life, disease, and environment penetrates every aspect of the TCM therapeutic strategy, described as principle–method–prescription–CMMs (Li-Fa-Fang-Yao in Mandarin). The foundational concepts and clinical practices of TCM simultaneously focus on handling the complicated relationships between different systems^[100] and emphasize restoring homeostasis, described as yin and yang in equilibrium. It can be said that the TCM complex system has four different levels: (1) complex adaptive system of human-to-natural environment; (2) various functional systems of the body, such as the visceral organs and relevant functions (Zangfu in Mandarin), different physiological systems involved in immunity (Defense), respiratory (Qi), digestion (Nutrient), circulation (Blood), and so on (Wei-Qi-Ying-Xue in Mandarin), meridian-collateral system (Jingluo in Mandarin); (3) four diagnostic methods for personalized therapy (inspection, listening and smelling, inquiry, and pulse-taking and palpation), syndrome differentiation through eight principles, and syndrome-based treatments; (4) the properties of CM including

the theory of flavor-meridian tropism (Xingwei-guijing in Mandarin), combination roles based on the compatibility of CMMs, and the diverse effects of different CMMs in a formula (sovereign–minister–assistant–courier).

Studies on TCM have employed complex network methods to illuminate the holistic properties of TCM at multiple levels and thus elucidate the TCM theory and clinical application, material basis, and relevant mechanism. This section mainly reviews the application of the complex network approach in TCM studies, primarily for investigating the biological mechanisms of syndromes, principles of clinical therapy, formulation theory, and CM-oriented compounds as well as bioactivities.

Exploring the biological mechanism of traditional Chinese medicine syndrome

As a fundamental principle of TCM for the prevention and treatment of disease, TCM syndrome (or pattern) differentiation plays a crucial role in making treatment decisions, guiding the administration of CMMs, and dispensing herbal formulae. Unlike Western medicine, which approaches disease from the perspective of anatomy, TCM syndrome is the comprehensive description of the outward manifestation of the pathological, physical, and psychological status of a specific environmental aspect. Thus, TCM syndrome can be characterized as a multidimensional complex system that is concerned with pathological and physical conditions simultaneously. The complex characteristics of a syndrome are as follows: (1) it emphasizes the integrity of the human body rather than a certain lesion distribution; (2) it is not only a stage of pathogenesis but also a progress in flux, and distinctive syndromes can be co-occurring or interconverting; (3) a modern disease can be differentiated into multiple syndrome types, and a syndrome is also involved in various modern diseases; and (4) the molecular mechanism of TCM syndrome is too complicated to be illustrated by current physiological or biochemical indexes.^[19,101] The holistic and complex properties of a syndrome coincide with the hypothesis about the biological network of network pharmacology.^[15] Thus, TCM complex network analysis might offer a new strategy for exploring the biomolecular mechanism of a syndrome and its relationships with diseases, CMMs, and CMFs.^[102]

Following the phenotype network–biological network–herb network structure, Li *et al.* used literature mining, network analysis, and topological comparison to explore the biomolecular basis of cold/hot syndromes within the context of the neuro-endocrine-immune system (NEI). The results *in silico* validated the different biological patterns identified in the cold/hot syndrome networks. An *in vivo* experiment further confirmed that some key genes and chemical messengers distinguished cold and hot syndromes through the corresponding cold/hot herbal treatment.^[19] Lu *et al.* integrated microarray technology and PPI network analysis to explore the distinct molecular signatures of TCM cold and hot patterns in rheumatoid arthritis (RA) patients. Their study indicated that the cold pattern of RA was related to the

Toll-like receptor signaling pathway, and the related pathways in the heat pattern involved the calcium signaling pathway, cell adhesion molecules, PPAR signaling pathway, and fatty acid metabolism.^[103] In addition, Lu *et al.* explored the correlations between the PPI network of an RA hot pattern and the target protein networks of four relevant CMMs through microarray technology, text mining, and complex network analysis. The mutual pathways of the RA hot pattern and CMMs include GM-CSF signaling, CLTA4 signaling in Cytotoxic T Lymphocytes, T cell receptor signaling, and CD28 signaling in T Helper cells, which were related to the cell survival, cell-mediated immune response, inflammatory response, and so on.^[104] Dai *et al.* conceived a two-level model, integrating a SVM-based diagnostic model and a symptom-gene-pathway multilayer correlation network, to detect the molecular mechanism of wind-phlegm collateral obstruction syndrome of acute ischemic stroke.^[105]

Discovering the underlying principle of traditional Chinese medicine therapy

The therapeutic purpose of TCM is to regulate homeostasis, remove pathogenesis, relieve symptoms, and finally promote physical and emotional health. The complex properties of TCM therapy can be further categorized as follows: (1) regaining the balance of the physiological functions of different subsystems at the global level; (2) making the TCM therapeutic schedule individualized and flexible on the basis of the pathogenic factors, the pathological process, physical and psychological conditions, and environmental aspects; and (3) identifying the individual subjective factors of TCM physicians and patients that affect the TCM clinical therapy. Restricting the worldwide application of TCM therapy are the lack of appropriate research approaches and a long history of an irreconcilable philosophical divergence between holistic CM and allopathic Western medicine. Yet modern medicine has gradually validated that most diseases, especially chronic diseases and complex diseases, are induced by various factors and have multiple mechanisms. Moreover, the perspective of network pharmacology acknowledges that a complex disease is caused by the perturbation of the biological network, while the random variation of individual genes or proteins has little effect on disease.^[15] Thus, the concept of TCM therapy aligns with the modern medical concept of complex diseases and the hypothesis about a biological network.

Complex network analysis provides a powerful tool for decoding the connotation of TCM therapy. The study of network analysis in relation to TCM therapy can adopt either a bottom-up or top-down approach according to the correlation among drugs, life, health, and disease.^[22] Gao *et al.* used complex network analysis to explore the syndrome–therapy–CM relationship within TCM therapy in the context of coronary artery disease (CAD). Moreover, they analyzed the topological structure of the syndrome–clinical therapy network to estimate the underlying treatments and CMMs that were not included in the TCM diagnostic standard of CAD.^[106] Furthermore, Li *et al.* explored the pharmacological

effect of the Bufei Yishen formula (BYF, Formula of Tonifying Lung and Replenishing Kidney) against chronic obstructive pulmonary disease (COPD) by integrating network analysis and bioinformatics. Their computational result uncovered the active compounds in BYF and the relevant potential targets through the compound–target network. Their experiment validated that the underlying mechanism of BYF against COPD might contribute to the inflammatory cytokine, hypertrophic factors expression, protease-antiprotease imbalance, and collagen deposition.^[107] Wang *et al.* took a novel approach to dissecting with holistic treatment in the TCM therapy of cardio-cerebrovascular diseases (CCDs) using systems pharmacology and complex network analysis. They screened the potential bioactive ingredients in the Xinnaoxin Pill by integrating the absorption–distribution–metabolism–excretion (ADME) model and complex network analysis based on the multiple layers of drug–target–pathway–organ, and further experimentally validated at the molecular level. Finally, they extracted a disease–therapeutic module for understanding the complex disease at the global level.^[108]

Understanding combinations in traditional Chinese medicine

The CM formula (Fufang in Mandarin), which follows the TCM therapeutic principle, can be characterized as the most typical treatment in the personalized therapy of TCM.^[109] With the purpose of synergy and attenuation, several CMMs are carefully dispensed into a specific prescription and play an integrative role for eliminating the symptoms and regulating the body's homeostasis. CMFs have been accumulated from clinical experience and verified in TCM therapy. However, we still lack a full understanding of the combination roles, dose-effect relationships, and molecular mechanisms relating to CMFs. And, furthermore, the complex properties of CMFs might also increase the difficulty of applying and modernizing TCM, which are as follows: (1) the pharmacological effects of CMFs depend on the combinational principles and status of different CMMs; (2) the pharmacological efficacy of CMFs is not a simple linear superposition but the synergistic activity of CMMs with multiple compounds; and (3) CMFs might be adjusted in CMMs or dosages to coincide with the patient's pathological and physiological status.

Complex network analysis plays an important role in revealing the complex properties of CMFs in the combination principle, active compounds, and biological mechanisms. For example, to identify useful relationships among herbs in numerous CMFs, Li *et al.* established a novel DMIM method combining mutual information entropy and “between-herb-distance” to score herb interactions and construct a herb network. The outcomes of this research were the construction of a herb network comprising 3,865 collaterals-related CMFs, the retrieval of herb pairs and formulae, and the generation of further novel anti-angiogenic herb ingredients.^[89] The researchers also integrated network-based methods to illustrate the network regulation mechanism and identify active ingredients as well as synergistic combinations for Qing-Luo-Yin (QLY, Drink

of Clearing Lung Collaterals), an anti-RA formula. Their research predicted synergetic activities and the combinatorial rule of QLY and identified several ingredient groups as active components through the use of cluster analysis.^[110] As the combination of CMMs in a CMF is essentially the combination of compounds, Ding *et al.* constructed a combination network of compounds based on the combinational relationship of CMMs in the CMF. In total, 1,588 compounds in 8 classic CMFs against CAD were clustered into 9 network communities using topological analysis, and 20 compounds with high centrality were screened out.^[111]

Exploring the material basis of traditional Chinese medicine

Abundant effective CMMs have been clinically validated and used for thousands of years under the theoretical system of TCM. Regular studies on CMMs have focused primarily on identifying the chemical ingredients and chemical structures, physicochemical properties, pharmacodynamics, and pharmacokinetic process. However, each CM can be regarded as a complicated chemical system with numerous compounds that are too complex to be investigated solely by using conventional empirical approaches. Moreover, the pharmacological activities and adverse effects of CMMs are mainly the result of the interactions between multiple compounds on multiple targets. The complex properties of the molecular basis of CMMs may include the following: (1) the compounds of CMMs vary in their chemical elements, chemical structures, physicochemical properties, and bioactivities; (2) the pharmacokinetic progress of multiple components is too complicated to be elucidated, and some metabolites of phytochemicals are also bioactive; and (3) the comprehensive bioactivities of CMMs are characterized as emergent due to the synergetic effects of compounds on multiple targets. Confronted with the complex issue of CMMs, the current reductionist approaches are limited to illustrating the molecular mechanisms from a global perspective.

Based on the correlations among disease, gene, target protein, and compound, a complex network analysis can be applied to analyze and dissect, with the molecular basis as well as the relevant biological mechanism, and provide theoretical and technical rationales for the efficiency and safety of CMMs or CMFs. Xu *et al.* elucidated the anti-cancer effects of the compounds in the Xiao-Chai-Hu Decoction (XCHT, Minor Bupleurum Decoction) by combining the methods of chemical space mapping, molecular docking, and network analysis. Their research enabled them to construct a compound–compound network based on multiple compound–target interactions and demonstrate the multi-compound combinations that might be effective on differentiated targets.^[65] Zhang *et al.* predicted the candidate targets for comprehensive compounds of the Wu-Tou Decoction (WTD, Aconite Main Root Decoction) against RA using the drugCIPHER-CS platform. They identified major hubs of the PPI network as candidate targets for WTD by analyzing the degree centrality, which was implicated in the NEI system and validated in further experiments.^[112] Yang

et al. unified the chemical analysis, prediction of ADME, and network pharmacology to highlight the active components in Dragon's blood tablet (DBT, Resina Draconis Tablet). Finally, they investigated 22 potentially absorbed components and 8 metabolites of DBT and determined that the molecular mechanism of these active components might be involved in the nucleotide-binding oligomerization domain-like receptor (NLRs) signaling pathway.^[113]

However, the complex network approach also provides an important clue for the toxicological mechanism of CMMs. For example, to explore the biomarkers and toxicity mechanism of processed *Aconitum carmichaelii* Debx tablet (Baifupian [BFP] in Mandarin), Zhang and Lu *et al.* comprehensively utilized serum metabolomics and complex networks to illustrate betaine and phosphatidylcholine as the biomarkers for the toxic responses of BFP. The toxic effects of BFP might be partially due to the perturbations of RhoA signaling, choline metabolism, and free radical scavenging.^[114]

CONCLUSION

Researchers have used complex network analysis to illustrate the complex correlations between different units and uncover the underlying principles of TCM theory and clinical practice. Despite the abundant achievements in the study of TCM network analysis, researchers have yet to clarify the deeper significance of TCM. They face many challenges as follows. First, although it is possible to use complex network analysis to derive the therapeutic role of TCM in treating diseases on the basis of the number of clinical practices, such an approach has yet to penetrate the scientific principles of TCM theory, such as TCM pharmacology, properties theory of CMMs, and combination role of CMFs. Second, based on the CM-compound-target-disease relationship, significant molecules as well as the bioactive mechanisms can be illustrated or predicted through complex network analysis. However, the comprehensive effects of activations/inhibitions/competitions of multi-compounds on the biological system are not a simple linear superposition, and we lack appropriate approaches for studying the synergetic effects of compounds. Third, an important property of TCM is its dynamic character. Many aspects of TCM can be characterized as dynamic systems including syndromes, TCM therapeutic schedules, the ADME progress of compounds in CMMs/CMFs, etc., However, the focus in the research involving TCM network analysis has tended to be on the static analysis of topological structure to investigate veiled herb pairs, chemical combinations, target groups, and so on, whereas dynamic network analyses of TCM are nearly absent. Fourth, having reliable data are the essential condition for a successful analysis of the TCM network. Although it is possible to retrieve abundant information about chemistry and biology from databases, literature, high-throughput experimentation, or computational modeling, the lack of sufficient interactions between different units, especially compounds and targets, might present an obstacle to constructing an integrated and predictable network. Finally,

the computational results of TCM network analysis should be validated by further supplementary experiments.

Although the TCM network analysis faces serious challenges in its infancy, its prospects are still promising, especially with the development of big data, computational capabilities, and experimental methods. In the future, pharmacodynamic material basis of CMMs, synergistic combinations among CMMs, pharmacological mechanisms of CMFs, and indications of TCM therapies may be elucidated through TCM network analysis. Thus, this approach is expected to bridge the gap between traditional medicine and modern medicine, allow for investigating the scientific basis of TCM theory, and accelerate the modernization of TCM.

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Conflicts of interest

There are no conflicts of interest.

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