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## Review

# Integrated Systems Biology and Chemical Biology Approach to Exploring Mechanisms of Traditional Chinese Medicines

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### ABSTRACT

After thousands of years of development, traditional Chinese medicines (TCMs) have evolved into a complete scientific system characterized by multiple components, targets, and pathways, which mediates numerous pharmacological activities and efficacies. The development of “-omics” technology, including systems biology and network pharmacology, has enabled the illustration of TCMs from a more systematic view. Although the network adequately reflects the overall philosophy of TCMs, its complexity hinders the relevant research to a hover. In addition, the strategies involved appear to be in contrast to the original concise and efficacious disease therapy oriented focus on classic Chinese material medica (CMM). Based on the established holistic view and reductionism, in this review, we discuss an integrated systems biology and chemical biology research approach that will facilitate and accelerate the understanding of the mechanisms of TCMs. Furthermore, we are optimistic that it will elucidate the associated interactions between active natural products and their targets, and ultimately improve the strategies for complex disease therapies.

#### Key words

chemical biology; network pharmacology; systems biology; traditional Chinese medicines

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## 1. Introduction

Traditional Chinese medicines (TCMs) have played an important role in the treatment of numerous complex diseases in the long history of its clinical use and been proved with reliable therapeutic efficacy. Currently, it constitutes a great wealth of therapeutic potentials for treatment of disease and sustainment of health. The continued investigation of TCM practices has enabled the characterization of their specific effects and low toxicity, which is increasingly attracting global attention (Dennis, 2003). In particular, Chinese scientist, You-you Tu, who is responsible for the discovery of

artemisin, was awarded the Nobel Prize in 2015, which advanced herbal medicines and drug discovery from natural-based drug products into a new golden age (Shen, 2015). However, in contrast to natural medicine which involves the use of plants and other remedies from natural sources, TCM is an ancient medical practice system that emphasizes the regulation of the integrity of the human body and its inter relationship with the natural environment (Wang and Xu, 2014a). By obeying the compatibility principles of “King (Jun), Minister (Chen), Assistant (Zuo), Guide (Shi)”, TCM creates an associated combination that jointly regulates disease-related multi-nodes and constitutes a comprehensive

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network. TCM prescriptions which constitute a complex system are the vectors of Chinese clinical therapy and are based on the original principles and theory that take the individual as a holistic system with different statuses and seek to regulate the networks and biological function of the body holistically. Although numerous TCMs have been proved to have the activities in modern pharmacological studies and clinical trials, the identity of the bioactive compounds in most TCM formulations remains to be characterized. The elucidation of the compatibility and interaction of these complex prescriptions is still a great challenge (Ge et al, 2012). Furthermore, complex system research requires a comprehensive strategy rather than a sophisticated mechanistic investigation of the interactions between small molecules and protein targets. By integrating traditional Eastern knowledge and modern Western science and technology, in this paper, we present a systematic approach which employs a wide range of research tools (e.g. from systems biology to chemical biology) for the exploration of TCM mechanisms.

## 2. Systems biology bridges modern science and traditional medicine practice

The dominant concept in modern drug discovery is the design of selective structures that act on drug targets. However, numerous active natural products act by regulating multiple proteins rather than single targets. Furthermore, TCM prescriptions have accumulated numerous herbal formulae, which introduce additional complications. Using the four diagnostic methods of observation, auscultation, interrogation, and palpation, Chinese medicine practitioners determine macroscopic symptoms and summarize the information required for issuing clinical therapy. This process embodies the advantages of the holistic concepts of Chinese medicine. In contrast, modern “-omics” technologies including chemomics, metabolomics, proteomics, transcriptomics, and network pharmacology could collect, screen, and analyze the body’s microscopic information by processing large data sets. After digitization, the information can be reconstructed into a new system for the diagnosis and treatment of disease. This appears to cut across the border between TCM theory and modern science. Hence, Wang (2007) pointed out that the concept of life science in the 21st century needs to incorporate the reductionist practice of analyzing and describing complex phenomena under the guidance of holism and systems theory. The philosophy of TCM is in considerable agreement with the key ideas of emerging network pharmacology and systems biology, and systematically adapts to the requirements of curing complex diseases.

Hopkins (2008) noted that integrating network biology and polypharmacology holds the promise of expanding the current opportunities for identifying drug targets, where network pharmacology can create a foundation for drug discovery. However, this paradigm has not been exploited over the past decades because of the lack of robust methods for systematic identification of complex networks. Currently, systems biology has proven to be a valuable tool and been greatly

facilitated by the advancement of comprehensive “-omics” in model technology (Buriani et al, 2012; Dou et al, 2008). Therefore, chemomics-integrated global systems biology has been presented as a method for studying the interactions between external intervention and biological response systems based on the fundamental principle of TCMs (Luo et al, 2007). Recently, the network pharmacology of TCM formulations has been developed rapidly, and related techniques have been used to investigate representative prescriptions such as Liu-Wei-Di-Huang (Liang et al, 2014), Siwu Tang (Fang et al, 2013), Qishen Yiqi (Li et al, 2014), and Qingluo Yin (Zhang et al, 2013), and the principles of herb combination were systematically clarified. The result suggested that the TCMs research strategy needed to be changed from a “single component and target” model to a “multiple components and network targets” model. Furthermore, the concept of systems biology played an important role in revealing the mechanisms underlying the effects of TCM formulations and, therefore, provided a new approach involving evidence-based medicine, which was developed based on the experience of medical research. Liu et al (2015a) noted that network pharmacology bridges the traditional application and modern development of TCMs and therefore, advocated the establishment of a linkage including network pharmacology, toxicology, and decoction pieces to support the safety and rational clinical use of TCMs. It is predicted that network pharmacology would play an important role in drug target discovery, mechanism investigation, pharmacokinetic/pharmacodynamics (PK/PD) analysis, safety and toxicity evaluation, quality control, and drug development. Subsequently, a set of TCMs network pharmacology methods (Li, 2015; Li and Zhang, 2013) were created for explaining network targets or effects/toxicities models such as prioritizing disease-associated genes, predicting target proteins and pharmacological actions, revealing drug-gene-disease co-module associations, and screening synergistic multi-compounds. Moreover, metabolomics also provides a dynamic picture of the phenotype of biosystems through the study of endogenous metabolites (Cao et al, 2015). Furthermore, it represents an opportunity to develop methods for the systematic analysis of metabolites and has been applied to identifying biomarkers and perturbed pathways.

Overall, systems biology integrates the advantages of chemical, pharmaceutical, and life sciences techniques, which is directed at revealing critical drug molecules and their pharmacodynamic modalities at the genomic, proteomic, metabolomic, and chemical genomic levels. This revelation is further targeted at interpreting the combinatorial rules and network regulatory effects of TCM formulae, as well as determining the macroscopic therapeutic underlying mechanisms or strategies for complex disease treatment.

## 3. Combination therapy: Requirements for complex disease therapy

Drug molecules usually induce concentration-dependent bioactivities. The introduction of a synergistic molecule can

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