

Network pharmacology: an important breakthrough in traditional Chinese medicine research

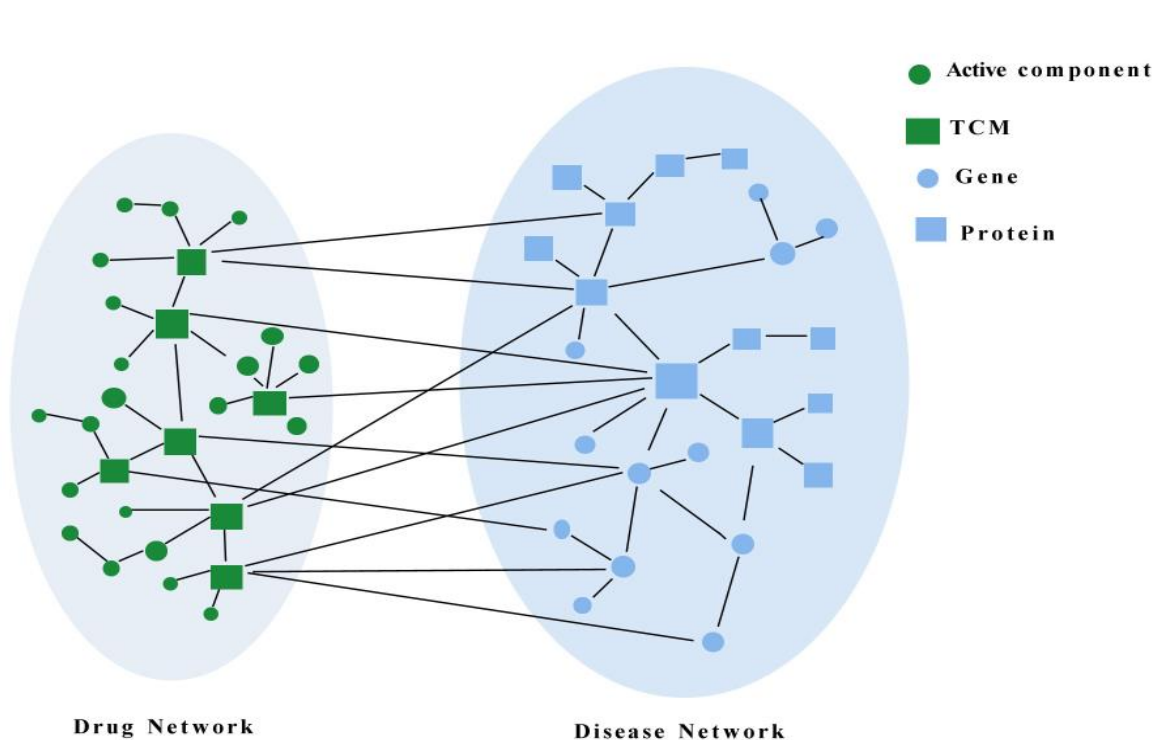
Jin-Wei Yuan¹, Jian Hao², Dan Chen³

¹School of Basic Medical Sciences, Tianjin Medical University, Tianjin, China. ²Tianjin Medical University Cancer Institute and Hospital, Tianjin, China.

***Correspondence to:** Dan Chen, School of Basic Medical Sciences, Tianjin Medical University, Qi-Xiang-Tai Road, Tianjin, China. E-mail: ilvcd@163.com

Highlights

Network pharmacology breaks through the traditional linear research model and coincides with the complexity of traditional Chinese medicine, provides technical support and new strategy in the research of traditional Chinese medicine.



Citation: Yuan JW, Hao J, Chen D. Network pharmacology: an important breakthrough in traditional Chinese medicine research. TMR Integrative Medicine 2018, 2(3): 92-98.

DOI: 10.12032/TMRIM201802026

Submitted: 27 July 2017, **Accepted:** 23 August 2017, **Online:** 13 September 2017.

Abstract

Objective: To study the relationship between traditional Chinese medicine (TCM) research and network pharmacology. **Methods:** Discuss the common features of TCM and network pharmacology through the analysis of the characteristics of TCM, the background of network pharmacology, so as better interpretation of TCM and in-depth understanding of TCM research and network pharmacology. **Results:** Multicomponent and multitarget characteristics of TCM as same as the study thought of network pharmacology. Network pharmacology breaks through the research model of linear and coincides with the complexity of TCM, provides technical support for rational design of TCM formulae, both and a new way in the research of TCM. It becomes a new strategy for modern TCM research. **Conclusion:** Network pharmacology is an important breakthrough in TCM research, its research promote modernization and internationalization process of TCM conduce to the research and development of TCM and have important significance for the integration of Chinese and Western medicine.

Keywords: Traditional Chinese medicine, Network pharmacology, Multicomponent, Multitarget

摘要

目的: 探讨中药研究与网络药理学的关系。

方法: 通过分析中医药的特点, 网络药理学的背景, 探讨中药与网络药理学的共性和个性, 从而更好地解读中医药的现代内涵, 使传承与创新结合, 深入了解中药研究与网络药理学的关系。

结果: 中药多成分多途径的特征与网络药理学的研究思路存在一定的共性, 网络药理学突破传统的线性研究模式, 暗合中药的复杂性, 为提高中医药的安全性和合理用药提供了技术支持, 为开展中医药研究提供了新的手段, 成为现代中医药研究的新策略。

结论: 网络药理学是中药研究重要突破口, 其研究策略促进了中医药的现代化和国际化进程, 有助于中药新药的研究开发, 对发展中医药的理论促进中西医药的融合具有重要意义。

关键词: 中药; 网络药理学; 多成分; 多靶点

Abbreviations: TCM, Traditional Chinese medicine.

Competing interests: The authors declare that there is no conflict of interests regarding the publication of this paper.

Copyright: © 2018 TMR Publishing Group Limited. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License.

Executive Editor: Chang Liu

Background

Currently, demand for TCM is increasing around the world. Various cultures and civilizations have encouraged the large-scale practice of TCM [1-2]. Characterized by holistic theory, and a rich experience in multicomponent therapeutics, TCM offer bright perspectives for treating complex diseases in a systematic manner. However, TCM has the characteristics of multicomponent and multitarget. Therefore, it is still a great challenge to clarify the mechanism of TCM under the background of modern science [3].

With the continuous progress of high-throughput omics data, the rapid development of computational methods and capabilities, human has entered a new era of bio-information. Network pharmacology, network medicine has gradually become a popular model of research, which has profound impact on drug research and new drug discovery [4-6]. Network pharmacology is a new discipline based on systematic biology and poly-pharmacology, which analyzes the network of biological system and chooses special signal nodes for drug molecular design of multitarget [7]. The holistic philosophy of TCM shares much with the key ideas of emerging network pharmacology and network biology, and meets the requirements of overcoming complex diseases, such as cancer, in a systematic manner. Thus, bridging the emerging network science and TCM will provide novel methodologies and opportunities for discovering bioactive components and biomarkers, potentially revealing mechanism of action, and exploring the scientific evidence of TCM formulae on the basis of complex biological systems.

TCM research from the perspective of modern science

TCM has developed over thousands of years and has accumulated abundant clinical experience, forming a comprehensive and unique medical system.

Just over 200 years ago, a 21-year-old pharmacist's apprentice named Friedrich Sertürner isolated the first pharmacologically active pure compound from a plant: morphine from opium produced by cut seed pods of the poppy, *Papaver somniferum* [8]. This initiated an era wherein drugs from plants could be purified, studied, and administered in precise dosages that did not vary with the source or age of the material. Pharmaceutical research expanded after the Second World War to include massive screening of microorganisms for new antibiotics because of the discovery of penicillin. By 1990, about 80% of drugs were either natural products or analogs inspired by them. Antibiotics (e.g., penicillin, tetracycline, erythromycin), antiparasitics (e.g., avermectin), antimalarials (e.g., quinine, artemisinin), lipid control agents (e.g., lovastatin and analogs), immunosuppressants for organ transplants (e.g., cyclosporine, rapamycins) and

anticancer drugs (e.g., taxol, doxorubicin) revolutionized medicine. Life expectancy in much of the world lengthened from about 40 years early in the 20th century to more than 77 years today. Although the expansion of synthetic medicinal chemistry in the 1990s caused the proportion of new drugs based on natural products to drop to about 50%, 13 natural products derived drugs were approved in the United States between 2005 and 2007, with five of them being the first members of new classes [9-10].

From the data presented, most drugs actually being either natural products or directly derived therefrom [11]. In the approved drugs, about 60% of the drugs are derived directly or indirectly from the natural products [12] (Figure 1).

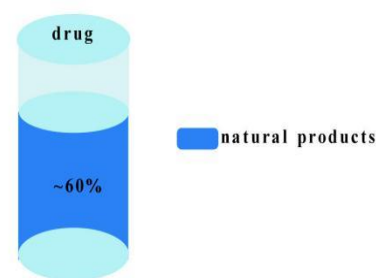


Figure 1 Source of small molecule approved drug

The complexity of mechanism in TCM

TCM formulae has been verified in clinical practice. It has high therapeutic value, and also is a treasure of medicine that has developed for several thousands of years. According to record of *Wushierbingfang* in the Han Dynasty of China (B.C. 206) and *Huangdineijing* in the Han Dynasty of China (B.C. 475), the total number of TCM formulae recorded in various literatures is more than 400,000 [13]. It has become major resource for the prevention and treatment of complex diseases, long-term clinical practice and the development of scientific research make people realize that TCM formulae plays a therapeutic role through accumulated synergy [14, 15].

Studies have shown that the efficacy of TCM formulae depends on the network interaction between the material foundation and act mechanisms [16] (Figure 2). TCM formulae usually contains hundreds of components. Identifying the active components is the basis for understanding the mechanisms of the whole formulae. Of course, research into a single component, such as artemisinin, has achieved great success. However, in many cases, the effect of a single

component is not ideal. The composition of formulae is an area of continuous exploration and involves accumulated synergy [17].

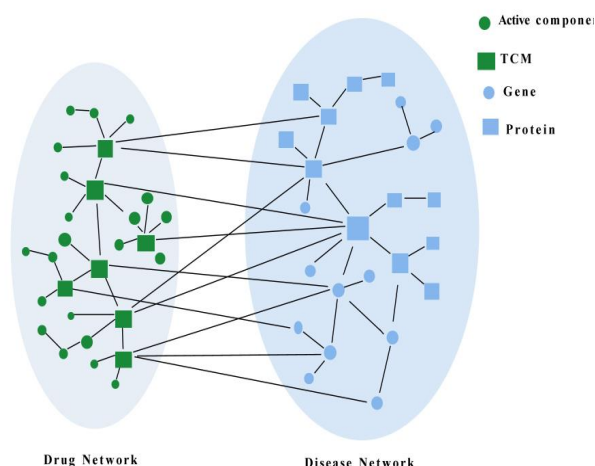


Figure 2 Network interaction between the material foundation and act mechanisms

TCM Network Pharmacology is an important breakthrough in TCM research

Early research on TCM was limited to single effective compounds; the results showed that this approach was not the correct one for modernizing TCM. Many effective drugs act via modulation of multiple proteins rather than single target. Advances in systems biology are revealing a phenotypic robustness and a network structure that strongly suggests that exquisitely selective compounds, compared with multitarget drugs, may exhibit lower than desired clinical efficacy [4]. Network biology analysis predicts that in most cases, deletion of individual nodes has little effect on disease networks, modulating multiple proteins may be required to perturb robust phenotypes. Network biology analysis shows that, in many cases, disease networks cannot be affected by individual nodes. Thus, identification and proof of combined nodes in a biological network with synergistic effects will produce a desired therapeutic outcome [18, 19]. Network pharmacology is new method and new strategy based on systematic biology and poly-pharmacology [20]. It integrates the network of biology and the network of drug, from single target to integrate network analysis [21]. Network pharmacology helps scientists analyze comprehensively the interactions among network parameters and potential drugs. It also allows examination of drugs' pharmaceutical effects and molecular mechanisms [22]. The holistic philosophy of TCM shares much with the key ideas of emerging network pharmacology and network biology, and meets the requirements of overcoming complex diseases, such as cancer, in a systematic manner. So network pharmacology is rapidly

becoming a cutting-edge research field in current drug studies and the next-generation mode of drug research.

Methodologies of TCM network pharmacology

Focusing on multicomponent, multitarget and system regulation of TCM [23], a set of TCM network pharmacology methods were created, we can divided into four steps: (1) Identify the active TCM components. (2) Identify the target of the active components. (3) Construct network of disease-target-drug. (4) Network analysis (Figure 3).

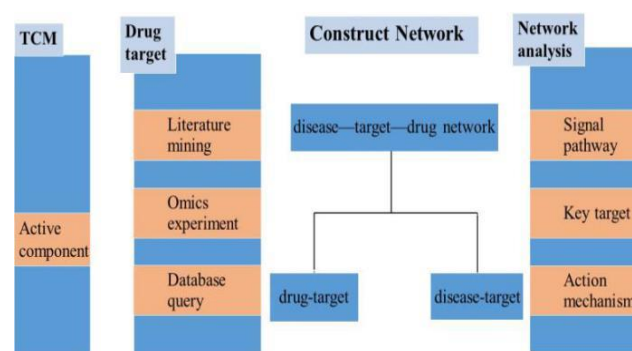


Figure 3 The research route of network pharmacology

Identify the active TCM components

One of the great challenges in the modernization of TCM is to identify the active TCM components and component pairs that produce the therapeutic effects or the adverse effects. And which is the basis for understanding the mechanisms of the TCM formulae. Scientists in the field of TCM and bioinformatics have done a great deal of work in the construction of TCM informatization, and constructed a large number of TCM databases. For example, TCM, 3D-MSDT, TCMID and TCM Database@Taiwan *et al*, the active components of TCM can be obtained through querying these databases [23-27].

Identify the target of the active components

Drug molecules through combining with specific proteins or nucleic acid targets, to regulate their biological activity, so as doing their work. Therefore, it is an essential step to understand the act mechanisms of TCM formulae to identify the target affected by the active components of TCM. Currently, the bioinformatics methods of identifying drug-targets include literature mining, omics experiment, calculation and prediction and database query [4]. In recent years, a large number of target data have been developed, such as DrugBank, TTD, STITCH, PDTD and HIT [28-31].

Construct network of disease - target - drug

Intuitively, the genes and proteins involved in the disease should be the target of the disease, but the fact is not so. The study group of Barabási constructed and analyzed the relationship between gene and disease [32]. It was found that a disease is rarely a consequence of an abnormality in a single gene [33]. The inherent mechanisms of a disease can be characterized with the biomolecular network model. Therefore, the identification of disease-related genes and the construction of disease-related networks, is one of the important element of network pharmacology research.

Information of disease-related gene can be obtained by database query and literature mining. The biomolecular network for disease-related gene or TCM components can be further constructed by the Cytoscape software. Finally, through integrating these datasets, a construction strategy for a network of a particular disease or TCM syndrome was proposed [34]. Various datasets have also been integrated to analyze and evaluate the network balance at the molecular and signaling pathway levels [35-38].

Network Analysis

Determining the signal pathway or sub-network regulated by the drug is the core of network pharmacology research. By making use of the network biology, the signal pathway or sub-network regulated by the drug was identified and interactions of the target proteins of active components were analyzed, which can help us to evaluate the effect of TCM on disease network, explore the mechanisms of the TCM formulae and syndrome relationship [4].

Applications of TCM network pharmacology

Discovery of active TCM components

Identification of active components and synergistic combinations: citing for the intervention of tumor angiogenesis as an example, core compatibility network are extracted from 3685 TCM formula. And some TCM formulae combinations which are of synergistic or antagonistic effects have been found in anti-angiogenic activities of various components estimated from those core compatibility networks [39].

Understanding the combinatorial rules of TCM formulae

Because many pathological processes are involved in a complex disease, and because they can be organized into different functional modules in a disease biomolecular network, it is reasonable to assume that the “Jun-Chen-Zuo-Shi” principle of TCM formulae can be explained by the actions of TCM on network-based functional modules. Given the ability to predict the target profiles of active components in TCM formulae, it is possible to reveal the combinatorial rule of “Jun-Chen-Zuo-Shi” based on the target interactions on the disease molecular network. Moreover, the interactions of the target proteins of active components may

contribute to the “Emergence” of the comprehensive effects of TCM formulae [40-41]. Therefore, it is promising to interpret the scientific basis and combinatorial rules of TCM formulae by the network target analysis of active components. By studying the characteristics of different combinatorial rules of TCM formulae, it is possible to explain the scientific connotation of combinatorial rules of TCM formulae from a new perspective.

Elucidation of the TCM formulae and syndrome relationship

TCM formulae is different from the individual component drug is characterized by the relationship between TCM formulae and syndromes. The formulae-syndrome relationship can be reflected by the rules of the “same treatment for different diseases” and “the same disease with different treatments” in TCM. Network pharmacology has been applied to explore the mechanisms as well as biomarkers of the TCM formulae and syndrome relationship, and they greatly facilitate the mechanistic interpretation of TCM formulae and syndrome.

Rational design and optimization of TCM formulae

TCM Network pharmacology can provide some feasible strategies and recommendations to increase the success rate of modern drug discovery as well as TCM network pharmacology can also be used to refine the experience by identifying and optimizing the synergistic and antagonistic combinatorial rules of TCM formulae, which in turn benefits combinatorial drug development. Therefore, rational design and optimization based on TCM network pharmacology is determining the best method of designing an optimal TCM formulae of multicomponent with a clear understanding of its pharmacology and potential drug-related adverse effects. In the future, two ways will be further explored as follows: (1) quantifying TCM formulae combinations with high efficacy and low side effects. (2) making use of the characteristics of the combinatorial rules of TCM formulae from a network perspective. Then, based on them, it is expected to develop a new algorithm for network targets suitable for rational design of TCM formulae.

Discussion

With continuous development of network pharmacology research, research methods will also show varied characteristics. The longstanding, successful application of TCM formulae makes it clear that phototherapy has synergistic effects: these occur when the efficacy of a formulae is greater than the summed effects of each individual component. Various constituents in a formulae may enhance the bioavailability or function on several targets instead of one to produce the synergistic effects [42-43]. Therefore, new drug development and research should first focus on the synergy among the

monomer components. Research into the synergistic actions of TCM can begin in a higher position, effectively standing on the shoulders of giants. One of those shoulders is the essence of TCM, the other is modern science and technology, such as network pharmacology. New drug strategies should be based on known effective TCM formulae in TCM. Such formulae provide a great many active components for further research and reduce many potential side effects. Solid basic research should be conducted to identify the active components preferably in the same formulae. Then, based on all the active components, combinations of two or three monomers should be screened out using the network pharmacology method. Subsequently, through structural modifications and improvements as well as adjusting the dosage and proportions of the species used, the efficacy of the drug group will be continuously improved, side effects will be constantly reduced, such that, finally, the optimal synergistic drug combination will result.

References

1. Qi FH, Wang ZX, Cai PP, *et al.* Traditional Chinese medicine and related active compounds: a review of their role on hepatitis B virus infection. *Drug Discov Ther* 2013, 7: 212-224.
2. Kim JY, Noble D. Recent progress and prospects in Sasang constitutional medicine: a traditional type of physiome-based treatment. *Prog Biophys Mol Biol* 2014, 116: 76-80.
3. Shang HC, Wu XZ, Qiu RJ, *et al.* Traditional Chinese medicine should not be ignored during the development of precision medicine with Chinese characteristics. *Tradit Med Res* 2016, 1: 105-114.
4. Hopkins A.L. Network pharmacology: the next paradigm in drug discovery. *Nat Chem Biol* 2008, 4: 682-690.
5. Barabasi AL, Gulbahce N, Loscalzo J. Network medicine: a network-based approach to human disease. *Nat Rev Genet* 2011, 12: 56-68.
6. Zhao J, Fang HY, Zhang WD, *et al.* Bioinformatics approaches in research on network pharmacology of traditional Chinese medicine. *Progr Pharm Sci* 2017, 38: 97-103.
7. Tang PP, Bai M, Miao MS. Traditional Chinese medicine research and network pharmacology. *Chin J Chin Med* 2012, 27: 1112-1115.
8. Hamilton GR, Baskett TF. In the arms of morpheus the development of morphine for postoperative pain relief. *Can J Anaesth* 2000, 47: 367-374.
9. Li JW, Vederas JC. Drug discovery and natural products: end of an era or an endless frontier? *Science* 2009, 325: 161-165.
10. Harvey AL. Natural products in drug discovery. *Drug Discov Today* 2008, 13: 894-901.
11. Newman DJ, Cragg GM. Natural products as sources of new drugs from 1981 to 2014. *J Nat Prod* 2016, 79: 629-661.
12. Newman DJ, Cragg GM. Natural products as Sources of new drugs over the 30 years from 1981 to 2010. *J Nat Prod* 2012, 75: 311-335.
13. Zhang JW, Lu ZL. Trace to the source of traditional Chinese medicine formulae. *Chin J Inf Tradit Chin Med* 2001, 3: 6-8.
14. Wang J, Wang YY. The theory of complex system and research on traditional Chinese medical formulae. *Chin J Inf Tradit Chin Med* 2001, 8:25.
15. Zhang BL, Wang YY. The basic research on the key scientific problems of formulae-development of modern Chinese medicine by component compatibility. *Chin J Nat Meds* 2005, 3: 258-261.
16. Fan XH, Cheng YY, Zhang BL. Network formulaology: a new strategy for modern research of traditional Chinese medicine formulae. *Chin J Chin Mat Med* 2015, 40: 1-6.
17. Yuan HD, Ma QQ, Cui HY. How can synergism of traditional medicines benefit from network pharmacology? *Molecules* 2017, 22: 1135-1140.
18. Csermely P, Agoston V, Pongor S. The efficiency of multi-target drugs: the network approach might help drug design. *Trends Pharmacol Sci* 2005, 26: 178-182.
19. Mayer LD, Janoff AS. Optimizing combination chemotherapy by controlling drug ratios. *Mol Interv* 2007, 7: 216-223.
20. Goh KI, Cusick ME, Valle D, *et al.* The human disease network. *Proc Natl Acad Sci USA* 2007, 104: 8685-8690.
21. Hopkins AL. Network pharmacology. *Nat Biotech* 2007, 25: 1110-1111.
22. Hoeng J, Deehan R, Pratt DA. Network-based approach to quantifying the impact of biologically active substances. *Drug Discov Today* 2012, 17: 413-418.
23. Zhao J, Jiang P, Zhang W. Molecular networks for the study of TCM pharmacology. *Brief Bioinform* 2010, 11: 417-430.
24. Ren TG, Liu XF, Gao JB. Introduction to traditional Chinese medicine basic database system. *Chin J Inf Tradit Chin Med* 2001, 8: 90-91.
25. Qiao X, Hou T, Zhang W, *et al.* A 3D structure database of components from Chinese traditional medicinal herbs. *J Chem Inf Comput Sci* 2002, 42: 481-489.
26. Xue R, Fang Z, Zhang M, *et al.* TCMID: traditional Chinese medicine integrative database for herb molecular mechanism analysis. *Nucleic Acids Res* 2013, 41: D1089-D1095.
27. Chen CY. TCM Database@ Taiwan: the world's largest traditional Chinese medicine database for drug screening in silico. *PLoS One* 2011, 6: e15939.
28. Wishart DS, Knox C, Guo A.C, *et al.* DrugBank: a comprehensive resource for in silico drug discovery and exploration. *Nucleic Acids Res* 2006, 34: 668-672.
29. Kuhn M, Mering C, Campillos M, *et al.* Stitch: interaction networks of chemicals and proteins.

- Nucleic Acids Res 2008, 36: D684-D688.
30. Gao Z, Li H, Zhang H, *et al*. PDTD: a web-accessible protein database for drug target identification. BMC Bioinformatics 2008, 19: 104.
 31. Ye H, Ye L, Kang H, *et al*. Hit: linking herbal active ingredients to targets. Nucleic Acids Res 2011, 39: D1055-D1059.
 32. Yildirim MA, Goh KI, Cusick ME, *et al*. Drug-target network. Nat Biotechnol 2007, 25: 1119-1126.
 33. Li S. Framework and practice of network-based studies for Chinese herbal formula. J Chin Integrat Med 2007, 5: 489-493.
 34. Li S, Wu LJ, Zhang ZQ. Constructing biological networks through combined literature mining and microarray analysis: a LMMA approach. Bioinformatics 2006, 22: 2143-2150.
 35. Huang Y, Li S. Detection of characteristic sub pathway network for angiogenesis based on the comprehensive pathway network. BMC Bioinformatics 2010, 11: S32.
 36. Gu J, Chen Y, Li S, *et al*. Identification of responsive gene modules by network-based gene clustering and extending: application to inflammation and angiogenesis. BMC Syst Biol 2010, 21: 47.
 37. Gu J, Li S. Toward integrative annotating of the cell-type specific gene functional and signaling map in vascular endothelial cells. Mol Biosyst 2012, 8: 2041-2049.
 38. Chen Y, Gu J, Li D, *et al*. Time-course network analysis reveals TNF-alpha can promote G1 / S transition of cell cycle in vascular endothelial cells. Bioinformatics 2012, 28: 1-4.
 39. Li S, Zhang B, Jiang D. Herb network construction and co-module analysis for uncovering the combination rule of traditional Chinese herbal formulae. BMC Bioinform 2010, 11: S6.
 40. Li S. Network target: a starting point for traditional Chinese medicine network pharmacology. Chin J Chin Mater Med 2011, 36: 2017-2020.
 41. Li S, Zhang B, Zhang NB. Network target for screening synergistic drug combinations with application to traditional Chinese medicine. BMC Syst Biol 2011, 5: S10.
 42. Zhao S, Li S. A co-module approach for elucidating drug-disease associations and revealing their molecular basis. Bioinformatics 2012, 28: 955-961.
 43. Li S, Zhao S. Network-based identification of drug target and drug action: China, 2010.