A Visual Analysis of Network Pharmacology Research Trends

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Objective: To understand the current situation of network pharmacology, and to analyze external and internal characteristics of literature, is of great significance for the development of network pharmacology in the future and its application in the modernization of Chinese medicine.

Methods: Bibliometrics were adapted to perform visual analysis on the research status of network pharmacology with Citespace and SPSS for windows 22.0 version (IBM, Armonk, New York, USA). Knowledge map was used to analyze the knowledge system in the field, to identify the research hotspots and dynamic frontiers, and to elaborate the research status and development trend of domestic network pharmacology.

Results: The research on network pharmacology in China is at the stage of the formation and construction of basic theories. At present, we focuses on the solution of actual disease problems and basic theoretical research, while the application in the research field of traditional Chinese medicine is a new hot spot and trend in the future development. Conclusions: It is important to pay attention to the connection and communication among the knowledge groups, so that a systematic knowledge system can be formed in the field of network pharmacology in domestic as soon as possible.

Keywords: Bibliometrics, network pharmacology, visual analysis

INTRODUCTION

Network pharmacology is a theory based on systems biology, network biology, and pharmacology. It uses network analysis methods to explain the complex relationships among genes, targets, drugs, and diseases, a new method for the development and design of new drugs.[1,2] This concept was first proposed by the pharmacologist Hopkins at the University of Dundee in the UK in 2007. He believes that the plight of drug development lies in the core issues and concludes that network pharmacology will become the next research paradigm for drug development. Compared to traditional pharmacology, the core idea of network pharmacology lies in “balance.” Network pharmacology does not focus on a target, but on the balance of the entire biological network, from disturbing the balance of the network and leading to disease, to understand the interaction between drugs and the body and to guide the development of new drugs by improving or restoring network balance.[3,4] This theory completely subverts the traditional concept of new drug development. Network pharmacology based on high-throughput network omics, network database and biological network construction on virtual computing also greatly saves the research and development costs, improving the success rate of new drug research and development in this concept. In the modernization of Chinese medicine, network pharmacology undoubtedly gave a brilliant inspiration. In recent years, the emerging network pharmacology methods have built a relatively stable network structure model of the complex interactions between the active ingredients, targets, related pathways, and diseases, so as to provide more scientific and efficient research ideas and methods for prediction of the active ingredients of traditional Chinese medicines (TCM), the screening of targets, and the discovery of new therapeutic effects.[5] Therefore, to analyze and evaluate the development history, knowledge system, and hot frontier topics of network Pharmacology in China through bibliometrics

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and visualization methods, and to conduct in-depth analysis of the similarities and differences at home and abroad, is of great significance for the modernized application of TCM.

**Materials and Methods**

**Sources of data**

The data in this study were collected from the Web of Science (TM) core collection database (including science citation index-expanded, current chemical reactions-expanded, and index Chemicus) under the Institute for Scientific Information platform.

**Strategy of search**

In order to ensure that the original data can fully cover the entire research field of network pharmacology, the keyword comprehensive search method was used on the basis of 21 keywords such as network pharmacology, polypharmacology, system pharmacology, and ligand-target network. We limited the country to Peoples R China and excluded research literature unrelated to network pharmacology, as well as news articles such as conference reports and reviews. Based on these search strategies, 3082 articles and 100,175 reference articles were retrieved in 2001–2017. The search time is May 10, 2017.

**Analysis of data**

Bibliometric analysis method with CiteSpace 3.7.R8 (Drexel University, Philadelphia, USA) was used to draw a knowledge map of domestic network pharmacology, and knowledge system, research hotspot, and frontier research of the domestic network pharmacology were further analyzed, and the result was compared with the results of international network pharmacology bibliometric visualization research.

**External characteristics of literature**

**Geographical distribution**

The literature on network pharmacology is distributed in 155 countries or regions internationally. The basic statistics and hierarchical clustering analysis were performed on the top 10 countries with the output. The results are shown in Table 1 and Figure 1. It can be seen that the research of network pharmacology on the international scale mainly focuses on North America, North America, Asia, and Europe. The U.S. is absolutely leading in all indicators, and it is far ahead of the research in network pharmacology. In the United Kingdom and Germany, the number of papers issued was ranked third and fourth respectively, and they come to a high level. On the contrary, although China has the second largest number of papers issued in the world, the actual research is at the same level as India, Japan, and it still lags behind that of developed countries. We can see that network pharmacology in China is very popular, but the research level and quality have yet to be improved.

**Institutional distribution**

The research literature of network pharmacology is distributed in 9437 research institutions internationally. The basic statistics and hierarchical clustering analysis were performed on the top 10 research institutions with the output. The results are shown in Table 2 and Figure 2. It can be seen that foreign research is mainly dominated by universities and their affiliated scientific research institutions, and forms a cooperative network. The University of California system is ranked first in all indicators and has the strongest research strength internationally. The clustering research institution which consists of Harvard

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**Table 1: Geographical distribution of international network pharmacology research literature**

| Country   | Output | The number of citations | The average number of citations | h-index |
|-----------|--------|-------------------------|---------------------------------|---------|
| America   | 7809   | 302,507                 | 38.74                           | 215     |
| China     | 3257   | 32,090                  | 9.85                            | 68      |
| Germany   | 2197   | 71,408                  | 32.5                            | 117     |
| England   | 1767   | 56,035                  | 31.71                           | 106     |
| France    | 1187   | 36,597                  | 30.83                           | 77      |
| Italy     | 1108   | 32,113                  | 28.98                           | 67      |
| Canada    | 988    | 34,175                  | 34.59                           | 89      |
| Spain     | 828    | 25,738                  | 31.08                           | 67      |
| Japan     | 822    | 20,341                  | 24.75                           | 55      |
| India     | 678    | 8716                    | 12.86                           | 35      |

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Figure 1: Hierarchical clustering analysis of geographical distribution of international network pharmacology research literature

Figure 2: Hierarchical clustering analysis of institutional distribution of international network pharmacology research literature
University and University of California San Diego is in second place, and the clustering research institution which includes French National Academy of Sciences, the Max Planck Society, the University of Toronto, and the Boston State Health Care System ranks third in output. The Chinese Academy of Sciences represents the highest level of domestic network pharmacology research. Its research strength is in a relatively backward cluster among 10 institutions together with the University of London and the National Institutes of Health. This not only indicates that the quality of the literature from China needs to be improved but also suggests that it is necessary to extensively build in cooperation with other top universities and research institutions.

Periodical distribution

A visual analysis of the journals of literature from the original data is shown in Figure 3. The left side represents the distribution of cited journals, and the right side represents the distribution of the journals of citing literature. The major subjects to which the network pharmacology related research literature belongs will be obtained by cluster analysis, which is the research foundation of network pharmacology.

As shown in Figure 3, the network pharmacology is applied in the main fields of biology, medicine, and chemistry. The application of biological fields is based on biological and molecular research, and mathematics, computer sciences, chemistry, and pharmacy are supplemented. The applications of medical fields are mainly based on biological and molecular disciplines, but they also require relevant knowledge in toxicology, mathematics, and economics. The research in the fields of chemistry is relatively decentralized, covering botany, mathematics, geography, computer sciences, toxicology, nursing, psychology, and so on. This shows that the three subjects of biology, chemistry, and medicine are the fundamental driving forces for the development. Moreover, the progress and development of toxicology, chemistry, computer sciences, clinical medicine, and other subjects provide the critical conditions and technical support for network pharmacology.

Internal characteristics of literature

Knowledge systems

In the dataset, the top 50 frequently cited articles in every 2 years were used to generate the co-citation network for that period, and the co-citation network of each period was

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Table 2: Institutional distribution of international network pharmacology research literature

| Institution                          | Output | The number of citations | The average number of citations | h-index |
|--------------------------------------|--------|-------------------------|---------------------------------|---------|
| University of California system      | 1089   | 62,650                  | 57.53                           | 115     |
| Harvard University                   | 575    | 34,961                  | 60.8                            | 87      |
| French National Academy of Sciences | 559    | 18,244                  | 32.64                           | 56      |
| Chinese Academy of Sciences          | 550    | 8139                    | 14.8                            | 42      |
| Max Planck Society                   | 453    | 18,941                  | 41.81                           | 68      |
| University of London                | 366    | 11,115                  | 30.37                           | 52      |
| University of California San Diego  | 353    | 31,876                  | 90.3                            | 83      |
| University of Toronto               | 326    | 18,223                  | 55.9                            | 64      |
| National Institutes of Health        | 305    | 11,824                  | 38.77                           | 56      |
| Boston State Health System           | 263    | 19,341                  | 73.54                           | 61      |

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Figure 3: Periodical distribution of international network pharmacology research literature
pruned and synthesized to obtain the document co-citation network. By using the Pathfinder and Pruning split networks algorithm to prune the network, and the document co-citation network [Figure 4] with 225 nodes and 331 lines was achieved. At the same time, we also get the main clustering information table. The top ten largest clusters, which cover 208 nodes and account for 92% of the total co-citation network, are the most representative ones [8-9] [Table 3].

After an in-depth analysis of the key node documents clustered in the group, the knowledge system in the field of domestic network pharmacology was obtained, which consists of five knowledge groups: Network theory, tool of software, genetic analysis theory, protein interaction theory, and drug discovery theory [10-14]. Based on the formation and development of each group, a knowledge system of domestic network pharmacology was obtained as shown in Figure 5. The knowledge system of network pharmacology research, based on network theory, obtained from the tool of software, supported by the research of gene analysis theory and protein interaction theory, will experience constant innovation and development.

**Research hotspot**

Taking the keyword as a network node, the co-occurrence network of the time slice is generated by taking the top 50 keywords that occur most frequently every 4 years. The co-occurrence network of each time slice is synthesized by using the Pathfinder and Pruning bellows networks algorithm to obtain a keyword co-occurrence network with 108 nodes, 163 lines, and an information table of the top 20 keywords cited as shown in Figure 6 and Table 4.

Through the analysis of the keyword co-occurrence network, we can see that “Expression” is cited the most frequently, indicating that gene expression is a major research hotspot in domestic pharmacology research. The research object is protein interaction network, metabolic network, biological network, and complex network. The research content mainly focuses on the network model, algorithm, recognition, expression, and pathway. The main research disease is cancer, and database is the main research source. It can be seen from “Saccharomyces cerevisiae” and “Yeast” that the research of domestic network pharmacology mainly focuses on yeasts as the research object.

**Research frontier**

The burst test was performed on the original data of the literature to explore keywords whose frequency suddenly increases in a short period to determine the research frontier in

| Cluster | Scale | S score | Cluster name                          |
|---------|-------|---------|----------------------------------------|
| #0      | 21    | 0.816   | Modules in Networks                    |
| #1      | 21    | 0.867   | Network Medicine                       |
| #2      | 20    | 0.904   | Drug Discovery                         |
| #3      | 20    | 0.724   | Community Structure in Networks        |
| #4      | 18    | 0.822   | Protein-Protein Interactions Networks  |
| #5      | 16    | 0.869   | Mathematical Tools                     |
| #6      | 15    | 0.907   | Computer Tools                         |
| #7      | 15    | 0.961   | Gene Analysis                          |
| #8      | 15    | 0.922   | Structure and Function of Complex Network |
| #9      | 13    | 0.918   | Statistical Mechanics of Complex Network |

| Keyword | Frequency | Keyword | Frequency |
|---------|-----------|---------|-----------|
| Expression | 419       | Model   | 193       |
| Protein interaction network | 330       | Cell     | 192       |
| Identification | 269       | Cancer   | 192       |
| Database | 237       | Gene     | 183       |
| Biological network | 230       | Yeast    | 161       |
| Network | 213       | Saccharomyces cerevisiae | 154 |
| Metabolic network | 212       | Protein | 146       |
| Pathway | 211       | Disease  | 146       |
| Gene expression | 209     | Algorithm | 144       |
| Complex network | 204     | Differentially expressed gene | 143 |

**Figure 4:** The clusters of knowledge system co-citation network

**Figure 5:** The picture of knowledge system
domestic network pharmacology. The information of emergent words in the past 5 years is obtained as shown in Table 5.

Among them, Systems Biology has the highest emergent rate. The co-occurrence words show that the research on diseases based on systems biology theory is the most prominent frontier trend in domestic network pharmacology research. The co-occurrence words of Yeast, Saccharomyces cerevisiae, Organization, Metabolic Network, Community Structure, Complexes, Mechanism, Functional module, and Algorithm are basically the same, illustrating that the study of the structure, function modules, mechanisms, and algorithms of complex networks or metabolic networks with yeasts and Escherichia coli as the research object is the research trend of domestic network pharmacology in recent years. The co-occurrence words of carcinoma and inflammation are comparatively less, indicating that the research on diseases has become the frontier trend of domestic network pharmacology research. The emergence of “TCM” and its co-occurrences shows that the use of network pharmacology theory and methods for research in the field of TCM has become a frontier trend in domestic network pharmacology research, and its purpose is to develop new drugs. The main tool used is the Cytoscape software and related databases. The research focuses on the study of the mechanism and signaling pathways.

![Figure 6: The keyword co-occurrence network](image)

### A comparative study of network pharmacology at home and abroad

#### Comparison of knowledge system

International and domestic network pharmacology research has roughly the same knowledge system. The difference is that the metabolic theory knowledge group in the field of international network pharmacology which dates back to 1994 is the earliest, largest, and most developed knowledge group in its knowledge system. The knowledge group of genetic analysis theory in the domestic knowledge system is a unique and emerging knowledge group. With the increase of research intensity and research efforts, the connection with other groups and scales have been increasing, and it has gradually become a symbolic group in the knowledge system of domestic network pharmacology.

The formation time of the group in the domestic knowledge system is generally later than international knowledge system, and the key node literature in the domestic group is also dominated by foreign documents which show that the establishment of the domestic knowledge system greatly depends on the international academic output and theoretical support. The researches on algorithms and theories mainly

| Emergent words            | Co-occurrence words                                                                 | Emergence rate | Frequency | Year |
|---------------------------|-------------------------------------------------------------------------------------|----------------|-----------|------|
| Systems biology           | Disease; Reconstruction                                                             | 11.9475        | 28        | 2012 |
| Organization              | Saccharomyces cerevisiae; Biological Network; Metabolic Network; Functional module; Complex Network; Community Structure; Discovery; Modularity | 11.5814        | 45        | 2012 |
| Yeast                     | Algorithm; Complexe; Genome; Identification; Saccharomyces cerevisiae; PPI Network; Interaction Network; Bioinformatics, et al. | 8.8882         | 89        | 2012 |
| Metabolic Network         | Complex Network; Organization; Identification                                       | 8.7317         | 83        | 2012 |
| Carcinoma                 | Differentially Expressed Gene; Expression                                           | 7.9276         | 38        | 2015 |
| Inflammation              | Cell                                                                                | 7.7172         | 38        | 2015 |
| Biology                   | Gene Ontology; Database                                                             | 5.9173         | 37        | 2012 |
| Community Structure       | Biological Network; Complex Network; Organization                                   | 5.8968         | 45        | 2012 |
| Complexes                 | PPI Network; Interaction Network; Algorithm; Yeast; Saccharomyces cerevisiae; Database | 5.8813         | 40        | 2014 |
| Saccharomyces cerevisiae  | Escherichia coli; Yeast; Genome; Identification; Database; Discovery; Organization; Protein-protein Interaction; Mass Spectrometry; Complex | 5.0836         | 88        | 2012 |
| Mechanism                 | Traditional Chinese Medicine; Apoptosis; Discovery                                  | 4.7501         | 57        | 2013 |
| Traditional Chinese Medicine | Drug Discovery; Network Pharmacology; Cytoscape; Database; Mechanism; Signaling Pathway, et al. | 2.6398         | 54        | 2013 |
| Functional module         | Organization; Identification; PPI Network; Algorithm; Interaction Network; Discovery; Biological Network; Database | 2.496          | 56        | 2012 |
| Algorithm                 | Discovery; Yeast; Prediction; Biological Network; Complex; PPI Network; Gene Ontology, et al. | 2.4669         | 100       | 2012 |

PPI: Protein-protein interaction
include argumentation, comparison, and application. This shows that domestic research on network pharmacology lacks independent innovation, and basic research is relatively weak, which leads to the delay in the development of tools and software knowledge groups and the lack in the support of databases and tools in the domestic network pharmacology knowledge system. Compared with the development of the international research, the domestic network pharmacology is still in the prototype stage.

**Research hotspot**

A comparative analysis of the hot spots in the field of pharmacological research at home and abroad shows that the international and domestic pharmacological network research focuses are roughly the same. The difference lies in the fact that the research targets of international network pharmacology include *E. coli* as well as yeast. In the study of diseases, not only cancers but other complex diseases are also hot topics in China. Although domestic and foreign research revolved around genetic research, the international research focus is more on system biology while domestic research focuses on cell, protein, and differential gene expression.

**Comparison of research frontiers**

The research of differently expressed genes based on interaction network analysis is the most prominent frontier trend in the field of international network pharmacology. The frequency of genome-wide network analysis, network reconstruction, and network structure research is high, and it is an emerging research focus and frontier trend of network pharmacology in recent years. Compared with the research frontier of international network pharmacology, domestic research focuses more on solving practical problems, that is, research on diseases. Among them, the application research in the TCM field is a characteristic domestic discipline, and it is also the frontier trend of domestic network pharmacology research.

**Discussion and Prospect**

Based on bibliometric visualization method, this study analyzes the research literature of network pharmacology in more than 10 years. Through co-citation analysis, cluster analysis, and literature analysis, the knowledge system in the field of domestic and international network pharmacology was determined; through the keyword co-occurrence analysis, the research hotspots of network pharmacology were identified; through the analysis of emergent words, the frontier trend of network pharmacology was analyzed. Compared with the international network pharmacology research, the problems and the unique characteristic advantages in domestic research are found.

The research field of the domestic network pharmacology has gradually formed a relatively complete knowledge system after more than 10 years of development, but it is still in its infancy compared with the international network pharmacology research. The knowledge group of genetic analysis theory is a unique and emerging knowledge group, and gene expression is a major research hotspot in the field of domestic network pharmacology. Compared with the research frontier of international network pharmacology, the domestic research focuses more on disease research, but the application of TCM is the hotspot and frontier in the future.

On the whole, the current status of domestic network pharmacology research lacks basic research, extended research among knowledge groups, and frontier branches. The future domestic network pharmacology must strengthen basic research, constantly improve the innovative power, and focus on exploratory research and integration of knowledge groups, so as to form a more complete knowledge system as soon as possible.

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**Conflicts of interest**

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