

General expert consensus on the application of network pharmacology in the research and development of new traditional Chinese medicine drugs

Shao Li, Wei Xiao

Citation: Shao Li, Wei Xiao, General expert consensus on the application of network pharmacology in the research and development of new traditional Chinese medicine drugs, *Chinese Journal of Natural Medicines*, 2025, 23(2), 129–142. doi: [10.1016/S1875-5364\(25\)60802-8](https://doi.org/10.1016/S1875-5364(25)60802-8).

View online: [https://doi.org/10.1016/S1875-5364\(25\)60802-8](https://doi.org/10.1016/S1875-5364(25)60802-8)

Related articles that may interest you

[Network pharmacology approaches for research of Traditional Chinese Medicines](#)

Chinese Journal of Natural Medicines. 2023, 21(5), 323–332 [https://doi.org/10.1016/S1875-5364\(23\)60429-7](https://doi.org/10.1016/S1875-5364(23)60429-7)

[TCM network pharmacology: A new trend towards combining computational, experimental and clinical approaches](#)

Chinese Journal of Natural Medicines. 2021, 19(1), 1–11 [https://doi.org/10.1016/S1875-5364\(21\)60001-8](https://doi.org/10.1016/S1875-5364(21)60001-8)

[Modern research thoughts and methods on bio-active components of TCM formulae](#)

Chinese Journal of Natural Medicines. 2022, 20(7), 481–493 [https://doi.org/10.1016/S1875-5364\(22\)60206-1](https://doi.org/10.1016/S1875-5364(22)60206-1)

[Traditional Chinese medicines derived natural inhibitors of ferroptosis on ischemic stroke](#)

Chinese Journal of Natural Medicines. 2024, 22(8), 746–755 [https://doi.org/10.1016/S1875-5364\(24\)60603-5](https://doi.org/10.1016/S1875-5364(24)60603-5)

[Transcriptional profiling and network pharmacology analysis identify the potential biomarkers from Chinese herbal formula Huosu Yangwei Formula treated gastric cancer *in vivo*](#)

Chinese Journal of Natural Medicines. 2021, 19(12), 944–953 [https://doi.org/10.1016/S1875-5364\(22\)60154-7](https://doi.org/10.1016/S1875-5364(22)60154-7)

[Ethnopharmacology, chemodiversity, and bioactivity of *Cephalotaxus* medicinal plants](#)

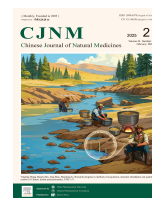
Chinese Journal of Natural Medicines. 2021, 19(5), 321–338 [https://doi.org/10.1016/S1875-5364\(21\)60032-8](https://doi.org/10.1016/S1875-5364(21)60032-8)



Wechat

Contents lists available at [ScienceDirect](https://www.sciencedirect.com)

Chinese Journal of Natural Medicines

journal homepage: www.cjnmcpu.com/

Guideline and consensus

General expert consensus on the application of network pharmacology in the research and development of new traditional Chinese medicine drugs

Shao Li^{a,*}, Wei Xiao^{b,*}^a Institute of TCM-X/MOE Key Laboratory of Bioinformatics, Bioinformatics Division, BNRIst/Department of Automation, Tsinghua University, Beijing 100084, China^b State Key Laboratory on Technologies for Chinese Medicine Pharmaceutical Process Control and Intelligent Manufacture, Jiangsu Kanion Pharmaceutical Co., Ltd., Lianyungang 222047, China

ARTICLE INFO

Article history:

Received 15 August 2024

Revised 25 September 2024

Accepted 8 October 2024

Available online 20 February 2025

Keywords:

Network pharmacology

Research and development of new traditional

Chinese medicine drugs

Expert consensus

ABSTRACT

The research and development of new traditional Chinese medicine (TCM) drugs have progressively established a novel system founded on the integration of TCM theory, human experience, and clinical trials (termed the “Three Combinations”). However, considering TCM’s distinctive features of “syndrome differentiation and treatment” and “multicomponent formulations and complex mechanisms”, current TCM drug development faces challenges such as insufficient understanding of the material basis and the overall mechanism of action and an incomplete evidence chain system. Moreover, significant obstacles persist in gathering human experience data, evaluating clinical efficacy, and controlling the quality of active ingredients, which impede the innovation process in TCM drug development. Network pharmacology, centered on the “network targets” theory, transcends the limitations of the conventional “single target” reductionist research model. It emphasizes the comprehensive effects of disease or syndrome biological networks as targets to elucidate the overall regulatory mechanism of TCM prescriptions. This approach aligns with the holistic perspective of TCM, offering a novel method consistent with TCM’s holistic view for investigating the complex mechanisms of TCM and developing new TCM drugs. It is internationally recognized as a “next-generation drug research model”. To advance the research of new tools, methods, and standards for TCM evaluation and to overcome fundamental, critical, and cutting-edge technical challenges in TCM regulation, this consensus aims to explore the characteristics, progress, challenges, applicable pathways, and specific applications of network pharmacology as a new theory, method, and tool in TCM drug development. The goal is to enhance the quality of TCM drug research and development and accelerate the efficiency of developing new TCM products.

The Communist Party of China Central Committee and the State Council prioritize the development of TCM, recognizing its significance in the country’s economic and social advancement. They have explicitly emphasized promoting TCM inheritance and innovative development¹⁻², as well as utilizing modern scientific methods to interpret TCM principles³⁻⁴. The National Medical Products Administration (NMPA), in accordance with the *Communist Party of China Central Committee and State Council on the Promotion of Chinese Medicine Inheritance and Innovative Development of the Views* document, is integrating modern scientific and technological achievements to reform and enhance the registration and management system of TCM⁵⁻⁸. As the reform of TCM’s registration and management system progresses, research and development (R&D) of new TCM drugs has begun to adopt a novel model based on the “Three Combinations”: TCM theory, human experience, and clinical trials. Despite the unique character-

istics of traditional Chinese medicine (TCM), such as its integrative approach to diagnosis and treatment, its multi-component formulations, and its focus on multiple therapeutic targets, the R&D of new TCM-based drugs face significant challenges. One of the primary obstacles is the insufficient understanding of the overall mechanisms of action, which leads to an incomplete evidence chain for supporting drug efficacy. Additionally, challenges persist in gathering reliable human clinical data, evaluating therapeutic outcomes, and ensuring the quality control of the bioactive components. These factors hinder the innovative development of new TCM drugs. To navigate the inherent complexity of TCM and make its foundational principles more accessible and understandable, it is essential to introduce innovative, multidisciplinary approaches. Exploring novel tools and methodologies, such as advanced analytical technologies or systems-based models, will be crucial for advancing TCM drug development and improving its scientific validation.

Investigating the scientific principles of TCM and exploring the intrinsic rules of its macro-phenotype and micro-molecular characteristics is crucial to unraveling the complexities of TCM. While TCM has amassed a substantial body of descriptive data at

* Corresponding author.

E-mail addresses: shaoli@mails.tsinghua.edu.cn (S. Li); kanionlunwen@163.com (W. Xiao)

the macroscopic level, there is a relative paucity of microscopic-level data accumulation. Consequently, interpreting the holistic characteristics of TCM from a microscopic and systematic perspective presents a significant challenge in current TCM research. The emergence of interdisciplinary fields such as computational biology, bioinformatics, artificial intelligence, and big data science has ushered medical and life science research into the era of big data. Disease and drug studies have shifted from reductionism to systematics and from isolated modes to diversified and systematic research approaches. Notably, analyzing the correlation mechanisms of diseases/syndromes and drugs from a biological network perspective, using networks to portray the whole, has further propelled the evolution of new pharmaceutical research models^{9,10}. This foundation has given rise to an emerging cross-disciplinary field known as “network pharmacology (NP)”, with “network target” as its core theory. NP transcends the limitations of the “single target” reductionist analysis research mode, emphasizing the integrated effects of disease or symptomatic biological networks as targets to characterize the overall regulatory mechanism of TCM prescriptions. This approach, which emphasizes the comprehensive effects of disease or syndrome biological networks as targets, is internationally recognized as the “next generation of drug research model”¹¹. NP is distinguished by its combination of computational and experimental methods, aligning with TCM’s holistic treatment concept. This alignment creates favorable conditions for exploring TCM characteristics and advancing toward international scientific and technological frontiers¹².

To promote the standardization of novel tools, methods, and standards for evaluating TCM and to address fundamental, critical, and cutting-edge technical challenges in TCM regulation, this consensus examines the characteristics, current progress, challenges, applicable pathways, and specific applications of NP in TCM drug development. Based on the “network target” theory, this approach aims to enhance the quality and efficiency of TCM drug R&D. This consensus integrates various regulatory documents and technical guidelines, including the *Special Provisions on the Administration of Registration of TCM*, the *Classification and Application Data Requirements for traditional Chinese Medicine Registration* (No. 68, 2020), the *Guiding Principles for Clinical Research and Development of New Drugs for Compound Preparations of TCM Based on the Experience of the Human Use of TCM*, the *Guiding Principles for the Research Techniques of New Drugs of Improved TCM* (for Trial Implementation), the *Provisions on the Administration of Simplified Registration and Approval of Compound Preparations of Ancient Classical Prescriptions of Chinese Medicines*, and the *Use of Artificial Intelligence and Machine Learning in the Research and Development of Pharmaceuticals and Biological Products*. Additionally, it incorporates findings from relevant projects and extensive deliberations by experts in the field.

1. Characteristics, current progress, and challenges in the application of NP to the development of new drugs of TCM

1.1. Characteristics of NP applied to the R&D of new drugs of TCM

NP aligns with the holistic perspective and systematic approach of TCM. It offers novel methodologies and tools for investigating the complex mechanisms of action in TCM and facilitates the R&D of new TCM drugs. This approach is grounded in the organism’s biological network, elucidating the intricate relationships between complex diseases, symptoms, prescriptions, and medicinal compounds, which is consistent with TCM’s holistic philosophy.

The central concept of NP, “network target”, encompasses the interconnected systems of biomolecular, cellular, and organ

interactions, along with their crucial sub-networks, modules, pathways, nodes, or node combinations that play a pivotal role in disease pathogenesis or syndrome formation. Herbal formulas, drug combinations, and compound groups may treat diseases or alleviate symptoms by systematically regulating these networks. The overall mechanism of action of TCM formulas in disease treatment can be elucidated by analyzing the structure and function of syndrome or disease network targets (including molecules, nodes, pathways, modules, and sub-networks) regulated by the entire formula and its individual components. This process involves integrating and quantitatively characterizing the perturbations, synergistic effects, and propagation dynamics among these various elements¹³.

The components of “network” in NP encompass herbal formulas (compound formulas, single-flavour medicines, extracts, components, and single compounds), targets (molecules, subcellular structures, cells, tissues, organs), phenotypes (molecular pathological markers, cellular behaviors, tissue properties, organ traits), evidence, diseases, and related elements. Utilizing these components and drawing from recent advancements in life sciences, chemistry, bioinformatics, and computer science, the interactions between TCM formulas and organisms are abstractly represented as networks. Network science and technology are then employed to analyze their connectivity, redundancy, multiplicity, emergence, complexity, and robustness (or self-stabilization) to investigate the interactions (efficacy, pharmacology, toxicology, and pharmacogenetics) between drugs and organisms, guiding the research and development of new TCM drugs. NP emphasizes the synergistic effects between drug components and targets, as well as the perturbation of network targets to restore or enhance network balance across organismal levels. This approach aligns with the holistic view intrinsic to Chinese medicine. This approach can facilitate the integration of clinical efficacy and basic theory in the development of new Chinese medicines. It promotes the combination of clinical efficacy and basic theory, macro-phenotype and micro-molecule, and pharmacological substance and pharmacology-toxicology during TCM drug R&D, thereby improving the efficiency of new TCM drug development. Recent breakthroughs in machine learning, particularly deep learning, have positioned artificial intelligence (AI) as a prominent research direction. AI algorithms can be applied to diverse data types using various strategies to perform tasks such as searching and discriminating, making them suitable for analyzing the massive data and complex relationships in NP research, thus advancing the development and application of NP in TCM. AI-oriented NP not only represents a breakthrough in cross-disciplinary research between AI and TCM but also provides a novel strategy for efficient and in-depth development of new TCM drugs¹⁴⁻¹⁶.

1.2. Research progress of NP applied to the R&D of new drugs of TCM

1.2.1. Development stages of NP

The evolution and utilization of NP can be categorized into three distinct phases: the initial exploration stage, the R&D stage, and the widespread application stage (Fig. 1).

The early exploration stage (1999–2008) marked the inception of network-based approaches in TCM. In 1999, Shao Li from Tsinghua University pioneered the hypothesis linking TCM to biomolecular networks¹⁷. In 2002, Li proposed that TCM formulas might modulate complex disease gene networks through a synergistic “multi-causal microeffects” mechanism¹⁸. Building on this foundation, Li initiated the development of a network-based navigation system for TCM in 2006¹⁹. The following year, Li conducted groundbreaking analyses of biomolecular network differ-

ences between TCM cold and hot syndromes, examining their macro-micro dynamic changes through network-contextualized information integration^{20, 21}. In October 2007, Hopkins introduced the term “network pharmacology”²², which was subsequently proposed as “the next paradigm in drug discovery” in 2008¹¹.

The research development stage (2009–2017) witnessed significant advancements in NP. In 2009, Shao Li introduced the “phenotypic network–biological network–herbal medicine network” model for TCM syndrome and formula research²³. Building on this foundation, Li proposed the “network target” concept in 2011 and developed a synergistic drug combination prediction algorithm, which was recognized as Essential Reading in the NP Field by Faculty of 1000²⁴. Du proposed NP as a novel strategy for drug discovery in 2010, moving beyond single-target approaches²⁵. Network scientist Barabási emphasized the importance of network medicine for identifying drug targets and biomarkers in complex diseases in 2011²⁶. Concurrently, Xiao et al. constructed a research model based on NP to elucidate the molecular mechanisms of Chinese patent medicines^{27, 28}. Zhou et al. published a review on NP concepts for drug understanding and discovery in 2012²⁹, while Sun et al. highlighted NP’s role in TCM modernization³⁰. Zhang proposed an NP-oriented strategy for TCM redevelopment in 2013³¹, and Li et al. further developed the “network target, multi-component drug” model¹³. Donald E. Mager introduced a new target discovery strategy based on complex disease-specific networks in the same year³². In 2014, Xiao and Wang et al. established the TCMN and TCMSp platforms, providing essential tools for TCM-related NP research³³⁻³⁵. Li proposed an on/off effect model based on network target in *Science* special issue in 2015³⁶, while Barabási introduced a systematic network-based approach for identifying disease modules³⁷. In 2017, Olivier proposed integrating biological and chemical structural features into a network-based model for active ingredient discovery and drug mechanism studies³⁸. These developments demonstrate that the “network target” concept, rooted in TCM’s original thinking, played a crucial role in NP’s origin and development. NP represents a promising area for China’s independent innovation in pharmaceutical science, integrating TCM principles with modern scientific interpretation.

The widely applied stage (2018–present) has seen significant advancements in NP. In 2019, Schmidt et al. utilized NP methods to predict synergistic targets³⁹, and in 2022, they proposed

shifting NP’s focus from treating symptoms to addressing root causes⁴⁰. Barabási et al., network scientists, applied NP methods in 2021 to predict the mechanism of action of natural polyphenolic constituents⁴¹. That same year, Xiao established an innovative R&D strategy for TCM driven by NP and centered on efficacy substances, publishing a monograph that provided a research paradigm for TCM innovation⁴². Li led the development of the first international standard for NP, the *Guidelines for Evaluation Methods of Network Pharmacology*, which was released in 2021⁴³⁻⁴⁵ and recognized as one of the Top Ten Academic Advances in TCM by the Chinese Society of Traditional Chinese Medicine. Concurrently, Li edited the first NP monograph published in both Chinese and English^{46, 47}, further standardizing and guiding NP research in Chinese medicine. In 2023, Huang employed an NP approach to predict potential bioactive components of Huashi Baidu Decoction⁴⁸. Researchers at the Dana-Farber Cancer Institute, in collaboration with the Boulder Institute, developed a context-aware, attention-based deep learning model that accelerated the discovery of key network modulators and candidate therapeutic targets⁴⁹. In 2024, Li proposed an AI-based framework for NP research¹⁵.

The origin and development of NP can be traced to the original concepts of TCM, leading to a paradigm shift in TCM research. NP has experienced rapid growth, with its application domains expanding significantly. It has made notable advancements in areas such as precision prevention and treatment in TCM, as well as innovative research and development of TCM. The field is progressing towards increased algorithmic precision, enhanced efficiency in translation and application, and elevated research standards. By maintaining a deep integration of TCM’s foundational principles with modern scientific and technological approaches, NP has the potential to foster independent innovation in China’s medical science and technology sector. This integration may catalyze the development of new, qualitative productivity in TCM and guide future paradigm shifts in medical research and practice.

1.2.2. Establishment of NP evaluation method guidance

The development of the *Network Pharmacology Evaluation Method Guidance*, the first formal international standard in the field of TCM for an emerging discipline, represents a significant advancement towards its robust development and application in TCM drug R&D. Grounded in the core theory of NP, “network tar-

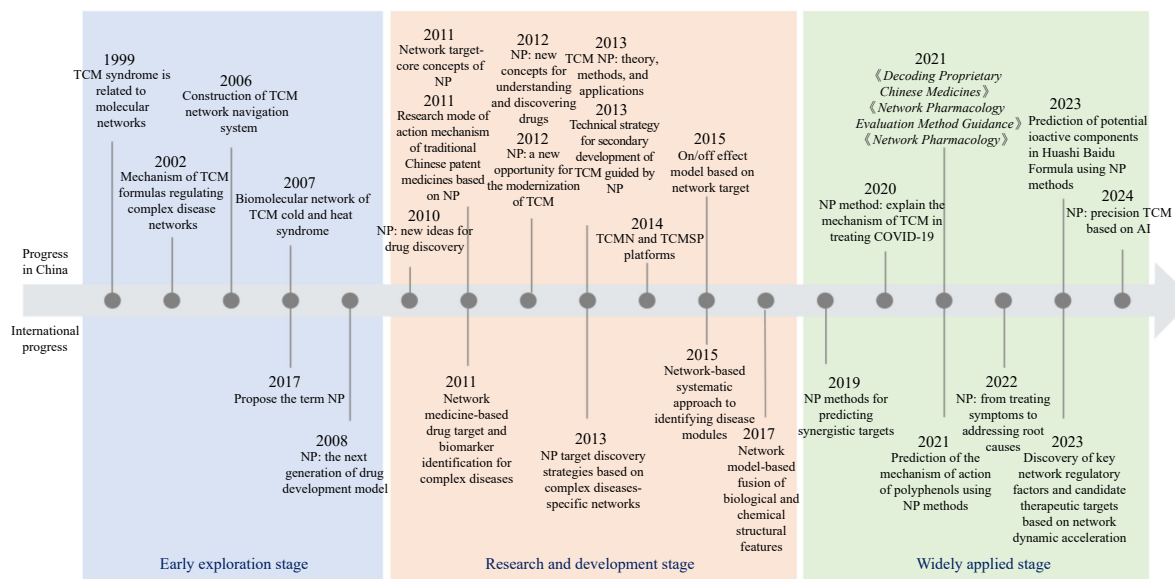


Fig. 1 Development and application of network pharmacology.

get”, this guidance establishes standardized criteria for evaluating NP and defines the reliability and accuracy of its technical methods. The formulation of these guidelines contributes to enhancing the overall research quality in NP, holding substantial practical significance in standardizing its application in TCM drug R&D. It has the potential to elevate the “network target-system regulation” based R&D model into a more rigorous, scientific, and universally applicable drug research paradigm. Furthermore, it promotes more standardized computational, experimental, and clinical applications of NP in the development of new TCM drugs⁴³⁻⁴⁵.

1.2.3. Publication of Chinese and English monographs of NP

Network Pharmacology is the first comprehensive book in China to systematically introduce the theory, methods, and applications of NP. Springer has published it globally, contributing significantly to the international dissemination and advancement of NP in China, as well as its application in the research and development of new TCM drugs. The book methodically presents the developmental history of NP and the core concept of “network target”, the application of NP based on AI algorithms in drug development, commonly used databases and software in NP, modernization of TCM based on NP, and the practical process of NP based on drugs and diseases. This publication offers a novel approach to deciphering TCM principles and provides digital, intelligent, and accurate solutions to the challenges of TCM inheritance, innovation, and development. It supports TCM research and development, clinical medicine use, and the training of related professionals, thereby fostering high-quality advancement in the field and industry of Chinese medicine^{46,47}.

1.2.4. Experimental platform for the application of NP to the development of new drugs of TCM

The Using Network Target for Intelligent and Quantitative Analysis on Drug Actions (UNIQ), an AI-enabled network target analysis platform, received the prestigious “Gold Medal of Special Mention by the Jury” at the 49th International Exhibition of Inventions in Geneva. This marks the first application of AI in TCM research independently developed by Shao Li’s team. The UNIQ system introduces a core algorithm for “relationship inference” between Chinese and Western medicine phenotypes, biomolecular networks, and Chinese and Western drugs. The algorithms, including CIPHER⁵⁰ and drugCIPHER⁵¹, have demonstrated remarkable precision, achieving 2.3 times the accuracy of the highest precision method reported in *Nature Biotechnology* for genome-wide prediction of disease-causing genes⁵² and 5.9 times that of a method reported in *Science* for prediction of drug targets⁵³. Utilizing these core algorithms, UNIQ localizes diseases and drugs at the molecular level and computationally predicts drug combinations and synergistic intervention modules, integrates information across phenotype–tissue–cell–molecule levels, and conducts comprehensive analyses of the relationships between Chinese and Western medicine phenotypes, cells, molecules, and drugs. The UNIQ system enables systematic analysis of disease–syndrome–prescription–medicine correlation mechanisms from a biological network perspective of disease–syndrome combinations. It establishes key technologies for scientific analysis of disease–syndrome combinations based on network targets, applicable to precise diagnosis, treatment, medication, and R&D in both Chinese and Western medicine. The network target theory bridges the gap between macroscopic and microscopic intrinsic correlation analyses, facilitating the integration of TCM and modern medicine. It provides new theories and methods for exploring TCM principles, while the UNIQ system offers a crucial technical support platform for applying network target theory.

Employing the UNIQ system to target angiogenesis mechan-

isms in rheumatoid arthritis, combined with global network target prediction screening and the expertise of renowned TCM practitioners, the Qingluo Decoction has been refined and enhanced. This process has yielded a modified Qingluo Decoction with a more precise mechanism and improved clinical efficacy. The UNIQ system has also been utilized to support the research and development of novel TCM drugs, such as Yinqiao Qingre Tablet and Yiqi Tongqiao Pill, as well as the advancement of established TCM formulations like Tian Shu Capsule and Xuebijing Injection. These efforts aim to elucidate the scientific principles underlying major TCM formulations, enhance their competitiveness, and establish a model for wider adoption and dissemination.

The UNIQ system has been evaluated as an integrated approach that combines macro- and micro-level data of TCM and disease–syndrome relationships. This system characterizes the overall regulatory mechanism of TCM formulas by targeting the comprehensive effects of disease or syndrome biological networks. Such an approach can guide the development of practical R&D strategies for new TCM drugs, thereby enhancing the specificity and precision of TCM drug R&D⁵⁴.

Various database platforms support the R&D of new TCM drugs. The ETCM database platform integrates standardized information on herbs, formulas, and their components, including TCM ingredients, medicinal flavors, properties, attributed meridians, and potential target genes. It constructs a network relationship mapping between TCM and formulas, ingredients, target genes, related pathways, and diseases. The platform encompasses 2079 Chinese herbal medicines, 48 442 ancient formulas, 9872 Chinese patent medicines, 38 298 Chinese medicinal ingredients, 1040 gene targets, and 8045 disease-related data verified or predicted by experiments⁵⁵. The TCMID database platform focuses on the collection of TCM-related chemical compositions and action targets⁵⁶. The SymMap database platform is specifically designed to explore the relationships between TCM syndromes and other medical entities, constituting a heterogeneous network of six entity types: TCM syndrome, herbal medicine, Western medicine symptoms, syndrome-associated diseases, herbal medicine components, and drug targets⁵⁷. TCM-PTD, a TCM potential target database, proposes a component pairing optimization strategy for the network balance construction algorithm and conducts experimental studies to create a comprehensive evaluation method of TCM efficacy based on network regulation and a multi-component/multi-target/multi-pathway network construction method. The TCMGeneDIT database platform constructs and evaluates relationships between TCM, genes, and diseases through literature mining⁵⁸. The INPUT platform stores data on Chinese medicines, diseases, active ingredients, and targets, integrating multiple bioinformatics methods to achieve automated analysis of NP, target gene function enrichment analysis, data querying and retrieval, and drug similarity analysis⁵⁹. The TCMN database platform stores data on Chinese medicines, source plants, ingredients, targets, biological pathways, clinical indicators, and standard transcriptome data from *in vitro* model screening. It links drug targets, diseases, and TCM components to predict activity and analyze mechanisms of TCM formulas and natural products, establishes optimization strategies for TCM components based on biological pathway networks, and achieves quantitative analysis of synergistic effects among TCM components. TCMSP and BATMAN-TCM focus on constituent-based target prediction and network analysis. These database platforms provide essential tools and technical means for NP utilization in the R&D of new Chinese medicines, serving as crucial support for NP research^{60,61}.

1.3. Challenges in the application of NP to the development of new drugs of TCM

The application of NP to the research and development of

new drugs in TCM represents an emerging research direction. This field currently faces numerous developmental opportunities and challenges in both theoretical and methodological aspects.

These challenges stem from two primary sources: firstly, the limitations of fundamental biological, medical, and pharmacological theoretical knowledge; secondly, the insufficient data accumulation, inadequate computational methods, and poorly defined research systems for NP. Consequently, some NP studies find themselves constrained by homogenization issues⁶².

Regarding data accumulation, public databases provide a foundation for NP. However, existing public databases face challenges in data quality and volume, which hinder researchers' ability to comprehensively and systematically integrate information from multiple sources and obtain reliable results. In the realm of computational methods, network-based approaches offer essential technical support for objective scientific pharmacological research. Nevertheless, several methodological challenges persist, including how to effectively highlight the holistic and systematic characteristics of NP, construct quantitative and dynamic network models, and enhance the applicability of NP methods in addressing complex diseases and facilitating new drug discovery and development. These areas require further in-depth consideration and exploration by researchers. Concerning the research system, high-level NP studies are characterized by the profound intersection of computation and experimentation, the integration of multi-omics data, and the convergence of mathematics and various biological disciplines. Further investigation into NP's potential for studying complex diseases, understanding syndrome mechanisms, and elucidating drug action mechanisms through the deep cross-fertilization of diverse information sources represents a noteworthy avenue for breakthrough research.

With the ongoing development of NP, the continuous accumulation of biological big data, and advancements in computational and experimental methods, this field is anticipated to provide increasingly reliable information for systematically understanding the interactions between diseases/syndromes and drugs. This progress is expected to offer crucial technical support for drug R&D, mechanism elucidation, drug efficacy evaluation, and precision medicine. Furthermore, it is likely to provide significant momentum for the widespread adoption and application of NP theories and technologies.

2. Application paths of NP in the R&D of new drugs of TCM

New drugs of TCM encompass innovative TCM drugs, modified new TCM drugs, and ancient classical formula TCM compound preparations. The National Medical Products Administration has issued regulations supporting the development of new TCM drugs based on ancient classical prescriptions, experienced prescriptions of renowned Chinese medicine practitioners, and TCM preparations formulated by medical institutions with extensive clinical experience. These regulations also encourage the application of emerging science and technology to study and elucidate the mechanisms of action of TCM. Network targets, a key technique in NP, play a crucial role in analyzing the overall mechanisms of action of TCM formulas. This approach elucidates the multi-component and multi-pathway regulatory effects on specific biological network targets related to diseases and syndromes. It contributes to deepening the understanding of pharmacological mechanisms, enhancing safety assessments, guiding formulation optimization, refining clinical trial design, and improving evaluation standards. By systematically analyzing the interactions between various components of the formulation and biological networks, NP reveals the multi-target and multi-pathway pharmacological mechanisms, assesses potential toxicological risks, and provides guidance for formulation optimization. Addi-

tionally, it offers a scientific basis for the design of clinical trials and helps to improve the standards and processes for evaluating hospital preparations. This approach enhances the scientific rigor and standardization of research and evaluation processes. NP aids in understanding and addressing the complexities of the chemical systems in TCM formulas and their interactions with biological systems. It provides a systematic perspective on the mechanisms of disease development and the overall therapeutic effects of TCM interventions from the viewpoint of biological network balance. This supports research into the theoretical foundations of traditional TCM preparations, accelerates the translation of clinical experience from renowned TCM practitioners, and offers robust theoretical support for the development of hospital preparations. Furthermore, it facilitates the deep integration of the industrial and innovation chains, promoting collaborative development between healthcare institutions.

2.1. Innovative drugs of TCM

Innovative TCM drugs encompass novel formulations that are not included in the *National Drug Standards*, the *Drug Registration Standards*, or the *Catalog of Ancient Classical Prescriptions* issued by the National TCM Authority. These formulations must demonstrate clinical value and should not have been previously marketed internationally. Innovative TCM drugs comprise:

Class 1.1: compound preparations formulated from multiple medicinal materials or extracts, guided by TCM theory.

Class 1.2: extracts and their preparations derived from individual plant, animal, or mineral sources.

Class 1.3: medicinal materials and their preparations, as well as novel medicinal components derived from animals or plants, which are not currently included in national or provincial drug standards.

Class 1.1 compound preparations may originate from various sources, including clinical experience formulas, medical institution preparations, modified classical formulas (excluding those in the classical formula catalog), and modern research-based scientific formulas. Clinical experience research plays a crucial role in preliminary assessments of a drug's efficacy, safety, and benefit-risk profile. The extent of clinical experience support may determine the necessity of subsequent pharmacodynamic tests and exploratory clinical trials. Comprehensive clinical experience information, encompassing prescription sources and evolution, key pharmaceutical data, clinical usage, and practice data, is instrumental in designing confirmatory clinical trials. This information aids in defining target populations, therapeutic ranges, dosages, endpoints, observation periods, follow-up nodes, and sample size parameters.

NP allows for an in-depth analysis of the complex formulations of Chinese herbal medicine by constructing multi-layered networks. These networks elucidate the multi-target modulatory effects of herbal compounds at various biological levels, from molecular interactions to systemic outcomes. By identifying key therapeutic targets and effective components, NP helps clarify the synergistic mechanisms underlying disease development and the therapeutic effects of Chinese herbal medicines. This approach is invaluable for both the pharmacological and toxicological research and evaluation of compound preparations. Furthermore, when integrated with clinical research based on human experience, NP can optimize prescription formulations through theoretical modeling and experimental verification of network targets, ultimately supporting the design of confirmatory clinical trials.

Furthermore, NP facilitates pharmaceutical research of Class 1.1, 1.2, and 1.3 innovative Chinese herbal medicine by identifying clinical efficacy components and establishing quality standards and control systems based on these identified components (Fig. 2).

2.2. Modified new drugs of TCM

Modified new drugs of TCM involve alterations to existing TCM products that enhance their clinical efficacy through changes in administration routes, dosage forms, or therapeutic functions. These modified new drugs of TCM encompass:

Class 2.1: formulations with altered administration routes.

Class 2.2: formulations with modified dosage forms.

Class 2.3: formulations with additional therapeutic functions.

Class 2.4: formulations with modified production processes or excipients that substantially affect the medicinal substance's fundamental properties or absorption characteristics.

Modified new drugs of TCM emphasize ongoing research and secondary development of marketed products, leveraging clinical advantages and product features through advancements in science and technology. NP, combined with AI, can predict drug metabolism and excretion network targets, supporting rational administration routes and dosage form development for Class 2.1 and 2.2 modified new drugs of TCM. Furthermore, drug repositioning can expand indications beyond those already marketed, aiding the development of Class 2.3 modified new drugs of TCM. NP can also construct disease network models and drug target spectra, identify potential efficacy components related to key disease network nodes, and optimize production processes and quality standards for Class 2.4 modified new drugs of TCM (Fig. 2).

2.3. Ancient classical formula TCM compound preparations

These preparations originate from ancient classical formulas. They encompass:

Class 3.1: compound preparations administered in accordance with the ancient classical formula catalog.

Class 3.2: classical formula compound preparations not regulated by the catalog and those derived from modified ancient formulas.

The development of classical formula compound preparations does not necessitate non-clinical efficacy studies or clinical trials. Instead, it involves two primary stages: establishing the "classic formula material benchmark" and developing the preparation, ensuring that key quality attributes align with those defined by the benchmark. NP, utilizing AI and big data analysis, addresses the complexity of quality attributes by analyzing the efficacy components of classical formula compound preparations, thereby supporting the selection of preparation processes and quality control indicators⁶³. Furthermore, it optimizes new effective compound prescriptions based on clinical experience and NP, enhancing the development quality of Class 3.2 classical formula new drugs. Ultimately, this approach supports the development of Class 3.1 and 3.2 classical formula TCM compound preparations (Fig. 2).

3. Application of NP in the development of new drugs of TCM

This section is structured according to the *Classification and Application Data Requirements for Traditional Chinese Medicine Registration* (No. 68, 2020) (hereafter referred to as *Requirements*). It is organized into relevant components for Module 3: pharmaceutical research, Module 4: pharmacological and toxicological research, and Module 5: clinical research.

3.1. Support for pharmaceutical research in Module 3 of TCM new drug registration

NP has the capacity to facilitate the evaluation of preparation process routes and the examination of process parameters in the preparation process materials of Module 3 of the *Requirements*.

Additionally, it can aid in the selection of quality control indicators within the research materials pertaining to formulation quality and quality standards (Fig. 3).

3.1.1. Design of preparation process

Efficacy substances (efficacy component groups) refer to the chemical components in TCM that exhibit clinical efficacy. These substances correlate the network target and complex component groups, addressing "disease-syndrome" through multi-dimensional network effects. They must reflect the characteristics of TCM composition, represent the overall efficacy intensity, and embody the specific therapeutic functions of TCM⁶⁴. Current quality standards often utilize indicators of specific ingredients, which may not fully capture the overall product quality. Consequently, targeted research should be conducted, integrating macroscopic syndromes with omics information such as genomics, transcriptomics, proteomics, metabolomics, and microbiomics. This approach aims to construct related disease-syndrome network models and drug target spectra, identify potential efficacy substances associated with key disease-syndrome network nodes, and establish methods and technical systems for analyzing TCM efficacy substances. The efficacy of TCM compounds results from the extensive regulation of biological networks (including DNA, RNA, proteins, small molecule metabolites, etc.) by their efficacy substances⁴². Therefore, evaluating the preparation process of TCM compounds using a single indicator can be limiting⁶⁵. NP aids in identifying substances related to TCM efficacy and understanding their mechanisms, which can inform extraction process design and quality standard establishment⁶⁶⁻⁶⁸. For instance, NP can predict the active components, potential targets, and mechanisms of action of Ziziphi Spinosae Decoction for insomnia. Under the Quality by Design (QbD) concept, this method facilitates the establishment of a robust design space for the extraction process, providing references for preparation process development⁶⁹.

3.1.2. Quality standard research

In recent years, TCM quality standards have evolved from single-indicator to multi-indicator controls. However, many controlled indicators remain unrelated to drug efficacy, and the overall control level of internal quality has not achieved significant breakthroughs. Furthermore, the inconsistency in raw material quality and inadequate quality control during production result in batch-to-batch variations, affecting drug efficacy and failing to meet international standards. Consequently, quality control issues represent the primary obstacle in TCM modernization and internationalization. By utilizing TCM formula-molecule-disease biological networks, key components or modules can be identified as quality control indicators to evaluate TCM clinical efficacy. This approach promotes precise quality control of TCM formulas and supports international clinical trials⁷⁰⁻⁷³.

A predictive analysis using NP was conducted on the active components and potential quality control indicators of Xiao'er Foshao Hezhong Granules for treating functional abdominal pain in children. The chemical constituents were analyzed using HPLC-Q-TOF-MS/MS technology. Active components were identified by combining results with oral bioavailability and drug-likeness screening, along with indicator components specified in the 2020 edition of the *Chinese Pharmacopoeia*. NP was then employed to predict the pharmacological basis for treating functional abdominal pain, leading to the identification of potential active components. The analysis revealed 72 active components in the formulation, with 13 identified as chemical constituents controlled by the current edition of the *Chinese Pharmacopoeia* for medicinal materials or decoction pieces. These include hesperidin from Citri Sarcodactylis Fructus (Foshou) as the chief herb; paeoniflorin from Paeoniae Radix Alba (Baishao), berberine, palmatine, cop-

tisine, and epiberberine from *Coptidis Rhizoma* (Huanglian) as minister herbs; forsythoside A and forsythoside E from *Forsythiae Fructus* (Lianqiao), and evodiamine, rutaecarpine, and limonin from *Euodiae Fructus* (Wuzhuyu) as adjuvant herbs; and glycyrrhizic acid and liquiritin from *Glycyrrhizae Radix et Rhizoma Praeparata Cum Melle* (Zhigancao) as envoy herbs. This comprehensive analysis supports the approval of Xiao'er Foshou San as a Class 1.1 TCM compound preparation and the initiation of clinical trials for treating functional abdominal pain with Qi stagnation syndrome in children. Similarly, Guizhi Fuling Capsules (originating from the *Jingui Yaolue* formula Guizhi Fuling Wan) utilized an integration of NP, computational molecular docking, and UPLC-QTOF/MS/MS techniques to identify quality control components related to efficacy. This approach elucidated the mechanisms of action for treating primary dysmenorrhea, pelvic inflammation, and uterine fibroids, addressing issues of unknown active components and quality standards that do not reflect product efficacy. Additionally, NP was employed to identify the core active components of Tianshu Capsules, enhancing quality standards and control. This led to its inclusion in the *Chinese Pharmacopoeia*, significantly improving the market competitiveness of the TCM product.

Furthermore, utilizing the network target-based intelligent and quantitative analysis system of NP, a predictive analysis was conducted on the active components and potential quality control indicators of Ji-chuan-jian Granules for treating slow-transit constipation. The analysis identified 36 active components. Of these, nine chemical constituents were recognized from medicinal materials or decoction pieces that are quality-controlled in the 2020 edition of the *Chinese Pharmacopoeia*. These include acteoside and echinacoside from the chief herb *Cistanches Herba* (Rou Cong Rong), ferulic acid from the minister herb *Angelicae Sinensis Radix* (Danggui), and β -ecdysterone from *Achyranthis Bidentatae Radix* (Niuxi). Moreover, isoferulic acid from the adjuvant herb *Cimicifugae Rhizoma* (Shengma), naringin and neo-

hesperidin from *Aurantii Fructus* (Zhiqiao), and 23-acetylalismol B and 23-acetylalismol C from *Alismatis Rhizoma* (Zexie) were also identified. This analysis supports the approval of Ji-chuan-jian Granules as a Class 3.1 traditional Chinese medicine compound preparation derived from ancient classical formulas.

3.2. Support for pharmacological and toxicological research in Module 4 of TCM new drug registration

NP technology can contribute to the pharmacological research of traditional Chinese medicine efficacy in Module 4 of the *Requirements*, as well as support toxicity research and safety evaluations in toxicology research materials.

3.2.1. Pharmacological research

Elucidating the integrated regulatory mechanisms of TCM compound efficacy substances is essential in pharmacological and efficacy research. The equilibrium between TCM efficacy component groups and disease target networks is fundamental to TCM disease treatment. Traditional pharmacological research often emphasizes single signaling pathways or pathological links, or solely differential gene changes post-intervention, lacking a comprehensive multi-component, multi-target, and multi-pathway perspective⁷⁴. NP offers a theoretical and technical framework to visualize the interaction between TCM efficacy components and disease target networks, with broad applications in studying the pharmacological mechanisms of TCM formulas, compounds, single herbs, and monomers. By integrating *in vivo* and *in vitro* experiments, this approach illuminates the relationship between the active components of TCM compounds, their molecular targets, associated biological pathways, and observed phenotypic outcomes, facilitating the understanding of their integrated regulatory mechanisms⁷⁵⁻⁷⁹. For instance, in investigating the mechanism of action of *Anchusa italica* Retz in treating cerebral ischemia-reperfusion injury, NP was employed to construct a net-

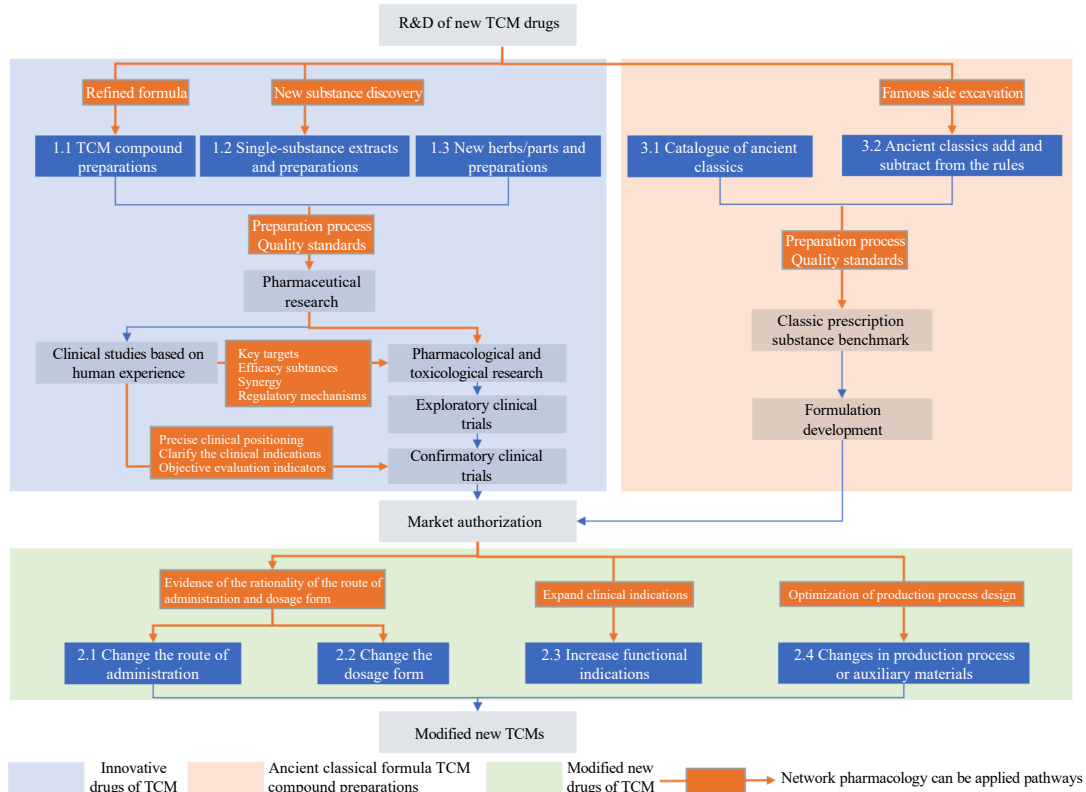


Fig. 2 Application of network pharmacology in the research and development pathway of new traditional Chinese medicine drugs.

work of cerebral ischemia-reperfusion injury and the target sites of active compounds in *Anchusa italica* Retz. The study revealed that administering *Anchusa italica* Retz significantly improved neurobehavioural dysfunction caused by cerebral ischemia-reperfusion injury and reduced brain tissue pathological damage. Furthermore, *Anchusa italica* Retz can regulate biological processes such as inflammation and apoptosis, and intervene in tumor necrosis factor, vascular endothelial growth factor, and hypoxia-inducible factor-1 signaling pathways through 143 ischemic stroke-associated targets⁸⁰. Utilizing NP research strategies, single-cell multi-omics, and target confirmation, researchers found that cycloastragenol, an active ingredient in the traditional Chinese medicine Astragali Radix, directly targets histone B to reduce MHC-I degradation on tumor cells, thereby enhancing CD8 T-cell-mediated anti-tumor immunity. This finding elucidated the scientific basis of Astragali Radix as “Strengthening the body and fighting cancer”⁸¹. Another study examining the overall mechanism of pediatric Jianpi Granules using NP found that its action may be related to regulating mast cell and Th17 cell-based immune cell activation and differentiation, inhibiting inflammation, interfering with serotonin and NO levels, improving intestinal immune and secretory environments, restoring gastric motility, alleviating gastric motility disorders and visceral hypersensitivity, and enhancing epithelial cell permeability. It also demonstrated potential stress and anxiety relief effects without significantly impacting children’s growth and organ development, contributing to its approval as a Class 1.1 Chinese medicine compound preparation. Additionally, NP methods revealed the inflammatory, immune, and antiviral modules of ReDuNing Injection for treating upper respiratory tract infections, providing insights into its mechanism of action⁸². NP has also elucidated the network regulation mechanism of Xuebijing Injection in treating systemic inflammatory response syndrome, sepsis, COVID-19 pneumonia, and other stasis-toxicity syndromes. It revealed that 24 components of Haemopigment Injection, including hydroxy saffron yellow pigment A and paeoniflorin, regulate inflammation, apoptosis, and coagulation, exerting the efficacy of “resolving stasis and detoxification”, providing crucial scientific evidence for treating critically ill patients⁸³. Furthermore, NP demonstrated how Xuanfei Baidu Decoction, through multi-component and multi-target regulation, balances immune-inflammatory responses, combats viral infections and protein transcription, and restores liver and bile metabolism and energy metabolism balance⁸⁴, supporting its approval as a Class 3.2 TCM new drug. NP also contributed to the approval of Fuzheng Jiedu Granules as a Class 3.2 an-

cient classical formula Chinese medicine compound preparation by revealing its intervention in neocoronavirus infections through modulation of four modules: immunity/inflammation, cardiovascular damage, nutrient metabolism, and energy metabolism.

3.2.2. Safety and toxicity evaluation

The intricate nature and specificity of TCM, coupled with the increasing prevalence of combined Chinese and Western medicine usage, lifestyle changes, and shifts in disease patterns, have significantly complicated the context and environment for TCM application. This complexity has led to a steep increase in safety risks, such as the irrational use of TCMs, resulting in frequent adverse reactions/events. These developments pose new challenges for scientifically understanding emerging situations and issues in TCM safety. NP can effectively elucidate the toxicity characteristics and modes of action of TCM from the perspective of TCM component-effect target interactions, revealing its influence on efficacy and toxicity⁸⁵. This approach provides technical references for constructing more scientific and effective compounding and toxicity reduction strategies and methods⁸⁶. For instance, in studying the hepatotoxicity mechanism of *Epimedium Folium*, NP was employed to construct a “hepatotoxicity–hepatotoxic components–hepatotoxic targets–hepatotoxic mechanism” network. This analysis identified icaritin as a key toxic component among various active ingredients in *Epimedium Folium*, closely related to several hepatotoxic targets. The study predicted icaritin as one of the main material bases of *Epimedium Folium*’s hepatotoxicity and found its toxicity mechanism closely related to cellular oxidative stress response and induced apoptosis, which was subsequently verified experimentally. These findings provide a reference for the safe clinical use of *Epimedium Folium*⁸⁷. Additionally, NP has been used to establish a “Chinese medicine–component–target–pathway” network, revealing the core target of Astragali Radix in intervening in the nephrotoxicity of *Tripterygium wilfordii*, thus providing a reference for its safe and rational use⁸⁸. In a study on the hepatotoxicity of *Polygonum multiflorum* Thunb components, a “toxicity–gene–target–drug” interaction network was established through NP to analyze adverse drug effects and evaluate TCM biosafety. This approach predicted potential key targets for *Polygonum multiflorum* Thunb-induced hepatotoxicity, suggesting that the toxicity mechanism may be related to oxidative stress and mitochondrial damage, potentially causing disturbances in bile acid, purine, energy, and lipid metabolism. Experimental validation confirmed dianthrone as possible components in the

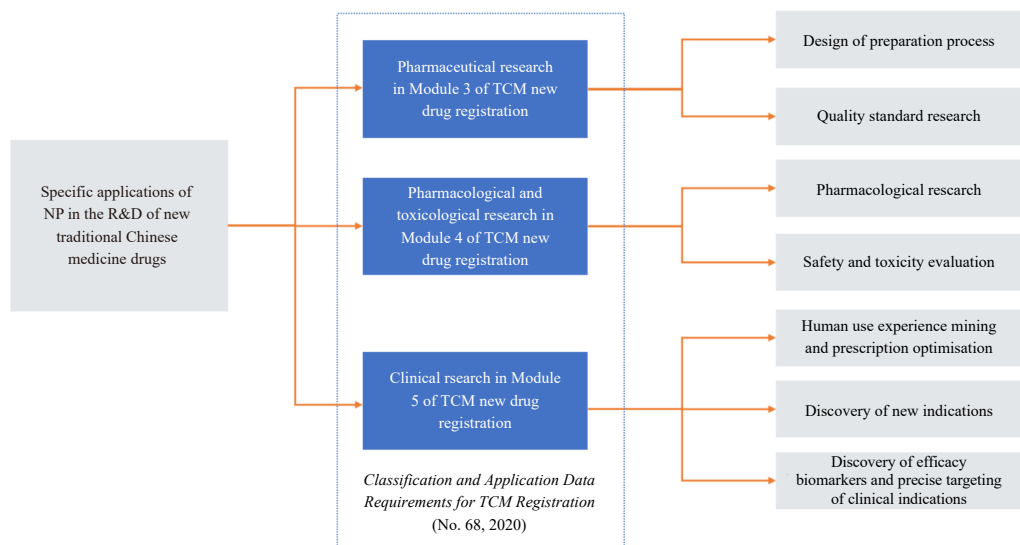


Fig. 3 Specific applications of network pharmacology in the research and development of new traditional Chinese medicine drugs.

hepatotoxicity induced by *Polygonum multiflorum* Thunb.⁸⁹. In ethnomedicine, NP has been used to explore the detoxification mechanism of *Chebulae Fructus* against *Aconiti kusnezoffii Radix* toxicity. By establishing an active ingredient–target–pathway network, it was found that *Chebulae Fructus* could regulate cardiac function to detoxify *Aconiti kusnezoffii Radix* through various biological processes and pathways⁹⁰. This approach provides insights into explaining safety and evaluating toxicity in new TCM R&D processes.

3.3. Support for clinical research in Module 5 of new TCM registration

NP can facilitate the investigation of human experiences, the development of functional indications, and the assessment of clinical value within the clinical research materials of Module 5 in the *Requirements*.

3.3.1. Human use experience mining and prescription optimization

The clinical experience of Chinese medicine practitioners is derived from a specific formula originating in clinical practice, combined with classical knowledge, repeatedly validated, and aligned with the inherent principles of Chinese medicine for disease prevention and control. This approach, formed according to Chinese medicine theories of identification and treatment, offers significant advantages in clinical application⁹¹. However, evaluating the efficacy of Chinese medicines from a holistic perspective and analyzing the intrinsic connection between formulas and symptoms remains a challenge in clinical research of Chinese medicine. NP effectively utilizes patient clinical big data and the expertise of renowned TCM practitioners. It elucidates the intervention effect of TCM on disease networks through the “disease–gene–target–drug” interaction network system and infers the causal relationship between TCM targets and efficacy by analyzing the regulatory effects of multi-target TCM modules at the network level. Furthermore, it explores the internal relationships and patterns between TCM formula compatibility and associated syndromes^{92, 93}, bridging theory, method, formula, and medicine. This approach not only enriches the fundamental theories of Chinese medicine and fosters innovative academic ideas⁹⁴, but also facilitates the integration of modern scientific techniques with human experience, offering new perspectives for the inheritance of renowned practitioners’ expertise and the precise development of TCM^{95, 96}. For instance, NP was employed to target a specific biological network of rheumatoid arthritis, leading to the precise optimization of the renowned Qingluo Decoction. This resulted in a modified Qingluo Decoction that targets angiogenesis in rheumatoid arthritis. Clinical studies have demonstrated that this modified formula improves clinical efficacy and enhances precise clinical positioning^{96, 97}. Another example involves the use of NP to discover a novel Liuwei Dihuang Formula (LW-AFC), composed of active ingredients from Liuwei Dihuang Wan (LWDH). This formula has shown potential in improving behavior and reducing pathological damage in Alzheimer’s disease model mice by regulating, restoring, and maintaining the neuroendocrine-immune regulatory network balance. These findings suggest that LW-AFC has potential clinical value for preventing and treating Alzheimer’s disease while also demonstrating the efficacy of NP in prescription optimization⁹⁸. By analyzing the pathological mechanism of chronic heart failure from a TCM perspective, a treatment principle of warming Yang and supplementing Qi, activating blood and eliminating stasis, dissolving phlegm, and promoting urination was identified. Formulae that reverse the dysregulated signaling pathway network of chronic heart failure were calculated through targeted transcriptome and pathway enrichment. Heihuang Chizhu Yin (HCY) was selected for anti-chronic heart failure based on expert experience and modifica-

tion of the calculated formulae. HCY can reverse more than 90% of the dysregulated pathways in chronic heart failure patients. This research aims to provide a novel approach to the development of innovative Chinese herbal medicine⁹⁹.

3.3.2. Discovery of new indications

Systems biology posits that health is founded on the equilibrium of biological networks, while disease stems from their imbalance. Drug therapy aims to restore this balance or mitigate its disruption. In treating complex diseases, drugs often modulate the entire “disease-causing network” rather than targeting a single gene, thus influencing the disease phenotype. NP can mechanistically link the clinical phenotypes of drugs and diseases, elucidating the biological network regulation mechanisms of Chinese medicines. This is achieved by analyzing the target spectrum of compounds in Chinese medicines, potential disease pathways, and the synergistic relationships of biological processes, providing a scientific basis for the clinical precision positioning of Chinese medicines and the discovery of new indications¹⁰⁰. For instance, NP was employed to uncover clinical evidence supporting the use of heat-clearing herbal medicines for coronavirus infections, which was subsequently included in WHO’s Clinical Management of COVID-19^{101, 102}. By constructing a cellular-molecular network related to immunoregulation of coronavirus infection, the efficacy and mechanism of ReDuNing Injection, a heat-clearing and detoxifying TCM, against the novel coronavirus were discovered. This research was incorporated into the *Coronavirus Disease-19 Prevention and Control-Consensus Diagnosis and Treatment of Coronavirus Disease-19* by the National Health Commission, providing a crucial scientific basis for the upgraded R&D of the TCM and its clinical application^{103, 104}. Another example involves the use of NP to discover that the core efficacy components of the compound Kushen Injection, such as picloram, oxidized picloram, sophoridine, and oxidized sophoridine, exhibit the “clearing heat and draining dampness” efficacy mechanism by interfering with oxidative stress, immune-inflammatory response, and other modules mediated by IL-1 β , MDM2, and related factors. This research led to the identification of the compound Kushen Injection as a potential treatment for radiological lung injury, refining its clinical positioning and providing a key scientific basis for its new indications to be declared for registration by the U.S. FDA. Additionally, NP research technology was utilized to elucidate the potential molecular mechanism of Ejiao compound for tumor treatment from a “multi-component, multi-target” perspective. The study revealed that Ejiao compound can directly regulate the differentiation, growth, proliferation, and apoptosis of cancer cells, exhibiting certain anti-tumor effects. Simultaneously, it can indirectly enhance the anti-tumor effect by tonifying the blood and improving immunity¹⁰⁵. These findings contributed to its approval as a new drug of Class 2.3 improved traditional Chinese medicine.

3.3.3. Discovery of efficacy biomarkers and precise targeting of clinical indications

Revealing the association mechanism between Chinese medicine and symptoms while promoting the precision of TCM diagnosis and treatment, is a critical challenge in improving TCM’s clinical efficacy. NP combines complex biological network analysis with artificial intelligence and multi-omics detection to intelligently analyze multimodal features related to symptoms. This approach quantitatively couples macro-phenotypic features of symptoms with microscopic information, such as cellular and molecular data, systematically elucidating the biological networks underlying symptoms. Consequently, NP can identify objective indicators for disease risk characterization¹⁰⁶, biomarkers for precise symptom diagnosis and treatment¹⁰⁷⁻¹¹¹, and establish a precise inference system for TCM prescriptions that in-

tegrates macroscopic and microscopic information. These advancements significantly enhance the clinical diagnosis and treatment capabilities of Chinese medicine for various illnesses and diseases¹¹².

Regarding efficacy biomarker discovery, NP methods have yielded significant insights. For instance, studies on Guizhi Fuling Capsule revealed its mechanism in alleviating primary dysmenorrhoea through regulation of intracellular calcium ion influx, interference with cyclooxygenase-2 (COX2) for anti-inflammatory and analgesic effects, and modulation of intrauterine circulation *via* endocrine hormone and microcirculation interference. The research identified a combination of efficacy biomarkers, including thromboxane B2 (TXB2), 6-Keto-PGF1 α , COX2, NO, ET-1, and intracellular calcium ions. Experimental data demonstrated that Guizhi Fuling Capsule significantly reduced plasma TXB2 and TXB2/6-Keto-PGF1 α ratio, elevated NO expression in uterine tissues, lowered ET-1 levels, and inhibited COX2 enzyme activity and intracellular calcium ions in uterine smooth muscle cells⁶⁴. Another notable application is the development of a Chinese and Western medicine precision prevention and treatment system for exceedingly early-stage gastric cancer. This innovative system incorporates intelligent early warning, extremely-early diagnosis, and precise prevention and treatment strategies. It introduces a novel staging system for exceedingly early-stage gastric cancer, characterizing the critical state of cancerous transformation. The system analyzes Chinese and Western clinical data from over 500 000 cases of gastritis cancer transformation, along with multi-histological data from typical sequential cases. It pioneered the construction of a multilevel biological network integrating Chinese and Western phenotype, cell, molecule, and medication data for gastritis cancer transformation. Through comprehensive analysis of this network, researchers identified “exceedingly early-stage gastric cancer cells” and achieved high-precision prediction and extremely-early stage diagnosis of gastric cancer¹⁰⁷. The system also uncovered Chinese and Western medicine features related to gastric cancer risk warning, enabling intelligent warning capabilities. Additionally, it identified traditional Chinese medicines targeting the exceedingly early-stage gastric cancer network, addressing a critical gap in extremely early prevention and treatment of gastric cancer. This system, developed by Shao Li’s group, has been implemented in numerous gastric cancer-prone areas and hospitals across China. The researchers propose that the “exceedingly early stage” may be a common phase in the development of various tumors, particularly gastrointestinal tumors. They suggest that the construction of such integrated Chinese and Western medicine systems for the prevention and treatment of exceedingly early-stage cancer represents a significant direction in clinical precision oncology research, warranting further investigation¹¹³. The National Natural Science Foundation of China (NSFC) has recognized this system as an example of a “paradigm shift in science” in its “case of concentration of scientific problems”¹¹⁴, indicating the broad potential of NP in enhancing TCM prevention and treatment strategies for tumors and other major diseases.

Regarding the precise targeting of clinical indications, NP has demonstrated significant advancements. For instance, in addressing the increasing prevalence of wind-heat and dryness type colds, which are challenging to treat due to limited therapeutic options, Academician Wang’s experiential formula for treating colds—Yinqiao Qingre Tablets—has been elucidated through NP. By constructing a biological network related to innate immunoregulation and adaptive immune response in wind-heat and dryness syndrome of colds, researchers have clarified the optimal clinical indications of this drug. Consequently, it has become the first Class 1.1 Chinese medicine new drug approved since the implementation of the new classification of registered TCM in 2020¹⁰⁴. Furthermore, NP has revealed the mechanism and clin-

ical indications of Yiqi Tongjiao Formula for treating seasonal allergic rhinitis, making it the first new Chinese medicine approved for this condition¹¹⁵. Another notable example is the study of Naoxingqing Tablets using NP. By constructing a biological molecular network for vascular stasis syndrome in ischemic stroke, researchers found that Naoxingqing could regulate oxidative stress and post-ischemic inflammation by modulating the secretion of cytokines, chemokines, and other potentially cytotoxic molecules by glial cells. Additionally, it demonstrated the ability to regulate T-cells to some extent, which could protect the cerebral vascular system and exhibit anti-inflammatory, anti-oxidative, and anti-ischemia/reperfusion injury effects, thus indicating potential therapeutic benefits in treating ischemic stroke. These findings provide a scientific basis for precisely identifying efficacy substances and positioning clinical indications, supporting the approval notification for the drug’s clinical trials.

4. Conclusion

The complexity of Chinese medicine research presents a significant challenge for the R&D of new Chinese medicinal products. Additionally, the scientific and objective evaluation of the effectiveness and safety of novel technologies and products in Chinese medicine has become a regulatory challenge. The holistic approach to clinical diagnosis and treatment in Chinese medicine has not only highlighted the limitations of reductionist medical research models but also fostered a new generation of research paradigms centered on biological networks and systems biology. These emerging approaches play a crucial role in the origin and development of NP. In recent years, the rapid advancements in artificial intelligence and machine learning have provided substantial support for the safe and effective R&D of medical products, becoming a significant focus in international drug and device regulation^{116, 117}. Encouraged by national policies promoting innovative development in Chinese medicine, a “Three Combinations” registration and review system has been established in accordance with Chinese medicine R&D principles. However, new methodologies and tools that fully integrate the characteristics of Chinese medicine to promote safe and effective R&D of new Chinese medicines have not yet been clearly incorporated into the regulatory framework. NP, by leveraging AI/ML technologies, can facilitate a more comprehensive and in-depth understanding of the complex effects of Chinese medicines, thereby accelerating the R&D process for new Chinese medicinal products.

NP has entered a crucial strategic period for innovative research in Chinese medicine within the information age. It demonstrates an advanced interplay between computation, fundamental biological experiments, and clinical trials, offering a viable approach to comprehensively analyze TCM evidence and efficacy mechanisms from extensive clinical and experimental data. Concurrently, the development of NP has witnessed the emergence of various Chinese medicine research models and AI algorithms based on network analysis. These methods have evolved from single-layer to multi-layer networks, integrating artificial intelligence, big data, and cutting-edge biological technologies such as neural networks, deep learning, and single-cell sequencing. This integration can further advance the modernization and internationalization of TCM, enhance the scientific interpretation of TCM principles, and facilitate new medicine R&D in TCM. As network target computational analysis methods deepen alongside basic biological experiments and clinical trials, NP based on network target theory continues to innovate and develop across the “industry-academia-research-application” spectrum, particularly with increasing applications in new Chinese medicine R&D. However, challenges persist, including the enhancement and innovation of prediction or analysis algorithms, understanding the relationship between TCM constituents and targets, deconstruct-

ing target networks, quantitatively analyzing nonlinear network changes and their relationship with efficacy, among other key scientific issues¹¹⁸. Nevertheless, with advancements in artificial intelligence and multimodal multi-omics technology, network targeting theory and technology have achieved the construction and in-depth analysis of Chinese and Western medicine phenotype-tissue-cell-molecule-medicines multilevel networks. These advancements have facilitated experimental validation at clinical, animal, cellular, and molecular levels, as well as high-throughput experimental verification, such as multi-component synergistic effect detection, and Chinese herbal medicine ingredient action profiling and targeting detection from a multimodal multi-omics perspective. The emergence of multimodal and multi-omics technologies in the past decade has provided an opportunity for TCM to accumulate massive, high-dimensional data at macro and micro levels. Network targeting integrated with artificial intelligence technology compensates for the lack of correlation between these data, analyzing the network regulation mechanism of TCM formulas to intervene in illnesses and diseases from a systemic viewpoint. Starting from the network regulation mechanism of prescription intervention, network targeting theory and technology enable the identification of key targets and efficacy substances, as well as the analysis of synergistic effects and regulation mechanisms of prescription components. As a novel theory, method, and tool, NP based on network target theory presents unlimited prospects for new Chinese medicine R&D, encompassing both opportunities and challenges. This Consensus Circular consolidates the expertise of domestic experts and scholars in NP and TCM, aiming to guide high-quality development of new drug R&D in TCM domestically and internationally, to achieve more rapid and substantial breakthroughs, and to continue promoting the inheritance, innovation, and development of TCM.

Consensus Project Leader: Shao Li (Tsinghua University).

Consensus Project General Counsellor: Wei Xiao (State Key Laboratory on Technologies for Chinese Medicine Pharmaceutical Process Control and Intelligent Manufacture)

Consensus Project Counsellor: Jinzhou Tian (Dongzhimen Hospital of Beijing University of Chinese Medicine), Shilin Chen (Chengdu University of TCM).

Consensus Authors (sort by first letter of surname): Liang Cao (State Key Laboratory on Technologies for Chinese Medicine Pharmaceutical Process Control and Intelligent Manufacture), Pan Chen (Nanjing University of Chinese Medicine), Qi Chen (Tsinghua University), Xu Chen (Tsinghua University), Yuanjia Hu (University of Macau), Jun Kang (Tianjin University), Ming Niu (Chinese PLA General Hospital), Deyang Sun (Tsinghua University), Li Tao (Yangzhou University), Xin Wang (Tsinghua University), Peng Zeng (University of South China), Bo Zhang (Tsinghua University), Peng Zhang (Tsinghua University), Pengfei Zhang (Tianjin Drug and Cosmetics Evaluation and Inspection Center).

Expert Participation in Consensus (sort by first letter of surname): Gang Bai (Nankai University), Yuefeng Bi (Zhengzhou University), Qian Cai (Liaoning University of Traditional Chinese Medicine), Gang Chen (Hubei University of Chinese Medicine), Huanwen Chen (Jiangxi University of Chinese Medicine), Lanying Chen (Jiangxi University of Chinese Medicine), Wansheng Chen (Shanghai University of Traditional Chinese Medicine), Haibo Cheng (Nanjing University of Chinese Medicine), Lufeng Cheng (Xinjiang Medical University), Xiaorui Cheng (Shandong University of Traditional Chinese Medicine), Jianye Dai (Lanzhou University), Jun Ding (Tianjin Drug and Cosmetics Evaluation and Inspection Center), Guanhua Du (Institute of Materia Medica, Chinese Academy of Medical Sciences & Peking Union Medical College), Qingfeng Du (Southern Medical University), Xiaohui Fan (Zhejiang University), Yue Gao (Beijing Institute of Radiation

Medicine), Hongwei Guo (Guangxi Medical University), Jiao Guo (Guangdong Pharmaceutical University), Erwei Hao (Guangxi University of Chinese Medicine), Wenbin He (Shanxi University of Chinese Medicine), Jingqing Hu (China Science and Technology Development Center for Chinese Medicine), Hua Hua (Sichuan Institute for Translational Chinese Medicine), Haixue Kuang (Heilongjiang University of Chinese Medicine), Jiansheng Li (Henan University of Chinese Medicine), Ping Li (China Pharmaceutical University), Xuejun Li (Peking University Health Science Center), Yubo Li (Tianjin University of Traditional Chinese Medicine), Zhe Lin (Changchun University of Chinese Medicine), Baoyan Liu (China Academy of Chinese Medical Sciences), Guilin Liu (Tianjin Drug Administration), Jianxun Liu (Xiyuan Hospital of CACMS), Liren Liu (Tianjin Medical University Cancer Institute), Yao Lu (Beijing University of Chinese Medicine), Shuangcheng Ma (Chinese Pharmacopoeia Commission), Hudan Pan (Guangdong Provincial Hospital of Traditional Chinese Medicine), Peng Cheng (Chengdu University of TCM), Dongzhu Renqing (Qinghai University), Si Lafu-Aibai (Xinjiang Institute of Traditional Uyghur Medicine), Weiwei Su (Sun Yat-sen University), Xiaobo Sun (Institute of Medicinal Plant Development), Yang Sun (Nanjing University), Jianyuan Tang (Hospital of Chengdu University of TCM), Li Tang (Minzu University of China), Zhishu Tang (Beijing University of Chinese Medicine), Qing Tian (Huazhong University of Science and Technology), Jiabo Wang (Capital Medical University), Tianfang Wang (Beijing University of Chinese Medicine), Wei Wang (Guangzhou University of Chinese Medicine), Xijun Wang (Heilongjiang University of Chinese Medicine), Yuhong Wang (Hunan University of Chinese Medicine), Zhibin Wang (Beijing Zhongyan Tongrentang Pharmaceutical R&D Co., Ltd.), Feng Wei (National Institutes for Food and Drug Control), Xu Wei (Wangjing Hospital of CACMS), Chengping Wen (Zhejiang Chinese Medical University), Jiarui Wu (Beijing University of Chinese Medicine), Rongwu Xiang (Shenyang Pharmaceutical University), Yaozu Xiang (Tongji University), Weilie Xiao (Yunnan University), Xiaohe Xiao (Chinese PLA General Hospital), Fan Xu (Anhui University of Chinese Medicine), Haiyu Xu (China Academy of Chinese Medical Sciences), Dong Yan (Tianjin Drug Administration), Hua Yang (China Pharmaceutical University), Minghui Yang (Chinese PLA General Hospital), Min Ye (Peking University), Wencai Ye (Jinan University), Jiangyong Yu (National Medical Products Administration), Bing Zhang (Beijing University of Chinese Medicine), Dejun Zhang (Qinghai University), Junhua Zhang (Tianjin University of Traditional Chinese Medicine), Qianru Zhang (Zunyi Medical University), Shengxi Zhang (Tianjin Drug Administration), Weidong Zhang (Naval Medical University), Xin Zhang (Tianjin Drug Administration), Yixin Zhang (Hebei University of Chinese Medicine), Hongjia Zhao (Fujian University of Traditional Chinese Medicine), Xiaoping Zhao (Zhejiang Chinese Medical University), Yanling Zhao (Chinese PLA General Hospital), Xuezhong Zhou (Beijing Jiaotong University).

This article was published in Chinese in *Chin J Chin Mater Med.* 2024;49(18):5055-5068. DOI:10.19540/j.cnki.cjcm.20240818.701.

Funding

This research was supported by the National Medical Products Administration Commissioned Research Project (No. 20211440216), the National Administration of Traditional Chinese Medicine Science and Technology Project (No. GZY-KJS-2024-03), the State Key Laboratory of Drug Regulatory Science Project (No. 2023SKLDRS0104), the Basic Research Program Natural Science Fund-Frontier Leading Technology Basic Research Special Project of Jiangsu Province (No. BK20232014), the Programs Foundation for Leading Talents in National Administra-

tion of Traditional Chinese Medicine of China “Qihuang scholars” Project, and the Tianjin Administration for Market Regulation Science and Technology Key Projects (No. 2022-W35).

Declaration of competing interest

The authors declare no conflicts of interest.

References

- The Central People's Government of China. Opinions of the Central Committee of the CPC and the State Council on Promoting the Development of Traditional Chinese Medicine Inheritance and Innovation. (2019-10-02) [2024-07-01]. <https://www.gov.cn/gongbao/content/2019/content5449644.htm>.
- General Office of the State Council. Several Policy Measures on Accelerating the Characteristic Development of Chinese Medicine. General Office of the State Council (Guo Ban Fa [2021] No. 3). (2021-01-22)[2024-07-01]. https://www.gov.cn/gongbao/content/2021/content_5588816.htm.
- Xinhua News Agency. The Central Committee of the Communist Party of China and the State Council have issued the “Healthy China 2030” Plan Outline. *State Council Bulletin of China*. 2016;32:5-20.
- The Standing Committee of the National People's Congress. *Traditional Chinese Medicine Law of China*. Beijing: China Traditional Chinese Medicine Press, 2017.
- National Medical Products Administration. Implementing Opinions on Promoting the Development of Traditional Chinese Medicine Inheritance and Innovation. (2020-12-25) [2024-07-01]. <https://www.nmpa.gov.cn/directory/web/nmpa/xxgk/gfwj/gzjw/gzwyyp/20201225163906151.html>.
- National Medical Products Administration. National Plan for Drug Safety and Promotion of Quality Development in the 14th Five-Year Plan. (2021-12-30) [2024-07-01]. <https://www.nmpa.gov.cn/directory/web/nmpa/zwgk/ghcw/ghjh/20211230192314164.html>.
- National Medical Products Administration. Several Measures on Further Strengthening the Scientific Supervision of Traditional Chinese Medicine and Promoting the Development of Traditional Chinese Medicine Inheritance and Innovation. (2023-01-04) [2024-07-01]. <https://www.nmpa.gov.cn/xxgk/gfwj/gzjw/gzwyyp/20230103172324162.html>.
- National Medical Products Administration. Special Provisions on the Administration of Registration of Chinese Medicines. (2023-02-10) [2024-07-01]. <https://www.nmpa.gov.cn/xxgk/gfwj/szhgfwj/20230210173401120.html>.
- Chen P, Wu BW, Zhang P, et al. Biological network-based exploration of the principles of traditional Chinese medicine. *Chin Sci Bull*. 2024;69(1):17-29. <https://doi.org/10.1016/j.scib.2023.11.054>.
- Tang JN, Sun Y. Application of computational biology in pharmaceutical research. *Acta Pharm Sin*. 2024;59(8):2192-2198. <https://doi.org/10.16438/j.0513-4870.2023.1256>.
- Hopkins AL. Network pharmacology: the next paradigm in drug discovery. *Nat Chem Biol*. 2008;4(11):682-690. <https://doi.org/10.1038/nchembio.118>.
- Han L, Cheng XR, Bo XC, et al. New situation and new strategy: network pharmacology and research and development of new drugs of traditional Chinese medicine. *Chin J Pharmacol Toxicol*. 2018;32(11):827-828. <https://doi.org/10.3867/j.issn.1000-3002.2018.11.001>.
- Li S, Zhang B. Traditional Chinese medicine network pharmacology: theory, methodology and application. *Chin J Nat Med*. 2013;11(2):110-120. [https://doi.org/10.1016/S1875-5364\(13\)60037-0](https://doi.org/10.1016/S1875-5364(13)60037-0).
- Lai X, Wang X, Hu Y, et al. Editorial: network pharmacology and traditional medicine. *Front Pharmacol*. 2020;11:1194. <https://doi.org/10.3389/fphar.2020.01194>.
- Zhang P, Zhang DF, Zhou W, et al. Network pharmacology: towards the artificial intelligence-based precision traditional Chinese medicine. *Brief Bioinform*. 2024;25(1):bbad518. <https://doi.org/10.1093/bib/bbad518>.
- Han L, Zhou WX. Artificial intelligence accelerates network pharmacology. *Chin J Pharmacol Toxicol*. 2023;37(S1):2-3.
- Li S. *Possible Association Between Chinese Medicine Evidence and Molecular Network Regulation. Scientific and Technological Progress and Socio-Economic Development for the 21st Century* (Upper Volume), Beijing: China Science and Technology Press, 1999:442.
- Li S, Wang YY, Ji L, et al. A discussion and case study of complexities in traditional Chinese medicine. *J Syst Simul*. 2002;11:1429-1431. <https://doi.org/10.16182/j.cnki.joss.2002.11.007>.
- Li S, Wu L, Zhang Z. Constructing biological networks through combined literature mining and microarray analysis: a LMMMA approach. *Bioinformatics*. 2006;22(17):2143-2150. <https://doi.org/10.1093/bioinformatics/btl363>.
- Li S. Computational systems biology-based TCM research: a case study of cold/hot zheng and associated formula. *Modern Tradit Chin Med Mater Med World Sci Technol*. 2007;9(1):105-111.
- Li S, Zhang ZQ, Wu LJ, et al. Understanding ZHENG in traditional Chinese medicine in the context of neuro-endocrine-immune network. *IET Syst Biol*. 2007; 1(1):51-60. <https://doi.org/10.1049/iet-syb:20060032>.
- Hopkins AL. Network pharmacology. *Nat Biotechnol*. 2007;25(10):1110-1111. <https://doi.org/10.1038/nbt1007-1110>.
- Li S. Concept and research on biological molecular network markers of traditional Chinese medicine syndrome. *J Tradit Chin Med*. 2009;50(9):773-776. <https://doi.org/10.13288/j.11-2166/r.2009.09.002>.
- Li S. Network target: a starting point for traditional Chinese medicine network pharmacology. *Chin J Chin Mater Med*. 2011;36(15):2017-2020. <https://doi.org/10.4268/cjcm20111502>.
- Liu AL, Du GH. Network pharmacology: new guidelines for drug discovery. *Acta Pharm Sin*. 2010;45(12):1472-1477. <https://doi.org/10.16438/j.0513-4870.2010.12.010>.
- Barabási AL, Gulbahce N, Loscalzo J. Network medicine: a network-based approach to human disease. *Nat Rev Genet*. 2011;12(1):56-68. <https://doi.org/10.1038/nrg2918>.
- Xiao W, Cao L, Fan QR, et al. Action mechanism studies of Guizhi Fuling Capsule: based on a bio-network analysis. *Comput Appl Chem*. 2012;29(12):1455-1459. <https://doi.org/10.16866/j.com.app.chem.2012.12.011>.
- Zhang XZ, Xiao W, Xu XX, et al. Study on mechanism of the Reduning Injection on the influenza virus using network pharmacology method. *Acta Phys Chim Sin*. 2013;29(7):1415-1420.
- Zhou WX, Cheng XR, Zhang YX. Network pharmacology: a new philosophy for understanding of drug action and discovery of new drugs. *Chin J Pharmacol Toxicol*. 2012;26(1):4-9. <https://doi.org/10.3867/j.issn.1000-3002.2012.01.002>.
- Liu ZH, Sun XB. Network pharmacology: new opportunity for the modernization of traditional Chinese medicine. *Acta Pharm Sin*. 2012;47(6):696-703. <https://doi.org/10.16438/j.0513-4870.2012.06.001>.
- Zhang BL, Fan XH, Liu Y, et al. Strategy and core technologies for the secondary development of Chinese patent medicine. *Chin J Chin Mater Med*. 2013;38(22):3797-3800. <https://doi.org/10.4268/cjcm20132201>.
- Harrold JM, Ramanathan M, Mager DE. Network-based approaches in drug discovery and early development. *Clin Pharmacol Ther*. 2013;94(6):651-658. <https://doi.org/10.1038/clpt.2013.176>.
- Ding W, Gu J, Cao L, et al. Traditional Chinese herbs as chemical resource library for drug discovery of anti-infective and anti-inflammatory. *J Ethnopharmacol*. 2014;155(1):589-598. <https://doi.org/10.1016/j.jep.2014.05.066>.
- Xiao W, Wu Y, Zhao BJ, et al. Development and industrialisation of a patent Chinese medicine Sanjie ZhenTong Capsule for the treatment of endometriosis//Chinese Society of Traditional Chinese Medicine. Proceedings of the Fourth Forum on Scientific and Technological Achievements of Chinese Traditional Medicine. Jiangsu Kang Yuan Pharmaceutical Co., [201401-04 ZY-02].
- Zhang X, Gu J, Cao L, et al. Insights into the inhibition and mechanism of compounds against LPS-induced PGE2 production: a pathway network-based approach and molecular dynamics simulations. *Integr Biol (Camb)*. 2014;6(12):1162-1169. <https://doi.org/10.1039/C4IB00141A>.
- Li S. Mapping ancient remedies: applying a network approach to traditional Chinese medicine. *Science*. 2015;350(6262):S72-S74.
- Menche J, Sharma A, Kitsak M, et al. Disease networks. Uncovering disease-disease relationships through the incomplete interactome. *Science*. 2015; 347(6224):1257601. <https://doi.org/10.1126/science.1257601>.
- Boezio B, Audouze K, Ducrot P, et al. Network-based approaches in pharmacology. *Mol Inform*. 2017;36(10):48. <https://doi.org/10.1002/minf.201700048>.
- Casas AI, Hassan AA, Larsen SJ, et al. From single drug targets to synergistic network pharmacology in ischemic stroke. *Proc Natl Acad Sci U S A*. 2019;116(14):7129-7136. <https://doi.org/10.1073/pnas.1820799116>.
- Nogales C, Mamdouh ZM, List M, et al. Network pharmacology: curing causal mechanisms instead of treating symptoms. *Trends Pharmacol Sci*. 2022;43(2):136-150. <https://doi.org/10.1016/j.tips.2021.11.004>.
- DO Valle IF, Roweth HG, Malloy MW, et al. Network medicine framework shows that proximity of polyphenol targets and disease proteins predicts therapeutic effects of polyphenols. *Nat Food*. 2021;2(3):143-155. <https://doi.org/10.1038/s43016-021-00243-7>.
- Xiao W. *Decoding Traditional Chinese Medicine*. Beijing: China Traditional Chinese Medicine Press, 2022.
- Li S. Network pharmacology evaluation methodology guidance. *World Chin Med*. 2021;16(4):527-532. <https://doi.org/10.3969/j.issn.1673-7202.2021.04.001>.
- Wang Z, Wang X, Zhang DY, et al. Traditional Chinese medicine network pharmacology: development in new era under guidance of network pharmacology evaluation method guidance. *Chin J Chin Mater Med*. 2022;47(1):7-17. <https://doi.org/10.19540/j.cnki.cjcm.20210914.702>.
- Li S. Network pharmacology evaluation method guidance-draft. *World J Tradit Chin Med*. 2021;7(1):148. https://doi.org/10.4103/wjtcn.wjtcn_11_21.
- Li S. *Network Pharmacology*. Beijing: Tsinghua University Press, 2022.
- Li S. *Network Pharmacology*. Springer Press & Tsinghua University Press, ISBN-10: 9811607524.
- Xu H, Li S, Liu J, et al. Bioactive compounds from Huashi Baidu Decoction possess both antiviral and anti-inflammatory effects against COVID-19. *Proc Natl Acad Sci U S A*. 2023;120(18):e2301775120. <https://doi.org/10.1073/pnas.2301775120>.
- Theodoris CV, Xiao L, Chopra A, et al. Transfer learning enables predictions in network biology. *Nature*. 2023;618(7965):616-624. <https://doi.org/10.1038/s41586-023-06139-9>.
- Wu X, Jiang R, Zhang MQ, et al. Network-based global inference of human disease genes. *Mol Syst Biol*. 2008;4:189. <https://doi.org/10.1038/msb.2008.27>.
- Zhao S, Li S. Network-based relating pharmacological and genomic spaces for drug target identification. *PLoS One*. 2010;5(7):e11764. <https://doi.org/10.1371/journal.pone.0011764>.
- Lage K, Karlberg EO, Størling ZM, et al. A human phenome-interactome network of protein complexes implicated in genetic disorders. *Nat Biotechnol*. 2007;25(3):309-316. <https://doi.org/10.1038/nbt1295>.
- Campillos M, Kuhn M, Gavin AC, et al. Drug target identification using side-

- effect similarity. *Science*. 2008;321(5886):263-266. <https://doi.org/10.1126/science.1158140>.
- 54 Zhao JN, Huang LQ. Traditional Chinese medicine regulatory science: an emerging convergence science in development. *Bull Natl Nat Sc Found Chin*. 2024;38(3):396. <https://doi.org/10.16262/j.cnki.1000-8217.20240209.003>.
- 55 Xu HY, Zhang YQ, Liu ZM, et al. ETCM: an encyclopaedia of traditional Chinese medicine. *Nucleic Acids Res*. 2019;47(D1):D976-D982. <https://doi.org/10.1093/nar/gky987>.
- 56 Huang L, Xie D, Yu Y, et al. TCMID 2.0: a comprehensive resource for TCM. *Nucleic Acids Res*. 2018;46(D1):D1117-D1120. <https://doi.org/10.1093/nar/gkx1028>.
- 57 Wu Y, Zhang F, Yang K, et al. SymMap: an integrative database of traditional Chinese medicine enhanced by symptom mapping. *Nucleic Acids Res*. 2019;47(D1):D1110-D1117. <https://doi.org/10.1093/nar/gky1021>.
- 58 Fang YC, Huang HC, Chen HH, et al. TCMGeneDIT: a database for associated traditional Chinese medicine, gene and disease information using text mining. *BMC Complement Altern Med*. 2008;8:58. <https://doi.org/10.1186/1472-6882-8-58>.
- 59 Li X, Tang Q, Meng F, et al. INPUT: an intelligent network pharmacology platform unique for traditional Chinese medicine. *Comput Struct Biotechnol J*. 2022;20:1345-1351. <https://doi.org/10.1016/j.csbj.2022.03.006>.
- 60 Ru J, Li P, Wang J, et al. TCMSP: a database of systems pharmacology for drug discovery from herbal medicines. *J Cheminform*. 2014;6:13. <https://doi.org/10.1186/1758-2946-6-13>.
- 61 Kong X, Liu C, Zhang Z, et al. BATMAN-TCM 2.0: an enhanced integrative database for known and predicted interactions between traditional Chinese medicine ingredients and target proteins. *Nucleic Acids Res*. 2024;52(D1):D1110-D1120. <https://doi.org/10.1093/nar/gkad926>.
- 62 Zeng P, Zhou H. Thoughts on the homogenization phenomenon of key component screening for "different diseases and different prescriptions" in network pharmacology. *Chin J Exp Tradit Med Form*. 2022;28(18):177-191. <https://doi.org/10.13422/j.cnki.syxj.20221114>.
- 63 Sun XB. Strategic thinking on high-quality development of traditional Chinese medicine new drugs derived from classic prescriptions. *Chin J Pharmacol Toxicol*. 2019;33(9):662.
- 64 Xiao W, Zhang XZ, Cao L, et al. Exploration of the whole-process quality control system of traditional Chinese medicine based on efficacy components. *J Nanjing Univ Tradit Chin Med*. 2022;38(9):743-747. <https://doi.org/10.14148/j.issn.1672-0482.2022.0743>.
- 65 Hou XJ, Zeng WJ, Ding JB, et al. Optimization of the process of antioxidant functional extracts of *Lycium barbarum* based on the concept of quality by design and information entropy assignment method. *Chin Mod Tradit Chin Med*. 2022;24(9):1745. <https://doi.org/10.13313/j.issn.1673-4890.20211014004>.
- 66 Hu M, Fu J, Hu JH, et al. Analysis of the components and mechanism prediction of Xiao'er Fu Shao He Zhong Granules for the treatment of functional abdominal pain based on HPLC-Q-TOF-MS/MS and network pharmacology. *Drug Eval Res*. 2023;46(5):997-1011. <https://doi.org/10.7501/j.issn.1674-6376.2023.05.009>.
- 67 Ke ZP, Zhang XZ, Ding Y, et al. Study on the pharmacodynamic material basis and molecular mechanism of Qigui Tongfeng Tablets based on network pharmacology. *Chin J Chin Mater Med*. 2015;40(14):2837-2842. <https://doi.org/10.4268/cjcm20151428>.
- 68 Huang M, Song YM, Wang XY, et al. Optimization of the ethanol extraction process of *Ziziphus jujuba* and *Schisandra chinensis* based on network pharmacology combined with response surface methodology. *Chin J Chin Mater Med*. 2023;48(4):966-977. <https://doi.org/10.19540/j.cnki.cjcm.20220712.303>.
- 69 Hu ZJ, Zheng LL, Xu GY, et al. Study on the extraction process of Zhishi Chi Tang based on network pharmacology and quality by design concept. *Chin Herb Med*. 2022;53(7):1973-1982. <https://doi.org/10.7501/j.issn.0253-2670.2022.07.006>.
- 70 Zhang SQ, Lai XX, Wang X, et al. Deciphering the pharmacological mechanisms of Guizhi-Fuling Capsule on primary dysmenorrhea through network pharmacology. *Front Pharmacol*. 2021;12:613104. <https://doi.org/10.3389/fphar.2021.613104>.
- 71 Xiao W. Establishment and application of modern TCM efficacy-related quality standards system using Guizhi Fuling Capsules as a model. Jiangsu Province, Jiangsu Kanion Pharmaceutical Co., Ltd., Jan. 1, 2010.
- 72 Chen S, Yang X, Wei Z, et al. Establishment of an anti-inflammation-based bioassay for the quality control of the 13-component TCM formula (Lianhua Qingwen). *Pharm Biol*. 2021;59(1):537-545. <https://doi.org/10.1080/13880209.2021.1917627>.
- 73 Ye J, Li RM, Zeng HW, et al. Discovery and research advances in quality markers of Chinese materia medica based on holistic characteristics. *Chin Tradit Herb Drugs*. 2019;50(19):4529-4537. <https://doi.org/10.7501/j.issn.0253-2670.2019.19.002>.
- 74 Fan XH, Cheng YY, Zhang BL. Network pharmacology: a new strategy for the modern research of Chinese medicinal formulas. *Chin J Chin Mater Med*. 2015;40(1):1-6. <https://doi.org/10.4268/cjcm20150101>.
- 75 Tao XQ, Ke ZP, Zhang XZ, et al. Study on the mechanism of Jinzheng Oral Liquid in the intervention of COVID-19 based on network pharmacology and molecular docking technology. *Chin Herb Med*. 2020;51(9):2326-2333. <https://doi.org/10.7501/j.issn.0253-2670.2020.09.006>.
- 76 Zhang XZ, Xiao W, Xu XJ, et al. Study on the molecular mechanism of Guizhi Fuling Capsules in the treatment of dysmenorrhea, uterine fibroids, and pelvic inflammatory disease based on network pharmacology. *Chin Herb Med*. 2016;47(1):81-94. <https://doi.org/10.7501/j.issn.0253-2670.2016.01.013>.
- 77 Li N, Zhang XZ, Wang YR, et al. Study on the mechanism of Tongsai Mai Pian in the treatment of atherosclerosis based on network pharmacology. *Chin J Chin Mater Med*. 2016;41(8):66-72. <https://doi.org/10.4268/cjcm20160922>.
- 78 Zhu Y, Ouyang Z, Du H, et al. New opportunities and challenges of natural products research: when target identification meets single-cell multiomics. *Acta Pharm Sin B*. 2022;12(11):4011-4039. <https://doi.org/10.1016/j.apsb.2022.08.022>.
- 79 Huang Y, Li S. Detection of characteristic sub pathway network for angiogenesis based on the comprehensive pathway network. *BMC Bioinformatics*. 2010;11(Suppl 1):S32. <https://doi.org/10.1186/1471-2105-11-S1-S32>.
- 80 Tann WT, Hu BJ, Huang B, et al. Effect of *Anchusa italica* Retz on cerebral ischemia-reperfusion injury in rats based on disease and active compound target network. *Her Med*. 2024;43(4):535-544. <https://doi.org/10.3870/j.issn.1004-0781.2024.04.009>.
- 81 Deng G, Zhou L, Wang B, et al. Targeting cathepsin B by cycloastragenol enhances antitumor immunity of CD8 T cells via inhibiting MHC-I degradation. *J Immunother Cancer*. 2022;10(10):e004874. <https://doi.org/10.1136/jitc-2022-004874>.
- 82 Zhang X, Gu J, Cao L, et al. Network pharmacology study on the mechanism of traditional Chinese medicine for upper respiratory tract infection. *Mol Biosyst*. 2014;10(10):2517-2525. <https://doi.org/10.1039/C4MB00164H>.
- 83 Zhou W, Lai XX, Wang X, et al. Network pharmacology to explore the anti-inflammatory mechanism of Xuebijing in the treatment of sepsis. *Phytomedicine*. 2021;85:153543. <https://doi.org/10.1016/j.phymed.2021.153543>.
- 84 Wang Y, Li X, Zhang JH, et al. Study on the mechanism of Xuanfei Baidu Decoction in the treatment of COVID-19 based on network pharmacology. *Chin J Chin Mater Med*. 2020;45(10):2249-2256. <https://doi.org/10.19540/j.cnki.cjcm.20200325.401>.
- 85 Tu C, Niu M, Li C, et al. Network pharmacology oriented study reveals inflammatory state-dependent dietary supplement hepatotoxicity responses in normal and diseased rats. *Food Funct*. 2019;10(6):3477-3490. <https://doi.org/10.1039/c8fo01974f>.
- 86 Bai ZF, Wang JB, Xiao XH. Cognition innovation of toxicity of Chinese medicine and safe and precise medication. *Chin J Chin Mater Med*. 2022;47(10):2557-2564. <https://doi.org/10.19540/j.cnki.cjcm.20220211.601>.
- 87 Zhang L, Wang T, Xu ZY, et al. Potential hepatotoxic compounds and mechanisms of Epimedium Folium based on network toxicology and cell experimental validation. *Chin J Chin Mater Med*. 2021;46(10):2413-2423. <https://doi.org/10.19540/j.cnki.cjcm.20210202.401>.
- 88 Wu X, Wu DL, Wei LB, et al. Mechanism of Astragalus Radix in reducing the nephrotoxicity of *Tripterygium wilfordii* based on network toxicology combined with network pharmacology and experimental verification. *Pharmacol Clin Chin Mater Med*. 2024;40(9):83-88. <https://doi.org/10.13412/j.cnki.zyyl.20240423.009>.
- 89 Jiang HY, Gao HY, Li J, et al. Integrated spatially resolved metabolomics and network toxicology to investigate the hepatotoxicity mechanisms of component D of *Polygonum multiflorum* Thunb. *J Ethnopharmacol*. 2022;298:115630. <https://doi.org/10.1016/j.jep.2022.115630>.
- 90 Li JL, Liang H, Cai SZ, et al. Mechanism of detoxification of Chebulae Fructus against Aconitum kusnezoffii Radix toxicity based on network pharmacology. *Acta Pharm Sin*. 2018;39(10):1670-1679. <https://doi.org/10.16438/j.0513-4870.2018-0506>.
- 91 Su SB, Lu A, Li S, et al. Evidence-based ZHENG: a traditional Chinese medicine syndrome. *Evid Based Complement Alternat Med*. 2012;2012:246538. <https://doi.org/10.1155/2012/246538>.
- 92 Wei FX, Liu HL, Fan YH, et al. Overview of mathematical models applying in property theory and compatibility rules of traditional Chinese medicines. *Drug Eval Res*. 2021;44(1):205-212. <https://doi.org/10.7501/j.issn.1674-6376.2021.01.029>.
- 93 Niu M, Zhang CE, Wu SN, et al. Evaluation of the "multi-efficacy of one drug" of traditional Chinese medicines based on the biological target network: towards precision medicine. *Modern Tradit Chin Med Mater Med World Sci Technol*. 2017;19(1):44-49. <https://doi.org/10.11842/wst.2017.01.006>.
- 94 Fu Y, Fan GJ, Huang HY, et al. Thinking of research methods on inheritance of famous TCM doctors' experience based on big data. *Chin J Tradit Chin Med Pharm*. 2017;32(4):1644-1646.
- 95 Zhou W, Yang K, Zeng J, et al. FordNet: recommending traditional Chinese medicine formula via deep neural network integrating phenotype and molecule. *Pharmacol Res*. 2021;173:105752. <https://doi.org/10.1016/j.phrs.2021.105752>.
- 96 Li Y, Wang X, Yang Z, et al. A new approach for optimizing empirical prescriptions of famous physicians based on network target: taking Qingluo Decoction as an example. *Chin J Chin Mater Med*. 2022;47(19):5264-5273. <https://doi.org/10.19540/j.cnki.cjcm.20220613.704>.
- 97 Zuo J, Wang X, Liu Y, et al. Integrating network pharmacology and metabolomics study on anti-rheumatic mechanisms and antagonistic effects against methotrexate-induced toxicity of Qing-Luo-Yin. *Front Pharmacol*. 2018;9:1472. <https://doi.org/10.3389/fphar.2018.01472>.
- 98 Wang JH, Lei X, Cheng XR, et al. LW-AFC, a new formula derived from Liuwei Dihuang Decoction, ameliorates behavioral and pathological deterioration via modulating the neuroendocrine-immune system in PrP^{Sc}APPswe/PS1^{ΔE9} transgenic mice. *Alzheimer's Res Ther*. 2016;8(1):57. <https://doi.org/10.1186/s13195-016-0226-6>.
- 99 Qiao LS, Li J, Xie L, et al. The exploration of a new approach for developing innovative Chinese herbal formulae by combining targeted transcriptome, expert experience and artificial intelligence: taking the development of antichronic heart failure innovative formula as an example. *J Tradit Chin Med*. 2023;64(3):217-224. <https://doi.org/10.13288/j.11-2166/r.2023.03.001>.
- 100 Liao S, Han L, Zheng X, et al. Tanshinol borneol ester, a novel synthetic small molecule angiogenesis stimulator inspired by botanical formulations

- for angina pectoris. *Br J Pharmacol*. 2019;176(17):3143-3160. <https://doi.org/10.1111/bph.14714>.
- 101 World Health Organization. Clinical Management of COVID-19: Living Guideline. <https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2023.2>. License: CC BY-NC-SA 3.0 IGO.
- 102 Li S, Wang R, Zhang Y, et al. Symptom combinations associated with outcome and therapeutic effects in a cohort of cases with SARS. *Am J Chin Med*. 2006;34(6):937-947. <https://doi.org/10.1142/S0192415X06004417>.
- 103 Corona Virus Disease-19 Prevention and Control-Consensus Diagnosis and Treatment of Corona Virus Disease-19 (9th trial edition). *Chin Med*. 2022;17(4):481-487. <https://doi.org/10.3760/j.issn.1673-4777.2022.04.001>.
- 104 Li S, Wang BY, Cao L, et al. Research and development practice of traditional Chinese medicine based on network target theory and technology. *Chin J Chin Mater Med*. 2023;48(22):5965-5976. <https://doi.org/10.19540/j.cnki.cjcmm.20230923.701>.
- 105 Xu HY, Wang SS, Yang HJ, et al. Study on action mechanism of adjuvant therapeutic effect compound Ejiao slurry in treating cancers based on network pharmacology. *Chin J Chin Mater Med*. 2014;39(16):3148-3151. <https://doi.org/10.4268/cjcmm20141628>.
- 106 Guo Y, Nie Q, Maclean AL, et al. Multiscale modeling of inflammation-induced tumorigenesis reveals competing oncogenic and onco-protective roles for inflammation. *Cancer Res*. 2017;77(22):6429-6441. <https://doi.org/10.1158/0008-5472.CAN-17-1662>.
- 107 Zhang P, Li S. Human cross-tissue cell atlases: unprecedented resources towards systematic understanding of physiology and diseases. *Signal Transduct Target Ther*. 2022;7(1):352. <https://doi.org/10.1038/s41392-022-01201-w>.
- 108 Hou SY, Zhang P, Yang K, et al. Decoding multilevel relationships with the human tissue-cell-molecule network. *Brief Bioinform*. 2022;23(5):bbac170. <https://doi.org/10.1093/bib/bbac170>.
- 109 Zhang P, Yang M, Zhang Y, et al. Dissecting the single-cell transcriptome network underlying gastric premalignant lesions and early gastric cancer. *Cell Rep*. 2019;27(6):1934-1947. <https://doi.org/10.1016/j.celrep.2019.04.052>.
- 110 Cui J, Cui H, Yang M, et al. Tongue coating microbiome as a potential biomarker for gastritis including precancerous cascade. *Protein Cell*. 2019;10(7):496-509. <https://doi.org/10.1007/s13238-018-0596-6>.
- 111 Guo JC, Zhang P, Zhou L, et al. Prognostic and predictive value of a five-molecule panel in resected pancreatic ductal adenocarcinoma: a multicentre study. *EBioMedicine*. 2020;55:102767. <https://doi.org/10.1016/j.ebiom.2020.102767>.
- 112 Zhang YX, Cheng XR, Zhou WX. Drug repositioning: an important application of network pharmacology. *Chin J Pharmacol Toxicol*. 2012;26(6):779-786. <https://doi.org/10.3867/j.issn.1000-3002.2012.06.001>.
- 113 Zhang P, Wang B, Li S. Network-based cancer precision prevention with artificial intelligence and multi-omics. *Sci Bull (Beijing)*. 2023;68(12):1219-1222. <https://doi.org/10.1016/j.scib.2023.05.023>.
- 114 National Natural Science Foundation of China. *Condensing the Case of Scientific Problems*. Beijing: Science Press, 2023.
- 115 Wang B, Zhang D, Zhang T, et al. Uncovering the mechanisms of Yi Qi Tong Qiao Pill in the treatment of allergic rhinitis based on network target analysis. *Chin Med*. 2023;18(1):88. <https://doi.org/10.1186/s13020-023-00781-1>.
- 116 U. S. Food & Drug Administration. Good Machine Learning Practice for Medical Device Development: Guiding Principles. <https://www.fda.gov/medical-devices/software-medical-device-samd/good-machine-learning-practice-medical-device-development-guiding-principles>.
- 117 European Medicines Agency. Multidisciplinary: Artificial Intelligence (AI). <https://www.ema.europa.eu/en/human-regulatory-overview/research-and-development/scientific-guidelines/multidisciplinary-guidelines>.
- 118 Wang Z, Liu J. Network pharmacology and drug discovery for new combinations in traditional Chinese medicine. *Chin J Pharmacol Toxicol*. 2018;32(11):862-864.