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Review

TCM network pharmacology: new perspective integrating network target with artificial intelligence and multi-modal multi-omics technologies

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ABSTRACT

Traditional Chinese medicine (TCM) demonstrates distinctive advantages in disease prevention and treatment. However, analyzing its biological mechanisms through the modern medical research paradigm of "single drug, single target" presents significant challenges due to its holistic approach. Network pharmacology and its core theory of network targets connect drugs and diseases from a holistic and systematic perspective based on biological networks, overcoming the limitations of reductionist research models and showing considerable value in TCM research. Recent integration of network target computational and experimental methods with artificial intelligence (AI) and multi-modal multi-omics technologies has substantially enhanced network pharmacology methodology. The advancement in computational and experimental techniques provides complementary support for network target theory in decoding TCM principles. This review, centered on network targets, examines the progress of network target methods combined with AI in predicting disease molecular mechanisms and drug-target relationships, alongside the application of multi-modal multi-omics technologies in analyzing TCM formulae, syndromes, and toxicity. Looking forward, network target theory is expected to incorporate emerging technologies while developing novel approaches aligned with its unique characteristics, potentially leading to significant breakthroughs in TCM research and advancing scientific understanding and innovation in TCM.

1. Traditional Chinese medicine (TCM) network pharmacology and network target

TCM represents a unique medical system developed through millennia of practical experience by the Chinese nation, serving a crucial role in disease prevention and treatment in China. TCM theory articulates the intricate relationships among diseases, syndromes, and medicines from a holistic perspective. The systematic nature of TCM contrasts with the reductionist approach prevalent in modern medical research, making it challenging to elucidate the mechanisms and biological foundations of TCM. Recent advances in bioinformatics, systems biology, artificial intelligence (AI), and related fields have facilitated comprehensive analysis of TCM's scientific principles and complex composition from a network perspective. These developments have led to the emergence and rapid evolution of network target theory and TCM network pharmacology (Fig. 1).

The network target theory originated from Li's hypothesis in 1999, which proposed a connection between TCM and biomolecular networks [1]. In 2002, Li examined how TCM formulae regulate biological networks of complex diseases and syndromes through their ingredients' "multiple factors and tiny effects" mechanism. He demonstrated that TCM ingredient targets exhibit synergistic and integrated effects on disease and syndrome biological networks, propagating through these networks to achieve "emerge" therapeutic effects [2]. In 2007, Li investigated the biological basis of cold syndrome and hot syndrome and the network regulatory effects of corresponding herbs from a biological network perspective [3], and established a network-based framework for understanding TCM formulae mechanisms [4], establishing the theoretical foundation for TCM network pharmacology. Subsequently, British pharmacologist Hopkins introduced the concept of "network pharmacology", emphasizing network methods for analyzing drug-target-disease interactions [5]. Network target encompasses key molecules, pathways, and network modules in biological networks that mechanistically link drugs and diseases, quantitatively representing drugs' holistic regulation mechanisms [6,7]. Network target theory and technology transcend the limitations of the reductionist "single gene, single target"medical research model, revealing correlations between complex diseases, syndromes, and TCM formulae through detailed analysis of multi-level modular biological networks. Network pharmacology and network target theory align with TCM's holistic perspective, establishing a new research paradigm for systematic interpretation of TCM principles and innovative development [8].

In recent years, network target methodology has become essential in TCM research, with related studies increasing substantially. TCM network pharmacology demonstrates integration of computational, experimental, and clinical approaches [9]. The 2021

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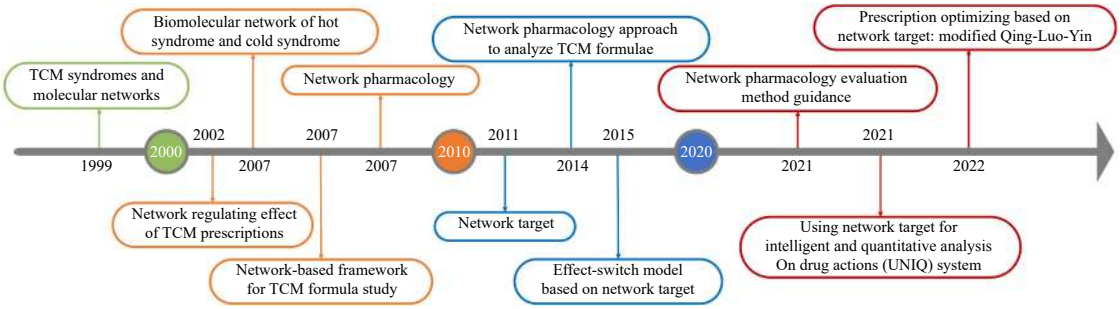

Fig. 1 Origin and development of TCM network pharmacology and network target theory.

publication of the *Network Pharmacology Evaluation Methodology Guidance* established evaluation standards for reliability, standardization, and rationality, marking a new phase of standardized development [10]. Network target methodology continues evolving through the integration of AI and multi-modal multi-omics technologies. High-throughput multi-modal data from transcriptomics, proteomics, and metabolomics, combined with advanced AI algorithms, enable analysis of multi-level biological networks of complex diseases and syndromes, precisely revealing intricate interactions among drugs, diseases, and biomolecules (Fig. 2). This comprehensive strategy enhances understanding of TCM theory while advancing precise TCM research, development, diagnosis, and treatment.

2. Representative methods and applications of network target

Since its inception, network target theory methodology has undergone continuous refinement, progressing from single-layer network analysis to comprehensive examination of multi-layer and dynamic networks, while incorporating novel computational and experimental techniques to enhance the research framework (Fig. 2). This section presents classic and representative methods and applications of network target, providing foundational knowledge for deeper understanding of the field. These studies aim to elucidate complex disease mechanisms and drug-disease regulatory relationships, demonstrating the network targeting theory's significance in understanding TCM's scientific principles and advancing its modernization.

Based on network target theory, our group has developed multiple algorithms to analyze the relationships within phenotype-tissue-cell-molecule-traditional Chinese and Western medicine multi-layer networks. We have accomplished the construction and analysis of biomolecular networks for specific phenotypes, TCM syndromes, and cell types [11], genome-wide target prediction for TCM components and Western medicines [12], gene network-based drug synergy prediction [13], drug-gene-disease co-module prediction [14], and TCM formula recommendation integrating macro and micro information [15]. These algorithms establish an efficient computational framework for analyzing the systematic mechanisms of Western medicines and TCM formulae, optimizing TCM formulae, and understanding the TCM principle of "different treatments for the same disease," which are critical issues in both traditional Chinese and Western medicine. Through emerging computational and experimental methods, our group developed a molecular-cellular-system dynamic network utilizing AI and multi-modal multi-omics integration analysis, providing a methodology for systematically understanding gastrointestinal tumor development [16]. We subsequently proposed methods based on graph convolutional neural networks and single-cell multi-omics to construct tissue-cell-molecule networks in gastric inflammation-induced tumorigenesis, establishing groundwork for mechanism resolution and biomarker discovery [17, 18]. Building upon this foundation, we developed the UNIQ (using network target for intelligent and quantitative analysis on drug actions) system by integrating high-precision prediction algorithms, network target quantitative modeling technologies, high-throughput experimental technologies, and multi-modal clinical databases of diseases and syndromes [19]. The UNIQ system enables systematic analysis of intrinsic network correlations across multi-level, multi-modal, and multi-omics data, demonstrating significant applications in TCM mechanism analysis, precision diagnosis and treatment, and innovative TCM research and development. This system shows promise as a crucial technology

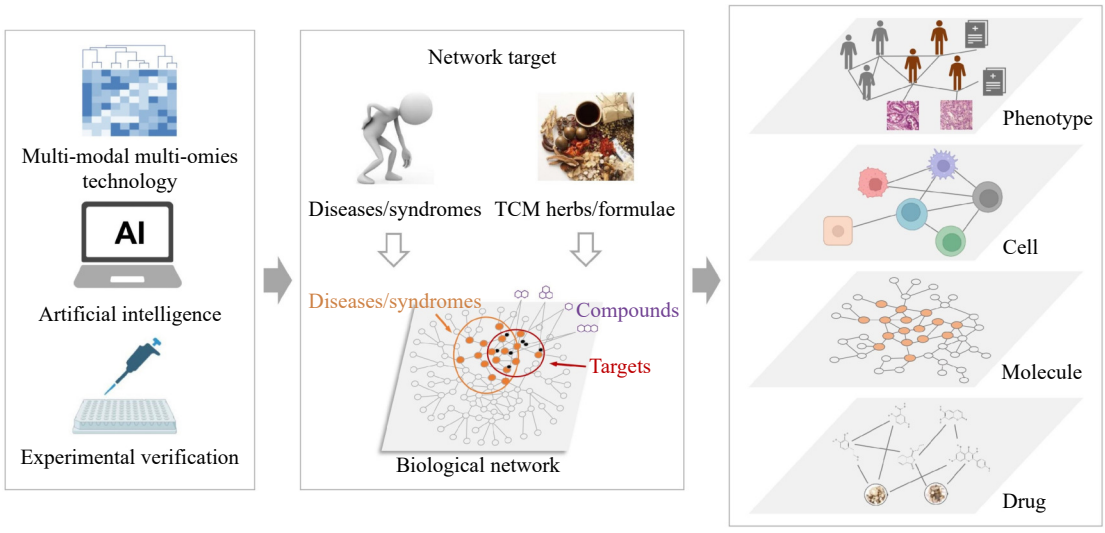

Fig. 2 Network target research framework combining multi-modal multi-omics technology, AI, and experimental verification.

platform for scientific interpretation of TCM mechanisms using AI. Additionally, researchers have investigated disease mechanisms and drug therapeutic mechanisms through topological analysis of multi-layer networks. A 2021 study constructed and analyzed a six-scale multi-layer biological network from genotype to phenotype to examine gene defect effects, utilizing disease modules to study rare disease mechanisms [20]. Ruiz et al. developed a multiscale interaction network integrating disease-perturbed proteins, drug targets, and biological functions, implementing a random walk approach to model drug effect propagation for predicting drug-treated diseases, identifying therapy-related proteins and functions, and predicting genes affecting efficacy and adverse effects [21]. Gan et al. created a network medicine framework for TCM efficacy prediction, demonstrating that TCM efficacy correlates with topological proximity of TCM targets to symptoms on protein interaction networks, validating findings with clinical data [22].

The network target theory aligns with TCM's holistic diagnosis and treatment principles and has gained widespread application in TCM research, providing robust methodological support for elucidating TCM's clinical experience through modern science and technology. Liang et al. investigated Liuwei-Dihuang Pill to explore novel TCM formula research approaches based on network pharmacology [23]. Guo et al. developed an analytical method incorporating genome-wide disease gene prediction and CRISPR-Cas9 technology to identify key molecular networks and genetic interaction modules in inflammation-induced tumorigenesis, subsequently identifying components within Liuwei-Dihuang that target metabolism-immunity and other synergistic modules to inhibit inflammatory bowel cell malignant transformation [24]. This research presents novel opportunities for understanding multiple TCM components' synergistic mechanisms. The network target theory and technology enable comprehensive analysis of network regulation mechanisms in formulae treating diseases and syndromes through multi-level biological network construction. Our group has successfully implemented network target methods combining computational and experimental approaches in studies examining TCM formulae mechanisms, including Guizhi-Fuling Capsule for primary dysmenorrhea [25], Weifuchun Capsule for chronic atrophic gastritis [26], Huashi-Baidu Decoction for COVID-19 [27], and Yiqi-Tongqiao Pill for allergic rhinitis (AR) [28].

Classical TCM formulae and renowned physicians' experiences contain valuable knowledge refined through extensive clinical practice, making it crucial to efficiently explore these experiences and establish precise TCM research methods that integrate traditional knowledge with modern technology. Using Qing-Luo-Yin, an empirical prescription for rheumatoid arthritis (RA), we explored prescription optimization approaches. Following the discovery of Qing-Luo-Yin's anti-angiogenesis effect [29] and elucidation of angiogenesis network mechanisms [30], network target methodology was employed to screen herbs targeting biological processes, including angiogenesis in RA. Incorporating expertise from renowned physicians, an optimized prescription of modified Qing-Luo-Yin was developed, demonstrating enhanced clinical efficacy and clearer mechanistic understanding [31]. This research establishes a novel method for precise TCM prescription optimization combining empirical evidence with network target theory and methodology, while providing innovative strategies for preserving and applying physician expertise in TCM research and development.

3. Network target approaches combined with AI

The integration of AI methodologies has brought new momentum to network target theory development. The proliferation of high-throughput experimental techniques and subsequent accumulation of high-dimensional data establishes a robust foundation for machine learning and deep learning applications. Through the integration and analysis of multi-level, large-scale experimental data, AI methodologies enable comprehensive analysis of multi-level biological networks in TCM. This provides novel perspectives on disease and syndrome mechanisms, systematic mechanisms of traditional Chinese and Western medicine, drug discovery, and drug repurposing (Fig. 3). This section examines TCM databases and research cases combining network target with AI (Table 1).

3.1. TCM database

TCM-related databases constitute essential data resources in network pharmacology research. The rapid evolution of network target theory and the emergence of extensive high-throughput data have accelerated database development, providing comprehensive information about syndromes, formulae, and herbs, along with their relationships to diseases, chemical components, and targets, thereby substantially supporting TCM network pharmacology advancement.

SymMap incorporates multiple types of associative information within a network, including syndromes, TCM phenotypes, phenotypes, diseases, drugs, and targets. It employs statistical methods to calculate relationships between indirectly connected data, such as syndromes and targets [32]. The SoFDA database offers detailed syndrome classifications, documenting primary and secondary symptoms, tongue and pulse characteristics, gene association information, and therapeutic formulae, providing molecular-level data support for TCM network pharmacology research [33]. TCMSSD integrates diverse TCM-related data and literature, constructs a TCM syndrome knowledge graph, and develops a syndrome prediction tool, addressing quantification and standardization limitations in existing TCM databases [34]. While most TCM databases emphasize association information centered on Chinese medicines, formulae, and components, some incorporate additional medical data, including metabolites and clinical treatment records. LTM-TCM, a comprehensive TCM platform, integrates high-quality data from 14 authoritative TCM databases and includes numerous clinical treatment records and ancient TCM texts [35]. The DCABM-TCM database focuses on blood-entry components and metabolites of Chinese medicines, systematically collecting and integrating data on blood components of TCM prescriptions and herbs to elucidate molecular mechanisms and discover bioactive compounds [36].

As experimental techniques advance and TCM-related research accumulates, several TCM databases have developed new-generation versions driven by additional data integration. HERB documents the efficacy and indications of numerous Chinese medicines, detailing corresponding targets and chemical components. The upgraded HERB 2.0, released in 2023, has refined the TCM component list and incorporated various TCM prescriptions [37]. TM-MC 2.0, expanding upon its initial version, has maximized compound information collection from Korean, Chinese, and Japanese pharmacopoeias, significantly enhancing data quantity and quality [38]. ETCM v2.0 facilitates quality control marker identification, derivative drug rediscovery, and pharmacological mechanism research. This upgrade has incorporated syndrome information and ancient TCM prescription data into the original database [39]. HIT 2.0, utilizing PubMed literature mining, acquires compound-target activity pairs, supporting TCM mechanism research and new drug development [40].

3.2. Prediction of disease/syndrome-related genes and biomarkers

The identification of disease and syndrome-related genes forms a crucial foundation for understanding disease mechan-

isms and achieving precision medicine. The integration of network target theory and AI techniques in analyzing extensive biomedical data enables the discovery of gene-disease and gene-syndrome associations, supporting the identification of diagnostic biomarkers and therapeutic targets.

KDGene, introduced by Wang et al., represents a knowledge graph completion framework for disease gene prediction. This framework achieves entity feature embedding through tensor decomposition of entities and their associations [41]. Rai et al. employed literature mining to fine-tune BERT on approximately 4.5 million PubMed abstracts describing gene-disease associations to predict previously unreported gene-disease associations [42]. While existing network-based gene prediction algorithms typically construct homogeneous networks or heterogeneous networks with customized meta-paths, the DGP-PGTN model developed by Li et al. utilizes parallel graph transformation networks to automatically learn latent disease-gene association information, including ontology and phenotype [43]. Xiang et al. introduced HyMM, which approaches prediction from a modular perspective, utilizing both local and global multiscale information for enhanced disease-gene association prediction [44]. Hou et al. constructed a comprehensive human multi-level heterogeneous biological network using neural network-based graph embedding, integrating disease phenotypes, tissues, cell types, and molecular interaction data. This method demonstrated superior performance across various tasks, including disease gene prediction, tissue-specific cell interactions, cell markers, and molecular interactions [18]. Wang et al. developed the PTsGene framework for predicting TCM syndrome-associated genes by extracting features from a heterogeneous drug-syndrome-disease-target network to rank syndrome-related gene correlations [45]. DAEMDA, introduced by Dong et al., represents a deep learning approach for micro ribonucleic acid (miRNA)-disease prediction, incorporating similarity and heterogeneity networks with parallel dual-channel feature encoders [46]. SFGAE presents an innovative miRNA-disease association prediction tool based on a self-feature graph autoencoder, addressing GNN model over-smoothing through self-feature embeddings independent of graph interactions [47].

Recent advances in large language models and foundational models have sparked interest in pre-trained models utilizing large-scale high-throughput data. Geneformer represents a pre-trained deep learning model employing self-supervised learning on approximately 30 million single-cell transcriptomes. This model enables context-specific predictions in data-limited network biology environments and enhances prediction accuracy in various downstream tasks through fine-tuning. The model has successfully identified candidate therapeutic targets in cardiomyopathy disease models, accelerating the discovery of key network regulatory factors and potential therapeutic targets [48]. Cui et al. developed scGPT, a generative pre-trained transformer model based on over 30 million cells. scGPT effectively extracts essential biological information of genes and cells, with performance optimization through transfer learning for various downstream tasks, including cell type annotation, perturbation response prediction, and gene network inference [49].

3.3. Drug discovery and drug repositioning

Network target theory emphasizes the systemic and multi-gene nature of diseases, enabling a comprehensive understanding of drug action mechanisms at the molecular level. As research increasingly focuses on identifying potential therapeutic targets within complex disease networks, network pharmacology demonstrates significant potential in drug discovery and drug repurposing.

Huang et al. created a deep transfer learning model incorporating Graph Transformer and a cross-attention mechanism for COVID-19 drug prediction [50]. Researchers explore new drug indications through drug-disease association prediction. HINGRL, developed by Zhao et al., identifies novel indications by constructing a heterogeneous drug-disease-protein interaction network and applying graph representation learning [51]. Yang et al. applied matrix decomposition theory to separate drug-disease association matrices into drug and disease features, enabling inference of unreported associations through feature extraction [52]. Xu et al. created DTIPred, a drug-target interaction prediction model integrating drug and protein features while considering topological information through a heterogeneous drug-protein-drug side effect network [53]. Wang et al. developed RDAU-Net, a deep learning model incorporating dynamic convolution and attention modules for organoid drug screening [54]. DeepMGM, a deep learning molecular generation model, utilizes LSTM to train drug-like molecules, facilitating bioactive drug molecule discovery [55].

In drug repurposing, integration of multiple drug-related features frequently yields superior prediction results. Pham et al. introduced a data augmentation method to enhance the L1000 dataset information and developed DeepCE, a model based on graph neural networks and a multi-head attention mechanism, to predict gene expression profiles under compound intervention, applying it to COVID-19 drug repurposing [56]. Malik et al. presented an omics integration strategy for predicting cancer patient survival rates and drug responses, addressing survival rate and drug response quantification [57]. Addressing antibiotic resistance, Stokes et al. developed a deep neural network method for antibacterial molecule prediction. This method screened over 107 million molecules in the ZINC15 database, identifying eight anti-

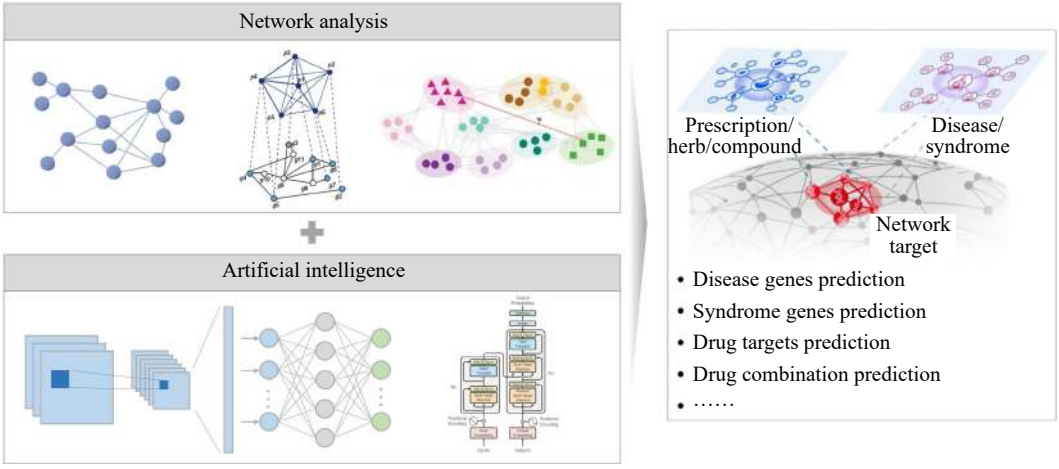

Fig. 3 Network target computing system: integrating network analysis with AI.

Table 1 Research cases of network target combined with AI.

Category	AI method	Prediction task	Ref.
Prediction of disease/ syndrome-related genes and biomarkers	Tensor decomposition	Disease genes	41
	Literature mining and BERT	Disease genes	42
	Parallel graph transformation networks	Disease genes	43
	Integrating multiscale module structure	Disease genes	44
	Multi-layer biological networks and a graph embedding algorithm	Disease genes	18
	Biological network-based framework	TCM syndrome genes	45
	Parallel dual-channel feature encoder and neural network classifier	Disease miRNAs	46
	Self-featured graphical autoencoder	Disease miRNAs	47
	Self-supervised deep learning model	Downstream tasks	48
	Generative pre-training model	Downstream tasks	49
Drug discovery and drug repositioning	Graph transformer and cross-attention	COVID-19 drugs	50
	Graph representation learning	New drug indications	51
	Matrix decomposition	New drug indications	52
	Random walk and CNN	Drug targets	53
	Convolution and attention modules	Drug screening	54
	LSTM	New drug molecules	55
	Graph neural network and multi-head attention mechanism	Drug repositioning	56
	Deep learning and multi-omics	Drug response	57
	Deep neural network	Antibacterial active molecules	58
Drug-drug interactions and drug combinations	Multi-modal inter-attentive network	Antitumor drug combinations	59
	Graph representation learning	Drug associations	60
	Tensor neural network	Drug-drug interactions	61
	Feature fusion and self-attention mechanism	Drug-drug interactions	62
	Supervised contrastive learning	Drug-drug interactions	63
	3D graph and neural network	Drug-drug interactions	64
	Representation learning	Drug-drug interactions	65
	Graph representation learning	Drug-drug interactions	66
	Multi-omics variational autoencoders	Drug-omics association	67
	Interpretable deep learning model	Drug responses and synergy	68
	Attention mechanism	Drug combination side effects	69
	Matrix factorization	Drug side effects	70

biotics and experimentally validating prediction accuracy [58].

3.4. Drug-drug interactions (DDIs) and drug combinations

Network target theory enables the analysis of interactions between multiple drugs based on biological networks, facilitating the identification of drug combinations that enhance therapeutic efficacy while minimizing adverse effects. SynergyX represents a multi-modal co-attention network developed to predict synergistic antitumor drug combinations [59]. Feng et al. modeled a signed directed network utilizing social network balance and status theories, considering pharmacological changes induced by drug interactions, and predicted drug interactions through graph representation learning [60]. Yu et al. proposed that drug interactions are determined by chemical substructures and mapped drugs into a substructure-related space to predict multi-type DDIs [61]. Lin et al. developed a method for predicting drug interactions by integrating multi-source drug fusion and multi-source feature fusion, validating their approach through case studies [62]. MDDI-SCL represents a supervised contrastive learning-based method for predicting drug interactions, achieving state-of-the-art results across three different tasks and demonstrating the effectiveness of supervised contrastive learning through ablation experiments [63]. He et al. developed a deep learning architecture comprising a 3D graph neural network and a pre-trained attention model, incorporating 3D molecular graph structure and positional information [64]. Zhang et al. developed a drug representation learning method based on a multi-modal autoencoder, capable of predicting drug interactions in large-scale, noisy, or sparse data [65]. GCN-BMP employs end-to-end graph representation learning for drug interaction prediction to mitigate noise-induced bias from drug-related features, demonstrating effectiveness on two real-world datasets [66]. Allesøe et al. developed MOVE, a deep learning model exploring drug-omics associations in type 2 diabetes patients, revealing novel connections between metformin and gut microbiota [67]. DrugCell represents an interpretable deep learning model of human cancer cells, trained on datasets of various drug interventions across different tumor cell lines, predicting therapeutic responses and elucidating biological mechanisms of drug responses [68]. In drug combination research,

understanding drug side effects remains crucial. DeepPSE presents an end-to-end deep learning method for predicting pairwise drug side effects, demonstrating model performance on large-scale multi-drug side effect benchmark datasets [69]. Galeano et al. eveloped a machine learning framework for drug risk assessment that applies matrix factorization to extract latent features of drug side effects, enabling the estimation of their frequency and providing evidence for the biological underpinnings of drug activity [70].

4. Network target approaches combined with multi-modal multi-omics technologies

Multi-modal samples from clinical cohorts, animal models, and cellular models integrated with multi-omics technologies, including transcriptomics, proteomics, and metabolomics, provide reliable experimental techniques for exploring the multi-layer phenotype-tissue-cell-molecule-traditional Chinese and Western medicine network from an integrated macroscopic and microscopic perspective. These approaches have become essential components of network target experimental methods. These omics technologies capture information at various levels, including RNA, protein, and metabolite profiles. Their integrated application enables researchers to comprehensively understand complex disease mechanisms and drug action mechanisms (Fig. 4). The following section presents recent advances in applying multi-modal multi-omics technologies to investigate therapeutic mechanisms of TCM formulae, biological bases of TCM syndromes, and toxicity mechanisms of TCM (Table 2).

4.1. Therapeutic mechanisms of TCM formulae

The integration of multi-omics technologies and network target theory has substantially advanced the understanding of TCM formulae mechanisms in treating diseases and syndromes. Multi-omics technologies reveal the intervention effects of TCM formulae across different dimensions, while network construction and analysis based on network target theory enable comprehensive and systematic analysis of pharmacodynamic substances, targets, and regulatory networks of TCM formulae in treating specific diseases. This approach assists researchers in identifying active ingredients, key targets, and mechanisms, thereby providing scientific evidence and theoretical support for TCM development and clinical application.

Lu et al. identified the targets of Xiaoyaosan in treating liver cirrhosis through dynamic network biomarker (DNB) analysis and network pharmacology based on transcriptomic data from patients with chronic liver disease, validating the results on a liver fibrosis rat model [71]. Through network pharmacology and metabolomics, Wang et al. discovered that the mechanism of Shenyan Kangfu Tablets in treating diabetic nephropathy correlates strongly with insulin resistance, identifying hexokinase 2 and maltase glucoamylase as key targets [72]. Chen et al. examined the protective mechanism of berberine against hyperlipidemia using network pharmacology and lipidomics, revealing that the key pathway of berberine's anti-hyperlipidemia effect involved glycerophospholipid and sphingolipid metabolism, while identifying the targets and metabolites regulated by berberine [73]. Liu et al. employed single-cell transcriptomics to investigate the synergistic mechanism of 11-keto-β-boswellic acid (KBA) and *Z*-guggulsterone (*Z*-GS), active components of frankincense and myrrh, on ischemic stroke, discovering that KBA and Z-GS regulated the expression of different genes and functioned in different microglia and astrocyte subtypes, with secreted phosphoprotein 1 identified as a key target [74]. Through network pharmacology and proteomics, Wang et al. investigated the potential mechanism of Biyuan Tongqiao Granule (BYTQ) in treating AR, demonstrating that BYTQ alleviated inflammatory response in AR mice by regulating the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) and STAT3/MAPK signaling pathways [75]. Yu et al. utilized a label-free quantitative proteomics approach to study the cardioprotective effects and potential mechanism of Shexiang Baoxin Pill (SBP) in myocardial infarction model rats, with network analysis revealing that SBP achieved its cardioprotective effect through preserving energy metabolism [76]. The mechanism of Dengzhan Shengmai Capsule on ischemic stroke was examined through a combination of network pharmacology with transcriptomics and metabolomics, and the key targets and active ingredients identified by network analysis were subsequently validated [77]. Zhao et al. investigated the mechanism of Bufei Yishen Formula (BYF) in treating chronic obstructive pulmonary disease (COPD) using network pharmacology combined with transcriptomics, proteomics, and metabolomics. Through proteomics analysis of COPD model rats and BYF-treated rats combined with multi-omics data and network analysis, findings indicated that BYF regulated genes, proteins, and metabolites related to lipid metabolism, inflammatory response, oxidative stress, and cell junction [78]. Research integrating network pharmacology, serum pharmacochemistry, and multi-omics analyses demonstrated that Qijiao Shengbai Capsule enhances hematopoiesis and alleviates leukopenia by suppressing inflammatory responses and modulating the leukotriene pathway. The study further identified potential active ingredients targeting the key enzyme arachidonate 5-lipoxygenase [79].

4.2. Biological bases of TCM syndromes

Syndrome represents a fundamental concept in TCM theory, encompassing a comprehensive consideration of multiple symptoms rather than a single symptom, and determines the choice and efficacy of therapy [80]. Syndromes in TCM emphasize a holistic perspective, with different syndromes often characterized by multi-dimensional biological distinctions. The network-target approach, when combined with multi-modal and multi-omics technologies, enables systematic investigation of the biological underpinnings of syndromes across multiple molecular layers, including RNA, proteins, and metabolites, thereby advancing the scientific basis of TCM syndrome differentiation and informing strategies for treating the same disease with different therapeutic approaches.

A network pharmacology strategy combining computational, clinical, and experimental approaches was employed to explore the biological basis of spleen qi deficiency (SQD) syndrome. Transcriptional profiles from patients with SQD indicated that SQD was closely associated with deficient immune response, while experiments verified that spleen qi reinforcing herb ingredients stimulated the proliferation of macrophages and lymphocytes [81]. Wang et al. utilized network pharmacology combined with metabolomics to analyze the biological mechanism of four typical cold property herbs in treating hyperthyroidism, revealing that cold property herbs alleviated hyperthyroidism symptoms by regulating energy metabolism and thyroid hormone synthesis, inhibiting inflammation and oxidative stress, while hot property herbs showed no effect. This provided scientific evidence for the "cold herbs treating hot syndrome" in hyperthyroidism treatment [82]. Lu et al. employed single-cell RNA sequencing technology to examine the correlation between TCM syndromes and tumor heterogeneity in colorectal cancer, identifying different cell subtypes, signal transduction pathways, and gene co-expression networks in excess, deficiency, and deficiency-excess syndromes [83]. Applying clinical transcriptomics and metabolomics to investigate the biological basis of cold-dampness syndrome and hot-dampness syndrome in RA, Ding et al. identified biomarkers for the two syndromes and validated them in an independent clinical cohort [84].

In research on coronary heart disease, network pharmacology combined with proteomics and metabolomics was utilized to explore the biological basis of two typical syndromes: cold congealing and qi stagnation (CCQS) and qi stagnation and blood stasis (QSBS), revealing the abnormal metabolic pathways and potential markers for each syndrome [85].

4.3. Toxicity mechanisms of TCM

Studies examining the toxicity and safety of TCM are essential for its modernization and international acceptance. The network target approach, combined with multi-omics technologies, facilitates the identification of toxic ingredients and their mechanisms through the construction of networks linking toxic herbs, targets, and pathways. This approach aids in identifying toxicity quality control ingredients and ensuring TCM safety. Network toxicology, developed from network pharmacology principles, has become widely implemented in TCM toxicity research [86]. Liu et al. examined the cardiotoxicity mechanism of celastrol, a component of *Tripterygium wilfordii* Hook F, utilizing network toxicology and metabolomics. Their research revealed that celastrol significantly elevated plasma palmitic acid levels in treated rats, leading to ROS overproduction and subsequent apoptosis *via* the TNF signaling pathway and caspase family. Prevention of cardiotoxicity from *Tripterygium wilfordii* Hook F may be achieved by interrupting this process [87]. Ge *et al.* explored the toxic components and mechanisms of tripterygium glycoside tablets (TGT) on male rat reproductive systems through combined network toxicology and metabolomics. Their methodology identified differential metabolites and metabolic pathways through metabolomics, while key toxic targets were identified through network analysis and validated by RT-qPCR [88]. The hepatotoxicity mechanism of component D of *Polygonum multiflorum* Thunb (PM-D) was investigated using network toxicology integrated with multi-omics. The construction of a PM-D hepatotoxicity network enabled analysis of biological functions and signaling pathways related to hepatotoxicity, while plasma metabolomics revealed risk characteristics in susceptible populations. Spatial metabolomics enabled visualization of metabolite distribution and identification of PM-D hepatotoxicity biomarkers [89]. Investigation of podophyllotoxin (PPT) nephrotoxicity mechanism employed a network strategy combining metabolomics and lipidomics, revealing PPT's primary effects on glycerophospholipid and sphingolipid metabolism pathways. The study demonstrated that PPT inhibited autophagy and induced oxidative stress in renal cells through PI3K/AKT/mTOR and Nrf2/HO1 pathways, resulting in renal tubular injury [90]. While some TCM herbs possess inherent toxicity, traditional processing or combination with other herbs can achieve detoxification. These traditional methods, based on extensive practical experience, have garnered increased attention regarding their mechanisms. Ren et al. investigated how Yunnan Baiyao (YNBY) detoxifies Caowu (CW, Aconiti Kusnezoffii Radix) through network pharmacology and metabolomics, demonstrating that core metabolites related to CW toxicity normalized in the YNBY group, leading to the identification of relevant metabolic pathways and targets [91].

5. Summary

The network target theory aligns with TCM's holistic perspective, offering an effective theoretical model and key technology for interpreting TCM principles. Recent years have witnessed significant advancement in network target theory and methodology, particularly through integration with AI and multi-modal multi-omics experimental technologies, providing robust support for TCM research. The implementation of multi-modal multi-omics technologies in TCM research has generated substantial high-throughput data, enabling enhanced integration of network target methods with sophisticated AI technologies. This integration facilitates efficient prediction of crucial TCM research aspects, including drug-target interactions and molecules associated with diseases and syndromes. Multi-modal multi-omics technologies establish a solid data foundation for network target computational system development while serving as a vital research method. These technologies advance the comprehensive analysis of TCM formulae mechanisms, systematic interpretation of disease and syndrome biological foundations, and identification of active and toxic TCM components through multi-perspective real-world information.

As network target methodology continues to advance and evolve, TCM research based on network targets has garnered increasing attention, with rapid growth in related studies and gradual improvement in overall quality. However, several challenges remain. Firstly, while high-throughput experimental technology has facilitated the rapid expansion of TCM data, the accuracy and completeness of TCM databases require enhancement. Inconsistencies in drug batch characteristics, extraction protocols, and testing methodologies result in discrepant records of identical herbs or formulas across different databases, complicating database utilization. Secondly, although existing AI tech-

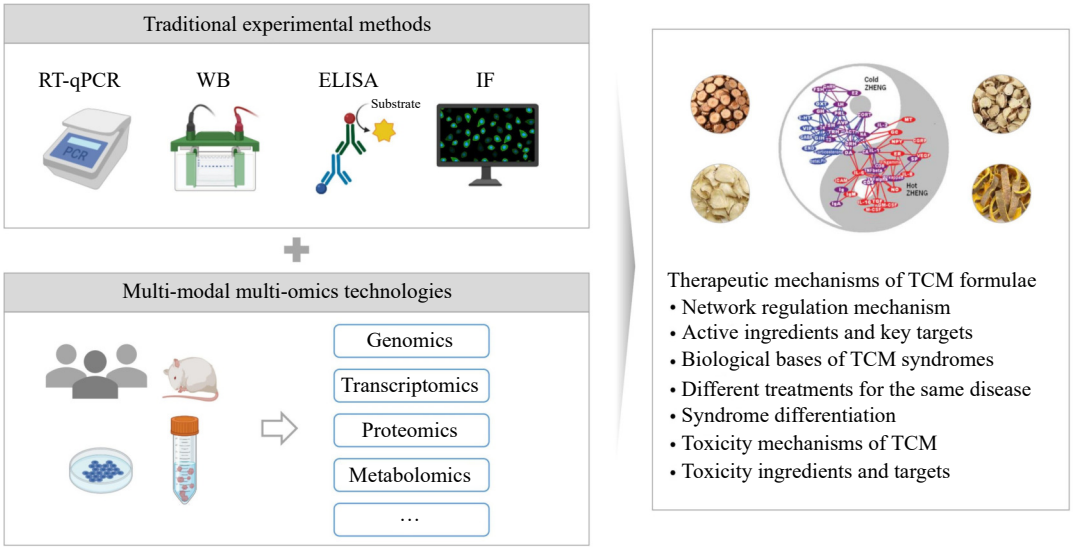

Fig. 4 Network target experimental system: integrating traditional experimental methods with multi-modal multi-omics technologies.

Table 2 Research cases of network target combined with multi-omics technologies

Category	Research object	Technology	Ref.
Therapeutic mechanisms of TCM formulae	Xiaoyaosan treating liver cirrhosis	Transcriptomics	71
	Shenyan Kangfu Tablets treating diabetic nephropathy	Metabolomics	72
	Berberine treating hyperlipidemia	Lipidomics	73
	Components of frankincense and myrrh treating ischemic stroke	Single-cell transcriptomics	74
	Biyuan Tongqiao Granule treating allergic rhinitis	Proteomics	75
	Shexiang Baoxin Pill treating cardiovascular diseases	Quantitative proteomics	76
	Dengzhan Shengmai Capsule treating ischemic stroke	Transcriptomics and metabolomics	77
	Bufei Yishen Formula treating chronic obstructive pulmonary disease	Transcriptomics, proteomics, and metabolomics	78
	Qijiao Shengbai Capsule treating leukopenia	Transcriptomics, proteomics, and metabolomics	79
Biological bases of TCM syndromes	Spleen qi deficiency syndrome and spleen qi reinforcing herbs	Transcriptomics	81
	Cold herbs treating hot syndrome in hyperthyroidism	Metabolomics	82
	Excess, deficiency, and deficiency-excess syndromes in colorectal cancer	Single-cell transcriptomics	83
	Cold-dampness syndrome and hot-dampness syndrome in rheumatoid arthritis	Transcriptomics and metabolomics	84
	Typical syndromes in coronary heart disease	Proteomics and metabolomics	85
Toxicity mechanisms of TCM	Cardiotoxicity mechanism of celastrol	Metabolomics	87
	Reproductive toxicity mechanism of tripterygium glycoside tablets	Metabolomics	88
	Hepatotoxicity mechanism of component D of *Polygonum multiflorum* Thunb	Plasma metabolomics and spatial metabolomics	89
	Nephrotoxicity mechanism of podophyllotoxin	Metabolomics and lipidomics	90
	Detoxification mechanism of Yunnan Baiyao Formulation	Metabolomics	91

niques have been applied directly to TCM research, the field's unique characteristics, such as prevalent few-shot and zero-shot learning scenarios, necessitate the development of specialized models tailored to TCM research requirements. Thirdly, as prediction methodologies evolve, more efficient experimental approaches, including comprehensive experimental design based on multi-omics data and novel TCM-specific experimental methods, are essential to bridge the computational-experimental gap. For instance, pull-down assay, thermal proteome profiling, and activity-based protein profiling facilitate high-throughput detection of TCM targets [92, 93]. Advanced gene editing technologies present new opportunities for investigating gene function, disease and syndrome genes, and drug targets [94]. Addressing these challenges will contribute to the further advancement of network target methodology and its practical applications in TCM research. The ongoing evolution of AI and multi-model multi-omics technologies continues to provide novel approaches and insights for TCM network pharmacology research. Large language models, representing the most significant recent AI advancement, have demonstrated considerable potential in identifying potential associations within extensive biological datasets. Additionally, single-cell and spatial multi-omics technologies enable precise network target navigation at single-cell and spatial resolutions. The integration of these technologies with network targets is expected to drive further innovation in TCM network pharmacology research.

The advancement of AI and multi-modal multi-omics experimental technologies has fostered innovation in network target computational systems and experimental techniques. Through comprehensive analysis of multi-level and multifaceted biological information, the network target method enables detailed examination of network regulation mechanisms in TCM formulae treating diseases and syndromes, establishing theoretical and experimental foundations for identifying key targets, pharmacodynamic substances, and synergistic effects of TCM components and herbs. This methodology provides robust support for advancing clinical precision diagnosis and treatment, precise TCM positioning, and research and development initiatives. The network target theory thus holds promise in providing a novel scientific basis for understanding TCM principles and promoting its modernization and internationalization.

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