

Review article

AI driven network pharmacology: Multi-scale mechanisms of traditional Chinese medicine from molecular to patient analysis

Guoqian Cui^{a,b,c,1}, Muzi Li^{b,c}, Wenbo Guo^{b,c,*}, Meng Gao^{b,c}, Qin Zhu^{a,**}, Jie Liao^{a,b,c,***}^a Hangzhou TCM Hospital Affiliated to Zhejiang Chinese Medical University, Hangzhou, Zhejiang 310007, China^b College of Pharmaceutical Sciences, Zhejiang University, Hangzhou, Zhejiang 310058, China^c Future Health Laboratory, Innovation Center of Yangtze River Delta, Zhejiang University, Jiaxing, Zhejiang 314100, China

ARTICLE INFO

Keywords:

Traditional Chinese medicine
Network pharmacology
Artificial intelligence
Multi-scale Mechanisms
Machine learning
Deep learning
Graph neural network
Systems biology
Precision medicine

ABSTRACT

Traditional Medicine (TM), especially Traditional Chinese Medicine (TCM), is renowned for its distinctive "multi-component-multi-target-multi-pathway" mode of action, which exhibits a unique overall regulatory therapeutic effect. However, the intricate nature of TCM poses significant challenges in identifying active components, elucidating mechanisms of action, and standardizing clinical practices. The advancement of modern science and technology has led to the gradual modernization of TCM research. Network pharmacology (NP) has emerged as a pivotal framework for comprehending the holistic mechanisms of TCM, offering a crucial avenue for unveiling intricate biological networks by integrating chemical information, omics data, and clinical efficacy evidence. Nevertheless, conventional NP approaches exhibit notable limitations, including substantial noise, high dimensionality, challenges in capturing dynamics and time series, and inadequate cross-scale integration, thereby constraining their utility in precise mechanism analysis and clinical translation. In recent years, artificial intelligence (AI), particularly machine learning (ML), deep learning (DL), and graph neural networks (GNN), have empowered NP in an unprecedented way, enabling it to systematically and accurately analyze the cross-scale mechanisms of TCM from molecular interactions to patient efficacy. This review will systematically examine the latest developments in artificial intelligence-network pharmacology (AI-NP) methodology, with a focus on typical research cases of multi-scale mechanism analysis at the molecular, cellular, tissue, and patient levels. It will systematically summarize the challenges currently faced and explore future development directions to fully unlock the systemic therapeutic wisdom of TCM.

1. Introduction

Traditional Medicine (TM), especially Traditional Chinese Medicine (TCM), an ancient medical system, has a long history and unique theories [1]. Its basic philosophy emphasizes holism and systematicity, believing that the human body is an organic whole, and the dynamic

balance between the internal and external environment of the body is crucial [2]. This concept is reflected in the cognition and treatment of diseases, and emphasizes achieving physical and mental harmony and health through various means when choosing therapies. [3]. But with the development of modern medicine, higher requirements have been put forward for the scientific verification and theoretical integration of

Abbreviations: AI, Artificial Intelligence; AI-NP, Artificial Intelligence-Network pharmacology; Attn, Attention Mechanism; CDDP, Compound Danshen Dripping Pills; CFDTD, Cangfu Daotan Decoction; CHM, Chinese Herbal Medicine; CM, Chinese Medicine; CNN, Convolutional Neural Network; DL, Deep Learning; GCN, Graph Convolutional Network; GNN, Graph Neural Network; EMR, Electronic Medical Record; KG, Knowledge Graph; LIME, Local Interpretable Model-agnostic Explanations; ML, Machine Learning; NLP, Natural Language Processing; NP, Network pharmacology; PPI, Protein-Protein Interaction; RF, Random Forest; ScRNA-seq, Single Cell RNA Sequencing; SHAP, SHapley Additive exPlanations; SVM, Support Vector Machine; TCM, Traditional Chinese Medicine; TM, Traditional Medicine; XAI, Explainable Artificial Intelligence.

* Corresponding author at: College of Pharmaceutical Sciences, Zhejiang University, Hangzhou, Zhejiang 310058, China.

** Corresponding author.

*** Corresponding author at: Hangzhou TCM Hospital Affiliated to Zhejiang Chinese Medical University, Hangzhou, Zhejiang 310007, China.

E-mail addresses: guo_wb@126.com (W. Guo), zhuqinfeifei@126.com (Q. Zhu), liaojie@zju.edu.cn (J. Liao).

¹ These authors contribute equally to this work

<https://doi.org/10.1016/j.csbj.2025.11.016>

Received 31 August 2025; Received in revised form 2 November 2025; Accepted 6 November 2025

Available online 11 November 2025

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TCM. Modern medicine places great emphasis on evidence-based methods, which determine the effectiveness of treatment measures through rigorous scientific evaluation of clinical efficacy and other factors. To promote the scientific process of TCM, its theory and practice need to be constantly adjusted to meet the standards of modern medicine [4,5]. Faced with the pressure of scientification, TCM urgently needs to organically combine modern scientific technology and verification methods to ensure the authenticity of the therapeutic effects and theories of CHM.

With the development of modern biology and the advancement of computer science, network pharmacology (NP) has emerged, which is based on systems biology and network science, and can realize multi-dimensional network relationships between drugs and diseases on this platform [6]. This method not only focuses on the effects of a single drug, but also comprehensively considers drug components, targets, and their interactions in biological networks, providing a new perspective for understanding complex diseases and treatments. At the same time, the core concept of NP is highly compatible with the theoretical basis of TCM, emphasizing holistic and multi-target treatment strategies. NP has gained unique therapeutic potential due to the multi-component, multi-target, and multi-pathway characteristics of CHM, while traditional single-target pharmacological research often fails to fully reveal these complex mechanisms. Recent reviews have systematically evaluated the current status of network pharmacology for herbal medicine, emphasizing both its achievements in mechanism elucidation and the need for methodological rigor and validation [7].

Based on TCM, NP can reveal the underlying principles of CM theory as a whole and help researchers discover more accurate conclusions in the drug-drug interaction network of complex diseases. CM emphasizes the synergistic effect of multiple components to treat diseases, while NP systematically analyzes the active ingredients and their mechanisms of action of CHM formulas by constructing a network model of "drug component target pathway" [8]. Although traditional NP can be used to study the networked mechanisms of multi-component drug systems, it has many drawbacks in practical applications, including uneven data quality, insufficient ability to interpret high-dimensional data, predominance of static analysis, and difficulty in connecting cross scale mechanisms. Similar methodological reflections have been made in recent reviews, which highlight both the progress and pitfalls of network pharmacology of natural products, emphasizing issues of data quality, reproducibility, and interpretability [9]. These issues not only affect the reliability of research results, but also constrain the further promotion and application of NP. Therefore, we should keep up with the pace of the times, improve NP technical standards and specifications on the basis of promoting NP development, and ensure the scientific rationality of research.

NP provides a systematic research paradigm for multi-target drug discovery by constructing interaction networks. However, traditional NP approaches face multiple challenges in the era of exponentially increasing high-throughput biological data, including limitations in data scalability, computational efficiency, and model generalization capacity [10]. These constraints hinder the effective analysis of the diversity and dynamic nature of complex diseases. With the rapid advancement of artificial intelligence (AI), AI-driven network pharmacology (AI-NP) has emerged as a promising direction in this field, integrating methodologies such as machine learning (ML), deep learning (DL), and graph neural networks (GNNs) [11].

The introduction of AI has led to a systematic transformation of NP in multiple key aspects, including multi-source data integration, predictive modeling, and drug screening [12]. First, at the data integration level, AI enables efficient processing of heterogeneous information derived from multi-omics and multimodal clinical data. Through advanced feature extraction and deep representation learning techniques, AI overcomes the traditional NP bottlenecks in multidimensional data integration and heterogeneous data association analysis, thereby constructing biologically meaningful multi-layered drug–target–disease networks. Second,

in predictive modeling, AI algorithms significantly enhance pattern recognition and predictive performance, allowing researchers to identify potential targets, elucidate molecular mechanisms, and visualize or quantify biological associations through interpretable models within complex biological systems. Finally, in the domain of drug discovery and design, AI-based approaches—such as virtual screening, molecular generation, and pharmacological activity prediction—greatly improve the efficiency and success rate of drug development. This enables AI-NP to perform intelligent molecular optimization and combinatorial innovation within vast chemical spaces, offering novel pathways for the secondary development of natural products and multi-component formulations. Overall, AI-NP not only facilitates a more efficient elucidation of complex biological interactions within molecular networks but also enhances the precision and effectiveness of drug discovery [13,14]. A structured comparative analysis between conventional network pharmacology and AI-driven network pharmacology is summarized in Table 1, outlining their respective challenges, advantages, and limitations.

A comprehensive literature search was conducted in PubMed, Web of Science, and Embase to identify studies published between January 2010 and June 2025 on AI-driven network pharmacology. The search strategy combined both controlled vocabulary and free-text terms, using Boolean operators (AND, OR) to ensure retrieval comprehensiveness. The specific search string was: ("network pharmacology" OR "systems pharmacology") AND ("artificial intelligence" OR "machine learning" OR "deep learning" OR "graph neural network" OR "AI") AND ("traditional Chinese medicine" OR "Chinese herbal medicine" OR "Chinese materia medica" OR "TCM"), with language restricted to English or Chinese articles with English abstracts. Inclusion criteria were: (1) original research articles or systematic reviews published in peer-reviewed journals; (2) studies focusing on the application of AI in network pharmacology to elucidate multi-scale mechanisms of TCM/CHM from molecular and cellular levels to patient outcomes; (3) research addressing drug screening, target prediction, mechanism exploration, formula optimization, or model development; (4) studies involving cell lines, animal models, or clinical data; and (5) full-text availability with clearly described study design and results. Exclusion criteria included: non-peer-reviewed publications (e.g., conference abstracts, theses, preprints, commentaries, editorials), studies not directly related to AI, network pharmacology, or TCM, research without experimental validation or purely theoretical studies, and studies with incomplete methods or data that precluded quality assessment. All retrieved records were imported into reference management software for deduplication. Titles and abstracts were screened, and potentially eligible studies underwent full-text review to confirm inclusion. The final set of included studies was systematically categorized and qualitatively analyzed to summarize the progress, application trends, and challenges of AI-driven network pharmacology in elucidating multi-scale mechanisms of TCM.

In summary, NP is more favored in integrating TCM experimental research and modern scientific technology in modern medical research. With the development of AI technology, AI-NP provides unprecedented opportunities for the multi-scale mechanism analysis of TCM. By combining advanced technologies such as ML, DL, and GNN, the complex mechanisms of action of traditional drugs can be explored more deeply and extensively in the context of multi-component, multi-target, and multi-pathway approaches. This article will focus on the core technology and methodology of AI-NP, systematically review its theoretical basis, key technologies, application cases, and future development directions, explore its potential and challenges in multi-scale mechanism analysis, and provide reference and guidance for future research.

2. Core technology and methodology progress of AI-NP

As an emerging research field, NP are gradually moving beyond the

Table 1
Structured comparison between NP and AI-NP.

Comparison Dimension	Network pharmacology	Artificial intelligence-network pharmacology	Remarks and Insights
Data Acquisition	Relies mainly on public databases (e.g., TCMSP, GeneCards, STITCH) and literature mining; data are fragmented and updated slowly.	Integrate multimodal data, including omics, graphical databases, text mining, etc., for dynamic and high-dimensional data fusion.	AI improves data integration depth and timeliness, strengthening the foundation of NP research.
Algorithmic Characteristics	Based on statistics, correlation networks, and topology analysis; relies on expert interpretation.	Utilizes ML, DL, and GNN to automatically identify complex patterns.	Shifts NP from experience-driven to data-driven discovery, enhancing prediction power.
Model Interpretability	Good interpretability but limited handling of nonlinear, high-dimensional data.	Complex models with weak interpretability, though XAI tools (SHAP, LIME) can enhance transparency.	Future trend: develop transparent and interpretable AI models.
Computational Efficiency and Scalability	Manual processing, low computational efficiency.	High-throughput parallel computing, suitable for large-scale networks.	AI improves automation and scalability, fitting complex pharmacological systems.
Clinical Translational Potential	Focuses on mechanistic validation and preclinical studies, limited predictive utility.	Integrates clinical big data, EMR, and RWD for precision prediction.	AI-NP bridges experimental research and clinical application.
Main Challenges	Data heterogeneity, lack of dynamic modeling, expert-biased results.	Model opacity, uneven data quality, limited clinical validation.	Future research should balance automation with interpretability and strengthen validation.

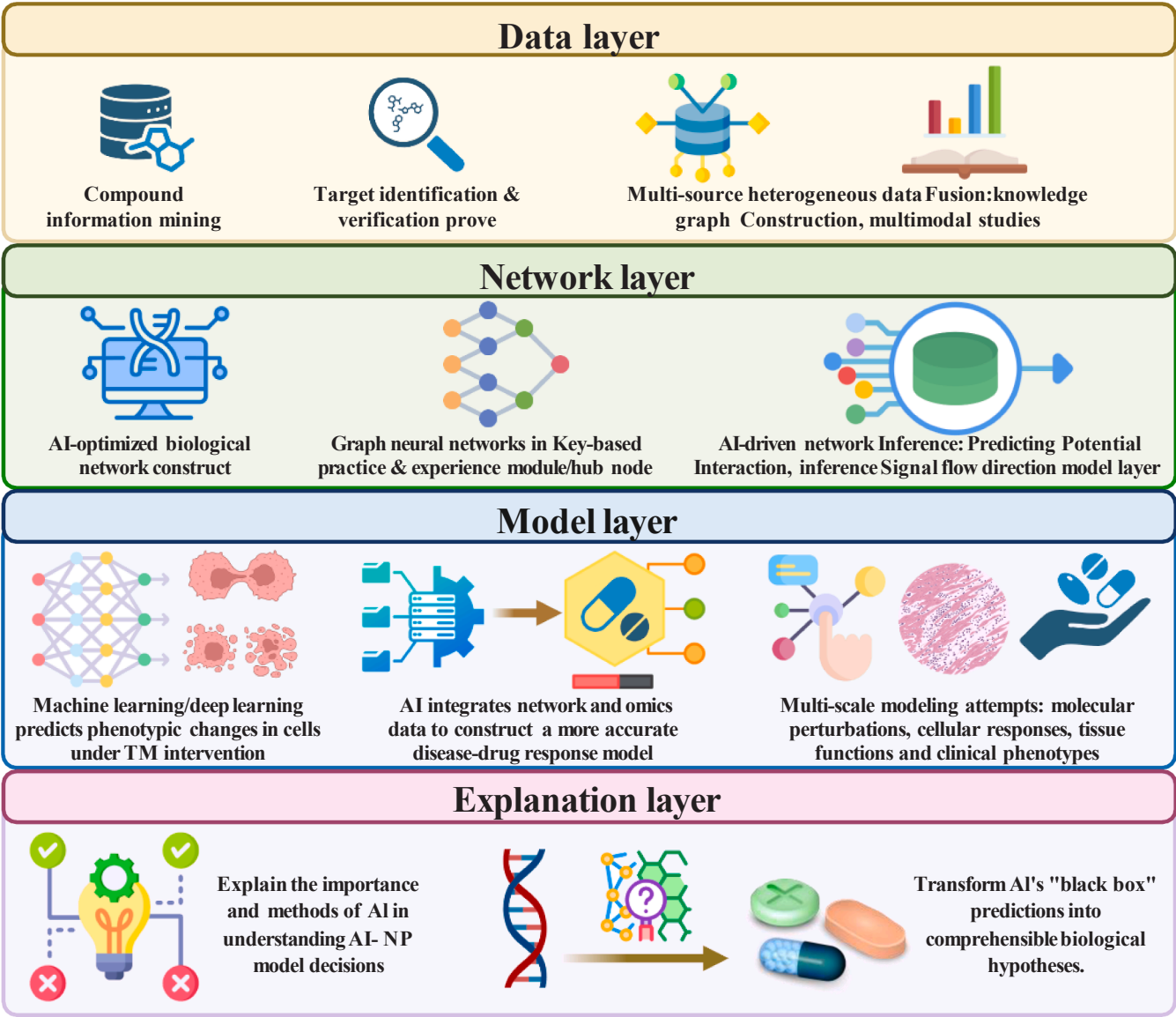


Fig. 1. Direction and progress of AI enhanced NP.

traditional “single-target, single-drug” paradigm of drug discovery and advancing toward a systems biology-based model characterized by “multi-component, multi-target networks” [15]. This paradigm shift has significantly deepened our understanding of complex diseases and facilitated progress in the design and development of multi-target therapeutics. In the era of big data and multi-omics, NP has vast amounts of data, but the efficient extraction, integration, and interpretation of these data remain major challenges.

To address the aforementioned challenges, has emerged as a powerful tool for acquiring and integrating data intelligence. AI can transform diverse and complex datasets into valuable information, effectively support data quality management, and integrate multi-modal information. Within NP research, AI technologies can be applied to predict the pharmacological substance basis and mechanisms of action of CHM formulas, providing some inspiration and reference for revealing the modern scientific connotation of CHM and its component groups [16]. Beyond data processing, AI has also been successfully employed in drug repositioning and novel target identification within the NP framework. Numerous successful applications of AI in data mining, bioinformatics, and related fields have increased the likelihood of drug discovery, particularly for complex diseases such as cancer [17, 18]. These advances suggest that AI is not only a technical aid but also a transformative force in modern NP research.

Overall, AI-enhanced NP is expected to be more extensively applied in future biomedical research, as illustrated in Fig. 1. With the continuous advancement of intelligent data acquisition and integration technologies, NP will be better positioned to serve clinical practice and play a pivotal role in new drug development, personalized diagnosis, and treatment planning. Future research should therefore prioritize further improvements in data quality and algorithmic accuracy, leverage the wealth of information embedded in big data, and explore novel therapeutic strategies to address currently intractable diseases. Such prospects underscore the transformative potential of integrating AI with NP in shaping the future of precision medicine.

2.1. Data layer: intelligent data acquisition and integration

NP offers an effective approach for investigating drug mechanisms and exploring multi-target synergies through big data, with an emphasis on integrating systems biology and systems informatics. The ultimate aim is to gain deeper insights into drug–target interactions within organisms by constructing complex biological networks [19]. This process entails not only the collection and analysis of biological data but also demands substantial computational power to process and interpret highly intricate biological information. As traditional data processing methods encounter increasing limitations, the incorporation of AI technologies has created new opportunities for advancing NP research.

In compound information mining, literature mining and information extraction are crucial processes. Automated techniques are increasingly utilized to retrieve data on specific compounds and their properties from vast scientific literature. Natural language processing (NLP) technologies are commonly employed to identify and extract relevant information, such as compound names, chemical structures, biological activities, and disease associations [20]. Notably, ML and DL have introduced new analytical paradigms for NP, enabling the efficient extraction, association, and prediction of drug actions from literature, databases, and multi-omics data sources [21]. DL, as a subset of ML, refers to machine learning approaches based on deep neural networks capable of automatically extracting complex features from data. In contrast, ML represents a broader field encompassing various algorithms and techniques that learn patterns and make decisions from data. ML focuses on mining latent patterns within heterogeneous datasets to improve predictive accuracy, thereby enhancing the efficiency and precision of novel drug discovery and clinical translation [22]. DL, through automatic feature extraction and multi-level representation learning, captures complex nonlinear relationships and strengthens the interpretability of

drug–disease networks [23]. For instance, some studies have applied DL algorithms to automatically identify compound bioactivities from scientific literature and to construct target-specific databases, thereby accelerating the drug discovery process [24]. AI-based approaches have significantly improved data processing efficiency and information integration. However, challenges such as semantic ambiguity and the lack of standardized data annotation still limit the accuracy of automated information extraction. Furthermore, the embedded application of AI in CHM databases, e.g., TCMID, TCMSP, has enabled intelligent compound screening and target prediction [25–27]. Nevertheless, high data heterogeneity among databases and biases in model training datasets remain major bottlenecks. Traditional ML algorithms, such as support vector machines (SVM) and random forests (RF), have also shown considerable potential in predicting compound bioactivity [28]. SVM constructs hyperplanes to classify data, making it particularly suitable for high-dimensional feature spaces and advantageous in handling molecular descriptors [29]. RF, by integrating multiple decision trees, enhances model stability and predictive accuracy, effectively mitigating overfitting when dealing with complex biological data [30]. In CHM component activity prediction, these traditional models utilize molecular descriptors to effectively evaluate bioactivity. For example, in predicting drug–compound interaction relationships, researchers have successfully applied SVM and RF models to screen candidate active compounds, achieving satisfactory outcomes [31].

In target identification, AI-NP facilitates the analysis of correlations between drug components and biological targets by constructing drug–component–target networks, thereby enabling the discovery of active components and mechanisms of action. This approach is particularly valuable for identifying novel drug targets and repurposing existing drugs [32]. In terms of structure prediction, AI can be used to predict the three-dimensional structure of the target, and molecular docking, computational simulation and other methods can better understand the mechanism of action between drug targets to optimize drug design. For example, studies of drug–target binding patterns can provide novel targets for drugs to improve efficacy and safety [33,34]. DL-based tools, such as AlphaFold, have shown excellent performance in structural prediction, and one of the keys to their success is to make full use of the attention mechanism (Attn). In AlphaFold, Attn constructs interaction maps between amino acids, enabling the generation of high-quality structural predictions within a short time frame. Notably, experimental validations have shown that AlphaFold’s predictions are highly consistent with empirical data, thereby enhancing our understanding of protein structures and offering novel insights for drug development and disease research [35]. However, models such as AlphaFold are primarily designed for static single-protein structures and still face limitations in predicting protein complex conformations and modeling dynamic molecular interactions. Integration with molecular dynamics simulations and NP approaches is therefore essential to overcome these challenges. In the field of novel target discovery, NP employs big data analysis and ML approaches to extract potential target information from extensive literature and database resources. This strategy not only improves the efficiency of target identification but also uncovers critical targets implicated in diverse diseases. For example, studies have revealed that CHM ingredients exert therapeutic effects on complex conditions such as diabetes and Alzheimer’s disease via multi-target mechanisms, thereby providing new directions for innovative drug design [36,37].

At the data fusion and reasoning level, AI has greatly facilitated the integration of multi-source heterogeneous data. The development of ML and DL technology makes it possible to mine useful information from a large amount of data in different formats. By leveraging these techniques, researchers can improve the efficiency of drug discovery and decision making at various stages of NP, including small molecule activity screening, target identification, metabolic pathway identification, protein–protein interaction network (PPI) analysis [38]. In the process of processing and reasoning multi-source heterogeneous data, knowledge graph (KG), as a research focus of AI, can better model complex data and

display data and relationships in a graphical way, making information acquisition and deduction more concise and transparent [39]. In processing and reasoning with multi-source heterogeneous data, the knowledge graph (KG) has emerged as a central focus of AI research. KGs can effectively model complex data and visualize both entities and their relationships in an interpretable graphical format, thereby making knowledge acquisition and inference more transparent [39]. The construction of KGs typically involves two key steps: entity recognition and relation extraction. The application of DL models such as BiLSTM-CRF has significantly improved the accuracy of entity recognition [40]. Meanwhile, relation extraction, which identifies associations among entities, is often implemented through graph neural networks (GNNs) or other ML approaches. Recently, graph convolutional network (GCN)-based methods for relation extraction have demonstrated excellent performance, particularly in resolving multi-relational graphs, thereby enhancing the efficiency of KG construction [41]. Multimodal learning techniques are widely used in drug retargeting, disease subtype classification and side effect prediction. Multimodal learning improves the predictive power and accuracy of models by fusing data from different sources and types, thus providing more effective support for drug development and disease treatment. For instance, the deep multimodal feature fusion framework DMFDDI integrates molecular structures, interaction networks, and biological features to significantly improve the accuracy of drug repositioning and side effect prediction. However, further validation is still required to enhance the model's biological interpretability and generalization performance [42].

Although AI technologies have greatly expanded the research boundaries of NP and made the systematic analysis of the complex CHM system possible, several critical issues have also emerged, including uneven data quality, insufficient model interpretability, lack of experimental validation, and weak standardization frameworks. Future research should focus on addressing these bottlenecks and challenges. Only in this way can AI-NP truly move from theoretical exploration toward clinical application, thereby providing a solid scientific foundation for the modernization of TCM.

2.2. Network layer: intelligent network construction and analysis

Current NP research is gradually evolving into an integrated system that combines multi-omics data to analyze disease and drug action processes from a dynamic perspective. For instance, multi-omics NP analyses focusing on cancer have revealed the dynamic remodeling of drug–target–signaling networks, providing a systematic perspective for elucidating the multilayered regulatory mechanisms of complex diseases [43]. Building on this foundation, the incorporation of AI technologies—particularly algorithms such as ML, DL, and GNN—has greatly enhanced the intelligence and dynamic modeling capabilities of NP, enabling the integration of multi-source heterogeneous biological information at higher dimensions.

In the construction of biological networks, AI-driven approaches have become an important means of overcoming the limitations of traditional NP methods. The complexity of biological networks arises not only from molecular interactions but also from factors such as cellular states, environmental changes, and external stimuli, which collectively impart pronounced spatiotemporal dynamics to these systems [44]. These factors drive dynamic changes in biological networks, presenting challenges for traditional network construction methods, including data noise, missing information, and the need for real-time updates. Advances in artificial intelligence, particularly DL and explainable artificial intelligence (XAI), have addressed many of these challenges, assisting in noise reduction, data completion, and dynamic network processing. This enables researchers to efficiently extract meaningful information from vast datasets and construct accurate, dynamic biological networks. For example, an AI-PPI network-based study on diabetic cardiomyopathy within the framework of systems pharmacology successfully identified potential therapeutic targets related to

glucose and lipid metabolism, demonstrating the potential of AI in disease network analysis [45]. Case studies of gene screening and network analysis show the value of AI in precision medicine and disease prediction. Through NP analysis, the research team found possible targets and signal pathways for berberine intervention in the process of atherosclerosis and the occurrence and development of various diseases, providing a new theoretical basis for further new drug development [46]. Collectively, these studies indicate that AI-empowered NP holds significant promise in precision medicine, while also underscoring the need for further improvement in data quality and model interpretability.

NP aims to elucidate the complex relational networks among drugs, genes, and diseases, providing a theoretical foundation for precision medicine research. Although NP has played a crucial role in integrating multidimensional biological data, traditional network analysis methods still face limitations, including low efficiency, difficulty in capturing higher-order topological structures, and inability to account for network dynamics. These limitations can lead to biased results and constrain in-depth exploration of drug mechanisms of action [47]. By aggregating information from neighboring nodes, GNNs allow each node to better reflect its position and functional role within the network [48]. This property allows GNNs to automatically capture higher-order topological features and identify critical hub nodes when analyzing complex biological networks. For instance, the DruGNNosis-MoA framework successfully classifies drug mechanisms of action by integrating GNNs with node features derived from large language models, enhancing understanding of therapeutic mechanisms and supporting precision medicine [49]. Additionally, the GRAF framework improves graph representation learning by transforming multiple heterogeneous networks into homogeneous networks, resulting in superior performance across diverse datasets [48].

In the analysis of drug–disease interactions, the application of AI technologies provides NP with a more comprehensive research perspective. Traditional NP approaches often face limitations such as inadequate data processing and low predictive accuracy, necessitating the development of novel techniques to address these shortcomings. The recent advancements in AI have brought transformative changes to NP. AI-driven network inference techniques can effectively integrate and analyze massive datasets, predict potential drug–target interactions, and infer the directionality of signaling flows, thereby enabling mechanistic-level system analyses. AI has demonstrated remarkable performance in predicting drug–target binding affinity. Conventional prediction methods typically rely on empirical data analysis, whereas AI approaches can leverage large-scale historical data to generate more accurate predictive models. For example, studies have shown that the magedTA models based on convolutional neural network (CNN) can predict drug–target binding affinities with high precision, significantly enhancing the efficiency and safety of drug development [50]. AI also plays a crucial role in inferring the directionality of signaling flows. By performing in-depth analyses of complex biological networks, AI can identify interactions among different signaling pathways and elucidate their roles in disease progression. For instance, applications of AI-NP in lung cancer research have revealed its potential in regulating signaling pathways and optimizing targeted therapeutic strategies [51].

However, AI-empowered NP still faces several critical challenges. First, the heterogeneity and noise inherent in biological data limit the stability and generalizability of AI models. Second, most AI models operate as “black boxes,” lacking biological interpretability regarding drug mechanisms of action. Finally, insufficient experimental validation of AI-derived predictions creates a disconnect between algorithmic outputs and underlying biological mechanisms. Overall, the introduction of AI has driven a shift in NP from static to dynamic analyses and from empirical to intelligent approaches, substantially enhancing the systematic understanding of disease mechanisms and the efficiency of drug discovery. From a critical perspective, however, the application of AI in NP remains in a transitional phase, moving from “tool-based” to “mechanism-oriented” research. In summary, the deep integration of AI

and NP represents not merely a technological convergence but a pivotal pathway for precision medicine to progress from “correlative discovery” toward “mechanistic elucidation.” Its future development is poised to play a central role in the study of complex diseases and the innovation of drug discovery.

2.3. Model layer: multiscale modeling and prediction

In recent years, driven by the rapid development of data science and related technologies, AI has seen substantial advancement in the biomedical field, thereby promoting innovations in NP methodologies and transforming drug discovery paradigms. The introduction of AI provides powerful technical support for NP, with its strengths in large-scale data processing, feature learning, and complex system modeling making it an essential tool for exploring drug–disease relational networks. However, despite the significant improvements AI has brought to the accuracy and efficiency of NP modeling, core challenges remain, including the efficient integration of heterogeneous data from diverse sources, enhancement of model generalizability and interpretability, and the realization of cross-scale predictive capabilities.

In TCM research, the application of CNNs offers a novel perspective for evaluating the effects of drug interventions on cellular phenotypes. CNNs can extract local spatial features from molecular images, structural fingerprints, or gene expression profiles, thereby enhancing the representation and predictive performance of drug–target pathway models [52]. For example, through DL-based analysis of cellular images, researchers can quantify morphological changes under CHM interventions, providing empirical support for investigating drug mechanisms [53]. High-throughput image analysis platforms, such as X-Profiler, combined with DL algorithms, can effectively remove noise and accurately identify cellular phenotypic features, substantially improving the utility of image data [54]. Furthermore, the transfer learning capabilities of CNNs are particularly valuable in CHM studies with limited sample sizes. Previous studies have employed models pre-trained on large-scale public datasets to perform transfer learning on small-sample cellular data, achieving high-precision classification under constrained data conditions and significantly reducing dependence on large annotated datasets [55]. This approach not only improves model accuracy but also enhances flexibility and efficiency in practical applications.

In the integration of multi-omics data and biological networks, the introduction of AI has significantly enhanced the predictive accuracy of disease–drug response models in NP. CNNs have demonstrated remarkable advantages in patient stratification and drug sensitivity prediction. These models can automatically learn complex feature representations, making them particularly well-suited for handling unstructured data such as genomic sequences and medical images. When applied to gene expression data, CNNs can effectively extract features associated with drug responses, thereby improving prediction accuracy [56]. For example, in the analysis of gene expression data from breast cancer patients, CNN models have successfully identified drug response-related features, achieving prediction accuracy substantially higher than that of traditional ML models [57]. Moreover, by integrating multi-layered biological data, including genomics, transcriptomics, and proteomics, AI can reveal system-level associations between individual variability and drug responses, demonstrating the feasibility of multi-omics AI models in clinical precision medicine [58]. These multi-omics models provide robust validation for the application of AI in clinical settings, supporting the advancement of personalized medicine through comprehensive data integration.

With the evolution of AI algorithms, NP is transitioning from the traditional “compound–target–pathway” framework toward multi-level system modeling encompassing “molecular perturbation–cellular response–tissue function–clinical phenotype.” Current AI-NP cross-scale modeling attempts are mainly reflected in many aspects. First, GNNs have been employed to integrate gene expression profiles induced by

CHM formulations with protein interaction networks to infer the perturbation effects of drugs on key cellular regulatory pathways. Studies have shown that embedding CHM components, gene expression, target interactions, and pathway annotation information into a unified KG using GNN models can successfully predict dynamic regulatory patterns of CHM formulations on inflammation networks, with partial validation in animal experiments [59]. Second, the combination of single cell RNA sequencing (scRNA-seq) technology with AI models can understand the basis of drug efficacy at the cellular level by characterizing the differential response of drugs in heterogeneous cell populations. For example, scRNA-seq technology was first integrated with NP prediction in the study of Cangfu Daotan Decotion, a classical Chinese medicine prescription, for the treatment of obese polycystic ovary syndrome, combined with AI algorithm to determine the regulation of specific immune cell subsets [60]. Finally, multimodal DL approaches can link drug-induced system-level responses with clinical phenotypes, allowing refinement and validation of efficacy prediction models. For instance, by leveraging inpatient electronic medical records (EMR) and time-series clinical features, Transformer- and GAN-based models have successfully predicted CM prescriptions, providing accurate and scalable recommendations for clinical decision support [61].

Although AI has facilitated the intelligence and systematization of cross-scale NP modeling, multiple bottlenecks remain. First, the spatiotemporal heterogeneity of cross-scale data is not fully captured by existing models, resulting in predictions that lack dynamic consistency. Second, when handling highly complex systems such as CHM formulations, AI models have yet to fully elucidate the systemic mechanisms involving multiple components, targets, and pathways. Third, the experimental validation of AI predictions is costly and time-consuming, creating a disconnect between model optimization and clinical translation. From a critical perspective, research in AI-NP still needs to transition from being “prediction-oriented” to “mechanism-driven,” emphasizing the enhancement of biological interpretability and the establishment of validation feedback loops. In the future, efforts should focus on developing high spatiotemporal-resolution, multimodal NP frameworks, integrating XAI techniques to improve model transparency, and implementing iterative cycles between AI predictions and experimental validation to achieve a systematic transition from algorithmic inference to mechanistic discovery.

2.4. Interpretative layer: interpretability of AI models

Driven by AI technologies, the scope and depth of NP applications have been significantly expanded. Leveraging its powerful data processing and pattern recognition capabilities, AI has greatly accelerated key processes such as drug target identification, mechanism of action elucidation, drug repositioning, and side effect prediction [62,63]. However, the “black-box” nature of AI models limits their interpretability, representing a major barrier to their widespread application in clinical practice and drug development. The lack of clear explanatory mechanisms not only undermines the credibility of AI predictions but may also introduce decision-making risks, potentially affecting patient safety and therapeutic efficacy [64,65]. Consequently, enhancing the interpretability and biological consistency of AI models has become a central focus of AI-NP research.

To address this challenge, the incorporation of explainable AI (XAI) has become a critical component in the development of AI-NP. XAI enhances model transparency, verifiability and scientific value by quantifying different features, such as components, targets, pathways, thereby revealing the key decision-making bases for models [66]. Common XAI methods include Shapley additive explanations (SHAP), local interpretable model-diagnostic explanations (LIME), Attn, etc. In practice, SHAP evaluates the predictive effectiveness of each feature for different combinations of features and calculates the marginal contribution of that feature relative to other features [67]. This approach ensures that SHAP provides reliable interpretation even when complex

correlations exist between features [68]. For example, in cancer prognosis analysis, SHAP identified the critical role of specific molecular features in predicting tumor recurrence risk, thereby supporting the selection of potential therapeutic targets [69]. The core function of LIME is to provide interpretability to individual predictions of complex models, which is critical for drug discovery and retargeting [70]. In Alzheimer's disease research, LIME successfully revealed associations between certain biomarkers and disease classification, offering new avenues for drug repositioning [71]. Attn assign different weights to input features, automatically highlighting the information most relevant to a specific task [72]. In drug target prediction, researchers can use Attn to dynamically adjust the focus of the model, focusing on targets that exhibit significant activity in specific biological environments [73]. In practical applications, the integration of self-attention layers enables adaptive feature selection, substantially improving the reliability of drug mechanism inference [74].

Although complex models perform well on large datasets, their “black-box” nature makes it difficult for users to understand the internal mechanisms and decision-making processes, and it can be challenging for researchers to validate the biological plausibility of predicted targets, potentially leading to off-target effects. To enhance the credibility and verifiability of AI-NP, biological consistency validation has emerged as an important complementary approach for evaluating model interpretability. This process assesses whether model predictions align with established biological knowledge, thereby evaluating their scientific rationality. In pharmacology and biomedical research, pathway enrichment analysis is a commonly used validation method, aiming to identify gene sets associated with specific biological processes or diseases [75]. This analysis can help researchers determine whether important features identified by AI models match known biological mechanisms, thereby enhancing the credibility and interpretability of models. For example, by using pathway enrichment analysis, researchers can verify whether the genes predicted by the model are concentrated in known disease-associated pathways, further supporting the biological soundness and clinical potential of the model [76,77]. In addition to pathway analysis, comprehensive biological consistency verification can combine bioinformatics tools with experimental data. This integrative approach improves validation reliability and uncovers underlying biological assumptions in AI models. For example, in drug discovery, by comparing the mechanism of action of existing drugs, researchers can confirm whether the target predicted by the model matches the known mechanism of action of the drug, thus providing clues for the development of new drugs [78]. A summary of the AI algorithms discussed above, including their primary functions, is provided in Table 2.

Overall, the introduction of XAI has shifted AI-NP from being “result-oriented” to “mechanism-oriented,” not only enhancing the transparency of AI models but also enabling biological interpretation and clinical translation. However, XAI currently remains at an “auxiliary explanation” stage, lacking unified validation standards and cross-modal adaptability, and its application in complex biological systems should be approached with caution. Future research should focus on developing multi-level, multimodal XAI frameworks that integrate causal inference with experimental validation, gradually transitioning from statistical explanations to mechanistic biological interpretations. Such advancements will drive AI-NP toward a more scientific, verifiable, and clinically applicable paradigm.

3. Analysis of multi-scale mechanism: application of AI-NP in TCM

TCM, as a treatment system with a long history, has the characteristics of multi-component, multi-target and multi-path treatment. NP provides a new perspective to understand and analyze the mechanism of TCM, and reveals the characteristics of TCM by constructing biological networks. This method can systematically integrate and analyze the

Table 2
Correlation algorithms applied by AI in NP.

No.	Name	Function	Ref.
1	ML	Utilizing multi-source complex data to mine potential patterns and improve prediction accuracy, thereby enhancing the efficiency and precision of new drug discovery and clinical translation	[21, 22]
2	DL	By using automatic feature extraction and multi-level representation learning, complex nonlinear relationships are constructed to enhance the analytical ability of drug disease networks	[21, 23]
3	GNN	Aggregate information from neighboring nodes to enable each node to better reflect its position and role in the network	[48]
4	SVM	Constructing hyperplanes for data classification is particularly suitable for classification problems in high-dimensional feature spaces and has advantages in processing molecular descriptors	[29]
5	RF	Integrating multiple decision trees to improve the stability and accuracy of the model, especially when dealing with complex biological data, can effectively avoid overfitting	[30]
6	KG	Better modeling of complex data and presenting data and relationships in a graphical manner, making information acquisition and deduction more concise and transparent	[39]
7	GCN	Effectively solving the problem of multiple relationship graphs, thereby greatly improving the efficiency of KG construction	[41]
8	CNN	Extracting local spatial features from molecular images, structural fingerprints, or gene expression profiles enhances the expression and predictive performance of drug target pathway models	[52]
9	Attn	By assigning different weights to different input features, it is possible to automatically identify and highlight important information related to specific tasks	[71]
10	SHAP	Evaluate the predictive performance of each feature under different feature combinations, and then calculate the marginal contribution of that feature relative to other features	[67, 68]
11	LIME	Providing interpretability for individual prediction results of complex models is crucial for drug discovery and repositioning	[70]
12	XAI	By quantifying different features such as components, targets, pathways, and other hierarchical levels, the key decision-making basis of the model is revealed, and the transparency, verifiability, and scientific value of the model are improved	[66]

components of CHM with related targets and their biological pathways, thus providing theoretical support and practical guidance for the modernization of CHM research [59,79]. With the birth of AI-NP, AI enables NP to inject powerful data analysis and modeling capabilities, significantly expanding the application boundaries in multi-group integration, complex network construction and cross-scale mechanism analysis.

Through the mining and analysis of massive data, AI efficiently processes the highly complex "multi-component-multi-target-multi-pathway" relationship network in TCM, improving the accuracy and systematicness of drug-target prediction, disease association analysis and potential pathway mining. And through advanced algorithms such as ML, DL and GNN, AI-NP can simulate the dynamic conduction path between molecules, cells, tissues and clinical phenotypes. The specific idea is shown in Fig. 2. In addition, combined with XAI, model predictions are translated into verifiable biological hypotheses, providing strong support for TM modernization, precision and mechanism-driven innovation. This process not only improves the efficiency of TCM research, but also provides a new perspective for individualized treatment and promotes precise treatment of TCM.

3.1. Molecular scale: revealing target interactions and molecular mechanisms of CHM components

AI-NP technologies have demonstrated significant potential in TCM

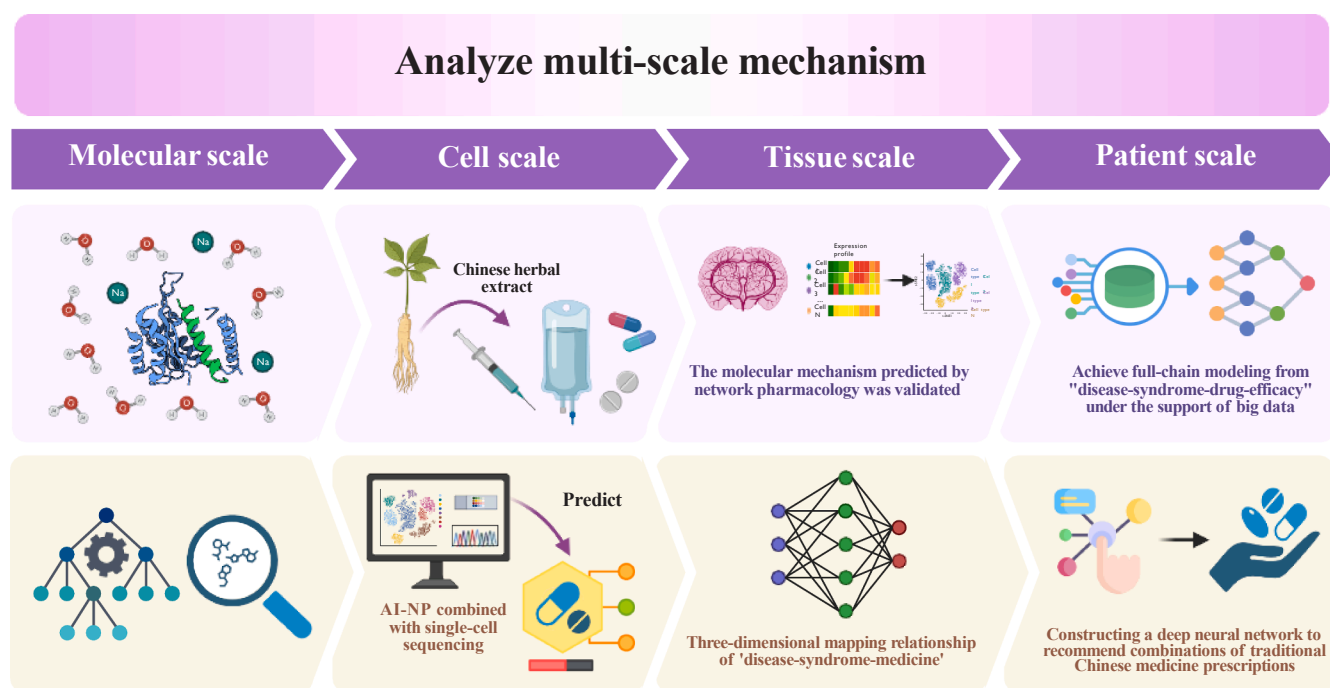


Fig. 2. Analysis of AI-NP cross-scale mechanism.

research, particularly in the analysis of signaling pathways. By analyzing gene expression profiles, AI-NP can elucidate the complex molecular networks regulated by CHM components, identify potential targets and underlying molecular mechanisms, and thereby provide a scientific basis for novel drug development.

A representative example is the target-prediction study of Quercetin in prostate cancer. Researchers employed network-pharmacology and ML-inspired methods to identify potential targets of quercetin, including EGFR, MAPK1 and other hub genes such as AKT1 and PARP1. Subsequent molecular docking revealed that quercetin could stably bind to the active sites of these proteins with favorable binding affinities. Molecular dynamics simulations using GROMACS further validated the structural stability of the quercetin–target complexes and supported the proposed multi-target mechanism of action [80]. In addition, quercetin-3-O- β -D-glucoside exhibited high binding free energy and structural stability with VEGF and HRAS proteins in cervical cancer natural product screening studies, and their binding tightness was verified by MM-GBSA analysis [81]. These findings demonstrate that the AI-NP-driven “prediction–docking–dynamic validation” integrated workflow can efficiently identify potential targets and binding modes, providing a novel paradigm for investigating the mechanisms of action of active CHM components.

In the study of CHM formulations, AI-driven molecular network analysis also holds significant value. Taking Compound Danshen Dripping Pills (CDDP) as an example, AI algorithms can be used to construct component–target–pathway networks, streamlining and optimizing processes such as data preprocessing, dimensionality reduction, and data analysis. At the same time, candidate drugs and candidate targets can be selected by fusion ML method. Under the guidance of various bioinformatics databases, effective targets and signal pathways can be screened and predicted. Studies have shown that multiple active components in CDDP synergistically regulate inflammatory responses, apoptosis pathways, and cardiomyocyte survival, thereby improving cardiac function [82–84]. This multi-component, multi-target mechanism aligns with the holistic philosophy of TCM and corresponds with the complex network regulation concept in modern systems pharmacology.

In recent years, the integration of DL with NP analysis has brought

new breakthroughs to CHM research [85,86]. AI-NP has demonstrated strong potential across multiple areas of CHM investigation. For instance, AI-NP can not only identify active CHM components and their targets but also, through pattern recognition, elucidate the regulatory mechanisms of CHM in complex diseases such as diabetic nephropathy, heart failure, and cancer, thereby facilitating the discovery of novel drug targets and candidate drug combinations [86,87]. In summary, AI-NP provides a novel perspective for elucidating the mechanisms of CHM and contributes to clarifying its underlying research mechanisms.

In AI-NP research, although many studies have demonstrated strong predictive capabilities, there remain instances of prediction failures or insufficiently validated hypotheses. For example, in quercetin target prediction studies, AI models initially predicted that quercetin could regulate multiple signaling pathways, including PI3K, EGFR, and MAPK1. However, subsequent experimental validation revealed that quercetin’s effect on EGFR was significantly lower than predicted in certain cell types, indicating limited model generalizability across different biological contexts [80]. Similarly, in studies investigating the mechanism of CDDP, network pharmacology analyses predicted that its components could substantially regulate apoptosis-related factors in cardiomyocytes. Yet, some in vitro experiments failed to fully reproduce the predicted target activities, highlighting the challenges of accurately modeling multi-component synergy and dose-dependency in computational predictions [82]. Furthermore, in AI-NP studies predicting the potential efficacy of TCM against diabetic nephropathy, certain models proposed novel targets and signaling pathways, but these hypotheses lacked sufficient in vivo or clinical validation, remaining largely theoretical [86]. These examples underscore the limitations of AI-NP in handling complex biological systems, including data heterogeneity, insufficient model interpretability, and inadequate experimental validation. Therefore, although AI-NP provides powerful predictive tools in network pharmacology, its findings require rigorous experimental design and multi-level validation to enhance reliability, thereby providing a more solid scientific foundation for mechanistic research and clinical application of TCM.

Overall, AI-NP technologies provide innovative approaches for elucidating the multi-target and multi-pathway action patterns of CHM, promoting the quantification and systematization of CHM mechanism

research. However, their scientific value remains dependent on the integration of high-quality data, algorithm interpretability, and experimental validation. Future efforts should emphasize interdisciplinary collaboration to establish verifiable, multimodal AI-NP frameworks, thereby facilitating the scientific translation of TCM from empirical knowledge to evidence-based practice.

3.2. Cell scale: understanding cell signaling pathway perturbations and phenotypic regulation under CHM intervention

CHM plays a critical regulatory role in cell fate determination, particularly in key biological processes such as stem cell differentiation, apoptosis, and autophagy. These processes often rely on intricate signaling pathways and molecular networks. AI-NP technologies provide researchers with precise tools for cellular identification and mechanistic validation, enabling the elucidation of CHM-induced pathway perturbations and phenotypic alterations at the cellular level. This approach not only advances the modernization of TCM theory but also provides a solid scientific foundation for its clinical applications.

A representative example is the study of *Polygonati Rhizoma* in regulating the tumor immune microenvironment. Using machine learning, researchers identified 38 potential bioactive compounds, among which eight were confirmed based on ADME criteria. These compounds exhibited significant inhibitory effects on HGC-27 gastric adenocarcinoma cells [88]. By integrating scRNA-seq technology, the study further revealed distinct target gene expression patterns across different cellular subpopulations, demonstrating the multi-target immunomodulatory and antitumor potential of *Polygonati Rhizoma* [88]. This research highlights the importance of CHM's multi-component and multi-target mechanisms in modulating the immune microenvironment and exerting antitumor effects.

The advantages of integrating AI-NP with scRNA-seq are further exemplified in studies of herbal formulations. For instance, in research on the Cangfu Daotan Decoction (CFDTD) for the treatment of obesity-related polycystic ovary syndrome, the combination of NP and scRNA-seq techniques predicted that its major flavonoid constituents—such as quercetin, carvacrol, β -sitosterol, and nobiletin—may act on targets including TP53, AKT1, STAT3, and JUN, thereby modulating the immune microenvironment through the TRC signaling pathway [60]. Single-cell analysis revealed that CFDTD significantly regulated specific immune cell subpopulations, which was highly consistent with the AI-based predictions. These findings indicate that the integration of AI-NP and scRNA-seq enables multiscale elucidation of CHM mechanisms, bridging molecular perturbations with cellular phenotypic responses.

The application of AI-NP in tumor microenvironment studies has further demonstrated its potential. For example, the high heterogeneity of immune cell subpopulations in lung adenocarcinoma has been revealed through scRNA-seq analysis [89]. Using a GNN-based model, researchers integrated the active components of the Astragalus-based formulation—such as quercetin and kaempferol—with known targets and signaling pathway data to predict that these compounds may regulate tumor-associated macrophage polarization via STAT1 and SPP1 pathways. Subsequent in vitro experiments confirmed that kaempferol significantly inhibited the formation of M2-type macrophages and reduced STAT1 activity, consistent with the model's predictions [89]. This case illustrates that combining AI-NP with scRNA-seq enables precise identification of CHM mechanisms within specific cellular subpopulations, offering new insights for precision drug development and personalized therapy.

Although NP has made notable progress in elucidating drug action mechanisms, several limitations remain. One major challenge lies in the fact that, while scRNA-seq reveals cellular heterogeneity, it provides limited temporal information, making it difficult to comprehensively capture the dynamic regulatory networks underlying cell fate decisions. In summary, the integration of AI-NP with scRNA-seq enables multiscale

analysis from molecular mechanisms to cellular phenotypes and unveils multi-target, multi-component regulatory networks. However, to achieve clinical translation and precision drug development, future research must incorporate dynamic and spatial information and develop more interpretable AI models to overcome current limitations.

3.3. Tissue scale: simulating the effect of CHM on tissue function and pathological state

In the field of CHM research, AI-NP technologies facilitate the elucidation of CHM mechanisms underlying tissue function modulation and pathological state regulation. By simulating the effects of CHM on specific disease conditions through NP modeling and leveraging the powerful data-processing capabilities of AI, researchers can efficiently identify the multi-target actions of CHM constituents and their interaction networks. This approach accelerates the scientific, modern, and international development of TCM.

The application of AI-NP in studies of cerebral ischemia–reperfusion injury highlights its value in investigating complex pathological conditions. For instance, in the study of the traditional Chinese prescription Naotai Fang, researchers employed AI-NP to integrate compound databases with disease-related targets, constructing a “drug–target–pathway” network that predicted its potential neuroprotective effects through signaling pathways such as STAT3 and PI3K/Akt [90]. Subsequent validation in a rat model demonstrated that Braintai Fang significantly improved neurological function scores, reduced infarct volume, and modulated the expression of apoptosis-related proteins, including Bcl-2, Bax, p-STAT3, and p-Akt. These findings suggest that the prescription exerts neuroprotective effects by regulating apoptotic signaling pathways [90]. This study not only validated the predictive capability of AI-NP but also provided a systematic modeling framework for elucidating CHM-mediated neuroprotection in brain injury.

The application of AI-NP in studies of CM syndromes has also made remarkable progress. According to relevant review reports, AI-NP has become an important way to reveal the molecular basis of traditional Chinese medicine “syndromes” such as cold syndrome/heat syndrome [91]. By integrating disease-related genes, syndrome-specific biomarkers, and CHM action networks, researchers have gradually established a three-dimensional “disease–syndrome–herb” mapping framework. For example, in hepatocellular carcinoma, PPI networks were constructed for different syndrome types—cold, heat, and damp-heat patterns—and key modules were identified using the random walk algorithm, revealing syndrome-specific signaling pathways and target clustering features [91]. Furthermore, a multi-graph convolutional network (multi-GCN) approach has been developed to model the relationships among symptoms, syndromes, and herbs in a graph-based structure, thereby providing data-driven support for CM diagnosis and personalized treatment [92]. These advances enable quantitative characterization of CM syndromes, inference of molecular mechanisms, and visualization of the “formula–syndrome correspondence” principle, transforming TCM syndrome research into a measurable and verifiable scientific process.

The value of AI-NP has also been demonstrated in the study of complex diseases and multitarget regulation. CHM exerts therapeutic effects through the coordinated modulation of multiple components, targets, and pathways. NP enables the construction of multidimensional network models to decipher the interactions among bioactive compounds and their corresponding targets, thereby elucidating the material basis of CHM efficacy and its correlation with disease mechanisms [93,94]. When integrated with AI—particularly ML and DL approaches—NP can efficiently assimilate multi-omics datasets, identify key regulatory molecules, and uncover the molecular essence of the holistic regulatory effects characteristic of CM [95–97]. Through network-based analyses, researchers can pinpoint potential targets and their roles across various signaling pathways, providing mechanistic insights into CHM's multitarget actions and establishing a theoretical foundation for

the modernization and clinical translation of TCM.

In summary, AI-NP provides a systematic framework for elucidating CHM mechanisms from molecular regulation to tissue-level function, effectively revealing the complex multitarget and multipathway regulatory networks underlying CHM efficacy. However, current disease and syndrome networks lack sufficient dynamic and spatiotemporal information, limiting comprehensive elucidation of pathological progression and CHM regulatory timing. Future studies should focus on improving data quality and integration, incorporating dynamic omics and spatiotemporal modeling techniques to refine the AI-NP framework and facilitate the transition of TCM from empirical knowledge to systematic science and clinical application.

3.4. Patient-scale: connection mechanism studies and clinical efficacy/safety

At the patient level, a critical challenge lies in effectively bridging molecular mechanistic studies with clinical practice. NP serves as an important intermediary by elucidating the complex network relationships between drugs and diseases, thereby helping clinicians better understand drug action mechanisms. The integration of AI further enhances the precision and efficiency of such studies, enabling the identification of biomarkers associated with drug responses within large-scale clinical and omics datasets. This, in turn, facilitates patient stratification and personalized therapeutic interventions [98,99].

AI-NP has demonstrated significant potential in predicting CHM clinical efficacy and individual patient responses. In one study on Long COVID, an interpretable model was constructed by integrating CM syndrome scores, patient clinical features, and AI algorithms to predict the therapeutic effects of CHM interventions. SHAP analysis identified key variables closely associated with efficacy, such as baseline symptom distribution and CM syndrome type, and a visual nomogram was employed to support individualized treatment recommendations [100]. Another study, based on a network medicine approach, predicted the therapeutic potential of CHM by calculating the topological proximity between CHM compound targets and disease symptom modules within protein–protein interaction networks. The results demonstrated a significant correlation between network proximity and symptom improvement, validating the effectiveness of this approach for herb–disease pair prediction [101]. These findings indicate that AI-NP is transitioning from mechanistic modeling to clinical efficacy prediction in CHM, enabling a fully data-driven modeling framework spanning “disease–syndrome–herb–effect.”

AI-NP has also demonstrated clinical value in disease prognosis and therapeutic efficacy prediction. In colorectal cancer, researchers developed a machine learning-based CHM prognostic model to assess post-operative recurrence and metastasis risk. The model integrated patients’ CM syndrome distributions, CHM intervention regimens, and clinical indicators, achieving high-precision recurrence risk prediction through multi-algorithm comparison [102]. The results showed that the AI model could predict 3-year and 5-year recurrence risks and revealed the potential independent contribution of CHM interventions to improved prognosis, providing data-driven support for establishing a causal pathway linking “patient characteristics–syndrome–CHM intervention–prognostic outcome.” This approach lays the foundation for individualized and evidence-based studies of CHM in long-term cancer management.

In the field of individualized formula recommendation, the application of deep learning within AI-NP has further expanded the boundaries of precision diagnosis and treatment. A representative example is the FordNet model, which integrates patient clinical phenotypes—including chief complaints, physical signs, and constitution types—with molecular features of CHM herbal components to construct a deep neural network for individualized formula combination recommendations [103]. The model maps symptom information from EMR and drug molecular features into a unified feature space, enabling

end-to-end prediction from “symptoms–herbs” to “formula–efficacy.” Experimental results demonstrated that FordNet achieved significantly higher recommendation accuracy across multiple CM indications compared to traditional rule-based or statistical models, marking a shift of CHM formula recommendation from experience-driven to data-driven and intelligent approaches.

Despite breakthroughs in the application of AI-NP for individualized CHM treatment and efficacy prediction, several challenges remain. First, model interpretability and clinical generalizability are still limited. Most studies rely on specific datasets or institutional cohorts, with limited external validation, posing risks of overfitting and bias. Second, clinical data quality is often uneven, and variable heterogeneity is substantial, particularly due to the subjective nature of CM syndromes, which compromises model robustness across diverse populations. Third, AI-NP predominantly operates at the level of statistical associations, lacking causal inference and mechanistic validation, which constrains its support for clinical decision-making. Finally, ethical and privacy concerns remain critical barriers in medical AI applications, especially when integrating multimodal data and constructing patient profiles, requiring stringent regulatory oversight.

Overall, AI-NP enables vertical integration from molecular and cellular mechanistic insights to tissue-level and patient-level physiological and clinical outcomes. At the molecular and cellular scales, AI-NP leverages ML, DL, and GNN algorithms in combination with multi-omics data to identify active CHM components, target interactions, and signaling pathway perturbations. These mechanistic insights provide a foundation for understanding the system-level effects of multi-component, multi-target, and multi-pathway regulation, and further guide the prediction of tissue function and clinical phenotypes. By integrating molecular docking, scRNA-seq, and clinical phenotypic data, AI-NP facilitates a seamless connection between mechanistic research and clinical translation, enabling efficacy prediction, prognostic evaluation, and individualized treatment. This multiscale integration highlights the capacity of AI-NP to bridge biological hierarchies, transforming dispersed molecular information into actionable clinical insights and advancing the modernization and precision application of TCM. A summary of representative AI-NP applications in TCM research is presented in Table 3, demonstrating the growing breadth of AI-NP utilization in this field.

4. Challenges and future directions

With the rapid development of information technology, AI-NP is gradually transforming the study of TCM. NP can systematically reveal the multi-target and multi-component mechanism of TCM, which promotes the combination of TM theory and modern pharmacology research [59]. Combined with AI technology, NP’s potential has been further enhanced, enabling effective processing and analysis of massive amounts of biomedical data to support drug development and personalized therapy. Advances in multi-omics technologies allow AI-NP to elucidate drug mechanisms more comprehensively by leveraging multimodal data [104]. For example, DL model can mine valuable information from large-scale biological datasets, deepening the understanding of disease mechanisms. Integrating multi-group data not only improves data utilization but also lays a foundation for precision medicine. Despite these advances, AI-NP still faces a series of challenges such as uneven data quality and insufficient interpretability of algorithms, and further research and innovation are urgently needed to overcome these obstacles [101,104].

Despite the rapid advancement of AI-NP in TCM research, instances of failed predictions and unverified hypotheses highlight ongoing challenges in the field and suggest the potential presence of publication bias. The previously described case studies not only reflect uncertainties in simulating multi-component, multi-target networks with AI-NP but also indicate that the literature may be skewed: studies are more likely to report positive results or successful predictions, whereas negative or

Table 3
Application cases of AI-NP in CHM research.

No.	Type	Example	Ref.
1	Monomer component	By predicting the proteins that quercetin may intervene through the ML model and validating	[80]
2	CHM Compound	Integrating ML methods to screen effective drugs, action targets, and related pathways in CDDP	[82–84]
3	Single herb medicine	Using ML algorithm to screen potential active ingredients in <i>Polygonati Rhizoma</i>	[88]
4	CHM Compound	Integrating AI-NP and scRNA seq techniques to determine the main components, target sites, and cell subpopulations of CFDTD	[60]
5	Single herb medicine	By using the GNN model, integrating the active ingredients, known targets, and pathway information in <i>Astrolus membranaceus</i> , it is predicted that it may regulate the polarization state of tumor associated macrophages through key targets	[89]
6	CHM Compound	Using AI-NP integrated component database and disease-related targets, predict the key signaling pathways that Naotaifang may regulate, and experimentally verify its anti-ischemia reperfusion injury effect	[90]
7	CM syndrome types	Based on different CM syndrome types, a protein interaction network containing candidate herbs and core genes of the syndrome was constructed, and a random walk algorithm was applied to identify key network modules clustered with specific syndrome types	[91]
8	Prescription recommendations	Constructing a multi-GCN model to construct a graph structure of symptoms, syndromes, and herbs to guide TM diagnosis assistance and personalized medication recommendation	[92]
9	Efficacy prediction	Constructed an interpretable model that combines CM syndrome scoring, patient clinical characteristics, and AI algorithms to predict the efficacy of CHM	[100]
10	Prognostic assessment	A ML based CHM prognostic model was constructed to preliminarily evaluate the independent effect of CHM intervention on improving prognosis	[102]
11	Prescription recommendations	The FordNet model integrates the clinical phenotype of patients with the molecular characteristics of CHMcomponents to construct a deep neural network for personalized recommendation of CHM compound combinations	[103]

inconclusive findings are often underreported, potentially leading to an overestimation of AI-NP reliability and generalizability. Therefore, although AI-NP offers powerful predictive tools, researchers must exercise caution in model development and experimental validation, emphasizing transparent reporting and the dissemination of negative results to ensure the scientific rigor and sustainable development of the field.

In conclusion, AI-NP provides new perspectives and methods for TCM research, new drug discovery, drug target prediction and clinical precision therapy. With ongoing advancements in theoretical knowledge and technology, AI-NP is poised to achieve further breakthroughs, continually revitalizing personalized medicine and the treatment of complex diseases.

4.1. Data challenges

Despite the considerable potential of AI-NP in CHM research, the field continues to face significant data-related challenges. These issues primarily stem from the diversity, complexity, and lack of standardization of the data, resulting in uneven data quality and difficulties in data integration, which in turn limit the predictive accuracy of models and their broader applicability [105].

First, the complexity of CHM components represents a critical bottleneck in the application of AI-NP. Herbal medicines typically contain multiple active compounds, and significant variability in component content exists across different sources and batches, leading to highly complex and diverse pharmacological effects. For example, approximately 400 chemical constituents have been identified in Chuanxiong, including phenolics, terpenoids, and alkaloids, which collectively determine its pharmacological activity through intricate interactions [106]. Advances in molecular biology and analytical chemistry continue to reveal new bioactive compounds, yet their precise mechanisms of action and target regulations remain incompletely understood, increasing the difficulty of CHM standardization and quality control. Moreover, certain structurally complex compounds, such as polysaccharides, pose additional challenges due to the diversity of glycosidic linkages, making isolation, identification, and quantification technically demanding [107]. In addition, commonly used chemical and TCM databases exhibit limitations in data completeness, standardization, and update frequency. Databases such as PubChem and ChEMBL provide high-quality standardized information on chemical structures, bioactivity assays, and biological target annotations, but they remain insufficient for describing the complex constituents of CHM. Conversely, TCM-specific databases like TCMID, TCMSP, and SymMap offer advantages in integrating herbal components, pharmacological targets, and formula information, supporting AI-NP applications in TCM research. However, these databases generally suffer from data redundancy, inconsistent nomenclature, limited experimental validation, and weak interoperability, which constrain the accuracy and interpretability of AI models. Therefore, in CHM research, the efficient extraction, identification, and quantification of complex components, along with enhanced database standardization and cross-platform integration, constitute essential prerequisites for improving the predictive accuracy and interpretability of AI-NP models.

Second, the complexity and unstructured nature of CM clinical data pose significant challenges for AI-NP applications. CM diagnosis and treatment are based on the syndrome differentiation and treatment framework, which emphasizes individual variability and holistic regulation, resulting in clinical records that contain rich information on symptoms, syndromes, therapeutic outcomes, and follow-up observations [108]. For instance, in the management of functional dyspepsia, practitioners may diagnose a patient with “Liver-Spleen disharmony” based on both physiological and emotional states, reflecting the multi-dimensional and dynamic characteristics of CM diagnosis. However, such complexity complicates linear modeling. Furthermore, most CM clinical records are unstructured text, lacking standardized coding or formatting, and considerable variation exists across different physicians and institutions, severely affecting data integration, sharing, and model training [109]. In particular, in multicenter studies, inconsistencies and poor comparability of clinical data constitute major barriers to the clinical validation and generalizability of AI-NP models.

Third, insufficient integration of multi-scale data represents a central bottleneck in the development of AI-NP. Current AI-NP studies must simultaneously handle heterogeneous data from multiple levels, including molecular omics, cellular omics, tissue imaging, and clinical records. Due to the lack of effective cross-scale modeling approaches and standardized data protocols, the generalizability and interpretability of models are often limited [110,111]. Single-source data cannot fully capture the complexity of biological processes, whereas NP approaches that integrate multi-dimensional data—such as genomics,

transcriptomics, and metabolomics—can partially enhance model systemicity and predictive performance [112,113]. Nevertheless, the absence of unified data standards and sharing mechanisms continues to constrain cross-domain collaboration and the translational application of AI-NP in precision medicine and drug mechanism research [114].

The current challenges of AI-NP in the TCM field are characterized by the coexistence of “data fragmentation and model black-boxing.” On one hand, insufficient standardization of CHM chemical constituents, pharmacological mechanisms, and clinical data undermines the reliability of model inputs. On the other hand, although AI models enhance analytical efficiency, they often lack interpretability, making it difficult to satisfy the scientific requirements for causal and mechanistic validation in TCM research. Furthermore, AI-NP studies currently lack unified regulations regarding data sharing ethics, intellectual property protection, and standards for multicenter collaboration, limiting the reproducibility and clinical translation of research findings. Overall, improving the quality of AI-NP research depends on the construction of high-quality, traceable, multi-scale CHM databases, the establishment of cross-platform data standardization protocols, and the development of interpretable AI algorithms capable of causal inference at the mechanistic level. Future efforts should strengthen multidisciplinary collaboration, integrating systems pharmacology, knowledge graphs, and clinical big data to advance AI-NP from theoretical modeling to practical validation, thereby promoting the standardization, systematization, and intelligent development of CHM research.

4.2. Algorithms and model challenges

Although AI-NP has achieved significant progress in drug screening, target prediction, and mechanism analysis, challenges remain in algorithm design and model construction. These challenges include data heterogeneity, poor model interpretability, and limited generalization. Studies have shown that current multi-omics-based drug sensitivity prediction models often suffer from overfitting, low interpretability, difficulty integrating heterogeneous data, and suboptimal prediction accuracy [114,115]. Consequently, designing more effective algorithms and constructing adaptive models has become a critical and challenging focus of current research.

Although complex AI-NP models offer performance advantages, their nonlinear characteristics and highly abstract representations make the decision-making process difficult to trace and interpret [116,117]. Clinicians often struggle to understand the underlying logic of model outputs, undermining the adoptability of AI predictions and clinical trust. This “high-accuracy–low-interpretability” paradox has become a central dilemma in AI-NP development. More critically, the reproducibility and causal verifiability of AI predictions are often limited, rendering some research findings difficult to translate into reliable clinical evidence. Therefore, ensuring model transparency and interpretability while maintaining predictive performance represents a key scientific challenge for the clinical application of AI-NP.

AI-NP still faces significant limitations in modeling dynamic and spatiotemporal networks. Drug actions *in vivo* are highly time-dependent and spatially specific, yet most current NP models are based on static network assumptions, making it difficult to capture multi-target synergistic effects over time [118]. Although modular pharmacology and multi-omics integration offer new avenues for dynamic system analysis, the high dimensionality of data and insufficient temporal resolution pose substantial modeling challenges [119]. Moreover, constructing spatiotemporal networks requires integrating multi-level data, including drug distribution, intercellular communication, and tissue microenvironment information [120,121], which static analysis methods often fail to accurately reflect. The absence of a spatiotemporal dimension creates an information gap when simulating the dynamic pharmacological effects of CHM, thereby limiting AI-NP’s ability to represent complex physiological systems.

Most existing AI-NP applications focus on complex data analysis or

model construction, whereas cross-scale causal inference remains methodologically underdeveloped. Cross-scale causal modeling involves capturing causal relationships from molecular and cellular levels to tissues and individual patients, requiring algorithms capable of handling heterogeneous, multimodal, and multi-level data [122]. For instance, a study on Ditan Decoction for treating intracerebral hemorrhage employed PPI and compound–target networks to identify core functional modules [123]. Although this approach revealed potential pathways, it did not establish cross-scale causal logic, remaining at the level of correlational interpretation. This illustrates that while AI-NP can integrate complex information, it remains immature in causal inference and mechanistic validation. Future models should incorporate structural causal models or interpretable graph learning to more accurately elucidate causal relationships between drug mechanisms and biological effects.

Insufficient validation of model generalizability and robustness represents a critical barrier to the practical application of AI-NP. Many AI models perform well on specific datasets, yet their performance deteriorates significantly when applied to data from different sources or heterogeneous contexts, indicating a strong tendency toward overfitting [124,125]. Moreover, these models often lack robustness against experimental noise, class imbalance, and data distribution shifts [126], resulting in unstable and non-reproducible predictions. For instance, in drug mechanism prediction, if the training data distribution differs from that of real-world clinical data, model performance can decline sharply, thereby undermining its practical utility.

The current technological bottlenecks in AI-NP do not merely stem from limitations in algorithmic capability but rather reflect an imbalance among data, models, and interpretability. On one hand, AI models often prioritize predictive accuracy at the expense of biological interpretability and experimental verifiability, resulting in a disconnect between scientific discovery and clinical application. On the other hand, AI-NP research generally lacks standardized datasets and unified evaluation frameworks, limiting model comparability and reproducibility of results. Furthermore, when addressing the unique complexities of TCM—such as multi-component, multi-target, and multi-pathway characteristics—AI models tend to rely on simplified assumptions, which may lead to predictions that deviate from actual physiological contexts. Therefore, future AI-NP research should focus on developing interpretable and verifiable hybrid intelligence models, incorporating dynamic and spatiotemporal modeling frameworks, and establishing multicenter, standardized open-access databases along with unified evaluation metrics. Only by addressing these challenges can AI-NP truly transition from theoretical innovation to clinical practice, thereby supporting a new phase of modernization and precision development in TCM.

4.3. Verification challenge

Despite significant advances in AI-NP for drug development and mechanistic research, a substantial gap remains between model predictions and experimental validation, which severely limits clinical translational potential. Many studies rely primarily on computational predictions, lacking systematic *in vitro*, *in vivo*, or clinical evidence to support their findings, leaving AI-NP outputs largely at the theoretical level and hindering the development of actionable intervention strategies [127]. This gap primarily arises from a structural tension between the high-throughput, system-level objectives of AI model predictions and the feasibility constraints of experimental validation, which is limited by cost, time, and technical conditions. Consequently, the validation process often lags behind computational progress, impeding the translation of AI-NP insights into practical clinical applications.

The high cost and long duration of experimental validation constitute a central barrier to the practical implementation of AI-NP research. While AI-NP has demonstrated the capacity to identify potential targets of natural products and small-molecule drugs in complex diseases, in

vivo validation of computational predictions remains particularly challenging. Animal experiments require model establishment, intervention administration, and long-term monitoring, often demanding substantial financial, human, and temporal resources [128–130]. Clinical trials, as a critical stage of drug development, face even greater constraints due to high costs and stringent ethical and regulatory requirements [131]. Furthermore, patient recruitment rates, adherence, and endpoint design all influence trial duration and data quality [132]. These practical limitations hinder the timely translation of AI-NP predictions into experimentally validated drug candidates or therapeutic strategies.

The absence of a robust biological validation system further undermines the credibility of AI-NP predictions. Although AI models are continuously optimized at the algorithmic level, predicted molecular mechanisms are difficult to establish as scientifically reliable without supporting experimental evidence [133,134]. Currently, most AI-NP studies lack a feedback loop connecting computational prediction, experimental validation, and model refinement, resulting in uncorrected prediction biases and model optimization without empirical grounding. Therefore, it is imperative to establish an integrated “dry-wet” validation framework (in silico–in vitro–in vivo) that dynamically links AI predictions with experimental validation [135].

Insufficient model interpretability and suboptimal experimental design are fundamental factors contributing to validation difficulties. Although current AI-NP models can efficiently identify potential targets, their decision-making processes are often complex and lack interpretability, making it challenging for researchers to assess the biological plausibility of predictions [133,136]. This directly affects the specificity and efficiency of experimental designs. Additionally, many experimental studies suffer from methodological shortcomings, such as inadequate randomization and lack of proper controls, resulting in poor reproducibility and limited reliability. These issues highlight a methodological imbalance in AI-NP research, characterized by “algorithmic advancement outpacing experimental validation.”

Insufficient data integration capabilities limit the establishment of a closed-loop AI-NP framework. AI-NP relies on multi-omics, high-dimensional, and heterogeneous data; however, current methods for data integration remain exploratory. Variations in data sources, inconsistencies in experimental conditions, and the unstructured nature of clinical data hinder the development of unified cross-platform models and validation. Without standardized strategies for data processing and integration, even highly accurate predictions are difficult to verify or apply across different experiments and institutions.

The AI-NP field currently exhibits a structural disconnection in the “prediction–validation–translation” pipeline, primarily due to a “technological rationality bias” that over-relies on computational outputs while neglecting experimental feedback. Some studies place excessive emphasis on model performance metrics, overlooking the biological and pharmacological interpretability, which may cause AI predictions to diverge from the actual pharmacodynamic basis. Moreover, experimental validation often aims merely to “verify model predictions” rather than pursue independent, hypothesis-driven scientific inquiry, potentially introducing result-dependent biases. This trend risks creating a self-consistent computational loop rather than a scientifically falsifiable validation cycle. Future AI-NP research should focus on establishing cross-level and multi-modal validation frameworks, incorporating interpretable AI approaches, optimizing experimental design standards, and promoting data standardization along with multi-center collaboration. Only by constructing a scientific closed loop of “algorithm–experiment–feedback” can AI-NP progress from theoretical exploration to verifiable and translatable applications.

4.4. Future direction

The deep integration of AI and NP is injecting new vitality into drug mechanism analysis, drug discovery and precision medicine, especially on the road of modernization of TM, showing a wide range of

application prospects. As technology evolves, more and more research are beginning to use AI technology to process complex biomedical data to reveal mechanisms of drug action and potential therapeutic targets. This integration could not only improve the efficiency of new drug development, but could also help personalize medicine. AI-NP future research directions should be as shown in Fig. 3.

Future development of AI-NP should focus on methodologically integrating cutting-edge AI technologies to enhance the analysis and predictive capabilities for complex CHM systems. GNN, with their superior performance in handling non-Euclidean data structures, are expected to play a key role in constructing multi-layer “component–target–pathway” networks [137]. Generative AI approaches, such as variational autoencoders and diffusion models, are emerging as powerful tools for CHM component structure optimization and virtual screening, providing innovative pathways for the design of “new CHMs” [138]. Reinforcement learning can be applied to simulate drug intervention trajectories and optimize dosing strategies in dynamic environments, thereby supporting individualized therapy planning [139]. Furthermore, large-scale pre-trained biomedical models demonstrate broad potential in CM semantic understanding, target prediction, and multi-source data integration. Through customized fine-tuning, AI-NP is poised to bridge the gap from “knowledge discovery” to “intelligent decision-making,” driving the modernization and precision development of TCM.

Another promising direction for AI-NP is to overcome the limitations of static mechanism inference and extend toward spatiotemporal dynamics and cellular heterogeneity. Most current studies predict CHM targets and pathways based on integrated omics data, often overlooking dynamic changes during disease progression and intercellular variability. Future efforts should combine AI models with scRNA-seq and spatial transcriptomics technologies to capture differential drug responses across cell types and spatial locations [140]. By constructing cell type-specific or region-specific action networks, it is possible to elucidate how CHM components regulate key cellular subpopulations within the disease microenvironment, enabling multi-dimensional modeling across the “component–target–cell–space” axis.

Developing a “causal AI-NP” framework centered on causal inference is a key direction for advancing from correlation-based to mechanism-driven insights. Current AI-NP approaches primarily rely on multi-omics and network data to identify statistical associations, which cannot distinguish direct effects from concomitant phenomena. Causal AI-NP aims to integrate causal graphs, structural equation models, instrumental variable analysis, and doubly robust estimation, combined with GNNs and time-series modeling, to identify direct intervention chains in dynamic networks [141]. For instance, in CHM compound studies, causal inference can verify whether a specific component directly drives phenotypic improvement through a particular signaling pathway, rather than merely co-occurring. By further integrating single-cell temporal and spatial omics data, it is possible to construct cross-scale causal intervention networks, providing robust scientific evidence for mechanism validation and precision therapy.

The “Digital Twin” technology offers a novel direction for AI-NP applications in TCM research. By integrating multi-omics, such as genomics, transcriptomics, metabolomics, imaging, and clinical phenotypic data, highly personalized and dynamically updatable virtual patient models can be constructed [142]. In CHM research, combining AI-NP with multi-component–multi-target–multi-pathway networks enable simulation of compound formula effects in virtual patients, predicting the impact of different formulations, dosages, and intervention timings on disease progression [143]. This approach has the potential to facilitate preclinical formula screening and efficacy prediction, thereby reducing the risks and costs associated with clinical trials.

The sustained development of AI-NP relies on an open, collaborative, and standardized scientific ecosystem. High-quality, openly accessible databases should be established, accompanied by rigorous data quality control and comprehensive metadata annotation systems.

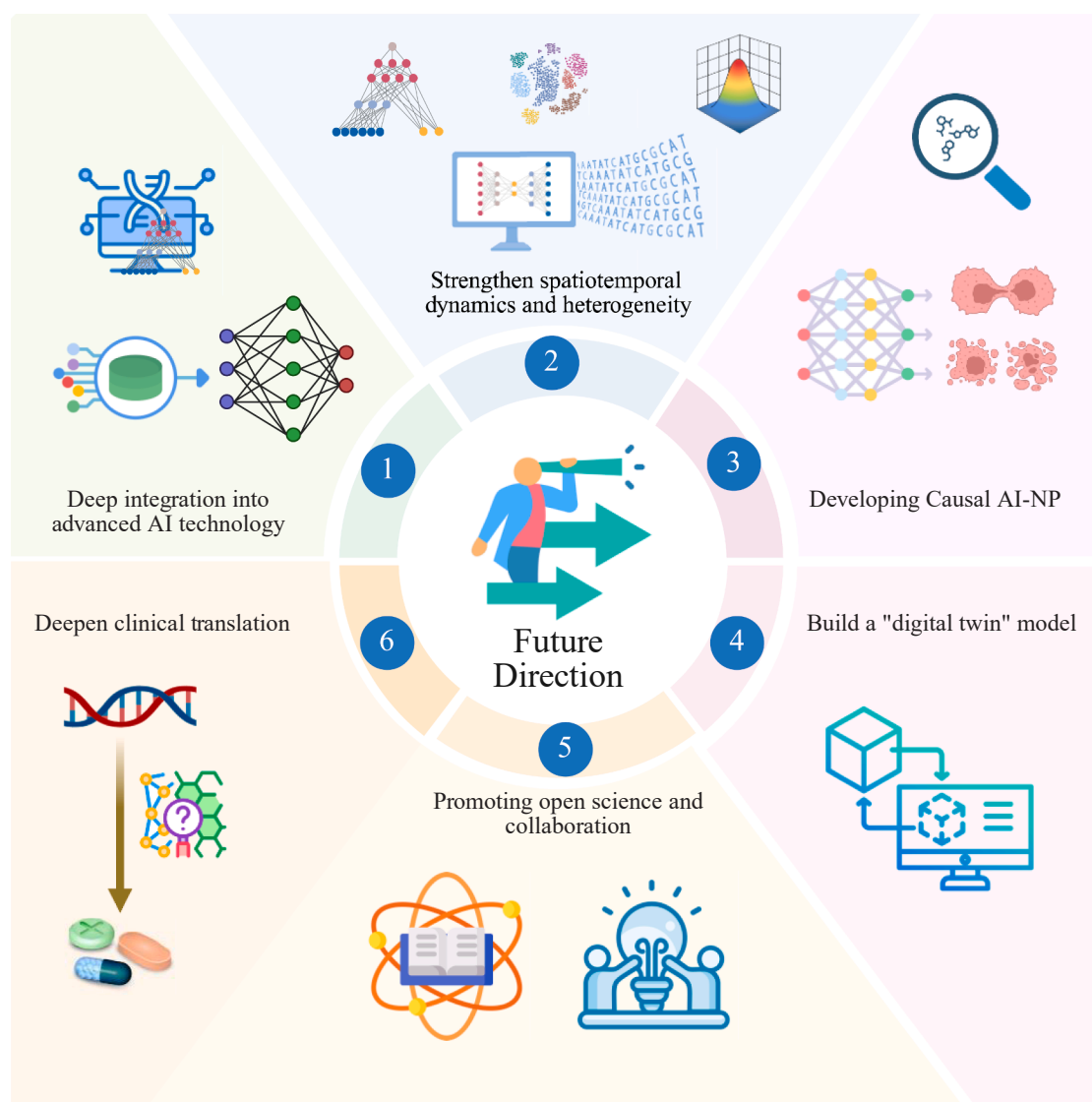


Fig. 3. AI-NP Future research directions.

Simultaneously, standardization of algorithmic frameworks and transparency in model evaluation processes are essential to enhance reproducibility and cross-platform comparability. Dedicated AI-NP platforms for TCM should integrate multi-source data management, network construction, model training, and visualization analysis to form an integrated research infrastructure.

More critically, in AI-NP research, model selection, data preparation, and validation standards are pivotal for ensuring the reliability and translational potential of study results. Regarding model selection, researchers should choose algorithms aligned with their research objectives and data characteristics. For complex multi-omics datasets and non-Euclidean molecular-target networks, GNN or DL models are preferred, whereas traditional ML models such as SVM or RF may be more robust for smaller or high-noise datasets. Data preparation must rigorously control quality, including removal of duplicates, handling of missing values, unification of data formats, and feature standardization, thereby minimizing the impact of data heterogeneity on model performance. For validation, a multi-tiered strategy should be adopted, encompassing cross-validation, independent external dataset testing, and in vitro or in vivo experimental verification, to ensure model generalizability and reproducibility. Moreover, researchers should meticulously document hyperparameter settings, training procedures, and performance metrics, and provide reproducible code and datasets

whenever possible, enabling clinicians and scientists to understand model decision logic and assess predictive reliability. When these foundational steps are secured, the ultimate goal of AI-NP is to support clinical decision-making. Future research should explore embedding model predictions into clinical trial design, incorporating identified key components, core pathways, and potential biomarkers into participant stratification and efficacy monitoring, thereby enhancing trial efficiency and success rates. In parallel, integration with EMR and real-world data can facilitate the development of real-time, individualized decision support systems, enabling AI-NP predictions to translate into optimized prescriptions and risk-assessed therapeutic interventions. This closed-loop framework, spanning methodology to application, not only strengthens the scientific rigor and reproducibility of AI-NP research but also builds a robust bridge between mechanistic insights and precision medicine.

5. Conclusion

With the rapid development of AI technology, the application of NP in TCM field is facing unprecedented opportunities. The integration of AI has overcome the limitations of conventional pharmacology in data integration, mechanistic exploration, and pattern recognition, enabling researchers to decipher the complex mechanisms of CHM with higher

precision. In particular, the combination of multi-omics integration and AI-driven approaches has transformed drug target identification, formula optimization, and safety assessment from experience-based practices to data-driven strategies, significantly enhancing both the systematic understanding and predictive accuracy of research. This shift not only reshapes the technological trajectory of TCM research but also reinforces its scientific standing within modern biomedical frameworks.

AI-NP enables the elucidation of TCM mechanisms across multiple biological scales, from molecules and cells to tissues and individual patients. Leveraging advanced algorithms such as ML, DL, and GNN, researchers can integrate chemical structures, multi-omics data, clinical phenotypes, and real-world evidence to construct systematic “compound–target–pathway–phenotype” networks [82,88,90,100]. Recent AI-NP studies combining single-cell and spatial multi-omics approaches have revealed the precise regulatory effects of CHM formulas on disease microenvironments and specific cell subpopulations. These findings not only advance the scientific interpretation of TCM’s holistic principles but also provide a data-driven framework for precision therapy and novel drug discovery. Collectively, AI-NP is transitioning from theoretical exploration toward experimentally verifiable systems and clinical translation, serving as a critical bridge between TCM and modern biomedical science.

With growing global attention on TCM, AI-NP can effectively identify the mechanism of action and potential targets of CHM components by integrating massive data and advanced algorithms, thus providing data support for modern research on TCM. This capability provides critical data support for modern TCM research, enhancing both scientific rigor and international recognition. AI-NP transforms traditional empirical medicine into precision medicine and demonstrates clear advantages in key areas such as drug target prediction, prescription optimization, mechanism analysis, and quality control [127]. Especially in drug target prediction, prescription optimization, mechanism analysis and quality control, the application of this model not only improves the research efficiency, but also provides a strong impetus for the scientization and internationalization of TCM [101]. By enabling rigorous, data-driven approaches, AI-NP holds broad strategic value and offers significant prospects for the future development and global integration of TCM.

However, the application of AI-driven network pharmacology (AI-NP) still faces several practical challenges. Data heterogeneity and uneven quality are major factors limiting model stability and generalizability. The decentralized sources and inconsistent collection standards make cross-platform integration and reproducibility difficult, thereby reducing the scientific reliability of predictions. Moreover, the limited interpretability of AI-NP models hinders clinical trust. Most current models operate as “black boxes,” achieving high predictive accuracy but lacking transparency in their internal logic, which constrains clinical adoption and regulatory approval [144]. In addition, a systematic cross-scale validation framework—from in silico predictions to in vitro, in vivo, and clinical verification—is generally absent, limiting both the translatability and external applicability of AI-NP findings.

To address these challenges, the future development of AI-driven network pharmacology (AI-NP) should focus on optimization at three levels. First, data standardization and sharing mechanisms should be strengthened by establishing high-quality, open-access databases with unified metadata annotation systems to support cross-institutional data integration and model retraining. Second, the application of explainable AI (XAI) in pharmacology should be promoted, incorporating causal inference and knowledge graph constraints to ensure that model predictions are biologically plausible and verifiable. Third, a multi-tiered validation framework should be established, combining in vitro experiments, animal models, and real-world clinical data to perform multi-dimensional cross-validation of AI predictions, thereby enhancing the scientific rigor and clinical credibility of the models.

It is noteworthy that the sustainable development of AI-driven network pharmacology (AI-NP) relies on interdisciplinary collaboration and clinical feedback mechanisms. The deep integration of

computer science, biology, pharmacology, and clinical medicine is a key driver of innovation in this field [145]. However, current collaborations often exhibit an imbalance, with technology development outpacing clinical demand. Without active participation from clinical settings and guidance from pharmacology, AI algorithms risk being “technologically advanced but difficult to implement.” Therefore, future efforts should focus on building clinically driven, interdisciplinary platforms that promote a closed-loop interaction among algorithm design, experimental validation, and clinical application, thereby facilitating the translation of AI-NP from model innovation to tangible medical value.

In conclusion, this review provides a systematic theoretical and technical framework reference for researchers in related fields, helping AI-NP to develop towards an intelligent and precise future. By integrating different research perspectives and findings, we not only gain a clearer understanding of the opportunities and challenges that AI-NP brings, but also outline meaningful guidance for future directions. In this rapidly evolving field, continuous research and collaboration will be key to achieving scientific breakthroughs and clinical applications.

Author agreement

The undersigned declare that this manuscript entitled “**AI driven Network Pharmacology: Multi-scale Mechanisms of Traditional Chinese Medicine from Molecular to Patient Analysis**” is original, has not been published before and is not currently being considered for publication elsewhere. We would like to draw the attention of Editor of *Computational and Structural Biotechnology Journal*. We confirm that the manuscript has been read and approved by all named authors. We further confirm that the order of authors listed in the manuscript has been approved by all of us. We understand that the Corresponding Author is the sole contact for the Editorial process. They are responsible for communicating with the other authors about progress submissions of revisions and final approval of proofs.

CRediT authorship contribution statement

Jie Liao: Writing – review & editing, Funding acquisition. **Meng Gao:** Writing – review & editing. **Qin Zhu:** Writing – review & editing. **Muzi Li:** Writing – review & editing. **Wenbo Guo:** Writing – review & editing. **Guoqian Cui:** Writing – review & editing, Writing – original draft.

Funding

This work was supported by the “Leading Goose” R&D Program of Zhejiang (2025C01133, J.L.), the National Natural Science Foundation of China (82474194, J.L.), and the Key Project of Zhejiang Provincial Administration of Traditional Chinese Medicine (GZY-KJS-ZJ-2025–071, J.L.).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

Thanks to all the authors for their important contributions to the writing and intellectual content of the article.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.csbj.2025.11.016](https://doi.org/10.1016/j.csbj.2025.11.016).

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