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Research progress in Fangjiomics: methodologies, applications, and perspectives

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ABSTRACT

Fangjiomics is a promising paradigm that enhances research on multi-omics-based pharmacological mechanisms of Fangji from holistic and systematic perspective. We reviewed recent advances in Fangjiomics, focusing on database and analysis platform development, methodological innovations, and translational applications. Through the integration of Fangji and multi-omics data, multi-level system analysis approaches were developed, encompassing single-target analysis, signaling pathways, multi-targeted network and modules. Fangjiomics has emerged as a key strategy in various areas of Fangji research. To support the high quality development of Fangjiomics, we propose principles and perspectives from the integrated, macro-level, and practical viewpoints.

1 Introduction

Millennia-old Chinese medicine has been treating diseases with Fangji to improve efficacy and/or reduce toxicity in clinical practice. Modern research into the pharmacological mechanisms of Fangji is crucial for decoding the scientific principles of traditional Chinese medicine (TCM), and represents a key area for both the inheritance and innovation of TCM research in the new era. Research based solely on single-target or pathway approaches may fail to elucidate the holistic, harmonious effects of Fangji. In the context of omics, Fangjiomics was proposed to systematically study myriad compatible combinations that may act through multiple targets and modes of actions, balancing on-targets with off-targets [1]. A variety of omics technologies and related analytical tools are integrated to reveal the complex relationships within the Fanjiome across different omics levels. In line with the holistic view and the TCM principle of treatment based on syndrome differentiation, Fangjiomics integrates multidisciplinary approaches such as systems biology, bioinformatics, chemical biology, and network pharmacology. These approaches bridge the gap between "disease-syndrome-target-prescription" and overcome the limitations of single-target research, enabling the exploration of Fangji's pharmacological mechanisms from a holistic and systematic perspective [2, 3].

Recent advances in bioinformatics and multi-omics research have led to significant progress in Fangjiomics, particularly in the integration of Zhenghou (signs), phenomics, and clinical applications. This emerging field holds promises as a paradigm for advancing the modernization of Fangji as part of the TCM.

With the development of multi-omics data and

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biological information technology, the integration of multi-omics data with interdisciplinary approaches, including bioinformatics, systems science, and computational science, has become increasingly prominent. This trend offers new opportunities to systematically elucidate the overall mechanisms of action and scientific foundations of Fangji. Guided by the original TCM theories and principles, Fangjiomics has gradually evolved into a new stage of systematic research. By focusing on the "relationship between Fangji and effects", it innovates research mechanisms on Fangji in two dimensions: high-throughput multi-omics data and target spectrum-efficacy relationships. These are analyzed across four levels: differentially expressed genes, pharmacological pathways, molecular networks, and targeted modules. In recent years, Fangjiomics has made progress in the development of databases and analysis platforms, methodological innovations, and translational applications (Figure 1).

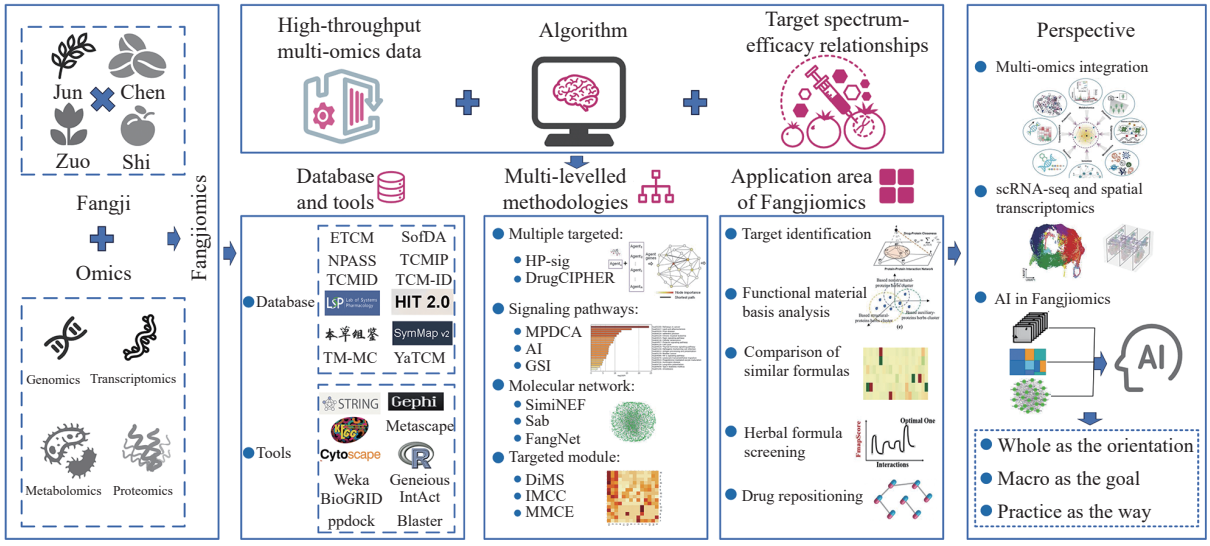

Figure 1 The progresses in and perspectives on Fangjiomics

2 Databases and tools for Fangjiomics research

As critical resources for Fangjiomics research, databases containing prescription information, herb components, herb targets and corresponding diseases, TCM syndrome and phenotypes have been developed and continue to emerge [4, 5]. Representative resources include the Encyclopedia of Traditional Chinese Medicine (ETCM), Symptom Mapping (SymMap), Traditional Chinese Medicine Integrated Database (TCMID), Bioinformatics Analysis Tool for Molecular mechanism of Traditional Chinese Medicine (BATMAN-TCM), Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP), Symptom Ontology and Disease Association (SoFDA) Platform, Traditional Chinese Medicine Medical Subject Headings (TCM-MeSH), High-throughput Experiment and Reference-guided Database of Traditional Chinese Medicine (HERB), Linking of Traditional Chinese Medicine with Modern Medicine at Molecular and Phenotypic Levels (LTM-TCM), Yet another Traditional Chinese Medicine (YaTCM), Herbal Ingredients' Targets (HIT) Platform, TCMBank, etc. These databases enable researchers to systematically investigate the mechanisms of action of Fangji. In addition, increasing amounts of disease and drug-related data at multiple omics levels like genome, transcriptome, proteome, and metabolome are becoming available in these databases, providing diverse omics-based information for TCM herbs or Fangji research [6]. Meanwhile, online analysis tools and platforms for target prediction, molecular docking, protein interaction, functional enrichment, network construction and visualization are continuously improving. These advancements offer researchers valuable tools for Fangjiomics. We have summarized representative databases and tools applicable to Fangjiomics in Table 1.

3 Multi-leveled methodologies of Fangjiomics

In the integrative research of Fangji and multi-omics data, various research methods have been proposed from multiple perspectives. For herb targets identification, computational methods such as DrugCIPHER [7] and Herb-Perturbation Signatures (HP-sig) [8] have been developed to identify potential targets the ingredients in the herb/formula based network analysis and omics data sets.

To examine the herb combination and compatibility mechanism of Fangji, the FangNet [9] platform was constructed to uncover hidden knowledge from clinically effective Fangji using structure network algorithms. The Sab algorithm [10] was employed to facilitate the synergistic mechanisms underlying herb combinations and

Table 1 Databases and tools for Fangjiomics

Type	Name	Data resource	Application	Website
Fangji database	Fangji database of TCM	There are 84 464 Fangji derived from more than 710 TCM ancient books	Multi-path retrieval of prescriptions	https://cintmed.cintcm.cn/cintmed
	Clinical Research Integrated Service (CRDS) database	Including 60 589 pieces of information about Chinese patent drug, involving more than 10 000 prescriptions of Chinese patent drug	Similarity analysis of prescriptions, compatibility rule analysis, function and indication analysis, etc.	http://crds.release.daodikeji. com/
	Fangji database of YAOZHI	Including 34 320 pieces of Fangji information from TCM ancient books, involving 20 kinds of efficacy classification	Searching for prescription names, herbal composition, functional indications, prescription classification, etc.	https://db.yaozh.com/fangji
Database of chemical components in TCM	Database of TCM and Chemical Components	Including more than 50 000 prescriptions, over 1 400 diseases and their medications, over 22 000 TCM herbs, and over 19 700 compounds	Retrieving information on disease medication, TCM, compound properties, and other related information	https://www.organchem.csdb.cn
	TCM Database@ Taiwan	Including 37 170 TCM compounds and their 2D and 3D structural files from 453 herbs	Molecular docking and molecular dynamics simulation	http://tcm.cmu.edu.tw/
	Natural Product Activity and Species Source 2.0 (NPASS 2.0)	There are 96 481 isolated natural products from 32 287 organisms, including the related 7 753 targets and 958 866 activity records	Retrieving detailed information on the species sources and biological activities of natural products	https://bidd.group/NPASS/
	Traditional Chinese Medicine Integrated Database 2.0 (TM-MC2.0)	Including 33 946 compounds of 635 herbs, which were derived from national pharmacopoeia of Northeast Asia	Retrieving information on the composition and compounds of traditional medical herbs included in the national pharmacopoeias of Northeast Asia	https://tm-mc.kr/
Comprehensive database of ingredients and targets	ETCM2.0	Including 402 herbs, 3 959 TCM formulas, 7 284 TCM components, 2 266 drug targets, and information on 4 323 related diseases	Retrieving standardized information on commonly used Chinese herbal medicines, Chinese herbal formulas, and their components, and to predict the targets of Chinese herbal ingredients	http://www.tcmip.cn/ETCM 2/front/#/
	SymMap	Establish associations between six major categories of databases, including 1 717 TCM symptoms, 961 western medicine symptoms, 499 TCM herbs, 19 595 drug ingredients, 4 302 drug targets, and 5 235 diseases	It can be used to integrate TCM symptoms and modern medicine information to serve drug screening research	http://www.symmap.org
	TCMID	Including about 46 929 prescriptions, 8 159 herbs, 25 210 compounds, 6 828 drugs, 3 791 diseases, and 17 521 human biological targets	Retrieving prescriptions, herbs, ingredients, diseases, drugs, and targets, and provides Java based online tools for network analysis	https://ngdc.cncb.ac.cn/databasecommons/database/id/437
	BATMAN-TCM	There are 8 159 TCM herbs and 46 914 formulas included in TCMID	Prediction and functional analysis of potential targets for TCM components and drugs, visualization of networks and pathways, and comparative analysis of different components of TCM	http://bionet.ncpsb.org.cn/batman-tcm/#/home
	TCMSP	Including 502 types of TCM herbs, including 13 729 TCM components, 3 339 targets, and 867 related diseases	It can be used to construct a drug target disease network, revealing the potential mechanisms of TCM and its formulations	https://old.tcmsp-e.com/tcmsp.php
	SoFDA	Including 319 TCM syndromes, 8 045 modern medical diseases, and 1 359 formulas	It can perform syndrome ontology information query and analysis, syndrome classification prediction, network visualization display, etc.	http://www.tcmip.cn/Syndrome/front

Table 1 Continued

Type	Name	Data resource	Application	Website
	TCM-MeSH	Including 6 235 TCM herbs, 383 840 compounds, 14 298 genes, 6 204 diseases, 144 723 gene disease associations, 3 440 231 gene interactions, 163 221 drug side effects, and 71 toxicity records	Construct network between TCM and the diseases it treats through network software, and analyze the potential mechanisms	http://mesh.tcm.micro-bioinformatics.org/
	HERB	Including high-throughput omics experimental data of TCM	It can quantitatively measure transcriptional responses and regulatory changes, thereby discovering potential drug targets and evaluating the therapeutic efficacy of drugs	http://herb.ac.cn
	LTM-TCM	Including 48 126 prescriptions, 9 122 TCM herbs, 34 967 TCM components, and 13 109 targets	Retrieving TCM, prescriptions, symptoms, active ingredients, and targets, and can perform compound reverse docking and ADME prediction analysis	http://cloud.tasly.com/#/tcm/home
Comprehensive database of ingredients and targets	YaTCM	Including 1 813 prescriptions, 6 220 herbs, 47 696 natural compounds, 18 697 targets, and 390 pathways	It can be used to analyze the mechanism of action of TCM or herbs, predict potential targets of Chinese medicine molecules, and discover compatible drug pairs	http://cadd.pharmacy.nankai.edu.cn/yatcm/home
	TCMID	There are 7 443 prescriptions, 2 751 TCM herbs, 7 375 TCM components, 768 targets, 366 diseases included in ICD10, and 27 716 human omics experimental sample data	Analyze basic information, targets, functional pathways, and related gene expression of prescriptions	http://bidd.group/TCMID/about.html
	HIT2.0	Including 1 250 TCM herbs, 1 237 TCM components, 2 208 biological targets, 10 031 component-target relationships, 1 231 therapeutic targets, and 56 miRNA targets	Retrieving information on TCM ingredients and targets	http://www.badd-cao.net:2345
	TCMBank	There are 9 192 herbs, 61 966 components, 15 179 targets, 32 529 diseases, and 3D structures of herbal active ingredients stored in mol2 format	Retrieving relevant data from existing databases related to TCM and publicly available biological databases, as well as algorithms for predicting adverse reactions between Chinese and western medicine	https://TCMBank.cn
	Online Mendelian Inheritance in Man (OMIM)	Including all known Mendelian diseases and information on over 16 000 genes	Retrieving human gene and genetic phenotype data	https://omim.org/
	Disease Gene Network (DisGeNET) (V7.0)	Including 1 134 942 gene-disease association (GDAs) and 369 554 variation disease associations (VDAs)	Molecular basis research on human diseases and their complications, as well as disease gene feature mining	https://disgenet.com/
Disease related gene database	MalaCards	There are 22 091 disease genes related information	Disease annotation resources for systematic analysis of diseases and gene function annotation research	https://www.malacards.org/
	Human Phenotype Ontology (HPO)	Including more than 13 000 terms and 156 000 genetic disease annotations in the fields of medicine, diseases, and related areas	Establishing the association between TCM symptoms and modern disease phenotypes, providing specific descriptions of disease symptoms and their related gene sets	https://hpo.jax.org/app

Table 1 Continued

Type	Name	Data resource	Application	Website
Disease related gene database	DigSee	Including disease related 14 608 human genes and their biological process	It can be used for text mining search, providing evidence text of disease-related genes	http://210.107.182.61/gene Search
Database of drug targets	Therapeutic Target Database (TTD)	Including 3 578 drug targets, 38 760 drugs, a large amount of drug molecular structure information, small molecule components, and drug information derived from natural products	Retrieving drugs, targets, pathways, molecular structures, etc., and can be used to create control datasets to obtain candidate target spectra for unknown drugs	http://db.idrblab.net/ttd
	DrugBank (V5.1.10)	Including 15 437 drug entries and 5 295 non redundant protein sequences	Providing biological and chemical information about drugs, targets, and effects, and providing functions such as drug retrieval, repositioning, drug metabolism prediction, and drug target prediction	https://go.drugbank.com/
	STITCH (V5.0)	Including more than 500 000 compounds and 9.6 million proteins, with over 1.6 billion interactions between compounds and proteins	Predicting the interactions between chemical drugs and target proteins	http://stitch.embl.de
	ChEMBL	Including 15 139 targets, over 2.3 million compounds, and more than 20 million information on active pharmaceutical ingredient (API)	It can be used to integrate chemical, biological activity, and genomic data, and query drug target or biological activity data	https://www.ebi.ac.uk/chembl
	Binding Database (BindingDB)	Including 2 656 564 protein targets and data of drug like small molecule binding	Retrieving the affinity for interactions between drug target proteins and drug like small molecules	http://www.bindingdb.org
Database of high throughput omics	Gene Expression Omnibus (GEO)	Including 4 348 GDS data, 24 832 GPL data, 195 165 GSE data, 5 566 359 GSM data	It can be used for high-throughput omics data mining, retrieval, and visualization expression	https://www.ncbi.nlm.nih.gov/geo
	ArrayExpress	There are 76 632 gene chip or high-throughput sequencing experimental research data, including 13 360 DNA data, 62 043 RNA data, and 191 protein data	Retrieving data from high-throughput functional genomic experiments	https://www.ebi.ac.uk/biostudies/arrayexpress
	Expression Atlas	Including 4 315 datasets related to RNA sequencing, proteomics, plant species, etc.	Retrieving information on gene and protein expression in biological samples under different cell types, body tissues, diseases, and other conditions	http://www.ebi.ac.uk/gxa
	Peoteomexchange	Including over 34 233 high-throughput proteomics research data, which containing various diseases and tissues	Retrieving disease and high-throughput proteomics research data	http://www.proteomexchange.org
	microRNA Sequence Database (miRBase) (V22.1)	Including 38 589 miRNAs from 271 species of organisms	Retrieving comprehensive miRNA data	http://www.mirbase.org
	Human Metabolome Database (HMDB) (V5.0)	There are 220 945 metabolite entries associated with 8 610 protein sequences, including water-soluble and lipid soluble metabolites	Retrieving data on small molecule metabolites found in the human body	https://hmdb.ca
	The Cancer Genome Atlas (TCGA)	Including over 20 000 patient tumor samples from 33 types of cancer	Retrieving clinical genomic research data related to cancer	https://www.cancer.gov/tcga

therapeutic effects of Fangji against various disease symptoms or phenotypes. To analyze the complex mechanisms of Fangji action, techniques such as the deep herb-graph method and the artificial intelligence neural network integrating phenotypic and molecular data have been explored in applications [11, 12].

Multi-level systematic methods from single target, signaling pathways, multi-targeted network and modules have been developed to investigate the synergistic mechanisms of Fangji compatibility from the perspective of holistic view. Global Similarity Index (GSI) [13], multiple-pathway-dependent comparison analysis (MPDCA) [14], additive index (AI) [15], similarity coefficient of network features (SimiNEF) [16], multiple modular characteristic fusing (MMCF) [17], and inter-module coordination coefficient (IMCC) [18] methods have been proposed to reveal the synergistic mechanism of Qingkailing formula. The driver-induced modular screening (DiMS) strategy has been applied to elucidate the additive mechanisms of Baicalin (BA) and Jasminoidin (JA) in cerebral ischemia therapy [19]. Modulome-Fangjiome Association Study (MoFAS) has revealed differential target distributions among four similar formulas from Qi-invigorating and blood-nourishing fangjiome [20]. In general, the study of Fangji compatibility and mechanisms of action has transitioned from a single-targeted structure-activity paradigm to a multi-targeted spectral and network-effect strategy. We have summarized the representative methods for Fangjiomics at multi-levels of single target, pathways, networks and modules in Table 2.

Table 2 Multi-levelled models, indicators, and methods for Fangjiomics

Level	Name	Principle	Application	Reference
Single target	Differential expression analysis	To identify genes, proteins, or metabolites whose expression levels are significantly altered under two or more conditions by statistical or other methods	Identify differentially expressed genes	[21]
	KGE-NFM	A framework combining Knowledge Graph (KG) with recommendation system, which firstly learns a low-dimensional representation for various entities in the KG, and then integrates the multimodal information via neural factorization machine (NFM)	Using heterogeneous data for drug-target interaction (DTI) prediction	[22]
	Herb-Target Interaction Network (HITNET)	Use node2vec, encode heterogeneous networks related to TCM and targets, and capture low dimensional feature vectors of TCM and proteins through network embedding	Perform TCM target prediction	[23]
	Herb-Perturbation Signatures (HP-sig)	Construct the initial perturbation characteristics of TCM components, convert them into a “perturbation” matrix, and obtain the final perturbation characteristics through thermal diffusion mode and protein-protain interaction (PPI) network	Indicate the therapeutic effect of TCM, and generate the perturbation signatures for each herb, which were represented the targets affected by the ingredients in the herb	[8]
	DrugBAN	Use Graph Convolutional Network (GCN) and Convolutional Neural Network (CNN) to encode local structures into two-dimensional molecular maps and one-dimensional protein sequences, and input the encoded local representation into the paired interaction module to learn the local interaction representation	Used for drug target prediction	[24]
Signaling pathway	GSI	To quantify the genotypic outcomes of gene expression profiles	For the spectral measurement of imbalance in biochemical pathways	[13]
	MPDCA	Qualitative comparison of the number of changes between multiple signaling pathways after different drug intervention	Exploring various pathway changes in drug combinations, so as to explain the mechanism of drug combination	[14]
	AI	On the basis of pathway-components-related variation, the additive index of any pathway in drug combination can be calculated quantificationally	To reveal the additive mechanism of drug combination based on variation of pathways and functional communities	[15]
	FangNet	Based on the symptom TCM network, use PageRank to rank the relative topological importance of TCM and construct a syndrome medicine network, and explore implicit knowledge of TCM through interactive visualization	Retrospective analysis of the prescription set for specific diseases and ranking of the relative importance of TCM	[9]
	FordNet	Develop a CNN based model to extract deep features and construct heterogeneous networks, and apply Network Embedding (NE) learning to integrate molecular information into the deep characteristics of TCM prescriptions	Intelligent recommendation of TCM prescriptions	[25]
	Sab	Measure the network proximity of drug-target modules A, B as reflected in their target localizations using the separation measure	Evaluate the degree of association between diseases, diseases and drugs, and drugs and drugs	[10]

Table 2 Continued

Level	Name	Principle	Application	Reference
Signaling pathway	CIPHER	Establish a regression model based on the hypothesis of molecular interaction network, evaluate the possibility of a gene participating in specific diseases and phenotypes, and use consistency score to quantitatively express it	Predicting uncharacterized phenotypes in genetics and conducting whole genome screening of disease genes	[26]
	Drug-CIPHER	Measure the similarity between drugs and the network distance between proteins and all other known drug targets	Inferring genome-wide drug target interactions	[7]
	PTsGene	Integrate data from multiple different sources to build a large-scale heterogeneous network, and using network embedding representation algorithm to learn low dimensional vector representations of each node in the network	Predicting and identifying genes for TCM symptoms	[27]
	Distance-based Mutual Information Model (DMIM)	Combining mutual information entropy and "distance between TCMs" to score the interactions between Chinese medicines and construct a network of Chinese medicine interrelationships	Elucidate known TCM pairs and formula combinations, and generate new combinations of TCM drugs	[28]
	Herb-Compound-Protein graph-based deep graph embedding method (HCP-DGE)	A preliminary docking diagram was constructed using virtual screening method, and a heterogeneous network was constructed based on four meta path embedding methods; use random walk algorithm to generate adjacency matrix S to calculate the similarity between nodes	Generate a list of candidate TCM rankings for structural, non structural, and auxiliary proteins	[29]
Module	MoFAS	Build a network and decompose it into modules; based on consistency scoring and richness analysis, construct a modular map with functional landscapes; and compare and evaluate using targeting rate (TR) matrix and Principal Component Analysis (PCA)	Study the differential target distribution and characteristic mechanism of Fangjis	[20]
	SimiNEF	Using similarity to quantify the relative overlap between modules by combining module nodes, edges, and Gene Ontology (GO) function similarity	Dynamic comparison and quantitative analysis of module topology changes in molecular networks	[16]
	MMCF	MMCF includes weighted degree, betweenness centrality, and PageRank	Identify core modules from the network	[17]
	IMCC	Combining quantitative methods with statistical analysis to construct coordination coefficients between modules	Accurately evaluate the relationships between modules	[18]
	DiMS	Integrate synergistic module and driver gene identification by modular similarity	Effectively identified targeted additive modules and driver genes based on networks	[19]

4 Expanding applications of Fangjiomics

Multi-omics based approaches, including genomics, proteomics, metabolomics, lipidomics, glycomics, epigenomics, metagenomics, microbiomics, and pharmacogenomics, have been applied to the research of Fangjiomics. For instance, in the study comparing the mechanisms of Zuogui Pill (左归丸) [Dihuang (Rehmanniae Radix), Shuyu (Dioscorea Yam), Gouqizi (Lycll Fructus), Shanzhuyu (Corni Fructus), Niuxi (Achyranthis Bidentatae Radix), Tusizi (Cuscutae Semen), Lujiaojiao (Cervi Cornus Colla), Guikejiao (Turtle Shell Gum)] and estradiol valerate in preventing and treating postmenopausal osteoporosis, ZHAO et al. [30] confirmed the role of Zuogui Pill and estradiol valerate in regulating inflammation and immune response through genomic methods, weighed gene co-expression network analysis (WGCNA) analysis, PPI network analysis and other bioinformatics methods. In another study, REN et al. [31] investigated Huatan Jiangzhuo Decoction (化痰降浊汤) [Baizhu (Atractylodis Macrocephalae Rhizoma), Chenpi (Citri Reticulatae Pericarpium), Banxia (Pinelliae Rhizoma), Fuling (Poria cocos), and Zexie (Alismatis Rhizoma)] by establishing a rat model of hyperlipidemia, based on the results of high-throughput transcriptome sequencing. They confirmed the therapeutic effect of Huatan Jiangzhuo Decoction on hyperlipidemia. Through proteomic analysis using tandem mass tag (TMT), SONG et al. [32] revealed that Jueyin Granules (决银颗粒) [Jinyinhua (Lonicerae Japonicae Flos), Lianqiao (Forsythiae Fructus), Juemingzi (Cassiae Semen), Banlangen (Isatidis Radix), Mudanpi (Moutan Cortex), Jianghuang (Curcumae Longae Rhizoma), Cheqianzi (Plantaginis Semen), and Sheshecao (Herba Hedyotidis Diffusae)] had a protective effect on a mouse model of imiquimod induced psoriasis by inducing autophagy. GO analysis and Kyoto Encyclopedia of Genes

and Genomes (KEGG) pathway analysis identified key pathways potentially involved in psoriasis treatment with Jueyin Granules. Furthermore, WEI et al. [33] established a stress-induced functional dyspepsia rat model and treated it with Weikangning (胃康宁) [Huangqin (Scutellariae Radix), Jianghuang (Curcumae Longae Rhizoma), Dangshen (Codonopsis Pilosula), Dahuang (Rhei Radix et Rhizoma), Beichaihu (Bupleurum Chinense), Houpo (Magnolia Officinalis), Shaoyao (*Paeonia lactiflora*)]. Differential proteins in drugs involved in the treatment of digestive disorders were analyzed using proteomic methods.

ZHANG et al. [34] applied metabolomics strategies to identify potential significant serum metabolites and metabolic pathways for the treatment of Alzheimer's disease with Bushen Tiansui Formula (补肾填髓方) [Yinyanghuo (Epimedii Folium), Heshouwu (Polygoni Multiflori Radix), Yuanzhi (Polygalae Radix), Guijia (Testudinis Carapax et Plastrum), Longgu (Os Draconis), Shichangpu (Acori Tatarinowii Rhizoma)]. The results indicated endogenous metabolites as potential biomarkers associated with the treatment of Alzheimer's disease with this TCM compound.

In addition, metabolomics was used to examine the effects of the TCM compound Huanglian Jiedu Decoction (黄连解毒汤) [Huangqin (Scutellariae Radix), Huanglian (Coptidis Rhizoma), Huangbo (Phellodendri Chinensis Cortex), and Zhizi (Gardeniae Fructus)] on lipopolysaccharide induced sepsis induced acute kidney injury. The findings showed that Huanglian Jiedu Decoction could significantly improve abnormal oxidative stress and energy metabolism disorders by regulating signaling pathways, effectively inhibiting acute kidney injury [35]. In spatial lipidomics, ZHANG et al. [36] revealed that the combined action of active ingredients in the TCM toad could regulate sphingolipid metabolism and glycerophospholipid metabolism. By driving cell apoptosis and disrupting tumor cell biofilms, it exerted anti-cancer effects at the level of lipid reprogramming. LIU et al. [37] used a multi-chromatographic technique based on glycomics strategy and found that sulfur fumigation of ginseng would reduce the total content and molecular weight of ginseng polysaccharides, alter the monosaccharide composition of ginseng polysaccharides, and evaluate the effect of sulfur fumigation on the overall quality of Sijunzi Decoction (四君子汤) [Shengjiang (Zingiberis Rhizoma Recens), Baizhu (Atractylodis Macrocephalae Rhizoma), Fuling (Poria), Gancao (Glycyrrhizae Radix et Rhizoma)]. In epigenetics, DONG et al. [38] used quantitative reverse transcription polymerase chain reaction to detect the expression levels of genes related to the treatment of liver fibrosis with Huangqi Decoction (黄芪汤), and identified potential therapeutic targets, indicating that Huangqi Decoction could inhibit the proliferation and activation of hepatic stellate cells. The TCM compound Naoluoxintong Fomula (脑络欣通方) [Huangqi (Astragali Radix), Sanqi (Notoginseng Radix et Rhizoma), Chuanxiong (Chuanxiong Rhizoma), Tianma (Gastrodiae Rhizoma), Honghua (Carthami Flos), Danggui (Angelicae Sinensis Radix), Wugong (Scolopendra)] could reduce the methylation level of NogoA pathway in rats with cerebral ischemia-reperfusion injury, inhibit the expression of NogoA/RhoA/ROCK protein, and alleviate apoptosis of glial cells [39]. When conducting research on Pien Tze Huang (片仔癀) [Shexiang (Moschus), Niudanzhi (Fel Bovis seu Bubali), Shedanzhi (Serpentis Fel), Sanqi (Notoginseng Radix et Rhizoma), etc.], GOU et al. [40] analyzed the fecal microbiota and metabolites of colorectal cancer mice using metagenomic sequencing and liquid chromatography-mass spectrometry. They found that Shaoyao (*Paeonia lactiflora*) increased the abundance of beneficial microbiota, elevated the expression of beneficial metabolites, and significantly restored intestinal barrier function.

CHENG et al. [41] used 16S rRNA sequencing analysis and targeted metabolomics methods to quantitatively analyze important microbial metabolites, and explored that the mechanism of action of Wutou Decoction (乌头汤) [Mahuang (Ephedrae Herba), Shaoyao (*Paeonia lactiflora*), Huangqi (Astragali Radix), Gancao (Glycyrrhizae Radix et Rhizoma), Chuanwu (Aconiti Radix)] against rheumatoid arthritis may be mediated by microorganisms. EFFERTH et al. [42] conducted systematic biological activity screening, chromatographic separation, and mass spectrometry analysis on commonly used TCMs through microbiome analysis. They found that the active ingredients contained in Shijunzi (Quisqualis Fructus) and Danshen (Salvia Miltiorrhizae Radix et Rhizoma) were possibly effective ingredients in inhibiting tumor proliferation.

In addition to synergistic compatibility and therapeutic mechanism research, Fangjiomics has been extended to be used for target identification, functional material basis analysis, comparison of similar formulas, drug repositioning, and new herbal formula screening. The concept of chemical functiomics was proposed to analyze the complex relationship between chemical components and functions of Fangji [43]. A comparative pharmacogenomic analysis based on molecular network modeling revealed the heterogenetic pharmacological molecular spectrum of three classic formulas for coronary heart disease [44]. The research paradigm of "target spectral effect of prescription" integrates omics technology with evidence-based principles revealed the precise clinical positioning of Qizhi Tongluo Formula (芪蛭通络方) [45]. Network target analysis integrated with machine learning algorithms were used to construct novel herbal formula prediction methods [46]. Fangjiomics has become one of the promising strategies in various areas of Fangji research.

5 Perspectives

The application of the concepts and research approaches of Fangjimocs has led to significant advances, yet several challenges remain. As a rapidly evolving research field, Fangjiomics needs to be integrated with more emerging omics technologies and deeply integrated with the theoretical foundations of TCM to uncover the underlying mechanisms. Beyond enhancing efficacy and reducing toxicity, the Fangji also contains rich contents such as the theory of Jun Chen Zuo Shi (君臣佐使) and Qi Qing (七情). A major challenge lies in explaining the scientific connotations of these issues.

Although vast amounts of omics data have been accumulated, further exploration is needed to improve the standardization, normalization and integrative analysis of these multi-omics data. With the rapid development of single-cell sequencing and spatial transcriptome technology, Fangjiomics needs to incorporate these spatio-temporal data to advance precise and individualized research of Fangji as well as TCM. In the era of artificial intelligence, Fangjiomics also needs to embrace neural networks, deep learning, large language model and other technologies to facilitate the intelligent development of Fangji research.

The development of Fangjiomics is integral, macro-level and practical. Given the vastness of omics big data, there is a risk of becoming overwhelmed by the data itself and losing sight of the original intention and direction. In the face of sophisticated modern technology, it is necessary to shift the research model for Fangji compatibility and pharmacological mechanisms from a focus on target-entity to target-relationship at micro, mesoscopic and macro levels. In the face of the local mathematical model, the synergistic and additional pharmacological effects must be viewed holistically and holographically, transitioning from the single pathway to the relationships between multiple pathways of Fangji. In the context of multi-model uncertainty and selection challenges, research should be grounded in practical application. This includes moving from the static analysis of efficacy substances, composition principles, target network topological structure to the dynamic evolution of related networks associated with clinical practice effect. The differences across various experiments must be reconciled with clinical practice. In summary, the high-quality development of Fangjiomics must adhere to the guiding principle of “taking the whole as the orientation, macro as the goal, and practice as the way” [47].

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Competing interests

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方剂组学的研究进展：方法、应用与展望

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【摘要】方剂组学作为一种新兴的研究范式，从整体和系统的角度探索了基于多组学的方剂药理机制的研究。本文回顾了方剂组学的最新进展，重点介绍了相关数据库和分析平台、方法创新及转化应用。通过整合方剂和多组学数据，研究者从单靶点分析、信号通路、多靶点网络和靶点模块等角度构建了多层次系统解析方法。方剂组学已成为方剂研究各个领域的重要策略，本文并从综合、宏观和实践的角度提出了方剂组学高质量发展原则和展望。

【关键词】方剂组学；多组学数据；方剂配伍；方剂数据库；网络药理学