Acupuncture and Herbal Medicine

Network pharmacology in food-medicine homology: AI-driven decoding of multi-target synergy from molecular networks to precision health

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Abstract

Network pharmacology provides a transformative framework for decoding multi-target, system-level mechanisms of the food-medicine homology (FMH) substances, overcoming the limitations of reductionist approaches by integrating multi-omics data, computational modeling, and network analysis. Central to this paradigm is the "Network Targets" theory, which conceptualizes therapeutic intervention as the reconfiguration of disease-associated biological networks rather than the modulation of isolated single targets. Artificial intelligence accelerates this process by enabling high-dimensional data integration, predictive modeling of synergistic combinations, and the identification of active constituents. This review outlines the key databases and computational tools that operationalize network pharmacology in FMH research and systematically categorizes their applications, including material screening, ingredient identification, synergy analysis, quality standard establishment, safety assessment, formula optimization, functional food discovery, and personalized recommendation, supported by experimental validation across numerous FMH items. Despite the challenges in data standardization and dynamic modeling, the integration of multi-omics, dynamic networks, and centralized repositories will further advance the field. Ultimately, network pharmacology will bridge traditional FMH wisdom with contemporary mechanistic rigor, positioning FMH as the cornerstone of precision nutrition and preventive medicine.

Keywords: Artificial intelligence, Food-medicine homology, Network pharmacology, Network targets

Graphical Abstract: https://links.lww.com/AHM/A223

Introduction

The paradigm of "food-medicine homology" (FMH) represents a cornerstone of holistic health systems, bridging nutritional sustenance and therapeutic intervention through a shared biological and philosophical framework. Rooted in ancient medical traditions, particularly traditional Chinese medicine (TCM), FMH posits that natural substances inherently play dual roles—nourishing physiological functions while correcting pathological imbalances. This integrative perspective, documented in foundational texts such as *The Inner Classic of Huangdi* and *the Shennong's Classic of Materia Medica*, underscores the dynamic equilibrium between humans and their environment, in which diet and medicine are not dichotomous but lie along a continuum. Globally analogous concepts, from Hippocratic dietary regimens to Ayurvedic Rasayana therapies, further validate the universality of FMH principles, reflecting humanity's enduring quest to harmonize preventive care with curative strategies.

Modern scientific exploration of FMH has gained momentum amid escalating interest in multi-target, system-level interventions for complex chronic diseases[1]. Unlike conventional pharmaceuticals, which often prioritize single-molecule specificity, FMH-derived bioactive compounds, including polyphenols, alkaloids, and polysaccharides, exert pleiotropic effects by simultaneously targeting diverse cellular targets. These interactions collectively modulate signaling pathways associated with inflammation, oxidative stress, and metabolic homeostasis, mimicking the body's intrinsic regulatory networks. However, the mechanistic elucidation of FMH substances remains fragmented and constrained by reductionist methodologies

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that overlook the emergent properties of multi-component synergies. Traditional analytical approaches, focusing on isolated compounds or linear cause-and-effect relationships, fail to capture the dynamic, context-dependent interplay between FMH agents and biological systems.

Emerging disciplines such as network pharmacology and systems biology have revolutionized this landscape. By integrating multi-omics data (eg, transcriptomics, metabolomics), computational modeling, and artificial intelligence (AI), these frameworks enable the deconvolution of FMH's "multi-component, multi-target, multi-pathway" architecture. Network-based analyses have revealed the mechanism by which FMH compounds reconfigure disease-associated molecular networks, restoring resilience through cooperative rather than isolated actions[2]. For instance, systemic inflammation may be mitigated not by targeting a single cytokine but by rebalancing immune-metabolic crosstalk across tissues. Such insights align with the holistic ethos of FMH while providing the mechanistic rigor demanded by contemporary biomedicine. Furthermore, advances in gut microbiome research have highlighted FMH's role in modulating microbial-host interactions, linking dietary interventions to systemic immune and metabolic outcomes.

This review synthesizes cutting-edge advancements at the intersection of FMH and network pharmacology and proposes a transformative framework to decode multidimensional health impacts. By unifying molecular granularity with organism-level complexity, we aim to redefine FMH's scientific legitimacy and translational potential, positioning it as a pivotal strategy for next-generation preventive and precision medicine.

This article is structured as follows: first, we outline the core theoretical framework of network pharmacology, particularly the "Network Targets" paradigm, and explore how AI accelerates its application in FMH research. Second, we introduce the key databases and computational tools that enable the translation of network pharmacology principles into actionable FMH studies. Third, we review the application scope of network pharmacology across FMH substances, supported by representative case studies illustrating its translational impact. This review was based on a search in mainstream academic databases and TCM-specialized databases from their inception to February 2026, including Web of Science Core Collection, PubMed/MEDLINE, Scopus, Embase, ScienceDirect, CNKI English Version, TCMSP, ETCM, SymMap, and BATMAN-TCM. Google Scholar and the official website of the National Health Commission of the People's Republic of China were used for supplementary searches. The search languages were restricted to English and Chinese. The core search terms included "food-medicine homology (FMH)," "network pharmacology," "network targets," "artificial intelligence (AI)," "multi-target synergy," "precision nutrition," "traditional Chinese medicine (TCM)," and "edible and medicinal herbs." Included studies comprised basic experimental studies, clinical trials, reviews, database construction, and computational modeling papers related to the application of network pharmacology in FMH, with clear experimental validation or data support. Conference abstracts, dissertations, and irrelevant studies were excluded. Fourth, we discuss prevailing challenges, such as data integration, standardization, and dynamic modeling, and propose future directions to improve multi-omics integration, temporal network analysis, and the development of centralized FMH repositories. Finally, we conclude by discussing the synergistic potential of network pharmacology in validating and modernizing FMH practices, emphasizing the need for interdisciplinary collaboration to advance global integrative health solutions.

Characteristics of network pharmacology in FMH

While traditional approaches to FMH research have long emphasized empirical observations and reductionist analyses, the advent of network pharmacology has offered a paradigm shift, unifying multi-target interventions with system-level mechanisms. By conceptualizing biological interactions as dynamic networks, this discipline bridges the gap between FMH's holistic principles and the molecular complexity underlying its therapeutic effects, thereby enabling the systematic decoding of multi-component synergies and emergent properties[3].

Core theory of network pharmacology: network targets

"Network Targets" constitute the core theory of Network Pharmacology. This refers to the establishment of mechanistic associations between drugs and diseases at the systemic level of biological networks, elucidating the mechanism by which drugs interact *via* multiple targets within a biological network, thereby generating an overall regulatory effect[4–5]. "Network Targets" can be understood from both narrow and broad perspectives. Narrowly defined, the "Network Targets" can be regarded as the crucial nodes within the disease biological network that are amenable to drug intervention. Broadly speaking, the "Network Targets" represents a research paradigm for establishing correlations between drugs and diseases. Specifically, it involves a qualitative and quantitative investigation of the network topology and dynamic characteristics of local biological network modules related to disease phenotypes within the disease-syndrome biological network, identifying their key mechanisms, and further designing drug interventions at critical junctures of the disease-syndrome biological network to achieve the overall regulation of disease-syndrome phenotypes[6].

The concept of "Network Targets" is fundamentally different from that of single and multiple targets. Single target refers to the selection of drugs with high affinity and high selectivity for a solitary target, treating a disease or syndrome by intervening with a single target. Multiple targets mean that a drug acts on two or more related targets simultaneously in the disease-syndrome biological network, generating a synergistic effect among the actions on each target, so that the overall effect is greater than the sum of the individual effects. The distinctions between "Network Targets" and single or multiple targets are as follows: single and multiple targets are defined from the perspective of the nature of drug action, whereas the "Network Targets" is defined from the angle of the interaction between drugs and the body, taking into account both drug action mechanisms and disease molecular mechanisms. Moreover, concepts such as single and multiple targets are explanatory and descriptive, lacking explicit quantification, whereas the "Network Targets" emphasizes qualitative and quantitative analysis of the overall drug

effect in terms of action mechanisms. Notably, network targets encompass not only endogenous human proteins but also the functional landscape of gut microbiota. The interplay between the components of flavonoid-rich medicinal herbs (FMH) and gut microbiota acts as the initial "filter" and "amplifier" for therapeutic signals, thereby modulating the subsequent efficacy of interventions.

AI: accelerating network pharmacology in FMH

The advent of AI has revolutionized network pharmacology, particularly in addressing the "high-dimensionality and high-complexity" challenges inherent to FMH research. Machine learning algorithms, including deep neural networks and graph convolutional networks (GCN), excel at distilling actionable insights from heterogeneous data streams, ranging from phytochemical databases to single-cell RNA-seq profiles. For example, unsupervised learning techniques can cluster FMH compounds based on their predicted polypharmacology, whereas reinforcement learning models optimize multi-component combinations by simulating their cooperative effects on network targets[7]. AI-driven platforms further enable *in silico* prediction of FMH–gut microbiome interactions, forecasting the mechanism by which dietary polyphenols modulate microbial metabolites to influence systemic inflammation or neuroendocrine signaling. Generative AI models are now being deployed to design novel FMH-inspired formulations, iteratively refining compound ratios to maximize network-level synergies while minimizing off-target risks[8–10].

The "Network Targets" paradigm is shifting from human-centric signaling toward a tripartite "Drug-Microbiota-Host" interaction framework. This evolution is particularly pertinent for FMH substances whose biological fate is often dictated by microbial intervention before systemic absorption. Rather than viewing the microbiome as a static entity, modern AI architectures—leveraging refined CIPHER frameworks and deep-learning metabolic encoders—characterize the gut as a dynamic "bioreactor." These models can simulate site-specific biotransformation pathways, such as the progressive deglycosylation of saponins into lipophilic aglycones by bacterial glycosidases[11]. By deploying multi-view graph neural networks (GNNs), current computational pipelines can bridge the gap between metagenomic fluctuations and host transcriptomic responses. This facilitates a closed-loop analysis in which microbial metabolites are identified as the actual systemic nodes that intercept host molecular networks[12].

These AI advancements enhance mechanistic interpretability and democratize FMH research by enabling hypothesis-free exploration of massive datasets[13]. For instance, natural language processing algorithms can mine ancient medical texts and contemporary biomedical literature in parallel, uncovering conserved network motifs that validate FMH's empirical wisdom through a modern lens. Meanwhile, explainable AI frameworks address the "black-box" critique by visualizing decision pathways[14]. By harmonizing data-driven discovery with mechanism-driven validation, AI-powered network pharmacology is poised to redefine FMH standardization, efficacy prediction, and personalized intervention strategies.

AI demonstrates practical value in FMH across the spectrum from disease interception to daily health management. AI-driven network pharmacology platforms such as the Using Network targets for Intelligent and Quantitative analysis on drug actions (UNIQ) system have been successfully applied to identify FMH substances for targeting complex conditions such as gastric cancer by deciphering disease-associated biological networks[2]. However, for personalized nutrition guidance, Retrieval-Augmented Generation (RAG) technology combined with Large Language Models (LLMs) offers a direct solution. A concrete implementation involves building a specialized TCM FMH knowledge base, utilizing the domain-optimized MedBERT model for accurate retrieval, and guiding LLMs with expert prompts to generate personalized dietary advice tailored to individual body constitutions[15]. These examples collectively highlight AI's dual role in FMH: enabling the mechanism-driven discovery of therapeutic substances and powering the knowledge-based delivery of personalized health recommendations.

Synergy between FMH and network pharmacology: a translational perspective

The integration of FMH and network pharmacology provides a robust framework for addressing multifactorial diseases using multi-target therapeutic strategies. The "multi-target synergy" is quantitatively characterized by the model's ability to capture non-linear interactions among targets within the biological network. The model achieves this not by merely adding scores, but by learning the complex dependencies and signal-propagation patterns within the network structure. By systematically decoding the interactions between FMH-derived compounds and biological networks, this approach facilitates the development of precision nutraceuticals and combinatorial therapies tailored to complex pathophysiological states. Traditional FMH formulations, once limited by empirical validation, now serve as blueprints for designing network pharmacological agents that simultaneously regulate disease-associated pathways while maintaining systemic homeostasis. AI-enhanced network models further enable the deconstruction of FMH formulations into modular pharmacophores, which are groups of bioactive compounds targeting complementary network subsystems that can be optimized for efficacy and safety in specific patient subpopulations[9]. This synergy not only advances drug discovery but also aligns with the growing demand for dietary interventions grounded in systems-level evidence, bridging the gap between empirical traditions and data-driven precision medicine.

Databases and tools of network pharmacology in FMH

The translation of network pharmacology principles into actionable FMH applications relies on computational platforms that are capable of integrating heterogeneous data, from phytochemical profiles to multi-omics dynamics. Specialized databases and AI-driven tools now serve as the backbone of this endeavor, transforming fragmented knowledge into interoperable networks that map FMH's multiscale mechanisms and accelerate precision intervention design (Table 1).

Table 1

Comparative summary of key databases and computational tools for network pharmacology in FMH research

Name	Type	Core data/algorithm	Key features and strengths	Limitations/considerations	Primary applicability in FMH
ETCM	Database	Standardized information on TCM herbs, formulas, components, properties (eg, taste, meridian tropism), and putative targets	Comprehensive and structurally organized; supports the construction of "herb-component-target-disease" networks, facilitating systematic inquiry	Focuses primarily on medicinal herbs; coverage of officially listed food-medicine homology items may be incomplete; target predictions are often putative and require validation	Constructing preliminary network relationships for FMH substances to generate mechanistic hypotheses
SymMap	Database	Associations linking TCM syndromes, modern diseases, FMH substances, and molecular targets	Uniquely bridges TCM syndrome patterns and modern biomedical diseases; enables the design of syndrome-specific dietary interventions	The relational network is complex; requires expertise in TCM theory for accurate interpretation; less focused on quantitative omics data integration	Designing personalized FMH dietary strategies tailored to an individual's TCM syndrome type
TCMSP/ BATMAN-TCM	Database & Tool	Phytochemical profiles, ADME properties, and target prediction algorithms for herbal compounds	User-friendly interface for compound screening and target prediction; widely adopted and validated in numerous pharmacological studies	More oriented toward drug discovery; may overlook the food matrix, processing effects, and complex bioavailability issues relevant to FMH	Initial screening and prioritization of potentially bioactive constituents within a given FMH substance
TCM-PTD	Tool	Network balance and optimization algorithms	Aims to optimize the composition of multi-herb formulas by balancing network signatures, potentially enhancing therapeutic robustness	Its application usually starts with an existing formula base; less suited for *de novo* discovery of food pairings from single ingredients	Refining and optimizing the component ratios of established FMH formulas or herbal pairs
UNIQ System	AI Platform	Core algorithms (CIPHER, drugCIPHER) that integrate multi-scale data from phenotype to molecule to model disease-drug networks	AI-driven; excels at predicting synergistic multi-component combinations and identifying key intervention modules from network topology, moving beyond single-target analysis	As a specialized platform, requires computational expertise for operation and interpretation of results	Mechanism-driven discovery of synergistic FMH combinations and decoding their network pharmacology mechanisms against complex diseases
RAG + LLMs (eg, with MedBERT)	AI Tool	Retrieval-augmented generation framework powered by domain-adapted language models (eg, MedBERT)	Grounds AI responses in a curated, authoritative knowledge base; generates personalized, contextual, and explainable dietary advice, lowering the barrier to professional knowledge	Performance is highly dependent on the quality, breadth, and structure of the underlying knowledge base and on careful prompt engineering	Translating classical and modern FMH knowledge into personalized, actionable dietary guidance for daily health management and preventive care

AI: Artificial intelligence; BATMAN-TCM: Bioinformatics Annotation daTabase for Molecular mechANism of Traditional Chinese Medicine; ETCM: Encyclopedia of Traditional Chinese Medicine; FMH: Food-medicine homolog; LLM: Large Language Model; RAG: Retrieval-augmented generation; TCM-PTD: Potential target database of Traditional Chinese Medicine; TCMSP: Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform; UNIQ: Using Network targets for Intelligent and Quantitative analysis on drug actions.

AI-powered network pharmacology platforms

Recent advancements in AI have catalyzed the development of integrated platforms for network pharmacology research on FMH. A representative example is the UNIQ system. It received the Gold Medal with Congratulations of the Jury at the 49th Geneva International Exhibition of Inventions, marking the first time AI-driven innovations in traditional medicine achieved this prestigious recognition. Central to UNIQ's success are its core algorithms, including CIPHER and drugCIPHER, which establish causal relationships between phenotypes, biomolecular networks, and therapeutic agents. These algorithms outperformed conventional methods, achieving 2.3-fold and 5.9-fold higher accuracy in genome-wide disease gene prediction and drug target enrichment analysis, respectively, compared to state-of-the-art approaches published in *Nature Biotechnology* and *Science*[16–17]. By integrating multiscale data from phenotypic traits to molecular interactions, UNIQ maps disease-syndrome-drug networks at an unprecedented resolution. It computationally predicts synergistic FMH combinations and identifies intervention modules by reconciling cross-hierarchical information spanning "phenotype-tissue-cell-molecule" dimensions. This enables a panoramic analysis of how FMH substances interact with biological systems, bridging the gap between traditional empirical knowledge and modern molecular pathophysiology. UNIQ further deciphers the "disease-syndrome-formula-drug" axis by modeling network targets, thereby establishing a mechanistic framework for evidence-based FMH applications[18].

Specialized databases for multi-dimensional FMH research

The systematic exploration of FMH mechanisms relies on curated databases that aggregate heterogeneous data on food-medicine substances, bioactive components,

and their biological interactions. The Encyclopedia of Traditional Chinese Medicine (ETCM) database platform integrates a large amount of standardized information on TCM, formulas, and their components, including Chinese medicine ingredients, medicinal materials, and formulas, as well as the taste, medicinal properties, meridian tropism, and potential target gene information of each Chinese medicine. Based on this, we explored and constructed a network relationship map between TCM and its formulas, ingredients, target genes, related pathways, and diseases[19]. Symptom Mapping (SymMap)[20] uniquely bridges TCM syndromes and modern diseases by constructing heterogeneous networks that link FMH substances, symptoms, and molecular targets, thereby enabling syndrome-specific dietary intervention design. The potential target database of Traditional Chinese Medicine (TCM-PTD) employs network equilibrium algorithms to optimize FMH formulations and balance multi-component synergies to enhance therapeutic robustness. Traditional Chinese Medicine Gene, Disease and Information database using Text mining (TCMGeneDIT)[21] leverages literature mining to prioritize FMH-gene-disease associations, whereas Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP)[22] and A Bioinformatics Annotation daTabase for Molecular mechANism of Traditional Chinese Medicine (BATMAN-TCM)[23] focus on target prediction and polypharmacology network visualization of FMH-derived compounds. Traditional Chinese Medicine Network Pharmacology Intelligent Information Platform (TCMN)[24] integrates multi-omics data to quantify component cooperativity and refine formulation ratios, whereas An Intelligent Network Pharmacology Platform Unique for Traditional Chinese Medicine (INPUT) automates the network pharmacology workflow through bioinformatics pipelines. These databases collectively address critical challenges, such as fragmented data and mechanistic opacity, by providing standardized, interoperable platforms for reconstructing FMH-component-target-disease networks. AI-driven tools further enhance their utility; for instance, GNNs analyze ETCM's data to predict novel FMH-disease links, while natural language processing cross-references historical texts with omics datasets to validate conserved network motifs. Together, these resources form an indispensable infrastructure for advancing FMH from tradition-guided practices to mechanism-driven precision medicine.

The application scope and typical cases of network pharmacology in FMH

The application scope of network pharmacology in FMH

Network pharmacology has been successfully applied to research and development within the domain of FMH substances. The official catalog published by the National Health Commission of the People's Republic of China (as of August 2024, comprising 106 distinct items) clearly defines the scope of medicinal materials that are legally permissible for use in food production. To summarize the diverse applications of network pharmacology across these items, the key areas are categorized below (Figure 1), with specific studies detailed in Table 2 and Table S1, https://links.lww.com/AHM/A224. Through network-based target mapping, studies have revealed that Hawthorn, Purslane, Lotus leaf, and Adzuki Bean address atherosclerosis and obesity by regulating lipid metabolism-related pathways, including phosphatidylinositol 3-kinase-serine/threonine protein kinase (PI3K-Akt), vascular endothelial growth factor (VEGF), and advanced glycation end-products-receptor for advanced glycation end-products (AGE-RAGE).

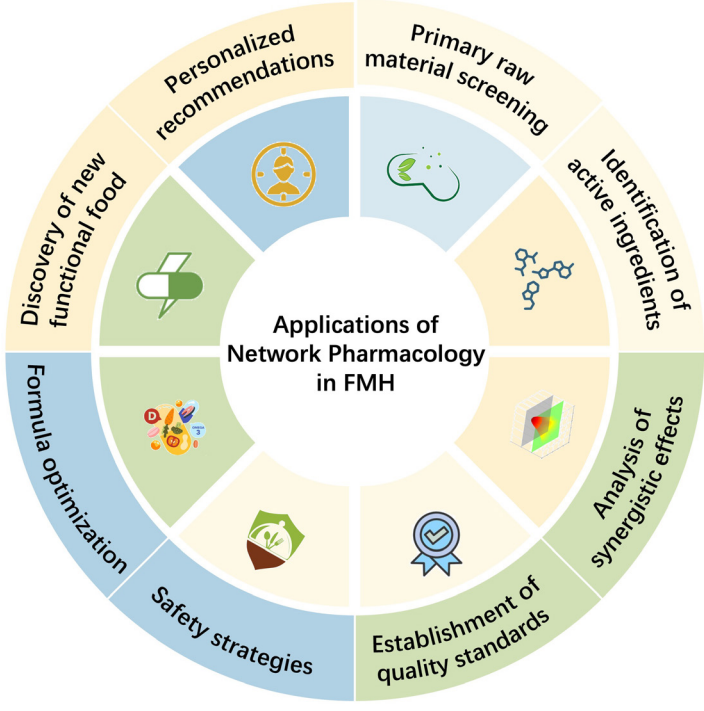

Figure 1. Applications of network pharmacology in FMH. FMH: Food-medicine homolog.

Table 2

Representative network pharmacology studies of FMH

Names of FMH	Major active ingredients	Targets and mechanisms	Disease	Validation techniques	Ref
Clove	Quinic acid, citric acid, gallic acid, eugenol, and other 21 ingredients	Pathways: PI3K/Akt, MAPK signaling	*Helicobacter pylori* infection	Western blot	[25]
Foeniculum vulgare (Fennel)	New compounds	Targets: TP53, SRC, AKT1	Inflammation	ELISA, HR-ESI-MS (new compound isolation)	[26]
Cirsium setosum	Naringenin, guanine, vitexin, etc	Targets: SRC, EGFR, etc Pathways: Coagulation-related	Coagulation diseases	Integrated metabolomics	[27]
Portulaca oleracea (Purslane)	Flavonoids, terpenoids, phenols, alkaloids	Targets: ABCA1, ABCG1, CD36 Pathways: Lipid and atherosclerosis	Atherosclerosis	Oil Red O, Western blot, serum lipid detection	[28]
Mume fructus (Dark Plum Fruit)	Citric acid, caffeic acid, coumaric acid, etc	Pathways: FAK/PI3K/AKT signaling	Crohn disease	Western blot, cell proliferation/migration	[29]
Carica papaya	Ursolic acid, quercetin, hesperidin	Targets: VEGFA, IL-10, CCL2	Anemia	Cell viability, migration, qPCR	[30]
Industrial hemp (Cannabis sativa)	Chlorogenic acid, gallic acid, luteolin	Pathways: Serotonin, dopamine	Inflammation/fungal	Anti-proliferative/inflammatory assays	[31]
Daidai flower	Hesperetin, neohesperidin, naringenin	Targets: AMPK, PPARα	Obesity	Lipase inhibition, animal experiment	[32]
Licorice	Liquiritin, glycyrrhizic acid, etc	Targets: NRIF2 Pathways: Nrf2/PINK1 signaling	Ulcerative colitis	Histology, IHC, TEM, ELISA, Western blot	[33]
Angelica Dahurica	Imperatorin, isoimperatorin, phellopterin, etc	Targets: STAT3, TNF, IL-1β, PTGS2	Wound healing (diabetes)	Wound analysis, histology, IF, WB	[34]
Lily bulb and Rehmannia	Palmitic acid, linoleic acid, arachidonic acid	Targets: MAPK3, RELA, AKT1 Pathways: Fatty acid metabolism, neuroinflammation	Depression	IF, gain/loss-of-function, UHPLC-Q-TOF/MS	[35]
Nutmeg	Myristicin, myrislignan, etc	Targets: Akt, JNK, Nrf2, HO-1 Pathways: Akt/JNK/Nrf2	Gastric ulcers	Western blot, ELISA, TUNEL, UHPLC-MS	[36]
Cinnamon	Cinnamic acid, cinnamaldehyde, coumarin	Targets: PPARγ, UCP1, PGC1-α Pathways: AMPK	Cold tolerance	IHC, Oil red O, ATP, mitochondrial potential, WB	[37]
Phyllanthus emblica	Gallic acid, corilagin, ellagic acid	Targets: ALOX5, PTGS2 Pathways: Linoleic acid/tryptophan metabolism	Alcoholic liver injury	Metabolomics, histopathology	[38]
Finger Citron	Scoparone, limonin, nomilin, and others	Targets: AKT, EGFR Pathways: Amino acid/lipid metabolism	Coughs (Phlegm)	Metabolomics, pharmacokinetics, WB	[39]
Adzuki bean	15 types of saponins	Targets: PI3K, Akt, GSK3β Pathways: PI3K/Akt/GSK3β/β-catenin	Obesity	Western blot, immunofluorescence, UHPLC-MS	[40]
Donkey-Hide Gelatin	PP-1, PP-2	Targets: NFE2L2, STAT3 Pathways: HIF-1, JAK-STAT, hematopoiesis	Myelosuppression	Peptidomics (LC-MS/MS), blood tests	[41]
Jujube	Jujuboside B	Targets: ALB, EGFR, SRC Pathways: Bax/Bcl-2/caspase-3	Alzheimer disease	Lifespan, ThT staining, ROS, ATP, qPCR	[42]
Jujube	20 Triterpenes	Targets: PI3K, Akt, NF-κB Pathways: PI3K/Akt/NF-κB	Colorectal cancer	MTT, WB, IHC, peptidomics	[43]
Bush cherry seed	Mandelonitrile, linalool, D-limonene	Targets: AKT1, TNF, STAT3 Pathways: PI3K/AKT	Ulcerative colitis	GC-MS, histology, biochem parameters	[44]
Honeysuckle	Kaempferol, luteolin, quercetin	Targets: TP53, TLR4, MYD88 Pathways: TLR4/MYD88	Sepsis	qPCR, MTT, ELISA	[45]
Hovenia dulcis seeds	Kaempferol, stigmasterol, naringenin	Targets: AKT1, IL-6, Caspase-3 Pathways: TNF, IL-17 signaling	Alcoholic liver disease	Antioxidant assays, histopathology	[46]
Wolfberry	Glycitein, quercetin, atropine, and others	Targets: IL-6, TNF, STAT3, SIRT1	Aging	WB, qPCR, ELISA, micronuclei determination	[47]

(Continued)

Table 2
(Continued)

Names of FMH	Major active ingredients	Targets and mechanisms	Disease	Validation techniques	Ref
Wurfbainia villosa	Tsaokopyranol N, hedycorofuran, etc	Targets: PGAM5 Pathways: Nrf2/HO-1	Oxidative stress	ROS assay, thermal shift assay, WB	[48]
Poria Cocos	Capsaicin, oleic acid, ellagic acid	Targets: XDH, FASN, ABCG2 Pathways: Purine/fatty acid metabolism	Hyperuricemia	Metabolomics (UHPLC-MS/MS), ELISA	[49]
Elsholtzia	Humulene, caryophyllene, etc	Targets: MAPK3, EGFR, CASP3 Pathways: Apoptosis	Hepatocellular carcinoma	GC-MS, MTT assay	[50]
Persicae semen	Amygdalin, myricetin, oleic acid	Targets: Wnt/β-catenin, VEGF	Androgenic alopecia	Organ culture, animal experiment, qPCR, IF, UPLC-MS	[51]
Mulberry leaf	Quercetin, kaempferol	Targets: PTP1B, PPAR, AMPK Pathways: mTOR, PI3K-Akt, PPAR	Alzheimer, diabetes	Western blot, tyrosine phosphorylation	[52]
Citrus reticulata pericarpium	Nobiletin, sinensetin, hispidulin	Targets: AKT1, VEGFA, EGFR Pathways: VEGF	Ulcerative colitis	Metabolomics, RAW 264.7 cells, animal experiment	[53]
Alpiniae Oxyphyllae	Cubebin, Chalcone base, etc	Targets: TP53, SRC, STAT3 Pathways: PI3K-Akt	Diabetic kidney disease	Serum pharmacochemistry (UHPLC-QTOF), WB	[54]
Lotus leaf	Quercetin, nuciferin, catechin	Targets: FGF15, FXR Pathways: AGE-RAGE, Insulin resistance	Obesity	Animal experiments	[55]
Nelumbinis Plumula	Neferine, liensinine, isoliensinine	Targets: SRC, PIM1, NOS3	Pulmonary hypertension	Animal (rat) and cell experiments	[56]
Alpinia officinarum	Quercetin, kaempferol, galangin	Targets: AKT1, IL-6, SRC Pathways: PI3K-AKT, AGE-RAGE	Diabetic gastroparesis	Animal experimental verification	[57]
Lophantherum gracile	Kaempferol, genistein, rutin	Targets: TNF, STAT3, IL-6 Pathways: NF-κB, MAPK	Inflammatory diseases	Animal and cell experiments	[58]
Fermented Soybean	Daidzein, genistein, glycitein	Targets: TP53, TNF, MMP9 Pathways: p53, IL-17, VEGF	Lung cancer	Molecular dynamics, *in vitro* validation	[59]
Flos Chrysanthemi	Luteolin, apigenin, chlorogenic acid	Targets: PTGS1, ALOX5, TNF Pathways: NF-κB, arachidonic acid	Inflammation	UPLC-MS/MS, cell experiments	[60]
Cichorium intybus	Cynarin, quercetin, esculin	Targets: AKT1, mTOR, STAT3 Pathways: PI3K-Akt, AGE-RAGE	Nephrotic syndrome	Metabolomics, Western blotting	[61]
Polygonati rhizoma	Agmatine, rutin, cafestol	Targets: ATK1, TNF, AChE Pathways: PI3K–Akt, TNF	Alzheimer disease	Metabolomics, animal and cell experiments	[62]
Perilla frutescens	Luteolin, rosmarinic acid	Targets: AKT1, TP53, IL-6, TNF Pathways: Apoptosis, PI3K-AKT, HIF-1	Chronic renal failure	HPLC, cell experiments	[63]
Perilla frutescens	Rosmarinic acid, tuberonic acid	Targets: FYN, PDGFRA Pathways: Prostate cancer, AMPK	Prostate cancer	HPLC, cell viability	[64]
Perilla seed	Luteolin, rosmarinic acid, ALA	Targets: IL-6, AKT1, MMP9 Pathways: PI3K-Akt, MAPK	IBD	Transcriptomics, UPLC-MS/MS, animal/cell experiments	[65]
Pueraria lobata	Puerarin, formononetin, genistein	Targets: NOS2, TNF-α, MMP9 Pathways: Arginine metabolism	Pulmonary fibrosis	Metabolomics, validation	[66]
Pueraria lobata	Formononetin, beta-sitosterol	Targets: AKT1, PPARG, TNF Pathways: PI3K-Akt	Obesity	UPLC-MS, animal and cell experiments	[67]
Black sesame	Sesamin	Targets: ACSL4, Hmox1, Map1lc3a Pathways: Ferroptosis, ROS	CV injury (PM2.5)	Transcriptomics, experimental verification	[68]
Sophora japonica flower	Linoleic acid, isorhamnetin	Targets: COX2, IL-6, TNF Pathways: Pro-inflammatory cytokine	Contact dermatitis	Animal experiments	[69]
Taraxacum (Dandelion)	Quercetin, apigenin, luteolin	Targets: TP53, CASP3, EGFR Pathways: PI3K-Akt, cancer	Lung cancer	Molecular dynamics simulation, cell viability	[70]

(Continued)

Table 2
(Continued)

Names of FMH	Major active ingredients	Targets and mechanisms	Disease	Validation techniques	Ref
Dandelion	Luteolin, apigenin	Targets: CDK1, CCNB1, P53 Pathways: Cell cycle, amino acid metabolism	Triple-negative breast cancer	LC-Q-TOF/MS, metabolomics	[71]
Torreya grandis	α-Pinene, D-limonene, and others (17 types)	Targets: TNF, STAT3, NF-κB1 Pathways: Th17, NF-κB, HIF-1	Skin inflammation	*In vitro* experiments	[72]
Ziziphi Spinosae Semen	Jujuboside A, B, and others	Targets: HTR1A, GABRA1 Pathways: GABAergic synapse	Insomnia	UHPLC-MS, animal experiments	[73]
Imperatae rhizoma	Gluconic acid, chlorogenic acid, and others (30+ types)	Targets: PPARG, NF-κB, TNF-α Pathways: NF-κB, PPAR	Nephrotic syndrome rats	Animal experiments	[74]
Rhizoma Phragmitis	Stigmasterol, coixol, etc	Targets: IL-6, TNF, MAPK14 Pathways: AGE-RAGE, IL-17	Chronic bronchitis	HPLC, cell experiments	[75]
Peppermint	Menthone, menthol	Targets: ZO-1, JNK, NF-κB Pathways: Tight junctions, MAPK	Allergic rhinitis	GC-MS, animal and cell experiments	[76]
Rubus chingii (Raspberry)	Kaempferol, quercetin, ellagic acid	Targets: AKT1, IL-6, STAT3 Pathways: PI3K/Akt, MAPK, HIF-1	Chronic kidney disease	Animal experiments	[77]
Raspberry	Kaempferol, epicatechin	Targets: AKT1, IL-6, VEGFA Pathways: AGE-RAGE, insulin resistance	T2DM	UPLC-MS, *in vitro* experiments	[78]
Agastache rugosa	Acacetin, calycosin, rosmarinic acid	Targets: AKT1, IL-1B, TLR4 Pathways: PI3K-Akt, NF-κB	Gastritis	UPLC, animal and cell experiments	[79]
Angelica sinensis	Polysaccharide	Targets: AMPK, PGC1α, Bax/Bcl-2 Pathways: AMPK-PGC1α, ER stress	Myocardial infarction	Animal and cell experiments	[80]
Angelica sinensis	Ferulic acid	Targets: RUNX2, HDAC4, SRC Pathways: Calcium, estrogen, PI3K-Akt	Bone metabolic diseases	Quantitative metabolic network, molecular docking, cell experiment	[81]
Kaempferia galanga	Luteolin, kaempferol	Targets: SRC, STAT3, AKT1 Pathways: PI3K-Akt, MAPK	Oxidative stress	DPPH, Zebrafish, and cell experiments	[82]
Saffron	N-Heptanal, crocetin	Targets: TP53, VEGFA, HIF1A Pathways: Apoptosis, TNF, p53	Glioma	Single-cell RNA sequencing, Lasso	[83]
Saffron	Crocin	Targets: PI3K, Akt Pathways: PI3K/Akt	Thyroid cancer	Cell experiments	[84]
Amomum tsaoko	Olefins, alcohols, aldehydes	Targets: TNF-α, EGFR, MAPK8 Pathways: TNF, PI3K-Akt	Acute gastritis	Animal experiments	[85]
Piper longum	Piperlongumine, piperine	Targets: MMP1, PTGS2 Pathways: Cancer, IL-17	Osteoarthritis	HPLC, animal and cell experiments	[86]
Cistanche deserticola	Acteoside, isoacteoside	Targets: TLR4, NF-κB, TNF Pathways: TLR4/NF-κB	NAFLD	UPLC-MS, animal and cell experiments	[87]
Cistanche deserticola	Echinacoside, acteoside	Targets: HIF-1α, IL-6, AKT1 Pathways: HIF-1, IL-17, PI3K-Akt	Periodontitis	UHPLC-MS, MD, cell experiments	[88]
Dendrobium officinale	Quercetin, fatty acids	Targets: MAPK3, PIK3R1, Nrf2 Pathways: PI3K/Akt/Nrf2/HO-1	Aging kidney injury	Antioxidant assays, animal and cell experiments	[89]
Dendrobium officinale	Arabinose, glucose, mannose	Targets: TLR4, MMP9, HSP90AA1 Pathways: TLR4, immune network	Intestinal immune function	Molecular dynamics simulation, animal experiments	[90]
Panax quinquefolium	Ginsenoside Rg3, Rg5, etc	Targets: VEGFA, STAT3, MET Pathways: Angiogenesis, energy metabolism	Heart failure	Metabolomics (UHPLC-MS), Zebrafish	[91]
Radix astragali	Formononetin, kaempferol	Targets: TNF, NF-κB1, HIF1A Pathways: NF-κB, IL-17, TLR	Allergic rhinitis	MD sim, cell experiments	[92]
Astragalus	Quercetin, formononetin	Targets: AR, ESR1, IL-1B Pathways: AGE-RAGE, cAMP, NF-κB	Alzheimer	MD sim, cell experiments	[93]

(Continued)

Table 2
(Continued)

Names of FMH	Major active ingredients	Targets and mechanisms	Disease	Validation techniques	Ref
Astragalus	Quercetin, kaempferol	Targets: HO-1, Nrf2, TP53 Pathways: Nrf2/HO-1	Osteoarthritis	Animal and cell experiments	[94]
Ganoderma lucidum	Ganoderic acid Mf, polysaccharide	Targets: TP53, TNF, CASP3 Pathways: AGE-RAGE, cAMP	Optic atrophy	Cell experiments	[95]
Cornus officinalis	Lauric acid, ellagic acid, rutin	Targets: IL-6, TNF, AKT1 Pathways: AGE-RAGE, TNF, IL-17	Ischemic stroke model: MCAO/R rats	UHPLC-Q-TOF-MS, animal experiments	[96]
Gastrodia elata	Benzyl ethers, palmitic acid	Targets: GAPDH, AKT1, STAT3 Pathways: PI3K-AKT, lipid/athero	Alcoholic liver injury Model: HepG2 cells	Molecular dynamics simulation, cell experiments	[97]
Gastrodiae Rhizoma	Gastrodin, parishin A/B/C/E	Targets: EGFR, SRC, MAPK8 Pathways: PI3K-Akt	Depression model: CMS mice, neural stem cells	Metabolomics, animal and cell experiments	[98]
Eucommia leaves	Iridoids, flavonoids, lignans	Targets: MMP2, MMP9, INSR Pathways: Estrogen, lipolysis	Diabetic nephropathy	UPLC-MS, cell experiments	[99]
Radix Rehmanniae	Echinacoside, acteoside	Targets: TGFB1, SMAD2, TNF Pathways: TGF-β, NF-κB	Multiple sclerosis	Transcriptomics, scRNA-seq, cell exp	[100]
Rehmannia glutinosa	Rehmaionoside a, etc	Targets: ADAM17, LCK, PRKCD Pathways: Th17, sepsis	Sepsis	scRNA-seq, RNA-seq, survival analysis	[101]
Ophiopogon japonicus	Ophiopogonin C, A, B	Targets: EGFR, TP53, STAT3 Pathways: Notch, apoptosis	Hepatocellular carcinoma	UPLC-MS, MD, animal and cell experiments	[102]
Exocarpium Citri	Naringenin, naringin	Targets: SREBP1, TfR, Fpn1 Pathways: Lipid/iron metabolism	NAFLD	UHPLC-HRMS, animal experiments	[103]

ABCA1: ATP-binding cassette transporter A1; ABCG1: ATP-binding cassette transporter G1; ABCG2: ATP-binding cassette transporter G2; AChE: Acetylcholinesterase; ACSL4: Acyl-CoA synthetase long-chain family member 4; ADAM17: ADAM metallopeptidase domain 17; AGE-RAGE: Advanced glycation end-products (AGE) and receptor for advanced glycation end-products (RAGE); AKT1: AKT serine/threonine kinase 1 (also known as protein kinase B alpha); Akt: Protein kinase B (also known as AKT); ALOX5: Arachidonate 5-lipoxygenase; ALB: Albumin; AMPK: AMP-activated protein kinase; AR: Androgen receptor; ATP: Adenosine triphosphate; Bax: BCL2-associated X protein; Bcl-2: B-cell lymphoma 2; β-catenin: Catenin beta-1; CASP3: Caspase 3; Caspase-3: Cysteine-aspartic protease 3; CCL2: C-C motif chemokine ligand 2; CCNB1: Cyclin B1; CD36: CD36 molecule; CDK1: Cyclin-dependent kinase 1; CMS: Chronic mild stress; COX2: Cyclooxygenase-2 (also known as PTGS2); CV injury: Cardiovascular injury; DPPH: 2,2-Diphenyl-1-picrylhydrazyl; EGFR: Epidermal growth factor receptor; ELISA: Enzyme-linked immunosorbent assay; ESR1: Estrogen receptor 1; FAK: Focal adhesion kinase; FASN: Fatty acid synthase; FGF15: Fibroblast growth factor 15; FMH: Food-medicine homolog; Fpn1: Ferroportin 1; FYN: FYN proto-oncogene, Src family tyrosine kinase; FXR: Farnesoid X receptor; GABRA1: Gamma-aminobutyric acid type A receptor subunit alpha1; GAPDH: Glyceraldehyde-3-phosphate dehydrogenase; GC-MS: Gas chromatography-mass spectrometry; GSK3β: Glycogen synthase kinase 3 beta; HDAC4: Histone deacetylase 4; HepG2: Human hepatocellular carcinoma cell line (used as a model); HIF-1: Hypoxia-inducible factor 1; HIF1A: Hypoxia-inducible factor 1 subunit alpha; HIF-1α: Hypoxia-inducible factor 1 alpha; Hmox1: Heme oxygenase 1; HO-1: Heme oxygenase 1; HPLC: High-performance liquid chromatography; HR-ESI-MS: High-resolution electrospray ionization mass spectrometry; HSP90AA1: Heat shock protein 90 alpha family class A member 1; HTR1A: 5-hydroxytryptamine receptor 1A; IBD: Inflammatory bowel disease; IF: Immunofluorescence; IHC: Immunohistochemistry; IL-10: Interleukin 10; IL-17: Interleukin 17; IL-1β: Interleukin 1 beta; IL1B: Interleukin 1 beta; IL-6: Interleukin 6; IL6: Interleukin 6; INSR: Insulin receptor; JAK: Janus kinase; JNK: c-Jun N-terminal kinase; Lasso: Least Absolute Shrinkage and Selection Operator; LCK: LCK proto-oncogene; Src family tyrosine kinase; LC-MS/MS: Liquid chromatography-tandem mass spectrometry; MAP1LC3A: Microtubule-associated protein 1 light chain 3 alpha (gene symbol Map1lc3a); MAPK: Mitogen-activated protein kinase; MAPK3: Mitogen-activated protein kinase 3 (also known as ERK1); MAPK8: Mitogen-activated protein kinase 8 (also known as JNK1); MAPK14: Mitogen-activated protein kinase 14 (also known as p38α); MCAO/R: Middle cerebral artery occlusion/reperfusion; MD: Molecular dynamics; MET: MET proto-oncogene, receptor tyrosine kinase; MMP1: Matrix metallopeptidase 1; MMP2: Matrix metallopeptidase 2; MMP9: Matrix metallopeptidase 9; MMP-9: Matrix metallopeptidase 9; mTOR: Mechanistic target of rapamycin kinase; MTT: 3-(4;5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; MYD88: MYD88 innate immune signal transduction adaptor; NAFLD: Nonalcoholic fatty liver disease; NFE2L2: Nuclear factor, erythroid 2-like 2 (also known as Nrf2); NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; NF-κB1: Nuclear factor kappa B subunit 1; NOS2: Nitric oxide synthase 2 (inducible NOS); NOS3: Nitric oxide synthase 3 (endothelial NOS); Nrf2: Nuclear factor erythroid 2-related factor 2; Nrf2: Nuclear factor erythroid 2-related factor 2; NRIF2: Possibly a typographical variant of Nrf2; if referring to a distinct gene, it may stand for neurotrophin receptor-interacting factor 2 (uncommon; in context likely Nrf2); p53: Tumor protein p53; PDGFRA: Platelet-derived growth factor receptor alpha; PGC1α: Peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PGC1-α: Peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PGAM5: PGAM family member 5, mitochondrial serine/threonine protein phosphatase; PI3K: Phosphoinositide 3-kinase; PIK3R1: Phosphoinositide-3-kinase regulatory subunit 1; PIM1: Pim-1 proto-oncogene, serine/threonine kinase; PINK1: PTEN induced kinase 1; PM2.5: Particulate matter with diameter ≤ 2.5 μm; PPAR: Peroxisome proliferator-activated receptor; PPARα: Peroxisome proliferator-activated receptor alpha; PPARG: Peroxisome proliferator-activated receptor gamma; PPARγ: Peroxisome proliferator-activated receptor gamma; PRKCD: Protein kinase C delta; PTGS1: Prostaglandin-endoperoxide synthase 1 (cyclooxygenase 1); PTGS2: Prostaglandin-endoperoxide synthase 2 (cyclooxygenase 2); PTP1B: Protein tyrosine phosphatase 1B (also known as PTPN1); qPCR: Quantitative polymerase chain reaction; RELA: RELA proto-oncogene; NF-kB subunit (also known as p65); RNA-seq: RNA sequencing; ROS: Reactive oxygen species; RUNX2: RUNX family transcription factor 2; scRNA-seq: Single-cell RNA sequencing; SIRT1: Sirtuin 1; SMAD2: SMAD family member 2; SRC: SRC proto-oncogene, non-receptor tyrosine kinase; SREBP1: Sterol regulatory element-binding transcription factor 1; STAT3: Signal transducer and activator of transcription 3; T2DM: Type 2 diabetes mellitus; TEM: Transmission electron microscopy; TfR: Transferrin receptor; TGFB1: Transforming growth factor beta 1; TGF-β: Transforming growth factor beta; Th17: T helper 17 cells; ThT: Thioflavin T; TLR4: Toll-like receptor 4; TNF: Tumor necrosis factor; TNF-α: Tumor necrosis factor alpha; TP53: Tumor protein p53; TUNEL: Terminal deoxynucleotidyl transferase dUTP nick end labeling; UCP1: Uncoupling protein 1; UHPLC-HRMS: Ultra-high-performance liquid chromatography–high-resolution mass spectrometry; UHPLC-MS: Ultra-high-performance liquid chromatography–mass spectrometry; UHPLC-MS/MS: Ultra-high-performance liquid chromatography–tandem mass spectrometry; UHPLC-Q-TOF/MS: Ultra-high-performance liquid chromatography quadrupole time-of-flight mass spectrometry; UHPLC-QTOF: Ultra-high-performance liquid chromatography quadrupole time-of-flight; UPLC: Ultra-performance liquid chromatography; UPLC-MS: Ultra-performance liquid chromatography–mass spectrometry; UPLC-MS/MS: Ultra-performance liquid chromatography–tandem mass spectrometry; VEGF: Vascular endothelial growth factor; VEGFA: Vascular endothelial growth factor A; WB: Western blot; Wnt: Wingless-related integration site; XDH: Xanthine dehydrogenase; ZO-1: Zonula occludens-1.

In parallel, network analyses have elucidated the anti-inflammatory actions of agents such as Licorice, Mume Fructus, Honeysuckle, and Perilla seed, demonstrating their ability to alleviate gastrointestinal and respiratory injuries by modulating critical signaling cascades like nuclear factor erythroid 2-related factor 2 (Nrf2), focal adhesion kinase (FAK)/PI3K/AKT, toll-like receptor 4 (TLR4)/nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), and mitogen-activated protein kinase (MAPK). Despite the widespread application of network pharmacology in FMH research, a prevalent limitation in the field is its heavy reliance on purely computational predictions or simple phenotypic observations, which often lead to uncertain molecular mechanisms. To address this concern and ensure the reliability of the summarized data, Table 2 prioritizes studies that

integrate rigorous wet lab validation over those based solely on *in silico* mining.

Primary raw material screening

Target-pathway prediction models were used to identify high-potential FMH resources. Zhao et al.[104] selected six FMHs reported to have anti-tumor activity (*Astragalus membranaceus, Ganoderma lucidum, Dioscorea opposita, Curcuma longa, Glycyrrhiza uralensis,* and *Pueraria lobata*) and identified differentially expressed genes in colorectal cancer from the Gene Expression Omnibus (GEO) database. Combined with weighted gene co-expression network analysis and targets from other public databases, a network pharmacology analysis was conducted on the six FMHs. Through network pharmacology, bioinformatics, and machine learning analyses, it was found that all six FMHs exhibited potential anti-colorectal cancer effects[18], and all of them were validated in *in vivo* experiments by different studies[105–109].

Identification of active ingredients

Network pharmacology and molecular docking enable the prediction of active ingredients in FMHs through molecular docking and network analysis, as well as the exploration of their medicinal potential. Identifying active ingredients also serves as a key strategy in the research and development of phytomedicinal drugs. Mao et al.[110] combined network pharmacology and molecular docking to verify the efficacy of *Pueraria Lobata Radix* in treating type 2 diabetes and found that puerarin and luteolin may be the main active ingredients. Recent studies have confirmed that puerarin and luteolin exert antidiabetic effects when administered alone[67,111–112]. Owing to the holistic concept of network pharmacology, many studies have identified not only a single compound but also a class of compounds. Ruan et al.[43] found that jujube extract had anti-colorectal cancer effects in an azoxymethane (AOM)/dextran sodium sulfate (DSS)-induced colorectal cancer mouse model. Subsequently, by combining different extraction conditions with network pharmacology analysis, they discovered that the triterpenes in it have anti-colorectal cancer effects and are a key class of anti-tumor compounds in jujube extract[43]. In addition to phytochemicals, animal-derived macromolecules can also be utilized in this strategy. Through liquid chromatography-mass spectrometry (LC/MS), zebrafish, rat, and mouse experiments, combined with network pharmacology, researchers have revealed that low-molecular-weight peptides derived from E-Jiao (LMEJ) can significantly alleviate bone marrow suppression by regulating key signaling pathways, such as Janus kinase-signal transducer and activator of transcription signaling pathway (JAK-STAT) and interleukin-17 (IL-17). They also identified specific peptides (PP-1 and PP-2) that exert these effects[41].

Analysis of synergistic effects

By evaluating the synergistic effects of different herbs or components on various targets or pathways, enhanced beneficial effects against specific diseases can be discovered. Zhang et al.[113] used cell models and 65 Chinese medicines with antioxidant potential were screened from 105 FMHs. Furthermore, a formula containing the five FMHs was designed using network pharmacology methods in combination with TCM. It has been confirmed in zebrafish and mouse models that this formulation helps clear particulate matter from the lungs and alleviates PM-induced lung injury[113]. In addition, FMH (such as goji berries, yams, and turmeric) usually contain multiple active ingredients (such as polysaccharides, flavonoids, and alkaloids). Network pharmacology can reveal FMH's multi-target synergistic mechanisms by constructing a "component-target-pathway-disease" network. Microvascular angina (MVA) is a common cause of myocardial ischemic chest pain in patients with nonobstructive coronary artery disease. Its pathogenesis is complex and involves coronary microcirculatory dysfunction, cardiac autonomic nervous system dysfunction, and insufficient estrogen levels. Thus, there is a lack of specific drugs. Researchers constructed an FMH database by searching 11 databases and composed an FMH formula for the treatment of MVA, which acts on estrogen-, inflammation-, and energy metabolism-related pathways simultaneously through network pharmacology methods, including frequency analysis, association rule analysis, and cluster analysis[114].

Establishment of quality standards

Network pharmacology helps to identify key active compound groups that are effective. Using these as quality markers (Q-markers) offers a practical way to standardize FMH products. *Gastrodia elata* is a FMH with various pharmacological activities. However, different drying methods for *G. elata* can lead to differences in the content of its components, which have different pharmacological effects. Therefore, it is particularly important to conduct quality control on the processing of *G. elata* for specific diseases. Yang et al.[115] used HPLC combined with network pharmacology analysis to investigate the effects of six different drying methods on the active components of *G. elata* with anti-type 2 diabetes mellitus (T2DM) effects. *In vitro* antioxidant experiments confirmed that steam freeze-drying helped retain the antidiabetic active components in *G. elata*[115]. During the reflux extraction of *Phyllanthus emblica*, a large amount of the tannin components can decompose into gallic acid, which affects the accuracy and specificity of content determination. Q-markers of *P. emblica* were determined by integrating chromatographic fingerprinting, serum pharmacochemistry, and network pharmacology. A component-target-disease-pathway network was constructed using network pharmacology to identify the 22 components responsible for the efficacy of *P. emblica*. Screening for more appropriate Q-markers will help to improve the quality standards of *P. emblica* and ensure its medicinal safety and efficacy[116].

Safety strategies

FMH Chinese herbs possess both medicinal efficacy and edible safety, making them widely used for disease prevention and adjuvant therapy[117]. However, owing to their complex compositions, co-administration with conventional drugs or multi-herb formulations is prone to inducing herb–drug interactions (HDIs), which may either produce therapeutic synergistic effects or trigger

potential toxicity risks. Therefore, the prediction and prevention of HDIs have become the core focus of safety research on FMH Chinese herbs[118]. The occurrence of HDIs is mainly related to the regulation of drug-metabolizing enzymes and transporters, among which the cytochrome P450 (CYP450) enzyme family (eg, CYP3A4 and CYP2C9) and transporters such as P-glycoprotein (P-gp) are key targets[119]. The active components of FMH Chinese herbs may induce or inhibit the activity of these targets, thereby altering the metabolism, absorption, and excretion of the co-administered drugs. For instance, formononetin and daidzein in *Astragali Radix* can inhibit CYP2C9, thereby affecting the efficacy and safety of the co-administered drugs[120]. Network toxicology deciphers the interaction network of "toxicity-(side effects)-genes-targets-drugs," enabling the sorting of chemical components in FMH and the construction of interaction networks to identify key components and targets triggering HDIs. AI models (eg, models integrating LLMs and variational graph autoencoders) further improve the accuracy of HDI prediction and can effectively distinguish between therapeutic synergy and potential toxicity[121]. Currently, HDI research on FMH Chinese herbs has limitations, including the lack of toxicological data for specific varieties, the impact of batch differences in Chinese herb components on model prediction, and the weak interpretability of AI models. In the future, it will be necessary to strengthen specialized HDI experiments between FMH and commonly used clinical drugs, accumulate high-quality data to optimize the prediction system, and achieve full-chain safety control, from early risk warning to formulation adjustment. In summary, integrating the HDI prediction capabilities of network toxicology and AI models, combined with the mechanistic analysis of key targets, such as CYP450 enzymes and transporters, can construct a multi-dimensional safety strategy for FMH Chinese herbs. This provides a new pathway for quality control and standardized development, ensuring its safe application in clinical practice and daily consumption.

Formula optimization

The FMH formulas are originate from long-term clinical practice. However, modern medicine increasingly demands higher precision in efficacy. How to optimize formulas and enhance clinical outcomes by leveraging modern technology has become a key research topic in FMH studies. Network pharmacology can integrate patients' clinical big data with the experiences of veteran TCM practitioners to construct a "disease-gene-target-drug" biological network. It enables in-depth analysis of disease mechanisms, gene-target associations, and interactions between drug components and targets[2]. By incorporating the target information of FMH Chinese herbs, formula optimization can be achieved by adjusting the proportion of herbs to enhance the effects of the active components, or by adding/removing herbs to reduce ineffective or harmful effects. The research team utilized their self-developed UNIQ system to predict disease-related targets of drug components, screen out highly relevant Chinese herbs, and adjust the formulation based on veteran TCM practitioners' experiences, resulting in precise formulas like "Jiawei Qingluo Yin (Modified Qingluo Decoction)." Finally, the efficacy mechanism was verified through clinical and experimental studies, realizing "data-driven + experience-inherited" formula upgrading[122]. Evidently, the application of network pharmacology in FMH formula optimization integrates traditional experiences with modern technologies. This not only improves the efficacy and precision of formulas but also provides strong support for the modernization of FMH formulas, promoting their wider application in clinical treatment.

Discovery of new functional foods

Health awareness is constantly increasing, leading to a growing demand for functional foods targeting specific diseases, such as diabetes and pneumonia. As a treasure trove of natural resources, Food-Medicine Homology (FMH) Chinese herbs are rich in potential functional components, holding broad prospects for the development of new functional foods. From the perspective of biological network regulation, network pharmacology can utilize target prediction technology to analyze the regulatory effects of Chinese herb components on disease-related biological networks, identify herbs that can effectively intervene in diseases, and further design targeted composite functional foods. Using Huangjing cake as an example, researchers identified 87 components using ultra-performance liquid chromatography quadrupole time-of-flight mass spectrometry (UPLC-Q-TOF-MS). Combined with network pharmacology, they screened 160 intersecting targets related to type 2 diabetes, with core involvement in the AGE-RAGE signaling pathway. Animal experiments further confirmed its ability to lower blood glucose levels, regulate blood lipids, and enhance antioxidant capacity, making it highly suitable for development as an adjunctive functional food for type 2 diabetes. For the herb–pair combination of *Platycodon grandiflorum* and *Lilium brownii*, 12 active components were screened, and 225 action targets were predicted, of which 22 overlapped with the pneumonia targets. Core targets such as tumor necrosis factor (TNF) and matrix metallopeptidase 9 (MMP9) are involved in inflammatory pathways like the TNF pathway, and *in vitro* experiments have verified their anti-inflammatory effects, laying a foundation for the research and development of pneumonia-related functional foods. The application of network pharmacology to the discovery of new FMH functional foods has clarified precise directions and provided scientific evidence for functional food research and development. This will facilitate the development of more effective and safe FMH functional foods targeting specific diseases that not only meet people's health needs but also promote the development of the functional food industry.

It should be noted that network pharmacology cannot fully replace clinical trials; instead, it requires scientific evidence regarding weight design and dynamic risk management. For example, by analyzing the predicted and verified results, feeding them back into the network pharmacology model, dynamically adjusting the research strategy, and ensuring the safety and effectiveness of the research can accelerate the process of research and translation of FMHs.

Personalized recommendations

Individuals exhibit differences in genetics, metabolism, and other aspects, leading to varying responses to FMH Chinese herbs among different people. Therefore, implementing personalized dietary interventions using FMH Chinese herbs is of great significance to improve their efficacy and to reduce adverse reactions[2]. Network pharmacology can integrate patients' genomic, metabolomic, and other omics data with FMH Chinese herb networks to construct personalized "omics-target-herb" association maps. The functional heterogeneity of the gut microbiota, which defines enterotypic distinctions, directly modulates the key metabolic pathways involved in FMH breakdown and bioactivation, underscoring the necessity of accounting for individual microbial profiles in tailored approaches. Based on each individual's genetic characteristics and metabolic traits, we analyzed the degree of matching between herbal components and individual targets, thereby providing precise recommendations for herbal combinations and ultimately achieving an individualized dietary design. For example, patients with different metabolic types show significant differences in their responses to FMH Chinese herbs. After obtaining individual characteristics through omics testing combined with network pharmacology analysis, FMH herbal combinations that regulate lipid metabolism targets can be recommended for obese patients with hyperlipidemia, whereas combinations that improve insulin sensitivity targets can be suggested for obese patients with insulin resistance[123]. However, the effectiveness of such personalized schemes has not yet been fully verified and should be confirmed through systematic intervention studies in the future. The application of network pharmacology to personalized recommendations for FMH Chinese herbs overcomes the limitations of the "one-size-fits-all" approach and moves toward individualized precision intervention. This study provides a new direction for personalized dietary interventions, enabling the customization of FMH herbal dietary plans according to each person's specific conditions, enhancing health management outcomes, and promoting the development of personalized medicine and precision nutrition.

The representative case of network pharmacology in FMH

Gastric cancer is highly prevalent in China, with an early diagnosis rate of <10% for a long time, posing a significant hazard to public health[124]. Based on the "network targets" theory, relevant studies have taken the gastritis-cancer transformation as the entry point and conducted long-term research focusing on the key issue of early diagnosis and treatment of gastric cancer. This study quantitatively depicted the dynamic evolutionary mechanism of gastritis-cancer transformation and identified FMH Chinese medicines that have the potential to inhibit this transformation process[13].

This study proposes an AI-based integrative approach combining traditional and Western medicine, termed AI-based Integration of Traditional and Western Medicine (AI-TWM). The UNIQ system was deployed as the core computational platform within the AI-TWM framework. The core of AI-TWM is the use of bio-network-informed AI algorithms to systematically analyze diagnostic and therapeutic patterns from multimodal big data related to tumorigenesis in both traditional and Western medicine. This enables intelligent early warning of cancer risk and precise discovery of interventional herbs. This approach has been successfully demonstrated in the prevention and management of gastric cancer, leading to the establishment of an intelligent and precision-based system for the early interception of gastric cancer at its critical transition stage—conceptualized as the "exceedingly-early stage" of gastric cancer. This represents a major paradigm shift in the introduction of a novel clinical staging system that captures the critical transition states during malignant transformation.

The AI-TWM system for gastric cancer prevention constitutes an integrated computational framework that employs a multi-modal fusion strategy to holistically capture the critical transition from premalignant lesions to malignancy. Its architecture utilizes cross-modal autoencoders and deep neural networks to integrate macroscopic clinical phenotypes from TCM, such as tongue-coating images, with microscopic single-cell and bulk omics data, as well as canonical risk factors. For cancer risk screening, a dedicated deep-learning model (eg, a convolutional neural network) was trained on a large-scale dataset of tongue images integrated with conventional risk factors, which significantly improved the prediction accuracy for progression from gastric precancerous lesions compared with models using conventional factors alone. To identify biomarkers for "exceedingly-early" diagnosis, the system analyzed single-cell transcriptomic profiles of gastric tissues from high-risk patients characterized by TCM "damp heat" syndromes, revealing a distinct epithelial cell population with enhanced stemness that served as a novel diagnostic biomarker.

Using the AI-TWM framework, the team systematically collected and computationally analyzed over 500,000 clinical cases of gastritis-to-gastric cancer progression, complemented by multi-omics data from representative sequential cases. This effort resulted in the construction of multilevel biological networks encompassing phenotypic, cellular, molecular, and pharmacological dimensions. Through in-depth analysis of these networks, the team identified integrated bio-signatures for gastric cancer risk warning and discovered "exceedingly-early gastric cancer cells" indicative of the critical transition state. Novel biomarkers were developed, and a multi-modal AI model integrating macroscopic clinical features and microscopic biological characteristics was established. This model enables the high-accuracy prediction of gastric cancer risk and supports an exceedingly accurate diagnosis. Furthermore, network pharmacology was employed to comprehensively predict and validate FMH, which targets the exceedingly early gastric cancer network. Subsequent randomized controlled trials (RCTs) confirmed that these herbs significantly inhibit the transition from gastritis to gastric cancer, thereby addressing a critical gap in early intervention strategies. This system has been implemented and promoted across multiple high-risk regions and hospitals in China, demonstrating substantial clinical benefits for gastric cancer prevention and treatment.

Challenges and future perspectives

Inadequacy of network pharmacology in FMH

The complexity of data integration arises as FMH datasets often differ in format, quality, and coverage, leading to challenges in constructing comprehensive interaction networks. Network pharmacology research relies on the systematic integration of multi-source heterogeneous data, including Chinese herbal medicine components, target molecules, disease genes, protein interactions, and clinical phenotype data. For example, at the compound data level, there are TCMSP/BATMAN-TCM[22,125], TCMID, ETCM, etc; at the drug target level, there are DrugBank, PubChem, HIT, etc; at the disease target level, there are DisGeNET, OMIM, etc; at the protein interaction level, there are STRING, BioGRID, etc; and at the biological pathway level, there are KEGG, GO, TCGA, etc. These databases have different formats for annotating TCM information, and the data sources (literature, experiments, and predictions) and quality screening standards vary across different databases. The same applies to food and medicine homogeneity. Data on natural product components, metabolic pathways, and traditional experiences are scattered across multiple databases, and there is a lack of data-sharing mechanisms, leading to obstacles in network modeling. With improvements in foundational infrastructure, such as one-stop analysis platforms, this issue may be addressed in the future.

Standardization gaps highlight the lack of standardized protocols for the quality control and bioactivity assessment of herbal mixtures. From the perspective of product forms in the terminal market, although medicinal and edible ingredients have been widely used in various carriers such as granules, capsules, tea drinks, meal replacement powders, biscuits, and jellies, their application has expanded from traditional fields such as alcoholic beverages and medicinal diets to emerging fields such as baking and snacks. During the food processing of medicinal and edible ingredients, the active compounds in these ingredients may be damaged or degraded through processes such as high-temperature heating, prolonged storage, and mechanical processing, resulting in a significant reduction in the content of active components. Product packaging often lacks specific labels indicating the components and their quantities, dosage guidelines, and efficacy verification. The absence of unified standards and regulations frequently results in unclear product efficacy and ambiguous components, making it difficult to gain widespread recognition from consumers and regulatory authorities. Therefore, it is imperative to establish standardized databases and protocols to establish quality control and efficacy evaluation standards for the active components in medicinal and edible ingredients and products of various forms, which may have different sources and preparation methods.

The limitations of dynamic network modeling mean that current models often overlook temporal changes in FMH systems, reducing the accuracy of predicting long-term effects and failing to capture adaptive responses to dietary interventions. Herbal ingredients with both medicinal and dietary uses are often incorporated into daily diets as functional components. These effects typically manifest gradually over time through prolonged and consistent consumption, representing a slow and gentle process of nourishment and regulation. In contrast, drug interventions often target specific diseases or symptoms, emphasizing the rapid onset of therapeutic effects within a short timeframe, to quickly alleviate or control the condition. There were significant differences between the two in terms of mechanism of action, dosage intensity, and temporal dimensions. Therefore, network pharmacology modeling of food medicine dual-use substances places greater emphasis on the dynamic changes in the body's ecological and metabolic networks and immune regulation over longer timescales. Traditional static network models cannot capture temporal changes, biological feedback, or individual differences, limiting the simulation and prediction of the long-term or personalized effects of food medicine interventions. Therefore, integrating dynamic networks requires combining multiple time-series omics data to reflect the progressive adaptation, metabolic transformations, and homeostatic regulation of the body, resulting in complex model construction and high data requirements.

The inherent chemical heterogeneity of FMH substances, arising from variations in origin, harvest time, and processing methods (Paozhi), poses a significant challenge to network pharmacology by introducing uncertainty into the fundamental chemical input for network construction. Current databases, which often rely on standardized or representative compound lists, struggle to capture this variability, leading to networks based on idealized chemical profiles that may not reflect real-world samples. To address this issue, future strategies must integrate quantitative chemical fingerprinting data with processing parameters. Modeling approaches, such as fuzzy logic, probabilistic graphical networks, and uncertainty-aware AI models, are promising avenues. These methods can transform binary component–target interactions into weighted or probabilistic relationships and provide confidence estimates for predictions, thereby explicitly accounting for compositional uncertainty. Advancing this direction is crucial for the evolution of FMH network pharmacology from a deterministic, idealized framework to a robust, quantitative, and real-world applicable discipline.

Future perspectives

Multi-omics integration involves combining transcriptomics, metabolomics, and gut microbiome data with network pharmacology to reveal FMH's holistic mechanism. Future research will focus on developing dynamic network modeling methods, combining time-series multi-omics data to achieve spatiotemporal dynamic characterization of the FMH system, providing a theoretical basis and technical support for precision nutrition and personalized dietary intervention.

Dynamic network modeling entails incorporating time-series data and machine learning to simulate FMH effects over time, enabling personalized nutrition-disease management strategies. The introduction of AI, particularly GNNs and GCNs, has provided powerful tools for integrating multi-layer network data and modeling complex relationships. GNNs can capture deep-level interactions within non-Euclidean structures between nodes, dynamically update node states, and are suitable for simulating multi-dimensional coupled processes of the microbiome, metabolism, and gene regulation in FMH systems. In addition, AI methods such as reinforcement learning can play

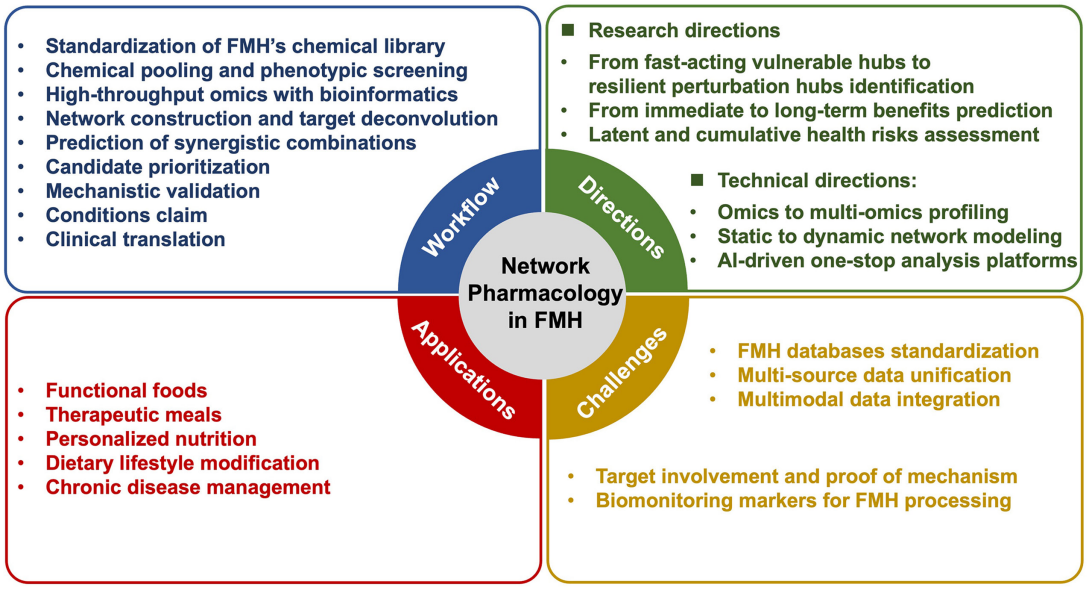

Figure 2. The schematic diagram of future perspectives for network pharmacology in FMH. FMH: Food-medicine homolog.

a role in optimizing personalized nutrition plans, enabling intelligent decision-making for precise nutritional interventions through continuous feedback adjustments. By combining methods, such as GNNs, dynamic efficacy prediction models that evolve over time can be established, enabling precise nutritional interventions for food-medicine products. A recent review has summarized prospects of scRNA-seq in clinical nutraceutical research, noting that single-cell technologies have the potential to clarify cellular responses to nutraceuticals and functional food components research. Similarly, pseudo-time analysis in single-cell transcriptomics reconstructs continuous trajectories of cell states from snapshot data, providing insights into the dynamic transitions along developmental or differentiation paths[126]. Thus, the direct application of dynamic network modeling to FMH research is still emerging, and it integrates time-series scRNA-seq data. Continuous dynamic models, particularly those based on ordinary differential equations (ODEs), have been widely used to model gene regulation and signaling kinetics. For example, dynamic time-order networks integrate ODEs with spline regression to reconstruct temporal regulatory trajectories from time-series expression data[127]. Moreover, temporal or time-varying network models allow the network topology to change over stages or conditions, thereby capturing rewiring events as cells develop or respond to stimuli. Complementing these approaches, hybrid methods combining machine learning and neural ODEs or graph-based ODE models have proven to be effective in learning hidden network dynamics from noisy longitudinal data. Importantly, concepts from critical transition theory, such as tipping points and critical slowing down, have been operationalized in biological systems using dynamic network biomarkers (DNBs). These methods can detect imminent state transitions, such as differentiation events, tumor progression, or epithelial-mesenchymal transition (EMT), from omics data, acting as early warning signals for network reorganization before phenotypic changes occur[128–129]. In parallel, probabilistic temporal frameworks, such as dynamic Bayesian networks (DBNs), are employed to capture time-dependent regulatory relationships, as demonstrated in yeast time-series data, and are enhanced with Monte Carlo sampling for improved inference[130]. Collectively, these frameworks illustrate how theoretical network dynamics can be grounded in concrete mathematical tools and real biological applications, thereby bridging the gap between time-course data and inference of FMH-regulating biological networks.

Standardized FMH databases involve the development of centralized repositories for FMH components, interactions, and clinical outcomes to streamline network construction and reproducibility. Advocate the construction of a standard database similar to DrugBank for food and medicine of the same origin, summarizing information such as ingredients, targets, indications, and toxicology to improve research reproducibility and provide an authoritative and reliable reference platform for academia and industry, thereby promoting scientific research and clinical application in the field of food and medicine of the same origin (Figure 2). In the future, methodological advances are expected to drive a systematic transition from single-omics analysis to comprehensive multi-omics profiling, thereby enabling a more holistic representation of biological complexities. Simultaneously, static network representations are increasingly being replaced by dynamic network modeling frameworks that explicitly incorporate temporal information, biological feedback, and adaptive system responses. Such developments also necessitate a conceptual shift in target identification strategies, moving from fast-acting vulnerable network hubs associated with acute therapeutic effects to resilient perturbation hubs that modulate systemic robustness and long-term homeostasis. Consequently, the predictive focus of network pharmacology is expected to evolve from immediate therapeutic outcomes to the prediction of long-term benefits, reflecting the gradual, cumulative, and regulatory effects of FMH interventions.

Discussion and conclusion

As public health awareness has significantly increased, the demand for food-medicine dual-use products has grown steadily. This industry also faces challenges, such

as insufficient basic research and unclear consumer understanding, particularly regarding the safety of medicinal and edible herbs. Many researchers believe that medicinal and edible herbs do not cause any toxicity or adverse reactions. Currently, there is a lack of long-term toxicological evaluations of FMH varieties, with most studies relying on short-term animal experiments and lacking human data and clinical validation. Key parameters such as dosage, frequency, and intake cycles lack scientific guidance. For example, red yeast rice, a fungus with medicinal and food properties, contains statin-like substances such as monacolin K in fermented health foods. When used in combination with lipid-lowering drugs, it can cause rhabdomyolysis syndrome and acute kidney injury. This highlights the urgent need to enhance the safety assessment of food-medicine dual-use varieties[26,131]. In this context, network pharmacology can reveal the complex relationships between components, targets, and toxicity pathways at a systemic level[27]. Big data technology can identify potential risk populations through real-world evidence, whereas AI models can further predict toxicity risks, uncover drug-food interaction signals, and provide decision support for personalized medication and dietary interventions. In the future, establishing an integrated system for intelligent safety assessment of food-medicine dual-use products by combining network pharmacology, big data, and AI will become a key direction for realizing their modernized and precise functions for safe population applications. A key quantitative limitation of the current network pharmacology is the lack of pharmacokinetic data on bioactive compounds. To mitigate this, the method leverages post-exposure omics data to prioritize targets *via* enrichment scoring and weighs network edges through link strength prediction, thereby constructing a functionally validated network that more accurately reflects system-level effects.

The synergistic potential of network pharmacology lies in its transformative role in validating and modernizing medicine-food homology practices. It promotes the development of food and medicine research toward precision, mechanism, and modernization, bridging the gap between traditional knowledge and modern mechanism research, and is a key path to promoting the modernization of FMH. Meanwhile, the translational imperative stresses the importance of bridging computational predictions with clinical trials and real-world applications; relying solely on computational predictions and network simulations is insufficient to fully reveal the actual efficacy and safety of food-medicine dual-use ingredients. The need for the translation from computational predictions to clinical validation suggests that computational simulations alone are insufficient. They must be combined with validation methods such as animal experiments, population studies, and clinical trials to create food medicine dual-use products that truly serve the cause of health. Finally, an interdisciplinary vision calls for collaborative efforts among TCM practitioners, pharmacologists, and data scientists to advance global integrative health solutions. We urge TCM scholars, bioinformaticians, nutritionists, and AI experts to work together to establish a new paradigm for FMH research.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

Deyang Sun contributed to the conceptualization, writing, and revision of the manuscript. Pan Chen contributed to the revision and editing of the manuscript. Li Tao contributed to the "Challenges and Future Perspectives" section. Peng Ma and Lichong Meng contributed to the investigation and writing of the specific applications. Shuting Yin contributed to the investigation of intestine-related materials. Bo Zhang and Shao Li supervised and guided the implementation of the manuscript.

Ethical approval of studies and informed consent

Not applicable.

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Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request. Additional information and supporting data can be found in the Supplementary Materials section of this article.

Declaration of generative AI in scientific writing

The conception and writing of this article were carried out collaboratively by all authors. Artificial intelligence was utilized exclusively for refining sentence coherence and amending punctuation. All citations in this manuscript were manually searched for and incorporated. After utilizing the aforementioned tools/services, the authors thoroughly reviewed and revised the content and take full responsibility for the entirety of this publication.

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