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REVIEW

Discovering the Molecular Secrets of Traditional Chinese Medicine: An Interpretation of Herbal Therapeutics Using Systems Biology

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Abstract: Systems biology is primarily concerned with the dynamic study of biochemical metabolic processes in physical systems, the interplay of multiple signal transduction routes, gene regulatory networks, and disease causes, among other things. Its most notable aspect is that it merges individual genes with protein studies into thousands of genes or proteins, resulting in "three-dimensional" research. The action advantage of Traditional Chinese Medicine (TCM) is in the integration and modulation of the impact of each individual medication. TCM active components are compatible and blended according to specified conditions, and the integrated medication action is characterized by multi-target and multi-way integration, which is consistent with system biology research theories. Actively introducing new concepts and approaches, such as system biology, will most likely lead to a breakthrough in advancing TCM modernization. This paper aims to review the application of systems biology technologies in TCM research, with a focus on unraveling the multi-component synergistic mechanisms, deciphering the molecular network regulatory patterns, and evaluating the safety and toxicity of TCM compounds, thereby illuminating the molecular basis of TCM's efficacy in improving complex diseases such as cardiovascular disease and cancer. By adopting the "three-dimensional" research framework of systems biology, this work intends to furnish advanced application references for the holistic view research strategy of Chinese medicine, thereby bridging the systemic research paradigm with traditional TCM theoretical frameworks.

Keywords: systems biology, traditional Chinese medicine, omics technologies, genomics, proteomics, metabolomics, microbiomics

Introduction

Traditional Chinese Medicine (TCM) boasts a rich history spanning thousands of years, establishing itself as an integral part of Chinese traditional culture that plays an indispensable role in the health and continuity of the Chinese population.[1] Central to TCM is the philosophy of "Heaven and man are identical", emphasizing a holistic approach and syndrome differentiation in prevention, diagnosis, and treatment of diseases.[2] This holistic principle, while rooted deeply in traditional Chinese culture, also underpins the foundational structure of TCM, shaping its evolution and objectives. Concurrently, modern medical practices recognize the merits of TCM's integrative approach. However, TCM's intricate theoretical constructs and the multifaceted nature of TCM compounds pose challenges. Assessing TCM exclusively within its own framework is tantamount to investigating a "black box", which potentially hampers its progression. Thus, it's essential to balance the preservation and transmission of TCM's rich heritage with modern advancements to foster its growth.[3–5]

In the aftermath of human genomic discoveries, systems biology has emerged as a multidisciplinary frontier, attracting considerable attention within the medical domain.[6] Systems Biology encompasses a diverse array of fields,

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including genomics, proteomics, transcriptomics, metabolomics, interaction omics, phenotypic omics, and computational biology. Each subset offers unique attributes and focuses.[7] Modern biology strives to move beyond singular entities like genes and proteins, aiming to decipher complex networks involving interactions among genes, proteins, metabolites, and other cellular components. By integrating multi-omics approaches and developing models—either graphical or mathematical—to depict system structures and behaviors, researchers can gain insights not only into the genetic makeup of organisms but also into the expression and interplay of proteins, metabolites, and other functional entities (Figure 1).[8–10]

TCM and systems biology, though stemming from disparate historical and cultural contexts, share intriguing similarities in their foundational principles. The convergence of these two fields can offer transformative insights for modern medical research. Integrating TCM's holistic and experiential wisdom with the data-driven methodologies of systems biology can pave the way for a more comprehensive understanding of health and disease. For instance, while

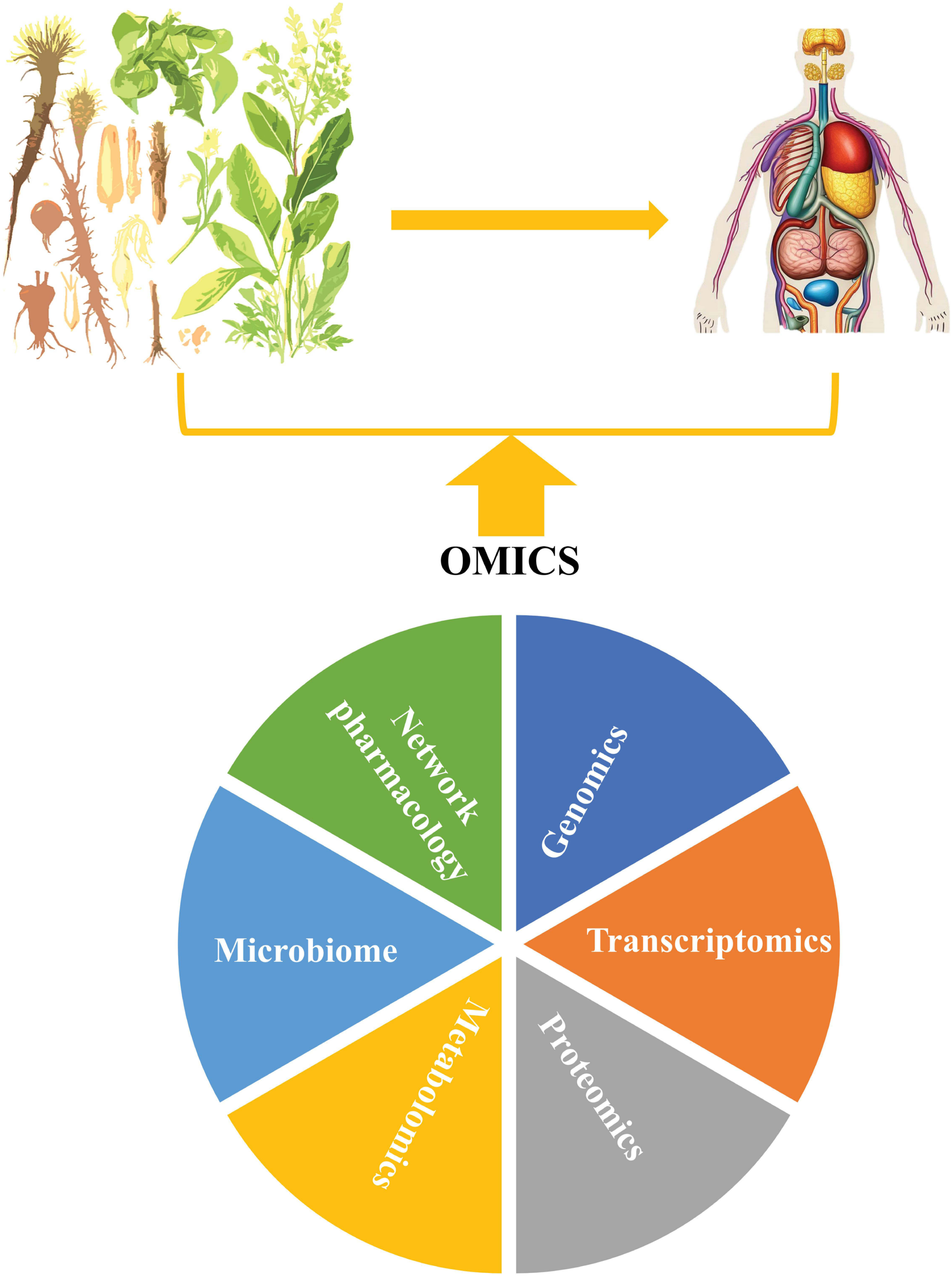

Figure 1 Application of Omics Technologies in Traditional Chinese Medicine (TCM) Research.

TCM may provide insights into how certain herbs or treatments can bring balance to the body, systems biology can elucidate the molecular and cellular mechanisms underpinning these effects. Moreover, the fusion of TCM and systems biology could usher in a new era of personalized medicine. By leveraging the holistic insights from TCM with the precision of systems biology, medical practitioners could tailor treatments based on an individual's unique biological makeup and the broader systems perspective. This blend could lead to more effective interventions, reduced side effects, and a deeper understanding of how treatments impact the body's equilibrium. Furthermore, in the realm of drug discovery, TCM's vast repository of herbal medicines can be explored through the lens of systems biology to decode their multifaceted effects on the human body. Through high-throughput screenings, network analyses, and multi-omics studies, the active compounds in these medicines can be identified, their mechanisms of action deciphered, and their therapeutic potential maximized.

System Biology Technology

Ludwig von Bertalanffy, an Austrian biologist, laid the groundwork for systems biology, with Leroy E. Hood later popularizing the term in 1999. This discipline in biology focuses on the structure, dynamics, and functions of biological system components. Characterized by its combination of systems theory, empirical methods, and computational approaches, systems biology has evolved from a localized view to a more holistic perspective of understanding biology, particularly in areas like cellular signal transduction and gene regulatory networks.[11,12] TCM offers a parallel in its perception of humans as organic wholes. In this framework, individuals are viewed as structurally unified entities with coordinated functions, affected in pathology. This holistic perception also emphasizes the intrinsic connection between individuals and their natural and social environments, leading to concepts like the "correspondence between man and nature" and the interplay of "three factors: time, place, and people".[13–15] In essence, the holistic views espoused by both systems biology and TCM align remarkably. The drive to modernise TCM has incorporated tools and methodologies from systems biology, such as transcriptomics, proteomics, metabolomics, genomics, network pharmacology, and epigenetics. Leveraging these advanced techniques, significant strides have been made in bridging ancient wisdom and modern scientific approaches.

Genomics Technology

Thomas H. Roderick, a renowned geneticist, introduced the concept of genomics in 1986. This field encompasses the study of an organism's genome, delving into nucleotide sequence analysis, gene localisation, and functional gene analysis. Genomics can be further classified into three main categories: structural genomics, comparative genomics, and functional genomics. These subdivisions primarily investigate the structure, function, evolution, positioning, and manipulation of genomes.[16,17] In Traditional Chinese Medicine (TCM) research, the most utilized genomic technologies include DNA molecular marker technology, gene chip technology, PCR technology, and DNA sequencing.

Emerging in the twilight of the 20th century, TCM genomics represents a convergence of ancient medicinal practices and modern scientific investigation. The inception and culmination of the human genome project marked a pivotal moment in our understanding of diseases and treatment modalities. This newfound appreciation for genomic technologies offers a more profound understanding of the intricate dynamics between our genetic makeup and health outcomes. In a similar vein, Chen et al launched the "Herbal Genome Project" in 2009, aiming to sequence the entire genome and conduct post-genomic research on economically valuable medicinal plants known for their distinctive secondary metabolic pathways.[18,19] This ambitious endeavor, reminiscent of the "Human Genome Project", seeks to deepen our comprehension of TCM. Upon its successful conclusion, the insights gleaned from projects like the "Herbal Genome Project" are expected to harness the potential of TCM further in treating human ailments.

Transcriptomics Technology

Transcriptomics delves into the study of gene expression at the mRNA level within a cell or tissue's genome. This field provides invaluable insights into the regulatory systems governing gene expression, as well as the functionality, interaction, and transcriptional regulation of proteins. In 1995, Velculescu's team first introduced the concept of the transcriptome during their research on Saccharomyces cerevisiae. As a holistic approach, transcriptomics has shifted the paradigm from the study of individual genes to an era characterized by rapid advancements in genomics research.[20,21] Unlike the static nature of the genome, the transcriptome is dynamic, with spatial and temporal variations. Some of the primary methodologies employed in transcriptomics research include Expression Sequence Tag technology (EST), Serial Analysis of Gene Expression (SAGE), DNA microarrays, Massively Parallel Signature Sequencing (MPSS), and RNA sequencing (RNA-seq).[22,23] In contemporary TCM research, the utilization of transcriptomics has become increasingly prevalent. Its applications span a diverse range of studies, such as evaluating the effects of TCM on disease-related gene expression, understanding TCM syndromes, elucidating the biosynthetic pathways of beneficial TCM compounds, and deciphering the underlying mechanisms of treatments like acupuncture and moxibustion.

Proteomics Technology

The "proteome"—the whole set of proteins produced by a cell, tissue, or organism's DNA—was initially defined by Australian researchers Wilkins and Williams in 1994. Proteomics analyses proteins in entire cells, tissues, and biological fluids, including qualitative characterization, quantitative measurement, and dynamic state changes. This study examines protein expression levels, post-translational modifications, protein-protein interaction networks, target protein quantitation, and global protein expression profiling.[24–26]

Currently, two-dimensional electrophoresis and mass spectrometry stand out as the primary analytical techniques in proteomics. Proteomics offers a comprehensive and systematic approach, leveraging high-efficiency, high-sensitivity, and high-throughput technologies to fully reveal the expression and functional dynamics of all proteins encoded by a biological genome throughout an organism's lifespan. Intriguingly, the overarching principles of proteomics align seamlessly with the holistic and systematic nature of TCM.[26,27] Harnessing the power of proteomic technologies in the realm of TCM pharmacological research holds immense promise. It is poised to shed light on the intricate mechanisms underpinning TCM's efficacy, facilitate the identification of therapeutic targets, and optimize the rational formulation and compatibility of TCM treatments.

Metabolomics Technology

Professor Nicholson of Ditong College, University of London, England, proposed metabolomics for the first time in 1999. It is a subfield of current biomedical research that examines the general biological condition and gene function regulation through the measurement of changes in bodily fluids and endogenous metabolites in tissues.[28,29] Metabolomics is a "top-down" approach to study metabolite sequences and metabolic pathways under normal or pathological situations. This study used advanced analytical technologies like nuclear magnetic resonance (NMR), liquid chromatography-mass spectrometry (LC-MS), gas chromatography-time-of-flight (GC-TOF-MS), ultra-high performance liquid chromatography-quadrupole time-of-flight (UPLC-Q-TOF-MS), FT-MS, and CE-MS. These methods were combined with multivariate statistical methods like PCA, PLS-DA, OPLS-DA, HCA, and SIMCA-P for data interpretation and analytical modelling.[30,31] Thus, the application of metabolomics in traditional Chinese medicine (TCM) research holds profound significance for deciphering the material basis of TCM's toxic and side effects, pharmacodynamic material basis, rational comprehension of medication dosage and treatment duration, as well as compatibility strategies for toxicity mitigation. This approach is also crucial for advancing TCM quality control, optimizing resource selection, and facilitating sustainable resource development, thereby providing critical support for the scientific advancement and ecological sustainability of TCM.

Microbiome Technology

In 1988, Whipps et al first defined the microbiome by studying the ecology of rhizosphere microorganisms, which they described as a combination of "microbe" and "biome". The notion of the human microbiome, which refers to the totality of all microorganisms in the human body and their genetic material, was first proposed in 2001.[32,33] In 2017, Chinese scientists Liu et al said that the microbiome is made up of all the microbes and their genetic information that live in a certain ecosystem or environment. This includes the number and types of cells that live there as well as their genetic material (genome). Functions of the body, including how microbes interact with their surroundings and hosts.[34] It described the microbiome and all of its genetic and physiological processes, as well as the interaction of microbes with their environment and host. Traditional culture, denaturing gradient gel electrophoresis, pyrosequencing, metagenomic technology, gene chip technology, nanopore sequencing, SMRT-DNA sequencing, and 16S rRNA sequencing are all microbiology methods. The National Institutes of Health launched the "Human Microbiology Project" in 2007 to explain the relationship between microbes and human health, which was followed by projects such as the Human Intestinal Metagenomics Alliance, the Irish Elderly Genomics Project, and the Canadian Microbiology Initiative. Because the findings demonstrate that the microbiome has a significant impact on human health and development, it has been dubbed the "barometer" of human health. The most fundamental property of the microbiome is that it is constantly changing, making it easier to adapt to disease incidence and medicine therapy. Microbiome research is a trendy topic, and intestinal flora is an essential component of the human microbiome; thus, it is critical to diagnose illnesses based on the microbiome and explore efficient methods of TCM.[35]

Network Pharmacology

The research on network pharmacology can be traced back to 1999. Li et al from Tsinghua University started a series of pioneering studies characterized by "network targets", and proposed to explore the integrated regulation of multi-targets in traditional Chinese medicine from the perspective of "relationship-network-function". The mechanism of action and the research ideas of the overall characteristics of the prescription and syndrome correspondence and disease syndrome correspondence.[36,37] In 2007, the biomolecular network of cold and heat in traditional Chinese medicine and the network regulation of cold and hot prescriptions were reported for the first time, and a research framework for Chinese medicine prescriptions based on biological networks was proposed. In the same year, Hopkins of the University of Dundee proposed the term "network pharmacology".[38] Network pharmacology is a multidisciplinary research field, which integrates a large amount of information to discover new drug targets and molecular mechanisms by combining calculations and experiments, that is, based on systems biology, genomics, and proteomics. Using high-throughput omics technologies, computational simulation, network database retrieval, and biological-pharmacological experiments to unravel the interactive network among drugs, genes, targets, and diseases. By deciphering these network relationships, it aims to predict drug efficacy mechanisms, evaluate therapeutic effects and adverse reactions, thereby facilitating the discovery of high-efficiency and low-toxicity pharmaceuticals.[39] The holistic, systematic, and comprehensive nature of network pharmacology closely parallels the multi-component, multi-target, and integrative attributes of traditional Chinese medicine, making network pharmacology a prevalent approach for investigating the molecular mechanisms of traditional Chinese medicine in recent years. Network pharmacology provides a comprehensive and holistic research approach for clarifying the mechanisms of efficacy and toxicity of traditional Chinese medicines (TCMs), especially Chinese medicine compound formulae. It also enables the evaluation of active constituents and the extraction of quality markers (Q-markers) for traditional Chinese medicines, offering a holistic method to reveal the multi-component, multi-target nature of traditional Chinese medicine systems.

Application of Systematic Biological Technology in the Material Basis Research of TCM

Application of Genomics Technology in TCM Research

Genomics can reveal the structural characteristics of the genomes of medicinal plants and the important role of functional genes in regulating plant growth, active ingredient synthesis and growth against adversity. Whole genome sequencing of plants can not only obtain the sequence information of the genome and important functional genes of the plant, which provides a certain basis for studying the molecular evolution, gene composition and gene regulation of plants at the molecular level, but also has important implications for the upcoming genomic studies of plants.

Gao et al[40] reported the complete chloroplast genome sequence of *Paeonia lactiflora* with a total genome length of 153405 bp, including a small single copy (SSC) region of 16969 bp and a large single copy (LSC) region of 84340 bp, separated by a pair of 26048 bp inverted repeat sequences (IRs). A total of 109 annotated genes were identified, including 76 protein-coding genes, 29 transfer RNAs (tRNAs), and 4 ribosomal RNAs (rRNAs). Additionally, 52 simple sequence repeats (SSRs) were detected in the chloroplast (cp) genome of *Paeonia lactiflora*. Notably, this study uncovered phylogenetic affinities between *P. lactiflora* and *P. fenugreek*, among other key findings. The full sequence of the *Epimedium brevicornu Maxim*. genome was determined by Zhang et al[41] with a full length of 159572 bp and GC The GC content was 38.83%, including four different regions: large single-copy region (86,535bp), small single-copy region (17641bp) and a pair of inverted repeat regions (27698bp). The chloroplast genome encodes 112 unique genes, including 78 protein-coding genes, 30 tRNA genes and 4 rRNA genes. Tan et al[42] sequenced the Psoralea corylifolia chloroplast's complete genome, revealing a 153,114-bp genome with two 25,557-bp inverted repeat (IR) sections surrounding a 17,885-bp SSC and 84,115-bp LSC. Genomic study found 98 SSRs, 14 forward, 2 inverted, 2 complementary, 32 palindromic, and 49 tandem repeats. Notably, four chloroplast DNA sequences (ycf1, matK, accD, ndhF) were verified as possible barcode markers, which would help understand this medicinal plant's genomic architecture and evolutionary history. Genomic technologies are essential for elucidating the biology of medicinal plants, allowing thorough examination of genome architectures and functional gene networks. Whole-genome and chloroplast genome sequencing methodologies enable researchers to delineate genomic architecture. These technological applications connect evolutionary biology with pharmaceutical research, establishing a basis for molecular breeding, active component biosynthesis investigations, and the conservation of medicinal plant resources.

Application of Transcriptomics Technology in TCM Research

The transcriptomic study can grasp the gene expression and regulation laws at the overall level, and the in-depth transcriptomic study of Chinese medicine basal plants can help to reveal the formation mechanism of active ingredients of Chinese medicine, elucidate the causes of the formation of the tractability of Chinese herbal medicine, provide basic data for the study of the biosynthetic pathway of active ingredients and the molecular mechanism of their formation, and provide reference for the breeding of medicinal plants. Therefore, the transcriptomic study of TCM plants has received much attention from researchers in TCM.

Jiang et al[43] identified a total of 9277 differentially expressed genes from *Perilla frutescens* by transcriptomics, and identified 77 single genes involved in encoding 15 enzymes, which are candidate genes for flavonoid biosynthesis in *Perilla frutescens* leaves. Candidate genes involved in flavonoid biosynthesis pathway in Perilla frutescens were revealed. Gao et al[44] conducted a transcriptomic and metabolomic investigation of Cinnamomum cassia and Cinnamomum cassia Presl var. Transcriptome analysis indicated that genes associated with photosynthesis and flavonoid biosynthesis were up-regulated in the variants, and that variations in essential oil content between the two varieties may be attributed to the phenylpropanoid metabolic pathway as opposed to the synthetic pathways of cinnamaldehyde and coumarin. This work elucidates the processes behind the phenylpropanoid metabolic pathway in Cinnamomum cassia Presl. Chang et al[45] investigated potential genes for tanninone biosynthesis by transcriptomic analysis was performed for two *Salvia miltiorrhiza* species. Differential expression profiling identified 2149 differentially expressed genes (DEGs) for subsequent functional characterization. Transcriptomic analysis further indicated that 25 cytochrome P450 enzymes (CYPs), three 2-oxoglutarate-dependent dioxygenases (2OGDs), one short-chain alcohol dehydrogenase (drs), and eight transcription factors were potential key players in tanshinone biosynthetic pathways. This study not only screened candidate genes involved in tanshinone biosynthesis but also laid a foundational framework for identifying genes associated with major bioactive components in other traditional Chinese medicine (TCM) plant species. Transcriptomic technologies facilitate the systematic profiling of gene expression patterns in medicinal plants, allowing for the analysis of active ingredient biosynthesis and regulatory networks. RNA-seq analyses identify differentially expressed genes (DEGs) associated with secondary metabolism. These applications underscore transcriptomics as a crucial method for elucidating the biosynthetic pathways of active components in traditional Chinese medicine, offering genetic targets for molecular breeding and metabolic engineering.

Application of Proteomics Technology in TCM Research

The study of proteins related to photosynthesis, energy, and metabolism in Chinese herbal medicines using proteomics can not only obtain the patterns of protein changes during the growth, development, maturation, and aging of Chinese herbal medicines, but also provide a theoretical basis for the targeted biosynthesis of active ingredients in Chinese herbal medicines. At the same time, the introduction of proteomics technology can overcome the above mentioned difficulties and explore the overall protein composition of herbal medicines themselves due to the relatively weak study of primary metabolites including proteins in plants.

Pedrete et al[46] examined the plant proteins of hypoglycemic agents used in folk medicine for diabetic therapy, namely "abajerú" (Chrysobalanus icaco) and "cow's paw" (Bauhinia forficata and Bauhinia variegata). Species distinction was conducted using proteomic characterization, resulting in the identification of 131 proteins via LC-MS/MS, mostly associated with cellular respiration, transport, metabolism, and photosynthesis, which may serve as a foundational reference for species assessment in Brazil. AngelaContreras et al[47] used a differential label-free quantitative proteomic methodology to investigate tanshinone biosynthesis-related proteins in extracts of Salvia miltiorrhiza hairy roots, identifying a total of 2650 proteins. A total of 2650 proteins were identified in root extracts, of which 893 demonstrated statistically significant ($p<0.05$) changes in relative abundance compared to control roots. A total of 251 proteins were upregulated, whereas 642 were downregulated. The up-regulated proteins were mostly classified into metabolism (47%), stress defence (18%), and redox homeostasis (10%). This study paves the way for enhancing tanshinone production through biotechnological strategies. Li et al[48] conducted a proteomic analysis of Panax ginseng and detected 2732 proteins in root tissues and 3608 proteins in shoot tissues, respectively. Their findings revealed that cytochrome P450 enzymes and UDP-glycosyltransferases were predominantly expressed in shoots rather than roots, indicating that ginsenoside glycosylation may occur in aboveground tissues during plant growth and then be translocated to roots during the wilting stage. This study provides critical insights for understanding the biosynthetic pathway of ginsenosides and optimizing artificial cultivation strategies. Proteomic technologies facilitate the systematic examination of protein profiles in Chinese medicinal plants, elucidating the mechanisms that govern photosynthesis, energy metabolism, and the biosynthesis of active ingredients. These applications underscore the significance of proteomics in elucidating biosynthetic pathways, enhancing cultivation methods, and facilitating molecular-level quality control in traditional Chinese medicine research.

Application of Metabolomics Technology in TCM Research

The chemical constituents of Chinese medicine serve as the material foundation for its therapeutic effects, exhibiting significant diversity in structure and composition. Given the complexity and variety of the chemical constituents in Chinese medicine, metabolomics technology is characterised by high throughput, a holistic approach, and objectivity, making it markedly advantageous for the investigation of multi-component and multi-target Chinese medicine.

Bai et al[49] used liquid chromatography-tandem mass spectrometry to perform Metabolomic analysis was performed and 16 potential biomarkers of roots from different origins were labeled, such as glycycoumarin, gancaonin Z, licoricone and dihydroxy kanzonol H were mainly present in Jiuquan samples; neoglycyrrhizin, 6′-acetylglycyrrhizin, glycyrrhizin chalcone B, isosiliconol, triglyceride, and methyl uralin were mainly present in licorice from Lanzhou; glycyrrhizic acid L, uralin, and glycyrrhizic acid I were first were mainly present in Wuwei-produced licorice, and the present work further promoted the utilization of licorice. Chen et al[50] picked Sophora flavescens as the focus of their research and devised a novel technique that integrates metabolomics and network pharmacology to investigate quality indicators. They used UHPLC/qms for the metabolomic analysis of 74 batches of 1–6-year-old flavonoids. Six prospective indicators were effectively screened, measured, and reverse-validated as the most significant active chemicals by UHPLC/QE-MS and multivariate statistical analysis. Li et al[51] characterised 50% methanolic extracts from Fritillaria thunbergii Miq bulbs (BFT) and flowers (FFT) using UHPLC-Q-Exactive Orbitrap MS/MS. They tested bulb and flower sample characterization using non-targeted UHPLC-HRMS metabolomics and molecular networking. The 31 substantially divergent alkaloids included seven cis-D/E-cevanine derivatives without C_{20}-OH, one trans-D/E-cevanine with C_{20}-OH, 13 trans-D/E-cevanines without C_{20}-OH, five cevanine N-oxides, and five cevanines. Eight alkaloids were more abundant in FFT than BFT. The research found that FFT has more flavonoids than BFT. Metabolomics technologies, characterized by high-throughput and holistic profiling, offer powerful tools for decoding the complex chemical landscapes of Chinese medicine (CM), enabling systematic identification of bioactive components and quality markers. These applications highlight metabolomics as a pivotal approach for CM research, enabling chemical fingerprinting, biomarker discovery, and quality assessment via high-resolution mass spectrometry and multi-omics integration.

Application of Network Pharmacology in TCM Research

The concept and associated research of quality markers (Q-Markers) in traditional Chinese medicine (TCM) have garnered extensive attention from scholars worldwide, emerging as a focal point in TCM research. As key indices for TCM quality control, Q-Markers are intricately linked to the production-processing workflows of TCM materials, decoction pieces, and patent medicines, as well as the efficacy attributes of TCM. The validation of Q-Markers plays a pivotal role in enabling systematic and in-depth investigations into TCM.

An integrated technique of plant metabolomics and target network pharmacology characterised Fritillaria cirrhosae bulbus (BFC) sources by Tian et al. Six BFC sources were characterised using multivariate statistical analysis, providing 12 chemical indicators. After screening 9 asthma-related components based on target network pharmacology, 9 were identified as prospective Q-Markers due to content differences and pharmacological activity.[52] Lan et al[53] predict rhubarb Q-Markers in Fengyin Decoction (FYD) using fingerprinting and network pharmacology and ultra performance liquid chromatography (UPLC). The potential Q-Markers of rhubarb in FYD were quantified by ultra performance liquid chromatography (UPLC) and network pharmacology, and a "component-target-pathway" network predicted rhubarb anthraquinones as potential Q-Markers, providing a reference for FYD quality control research and laying the groundwork for its mechanism of action study. Liao et al[54] used network pharmacology and chemical analysis to develop a "effect-compound-target-fingerprint" technique to identify Alisma orientalis quality indicators. Lipid-lowering activity was highest in 50% ethanol extract. Network pharmacology revealed Q-Marker's unique link to their pharmacological actions. Q marker-based chromatographic fingerprint and herbal medicine quality evaluation were developed. Network pharmacology has become an essential method for validating quality markers (Q-Markers) in traditional Chinese medicine (TCM) through the integration of chemical profiling and biological pathway analysis. The applications illustrate the role of network pharmacology in systematically identifying Q-Markers through the integration of multi-omics data, the establishment of correlations between chemical constituents and therapeutic targets, and the facilitation of scientific quality assessment of TCM materials and formulations.

Application of Systems Biology Techniques in Pharmacodynamic and Toxicological Studies of TCM

Application of Genomics Technology in TCM Research

TCM's pharmacodynamic and toxicological processes are complicated and difficult to completely describe. Genomics technology has high throughput, multiple factors, rapidity, and sensitivity, and may acquire a large number of associated differentially expressed genes in a short period of time, which corresponds to TCM's multi-component, multi-channel, and multi-target effects. When combined with biological data analysis technologies, it has the potential to show the whole set of associated systems. According to reports, genomics is being utilized to assess the therapeutic efficacy of TCM and to uncover the mechanism of action of TCM at several levels.

Gu et al[55] employed gene microarray technology to explore the therapeutic mechanisms of Indigo naturalis (IN) in ulcerative colitis treatment. The researchers screened and validated 10 key active constituents and 184 compound targets for IN-UC, of which 43 core targets were identified. These targets are implicated in systemic immune activation, Th17 cell differentiation, and signaling pathways including IL-17, Jak-STAT, Toll-like receptor (TLR), and NOD-like receptor (NLR) pathways, which regulate innate immune responses. Additionally, they are involved in biological processes such as nuclear transcription regulation, protein phosphorylation, cytokine activity modulation, reactive oxygen species metabolism, epithelial cell proliferation, and apoptosis. This study provides a theoretical basis for subsequent investigations into IN's effective components and therapeutic mechanisms in ulcerative colitis. Lin et al[56] used DNA microarray analysis to show that Psoralea corylifolia treatment resulted in the upregulation of 944 genes and the downregulation of 872 genes, and increased the expression of several genes related to cytokines, transcription factor activation, cell viability, DNA damage, cell cycle and autophagy. Evodiamine (EVO) was tested on tongue squamous cell carcinoma using microarray analysis and gene chip technology by Wu et al. The results showed that 1243 genes were differentially expressed after treating CAL-27 cells with EVO, 684 were up-regulated and 559 were down-regulated, and screened out abnormally expressed genes in TSCC treated with EVO, indicating that EVO's anticancer activity is the result of multiple targets' interaction and regulation, providing a new research direction for EVO's anticancer mechanism.[57] Genomics technologies have become essential in understanding the complex, multi-target mechanisms of traditional Chinese medicine (TCM), utilising their high-throughput, sensitive, and multifactorial capabilities to analyse gene expression patterns. These applications illustrate the utility of genomics in connecting TCM components to gene regulatory networks, offering molecular insights into therapeutic efficacy and toxicological mechanisms within immune, inflammatory, and oncogenic pathways.

Application of Transcriptomics Technology in TCM Research

Using transcriptomics to study the pharmacodynamic mechanism of TCM can comprehensively observe the influence of TCM on the disease process, identify differentially expressed transcription genes, and then predict the pharmacodynamic activity and mechanism of TCM because transcriptomics can monitor and analyze disease occurrence in different time and space.

Han et al[58] confirmed 370 differentially expressed genes after Sanhuang decoction (SHD) treatment through transcriptomic analysis, and they were mainly enriched in signaling pathways related to inflammation and immune response. Response and mucosal innate immune response, Toll-like receptors and PI3K-Akt signaling pathway are the main pathways of SHD in the treatment of fungal ulcerative colitis. Jiang et al[59] used lncRNA, mRNA, and microRNA sequencing of kidney tissue to generate multi-level transcriptome data sets, established a multi-level transcription regulation network to clarify the pathogenesis of fibrosis and the core factors of therapeutic regulation, and revealed the potential mechanism of Kangxianling(KXL), a TCM, inhibiting the renal interstitium. Zheng et al[60] utilized network pharmacology combined with mRNA transcriptome analysis to explore the multi-target therapeutic mechanisms of ELeng capsule, identifying 40 active compounds and 75 targets that overlapped with endometriosis-related proteins. The study revealed that ELeng capsule exerts its therapeutic effects on endometriosis through functional modules including apoptosis induction, angiogenesis inhibition, and immune regulation. Key signaling molecules and pathways were identified, such as neuroactive ligand-receptor interactions, toll-like receptor signaling pathways (immune system-related), vascular endothelial growth factor (VEGF) signaling, and MAPK pathways. These findings not only offer novel insights into the mechanism of TCM in treating endometriosis but also provide a viable approach for the discovery and development of new TCM formulations. Transcriptomics facilitates the systematic investigation of pharmacodynamic mechanisms in traditional Chinese medicine (TCM) through the profiling of gene expression dynamics in various disease contexts, the identification of differentially expressed genes (DEGs), and the association of these genes with functional pathways. These applications underscore transcriptomics as a crucial instrument for elucidating the multi-component, multi-target effects of TCM by associating gene expression profiles with therapeutic mechanisms in inflammatory, fibrotic, and oncogenic diseases.

Application of Proteomics Technology in TCM Research

TCM, being a complex chemical composition system, incorporates various processes by managing multiple targets. Researchers have long struggled to understand its process. We may examine the control of TCM at the protein level using protein omics technology by assessing the function of proteins with considerable differential expression or further investigating similar methodologies. Differential proteomics in proteins offers a practical and effective technique for identifying targets in TCM and aids in understanding TCM's therapeutic impact at the molecular level.

Yao et al[61] identified the tropomyosin positive regulation complex interaction network in Deer antler extract serum protein spectrum using isobaric labelling relative and absolute quantification (iTRAQ) technology, systematic bioinformatics analysis, and verification methods, negative control of 2-macroglobulin (A2m), serine protease inhibitor A3n, and apolipoproteins (Apo and Apof), which interact well with several proteins and signalling pathways. Deer antler extract modulates serum proteins and signal pathways that regulate osteoblast and osteoclast activity to regulate bone synthesis and remodelling, treating bone diseases. Liu et al[62] used iTRAQ labelling and intelligent pathway analysis to study Gubenfangxiao decoction (GBFXD)'s effect on asthmatic mice. Modelling and evaluating protein before and after therapy revealed 75 differentially expressed proteins. The IPA investigation found that mitochondrial dysfunction and oxidative phosphorylation greatly influenced GBFXD's asthma treatment effects. GBFXD dramatically decreased M2

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macrophage polarisation, revealing its protective mechanism. According to TCM, the two deconstructed formulas of Chaihu-Shugan-San have synergistic benefits, especially Shu Gan (relieving sluggish liver qi) and Rou Gan (nourishing the liver to relieve pain). Zhu et al[63] found that Chaihu-Shugan-San, Shu Gan, and Rou Gan controlled 110, 12, and 407 DEPs. Chaihu-Shugan-San therapy regulated 22 proteins, whereas solo Shu Gan or Rou Gan changed 323 proteins. These data imply that Chaihu-Shugan-San cures depression via many targets and pathways, providing empirical proof and a theoretical framework for therapeutic use. Proteomic technologies have become a significant method for elucidating the multi-target mechanisms of traditional Chinese medicine (TCM), facilitating systematic analysis of protein expression profiles to connect therapeutic effects with molecular pathways. These applications demonstrate proteomics as a crucial method for elucidating the synergistic effects of TCM by correlating protein expression dynamics with functional networks, thereby facilitating a molecular-level comprehension of its therapeutic mechanisms in disease disorders.

Application of Metabolomics Technology in TCM Research

Metabonomics bypasses life's intricate regulating process and provides the final and overall findings through metabolite analysis. This method, which reveals the internal dynamic changes of organisms as a whole, eliminates the drawbacks of previous studies that used a single or a few markers to examine specific physiological and pathological changes. As a result, it incorporates an entire, dynamic, comprehensive, and analytic technique, which is consistent with the notion of holistic perpetual motion in TCM. It is a technically adequate technique for doing TCM research.

Sun et al[64] used the metabolomics technology of UPLC-HDMS to discover metabolic profiles, biomarkers and related metabolic pathways in coronary heart disease models, and evaluated the influence of Jing Zhi Guan Xin Pian (JZGXP) on them. At the same time, the targets of JZGXP in the treatment of coronary heart disease were analyzed, and 25 biomarkers related to coronary heart disease model were finally identified, involving 9 metabolic pathways in the body, and it was found that JZGXP could awaken 21 biomarkers in the urine of model rats, which involved 9 metabolic pathways. Effectively explore the potential biomarkers related to syndrome or disease and the therapeutic mechanism of traditional Chinese medicine preparations. Jiao et al[65] constructed a rat depression model using chronic unpredictable moderate stress and ultra-performance liquid chromatography-quadrupole time-of-flight mass spectrometry (UPLC-TOF-MS). The metabolic spectrum of rat blood samples was then studied using non-targeted metabonomics, which evaluated the changes in metabolites in serum samples before and after Jiaotaiwan Pill administration using different statistical approaches. Jiaotaiwan therapy improved the metabolic phenotype of depression, according to principal component analysis and partial least squares discriminant analysis. According to the route study, Jiaotaiwan Pill's antidepressant impact may entail modulating amino acid metabolism, glycerol phospholipid metabolism, and energy metabolism. These discoveries will help researchers better understand the pathophysiology of depression and identify targets for clinical diagnosis and therapy. At the same time, it laid the groundwork for the use of Jiaotaiwan as an antidepressant. Wang et al[66] used a urine metabonomics approach based on mass spectrometry to investigate the action mechanism of Radix ginseng-Schisandra chinensis medication in treating Alzheimer's disease. Urine included sixteen endogenous potential biomarkers. The pathogenic symptoms in the brains of model rats were visibly improved before and after injection, whereas possible biomarkers were obviously downregulated. Endogenous biomarker metabolic pathways included phenylalanine and tyrosine metabolism, tryptophan metabolism, purine metabolism, and so forth. It can be noted that the Radix ginseng-Schisandra chinensis medication combination is primarily achieved in the treatment of Alzheimer's disease by controlling aberrant energy metabolism, lowering inflammation, regulating intestinal flora, and increasing neurotransmitters. Metabonomics has become an essential instrument in the study of traditional Chinese medicine (TCM), providing comprehensive insights into therapeutic mechanisms through the profiling of metabolic signatures and their association with physiological and pathological conditions. Wang et al[67] utilized UPLC-HR MS/MS to detect 260 chemical components and 41 absorbed components in Da-Chai-Hu Decoction (DCHD)-treated plasma for the first time. Furthermore, in vivo experiments demonstrated that DCHD can regulate glucose/lipid metabolism and ameliorate renal dysfunction. In addition, comprehensive analysis using untargeted urine metabolomics and function-guided and network-based complementary methodology (FNICM) methods identified a total of 33 differential metabolites, which were classified as core metabolites. Finally, combined studies of FNICM, network pharmacology, and experimental pharmacology indicated that DCHD may regulate the AGEs/RAGE/AKT pathway to combat diabetic nephropathy (DN). It was found that DCHD treats DN by inhibiting the AGEs/RAGE/AKT pathway and regulating the metabolic profile. These studies illustrate the integration of metabonomics with the holistic principles of traditional Chinese medicine, facilitating the identification of diagnostic biomarkers and the characterization of multi-component therapeutic effects in cardiovascular, psychiatric, and neurodegenerative diseases.

Application of Microbiomics Technology in TCM Research

The term "human microbiome" refers to the total number of microorganisms residing in the human body, which may be found in the skin, gastrointestinal system, oral cavity, and other areas, with different microbes inhabiting various areas. Intestinal flora has been linked to digestive tract disorders (inflammatory bowel disease), metabolic diseases (type 2 diabetes), cardiovascular and cerebrovascular diseases (Parkinson's syndrome), and other diseases. TCM (TCM), which is often used as a tonic, has been used in enormous amounts for a long time. Its pharmacological and toxicological effects are influenced by intestinal flora once it is administered orally into the gastrointestinal system.

Evidence indicated that the ZiBuPiYin recipe (ZBPYR) caused enduring modifications in gut microbiota composition and metabolic profiles, which indirectly influenced hippocampal metabolic changes to improve memory deficits and reverse β-amyloid accumulation and insulin resistance in the brains of ZDF rats during the progression from type 2 diabetes mellitus (T2DM) to diabetes-associated cognitive decline (DACD). The therapeutic effects were associated with a series of metabolic reprogramming driven by the intestinal microbiome, particularly concerning the metabolism of alanine, aspartic acid, and glutamic acid; branched-chain amino acids; short-chain fatty acids; and linoleic/unsaturated fatty acids. This study emphasised that the prevention of diabetes-induced cognitive decline is partially dependent on the gut microbiome, with metabolites derived from bacteria and the regulation of the microbiome-gut-brain axis recognised as essential protective mechanisms of ZBPYR, thereby offering mechanistic insights into its therapeutic effectiveness. Feng et al[68] employed 16S rDNA sequencing to investigate the effect of realgar on mitigating neuroinflammation induced by a high-protein, high-calorie diet, yielding a total of 35,906 operational taxonomic units (OTUs). Bacteroides, Sclerotinia, Proteus, and verrucous microbes are the richest phyla in these groupings, according to research. Realgar has a neuroprotective impact on Gastrointestinal heat retention syndrome (GHRS) animals through modulating the microbiome-gut-brain axis, according to the findings. Zhang et al[69] employed 16S rRNA gene sequencing combined with shotgun metagenomics to characterize the microbial community in rat fecal samples. Their findings showed that Shen-Ling-Bai-Zhu-San (SLBZS) alleviated dyspeptic symptoms in functional dyspepsia model rats and restored intestinal ecological balance. Mechanistic investigations revealed that SLBZS exerts its therapeutic effects by upregulating energy metabolism pathways, reducing oxidative stress, and inhibiting pathogenic bacteria, providing insights into the role of intestinal microbiota in its mechanism of action against functional dyspepsia. Microbiomics serves as a crucial instrument in elucidating the therapeutic mechanisms of traditional Chinese medicine (TCM) through the characterization of gut microbiota dynamics and their functional associations with disease modulation. Technologies like 16S rDNA sequencing and shotgun metagenomics facilitate systematic profiling of microbial communities, as demonstrated in research investigating TCM's influence on the microbiome-gut-brain axis. These applications demonstrate microbiomics as a significant method for connecting TCM formulas to microbial-mediated therapeutic effects, revealing mechanisms that regulate metabolic, inflammatory, and neurological pathways.

Application of Network Pharmacology in TCM Research

The total of all the beneficial components of Chinese medicine that have an impact on a certain ailment is the material foundation of Chinese medicine's effectiveness. Systematic separation, serum pharmacochemistry, spectrum-effect correlation, and pharmacokinetics-pharmacodynamics are now used to investigate the substance foundation of Chinese medicine effectiveness (PK-PD). With the advancement and popularization of network pharmacology, it has become fashionable to employ network pharmacology to forecast the material basis and mechanism of action of TCM.

Jin et al[70] used network pharmacology to discover 71 active components and 20 potential anti-colorectal cancer targets in Xiao-Chai-Hu-Tang (XCHT) for colorectal cancer treatment. Crucial targets included PTGS2, NR3C2, CA2, and MMP1, as well as quercetin, stigmasterol, kaempferol, baicalein, and albizzine. The research identified 11 KEGG

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signalling pathways, including Toll-like receptor and NF-κB pathways, that contribute to XCHT's therapeutic actions. Modulating signal pathways, XCHT may treat colorectal cancer. Jin et al[71] predicted the effective ingredients and mechanism of action of ZaoRenDiHuang (ZRDH) capsule in insomnia treatment using network pharmacology, selected 61 anti-insomnia components and 65 targets through database mining, and identified 65 key targets through topological analysis. Data mining and network analysis demonstrated that neuroactive ligand-receptor interactions, serotonergic synaptic CAMP signalling, hif1a signalling, and toll-like receptor signalling pathways can prevent insomnia. It references future research on ZRDH Capsule's insomnia treatment mechanism. Wei et al[72] investigated Zuojin Pill (ZJP)'s active components and ulcerative colitis treatment mechanism using network pharmacology. They found 14 potential therapeutic ingredients and 26 key targets of ZJP, including signal transduction, MAPK cascade, inflammatory reaction, immune reaction, and ulcerative colitis apoptosis, and predicted that the PI3K-Akt, MAPK, toll-like receptor, and prolactin signal pathways, respectively. Network pharmacology has become a pivotal approach for deciphering the material basis and action mechanisms of CM formulas, enabling systematic identification of active components, targets, and signaling pathways involved in disease treatment.

Application of Multi-Omics in TCM Research

On multiple levels, genomic assays such as genomics, transcriptomics, metabolomics, and proteomics may characterize intracellular life processes. Data from various histologies can be integrated based on complex pathways and network associations to reveal the effects of drugs on living systems by collating, statistically and computationally demonstrating the regulatory relationships between the data, and studying disease pathogenesis and drug treatment mechanisms (Figure 2).

Cao et al[73] hypothesized that Zexie-Baizhu (ZXBZ) decoction might regulate lipid and glucose metabolism using metabolomics and transcriptomics analysis, and the study results showed that ZXBZ decoction reduced non-alcoholic metabolism. Yan et al[74] found 567 target genes and 377 target proteins for ursolic acid's hepatoprotective action using transcriptome and proteomic analysis. The proteins were mostly involved in cellular processes, fractionation, and binding. After data integration, 56 co-regulatory targets were examined, including ADH4, CYP450 enzymes, NQO1, apolipoprotein, and glutathione S-transferase. Both mRNA and protein levels were regulated consistently. Oncogenic effects, retinol metabolism, and the CYP450 metabolic pathway affect KEGG pathway 70, which has co-regulated targets. Ursolic acid ingestion reduces chronic alcohol-induced liver damage, giving important insights for treating alcoholic liver disease. Wang et al[75] used non-targeted metabolomics method based on LC-MS and quantitative proteomics technology based on tandem mass label (TMT) to analyse 110 metabolites and 359 differential proteins from brain tissue. The metabolites were mostly related to complement and clotting cascade reaction, sphingoid metabolism, glycerol phospholipid metabolism, glutathione metabolism, and platelet activation.

Prickly ash improves non-alcoholic fatty liver, according to Huang et al's transcriptome, microbiome, and untargeted metabolomics studies In HFD-induced non-alcoholic fatty liver mice, Zanthoxylum bungeanum Maxim. (ZBM) regulates fatty acid and cholesterol metabolism, intestinal microbiota, and metabolic pattern. Biochemical and clinical signs and differential metabolic biomarkers were substantially linked with intestinal microbiota. ZBM improves HFD-induced non-alcoholic fatty liver disease by altering fatty acid/cholesterol metabolism, intestinal flora, and metabolic profiles.[76] Chaihu-Shugan-San's anti-fibrosis mechanism was discovered by Xie et al using network pharmacology, single cell, and batch transcriptomics. We examined 134 ginsenosides and predicted 1150 CHSGS target genes and 625 liver fibrosis genes. The analysis showed that CHSGS's core targets were mainly regulating inflammatory response, inhibiting angiogenesis, and regulating extracellular matrix remodelling, with the most important mechanism being the latter. This suggests that CHSGS may be an effective liver fibrosis treatment.[77]

To study breast cancer gene profiles from The Cancer Genome Atlas (TCGA), Liu et al employed network pharmacology. Integrative DEGs network analysis indicated key targets for Astragalus polysaccharides (APS) breast cancer treatment. This proves that APS can cure breast cancer and that network pharmacology can use large-scale target data to study natural product effects.[78] Liu et al[79] investigated the mechanism of action of Tripterygium Wilfordii Hook F (TwHF) pill in the therapy of INRs using transcriptome, proteomic, and network pharmacology. Multi-omics analysis revealed that interferon administration significantly inhibited the IFN-signaling pathway, and network pharmacology

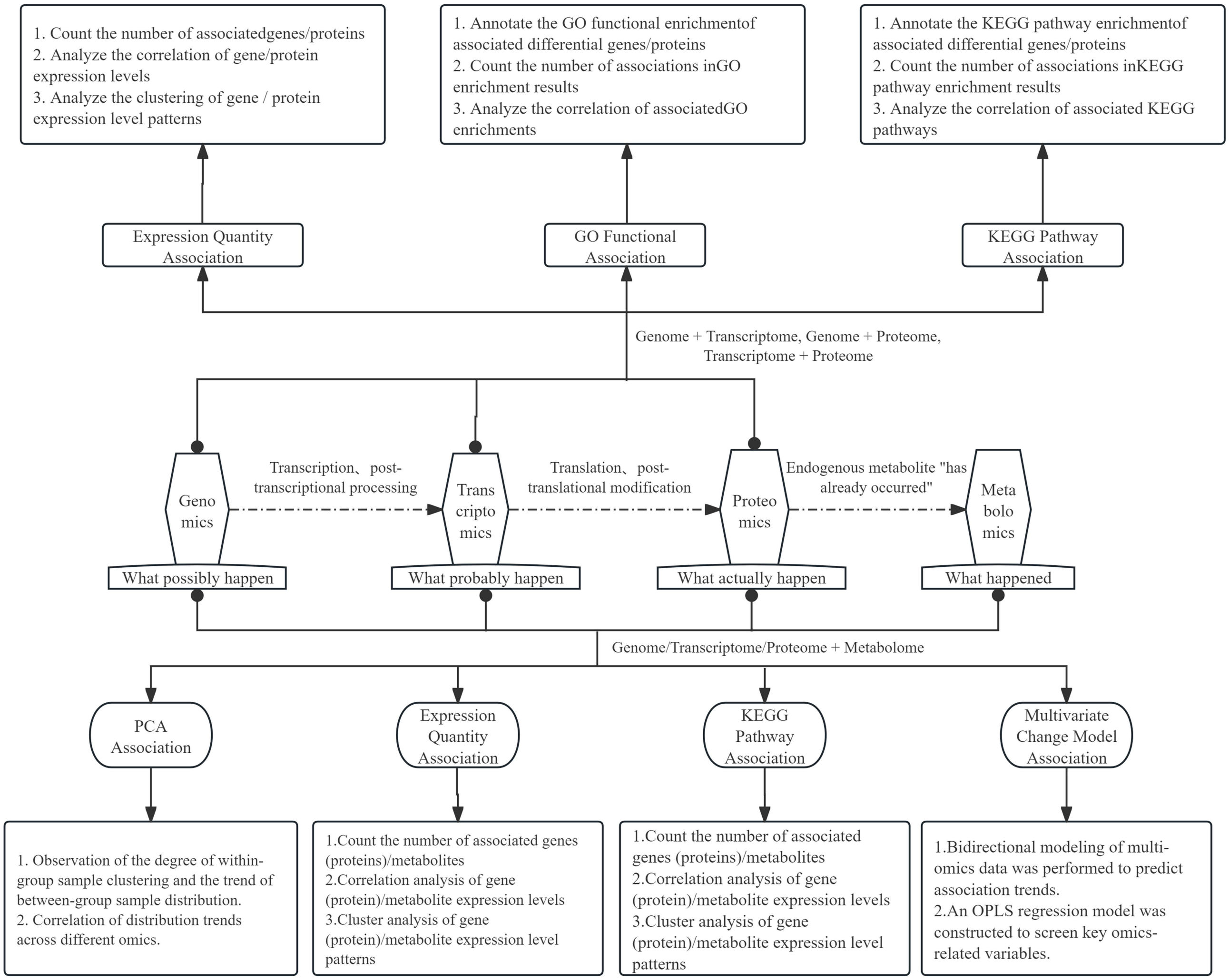

Figure 2 Current common research design for integration strategy of multi-omics.

analysis identified the signal transducer and activator of transcription 1 (STAT1) in the "TwHF-compound-target-INR" network, which systematically validated TwHF mechanism of INR treatment. Chu et al[80] addressed DNA methylation and He Qi San (HQS)'s impact on glycolipid metabolism in type 2 diabetes. In 682 genes, 426 had high CpG promoters, 150 had medium, and 106 had low. HQS regulates AMPK gene DNA methylation, insulin signalling pathway, and terpenoid skeleton production to enhance glycolipid metabolism in T2DMPBSS patients.

Miao et al[81] found that rhubarb, used to treat cardiovascular diseases, cancer, liver and kidney diseases, etc., integrates metagenomics, genomics, transcriptomics, metabolomics, and proteomics to reveal its therapeutic mechanisms. Metagenomics (gut microbiomics) is core: it reshapes microbial dysbiosis, regulates gut-heart/liver/kidney axes, adjusts beneficial/harmful bacteria ratios, and improves microbe-derived metabolites like SCFAs and TMAO for multi-organ protection. Genomically, GWAS identifies gene polymorphisms (eg, UGT2B7, CYP2C19) related to rhubarb components (emodin, rhein), clarifying gene regulation in efficacy and toxicity. Transcriptomics focuses on ncRNAs, with rhubarb restoring abnormal miRNAs (miR-26b-5p, miR-133) and lncRNAs (TUG1) to inhibit inflammation and fibrosis via PI3K/Akt pathways. Metabolomics confirms rhubarb corrects amino acid/lipid metabolic disorders and restores TCA cycle balance. Proteomics reveals its regulation of mitochondrial function and oxidative stress-related proteins (SOD, Bcl-2) for anti-apoptotic and antioxidant effects. These multi-omics technologies synergize to decode rhubarb's "reshaping microflora - regulating genes - repairing metabolism - regulating proteins" pathway, providing scientific support for clinical application.

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Zhao et al[82] have reported that studies related to the treatment of diseases with traditional Chinese medicine (TCM) have mainly utilized proteomics, metabolomics, mass spectrometry imaging (MSI), and multi-omics integration technology. Proteomics aids in the identification of TCM's action targets and the analysis of its mechanisms by comparing differential protein expression before and after drug administration, such as clarifying the regulation of TCM components on signaling pathways and protein networks. Relying on technologies like mass spectrometry, metabolomics enables high-throughput detection of TCM components, screening of quality markers, and analysis of metabolic pathways, revealing TCM's regulatory effect on metabolic disorders in the organism. Mass spectrometry imaging technology intuitively presents the spatial distribution of TCM's active components in tissues, providing a basis from the spatial dimension for research on pharmacological mechanisms. In addition, the studies have systematically analyzed the multi-target and multi-pathway therapeutic characteristics of TCM at multiple molecular levels by integrating multi-omics data and combining bioinformatics with artificial intelligence technologies. This has provided comprehensive scientific support for TCM modernization, clinical application, and new drug development.

Qiao et al[83] mainly integrated genomics, metabolomics-related multi-omics technologies in the study of Compound Qingdai Capsule (CQC) for treating psoriasis, and conducted mechanism analysis combined with verification at the transcriptional and protein levels. First, the study obtained differentially expressed genes (DEGs) and differentially expressed microRNAs (DEMs) through differential expression analysis by mining psoriasis-related mRNA dataset (GSE201827) and miRNA dataset (GSE174763) from the GEO database, and constructed a psoriasis pathogenic pathway network, which belongs to the application at the genomics level. It identified the material basis of CQC by detecting 29 main components using ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) technology, involving metabolomics-related component analysis. Subsequently, quantitative real-time reverse transcription polymerase chain reaction (qRT-PCR) and enzyme-linked immunosorbent assay (ELISA) were used to detect the mRNA and protein expression levels of core targets respectively, realizing verification at the transcriptomics and proteomics levels. Meanwhile, the study combined multi-omics data with systems pharmacology and machine learning algorithms to screen out core targets such as AURKB and CCNB1, comprehensively revealing the molecular mechanism of CQC in treating psoriasis through multi-components, multi-targets, and multi-pathways, and providing scientific support for the clinical application and modernization of traditional Chinese medicine.

Multi-omics technologies integrating genomics, transcriptomics, proteomics, metabolomics, and microbiomics have revolutionized the landscape of traditional Chinese medicine (TCM) research, enabling systematic dissection of the multi-component and multi-target therapeutic mechanisms of TCM. These studies exemplify how multi-omics integration uncovers the systemic regulatory effects of TCM at the genetic, transcriptional, proteomic, and metabolic levels, providing mechanistic insights for drug development and precision TCM therapy. However, constrained by the dual limitations of TCM's inherent complexity and the technical characteristics of multi-omics itself, significant limitations remain.

TCM formulas are composed of complex components and exert synergistic effects through a "multi-component, multi-target, and multi-pathway" mode, resulting in large volumes and high heterogeneity of multi-omics data. Coupled with the lack of unified standardization norms, systematic biases exist across different detection platforms, leading to potential false positives during data integration and making it difficult to accurately delineate the component-target-pharmacodynamic causal chain. Derived from the reductionist thinking of Western medicine, the technical logic of multi-omics is insufficiently compatible with TCM's core concepts of "holism" and "syndrome differentiation and treatment". While it can detect changes in metabolites or proteins induced by TCM, it struggles to capture the dynamic and holistic changes brought about by processing and compatibility nor can it effectively link TCM syndrome types with molecular mechanisms.

At the sample level, significant individual differences and the scarcity of rare syndrome type samples make it difficult to meet the large sample size requirements for multi-omics analysis. Additionally, the disconnect between animal models and human syndrome differentiation further exacerbates interpretation biases.

Furthermore, multi-omics can only reveal correlations among differential molecules but fails to clarify the upstream-downstream regulatory causal chains. High technical costs, barriers to professional talents, and inadequate data sharing limit its widespread application. Meanwhile, it tends to overlook core TCM characteristics such as compatibility and processing, requiring breakthroughs in overcoming barriers related to technical adaptation, data integration, and conceptual integration.

Conclusion and Future Perspective

In recent years, TCM research has received unprecedented attention and rapid development worldwide, and it can be said that TCM research is in the best development opportunity in history. It is possible to argue that TCM research is experiencing its most prosperous time in history. However, in order to promote the scientific development and rapid development of TCM, it is necessary to innovate in methodology, identify the key scientific problems to be solved, propose corresponding countermeasures, and establish an innovative method system of TCM that conforms to the basic characteristics and laws of TCM and can fully integrate and utilize the most recent modern scientific and technological advances. TCM is a complicated system, with the "holistic perspective", "dynamic view", and "dialectical view" being the primary distinguishing elements of traditional Chinese medical ideas. The use of concepts and procedures from systematic biology is a key strategy in TCM research. It is envisaged that the "complex system-complex system" research approach would be a breakthrough in promoting TCM modernization and the study and clinical application of core TCM ideas.

In this review, we explore systematic biology technology and its use in TCM research. Biology is defined by holistic study, and biological information technology is the primary way of connecting "reduction" and "wholeness", which has many parallels with TCM philosophy. The merger of TCM and system biology will provide both opportunities and challenges for TCM to establish and develop its unique qualities. The integration of diverse omics and bioinformatics research allows us to build a prediction model, simulate illness development and medication therapy, and forecast disease prognosis, providing objective proof to TCM research and ending the era of relying solely on experience. Aiming for a match between the concept of "omics" in system biology and the characteristics of "multi-component, multi-effect, multi-target, and overall regulation" of TCM, system biology technology was applied to TCM research, and the model predicted the design and treatment process of compound prescriptions, the treatment plan was optimized, the individualized treatment was guided, and the side effects were minimized.

Even though each omics approach exists independently, they represent biological properties from various perspectives. Methods and technology should be chosen for each study based on the research topic and purpose. A single omics technique is frequently insufficient for studying TCM. Multi-omics approaches should be used to validate the study findings, and multi-center and multi-level research strategies should be used to evaluate changes in the level of consistency of gene-protein metabolites. The ideal multi-omics integration comprehensively integrates the omics data from various levels, allowing for the full spectrum analysis of genes, proteins, transcription factors, and metabolites of diseases or drugs, as well as the development of the relationship between molecular regulation and phenotype and the comprehensive analysis mechanism. However, the most popular multimomics integration technique at the moment is to combine the genome and transcriptome to discover novel important genes, or to combine the genome, transcriptome, and protein group to identify biomarkers, or to integrate the above three with metabolomics to uncover gene functions. Currently, the most common multi-omics integration strategy is to analyze the correlation or causality of multi-type omics data, build a linear model, a tree model, or a network model, and incorporate variables like statistics, biology, literature reports, and all-inclusion methods to make statistics, predict the results, discover the biological regulation relationship, and finally find the influencing factors related to the research purpose. As system biology advances, there will be an increasing number of developing omics. Biology's research concepts and technology will increasingly be utilized for TCM study. The integration of systems biology and traditional Chinese medicine (TCM) is an inevitable trend in the modernization of TCM. In the future, focus will be placed on technological innovation, theoretical interpretation and clinical transformation. Multi-omics and intelligent technologies will be used to deepen mechanism research, promote precision medicine and new drug research and development, facilitate the internationalization of TCM, and provide characteristic solutions for the prevention and treatment of complex diseases worldwide.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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