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REVIEW

Metabolomics-Driven Precision Prevention and Treatment of Heart Failure with Traditional Chinese Medicine: From Mechanistic Insights to Metabolic Network Regulation

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Abstract: Heart failure (HF), as the terminal clinical stage of diverse cardiovascular diseases, involves complex pathological mechanisms. Conventional Western medicines, which typically target individual molecules or pathways, may have limitations in comprehensively halting disease progression and can be associated with adverse effects. In contrast, Traditional Chinese Medicine (TCM) employs a holistic treatment strategy based on a "multi-component, multi-target, multi-pathway" principle (eg, Shenfu Injection, Linggui Zhugan Decoction), which may align more closely with the multifaceted pathophysiology of HF. However, the specific mechanisms underlying the therapeutic benefits of TCM have remained largely unclear, and most existing evidence is correlative rather than causal. Metabolomics, with its inherent strengths for holistic and dynamic analysis, offers a methodological framework for investigating the comprehensive effects and potential mechanisms of TCM interventions in HF. This review outlines the evolution of metabolomics technology platforms and their complementary applications in tackling the chemical complexity of TCM formulations, interpreting in vivo metabolic responses, and revealing spatial metabolic heterogeneity. The convergence of these technologies provides a foundation for a research paradigm centered on "problem orientation, technology matching, data integration, and hypothesis generation for mechanism elucidation". Furthermore, this paradigm has suggested potential synergistic mechanisms through which TCM regulates cardiac metabolism across multiple levels—from single active compounds and individual herbs to complex formulae. Collectively, these advances offer a useful reference for future research aimed at improving the precision and broader applicability of TCM in HF management, although most metabolomic findings remain associative and require validation through flux analysis, intervention studies, or clinical endpoint trials.

Keywords: metabolomics, heart failure, traditional Chinese medicine, multi-omics integration, metabolic network regulation

Introduction

Heart failure (HF), representing the final phase of numerous cardiac conditions, is a clinical syndrome where compromised cardiac contraction and/or relaxation fails to meet the body's metabolic requirements. It constitutes a primary reason for the elevated morbidity post-myocardial infarction and rising patient mortality.[1] Contemporary management of HF has evolved far beyond simple single-target approaches into a sophisticated, multi-modal, and guideline-directed medical therapy (GDMT). Current standard Western treatments encompass a broad arsenal including ARNI/ACEI/ARB,

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beta-blockers, mineralocorticoid receptor antagonists (MRA), and SGLT2 inhibitors. Furthermore, management is augmented by diuretics for congestion relief, iron supplementation when indicated, device therapies (such as CRT and ICD), and structured multidisciplinary care. While these comprehensive strategies significantly improve outcomes, challenges such as residual risk, polypharmacy, and dose-limiting adverse effects (eg, hyperkalemia, hypotension, and electrolyte disturbances) persist in certain populations, driving the pursuit of safer, adjunctive strategies.[2–4]

The core pathophysiology of chronic heart failure (CHF) centers on a self-perpetuating cycle of excessive neuroendocrine activation and ventricular remodeling—an intricate network involving multiple physiological systems and signaling pathways.[5] Although modern GDMT targets multiple pathways concurrently, the holistic "multi-component, multi-target, multi-pathway" paradigm of Traditional Chinese Medicine (TCM) offers a unique perspective for systemic regulation. Research indicates that many active compounds from Chinese medicinal herbs can modulate neuroendocrine activity, curb inflammation,[6–8] as well as offering further cardioprotection by enhancing myocardial energy metabolism and preventing cardiomyocyte apoptosis.[9] Qili Qiangxin Capsule (proven effective in a multicenter RCT for CHF) significantly reduced NT-proBNP and improved cardiac function.[10] However, the precise mechanisms underlying these systemic effects often resemble a "black box", posing a challenge for conventional investigative approaches.

The advent of metabolomics has furnished vital methodological support for systematically unraveling the global impact and mechanisms of TCM in HF management. This discipline contributes a molecular basis for TCM syndrome differentiation by discovering syndrome-associated biomarkers, thus refining the comprehension of the biological underpinnings of syndromes.[11] Moreover, through systematic analysis of the synergy within formulas, it aids in uncovering their comprehensive regulatory networks.[12] Ultimately, by verifying the beneficial effects of TCM interventions on definitive clinical endpoints, it robustly accelerates the clinical translation and practical application of TCM.[13]

This review aims to consolidate key breakthroughs in TCM research for HF from a metabolomics standpoint. We will emphasize strategies for employing integrated, multi-platform metabolomic technologies to methodically clarify the holistic mechanisms of Chinese medicines, with the goal of providing novel perspectives and a structured framework for future HF investigation.

Literature Search Strategy and Study Selection

This narrative review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines to ensure transparency.[14] A systematic literature search was performed in the PubMed and Web of Science databases from inception to January 2026. The search strategy employed Boolean operators to combine terms from three core domains: (1) heart failure (eg, "heart failure", "cardiac remodeling", "HF"); (2) metabolomics technologies (eg, "metabolomics", "LC-MS", "NMR"); and (3) traditional Chinese medicine (eg, "traditional Chinese medicine", "TCM formula", "natural compound"). The detailed search strategy is presented in Table S1.

The initial search identified 2360 records. After removing 425 duplicates, the remaining 1935 records were screened by title and abstract, of which 1250 were excluded because they were irrelevant to the topic, lacked metabolomics data, were non-clinical or non-human studies, or were inappropriate document types (eg, reviews, editorials). The full texts of the remaining 685 articles were then assessed for eligibility; 573 were further excluded due to inaccessible full texts, incomplete outcome measures, or missing key information. Finally, a total of 112 articles were included in this narrative review to provide a comprehensive overview of the current state of research in this field. The detailed study selection flow diagram is shown in Figure 1.

Metabolomics Technology Platforms and Their Tailored Strategies in TCM HF Research

Analytical Platforms for Deciphering "Complex Chemical Composition"

Liquid Chromatography-Mass Spectrometry (LC-MS)

LC-MS has become a widely used platform in TCM metabolomics research, owing to its analytical capabilities.[15] The evolution of this technology, from standalone separation techniques to highly efficient hyphenated systems, benefited from developments in the late 1980s with the maturation of soft ionization methods like electrospray ionization (ESI) and

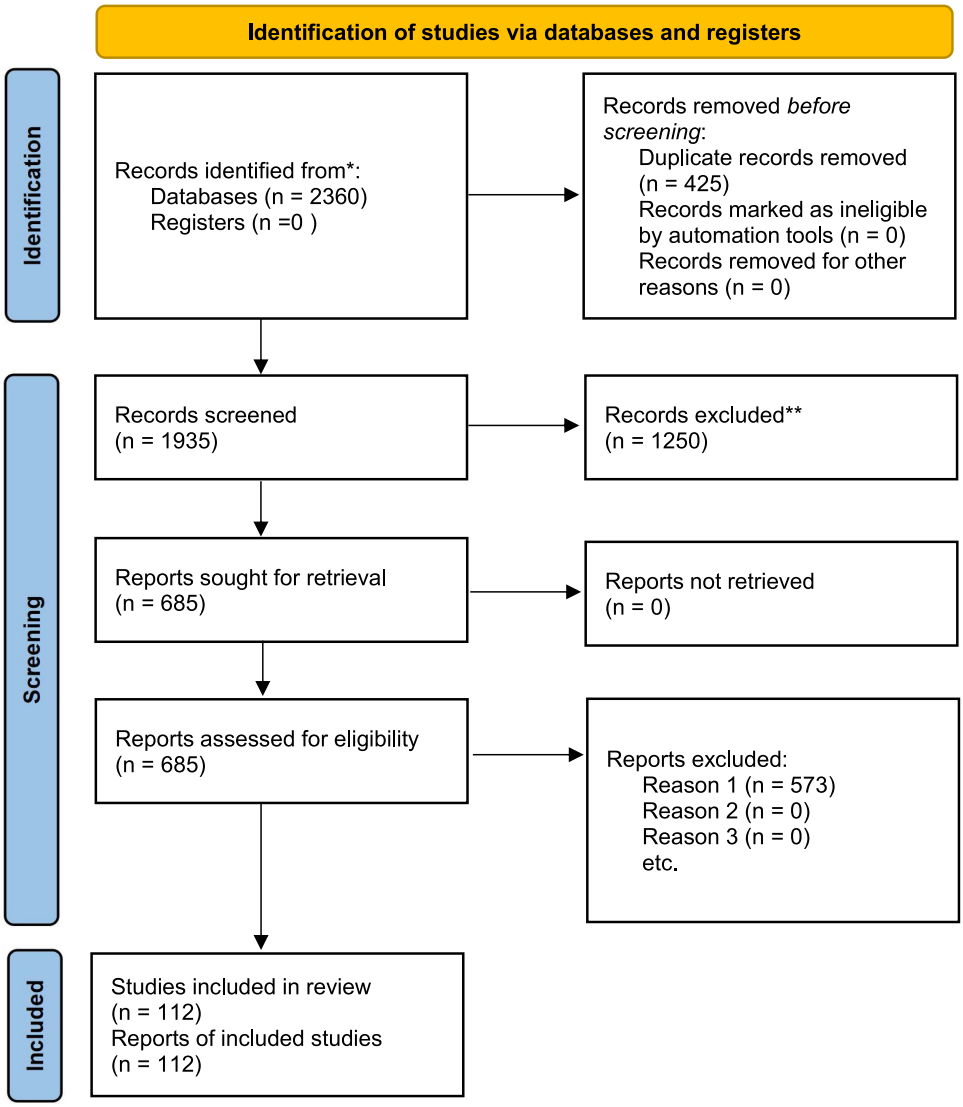

Figure 1 PRISMA 2020 flow diagram of study selection for this narrative review.

atmospheric pressure chemical ionization (APCI).[16] These advances enabled the online coupling between liquid chromatography and mass spectrometric detection, thereby facilitating the efficient analysis of non-volatile and highly polar metabolites within complex biological matrices. This achievement contributed to the development of metabolomics.[17] Subsequent technological innovations have continuously enhanced both separation and detection capabilities. The advent of ultra-high-performance liquid chromatography (UHPLC), which utilizes small-particle-size stationary phases and high-pressure systems, has improved separation efficiency and resolution.[18] Concurrently, the introduction of high-resolution mass (HRMS) spectrometers, such as time-of-flight (TOF) and Orbitrap analyzers, has provided high mass accuracy and resolving power, which can aid in the identification of chemical constituents and their metabolites in intricate TCM systems.[19] Leveraging UPLC-HRMS, investigators can simultaneously profile endogenous metabolites and exogenous TCM compounds in diverse samples, including cells, animal tissues, and clinical specimens.[15] Implementing rigorous quality control (QC), standardized data processing, multivariate statistics, and pathway analysis enables the detection of differential metabolites and the preliminary interpretation of their biological roles. However, such pathway analyses are correlative and do not establish causality; they generate hypotheses that require experimental validation.[20] This workflow provides a technical framework from chemical profiling to hypothesis generation for further mechanistic studies.

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Ion Mobility Spectrometry-Mass Spectrometry (IMS-MS)

The application of IMS-MS represents an advance in multidimensional separation in metabolomics research. This technique incorporates the collision cross-section (CCS), an intrinsic physicochemical parameter determined by an ion's size, shape, and charge, adding a third qualitative dimension for metabolite identification alongside retention time (RT) and mass-to-charge ratio (m/z).[21] One of its useful features lies in its ability capability to resolve isomeric compounds. Notably, novel IMS configurations such as Trapped Ion Mobility Spectrometry (TIMS) and Travelling Wave Ion Mobility Spectrometry (TWIMS) effectively discriminate between TCM isomers (eg, saponins and alkaloids) that pose challenges for conventional LC-MS.[22,23] For instance, in analyzing the chemical constituents of *Gynostemma pentaphyllum* (Jiaogulan), IMS-MS has been used to differentiate several co-eluting, structurally analogous saponins based on their distinct CCS values, providing an approach to address co-elution issues inherent in complex TCM matrices.[24] Current cutting-edge developments are concentrated on enhancing resolution and achieving deeper integration of multidimensional data. High-resolution cyclic IMS (cIMS) technology, which enables ions to undergo multiple passes, can improve separation power compared with conventional techniques.[25] Furthermore, combining standardized CCS measurement with artificial intelligence (AI)-based prediction algorithms is accelerating the transition towards automated and intelligent metabolite annotation.[26] The continuous expansion of CCS databases may further support its role as a pivotal search parameter, on par with m/z and RT, potentially contributing to the accuracy and reliability of identifications.[22]

Liquid Chromatography-Nuclear Magnetic Resonance (LC-NMR)

LC-NMR combines the high separation efficiency of liquid chromatography with the non-destructive analytical capabilities of NMR. Evolving since the 1980s, an important development was the successful online coupling of the two modules, which enables an approach for the direct structural elucidation of components within complex mixtures.[27] A useful feature of LC-NMR lies in its capacity for in-situ structural characterization of mixture constituents, yielding comprehensive structural data without the need for laborious isolation and purification steps. This is potentially valuable for distinguishing the numerous isomers prevalent in TCM systems.[28,29] For example, operating in stopped-flow mode, LC-NMR can be used to double-bond configurations by analyzing parameters such as proton coupling constants, and has been used to study dihydroartemisinin epimer conversion.[30] However, the application of LC-NMR confronts challenges, including relatively modest sensitivity, high instrumentation costs, and limited analytical throughput.[31] To address these constraints, newer configurations like LC-solid phase extraction-nuclear magnetic resonance (LC-SPE-NMR) (incorporating online solid-phase extraction) can improve detection sensitivity through metabolite pre-concentration.[32] Concurrently, advancements in microfluidic chip integration, improved cryogenic probes, and the deployment of higher magnetic field strengths may contribute to better sensitivity and resolution.[33]

Gas Chromatography-Mass Spectrometry (GC-MS)

In studying the metabolic mechanisms of HF, GC-MS is a useful tool due to its analytical capabilities for specific metabolites. HF is accompanied by profound metabolic remodeling, particularly involving impaired fatty acid oxidation and substrate switching.[34–36] The development of GC-MS, especially the high separation efficiency brought by the invention of capillary columns and the precise qualitative ability achieved through its coupling with mass spectrometry, contributed to its widespread use for the early quantitative analysis of key energy metabolism products (eg, fatty acids, organic acids, ketone bodies) in myocardial tissue and plasma.[36,37]

Currently, GC-MS, with its high sensitivity and resolution for volatile and derivatizable non-polar small molecule metabolites, is suitable for characterizing changes in specific pathways such as fatty acid oxidation and branched-chain amino acid metabolism.[38] Furthermore, it possesses well-established, cross-laboratory comparable Electron Ionization (EI) mass spectral libraries, which can aid in metabolite identification and verification. Although LC-MS has become the mainstream platform in metabolomics in recent years due to its broader polarity coverage, GC-MS remains a complementary technique for analyzing volatile metabolites, short-chain fatty acids, and similar compounds.[39] The ongoing integration of GC-MS with high-resolution mass spectrometry, enabling more accurate non-targeted screening, may help to identify metabolic heterogeneity in HF and potential therapeutic response biomarkers.[40]

Presently, GC-MS-based metabolomics can provide information that links clinical manifestations of HF with its underlying metabolic mechanisms. With the further development of portable GC-MS devices and AI data analysis algorithms, this technology may have potential applications in the early warning, precise phenotyping, and efficacy evaluation of heart failure, although these possibilities require further investigation and validation in clinical settings.[41]

Deciphering "in vivo Metabolic Response"

Following the characterization of the chemical basis of TCM formulae, the central focus of research can shift towards elucidating their in vivo pharmacological effects and mechanisms of action in HF. Metabolomics provides a method for monitoring system-wide dynamic alterations within the endogenous metabolic network of a living organism, although the observed changes are correlative and do not by themselves demonstrate causality.

Capillary Electrophoresis-Mass Spectrometry (CE-MS)

A useful feature of CE-MS lies in the orthogonality and complementarity of its separation mechanism to that of LC-MS. While LC-MS primarily separates compounds based on their hydrophobicity, CE-MS achieves separation according to a molecule's net charge and its conformation in solution (ie, its charge-to-mass ratio).[42] This fundamental distinction makes CE-MS particularly suitable for analyzing substances that are challenging for LC-MS, such as highly polar small molecule metabolites (eg, amino acids, nucleotides) and intact biomacromolecules (eg, proteins, polysaccharides), thereby addressing a part of the analytical blind spot of mainstream LC-MS techniques.[43] CE-MS-based metabolomics profiling can detect dynamic alterations in energy metabolism biomarkers in HF following TCM intervention, which may generate hypotheses for understanding how TCM might multi-targetedly regulate energy metabolism.[42,44] However, CE-MS application is constrained by limitations including modest absolute sensitivity and susceptibility to variations in methodological reproducibility. Overcoming these challenges may require targeted improvements, such as the development of online enrichment strategies and the promotion of automated, standardized operational protocols.[45]

Nuclear Magnetic Resonance (NMR) Spectroscopy

NMR Spectroscopy, valued for its non-destructive nature, reproducibility, and capacity for absolute metabolite quantification, can serve as a useful analytical platform aligned with the holistic perspective of TCM research.[46,47] An important development in the technology's evolution occurred in the 1970s, marked by the implementation of Pulsed Fourier Transform (PFT) techniques and widespread adoption of high-field superconducting magnets. These advancements improved sensitivity and resolution, allowing for the acquisition of comprehensive molecular structural and dynamic information of metabolites.[48,49] In HF metabolism studies, NMR technology, particularly via ^{1}H-NMR metabolomics, can capture global alterations in the host's metabolic network following TCM intervention. It is suitable for monitoring dynamic remodeling of key pathways such as energy metabolism, amino acid metabolism, and gut microbiota-host co-metabolism.[50] One hypothesis in systems biology suggests that correction of metabolic disturbances often precedes and may underlie physiological improvement, serving as a sensitive indicator of early efficacy.[51] Consistent with this hypothesis, an NMR-based metabolomic study in an HF model revealed that the restoration of key amino acid and energy metabolite levels following Shenmai Injection intervention occurred prior to observable improvements in cardiac functional parameters.[50] This finding may provides clues for generating hypotheses about the early-effect targets of TCM formulae.[52]

Current advancements in NMR focus on overcoming its sensitivity limitations through the deployment of ultra-high-field magnets, refined cryogenic probes, and the development of hyperpolarization techniques like dynamic nuclear polarization. The integration of these technological improvements with multidimensional NMR experimental methods and automated analytical workflows may enable broader application of NMR in TCM metabolomics research.[48,53,54]

Platforms Addressing the Challenge of "Spatial Distribution and Cellular Heterogeneity"

While traditional metabolomics based on bodily fluids or tissue homogenates can provide information on the metabolic changes associated with TCM interventions on heart failure from a global perspective, it inevitably obscures the spatial

heterogeneity of cardiac tissue. To clarify whether the therapeutic efficacy of TCM stems from broad regulation at the overall cellular level or precise targeting of specific cellular subpopulations, it is necessary to introduce metabolic visualization techniques possessing spatial resolution and single-cell precision.

Mass Spectrometry Imaging (MSI)

MSI represents a spatially resolved analytical technique that integrates mass spectrometry with visual mapping, enabling the direct acquisition of spatial distribution, relative abundance, and structural information of metabolites directly from their native locations within biological tissue sections, without the need for labeling. Originating in the late 1990s, the development of MSI was primarily propelled by innovations in soft ionization techniques, notably matrix-assisted laser desorption/ionization (MALDI) and desorption electrospray ionization (DESI).[55–57] The technique operates by performing sequential point-by-point analysis of tissue sections, collecting mass spectral signals at each pixel, and subsequently converting the intensity of ions with specific mass-to-charge ratios (m/z) into two-dimensional or three-dimensional distribution images. This process allows for simultaneous visualization and analysis of hundreds of metabolites across the tissue sample.

In metabolomics research investigating TCM for HF treatment, an application of MSI lies in its capacity to visualize spatial heterogeneity within metabolic networks. Studies have demonstrated that intervention with Xinshoubao Tablets is associated with improved myocardial metabolic homeostasis. Spatial metabolomic imaging (MALDI-MSI) has shown that this drug is associated with changes in the distribution of lipid metabolites in the peri-infarct zone, providing spatial evidence for how TCM alleviates myocardial "energy starvation" and metabolic disorders.[58,59] Furthermore, high spatial-resolution techniques like secondary ion mass spectrometry (SIMS), which achieves nanometer-scale resolution, can be used to localize the distribution of TCM active ingredients within subcellular structures such as mitochondria, providing correlative spatial information that links TCM intervention to observations the organelle level.[60]

To address the challenges MSI faces in HF research involving TCM—including limited quantitative accuracy, insufficient differentiation of isomeric metabolites, and difficulties in data interpretation—several strategies are required. These involve technological integration and innovation, multi-dimensional data fusion, and the establishment of standardized protocols.[61–63]

Single-Cell Metabolomics (SCM)

Leveraging its single-cell resolution, SCM offers a perspective technological perspective for investigating the multi-targeted and holistic effects of TCM in treating HF at the cellular scale. Building on analytical platforms such as chromatography-mass spectrometry couplings (eg, LC-MS, GC-MS) and microfluidics, SCM can provide broader metabolite coverage and higher analytical throughput, allowing for characterization of metabolic response heterogeneity across different myocardial cell subpopulations following TCM intervention at the single-cell level.[64,65] This capability allows SCM to detect heterogeneous perturbations in key HF pathways—such as energy metabolism, lipid metabolism, and oxidative stress—at single-cell resolution, generating correlative data that may help to generate hypotheses about the mechanisms by which TCM formulations might influence myocardial energy metabolism.[66–68] By accurately correlating metabolic phenotypes with specific cell types, the technology can be used to explore the cellular basis underlying TCM's "multi-component, multi-target" actions. For example, studies have reported that formulas containing *Astragalus* (Huangqi) and Shenfucan are associated with changes in amino acid metabolism in cardiomyocytes and changes in the lipid-inflammatory state of macrophages.[69,70] Despite challenges such as high technical complexity and limited throughput, the integration of SCM with microfluidics, ion mobility-MS, and machine learning may contribute to further developments in TCM HF research into the era of single-cell precision.[71–73]

Market Landscape and Industrial Prospects of Metabolomics Technology Platforms

Currently, mass spectrometry-based metabolomics research often uses mature commercial platforms provided by leading companies such as Thermo Fisher Scientific, Waters Corporation, and Bruker Corporation (eg, Orbitrap, Q-TOF, timsTOF systems). These platforms constitute an end-to-end technological foundation spanning from sample separation to data acquisition. Concurrently, to ensure the comparability and reproducibility of data generated across different platforms and

laboratories, the metabolomics community is actively engaged in establishing and promoting unified reporting standards and best practices.[74] At the technological frontier, the evolution of these platforms is clearly oriented towards the integration of multidimensional separation techniques, such as liquid chromatography-ion mobility-mass spectrometry (LC-IMS-MS), with intelligent detection capabilities.[75] Therefore, a clear understanding of this technological landscape is essential for platform selection and ensuring long-term data comparability in TCM metabolomics research.

Innovations and Development Trends of Metabolomics Technology in TCM Heart Failure Research

Metabolomics technology has enabled TCM HF research to move toward multidimensional and more analyses, with ongoing developments in three areas: technological iteration, data intelligence, and clinical integration.

Evolution Trends of Technology Platforms

Metabolomics technology is transitioning from single detection modalities towards multidimensional and dynamic analytical frameworks. In terms of resolution and temporal dimensions, existing high-resolution techniques such as cIMS have shown powerful capabilities for isomer discrimination. However, opportunities remain for enhancing detection sensitivity and throughput. The evolution and convergence trends of technology platforms will be illustrated in Figure 2. Future efforts may focus on the development of dynamic multi-modal integrated technologies that organically combine spatial resolution, temporal resolution, and molecular specificity.[76,77]

Furthermore, the integration of spatial metabolomics with single-cell technologies, for instance, combining MALDI-MSI with single-cell sorting, can be used to investigate the distribution differences of TCM components within specific myocardial cell subpopulations (eg, fibroblasts and cardiomyocytes), providing correlative spatial information for heterogeneous cellular regulation[78] Advancing such integrated technologies may require overcoming bottlenecks like the insufficient sensitivity for detecting low-abundance metabolites, which could be addressed by strategies such as utilizing nanomaterials to enhance ionization efficiency and boost signal intensity.[79]

Intelligent Pathways for Data Integration

At the level of data integration, future efforts may concentrate on constructing multi-omics correlation models and fostering deeper involvement of AI. The “multi-component, multi-target” mode of action of TCM and the systemic disease characteristics of HF mean that data from any single omics layer is likely insufficient for capturing the pathological mechanisms. The intelligent pathway for interpreting integrated multi-omics data is shown in Figure 3. Current research has begun to explore strategies for associating TCM improves cardiac function, inhibits ventricular remodeling, and ameliorates myocardial energy metabolism by integrating multidimensional data from metabolomics, transcriptomics, and network pharmacology. For instance, Wang et al combined machine learning with molecular pathway analysis to construct an anti-arrhythmic target network for the compound TCM Wenxin Keli, demonstrating the feasibility of AI-driven network pharmacology in cardiovascular disease research.[71] To better explore multi-pathway synergistic effects in the future, it may be useful to flexibly adopt various integration strategies, including vertical, spatiotemporal, and network-based integration.[80–83]

Given the complexity of extracting insights from massive datasets, the introduction of AI may help to reduce workload and support TCM toward precision medicine. When dealing with vast multi-omics data, machine learning models can identify non-linear syndrome-metabolite associations beyond the reach of traditional statistical methods, thereby saving time and costs.[84] For instance, Liu et al utilized algorithms including Multi-layer Perceptron (MLP), Support Vector Regression (SVR), Decision Tree Regression (DTR), and Gradient Boosting Regression (GBR) to construct a multi-target pharmacological prediction (mTPP) model, which identified 20 candidate compounds with potential drug-induced liver injury (DILI) effects.[80,85]

However, inconsistent standardization across different omics datasets constrains integration efficacy. Establishing TCM-specific data repositories—for instance, incorporating mass spectral libraries for compounds like berberine and astragaloside IV—constitutes a fundamental prerequisite for supporting reproducible analysis.[86,87] This requirement, in

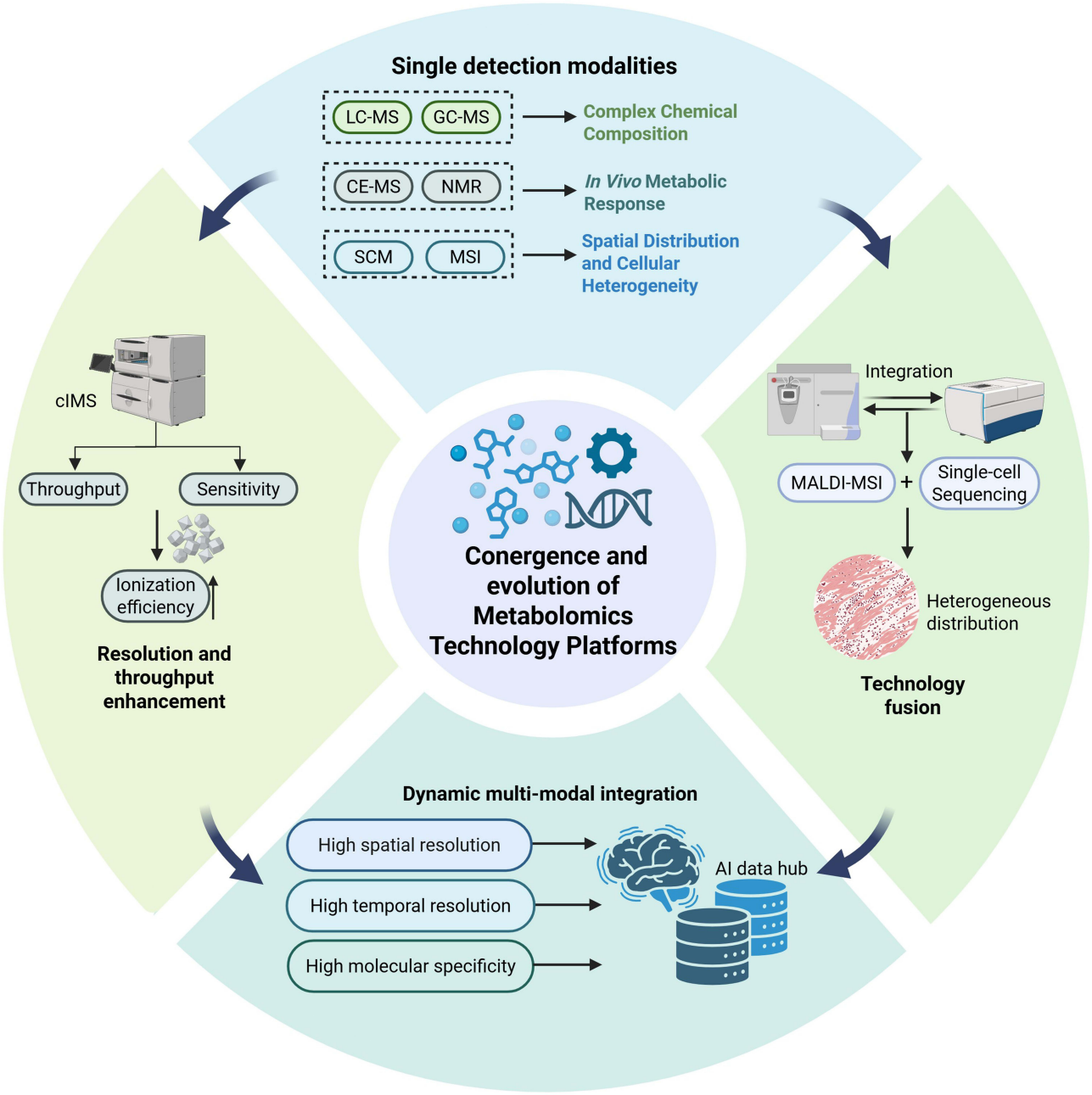

Figure 2 The convergence and evolution trends of technology platforms. Conceptual diagram illustrating the paradigm shift from isolated analytical techniques to an integrated technological ecosystem. Core targets include deciphering TCM formulas, monitoring in vivo responses, and resolving spatial heterogeneity. Upward arrows (↑) denote advancements in cIMS and performance metrics; convergent arrows (→) show MALDI-MSI fusion with single-cell sequencing; downward arrows (↓) represent integration into AI-orchestrated systems for high-resolution, dynamic analysis. The flow emphasizes directional synergy from discrete tools to unified application. Created with BioRender.com.

turn, further reinforces the reliance on intelligent data integration tools. Such intelligent analytical capabilities are crucial for realizing the individualized diagnosis and treatment embodied in the TCM principle of "treating the same disease with different therapies".

From Biomarker Validation to Clinical Translation

The clinical translation of TCM research in HF has long-faced challenges related to fragmented evidence chains and insufficient individualization in application. On one hand, translating metabolic biomarkers from discovery to clinical implementation must

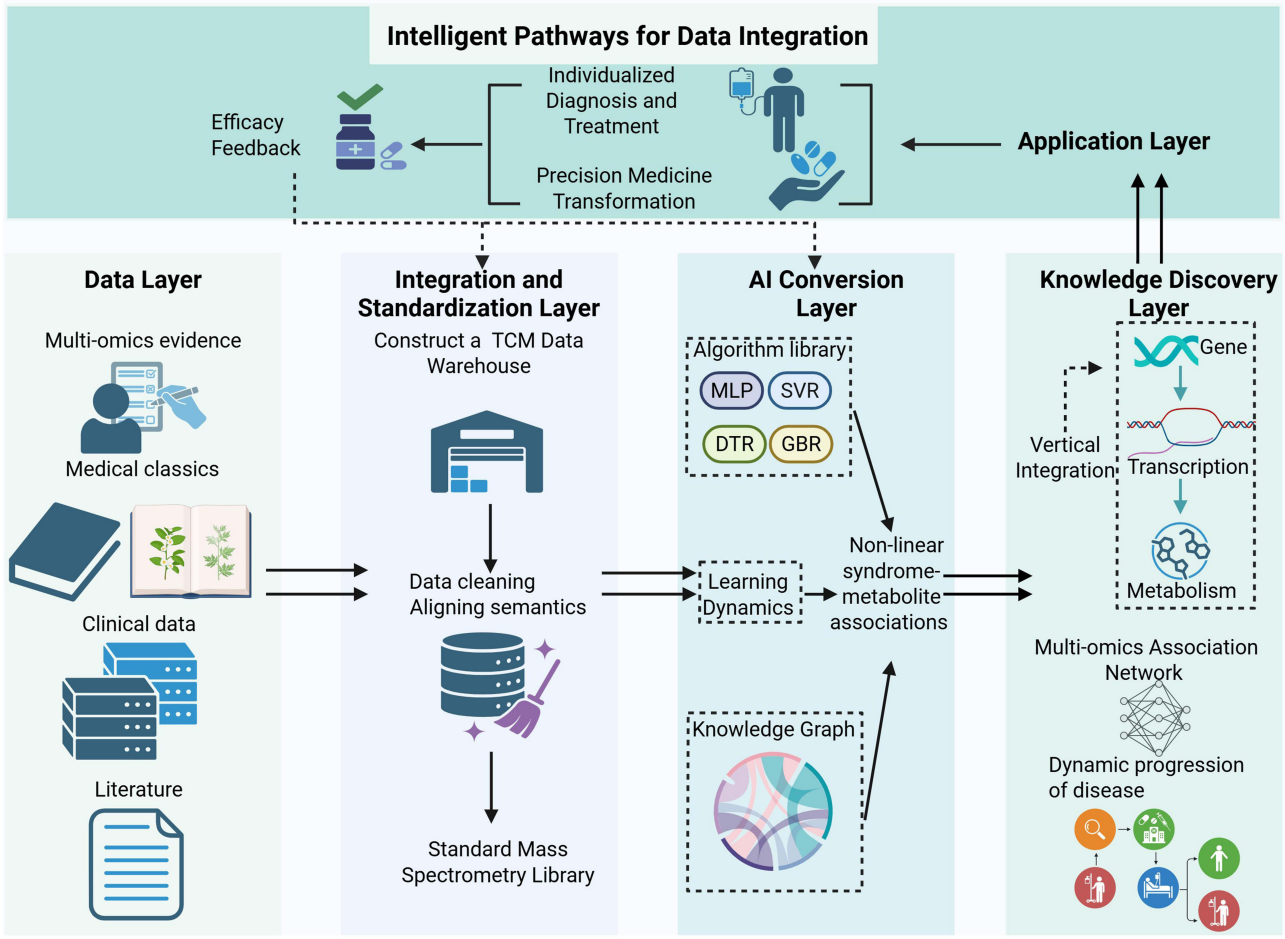

Figure 3 The intelligent pathway for interpreting integrated multi-omics data. The intelligent pathway for interpreting integrated multi-omics data is an intelligent framework bridging multi-omics data and clinical decision-making. It follows a bottom-up structure: first, the Data Layer aggregates multi-omics, clinical, and library evidence; then, the AI Conversion Layer uncovers non-linear syndrome-metabolite links, the Knowledge Discovery Layer integrates networks and spatiotemporal dynamics, the Application Layer drives individualized diagnosis and precision medicine. Created with BioRender.com.

overcome multiple barriers, including validation of biological relevance, confirmation of clinical utility, and individual patient matching.[36] On the other hand, the TCM concept of "treatment based on syndrome differentiation" requires translating population-level evidence into individualized treatment plans, yet traditional evaluation systems lack objective indicators for support.[11] Therefore, a systematic three-tier "discovery-validation-application "pipeline is needed to establish a complete pipeline from biomarker identification to precision diagnosis and treatment. The pathway from biomarker discovery to individualized application will be depicted in Figure 4.

In the discovery phase, it is important to validate the association between metabolites and hard endpoints through prospective cohorts (eg, multicenter registry studies), such as establishing causal links between acylcarnitine profiles and heart failure rehospitalization rates, to assess the clinical relevance of the biomarkers. In the validation phase, the focus shifts to confirming the efficacy of biomarker-guided therapy through randomized controlled trials (RCTs) and similar designs, laying the foundation for individualized application.[51] In the application phase, innovating efficacy evaluation systems is crucial. For instance, incorporating dynamic metabolic parameters (eg, mitochondrial respiratory-chain flux) as surrogate endpoints could eventually complement traditional subjective scores, although technical challenges related to high intra-individual variability need to be overcome.[62,63]

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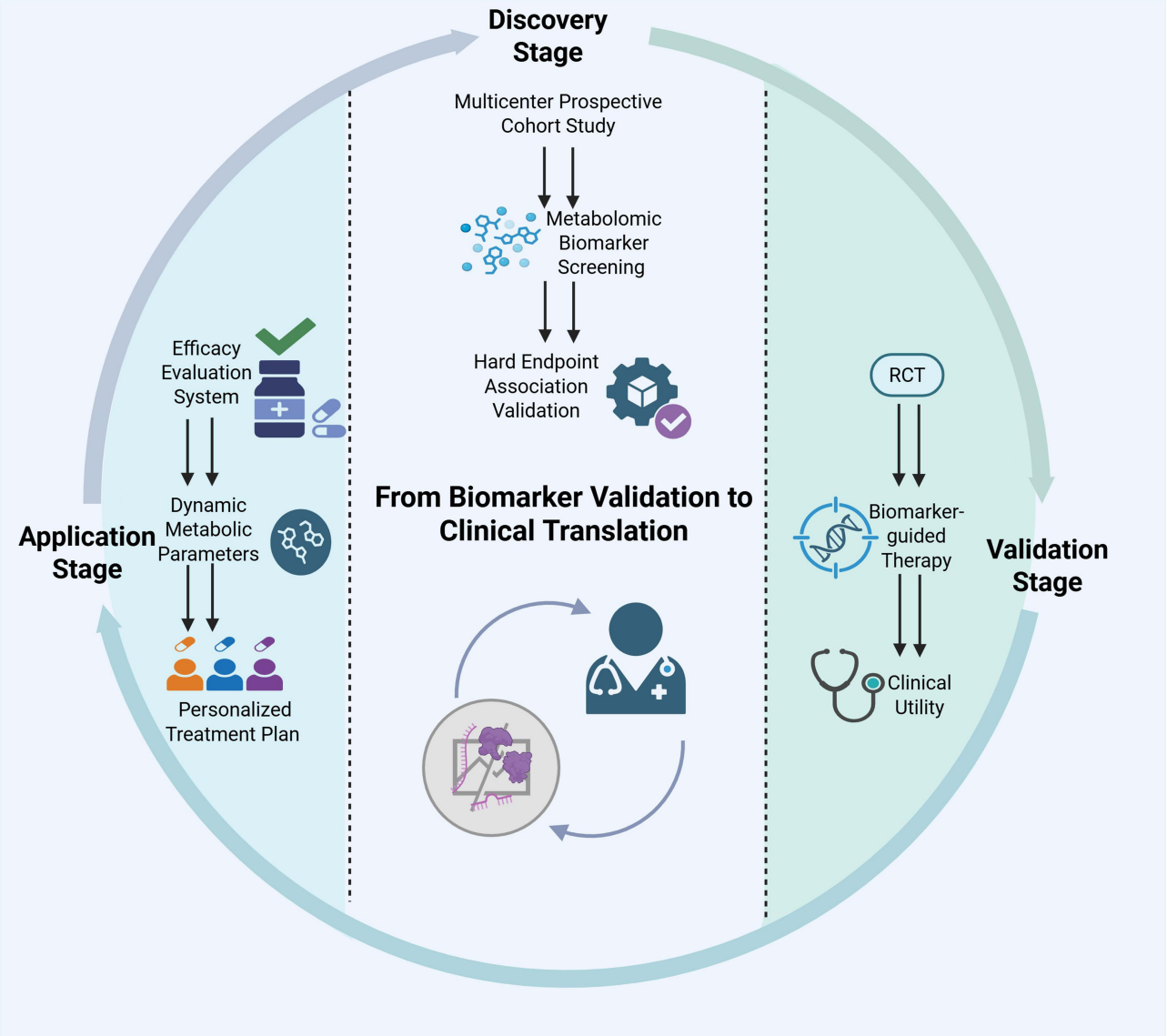

Figure 4 The pathway from biomarker discovery to individualized application. A three-stage bidirectional workflow integrating metabolomic biomarkers into clinical practice follows a forward translational structure: first, multicenter cohort studies are conducted to discover HF-associated biomarkers; then, randomized controlled trials are performed to validate the utility of biomarker-guided therapy; finally, dynamic metabolic parameters are applied to establish personalized treatment plans, with horizontal arrows (→) denoting forward translation and curved arrows (∪) representing bidirectional iteration between stages to emphasize an adaptive, cyclic clinical translation. Created with BioRender.com.

Metabolic Regulatory Mechanisms of TCM Intervention in HF

Modern metabolomics technologies have generated correlative evidence that helps to map the metabolic regulatory mechanisms by which TCM treats HF.[88] Multi-platform analytical strategies, represented by IMS, high-resolution LC-MS, and NMR, can capture dynamic changes of metabolites in living organisms and may bridge the holistic therapeutic efficacy of TCM with micro-level metabolic reprogramming processes. This integration provides a framework for interpreting the "multi-component, multi-target, holistic regulation" paradigm of TCM action. Utilizing these technological platforms, associations have been reported TCM intervention in HF can be elucidated across multiple dimensions, including energy metabolism, amino acid metabolism, fatty acid metabolism, and gut microbiota metabolism. These findings suggest a systems-level pattern through which TCM might alleviate myocardial energy starvation, oxidative stress, and fibrosis via potentially synergistic effects across multiple pathways.[89–92] However, metabolomic data alone do

not establish causality; targeted intervention studies, flux analysis, and clinical endpoint validation are needed to confirm mechanistic hypotheses.

Synergistic Regulation of HF Metabolic Network by Single Herb and Compound Formulae

Single herbs and compound formulae, as the core modalities of TCM in treating HF, are believed to exert their therapeutic effects through the synergistic actions of multiple components to regulate various HF-related metabolic pathways, thereby reflecting the concept of holistic regulation. Single herbs, such as *Astragalus* (Hugqi) and *Aconite* (Fuzi), directly target specific pathways like energy metabolism and amino acid metabolism through their distinctive active constituents. In contrast, compound formulae, through principled herb combination, may amplify synergistic effects and engage a broader metabolic network encompassing lipid metabolism, inflammatory response, and gut microbiota metabolism. The core mechanisms and associated metabolites involved in this synergistic regulation are summarized in Table 1.

Table 1 Comparison of Key Metabolomics Technology Platforms in Heart Failure Research

Platform	Key Strengths	Typical Samples	Primary Analytes	Main Technical Considerations	Reference
Liquid Chromatography-Mass Spectrometry (LC-MS)	Broad metabolite coverage, high sensitivity, excellent for non-volatile and polar compounds.	Polar compounds. Serum, plasma, urine, tissue homogenates, cell lysates.	A wide range of small molecule metabolites (lipids, amino acids, organic acids, etc).	Requires method optimization for different compound classes, and targeted analysis.	[15]
Gas Chromatography-Mass Spectrometry (GC-MS)	High separation efficiency, excellent reproducibility, robust compound identification via standard libraries (eg, NIST).	Serum, plasma, and urine after derivatization.	Volatile compounds, organic acids, fatty acids, sugars, amino acids (after derivatization).	Derivatization essential but time-consuming; ideal for targeted quantification.	[94]
Capillary Electrophoresis-Mass Spectrometry (CE-MS)	High efficiency for charged/ionic species, minimal sample volume requirement.	Polar/ionic metabolites in trace samples (eg, single-cell analysis).	Polar metabolites, amino acids, organic acids, nucleotides, carbohydrates.	Sensitive to sample matrix, lower peak capacity compared to LC.	[43]
Nuclear Magnetic Resonance (NMR) Spectroscopy	Non-destructive, quantitative, high reproducibility, provides structural information.	Fresh-frozen or formalin-fixed tissue sections.	Intact biofluids (serum, urine), tissue extracts, in vivo applications (MRS).	Lower sensitivity vs. MS, limited dynamic range but excellent for absolute quantification.	[46]
Mass Spectrometry Imaging (MSI)	Provides spatial distribution of metabolites directly from tissue sections, label-free.	Provides spatial distribution of metabolites directly from tissue sections, label-free.	Lipids, peptides, small molecules, distribution mapped across tissue architecture.	Semi-quantitative, spatial resolution vs. sensitivity trade-off, complex data analysis.	[95]
Liquid Chromatography-Nuclear Magnetic Resonance (LC-NMR)	Direct structural elucidation of unknown compounds from mixtures without isolation.	Fractions from LC separation of complex mixtures (eg, herbal extracts).	Unknown or novel compounds requiring de novo structure identification.	Low sensitivity, requires specialized equipment, typically used for specific, targeted analysis.	[27]

(*Continued*)

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Table 1 (Continued).

Platform	Key Strengths	Typical Samples	Primary Analytes	Main Technical Considerations	Reference
Ion Mobility Spectrometry-Mass Spectrometry (IM-MS)	Adds a separation dimension based on ion shape/size (Collision Cross Section, CCS), improves isomer separation.	Complex biological matrix samples (eg, cardiac tissue extracts).	Isomeric lipids, glycans, metabolites with similar m/z.	Increases analysis specificity, CCS value is a reproducible identifier for compound annotation.	[96]
Single-Cell Metabolomics (SCM)	Reveals cellular heterogeneity, identifies rare subpopulations, avoids population averaging, can correlate with cell function, provides spatial metabolic information (eg, via MALDI-MSI).	Primary cells (eg, cardiomyocytes, fibroblasts), cell lines, oocytes, neurons, immune cells, plant protoplasts.	Covers hundreds of metabolites per cell, from high-abundance (eg, amino acids) to lipids (eg, phospholipids), low-abundance signal detection remains challenging.	Relies on nano-LC/MS, requires extreme sensitivity, faces bottlenecks in sample preparation, throughput, and data complexity, microfluidics/AI are future directions.	[73]

Metabolic Regulation by Single Herbs

As the fundamental therapeutic units in TCM for treating HF, single herbs have been shown to achieve focused modulation of HF-related metabolic pathways through their defined active constituents. *Aconiti Lateralis Radix Praeparata* (Fuzi), a key herb for restoring vitality, has been associated with significant improvement in cardiac function. This effect has been primarily associated with the regulation of the PI3K/AKT/Bnip3 signaling axis, which in animal studies has been suggested to suppresses excessive mitophagy, improve myocardial energy metabolism, and reduce oxidative stress damage. Metabolomic analyses have further indicated that Fuzi is associated with the levels of key metabolites such as tetrahydrooxycorticosterone and decaprenylubiquinone, suggesting involvement of pathways such as arachidonic acid metabolism. In vitro experiments have also reported that Fuziprotects can protect cardiomyocytes and help maintain mitochondrial functional integrity. This research systematically elucidates, from a modern scientific perspective, the underlying molecular mechanisms of Fuzi's traditional efficacy of "restoring vitality and rescuing from collapse", highlighting its unique advantage in multi-component, multi-target integrated regulation.[97,98]

Metabolic Regulation by Compound Formulae

Current research demonstrates that although different categories of TCM formulae exhibit distinct therapeutic characteristics, they may all function through multi-target and multi-level regulation of energy metabolism, amino acid metabolism, and lipid metabolism networks. This concerted action is associated with the HF state, offering metabolomic-level observations consistent with the "holistic regulation" advantage of TCM.(eg, Shengmai Yin/San for amino acid metabolism and anti-fibrosis, Shenfu Injection for energy metabolism restoration, and Qiangxin Bushen Decoction for ferroptosis inhibition).

Regarding energy metabolism, multiple studies have revealed the corrective effects of various TCM formulae are associated with changes in energy supply parameters in the failing heart. For instance, Shenfu Injection significantly restored the levels of nine key metabolites (eg, lactate, malate, and anserine) in myocardial tissue of rats with chronic HF models. These metabolites are enriched in core energy-producing pathways such as pyruvate metabolism, histidine metabolism, and the citric acid cycle.

At the level of amino acid metabolism and immune-inflammatory regulation, TCM formulae have been reported to affect specific pathways. Research on Shengmai Yin found that it was associated with restore levels of key metabolites like kynurenine, tryptophan, and 5-hydroxyindoleacetic acid, suggesting modulation of the tryptophan metabolism pathway and its associated inflammatory response network. This effectively has been hypothesized to link the regulation of amino acid metabolism to the inhibition of myocardial fibrosis.[99] Yixin Fumai Lyophilized Powder, by being associated with by restoring metabolites such as L-valine, L-isoleucine, and taurine, may systemically influence multiple

amino acid metabolic pathways, potentially contributing to in an overall amelioration of amino acid metabolism and energy supply disorders.[100]

At the more complex level of lipid metabolism and cellular fate regulation, Linggui Zhugan Decoction exhibits value. It can restore a wide range of differential metabolites (eg, LysoPCs, arachidonic acid, and phenylalanine) with a focus on intervening in glycerophospholipid and arachidonic acid metabolism pathways, thereby suggesting an effect on lipid disorders at the metabolic level in HF.[101] Research on Qiangxin Bushen Decoction has provided further observations. Beyond associations with restored specific metabolites, it has been reported to activate the AMPK/FOXO1 pathway and to be associated with inhibiting ferroptosis and increase GPX4 expression, suggesting potential cross-level and multi-organ protection spanning from energy metabolism to cell death programs.[102] The clinical study on Qishen Yiqi Dripping Pills provides an example of translational research from discovery to validation. Based on serum metabolomics findings from clinical patients, this formulation has been reported to be associated with restored metabolites such as lactate, phenylalanine, and proline, and modulates LysoPCs and glycerophospholipid metabolism networks, suggesting a holistic effect on the disordered patterns of amino acid, lipid, and energy metabolism in HF patients.[103–105]

From a metabolomics perspective, single herbs and compound formulae each exhibit distinct advantages in HF therapy. Single herbs provide targeted regulation through well-characterized active constituents. For instance, *Astragalus* (Huangqi) enhances energy supply by modulating branched-chain amino acid and taurine metabolism, while *Aconite* (Fuzi) improves myocardial contractility via purine metabolism regulation by its water-soluble alkaloids, reflecting focused bioactivity. In contrast, the compound formulae display broad-spectrum effects. Shenfu Injection has been shown to concurrently normalize multiple energy metabolism pathways, including pyruvate metabolism and the TCA cycle. Linggui Zhugan Decoction has been associated with changes in lipid profiles through glycerophospholipid metabolism, and Qiangxin Bushen Decoction has been reported to extend its associated regulatory scope from energy metabolism to ferroptosis inhibition, suggesting combined cardio-renal protection. This multi-component, multi-target, multi-pathway observed network is consistent with the holistic therapeutic principle of TCM at a metabolomic level.[100–102,106] The targeted associations of single herbs and the systemic influences of compound formulae are thus seen as complementary, collectively forming an integrated metabolic intervention strategy for HF that warrants further mechanistic validation.[107]

Metabolic Regulatory Effects of Monomer Components

Building upon observations of TCM's holistic regulation of HF metabolic networks, natural compounds serving as the active monomeric components of Chinese herbs achieve synergistic intervention from the macroscopic whole to microscopic precision by precisely targeting key metabolic pathways and signaling molecules, suggesting a potential for targeted intervention from a systems level to specific molecular targets.[99,100] Based on their core targets of action in the pathological process of HF, representative monomer components are categorized into the following three types for elaboration. Their core mechanisms and associated metabolites are summarized in Table 2.

Improving Myocardial Contraction and Energy Metabolism

This category of active monomers has been studied for its potential to address the core pathology of HF—"energy deficit"—by enhancing myocardial contractility and optimizing the energy metabolism of cardiomyocytes. Astragaloside IV has been reported to be associated with improved myocardial energy supply primarily through activating the AMPK/PGC-1α signaling pathway, thereby promoting mitochondrial biogenesis.[59,108] Targeted metabolomics studies have reported that it is associated with upregulate the acylcarnitine profile and downregulate lysophosphatidylcholines. These changes involve the PPAR signaling pathway and glycolytic providing correlative metabolomic observations that are consistent with its potential role in improving cardiac energy metabolism.[70,109]

Conversely, Ginsenoside Rg3 has been reported to optimize energy supply in association with modulating amino acid metabolism and purine metabolism. Metabolomic pathway analysis reveals significant enrichment of the purine metabolism and TCA cycle pathways following its intervention. These findings, which are correlative, suggest that by enhancing mitochondrial function and influencing the energy metabolic system, this compound may contribute to the improvement of myocardial contractile function.[110]

Table 2 Metabolic Mechanisms of Selected TCM Interventions in Heart Failure Models

Compound Recipe	Component/ Active Ingredient	Model Type	Sample Size (Treatment Group)	Dosage/Duration	Reverted Metabolites	Technology Platform	Efficiency	References
Aconite	Aconite Water Extract	In vivo, TAC-induced chronic HF mice			↓: Tetrahydrooxycorticosterone, Decaprenylubiquinone, Taurocholic acid (20 key metabolites reversed)	UPLC-Q-Orbitrap-HRMS	Activates PI3K/AKT, inhibits Bnip3-mediated mitophagy, improves energy metabolism and cardiac function.	[97]
		In vitro, NE-stimulated H9c2 cells	In vivo, 8–10/ group	2g/kg/day (Crude drug, ig) or 05–2 mg/ kg/day (Total alkaloids, ig), 21 days				
Shenfu Injection	Red Ginseng, Aconite	In vivo, Surgery-induced HF model in SD rats	In vivo, 9/ group	60 mL·kg^{-1}, ip, q.d., 15 days	↑: Leucine/Isoleucine, Anserine, Lactate, Malate	UHPLC-QE-MS	Reverses energy metabolism remodeling, repairs mitochondrial structure, improves cardiac function, reduces NT-proBNP and pathological damage.	[96]
Shengmai Injection	Red Ginseng, Ophiopogon	In vivo, Salt-sensitive hypertensive HF rats	In vivo:, 8/ group	6.0 mL/kg, ip, q.d., 15 days	↑: TMAO, TMA, Histamine, 5-Hydroxytryptamine, L-Threonine ↓: GABA, Glutamate, D-Glucuronic acid, Creatine, Cholic acid, Chenodeoxycholic acid, L-Valine, Ketoleucine	UPLC-MS /MS, UHPLC-MRM-MS/MS	Modulates gut microbiota, restores energy/amino acid/bile acid/methylamine metabolism, reduces serum TMAO, improves cardiac/intestinal barrier function, alleviates inflammation/fibrosis.	[95]
Linggui Zhugan Decoction	Poria, Cinnamon Twig, Atractylodes, Licorice	In vivo, Doxorubicin-induced heart failure mouse model	In vivo:, 8–10/ group	66 g/kg/day, ig, 21 days	↑: 15-HPETE, Uric acid, Phenylalanine ↓: Arachidonic acid	UHPLC-QTOF-MS	Regulates glycerophospholipid and arachidonic acid metabolism, inhibits inflammation, improves cardiac function, alleviates injury	[100]
Yixin Fumai Lyophilized Powder	Red Ginseng, Ophiopogon, Schisandra	In vivo, Coronary artery ligation-induced chronic HF mice	In vivo, 6–8/ group	0.53 g/kg/day, ip, 14 days	↑: L-Isoleucine, Taurine, Theophylline ↓: Quinic acid, Uric acid, Creatine	HPLC-QTOF /MS	Regulates amino acid metabolism, inhibits TGF-β1/Smad3 signaling, improves cardiac function, reduces fibrosis.	[99]
		In vitro, Ang II–induced cardiac fibroblasts	In vitro, 3 indep. exp	400 μM YQFM for 24 hours				
Qiangxin Bushen Decoction	Ginseng, Aconite, Dalbergia odorifera, Cornus, Red Peony, Poria, Ephedra, Astragalus, Cinnamon Twig, Asarum, Rehmannia, Polygonatum	In vivo, CRS2-induced cardiorenal syndrome mouse model	In vivo, 8–10/ group	High/Low dose, ig, 4 weeks	↑: 2-Oxocarboxylic acid metabolism, Adrenergic signaling, Amino acid biosynthesis, β-Alanine metabolism ↓: Isoproterenol, L-Methionine, γ-Glutamylvaline, Melitric acid B	UPLC-Q-TOF-MS	Activates AMPK/FOXO1 pathway, inhibits ferroptosis in heart/kidney, regulates energy metabolism, improves cardiorenal function/structure.	[101]

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Amino Acid Metabolism and Immune-Inflammatory Regulation

This category of active monomers exerts significant effects in inhibiting myocardial fibrosis and modulating immune responses, potentially through regulating the crosstalk between amino acid metabolism and immune-inflammatory processes. Notoginsenoside R1 demonstrates protective effects by being associated with modulating phospholipid metabolism and inflammatory responses. Based on UPLC-Q-TOF/MS-based metabolomics research, this component significantly reduces serum levels of lysophospholipids and arachidonic acid metabolites in heart failure rats. These changes involve the glycerophospholipid metabolism and arachidonic acid metabolism pathways, suggesting a potential mechanism for suppressing inflammation-mediated myocardial injury.

Lipid Metabolism and Cell Fate Regulation

This category of monomeric components has been studied for its potential to protect cardiomyocytes by regulating lipid metabolism homeostasis and by influencing cell death programs.

Hydroxysafflor Yellow A (HSYA) not only promotes angiogenesis by activating the HIF-1α-VEGFA-Notch1 signaling axis but also counteracts fibrosis in association with modulating lipid metabolism and directly inhibiting cardiac fibroblast activation. As a natural allosteric activator of malate dehydrogenase 1 (MDH1), it directly improves mitochondrial energy metabolism in cardiomyocytes, achieving multi-level protection spanning from energy metabolism to cell fate determination.[111]

Icariin has been reported to enhance mitochondrial function via the Apelin/Sirt3 signaling pathway. Metabolomic analyses have suggested its ability to be associated with restoration of the levels of L-arginine, uric acid, and sphingosine-1-phosphate, with pathway enrichment primarily in arginine biosynthesis and glutathione metabolism. These alterations are associated with changes in the cellular metabolic state and have been hypothesized to influence the decision-making process governing cell survival and death through inhibition of cardiomyocyte apoptosis.[112]

Monomer components offer certain features in HF treatment. Their targeted mechanisms involve specific pathways such as energy metabolism and oxidative stress, potentially enhancing therapeutic efficacy while possibly reducing the risk of off-target effects.[69] These components possess well-defined chemical structures, clear structure–activity relationships, and quantifiable pharmacokinetic profiles and metabolic pathways, which align with international drug evaluation standards. Monomer components and compound formulae complement each other: monomers address individual variability, while formulae provide a foundation for holistic regulation. This multi-tiered model may support TCM's role in more individualized approaches, may help integration with Western medicine through better understanding of mechanisms, and could contribute to TCM's standardization and broader recognition, although these possibilities require further clinical validation.[94,103,109]

Discussion

This study systematically reviews the paradigm shift in HF research within TCM, driven by metabolomics technology. At its core, this shift lies in the transition of research focus from the discovery of single metabolite markers to the analysis of the remodeling patterns of the entire metabolic network under TCM intervention. The novelty of this review is the construction of an integrated "Technology-Strategy-Mechanism" framework that proceeds stepwise into greater depth: (1) By systematically elaborating the complementary application of multi-platform metabolomics technologies, it provides a methodological foundation for analyzing the complex system of TCM. (2) It proposes a "problem-oriented" integration strategy, providing a research blueprint for investigating HF-related metabolic disorders and potential mechanisms of TCM intervention across different spatial scales and biological levels. (3) Through systematic analysis of the multi-level metabolic regulatory network—from single compounds to single herbs and complex formulae—it presents metabolomics-derived evidence that is consistent with "multi-component, multi-target, holistic regulation" from multiple dimensions, including energy metabolism, oxidative stress, and inflammatory response.

While the aforementioned framework highlights the potential of metabolomics in advancing TCM HF research, it must be objectively recognized that the transition from a conceptual framework to mature application still faces a series of challenges. These challenges essentially stem from the interplay between technological bottlenecks and the inherent complexity of TCM itself: (1) Technically, cutting-edge technologies like IMS and SCM still have room for improvement

in resolution and sensitivity, making it difficult to fully eliminate interference from complex biological matrices. Absolute quantification and deep coverage of metabolites remain significant challenges. (2) Heavy reliance on biofluids like serum and urine metabolomics data, while reflecting systemic metabolic responses of the organism, cannot distinguish whether metabolite changes stem from the direct action of TCM components on the heart or from indirect effects, such as through improved renal function, modulation of gut microbiota, or influence on the neuroendocrine system. This may lead to misinterpretation of the core pharmacodynamic mechanisms. (3) After TCM intervention, the concentrations of TCA cycle intermediates (eg, malate, succinate) have been reported to return to normal levels, but the temporal sequence of these concentrations increases remains unknown. This lack of temporal resolution limits the depth of mechanistic interpretation from "correlation" to "causation".

However, it is precisely this recognition of the limitations that suggests directions for focused optimization in technological development and research design, potentially moving the field towards more reliable and refined goals: (1) Developing high-resolution cyclic ion mobility spectrometry, optimizing single-cell pre-processing workflows, and incorporating stable isotope labeling to enhance analytical performance. (2) In studies on the same individual, synchronously collecting and analyzing serum, cardiac tissue, urine, and even bile samples. By comparing metabolite change patterns across different sample types, the origin and propagation pathways of metabolic disturbances may be inferred. In animal experiments, simultaneously collecting coronary sinus blood and arterial blood allows for calculating the arteriovenous concentration difference of specific metabolites, directly quantifying myocardial uptake or release of the substance, thereby providing more direct evidence for "TCM-heart" interaction (3) In cell or animal models, while administering TCM, providing tracer substrates such as ^{13}C-labeled glucose or ^{15}N-labeled glutamine. Using LC-MS to track the incorporation rate and pattern of these labeled atoms into metabolites (eg, in the TCA cycle, amino acids, nucleotides) over time.

Conclusion

This review summarizes that metabolomics technology provides methodological support and a framework for investigating the complex mechanisms associated with TCM intervenes in HF. Confronted with HF as a complex clinical syndrome involving multiple systems and pathways, and considering the limitations of single-target Western drug therapies, the holistic regulatory approach of TCM—characterized by "multi-component, multi-target, multi-pathway" actions—shows potential advantages. However, its specific mechanisms of action had long been regarded as a "black box". Metabolomics, leveraging its holistic and dynamic technical features, is compatible with holistic philosophy of TCM. By integrating multi-dimensional platform technologies such as LC-MS, IMS, NMR, MSI, and single-cell metabolomics, it has contributed to a systematic research strategy. This strategy spans from parsing complex chemical components and monitoring in vivo metabolic responses to visualizing spatial distribution and cellular heterogeneity.

This strategy has been applied in multi-level research involving "single compounds, single herbs, and compound formulae". From various dimensions, including energy metabolism, amino acid metabolism, lipid metabolism, and gut microbiota metabolism, it has provided observations consistent with metabolic reprogramming mechanisms through which TCM interventions that may ameliorates cardiac function and curbs ventricular remodeling, involving the synergistic regulation of key processes such as myocardial energy supply, inhibition of oxidative stress and inflammatory responses, and intervention in cell fate decisions. Among these, active ingredients that regulate branched-chain amino acid and tryptophan metabolism or target acylcarnitine profiles (eg, astragaloside IV), as well as compound formulas (eg, Shenfu Injection, Linggui Zhugan Decoction), have shown potential in improving myocardial energy metabolism and inhibiting fibrosis, warranting further validation.

Despite existing challenges in areas such as technical sensitivity, clinical sample heterogeneity, and inferring causal mechanisms, the integrated research strategy driven by metabolomics provides a useful framework for further exploring the scientific essence of TCM in treating HF and for advancing its clinical precision and international integration. Realizing these possibilities will require rigorous validation that moves beyond correlation toward causation—through flux analysis to trace metabolic pathways, targeted intervention experiments (genetic or pharmacological) to test key pathways, temporal studies to determine the sequence of metabolic changes relative to phenotypic improvement, and clinical cohort studies with Mendelian randomization to assess causal associations.

Abbreviations

HF, Heart failure; TCM, Traditional Chinese Medicine; CHF, chronic heart failure; LC-MS, Liquid Chromatography-Mass Spectrometry; ESI, electrospray ionization; APCI, atmospheric pressure chemical ionization; UHPLC, ultra-high-performance liquid chromatography; TOF, time-of-flight; QC, quality control; IMS-MS, Spectrometry-Mass Spectrometry; CCS, collision cross-section; RT, retention time; TIMS, Trapped Ion Mobility Spectrometry; TWIMS, Travelling Wave Ion Mobility Spectrometry; cIMS, High-resolution cyclic IMS; LC-SPE-NMR, liquid chromatography-solid phase extraction-nuclear magnetic resonance; LC-NMR, Liquid Chromatography-Nuclear Magnetic Resonance; CE-MS, Capillary Electrophoresis-Mass Spectrometry; NMR, Nuclear Magnetic Resonance; PFT, Pulsed Fourier Transform; MSI, Mass Spectrometry Imaging; MALDI, Matrix-Assisted Laser Desorption/Ionization; DESI, Desorption Electrospray Ionization; SCM, Single-Cell Metabolomics; LC-IMS-MS, liquid chromatography-ion mobility-mass spectrometry; MLP, Multi-layer Perceptron; SVR, Support Vector Regression; DTR, Decision Tree Regression; GBR, Gradient Boosting Regression; mTPP, multi-target pharmacological prediction; DILI, drug-induced liver injury; RCTs, randomized controlled trials.

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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 agreed to be accountable for all aspects of the work.

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