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Traditional Chinese medicine phenomics research on glycolipid metabolism disorder: a review

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ABSTRACT

Traditional Chinese medicine (TCM) has demonstrated unique advantages in the prevention and treatment of chronic diseases such as glycolipid metabolism disorder. However, its widespread application has been hindered by the unclear biological essence of TCM syndromes and therapeutic mechanisms. As an emerging interdisciplinary field, phenomics integrates multi-dimensional data including genome, transcriptome, proteome, metabolome, and microbiome. When combined with TCM's holistic philosophy, it forms TCM phenomics, providing novel approaches to reveal the biological connotation of TCM syndromes and the mechanisms of herbal medicine. Taking glycolipid metabolism disorder as an example, this paper explores the application of TCM phenomics in glycolipid metabolism disorder. By analyzing molecular characteristics of related syndromes, TCM phenomics identifies differentially expressed genes, metabolites, and gut microbiota biomarkers to elucidate the dynamic evolution patterns of syndromes. Simultaneously, it deciphers the multi-target regulatory networks of herbal formulas, demonstrating their therapeutic effects through mechanisms including modulation of insulin signaling pathways, improvement of gut microbiota imbalance, and suppression of inflammatory responses. Current challenges include the subjective nature of syndrome diagnosis, insufficient standardization of animal models, and lack of integrated multi-omics analysis. Future research should employ machine learning, multimodal data integration, and cross-omics longitudinal studies to establish quantitative diagnostic systems for syndromes, promote the integration of precision medicine in TCM and western medicine, and accelerate the modernization of TCM.

1 Introduction

Traditional Chinese medicine (TCM) stands as a treasure of the Chinese nation. Its concepts of “correspondence between humanity and the universe (天人相应)” and “the

holistic approach to treatment (整体论治)”, as well as the idea of “addressing disease before its onset and halting its progression (未病先防-既病防变)”, have demonstrated unique advantages in the comprehensive prevention and treatment of chronic conditions such as glycolipid

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metabolism disorder. However, the limited understanding of TCM means that the intrinsic essence of TCM syndromes remains ambiguous, and the biological mechanisms underpinning its precise efficacy have yet to be fully elucidated. This obscurity has hindered the broader adoption and application of TCM in addressing glycolipid metabolism disorder. As an emerging research direction in the field of life sciences, phenomics has developed rapidly since its conceptual inception by Prof. Steven A. Garan of the University of California, USA, in 1996, providing solid support for the realization of precision medicine [1]. In recent years, phenomics technology has been prevalently applied in TCM, giving rise to TCM phenomics. This integrative approach elucidates the scientific connotation of TCM across multiple scales and dimensions, thereby advancing its modernization and precision development. Using glycolipid metabolism disorder as a case study, this paper systematically examines the current application of phenomics in TCM to provide an objective scientific basis for the prevention and treatment of glycolipid metabolism disorder in TCM.

2 The concept of TCM phenomics

As life science research advances into the post-genomic era, the “phenome” has emerged as the next strategic frontier in the field of life science and human health, following the “genome”, and represents the “key” to further deciphering the complexities of human health [2]. Academician Jin LI’s team at the Institute of Human Phenomics, Fudan University, defines the phenome as a collection of quantifiable characteristics encompassing individuals’ and groups’ physical, chemical, and biological attributes. These traits arise from the dynamic interplay of genetic factors, epigenetic modifications, symbiotic microbial communities, dietary influences, and environmental factors [3]. Phenomics, an emerging transdisciplinary field, is dedicated to the systematic, genome-wide study of phenotypes [4]. By constructing cross-scale associations among genes, phenotypes, and environments, as well as between micro- and macro-phenotypes, phenomics offers a novel framework for deciphering the code of life.

Phenomics is characterized by its complexity, cross-scale nature, and dynamic character. Its research scope spans micro-phenotypes, such as transcription, protein, and metabolism, as well as macro-phenotypes, including behavior, psychology, and language [5, 6]. It emphasizes the entire life cycle and the impact of spatial and temporal dynamics, such as altitude, temperature, and humidity, on the phenome. This holistic and systematic approach to understanding life resonates profoundly with the holism concept and correspondence between humanity and the universe in TCM [7]. Both TCM and phenomics focus on phenotypic characteristics and

patterns of changes within the human body, and their concepts and methodologies can mutually inform and complement each other. TCM provides a reference for human phenomics in terms of disease cognition. Besides, phenomics offers critical technical tools for elucidating the cognitive perspectives and the complex action systems of TCM [8] (Figure 1). In recent years, the iterative development and deepening of the interdisciplinary research between TCM and phenomics have given rise to the nascent field of TCM phenomics. TCM phenomics is rooted in the core theories of TCM and employs modern multi-omics technologies to measure phenotypic profiles during the progression of TCM syndromes from both macroscopic and microscopic perspectives. It aims to elucidate the essence of TCM syndromes and the transition mechanisms under herbal medicine interventions, thereby facilitating the integration and mutual enhancement of TCM and western medicine [9].

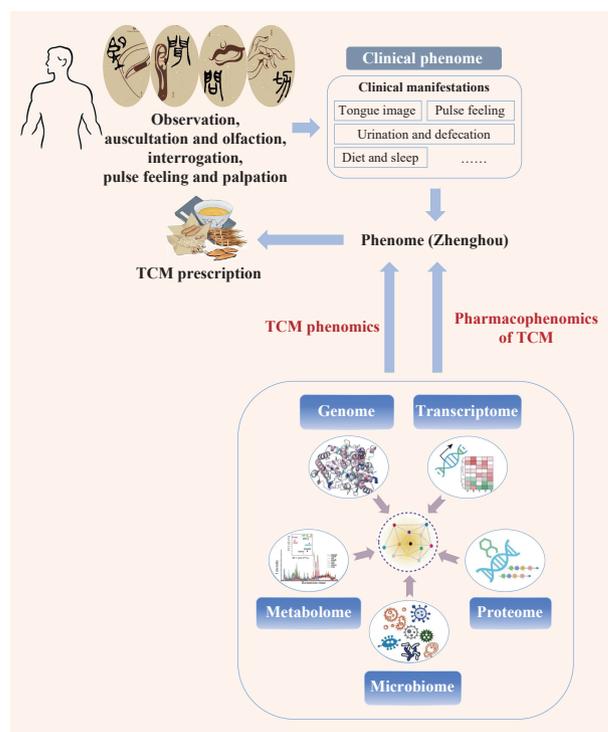


Figure 1 Overview of TCM phenomics

3 TCM phenomics and the diagnosis and treatment of glycolipid metabolism disorder

The prevalence of diseases related to glycolipid metabolism disorder is escalating, driven by multifaceted factors such as lifestyle changes and population aging [10]. Glycolipid metabolism disorder is characterized by dysregulation in glucose and lipid homeostasis, with primary clinical manifestations including type 2 diabetes mellitus (T2DM), dyslipidemia, obesity, or overweight, which may present either individually or in combination. Glycolipid metabolism disorder is characterized by complex core pathomechanisms, a large patient base, low

rates of awareness, treatment and control, a wide variety of complications, and high morbidity and mortality rates, creating a pressing challenge for disease prevention and management. The treatment model of glycolipid metabolism disorder has transitioned from single-disease, single-target interventions to multi-disease, multi-target synergistic approaches, emphasizing early intervention, glucose-lipid co-regulation, and integrated prevention and treatment strategies [11]. Glycolipid metabolism disorder falls under the categories of “Pidan (脾瘵)” “Gaozhuo (膏浊)” and “Danzhuo (瘵浊)” in TCM. They are primarily attributed to overconsumption of greasy food, imbalances between work and rest, obstruction of Qi flow in the middle Jiao, impaired transportation and transformation, and the accumulation of pathological Gaozhuo, leading to the endogenous production of phlegm, turbidity, dampness, toxicity, and blood stasis. The core pathogenesis involves internal heat and fullness in the middle energizer, as well as the accumulation of Gaozhuo. Clinically, these disorders are commonly manifested as syndromes of gastrointestinal excess heat, liver and stomach heat stagnation, and phlegm-heat intermingled syndrome [12]. Multiple high-quality, evidence-based medical studies have demonstrated that TCM significantly ameliorates glycolipid metabolism disorder through simultaneous regulation of blood sugar, blood lipids, and obesity [13-15]. However, the basis of its effective substances, mechanisms of action, and network of intervention targets have not been fully elucidated.

TCM phenomics, as an essential research tool to explore the mysterious “black box” of TCM, not only clarifies the scientific connotation of TCM syndrome differentiation in improving glycolipid metabolism disorder from a holistic perspective but also focuses on identifying key targets with TCM in the systemic regulatory network of diseases. Ultimately, it aims to elucidate the therapeutic mechanisms and address the bottlenecks hindering TCM research in treating glucose and lipid metabolism disorders [16]. TCM phenomics includes syndrome phenomics, pharmacophenomics of TCM, and other domains [17]. Syndrome phenomics employs phenomics technology to analyze the biological manifestations and their evolutionary trends during the existence and progression of syndromes. Identifying molecular-level biomarkers associated with syndromes seeks to decipher the essence and connotation of various syndromes related to glycolipid metabolism disorder. Furthermore, it aims to establish a diagnostic framework for TCM syndromes that correlates syndromes with their corresponding phenotypes, thereby promoting objectivity and standardization in the TCM syndrome differentiation of glycolipid metabolism disorder [18]. Pharmacophenomics of TCM, through the application of diverse histological techniques and analytical tools, reconstructs the “sovereign-minister-assistant-courier (君-臣-佐-使)” principle and the multi-target

pharmacological mechanisms of TCM prescriptions. Guided by the holistic view and syndrome differentiation, it validates the clinical application of TCM in the prevention and treatment of glycolipid metabolism disorder and provides objective criteria for evaluating drug efficacy [19, 20]. Therefore, TCM phenomics research on glycolipid metabolism disorder enhances the precision of TCM treatment, propelling TCM toward a more targeted and refined approach.

4 Research status of TCM phenomics in glycolipid metabolism disorder

4.1 Application of TCM syndrome phenomics in glycolipid metabolism disorder

4.1.1 Transcriptomics Researchers employed transcriptomics sequencing to screen for differentially expressed genes (DEGs) in a rat model combining the syndrome of Qi and Yin deficiency with T2DM. Their findings suggest that T2DM associated with Qi and Yin deficiency syndrome may be linked to the upregulation of early growth response 2 (*EGR2*), insulin-like growth factor binding protein 1 (*IGFBP1*), and a disintegrin and metalloproteinase with thrombospondin motifs 4 (*ADAMTS4*) genes, as well as the downregulation of G0/G1 switch 2 (*G0S2*), MID1 interacting protein 1 (*MID1IP1*), and basic helix-loop-helix family member E40 (*BHLHE40*) genes [21]. Utilizing RNA-seq technology, transcriptomic profiling of macrophages was conducted to delineate DEGs and associated biological pathways in dyslipidemia, with a particular focus on its correlation with phlegm-dampness retention (PDR) syndrome and spleen-kidney Yang deficiency (SKYD) syndrome. The transcriptomic analysis of macrophages revealed proinflammatory effects on the vascular endothelium in dyslipidemic mice exhibiting both PDR and SKYD syndromes, albeit through distinct pathways. In PDR syndrome, macrophages exhibited increased interferon (IFN)- γ and IFN- β expression, contributing to endothelial inflammation. In contrast, in SKYD syndrome, enhanced macrophage chemotaxis and taxis were observed, driving similar inflammatory responses in the endothelium. Additionally, while the vascular endothelium in both PDR and SKYD syndromes mice demonstrated protective mechanisms, these mechanisms differed significantly between the two conditions. On one hand, in dyslipidemic mice exhibiting PDR syndrome, macrophages exhibited elevated levels of arachidonic acid metabolic processes and the epoxygenase P450 pathway, which protected the vascular endothelium. On the other hand, in dyslipidemic mice with SKYD syndrome, macrophages were predominantly enriched in biological processes such as angiogenesis, blood vessel morphogenesis, response to growth factors, and cellular response to growth factor stimuli. These processes revealed significantly higher activity levels than those

observed in the PDR group, contributing to enhanced angiogenesis and vascular repair [22].

4.1.2 Proteomics Using isobaric tags for relative and absolute quantitation (iTRAQ) technology, a material-based study was conducted on the salivary proteome of patients with T2DM and spleen deficiency syndrome. Multiple differential proteins were screened and found to be enriched in three metabolic pathways: the complement and coagulation cascades, fat digestion and absorption, and vitamin digestion and absorption. These differential proteins primarily include plasma kallikrein (KLKB1), complement C3 (C3), plasma serine protease inhibitor (SERPINA5), heparin cofactor 2 (SERPIND1), apolipoprotein B-100 (APOB), and apolipoprotein A-I (APOA1), which may be closely related to the occurrence and development of T2DM with spleen deficiency syndrome [23].

4.1.3 Metabolomics A metabolomic analysis was conducted to assess plasma fatty acid concentrations in T2DM patients presenting with three distinct TCM syndrome patterns, aiming to determine if fatty acid signatures could serve as discriminative markers among these syndromes. In comparing the two groups of Qi deficiency and Qi with Yin deficiency, γ -linolenic acid (C18:3), arachidonic acid (C20:2), triglycerides (TG), and low-density lipoprotein (LDL) emerged as potential biomarkers. The candidate biomarkers identified for Qi-deficiency and damp-heat were eicosapentaenoic acid (C20:5), triglycerides (TG), and high density lipoprotein (HDL). Conversely, myristic acid (C14:0), palmitic acid (C16:0), oleic acid (C18:1), linoleic acid (C18:2), and high density lipoprotein (HDL) were the primary classification indicators for Qi and Yin deficiency and damp-heat [24]. CHEN et al. [25] investigated the features of serum metabolomic profiles in individuals exhibiting dyslipidemia across various syndrome types, utilizing nuclear magnetic resonance (NMR) technology. From a metabolite standpoint, individuals exhibiting phlegm-dampness retention syndrome primarily displayed an aggregation of harmful metabolic byproducts. Conversely, those with spleen and kidney Yang deficiency syndrome were characterized by a deficiency in protective metabolites. Regarding metabolic pathways, variations were observed in liver function, oxidative stress, inflammatory responses, and energy utilization among dyslipidemia patients across different syndromes. CHU et al. [26] employed NMR to investigate patients with T2DM and blood stasis syndrome (BSS) plasma metabolomic characteristics. Their findings revealed that patients with T2DM with BSS exhibited higher levels of acetone, acetoacetate, α -hydroxybutyric acid, α -hydroxyisovaleric acid, β -hydroxybutyric acid, α -ketoisocaproate, 3-methyl-2-oxovalerate, 3-hydroxyisobutyric acid, and glycine compared with those in the non-BSS group. Conversely, fumaric acid, citric acid,

N-acetylmethionine, pyroglutamic acid, and methionine levels were lower in the BSS group than in the non-BSS group.

Using serum metabolomics technology, HUANG et al. [27] investigated the relationship between the syndrome manifestations and the changes in serum differential metabolites and related metabolic pathways in a rat model of T2DM with Qi and Yin deficiency syndrome. The results indicated that the syndrome manifestations in the rat model of T2DM with Qi and Yin deficiency syndrome may be associated with the metabolic pathways of D-glutamine and D-glutamic acid, arachidonic acid metabolism, alanine, aspartate, and glutamate metabolism, and arginine biosynthesis. L-glutamic acid and arachidonic acid may be potential characteristic metabolites for T2DM with Qi and Yin deficiency syndrome. Using liquid chromatography-mass spectrometry (LC-MS) technology, QIU et al. [28] conducted a non-targeted metabolomics study on the urine of rats with T2DM and Qi and Yin deficiency syndrome. They found that the biological model of T2DM with Qi and Yin deficiency syndrome exhibited disorders in carbohydrate metabolism, lipid metabolism, amino acid metabolism, and bioenergetic metabolism. YANG et al. [29] utilized ultra-performance liquid chromatography coupled with quadrupole time-of-flight mass spectrometry (UPLC/Q-TOF-MS) to identify potential biomarkers and related metabolic pathways for T2DM with Qi and Yin deficiency syndrome. Their research revealed significant differences in the serum metabolic profiling of rats with T2DM and Qi and Yin deficiency syndrome compared with the normal group. Specifically, disorders were observed in carbohydrate metabolism, lipid metabolism, protein metabolism, oxidative stress, the tricarboxylic acid cycle, and bioenergetic metabolism. Using rats with metabolic syndrome (MetS) and phlegm dampness syndrome as the research subjects, changes in the metabolite profile were analyzed through the UPLC/Q-TOF-MS. The results indicated the presence of disorders in amino acid metabolism, lipid metabolism, bile acid metabolism, oxidative stress, phospholipid metabolism, carbohydrate metabolism, and energy metabolism in rats with MetS and phlegm dampness syndrome [30]. Using metabolomics technology with the UPLC/Q-TOF-MS, YANG et al. [31] investigated changes in small molecule metabolites in the serum of rats with MetS and intermingled phlegm and blood stasis syndrome. The identified potential biomarkers primarily included lysophosphatidylcholines, phenylalanine, tyrosine, tetradecanoic acid, stearic acid, D-gluconic acid, and prostaglandin B1.

4.1.4 Microbiomics Selecting the bacterial V3-V4 region of the 16S rRNA gene for high-throughput sequencing, YIN et al. [32] analyzed the patterns of gut microbiota imbalance and functional changes in patients with T2DM of different TCM syndromes. The research revealed that

Faecalibacterium is a representative genus for the syndrome of Yin-Yang deficiency. At the same time, *Clostridium* sp. is a marker species for Yin deficiency syndrome with excessive heat.

4.1.5 Multi-omics By conducting metabolomic and proteomic analyses on the serum of T2DM patients, both with and without damp-heat syndrome, it was observed that the proteins showing differential abundance were primarily linked to the renin-angiotensin system, vitamin digestion and absorption, and hypertrophic cardiomyopathy, among others. Additionally, the metabolites that exhibited differential abundance were mainly amino acids connected to CoA and pantothenate biosynthesis and the metabolic pathways of phenylalanine, beta-alanine, proline, and arginine. Integrative analysis indicated that the vitamin metabolism pathway was the most significantly impacted [33]. The metabolic and protein expression patterns in patients with T2DM exhibiting kidney Yin deficiency syndrome (KYDS) were evaluated through a combination of NMR-based metabolomic approaches with multivariate analysis and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS)-based proteomic techniques. Analysis of protein expression between the KYDS and non-KYDS cohorts revealed no significant differences in peptide expression. However, notable metabolic changes were identified that differentiated the two groups. Specifically, KYDS patients showed reduced concentrations of creatinine, citrate, trimethylamine N-oxide (TMAO), phenylalanine, and tyrosine, while alanine, glycine, and taurine levels were elevated [34].

By integrating advanced phenomics technologies, including transcriptomics, proteomics, metabolomics, and microbiomics, we can uncover the biological alterations associated with syndromes of glycolipid metabolism disorder. This includes identifying differences in specific gene or protein expression, shifts in metabolite levels, and imbalances in gut microbiota. Such an integrated approach offers profound insights into the role and mechanisms of TCM syndromes in the occurrence and development of glycolipid metabolism disorder, thereby advancing the integration of disease and syndrome-based approaches in TCM. While significant strides have been made in linking TCM syndromes with phenotypes through phenomics research, several issues, and challenges remain. First, diagnosing TCM syndromes is highly subjective due to the lack of quantitative standards, which poses difficulties in exploring the matching between syndromes and clinical phenotypes. Second, the preparation of animal models for TCM syndromes lacks standardized protocols. Third, there is a paucity of multi-omics studies on TCM syndromes, which hinders a holistic and dynamic understanding of the biological essence of these syndromes. To address the three major bottlenecks

in future research, the following strategies can be adopted. First, integrate multimodal data from the four diagnostic methods (inspection, auscultation, inquiry, and palpation) with multi-omics biomarker screening and leverage machine learning to construct quantitative diagnostic models for syndrome differentiation. Second, establish “disease-syndrome combination (病证结合)” animal models and implement standardized model validation through dynamic monitoring and multidimensional evaluation systems. Third, conduct longitudinal multi-omics studies (integrating transcriptomics, proteomics, metabolomics, and microbiomics) to dynamically dissect the core regulatory networks underlying syndrome evolution. By integrating systems biology technologies into TCM syndrome phenomics research, this approach will provide theoretical and methodological foundations for elucidating the scientific essence of TCM syndromes and advancing precision medicine through the integration of traditional Chinese and western medicine.

4.2 Application of pharmacophenomics of TCM in glycolipid metabolism disorder

4.2.1 Transcriptomics ZHANG et al. [35] discovered the component of Wacao pentacyclic triterpenoid saponins (WPTS) from *Silene viscidula*. This component rapidly reduces blood glucose levels in mouse models with severe insulin resistance, exhibiting a significantly superior hypoglycemic effect compared with metformin and rosiglitazone. Furthermore, they systematically elucidated the mechanism of action of WPTS in treating T2DM using transcriptome technology. Transcriptomic results revealed that WPTS down-regulated monoacylglycerol O-acyltransferase 1 (*MOGAT1*), hepatic lipase (*LIPC*), and sphingomyelin phosphodiesterase 4 (*SMPD4*) and upregulated glucose transporter type 4 (*SLC2A4/GLUT4*), insulin receptor substrate 1 (*IRS1*), and components of the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) signaling pathway to regulate lipid metabolism and improve insulin resistance.

4.2.2 Proteomics ZHAO et al. [36] used the serum proteome labeled by iTRAQ to identify the therapy target of Yiqi Yangyin Huatan Quyu Recipe (益气养阴化痰祛瘀方) on T2DM. In this study, the therapy effect of the recipe on T2DM was confirmed, and therapy targets [cell division control protein 42 homolog (CDC42) and ras homolog gene family member A (RhoA) proteins] were identified. Proteomics technology was employed to analyze the changes in the proteome in the serum of diabetic rats after treatment with Yitangkang (益糖康). The study revealed that a total of 40 differential proteins were obtained between the drug treatment group and the control group, among which 11 proteins were upregulated more than 1.5 times, including carnitine acetyltransferase, and 29 proteins were down-regulated less than 0.75 times,

including epidermal growth factor receptor [37]. iTRAQ quantitative analysis was performed to evaluate proteomic abundance changes in the serum of patients with T2DM after treatment with Xiaoke Pill (消渴丸) containing Chinese herbal extracts and glibenclamide. The findings revealed that, among patients without hypoglycemia, 25 proteins and, in those with hypoglycemia, 21 proteins exhibited differences after treatment with the Xiaoke Pill. In contrast, treatment with glibenclamide resulted in differences among 24 proteins in patients without hypoglycemia and 25 proteins in those with hypoglycemia. In the groups without hypoglycemia, five proteins—inter-alpha-trypsin inhibitor heavy chain H4, cholesteryl ester transfer protein, apolipoprotein C, histone H2B, and alpha-2-macroglobulin—showed consistent abundance responses to both medications. In the groups experiencing hypoglycemia, eight proteins—histone H2B, apolipoprotein C, alpha-2-macroglobulin, inter-alpha-trypsin inhibitor heavy chain H1, inter-alpha-trypsin inhibitor heavy chain H4, complement component C9, biotinidase, and complement component C8 gamma chain—displayed similar abundance changes across the two groups [38].

4.2.3 Metabolomics Metabolomics was performed to investigate the antidiabetic effect of radix ginseng extract in T2DM rats based on high-performance liquid chromatography-tandem mass spectrometry (UHPLC-MS). It was found that the extract of red ginseng could improve the condition of blood glucose and lipids, and regulate the metabolic pathway related to T2DM. These include D-arginine and D-ornithine metabolism, D-L-glutamine and D-glutamate metabolism, taurine and sub-aurine metabolism, arginine biosynthesis, and tryptophan metabolism [39]. Using UHPLC-MS for metabolomics analysis of urine samples from T2DM rats, it was confirmed that Huanglian Decoction (黄连汤) regulates glyoxylic acid and dicarboxylate metabolism, L-phenylalanine metabolism and biomarkers in the tricarboxylic acid (TCA) cycle. Such applicable examples include cytosine, carnitine, betaine, L-phenylalanine, L-phenylalanine, glucose, citrate, 3-phenylpyruvic acid, and equine [40].

4.2.4 Microbiomics The molecular mechanisms underlying the therapeutic effects of Scutellaria-Coptis (SC) on T2DM were investigated through 16S rRNA high-throughput sequencing. The findings revealed that SC significantly decreased the levels of gut-associated pathogenic bacteria, such as *Proteobacteria*, *Enterobacteriaceae*, *Enterococcus*, *Escherichia-Shigella*, and *Enterobacter*, while enhancing the proliferation of certain bacterial genera within the *Lachnospiraceae* and *Prevotellaceae* families [41]. To assess changes in gut microbial diversity and composition in T2DM rats following Baihu Ren-shen Decoction (白虎人参汤, BHRS) administration, 16S rRNA gene sequencing was performed. The study

revealed that BHRS intervention modified the gut microbial ecosystem, notably reducing the *Firmicutes/Bacteroidetes* (F/B) ratio at the phylum level. Furthermore, the taxonomic analysis demonstrated that BHRS administration elevated the proportional representation of *Lactobacillus*, *Blautia*, and *Anaerostipes* genera while reducing the prevalence of *Allobaculum*, *Candidatus Saccharimonas*, and *Ruminococcus* at the genus level [42]. TIAN et al. [43] investigated the effects of Gegen Qinlian Decoction (葛根苓连汤, GGQLD) on the gut microbiota of diabetic rats. They found that the administration of GGQLD was observed to significantly enhance the population of beneficial bacteria, including *Flavonifractor* and *Acetatifactor*, which are known for their roles in producing short-chain fatty acids (SCFAs) and exhibiting anti-inflammatory properties. Concurrently, it reduced the presence of potentially harmful bacteria, such as *Anaerofustis* and *Gammaproteobacteria*. Through 16S rRNA sequencing, it was demonstrated that the structural changes in the gut microbiota caused by the Chinese herbal formula GGQLD are linked to its antidiabetic properties. Notably, this intervention increased the abundance of beneficial microbes like *Faecalibacterium* spp. in the intestinal environment [44]. Additionally, TONG et al. [45] utilized 16S rRNA sequencing to reveal that the herbal formula could ameliorate T2DM accompanied by hyperlipidemia by promoting the growth of beneficial bacterial species, including *Blautia* and *Faecalibacterium* spp.

4.2.5 Multi-omics XU et al. [46] conducted a study to assess the impact of GGQLD and its presumed primary active component, berberine, on a diabetic rat model. Through extensive analysis of gut microbiota, short-chain fatty acids, proinflammatory cytokines, and ileum transcriptomics, they discovered that berberine and GGQLD treatments led to notable changes in the gut microbiota composition. Notably, the abundance of butyrate-producing bacteria, such as *Faecalibacterium* and *Roseburia*, was markedly increased. This shift contributed to reduced intestinal inflammation and improved glucose regulation. Additionally, the levels of short-chain fatty acids in the rats' feces were significantly higher following treatment with berberine or GGQLD. The study also reported a substantial reduction in serum proinflammatory cytokines and the expression of immune-related genes, including nuclear factor kappa B subunit 1 (*NFKB1*), signal transducer and activator of transcription 1 (*STAT1*), and interferon gamma receptor 1 (*IFNGR1*), in the pancreatic islets after treatment. In another investigation, the db/db mouse model of T2DM was employed to evaluate the pharmacodynamic properties of polysaccharides derived from Gegen [*Pueraria lobata* (Willd.) Ohwi, GG] and Fenge [*Pueraria thomsonii* Benth., FG]. The study aimed to explore their antidiabetic mechanisms through metabolomic profiling and intestinal microbiota analysis. On one hand, GG polysaccharide lowered serum

taurocholic acid levels by enhancing the population of *Romboutsia*, thereby modulating the PPAR signaling pathway and alleviating insulin resistance. On the other hand, FG polysaccharide decreased serum uric acid concentrations by reducing the abundance of *Klebsiella*, subsequently regulating the PPAR signaling pathway to improve insulin resistance [47]. TAWULIE et al. [48] elucidated the potential mechanism of the Jiangtang Sanhuang Pill (降糖三黄片, JTSHP) in treating T2DM through 16S rRNA sequencing and UPLC-MS/MS. They demonstrated that JTSH treatment can regulate intestinal dysbiosis by preferentially increasing bacteria with bile salt hydrolase activity, such as *Bacteroides*, *Lactobacillus*, and *Bifidobacterium*. This, in turn, may result in the accumulation of unconjugated bile acids (BAs) in the ileum, such as chenodeoxycholic acid (CDCA) and deoxycholic acid (DCA), and further upregulate intestinal farnesoid X receptor/fibroblast growth factor 15 (FXR/FGF15) and G protein-coupled bile acid receptor 5/glucagon-like peptide-1 (TGR5/GLP-1) signaling pathways. FANG et al. [49] employed metabolomics and metagenomics to explore the mechanism of berberine in ameliorating glycolipid metabolism disorder. After berberine treatment, the structure of gut microbiota altered, reducing microbial richness and diversity, and bacteria such as *Akkermansia*, *Eubacterium*, and *Ruminococcus* were enriched. Concurrently, the levels of metabolites such as L-isoleucine, L-phenylalanine, and hydroquinone O-beta-D-glucopyranoside were decreased. Combining 16S rDNA gene sequencing and metabolomics analysis, the potential mechanism of Shenqi Compound (参芪复方, SQC) in treating T2DM was revealed. SQC intervention modulated the structure of gut microbiota, increasing the ratio of *Bacteroidetes/Firmicutes* and regulating the relative abundance of *Prevotellaceae*, *Butyrivimonas*, *Bacteroides*, *Blautia*, *Roseburia*, *Lactobacillus*, and *Rothia*, and improve the expression of 40 metabolites. These effects mainly influenced pathways such as gluconeogenesis/glycolysis, amino acid metabolism, lipid metabolism, citrate cycle, and butanoate metabolism [50]. To assess the impact of Purendan (普仁丹, PRD) on the gut microbiota and their metabolic byproducts in rats with T2DM, a metagenomic approach alongside UPLC-MS/MS was utilized. Key microbial species influenced by PRD included *Prevotella* sp. 10(H), *Parabacteroides* sp. SN4, *Flavobacteriales bacterium*, *Bacteroides*, *Alistipes indistinctus*, and *Ruminococcus flavefaciens*. Furthermore, PRD was found to modulate concentrations of microbial metabolites such as pantothenic acid, 1-methylhistamine, and 1-methylhistidine, which play roles in the biosynthesis pathways of pantothenate and coenzyme A, histidine degradation, and the synthesis of secondary bile acids [51]. Based on metagenome sequencing and targeted metabolomics, it was discovered that the modified GGQLD could effectively regulate the gut microbiota, improve bile acid metabolism, activate the Takeda G

protein-coupled receptor 5 (TGR5)/cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA)/cAMP response element-binding protein (CREB) signaling pathway, stimulate glucagon-like peptide-1 (GLP-1) secretion, and exhibit therapeutic effects on T2DM mice [52].

Combining metabolomics and transcriptomic, Jinqi Jiangtang Tablets (金芪降糖片) were shown to improve insulin resistance in T2DM mice by regulating the insulin signaling pathway, enhancing glycogen synthesis and glycolysis, and increasing hepatic triglyceride and fatty acid metabolism [53]. Metagenomics, transcriptomics, and targeted metabolomics were integrated to reveal the underlying mechanisms of the total alkaloids of *Berberidis Cortex* for T2DM treatment. The research demonstrated that total alkaloids of *Berberidis Cortex* notably alleviates hyperglycemia, insulin resistance, hyperlipidemia, and inflammation in rats with T2DM. Its mechanism involves modulating various processes, such as restoring gut microbiota balance, enhancing intestinal barrier function through increased expression of tight junction proteins, mitigating inflammation by suppressing the lipopolysaccharide (LPS)/toll-like receptor 4 (TLR4)/myeloid differentiation primary response 88 (MyD88)/nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) pathway and reducing liver gluconeogenesis via the regulation of BAs/FXR/FGF15 and cAMP responsive element binding protein 1 (CREB1)/peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 α) signaling pathways [54].

Currently, the application of pharmacophenomics of TCM in glycolipid metabolism disorder is extensive, primarily used to unravel the therapeutic mechanisms of Chinese medicine compounds, pairs, single herbs, and monomers in improving glycolipid metabolism disorder. However, pharmacophenomics of TCM is still in its early stages of development, and relevant research still faces certain limitations. First, the chemical composition of Chinese medicine is complex, and a systematic approach to studying its pharmacologically active components and pharmacological mechanisms has yet to be established. Second, there are relatively few clinical studies on pharmacophenomics of TCM. Third, there is a lack of research combining TCM syndrome phenomics with the pharmacophenomics of TCM. To address the three major limitations of TCM pharmacophenomics in the study of glycolipid metabolism disorder, modern analytical technologies such as high-throughput screening and network pharmacology can be integrated to systematically elucidate the relationship between the complex chemical components of TCM and their pharmacological effects. Additionally, large-scale, multicenter clinical trials should be conducted, combining multi-omics technologies with TCM syndrome research to validate the therapeutic efficacy and mechanisms of action of TCM in different syndromes associated with glucose and lipid metabolism disorders.

5 Conclusion and prospects

As an emerging discipline, TCM phenomics bridges the realms of TCM, genomics, proteomics, metabolomics, epigenomics, and metagenomics. It forms a holistic framework to explore the intricate relationships among cross-scale phenotypes, thereby promoting the modernization of TCM theory [55]. TCM has demonstrated remarkable efficacy in the management of glycolipid metabolism disorder. However, there is an urgent imperative to conduct standardized research in TCM phenomics to clarify the scientific underpinnings of TCM syndrome differentiation and treatment, thereby fostering the development of precision medicine within TCM. Moving forward, the integration of TCM phenomics with pharmacology, bioinformatics, integrated large-scale TCM databases, artificial intelligence, and machine learning holds immense potential to reveal the molecular mechanisms underlying the formation of TCM syndromes in glycolipid metabolism disorder, as well as the mechanisms of action of TCM interventions across different scales. By leveraging phenotype-pharmacodynamics relationships, new drug targets can be identified, paving the way for enhanced clinical efficacy and new drug development. Such advancements will transform the traditional research paradigm of TCM, elevating the TCM research and accelerating the modernization of TCM's applications in the prevention and treatment of glycolipid metabolism disorder.

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Competing interests

The authors declare no conflict of interest.

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糖脂代谢紊乱的中医表型组学研究概况

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【摘要】 中医药在防治糖脂代谢紊乱等慢性病中展现出独特优势, 但受限于中医证候本质及疗效机制的不明确, 推广应用受阻。表型组学作为新兴交叉学科, 通过整合基因组、转录组、蛋白质组、代谢组及微生物组等多维度数据, 与中医学整体观结合, 形成中医表型组学, 为揭示中医证候生物学内涵及中医药作用机制提供了新路径。本文以糖脂代谢紊乱为例, 探讨中医表型组学在糖脂代谢紊乱中的应用。中医表型组学通过分析糖脂代谢紊乱相关证候的分子特征, 筛选差异表达基因、代谢物及肠道菌群标志物, 阐明证候动态演变规律; 同时解析中药复方的多靶点调控网络, 证实其通过调节胰岛素信号通路、改善肠道菌群失衡、抑制炎症反应等机制改善糖脂代谢。然而, 当前研究仍面临证候诊断主观性强、动物模型标准化不足、多组学联合分析缺乏等挑战。未来需结合机器学习、多模态数据整合及跨组学纵向研究, 构建证候量化诊断体系, 推动中西医精准诊疗融合, 加速中医药现代化进程。

【关键词】 中医药; 表型组学; 多组学; 糖脂代谢紊乱; 证候