Diabetes, Metabolic Syndrome and Obesity

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REVIEW

Application of Metabolomics and Traditional Chinese Medicine for Type 2 Diabetes Mellitus Treatment

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Abstract: Diabetes is a major global public health problem with high incidence and case fatality rates. Traditional Chinese medicine (TCM) is used to help manage Type 2 Diabetes Mellitus (T2DM) and has steadily gained international acceptance. Despite being generally accepted in daily practice, the TCM methods and hypotheses for understanding diseases lack applicability in the current scientific characterization systems. To date, there is no systematic evaluation system for TCM in preventing and treating T2DM. Metabonomics is a powerful tool to predict the level of metabolites in vivo, reveal the potential mechanism, and diagnose the physiological state of patients in time to guide the follow-up intervention of T2DM. Notably, metabolomics is also effective in promoting TCM modernization and advancement in personalized medicine. This review provides updated knowledge on applying metabolomics to TCM syndrome differentiation, diagnosis, biomarker discovery, and treatment of T2DM by TCM. Its application in diabetic complications is discussed. The combination of multi-omics and microbiome to fully elucidate the use of TCM to treat T2DM is further envisioned.

Keywords: metabolomics, traditional Chinese medicine, type 2 diabetes mellitus, diabetic complications, diagnosis

Introduction

Diabetes, a complex metabolic disorder, involves imbalances in blood sugar, insulin resistance, and dysfunction of islet β-cells. Over 90% of diabetes cases are type 2 diabetes (T2DM).[1,2] T2DM stems from disruptions in pancreatic hormone secretion, insulin action on target tissues, and defects in insulin signaling mechanisms, impacting carbohydrate and lipid metabolism.[3] This condition significantly impairs patients' quality of life, and its prevalence and treatment costs pose substantial social and economic burdens. Advanced T2DM can lead to severe complications and death, yet suitable prevention and treatment approaches remain elusive.[4]

In traditional Chinese medicine (TCM), diabetes is considered as Xiaoke, which means "consumptive thirst". It can be differentially diagnosed based on its various symptoms and patterns. One common type is the yin deficiency and fire pattern, which is characterized by polydipsia, polyuria, red cheeks, irritability, a red tongue with yellow fur, and a rapid pulse.[5] TCM has a long history of treating diabetes and its complications. The multiple component and target characteristics of TCM have unique advantages in the prevention and control of complex diseases such as diabetes.[6,7] However, due to the lack of scientific and modern evidence, TCM is also facing serious challenges in the diagnosis and treatment of diabetes. New technologies must be developed quickly to improve the detection of T2DM risk factors and the T2DM prevention, diagnosis, and prognosis of TCM, potentially impacting the early diagnosis and personalized care of patients with T2DM.

Received: 21 September 2023
Accepted: 21 November 2023
Published: 28 December 2023

Metabolomics can systematically evaluate the changes of metabolites in the body and screen metabolic biomarkers, thereby enhancing the effectiveness of disease diagnosis and treatment.[8] Its approach and properties are similar to TCM's holistic concept, which offers opportunities and challenges for TCM modernization.[9–11] Metabolomics can benefit from the systematic analyses of metabolites and the discovery of various biomarkers and interfering pathways in TCM syndromes or after TCM treatment to clarify the mechanism of TCM and the significance of evidence-based TCM.[12] Metabolomics has the potential as a holistic approach for clinical diagnosis and care and as a way to better elucidate the pathological mechanism of T2DM.

In this context, our discussion revolves around the application of metabolomics to elucidate TCM's principles in T2DM syndrome differentiation, diagnosis, and anti-diabetic mechanisms. We explore its potential in treating diabetic complications and propose the integration of multi-omics and microbiomes to comprehensively understand the mechanisms underlying TCM's preventive and therapeutic approaches for T2DM. This not only provides a theoretical basis but also introduces a novel perspective for the modernization of TCM.

Metabolomics in TCM Syndrome Differentiation of T2DM

In TCM, diabetes, known as xiaokezheng, is characterized by symptomatic polydipsia with an extensive treatment history.[13] TCM emphasizes syndrome differentiation as the foundation for treating diseases, including diabetes.[14] According to TCM theory, diseases result from imbalances in Yin, Yang, Qi, blood, organs, and meridians,[15] with diabetes pathogenesis involving Yin deficiency and excessive heat syndrome in the early phase, deficiency of Qi and Yin syndrome in the middle stage, and deficiency of Yin and Yang syndrome in the later phase.[16] Inconsistent T2DM diagnoses among TCM physicians highlight the need for objective indicators to enhance syndrome accuracy.[17,18]

TCM syndromes and metabolic characteristics are interconnected, providing mutual validation and aiding modern biology in confirming TCM syndromes for diabetes diagnosis and treatment. Metabolomics, a systematic study of metabolites after environmental stimulation, allows a holistic investigation of changes in human metabolism concerning diseases.[19] This holistic view aligns with TCM concepts and scientifically conveys the sense of TCM syndromes.[20] Analysis of endogenous plasma metabolites in patients with Kidney-Yin Deficiency Syndrome (KYDS) and diabetes revealed specific changes, supporting the syndrome differentiation principle in TCM.[21]

While metabonomics alone has limitations in clarifying the biological essence of syndromes, future research should target upstream functional proteins and genes based on metabolic markers. This approach promises a more in-depth and specific analysis of syndromes, leading to more accurate treatments due to the complexity of syndromes.

Application of Metabolomics in the Diagnosis of T2DM

Pre-diabetes is an intermediate stage between normal glucose tolerance (NGT) and T2DM,[22] which is often difficult to diagnose accurately. T2DM increases the risk of cardiovascular disease (CVD) and microvascular complications by 2- to 4-fold, which may have existed before diagnosis.[23] Since early intervention may be the most effective way to delay the progress of T2DM, it is crucial to develop sensitive biomarkers for early diagnosis of various pathologies related to T2DM. Metabolomics is a powerful method to find biomarkers. It can acquire a new view of disease pathophysiology and identify individual metabolites or their profiles as potential biomarkers to distinguish normal and pathological states.[24] Accurate biomarkers are necessary for better diagnosis and prognosis, guiding molecular targeted therapy and exploring treatment response and results.[25] One of the significant breakthroughs in enhancing the diagnosis of risk factors for T2DM was the discovery and validation of biomarkers. The identified potential biomarkers in metabolomics-based T2DM in the last five years have been summarized in Table 1. These findings help elucidate the pathogenic mechanisms underlying T2DM and may aid in diagnosing and treating T2DM patients.

Metabolomic Profiles for the Prediction of T2DM

In the early stages, numerous studies have indicated elevated levels of branched-chain amino acids (BCAAs), their derivatives, aromatic amino acids, and α-hydroxybutyrate in plasma before T2DM, while glycine and glutamine show negative associations.[49–51] Additionally, noticeable changes in serum concentrations of glycerophospholipids and sugar metabolites, including deoxyhexose sugars and sugar alcohols, occurred six years before the onset of T2DM.[52] Notably,

Table 1 Biomarker Discovery in T2DM

Prediction	Detective Method	Metabolic biomarkers	Ref.
Pre-diabetes	LC-MS	Valine, isoleucine, tryptophan, lysine, arginine, proline	[26]
Pre-diabetes	LC-MS	Hexose, 2-hydroxybutyric/2-hydroxyisobutyric acid, and phenylalanine	[27]
Pre-diabetes	1D 1H NMR, FIA-MS, LC-MS	BCAAs, trimethyl uric acid, trimethylamine N-oxide, lysophosphatidylcholines, β-hydroxybutyrate, phosphatidylcholines, Alanine, acylcarnitine, sphingomyelins, amino acids; Glutamine and SM.C16.1, Lyso.PC.a.C18.0, PC.ae.C34.2, C3. DC. C4.OH,	[28]
Pre-diabetes	GC–MS	Tyrosine, lysine, alanine, valine, proline, phenylalanine, tryptophan, hexadecanoic acid, alpha-ketoglutaric acid, myristic acid, octadecanoic acid, uric acid	[29]
Pre-diabetes and T2DM	LC-MS	Ceramides, saturated sphingomyelins, unsaturated sphingomyelins, hydroxyl-sphingomyelins, and a hexosylceramide	[30]
Pre-diabetes	LC-MS	N2, N2-dimethylguanosine, 7-methylguanine and 3-hydroxytrimethyllysine	[31]
Pre-diabetes	LC-MS	A cluster of saturated sphingomyelins	[32]
Pre-diabetes	1H-NMR	Lipids in HDL subtypes, citrate, glycoprotein acetyls, branched-chain amino acids, VLDL lipids	[33]
Pre-diabetes	LC-MS	Alanine, aspartate, glutamate, isoleucine, leucine, phenylalanine, tyrosine, tryptophan, and valine	[34]
Pre-diabetes	GC-MS and LC-MS	1,5-anhydroglucitol	[35]
Pre-diabetes	HPLC-MRM	TAGs, lyso-phosphatidylinositols, phosphatidylcholines, PUFA-PEps, cholesteryl esters	[36]
Pre-diabetes	CIL-LC-MS	Methionine (Met) sulfoxide, amino acids (Asn, Gln, and His), 2-methyl-3-hydroxy-5-formylpyridine-4-carboxylate, L-2-amino-3-oxobutanoic acid, serotonin, and 4,6-dihydroxyquinoline.	[37]
Pre-diabetes	GC-MS and LC-MS	Lysophosphatidylcholines (muscle), glycodeoxycholic acid (liver)	[38]
Pre-diabetes and diabetes	GC-MS	Maltose, glucose, trehalose, an unknown sugar compound (U15), mannose, fructose, sedoheptulose, and 1,5 anhydroglucitol,	[39]
T2DM	CIL-LC-MS	Amino acids, amino acids metabolites, and dipeptides.	[37]
T2DM	GC-MS and LC-MS	Carnitines (liver), lysophosphatidylcholines (muscle and serum)	[38]
T2DM	LC-MS	Alanine, 3-methyl histidine, glutamic acid, arginine, tryptophan, and ethanolamine sarcosine	[40]
T2DM	1H-NMR and 2D-NMR	61 distinct metabolites	[41]
Pre-diabetes and diabetes	LC-MS	Oxidized glycerophosphatidylcholines	[42]
Obese insulin sensitive (OIS)	LC-MS	Phospholipid metabolites, including choline, glycerophosphoethanolamine, and glycerophosphorylcholine	[43]
T2DM	GC-MS	Tyrosine, alanine, valine, tryptophan, and alpha-ketoglutaric acid	[29]
T2DM	LC-MS	Organophosphate flame retardant (OPFR) diesters	[44]
T2DM	LC-MS	Dimethylguanidino valerate, acisoga, acylcarnitine C10:3, homocitrulline, N2, 1-methyladenosine, N2-dimethylguanosine, hippurate, urobilin, threonine, lysine and tryptophan	[45]
T2DM	LC-MS	Urine 3-hydroxyundecanoyl-carnitine	[46]
Pre-diabetes and T2DM	NMR	Branched-chain, aromatic amino acids, linoleic n-6 fatty acid, triacylglycerol within VLDL particles, and non-esterified cholesterol in large HDL particles	[47]
T2DM	GC-MS	Lysophosphatidylcholine, deoxycholic- and glycodeoxycholic acid, all BCAAs, and their catabolic intermediates	[48]
Pre-diabetes	GC-MS	Lysophosphatidylcholine, ursodeoxycholic- and chenodeoxycholic acid, leucine and its catabolic intermediates (ketoleucine and C5-carnitine)	[48]

glyoxylate levels in human serum significantly increased up to three years before a T2DM diagnosis, suggesting its potential role in guiding novel antidiabetic therapies.[53]

Recent advancements in metabolomics have significantly contributed to pre-diabetes biomarker recognition.[26,27,29–34,38] Li et al utilized non-targeted and targeted metabolomics to identify novel plasma biomarkers in lean β-Phb2-/- mice and obese db/db mice. The study highlighted 1,5-anhydroglucitol's association with the loss of functional β-cell mass, revealing metabolic similarities between the liver and plasma.[35]

Lipidomics, a vital branch of metabolomics, demonstrated its significance in assessing lipid co-regulation changes before T2DM treatment. Lu et al employed a high-coverage targeted HPLC-MRM lipidomics method, revealing 38 lipids significantly related to T2DM, outperforming traditional clinical indices in predicting incident T2DM.[36]

Obesity, a key factor in metabolic diseases, including T2DM, is often associated with insulin resistance (IR). IR occurs several years before the clinical symptoms of T2DM, but due to hyperglycemia, IR prediction, diagnosis, and treatment have been delayed.[54] Gu et al identified IR candidate biomarkers in serum, including methionine sulfoxide,

L-2-amino-3-oxobutanoic acid, amino acids (Asn, Gln, and His), serotonin, and 2-methyl-3-hydroxy-5-formylpyridine-4-carboxylate, emphasizing the importance of early detection and intervention.[37]

Yun et al utilized high-coverage targeted lipidomics to identify sphingolipids associated with incident T2DM, providing insights into potential biochemical processes during pre-diabetes progression.[30] These metabolomics findings offer guidance for early intervention strategies to delay T2DM onset.

Metabolomic Profiles for the Diagnosis of T2DM

Commonly used screening methods for T2DM, such as fasting plasma glucose (FPG) or glycated hemoglobin (HbA1c) analysis, often miss many affected individuals.[27] Developing specific T2DM biomarkers is critical. High-throughput metabolomics studies systematically reviewed and meta-analyzed the relationship between metabolites and T2DM. Some metabolites, including alanine, leucine, glutamate, and others, were found to increase the risk of T2DM, while others like glutamine, serine, and lysophosphatidylcholine C18:2 were associated with reduced risk.[55]

Recent investigations have extensively studied diagnostic biomarkers associated with T2DM.[41–45] Gu et al identified significant associations between 42 metabolites, including dipeptides and amino acids, in T2DM.[37] Diamanti et al found higher carnitine levels in the liver of T2DM patients and lower lysophosphatidylcholines in muscle and serum.[38] Mack et al discovered potential biomarkers, such as trehalose and various sugars, using semi-targeted GC-MS.[39] A targeted metabolomics approach in functionally impaired older persons revealed specific amino acid and derivative profiles in those with T2DM.[40]

Furthermore, Zeng et al linked lysophosphatidylcholine, bile acids, and branched-chain amino acids (BCAAs) to T2DM in black South African women.[48] Large-scale studies on urinary metabolomics identified 3-hydroxyundecanoyl-carnitine as a potential biomarker.[46] Another analysis of four Finnish cohorts revealed potent T2DM risk biomarkers, including branched and aromatic amino acids and specific lipids.[47]

In summary, these studies highlight the association between metabolic alterations and T2DM. The metabolomics platform emerges as a powerful tool for T2DM screening.

Metabonomics Reveals the Efficacy and Mechanism of TCM in Treating T2DM

T2DM is a global health challenge commonly managed with oral hypoglycemic drugs and insulin injections.[56] Chinese medicine, with its unique theories and extensive clinical applications, is gaining popularity globally.[57] Metabolomic studies play a crucial role in understanding disease mechanisms, diagnostic markers, and the action of TCM, offering valuable insights for TCM research.[58–60] Table 2 summarizes several groups' experimental designs and metabolomics results.

TCM, either alone or in combination, induces changes in a broad spectrum of metabolites. Huanglian Decoction (HLD), a traditional TCM formulation used for centuries, was investigated for its therapeutic effects on T2DM in rats. Urinary metabolomics revealed biomarkers associated with glyoxylate and phenylalanine metabolism, dicarboxylate metabolism, and the tricarboxylic acid (TCA) cycle, providing dynamic insights into HLD's therapeutic impact.[63] Another TCM preparation, Hypoglycemic decoction (HD), exhibited significant therapeutic effects on T2DM. Metabolomics analysis identified potential biomarkers linked to phenylalanine metabolism, TCA cycle, glyoxylate metabolism, and dicarboxylate metabolism.[71]

Dendrobium officinale polysaccharide (DOP), a key ingredient in D. officinale with metabolism-modulatory activities in T2DM, was studied for its impact on liver lipidomics and metabolomics. The results indicated that DOP can modulate glycerolipid, fatty acid, glycerophospholipid, ceramide, and bile acid metabolism, presenting a potential avenue for managing T2DM.[74] Litchi chinensis Sonn. seed extract (LSE), commonly used in TCM to mitigate diabetic risk factors, demonstrated its hypoglycemic mechanism through broad-spectrum metabolic changes in T2DM rats.[75]

Different TCMs chosen in the same stage of T2DM disease caused a similar metabolic response. Whether these pathways or metabolites constitute a shared mechanism for various therapies is unknown. Understanding this may help us investigate new T2DM therapeutics or develop new drugs. These studies indicated that metabolomics, one of the most critical systems biology platforms, can identify and characterize the organism's biochemical responses to TCM. This approach provided a practical method for future interventions and TCM assessments.

Table 2 Treatments for T2DM Evaluated by Metabolomics Approaches

TCM	Sample Sources	Biological Samples	Detection Method	Metabolic Biomarkers	Metabolic Pathways	Ref.
Cicer arietinium L.	T2DM rats	Urine	LC-MS	Acylcarnitines, amino acid-related metabolites, and organic acids	Dicarboxylate and glyoxylate metabolism, vitamin B6 metabolism, tricarboxylic acid cycle, and energy metabolism	[61]
Naoxintong Capsule (NXT)	T2DM rats	Serum	LC-MS	L-carnitine, tyrosine, Tryptophan, Indoleacrylic acid, 11-Dehydrothromboxane B2, 3-Hydroxysebacic acid, etc.	Tyrosine, Phenylalanine, and tryptophan biosynthesis, glycerophospholipid metabolism, arachidonic acid metabolism, tyrosine metabolism, tryptophan metabolism, sphingolipid metabolism, and primary bile acid biosynthesis	[62]
Huanglian Decoction (HLD)	T2DM rats	Urine	LC-MS	Cytosine, L-carnitine, betaine, phenylalanine, glucose, citrate, phenylpyruvate, and hippuric acid	Glyoxylate and dicarboxylate metabolism, phenylalanine metabolism, and tricarboxylic acid (TCA) cycle	[63]
Astragalus Radix (HQ) and Dioscoreae Rhizoma (SY)	T2DM rats	Serum	1H-NMR	Monoamine oxidases B, acetyl-CoA carboxylase 1, carbonic anhydrase 2, and catalase	Aminoacyl-tRNA biosynthesis, Valine, leucine, and isoleucine biosynthesis, Nitrogen metabolism, etc.	[64]
Melastoma dodecandrum Lour. (Melastomataceae)	T2DM rats	Serum	LC-MS	Cholic acid, taurine, nicotinuric acid, hippuric acid, phosphohydroxypyruvic acid, tyrosine, arachidonic acid, PGE2, phenylalanine, glucuronide, carnitine, phosphatidylethanolamine, phosphatidylcholine, and phosphatidylinositol	Lipid, amino acid, arachidonic acid, taurine, and nicotinic acid metabolism	[65]
Gardenia jasminoides fruits	T2DM rats	Urine	LC-MS	Kynurenic acid, 3-Oxo-4,6-choladienoic acid, Xanthurenic acid, Creatinine, Phenylacetylglycine, etc.	Bile acid biosynthesis, amino acid metabolism, vitamin B metabolism, taurine metabolism, etc.	[66]
Ginseng berry	T2DM rats	Serum	LC-MS	Shikimic acid, 5' -Methylthioadenosine, 2-Isopropyl-3-oxosuccinate, Liothyronine, Glycocholic Acid, etc.	Bile acid metabolism, arachidonic acid metabolism, glucuronization	[67]
Lycii Cortex (LyC)	(db/db) mouse db/db mice	Serum	LC-MS	Circulating triglycerides, cholesterol, phosphatidylethanolamine, phosphatidylcholines, acylcarnitines	Regulating nuclear transcription factors	[68]
Mulberry (Morus multicaulis) branch bark powder	T2DM mice	Serum	GC-MS	Sugars, fatty, sugar alcohols, amino acids, and organic.	Lipid metabolism, carbohydrate metabolism, energy metabolism, protein metabolism, oxidative stress	[69]
BuZangTongLuo Formula (BZTLF)	T2DM mice	Serum	LC-MS	Geranylfarnesyl diphosphate (GFPP), enterobactin, lasaloid, deferoxamine, vanillic acid, 11-Hydroxyeicosatetraenoate glyceryl ester, cucurbitacin C, and angiotensin IV, koenigicine, 18-Carboxydinor-LTE4 and Ursodeoxycholic acid 3-sulfate	Glutathione metabolism, phosphatidylcholine biosynthesis, and tryptophan metabolism	[70]
The hypoglycemic decoction (HD)	T2DM rats	Urine	LC-MS	L-carnitine, 1-methyladenosine, 1-methylhistamine, 3-indoleacrylic acid, riboflavin, phenylalanine, atrolactic acid, 2-oxoglutarate, citrate, isocitrate, cortisol, and glucose	Glyoxylate metabolism, Tricarboxylic acid cycle, phenylalanine metabolism, and dicarboxylate metabolism	[71]
Huang-Lian-Jie-Du Decoction (HLJDD)	db/db mice	Plasma	LC-MS	D-Galactose, Vigabatrin, D-Glucose, Indoxyl sulfate, LysoPC, Eicosapentaenoic acid, Retinyl acetate, 2-oleoylglycerol, Docosapentaenoic acid	Fatty acid β-oxidation, glycerophospholipid metabolism, glucose metabolism, linoleic acid metabolism, and glutathione metabolism	[72]
Xiaokeyinshui extract combination (XEC)	T2DM mice	Plasma	LC-MS	Carbohydrates, lipids, and amino acids	Fructose and mannose metabolism, galactose metabolism, arachidonic acid metabolism, TCA cycle, glycerolipid metabolism, sphingolipid metabolism, glycerophospholipid metabolism, and amino acid metabolism	[73]
Dendrobium officinale stem (DOP)	T2DM rats	Liver	LC-MS	Cholic acid, deoxycholic acid, glycerophospholipids, lysophosphatidylcholine (LPC), and phosphatidylethanolamines	Fatty acid, glycerolipid, glycerophospholipid, ceramide, and bile acids metabolism	[74]
Litchi chinensis Sonn (LSE)	T2DM rats	Serum and urine	LC-MS GC-MS	Carbohydrate, organic acids, amino acids, etc.	Serine, glycine, arginine, threonine, proline, alanine metabolism, etc.	[75]

https://doi.org/10.2147/DMSO.S441399 DovePress

Metabolomics Studies of TCM Treating Diabetic Complications

Long-term insulin deficiency leads to macrovascular and microvascular complications and even death in patients with diabetes. Microvascular complications in patients with T2DM causing renal failure, blindness, and non-traumatic amputations, are effective predictors of cardiovascular complications.[76] There is no available treatment when the disease is diagnosed, but early treatment at a subclinical level can prevent or at least delay disease progression. Thus, it is vital to identify early biomarkers to inhibit the disease. Metabolomics has been used to classify the metabolic characteristics of T2DM in many different biological systems. Current challenges include linking these biomarkers to specific complications to better predict future risks and disease progression.[77]

Diabetic complications are usually treated with western medicine or surgery.[78–81] However, effective prevention and treatment methods are lacking. Effective medications with fewer side effects need to be discovered. The efficacy and mechanism of TCM on T2DM and diabetic complications have been gradually recognized and clarified. However, the composition of TCM is complex, and it is challenging to elucidate the treatment mechanism. Strategies and methods appropriate for complex system analysis are required to further explain TCM's mechanism of action and investigate pharmacodynamics' basis. Considering its advantages, metabonomics has become the research focus to reveal the mechanism of action of TCM.

Diabetic Retinopathy

Diabetic retinopathy (DR), a leading cause of adult blindness globally, stems from alterations in retinal microvasculature.[82] Proliferative diabetic retinopathy (PDR), characterized by retinal neovascularization (NV), is a common cause of vision loss in diabetic patients. Metabolomics-based studies on DR biomarkers have gained interest (Table 3).

Tomita et al investigated DR metabolites in vitreous samples from patients with PDR, identifying 158 potential biomarkers associated with the anti-DR effect, including pyruvate, lactate, proline, allantoin, and creatine. Creatine supplementation may inhibit NV in PDR, suggesting its potential therapeutic benefit.[83] Another study by Xuan et al conducted serum metabolic profiling in diabetic patients without DR (NDR) and with different stages of DR. Biomarkers, such as 12-hydroxyeicosatetraenoic acid (12-HETE) and 2-piperidone, outperformed hemoglobin A1c (HbA1c) in differentiating DR from diabetes and detecting early-stage DR.[86]

While most research focuses on discovering early biomarkers for inhibiting DR progression, there's a gap in understanding the metabolomic mechanisms of traditional Chinese medicine (TCM) effects. Bushen Huoxue Prescription (BP), comprising Salviae Miltiorrhizae Radix et Rhizoma, Rehmanniae Radix, Puerariae Lobatae Radix, and Ginseng Radix et Rhizoma, has shown promise in DR prevention and treatment. Using urine metabolomics, BP's

Table 3 Biomarker Discovery in Diabetic Retinopathy

Prediction	Detective Method	Metabolic Biomarkers	Ref.
Proliferative diabetic retinopathy (PDR)	LC-MS	Pyruvate, lactate, proline, allantoin, creatine	[83]
DR	LC-MS	Total DMA, tryptophan, and kynurenine	[84]
PDR	LC-MS	Inosine, hypoxanthine, urate, allantoate	[85]
DR	GC-MSM, LC-MSM, and LC-MSL	2-piperidone and 12-hydroxyeicosatetraenoic acid (12-HETE)	[86]
PDR	LC-MS	Fumaric acid, uridine, acetic acid, and cytidine	[87]
DR	LC-MS	Arginine, citrulline, glutamic γ-semialdehyde, and dehydroxycarnitine	[88]
PDR	LC-MS	Arginine and Carnitine	[88]
DR	1 H-NMR	Lactate, succinate, 2-hydroxybutyrate, asparagine, dimethylamine, histidine, threonine, and glutamine	[89]
DR	GC-MS	Threonic acid, d-2,3-Dihydroxypropanoic acid, l-Lactic acid, isocitric acid, fructose 6-phosphate, l-threonine, ornithine, l-glutamine, pyroglutamic acid, pyruvic acid, and l-alanine	[90]
DR	GC-MS, LC-MS	Plasma glutamine, glutamic acid, and their ratio	[91]
DR	LC-MS	FAS, LPCs, LPC-Os, LPEs, LPE-ps, Cers, CerG1s, etc	[92]

anti-DR effect was linked to nine small-molecule metabolites, indicating its potential to regulate gut microbial metabolism, lipid metabolism, and tryptophan metabolism in treating DR.[93] These findings underscore the need for more research to elucidate the molecular effects of TCM on DR's physiological changes.

Diabetic Nephropathy

Diabetic nephropathy (DN), characterized by decreased glomerular filtration rate and increased urinary albumin excretion, poses a significant risk,[94] affecting about 30% of diabetic patients and potentially progressing to end-stage kidney disease. The associated cardiovascular death risk is notably higher than in individuals with normal renal function.[95] Table 4 summarizes the metabolomics of DN patients.

Existing literature and recent studies have identified potential metabolites for monitoring DN.[102] Representative studies include Zhang et al, who used gas chromatography coupled with time-of-flight mass spectrometry to identify serum and urine metabolites distinguishing DN from T2DM.[96] Tofte et al utilized nuclear magnetic resonance spectroscopy, linking 125 metabolites strongly to estimated glomerular filtration rate, revealing associations with glycoprotein acetyls, amino acids, triglycerides, lipids, and fatty acids.[99]

Metabolomics has also been applied to TCM research in addressing diabetic nephropathy issues.[103–105] Notably, Salvia miltiorrhiza Bunge (SM) has shown therapeutic effects on various T2DM complications, including diabetic nephropathy. Xiang et al investigated the metabolic changes induced by SM in plasma, urine, and renal tissues of DN rats. SM extracts alleviated renal injury and regulated glycolipid metabolism, triggering significant metabolic alterations in serum, urine, and kidney tissues. This metabolic network, including phospholipid, arachidonic acid, and pyrimidine metabolisms, supports the protective effects of SM in DN rats.[106–109]

While initial studies demonstrate the potential of metabolomics in understanding DN's metabolic patterns, development, and differentiation, further research is necessary for a more accurate analysis.

Diabetic Peripheral Neuropathy

Diabetic peripheral neuropathy (DPN), a common complication of pre-diabetes and T2DM, significantly contributes to lower-limb amputation and neuropathic pain.[110] Recent metabolomic studies on DPN patients have highlighted abnormal concentrations of glucosamine,[111] 1-deoxydihydroceramides,[112] and sphingosine[113] in sciatic nerves. A meta-analysis emphasized the correlation between histidine, pyruvate, alanine, tyrosine, leucine, and valine levels in cerebrospinal fluid and plasma with the presence of DPN, shedding light on potential metabolic disorders[114] (Table 5).

TCM, with its rich bioactive compounds and holistic approach, presents a promising avenue for addressing DPN. Jin-Mai-Tong (JMT) decoction, consisting of 12 diverse components, has been studied for its neuroprotective effect on diabetic

Table 4 Biomarker Discovery in Diabetic Nephropathy

Prediction	Detective Method	Metabolic Biomarkers	Ref.
DN	GC-MS	Serum: benzoic acid, glycerol 1-octadecanoate, fumaric acid, erythrose, L-glutamic acid/pyroglutamic acid, fructose 6-phophate, L-Arabitol, taurine, and L-glutamine. Urine: D-glucose, gluconic acid, L-histidine, L-valine, sucrose, glycine, L-xylonate-2, L-asparagine/L-aspartic acid, and oxalic acid.	[96]
DN	LC-MS	Tyrosine	[97]
DN	LC-MS	Linolelaidic Acid (C18:2N6T), 6-Aminocaproic Acid, Hexadecanoic Acid (C16:0), Trans-4-Hydroxy-L-Proline, L-Dihydroorotic Acid, Azoxystrobin Acid, Linoleic Acid (C18:2N6C), 6-Methylmercaptopurine, Lysopc 20:4, Piperidine, and Cuminaldehyde	[98]
DN	NMR	Glycoprotein acetyls, branched-chain and aromatic amino acids (AAAs), triglycerides (TGs), lipids in very low-density lipoproteins (VLDL), cholesterol, fatty acids, and phospholipids in high-density lipoproteins (HDL) and apolipoprotein A1.	[99]
DN	LC-MS	3-methylcrotonyglycine, 3-hydroxyisobutyrate (3-HIBA), citric and aconitic acid	[100]
DN	LC-MS	Pantothenic acid	[101]

Table 5 Biomarker Discovery in Peripheral Neuropathy

Prediction	Detective Method	Metabolic Biomarkers	Ref.
DPN	LC-MS	Glucosamine	[111]
DPN	LC-MS	1-deoxydihydroceramides	[112]
DPN	LC-MS	Sphingosine	[113]
DPN	HNMR	Alanine, histidine, leucine, pyruvate, tyrosine, and valine	[114]

peripheral neuropathy rats.[115,116] Metabolomics revealed 21 potential biomarkers associated with JMT's therapeutic effect, primarily involving the tricarboxylic acid (TCA) cycle, lipid metabolism, and amino acid metabolism. This suggests that JMT decoction improves the metabolism of diabetic rats with peripheral neuropathy, countering DPN.[117]

Despite increasing attention to diabetic complications, the underlying mechanisms remain unclear. Prospective human sample studies and investigations into diabetic complications within metabonomics research are still limited. Identifying potential biomarkers for T2DM and its complications holds promise for prediction and prevention. While TCM's efficacy in treating microvascular complications has been explored, the metabolic response to these complications is seldom reported in metabolomic studies. Utilizing metabolomics to delve into TCM mechanisms in humans, although in its early stages, has the potential to inform clinical practice and drug discovery. Future research should extend beyond isolated pharmacodynamic studies, establishing robust connections between symptom improvement and metabolome restoration.

Prospects: Potential of Multi-Omics and Microbiome Integration in TCM Treating T2DM

While metabonomics provides insights into metabolites and pathways, its capacity to fully unravel the therapeutic mechanism of TCM for T2DM is limited. To address this, integrating omics and systems biology techniques with traditional methods is imperative (Figure 1).

Omics technologies—genomics, proteomics, transcriptomics, and metabolomics—serve as invaluable tools for studying biological systems, especially in the TCM context.[118,119] A comprehensive understanding necessitates merging data from diverse omics approaches. Metabolomics complements other omics data, forming a foundational understanding via gene-transcript-protein-metabolite profiles in human tissues,[120–123] elucidating the mechanism of TCM treatment for T2DM and identifying therapeutic targets.

Key biomarkers in TCM treatment for T2DM, such as acetate, organic acids, pyruvate, and others, reflect endogenous metabolites influenced by both the host and commensal microorganisms.[124–127] TCM induces significant shifts in gut microbiota,[128] particularly in the gastrointestinal microflora, influencing T2DM etiology and pathology.[129–132]

Host genomics, pivotal in microbiome composition determination,[133] can be effectively studied through metagenomics, which collectively examines microbial genomes. Integrated with host transcriptome analysis, this approach reveals molecular mechanisms and the impact of microbial variation on gene expression. Proteomics, complementing metagenomics, offers a detailed analysis of microbiome structure and function, illustrating its relationship with the human body.[134] The functional influence of the microbiome on metabolic pathways explains its significant association with disease.

In summary, understanding the intricate interactions between the host's multi-omics and microbiome provides novel insights into TCM's efficacy in treating T2DM.[135,136] The absence of a systematic approach to integrate TCM, microbiome, and in-depth multi-omics in T2DM patients unveils opportunities for studying human wellness and disease. The integration of multi-omics and microbiomes holds promise in developing individualized medicine for T2DM, representing a crucial research direction for the future of TCM in T2DM treatment.

Conclusion

Early management of T2DM is pivotal for averting complications and mortality. Despite advancements in prevention and therapy, persistent diabetic complications underscore the need for novel therapeutic targets. Metabonomics, employing a top-down strategy, systematically delineates body function and detects holistic metabolic changes. By quantifying

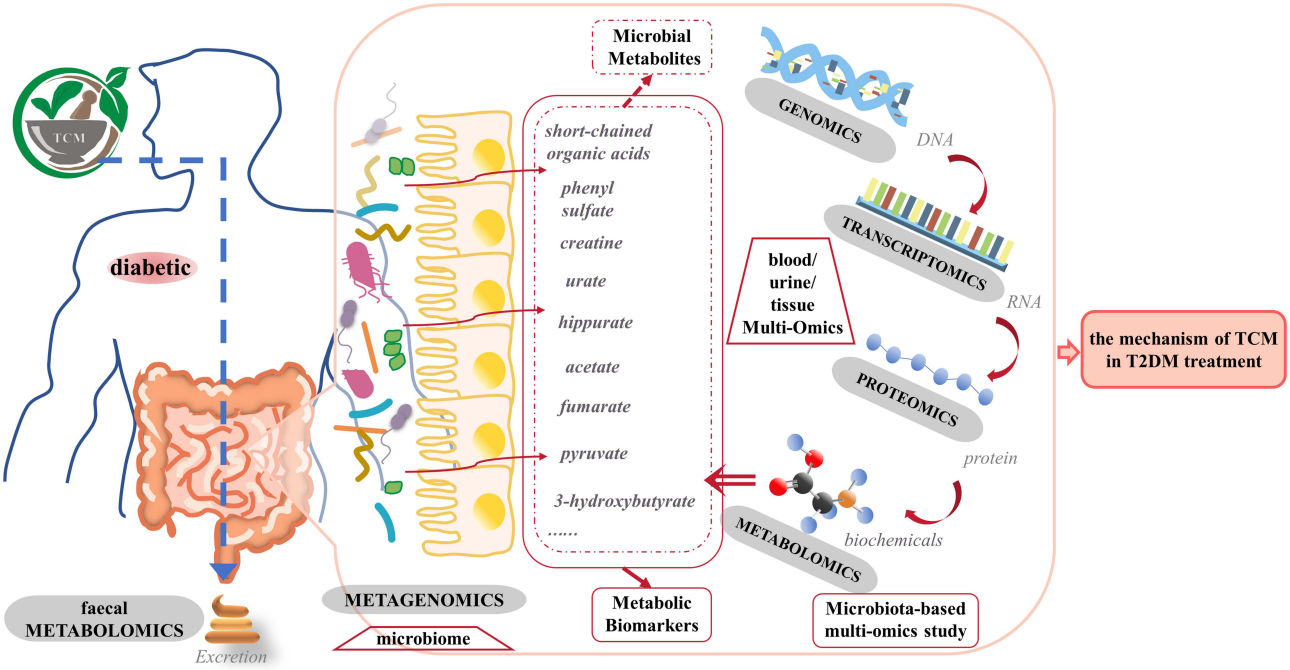

Figure 1 Application of Multi-Omics and microbiome Integration in TCM Treating T2DM. The human microbiome plays a role in the etiology and pathology of T2DM and its complications. Metabolites originating from microorganisms are potentially important compounds that mediate microbiota-host interactions in health and disease. External factors such as TCM and internal factors such as the host genome can influence microbial diversity. Changes in the microbiome later affect the metabolites that they produce. Metagenomics is suitable for determining intestinal microbiota composition, while metabolomics can find functional endpoints. Genomics obtained candidate genes related to transcriptomics, while transcriptomics obtained functional gene clusters related to disease pathogenesis. Proteomics can analyze expressed proteins and protein function in a cellular context. It will be vital to reveal the role of the microbiome in T2DM and the mechanism of traditional Chinese medicine in T2DM treatment by integrating metagenomic data and data generated by host omics in the future.

circulating metabolites across pathways, this approach facilitates early identification of high-risk individuals. Metabolomics provides profound insights into T2DM pathogenesis, treatment, and the mechanisms of TCM. As metabolomics advances, TCM modernization progresses, revealing biomarkers for diverse T2DM types and stages. Strengthening TCM modernization studies is imperative. The metabonomics strategy emerges as a potent tool for exploring TCM's therapeutic basis, promising significant strides in advancing T2DM diagnosis, prevention, and treatment, thereby offering vital guidance for clinical practice.

Funding

This review was funded by the Science and Technology Research Project of the Education Department of Jilin Province (Under grant No. JJKH20210989KJ) and the Traditional Chinese Medicine Research Project in Qingdao (Under grant No. 2019-zyy033).

Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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