Review

Applications of metabonomics in traditional Chinese medicine

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Abstract

Metabonomics, a key aspect of systems biology, offers novel approaches for early diagnosis, pharmacotherapy, and health management in Traditional Chinese Medicine (TCM). This paper summarizes its applications in establishing TCM quality standards, exploring material basis, clarifying mechanism, and assessing toxicity. By profiling TCM and its metabolites, metabonomics comprehensively captures chemical traits, enhancing quality evaluation precision. It also tracks metabolic dynamics to understand TCM's absorption, distribution, metabolism, excretion, thereby facilitating the identification of active components and their underlying mechanisms. In toxicity assessment, metabonomics uncovers hepatic and renal toxicity while elucidating potential mechanisms. In summary, metabonomics fosters TCM modernization and globalization, serving as a pivotal tool for advancing research and development.

Keywords: metabonomics; traditional Chinese medicine; quality control; pharmacodynamic mechanism; toxicity evaluation

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1 Introduction

With the rapid development of modern scientific and technological research, biomedical research methods are constantly updated and reformed. Metabonomics, as an important part of systems biology, is characterized by the holistic, diverse, dynamic, and complex nature, and has garnered widespread attention since its inception. In recent years, the integrated application of metabonomics, genomics, transcriptomics and protein genomics has provided a more comprehensive perspective for systems biology. For example, by combining metabonomics and transcriptomics data, researchers can analyze the dynamic changes of metabolic pathways from the level of gene expression regulation, so as to identify the target of action of traditional Chinese medicine compound more accurately. This multi-omics integration strategy not only strengthens the explanatory power of metabonomics, but also makes up for the limitations of single omics technology in the study of complex biological systems, which provides methodological support for the holistic TCM study. Through comprehensive and systematic analysis of small molecular metabolites within organisms, metabonomics technology offers innovative ideas and methodologies for early disease

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diagnosis, drug treatment, and health maintenance. In recent years, it has also demonstrated significant potential in the realm of TCM research [1].

As an artistic treasure of the Chinese nation, TCM has a broad application prospect in clinical practice with its unique curative effect and minor side effects, and has been paid more and more attention both home and abroad in recent years. TCM usually contains a variety of chemical components, which interact with each other in organisms and play a therapeutic role together. Traditional research methods are often difficult to comprehensively analyze the efficacy mechanism and toxicity mechanism of TCM [2]. In addition, the sources of TCM are extensive, and the growth environment is not the same, resulting in its complex and changeable components, and making difficult the quality control of TCM [3]. This review systematically summarized the application status and research progress of metabonomics technology in TCM quality standards establishment, the study of material basis and mechanism of action, and toxicity evaluation (Fig. 1). It is expected that this review will provide more convenient ideas for the related research of Chinese pharmacy and promote the modernization and internationalization of the future development of Chinese pharmacy [4].

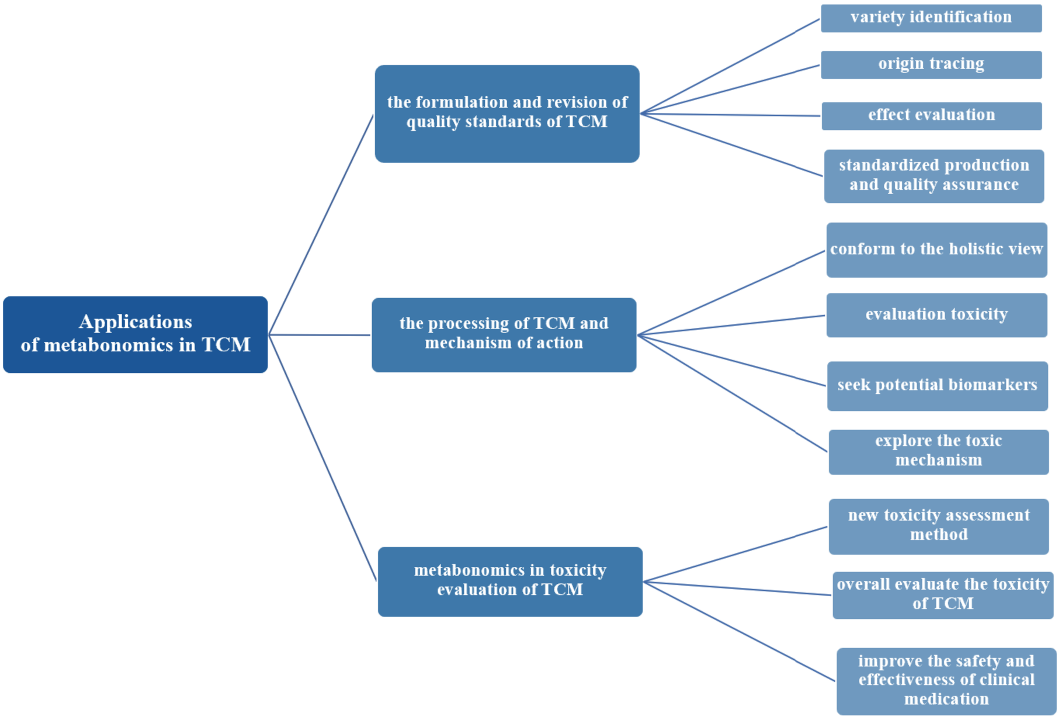

Fig. 1 Application of metabonomics in traditional Chinese medicine

2 Application status

2.1 Application of metabonomics in the formulation and revision of quality standards of TCM

With the rapid development of Chinese medicine, the formulation and revision of quality standards for Chinese herbal medicines has become the key to the sustainable and high-quality development of Chinese medicine industry [5]. Metabonomics has important application value and prospect in TCM quality evaluation. By comprehensively analyzing the metabolites in medicinal materials, metabonomics can reflect the overall chemical characteristics of medicinal materials, rather than the chemical characteristics of a single component, which improves the accuracy and objectivity of evaluation and provides strong support for the modernization and internationalization of TCM [6].

The choice of metabonomics technology needs to be flexibly adjusted according to the research objectives. For example, nuclear magnetic resonance (NMR) technology is suitable for panoramic analysis of non-targeted metabolites, with high repeatability and low sample destructiveness, but low sensitivity; liquid chromatography-mass spectrometry (LC-MS) technology is outstanding in high-sensitivity targeted quantitative analysis, especially suitable for the detection of low-abundance metabolites; gas chromatography-mass spectrometry (GC-MS) has unique advantages in the analysis of volatile metabolites. The complementarity of different technologies provides multi-dimensional data support for the establishment of TCM quality standards.

Tang et al. pointed out that metabonomics technology, combined with multivariate statistical analysis methods, could effectively identify the varieties and origin of TCM by detecting small molecular metabolites in TCM, so as to improve the accuracy of quality evaluation of TCM [7]. Shi et al. demonstrated that dozens of metabonomics studies focused on proving the efficacy and safety of TCM, exploring its potential mechanism, and identifying potential biomarkers to obtain the target of TCM, and have achieved fruitful results [8]. Li et al. established the quality evaluation method of Gastrodiae rhizoma tuber by using QMS method combined with HPLC fingerprint analysis, and analyzed Rhizoma Gastrodiae tuber from different habitats using HPLC fingerprint [9]. At the same time, the content of seven components in Rhizoma Gastrodiae tuber samples were identified by QMS method, providing favorable basis for its future research. In addition, Jiang used UPLC-Q-TOF-MS technology to analyze the metabolic profile and chemical composition differences, and the genetic and chemical material basis of genuine Scutellariae radix was discussed, which provided scientific basis for the introduction, cultivation and variety breeding of Scutellaria baicalensis Georgi and laid a research foundation for the protection and utilization of Scutellaria baicalensis Georgi germplasm resources [10]. This shows that metabonomics also has an important application in the study of authentic Chinese herbal medicine.

Metabonomics has shown great value and broad prospects in TCM quality evaluation By comprehensively analyzing the metabolites of medicinal materials to reflect the overall chemical characteristics, it has improved the accuracy and objectivity of evaluation and provided support for TCM modernization and internationalization. Metabonomics, combined with multivariate statistical analysis, can effectively identify the varieties and producing areas of traditional Chinese medicine and improve the accuracy of quality evaluation. At the same time, it has also achieved fruitful results in exploring the effectiveness, safety, mechanism of action and biomarker identification of traditional Chinese medicines, and played an important role in the authentic research of traditional Chinese medicines, which may provide scientific basis for the introduction, cultivation and variety selection of some traditional Chinese medicines.

2.2 Metabonomics in the processing of TCM and mechanism of action

Metabonomics technology has become a pivotal tool to clarify the holistic mechanism of TCM. By dynamically monitoring endogenous metabolites *in vivo*, this approach can comprehensively analyze the absorption, distribution, metabolism, and excretion (ADME) processes of TCM bioactive components, while simultaneously evaluating their regulatory effects on physiological functions [11]. By comparing the changes of metabolites in organisms before and after treatment with TCM, we can identify the effective components of TCM and reveal its mechanism of action.

Cui et al. concluded that metabonomics technology helped accurately analyze the functional level of biological system and the changes of metabolites, which provides a new method for understanding the complex mechanism and scientific connotation of TCM from a micro perspective [12]. They also mentioned a number of specific studies, which combined targeted and non-targeted metabonomics methods to analyze the clinical serum samples of angina pectoris with excess and deficiency syndrome of stable coronary heart disease, and revealed the metabolic characteristics of different syndrome types. The integration of metabonomics with gut microbiota research has opened new frontiers in cardiovascular TCM studies. In addition, Zhang et al. applied metabonomics method to the research of Chinese medicine, revealing the relationship between the occurrence and development of HF and the body's energy metabolism and providing basis for the clinical application of Chinese medicine [13]. Intestinal flora is closely related to the occurrence and development of cardiovascular diseases. Research on the combination of metabonomics and intestinal flora has opened up new ideas for the mechanism of TCM diagnosis and treatment of HF. Based on ultra performance liquid chromatography-triple quadrupole mass spectrometry platform, Mai et al. studied the influence of active components of TCM on lipopolysaccharide-induced inflammation model and the metabolic changes of eicosanoid in raw 264.7 cell inflammation model induced by KDO 2-lipida [14]. It was found that Curcumae longae rhizoma could exert anti-inflammatory activity by inhibiting Cox-2 activity. Advanced analytical platforms have further enhanced metabonomics' resolution in neuroprotection studies. Yang used 1H-NMR to explore the protective mechanism of Ginseng radix et rhizoma Rb1 on glutamate-induced apoptosis of SH-SY5Y cells by cytometabonomics [15]. The survival rate and apoptosis rate of SH-SY5Y cells before and after modeling and administration were analyzed by MTT colorimetry and flow cytometry. Results showed that Ginseng radix et rhizoma Rb1 could protect SH-SY5Y cells from apoptosis induced by glutamic acid, and could also protect nerve cells from oxidative damage mainly by affecting various energy and amino acid metabolism. Guo et al. [16] studied the protective mechanism of cycloastragenol (CAG) on mouse podocyte (MPC5) injury induced by doxorubicin (DOX) based on LC-MC cell metabonomics [17]. They put forward certain attenuation mechanism and pointed out that metabonomics could be used to clarify how the processing technology (such as honey processing of Astragli radix) could promote the conversion of saponins into aglycones with higher activity (such as CAG), thus enhancing the efficacy. To sum up, the application of metabonomics in the processing research of TCM is deepening, and its multi-dimensional analysis ability can not only accurately analyze the *in vivo* behavior of active components of traditional Chinese medicine, but also reveal the dynamic change law of the material basis of efficacy before and after processing of traditional Chinese medicine, which provides strong technical support for the modern interpretation and practical application of traditional Chinese medicine processing theory.

2.3 Application of metabonomics in toxicity evaluation of TCM

Metabonomics plays an important role in various usage scenarios of TCM, especially for the safety of special people [18]. At present, the research progress on the application of metabonomics in toxicity evaluation of TCM extracts is shown in Table 1.

Table 1 Application of metabonomics in toxicity evaluation of TCM

Medicine	Animal sample	Research method	Research conclusion	References
Water extracts of Stephaniae tetranidae radix	Rat blood, urine	NMR	Drugs changed the contents of citric acid, 2-ketoglutarate, taurine, hippuric acid, TMAO and creatinine in urine of rats. The main metabolites in blood are unsaturated fatty acids, 3-hydroxybutyric acid, acetone, acetoacetic acid, creatinine, NAC and OAC. It is suggested that drugs mainly affect the excretion function of renal tubules, and continuous long-term administration can cause damage to the filtration function of renal tubules, renal medulla and glomerulus.	[19,20]
Supercritical extract of Cndii frustus	Rat urine	UPLC / Q-TOF / MS	The drug increased the levels of eicosapentaenoic acid, coenzyme Q and phosphorylcholine in rat urine, suggesting that its toxicity may be related to its destruction of cell membrane structure and interference with energy metabolism.	[21,22]
Akebiae caulis decoction	Rat urine	NMR	Trimethylamine oxide and taurine in urine samples of rats after exposure decreased, and the metabolites of citric acid, creatinine and 2-ketoglutarate also decreased in different degrees. Acetic acid and alanine increased significantly, indicating that animals may have tubular necrosis, and drugs interfered with their energy metabolism and affected intestinal flora.	[23]
Dioscorea panthaicae rhizoma decoction	Rat urine	NMR	The levels of taurine, creatinine, cyclamate, dimethylglycine (DMG), acetic acid and glycine in the urine of rats in Huangyaozi group increased, while the contents of α-ketoglutarate, succinic acid, citric acid, hippurate and urea decreased. It is suggested that tricarboxylic acid cycle of the body is weakened, mitochondrial function is reduced, liver function is damaged.	[24]
Aconiti radix lateralis praeparata decoction	Rat blood	UPL-Q-TOF-HDMS	Most biomarkers are lysophosphatidylcholine, tryptophan, etc., suggesting that their toxicity is related to their effects on glycerol phospholipid metabolism, lipid metabolism, tryptophan metabolism and aminoacyl tRNA biosynthesis.	[25]
Yishun tablet decoction	Rat urine, blood plasma	NMR	Drugs can cause obvious changes in metabolomics, especially taurine content, suggesting that drugs can cause toxicity in heart and liver.	[26]
Cinnabaris suspension	Rat urine, serum	NMR	Drugs increase the contents of creatinine, ethyl acetate and taurine in urine, but decrease the contents of hippuric acid, phenylacetylglycine, dimethylglycine and tricarboxylic acid cycle intermediates (citrate, 2-ketoglutarate and succinic acid). After administration, the concentrations of ketone bodies, branched-chain amino acids, choline and creatine in serum of rats increased, while the concentrations of blood sugar, blood lipid and lipoprotein decreased. It is suggested that cinnabar may interfere with energy metabolism, amino acid metabolism and intestinal bacteria environment, and cause slight damage to liver and kidney.	[27]
Realgar CMC -Na suspension	Rat urine, serum	NMR	Drugs increase the levels of ketone bodies in urine and serum, and decrease the levels of glucose and glycogen in liver, suggesting that realgar interferes with energy metabolism; The decrease of phenylacetylglycine, trimethylamine-*N*-oxide and hippuric acid in urine suggests the influence of realgar on intestinal microecological environment. The decrease of serum alanine level and the increase of glutamic acid and methionine levels suggest that realgar interferes with amino acid metabolism.	[28]

(to be continued)

Continued Table 1

Medicine	Animal sample	Research method	Research conclusion	References
Polygoni multiflori radix	Rat serum	UHPLC-Q-Obitrap-MS/MS	Emodin and THSG cause liver and kidney damage in rats to varying degrees by disrupting metabolic pathways, and the combined exposure of emodin and THSG reduces liver and kidney toxicity by restoring metabolic disorders, which plays an antagonistic role.	[29]
Euodiae fructus	Rat serum	LC-GC-MS, NMR	The potential hepatotoxic substances in EVOdia rutaecarpa suggest a link between Evo's hepatotoxicity and abnormal steroid hormone synthesis/bile secretion due to mitochondrial damage.	[30]

The advantage of metabonomics in toxicity evaluation lies in its dynamic monitoring ability. For example, UPLC-Q-TOF-MS technology can capture the temporal changes of metabolic network after drug exposure in real time, and, combined with pathway analysis (such as KEGG and MetPA), it can systematically identify toxicity-related metabolic disturbances. In addition, the correlation analysis of metabonomics data with histopathological and biochemical indexes can improve the credibility of toxicity mechanism explanation. For example, the study of Tripterygium wilfordii in Table 1 shows that the molecular basis of mitochondrial dysfunction can be more clearly revealed if the data of liver transcriptome are further integrated.

At the same time, as an important part of metabonomics, spatial metabonomics provides a more accurate and scientific method for analyzing the drug-induced components and their regulatory mechanisms for adverse reactions or diseases in organisms by constructing an interactive network of “drug delivery molecular structure/drug-induced molecular structure-content change-spatial distribution-metabolic pathway” [31]. Metabonomics technology is used to deeply explore the different components of endogenous small molecular substances, drugs and their metabolites in the region, and bioinformatics analysis methods are used to deeply explore the characteristics and correlation of these components. Besides, mass spectrometry imaging technology enables the precise mapping of metabolites distribution across entire tissue sections or specific micro-regions while preserving sample structural integrity. In this way, the potential mechanism of the content change of various substances can be analyzed. This technology can also relate the spatial distribution information of the compounds to be tested in tissues with the anatomical characteristics and biological functions of biological tissues [32]. By analyzing the spatial distribution pattern of metabolites alongside anatomical characteristics and biological functions within tissues, spatial metabonomics deeply analyzes the driving mechanism behind the dynamic changes of metabolites. This approach provides an innovative research paradigm for accurately locating the toxicity and therapeutic targets of drug components and explaining their mechanism of action. It strongly promotes the development of drug research and toxicology in the direction of precision and visualization, while also providing important technical support and theoretical basis for identifying key metabolic control nodes in the process of disease occurrence and development [33,34].

The above research demonstrates the active application of metabonomics in studying the multi-target and multi-channel toxicity of TCM, and also indicates that metabonomics correlates with classical toxicology indexes and helps to clarify the toxicity of TCM [35]. Metabolomics, as a systematic approach, mainly focuses on comprehensively studying metabolites and their functions in biological systems. By quantitatively measuring a large number of low molecular endogenous metabolites involved in metabolic pathways, it reflects the basic metabolic state of the body. The systematic study of metabonomics conforms to the theory of TCM and it may be the best way to conform to the overall concept of TCM. Therefore, metabonomics analysis is an appropriate tool to systematically evaluate toxicity, find potential biomarkers and explore the toxicological mechanism of TCM [36].

3 Conclusion

This study systematically explores the application of metabonomics in TCM research, highlighting its significant role in advancing TCM modernization and internationalization. By comprehensively analyzing the metabolites within medicinal materials, metabonomics provides an accurate map of the chemical panorama of traditional Chinese medicine. This significantly improves the accuracy and objectivity of TCM quality evaluation, thereby providing robust scientific support for optimizing and updating TCM quality standards. In TCM processing research, metabonomics technology systematically explains the pharmacokinetic characteristics and physiological regulation effects of active components of traditional Chinese medicine by monitoring the dynamic changes of endogenous metabolites in real time, and deeply analyzes the multi-target and multi-channel action mechanism of traditional Chinese medicine. Metabonomics also shows excellent efficacy in the field of TCM toxicity evaluation. Its highly sensitive dynamic monitoring system can timely capture the subtle fluctuations of the metabolic network after drug intervention. Integrated with pathway enrichment analysis, it precisely identifies toxicity-related metabolic abnormal nodes. This establishes a quantitative and visual technical platform for TCM safety evaluation, and strengthens the ability to accurately analyze the mechanism of drug action. Generally speaking, the in-depth application of metabonomics in TCM research provides an innovative research paradigm for revealing the material basis, mechanism and toxicity characteristics of traditional Chinese medicine. It also facilitates the modern interpretation of TCM theory and provides a standardized and objective research tool for TCM's global development, continuously enhancing innovative TCM development within contemporary life sciences.

Based on the above conclusions, this paper puts forward the following prospects for the application of metabonomics in TCM:

First of all, researchers should further explore the deep integration of TCM theory and metabonomics, and integrate the core concepts of TCM, such as syndrome differentiation and treatment, into metabonomics research, so as to reveal the mechanism of action and pharmacodynamic characteristics of TCM more comprehensively. Secondly, metabonomics should be combined with other omics technologies (such as genomics, transcriptomics and protein genomics) to form a multi-omics integrated research platform, such as “metabonomics-protein Group-Transcriptome” combinatorial analysis platform, which can comprehensively analyze the regulatory effect of traditional Chinese medicine components on biological networks, so as to further analyze the biological basis of complex TCM systems. This will help to reveal the mechanism of action of traditional Chinese medicine at multiple levels and provide strong support for TCM modernization and internationalization. In addition, it is necessary to strengthen the interpretation of metabolomics data and knowledge mining in the future TCM development. By establishing the database and analysis platform of metabolites with TCM characteristics, the metabonomics data can be deeply excavated and effectively utilized, and more valuable information and clues can be obtained for TCM research. Finally, the application of artificial intelligence (such as machine learning) in metabonomics big data mining will also be expected to further improve the accuracy of toxicity prediction and efficacy evaluation.

In summary, metabonomics technology has a broad application prospect in the research of TCM, which provides a new perspective and method for the quality control of traditional Chinese medicine, the basic research of pharmacodynamic substances, the explanation of action mechanism and toxicity evaluation. Future research should focus on the application of metabonomics technology in the field of TCM, optimize analysis methods, improve data analysis ability, and achieve more accurate efficacy evaluation and toxicity prediction.

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