

Overview on metabolomics in traditional Chinese medicine

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ization of TCM. This review summarizes potential applications of metabolomics in the area of TCM. Guidelines for good practice for the application of metabolomics in TCM research are also proposed, and the special role of metabolomics in TCM is highlighted.

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Core tip: Traditional Chinese medicine (TCM) has been used for thousands of years to treat or prevent diseases. Actual value of TCM has not been fully recognized worldwide due to the lack of scientific approaches. Metabolomics has become a hot topic in TCM research. Metabolomics is the best method to fit the holistic concept of TCM, and it can not only interpret the essence of syndrome but also elucidate the scientific connotation of prescription. This combination of TCM with metabolomics in modern health care systems may lead to a revolution in TCM therapy.

Abstract

Metabolomics has been widely used in the modern research of traditional Chinese medicine (TCM). At the same time, the world is increasingly concerned about TCM, and many studies have been conducted to investigate different aspects of TCM. Among these studies, metabolomic approach has been implemented to facilitate TCM development. The current methods for TCM research are diverse, including nuclear magnetic resonance, gas chromatography-mass spectrometry, and liquid chromatography-mass spectrometry. Using these techniques, some advantageous results have been obtained in the studies of TCM, such as diagnosis and treatment, quality control, and mechanisms of action. It is believed that the further development of metabolomic analytical techniques is beneficial to the modern-

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INTRODUCTION

Traditional Chinese medicine (TCM) has been important in health protection and disease control in East Asia for thousands of years. Now, it is getting more and more popular in the whole world for improving health conditions of human beings and preventing or healing diseases. Moreover it shows some advantages in early intervention, individuation medicine and combination therapies. TCM has a distinctive feature, *i.e.*, its systems

theory, which includes the holistic view and the dialectical view. It takes the human body as a whole from the key concepts of “qi, blood, yin-yang, viscera (Zang-Fu), and meridian and channel”^[1]. TCM is also a natural combination of philosophy and ancient science disciplines. The overall concept and differential treatment are the most basic features. Chinese herbal medicine treats a disease by regulating and mobilizing the whole body rather than just regulating a single factor. However, the development of TCM is restricted in the world. The lack of scientific and technologic approaches makes TCM face serious challenges and suffer from inadequate modern research.

Metabolomics is a new subject concerned with the comprehensive characterization of the small molecule metabolites in biological systems. It can distinguish between diseased and non-diseased status information through the assessment of global metabolic profiles in approximative biofluids and biomarker discovery^[2]. Studying the metabolome can highlight changes in networks and pathways and provide advice to physiological and pathological states^[3]. New dimensions are adding to the field of metabolomics by developments in new technology, flux analysis and biochemical modeling^[4-6]. The holistic analyses in the context of metabolomics will give the current essay and the foreseeable developments some relatively clear conclusions^[7].

TCM recognizes the human body by system discrimination and in a cybernetic way. TCM can be characterized as holistic, emphasizing the integrity of the human body. It also pays close attention to the relationship between human and their social and natural environment^[8]. Metabolomics is a promising way for research of TCM and opens a new way for using metabolomic platform to resolve TCM issues^[9]. The metabolomic platforms provide a way to extend the understanding of the mechanisms of action of TCM formulae and the analysis of Chinese herbs, TCM syndromes, mineral medicine, and acupuncture^[10]. They offer a useful tool to identify biomarkers and provide a new method for studying the efficacies and mechanisms of TCM in treating diseases^[11]. Conclusively, metabolomics has become a key to resolving special TCM issues. Here, we give an overview of the applications of metabolomic approaches in research of TCM in recent years.

METABOLOMICS IN DIAGNOSIS AND TREATMENT IN TCM

The superiority and soul of TCM are diagnosis and treatment, and syndrome is the basic concept of the theory. The accuracy of syndrome differentiation determines the effectiveness of TCM treatment. The metabolomic technologies have been used in objectively differentiating syndromes and exploring their biological mechanisms by studying the functional activities of the human body from a system-wide perspective. It will impact our understanding of the theory behind the evidence-based Chinese medicine^[12]. Lu *et al.*^[13] performed the overall biological

characterization of the urine of psoriasis patients with Blood Stasis Syndrome. Simultaneously, they investigated the therapeutic metabolomic mechanism of the Optimized Yinxieling formula. The findings enhanced the understanding of the metabolic influence in Blood Stasis Syndrome in psoriasis patients and the mechanism of action of optimized Yinxieling^[13]. In addition, that study demonstrated that metabolomics was a powerful tool in diagnosis and treatment of primary dysmenorrhea by providing information on changes in metabolites and endocrinal, neural and immune pathways. Xiang-Fu-Si-Wu Formula intervention can affect some significant perturbations in sphingolipid metabolism, glycerophospholipid metabolism and steroid hormone biosynthesis to make the metabolic discrepancy return to the normal level^[14].

The personalized diagnosis in TCM can help to distinguish different types of diabetics. Metabolomics provides biomarkers for disease subtypes as a potential platform. It has been proved that combining metabolomics with TCM diagnosis can reveal metabolic characteristics for pre-diabetic subtypes^[15]. Xu *et al.*^[16] used the orthogonal signal correction-partial least squares method to confirm the existence of metabolite differences among different TCM syndromes. Additionally, a new method has been developed to distinguish the difference between healthy controls and patients with TCM deficiency syndromes by uncorrelated linear discriminant analysis. It provides important information assisting TCM clinical diagnosis^[16]. Metabolomics has the potential to become a diagnostic tool for diseases and provide a new way to understand pathophysiologic mechanisms. Metabolic pathways including alanine and aspartate were found to be disturbed in jaundice syndrome patients. Using this method, 44 marker metabolites have been identified to distinguish patients with jaundice syndrome from matched healthy controls^[17].

METABOLOMICS IN ACUPUNCTUROLOGY

Acupuncture, as an alternative and complementary therapy, has been used for disease treatment and prevention in TCM^[18]. But, the underlying mechanism of acupuncture is unclear, which precludes its widespread use. Metabolomics is similar to acupuncturology in terms of dynamic changes and comprehensiveness^[19]. The high-throughput metabolomics can identify potential factors for acupuncture effects and provide valuable information towards understanding therapeutic mechanisms. Wang *et al.*^[17] assessed the acupuncture treatment at the “Zusanli” acupoint *via* marker metabolites, based on the perturbed signatures and pathways after acupuncture^[20,21].

Many studies show the potential of an NMR-based metabolomic approach in the research of biological effects of acupuncture. It was used to investigate the metabolic change of plasma before and after electro-acupuncture in senescence-prone mice, providing a method to assess the effects of acupuncture and to understand the

underlying mechanism in neurodegenerative diseases^[22]. Wu *et al*^[23] have shown that acupuncture demonstrates its therapeutic effects in the relief of functional dyspepsia symptoms. After treatment, the levels of leucine/isoleucine, lactate and glucose in patients significantly changed and lipid levels slightly changed towards those of the healthy controls^[23]. Acupuncture could make the metabolite network recover. An UPLC-MS-based metabolomic method has been developed to investigate the biological effect of acupuncture in acute gouty arthritis and to understand the underlying mechanism^[24].

APPLICATION OF METABOLOMICS TO MATERIAL FOUNDATION

Metabolic profiling is benefit to screening active components in medicinal plants. Li *et al*^[25] have used metabolomics to find metabolites with antitussive and expectorant activities. It has been shown that chlorogenic acid, 3,5-dicaffeoylquinic acid, and rutin may be closely associated with the antitussive and expectorant activities^[25]. Wang *et al*^[26] established a UPLC/MS method for analyzing the chemical constituents after oral administration of Yinchenhao Tang (YCHT), which was used for treatment of jaundice syndrome. Forty-five compounds *in vitro* and 21 compounds *in vivo* were detected^[26,27]. The three components of YCHT are *Artemisia annua* L., *Gardenia jasminoides* Ellis, and *Rheum Palmatum* L., whose major active ingredients are 6,7-dimethylesculetin (D), geniposide (G), and rhein (R), respectively. The D/G/R combination had a more robust synergistic effect than any one or two of the three individual compounds by acting upon multiple target proteins^[28].

ACTION MECHANISM RESEARCH

Action mechanisms of most of Chinese medicines are difficult to determine. In an attempt to address the benefits of Chinese medicine using current biomedical approaches, we regard the metabolomics technology as a powerful tool. Metabolomic techniques are promising for identifying biomarkers, clarifying mechanisms of disease, and highlighting insights into drug discovery. Zhao *et al*^[29] identified 19 metabolites as potential biomarkers of chronic kidney disease, and 10 biomarkers returned to the control levels in *Poria cocos*-treated groups. Furthermore, they found that topical treatment with *Poria cocos* intervenes some primary metabolic pathways^[29]. Scoparone has a potential effect against carbon tetrachloride-induced liver injury through regulating multiple perturbed pathways to the normal state^[30]. The dried root of *Kansui* (*Euphorbia kansui* L.), an effective TCM, has been researched by NMR analysis. It provides new clues to the toxicity of *Kansui* from a systematic and holistic view^[31].

Modified Sinisan can have an effect on liver injury through partially regulating the perturbed pathways, such as phenylalanine metabolism, tyrosine and tryptophan biosynthesis, tryptophan metabolism, retinol metabolism,

and tyrosine metabolism^[32]. Gou *et al*^[33] investigated the effect of Xia Yu Xue Decoction on liver fibrosis by a urinary metabolomic method, based on gas chromatography coupled with GC/MS. It was suggested that the mechanism of action of Xia Yu Xue Decoction may affect ten potential biomarkers associated with microflora metabolism^[33]. Chen *et al*^[34] have studied the therapeutic mechanism of a traditional Chinese medicine Jiu Wei Qiang Huo decoction effects against H1N1-induced pneumonia by a metabolomic approach. The findings provided a systematic view and a basis for understanding of prevention and treatment^[34].

POTENTIAL OF METABOLOMICS FOR STUDING CHINESE MEDICAL FORMULAE

Chinmedomics, defined as “elucidating the therapeutic and synergistic properties and metabolism of traditional Chinese medical formulae (chinmediformulae) and related metabolic analysis by modern techniques”, has recently showed potential in evaluating TCM^[35]. It supplies a way to translate chinmediformulae into practices. TCM therapy will be revolutionized by the way, which combines chinmedomics with chinmediformulae in modern health care systems^[36]. A developed and validated UPLC-MS/MS method has been used to test the plasma pharmacokinetics, tissue distribution and excretion of schisan-drin (the main component of shengmaisan) in rats after oral administration of shengmaisan. This method can be used to investigate the *in vivo* behaviors of the TCM components in formulae^[37]. The pathogenic mechanism of yinhuang syndrome was investigated by a metabolomics method, which had identified 19 biomarkers for the progression of the yinhuang syndrome^[38].

METABONOMICS IS A ROAD TO QUALITY CONTROL OF TCM

The quality control of Chinese medicine, referring to the TCM preparations comprising more than one herb, is challenging due to their extreme chemical complexity. A chemical fingerprint technique for quality control has been established for identifying herbs from different origins. Fingerprinting analysis could provide a platform to identify herbs from different origins by GC-MS, which is beneficial to quality control. In this way, *Longae rhizome* samples have been indentified as the characteristic components for distinguishing these samples of various geographical origins, which is good for quality control^[39]. A practical quality control method for *A. Radix* has been set up by recognizing GC-based metabolic markers. It identified sorbitol and a glucose/4-aminobutyric acid combination as bio-markers for discriminating species and cultivation area^[40].

Twelve active components in a methanol extract of Weichang'an pill were simultaneously determined using the HPLC-DAD-ESI-MS/MS technique^[41]. Wang *et al*^[42]

have separated and determined 18 major active ingredients of Banxia Xiexin decoction in order to achieve quality control by UPLC-MS/MS. A fingerprint profile of Niu Huang Shangqing pill has been established and 190 compounds was characterized by HPLC/qTOF-MS. It is a significant method to implement and provides a potential approach to achieve the holistic quality control of complex TCM preparations^[43].

METABONOMICS PROVIDES INSIGHTS INTO THE GLOBAL ISSUES OF TCM TOXICOLOGY

Metabolomics has showed potential to improve the discovery of biomarkers for detection of toxicity. Dong *et al*^[44] utilized global metabolomics to find 17 metabolites, which were regarded as phenotypic biomarkers for toxicity of Chuan Wu. Additionally, the mechanisms of Fuzi's toxicity and potential tissue-specific biomarkers for the toxicity have been explored by metabolomics. Significant changes of 14 lipid metabolites were considered the potential biomarkers for toxicity of Fuzi^[45].

In TCM, a principle called “Jun-Chen-Zuo-Shi” may be used to formulate a herbal formula that can mitigate the toxicity of the main ingredient. NMR-based metabolomics approach has been used to research the toxicity of realgar after being counterbalanced by other TCMs in a TCM prescription named Niu Huang Jiedu Tablet. The counterbalanced realgar in Niu Huang Jiedu Tablet was more secure and much less toxic^[46]. A TCM Paozhi approach can increase potency and reduce toxicity. An RPLC-Q-TOF/MS method based on metabolomic analysis has been explored to help improve the understanding of the transformation mechanisms underlying Paozhi. Twenty-two key biomarkers responding to detoxifying actions of Paozhi were identified^[47]. Sun *et al*^[48] also proved that metabolomic method greatly contributes to the investigation of processed Fuzi and provides useful information for the potential activity and toxicity of processed Fuzi.

CONCLUSION

Metabolomics is a modern technology in the post-genome era and has been being used widely in modern Chinese medicine^[49,50]. Metabolomics reflects the function of organisms from terminal symptoms of metabolic network and can help understand metabolic changes of a complete system caused by interventions in the holistic context. Its character is consistent with the whole thinking of TCM, and it may be beneficial to provide an opportunity to scientifically express the meaning of evidence-based Chinese medicine. It shows potential in both TCM research and drug discovery. Metabolomic applications in TCM field related to drug development from natural sources and drug discovery aim at raising the potential of metabolomics in reducing the gap between

TCM and modern drug discovery, and highlight the key role of biomarkers for drug discovery and development of traditional oriental medicine. It is expected that current metabolomic technologies can impel the development of TCM, especially in the understanding of the concept of Chinmedomics. Currently, systems biology is in accordance with the holistic concept and practices of TCM and will help to understand the mechanisms of TCM. As one part of “Omic”, metabolomics, playing an import role in systems biology, has a non-selective approach and can thus lead to the identification of all the metabolites. Metabolomics should be devoted to establishing and improving its own databases, linking other genomics together to solve the problems of TCM, in order to enhance its self-worth in the field of TCM research. Overall, incorporation of metabolomics technologies into TCM can make it possible to study the mechanism of TCM.

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