Metabolomics and traditional Chinese medicine

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ABSTRACT

Traditional Chinese medicine (TCM) has attracted increasing interest throughout the world because of its potential as complementary therapy of choice and a source for discovery of new drugs. However, the analytical characterization of TCM is still in its infancy due to its chemical nature of multi-component mixtures that often possess their own inherent holistic bioactivities. Metabolomics incorporates state-of-the-art approaches enabling systemic molecular characterization in complex samples and provides the option for an integrated view of the biochemistry in TCM. In this review, we present current metabolomics technologies in research on TCM related to chemical composition, bioactive components and efficacy. We also highlight the potential role of metabolomics technologies in evidence-based studies of TCM syndromes.

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1. Introduction

Interest in study of traditional Chinese medicines (TCMs), or so called Chinese herbal medicines (CHMs), recently became widespread due to their potential as a source of new drug discovery and complementary therapy of choice, although the history of TCM can be dated back to thousands of years ago. TCM holds a holistic health care philosophy (i.e., looking at the behavior of the system as a whole). It regards disease as energetic imbalance and adheres to the concept of cure instead of treatment. The components of CHM are very complex; CHMs usually consist of hundreds or even thousands of different compounds. The therapeutic effects of CHM can usually be attributed to the combination of multiple elements

(i.e., multi-component mixture) of the herb or the formula acting together.

Traditionally, a TCM is administered as an individually prepared water decoction containing multiple herb materials in certain proportions. Notably, the final item that is taken orally by a patient is an extract of herbs that is influenced by not only the botanical origin of its herbal components but also the procedure that is used to treat the herbal material [1]. Any minor changes in these two aspects will greatly affect the therapeutic efficacy of the products. Such complexity in TCM administration brings a great challenge in establishing suitable analytical approaches for the development of modernization and standardization of TCMs and their natural products. Besides, TCM possesses two unique features – multidimensional pharmacology {i.e., synergetic effects [2], and combinatorial effects and opposing principles [3]} and personalized or individual treatment. Such features of TCM determine that the traditional analysis based on major components is not sufficient to provide information on bioactivity of herbal products. Analytical characterization of TCM is still in its infancy due to the chemical nature of multi-component mixtures that often possess inherent holistic bioactivities.

To meet this challenge, metabolomics which aims at comprehensive characterization of the total metabolome in a biological system and dynamic metabolomics responses to alterations of inner and/or external factors [4] is in great demand. As an emerging field of science in the post-genomics era, metabolomics has been broadly applied in many fields {e.g., toxicological survey [5], functional genomics [6,7], clinical diagnostics [8], plant and microbes [9–11], and nutritional biochemistry [12,13]}. The most commonly used two technologies in metabolomics applications are nuclear magnetic resonance (NMR) [14] and mass spectrometry (MS) [15]. Although its sensitivity is less than that of MS, NMR is still popular in many applications due to its rapidity, high throughput, easy operation, being non-destructive of samples, and quantitation of metabolites from different groups. However, in most cases, MS is preferred because of its advantages of unparalleled sensitivity, super resolution and structural specificity. In practical applications, chromatographic separation technologies [e.g., gas chromatography (GC), liquid chromatography (LC) and capillary electrophoresis (CE)] are often coupled to MS depending on the properties of the analytes being measured.

As the data matrix generated in metabolomics studies is usually very large, data processing and data analysis are crucial for their final outcome. Many available software packages {e.g., JDAMP [16], MetAlign [17], MSFACTs [18], Mzmine [19], and XCMS [20]} were developed for processing raw data from metabolomics. On this basis, multivariate (e.g., PCA, PLS-DA, PLS, and OPLS) and univariate (e.g., T-test and ANOVA) analyses were carried out for classification and differential metabolite discovery. In combination with advanced bioinformatics tools, many studies demonstrated that metabolomics incorporating state-of-the-art analytical approaches enables systemic molecular characterization of complex samples [21,22] and provides an integrated biochemical view of TCM.

In this review, we summarize metabolomics methods based on GC-MS and LC-MS and applied in research on TCM. We highlight the subjects related to chemical composition, bioactive components and the efficacy of CHM, and metabolomics applications in evidence-based studies of TCM syndromes.

2. Advances in metabolomics technologies

As early as the 1970s, the embryonic form of metabolomics (at that time called "metabolic profile") was coming into being. A typical example is that GC-MS became feasible to measure qualitatively and quantitatively metabolic profiles of body fluids and tissue extracts. Concurrently, rapid improvement was achieved in NMR spectroscopy due to the increasing strengths of magnetic field and magic angle spinning, which remarkably improved the sensitivity and made NMR a leading analytical tool to detect metabolites of many different classes in biological samples.

The initiation of study on MS-based metabolomics in a real sense was carried out by van der Greef et al. using field desorption and fast atom bombardment (FAB)-MS for profiling complex, non-volatile metabolites in body fluids to study gender difference [23]. They pioneered the utilization of pattern-recognition techniques to MS-based datasets. Meanwhile, the NMR-based metabonomics approach was pioneered in the study of vertebrate blood and plasma by Nicholson et al. [24].

Although there were some sporadic applications, the limitation in early analytical technologies (e.g., low sensitivity, low specificity and low throughput) made it a big challenge to qualify and to quantify complex metabolites in biological samples. Analytical techniques with super sensitivity and selectivity, high specificity, good reliability, and easy automation are required to detect and to identify metabolites in complex biological systems. The revolution in soft-ionization technologies for MS included matrix-assisted laser desorption/ionization (MALDI) [25] and electrospray ionization (ESI) [26] as well as atmospheric pressure chemical ionization (APCI) [27]. Metabolomics has largely been driven by these technologies, as they possess better resolution and sensitivity, and higher specificity and mass accuracy than earlier technologies. These MS instruments are still undergoing rapid advances in terms of sensitivity, resolution, mass accuracy and dynamic range.

As complexity increases in the composition of metabolome – the whole set of endogenous and exogenous metabolites with small molecular weight in an individual organism – modern technologies that allow for qualitative and quantitative measurement of a vast number of metabolites in complex biological systems are required for metabolomics studies. Modern metabolomics platforms usually comprise approaches using chromatography-based technologies such as GC and LC, including high-performance LC (HPLC), ultra-performance LC (UPLC), hydrophilic interaction chromatography (HILIC)) and CE coupled to MS or MS/MS. Notably, frequently used ion sources are, for GC-related techniques, electron ionization (EI), and, for LC- and CE-based MS systems, ESI. Occasionally, APCI and atmospheric pressure photoionization (APPI) are coupled to LC for detection of non-polar compounds. Frequently used mass analyzers in current metabolomics include quadrupole (Q), ion trap (IT), time-of-flight (TOF), Fourier transform ion cyclotron resonance (FT-ICR), orbital trap and a combination of them [e.g., triple quadrupole (QQQ), Q-TOF, IT-TOF, IT-FT-ICR].

Besides, NMR is also frequently applied in modern metabolomics studies. In recent decades, many studies using NMR for metabolomics were carried out by Nicholson and his group. The related metabolomics studies generated many valuable findings, ranging from early diagnosis to disease treatment, drug toxicity, gene function, microbial, physiological and epidemiological aspects [6,28–31].

3. Applications of metabolomics in systems-based TCM

Differing from Western medicine (WM) that is based on the concept of "one size fits all" (i.e., 1 disease – 1 target – 1 drug), TCM follows the principle of multiple components – multiple target interactions – and has been developed into a holistic healthcare system [32]. Although attractive worldwide as a rich source of leading molecules for complementary and alternative medicine, TCM suffers from inextricable obstacles in modern CHM research [33]. In CHM, most of the active components are not well defined. The constituents and their related concentrations in each herbal medicine can vary greatly {e.g., depending on species [34], plant-growth conditions, and processing procedure [35]}. Metabolomics provides a valuable chance for studying TCM in terms of characterizing the chemical components, defining the multiple active components and evaluating the