Review

Chinmedomics: Newer Theory and Application

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ABSTRACT

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The scientific interpretation of the effectiveness of traditional Chinese medicine (TCM) is a communication channel between Chinese medicine and modern medicine. The evaluation of TCM efficacy is an important prerequisite for discovering active constituents. Therefore, there is an urgent need to establish a biological language for scientific explanation of the effectiveness of TCM, and modern scientists can further accept the significant value of TCM theory and its clinical practice. The syndrome and corresponding formulation are two important parts in TCM, and they are directly related to the effectiveness of TCM. Our team has taken syndrome and formulation as the research objects, integrated serum pharm-chemistry of TCM with metabolomics technology, developed a new platform termed Chinmedomics, which is capable of evaluating effectiveness of TCM and discovering the syndrome biomarkers as well as the effective substances. The correlation between the endogenous biomarkers of syndrome and exogenous constituents of formulation is analyzed to find the highly associated compounds as the effective substances, and further clarifying their activities, and may discover lead compounds. This effective strategy could speed the drug discovery from natural resources. This article systematically introduced the establishment and application of Chinmedomics theory, in order to provide references for studies on TCM, and some characteristic examples are presented to highlight the application of this new strategy for discovering the potential active constituents of TCM.

Key words
active constituents; biomarkers; Chinmedomics; effectiveness; traditional Chinese medicine

1. Introduction

The efficacy of traditional Chinese medicine (TCM) depends on the wonderful combination of multiple herbs under TCM theory, however, understanding such effects is very difficult in the search for the effective substances of TCM. Single herb already contains thousands of compounds, and formulation consisting of multi-herbs has become the giant system of chemical composition. Elucidation of the efficacy on TCM is important to understand the scientific value of TCM (Cao et al, 2010; Zhang et al, 2013a). It is necessary to have a biological language to scientifically describe the efficacy of TCM. The efficacy of TCMs is directly related with syndrome and formulation, but the vagueness of syndrome

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and complexity of formulation makes the diagnosis and efficacy evaluation difficulty, greatly limits the discovery of active constituents from TCM.

The biological characters of syndrome and formulation efficacy are important for discovery of effective substances from TCM. Therefore, researchers have exerted their efforts to innovating the research methods of TCM, aiming to solve the chemical and biological essence of syndrome and efficacy of TCM formulation (Jiang et al, 2012; Liu et al, 2013). Under this background, Chinmedomics (Chinese Medicine Metabolomics) has been proposed by our team (Wang et al, 2012a), and it is newer theory and methodology for expressing the TCM efficacy based on discovery of the syndrome biomarkers, and then for shedding new lights on the efficacy of TCM to discover effective constituents, finally to elucidate the scientific value of TCM. Therefore, this paper outlines the current progress and application of Chinmedomics, and proposes an integrated strategy for facilitating drug discovery and development from TCM.

2. Establishment and development of Chinmedomics

Even though the efficacy is embodying of TCM advantage, but it is difficult to scientifically express the efficacy of TCM, which restricts scientist to further understand and accept TCM. In early 1990s, we firstly established the theory and method on serum pharm-chemistry of TCM (SPT) (Wang et al, 2006), providing methodology for discovering constituents in vivo originated from TCM, but these constituents had not been linked with clinical efficacy of formulation due to the lack of syndrome biomarkers.

In the 21st century, we integrated serum pharm-chemistry of TCM (SPT) with metabolomics to develop a new theory and method for solving the efficacy and safety issues of TCM, and this theory have been defined as Chinmedomics (Wang et al, 2012a). In brief, using metabolomics technology to clarify the biomarkers of syndrome, take the biomarkers as targets to evaluate the efficacy of TCM formulation, under the condition of effective treatment to identify the active form of constituents in vivo originated from formulation, and further analyzing the correlation between the exogenous constituents in vivo and endogenous biomarkers to discover the constituents which are highly associated with formulation efficacy as the active constituents (Zhang et al, 2015).

The idea of Chinmedomics initially formed in 2004. In the end of 2011, the theory and method were formally defined as Chinmedomics, its academic connotation and research method has been published in “omics” (Wang et al, 2012a). The overall procedure of the Chinmedomics analysis is shown in Figure 1. This innovation includes four core elements: metabolic biomarker discovery based on metabolomics technology; syndrome model preparation based metabolic biomarkers; identification of the active constituents in vivo using SPT; correlation analysis between the constituents in vivo and endogenous markers (Wang et al, 2016a). They together formed the core technology of Chinmedomics. The book Chinmedomics: The Integration of Serum Pharmacochemistry and Metabolomics to Elucidate the Scientific Value of Traditional Chinese Medicine (ISBN: 978-0-12-803117-9) has been published by Elsevier. Chinmedomics is a newly established language which can express the TCM efficacy. It allows the experts in life science to deeply understand and accept the scientific value of TCM theory and experience.
$D$-glutamine and $D$-glutamate metabolism, synthesis, and degradation of ketone body, alanine metabolism, aspartic acid and glutamic acid metabolism, vitamin B6 metabolism, etc. In the same way, 49 metabolites were found contributing to YIH syndrome, such as $L$-homocysteine, $\beta$-citryl-$L$-glutamic acid, $L$-$\beta$-aspartyl-phenylalanine, $\alpha$-$N$-phenylacetly-$L$-glutamine, cholesterol, palmitic acid, which were related with $D$-glutamic acid, arginine metabolism, proline metabolism, and steroid hormone synthesis, bile acid biosynthesis, cysteine and methionine metabolism, etc. NSFC has inspiringly commented this research and China News of TCM has evaluated “Connotation interpretation of TCM with metabolomics language”.

2.2 Syndrome models based on metabolic biomarkers

Metabolic biomarker is used as bridge to prepare the relevant animal model of TCM syndrome, and then to establish the biological evaluation system for formulation efficacy. This innovation is taking candidate biomarkers obtained from clinical cases as targets, based on pathogenesis theory of TCM syndrome, combining the preparation method of related disease models, to create a new way for preparing the animal model of syndrome. By this research design, we firstly investigated the specific metabolite profiles and biomarkers of the liver injury induced by chemicals, and comparing metabolomic characteristics of the liver injury with those of clinical Huang-dan syndrome (Wang et al, 2014a), to select a proper animal model of the YAH or YIH syndrome. According to the changes in endogenous metabolites of the liver injury induced by chemicals, we successfully prepared the YAH animal model, among the 40 marker metabolites of YAH, and 33 metabolic markers, such as porphobilinogen, dimethylglycicosides, $L$-$\gamma$-glutamyl-$L$-valine, $S$-(4-nitro)-glutathione, benzylsucinic acid, sphingosine galactosidase sulfates, etc., were identified and consistent with the major biomarkers with YAH in clinic. Particularly, after treatment by Yinchenhao Decoction (YCHD) that is an effective formulation for the treatment of YAH, 33 biomarkers were adjusted almost to the level of normal animals (Wang et al, 2008a). In the same way, according to the 49 marker metabolites of clinical YIH syndrome, we successfully prepared YIH relevant animal model, and 39 biomarkers of YIH syndrome animal model were identified, such as 3-methyl-guanine, glycocholic acid, N-methyl-1-naphthalenemethyl amine, 3-methyl-2-oxo-indole, oxidation N-methyl-1-naphthalene methanamine, 3,5-dihydroxysuccinaic acid, carbamate, 5-$L$-glutamyl taurine, etc, which was capable to represent the development process of the YIH syndrome. Traditionally, Yinchen Sini Decoction is used for the treatment of YIH. By comparing the level of the identified biomarkers, the most of them were reset to a normal state after the administration of Yinchen Sini Decoction (Tong et al, 2011).

2.3 Analysis on constituents in vivo using SPT

Traditional research method guided extraction and separation could not reflect the overall efficacy of formulation. Many ingredients in TCM could produce an effect after absorption into the blood. The blood-contained ingredients may be the effective substances. Therefore, the efficacy material basis of TCM must be carried out in serum after the administration of TCM. In the early 1990s, we firstly established the SPT that could reflect the drug action, absorption, distribution and interaction in the body. SPT could isolate and identified the efficacy basis from serum after oral formulation, reflect the state of active constituents in vivo of formulation, and effectively guide the modern and innovative drug design (Figure 3). With the development of more than 20 years, it has become the key technology for in vivo analysis of active ingredients of TCM (Yan et al, 2015). SPT is based on comprehensive analysis of compounds into the blood, and to determine the dynamics and interaction of the main substances related with the efficacy, finally elucidates the mechanism of TCM compatibility.
SPT has been used for the screen and analysis of active constituents in TCM famous herb formulation. In a work, we have established the SPT method for analyzing the constituents after oral administration of YCHD, in order to identify the potentially effective constituents of TCM formulation in vivo (Wang et al, 2008b). The constituents of YCHD both in vitro and in vivo were well detected. The fingerprints of the samples were established, with 45 compounds in YCHD and 21 compounds in vivo were identified. Two of 21 compounds in vivo were metabolites and others were of the original form of the compounds in vitro. The present work was successfully applied for rapid discovery of bioactive components and metabolites from YCHD. The proposed SPT approach has been successfully applied on identification and characterization of multi-component in vivo after oral formulation, screening the active ingredients from Chinese medicinal formulations such as Sheng-mai San (Wu et al, 2011), Kai-xin Powder (Liu et al, 2015), Si-miao Pills (Zhang et al, 2014), Shaoyao Gancao Decoction (Wang et al, 2014b), etc.

2.4 Correlation analysis on constituents in vivo and biomarkers

In the early 1990s, we firstly proposed and established the theory and method of SPT, found the direct acting substances in vivo originated from formula after oral administration. However, due to the evaluation system of formulation efficacy not being established, we can only simply analyzing constituents and their time course in vivo, and it failed to link the constituents in vivo with the clinical efficacy of TCMs. Therefore, we integrated syndrome biomarkers found by metabolomics and constituents analysis in vivo using SPT. Meanwhile, evaluating the efficacy of formulation, we obtained the active form of the constituents under the therapeutically effective condition of formulation. To mining the correlation between the exogenous constituents in vivo after oral formulation and endogenous markers, the method based on the classical Pearson regression was defined as Plotting of Correlation between Metabolite Markers with Serum Constituent Originated from TCMs (PCMS) which has been developed into software application, and may be a new way to discover the active constituents related to clinical efficacy (Figure 4). The developed PCMS analysis software was awarded national invention patent and software copyright. To determine which constituents contributed to the therapeutic effect of formulation, for example, PCMS was performed using the coefficient described the degree of correlation between two variables: all the exogenous constituents in vivo and the endogenous biomarkers in vivo. According to the correlation coefficient, the constituents in vivo were positively and negatively correlated to syndrome biomarkers, contributed to the therapeutic effect.
Using the prepared rat model of the Huang-dan syndrome, we have evaluated the efficacy of YCHD based on the previously identified 33 metabolic biomarkers, and found that YCHD targeted the key regulatory pathways, thereby helping to restore the metabolic function (Zhang et al, 2013c). Further, the absorbed constituents have been analyzed under the effective treatment conditions of YCHD, 21 compounds in vivo derived from YCHD were identified. Interestingly, eight of the 21 compounds in vivo, such as genipin 1-gentiobioside, capillarisin, etc, could be absorbed only under the compatibility of whole formulation, showing scientific significance of compatibility. On the premise of the curative effect of YCHD, correlation analysis between the exogenous ingredients and endogenous marker metabolites from a single drop of blood is used to clarify the effective substances (Figure 5). To determine the constituents contributed to the therapeutic effect, we extracted the relevant chemical component data and then identified the individual components using the PCMS. It showed that, top three constituents had an extremely positive and negative relationship with therapeutic effect (Wang et al, 2013). The combination can more significantly increase the plasma level, decrease elimination rate than any one or two of the three individual compounds (Zhang et al, 2011). They can exert a more robust synergistic effect than any one or two of the three individual compounds by hitting multiple targets and activating an array of factors that are involved in energy, amino acid, nucleotide, fatty acid, cofactors, and vitamin metabolism.

3. Application of Chinmedomics

Chinmedomics was applied to clarify the metabolic profiling and biomarkers of TCM syndromes, dissect the therapeutic efficacy of the related formulations, and develop the significant value of clinical experience. Clarifying the effective substances by applying the Chinmedomics may discover lead compounds and the innovative drug based on TCM clinical experiences. Some studies showed that Chinmedomics strategy may provide the effective tool for exploring the essence of syndromes, discovery and screening of the active constituents from herbal formulation.
3.1 Chinmedomics analysis of Wen-xin formulation

Chinmedomics method was used to analyze the serum metabolome of 475 cases of patients suffered from the Xin-yang deficiency syndrome along with coronary heart disease. Interestingly, 38 metabolite biomarkers, such as D-galactose, 17α,21-dihydroxyprog-nenolone, lactosylceramide, inoleic acid, cystidine, D-tryptophan, L-glutamin, 4-hydroxybenzaldehyde, 4-hydroxybenzoic acid, pregnanediol-3-glucuronide, 2-phenylacetamide, etc, were detected and indentified (Cao et al, 2014). These metabolites were mainly related to glutamate, phenylalanine and tyrosine metabolism, glycerol phospholipid metabolism, pyruvate metabolism, etc, and 23 biomarkers after the treatment with WXF were significantly regulated to normal levels by re-balancing the perturbed pathways. Under the effective condition, 20 compounds were identified from the blood of patients treated with Wen-xin formulation. PCMS correlation model between the marker metabolites and constituents in vivo was established, and six potentially active constituents such as albiflorin, paoniflorin, coptisine, berberine, palmatine, and ginsenoside Rg1, were highly linked with the adjustment of biomarkers. These compounds were validated by biological test to define as effective material basis of Wen-xin formulation protecting against Xin-yang deficiency syndrome.

3.2 Kidney-yang deficiency syndrome with targeting actions

A TCM formulation (AS135) is consisted of eight herbs, but the therapeutic mechanism, effective constituents, and potential targeting actions of AS135 on “Kidney-yang deficiency syndrome” (KYDS) are unclear. In a study, Chinmedomics strategy was designed to explore the active components and potential targeting actions of AS135 on KYDS (Wang et al, 2016b). Serum samples were analyzed to identify the biomarkers related to the therapeutic effects. Interestingly, 48 marker metabolites were identified and associated with alpha-linolenic acid metabolism, fatty acid metabolism, sphingolipids metabolism, phospholipid metabolism, steroid hormone biosynthesis, and amino acid metabolism. The correlation coefficients between the constituents in vivo and the changes of biomarker metabolites were calculated and the potentially effective constituents of AS135 were also confirmed. The effective substances of AS135 including betaine, scoparone, clovene, stepharine, longipedumin C, gomisin S, schizandrin, auxin A, and 1,11-undecanedicarboxylic acid were extracted by PCMS analysis method (Figure 6). These components in AS135 protects against KYDS by re-balancing metabolic disorders of fatty acid metabolism, lipid metabolism, steroid hormone biosynthesis,
3.3 Therapeutic effect of Kai-Xin-San treated on Alzheimer’s disease

Kai-Xin-San (KXS), originally recorded in the Chinese ancient medical formulation book *Qian-Jin-Yao-Fang* by Si-mao Sun for centuries ago, is a TCM formulation consisting of four herbs, *Ginseng Radix*, *Polygala Radix*, *Poria*, and *Acori Tatarinowii Rhizoma*. Moreover, it has been used for the treatment of neurasthenia and Alzheimer’s disease. We found that KXS significantly improved cognitive impairment, attenuated hippocampal histopathological abnormalities, reduced Aβ1-40 levels, and increased Bcl-2 and ChAT expression in the hippocampus (Chu et al, 2016). Metabolomics technology was used to reveal the potential biomarkers of AD and influenced metabolic pathways by KXS (Figure 7). The chemical composition of KXS was analyzed by UPLC-MS technology. A total of 106 compounds were identified, including 34 from ginseng which mainly for saponins, 23 derived from *Poria*, 35 from *Polygala Radix*, 15 from *Acori Tatarinowii Rhizoma*. SPT was introduced to...
investigate the constituents absorbed into blood after oral administration of KXS. Sixty-seven constituents were screened and including 46 prototypes in vitro and 20 metabolites which originated from KXS. Changes in metabolic profiling of AD were close to normal states through regulating multiple perturbed pathways after KXS treatment. Based on PCMS, it was found that 25 constituents were most associated with potential biomarkers which may be the effective substance of KXS against AD.

4. Discussion and conclusion

TCM is a healthcare system with rich experience over 3000 years of continuous practice and refinement. With the improvement of omics (including genomics, proteomics, transcriptomics, and metabolomics) technologies, scientists have gradually realized that these omics technology-based diagnostic principles can be used as a bridge between TCM and modern medicine and life sciences. At present, though the applications of omics technologies on TCM are much less popular than on modern medicine, preclinical and clinical TCM studies by omics technologies have also achieved great successes.

Recent omics technological advances have helped cast light on the essence and molecular basis of TCM. Specially, in the 21st century, we have made SPT integrated with metabolomics, developed Chinmedomics methodology, contributed to investigate the molecular mechanisms and effective substances of TCM. It has opened the new gate-ways in therapeutics and drug discovery and development. The establishment and implementation of Chinmedomics had made the innovative achievements in solving key scientific problems about the efficacy aspect of TCM. At the end of 2015, Nature (Wang, 2015) gave a systematic presentation on our research work, and commented that “Chinmedomics provides a powerful approach to evaluate the efficacy of TCM formulation; The Chinmedomics approach will contribute to finding a common language to bridge TCM and Western medicine”. Therefore, this paper outlines the current progress of Chinmedomics, proposes an integrated strategy for facilitating drug discovery and development from TCM. We sincerely hope that the Chinmedomics could mine the scientific values of TCM formulation, innovative drug design based on clinical experience, and enhance the academic level and clinical efficacy of Chinese medicine.

Conflict of interest statement

The authors declare no competing financial interests.

References


