Recent Advances in ZHENG Differentiation Research in Traditional Chinese Medicine

Review Article

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Abstract ZHENG, also known as traditional Chinese medicine (TCM) syndrome or TCM pattern, is an integral and essential part of TCM theory. A TCM ZHENG, in essence, is a characteristic profile of all clinical manifestations that can be identified by a TCM practitioner. Clinical treatments of a patient rely on the successful differentiation of a specific ZHENG. Recently, some new technologies and methods such as the System-Omics approach were introduced in ZHENG research, which significantly facilitate the development of ZHENG theory. This review focuses on a brief introduction of these new technologies and methods and their application in TCM ZHENG differentiation research. Also, some of the latest progress and applications in this area, such as ZHENG measurement, information collection, data analysis and mining, ZHENG differentiation based TCM treatment, and mechanisms of ZHENG differentiation based on biological networks reviewed.

Keywords ZHENG, Traditional Chinese Medicine, ZHENG Differentiation, TCM Treatment

1. Introduction

Traditional Chinese medicine (TCM) ZHENG, also known as TCM syndrome or TCM pattern, is an integral and essential part of TCM theory [1]. ZHENG is a profile of symptoms and signs as a series of clinical phenotypes, which reflects the essence of pathological changes at a certain stage in the process of disease occurrence and development and plays an important role in understanding the human homeostasis and guiding the applications of TCM treatment. The diagnostic and therapeutic methods of TCM practice are based on ZHENG differentiation; this concept has been used for approximately one thousand years in China [2]. In order to facilitate the development and application of TCM ZHENG, scientific evidence for ZHENG differentiation is essential. Such evidence would also be beneficial for understanding the essence of ZHENG.

Recently, studies of TCM ZHENG have dramatically increased in number. A literature analysis of TCM ZHENG [3] found 275,408 Chinese-language studies in the SinoMed database (CBM) and 28,103 English-
language studies in the PubMed database. In addition, the proportion of clinical studies has substantially increased. The advantages of integrating TCM ZHENG with biomedical disease diagnoses has been emphasized in recent years and a number of novel achievements have been acquired in this field.

The increase in the number of TCM ZHENG studies occurred in conjunction with advances in biomedical technologies and analytic methods [4]. Advances in systems biology in particular have allowed the application of new phenotype technologies in the study of ZHENG differentiation with plausible biological interpretations. Understanding the characteristic changes in biochemistry associated with a specific TCM ZHENG will facilitate the development of ZHENG identification, as well as a novel disease diagnostic and stratification approach that will potentially lead to personalized healthcare strategies for a range of diseases that lack therapeutic solutions [1].

Since ZHENG differentiation is a process from ZHENG information collection to identification, here we have reviewed the recent advances in ZHENG research, including the measurement of a patient’s symptoms and signs, information collection, and data analysis and mining. Furthermore, advances in the mechanisms of ZHENG differentiation, ZHENG differentiation based treatment, and animal models of ZHENG are also introduced.

2. Clinical ZHENG measurement and information collection

In TCM, the clinical diagnosis of ZHENG relies on the gathering of clinical information through four traditional diagnostic methods: inspection, auscultation and olfaction, inquiry, and palpation. For ZHENG identification, the objective and quantified collection of clinical ZHENG information, in other words, a patient’s symptoms and signs, using appropriate technologies or methods is required. Clinical ZHENG measurement and information collection is accomplished mainly through the establishment of a TCM questionnaire and improvement of the four diagnostic methods.

For the acquisition of ZHENG-related clinical information, Zhang H et al. [5] established a TCM liver disease questionnaire (TCMLDQ) with a ZHENG scale for ZHENG measurement in patients with post-hepatic cirrhosis. When compared to the chronic liver disease questionnaire (CLDQ), they found that the two scales show good consistency in the evaluation of severity and quality of life of liver cirrhosis patients. Zhao H et al. [6] developed and evaluated a TCM questionnaire with 50 items that embodies the features of ZHENG diagnosis for measuring sub-optimal health status (SHS), indicating that it is a reliable and valid instrument for ZHENG measurement in SHS.

The four traditional diagnostic methods are dependent upon the TCM practitioner’s clinical observations: listening, smelling, asking, feeling, and judgments based on experience. Researchers have focused on the improvement of the four traditional diagnostic methods. Li F et al. [7] designed a computer-assisted classification model to provide an automatic and quantitative approach for the diagnosis of TCM based on images of the lip. Yue X Q et al. [8] and Pang B et al. [9] digitalized tongue images using computer technology in order to obtain semi-quantitative measurements using tongue observations. Instead of pulse diagnosis relying on the tactile sense of the TCM practitioner, a TCM pulse detector was established and utilized to improve the accuracy and repeatability of pulse diagnosis [10]. Furthermore, Niu X et al. [11] and Wang Y et al. [12] introduced the digitalization and quantification of techniques of auxiliary diagnosis based on the combination of the four TCM diagnostic methods. In addition, semi-quantitative research on the symptoms and signs as a grading and scoring method [13] and the grading and score combined weighting factor method [14] have been reported.

3. Data analysis and mining for ZHENG differentiation

ZHENG is not merely an assembly of various disease symptoms, but is also an organization of interrelated clinical manifestations following the TCM theory. The interrelated symptoms and signs of diseases in ZHENG measurement should be analysed using appropriate statistical tools to better understand ZHENG differentiation.

Recent research has presented clinical information dimensionality reduction and data mining for ZHENG differentiation. Information dimensionality reduction is extracting the related characteristic factors of symptoms and signs from clinical information using rough set [15, 16], Shannon entropy [17, 18], association rules [19], mutual information and minimum redundancy maximum relevance [20], factor analysis [21, 22], the dynamic correlation coefficient cluster method [23], and other methods.

Data mining for ZHENG differentiation has been carried out using the combination of rough set and Bayesian model [15] or support vector machines (SVM) [16] in post-hepatic cirrhosis; Bayesian network in depression patients [9, 24]; Bayesian network combined with SVM in coronary artery disease [25]; decision trees and relation rules [26] and multi-label learning using the relevant feature for each label algorithm [20] in gastritis; artificial neural network [27] and wavelet packet transform
combined with sample entropy [28] in coronary heart disease (CHD); structural equation modelling in menopause syndrome [29, 30]; logistic regression [31, 41] in stomach cancer; entropy cluster algorithm in five different diseases [32] and in chronic gastritis [33]; and partial least squares [34], soft independent modelling of class analogy [35], and fuzzy recognition [22] in posthepatic cirrhosis. In addition, information entropy was also applied in the correlation between ZHENG and seasonal change [36].

4. ZHENG identification following the System-Omics approach

Systems biology and Omics, a System-Omics approach, mainly include genomics, transcriptomics, proteomics, and metabolomics, which are rapidly growing large-scale detection technologies [37]. Genomics indicates what can occur; transcriptomics indicates what is going to happen; proteomics indicates what happened; and metabolomics indicates what has happened [38]. Genomics focuses on gene networks, pathways, metabolites, and molecular targets of whole bodies from a top-to-bottom view. With the features of non-destructiveness, integrity, multi-target, high-throughput, and digitalization, it may be feasible to investigate TCM ZHENG using System-Omics technologies, which would be characterized by multi-factors, multi-phenotypes, and dynamic status [2, 39]. This could provide helpful tools for TCM ZHENG research.

4.1 Genomic research

Genomics, also known as gene polymorphism, is a tool for evaluating the correlation between genotypes and phenotypes of disease or health. The technologies include polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP), PCR-ligase detection reaction (PCR-LDR), single nucleoside polymorphisms shot (SNPshot) technology platform, gene chip, and gene sequencing. Wu Y et al. [40] assessed the correlation between genetic variations of metabolic genes and TCM constitutions, and observed that SNPs and haplotypes of PPARD, PPARG, and APM1 may underlie the genetic basis of ZHENG classification. Li QY et al. [41] revealed the interleukin 10-819 C/T genotype was probably correlated to Deficiency syndrome in hepatitis B-caused cirrhosis. Moreover, APOE polymorphisms have been reported to associate with TCM syndrome types in type II diabetes [42] and in primary hyperlipidaemia [43]. Angiotensinogen gene M235T [44] and angiotensin II type I receptor gene A1166C polymorphisms [45] are associated with ZHENG types in essential hypertension. Leukocyte antigen (HLA) class II polymorphisms were reported to associate with the physiologic characteristics defined by TCM [46]. In addition, linkage disequilibrium SNPs from a Kidney-Yang deficiency syndrome pedigree has been identified [47].

4.2 Transcriptomic research

Transcriptomics, also known as global gene expression profile in transcriptional levels, is a tool for evaluating the expression levels of thousands of mRNAs in parallel. Technologies such as gene chip and gene sequencing are usually applied. Lu C et al. [48] examined gene expression profiles in CD4+ T cells to classify cold and heat syndromes using gene chips. Li S et al. [49, 50] explored the essence of cold and heat syndromes in TCM through the Neuro-Endocrine-Immune (NEI) system and found that 25 specific modulations of genes occurred in the cold syndrome and were mainly concentrated with energy metabolism function. Ma XJ et al. [51] compared the differential gene expression profiles in CHD patients with and without blood stasis syndrome and found that the inflammatory- and immune-related genes were correlated with blood stasis syndrome. Guan Y et al. [52] analysed differential gene expression profiles in chronic hepatitis B patients with different TCM syndromes and found that there is a molecular foundation in the ZHENG classification. Weng L et al. [53] first described the characteristic genomics in hepatocellular carcinoma patients with liver-kidney yin deficiency syndrome. Additionally, the molecular mechanisms of “Same ZHENG for Different Diseases” and “Different ZHENGs for Same Disease” in chronic hepatitis B and liver cirrhosis [54] have also been reported. The results show that the difference between chronic hepatitis B and liver cirrhosis was the gene expression level and the difference between liver-gallbladder dampness-heat syndrome and liver depression and spleen deficiency syndrome was gene co-expression in the G-protein-coupled receptor protein-signalling pathway.

4.3 Proteomic research

Proteomics, a rapidly evolving tool in systems biology for analysing protein expression to a comprehensive degree, is widely applied for disease-ZHENG diagnosis and prognosis. It has been defined as the science and technologies associated with mapping, visualizing, and/or quantitating the expression of all or a majority of the proteins in living systems [55]. Technologies used in proteomics include two-dimensional polyacrylamide gels (2DE) combined with mass spectrometer (MS) or liquid chromatography (LC), matrix-assisted laser desorption/ionization time-of-flight mass spectrometer (MALDI-TOF-MS) and so on. Liu YP et al. [56] used 2DE combined with MALDI-TOF-MS to evaluate the levels of plasma proteins in healthy donors and chronic hepatitis B patients with different ZHENGs, and Xiong XG et al. [57] and Ou JG et al. [58] investigated the essence of wind syndrome caused by gan-yang hyperactivity in multiple diseases. Wu et al. [59] analysed the plasma of CHD patients and found that fibrinogen and granzyme related three decreased proteins and six increased proteins in
BSS. Chu YG et al. [60] measured the serum proteomes of essential hypertension patients and found 102 differentiated protein peaks between abundant phlegm-dampness and control group, among which the combination of four protein peaks found by Biomarker Patterns Software (BPS) could induce abundant phlegm-dampness. Liu JL et al. [61] found differential plasma protein profiles in patients with hyperlipidaemia and atherosclerosis of different patterns of phlegm-stasis syndrome. In addition, ZHENG classification in chronic hepatitis B [62] and the protein profiles of blood stasis [63] of patients by SELDI-based protein chip analysis have been also discussed.

4.4 Metabonomics research

Metabonomics is the study of global metabolite profiles in a biological system under a given set of conditions [64]. Gas chromatography-mass spectrometry (GC-MS), liquid chromatography-mass spectrometry (LC-MS), (UPLC-QTOF-MS), and nuclear magnetic resonance (NMR) are widely applied in this area. Using these technologies, several researchers have detected and classified metabolism profiles and observed significantly differential metabolites or metabolic pathways in the plasma of rheumatoid arthritis patients with cold and heat syndromes [65], in urine samples from knee osteoarthritis patients with two kinds of TCM syndrome [66], in angina pectoris of CHD patients with three kinds of blood stasis [67], in hypertension with Yin deficiency and Yang hyperactivity syndrome [68], hyperlipidaemia and atherosclerosis [69], and tumour [70] patients with phlegm and blood stasis evolution syndromes, in diabetes mellitus patients with deficiency and excess syndromes [71] and Qi deficiency syndrome, in Qi and Yin deficiency and dampness syndromes [72], in hepatitis B caused by cirrhosis with multiple ZHENGs [73], and in liver-stagnation and spleen-deficiency syndrome in different diseases [74]. Recently, a NOESY pulse NMR has been also applied in a metabonomics study of CHD myocardial ischemia with BSS [75].

5. ZHENG differentiation based TCM treatment

ZHENG differentiation, also called “Bian ZHENG”, is the comprehensive analysis of clinical information and is used to guide the choice of treatment either by TCM herbal formulae or acupuncture. ZHENG differentiation can be used for further stratification of a patient’s condition with a certain disease, identified by orthodox medical diagnosis, which could help improve the efficacy of the selected intervention. In modern TCM research it is possible to integrate syndrome differentiation with orthodox medical diagnosis, leading to new scientific findings in overall medical diagnosis and treatment [76].

Recently, some clinical research has focused on the better effectiveness of TCM treatment based on ZHENG differentiation. Li SY et al. [77] conducted a four-centre, open-label, randomized, controlled study and found that, based on the TCM patterns, Bu-Fei Jian-Pi granules, Bu-Fei Yi-Shen granules, and Yi-Qi Zi-Shen granules had beneficial effects on measured outcomes in stable chronic obstructive pulmonary disease patients over the six-month treatment and 12-month follow-up. Yu L et al. [78] performed a randomized, controlled trial which compared Western medicine treatment to Chinese medicine treatment based on ZHENG differentiation to determine which is more effective at improving cognitive function in Alzheimer’s disease patients observed using a resting-state functional magnetic resonance imaging technique. Pan H [79] reported that herpes zoster treated with acupuncture based on ZHENG differentiation combined with prickling and cupping therapy is highly pertinent and effective and that post-herpetic neuralgia could be significantly reduced. In addition, a clinical study [80] reported the survival benefit of using ZHENG differentiation treatment for elderly patients with stage II or III colorectal cancer.

On the other hand, the ZHENG related therapeutic efficiency of TCM treatment was evaluated using the System-Omics approach. Sun P et al. [81] reported on the effect of JingQianPing Keli in treating liver-Qi invasion patients with premenstrual syndrome by metabolic analysis, and found that the endogenous metabolite disorder was repaired in these patients. Sun S et al. [82] investigated urine metabolic materials in ZHENG differentiation and found that the efficacy of Fuzhenghuayu (FZHY) tablets in patients with cirrhosis caused by hepatitis B, patients with spleen deficiency, with dampness encumbrance syndrome, and patients with liver-kidney yin deficiency syndrome was better than that of other syndromes. Furthermore, Yu S et al. [83] combined ZHENG differentiation and high-throughput gene chip data to perform predictions and found FZHY had new effects on diabetes and dyslipidaemia. Xue M et al. [84] examined the effects of Xuefu Zhuyu Oral Liquid on haemorheology in patients with blood-stasis syndrome due to coronary disease and their relationship with human platelet antigen-3 polymorphism. Animal models of ZHENG have been established in order to experimentally evaluate TCM ZHENG differentiation and ZHENG-based treatment, and an established methodology and criteria for ZHENG animal models in rats and mice have been reported [85]. Recently, Chen Z et al. [86] established mouse xenograft pancreatic cancer models with dampness-heat, spleen-deficiency, and blood-stasis syndromes, and found that they correlated with the treatment response to herbal medicine. Zhao HY et al. [87] investigated the protective effect of Yi Shen Juan Bi Pill in arthritic rats with castration-induced kidney deficiency syndrome, and reported that its
pharmacological mechanism was partially associated with lipid metabolites involving free fatty acid and lysophosphatidylcholine. Moreover, it has also been reported that metabolic profiling revealed the therapeutic effects of Herba Cistanches [88] and Rhizoma Drynariae extracts [89] in an animal model of hydrocortisone-induced kidney-deficiency syndrome, and that the disorder of endogenous metabolites in the urine gradually returned to normal after the intervention.

6. Mechanisms of ZHENG differentiation based on biological networks

ZHENG is a kind of phenotype underlying the interaction of multi-level factor disorder in the body, which suggests an imbalance in the biological network at the system level. The biological network [90], which is based on system biology and Omics, as a network mode of “multiple factor interaction-biological network-multiple function” afforded a new research approach for diseases - ZHENG research, and the ZHENG-oriented effects of Chinese herbal medicine or formula research for understanding the mechanism [91]. In addition to the system biology and Omics, biological network technologies mainly involve data acquisition and validation, such as high-throughput and high-content screening technology, dual high-throughput gene expression detection technology and molecular interaction validation, database construction, network analysis, and visualization techniques [92].

TCM database construction is a prerequisite for ZHENG research using biological networks. Li S et al. [93] combined the Chinese herbal literature and microarray gene-expression data to develop a literature mining and microarray analysis (LMMA) method, which was successfully used in the construction and analysis of a specific disease-syndrome network as well as a tumour angiogenesis related biological network, and found the multiple signalling pathways had a synergistic effect. Furthermore, this research group has established a TCM cold syndrome and hot syndrome network model based on the Nerve-Endocrine-Immune (NEI) interaction [49]. Network structure analysis has revealed that cold syndrome and hot syndrome are related to different regulated modes of the NEI network. Network properties analysis has also found that cold syndrome and hot syndrome networks have the characteristics of complex networks, suggesting that formation of the syndrome is due to multiple factors and specific combination disorders, and that the network function depends on the part of the function modules and the key node.

Furthermore, Jiang M et al. [94] reported on the effectiveness of treating rheumatoid arthritis patients in a randomized clinical trial as reanalysed after the patients were classified into different TCM patterns, and found that the pharmacological network of TCM intervention merged well with the molecular network of TCM hot pattern, and the pharmacological network of biomedical therapy merged well with the network of cold pattern. In addition, data mining combined with the network visualization technique has also been applied in TCM ZHENG research. Shi Q et al. [95] utilized a complex network and CHAID decision tree to identify the TCM core ZHENG in CHD patients and to establish ZHENG identification modes of CHD based on biological parameters.

7. Discussion

In order to obtain a better therapeutic effect, ZHENG differentiation and ZHENG-based treatment are usually carried out in TCM clinical practice. The traditional four diagnostic methods are dependent upon the TCM practitioners’ clinical observations, as well as listening, smelling, asking, feeling, and judgments based on experience, in which objective criteria and repeatability are absent. Though previous research has attempted to differentiate ZHENG from different points of view and different methods, unified standards for ZHENG measurement and information collection, data analysis and mining, and so on, are still lacking. Exactly how to establish unified objective criteria for ZHENG differentiation, find the characteristics of ZHENG and guide TCM treatment in various diseases are all important research topics for ZHENG differentiation in the future.

To clarify the mechanisms in occurrence, development and evolution of TCM ZHENG in various diseases, and the pharmacological and safety evaluation of TCM treatment or new drug discovery, TCM ZHENG animal models as well as disease models are required. However, it is difficult to accurately embody the information obtained from patients by the four diagnostic methods, including symptoms, tongue presentation, and pulse conditions, in animal disease models. This is the key problem related to obtaining the ZHENG characteristics of animal disease models from traditional methods [96]. Since TCM ZHENG is a kind of clinical phenotype of disease, there should be a biological basis in ZHENG as well as human diseases. Following the development of biomedical techniques, it is possible to analyse the ZHENG characteristics of animal disease models using biological parameters. It is important to find ZHENG biological characteristics in animal disease models.

With a holistic feature in TCM ZHENG, it is important to evaluate ZHENG differentiation and ZHENG-based TCM treatment through the System-Omics approach. Previous research has revealed that System-Omics methods are suited for ZHENG global evaluation and biomarker screening, indicating that there is a molecular basis in
ZHENG classification, that there are differential expression profiles in different molecular levels and differential genes, proteins and metabolites among ZHENGs in diseases, and that there is the un-regulation of multi-molecular, multi-function and multi-pathway among ZHENGs in diseases. How to integrate systematically the information from genomics, transcriptomics, proteomics, metabonomics, etc., and find biomarkers for evaluating the advantages of ZHENG differentiation and ZHENG-based TCM treatment will be meaningful in future ZHENG research and clinical practice.

Since a feature of dynamical change in TCM ZHENG, the dynamical profiles of ZHENG differentiation and ZHENG-based TCM treatment in the process of diseases should be evaluated. Previous research has established a ZHENG dynamical variation based TCM therapeutic effects evaluation method for virus pneumonia [97], as well as a similarity match measure based dynamical TCM ZHENG therapeutic effects evaluation method for cirrhosis caused by hepatitis B [98]. However, there is still a lack of methods for evaluating dynamical changes in ZHENG differentiation and ZHENG-based TCM treatment. Moreover, due to the integrity, dynamic, and complexity features of TCM ZHENG, it is difficult to clarify the essence of ZHENG. In the future, conducting an international collaborative study that examines both a disease and ZHENG or ZHENG-based availability between TCM researchers and biomedical scientists would be beneficial.

In summary, the concept of TCM ZHENG, as a diagnostic approach in TCM, should provide invaluable guidance about therapeutic choices and personalized disease management, not only in traditional medical practices but also in modern healthcare systems. We hope clinical trials larger in both size and number utilizing TCM ZHENG will be conducted in the future to further promote the development of evidence-based personalized medicine.

8. References


