Journal of Ethnopharmacology

Syndrome differentiation in modern research of traditional Chinese medicine

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ARTICLE INFO

ABSTRACT

Syndrome differentiation (*Bian Zheng*) in traditional Chinese medicine (TCM) is the comprehensive analysis of clinical information gained by the four main diagnostic TCM procedures: observation, listening, questioning, and pulse analysis, and it is used to guide the choice of treatment either by acupuncture and/or TCM herbal formulae, that is, Fufang. TCM syndrome differentiation can be used for further stratification of the patients' conditions with certain disease, identified by orthodox medical diagnosis, which could help the improvement of 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. In this review, the focus is to screen published evidence on the role of syndrome differentiation in modern TCM research with particular emphasis on basic and clinical research as well as, pharmacological evaluation of TCM herbal formulary for drug discovery.

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1. Introduction

Currently traditional Chinese medicine (TCM) is an essential part of the healthcare system in several Asian countries, and is considered a complementary or alternative medical system in most Western countries (Jiang et al., 2010a). The general practice of TCM depends on the accurate diagnosis and treatment procedures known as Bian Zheng Lun Zhi (syndrome differentiation followed by treatment procedures). Syndrome differentiation is one of most important concepts in the practice of TCM that consists of a series of diagnostic procedures. Syndrome differentiation is different from the conventional diagnosis methodology used in orthodox medical practice. It is the process of comprehensive analysis of clinical information obtained by the four main diagnostic TCM procedures: observation, listening, questioning, and pulse analyses. It is used to guide the choice of TCM treatment using acupuncture and or TCM herbal formulae, that is, Fufang. Thus the complete TCM process is known as *Bian Zheng Lun Zhi*, "Treatment based on syndrome differentiation". Correct TCM syndrome differentiation is the most

important principle that guides the prescribing of Chinese herbal formulae (Bao et al., 2010). It is possible to integrate TCM syndrome differentiation and biomedical diagnosis in modern clinical practice. As shown in Fig. 1, diseases diagnosis shown in the transversal way for patient classification and TCM syndrome differentiation shown in the longitudinal way indicate a cross relationship. A patient can suffer from 2 or more diseases at same time, and one disease can show 2 or more TCM syndromes. Similarly a patient can show a mixture of TCM syndromes (2 or more syndrome), and one TCM syndrome can be shown in different diseases. Moreover, syndrome differentiation is dynamic, and one syndrome could be altered after TCM treatment according to the previous TCM diagnostic pattern (symptoms, signs, tongue appearance and pulse feelings).
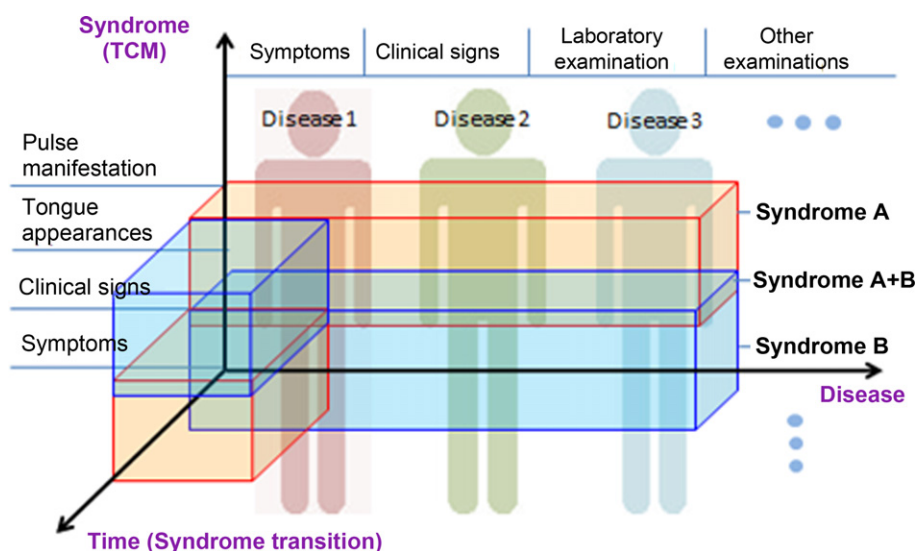
The information obtained from syndrome differentiation, including symptoms, pulse feelings and tongue appearance, is often considered to be subjective. Patients' responses to treatment and their feelings can be recorded objectively in terms of patients' reported outcomes (PROs), using instruments such as the scaling ruler and questionnaires (Zhao and Chan, 2005). Recently TCM syndromes were detected and verified in many diseases, including Fibromyalgia Syndrome (Aliyev et al., 2010), amnestic mild cognitive impairment and Alzheimer's dementia (Miao et al., 2009), hyperlipidaemia (Xue et al., 2010), gastric mucosal dysplasia (S.W. Shen et al., 2011), thoracic diseases (Fu et al., 2011). Some correlations between certain TCM syndrome and the disease were also validated: the association between *Shen (kidney)* deficiency syndrome and postmenopausal osteoporosis (Chen et al., 1999), *Xue Yu* (blood stasis) syndrome and coronary heart disease (Chen et al.,

Fig. 1. Concept of TCM syndrome differentiation and its correlations to biomedical disease diagnosis. TCM syndrome and biomedical disease are classified basing on different parameters, and they can be linked to each other as shown; TCM syndrome also exhibits transitional changes during the treatment of the illness.

2011). Such observations have provided the substantial evidence for the objectiveness of TCM syndrome differentiation.

TCM has its origins in China and the information for the TCM syndrome differentiation is used in the past by the Chinese based on the Chinese cultural development and understanding of TCM and its philosophies. The medical service based on TCM syndrome differentiation may be difficult to be understood in the west, but in the recent years where TCM practice outside China is widespread, the TCM concepts have been adopted and practised gradually. However scientists in the west may not be familiar with the intricacies of the syndrome differentiation and have generally focused on phytochemical approaches on Chinese materia medica (CMM) with no reference on TCM syndrome differentiation research. Yet recently researchers outside China have demonstrated that the TCM syndromes can be observed in patients who are not of Chinese origin. For instance, evidence was observed in the distribution of similar TCM syndromes in Australian and Chinese women with primary dysmenorrhoea (Zhu et al., 2009); the *Shen* deficiency syndrome could be diagnosed in both German and Chinese menopausal women under the same diagnostic criteria (Rampp et al., 2008). TCM syndrome differentiation, if adopted as the diagnostic method for the substantial part in modern TCM research, would lead to new scientific findings for medical sciences. In this review, we have explored its roles on modern TCM research and particularly focused on its innovative impacts on medical research.
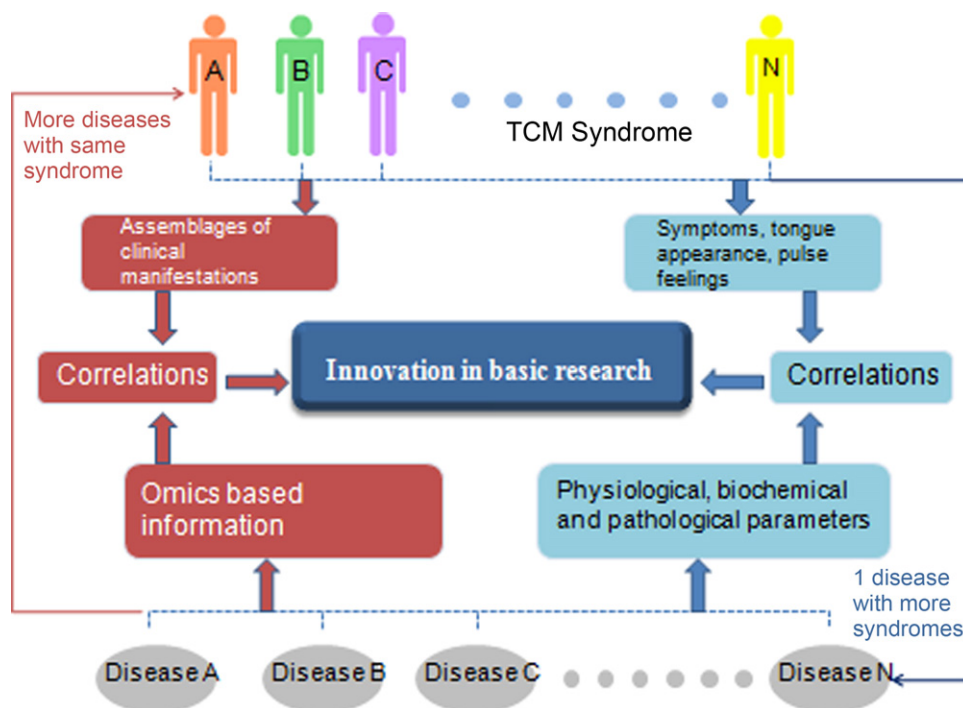
2. Syndrome differentiation and modern research in TCM diagnosis

One TCM syndrome differentiation can be observed in different diseases as identified by western medicine (WM), and different syndrome differentiation can be shown in one WM-disease (biomedical disease). Thus it is not necessary to have a "one to one" correlation between the TCM syndrome and the biomedical disease. In the clinical practice in China, both the biomedical diagnosis for the disease and TCM syndrome differentiation are often incorporated, and the correlation between the biomedical disease and TCM pattern is considered as the most important approach for modern TCM diagnosis research. Fig. 2 indicates how the correlation between TCM syndrome differentiation (e.g. tongue appearance or pulse feeling) and the biomedical parameters (the diagnosis information obtained from laboratory parameters and

omics/biomarkers data related to the biomedical disease) can be explored and further focused.

Considerable achievements have been made in correlating TCM syndromes differentiation with measurable modern biomedical indexes. The observations include: the linkage between sex hormones and *Shen deficiency* syndrome was identified in chronic nephritis (Zhang et al., 1990); between C-reactive protein and *Han/Re* (cold/hot) syndrome in rheumatoid arthritis (RA) (Zhao et al., 2006); between *Qi-Yin* deficiency syndrome in type 2 diabetes mellitus patients (Xie et al., 2011); between carotid intima–media thickness (IMT), triglyceride (TG) and blood rheology with certain TCM syndrome (Lei et al., 2009); between *blood stasis* syndrome score with 24-h urine protein ration, cholesterol, estimation of glomerular filtration rate (eGFR) in the primary glomerular diseases (Li et al., 2009); between the bone mineral density and *Shen deficiency* syndrome in chronic obstructive pulmonary disease (COPD) (Wang et al., 2005); between serum level of eosinophil cationic protein in asthmatic patients and the development of "*heat*" syndrome manifestations (Hsu et al., 2003); between the decrease in skin electrical conductance and the severity of *Qi deficiency* syndrome (Yu et al., 1998). More studies are in progress to explore the correlations between TCM syndrome and the biological indexes. We believe that, following the use of data mining techniques and bioinformatics approaches, the biological basis of TCM syndrome would be further clarified.

Systems biology approaches have recently been innovatively utilized in the TCM syndrome differentiation studies. Systems biology is similar to the views of the holistic approaches and syndromes differentiation of TCM. It has been pointed out these systems biology-based diagnostic principles can be used as pillars of the bridge between TCM and biomedicine (Xue et al., 2006; van der Greef et al., 2010). From the view of the gene expression profile, the TCM syndrome differentiation has close intrinsic relations with not only the difference of gene expression but also the gene polymorphisms. Therefore, applying the advanced microarray and sequencing techniques can help clarify the biological basis of TCM syndrome (Xue et al., 2006). By using the microarray, RT-PCR and ELISA technologies, it was explored that *Shen Yang deficiency* syndrome is involved in special SNP linkage disequilibrium (LD) in the intragenic level (Ding et al., 2009b), and the marked low level of energy output in *Shen Yang deficiency* syndrome may be primarily attributed to the insufficient activity of the MAPK pathway (Ding et al., 2009a). The correlation of
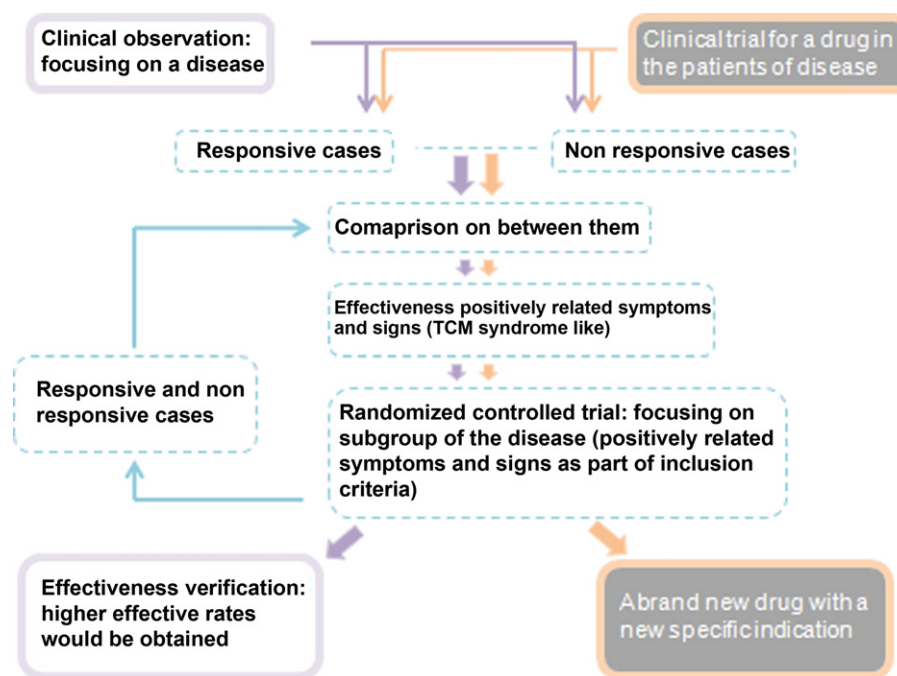
Fig. 2. Application of TCM syndrome differentiations in modern innovative research in TCM. The correlation can be applied either between TCM symptoms (including tongue appearance and pulse feeling) and biological parameters in biomedicine, or between TCM syndrome (assemblages of clinical manifestation) and omics parameters/biomarkers in biomedicine.

inflammatory- and immune-related genes with coronary heart disease (CHD) patients of *blood-stasis* syndrome was revealed at the level of nucleic acid, and the target gene IL-8 could play a role in the pathology of CHD with *blood-stasis* syndrome (Ma et al., 2009). The *cold* syndrome was discovered to be possibly caused by the physiological imbalance and/or the disorder of metabolite processes by the microarrays technology (Yang et al., 2007). Similarly, a wide range of metabolomics analytical techniques are widely used in the modern research of TCM syndrome (Liang et al., 2010). For example, the metabolomics method, ultra performance liquid chromatograph/time of flight mass spectrometer (UPLC/TOF-MS) was successfully used in evaluating the animal model of TCM syndrome differentiation (Tong et al., 2011). A urinary metabolomics method based on ultra-performance liquid chromatography coupled with mass spectrometry (UPLC/MS) was developed to study metabolomic characters of the 'Shen Yang deficiency syndrome' rats (X. Lu et al., 2011). By metabolite profiles measured in plasma using GC/MS, molecular differences between the *Cold and heat* syndrome in RA patients were found, which suggest differences in apoptotic activity (van Wietmarschen et al., 2009). Using the GC/TOF-MS-based metabolomic method, the metabolites contributing most to the classification between the *Xin blood stasis obstruction* and *Qi-Yin deficiency* syndrome rats were identified as the potential biomarkers (Yan et al., 2009). A urinary metabolomics method based on the ultra-performance liquid chromatography combined with quadrupole time-of-flight tandem mass spectrometry (UPLC Q-TOF MS) was used to evaluate the efficacy and study the mechanism of TCM herbal preparation in treating the *blood stasis* syndrome (Zhao et al., 2008). Proteomics has recently received extensive attention in the area of medical diagnosis and drug development, and the proteomics data could also contribute to the TCM syndrome differentiation research. We believed that with further development of analytical techniques, systems biological approaches and omics data will greatly promote TCM syndrome differentiation research and be beneficial to the modernization of TCM diagnosis.

The "correlation exploration" studies between TCM syndrome differentiation and biomedical disease not only elucidate the biological basis for TCM syndrome differentiation, but also can help innovative study in biomedicine, and more importantly help the further accurate stratification of patients for intervention selection by fully integrating of the TCM syndrome differentiation and biomedical diagnosis.

3. Syndrome differentiation and modern clinical research in TCM

More and more clinical trials of TCM have been conducted and reported in China and abroad in the last decade with diversified results (Jiang et al., 2010a). The key issue in clinical research in TCM is how to apply TCM syndrome differentiation in the clinical trial design. TCM syndrome differentiation, as a method of patient stratification, could change clinical trial strategy and help design better clinical trials. This could be included in the clinical trial, as TCM syndrome differentiation, can help choose the most appropriate patients for the intervention. The concept behind TCM syndrome differentiation and biomedical disease based efficacy evaluations may optimize clinical trial design by identifying the responsive cases which might be categorized in a certain TCM syndrome differentiation. Fig. 3 indicates, in a clinical trial focusing on a disease, there will always be the responsive and non-responsive cases to one intervention. The comparison analysis between the responsive and non-responsive cases can help detect the effectiveness related symptoms and signs (which might be different from typical TCM syndrome differentiation but homologous with and rooted from TCM syndrome differentiation). Then a next round of clinical trial can be conducted focusing on this subgroup of patients with the positively related symptoms and signs as part of inclusion criteria. We can therefore anticipate that a higher effective rate would be obtained in the second round of clinical trial since the patients have been further stratified with the responsive related factors. This

Fig. 3. Application of the TCM syndrome differentiation in clinical trial design. The left portion illustrates the intervention with TCM syndrome can be obtained from a clinical trial by comparing the differences between responsive cases and non-responsive cases, and the incorporation of the TCM syndrome information for further verification in second clinical trial. The right portion indicates that if the clinical trial is aimed to evaluate the effectiveness of an old drug, the old drug can be assessed to have more specific indication after incorporation of TCM syndrome differentiation via the new clinical trial design.

innovative clinical trial design can also be used for the clinical efficacy evaluation of "old" drug to "renew" its indication (the right part in Fig. 3). Recently a two-stage clinical trial of TCM therapy for the management of RA has been designed (Zhang et al., 2011). The stage one trial is an open-label trial and aims to explore what groups of TCM information (such as symptoms) correlates with better efficacy, and the stage two trial is a randomized, controlled, double-blind clinical trial that incorporates the efficacy-related information identified in the stage-one trial into the inclusion criteria. This design, though not defining the TCM syndrome criteria, does include TCM syndrome differentiation concept.

In the clinical studies which employed TCM syndrome differentiation in the design, the desirable outcomes are found easier to be achieved. For instance, in a double-blinded and randomized clinical trial, *Fufangkushen* enteric-coated capsule was proved to be similarly effective and safe in the treatment of active ulcerative colitis (UC) with TCM syndrome of *damp-heat accumulation interior* compared with a mesalamine enteric-coated tablet, and it even indicated preferable effect in the treatment of UC with inflamed area of the left hemicolon (Gong et al., 2011). In a prospective RCT, *Tanreqing Injection* was proved to be able to improve the TCM signs and symptoms in the patients with acute exacerbation of chronic obstructive pulmonary disease and TCM syndrome of *retention of phlegm and heat in Fei (Lung)* (Li et al., 2010). Good effectiveness was objectively shown in the TCM treatment of children's respiratory syncytial viral pneumonia with *phlegm-heat blocking Fei (Lung)* syndrome in 206 children with a single-blinded multi-center, blocked, randomized and parallel-controlled trial (Yang et al., 2009). In a 108 patients with psoriasis of *blood-heat* syndrome clinical study, a new Pulian Ointment (NPLO) showed a reliable therapeutic efficacy and good safety for the treatment of psoriasis with TCM *blood-heat* syndrome (Zhou et al., 2009). Another RCT proved the definite therapeutic effect and high safety can be achieved in using the TCM therapy to treat RA with syndrome of *damp-heat obstruction* (H.B. Shen et al., 2011). A clinical investigation indicated that a more effective treatment rate could be achieved for RA patients when

co-diagnosed and treated based on their TCM syndrome differentiation classification (Zha et al., 2006). Though some clinical trials and systematic reviews reported that it was difficult to show rigorous evidence for the effectiveness and safety of herbal medicine (M.M. Zhang et al., 2004; Chen et al., 2006; Leung et al., 2006), randomized controlled clinical trials (RCTs) with specific assessment criteria and diagnostic criteria are considered as being able to close the gap between TCM and evidenced-based medicine (Zheng et al., 2011). Therefore the incorporation of TCM syndrome differentiation for further stratification of the patients could improve the efficacy of a certain intervention in clinical practice.

The safety evaluation of a TCM intervention can be conducted basing on the same principle. Through the thousands of years of experience based practice, a full-grown TCM intervention usually possesses a good safety profile when used for its corresponding TCM syndrome differentiation. Some symptoms are proved to be predictive factors/risk factors for the drug adverse reactions (ADRs) in RA patients treated with both TCM and biomedical combination therapy (Jiang et al., 2011b), and there have been documented evidence showing correlations between gastrointestinal ADRs with clinical efficacy in RA patients treated with biomedical combination therapy (Jiang et al., 2010b). Thus the evaluation of TCM treatment efficacy and safety should focus on a specific subgroup of patients with its corresponding TCM syndrome differentiation.

4. Syndrome differentiation and modern pharmacological research in TCM

The clinical application of Chinese herbal medicine (CHM) should be based on syndrome differentiation in TCM, and the pharmacological evaluation of CHM should be also based on the TCM syndrome differentiation. To clarify the CHM pharmacological activity is not only the requirement for TCM globalization, but is also important for guiding the clinical application of CHM. Thus the method of characterizing of the TCM syndrome differentiation in animal disease models becomes the key issue in pharmacological

evaluation. In the past years, some studies have reported that some conditions induced by chemicals could be considered having similar TCM syndrome differentiation since the conditions showed certain clinical manifestations similar to the patients with the TCM syndrome differentiation, and the condition could be reversed by the corresponding CHM. For example, TCM *Pi deficiency (Pi Xu)* rat, induced by reserpine administration, could be treated with the *Lizhong* Pill which can reinforce the *deficient Pi* (Zhao et al., 2011). Rodents with liver injury induced by carbon tetrachloride could be regarded as suffering from the *dampness-heat* syndrome (Cao et al., 2009). A novel mice model induced by chronic intermittent hypoxia showed similar symptoms and signs accorded with the clinical features of *Deficiency of both Qi and Yin* syndrome (Chai et al., 2010). Rats with subcutaneous tumor of pancreatic cancer can be regarded as suffering from syndromes of *Damp heat (Shi-Re) and Pi deficiency* (Dai et al., 2010). Based on the animal models with induced TCM syndrome differentiation, pharmacological evaluations have been conducted on CHM. Using the *Qi deficiency and blood stasis* syndrome rats model, the effects of *Buyang Huanwu* decoction on CHD were proved to be associated with the inhibition of C-reactive protein (CRP) and vascular endothelial regulators (Zhang et al., 2010). More directions on how to integrative TCM syndrome and biomedical disease in animals have been conducted (Chai et al., 2009) and the establishment of the disease with TCM syndrome differentiation induced model could provide new concepts and method for evaluation of CHM (Ma and Zhai, 2010).

However the TCM syndrome differentiation is not only complicated, but also based on the information generated by experience-based TCM diagnostic methods mainly from diagnosis through interrogation. Thus the pharmacological evaluation on CHM using these types of animal models could provide an alternative way. However it is necessary to develop more TCM syndrome differentiation animal models based on the phenotype clinical manifestations, and verified with the positive responses induced by the TCM syndrome differentiation corresponding CHM. On the other hand, following the development of biomedicine, one important way to clarify the TCM syndrome differentiation characteristics of the animal disease model in the pharmacological evaluation is to compare the differences between the responsive and non-responsive animals to a certain intervention, and to find out the responsiveness-related biomedical characteristics, which can be regarded as the essentials of the corresponding TCM syndrome differentiation. The biomedical characteristics can then be applied as the text parameters for the pharmacological evaluation of a related CHM.
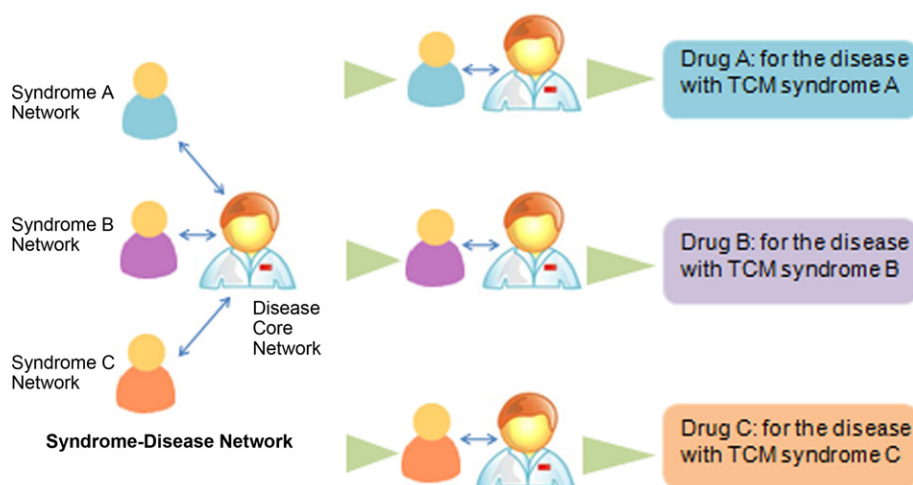
5. Syndrome differentiation and modern new drug discovery in TCM

In orthodox medical practice any agent intended for human use as a prescribed drug often consists of a single chemical compound for the treatment of a specific disease diagnosed by biomedical method. In TCM practice after diagnosis of patient's conditions according to specific syndrome differentiation, multiple component Fufang consisting of several CMM is prescribed to restore the patient's imbalanced conditions. The multiple compounds in Fufang, targeting on the biological network within the human body can be analysed for new drug discovery if their concerted actions can be recorded in terms of network pharmacology that links with the biological networks of disease, the drug and drug-disease interaction, and could provide the leads of becoming the next paradigm in drug discovery as described by Hopkins (2007). Hence new drugs can be discovered from the "old" drugs if they can be redefined with the newly prescribed conditions which are based on the integration of biomedical disease and TCM syndrome differentiation.

Syndrome differentiation should be taken into consideration in new drug discovery since TCM syndrome differentiation is involved in diagnosis and treatment in TCM practice. All natural products can act as drugs for the treatment of disease when they are found effective in certain patients with corresponding TCM syndrome, and such approaches focus on tailoring drug treatment prescribed to the patients. Thus it is possible to find new indication of a certain drug in a clinical trial based on TCM syndrome differentiation concept. Consecutive clinical trials can be employed to find "new" drugs by revealing the TCM syndrome related indications of existing "old" drugs. As shown in the right part of Fig. 3, the findings of the new indication can be realized by determining what are positively or negatively related to the effectiveness. The correlated factors could be obtained by comparing the differences between the effective cases and non-effective cases in the view of syndrome differentiation. Our previous study showed that RA patients with cold syndrome had a significantly higher response rate to the biomedical therapy (consisting of diclofenac, methotrexate, and sulfasalazine) than RA patients with hot syndrome (Lu et al., 2009), and this can give rise to the therapy that could lead to a new drug discovery since its indication was redefined with the TCM cold syndrome. All medicines should be rigorously tested in the clinical trials (Angell and Kassirer, 1998; Tsang, 2007), and potential clinical trials based on TCM syndrome differentiation could be a way for new drug development by referring to the biomedical disease indications.

Network pharmacology, a systems biology based methodology, is a new TCM approach to drug design that encompasses the construction of disease network, drug–target network, drug–disease network. It offers the concept of drug discovery that simultaneously considers the improvement of clinical efficacy and reduction of side effects and toxicity, which are the most important reasons for failure in R&D of new drug (Sams-Dodd, 2005; Hopkins, 2008). Based on TCM network pharmacology, the molecular network of disease diagnosed by TCM syndrome and pharmacological network that relates the herbal formula (mainly multiple herbal compounds) are important key factors for consideration. Information for a disease could be collected and accumulated to build up the molecular network of that particular disease as identified in orthodox medicine. For example, the molecular network has been built up on rheumatoid arthritis (RA) (Wu et al., 2010). The network of a disease could be linked to locate the corresponding pharmacological network of drug treatment (intervention) by merging the disease network with the intervention network. In recent years, scientists focused on the molecular network build-up using TCM pattern differentiation for certain diseases (Zhao et al., 2010). For instance, RA can be differentiated into two major TCM patterns: cold and hot patterns, which can be shown in terms of molecular networks (Jiang et al., 2011a). Separate TCM formula used for intervention of RA of cold or hot patterns, with multiple herbal compounds, are targeting on separate biological networks pharmacologically. Thus building-up of pharmacological network of TCM formula is a good way to find new potential multiple compound medicines for a TCM syndrome in a disease or new targeted TCM syndrome for an "old" drug. Advance information on genomics, proteomics and metabolomics has enabled scientists to correlate proper methodology for building up the molecular pharmacological network in combinational TCM therapy. For example, we have successfully combined text-mining with bioinformatics to build up the functional networks for Salvia miltiorrhiza radix (SM) and Panax notoginseng radix (PN) combination in the TCM intervention of coronary heart diseases by the SM–PN herbal-pair formula (Gao and Aiping, 2011).

By linking the molecular disease network, TCM syndrome with the pharmacological network of the potential TCM formula, we can locate which formula would be the best in treating the disease with the identified TCM syndrome and in terms of molecular disease network. Such approach will further help to choose the right

Fig. 4. Application of TCM syndrome differentiation and new drug discovery. A patient with a certain disease associated with TCM syndrome may show certain characteristics in the disease-based network and syndrome characteristics in TCM syndrome network. Based on the network pharmacology of a drug built up by systems biology approaches, the new drug could be developed with targeting on specific TCM syndrome in a certain disease by comparing and merging the pharmacological network of a new drug candidate with the characteristics in the TCM syndrome network in a disease-based network. The pharmacological networks of potential candidate A, B and C were merged with the molecular networks of TCM syndrome A, B and C in the disease respectively.

new drug candidates for further pre-clinical study (discovering new chemical compounds) or clinical study (for defining the new indication with TCM syndrome for that "old" drug). As shown in Fig. 4, TCM syndrome differentiation network incorporated in the disease biological network can: generate the investigating path for potential drug candidates or locate existing "old" drugs via the merging of TCM syndrome with identified disease biological network and identify the pharmacological networks of tested candidates. More importantly, there are many herbal formulas such as the SM–PN herbal pair, and the herbal formulas would be a great source for new multiple compound drug discovery. The network pharmacology would be helpful in finding the right multiple compound drug candidates from herbal formula for further new drug development.

6. Syndrome differentiation and novel medical equipment development in TCM

The advances in medical technological diagnosis equipment used in monitoring of disease patterns can certainly help modernization of TCM diagnosis and treatment processes. It is recognised that TCM syndrome differentiation is a complicated and experience-based process. To have a generalised and agreed method of diagnosis using novel diagnostic equipment on TCM tongue and pulse diagnosis will assist further development towards objective measurement.

Tongue appearance has some specific features and could be simplified for clear identification in clinical practice though there is a relatively poor consistency in the results of TCM syndrome differentiation due to the subjective nature of assessing complicated tongue appearance and pulse (G.G. Zhang et al., 2004; Zhang et al., 2005). Previous study suggests that tongue coating and tongue body colour might be used to help identify a subset of RA patients for certain interventions (Jiang et al., 2011c). More efforts are needed for research into the diagnostic equipment for accurate measurement of the tongue and pulse diagnosis. It was reported that a digital analysis instrument for the tongue image can objectively describe the tongue features of patients with different syndromes of lung cancer (Su et al., 2011). Efforts have been made to build up a feasible and effective model for pulse analyses in order to facilitate its clinical application. These models were introduced or constructed based on an artificial neural network (Tang et al., 2012), Bayesian networks (Wang and Cheng, 2005) and the ensemble empirical mode decomposition (Yan et al., 2011).

Comprehensive equipment or diagnostic systems on "combination of four examination methods, including inspection, auscultation, interrogation, and pulse-feeling and palpation" for TCM syndrome differentiation are being developed by integrating modern medical techniques. One such system had entered the market in China last year (http://www.daosh.com/s.asp?id=79). The feasibility and usefulness of this system is being tested. We believe that from this launch, more novel diagnostic equipment for TCM syndrome differentiation will be developed and assessed for their usefulness in TCM syndrome differentiation in the near future.

7. Major issues in modern TCM syndrome differentiation research

TCM focuses attention to the integrity of the whole human body and its interrelationship with nature. The component parts of the human body are inseparable and are functionally coordinative and mutually beneficial whilst affecting each other pathologically. Modern biomedical research has entered an era of integrating various research technologies and methods to analyse difficult biological problems at molecular level as a whole, which is shown by studies in terms of genomics, metabolomics and proteomics. Accordingly the application of molecular biology is to study life phenomena and nature of diseases, governing and controlling the development and progression of systems processes. Thus modern research on TCM syndrome differentiation should lead to better progress and understanding of TCM diagnostic approaches. However, there has been few progress in research based on the modern TCM syndrome differentiation. Recently more issues have been taken into consideration for clinical trial design, systems biology technique application and data mining approach applications. These will form the major areas for the improvement of modern TCM syndrome differentiation research.

The key challenge in TCM syndrome differentiation research is how to standardize the diagnostic procedure for syndrome. TCM syndrome is differentiated from the clinical manifestations, and the diversified manifestations would make the TCM syndrome in a patient appearing in syndrome combination or mixed syndromes (we can define the simple syndrome as a syndrome unit in a patient). Some clinical manifestations for TCM syndrome

differentiation are subjective, such as pulse feelings, which might provide different understandings about the pulse feelings in the syndrome differentiation by different doctors. Therefore modern TCM syndrome differentiation research should focus on the typical (easy to be differentiated) and most important TCM syndromes in a disease. For example, RA syndrome research should focus on cold and hot syndrome as they are most important syndromes for RA, similarly _Xue-Yu_ syndrome should be related to coronary heart disease. In some instance, major objective clinical manifestations are considered as bases for TCM syndrome differentiation understandable and simpler. For example, the cold and hot syndromes in RA were differentiated by analysing 13 symptoms, which are objective measures in the score scale system as assessment for evaluation purposes (Lu et al., 2009). Another way for modern TCM syndrome differentiation research is to define the corresponding TCM syndrome when it has positively responded to the intervention (drug treatment or other therapy). In TCM, the choice of herbal formula is closely related to the TCM syndrome, that is, the herbal formula must be effective in treating the patients if they are correctly differentiated according to TCM syndrome. Similarly, the TCM syndrome in the responsive case to an intervention should be the corresponding TCM syndrome for that intervention. At present very limited examples can be identified to be corresponding to TCM syndrome for many interventions (biomedicines included). Therefore the exploration of TCM syndrome via clinical trials that are linked to biomedical diagnosis should be the key topics in modern TCM syndrome differentiation research.

A properly conducted clinical trial is one of the most important methods that measure the success of conventional medical practice and clinical trials involving TCM syndrome differentiation will be the most important method to assess the efficacy of TCM treatment in the future. Due to the complicated and experience-based involvement in the TCM syndrome differentiation, it is preferable to start the TCM syndrome differentiation research at a level that can be incorporated in clinical trial to demonstrate the importance of stratification into different TCM syndromes amongst patients. An example to illustrate such approach would be to focus on the RA, a disease that has definite measureable clinical/biomedical features in conventional medical practice. TCM syndrome differentiation related information can be collected from thousands of RA patients from either expert consensus on the TCM syndrome differentiation or from TCM syndrome differentiation generated using statistical analysis (Li et al., 2006; Lu, 2006). This two stage clinical trial design including TCM syndrome differentiation concept can be integrated (Lu and Li, 2010; Zhang et al., 2011) into the clinical trial (see Fig. 4).

Systems biology is a general trend of contemporary scientific development (Wang et al., 2009). The advances of the "Omics" revolution and methodology in the post-genomic era of life science research, bioinformatics and systems biology have all collectively offered an opportunity to integrate multi-dimensional and multiple data from medical practices. The capturing of these unprecedented opportunities and challenges will provide a platform for research to understanding of the principles of TCM practice. Thus systems biology approaches are expected to open the way to a new convergence of TCM syndrome differentiation information. By analysing microarray, metabolomic data obtained from literature, the TCM syndrome differentiation could be related to biomarkers or biological networks (Cheng et al., in press; Jiang et al., 2011a; A. Lu et al., 2011). Furthermore, systems biology approaches can assist in identifying the therapeutic mechanism of multiple component herbal drugs, including the build-up of the pharmacological networks of the herbal drugs, which can be merged with the TCM syndrome differentiation network in certain diseases to explore the therapeutic mechanism and the biomarkers for specific indication.

Confronted with the increasing popularity of TCM and the huge volume of TCM data, both historically accumulated and recently obtained, there is an urgent need to explore these resources effectively by the techniques of knowledge discovery in database (KDD) (Feng et al., 2006). A series of KDD methods are used in existing knowledge discovery in TCM researches, ranging from conventional frequent item set mining to state of the art latent structure models. Yet few or no obvious progress has been made in TCM practice with KDD techniques. Thus the integrated data mining approaches should be used with the extensively integrated databases, such as the TCM data base in Chinese patients with TCM syndrome differentiation and clinical observation, accumulated case reports in the TCM clinical practice, PubMed in English on biomedicine, and PubChem in English on herbal chemistry and protein targets. We believe that integrated data mining approach application in analysis of the integrated TCM and biomedical and chemical databases would lead to progress in modern TCM research. These may include: the finding of the basic rule for herbal prescription targeting to the corresponding TCM syndrome differentiation in a certain disease, the build-up of the biological network of the disease, and the potential pharmacological network of the herbal prescription.

8. Concluding remarks

Over the past decades, we have identified increasing numbers of clinical trials on TCM treatment efficacy with unsatisfactory RCT designs due mainly to the lack of stratification using TCM syndrome differentiation. We expect higher quality RCT in the future to meet the needs of modern research and development. Such approaches will add more weight to the evidence-based medical practice in TCM. However, it is crucial that the concept of TCM syndrome differentiation should be made understood and substantiated with biomedical evidence in the medical science arena. We have initiated some background work in these areas. Published data have also been initiated by biomedical scientists and researchers in China and worldwide to provide information towards these directions. More effort will be required to substantiate such findings to support the concepts.

The TCM syndrome differentiation uses phenotype-like clinical manifestation to classify patients, which would further assist in stratification for the intervention in order to improve the efficacy of the intervention based on the TCM syndrome differentiation related clinical trial strategy. Research in TCM syndrome differentiation will provide the basis of the molecular network of TCM syndrome differentiation for certain disease types, which will assist in defining the potential mechanism of Chinese herbal medicines. The incorporation of TCM syndrome differentiation into biomedical disease diagnosis will lead to a new era in the development of medical sciences to research in the diagnosis, clinical trial, and new drug discovery in TCM. The way forward to identify evidence-base of TCM syndrome differentiation in TCM practice requires multidisciplinary collaborations amongst different professionals, researchers and scientists of both conventional medical and TCM practices with expertise from biomedical, bioinformatics, medical, pharmaceutical and TCM disciplines.

References

Aliyev, R., Vieth, T., Geiger, G., 2010. Traditional Chinese medicine in diagnosis and treatment of fibromyalgia syndrome. Georgian Medical News, 38–45.

Angell, M., Kassirer, J.P., 1998. Alternative medicine—the risks of untested and unregulated remedies. The New England Journal of Medicine 339, 839–841.

Bao, H., Gao, J., Huang, T., Zhou, Z.M., Zhang, B., Xia, Y.F., 2010. Relationship between traditional Chinese medicine syndrome differentiation and imaging characterization to the radiosensitivity of nasopharyngeal carcinoma. Chinese Journal of Cancer 29, 937–945.

Cao, H.X., Sun, H., Jiang, X.G., Lu, H.T., Zhang, G.M., Wang, X.J., Sun, W.J., Wu, Z.M., Wang, P., Liu, L., Zhou, J., 2009. Comparative study on the protective effects of Yinchenhao Decoction against liver injury induced by alpha-naphthylisothiocyanate and carbon tetrachloride. Chinese Journal of Integrative Medicine 15, 204–209.

Chai, C., Kou, J., Zhu, D., Yan, Y., Yu, B., 2009. Thinking of current situation of animal model of tradition Chinese medicine combining disease and syndrome. Zhongguo Zhong Yao Za Zhi 34, 2673–2675.

Chai, C., Kou, J., Zhu, D., Yan, Y., Yu, B., 2010. Mice exposed to chronic intermittent hypoxia simulate clinical features of deficiency of both Qi and Yin syndrome in traditional Chinese medicine. Evidence-Based Complementary and Alternative Medicine [Epub ahead of print].

Chen, K.J., Shi, D.Z., Xu, H., 2011. The criterion of syndrome differentiation and quantification for stable coronary heart disease caused by etiological toxin of Chinese medicine. Zhongguo Zhong Xi Yi Jie He Za Zhi 31, 313–314.

Chen, X., Wu, T., Liu, G., 2006. Chinese medicinal herbs for influenza: a systematic review. Journal of Alternative and Complementary Medicine 12, 171–180.

Chen, Y.Y., Hsue, Y.T., Chang, H.H., Gee, M.J., 1999. The association between postmenopausal osteoporosis and kidney-vacuity syndrome in traditional Chinese medicine. The American Journal of Chinese Medicine 27, 25–35.

Cheng, L., Xuyan, N., Cheng, X., Gao, C., Qinglin, Z., Hongtao, G., Miao, J., Aiping, L. Network-based gene expression biomarkers for traditional Chinese medicine cold and heat pattern in rheumatoid arthritis. Evidence-Based Complementary and Alternative Medicine, in press.

Dai, H.Y., Wang, P., Feng, L.Y., Liu, L.M., Meng, Z.Q., Zhu, X.Y., Wang, K., Hua, Y.Q., Mao, Y.X., Chen, L.Y., Chen, Z., 2010. The molecular mechanisms of traditional Chinese medicine ZHENG syndromes on pancreatic tumor growth. Integrative Cancer Therapies 9, 291–297.

Ding, W.J., Yan, S.L., Zeng, Y.Z., Li, W.H., Duan, A., Zheng, T.E., Liu, M., Tan, C.E., Teng, X., Wan, J., 2009a. Insufficient activity of MAPK pathway is a key monitor of Kidney-Yang Deficiency Syndrome. Journal of Alternative and Complementary Medicine 15, 653–660.

Ding, W.J., Zeng, Y.Z., Li, W.H., Zhang, T.E., Liu, W.W., Teng, X.K., Ma, Y.X., Yan, S.L., Wan, J.M., Wang, M.Q., 2009b. Identification of linkage disequilibrium SNPs from a Kidney-Yang Deficiency Syndrome Pedigree. The American Journal of Chinese Medicine 37, 427–438.

Feng, Y., Wu, Z., Zhou, X., Zhou, Z., Fan, W., 2006. Knowledge discovery in traditional Chinese medicine: state of the art and perspectives. Artificial Intelligence in Medicine 38, 219–236.

Fu, X.Q., Yang, Y., Dong, L.W., Cheng, G.M., Wang, J., 2011. Rule of Chinese medicine syndrome differentiation in the patients with thoracic diseases at perioperation stage. Chinese Journal of Integrative Medicine 17, 351–354.

Gao, C., Aiping, L., 2011. Prediction of the mechanisms of *Salvia miltiorrhiza* against atherosclerosis using text mining and network-based analysis. Journal of Algorithms & Computational Technology 5, 161–166.

Gong, Y., Zha, Q., Li, L., Liu, Y., Yang, B., Liu, L., Lu, A., Lin, Y., Jiang, M., 2011. Efficacy and safety of Fufangkushen colon-coated capsule in the treatment of ulcerative colitis compared with mesalazine: a double-blinded and randomized study. Journal of Ethnopharmacology [Epub ahead of print].

Hopkins, A.L., 2007. Network pharmacology. Nature Biotechnology 25, 1110–1111.

Hopkins, A.L., 2008. Network pharmacology: the next paradigm in drug discovery. Nature Chemical Biology 4, 682–690.

Hsu, C.H., Yu, M.C., Lee, C.H., Lee, T.C., Yang, S.Y., 2003. High eosinophil cationic protein level in asthmatic patients with "heat" Zheng. The American Journal of Chinese Medicine 31, 277–283.

Jiang, M., Xiao, C., Chen, G., Lu, C., Zha, Q., Yan, X., Kong, W., Xu, S., Ju, D., Xu, P., Zou, Y., Lu, A., 2011a. Correlation between cold and hot pattern in traditional Chinese medicine and gene expression profiles in rheumatoid arthritis. Frontiers of Medicine 5, 219–228.

Jiang, M., Yang, J., Zhang, C., Liu, B., Chan, K., Cao, H., Lu, A., 2010a. Clinical studies with traditional Chinese medicine in the past decade and future research and development. Planta Medica 76, 2048–2064.

Jiang, M., Zha, Q., He, Y., Lu, A., 2011b. Risk factors of gastrointestinal and hepatic adverse drug reactions in the treatment of rheumatoid arthritis with biomedical combination therapy and Chinese medicine. Journal of Ethnopharmacology [Epub ahead of print].

Jiang, M., Zha, Q., Lu, C., He, Y., Lu, A., 2011c. Association between tongue appearance in traditional Chinese medicine and effective response in treatment of rheumatoid arthritis. Complementary Therapies in Medicine 19, 115–121.

Jiang, M., Zhao, J., Lu, A., Zha, Q., He, Y., 2010b. Does gastrointestinal adverse drug reaction influence therapeutic effect in the treatment of rheumatoid arthritis? Journal of Alternative and Complementary Medicine 16, 143–144.

Lei, Y., Wang, Z.H., Zhao, H., Liu, J.G., 2009. Study of the relationship between carotid intima–media thickness and traditional Chinese medicine syndrome of dyslipidemia. Chinese Journal of Integrative Medicine 15, 112–116.

Leung, W.K., Wu, J.C., Liang, S.M., Chan, L.S., Chan, F.K., Xie, H., Fung, S.S., Hui, A.J., Wong, V.W., Che, C.T., Sung, J.J., 2006. Treatment of diarrhea-predominant irritable bowel syndrome with traditional Chinese herbal medicine: a randomized placebo-controlled trial. The American Journal of Gastroenterology 101, 1574–1580.

Li, S., Rao, X.R., Wang, S.X., Zhang, G.H., Li, X.M., Dai, X.W., Chen, K.J., 2009. Study on the relationship between blood stasis syndrome and clinical pathology in 227 patients with primary glomerular disease. Chinese Journal of Integrative Medicine 15, 170–176.

Li, W., Mao, B., Wang, G., Wang, L., Chang, J., Zhang, Y., Wan, M.H., Guo, J., Zheng, Y.Q., 2010. Effect of Tanreqing Injection on treatment of acute exacerbation of chronic obstructive pulmonary disease with Chinese medicine syndrome of retention of phlegm and heat in Fei. Chinese Journal of Integrative Medicine 16, 131–137.

Li, Y., Li, S., Lu, A.P., 2006. Comparative analysis via data mining on the clinical features of Western medicine and Chinese medicine in diagnosing rheumatoid arthritis. Zhongguo Zhong Xi Yi Jie He Za Zhi 26, 988–991.

Liang, Y.Z., Xie, P.S., Chan, K., 2010. Perspective of chemical fingerprinting of Chinese herbs. Planta Medica 76, 1997–2003.

Lu, A., Jiang, M., Zhang, C., Chan, K., 2011. An integrative approach of linking traditional Chinese medicine pattern classification and biomedicine diagnosis. Journal of Ethnopharmacology [Epub ahead of print].

Lu, A.P., 2006. Making repeated clinical trials aiming at finding specific indications is the way for improving clinical efficacy of traditional Chinese medicine. Zhongguo Zhong Xi Yi Jie He Za Zhi 26, 588–589.

Lu, A.P., Li, S., 2010. Principle and application of Chinese medicine syndrome differentiation and disease classification. Zhongguo Zhong Xi Yi Jie He Za Zhi 30, 84–86.

Lu, C., Zha, Q., Chang, A., He, Y., Lu, A., 2009. Pattern differentiation in Traditional Chinese Medicine can help define specific indications for biomedical therapy in the treatment of rheumatoid arthritis. Journal of Alternative and Complementary Medicine 15, 1021–1025.

Lu, X., Xiong, Z., Li, J., Zheng, S., Huo, T., Li, F., 2011. Metabonomic study on 'Kidney-Yang Deficiency syndrome' and intervention effects of Rhizoma Drynariae extracts in rats using ultra performance liquid chromatography coupled with mass spectrometry. Talanta 83, 700–708.

Ma, M., Zhai, H.N., 2010. Thinking path and method for establishing the disease/Chinese medicine syndrome conjugated pattern of a mammary hyperplasia animal model. Chinese Journal of Integrative Medicine 16, 457–463.

Ma, X.J., Yin, H.J., Chen, K.J., 2009. Differential gene expression profiles in coronary heart disease patients of blood stasis syndrome in traditional Chinese medicine and clinical role of target gene. Chinese Journal of Integrative Medicine 15, 101–106.

Miao, Y.C., Tian, J.Z., Shi, J., Mao, M., Zhao, X.D., Fang, L.Y., Zeng, C.Y., Liu, J.P., Wang, Z.L., Li, X.B., 2009. Correlation between cognitive functions and syndromes of traditional Chinese medicine in amnestic mild cognitive impairment. Zhong Xi Yi Jie He Xue Bao 7, 205–211.

Rampp, T., Tan, L., Zhang, L., Sun, Z.J., Klose, P., Musial, F., Dobos, G.J., 2008. Menopause in German and Chinese women—an analysis of symptoms, TCM-diagnosis and hormone status. Chinese Journal of Integrative Medicine 14, 194–196.

Sams-Dodd, F., 2005. Target-based drug discovery: is something wrong? Drug Discovery Today 10, 139–147.

Shen, H.B., Bai, Y.J., Huo, Z.J., Li, W.N., Tang, X.P., 2011. Assessment of clinical effect of therapy combining disease with syndrome on rheumatoid arthritis. Journal of Traditional Chinese Medicine 31, 39–43.

Shen, S.W., Hui, J.P., Yuwen, Y., Wang, J.H., Chen, L.Y., Niu, Y., Peng, N., Yang, Z.H., Zhao, Y., 2011. Study on canceration law of gastric mucosal dysplasia based on syndromes of Chinese medicine. Chinese Journal of Integrative Medicine 17, 346–350.

Su, W., Xu, Z.Y., Wang, Z.Q., Xu, J.T., 2011. Objectified study on tongue images of patients with lung cancer of different syndromes. Chinese Journal of Integrative Medicine 17, 272–276.

Tang, A.C., Chung, J.W., Wong, T.K., 2012. Validation of a novel traditional Chinese medicine pulse diagnostic model using an artificial neural network. Evidence-Based Complementary and Alternative Medicine 2012, 685094.

Tong, X., Sun, H., Yan, G.L., Dong, W., Sun, W.J., Yu, Y., Wang, P., Han, Y., Wang, X.J., 2011. Evaluation study on urine metabolomics in yinhuang rat model induced by triplet factors of rhubarb, ethanol, and alpha-nephthylisothiolyanate. Chinese Journal of Integrative Medicine 17, 369–375.

Tsang, I.K., 2007. Establishing the efficacy of traditional Chinese medicine. Nature Clinical Practice. Rheumatology 3, 60–61.

van der Greef, J., van Wietmarschen, H., Schroen, J., Wang, M., Hankemeier, T., Xu, G., 2010. Systems biology-based diagnostic principles as pillars of the bridge between Chinese and Western medicine. Planta Medica 76, 2036–2047.

van Wietmarschen, H., Yuan, K., Lu, C., Gao, P., Wang, J., Xiao, C., Yan, X., Wang, M., Schroen, J., Lu, A., Xu, G., van der Greef, J., 2009. Systems biology guided by Chinese medicine reveals new markers for sub-typing rheumatoid arthritis patients. Journal of Clinical Rheumatology 15, 330–337.

Wang, G., Li, T.Q., Mao, B., Wang, L., Wang, Z.A., Chang, J., Xiong, Z.Y., Yang, D.Z., 2005. Relationship between bone mineral density and syndrome types described in traditional Chinese medicine in chronic obstructive pulmonary disease: a preliminary clinical observation. The American Journal of Chinese Medicine 33, 867–877.

Wang, H., Cheng, Y., 2005. A quantitative system for pulse diagnosis in Traditional Chinese Medicine. In: Conf. Proc. IEEE Eng. Med. Biol. Soc., vol. 6, pp. 5676–5679.

Wang, J., van der Heijden, R., Spruit, S., Hankermeier, T., Chan, K., van der Greef, J., Xu, G., Wang, M., 2009. Quality and safety of Chinese herbal medicines guided by a systems biology perspective. Journal of Ethnopharmacology 126, 31–41.

Wu, G., Zhu, L., Dent, J.E., Nardini, C., 2010. A comprehensive molecular interaction map for rheumatoid arthritis. PLoS One 5, e10137.

Xie, Y.Q., Wang, H., Wu, Y.P., Yin, D.H., Wang, Z.S., Huang, Y.H., 2011. Association of APOE polymorphisms and insulin resistance with TCM syndromes in type 2 diabetes patients with macroangiopathy. Molecular Medicine Reports 4, 1219–1223.

Xue, J., Wang, Y., Han, R., 2010. Factor analysis on the distribution of Chinese medicine syndromes in patients with hyperlipidemia in Xinjiang region. Zhongguo Zhong Xi Yi Jie He Za Zhi 30, 1169–1172.

Xue, M., Yin, H.J., Chen, K.J., 2006. Some thoughts on studying essence of syndromes based on genomics. Zhongguo Zhong Xi Yi Jie He Za Zhi 26, 88–90.

Yan, B., A, J., Hao, H., Wang, G., Zhu, X., Zha, W., Liu, L., Guan, E., Zhang, Y., Gu, S., Huang, Q., Zheng, Y., 2009. Metabonomic phenotype and identification of "heart blood stasis obstruction pattern" and "qi and yin deficiency pattern" of myocardial ischemia rat models. Science in China Series C: Life Science 52, 1081–1090.

Yan, H., Qin, K., Wang, Y., Li, F., Run, F., Hong, Y., Hao, J., 2011. Research of the EEMD method to pulse analysis of traditional Chinese medicine based on different amplitudes of the added white noise. Sheng Wu Yi Xue Gong Cheng Xue Za Zhi 28, 22–26.

Yang, L., Wang, M., Wu, W., Zhang, L., 2007. Transcriptome analysis of cold syndrome using microarray. The American Journal of Chinese Medicine 35, 609–620.

Yang, Y., Wang, S.C., Bai, W.J., Li, R.L., Ai, J., 2009. Evaluation by survival analysis on effect of traditional Chinese medicine in treating children with respiratory syncytial viral pneumonia of phlegm-heat blocking Fei syndrome. Chinese Journal of Integrative Medicine 15, 95–100.

Yu, H.M., Chang, H.H., Liou, S.Y., Li, S.F., Hou, M.M., Chen, M.F., 1998. The correlation between skin electrical conductance and the score of qi vacuity. The American Journal of Chinese Medicine 26, 283–290.

Zha, Q., He, Y., Yu, J., Yan, X., Su, L., Song, Y., Zeng, S., Liu, W., Feng, X., Qian, X., Zhu, W., Lin, S., Lv, C., Lu, A., 2006. Correlations between diagnostic information and therapeutic efficacy in rheumatoid arthritis analyzed with decision tree model. Zhongguo Zhong Xi Yi Jie He Za Zhi 26, 871–876.

Zhang, C., Jiang, M., Lu, A., 2011. A traditional Chinese medicine versus Western combination therapy in the treatment of rheumatoid arthritis: two-stage study protocol for a randomized controlled trial. Trials 12, 137.

Zhang, G.G., Lee, W., Bausell, B., Lao, L., Handwerger, B., Berman, B., 2005. Variability in the traditional Chinese medicine (TCM) diagnoses and herbal prescriptions provided by three TCM practitioners for 40 patients with rheumatoid arthritis. Journal of Alternative and Complementary Medicine 11, 415–421.

Zhang, G.G., Lee, W.L., Lao, L., Bausell, B., Berman, B., Handwerger, B., 2004. The variability of TCM pattern diagnosis and herbal prescription on rheumatoid arthritis patients. Alternative Therapies in Health and Medicine 10, 58–63.

Zhang, H., Wang, W.R., Lin, R., Zhang, J.Y., Ji, Q.L., Lin, Q.Q., Yang, L.N., 2010. Buyang Huanwu decoction ameliorates coronary heart disease with Qi deficiency and blood stasis syndrome by reducing CRP and CD40 in rats. Journal of Ethnopharmacology 130, 98–102.

Zhang, M.M., Liu, X.M., He, L., 2004. Effect of integrated traditional Chinese and Western medicine on SARS: a review of clinical evidence. World Journal of Gastroenterology 10, 3500–3505.

Zhang, Q., Wu, Z., Feng, Y., Shi, J., 1990. Levels of sexual hormones in relation with syndrome-differentiation of TCM in patients of chronic renal failure. Journal of Traditional Chinese Medicine 10, 132–135.

Zhao, J., Jiang, P., Zhang, W., 2010. Molecular networks for the study of TCM pharmacology. Briefings in Bioinformatics 11, 417–430.

Zhao, L., Chan, K., 2005. Patient-reported outcomes (PROs): an approach to evaluate treatment efficacy of Chinese medicine or integrative medicine. Chinese Journal of Integrative Medicine 11, 151–153.

Zhao, L., Yan, X., Jianming, W., Zhang, Y., Dong, Q., Zha, Q., Lv, C., Xiao, C., Lu, A., 2006. Correlation between pathophysiology features and Chinese medical four diagnostic information in rheumatoid arthritis. Guangzhou Zhongyiyao Daxue Xuebao 23, 112–117.

Zhao, N., Zhang, W., Guo, Y., Jia, H., Zha, Q., Liu, Z., Xu, S., Lu, A., 2011. Effects on neuroendocrinoimmune network of Lizhong Pill in the reserpine induced rats with spleen deficiency in traditional Chinese medicine. Journal of Ethnopharmacology 133, 454–459.

Zhao, X., Zhang, Y., Meng, X., Yin, P., Deng, C., Chen, J., Wang, Z., Xu, G., 2008. Effect of a traditional Chinese medicine preparation Xindi soft capsule on rat model of acute blood stasis: a urinary metabonomics study based on liquid chromatography–mass spectrometry. Journal of Chromatography B: Analytical Technologies in the Biomedical and Life Sciences 873, 151–158.

Zheng, L.W., Hua, H., Cheung, L.K., 2011. Traditional Chinese medicine and oral diseases: today and tomorrow. Oral Diseases 17, 7–12.

Zhou, N., Bai, Y.P., Man, X.H., Zhang, Y.B., Kong, Y.H., Ju, H., Chang, M., 2009. Effect of new Pulian Ointment ( ) in treating psoriasis of blood-heat syndrome: a randomized controlled trial. Chinese Journal of Integrative Medicine 15, 409–414.

Zhu, X., Bensoussan, A., Zhu, L., Qian, J., Xu, M., Zhou, C., Chao, P., Lo, S., 2009. Primary dysmenorrhoea: a comparative study on Australian and Chinese women. Complementary Therapies in Medicine 17, 155–160.

Glossary

Syndrome: also called *Zheng*. It is a state defined by TCM based on its own theory after analysis on the symptoms, tongue appearance and pulse feelings.

Syndrome differentiation: also called *Bian Zheng*, or *pattern classification*. It is a process to define the syndrome (*Zheng*).

Bian Zheng Lun Zhi: it means treatment based on Syndrome Differentiation.

Shen deficiency syndrome: one kind of TCM syndromes. It is also called *kidney deficiency syndrome*, and it can be classified into 2 major categories, *kidney Yang deficiency* and *kidney Yin deficiency*.

Shen Yang deficiency syndrome: one kind of TCM syndromes, and also called *kidney Yang deficiency syndrome*.

Shen Yin deficiency syndrome: one kind of TCM syndromes, and also called *kidney Yin deficiency syndrome*.

Xue-Yu syndrome: one kind of TCM syndromes, and also called *blood stasis syndrome*.

Fufang: TCM herbal formulae.

Han/Re syndrome: two kinds of TCM syndromes with opposite clinical manifestations, also called *cold/hot syndrome*, or *cold/heat syndrome*.

I-Yin deficiency syndrome: also called *Deficiency of both I and Yin syndrome*. It is a combined TCM syndrome consisted of manifestations on both *I deficiency and Yin deficiency syndromes*.

I deficiency syndrome: one kind of TCM syndromes.

Shi-Re accumulation interior syndrome: one kind of TCM syndromes. It is also called TCM *syndrome of damp-heat accumulation interior*.

Tan-Re zoo Fei syndrome: one kind of TCM syndrome, and also called *phlegm-heat blocking Fei (Lung) syndromei*.

Xue-Re syndrome: one kind of TCM syndromes, and also called *blood-heat syndrome*.

Shi-Re syndrome: one kind of TCM syndromes, and also called *damp-heat obstruction syndrome*.

Pi-CSU syndrome: one kind of TCM syndrome, and also called *spleen deficiency syndrome*.

Qi-Xu and Xue-Yu syndrome: one kind of TCM syndrome, and also called Qi deficiency and blood stasis syndrome.

Lizhong Pill: one type of TCM proprietary medicines.

Tanreqing Injection: one type of TCM proprietary medicines.

Buyang Huanwu Tang: also called *Buyang Huanwu decoction*. It is a TCM formula.

Fufangkushen enteric-coated capsule: one type of TCM proprietary medicines.