Methodology of pharmacodynamic evaluation on Chinese herbal medicine based on syndrome differentiation

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Abstract: The clinical application of Chinese herbal medicine should be based on syndrome differentiation in traditional Chinese medicine (TCM), and the pharmacological evaluation of herbal medicine in new drug discovery should be also based on the TCM syndrome differentiation. To clarify the Chinese herbal characteristics and mechanisms of action through pharmacological experiments is not only the inevitable requirement for Chinese herb modernization and internationalization, but also the key way to direct the clinical rational administration. Thus how to characterize the syndrome type in commonly used animal disease models becomes the key issue in pharmacological evaluation. Following the development of biomedicine, one important way to clarify the syndrome characteristics of animal disease model in the pharmacological evaluation is to compare the differences between the responsive and non-responsive animals, and to find out the responsiveness-related biocharacteristics. An important approach to set up the Chinese herbal pharmacological evaluation which is suitable for Chinese medicine differentiation is to utilize the method of surveying syndrome type with Chinese herb formula and select the responsive animal model to reflect certain syndrome type, and furthermore to clear up the syndrome characteristics of the animal model by investigating its modern biological basis and establishing the correct indications of special TCM syndrome type. This pharmacological evaluation way based on finding out the responsiveness-related biocharacteristics of herbal medicine could become more effective in evaluating drug effects, further improving the new drug discovery, and developing Chinese herbal medicine.

Keywords: Chinese herbal drugs; treatment effectiveness; syndrome; models, animal

基于疾病中医证候分类的中药药效评价研究思路和方法

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摘要: 中药的临床应用建立在辨证的基础上, 因此其药效评价也应该建立在中医证候分类的基础之上。通过药效学实验阐明中药治疗疾病的药效作用特点及其机制，揭示中药作用机制的科学内涵，是中药现代化和国际化的必然要求，也是探索药物作用靶点，指导临床合理用药的关键所在。如何利用现代疾病动物模型，并明确其证候特征，是中药药效评价研究的关键问题。随着生物医学的发展，通过研究疾病动物模型的生物学指标有可能分析得出该疾病动物模型的证候特征。利用以方测证方法，建立针对该疾病常见证候类型且临床验证有效的中药干预疾病动物模型，并将治疗有效的动物作为体现相应证候特征的动物模型，通过探寻其现代生物学基础，确立相应的中医证候特征相关指标，从而明确疾病动物模型的证候特征，是建立适合辨证论治中药药效评价动物模型的重要途径。建立基于中医证候分类的中药药效评价研究方法，将有助于从中医理论出发提高我国中药研发水平。

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The first role of drug is to treat diseases. So the purpose of pharmacodynamic evaluation on Chinese herbal medicine is to clarify the characteristics and action mechanisms of Chinese herbal medicine. It is a request for traditional Chinese medicine (TCM) modernization and a key part in clinic to focus on pharmacodynamic evaluation on Chinese herbal medicine. In present, a lot of results on Chinese herb pharmacodynamic evaluation are not satisfied. Meanwhile, these results can not be used to instruct the clinical trials. The main reason is that they ignore the TCM basic theory, which is closely related to syndrome differentiation. The clinical application of Chinese herbs must be established in accordance with syndrome differentiation, i.e., Chinese herb has its own indications. Hence, the key scientific problem of pharmacodynamic evaluation on Chinese herb is to clarify the Chinese herb action based on TCM syndrome differentiation.

1 Syndrome classification and Chinese herb pharmacodynamic evaluation

Syndrome classification is a kind of way to carry out categorization for different individual physiology and pathology functional status. It is the diagnostic model and efficacy basis in TCM. Chinese medicinal formula is the main form in clinical application of Chinese herbs. It is the key factor to set up syndrome differentiation system which composes special formula based on syndrome differentiation. The process of syndrome differentiation is to clear up syndrome classification first, and then to establish principle based on syndrome type and to determine the formula based on principle finally. Thereby, the fine therapeutic action of Chinese herb can be displayed.

It is a certain request for syndrome differentiation to build “formula-syndrome” correspondence. “Formula-syndrome” correspondence is the premise and basis for inducing Chinese herb efficacy. The highlight is “selecting certain formula based on certain syndrome”. Ignoring syndrome type to evaluate Chinese herb action single-handedly can not display objectively. Thus the results can not guide the clinical practice. Hence, the clinical application of Chinese herb closely relates to syndrome differentiation and the potency of Chinese herb should be exhibited under the special syndrome type.

2 Animal model and pharmacodynamic evaluation on Chinese herbal medicine

The final purpose of selecting drug is to get fine therapeutic effects. The main aim for pharmacodynamic evaluation on Chinese herbal medicine is to assess its effects systematically. Hence, the animal disease model is an important target. Chinese herbs are normally used to treat only definite patients with definite syndrome type. Research showed that the Chinese herb effects were not satisfactory without the direction of syndrome theory. And the results could not guide the clinical practice based on syndrome classification. Hence, seeking the syndrome characteristics of animal disease model is the important content for Chinese herb pharmacodynamic evaluation.

It is the key problem for Chinese herb pharmacodynamic evaluation to set up animal disease model with syndrome characteristics. It is difficult to embody the information obtained from patients by four diagnostic methods, including symptoms, tongue presentation, pulse conditions and so on, in an animal disease model. So it is not easy to get syndrome characteristics of the animal disease model from traditional methods. Following the development of biomedicine, it is possible to analyze the syndrome characteristics of animal disease model by biological parameters. The syndrome characteristics of animal disease model can be explored by the method of “measuring syndrome type by means of prescription”. Using clinically approved effective herbal medicine to intervene the related animal disease model and finding out the responsiveness-related biomedical parameters would be a way to define the animal disease model with TCM syndrome related to the herbal medicine. Utilizing the animal model with syndrome characteristics to carry out Chinese herb pharmacodynamic evaluation will reveal the advantage of syndrome differentiation and direct the clinical practice in selecting suitable patients with correct indications.

Some progress has been made on establishment of animal models for both disease and TCM syndrome type, and also some pharmacological evaluation on such animal models for herbal medicine has been conducted, however it is still hard to define the TCM syndrome characteristics, which directly influence the guiding role for clinical trial or clinical practice since TCM syndrome type is differentiated on TCM information which is mainly not shown in animals. Thus similar approaches could be used to further clarify the syndrome characteristics of the animals with certain disease and TCM syndrome type.

The pharmacological evaluation of herbal medicine on animal disease model is important for TCM modernization, and also for new herbal medicine research and marketing development nationally and internationally. Comparing the responsive and non-responsive animals after herbal medicine intervention and finding out the
differences in biological characteristics is a scientific way to clarify the pharmacological mechanisms of herbal medicine and further to guide the clinical practice. Based on TCM syndrome classification, finding out the correlated biomedical characteristics of responsive animals treated with herbal medicine is an important task in pharmacological study of herbal medicine.

3 To obtain the biological features of responsive animals with disease after intervention of herbal medicine is a feasible way to conduct pharmacological evaluation of TCM syndrome type

TCM syndrome information obtained by TCM approaches can not be obtained from animal disease model, and TCM syndrome characteristics on animal disease model could be only shown with biological parameters. Pharmacological evaluation for herbal medicine on animal disease model is also shown with biological changes. Because the diagnostic indexes in one disease are the common in all patients (or all animal disease model) with the disease, the other non-diagnostic biological parameters might be a way to support the findings of biological characteristics of TCM syndrome type. The progress in basic research in life sciences, such as progress in omics, could be helpful in such a finding for biological characteristics of TCM syndrome type.

The non-diagnostic biological indicators are diversified and complicated, and it is difficult to set a limitation for biological parameters for TCM syndrome characterization and it is impossible to test all parameters. Thus to find the potential biological parameters or pathways for TCM syndrome with some approaches could be important for TCM syndrome differentiation in the pharmacological evaluation. Following large amount of data accumulation in life sciences and progress in data analysis technique, it is possible to find the potential syndrome index from disease research data. According to TCM syndrome research results, gathering all the research findings which have been found from the animal disease model and using text data mining technology might be a way to explore the potential relationships among the modern biological indicators for the disease, and also to explore the similarity in biological characteristics between different diseases if they share same TCM syndrome type in some way. Those biological characteristics might be included for the pharmacological evaluation of herbal medicine on animal disease model. Text data mining is the process to get out understandable, unknown, and ultimately available knowledge from a large number of text data. It combines artificial intelligence, machine learning, natural language processing, data mining and automatic text processing such as information extraction, information retrieval and text classification together. Text mining has an important value in exploration of potential knowledge. At present, the application of text data mining technology in the biological database with huge amount of data to find potentially useful knowledge has become a focus of medical research. We preliminarily investigated the similar biological characteristics and pathways between rheumatoid arthritis (RA) and ulcerative colitis (UC) with text mining technique since RA and UC share similar TCM syndrome type, and a number of potential common biological characteristics and pathways were found. In addition, exploration of biomarkers of TCM syndrome type in diseases with systems biology approaches, such as combining with genomics, proteomics, metabolomics and other omics technologies and methods, becomes the hot spots in TCM syndrome research. Our previous results showed that there were significant differences in genomic profile and metabolomical profile between cold and heat syndrome in RA patients, which suggests that omics might be helpful in clarification of TCM syndrome.

Pharmacological evaluation for herbal medicine is one of the most important research areas in TCM modernization and new herbal medicine discovery. The pharmacological evaluation for herbal medicine should be based on TCM syndrome type, which is the only way to show up the specific indication for herbal medicine based on the syndrome differentiation, and the only way to take TCM advantages in herbal medicine research and development, and the only way to improve capacity of new herbal medicine discovery in China.

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