Pharmacokinetics Applications of Traditional Chinese Medicines

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ABSTRACT

Traditional Chinese medicine (TCM) has been widely used in many oriental countries for thousands of years and played an indispensable role in the prevention and treatment of diseases, especially the complicated and chronic ones. It is a very complex mixture containing hundreds or thousands of different components. Pharmacokinetic study on active constituents in TCM preparations is a good way for us to explain and predict a variety of events related to the efficacy and toxicity of TCM. In the drug discovery phases, pharmacokinetics is a key to guide medicinal chemists in the optimization process of a chemical series and to assist pharmacologists to design in vivo studies. To explore the potentially bioactive components in TCM, it is necessary to further study the in vivo pharmacokinetic characteristics of multiple absorbed components and find out the optical time-course behavior to providing more substantial research for new leads in drug discovery. Pharmacokinetics screening method could provide a reliable means of prospecting natural products in the search for new leads in drug discovery. This review summarizes the research progress of PK on TCM in the search for suitable lead compounds in recent years.

Key words: Traditional Chinese medicine, Pharmacokinetics, Drug discovery, Active constituents

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INTRODUCTION

In the long history of several thousand years, traditional Chinese medicine (TCM) has played a positive role to the health industry of human. It originated in ancient China, has been widely used for the prevention and treatment of various diseases in China and Western countries. With the passage of time, it has developed its own coherent theories with regard to precaution, diagnosis, and treatment of disease and been accepted by the academic community and patients, in particular chronic diseases and metabolic syndromes. It is the so-called “holistic view”[1–2]. Consequently, for the study of TCM, we also should depend on the basis of the overall concept. For example, the therapeutic efficacy of TCM usually is attributed to the combined action of a mixture of constituents, rather than a single component[3]. Moreover, because of the complexity of the ingredient of TCM and the global thinking of TCM, the pharmacokinetic study of TCM and chemical medicine have very big difference[4–5]. Therefore, it is necessary to clarify and analyze the pharmacokinetic characteristics of TCM to ensure the reliability of the clinical application and a better understanding of pharmacology foundation[6–7].

All the time, as a discipline, pharmacokinetics (PK) is based on the principle of dynamics to research the dynamic change rule and its quantity - timing exists in the absorption, distribution, metabolism and excretion (ADME) of drugs in vivo and to use mathematical function to quantitative description[8]. PK is widely used in the field of chemical medicine, especially in new drug development, the changing process of drug in vivo, etc[9–10]. With the development of medicinal chemistry, the human health level has unceasing enhancement, so for the market prospect of the newly researched drugs, we demand them not only curative effect are good, and side effects are small, but also have good PK properties[11].

However, unlike chemical drug research, the PK of TCM can be simply divided into four parts, which are the PK of single ingredients, the multi-component PK, the PK of single drug and the PK of Chinese medicines formulae[12]. But for a long time, one method of measuring a certain component concentration in plasma has been commonly used in PK of TCM as same as chemical medicine[13]. Even though, classic pharmacokinetic theory is established on the basis of determination of plasma drug concentration, it is hard to predict the effects of the drug in the body really and effectively[14]. Similarly, measuring the concentration of an ingredient in plasma cannot completely represent the single Chinese medicine to say nothing of formulae Chinese medicines, due to the action principles of TCM which were multi-component, multi-target, and diversity function[15]. So a lot of new methods and new ideas have been presented by researchers, in order to solve the problems existing in the present situation of PK of TCM. This article summarized the pharmacokinetic research methods and application of TCM in recent years, combined the basic theory and the overall concept of TCM, and discussed the pharmacokinetic development prospects of TCM in the future.
METHOD OF PHARMACOKINETICS OF TRADITIONAL CHINESE MEDICINES

1. Plasma concentration
At present, the plasma concentration is a classic method in the pharmacokinetic study of TCM, especially for the effective components have been identified of one Chinese medicine and its formulae preparations\(^\text{[16]}\). In a certain period of time after oral administration, researchers determines the concentration of a particular component or multiple components in plasma, body fluids, or other organizations of a person or animal, then on the basis of it drawing one drug concentration-time curve, and finally calculating the PK parameters\(^\text{[17]}\). Yin et al have investigated the in vivo plasma PK and tissue distribution characteristics of scoparone after oral administration which were measured by a rapid and sensitive UPLC–MS/MS method. In the end, according to the PK parameters, they found that scoparone was distributed and eliminated rapidly in plasma of rats and the result of tissue distribution showed the maximum level was observed in liver, supporting it was the effective ingredient of Yinchenhao- Decoction for the treatment of liver injury\(^\text{[18]}\). Similarly, Lu et al have investigated the plasma PK, tissue distribution and excretion of the main component- schisandrin in rats after oral administration of a classical TCM prescription, ShengMaiSan (SMS). It can be seen from the figure 1, 2, PK results showed a rapid absorption and a relatively slow elimination proceeding. The tissue distribution showed the maximum concentration distributions were in the small intestine, and there is less in the feces and urine\(^\text{[19]}\). At the same time, a rapid and special recognized UPLC - Q - TOF/MS method has been developed and applied to the simultaneous determination of rat plasma contents of five main effective component, namely, schisandrin, schisandrol B, schisantherin, deoxyschisandrin, schisandrin B, after oral administration of the SMS\(^\text{[20]}\). Although to some extent, the multi-component PK of TCM reflected the Chinese medicine overall point of view, there was no detailed instructions for the choice of components\(^\text{[21]}\).

2. Biological effect
For the active ingredients of one Chinese medicine and its formulae preparations are unclear, the method of biological effect is often used to study the PK of TCM, including toxicology effects, pharmacological effects, microorganism indexes and so on\(^\text{[22]}\). Yu J et al have monitored the exposure level of ‘SHENMAI’ injection (SMI) during a one-month toxicology experiment. The levels of some certain toxicology indicators were measured to explore pharmacokinetic changes of SMI in rats\(^\text{[23]}\). Similarly, most scholars are willing to measure the pharmacological effects of TCM in animals to reflect their pharmacokinetic characteristics\(^\text{[24]}\). For example, Pan L and his colleagues have tested the time-antioxidant efficacy, it is the levels of superoxide dismutase (SOD) which were calculated by ELIASA, after oral administration of Huanglian-Zhizi couplet medicine from Huang-Lian-Jie-Du-Tang in MCAO rats\(^\text{[25]}\). In recent years, some scholars indirectly showed the pharmacokinetic characteristics of TCM through the determination of antibacterial activity of components\(^\text{[26]}\). Some Turkish researchers try to find out the
possible antibacterial active ingredients of methanol extracts from Physalis alkekengi L. (Solanaceae), then according to the antimicrobial activity to show the process of absorption, distribution, metabolism and excretion of Physalis alkekengi L. in vivo\[^{27}\]. Before this, the Kataoka M experimental team has also adopted the same approach to study the PK of tryptanthrin and kaempferol, isolated from the indigo plant (Polygonum tinctorium Lour)\[^{29}\].

3. TCM multi-component integrated PK
For the first time, the team of Wang GJ professor, who come from Chinese pharmaceutical university, put forward the concept of multi-component integrated PK of TCM. Its main idea was drawing only one drug concentration-time curve to represent the whole TCM resides in the body, making the PK of TCM from the “single” to “complex”\[^{29}\]. In the meantime, the experimental group through calculating the PK parameters of five iconic compositions in Xuesaitong in rats, drew all the ingredients of medication in one concentration-time curve, and every point of five monomer compositions of plasma concentration were assigned to their respective weight coefficient to achieve the integration concentration-time curve of total saponin of notoginseng. The final results showed that the obtained parameters can maximum the overall treatment regularity of TCM\[^{30}\]. However, many scholars found that the TCM multi-component integrated PK thoughts have certain restriction, it can only made the similar ingredients in structure or efficacy together\[^{31}\].

4. Pharmacokinetic markers
Academician Liu, who come from Tianjin medicine research institute, has proposed the concept of “PK markers”. PK markers may be used to display overall exposure to the Chinese herbal medicine in body of animals or humans. Active ingredients that own good PK character, including a prominent dose-dependent and an advisable elimination half-life can be used as the PK markers of TCM. The active constituent was unknown or a suitable assay was not feasible, the main chemical composition or metabolites tested in plasma or urine may be assessed as the substitute PK markers\[^{32-33}\]. Firstly, H. Lv \textit{et al} select the 6,7-dimethyleculetin and geniposide, which respectively from the Yin Chen Hao(YCH) and Zhi Zi (ZZ), but also mainly hepatoprotective constituents in Yin-Chen-Hao-Tang (YCHT), and then through the PK study in rat after oral administration of YCH, YCH + ZZ, YCH + Da Huang DH, YCHT, ZZ, respectively. It reveals that the compatibility of TCM can affect the whole process of absorption, distribution, metabolism and excretion of the drug active ingredient, which compared with a single herb\[^{34}\]. Then some researchers have monitored simultaneously the PK time-course of 21 in rat plasma, after a single oral administration of YCHT, compared the body dynamics of each composition, and chose nine compounds as the candidate components\[^{35}\]. Whereafter, Zeng L \textit{et al} have carried out simultaneous measurement and PK investigation of the eight PK markers in rats following an intravenous administration of Ying-zhi-huang injection\[^{36}\]. Moreover, Huang \textit{H et al} have chosen five bufadienolides and four volatile compounds as the PK markers to carry out the PK and tissue distribution of Shexiang Baoxin Pill in rat plasma after oral administration of the Chinese medicine formula\[^{37-38}\].

Above all, in the existing PK analytical methods of TCM, the PK markers not only reflects the whole theory of TCM, but also thinks over the drug effect in selecting markers at the same time, finally applies to determine the plasma concentration to reflect the PK of TCM, which is the classic PK method.

APPLICATION OF PK OF TCM
In the early studies, as a method, the PK of TCM always used alone, so it was often not enough comprehensive and reliable to clarify the meaning of the research of TCM\[^{39-40}\]. In the recent years, some new research thoughts and PK of TCM combined application, have brought new breakthrough to pharmacokinetic research of TCM.

1. PK associated application with metabonomics
Metabolomics was originally proposed as a method of functional genomics\[^{41}\], and represented a global understanding\[^{42}\] of metabolite complement of completed living systems and the dynamic change process of the external and internal factors and has many promising applications and preponderance for the research of complex systems\[^{43}\]. Studying the metabolomics can highlight changes in networks and pathways and provide advice to physiological and pathological states\[^{44}\]. So making the metabolomics and PK of TCM combined application can be more comprehensive to clarify some related issues in the research of TCM. Wang \textit{et al} have used metabolomics technology to study the therapeutic effect of Liu-Wei-Di-Huang pill (LW) based on the male rat model of kidney yin deficiency\[^{45}\]. Meanwhile, Zhang \textit{et al} have researched the PK characters of the three main compounds 5-hydroxymethyl-2-furoic acid, paenol and loganin in the plasma of rats which have oral LW. Combined the two methods not only illustrated the long-lasting and steady pharmacological characteristic, but they also demonstrated the important meaning of the compatibility of TCM\[^{46}\]. In recent years, some researchers have introduced that the drugs effect index or diagnostic index can be replaced by the endogenous biomarkers which were found by metabolomics and PK of TCM combined application, to clarify the problem such as the mechanism of TCM\[^{47}\].

2. PK with pharmacodynamics
PK of TCM and pharmacodynamics (PD) combined application to elucidate the mechanism of Chinese medicine has been generally recognized by many scholars\[^{48-49}\]. What’s more, a growing body of evidence has demonstrated that monitoring plasma concentrations of TCM using a modern PK and PD is essential to ensure optimal drug efficacy and to assess therapeutic efficacy, especially in vivo\[^{50-51}\]. Sun \textit{et al} have researched the plasma PK and PD characteristics of
Zhi Zhu Wan (ZZW) after oral administration, valuated and clarified the effect of ZZW on small intestinal movement. It was found that ZZW can precipitate intestinal peristalsis of mice and will be a promising prescription to treat intestinal disease\(^{52}\).

### 3. Other application

With the research of TCM, the emergence of various theories and PK of TCM joint application lead to better development. To research TCM from a holistic view, the appearance of Network pharmacology of TCM has broken the partial and limited study of TCM to some extent\(^{53-54}\). The essence of network pharmacology and PK of TCM combined application is another form of PK-PD\(^{55-56}\). Furthermore, the fingerprintology of TCM was a novel system, in which the pharmacologic substance bases and mechanism, especially the law of PK on TCM were systematically and integrally studied\(^{57-58}\). In addition, physiologically based pharmacokinetic (PB-PK) model has been proposed, which based on physiological anatomy data and the physical and chemical properties of medicine to analyse data, the resulting parameters had more actual physical meaning, more advantage and practical value compared with the classical atrioventricular model\(^{59}\). Besides, the technology of dynamic intravital imaging through the markers after fluorescent dying, can be observed from the level of cell disease processes and the treatment progress of drugs\(^{60}\).

### CONCLUSION AND FUTURE PROSPECTS

The rapid economic growth of mainland China has caused TCM to be noticed beyond Chinese-speaking countries, in recent years\(^{61}\). However, the lack of scientific and technologic approaches makes TCM facing serious challenges. With the modernization of TCM, advanced instrument such as ultra high performance liquid and mass spectrometry, gas phase mass spectrometry, liquid phase and nuclear magnetic resonance spectrometry, micro dialysis technology and capillary electrophoresis on the PK of TCM was gradually promote the use, to some extent which broaden the train of thought for studying the PK of TCM\(^{62-66}\). Thus, pharmacokinetics can provide a reliable suitable and means of screening and identifying potential bioactive components contributing to pharmacological effects of TCM, further prospecting natural products in the search for new leads in drug discovery.

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### COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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