DOCTORAL THESIS

# Studies on the quality control and pharmacokinetics of QFGJS capsule, an anti-arthritic Chinese herbal preparation

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*Date of Award:*
2007

# Studies on the Quality Control and Pharmacokinetics of QFGJS Capsule, an Anti-Arthritic Chinese Herbal Preparation

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**A thesis submitted in partial fulfillment of the requirements**

**for the degree of**

**Doctor of Philosophy**

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**Hong Kong Baptist University**

**November 2007**

## ABSTRACT

Interests and applications of herbal medicinal products (HMPs) have been markedly increased worldwide in the past decades, as HMPs demonstrated great potential for treatment of complicated diseases and for improvement of health. Qingfu Guanjieshu (QFGJS) capsule derived from five well-documented herbs is developed for treating human rheumatoid arthritis. Previous studies conducted by our research group showed that QFGJS had significant anti-arthritic, anti-inflammatory and analgesic effects. Those effects depend on a reproducible and consistent quality of the products. Thus, establishment of quality control methods and standard of QFGJS is a key issue for safe and effective clinical usage of the product. However, due to the chemical complexity and the potential interactions among chemicals and trace concentrations of analytes, studies on systematic quality control of HMPs are particularly difficult. The current work aims to develop methods for ensuring the quality and safety of QFGJS, which includes a series of quantitative and qualitative chemical analyses, and pharmacokinetic studies.

The processed aconite (Ranunculaceae) root, one of the five herbs in the formula of QFGJS, is widely used to treat joint pain and arthritic diseases, but contains toxic *Aconitum* alkaloids, i.e., aconitine, mesaconitine, and hypaconitine. To control the quality of the processed aconite roots for ensuring safe usage of QFGJS, a sensitive HPLC method was developed for determining those alkaloids by using a $C_{18}$ column gradient eluted with acetonitrile and 10mM ammonium bicarbonate buffer. The results showed that contents of those toxic alkaloids in different batches of the herbal samples varied significantly. Moreover, for HMPs containing aconite roots, a modified HPLC method was developed for simultaneous determination of six *Aconitum* alkaloids, i.e., three toxic alkaloids and their corresponding hydrolyzed products. The results showed that the contents of all six alkaloids in twelve Chinese proprietary products containing aconite roots varied markedly. This developed method has provided a technical platform to manufacturers for controlling the content limits of those toxic alkaloids in HMPs. By using this modified HPLC method to determine toxic *Aconitum* alkaloids in QFGJS, only trace contents are observed, which are within the limits stipulated by Chinese Pharmacopoeia, suggesting good safety of QFGJS in clinical use.

In order to evaluate the quality consistency of QFGJS from batch-to-batch and its stability after production, an HPLC-DAD method for quantitative and qualitative analysis of QFGJS was established. Simultaneous determination of four marker compounds, i.e., sinomenine, paeoniflorin, paeonol, and curcumin in QFGJS, was conducted by using this method. Qualitative chromatographic fingerprint analysis of QFGJS was carried out at the same time, showing the chemical characteristics of the four out of five herbs in the herbal formula (except the processed aconite roots) of QFGJS in the HPLC fingerprint chromatograms. This comprehensive HPLC analytical evaluation showed that both the contents of four marker compounds and the HPLC fingerprint profiles were consistent in all three batches of QFGJS products and also almost unchangeable in samples subject to the stability tests, which indicates that the quality of QFGJS was reproducible and consistent in the manufacturing processes. In this study, the way to develop an HPLC method providing both quantitative determination and qualitative fingerprint analysis as well as conducting methodology validation was investigated, which would be useful for quality assessment of other HMPs.

To evaluate the bioavailability of QFGJS, pharmacokinetic studies were carried out through investigating the concentration time course of bioactive compounds and metabolites. By using the developed sensitive HPLC methods, plasma concentrations of sinomenine, paeoniflorin, and paeonol were successfully determined after oral administration of QFGJS in the jugular-catheterized moving rats. It was found that three compounds were absorbed into blood, but their pharmacokinetic behaviors were different from those of the pure compounds described in the references. To further investigate the differences in the pharmacokinetic behavior of paeonol in QFGJS, the plasma concentrations of paeonol were determined after oral administration of pure paeonol and QFGJS. The results showed that both the plasma concentration and AUC of paeonol were significantly elevated in rats treated with QFGJS compared with those treated with pure paeonol at a comparable dosage, while the $T_{max}$, $T_{1/2}$, and MRT were showed to be similar in two groups. Moreover, the concentrations of four metabolites of paeonol detected by using LC-ESI-Q/TOF/MS were found to be higher in rat plasma treated with QFGJS, indicating that the increased concentration of paeonol in plasma did not result from the inhibition of metabolism. Thus, those differences in pharmacokinetics of paeonol might be caused by other co-existing chemicals in QFGJS.

To investigate whether there are cross-influences among the chemicals in QFGJS on toxicity, aconitine and paeoniflorin were employed for the study. The preliminary results showed that paeoniflorin could markedly increase the value of $LD_{50}$ of aconitine and reduce the death ratio of mice caused by orally taking aconitine. By using a cardiac arrhythmia model induced by aconitine on rat right atria to further investigate the possible detoxifying mechanisms of paeoniflorin, the results showed that paeoniflorin could significantly inhibit cardiac arrhythmias caused by aconitine, which indicates that the detoxifying effect of paeoniflorin could be derived from chemical-chemical interactions in QFGJS.

In summary, a comprehensive quality control system has been successfully established for ensuring the quality and safety of QFGJS in this thesis, in which the chemical analytical method, chromatographic fingerprint analysis, pharmacokinetic study and toxicological test have been taken into account.

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