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Review Article

# Pharmacokinetic interactions of herbal medicines for the treatment of chronic hepatitis

*Tun-Pin Hsueh* [a,b], *Wan-Ling Lin* [c], *Tung-Hu Tsai* [a,d,e,*]

[a] *Institute of Traditional Medicine, School of Medicine, National Yang-Ming University, Taipei, Taiwan*
[b] *Department of Chinese Medicine, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung, Taiwan*
[c] *Department of Chinese Medicine, E-DA Hospital, I-Shou University, Kaohsiung, Taiwan*
[d] *Department of Chemical Engineering, National United University, Miaoli, Taiwan*
[e] *School of Pharmacy, College of Pharmacy, Kaohsiung Medical University, Kaohsiung, Taiwan*

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ABSTRACT

Chronic liver disease is a serious global health problem, and an increasing number of patients are seeking alternative medicines or complementary treatment. Herbal medicines account for 16.8% of patients with chronic liver disease who use complementary and alternative therapies. A survey of the National Health Insurance Research Database in Taiwan reported that Long-Dan-Xie-Gan-Tang, Jia-Wei-Xia-Yao-San, and Xiao-Chai-Hu-Tang (Sho-saiko-to) were the most frequent formula prescriptions for chronic hepatitis used by traditional Chinese medicine physicians. Bioanalytical methods of herbal medicines for the treatment of chronic hepatitis were developed to investigate pharmacokinetics properties, but multicomponent herbal formulas have been seldom discussed. The pharmacokinetics of herbal formulas is closely related to efficacy, efficiency, and patient safety of traditional herbal medicines. Potential herbal formula–drug interactions are another essential issue during herbal formula administration in chronic hepatitis patients. In a survey with the PubMed database, this review article evaluates the existing evidence-based data associated with the documented pharmacokinetics profiles and potential herbal–drug interactions of herbal formulas for the treatment of chronic hepatitis. In addition, the existing pharmacokinetic profiles were further linked with clinical practice to provide insight for the safety and specific use of traditional herbal medicines.



* *Corresponding author*. Institute of Traditional Medicine, School of Medicine, National Yang-Ming University, 155, Li-Nong Street Section 2, Taipei 112, Taiwan.
E-mail address: thtsai@ym.edu.tw (T.-H. Tsai).

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## 1. Introduction

Traditional herbal medicines are increasingly used worldwide. A 2007 survey of the National Center for Health Statistics revealed that nearly four of 10 adults had used complementary and alternative medicine (CAM) therapy in the previous 12 months, and the most common CAMs were natural products (17.7%) [1]. Chinese medicine is a popular CAM frequently used by CAM users in Asia, including China, Hong Kong, Taiwan, Japan, and Korea. Chinese medicine accounts for 88% of CAM users in Singapore and covers 40% of healthcare in China [2,3]. In Taiwan, Chinese herbal medicine was estimated to account for 68.4–72.7% of CAM users in 2003 [4]. Chinese medicinal herbs contain more than 13,000 medicinal properties, including plants, animals, and minerals. Each herb can contain dozens of active ingredients that vary depending on the season, place of production, and other factors. More than 80% of the ingredients in Chinese herbs have not been isolated, and their metabolites have not been characterized despite the prevalence of modern chemical analytical techniques. The pharmacokinetics study of herbal medicines is one comprehensive way of determining how our bodies act under the specific agent after administration.

The administration of herbal formulas follows pharmacokinetic principles, which are absorption, distribution, metabolism, and excretion. As an overwhelming majority of herbal formulas are administered orally, the ability of the compounds within a formula to exhibit activity along the gastrointestinal tract after administration is imperative. The pharmacokinetic parameter bioavailability ($F$) represents the sum result of the combination of compounds that across the intestinal wall ($F_a$) and escape the presystemic gut wall ($F_g$) and hepatic first-pass metabolism ($F_h$). The equation comes to:

$$F = F_a \times F_g \times F_h \quad (1)$$

The area under the concentration versus time curve (AUC) in the pharmacokinetic figure is primarily proportional to the extent of bioavailability. Some compounds in the herbal formula may lose part of the administered dose owing to elimination by enzymes or degradation in the gastrointestinal tract, which prevents detection in plasma and reduces the concentration of active compounds at active sites. For instance, *Rheum officinale* Bail was found to reduce the bioavailability of geniposide, resulting in an inferior absorption [5]. This further indicates that herbal formulas containing more than a single herb or pure compound may contribute to synergetic, specific chemical absorption, and antagonistic effects.

The rationales for pharmacokinetics are crucial and applicable to the identification of compounds in herbal formulas. Compounds enter the systemic circulation and distribute into various tissues and body fluids via passive diffusion, ion trapping, or protein transport. The metabolism of compounds depends on the nature of the compound, and it is a multifactorial process that involves multiple pathways. Compounds with low molecular weight that are not bound to plasma proteins are filtered via the glomerula. Compounds that are metabolized by enzyme families, such as the cytochrome P-450 (CYP) system, are often excreted via the bile into the intestinal tract. Ingredients in the herbal formula are eventually excreted in the form of free drug or metabolites via urine, feces, or rarely skin or lung. Systemic clearance (CL) is the production of all organ clearance that contributes to the elimination of the compound, and it is affected by dose ($D$), bioavailability ($F$), and AUC:

$$\mathrm{CL} = \frac{F \times D}{\mathrm{AUC}} \quad (2)$$

When there is no intravenous (i.v.) form of herbal formula available and the absolute bioavailability of the formula is not known, the oral clearance (CL/$F$) is determined by the ratio of the AUC and extravascular dose of administration. Body clearance could also be altered by drug–drug interactions; for example, clozapine increased clearance by three-fold as rhein pretreatment increased in rat medial prefrontal cortex dialysate [6]. The pharmacokinetic parameters not only scheme how our bodies respond to drugs or compounds, but also outline the alterations of drug–drug or herb–drug interactions that are administered in combination. The dynamic process of plasma concentrations versus time in distribution is illustrated in Figure 1.

Quantitative monitoring changes of bioactive compounds within herbal medicines in pharmacokinetics is important as both herbs and drugs contribute to the overall pharmacodynamic outcome. Many systems are developed for quantification without interference, such as gas chromatography (GC), high-performance liquid chromatography (HPLC), ultra-pressure liquid chromatography (UPLC), or the combination of GC and LC with mass spectrometric (MS) procedures. A few methods such as HPLC or UPLC can achieve the sensitivity required to detect the low plasma concentrations of chemical compounds after the administration of herbal medicines in animals or humans. The lowest concentration of hepatoprotective chemical compounds in biosamples determined by HPLC coupled with ultraviolet detection system (HPLC-UV) varies from 10 ng/mL to 500 ng/mL [7,8]. The analytical method commonly used to provide good limits of quantification (LOQs) with higher selectivity and sensitivity for chemical compounds within herbal medicines is HPLC coupled with mass spectrometry (HPLC-MS).

MS is often used for quantitative and qualitative analyses of herbal medicines by its ion signal intensity and mass/charge ratio ($m/z$). MS is capable of accessing the specific mass/charge ratio of an analyte that can reduce the noise interference caused by the matrix to provide its high specificity and sensitivity. HPLC-MS is suitable for pharmacokinetics studies not only because of the nature and complexity of the blood or urine matrix, but also the availability of detecting low doses of herbal drugs and long-time data points. LC-MS combined with a triple quadrupole mass spectrometer generally affords very good LOQs of 0.5–50 ng/mL after oral administration, and for added specificity, HPLC coupled with tandem mass spectrometry (HPLC-MS/MS) is usually used for quantification of bioactive compounds in herbs [9].

Ultraperformance liquid chromatography coupled with mass spectrometry (UPLC-MS), using special particles with internal diameters smaller than 2 mm, offers a faster analysis, higher selectivity, and sensitivity with improved resolution than conventional HPLC-MS [10]. The chromatography