Review Article

Pharmacokinetic interactions of herbal medicines for the treatment of chronic hepatitis

Q4 Tun-Pin Hsueh [a,b,c], Wang-Ling Lin [d], Tung-Hu Tsai [a,e,f,*]

[a] Institute of Traditional Medicine, School of Medicine, National Yang-Ming University, Taipei, Taiwan
[b] Department of Traditional Chinese Medicine, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan
[c] Chang Gung University College of Medicine, Kaohsiung, Taiwan
[d] Department of Chinese Medicine, E-DA Hospital, I-Shou University, Kaohsiung, Taiwan
[e] Department of Chemical Engineering, National United University, Miaoli, Taiwan
[f] Department of Education and Research, Taipei City Hospital, Taipei, 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).

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:

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

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:

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

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 Q1 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), ultrapressure 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
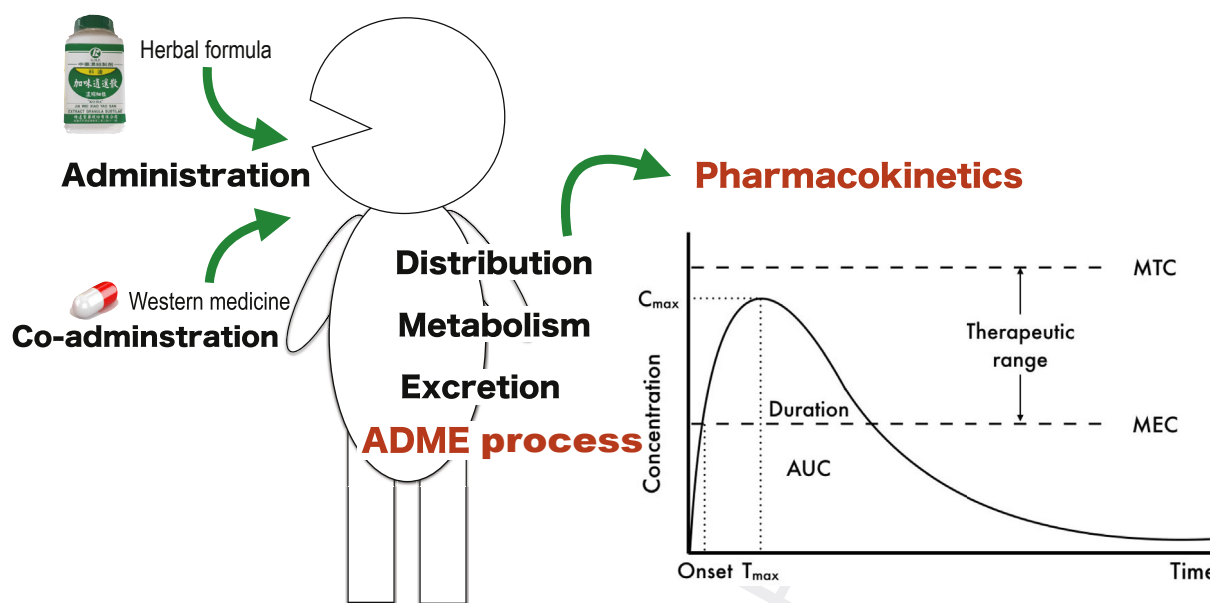
Figure 1 — Typical plasma concentration versus time profiles after oral administration. AUC = area under the curve; C_{max} = maximum plasma concentration; MEC = minimum effective concentration; MTC = maximum toxic concentration; $t_{1/2}$ = half-life; T_{max} = time to C_{max}.

improvement of using rapid UPLC-MS analysis without loss of resolution also helps minimize matrix effects such as ion suppression from biosamples. A 20% increase of detected analytes by UPLC-MS has been demonstrated compared with a similar HPLC-MS approach [11]. UPLC with electrospray ionization tandem mass spectrometry (UPLC-MS/MS) methods for pharmacokinetics have been developed for excellent quantitative analysis of detecting active compounds in herbal medicines in rat plasma extracts [12,13].

Reliable results of qualitative and quantitative analyses of herbal medicines depend on the validation of the analytical methods. The United States Food and Drug Administration published a guide for bioanalytical method validation that generally applies to bioanalytical procedures. The standard guidelines of method validation include selectivity, calibration curve, extraction recovery, repeatability of accuracy and precision, stability in all operations and storage conditions, and the matrix effect of study samples. Sample pretreatments that involve removal of endogenous interferences, such as protein precipitation, liquid—liquid extraction, and solid-phase extraction, are important aspects that could affect the analytical results and method validation procedures. Method validation and optimization are time-consuming processes during biological analyses but are the most reliable methods for qualifying an herbal medicine, and even an herbal formula composed of several herbs that are used in humans.

The aim of this article is to evaluate the existing evidence-based data associated with documented pharmacokinetics profiles of herbal formulas for the treatment of chronic hepatitis as well as their potential herbal—drug interactions. Various articles were surveyed on the PubMed database by using keywords such as pharmacokinetic, herbal formula, Chinese medicine, and herb—drug interaction. The content herbal formulas in these published studies relating to chronic hepatitis were selected for references. The article briefly introduces the analytical instruments, discusses the pharmacokinetic principles, and summarizes the dose of administration and intended analytical marker compounds of herbal formula frequently applied on chronic hepatitis. Moreover, the contents focusing on the existing pharmacokinetic profiles of herbal formulas are further linked with clinical practice to provide insight for the safety and specific use of traditional herbal medicines.

2. Chronic hepatitis

Chronic hepatitis, including viral hepatitis B or C, is a serious health problem in Eastern and Western countries. It is also the leading cause of hepatocellular carcinoma (HCC) in Asian countries [14,15]. There is a 9.6% relative risk of HCC for males who are hepatitis B surface antigen (HBsAg)-positive alone and a 60.2% relative risk for males who are positive for HBsAg and hepatitis B e antigen (HBeAg) in Taiwan [16]. Hepatitis B accounts for approximately one-third of liver cirrhosis cases and more than one-half of HCC cases in Asian areas [17]. The development of liver cirrhosis and HCC in patients with coinfections of hepatitis B and C is generally more severe than that in patients with hepatitis B or hepatitis C alone [18]. The proposed guidelines for the management of hepatitis B in Asia Pacific regions include antiviral agents (nucleotide analogs) and immune-based therapies [interferon (IFN)-α or pegylated-IFN-α] [19]. Nevertheless, pharmacokinetic behavior varies from the extent of different liver functions. The elimination half-life ($t_{1/2}$) of glycyrrhizin in the hepatitis and cirrhosis groups varied about twice and eight times, and total body clearance rates were about 0.7 times and 0.23 times versus those in normal individuals, respectively [20]. Alterations of the liver structure in HCC or cirrhosis could consequentially affect the metabolization and transfer of drug by enzymes. Q2

The metabolism of hepatitis C virus (HCV) drugs involves enzymes such as CYP3A4, CYP2C8, or CYP2C19 [21]. The pharmacokinetics of asunaprevir, a protease inhibitor metabolized by CYP3A4 and 98.8% bound to serum proteins, showed a 10-fold increase in maximum concentration and 5-fold AUC in Child B patients, as well as 23- and 32-fold increase in Child C patients, respectively [22,23]. A Miao medicinal plant, *Polygonum capitatum*, could also induce CYP2C9 and CYP3A4, which may result in reduced effective concentrations of drugs metabolized by these enzymes [24]. Therefore, pharmacokinetic studies, whether herbs or drugs, for treating liver disease should never be the last issue that should be considered.

3. Herbal medicine treatment on chronic hepatitis

An increasing number of patients seek alternative medicine or complementary treatment despite the implementation of strategies for the treatment of patients with chronic viral hepatitis. Herbal medicines account for 16.8% of patients with chronic liver disease who use complementary and alternative therapies [25]. Several single herbal medicines are used to treat or prevent liver disease. Silibinin or silybinin, which is the primary component of silymarin, exerts hepatoprotective properties [26]. The root of *Scutellaria baicalensis* (Chinese herbal name: Huang Qin) contains baicalin and baicalein, which inhibit oxidation and nitration in liver cells [27]. *Schisandra chinensis* (Wu-Wei-Zi), which is the primary component of the Kampo medicine TJ-108, exhibited liver protection and inhibited HCV infection [28]. Salvianolic acid B, which is obtained from the water extract of *Salvia miltiorrhiza* (Dan-Shen), reversed liver fibrosis in chronic hepatitis B patients with slight liver injury [29]. However, as herbal medicines contribute to the pharmacodynamic outcomes, coadministration of herbs and drugs may alter their pharmacokinetics, in which one could increase or decrease the therapeutic properties of the other. For example, silymarin could increase the clearance of metronidazole and hydroxymetronidazole by 29.51% and 31.90%, respectively [30]; it may also affect the distribution ratios of pyrazinoic acid through hepatobiliary elimination [31]. The anti-inflammatory effects of Radix *S. baicalensis* extract with mefenamic acid was potentiated and prolonged through PEG2 inhibition [32]; *S. miltiorrhiza* may induce CYP3A4 in the gut that therefore prolongs the effects of warfarin [33]. The pharmacokinetic and subsequent pharmacodynamic properties of these single medicinal herbs could be changed by other drugs, not to mention the multicomponent herbal medicines. Recognizing the pharmacokinetics properties of these herbal medicines by bioanalytical methods that have been developed are the basic issue of high priority.

4. Pharmacokinetics of herbal medicines used for chronic hepatitis

The National Health Insurance Research Database in Taiwan reported that the most frequently prescribed Chinese herbal formulas for chronic hepatitis were Long-Dan-Xie-Gan-Tang (LDXGT), which contains 10 herbs, followed by herbal formulas including Jia-Wei-Xiao-Yao-San (JWXYS; contains 10 herbs), Xiao-Chai-Hu-Tang (XCHT) (Sho-saiko-to; contains 7 herbs), and Yin-Chen-Wu-Ling-San (contains 6 herbs) [34]. Each formula accounted for at least 10% of all formulas prescribed for chronic hepatitis in Taiwan in 2002. The prescribing patterns of Chinese herbal formulas for the treatment of chronic hepatitis were revealed, but the pharmacokinetic parameters of these formulas—including absorption, distribution, metabolism, and excretion, as well as their possible herbal formula–drug interactions—should be considered in clinical practice.

4.1. Long-Dan-Xie-Gan-Tang

LDXGT originated from *Yi-Zong-Jin-Jian* (*Golden Mirror of Medicine*) during the Ching dynasty in approximately 1739. LDXGT contains 10 herbal medicines: *Gentiana scabra* (Long-Dan-Cao), *Alisma orientalis* (Ze-Xie), *Bupleurum chinense* (Chai-Hu), *S. baicalensis* (Huang-Qin), fruits of *Gardenia jasminoides* (Zhi-Zi), *Clematis montana* (Mu-Tong), seeds of *Plantago asiatica* (Che-Qian-Zi), *Angelica sinensis* (Dang-Gui), *Rehmannia glutinosa* (Di-Huang), and *Glycyrrhiza uralensis* (Gan-Cao), in a weight ratio of 4:4:4:2:2:2:2:2:2:2, respectively.

LDXGT treatment is used for acute or chronic hepatitis and accounts for 23.5% of the herbal formula prescriptions for chronic hepatitis in Taiwan [34]. The anti-inflammatory and antiherpetic virus effects of LDXGT have been reported previously [35]. These properties contribute to the herbal medicines contained in this formula, which exhibit antihepatitis B and C virus effects, other antiviral effects (*S. baicalensis*, *Glycyrrhiza uralensis*, and *G. scabra*) [36–39], anti-inflammatory effects (*B. chinense*, *G. scabra*, and *G. jasminoides*) [37,40–42], and antioxidation effects (*B. chinense*) [43]. *G. scabra* treatment may reverse hepatic fibrosis [44]. LDXGT is also widely used as a treatment for jaundice, cystitis, chronic pelvic inflammation, and scrotal and extremity inferior eczema [45–47].

The active compounds isolated from the LDXGT formula include gentiopicroside and swertiamarin, which are derived from *G. scabra*. Geniposide is isolated from *G. jasminoides*, and baicalin is derived from *S. baicalensis*. A pharmacokinetic study in freely moving rats after the oral administration of 10 g/kg LDXGT revealed that baicalin was absorbed rapidly and exhibited sustained levels among all of the notable compounds in LDXGT, with a t_{max} of 15.8 ± 9.0 minutes and $t_{1/2}$ of 314 ± 56.3 minutes in the concentration–time curve in plasma [48]. The bimodal phenomenon of baicalin represented variable gastric emptying, enterohepatic recycling, or different absorption sites along gastrointestinal segments. Baicalin isolated from *S. baicalensis* also exhibited the longest elimination time of all compounds. Gentiopicroside and swertiamarin are derived from *Gentiana* species. Swertiamarin exhibited the least prolonged t_{max} at 97.5 ± 14.4 minutes and the lowest AUC (2.5 ± 0.1 min μg/mL), which indicated a rapid metabolization or biotransformation of this compound. Gentiopicroside showed the highest C_{max} (5767 ± 412 ng/mL) and the highest AUC, which were significantly different from those of other active compounds. Gentiopicroside is protective against hepatitis and exhibits free-radical-scavenging activity [49,50]. These descriptive phenomena confirmed the

role of the medicinal *G. scabra* and may explain the protective and immunological effects of LDXGT for hepatic disease.

4.2. Jia-Wei-Xiao-Yao-San

JWXYS was first developed by the official pharmacy "He-Ji-Ju" (Grace Pharmacy) in the Song Dynasty (960—1279 BC). The composition of JWXYS includes 10 herbal medicines: Cortex *Moutan Radicis* (Mu-Dan-Pi), Fructus *Gardeniae* (Shan-Zhi-Zi), Radix *Bupleuri* (Chai-Hu), Radix *Angelicae Sinensis* (Dang-Gui), Radix *Paeoniae Alba* (Shao-Yao), *Poria* (Fu-Ling), Rhizoma *Atractylodis Macrocephalae* (Bai-Zhu), Rhizoma *Zingiberis Recens* (Wei-Jiang), *Herba Menthae* (Bo- He-Ye), and Radix *Glycyrrhizae* (Zhi-Gan-Cao), in a weight ratio of 2.5:2.5:4:4:4:4:4:4:2:2, respectively. This is the most frequently prescribed herbal formula according to the National Health Insurance Research Database of Taiwan [51]. JWXYS prevents dimethylnitrosamine-induced hepatic fibrosis in rats [52], and it is widely used in chronic hepatitis [34], climacteric symptoms [53], insomnia [54], and breast cancer [55].

The only pharmacokinetic study of JWXYS was performed on puerarin, which is derived from Radix Paeoniae Alba. Puerarin exhibited a mean absorption time to C_{max} of 51 minutes after oral administration of 5 g/kg medicinal powder to 11 individuals (6 functional dyspepsia patients and 5 healthy volunteers) [56]. The study revealed alternative pharmacokinetic variations of JWXYS between the two different patient conditions, but it did not clarify the full therapeutic picture of this formula because only a single component was analyzed.

4.3. XCHT (Sho-saiko-to)

XCHT was first developed by Zhang Zhongjing during the Han Dynasty (150—215 AD) and is described in his book, *Shang-Han-Lun* (*Treatise on Cold Damage Diseases*). XCHT was originally developed for the treatment of patients with alternating chills and fever, chest tightness, bitter taste, and poor appetite with or without nausea and vomiting, which are similar to the symptoms exhibited by patients with cholecystitis or hepatitis. Many studies were performed on XCHT, and the results demonstrated therapeutic effects on chronic hepatitis [57—59], depression [60], renal protection of type 1 diabetic mice [61], and ovarian cancer [62]. XCHT was also frequently used as a treatment for migraine [63]. XCHT contains seven medicinal herbs: Radix *Bupleurum falcatum* (Chai-Hu), Radix *S. baicalensis* (Huang-Qin), Radix *Panax ginseng* (Ren-Shen), Fructus *Zizyphus jujuba* (Da-Zao), *Pinellia ternate* (Ban-Xia), *Zingiber officinale* (Sheng-Jiang), and *Glycyrrhiza glabra* (Zhi-Gan-Cao). Severe adverse effects of interstitial lung fibrosis [64] and acute hepatitis [65,66] were reported following the administration of this formula. An *in vivo* study demonstrated that a dose level less than 2 g/kg/d during a 13-week oral administration of XCHT in rats did not produce adverse effects [67]. The toxicity of XCHT may be related to administration duration and dose. Therefore, the pharmacokinetic profiles of XCHT should delineate its bioavailability in human studies.

Pharmacokinetic analyses of baicalin and wogonoside isolated from Radix *scutellariae* after oral administration of 2 mL/100 g XCHT (which contained 265.4 mg/kg of baicalin and 58.78 mg/kg of wogonoside) to Sprague—Dawley rats demonstrated that these isolates exhibited double-peak phenomenon that was likely the result of enterohepatic circulation. The t_{max} 1 and t_{max} 2 of baicalin in XCHT was 7.8 ± 2.8 minutes and 384 ± 100.2 minutes, respectively. The t_{max} 1 and t_{max} 2 of wogonoside was 12.6 ± 12 minutes and 336 ± 100.2 minutes, respectively [68]. The half-life of baicalin and wogonoside in XCHT was 3.6 hours and 4.9 hours, respectively. The pharmacokinetic parameters of baicalin and wogonoside support the notion that XCHT has a rapid onset and sustained effect during treatment. However, baicalin and wogonoside were derived from the same herbal medicine, and different compounds from various herbs in XCHT should be investigated to further reveal the pharmacokinetic properties of XCHT.

4.4. Yin-Chen-Hao-Tang

Yin-Chen-Hao-Tang (YCHT) also originated from *Shang-Han-Lun* (*Treatise on Cold Damage Diseases*), written during the Han Dynasty (150—215 A.D.). YCHT is used to treat patients with jaundice, dysuria, and thirst, which correlates to the Chinese medicine pattern of damp heat. The formula contains three medicinal herbs: *Artemisia capillaris* Thunb (Yin-Cen-Hao), *G. jasminoides* Ellis (Zhi-zi), and *R. officinale* Baill (Da-huang) in a weight ratio of 4:3:1. Many studies reported potent effects of antihepatic fibrosis, antihepatic apoptosis, and alleviation of hepatic oxidative stress [69—71]. An *in vitro* study also demonstrated that the water extract of YCHT diminished the infectivity of herpes simplex virus (HSV), especially that of HSV-2 [72]. YCHT is also the basic composition formula of Yin-Chen-Wu-Ling-San (YCWLS), which was the fourth leading herbal formula prescribed for chronic hepatitis in Taiwan [34]. YCWLS is also the chosen formula for the damp-heat pattern that is frequently observed in cirrhosis [73].

The pharmacokinetic profiles of YCHT demonstrated that the t_{max} was approximately 35 minutes via measurement of the compound 6,7-dimethylesculetin, which is derived from *A. capillaris*, after oral administration of YCHT containing 12.0 mg/kg of 6,7-dimethylesculetin or 35.5 mg/kg of geniposide. The pharmacokinetic parameters of geniposide isolated from *G. jasminoides* demonstrated that the C_{max} and t_{max} were 11.54 ± 2.73 μg/mL and 16.2 ± 3.6 minutes, respectively [5]. Another pharmacokinetic study of YCHT reached the same conclusion of a synergistic effect of the combination of these three herbs, and YCHT exhibited an increased plasma level and delayed elimination rate of 6,7-dimethylesculetin compared to the other one or two individual herbs combined [74]. These studies lacked a validated internal standard compound, but the interaction of active compounds within the same formula could alter the therapeutic effectiveness of traditional herbal formulas.

5. Pharmacokinetic interaction of herbal medicines with Western drugs for chronic liver disease

The interaction between Chinese herbal medicines and Western drugs affects the pharmacokinetics and pharmacodynamics in human bodies regardless of the multiple

components of herbal formulas. Different concentrations of active compounds and drugs result from the pharmacokinetic and pharmacodynamic interactions, which alters the absorption, distribution, metabolism, and excretion of these substances, and leads to synergistic or reduced effects. Studies on herbal formula–drug interactions would affect clinical practice and provide a relatively safe method for the coadministration of herbs and drugs.

5.1. LDXGT coupled with lamivudine

LDXGT is the leading prescription for chronic hepatitis in Taiwan. Patients with chronic hepatitis may seek complementary and alternative therapies, which expose them to risk of potential herbal formula–drug interactions, especially patients with poor liver function. One potential drug interaction in patients with chronic hepatitis stems from lamivudine, which is a nucleoside analog and reverse transcriptase inhibitor that is used to treat patients with hepatitis B virus infection. An *in vivo* study of the interaction of LDXGT and lamivudine revealed that the pharmacokinetic parameters of lamivudine were not significantly altered by the oral administration of 1.23 g/kg or 2.46 g/kg LDXGT in Sprague–Dawley rats, but the volume of distribution (V_d) was slightly increased at a high dose of lamivudine (up to 30 mg/kg) [75]. The pharmacokinetics of lamivudine in rat plasma or liver was not altered by LDXGT, even at a dose of 2.46 g/kg/d in rats, which corresponded to 23.9 g/d for a 60-kg human. LDXGT is also used for the treatment of insomnia and herpes zoster [47,54]. Potential herbal formula–drug interaction studies in other disease states should be examined for future clinical implications.

5.2. JWXYS coupled with 5-fluorouracil or etizolam

The potential interactions between the herbal formula JWXYS and drugs are based on clinical situations. JWXYS is widely used to treat functional dyspepsia, chronic hepatitis, hepatic fibrosis, and chronic renal disease [52,76–78]. Current research also revealed that JWXYS was the most frequently prescribed formula for climacteric women and patients with breast cancer, and it is the second most common prescription for insomnia [53–55]. One study used multiple microdialysis probes to monitor the interaction of JWXYS and 5-fluorouracil (5-FU) in rat plasma and brain [79]. The results revealed that JWXYS did not alter the AUC or C_{max} of 5-FU in plasma or brain, but it did increase the elimination half-life in the blood and brain at a dose of 2.4 g/kg/d orally, which corresponded to the maximum doses of 23.4 g/d for a 60-kg person. This maximum dose of JWXYS also increased the volume distribution in the blood and reduced clearance in the brain. A possible leading cause of increased $t_{1/2}$ and clearance reduction is that JWXYS, which contains sufficient concentrations of flavonoids, 18-β-glycyrrhetic, acid or other compounds, inhibited the removal of 5-FU by P-glycoprotein in the brain. The suppressive effect of JWXYS on CYP1A2 expression at a high dose reduced the metabolic efficiency of 5-FU, which provides an additional explanation of the increase in $t_{1/2}$ and the volume of distribution.

JWXYS, known as Kamisyoyosan (KSS) in Japan, is also clinically used to treat women with climacteric disturbance. Climacteric problems, such as hot flash, panic, insomnia, and emotional disturbance, were relieved by JWXYS in clinical studies [80,81]. Women with climacteric symptoms of emotional disturbance may receive the benzodiazepine etizolam for symptom relief. Makino et al [82] examined potential herbal formula–drug interactions and demonstrated that oral administration of 1 g/kg KSS did not alter plasma concentrations of etizolam in rats. This result suggests that a common clinical dosage of KSS that corresponds to 9.73 g/d for a 60-kg human would not cause pharmacokinetic interactions with etizolam. The herbal formula JWXYS exhibited relative safety with drug coadministration for this condition.

5.3. XCHT and carbamazepine

XCHT exhibits renal protective, antidepressant, antihepatitis C, and antiseptic shock properties [59–61,83], but severe herbal hepatotoxicity was reported with an odds ratio of 2.19 for HBV-infected patients in a dose–response relationship with *Bupleurum* (Chai Hu) [84]. Drugs that cause liver injury or are primarily metabolized by the liver should be used with caution for coadministration with XCHT. An *in vivo* study orally administered the Kampo medicine Sho-saiko-to (XCHT) to rats for 2 weeks followed by treatment with carbamazepine (CBZ), which is a substrate of P450 and an anti-epilepsy drug. The results revealed no alternative pharmacokinetic parameters of CBZ or its toxic metabolite carbamazepine-10, 11-epoxide (CBZ-E). However, simultaneous oral administration up to 1 g/kg of XCHT in rats significantly decreased the C_{max} of CBZ and the AUC of CBZ-E [85]. These phenomena may result from gastric emptying induced by XCHT and the slowed absorption of CBZ. XCHT is applicable in patients receiving CBZ because no interference was noted in the metabolism of CBZ, which is metabolized by CYP3A4.

6. Conclusion

We reviewed current studies of the pharmacokinetic profiles and herbal formulas versus drugs interaction in chronic liver disease. The results of current herbal formula–drug interaction studies revealed no significant changes in pharmacokinetic parameters during the coadministration of the following herbal formulas and drugs: LDXGT coupled with lamivudine, Jia-Wei-Xiao-Yao-San (JWXYS) coupled with 5-FU or etizolam, and XCHT and CBZ. However, JWXYS (up to 23.4 g/d) delayed the elimination $t_{1/2}$ of 5-FU in blood and brain and reduced clearance in the brain, and XCHT (up to 9.73 g/d for a 60-kg adult) decreased the maximum concentration of CBZ and the bioavailability of its metabolites. The possible herb–drug interactions based on the current literature are summarized in Table 1.

In conclusion, the quality and quantity of the prescribed herbal remedies and randomized clinical trials should be required to ensure the efficacy of Chinese herbal medicine. An increased understanding of the pharmacokinetics and bioavailability of herbal formulas helps physicians efficiently determine the dose and efficacy of therapies. However, studies on pharmacodynamics are lacking. Therefore, specific

Table 1 – Interaction effects of drugs with herbal formula for chronic liver disease on pharmacokinetic parameters.				
Drugs (dose)	Lamivudine (30 mg/kg, i.v.) [75]	5-FU (100 mg/kg, i.v.) [79]	Etizolam (10 mg/kg, p.o.) [82]	Carbamazepine (50 mg/kg, p.o.) [85]
Pretreated herbs (dose)	LDXGT (1.23 g/kg)	JWXYS (2.4 g/kg/d)	KSS (1 g/kg)	TJ-9 (1 g/kg)
C_{max} (μg/mL)	87.8 (C_0)	107 (C_0)	0.651	↓ 11.5
T_{max} (min)	—	—	11.9	180
$t_{1/2}$ (min)	7.74 and 49.2	↑ 25.6 (↑ brain 47.2)	44.9	192
AUC (min μg/mL)	1449	6159	30.5	5136 (↓CBZ-E 4050)
Cl (mL/min/kg)	21.2	17.6 (↓brain 82.9)	na	na
V_d (mL/kg)	↑ 718	↑ 575	na	na
Notes	Possible affect drug-metabolizing genes	Possible inhibit P-glycoprotein		Possible reduce carbamazepine absorption

Data are expressed as mean value. The arrow signs in the table indicate increase or decrease when combined with herbal medicine compared to the drug alone.

5-FU = 5-fluorouracil; AUC = area under the curve; CBZ-E = carbamazepine-10,11-epoxide; Cl = clearance; C_{max} = maximum plasma concentration; JWXYS = Jia-Wei-Xiao-Yao-San; KSS = Kamisyoyosan; LDXGT = Long-Dan-Xie-Gan-Tang; na = data not available; TJ-9 = Sho-saiko-to; $t_{1/2}$, half-life; T_{max} = time to C_{max}; V_d = volume distribution.

therapeutic or adverse effects of herbal medicines, *in vivo* synergetic effects, and herb—drug interactions remain ambiguous. Future studies of herbal remedies should concentrate on the integration of pharmacokinetics and pharmacodynamics for the safety and specific use of traditional medicines.

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Acknowledgments

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