Influence Factors of the Pharmacokinetics of Herbal Resourced Compounds in Clinical Practice

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Herbal medicines have been used to prevent and cure diseases in eastern countries for thousands of years. In recent decades, these phytotherapies are becoming more and more popular in the West. As being nature-derived is the essential attribute of herbal medicines, people believe that taking them for diseases treatment is safe enough and has no side-effects. However, the efficacy of herbal resourced compounds (HRC) depends on the multiple constituents absorbed in the body and their pharmacokinetics. Thus, many factors will influence the clinical practice of HRC, i.e., their absorption, distribution, metabolism, and excretion (ADME). Among these factors, herb-drug interaction has been widely discussed, as these compounds may share the same drug-metabolizing enzymes and drug transporters. Meanwhile there are many other potential factors that can also change the ADME of HRC, including herb pretreatment, herb-herb interactions, pathological status, gender, age of patient, and chemical and physical modification of certain ingredients. With the aim of ensuring the efficacy of HRC and minimizing their clinical risks, this review provides and discusses the influence factors and artificial improvement of the pharmacokinetics of HRC.

1. Introduction

The history of people employing herbal medicines can be dated back as early as 2100 B.C. in ancient Asian countries [1]. Nowadays, approximately 25% of common medications contain herbs, and this proportion has been elevated to 30% and to 50% in China, especially [2]. Not only in the East, herbal medicines have contributed the largest proportion to complementary and alternative medicine consumption in the United States and about 20% of people have taken some herbal supplementation [2, 3].

With the increasing knowledge of diseases treatment, people found that pharmacokinetics of HRC and their tissue distribution behaviors are crucial to their pharmacological efficacy [4]. For instance, differences in physiological status of body such as gender, age, diseases, and external stimulus may influence the oral bioavailability, tissue distribution, half-time (t1/2), maximum plasma concentration (Cmax), and time to reach Cmax (Tmax), etc. of drugs or herbal medicines, and these changes in intrinsic pharmacokinetic parameters will cause variations in their therapeutic effects [4–8].

Meanwhile, unlike the widely employed chemical drugs, herbal medicines containing thousands of constituents are regarded as performing holistic effects through interactions among multiple active components and multiple targets [9]. Meanwhile, the internal metabolism processes of herbal medicines are complex due to these interactions, which may influence metabolism-related biological active substances, such as cytochrome P450 enzyme (CYP450) and P-glycoprotein (P-gp) [10]. Certainly, if herbal medicines were applied in combination with conventional drugs, the risk of possible interactions between constituents is increased. In addition, not all herb-drug or herb-herb interactions are harmful. Under some circumstances, these interactions can improve the bioavailability of target compounds and minimize side-effects of toxic ingredients [11, 12].

The pharmacokinetic changes of HRC are closely related to its pharmacodynamics, and the factors affecting the process in vivo are very complex and easy to be ignored. Thus, the aim of this review is to describe the common factors that influence the pharmacokinetics of HRC, thereby giving
some references to ensure the safety and efficacy of these medications.

2. The Influence of Processing on the HRC Pharmacokinetics

The processing of traditional Chinese medicines (TCM) is a routine procedure and is usually performed on raw herbs before clinical use. Various traditional methods have been applied to herbs processing, such as sautéing with Chinese rice wine or brine solution, stir-heating, frying with sand, salt, honey or bile, steaming with water, ginger juice or vinegar, and sulfur fumigation [13–19]. The purpose of herb processing is modifying the nature of crude herbal materials, which results in enhancing their therapeutic effects, as well as reducing their toxicity. The content of some ingredients in herbs may increase, and others may decrease or even disappear after processing. Changing the chemical profile usually influences the pharmacokinetics of HRC.

Wine is one of the most popular processing adjuvants. Tao et al. [20] compared the pharmacokinetic differences between crude and wine-processed Dipsacus asper (DA) in rats. After being processed, the contents of phenolic acids of DA were decreased more than those of the crude herb, while the contents of saponins and iridoids were increased significantly. Compared to rats in the group of crude herb administration, area under the plasma concentration-time from zero to the last quantifiable time-point (AUC0–t) values along with Cmax values of most compounds increased remarkably after wine-processed DA aqueous extracts administration. These differences might be attributed to the facilitating effect of wine that made ingredients absorb into the circulation more easily. Wine-processed herb exhibited more loose tissues, more small pores, larger total surface area, and smaller fractal dimension than those of crude herb, which allows the solvent to penetrate the loose tissue and to change internal structure, then increasing dissolution of herb containing components [21], and this might be another reason to explain this phenomenon. Similar results were observed in wine-processed Rhizoma Coptidis and Schisandra Chinensis fructus [22, 23].

The same adjuvant used in herbal materials processing can have different effects on pharmacokinetics of herbs. Vinegar-baked is another routine technology for herb preparation. On the one hand, during the procedure of vinegar processing, the hydrolyzation of saponins, flavonoids, and polysaccharides occurs, and the content of these components may be changed, because the main component of vinegar is acetic acid; this will result in deglycosylation of natural products with glycoside structure. The reaction makes the pharmacokinetic parameters of compounds significantly different between crude and vinegar-processed herbs and strengthens the effect of processed herbs [24]. On the other hand, some vinegar-processed herbs show less toxicity than crude herbs. This may be caused by the destruction of prototypes of some ingredients possessing the most toxicity and decreasing the bioavailability of toxic components after processing [14].

Animal-derived materials, such as pig's bile and mutton-fat, are a class of distinctive adjuvants in herb processing. There are researchers believing that bitter bile could increase the Cold nature of herbs and influence the energy metabolism of experimental animals [25]. Furthermore, a comparative pharmacokinetic study revealed that bile-processed Rhizoma Coptidis could increase the absorption rate of main active alkaloids into the plasma of heat syndrome rats more than raw herb [19]. These results are probably because alkaloids in Rhizoma Coptidis are hydrophobic, but when they meet the bile acids in processing adjuvant pig's bile, soluble salts are formed and then facilitate the water dissolving of these alkaloids, which finally leads to the absorption rate improvement of alkaloids by rats and strengthens their specific therapeutic effects.

In recent decades, a controversial processing technology named sulfur fumigation has taken the place of natural drying of postharvest medicinal herbs under sun or in the shade [26]. For one thing, this operation can make herbs look whiter and prettier and prevent them from insects and mildew with shortened drying time. For another, this processing procedure can cause chemical alteration of the herbs’ origin ingredients, generate sulfonated derivatives, and then influence the pharmacokinetics of certain components [26–28]. Radix Paeoniae Alba (the root of Paeonia lactiflora Pall., PA) is the most representative medicinal herb that is always processed by sulfur fumigation. Some researchers suggested that sulfur fumigation could increase the absorption time and improve the bioavailability of the active components of PA [29], whereas another study showed that the safety and efficacy of PA were reduced after this processing procedure [28]. In consideration of the debatable safety of sulfur-fumigated medicinal materials, most herbs are forbidden to be processed by sulfur fumigation in China now. Meanwhile, the permitted herbs should have sulfur dioxide residual amount less than 400 mg/kg, but this residue limitation lacks scientific evidence [26]. Overall, in order to standardize the practice of sulfur fumigation and ensure the safety and efficacy of sulfur-fumigated herbs, further studies are needed.

Different from traditional processing, new methods like ultrafine powders of Chinese herbs (D 90 < 45 μm) have made great progress in clinical use for their convenience for carrying and oral administration [30]. As the pulverized herbal medicine owns a relatively larger surface area than traditional applied forms, bioavailability of many constituents in vivo increased [30, 31]. Consequently, this feature will help patients in taking lower dosage of herbal medicine in prescriptions and saving cost, which may improve medication compliance to ensure therapeutic effects.

3. The Influence of Coadministration with Herbal Medicines or Drugs

In general, many people believe that herbal remedies present moderate and harmless effects to patients. Admittedly, the use of herbal medicines alone may not be dangerous, but they ignore the fact that herbal medicines contain various constituents with multiple pharmacological actions on the body. If conventional drugs are taken in combination,
probable interactions of pharmacokinetics and/or pharmacodynamics may occur between them. A report reveals that nearly 80% of the world’s population take herbs as their primary medications. In particular, older people tend to become the largest consuming groups of herbal prescriptions due to their commonly multiple health problems, such as chronic diseases [32]. They often take herbal medicines coupled with conventional medications, which is raising the potential for herb-drug interactions. Therefore, the risk of possible interactions between drug and co- or pre-administration herbal medicine, single substance, and other components in traditional herbal compound prescriptions, even occurring in the multiconstituent herb itself, should not be disregarded. Several reviews have discussed the issue of herb-drug interactions [3, 10, 32–35]. In these reviews, they mainly focus on the effects of natural products on the pharmacokinetics or pharmacodynamics of drugs. However, on the one hand, the coadministration of chemical drug may also influence the pharmacokinetics of HRC; on the other hand, the interactions between HRC are also little discussed. Hence, we will place especial emphasis on herb-herb interactions and multicomponent interaction in an herb in this section.

3.1. Herb-Drug Interaction. The metabolism of HRC in vivo mostly depends on common drug-metabolizing enzymes and transporters, such as CYP450 or P-gp. Many papers reported that the coadministration of herbal medicines interferes in the pharmacokinetics of chemical drugs because of their sharing the same metabolizing enzymes and transporters, while the chemical drugs would also affect the pharmacokinetics of HRC by the same mechanism. Therefore, intensive studies are needed to ensure the safety and effectiveness of drugs when they coadministrated with herbal medicines.

CYP450 is a group of oxygenases, which plays a key role in the metabolism of endogenous substances and xenobiotics. Meanwhile, approximately 90% of current drugs are metabolized by CYP450 subtypes [10]. If the chemical drugs induced or inhibited specific CYP450 isoforms, the metabolism of coadministration HRC would be influenced. Yin and Cheng et al. [36] used CYP450 probe drugs as a tool to investigate the effects of notoginsenoside R1 on the activities of several CYP450 isoforms in vivo. The results exhibited that compared with the pharmacokinetic parameters of the control group, the Cmax and area under the plasma concentration-time from zero to infinity (AUC(t,∞)) of caffeine, which is mainly metabolized by CYP1A2, were increased, while the total plasma clearance (CL) was decreased in the notoginsenoside R1 treated group. However, other probe drugs corresponding to CYP2C11, CYP2D1, and CYP3A4/5 like tolbutamide, metoprolol, and dapsone were not affected by notoginsenoside R1 administration. These consequences indicated that patients who took drugs metabolized by CYP1A2 together with notoginsenoside R1 should evaluate the potential herb-drug interactions and be paid more attention.

Drug transporters are another important group that affects the metabolism of drugs. Until now, a lot of transporters have been characterized in humans, while P-gp is the most extensively studied one and affects the bioavailability of many oral medications [33]. Schisandra chinensis is a commonly used herb and its extract was reported to regulate P-gp along with other transporters such as multidrug resistance-associated proteins and organic anion transporting polypeptides, as well as some drug-metabolizing enzymes. Therefore, coadministration of Schisandra chinensis and other drugs which are substrates of the reported transporters and enzymes may cause unfavorable herb-drug interactions [37].

Although many studies indicate that herbal medicines could alter the pharmacokinetics of coadministration drugs [38, 39], there are still some reports suggesting that no significant influence is observed in combination use of herbs with drugs [40, 41].

3.2. Herb-Herb Interaction. According to many fork medicine theories, the most dominant clinical application form of herbal medicines is “formula”, which is prescribed in combination of two or more herbs. Compatibility of multiple herbs is a key characteristic of formula and has exhibited its enormous influence in long-term clinical practices. It depends on both the clinical efficacy and the properties of each herb and possesses intention to obtain synergistic therapeutic effects and minimize or diminish the possible side-effects [42–44]. The chemical material basis of compatibility may be due to their interactions between the multiple constituents in the compound prescription, sequentially influencing the ADME of individual active ingredients. Hence, it is meaningful to reveal the complex mechanism of formula compatibility. Some common herb-herb interactions are summarized in Table 1.

Many works have been demonstrated to study the regularity of recipe composition. Da Chuanxiong decoction consists of Gastrodia elata Bl. (GE) and Ligusticum chuanxiong Hort. (LC), and Hu et al. compared the pharmacokinetics of gastrodin after orally administrating GE extract alone and in combination with different components of LC in rats [54]. They found that total phenolic acids and alkaloids but not tetramethylpyrazine of LC significantly affected the pharmacokinetic parameters of gastrodin. Another case investigated the pharmacokinetic compatibility of several ingredients in Sheng Mai San, a compound prescription consisting of Panax ginseng, Ophiopogon japonicus, and Schisandra chinensis and exhibiting curative effects on cardiovascular diseases [44]. Experiment results showed that Schisandra lignans extract could significantly enhance the exposure of several ginsenosides both in vitro and in vivo. Recently, a comparative pharmacokinetic study in rats was carried out to evaluate the herb-herb interactions in Guanxin Shuting Capsule (GSC) following oral administration of single herb extract and different herb extract combinations [45]. With the composing of Choerospondias axillaris, Salvia miltiorrhiza Bunge, Syzigium aromaticum (SA), Borneolium synthetica, and Tabaschir, GSC has been used for treating cardiovascular-related disease in clinical practice. As a result, GSC treated group showed significant promotion of the bioavailability of eugenol and reduction of the rate of its elimination processes, and the AUC0-∞, AUC0-∞, and Cmax of bicyclic monoterpenes (isoborneol, borneol, and camphor) were more prominently
Table 1: Possible herb-herb interactions.

| Herb1                         | Herb2                           | Monitoring indexes | Pharmacokinetic parameters of indexes comparing to administration herb1 alone | Ref. |
|-------------------------------|---------------------------------|--------------------|-----------------------------------------------------------------------------|------|
|                               |                                 | AUC<sub>0-1</sub> | AUC<sub>0-0</sub> | t<sub>1/2</sub> | T<sub>max</sub> | C<sub>max</sub> | MRT<sub>0-0</sub> | MRT<sub>0-1</sub> | K | V<sub>d</sub> | CL |
| Borneolum                     |                  GuanxinShutong Capsule | Camphor            | ↓                        | ↓                        | ↓                        |
|                               |                   Isoborneol         | ↓                        | ↑                        | ↑                        | ↓                        |
|                               |                   Borneol           | ↓                        | ↑                        | ↑                        | ↓                        |
|                               |                   Eugenol           | ↑                        | ↑                        | ↑                        | ↓                        |
|                               |                   Camphor           | ↓                        | ↓                        | ↑                        | ↓                        |
|                               |                   Isoborneol         | ↓                        | ↓                        | ↑                        | ↓                        |
|                               |                   Borneol           | ↓                        | ↓                        | ↑                        | ↓                        |
|                               |                   Eugenol           | ↑                        | ↑                        | ↑                        | ↓                        |
| Syzygium aromaticum           |                  Borneol           | Rosmarinic acid       | ↑                        | ↑                        | ↑                        | ↑                        | [45] |
|                               |                  Isoborneol         | ↑                        | ↑                        | ↑                        | ↑                        | ↑                        | [46] |
|                               |                  Borneol           | ↑                        | ↑                        | ↑                        | ↑                        | ↑                        | [43] |
| Salviae miltiorrhizae         |                  Borneol           | Chrysophanol         | ↓                        | ↓                        | ↑                        | ↑                        |
|                               |                  Physcion          | ↑                        | ↑                        | ↑                        | ↑                        | ↑                        |
| Radix et Rhizoma Rhei         |                  Dahuang-Fuzi Decoction | Salvanolic acid A     | ↑                        | ↑                        | ↑                        | ↑                        |
|                               |                  Physcion          | ↑                        | ↑                        | ↑                        | ↑                        | ↑                        |
| Paeonia lactiflora            |                  ZengnianYiliu Formula | Albaflorin           | ↓                        | ↓                        | ↑                        | ↑                        | ↑                        | [47] |
|                               |                  Paeoniflorin       | ↓                        | ↓                        | ↑                        | ↑                        | ↑                        | [47] |
| Radix Kansui and Radix et Rhizoma Glycyrrhiza | Gansui-Banxia Decoction | Liquiritigenin       | ↑                        | ↑                        | ↑                        | ↑                        | ↑                        | [48] |
|                               |                   Isoliquiritigenin | ↑                        | ↑                        | ↑                        | ↑                        | ↑                        | [48] |
|                               |                   Liquiritin      | ↑                        | ↑                        | ↑                        | ↑                        | ↑                        | [48] |
|                               |                   Glycyrrhetinic acid | ↑                        | ↑                        | ↑                        | ↑                        | ↑                        | [48] |
|                               |                   Glycyrrhizic acid  | ↑                        | ↑                        | ↑                        | ↑                        | ↑                        | [48] |
| Radix Paeoniae                |                  Radix et Rhizoma Glycyrrhiza | Liquiritigenin       | ↑                        | ↑                        | ↑                        | ↑                        | ↑                        | [48] |
|                               |                   Isoliquiritigenin | ↑                        | ↑                        | ↑                        | ↑                        | ↑                        | [48] |
|                               |                   Liquiritin      | ↑                        | ↑                        | ↑                        | ↑                        | ↑                        | [48] |
|                               |                   Glycyrrhetinic acid | ↑                        | ↑                        | ↑                        | ↑                        | ↑                        | [48] |
|                               |                   Glycyrrhizic acid  | ↑                        | ↑                        | ↑                        | ↑                        | ↑                        | [48] |
| Cortex Mori                   |                  Radix Pueraria Flavonoids | l-deoxynojirimycin    | ↑                        | ↑                        | ↑                        | ↑                        | ↑                        | [49] |
Table 1: Continued.

| Herb1                  | Herb2               | Monitoring indexes | Pharmacokinetic parameters of indexes comparing to administration herb1 alone | Ref.  |
|------------------------|---------------------|--------------------|--------------------------------------------------------------------------------|-------|
|                        |                     |                    | AUC<sub>0-<inf>t</inf> | AUC<sub>0-<inf>∞</inf> | t<sub>1/2</sub> | T<sub>max</sub> | C<sub>max</sub> | MRT<sub>0-<inf>t</inf></sub> | MRT<sub>0-<inf>∞</inf></sub> | K | V<sub>d</sub> | CL |     |
| Ramulus Cinnamomi      | Ephedrae Herba     |                    | ↑↑ | ↑ | ↓ | ↑ | ↑ | ↑ | ↑ | [50] |     |     |     |
|                        |                     |                    | Cinnamic acid | ↑ | ↓ | ↓ | ↑ | ↑ | ↑ |     |     |     |     |
|                        |                     |                    | Cinnamic alcohol | ↑ | ↑ | ↓ | ↑ | ↑ | ↑ |     |     |     |     |
| Huoluo Xiaoling Dan    | Radix Paeoniae Rubra |                   | Paeoniflorin | ↓ | ↓ | ↓ | ↑ | ↑ | ↑ |     |     |     |     |
|                        |                     |                    | Albisflorin | ↓ | ↓ | ↓ | ↑ | ↑ | ↑ |     |     |     |     |
|                        |                     |                    | Oxyflorin | ↑ | ↑ | ↓ | ↑ | ↑ | ↑ |     |     |     |     |
|                        |                     |                    | Tetrahydroflavonol | ↑ | ↑ | ↓ | ↑ | ↑ | ↑ |     |     |     |     |
|                        |                     |                    | Corydaline | ↑ | ↑ | ↓ | ↑ | ↑ | ↑ |     |     |     |     |
|                        |                     |                    | Dehydrocorydaline | ↑ | ↑ | ↓ | ↑ | ↑ | ↑ |     |     |     |     |
|                        | Huoluo Xiaoling Dan |                   | Senkyunolide A | ↑ | ↑ | ↓ | ↑ | ↑ | ↑ |     |     |     |     |
|                        |                     |                    | Ligustilide | ↑ | ↑ | ↓ | ↑ | ↑ | ↑ |     |     |     |     |
|                        |                     |                    | Butylideneflavonol | ↑ | ↑ | ↓ | ↑ | ↑ | ↑ |     |     |     |     |
|                        |                     |                    | 3-butyl-flavonol | ↑ | ↑ | ↓ | ↑ | ↑ | ↑ |     |     |     |     |
|                        | Huoluo Xiaoling Dan | Radix Angelica sinensis and Rhizome Ligusticum chuanxiong | Ginsenoside Rb<sub>2</sub><sup>d</sup> | ↑ | ↑ | ↓ | ↑ | ↑ | ↑ |     |     |     |     |
|                        |                     |                    | Ginsenoside Re<sub>2</sub><sup>d</sup> | ↑ | ↑ | ↓ | ↑ | ↑ | ↑ |     |     |     |     |
|                        |                     |                    | Ginsenoside Rd<sub>2</sub><sup>d</sup> | ↑ | ↑ | ↓ | ↑ | ↑ | ↑ |     |     |     |     |
|                        |                     |                    | Gastrodin | ↑ | ↑ | ↓ | ↑ | ↑ | ↑ |     |     |     |     |
|                        | Panax Ginseng glycosides | Schisandra lignans | Gastrodin | ↑ | ↑ | ↓ | ↑ | ↑ | ↑ |     |     |     |     |
|                        |                     |                    | Gastrodin | ↑ | ↑ | ↓ | ↑ | ↑ | ↑ |     |     |     |     |
|                        | Quercetin and Rutin Leaves of Bacopa onnieri, Fruits of Hippophae rhamnoides and Bulbs of Dioscorea bulbifera | | Quercetin | ↑ | ↑ | ↓ | ↑ | ↑ | ↑ |     |     |     |     |
|                        | Radix Paeoniae Alba and Radix et Rhizoma Glycyrrhizae (1:1) | | Rutin | ↑ | ↑ | ↓ | ↑ | ↑ | ↑ |     |     |     |     |
|                        |                     |                    | Albin | ↑ | ↑ | ↓ | ↑ | ↑ | ↑ |     |     |     |     |
|                        |                     |                    | Oxyflorin | ↑ | ↑ | ↓ | ↑ | ↑ | ↑ |     |     |     |     |
|                        | Radix Paeoniae Alba and Radix et Rhizoma Glycyrrhizae (4:1) | | Paeoniflorin | ↑ | ↑ | ↓ | ↑ | ↑ | ↑ |     |     |     |     |
|                        |                     |                    | Licoricein | ↑ | ↑ | ↓ | ↑ | ↑ | ↑ |     |     |     |     |
|                        | Rhizoma Tiansianna | Total phenolic acid of Rhizoma Chuanxiong | Gastrodin | ↑ | ↑ | ↓ | ↑ | ↑ | ↑ |     |     |     |     |
|                        |                     |                    | Gastrodin | ↑ | ↑ | ↓ | ↑ | ↑ | ↑ |     |     |     |     |
|                        | Rhizoma Tiansianna | Total alkaloids of Rhizoma Chuanxiong | Gastrodin | ↑ | ↑ | ↓ | ↑ | ↑ | ↑ |     |     |     |     |

Blanks are no mention or no significant changes
a. decreased in elimination rate constant
b. decreased in distribution/absorption rate constant
c. decreased in elimination half-life and increased in distribution half-life
d. single dose
e. multiple dose
decreased than in SA-BS coextract treated group. As the accumulation of bicyclic monoterpene proved to be toxic in long-term administration, the reduced absorption of these compounds owing to the herb-herb interactions in GSC could alleviate the toxicity of bicyclic monoterpene to some extent. From the cases discussed above, we can speculate that improving the exposure of some bioactive components and reducing toxic ingredients absorption may be possible explanations to elucidate the mechanism of formula compatibility.

Although many researchers suggested that interactions between herbs in compound prescriptions are of common occurrence [44–47, 50–54], herbs demonstrate almost no interference with each other in some cases. Li et al. [61] reported that Honghua constituents demonstrated nearly no influences on the metabolism of Danshen polyphenols from Danhong injection via monitoring the plasma concentrations of eight Danshen polyphenols and comparing their pharmacokinetic parameters between Danshen injection and Danhong injection treated rats. Therefore, the interaction among herbs cannot be generalized, and specific discussion is required.

Nowadays, the safety of herbal medicines has been attracted more and more attention, and confirming the compatibility of herbs is a key point to ensure the safety of clinical usage of herbal remedies. “Eighteen Incompatible Medicaments” is the typical representative of TCM incompatibility. The theory proposes that specific agents in the eighteen-herb list can produce toxicity if they were used in combination. Gansui-Gancao is an incompatible herb pair recorded in “Eighteen Incompatible Medicaments”. Gansui is the root of *Euphorbia kansui* T.N. Liu ex T.P. Wang (GS) and exhibited a notable efficacy in treating malignant pleural effusion, but its efficacy could be weakened and even caused serious toxicity when used in combination with gancao, the root of *Glycyrrhiza uralensis* Fisch. or *Glycyrrhiza glabra* L (GC) [62, 63]. In general, these two herbs will not appear in one TCM formulae. Interestingly, a compound prescription called Gansui-baixia decoction (GSD) is composed of the tuber of *Pinellia ternata* (Thunb.) Breit. (BX) and the root of *Paeonia lactiflora* Pall. (SY), along with the incompatible herb pair of GS and GC, and the decoction exhibits great curative effect on phlegm retention syndrome. This is a surprising example, and it seems to violate the principles of formulating prescription. Cui et al. [48] elucidated the reasonability of this application of GSD from the pharmacokinetic prospective. They found that GS could inhibit the absorption of liquiritigenin, isoliquiritigenin, liquiritin, glycyrrhetinic acid, and glycyrrhizic acid of GC, which reduced the detoxification ability of GC and increased the toxicity of GS immediately. Nevertheless, SY demonstrated the opposite effects on the bioavailability of the main bioactive components of GC and alleviated the absorption inhibition of GS on GC in GSD. These results provided a possible explanation of this application of the incompatible herb pair.

Synergistic effect is another pivotal characteristic of TCM and demonstrates enhancement of their therapeutic effects; for example, Danshen-Sanqi (the root and rhizome of *Salvia miltiorrhiza* Bge. and the root and rhizome of *Panax notoginseng* (Burk.) F. H. Chen) and Zhishi-Baizhu (the immature fruit of *Citrus aurantium* L. or *Citrus sinensis* Osbeck and the root of *Atractylodes macrocephala* Koidz) exert synergistic actions to treat coronary heart disease and functional dyspepsia, respectively [64, 65]. *Cortex Mori* (CM), the root bark of *Morus alba* L, exhibits α-glycosidase inhibition effect and plays an important role in regulating the postprandial blood glucose level. As the main biological active constituent of CM, 1-Deoxynojirimycin (DXM) is considered as a potent α-glycosidase inhibitor. Coadministration of *Radix Pueraria* (the root of *Pueraria lobata* (Wild) Ohwi, RP) flavonoids with CM extract could reduce the absorption rate of DXM significantly and thus elevate the relative concentration and duration of DMX in small intestine, which demonstrated a stronger hypoglycemic effect of CM extract compared with the herb administration alone [49]. These results agree with the principle of composition of TCM, referring to enhancing the efficacy and reducing the toxic side-effects.

### 3.3. Multicomponent Interaction in an Herb

Since multiple components constitute the connotation of herbal medicines, possible interactions between complex ingredients in a single herb may occur. Ma et al. [12] reported that interaction between stilbene glucoside and emodin, two major constituents of *RadixPolygoni Multiflori* (the root of *Polygonum multiflorum* Thunb.), was observed. This interaction subsequently elevated the degree of absorption of emodin into rat plasma and prolonged its duration time in vivo after the stilbene glucoside treatment. The mechanism might involve inhibition of UDP-glucuronosyl-transferases IA8 and thus prohibit the glucuronidation of emodin. Sinomenine is the prime alkaloid of *Sinomenium acutum*, Rehder & E.H. Wilson (SA). Co-dosing sinomenine with SA extract reduced the *C*max and AUC0–t in rat plasma by comparison with pure sinomenine treated group, especially at the higher dosage of 60 mg/kg. These results suggested that the SA extract was able to decrease the bioavailability of its main constituent [60]. Similar results were observed in coadministration of pure osthol and *Libanotis buchtormensis* supercritical extract [55]. Of course, there are studies suggesting that interactions between components can also increase the absorption and improve the bioavailability of other components [11, 56, 57]. In addition, some reports indicate that the pharmacokinetic parameters of a class of compounds having similar characteristics, like flavonoids, tend to be affected together by coexisting compounds in rats [58, 59]. These results may be attributed to the competition or inhibition of the same transporters between those certain group compounds and other complex ingredients in one herb. The function and direction of interaction are uncertain, further studies should be carried out monitoring the clinical use of herbal medicines to ensure their safety and efficacy. Table 2 represents possible interactions among multiple components in single herb.

### 4. The Influence of Pathological Status

Pharmacokinetics of certain compounds may be influenced by the pathological status of host [5, 66]. For the past few years, many researches have focused on this issue. They found that pathological factors such as liver injury, diabetes, stroke,
Table 2: Possible multi-components interaction in an herb.

| HRC1 | HRC2/Herb | Monitoring indexes | Pharmacokinetic parameters of indexes comparing to administration of HRC1 alone | Ref. |
|------|-----------|--------------------|--------------------------------------------------------------------------------|------|
|      |           |                    | AUC<sub>0-∞</sub> | AUC<sub>0-t</sub> | t<sub>1/2</sub> | T<sub>max</sub> | C<sub>max</sub> | MRT<sub>0-∞</sub> | MRT<sub>0-t</sub> | V<sub>d</sub> | CL   |
| Osthole | *Libanotis buchtormensis* | Osthole | ↓ | ↑ | ↓ | ↓ | ↑ | [55] |
| Epimedin C | *Herba Epimedii* | Epimedin C | ↓ | ↓ | ↓ | ↑ | [56] |
| Tectoridin | *Iris tectorum* | Tectoridin | ↑ | ↑ | ↑ | ↑ | ↑ | [57] |
| Emodin | *Stilbene glucoside of Radix Polygoni Multiflori* | Emodin | ↓ | ↑ | ↓ | ↑ | [12] |
| Magnoflorine | *Cortex Phellodendri* | Magnoflorine | ↑ | ↓ | ↑ | ↑ | ↑ | [11] |
|           |           | Magnoflorine | ↑ | ↑ | ↓ | ↑ | [11] |
|           |           | Rutin | ↓ | ↑ | ↑ | ↑ | [58] |
|           |           | Isoquercitrin | ↓ | ↑ | ↑ | ↑ | [58] |
|           |           | Hibifolin | ↓ | ↑ | ↑ | ↑ | [58] |
|           |           | Quercetin-3'-O-glucose | ↓ | ↑ | ↑ | ↑ | [58] |
| Favonoid fraction of *Abelmoschus manihot* | | | | |
|           |           | Rutin | ↓ | ↑ | ↑ | ↑ | [58] |
|           |           | Hyperide | ↑ | ↑ | ↑ | ↑ | [58] |
|           |           | Isoquercitrin | ↑ | ↑ | ↑ | ↑ | [58] |
|           |           | Hibifolin | ↑ | ↑ | ↑ | ↑ | [58] |
|           |           | Myricetin | ↑ | ↑ | ↑ | ↑ | [58] |
|           |           | Quercetin-3'-O-glucose | ↑ | ↑ | ↑ | ↑ | [58] |
|           |           | Quercetin | ↑ | ↑ | ↑ | ↑ | [58] |
| Small molecule fraction of *Abelmoschus manihot* | | | | |
|           |           | Rutin | ↑ | ↑ | ↑ | ↑ | [58] |
|           |           | Hyperide | ↑ | ↑ | ↑ | ↑ | [58] |
|           |           | Isoquercitrin | ↑ | ↑ | ↑ | ↑ | [58] |
|           |           | Hibifolin | ↑ | ↑ | ↑ | ↑ | [58] |
|           |           | Myricetin | ↑ | ↑ | ↑ | ↑ | [58] |
|           |           | Quercetin-3'-O-glucose | ↑ | ↑ | ↑ | ↑ | [58] |
|         |           | Quercetin | ↑ | ↑ | ↑ | ↑ | [58] |
| Macromolecular and Small molecule fraction of *Abelmoschus manihot* | | | | |
| Ginkgo flavonoids | *Ginkgo biloba* | | | | | | | | | | [59] |
| Sinomenine | *Sinomeniuncatum* | | | | | | | | | | [60] |
f squirt fever, rheumatoid arthritis, migraine, coronary atherosclerotic heart disease, cancer, and neurodegenerative diseases demonstrate deep impact on metabolism of HRC [8, 67–75]. Hepatocytes are the parenchymal cells of liver which can improve the excretion of xenobiotics through urine or feces by modifying their structure, including phase I xenobiotic metabolism like oxidation or hydrolysis, followed by phase II metabolism like glucuronidation, sulfation, acetylation, or glutathione conjugation. Meanwhile, cytochrome P450 enzymes are mainly located in the pericentral area of the liver lobule, and glutathione peroxidase shows a higher expression in periportal zone [76]. So drugs are primarily metabolized in liver as this important organ generates the highest drug-metabolizing activity. Therefore, liver lesions will result in changing the pharmacokinetics of drugs [8, 77]. For instance, dl-Praeruptorin A (PA) is the prime active ingredient of Peucedanum praeruptorum Dunn and the substance of CYP 450 isozyme 3A1 and 3A2 in rats. A comparative pharmacokinetic experiment was conducted in liver cirrhosis and normal rats with single-dose intravenous administration to evaluate the pharmacokinetic variability of PA under hepatic damage condition. Compared to the control group, PA exhibited significant higher AUC$_0$–$_\infty$ and slower hepatic elimination rate in model group. Those results might be partly caused by the lower hepatic blood flow rate and levels of CYP450 isoforms in liver cirrhosis rats [78].

Diabetes mellitus has become one of the most widespread metabolic diseases in the world, and patients suffering from type 2 diabetes mellitus (T2DM) approximately account for 90% of the diabetic totality [79]. In terms of metabolism, T2DM can induce gastrointestinal impairments, resulting in changes of the gut microbiome and slowing gastric emptying. Meanwhile, nephropathy and liver disease can be also observed in T2DM patients [80–82]. These physiological changes will affect the ADME of HRC. Wei et al. [80] invested the pharmacokinetic alteration of Sanhuang Xieixin decoction (SXD) extracts between T2DM and normal rats. They found that, compared to the control group, the AUC, $C_{\text{max}}$, $T_{1/2}$, and $T_{\text{max}}$ of the six main components of SXD, namely, rhein, baicalin, wogonoside, berberine, palmatine, and coptisine, were remarkably enhanced in T2DM rats after oral administration of SXD. These results indicated that the bioavailability of the target compounds was improved and the elimination was slower in T2DM rats. Similar metabolism process in vivo was observed in cyanidin-3-O-glucoside and Maydis stigma extract treated T2DM rats [82, 83].

Stroke is one of the most serious causes of death in China and the United States [84]. Moreover, this malignant disease can cause hepatic dysfunction, affecting the secretion of glucocorticoid and gastric mucus, suppressing the gastric mucus bicarbonate barrier function and the peristalsis of stomach and small intestine. These alterations may increase bioavailability of HRC and prolong their retention time in the body [70, 85]. Meanwhile, stroke can activate a sequence of cascade reactions and damage the blood brain barrier (BBB). This makes it easier for HRC to cross BBB, thus changing the distribution of HRC [84].

It is worth noting that some model-inducement agents, such as streptozotocin and nitroglycerin, can elicit liver and kidney damage and increase microvascular permeability [80, 86]. Streptozotocin induces insulin deficiency due to its selective pancreatic $\beta$-cell cytotoxicity caused by DNA alkylation and nitric oxide generation. And diabetes causes structural and functional abnormalities in the liver by affecting glycogen and lipid metabolism. Nitroglycerin will induce vasodilation due to the vascular dilatary response of the brachial artery. These compounds also affect the metabolism of HRC. The metabolic changes caused by model-inducement agents do not agree with normal pathological process; perhaps some of the metabolism changes are not caused by the diseases themselves, so the results in these studies inducing models with nonself substances should be confirmed and evaluated.

5. The Influence of Physical and Chemical Modifications of Natural Product

Although many herbal medicines demonstrate good biological activities in tests in vitro, the in vivo assays do not exhibit reproducible results [87]. This may be attributed to the diversity of various constituents of herbal remedies, which affect the bioavailability, the internal duration, and the amount reaching the target tissue of the curative compounds. Many efforts have been made trying to solve the mentioned problems above, concerning physical and chemical modifications of active candidates derived from herbal medicines, to develop various drug delivery systems, (DDS) and change their properties and behaviors in vivo.

5.1. Promoting Bioavailability and Internal Duration of Natural Products. Most HRCs, such as flavonoids, tannins, and terpenoids, possess high water solubility or high molecular size; thus it is difficult for them to cross cell lipid membranes, leading to decreased bioavailability and efficacy [87]. Nevertheless, ingredients with hydrophobic property, like $\beta$-elemene, also affect their oral absorption due to the poor water solubility [88]. Low bioavailability seems to become the biggest obstacle of herbal medicines application in treating disease and brought about many problems in clinical trials [89]. Meanwhile, fast systemic clearance of HRCs also limits their therapeutic usage [90].

Poly lactic-co-glycolic acid (PLGA) is a widely used class of polymers and has been approved by US Food and Administration and European Medicine Agency for developing therapeutic nanoparticle DDS for their good biocompatible and biodegradable properties. The biodegradation process of PLGA occurs by hydrolysis and generates lactic acid and glycolic acid, which finally enter the tricarboxylic acid cycle being metabolized into carbon dioxide and water [91–93]. So, the polymers are safe enough and usually used to improve bioavailability and solubility of certain drugs [94]. Solvent evaporation, nanoprecipitation, and emulsification-diffusion technologies are commonly employed methods of PLGA nanoparticles synthesis [91]. Curcumin is a widely concerning polyphenol, which is derived from the herbal spice Curcuma longa L., and exhibits many physiological activities such as antioxidant, anti-inflammation, and antitumor. However, this promising bioactive compound exhibits
low bioavailability and a short half-life [92]. To overcome the shortages of curcumin and improve its therapeutic effect, Tsai et al. [92] designed curcumin-loaded PLGA nanoparticles (C-NPs). The in vivo test results showed that the curcumin exposure (AUC/dose) dramatically increased, 55% and 21-fold, after intravenous and oral administration of C-NPs more than conventional curcumin in rats, respectively. Meanwhile, C-NPs treated rats demonstrated 22-fold relative higher oral bioavailability, extended retention time, and decreased excretion of curcumin than those of rats in the control group. All the results above revealed that C-NPs could prolong intestinal retention time and elevate bioavailability of curcumin. Another attempt aiming to improve the oral bioavailability of resveratrol, a poorly water-soluble anti-inflammatory and antioxidant compound, was performed via formation of resveratrol-loaded galactosylated PLGA nanoparticles (RGP-NPs) [95]. These newly synthesized RGP-NPs exhibited more than 3 times higher oral bioavailability of resveratrol than those of rats dosing resveratrol suspensions alone, as well as exhibiting increased anti-inflammatory efficacy. From these examples, we can see clearly that PLGA-conjugates significantly affect the metabolism of modified HRC.

Emulsions are a class of mixtures consisting of two immiscible liquids and stabilizing with surfactants or emulsifiers. These DDS can be divided into two types, oil-in-water (O/W) and water-in-oil (W/O), and O/W type holds dominant position in parenteral or oral administration [91, 96]. Due to the hydrophilic property and smaller particle size, emulsions can be used to deliver many hydrophobic HRCs and enhance their bioavailability and in vivo duration time by turning them into dissolved forms, increasing their intestinal epithelial permeability, and decreasing their hepatic uptake [97–100]. The common methods to prepare emulsions in laboratory are sonication and homogenization, with high-pressure homogenization and microfluidization on a large scale [91]. Ligustrazine is an active alkaloid derived from Ligusticum wallichii Franchat and has various biological effects on cardiovascular and neurovascular disorders. However, like curcumin, the low oral bioavailability and short in vivo half-life of ligustrazine require multiple doses to obtain optimum clinical efficacy, but this application also ascends the its toxic risk to patients [100]. Wei et al. developed a ligustrazine-loaded lipid emulsion (LLE) and invested the influence of pharmacokinetics and tissue distribution of this application form on ligustrazine. Compared with routine ligustrazine injection, the optimized LLE demonstrated a sustained release profile in vitro, as well as an enhanced bioavailability and improved distribution pattern in all rat tissues in vivo. These results made lipid emulsion a potential delivery system of ligustrazine for its clinical use [100]. Moreover, Ke et al. [99] designed a cycloviolubuxine D-loaded self-nanoemulsifying DDS and significantly enhanced the relative bioavailability of the loaded drug to 200.22% in comparison with the commercial dosage form in rabbits. Besides carrying monomers, emulsion DDS can be also loaded with multiple phytochemicals like the total flavones of Hippophae rhamnoides L. and Corydalis decumbens (Thunb.) Pers. extracts, improving the relative bioavailability of those hydrophobic ingredients [98, 101]. These results show the great potential of emulsion in developing DDS for poorly water-soluble HRC.

PEGylation technique, which refers to covalent attachment of polyethylene glycol (PEG) chains to target compound with ester bonds, is a widely used chemical functionalization method of biomolecules to improve their stability, water solubility, and pharmacokinetic properties such as $t_{1/2}$ and CL [102, 103]. Moreover, PEGylation molecules often demonstrated advantages in being protected against enzymatic degradation, as well as reducing immunogenicity and toxicity compared to their parent compounds [103, 104]. So many distinguishing properties make PEGylation technology very suitable to be applied to HRC modification. Lu et al. [102] synthesized PEGylated triacotanol (PEG-TA) as prodrug of triacotanol (TA), which exhibited antibacterial, antioxidant, anti-senescence, etc. activities with low water solubility, established a gas chromatography tandem mass spectrometric method, and finally applied it to the pharmacokinetic study of PEG-TA and its metabolite TA in rats. Comparing the pharmacokinetic parameters, involving $C_{\text{max}}$, $T_{\text{max}}$, AUC, and mean residence time (MRT), between PEG-TA and TA treated rats via oral dosing and intravenous injection, they found that administration of PEG-TA in both ways conspicuously enhanced exposure levels and prolonged plasma half-life of TA. Namely, these results indicated that PEGylation might be a potential way to improve the pharmacodynamic properties of TA and promote its application. Radix Ophiopogonis polysaccharide (ROP) is a natural fraction possessing great therapeutic efficacy on myocardial ischemia. However, the poor oral bioavailability and short half-life limit its clinical application. In consideration of overcoming aforementioned shortages of ROP, Lin et al. synthesized two forms of PEGylated ROP. Finally, they found that these two newly synthesized conjugates exhibited approximate 11-13 times longer $t_{1/2}$ in vivo than ROP alone, showing good absorption following subcutaneous administration [105]. In addition, other technologies like micronization, salt formation, and hydroxypropyl-β-cyclodextrin inclusion were reported to enhance oral bioavailability of target compounds [106].

5.2. Target Delivering of HRC. The poor concentration of drug in target tissue prevents many drugs from exerting their therapeutic effects [107]. Hence, researchers took more and more attempts to apply plenty of methods to solve this problem. Among them, drug-targeting, including passive targeting and active targeting, is a promising technology that improves the bioavailability of HRC in desired loci in vivo, as well as reducing toxicity due to the localized area release of certain constituents of herbal medicines [89].

Since tissue lesions are direct manifestations of many diseases, tissue-targeting is the most important strategy in targeting DDS design. Meanwhile, the changes of tissue distribution of loaded HRC are obvious. For instance, Huang et al. [108] developed a bone-targeting liposome loaded with icaritin, an osteogenic flavonoid isolated from Herba Epimedii. They found that the developed targeting DDS could increase distribution of icaritin to the bone and enhance bone
formation in ovariectomized mice compared to the control group. In addition, other cases also indicated tissue-targeting DDS can enhance the therapeutic effects of loaded HRC on certain disease and, of course, proved changes of their tissue distribution indirectly [109–111].

Cells are the basic structures and functional units of organisms. Interfering with the physiological activities of pathological cells has become one of the means to treat diseases, especially in cancer therapy. Therefore, many cell-targeting DDS are developed to improve the bioactive HRC uptake into concerning cells. These attempts will change the distribution of loaded components between normal and diseased cells. Recognized as an anti-inflammation and anti-cancer agent, celastrol, an active constituent of Tripterygium wilfordii Hook. F., possesses the property of poor water solubility and target selectivity [112]. To surmount these challenges, Niemelä et al. designed sugar-decorated mesoporous silica nanoparticles (SDMSN) as vectors of celastrol and investigated the target-specific efficacy on induction of apoptosis of cancer cells. Consequently, the uptake of SDMSN in HeLa and A549 cancer cells was four and five times higher than mouse embryonic fibroblasts and shows no toxicity to normal cells [112]. As tumor cells extensively produce acidic metabolites and export acid to the extracellular space, these characteristics result in a peripheral acidic microenvironment around tumor cells [113]. Based on this feature of tumor cells, researchers have developed pH-sensitive DDS, and the loaded HRC release is facilitated in the acidic microenvironment of tumor, rather than normal cells, thereby changing the distribution of curative compounds and enhancing their target-specificity [114].

Organelles are fundamental structures of cells and keep cells working normally. Among them, mitochondria are very important organelles and their dysfunctions are linked with cancer, diabetes, and other diseases [115]. More and more attention has been attracted by mitochondria-mediated apoptosis of tumor cells, and researchers believe that this may be a promising approach in cancer therapy. Therefore, mitochondria-targeting DDS emerge at the right moment. Recently, glycyrrhetinic acid [116] and hypericin [117] functionalized graphene oxide carriers were reported to exhibit mitochondria-targeting property, improve mitochondrial permeability, and enhance the uptake of loaded drug into mitochondria.

6. Influence of Other Factors

Gender is a very important influence factor in drug metabolism, especially for women. The inter-gender pharmacokinetic alterations are mainly attributed to the differences of sex hormones secretion, the variety of intestinal and hepatic CYPs and transporters, the body fat percentage and the average body weight, plasma volume, and organ blood flow between male and female [118, 119]. These discrepancies have overall effects on drug ADME. Some reports indicate that women suffered high risk of adverse drug reaction in certain circumstances than men [118, 120]. Therefore, it is particularly important to study the sex-based impact on drug metabolism.

Yang et al. [6] performed a study to investigate the gender-related differences of pharmacokinetics of diosbulbin B (DB) in rats. As a result, the female rats exhibited approximately 7 times higher oral absolute bioavailability of DB than male rats. Moreover, a bigger apparent volume of distribution (Vd), longer internal retention, and faster clearance were observed in female group after intravenous administration of DB. Xu et al. [9] explored the sex-related pharmacokinetic differences of Schisandra lignans after oral-dose of Schisandra chinensis extract in rats and found that female rats demonstrated a higher internal amount and slower elimination rate of focused compounds than male group. In detail, the $t_{1/2}$ of all the five marker ingredients, namely, schisandrin, schisandrol B, deoxyxschisandrin, $\gamma$-schisandrin, and schisantherin A, was 2-9 times longer, along with 5-50 times higher $C_{\text{max}}$ and $\text{AUC}_{0-\text{t}}$ of the tested compounds except schisantherin A, compared to those achieved in male rats. Nevertheless, it has been pointed out that gender difference did not significantly influence the pharmacokinetic parameters of paeoniflorin [121]. As the results showed above, the gender-related changes of pharmacokinetics seem to be unpredictable, so more attention is needed to explore the differences of herbal medicine applications between genders.

Age appears to be another influence factor of pharmacokinetics, for the age-related differences in gastric emptying rate, the concentration of serum proteins, and the activity levels of drug-metabolizing enzymes, as well as the function of liver and kidney [122, 123]. Specifically, children exhibit increased CL of certain drugs, while elders show the opposite trend. Meanwhile, elder people show decreased absorption rate and increased unbound drug concentration in plasma due to the slower gastric emptying and lower concentration of serum proteins than adults [122]. A population pharmacokinetic study suggested that the population estimate of the Vd of artemesunate and dihydroartemisinin, two derivatives of artemisinin treating severe malaria, was higher in adults than children, but CL was not significantly changed [124]. Another population pharmacokinetic study concerning daikenchuto, a traditional Kampo used in Japan to treat various gastrointestinal complications, also revealed that age is an important index in drug metabolism [125]. In summary, dosage adjusting to different age is a vital issue during the drug treatment, and age-related pharmacokinetic changes should be taken into account.

Acupuncture is a traditional therapy and has been used in China for thousands of years. It is always applied by inserting thin needles into specific points, which is called “acupoints”, of the body of people being treated and then rolling the needles manually or simulating by electricity [126, 127]. Due to the oddity of its theory and operation method, it was considered to be a Chinese equivalent of voodoo decades ago [128]. Nevertheless, acupuncture is becoming a distinguished alternative therapy and being adopted in countries worldwide to treat chronic pain, osteoarthritis, asthma, rhinitis, heroin addiction, rheumatoid arthritis, etc. [127–129]. Moreover, acupuncture is the most popular alternative treatment in US fertility clinics for couples desiring fertility care [130]. Additionally, evidence shows that acupuncture can promote the release of several neuropeptides in the central nervous system.
and demonstrate meaningful physiological effects [131]. In a word, acupuncture shows great potential therapeutic effect on certain body disorders. As acupuncture is an external stimulus, it can disturb the internal balance of the body and affect the metabolism of herbal medicines. Zhou et al. [132] reported that acupuncture could improve the absorption and reduce the elimination of baicalin in normal rats, and they found that stimulating specific acupoints, such as Jizhong (Du6), Dazhui (Du14), and Zhongwan (Ren12), was able to cause a bimodal phenomenon of the concentration-time course of baicalin. The synergistic effect on pharmacokinetics was also observed in combination with acupuncture at Zusanli (ST36) and oral administration of *Schisandra chinensis* in rats, as well as improving the target tissue distribution of three main lignans of *Schisandra chinensis*, namely, schisandrin, deoxyschisandrin, and schisandrin B, in comparison with the herb-alone treated group [4, 127]. All the published data above suggests that acupuncture seems to be able to decrease the required dosage of herbal medicines, thus economizing the total amount of herb consumption and reducing the possibility of adverse drug reactions.

7. Conclusion

According to evidence presented in this review, numerous factors like preliminary treatment, combination with drugs or herbs, pathological status, chemical or physical modifications, age, gender, and acupuncture will influence the pharmacokinetics of herbal medicines. In particular, as aging society is coming, the population of elder people with multiple health disorders and taking multiple medications is growing larger and larger. The occurrence of interactions between herbal medicines and drugs or internal body environment should be paid more attention particularly. Knowledge of factors affecting the pharmacokinetics of herbal medicines can lead to better guidance of their rational administration, whereas studies of these factors are mainly limited to animals at present and clinical research is lacking. Therefore, clinical research is required to focus in the future on elucidating and verifying the mechanism of the interactions between the influence factors and herbal medicines. The better knowledge of factors affecting the pharmacokinetics of herbal medicines we gain, the better guidance of their rational administration we can apply.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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References

[1] D. Schuppan, J. I.-D. Jia, B. Brinkhaus, and E. G. Hahn, “Herbal products for liver diseases: a therapeutic challenge for the new millennium,” *Hepatology*, vol. 30, no. 4, pp. 1099–1104, 1999.

[2] R. Liperoti, D. L. Vetrano, R. Bernabei, and G. Onder, “Herbal medications in cardiovascular medicine,” *Journal of the American College of Cardiology*, vol. 69, no. 9, pp. 1188–1199, 2017.

[3] A. Tachjian, V. Maria, and A. Jahangir, “Use of herbal products and potential interactions in patients with cardiovascular diseases,” *Journal of the American College of Cardiology*, vol. 55, no. 6, pp. 515–525, 2010.

[4] X. Wu, Y. Zhou, F. Yin et al., “Comparative pharmacokinetics and tissue distribution of schisandrin, deoxyschisandrin and schisandrin B in rats after combining acupuncture and herb medicine (schisandra chinensis),” *Biomedical Chromatography*, vol. 28, no. 8, pp. 1075–1083, 2014.

[5] M. D’Archivio, C. Filesi, R. Vari, B. Scaccuzio, and R. Masella, “Bioavailability of the polyphenols: Status and controversies,” *International Journal of Molecular Sciences*, vol. 11, no. 4, pp. 1321–1342, 2010.

[6] B. Yang, X. Wang, W. Liu et al., “Gender-related pharmacokinetics and absolute bioavailability of diosbulbin B in rats determined by ultra-performance liquid chromatography–tandem mass spectrometry,” *Journal of Ethnopharmacology*, vol. 149, no. 3, pp. 810–815, 2013.

[7] L. Zhou, J. Li, and C. Yan, “Simultaneous determination of three flavonoids and one coumarrin by LC–MS/MS: Application to a comparative pharmacokinetic study in normal and arthritic rats after oral administration of Daphne genkwa extract,” *Biomedical Chromatography*, vol. 32, no. 7, Article ID e4233, 2018.

[8] T. Yang, S. Liu, C.-H. Wang, Y.-Y. Tao, H. Zhou, and C.-H. Liu, “Comparative pharmacokinetic and tissue distribution profiles of four major bioactive components in normal and hepatic fibrosis rats after oral administration of Fuzheng Huayu recipe,” *Journal of Pharmaceutical and Biomedical Analysis*, vol. 114, pp. 152–158, 2015.

[9] H. Xu, J. Gan, X. Liu et al., “Gender-dependent pharmacokinetics of lignans in rats after single and multiple oral administration of Schisandra chinensis extract,” *Journal of Ethnopharmacology*, vol. 147, no. 1, pp. 224–231, 2013.

[10] S. Soleymani, R. Bahramsoltani, R. Rahimi, and M. Abdollahi, “Clinical risks of St John’s Wort (Hypericum perforatum) co-administration,” *Expert Opinion on Drug Metabolism & Toxicology*, vol. 13, no. 10, pp. 1047–1062, 2017.

[11] X. Tian, Z. Li, Y. Lin, M. Chen, G. Pan, and C. Huang, “Study on the PK profiles of magnoflorine and its potential interaction in Cortex phellodendri decoction by LC-MS/MS,” *Analytical and Bioanalytical Chemistry*, vol. 406, no. 3, pp. 841–849, 2014.

[12] J. Ma, L. Zheng, T. Deng et al., “Stillbene glucoside inhibits the glucuronidation of emodin in rats through the down-regulation of UDP-glucuronosyltransferases IA8: application to a drug–drug interaction study in Radix Polygani Multiflori,” *Journal of Ethnopharmacology*, vol. 147, no. 2, pp. 335–340, 2013.

[13] X.-B. Cui, X.-C. Qian, P. Huang et al., “Simultaneous determination of ten flavonoids of crude and wine-processed Radix Scutellariae aqueous extracts in rat plasma by UPLC-ESI-MS/MS and its application to a comparative pharmacokinetic study,” *Biomedical Chromatography*, vol. 29, no. 7, pp. 1122–1123, 2015.

[14] Y. Tao, D. Su, W. Li, and B. Cai, “Pharmacokinetic comparisons of six components from raw and vinegar-processed Daphne
genkwa aqueous extracts following oral administration in rats by employing UHPLC–MS/MS approaches,” Journal of Chromatography B, vol. 1079, pp. 34–40, 2018.

[15] Y. Cheng, Y. Zhang, H. Xing, K. Qian, L. Zhao, and X. Chen, “Comparative pharmacokinetics and bioavailability of three ephedrines in rat after oral administration of unprocessed and honey-fried ephedra extract by response surface experimental design,” Evidence-Based Complementary and Alternative Medicine, vol. 2017, Article ID 2802193, 12 pages, 2017.

[16] Y. Tao, Y. Du, W. Li, and B. Cai, “Development and validation of an UHPLC–MS/MS approach for simultaneous quantification of five bioactive saponins in rat plasma: Application to a comparative pharmacokinetic study of aqueous extracts of raw and salt-processed Achyranthes bidentata,” Journal of Pharmaceutical and Biomedical Analysis, vol. 151, pp. 164–169, 2018.

[17] W. Gu, J. C. Li, D. Ji et al., “Pharmacokinetic comparisons of typical constituents in curcuma rhizoma and vinegarp-processed curcuma rhizoma after oral administration to rats,” Evidence-Based Complementary and Alternative Medicine, vol. 2018, Article ID 6809497, 11 pages, 2018.

[18] R. Guo, H. Wu, X. Yu et al., “Simultaneous determination of seven anthraquinone aglycones of crude and processed semen cassiae extracts in rat plasma by UPLC-MS/MS and its application to a comparative pharmacokinetic study,” Molecules, vol. 22, no. 11, Article ID 1803, 2017.

[19] Y. Zi-Min, C. Yue, G. Hui, L. Jia, C. Gui-Rong, and J. Wang, “Comparative pharmacokinetic profiles of three protoberberine-type alkaloids from raw and bile-processed Rhizoma cop- tidis in heat syndrome rats,” Pharmacognosy Magazine, vol. 13, no. 49, pp. 51–57, 2017.

[20] Y. Tao, Y. Ren, W. Li et al., “Comparative pharmacoki-netic analysis of extracts of crude and wine-processed Dip-sacus asper in rats by a sensitive ultra performance liquid chromatography–tandem mass spectrometry approach,” Journal of Chromatography B, vol. 1036-1037, pp. 33–41, 2016.

[21] C. L. Cui, X. He, C. L. Dong et al., “The enhancement mechanism of wine-processed Radix Scutellaria on NTG-induced migraine rats,” Biomedicine and Pharmacotherapy, vol. 91, pp. 138–146, 2017.

[22] X.-C. Qian, L. Zhang, Y. Tao et al., “Simultaneous determination of ten alkaloids of crude and wine-processed Rhizoma Coptidis aqueous extracts in rat plasma by UHPLC-ESI-MS/MS and its application to a comparative pharmacokinetic study,” Journal of Pharmaceutical and Biomedical Analysis, vol. 105, pp. 64–73, 2015.

[23] K. Liu, Y. Song, Y. Liu et al., “An integrated strategy using UPLC–QTOF-MSE and UPLC–QTOF-MRM (enhanced tar-get) for pharmacokinetics study of wine processed Schis-an-dra Chinensis fructus in rats,” Journal of Pharmaceutical and Biomedical Analysis, vol. 139, pp. 165–178, 2017.

[24] T. Lei, D. Zhang, K. Guo et al., “Validated UPLC-MS/MS method for simultaneous quantification of eight saikosaponins in rat plasma: Application to a comparative pharmacokinetic study in depression rats after oral administration of extracts of raw and vinegar-baked Bupleuri Radix,” Journal of Chromatography B, vol. 1060, pp. 231–239, 2017.

[25] C. Zhou, J. Wang, X. Zhang et al., “Investigation of the differences between the “Cold” and “Hot” nature of Coptis chinensis Franch and its processed materials based on animal’s temperature tropism,” Science in China Series C: Life Sciences, vol. 52, no. 11, pp. 1073–1080, 2009.

[26] W. L. T. Kan, B. Ma, and G. Lin, “Sulfur fumigation processing of traditional Chinese medicinal herbs: beneficial or detrimental?” Frontiers in Pharmacology, vol. 2, article 84, 2011.

[27] K. Cheng, H. Cai, X. Liu et al., “Evaluation of the influence of sulfur fumigation on the pharmacokinetics of four active ingredients in Si Wu Tang,” Journal of Separation Science, vol. 38, no. 1, pp. 25–33, 2015.

[28] M. Kong, H. H. Liu, and J. Wu, “Effects of sulfur-fumigation on the pharmacokinetics, metabolites and analogesic activity of Radix Paeoniae Alba,” Journal of Ethnopharmacology, vol. 212, pp. 95–105, 2018.

[29] Y. S. Cheng, C. Peng, F. Y. Wen, and H. Zhang, “Pharmacokinetic comparisons of typical constituents in white peony root and sulfur fumigated white peony root after oral administration to mice,” Journal of Ethnopharmacology, vol. 129, no. 2, pp. 167–173, 2010.

[30] H. Zhi, Z. Li, Y. Deng et al., “Comparative in vivo constituents and pharmacokinetic study in rats after oral administration of ultrafine granular powder and traditional decoction slices of Chinese Salvia,” Biomedical Chromatography, Article ID e4385, 2018.

[31] Y. Tao, S. Huang, G. Yang, W. Li, and B. Cai, “A simple and sensitive LC-MS/MS approach for simultaneous quantification of six bioactive compounds in rats following oral administration of aqueous extract and ultrafine powder of Astragalus propinquus: application to a comparative pharmacokinetic study,” Journal of Chromatography B, vol. 1096, pp. 31–38, 2018.

[32] E. M. Alissa, “Medicinal herbs and therapeutic drugs interactions,” Therapeutic Drug Monitoring, vol. 36, no. 4, pp. 413–422, 2014.

[33] S. Shi and U. Klotz, “Drug interactions with herbal medicines,” Clinical Pharmacokinetics, vol. 51, no. 2, pp. 77–104, 2012.

[34] D. Singh, R. Gupta, and S. A. Saraf, “Herbs-are they safe enough? An overview,” Critical Reviews in Food Science and Nutrition, vol. 52, no. 10, pp. 876–898, 2012.

[35] A. Di Minno, B. Frigerio, G. Spadarella et al., “Old and new oral anticoagulants: food, herbal medicines and drug interactions,” Blood Reviews, vol. 31, no. 4, pp. 193–203, 2017.

[36] S. Yin, Y. Cheng, T. Li, M. Dong, H. Zhao, and G. Liu, “Effects of notoginsenoside R1 on CYP1A2, CYP2C11, CYP2D1, and CYP3A1/2 activities in rats by cocktail probe drugs,” Pharmaceutical Biology, vol. 54, no. 2, pp. 231–236, 2016.

[37] J.-L. He, Z. W. Zhou, J.-J. Yin et al., “Schisandra chinensis regulates drug metabolizing enzymes and drug transporters via activation of Nrf2-mediated signaling pathway,” Drug Design, Development and Therapy, vol. 9, pp. 127–146, 2015.

[38] Y. Liu, S. Liu, Y. Shi, M. Qin, Z. Sun, and G. Liu, “Effects of sawflower injection on the pharmacodynamics and pharmacoki-netics of warfarin in rats,” Xenobiotica, vol. 48, no. 8, pp. 818–823, 2018.

[39] T. H. Kim, S. Shin, J. C. Shin et al., “Effect of sipiondea-botang on the pharmacokinetics of S-1, an anticancer agent, in rats evaluated by population pharmacokinetic modeling,” Molecules, vol. 22, no. 9, Article ID 1488, 2017.

[40] C.-M. Lu, M.-L. Hou, L.-C. Lin, and T.-H. Tsai, “Development of a microdialysis system to monitor lamivudine in blood and liver for the pharmacokinetic application in herbal drug interaction and the gene expression in rats,” Journal of Pharmaceutical and Biomedical Analysis, vol. 96, pp. 231–240, 2014.

[41] C. T. Ting, Y.-Y. Cheng, and T. H. Tsai, “Herb-drug interaction between the traditional hepatoprotective formulation and
sorafenib on hepatotoxicity, histopathology and pharmacokinetics in rats," *Molecules*, vol. 22, no. 7. Article ID 1034, 2017.

[42] W. Ma, W. Wang, Y. Peng et al., "Ultra-high performance liquid chromatography with tandem mass spectrometry method for the simultaneous quantitation of five phthalides in rat plasma: application to a comparative pharmacokinetic study of Huo Luo Xiao Ling Dan and herb-pair extract," *Journal of Separation Science*, vol. 39, no. 11, pp. 2057–2067, 2016.

[43] X. Liu, H. Li, L. Wu et al., "Simultaneous quantification of chrysophanol and physcion in rat plasma by ultra fast liquid chromatography-tandem mass spectrometry and application of the technique to comparative pharmacokinetic studies of *Radix et Rhei Rhzoma* extract alone and Dahuang Fuzi Decoction," *Journal of Chromatography B*, vol. 980, pp. 88–93, 2015.

[44] Y. Liang, Y. Zhou, J. Zhang et al., "Pharmacokinetic compatibility of ginsenosides and Schisandra Lignans in Shengmai-san: from the perspective of p-glycoprotein," *PLoS ONE*, vol. 9, no. 6. Article ID e98797, 2014.

[45] J. Mu, X. Gao, Q. Li et al., "Vortex-ultrasound-assisted dispersive liquid–liquid microextraction coupled with gas chromatography–mass spectrometry for the analysis of volatile bioactive components and comparative pharmacokinetic study of the herb–herb interactions in Guanxin Shutong Capsule," *Journal of Separation Science*, vol. 40, no. 16, pp. 3267–3278, 2017.

[46] X.-J. Lai, L. Z. Zhang, J.-S. Li et al., "Comparative pharmacokinetic and bioavailability studies of three salvianolic acids after the administration of *Salviae miltiorrhizae* alone or with synthetic borneol in rats," *Fitoterapia*, vol. 82, no. 6. pp. 883–888, 2011.

[47] C. Gong, H. Yang, H. Wei, C. Qi, and C.-H. Wang, "Pharmacokinetic comparisons by UPLC-MS/MS of isomer paenoniflorin and albiflorin after oral administration decoctions of single-herb *Radix Paeoniae Alba* and Zengmian Yiliu prescription to rats," *Biomedical Chromatography*, vol. 29, no. 3, pp. 416–424, 2015.

[48] Y. Cui, T. Liu, Y. Zhang et al., "Simultaneous determination of five bioactive components of *Gancao* in rat plasma by UHPLC-MS/MS and its application to comparative pharmacokinetic study of incompatible herb pair Gansui-Ganco and Gan-subanxia Decoction," *Journal of Pharmaceutical and Biomedical Analysis*, vol. 159, pp. 318–325, 2018.

[49] B.-X. Xiao, Q. Wang, L.-Q. Fan, L.-T. Kong, S.-R. Guo, and Q. Chang, "Pharmacokinetic mechanism of enhancement by *Radix Pueraria* flavonoids on the hyperglycemic effects of *Cortex Moris* extract in rats," *Journal of Ethnopharmacology*, vol. 151, no. 2, pp. 846–851, 2014.

[50] P. Wei, Q.-F. Tang, H.-L. Huo et al., "Comparative pharmacokinetics of three phenylpropanoids in rat plasma after oral administration of *Ramulus Cinnamomami* and *Ramulus Cinnamomami-Ephedrae Herba* herb-couple extract," *Chinese Journal of Integrative Medicine*, pp. 1–7, 2017.

[51] Y. Ai, Y. Wu, F. Wang et al., "A UPLC-MS/MS method for simultaneous quantitation of three monoterpene glycosides and four alkaloids in rat plasma: Application to a comparative pharmacokinetic study of *Huo Luo Xiao Ling Dan* and single herb extract," *Journal of Mass Spectrometry*, vol. 50, no. 3, pp. 567–577, 2015.

[52] A. K. Kammalla, M. K. Ramasamy, J. Chintala, G. P. Dubey, A. Agrawal, and I. Kaliappan, "Comparative pharmacokinetic interactions of Quercetin and Rutin in rats after oral administration of European patented formulation containing Hippophae rhamnoideae and Co-administration of Quercetin and Rutin," *European Journal of Drug Metabolism and Pharmacokinetics*, vol. 40, no. 3, pp. 277–284, 2015.

[53] C.-H. Xu, P. Wang, Y. Wang et al., "Pharmacokinetic comparisons of two different combinations of *Shaoyao-Gancao Decoction* in rats: competing mechanisms between paenoniflorin and glycyrrehetic acid," *Journal of Ethnopharmacology*, vol. 149, no. 2, pp. 443–452, 2013.

[54] P.-Y. Hu, P.-F. Yue, Q. Zheng et al., "Pharmacokinetic comparative study of gastrodin after oral administration of *Gastrodia elata* Bl. extract and its compatibility with the different indigents of *Ligusticum chuanxiong* Hort. to rats," *Journal of Ethnopharmacology*, vol. 191, pp. 82–86, 2016.

[55] J. Shi, Q. Fu, W. Chen et al., "Comparative study of pharmacokinetics and tissue distribution of osthole in rats after oral administration of pure osthole and *Lanbaniotis buchtormensis* supercritical extract," *Journal of Ethnopharmacology*, vol. 145, no. 1, pp. 25–31, 2013.

[56] C.-J. Lee, Y.-T. Wu, T. Y. Hsueh, L.-C. Lin, and T.-H. Tsai, "Pharmacokinetics and oral bioavailability of epimedin C after oral administration of epimedin C and Herba Epimedi extract in rats," *Biomedical Chromatography*, vol. 28, no. 5, pp. 630–636, 2014.

[57] M. Yang, X. Yang, J. An et al., "Comparative pharmacokinetic profiles of tectorigenin in rat plasma by UPLC-MS/MS after oral administration of *Iris tectorum* maxim extract and pure tectoridin," *Journal of Pharmaceutical and Biomedical Analysis*, vol. 114, pp. 34–41, 2015.

[58] L. Lu, D. Qian, J. Guo et al., "Abdomschi Corolla non-flavonoid components altered the pharmacokinetic profile of its flavonoids in rat," *Journal of Ethnopharmacology*, vol. 148, no. 3, pp. 804–811, 2013.

[59] T. Wang, J. Xiao, H. Hou et al., "Development of an ultra-fast liquid chromatography–tandem mass spectrometry method for simultaneous determination of seven flavonoids in rat plasma: application to a comparative pharmacokinetic investigation of *Ginkgo biloba* extract and single pure *ginkgo* flavonoids after oral administration," *Journal of Chromatography B*, vol. 1060, pp. 173–181, 2017.

[60] M.-F. Zhang, Y. Zhao, K.-Y. Jiang et al., "Comparative pharmacokinetics study of sinomenine in rats after oral administration of sinomenine monomer and sinomenium acutum extract," *Molecules*, vol. 19, no. 8, pp. 12065–12077, 2014.

[61] X. Li, F. Du, W. Jia et al., "Simultaneous determination of eight Danshen polyphenols in rat plasma and its application to a comparative pharmacokinetic study of *DanHong* injection and Danshen injection," *Journal of Separation Science*, vol. 40, no. 7, pp. 1470–1481, 2017.

[62] J. Shen, J. Wang, E.-X. Shang et al., "The dosage-toxicity-efficacy relationship of kansui and licorice in malignant pleural effusion rats based on factor analysis," *Journal of Ethnopharmacology*, vol. 186, pp. 251–256, 2016.

[63] X. Zhang, Y. Wang, Q. Liang et al., "The correlation between chemical composition, as determined by UPLC-TOF-MS, and acute toxicity of *Veratrum nigrum* L. and *Radix paonieae alba*," *Evidence-Based Complementary and Alternative Medicine*, vol. 2014, Article ID 892797, 13 pages, 2014.

[64] X. Zhou, V. Razmowski- Naumovski, D. Chang et al., "Synergistic effects of danshen (salvia miltiorrhiza radix et rhizoma) and sanqi (notoginseng radix et rhizoma) combination in inhibiting inflammation mediators in RAW264.7 cells," *Bioned Research International*, vol. 2016, Article ID 5758195, 12 pages, 2016.
[65] C. Wang, Q. Ren, X. T. Chen et al., “System pharmacology-based strategy to decode the synergistic mechanism of Zhi-zhu Wan for functional dyspepsia,” Frontiers in Pharmacology, vol. 9, Article ID 841, 2018.

[66] Y. Wang, M. Zhao, H. Ye et al., “Comparative pharmacokinetic study of the main components of cortex fraxini after oral administration in normal and hyperuricemic rats,” Biomedical Chromatography, vol. 31, no. 8, Article ID e3934, 2017.

[67] X.-K. Huo, B. Wang, L. Zheng et al., “Comparative pharmacokinetic study of baicalin and its metabolites after oral administration of baicalin and Chaqin Qingning capsule in normal and febrile rats,” Journal of Chromatography B, vol. 1059, pp. 14–20, 2017.

[68] Y. Wu, Y. Ai, F. Wang et al., “Simultaneous determination of four secoiridoid and iridoid glycosides in rat plasma by ultra performance liquid chromatography-tandem mass spectrometry and its application to a comparative pharmacokinetic study,” Biomedical Chromatography, vol. 30, no. 2, pp. 97–104, 2016.

[69] B. Kamble, A. Gupta, I. Moothedath et al., “Effects of Gymnema sylvestre extract on the pharmacokinetics and pharmacodynamics of glimepiride in streptozotocin induced diabetic rats,” Chemico-Biological Interactions, vol. 245, pp. 30–38, 2016.

[70] Y. Li, Y. Lu, J. Hu et al., “Pharmacokinetic comparison of scutellarin and paenoflorin in sham-operated and middle cerebral artery occlusion ischemia and reperfusion injury rats after intravenous administration of xin-shao formula,” Molecules, vol. 21, no. 9, Article ID 1911, 2016.

[71] J. Guan, X. Zhang, B. Feng et al., “Simultaneous determination of ferulic acid and gastrodin of Tianshu Capsule in rat plasma by ultra-fast liquid chromatography with tandem mass spectrometry and its application to a comparative pharmacokinetic study in normal and migraine rats,” Journal of Separation Science, vol. 40, no. 21, pp. 4120–4127, 2017.

[72] X. Gao, J. Mu, S. Guan et al., “Simultaneous determination of phenolic acids and diterpenoids and their comparative pharmacokinetic study in normal and acute blood stasis rats by UFLC–MS/MS after oral administration of Guan-Xin-Shu-Tong capsules,” Journal of Chromatography B, vol. 1072, pp. 221–228, 2018.

[73] W. Chen, J. Li, Z. Sun et al., “Comparative pharmacokinetics of six coumarins in normal and breast cancer bone-metastatic mice after oral administration of Wenshen Zhanguo Formula,” Journal of Ethnopharmacology, vol. 224, pp. 36–44, 2018.

[74] Y. Shi, C. Cao, Y. Zhu et al., “Comparative pharmacokinetic study of the components of Jia-Wei-Kai-Xin-San in normal and vascular dementia rats by ultra-fast liquid chromatography coupled with tandem mass spectrometry,” Journal of Separation Science, vol. 41, no. 12, pp. 2504–2516, 2018.

[75] X. Wang, Y. Zhang, H. Niu et al., “Ultra-fast liquid chromatography with tandem mass spectrometry determination of eight bioactive components of Kai-Xin-San in rat plasma and its application to a comparative pharmacokinetic study in normal and Alzheimer’s disease rats,” Journal of Separation Science, vol. 40, no. 10, pp. 2131–2140, 2017.

[76] A. Schenk, A. Ghallab, U. Hofmann et al., “Physiologically-based modelling in mice suggests an aggravated loss of clearance capacity after toxic liver damage,” Scientific Reports, vol. 7, no. 1, Article ID 6224, 2017.

[77] K. Thelen and J. B. Dressman, “Cytochrome P450-mediated metabolism in the human gut wall,” Journal of Pharmacy and Pharmacology, vol. 61, no. 5, pp. 541–558, 2009.

[78] Z. Zhang, X. Liang, M. Su et al., “Pharmacokinetics of dl-praeruptorin A after single-dose intravenous administration to rats with liver cirrhosis,” DARU Journal of Pharmaceutical Sciences, vol. 19, no. 3, pp. 210–215, 2011.

[79] S. Sun, Z.-S. Xie, E.-H. Liu, Y.-T. Yan, X.-J. Xu, and P. Li, “Chemical profiling of Jinqi Jiangtang tablets by HPLC-ESI-Q-TOF/MS,” Chinese Journal of Natural Medicines, vol. 12, no. 3, pp. 229–240, 2014.

[80] X.-Y. Wei, J.-H. Tao, X. Cui, S. Jiang, D.-W. Qian, and J.-A. Duan, “Comparative pharmacokinetics of six major bioactive components in normal and type 2 diabetic rats after oral administration of Sanhuang Xie Xin Decoction extracts by UPLC-TQ MS/MS,” Journal of Chromatography B, vol. 1061-1062, pp. 248–255, 2017.

[81] X. Zhang, L. Wang, Z. Zheng, Z. Pi, Z. Liu, and F. Song, “Online microdialysis-ultra performance liquid chromatography–mass spectrometry method for comparative pharmacokinetic investigation on iridoids from Gardenia jasminoides Ellis in rats with different progressions of type 2 diabetic complications,” Journal of Pharmaceutical and Biomedical Analysis, vol. 140, pp. 146–154, 2017.

[82] B. B. Wei, Z. X. Chen, M. Y. Liu, and M. J. Wei, “Development of a UPLC-MS/MS method for simultaneous determination of six flavonoids in rat plasma after administration of maydis stigma extract and its application to a comparative pharmacokinetic study in normal and diabetic rats,” Molecules, vol. 22, no. 8, Article ID 1267, 2017.

[83] C. Yang, Q. Wang, S. Yang, Q. Yang, and Y. Wei, “An LC–MS/MS method for quantitation of cyanidin-3-O-glucoside in rat plasma: Application to a comparative pharmacokinetic study in normal and streptozotocin-induced diabetic rats,” Biomedical Chromatography, vol. 32, no. 2, Article ID e4042, 2018.

[84] L. Yu, H. F. Wan, C. Li et al., “Pharmacokinetics of active components from guhong injection in normal and pathological rat models of cerebral ischemia: a comparative study,” Frontiers in Pharmacology, vol. 9, Article ID 493, 2018.

[85] S. Chen, M. Li, Y. Li et al., “A UPLC-ESI-MS/MS method for simultaneous quantitation of chlorogenic acid, scutellarin, and scutellarein in rat plasma: application to a comparative pharmacokinetic study in sham-operated and MCAO rats after oral administration of erigeron breviscapus extract,” Molecules, vol. 23, no. 7, Article ID 1808, 2018.

[86] X. Zhao, T. Ma, C. Zhang et al., “Simultaneous determination of senkyunolide I and senkyunolide H in rat plasma by LC-MS: Application to a comparative pharmacokinetic study in normal and migrainous rats after oral administration of Chuanxiong Rhizoma extract,” Biomedical Chromatography, vol. 29, no. 9, pp. 1297–1303, 2015.

[87] B. V. Bonifacio, P. B. Silva, M. A. Ramos et al., “Nanochemistry-based drug delivery systems and herbal medicines: a review,” International Journal of Nanomedicine, vol. 9, pp. 1–15, 2014.

[88] M. Chen, S. Wang, M. Tan, and Y. Wang, “Applications of nanoparticles in herbal medicine: Zedoary turmeric oil and its active compound β-elemene,” American Journal of Chinese Medicine, vol. 39, no. 6, pp. 1093–1102, 2011.

[89] R. Watkins, L. Wu, C. Zhang, R. M. Davis, and B. Xu, “Natural product-based nanomedicine: recent advances and issues,” International Journal of Nanomedicine, vol. 10, pp. 6055–6074, 2015.

[90] M. Namdari, A. Eatemadi, M. Soleimanejad, and A. T. Hammed, “A brief review on the application of nanoparticle
enclosed herbal medicine for the treatment of infective endocarditis,” *Biomedicine & Pharmacotherapy*, vol. 87, pp. 321–331, 2017.

[91] S. Wang, R. Su, S. Nie et al., “Application of nanotechnology in improving bioavailability and bioactivity of diet-derived phytochemicals,” *The Journal of Nutritional Biochemistry*, vol. 25, no. 4, pp. 363–376, 2014.

[92] Y. Tsai, W. Jan, C. Chien, W. Lee, L. Lin, and T. Tsai, “Optimised nano-formulation on the bioavailability of hydrophobic polyphenol, curcumin, in freely-moving rats,” *Food Chemistry*, vol. 127, no. 3, pp. 918–925, 2011.

[93] L. Zou, F. Chen, J. Bao et al., “Preparation, characterization, and anticancer efficacy of eudiamine-loaded PLGA nanoparticles,” *Drug Delivery*, vol. 23, no. 3, pp. 908–916, 2016.

[94] Y.-Y. Wu, J.-H. Zhang, J.-H. Gao, and Y.-S. Li, “Aloe-emodin (AE) nanoparticles suppresses proliferation and induces apoptosis in human lung squamous carcinoma via ROS generation in vitro and in vivo,” *Biochemical and Biophysical Research Communications*, vol. 490, no. 3, pp. 601–607, 2017.

[95] F. Y. Siu, S. Ye, H. Lin, and S. Li, “Galactosylated PLGA nanoparticles for the oral delivery of resveratrol: enhanced bioavailability and in vitro anti-inflammatory activity,” *International Journal of Nanomedicine*, vol. 13, pp. 4133–4144, 2018.

[96] Y. Cai, W. Zhang, Z. Chen, Z. Shi, C. He, and M. Chen, “Recent insights into the biological activities and drug delivery systems of tanshinones,” *International Journal of Nanomedicine*, vol. 11, pp. 121–130, 2016.

[97] N. Chouhan, V. Mittal, D. Kaushik, A. Khatarek, and M. Raina, “Self-emulsifying drug delivery system (SEDDS) for phytoconstituents: a review,” *Current Drug Delivery*, vol. 12, no. 2, pp. 244–253, 2015.

[98] R. Guo, X. Guo, X. Hu et al., “Fabrication and optimization of self-microemulsions to improve the oral bioavailability of total flavones of Hippophae rhamnoides L.,” *Journal of Food Science*, vol. 82, no. 12, pp. 2901–2909, 2017.

[99] Z. Ke, X. Hou, and X.-B. Jia, “Design and optimization of self-nanoemulsifying drug delivery systems for improved bioavailability of cyclovirobuxine D,” *Drug Design, Development and Therapy*, vol. 10, pp. 2049–2060, 2016.

[100] L. J. Wei, N. Marasinh, G. Li et al., “Development of ligustrazine-loaded lipid emulsion: formulation optimization, characterization and biodistribution,” *International Journal of Pharmaceutics*, vol. 437, no. 1-2, pp. 203–212, 2012.

[101] H. Ma, Q. Zhao, Y. Wang et al., “Design and evaluation of self-emulsifying drug delivery systems of Rhizoma cordyalis decumbents extract,” *Drug Development and Industrial Pharmacy*, vol. 38, no. 10, pp. 1200–1206, 2012.

[102] X. Lu, M. Fang, Y. Dai et al., “Quantification of triacontanol and its PE-gylated prodrug in rat plasma by GC-MS/MS: application to a pre-clinical pharmacokinetic study,” *Journal of Chromatography B*, vol. 1089, pp. 8–15, 2018.

[103] P. Esposito, L. Barbero, P. Caccia et al., “PEGylation of growth hormone-releasing hormone (GHRH) analogues,” *Advanced Drug Delivery Reviews*, vol. 55, no. 10, pp. 1279–1291, 2003.

[104] G. Pasut and F. M. Veronese, “State of the art in PEGylation: the great versatility achieved after forty years of research,” *Journal of Controlled Release*, vol. 161, no. 2, pp. 461–472, 2012.

[105] X. Lin, Z.-J. Wang, F. Huang et al., “Long-circulating delivery of bioactive polysaccharide from radix ophiopogonis by PE-gylation,” *International Journal of Nanomedicine*, vol. 6, pp. 2865–2872, 2011.

[106] J. Huang, Y. Liu, X. Li et al., “Comparative pharmacokinetic profiles of five poorly soluble pulchinenosides in different formulations from Pulsatilla chinensis saponins extracts for enhanced bioavailability,” *Biomedical Chromatography*, vol. 29, no. 12, pp. 1885–1892, 2015.

[107] T. Chen, C. Li, Y. Li, X. Yi, S. M.-Y. Lee, and Y. Zheng, “Oral delivery of a nanocrystal formulation of sanchisantherin a with improved bioavailability and brain delivery for the treatment of Parkinson’s disease,” *Molecular Pharmaceutics*, vol. 13, no. 11, pp. 3864–3875, 2016.

[108] L. Huang, X. Wang, H. Cao et al., “A bone-targeting delivery system carrying osteogenic phytomolecule icaritin prevents osteoporosis in mice,” *Biomaterials*, vol. 182, pp. 58–71, 2018.

[109] H. Wu, T. Yu, Y. Tian, Y. Wang, R. Zhao, and S. Mao, “Enhanced liver-targeting via coadministration of 10-Hydroxycamptothecin polymeric micelles with vinegar baked Radix Bupleuri,” *Phytommediine*, vol. 44, pp. 1–8, 2018.

[110] S. Yum, S. Jeong, S. Lee et al., “Colon-targeted delivery of picratannol enhances anti-colic effects of the natural product: Potential molecular mechanisms for therapeutic enhancement,” *Drug Design, Development and Therapy*, vol. 9, pp. 4247–4258, 2015.

[111] J. H. Park, H. A. Kim, J. H. Park, and M. Lee, “Amphiphilic peptide carrier for the combined delivery of curcumin and plasmid DNA into the lungs,” *Biomaterials*, vol. 33, no. 27, pp. 6542–6550, 2012.

[112] E. Niemelä, D. Desai, Y. Nkizinkiko, J. E. Eriksson, and J. M. Rosenholm, “Sugar-decorated mesoporous silica nanoparticles as delivery vehicles for the poorly soluble drug celastrol enables targeted induction of apoptosis in cancer cells,” *European Journal of Pharmaceutics and Biopharmaceutics*, vol. 96, pp. 21–21, 2015.

[113] I. Böhme and A. K. Bosserhoff, “Acidic tumor microenvironment in human melanoma,” *Pigment Cell & Melanoma Research*, vol. 29, no. 5, pp. 508–523, 2016.

[114] X. Wang, F. Wu, G. Li et al., “Lipid-modified cell-penetrating peptide-based self-assembly micelles for co-delivery of narce- lamine and siULK1 in hepatocellular carcinoma therapy,” *Acta Biomaterialia*, vol. 74, pp. 414–429, 2018.

[115] L. Saso and O. Firuzi, “Pharmacological applications of antiok- dants: lights and shadows,” *Current Drug Targets*, vol. 15, no. 13, pp. 1177–1199, 2014.

[116] C. Zhang, Z. Liu, Y. Zheng et al., “Glycyrrhetinic acid function- alized graphene oxide for mitochondria targeting and cancer treatment in vivo,” *Small*, vol. 14, no. 4, Article ID 1703306, 2018.

[117] C. Han, C. Zhang, T. Ma et al., “Hypericin-functionalized graphene oxide for enhanced mitochondria-targeting and syn- ergistic anticancer effect,” *Acta Biomaterialia*, vol. 77, pp. 268–281, 2018.

[118] M. Gandhi, F. Aweeke, R. M. Greenblatt, and T. F. Blaschke, “Sex Differences in Pharmacokinetics and Pharmacodynamics,” *Annual Review of Pharmacology and Toxicology*, vol. 44, pp. 499–523, 2004.

[119] F. Hu, J. An, W. Li et al., “UPLC-MS/MS determination and gender-related pharmacokinetic study of five active ingredients in rat plasma after oral administration of Eucommia cortex extract,” *Journal of Ethnopharmacology*, vol. 169, pp. 145–155, 2015.

[120] R. G. Ulrich, “Idiosyncratic toxicity: a convergence of risk factors,” *Annual Review of Medicine*, vol. 58, pp. 17–34, 2007.
paeoniflorin after oral administration with Samul-tang in rats,” 
*Journal of Ethnopharmacology*, vol. 142, no. 1, pp. 161–167, 2012.

[122] C. J. Landmark, S. I. Johannessen, and T. Tomson, “Host factors affecting antiepileptic drug delivery—pharmacokinetic variability,” *Advanced Drug Delivery Reviews*, vol. 64, no. 10, pp. 896–910, 2012.

[123] H. Soraoka, K. Oniki, K. Matsuda et al., “The effect of Yokukansan, a traditional herbal preparation used for the behavioral and psychological symptoms of dementia, on the drug-metabolizing enzyme activities in healthy male volunteers,” *Biological & Pharmaceutical Bulletin*, vol. 39, no. 9, pp. 1468–1474, 2016.

[124] J. A. Simpson, T. Agbenyega, K. I. Barnes et al., “Population pharmacokinetics of artesunate and dihydroartemisinin following intra-rectal dosing of artesunate in malaria patients,” *PLoS Medicine*, vol. 11, no. 3, Article ID e444, 2006.

[125] M. Munekage, K. Ichikawa, H. Kitagawa et al., “Population pharmacokinetic analysis of daikenchuto, a traditional Japanese medicine (kampo) in Japanese and US health volunteers,” *Drug Metabolism and Disposition*, vol. 41, no. 6, pp. 1256–1263, 2013.

[126] L. Cavalli, L. Briscese, T. Cavalli, P. Andre, and M. C. Carboncini, “Role of acupuncture in the management of severe acquired brain injuries (sABIs),” *Evidence-Based Complementary and Alternative Medicine*, vol. 2018, Article ID 8107508, 10 pages, 2018.

[127] D. Ji, Z. Ning, C. Mao et al., “Effects of acupuncture at ST36 on pharmacokinetics of Schisandra lignans in rats,” *Acupuncture in Medicine*, vol. 33, no. 3, pp. 223–229, 2015.

[128] T. J. Kaptchuk, “Acupuncture: theory, efficacy, and practice,” *Annals of Internal Medicine*, vol. 136, no. 5, pp. 374–383, 2002.

[129] F. Zhang, J. Ma, Y. Lu et al., “Acupuncture combined with curcumin attenuates carbon tetrachloride-induced hepatic fibrosis in rats,” *Acupuncture in Medicine*, vol. 30, no. 2, pp. 132–138, 2012.

[130] E. Manheimer, D. van der Windt, K. Cheng et al., “The effects of acupuncture on rates of clinical pregnancy among women undergoing in vitro fertilization: a systematic review and meta-analysis,” *Human Reproduction Update*, vol. 19, no. 6, pp. 696–713, 2013.

[131] J. S. Han, “Acupuncture: neuropeptide release produced by electrical stimulation of different frequencies,” *Trends in Neurosciences*, vol. 26, no. 1, pp. 17–22, 2003.

[132] J. Zhou, F. Qu, E. Burrows, Y. Yu, and R. Nan, “Acupuncture can improve absorption of baicalin from extracts of Scutellaria baicalensis Georgi in rats,” *Phytotherapy Research*, vol. 23, no. 10, pp. 1415–1420, 2009.