Review article

Pharmacokinetic profile of phytoconstituent(s) isolated from medicinal plants—A comprehensive review

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A R T I C L E   I N F O

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A B S T R A C T

Herbal medicine, the backbone of traditional medicine, has played an important role in human health and welfare for a long period. Traditional therapeutic approaches of regional significance are found in Africa, South and Central America, China, India, Tibet, Indonesia, and the Pacific Islands. The considerable scientific significance and commercial potential of traditional medicines have resulted in increased international attention and global market demands for herbal medicines, especially Chinese herbal medicines. Herbal medicines currently are the primary form of health care for the poor in the developing countries, and also are widely used as a supplement or substitute for conventional drugs in developed countries. These traditional medicines have a pivotal role in the treatment of various ailments and more than 50% of drugs used in Western pharmacopoeia are isolated from herbs or derived from modifications of chemicals found in plants. Herbal medicines usually contain a complex mixture of various bioactive molecules, which make its standardization complicated, and there is little information about all compounds responsible for pharmacological activity. Several research papers have been published that claim pharmacological activity of herbal medicines but few are discussing the role of the exact phytoconstituent. Understanding the pharmacokinetic profile of such phytoconstituents is essential. Although there are research papers that deal with pharmacokinetic properties of phytoconstituents, there are a number of phytoconstituents yet to be explored for their kinetic properties. This article reviews the pharmacokinetic profile of 50 different therapeutically effective traditional medicinal plants from the year 2003 onward.

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1. Introduction

Herbal medicines are known to have a strong reputation throughout history and within every culture to provide first-line and basic health services for patients with numerous disease conditions. The roots of herbal medicine are at the very beginning of human history. These are the oldest form of medicine for welfare of mankind, and they play a paramount role in culture-specific traditional medicinal systems (TMS), i.e., Ayurveda (India) and traditional Chinese medicine (China). Herbal medicine is an umbrella term that encompasses an array of treatment options to supplement conventional and nonconventional therapies. Herbal medicine approaches are completely different from modern orthodox medicines. The historical background of herbal medicine begins with ethnopharmacology, a term introduced in 1967, which mainly deals with the scientific study of the traditional medicinal plants. It can be defined as ‘the scientific study of materials used by ethnic and cultural groups as medicines’ and in most instances this is synonymous with the study of traditional medicine. Phytochemicals, phytomedicine, natural remedies, natural products and their chemistry, and various other subjects are present in the realm of herbal medicines and are beyond the scope of this article. Basically, medicinal plants are a huge source of chemical compounds, including primary and secondary metabolites, alkaloids, flavonoids, and lignin. These medicinal plants and their extracts...
yield promising leads (active principals) to further strengthen the medicinal system. These natural bioactive compounds play a central role in combating many human diseases. More than 50% of drugs used in Western pharmacopoeia are isolated from herbs or derived from modification of phytoconstituents. Recent studies have stated that 75–90% (developing world) and 80% (less developed/developing countries) of the current world population relies on the use of herbal medicines for their primary health care and other needs, which signifies the scope of TMS, where 85% of medicinal plants of TMS involve the use of plant extracts. These phytochemicals show a more complex pharmacokinetic profile (the study of the time course of phytochemicals, absorption, distribution, metabolism, and excretion). This pharmacokinetic profile helps to elaborate the relationship between intensity and time course of pharmacology, the toxicological effects of phytochemicals in the human body, and extends the scope of the use and acceptance by different regulatory bodies. As pointed out by the World Health Organization, there is very limited knowledge about the chemical compositions, pharmacokinetics, pharmacodynamics, and metabolomics of TCM plants; the data about authentication, efficacy, and safety of TCM are known and are far from satisfactory to meet the required criteria for worldwide use. To provide satisfactory data about safety and efficacy of these medicinal plants and for pharmacokinetic profile, we have gathered information from various search engines and other possible sources from 2003 onward to provide a detailed picture on ADME parameters (absorption, distribution, metabolism, and excretion) of some phytoconstituents. The review elaborates pharmacokinetic profile of 50 medicinally important phytoconstituents from different medicinal plants.

2. Pharmacokinetic profile of drugs

2.1. Ammi visnaga L. (阿密香 e mì xiāng)

Visnagin is a furanocoumarins derivative and one of the major constituents in Ammi visnaga L. (Apiaceae). It is commonly known as Khella. It was used by ancient Egyptians as a treatment for kidney stone disease. Visnagin has cardiovascular effects due to calcium channel blocking actions. Visnagin also has negative chronotropic and isotropic effects and reduces peripheral vascular resistance. Its extract prevents urolithiasis (kidney stone formation) by decreasing calcium oxalate crystal growth in the stone-forming rat model.

A sensitive and highly selective liquid chromatography-tandem mass spectrometry (LC-MS) method was used to determine visnagin in rat plasma. Chromatography was performed on a Phenomenex Gemini column (2.0 × 50 mm i.d., 5 μm, Torrance, CA, USA) analytical column at ambient temperature. The mobile phase used for analysis was 0.1% formic acid, 5mM ammonium acetate in deionized water and methanol (15:85, v/v) delivered at a flow rate of 0.2 mL/min. For quantitative determination of visnagin in a rat plasma, a 50-μL sample is required. Pharmacokinetic parameters after oral administration of visnagin are provided in Table 1.

2.2. Apium graveolens, Ligusticum sinensis, and Ligusticum wallichii (芹菜 qín cài), Ligusticum sinensis (霧木 gào bēn) and Ligusticum wallichii (川芎 chuān xiāng)

3-n-Butylphthalide is a volatile chemical present in several plants including Apium graveolens, Ligusticum sinensis, and Ligusticum wallichii. In China 3-n-butylphthalide [(±)-NBP] may be a promising new drug for the treatment of ischemic cerebral diseases, such as stroke.

| Parameter | Values |
|-----------|--------|
| Peak plasma concentration (Cmax) (ng/mL) | 2969 |
| Time of peak plasma concentration (tmax) (h) | 0.33 |
| Area under the concentration-time curve (trapezoidal rule) (h × mg/L) | 11.9 |
| Apparent clearance (CL/F) (L/kg) | 0.84 |
| The terminal elimination half-life (h) | 2.3 |

A high-performance liquid chromatography (HPLC)-mass spectrometry (MS)/MS with positive ionization mode was adopted to determine 3-n-butylphthalide in rat plasma. The system was equipped with an ACQUITY UPLC T M BEH C18 (50 × 2.1 mm i.d., 1.7 μm) column. Gradient mobile phase composed of acetonitrile (ACN) and water containing 0.1% formic acid was used. The separated compounds were detected by a Waters Tandem Quadrupole (TQ) Detector (Waters, Milford, MA). The column temperature, flow rate, and chromatographic run time per sample used was 35°C, 0.2 mL/min, and 3.0 minutes, respectively. The lower limit of quantification (LLOQ) value was 5.57 ng/mL. Pharmacokinetic parameters after intravenous administration of 3-n-butylphthalide (5 mg/kg) are provided in Table 2. 3-n-Butylphthalide followed extensive metabolism in humans and produced four metabolites, i.e., 10-keto-NBP, 3-hydroxy-NBP, 10-hydroxy-NBP, and NBP-11-oic acid.

2.3. Atractylodes macrocephala Koidz (白朮 bái zhú)

Atractylodes macrocephala Koidz is one of the TCMs listed in Chinese pharmacopoeia. It exhibits antitumor, anti-inflammatory, and antibacterial properties. The anticancer effect of atractylenolide I has been proved in different cancer cells.

The HPLC-MS/MS method was reported for quantification of atractylenolide I in Wistar rat plasma after oral administration of the ethanol (95%) extract of atractylodis. The MS was operated in the positive electrospray ionization (ESI) mode with multiple reaction monitoring (MRM). The LC system was equipped with a Phenomenex Gemini column (2.0 × 50 mm i.d., 5 μm, Phenomenex Company, CA, USA). The mobile phase consisted of a mixture of 0.1% formic acid in water and 0.1% formic acid in methanol. The flow rate was set at 0.4 mL/min, and column temperature and injection volume are 25°C and 10 μL, respectively. The limit of detection (LOD) and the limit of quantification (LOQ) are 0.6 ng/mL and 2.0 ng/mL, respectively. The pharmacokinetic parameters of atractylenolide I after oral administration of ethanol (95%) atractylodis extract are presented in Table 3. The pharmacokinetic data indicate that atractylenolide I was absorbed very quickly in the body.

When simultaneous determination for atractylenolide I, II, and III was performed in blank rat plasma, atractylenolide II was found in real samples, atractylenolide III was found in plasma at different time points, and the pharmacokinetic curve of atractylenolide III showed an irregular pattern.

| Parameter | Values |
|-----------|--------|
| AUC0–6h (ng-h/mL) | 1140.16 |
| Apparent volume of distribution (Vc) (L/kg) | 1.22 |
| Half-life (t1/2) (distribution) (h) | 0.098 |
| t1/2 (elimination) (h) | 2.62 |
| Clearance (CL) (L/h kg) | 3.67 |

AUC – area under the concentration-time curve.
Table 3
Pharmacokinetic parameters of atractylenolide I after oral administration of Atractylodis extract (20 g/kg) to rats (n = 6, mean ± standard deviation).

| Parameters | Values |
|------------|--------|
| Elimination rate constant (Ke) (h⁻¹) | 0.365 ± 0.06 |
| AUC∞ (ng·h/L) | 22.2 ± 1.9 |
| AUCC (ng·h/L) | 22.6 ± 1.8 |
| Tmax (h) | 0.81 ± 0.11 |
| Cmax (ng/L) | 7.99 ± 1.2 |
| V1 (L/kg) | 2768.6 ± 751.5 |
| CI (L/h/kg) | 978.2 ± 117.3 |
| t1/2 (h) | 1.94 ± 0.27 |

AUC = area under the concentration-time curve; CI = clearance; T_max = peak plasma concentration; Tmax = time of peak plasma concentration.

2.4. Artemisia annua L. (黃花蒿 huáng huā hāo)

Artemisia annua L. (annual wormwood) contains the antimalarial artemisinin. Aqueous preparations of the dried herb are included in the pharmacopoeia of the People’s Republic of China for the treatment of fever and malaria.

A reverse-phase HPLC was used to determine artemisinin in blood samples of healthy male volunteers receiving 9 g of Artemisia annua L. The system is equipped with 250 × 4.6 mm Multhope RP-18, 5-μm column (Chromatography Service, Langenwehe, Germany). A linear gradient of 45–100% acetonitrile in water (20 minutes, 1 mL/min) was used. For online postcolumn derivatization, 0.3 M aqueous potassium hydroxide was added to the elute at a rate of 0.2 mL/min. The resulting mixture was passed through a 5-m steel capillary (0.5 mm internal diameter) immersed in a water bath of 70°C. Ultraviolet absorption was monitored at 289 nm. The pharmacokinetic parameters of artemisinin are provided in Table 4. The overall picture of pharmacokinetic data revealed that artemisinin plasma concentrations after intake of the given herbal tea are sufficient for clinical effects, but insufficient to recommend such preparations as equivalent substitutes for modern artemisinin drugs in malaria therapy.10

2.5. Aristolochia fangchi (防己馬兜鈴 fāng jǐ mǎ dōu líng)

Aristolochic acids (AAs) are found primarily in the plant genera Aristolochia and Asarum. AAs exhibit anti-inflammatory, antitussive, and antiplatelet aggregation pharmacologic properties and are also used as pain relievers. AAs have proved to be the major components that cause renal fibrosis problems. AAs are a mixture of structural-related 10-nitrophenanthrene 1-carboxylic acids, where AAI, the 8-methoxy-3,4- methylene dioxy derivative, and AAII, the 3,4-methyleneedioxy derivative, are the major components in the Aristolochia species.

Ultra high-performance liquid chromatography (UHPLC)-MS/MS with a Quatro Micro triple-quadrupole mass spectrometer (Micromass, Manchester, UK) operating at positive ion electrospray mode has been reported to determine the pharmacokinetic parameters. The system was equipped with an Acquity BEH C18 column (100 × 2.1 mm i.d., 1.7 μm, Waters) for separation of aristolochic acids. The mobile phase was composed of 10 mM ammonium formate (pH 3.0) (solvent A) and ACN (solvent B). The gradient profile was 0–2 min: 34% B; 2–10.5 min: linear from 34% to 36% B; 10.5–10.6 min: linear from 36% to 34% B and then re-equilibrium of the column. The flow rate was kept at 0.3 mL/min. The column oven and autoinjection system are set at 40°C and 4°C respectively. Partial loop with needle over fill mode was used for sample injection, and the injection volume was 5 μL. The LOD was 0.14 ng/mL for AAI and 0.26 ng/mL for AAII. The pharmacokinetic parameters after single oral administration of 10 mg/kg standard in female Wistar rats are presented in Table 5.

The pharmacokinetic data revealed that AAs could be quickly absorbed in the gastro-intestinal tract. The hepatic enzymes P450 1A1 and 1A2 help to detoxify AAI through the metabolism of AAI into less toxic metabolites aristolactam I (AL I).11

2.6. Anemarrhena asphodeloides (知母 zhī mǔ)

The Chinese herb named as Zhi-Mu, mangiferin (2-b-o-glucopyranosyl-1,3,6,7-tetrahydroxanthene-9-one) has been isolated from the herbal root of Anemarrhena asphodeloides Bung showing antioxidant, antiviral, and anticancer activity.

A HPLC tandem MS with in vivo microdialysis sampling method was used for continuous monitoring of free mangiferin in rat blood. Mangiferin was separated by a reverse-phase C microbore column (15031 mm) from dialysate within 10 minutes. The mobile phase consisted of 18 acetonitrile-0.05% phosphoric acid-tetrahydrofuran (10:75:15, v/v/v) with a flow rate of 0.05 mL/min. Multiparameter detection was set at 257 nm. The LOQ and retention time were 0.05 mg/mL and 6.0 minutes, respectively. The pharmacokinetic parameters for mangiferin are provided in Table 6. The study results revealed that mangiferin cannot cross the blood-brain barrier because it was not detected in the bile and brain for all dosage treatments. Mangiferin metabolites are formed by methylation and phase II sulfation and glucuronidation are found in rat bile.12

2.7. Baphicacanthus cusia (Nees) Bremek. (馬藍 mǎ lán; Polygonum tinctorium Ait. (蓼蓝 liǎo lán) and Isatis indigotica Fort. (菘蓝 sōng lán)13

Indirubin, a 3,20-bisindole isomer of indigo, exists in several medicinal plants such as Baphicacanthus cusia (Nees) Bremek, Polygonum tinctorium Ait., and Isatis indigotica Fort. It is one of the compounds that exhibits antileukemic action more specifically effective against chronic granulocytic leukemia. In addition, it is useful as an antiproliferative and an anti-inflammatory agent.

HPLC was adopted to determine the pharmacokinetic parameters of indirubin in a rat after intravenous and intraperitoneal administration. It was equipped with a Zirchrom Kromasil ODS column (200 × 4.6 mm i.d., 5 mm) and protected by a guard

Table 4
Pharmacokinetic parameters of artemisinin.

| Parameter | Values |
|-----------|--------|
| Mean ± SD (ng/mL) | 240 ± 75 |
| (Maximum plasma concentration of artemisinin) | |
| Mean ± SD (ng/mL × h) | 336 ± 71 |
| (Area under the plasma concentration-time curve) | |
| Tmax (h) | 0.6 ± 0.2 |
| Cmax (ng/L) | 7.99 ± 1.2 |
| V1 (L/kg) | 2768.6 ± 751.5 |
| CI (L/h/kg) | 978.2 ± 117.3 |
| t1/2 (h) | 1.94 ± 0.27 |

Table 5
Pharmacokinetic parameters after single oral administration of 10 mg/kg standard in female Wister rats.

| Parameter | AAII | AAII |
|-----------|------|------|
| Tmax (min) | 30 | 45 |
| Cmax (ng/mL) | 7249.3 | 77.7 |
| AUC (ng/mL × min) | 716,936.3 | 31,344.8 |
| CI (L/h/kg) | 234.6 | 800.7 |
| Rate constant (k) (min⁻¹) | 0.003 | 0.0009 |
| Oral clearance (ml/min) | 2.9 | 66.0 |

AA = aristrolic acid; AUC = area under the concentration-time curve; Cmax = peak plasma concentration; Tmax = time of peak plasma concentration.
Table 6
Pharmacokinetic parameters following mangiferin administration (10, 30, and 100 mg/kg, intravenously) (z = 6).

| Parameters | 10 mg/kg | 30 mg/kg | 100 mg/kg |
|------------|----------|----------|-----------|
| AUC (min mg/mL) | 122.96171 | 452.56398 | 2424.26196.7 |
| Half-life of slow distribution phase | 28.5635 | 35.0635 | 47.8641* |
| (t 1/2 b) (min) | 1/2b |
| Steady-state volume of distribution | 3.0603 | 2.5603 | 2.0603 ss |
| (Vss) (L/kg) | |
| Cl (mL/min/kg) | 90.161.26 | 69.166.5 | 43.2643* |
| Mean residence time (min) | 35.065.22 | 35.962.8 | 45.8648* |

AUC – area under the concentration-time curve; Cl – clearance.

* Denotes the, significantly different (p = 0.05) from the dose of 10 and 30 mg/kg (Student’s t test) and SS denotes the steady-state.

§ Significantly different (p = 0.05) from the dose of 10 30 mg/kg (Student’s t test).

Table 7
Mean pharmacokinetic parameters of indirubin after intravenous injections at doses of 5.6 and 2.8 mg/kg and intraperitoneal injections at dose of 5.6 mg/kg in rats.

| Parameters | Doses | Value |
|------------|-------|-------|
| 5.6 mg/kg (i.v.) | 2.8 mg/kg (i.v.) | 5.6 mg/kg (i.p.) |
| AUC0–∞ (ng h/mL) | 308 ± 75.0 | 130 ± 47.83 | 25.9 ± 74.9 |
| AUC0–t (ng h/mL) | 295 ± 745.3 | 12.7 ± 74.33 | 22.6 ± 75.2 |
| Cmax (ng/mL) | 201 ± 723.7 | 155 ± 717.7 | 20.87 ± 7.6 |
| Tmax (h) | 0.017 | 0.017 | 0.010 |
| Ke (h⁻¹) | 0.670 ± 70.2 | 0.6837 ± 0.2 | 0.6407 ± 0.5 |
| t1/2 | 1.0307 ± 0.2 | 1.0207 ± 0.2 | 1.0870 ± 0.4 |
| MRT (h) | 1.7507 ± 0.3 | 1.5107 ± 0.3 | 0.777 ± 1.1 |

AUC – area under the concentration-time curve; Cmax – peak plasma concentration; i.p. – intraperitoneal; i.v. – intravenous; MRT – mean residence time; Tmax – time of peak plasma concentration.

Table 8
The main pharmacokinetic parameters of CXB after a single intravenous administration of 5.0 mg/kg CXB in six male rats.

| Parameter | Value |
|-----------|-------|
| Vc (L/kg) | 2.60 ± 1.88 |
| t1/2 pi (h) | 0.109 ± 0.058 |
| Half-life of rapid distribution phase (t1/2 s) (h) | 0.503 ± 0.173 |
| t1/2 s (h) | 1.87 ± 0.99 |
| K12 (1/h) | 1.38 ± 1.36 |
| K3 (1/h) | 2.24 ± 1.77 |
| K13 (1/h) | 1.17 ± 0.178 |
| K15 (1/h) | 0.113 ± 0.021 |
| C1 (L/kg/h) | 4.53 ± 1.65 |
| CI (L/kg/h) | 5.92 ± 1.73 |
| AUC0–t (ng h/mL) | 5660 ± 76.4 |
| AUC0–∞ (ng h/mL) | 583.1 ± 79.7 |

AUC – area under the concentration-time curve; CI – clearance.

Table 9
Selected pharmacokinetics parameters of nobiletin in male Sprague Dawley rats following oral administration of nobiletin at 50 mg/kg (n = 3/time point).

| Parameters | Plasma | Brain |
|------------|--------|-------|
| AUC0–t (µg h/mL) | 7.49 | 20.66 |
| AUC0–∞ (µg h/mL) | 7.84 | 23.20 |
| Cmax (µg/mL) | 1.78 | 4.20 |
| Tmax (h) | 1.00 | 1.00 |
| Kel (1/h) | 0.39 | 0.06 |
| t1/2 (h) | 1.80 | 11.42 |

AUC – area under the concentration-time curve; Cmax – peak plasma concentration; Tmax – time of peak plasma concentration; Kel – elimination rate constant.

Column (Phenomenex Security Guard TM, ODS, 4 × 30 mm, Cheshire, UK). The mobile phase contains a mixture of methanol-water (75:25, v/v). The flow rate and wavelength for detection are 1 mL/min and 289 nm at room temperature, respectively. The LLOQ was found to be 6.5 ng/mL. The mean pharmacokinetic parameters of indirubin after intravenous injections and intraperitoneal injections at doses 2.8, 5.6, and 5.6 mg/kg, respectively, in rats are provided in Table 7. The parent molecule of indirubin metabolized and excreted fast as compared with its metabolites. Indirubin showed a relatively low bioavailability of 8.40% in rats when it was intraperitoneally administered, and to enhance its therapeutic efficacy design of appropriate dosage form or delivery system or structural modification may be required.

2.8. *Cudrania tricuspidata* (Carr.) Bur. (ｆｕｋｕ 桑 ｚｈｅ ｓｈù)

*Cudrania tricuspidata* (Carr.) Bur. is a deciduous shrub or tree distributed over China, Korea, and Japan. The root of the plant is used for gastric carcinoma. Among the active compounds, cudranictsxanthone B (CXB) is found to be the most promising.

A HPLC-ESI-tandem MS was used to evaluate the pharmacokinetic characteristics of CXB after intravenous administration in the rat. The system was equipped with a Venusil XBP-PH C18 column (2.1 × 100 mm i.d., 5 µm) coupled with a Phenomenex C18 guard column (4.0 × 30 mm i.d., 5 µm) and the temperature was set at 40°C. The mobile phase was 0.5% formic acid in methanol at a flow rate of 0.3 mL/min. Acquisition of MS data for CXB and internal standards was performed in positive ionization mode. The study used 5.0 mg/kg CXB in rats, which was administered via the tail vein. Blood samples (about 50 mL at 0.083 and 0.25 h, and about 200 mL at other points) are drawn from the retro-orbital plexus before dosing and at 0.083, 0.25, 0.5, 1, 2, 3, 4, 6, 9, 15, and 24 hours after dosing. The compartment model for pharmacokinetic parameters of CXB was chosen according to the lowest Akaike information criterion (AIC) value. The (AUC0–t) and infinity (AUC0–∞) are calculated using the linear trapezoidal rule with a non-compartment model, and other parameters are estimated with a three-compartment model. The method was sensitive with an LLOQ at 1.0 ng/mL for CXB using 100 µL of rat plasma. The pharmacokinetic parameters of CXB after a single intravenous administration are given in Table 8. CXB after a single intravenous administration indicate the rapid distribution followed by a slow elimination."
Elimination of nobelitin from the brain was slower in comparison with plasma. The AUC and \( t_{1/2} \) indicated that the brain exposure of nobelitin is approximately three times higher than the plasma.\(^{15}\)

2.10. *Cynomorium songaricum* Rupr. (鍋蕨 suò yang)

*Cynomorium songaricum* Rupr. (Suoyang) is one of the known medicinal parasitic plants from TCM. The catechins isolated from *C. songaricum* include catechin, epicatechin, and epicatechin gallate. Catechin and epicatechin are useful in atherosclerosis and cancer treatment, respectively.

The LC-MS/MS method was used for simultaneous determination of pharmacokinetic parameters catechin, epicatechin, and epicatechin gallate after oral administration of alcoholic *C. songaricum* extract in rats. The system was equipped with an Eclipse Plus (Agilent, USA) C18 (4.6 × 100 mm, 1.8 μm) column with a security guard C18 (2.1 × 12.5 mm i.d., 5 μm) column. The mobile phase involves formic acid aqueous solution (0.1%) (A) and acetonitrile (B) using a gradient elution of 20–44% B at 0–8 min, 44–80% B at 8–12 min, 80–20% B at 12–13 min, and the re-equilibration time of gradient elution is 5 minutes. The flow rate, column temperature, and injection volume are 0.3 mL/min, 25°C, and 10 μL, respectively. \( C_{\text{max}} \) of catechin, epicatechin, and epicatechin gallate in rat plasma is 86.69 ± 38.65, 32.57 ± 15.00, and 36.93 ± 12.62 ng/mL, respectively. \( T_{\text{max}} \) values are 0.15 ± 0.08, 0.20 ± 0.10 and 0.20 ± 0.13 hours, respectively. The LLOQ value is 2 ng/mL. The pharmacokinetic parameters of catechin, epicatechin, and epicatechin gallate after oral administration are provided in Table 10. Catechin, epicatechin, and epicatechin gallate demonstrated rapid absorption in rat plasma after oral administration of *C. songaricum* extracts.\(^{16}\)

2.11. *Curcuma longa* L. (薑黃 jiàng huáng)

*Curcuma*(1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) is a phenolic substance derived from spice herb *Curcuma longa* L. Curcumin is widely used in the food industry as a natural food coloring agent and curry powder. In addition, curcumin has the anticancer, antiviral, and anti-infectious properties, anti-amyloidogenic effects, and wound healing qualities and it is also useful in treating Alzheimer disease.

A LC-MS/MS with an orthogonal Z-spray electrospray interface system was used to determine the pharmacokinetics and oral bioavailability of curcumin and demethoxycurcumin from *C. longa*. The system was equipped with a ZORBAX SB-C18 column (150 × 2.1 mm i.d., 1.8 μm) (Agilent Technologies). The MS was used in the negative mode. The mobile phase consisted of acetonitrile (A) and water containing 0.1% formic acid (B) and it is eluted as follows: 0 min (23%, A), 2 minutes (23%, A), 3.5 minutes (10%, A), 5 minutes (20%, A), 10.5 minutes (20%, A), 14 minutes (70%, A), 14.01 minutes (23%, A), and 18 minutes (23%, A). The flow rate and column temperature were 0.2 mL/min and 30°C, respectively. The plasma sample was prepared using a liquid-liquid extraction method and the recovery rate for the four analytes was around 80%. The calibration curves are linear over a concentration range of 10.6–1060.0 ng/mL for 3,4-DCQA, 19.2–192.00 ng/mL for 1,5-DCQA, 14.0–2900.0 ng/mL for 3,5-DCQA, and 9.7–970.0 ng/mL for 4,5-DCQA. The intraday and interday precision was less than 15% and the relative error (RE) was within ±15%. The four DCQAs were not stable after three complete freeze/thaw cycles (−80°C to 23°C). However, they were stable after long-term sample storage (−80°C for 30 days) and bench-top (23°C for 2 hours). The extracted samples on the auto sampler rack at 4°C are stable for 6 hours. The LLOQ was as follows: 10.6 ng/mL for 3,4-DCQA, 19.2 ng/mL for 1,5-DCQA, 14 ng/mL for 3,5-DCQA, and 9.7 ng/mL for 4,5-DCQA, which was sufficiently sensitive to measure relatively low concentrations of DCQA in plasma with a simple liquid-liquid extraction procedure using as little as 50 μL plasma. The typical plasma concentration-time profiles indicate that 3,4-DCQA, 3,5-DCQA, and 4,5-DCQA may transform to 1,5-DCQA in vivo because the content of 1,5-DCQA in the extract was very low.\(^{17}\)

3. Dicaffeoylquinic acids

Dicaffeoylquinic acids (DCQAs) are a class of natural polyphenolic compounds widely distributed in many herbs. 3,4-DCQA, 1,5-DCQA, 3,5-DCQA, and 4,5-DCQA are the typical analogs of DCQAs. Large amounts of such polyphenolic compounds have been extracted from *Ainsliaea fragrans champ.* (兔耳風 tù é fēng) These compounds exhibit various biological actions such as antibacterial, antiviral, anti-inflammatory, and antioxidative stress effects.

The HPLC-MS/MS method was used for simultaneous estimation of pharmacokinetic activity of four DCQAs in Dawley rat plasma. The system was equipped with an Agilent (Santa Clara, CA) ZORBAX SB-C18 column (150 × 2.1 mm i.d., 1.8 μm) (Agilent Technologies). The MS was operated in the negative mode. The mobile phase consisted of acetonitrile (A) and water containing 0.1% formic acid (B) and it is eluted as follows: 0 min (23%, A), 2 minutes (23%, A), 3.5 minutes (10%, A), 5 minutes (20%, A), 10.5 minutes (20%, A), 14 minutes (70%, A), 14.01 minutes (23%, A), and 18 minutes (23%, A). The flow rate and column temperature were 0.2 mL/min and 30°C, respectively. The plasma sample was prepared using a liquid-liquid extraction method and the recovery rate for the four analytes was around 80%. The calibration curves are linear over a concentration range of 10.6–1060.0 ng/mL for 3,4-DCQA, 19.2–192.00 ng/mL for 1,5-DCQA, 14.0–2900.0 ng/mL for 3,5-DCQA, and 9.7–970.0 ng/mL for 4,5-DCQA. The intraday and interday precision was less than 15% and the relative error (RE) was within ±15%. The four DCQAs were not stable after three complete freeze/thaw cycles (−80°C to 23°C). However, they were stable after long-term sample storage (−80°C for 30 days) and bench-top (23°C for 2 hours). The extracted samples on the auto sampler rack at 4°C are stable for 6 hours. The LLOQ was as follows: 10.6 ng/mL for 3,4-DCQA, 19.2 ng/mL for 1,5-DCQA, 14 ng/mL for 3,5-DCQA, and 9.7 ng/mL for 4,5-DCQA, which was sufficiently sensitive to measure relatively low concentrations of DCQA in plasma with a simple liquid-liquid extraction procedure using as little as 50 μL plasma. The typical plasma concentration-time profiles indicate that 3,4-DCQA, 3,5-DCQA, and 4,5-DCQA may transform to 1,5-DCQA in vivo because the content of 1,5-DCQA in the extract was very low.\(^{17}\)

### Table 10

| Parameters | Catechin | Epicatechin | Epicatechin gallate |
|------------|----------|-------------|---------------------|
| \( \text{MRT}_{1/2} \) (h) | 3.98 ± 0.33 | 4.54 ± 0.66 | 3.85 ± 0.78 |
| \( T_{1/2} \) (h) | 0.13 ± 0.12 | 0.60 ± 0.34 | 0.51 ± 0.36 |
| \( T_{\text{max}} \) (h) | 6.38 ± 4.20 | 34.80 ± 25.30 | 4.70 ± 4.24 |
| \( \text{AUC}_{\text{C}} \) (ng/mL) | 1097.7 ± 57.0 | 67.66 ± 16.99 | 72.44 ± 48.93 |
| \( \text{AUC}_{\text{E}} \) (ng/mL) | 1540.0 ± 97.2 | 2140.0 ± 161.7 | 91.01 ± 67.99 |

AUC = area under the concentration-time curve; MRT = mean residence time.

### Table 11

| Parameters | Curcumin |
|------------|----------|
| 10 mg/kg, i.v. | 500 mg/kg, p.o. |
| AUC (min μg/mL) | 7.2 ± 1.2 | 3.6 ± 0.6 |
| \( t_{1/2} \) (min) | 28.1 ± 5.6 | 44.5 ± 7.5 |
| \( C_{\text{max}} \) (μg/mL) | 0.36 ± 0.05 | 0.06 ± 0.01 |
| \( T_{\text{max}} \) (min) | – | 41.7 ± 5.4 |

AUC = area under the concentration-time curve; \( C_{\text{max}} \) = peak plasma concentration; i.v. = intravenous; p.o. = by mouth; \( T_{\text{max}} \) = time of peak plasma concentration.

Longxuejie is a resina moiety isolated from the *Dracaena cochinchinensis* (Lour.) S.C. Chen which is also called ‘dragon’s blood’ in TCM. Longxuejie is clinically used in the treatment of cerebral arterial thrombosis, ischemic heart disease, and peptic ulcer. Loureirin B is the single active component isolated form of longxuejie that has shown good therapeutic actions.
A HPLC (Shimadzu LC-20AD, Japan) was used to analyze the Loureirin B after oral administration of longxuejie. The MS was operated in the positive ESI mode with multiple reaction monitoring (MRM) at unit resolution. The system was equipped with an Agilent XDB-C18 column (4.6 × 50 mm i.d., 5 μm) maintained at 20 °C. The mobile phase was composed of water containing 0.1% formic acid (A) and methanol containing 0.1% formic acid (B) and with flow rate of 0.4 mL/min. After oral administration of 16 g/kg longxuejie to rats through lavage, serial blood samples (0.3 mL) are collected by retro-orbital puncture at 0, 0.083, 0.17, 0.33, 0.5, 0.75, 1, 2, 4, 6, 8, 12, and 18 hours, and then centrifuged at 5000 rpm for 5 minutes immediately afterward. All plasma samples are stored at −20 °C until analysis. The concentration range of 0.08–100 ng/mL. The LOD and LOQ were 0.03 and 0.08 ng/mL, respectively. The pharmacokinetic parameters of loureirin B after oral administration of longxuejie are provided in Table 12.20 In this study, apart from free loureirin B, conjugated metabolites of loureirin B such as sulfate and glucoside metabolites were also detected in rat plasma samples, and the study suggests the necessity of further detailed study of the metabolites.

3.2. Dioscorea nipponica (柴龍 çaí lóng)

Protodioscin (3-O-[α l-rhamnopyranosyl-(1→2)-[α l-rhamnopyranosyl(1→4)]-β-D-glucopyranosyl]-26-O-[β-D-glucopyranosyl]-25R-furost-5-ene-3β,26-diol) is a typical example of a furostan saponin, which is isolated from the roots of Dioscorea nipponica Makino, and it also comprises Oriental vegetables and medicinal plants. Protodioscin is found to be one of the potent anticancer agents and in China its formulation is commercially available.

HPLC-tandem MS with positive ion detection mode was used to determine the pharmacokinetics of protodioscin after intravenous administration in rats. The system was equipped with a Carbosorb ODS-3 column (50 × 2.0 mm i.d., 5 μm) and a security guard C18 guard column (4 × 2.0 mm i.d.) using a mobile phase of acetonitrile-water-formic acid (80:20:0.1, v/v/v). The liquid flow rate, column temperature and volume of distribution at steady state are 1.0 mL/min, 10 μL, and 25°C, respectively. To maintain the flow rate of 0.25 mL/min and to avoid differences in nebulization efficiency, a postcolumn split was used. The LOD and LOQ (pooled plasma samples) values were 0.00234, 0.00184, 0.00217, 0.000433, and 0.00772, 0.00606, 0.00716, and 0.00143 μg/mL, respectively. The pharmacokinetic parameters of the four saponins after oral (2 g extract/kg) administration are presented in Table 14. In this study double peaks were observed in both individual and mean plasma concentration curves of the four saponins except for macranthoside B. This type of diversity of pharmacokinetics of various components is influenced by the complicated interactions among compounds during the process of absorption, distribution, metabolism and excretion.22

3.4. Forsythia suspensa (Thunb) (連翘 lián qiáo)

Forsythia, a phenylethanoid glycoside, is the most abundant constituent in the fruit of Forsythia suspensa (Thunb) Vahl. Forsythia is able to show the antipyretic, antidote, and anti-inflammatory properties in the treatment of various infections, especially acute upper respiratory tract complaints caused by viruses and/or bacterial infection.

A LC/MS with an ESI negative mode was used to determine the pharmacokinetic parameters of four saponins after oral administration. The system is equipped with an Agilent Zorbax C18 guard column (12.5 × 4.6 mm i.d., 5 μm) and a Shim-Pack CLC-ODS column (150 × 6.0 mm i.d., 5.0 μm). The mobile phase was composed of 0.2% acetic acid water (A) and acetonitrile (B) using a gradient elution of 27–29% (v/v) B at 0–6 minutes; 29–33% B at 6–14 minutes; 33–50% B at 14–20 minutes; 50–80% B at 20–30 minutes. The mobile phase flow rate, injection volume, and column temperature are 1.0 mL/min, 10 μL, and 25°C, respectively. To maintain the flow rate of 0.25 mL/min and to avoid differences in nebulization efficiency, a postcolumn split was used. The LOD and LOQ (pooled plasma samples) values were 0.00234, 0.00184, 0.00217, 0.000433, and 0.00772, 0.00606, 0.00716, and 0.00143 μg/mL, respectively. The pharmacokinetic parameters of the four saponins after oral (2 g extract/kg) administration are presented in Table 14. In this study double peaks were observed in both individual and mean plasma concentration curves of the four saponins except for macranthoside B. This type of diversity of pharmacokinetics of various components is influenced by the complicated interactions among compounds during the process of absorption, distribution, metabolism and excretion.

Table 13 Pharmacokinetic parameters of protodioscin in rats after intravenous administrations.

| Parameter       | Dose (mg/kg) |
|-----------------|--------------|
|                 | 0.5          | 1            | 3            |
| t1/2 (min)      | 78 ± 12      | 58 ± 11      | 27 ± 19      |
| kel (1/min)     | 0.0089 ± 0.0056 | 0.012 ± 0.042 | 0.029 ± 0.009 |
| Cmax (μg/mL)    | 70 ± 9       | 116 ± 15     | 378 ± 10     |
| Vss (mL/kg)     | 71.6 ± 13    | 49 ± 21      | 23.5 ± 9     |
| CI (mL/min/kg)  | 0.67 ± 0.19  | 0.598 ± 0.05 | 0.681 ± 0.06 |
| AUC0-18 (μg min/mL) | 732 ± 82 | 1406 ± 107 | 4196 ± 245 |
| AUC0-∞ (μg min/mL) | 785 ± 94 | 1673 ± 195 | 4406 ± 209 |

Table 14 Pharmacokinetic parameters of the four saponins after oral administration of 2 g extract/kg, each value represents the mean ± standard deviation (n = 5).

| Compound        | Cmax (μg/mL) | Cmax (μg/mL) | T1/2 (h) | T1/2 (h) | AUC0-18 (μg h/mL) |
|-----------------|--------------|--------------|----------|----------|-------------------|
| Macranthoside B | 1.39         | 1.30         | 5        | 18       | 22.79             |
| Macranthoside A | 1.88         | 2.35         | 5        | 18       | 39.01             |
| Diphascoside B  | 1.73         | 2.20         | 5        | 18       | 39.62             |
| Macranthoside B | 0.10         | 0.64         | –        | 18       | 19.52             |

AUC – area under the concentration-time curve; CI – clearance; Cmax – peak plasma concentration; Vss – volume of distribution at steady state.

which are useful in alleviating acute fever, headache, pharyngodynia, respiratory infection, pyocutaneous disease, and epidemic disease and are also helpful in treating hepatic injury caused by acetaminophen, Cd and CCl4, and conspicuous depressant effects on swelling of ear croton oil. A LC/MS with an ESI negative mode was used to determine the pharmacokinetic parameters of four saponins after oral administration. The system is equipped with an Agilent Zorbax C18 guard column (12.5 × 4.6 mm i.d., 5 μm) and a Shim-Pack CLC-ODS column (150 × 6.0 mm i.d., 5.0 μm). The mobile phase was composed of 0.2% acetic acid water (A) and acetonitrile (B) using a gradient elution of 27–29% (v/v) B at 0–6 minutes; 29–33% B at 6–14 minutes; 33–50% B at 14–20 minutes; 50–80% B at 20–30 minutes. The mobile phase flow rate, injection volume, and column temperature are 1.0 mL/min, 10 μL, and 25°C, respectively. To maintain the flow rate of 0.25 mL/min and to avoid differences in nebulization efficiency, a postcolumn split was used. The LOD and LOQ (pooled plasma samples) values were 0.00234, 0.00184, 0.00217, 0.000433, and 0.00772, 0.00606, 0.00716, and 0.00143 μg/mL, respectively. The pharmacokinetic parameters of the four saponins after oral (2 g extract/kg) administration are presented in Table 14. In this study double peaks were observed in both individual and mean plasma concentration curves of the four saponins except for macranthoside B. This type of diversity of pharmacokinetics of various components is influenced by the complicated interactions among compounds during the process of absorption, distribution, metabolism and excretion.22

3.4. Forsythia suspensa (Thunb) (連翘 lián qiáo)

Forsythia, a phenylethanoid glycoside, is the most abundant constituent in the fruit of Forsythia suspensa (Thunb) Vahl. Forsythia is able to show the antipyretic, antidote, and anti-inflammatory properties in the treatment of various infections, especially acute upper respiratory tract complaints caused by viruses and/or bacterial infection.

A LC/MS/MS method was used to determine the pharmacokinetic and oral bioavailability of forsythiaside in rats. The system
was equipped with a Thermo Hypersil reverse-phase C18 column (250 × 4.6 mm i.d., 5 μm, San Jose, CA, USA), which was eluted with a gradient mobile phase of acetonitrile (A) and water (B) both containing 0.2% formic acid. The solvent A was 15% (v/v) at the beginning and linearly increased to 35% over 7 minutes, and then returned to 15% by 3 minutes. The mobile phase was delivered at a flow rate of 1 mL/min and 40% of elute was introduced to an Applied Biosystem 3200 Q-Trap mass spectrometer (Foster City, CA, USA) with ESI source. The detection was performed by negative ion ESI in multiple reaction monitoring mode. To calculate the parameters in noncompartmental models and plasma concentration versus time profiles, Win-Nonlin software (Pharsight Corporation, Mountain View, CA, USA, Version (2.1)) was used. The LOD and LOQ were 0.2 and 1.0 ng/mL, respectively, when 100 μL of plasma was used for assay. The pharmacokinetic parameters of forsythiaside in rats following intravenous and oral administration are presented in Table 15. From pharmacokinetic parameters it is clear that forsythiaside is rapidly absorbed into the circulation system and reached its peak concentration at around 20 minutes after oral administration but because of potential hydrolysis in the gastrointestinal tract, poor permeability through the intestinal epithelial membrane and first-pass effect in the liver might be responsible for the low bioavailability of the compound.25

3.5. Flos Lonicerae: Flos Lonicerae (金银花 jin yin hua)

_Flos Lonicerae_ is one of several herbs present in TCM. It mainly consists of a series of water-soluble phenolic components. Chlorogenic acid is the main constituent of _Flos Lonicerae_, which has been reported to have activity of suppressing the N-nitrosating reaction and inhibiting hepatic glucose 6-phosphatase.

A HPLC with UV detector was used to determine the pharmacokinetic parameters of _Flos Lonicerae_ after administration of water extract to rabbits. The system was equipped at room temperature with an analytical column (MTPER SIL BDS C18, 250 × 4.6 mm i.d., 5 μm). The mobile phase consisted of a mixture of acetonitrile-0.2% H3PO4 (11:89, v/v) adjusted to pH 3.0 with sodium hydroxide (0.2 g/mL). The solvent A was 15% (v/v) at the beginning and linearly increased to 35% over 7 minutes, and then returned to 15% by 3 minutes. The mobile phase was delivered at a flow rate of 1 mL/min and 40% of elute was introduced to an Applied Biosystem 3200 Q-Trap mass spectrometer (Foster City, CA, USA) with ESI source. The detection was performed by negative ion ESI in multiple reaction monitoring mode. To calculate the parameters in noncompartmental models and plasma concentration versus time profiles, Win-Nonlin software (Pharsight Corporation, Mountain View, CA, USA, Version (2.1)) was used. The LOD and LOQ were 0.2 and 1.0 ng/mL, respectively, when 100 μL of plasma was used for assay. The pharmacokinetic parameters of forsythiaside in rats following intravenous and oral administration are presented in Table 15. From pharmacokinetic parameters it is clear that forsythiaside is rapidly absorbed into the circulation system and reached its peak concentration at around 20 minutes after oral administration but because of potential hydrolysis in the gastrointestinal tract, poor permeability through the intestinal epithelial membrane and first-pass effect in the liver might be responsible for the low bioavailability of the compound.25

### Table 15

| Parameters | The route of dosing | Oral |
|------------|---------------------|------|
| C_{max} (ng/mL) | – | 122.2 ± 45.4 |
| T_{max} (min) | 0.0 | 20.0 ± 0.0 |
| Initial plasma concentration (C_{0}) (μg/mL) | 64.2 ± 36.1 | – |
| t_{1/2} (μg/mL) terminal elimination half-life | 76.8 ± 26.5 | 74.7 ± 13.3 |
| AUC_{0-∞} (μg min/mL) | 570.5 ± 69.4 | 13.9 ± 5.2 |
| AUC_{0-β} (μg min/mL) | 570.8 ± 69.2 | 14.6 ± 5.7 |
| CL/F (mL/min/kg) | 35.5 ± 4.2 | 39.4 ± 15.9 |
| Volume of distribution (Vd) | 4.0 ± 1.8 | 4.2 ± 1.9 |
| Absolute bioavailability (F%) | – | 0.48 ± 0.12 |

All data are expressed as mean ± standard deviation (n = 5). AUC – area under the concentration-time curve; C_{max} – peak plasma concentration; i.v. – intravenous; T_{max} – time of peak plasma concentration; CL/F – apparent plasma clearance.

### Table 16

Pharmacokinetic parameters obtained by analyzing plasma samples after administration of 10 mg/kg Flos Lonicerae extract to rabbits (n = 4).

| Parameters | Values |
|------------|--------|
| AUC (min/mL) | 140 ± 65.9 |
| Area under first moment curve (AUMC) (μg min²/mL) | 2.80 × 10⁵ ± 1.73 × 10⁴ |
| MRT (min) | 190 ± 38.3 |
| Variance of the mean residence time (VRT) (min/min) | 1.28 × 10⁵ ± 2.56 × 10³ |
| Kel (l/min) | 0.0130 ± 0.0023 |
| T_{max} (min) | 34.7 ± 1.09 |
| C_{max} (μg/mL) | 0.839 ± 0.350 |

AUC – area under the concentration-time curve; C_{max} – peak plasma concentration; MRT – mean residence time; T_{max} – time of peak plasma concentration; Kel – elimination rate constant.

### 3.6. Ginkgo biloba (银杏 yín xìng)

_Ginkgo biloba_ is a TCM herb mostly used to treat various diseases. It contains mixtures of terpenoids and flavonoids. The flavonoids, including flavones (quercetin, kaempferol, and isorhamnetin) and flavonol glycosides are responsible for the free radical scavenging effects of _G. biloba_, whereas the ginkgolides are potent antiplatelet factor (PAF) antagonists. However, the oral bioavailability of flavonoids is relatively low because of their low liposolubility and poor solubility, which severely limits their ability to pass across the lipid-rich biological membranes, resulting in poor bioavailability. In order to improve the absorption of ginkgo flavonoids in vivo, _Ginkgo biloba_ extract (GBE), _G. biloba_ extract phospholipid complexes (GBP), and solid dispersions (GBS) are formulated.

HPLC composed of an LC-20AB with SPD-20A (Shimadzu) was used to determine the pharmacokinetic characteristics and bioavailability of isorhamnetin, quercetin, and kaempferol after oral administration of GBE, GBP, and GBS in rats. The system was equipped with a Hexed ODS-2 column (250 × 4.6 mm i.d., particle size 5 μm, Dalian Elite, China). The mobile phase composed of a mixture of methanol and 0.4% phosphoric acid (60:40, v/v). The flow rate and column temperature are 1.0 mL/min and 35°C, respectively. The wavelength of UV detector was set at 360 nm. Based on a signal-to-noise ratio (S/N = 10), the LLOQ for isorhamnetin, quercetin, and kaempferol were 0.039, 0.056, and 0.048 μg/mL, respectively. The main pharmacokinetic parameters of isorhamnetin, quercetin, and kaempferol in rats are presented in Tables 17, 18, and 19, respectively. In comparison with GBE, both GBS and GBP showed better bioavailability, and the bioavailability of GBP is more than that of GBS. The key parameter in _G. biloba_ flavonoids is the modification of liposolubility to enhance their bioavailability.25

### Table 17

The main pharmacokinetic parameters of isorhamnetin in rats.

| Parameter | GBE | GBP | GBS |
|-----------|-----|-----|-----|
| Ke (1/h)  | 0.0321 | 0.1135 | 0.0644 |
| Absorption rate constant (Ka) (1/h) | 0.2034 | 1.0512 | 0.6374 |
| T_{max} (h) | 7.21 | 4.32 | 6.16 |
| C_{max} (ng/mL) | 195.96 | 672.29 | 291.57 |
| AUC (0–T) (ng h/mL) | 1153.66 | 2722.37 | 1738.889 |
| MRT (0–T) (h) | 6.3332 | 5.1331 | 5.2323 |
| CL/F(h) (ng h/(ng/mL)) | 0.00022 | 0.00037 | 0.00041 |

AUC – area under the concentration-time curve; C_{max} – peak plasma concentration; GBP – _Ginkgo biloba_ extract phospholipid complexes; GBS – _G. biloba_ extract solid dispersions; MRT – mean residence time; T_{max} – time of peak plasma concentration; CL/F – Apparent clearance; Ke – elimination rate constant.
Table 18
The main pharmacokinetic parameters of quercetin in rats.

| Parameter            | GBE   | GBP   | GBS   |
|----------------------|-------|-------|-------|
| Ke (1/h)             | 0.0541| 0.1909| 0.1124|
| Ka (1/h)             | 0.6376| 1.4162| 1.3592|
| Tmax (h)             | 1.21  | 1.02  | 0.63  |
| Cmax (ng/mL)         | 179.21| 724.89| 419.02|
| AUC (0-T) (h)        | 1368.26| 3321.05| 2841.63|
| MRT (0-T) (h)        | 5.4791| 4.1442| 4.6633|
| CL/F (ng/h/(ng/mL))  | 0.0015| 0.0033| 0.0038|

AUC = area under the concentration-time curve; Cmax = peak plasma concentration; GBE = Ginkgo biloba extract; GBP = G. biloba extract phospholipid complexes; GBS = G. biloba extract solid dispersions; MRT = mean residence time; Tmax = time of peak plasma concentration; CL/F = Apparent clearance; Ke = elimination rate constant.

Table 19
The main pharmacokinetic parameters of kaempferol in rats.

| Parameter            | GBE   | GBP   | GBS   |
|----------------------|-------|-------|-------|
| Ke (1/h)             | 0.1641| 0.3412| 0.2875|
| Ka (1/h)             | 0.2029| 0.8891| 0.5570|
| Tmax (h)             | 6.32  | 5.83  | 1.33  |
| Cmax (ng/mL)         | 180.23| 323.56| 280.54|
| AUC (0-T) (h)        | 1139.59| 2228.21| 1630.94|
| MRT (0-T) (h)        | 6.1712| 5.5662| 5.3033|
| CL/F (ng/h/(ng/mL))  | 0.0013| 0.0028| 0.0017|

AUC = area under the concentration-time curve; Cmax = peak plasma concentration; GBE = Ginkgo biloba extract; GBP = G. biloba extract phospholipid complexes; GBS = G. biloba extract solid dispersions; MRT = mean residence time; Tmax = time of peak plasma concentration; CL/F = Apparent clearance; Ka = absorption rate constant and Ke = elimination rate constant.

3.7. G. biloba extract

G. biloba extract is one of the known remedies for treatment of various conditions. The standard ginkgo biloba extract, (Egb 761), contains 22–27% flavonoids and 5–7% lactones. Aglycones comprise less than 0.1% in the extract. G. biloba extract is extensively used therapeutically to increase peripheral and cerebral blood flow as well as for the treatment of dementia. G. biloba extract was reported to show interactions with other drug categories such as antiplatelet, antidepressant, diuretic, and non-steroidal anti-inflammatory drugs. In addition, it shows significant interaction with human cytochrome P450. Considering consumer safety the kinetic behavior of the flavonoids in vivo was studied using the following method.

A HPLC with a diode-array detector was used to determine the total flavonoids in plasma after intravenous administration of G. biloba. The system was equipped with a C18 (4.6 × 150 mm, 5 μm, Waters) column with a guard C18 (4 × 15 mm i.d., 5 μm) column. The mobile phase consisted of an acetonitrile-0.02 mol/L sodium dihydrogen phosphate solution, containing 0.2% phosphoric acid, pH=2.0, (35:65, V/V). The flow rate, column temperature and detection wavelength were 1.0 mL/min, 30 °C, and 360 nm respectively. The injections are administered to 55 male Wistar rats at doses of 50 mg/kg (containing 18 mg/mL flavonoids) via the thigh vein. Blood was collected from abdominal aorta by heparinized needles and syringes after 15, 25, 30, 60, 90, 120, 240, 360, 480, 600, and 720 min of administration from five rats each time. Then the blood was centrifuged at 3000 g for 15 minutes to obtain the plasma samples, which are stored at –80 °C until assaying. The detection limits are 20 ng/mL for quercetin, 20 ng/mL for kaempferol, and 50 ng/mL for isorhamnetin. The pharmacokinetic parameters are calculated using a two-compartment model. The initial concentration in the plasma was 171.22 μg/mL. The half-life of the flavonoids in the first compartment (distribution) the second compartment (elimination) are 0.07 hours and 4.51 hours, respectively, whereas AUC0→∞, apparent volume of distribution and total body clearance are found to be 1711.06 μg min/mL, 0.11 L/kg, and 10.52 mL/(min·kg), respectively. The coingestion of 120 mg of Egb 761 and 500 mg of metformin did not significantly affect the pharmacokinetic properties of metformin.

3.8. Gardenia jasminoides (栀子花 zhi zi hua)

Geniposide is an iridoid glycoside extracted from the fruit of Gardenia jasminoides. It is a well-known TCM herbal plant. It is used to treat disorders of the liver and gallbladder and also is known for its antihyperbilirubinemic action. Long-term use of the Gardenia extract and geniposide could induce hepatic pigmentation in pigs and mice and produce a hepatotoxic effect, respectively.

A LC system was coupled with multiple microdialysis probes to determine the amount of geniposide in the blood, liver, brain, and bile of anesthetized rats. The system was equipped with a Nova-Pak (Waters, Milford, MA, USA) reverse-phase column RP-C18 (150 × 3.9 mm i.d.; 5 μm) at ambient temperature (24 ± 1 °C). The mobile phase consists of acetonitrile-methanol-5mM monosodium phosphate (pH 4.6; 5:15:80, v/v/v), and the flow rate of the mobile phase was 1 mL/min. The maximum UV absorbance for geniposide was tested at a wavelength of 240 nm. Method helps to know the pharmacokinetics of geniposide and its influence by the treatment of acupuncture. The pharmacokinetic data on geniposide in rat blood following geniposide administration are presented in Table 20. The above data does not affect the pharmacokinetics of the herbal ingredient geniposide. However, several questions remain, and the most important is, Do these results reveal the independent effects between acupuncture and the pharmacokinetics of herbs?

4. Homoeriodictyol-7-O-β-D-glucopyranoside

Homoeriodictyol-7-O-β-D-glucopyranoside (flavone 4′,5,7-trihydroxy-3′-methoxy-7′-O-β-D-glucopyranoside, HEDT-Glu) isolated from the TCM herb Viscum coloratum and Viscum album (槲寄生 hú jì shēng). HEDT-Glu can inhibit platelet aggregation induced by platelet-activating factor. Phytochemical investigations indicated that Viscum coloratum helps to show the inhibitory effect on PAF and also the antioxidative activities.

A HPLC with UV detector was used to determine the pharmacokinetic parameters of HEDT-Glu (13.2 mg/kg) after intravenous injection. The system was equipped with a Diamonsil C18 column (200 × 4.6 mm i.d., 5 μm). A mobile phase consisted of methanol-water-glacial acetic acid (45:55:0.5, v/v/v). The flow rate, column temperature, and UV detector wavelength are 1.0 mL/min, 30 °C, and 284 nm, respectively. HEDT-Glu identification was carried out by MS (Finnigan TSQ), 1H- and 13C-NMR spectra (Bruker AVANCE-300). The LOQ in plasma and tissue samples are 1 and 0.5 ng, respectively. The main pharmacokinetic parameters of HEDT-Glu, are presented in Table 21. Low levels of the HEDT-Glu remained in the blood even 5 hours after intravenous administration. When s cleared from the blood, it is distributed to the liver and small intestine.

4.1. Helicia nilagirica Bedd (山龍眼科 shān lóng yè kē)

Helicid is the main chemical constituent extracted from the herb Helicia nilagirica Bedd of TCM. It is used to treat neurasthenia, neurasthenia syndrome, and vascular headache. From clinical practice it was found that helicid has significant healing effects, with no side effects on patients.

LC-ESI-MS method with negative ionization mode was used for identification and quantification of helicid in rat plasma. The pharmacokinetic parameters are also determined in rats after
Table 20
Estimated pharmacokinetic data on geniposide in rat blood following geniposide administration (10, 30, and 100 mg kg⁻¹, intravenously).

| Parameters          | Geniposide 10 mg/kg⁻¹ | Geniposide 30 mg/kg⁻¹ | Geniposide 100 mg/kg⁻¹ |
|---------------------|-----------------------|-----------------------|------------------------|
|                     | Without acupuncture   | With acupuncture      | Without acupuncture   | With acupuncture      | Without acupuncture   | With acupuncture      |
| A. Blood            |                       |                       |                        |                        |                        |                        |
| AUC (min μg/ml⁻¹)   | 417 ± 17              | 486 ± 59              | 1102 ± 32              | 1235 ± 128             | 4759 ± 601             | 4233 ± 411             |
| MRT (min)           | 15 ± 1                | 15 ± 1                | 18 ± 1                 | 17 ± 2                 | 17 ± 2                 |                        |
| Cl (ml min⁻¹ kg⁻¹)  | 24 ± 2                | 22 ± 2                | 27 ± 1                 | 26 ± 3                 |                        |                        |
| B. Liver            |                       |                       |                        |                        |                        |                        |
| AUC (min μg/ml⁻¹)   | 550 ± 107             | 637 ± 76              | –                      | –                      | –                      | –                      |
| MRT (min)           | 16 ± 2                | 19 ± 3                | –                      | –                      | –                      | –                      |
| C. Bile             |                       |                       |                        |                        |                        |                        |
| AUC (min μg/ml⁻¹)   | 1039 ± 136            | 1001 ± 90             | –                      | –                      | –                      | –                      |
| MRT (min)           | 37 ± 2                | 39 ± 1                | –                      | –                      | –                      | –                      |
| AUC liver/AUC blood | 1.34 ± 0.27           | 1.41 ± 0.24           | –                      | –                      | –                      | –                      |
| AUC bile/AUC blood  | 2.50 ± 0.33           | 2.10 ± 0.10           | –                      | –                      | –                      | –                      |

Data are expressed as mean ± standard error of the mean from six individual micro-dialysis experiments at each dose treatment.

AUC – area under the concentration-time curve; Cl – clearance; MRT – mean residence time.

intragastric administration of helicid with a single dose 50 mg/kg. The system was equipped with a Luna C18 column (150 × 2.00 mm i.d., 5 μm). A mobile phase composed of acetonitrile-0.1% ammonia solution (20:80, v/v) at a flow rate of 0.3 ml/min. The LLOQ was found to be 1 μg/L. The pharmacokinetic parameters of helicid after oral administration are presented in Table 22. The plasma concentration of helicid was much lower in humans in comparison with rats and dogs, which suggests the existence of species differences but there is no significant species difference between human and rats for the plasma protein binding of helicid.29

5. Hawthorn (山楂 shan zha)

Hawthorn (Crataegus) is widely used as a medicinal plant in folk and official medicine. There are about 16 species in China, where Crataegus Pinnatifida Bge. Var. Major N. E. Br. and Crataegus Pinnatifida Bge. (山黑果 shan li hong guo) are the two major species, named as Shanlihong and Shanzha, respectively. Hawthorn leaves flavonoids (HLF) include many types of flavonoids, e.g., vitexin-4”–O-glucoside (VGL), vitexin-2”–O-rhamnoside (VRH), vitexin, vitexin-6”–O-acetyl, rutin, hyperoside, quercitrin, and quercetin.

Table 22
Pharmacokinetic parameter of helicid after oral administration of a single dose of 100 mg.

| Parameter          | Values                        |
|--------------------|-------------------------------|
| Cmax (μ g/L)       | 10.6 ± 3.11                   |
| Tmax (h)           | 1.08 ± 0.47                   |
| t1/2 (h)           | 5.72 ± 0.89                   |
| AUC0–24 (μ g h/L)  | 37.25 ± 5.33                  |
| AUC0–∞ (μ g h/L)   | 40.34 ± 6.04                  |
| F (%)              | 48.34 in rats and 22.85 in dogs |

AUC – area under the concentration-time curve; Cmax – peak plasma concentration; Tmax – time of peak plasma concentration; t1/2 – half life; F – absolute bioavailability.

The HPLC with UV detector was used to determine the pharmacokinetic parameters of HLF. The system was equipped with reverse-phase Diamonsil TM C18 (200 × 4.6 mm i.d., 5 μm) column in presence of a guard column (Easy Guard C18 Kit, 8 × 4 mm, Dikma Technologies Inc.). The mobile phase composed of methanol-acetonitrile-tetrahydrofuran-0.5% acetic acid (1:1:19:78.6, v/v/v/v). The flow rate, column temperature, and UV detection are 0.8 ml/min, 30°C, and 330 nm, respectively. The sample injection and plasma required for both compounds are 20 μL and 100 μL, respectively. The LOQs are 0.23 μg/mL for VGL and 0.36 μg/mL for VRH and the relative standard deviations (RSDs) for both compounds are less than 20%. The pharmacokinetic parameters and dose-linear pharmacokinetics are carried out by compartmental, statistical moment (i.e., noncompartmental) analysis and least squares regression analysis, respectively. With minimum AIC values, a three-compartment open pharmacokinetic model was proposed and validated through the DAS 2.0.1. The pharmacokinetic parameters for VGL and VRH after a single intravenous administration of HLF are provided in Table 23. From the results it is found that the plasma concentrations and AUC of VGL and VRH in rat plasma were proportional to the administered doses.30

5.1. Huperzia serrata (Thumb) (千層塔 qiān céng tǎ)

Huperzia serrata (Thumb.) Trev. is a well-known TCM plant used to relieve contusions, strains, and swelling, and to treat schizophrenia. As the peripheral cholinergic effect are often observed as the main side effect for this herb in clinic practice, it was suggested that the active component from H. serrata might be studied as a new drug for the treatment of neurodegenerative disorder such as Alzheimer disease. Bis(12)-hupyridone (B12H), a homodimer by linking two hupyridone fragments derived from Hup A, is a promising candidate for acetylcholinesterase (AChE) inhibition. In addition, as a more potent and selective anti-AChE agent, chemically synthesized B12H can be more easily prepared for its further commercialization and clinical use.

A HPLC DAD system was used to determine the pharmacokinetic profiles of B12H after intravenous (5 mg/kg and 10 mg/kg) and intra-peritoneal (20 mg/kg) administration to rats. The system was equipped with an Agilent Extend C-18 analytical column (250 × 4.6 mm i.d., 5 μm) and protected with an Agilent Extend C-18 guard-column (12.5 × 4.6 mm i.d., 5 μm) maintained at 25°C. The iso-critical elution with a mobile phase of water-ACN-trifluoroacetic acid (TFA) (81:19:0.04, v/v/v) was used at a flow rate of 1.0 ml/min for the separation of analytes. The UV detector
wavelength was set at 229 nm. Pharmacokinetic parameters are calculated with a two-compartmental and/or noncompartmental approach. The LOD and LOQ of this method are 0.05 μg/mL and 0.1 μg/mL, respectively. The pharmacokinetic parameters are presented in Table 24. The pharmacokinetic data indicated that after extravascular injection B12H could be well absorbed and most of the administered drug could enter into the systemic circulation.31

### 5.2. *Isodon rubescens* (Hemsli.) (冬凌草 dòng líng cǎo)

*Isodon rubescens* (Hemsli.) Harra (Labiateae) is a perennial herb, native to China. It is one of the folk remedies for respiratory and gastrointestinal bacterial infections, inflammation, and cancer. The different diterpenoids found in the plants are lasiodonin, oridonin, poniconin, and rabdoterin A. These compounds are able to show a variety of biological actions such as antitumor, antimicrobial, anti-inflammatory, anticatastrophe, and antioxidation effects.

HPLC-ESI-MS method with positive ionization mode was used to determine pharmacokinetic profiles four diterpenoids in rat plasma after the single oral administration of *I. rubescens* ethanol extract. The system was equipped with a Diamonsil C18 (250 × 4.6 mm i.d., 5 μm) column. The mass spectrometer was operated in the chemical determination process, which was divided into three periods. A linear gradient elution of methanol containing 0.1% formic acid (A) and 0.1% [v/[v] aqueous formic acid (B) was used for the separation. The solvent flow, column temperature, and total run time between injections are 0.8 mL/min, 25°C, and 13.5 minutes, respectively. Over the range from 0.0 to 10.5 min, lasiodonin, oridonin, and internal Standards are easily detected. The pharmacokinetic parameters of the four diterpenoids after single oral administration of *I. rubescens* ethanol extract are presented in Tables 25 and 26. All four diterpenoids show good absorption with oral administration. They are easily detected in plasma after 10 minutes and eliminated quickly at a similar rate.32

### 5.3. *Isatis indigotica* L. (菘蓝 sēng lán)

Indolinone [(E,Z)-3-(4-hydroxy-3,5-dimethoxybenzylidene)indolin-2-one], is an alkaloid present in the TCM different herbs. It is present in the dried roots of *I. indigotica* L. (Brassicaceae) (板蓝根 bǎnlán gēn) and in leaves of *I. tinctoria* L. (European woad) (板蓝葉 bǎnlán yè). Indolinone is useful in the inhibition of mast cell degranulation as well as block immunoglobulin E (IgE) mediated degranulation of sensitized mast cells.

An UPLC-MS/MS method with positive ionization mode was used to determine the pharmacokinetic parameters after a single intravenous of indolinone in rats. The system was equipped with a Waters UPLC HSS T3 column (100 × 2.1 mm i.d., 1.8 μm) protected by an Acuity UPLC column in-line filter unit (0.2 μm in-line frit). Seal wash solvent was water-acetonitrile (70:30, v/v), weak and strong wash solvents was water-acetonitrile (50:50, v/v; containing 0.2% TFA) and acetonitrile-isopropanol-acetone (40:30:30, v/v/v; containing 0.2% TFA), respectively. The flow rate was set as 0.5 mL/min. The standard calibration curve of indolinone generated between 30.0 and 3000 ng/mL was found to be quadratic. The LOQ was found to be 30.0 ng/mL. Indolinone was found to be stable in rat plasma samples kept for 4 hours on the bench at room temperature, after three successive freeze/thaw cycles, and in processed plasma samples stored at circa 10°C for 4 days. The main pharmacokinetic parameters of indolinone calculated by non-compartmental analysis using Win-Nonlin software. The pharmacokinetic parameters after a single intravenous of indolinone in rats are presented in Table 27. The pharmacokinetic data indicate short half-life and a relatively high clearance.33

### 5.4. *Mangifera indica* (檬果 měng guǒ)

Mangiferin (1,3,6,7-tetrahydroxyxanthone-C-2-β-D-glucoside) is a natural glucosyl obtained from the TCM herb, *Mangifera indica*. Recently, it is found that mangiferin is a promising agent for oral diabetes treatment.

#### Table 23

Pharmacokinetic parameters for VGL and VRH in SD rats (mean ± standard deviation, n = 6) after a single intravenous administration of Hawthorn leaves flavonoids.

| Pharmacokinetic parameter | VGL (mg/kg) | VRH (mg/kg) |
|---------------------------|-------------|-------------|
| t1/2 (h)                  | 0.028 ± 0.002 | 0.029 ± 0.006 |
| tβ (h)                    | 0.251 ± 0.004 | 0.25 ± 0.037 |
| Half-life of elimination phase (t1/2 γ) (h) | 2.671 ± 0.087 | 2.146 ± 0.137 |
| Apparent volumes of distribution of the central compartments (V1) (L/kg) | 0.021 ± 0.004 | 0.024 ± 0.001 |
| CL (L/h/kg)               | 0.096 ± 0.013 | 0.101 ± 0.014 |
| AUC∞ (mg h/L)             | 4.492 ± 0.54 | 9.337 ± 1.215 |
| AUC0 (mg h/L)             | 5.60 ± 0.778 | 10.578 ± 1.507 |
| MRT (h)                   | 1.268 ± 0.0 | 1.478 ± 0.032 |

AUC – area under the concentration-time curve; MRT – mean residence time.

#### Table 24

Pharmacokinetic parameters were calculated with two-compartmental and/or noncompartmental approach. Absolute bioavailability (F) was calculated as the ratio of the dose-normalized AUC0–∞ after i.p. injection (10 or 20 mg/kg) to that after bolus intravenous injection (5 mg/kg) of B12H.

| Pharmacokinetic parameters | Route of administration | VGL (5 mg/kg) | VGL (10 mg/kg) | VGL (20 mg/kg) |
|----------------------------|-------------------------|---------------|----------------|---------------|
| A z (L/min)                | Intravenous             | 0.0050 ± 0.0005 | 0.0045 ± 0.0009 | 0.0059 ± 0.0008 |
| AUC0–∞ (min μg/mL)         | Intrapertioneal         | 62.62 ± 5.47  | 96.15 ± 20.67  | 219.92 ± 8.78  |
| AUC0–∞ (min μg/mL)         | Intravenous             | 82.50 ± 8.55  | 125.73 ± 28.92 | 266.12 ± 13.14 |
| MRT (h)                    | –                       | 2.67 ± 0.18    | 3.84 ± 0.37    | 3.14 ± 0.37    |
| Cmax (μg/mL)               | –                       | 0.93 ± 0.23    | 1.91 ± 0.29    |
| tmax (min)                 | –                       | 9.33 ± 6.25    | 4.75 ± 2.36    |
| t1/2 (h)                   | –                       | 2.35 ± 0.29    | 2.63 ± 0.49    | 1.99 ± 0.29    |
| CL (L/kg min kg)           | –                       | 0.061 ± 0.006  | 0.055 ± 0.016  | 0.093 ± 0.005  |
| Vd (L/kg)                  | –                       | 12.35 ± 1.24   | 12.09 ± 1.72   | 16.06 ± 1.86   |
| F (%)                      | –                       | 76.2           | 80.7           |

AUC – area under the concentration-time curve; MRT – mean residence time; Cmax – maximum blood concentration; tmax – time to peak concentration; t1/2 – elimination half-life; Vd – the volume of distribution; CL – total blood clearance; F – absolute bioavailability.

#### Table 25

Pharmacokinetic parameters of the four diterpenoids after single oral administration of *I. rubescens* ethanol extract are presented in Tables 25 and 26. All four diterpenoids show good absorption with oral administration. They are easily detected in plasma after 10 minutes and eliminated quickly at a similar rate.

#### Table 26

Waters Corp., Milford, MA, USA) at 4°C. The 5.3. Isatis indigotica L. (菘蓝 sēng lán)

Indolinone [(E,Z)-3-(4-hydroxy-3,5-dimethoxybenzylidene)indolin-2-one], is an alkaloid present in the TCM different herbs. It is present in the dried roots of *I. indigotica* L. (Brassicaceae) (板蓝根 bǎnlán gēn) and in leaves of *I. tinctoria* L. (European woad) (板蓝葉 bǎnlán yè). Indolinone is useful in the inhibition of mast cell degranulation as well as block immunoglobulin E (IgE) mediated degranulation of sensitized mast cells.

An UPLC-MS/MS method with positive ionization mode was used to determine the pharmacokinetic parameters after a single intravenous of indolinone in rats. The system was equipped with a Waters UPLC HSS T3 column (100 × 2.1 mm i.d., 1.8 μm) protected by an Acquity UPLC column in-line filter unit (0.2 μm in-line frit). Seal wash solvent was water-acetonitrile (70:30, v/v), weak and strong wash solvents was water-acetonitrile (50:50, v/v; containing 0.2% TFA) and acetonitrile-isopropanol-acetone (40:30:30, v/v/v; containing 0.2% TFA), respectively. The flow rate was set as 0.5 mL/min. The standard calibration curve of indolinone generated between 30.0 and 3000 ng/mL was found to be quadratic. The LOQ was found to be 30.0 ng/mL. Indolinone was found to be stable in rat plasma samples kept for 4 hours on the bench at room temperature, after three successive freeze/thaw cycles, and in processed plasma samples stored at circa 10°C for 4 days. The main pharmacokinetic parameters of indolinone calculated by non-compartmental analysis using Win-Nonlin software. The pharmacokinetic parameters after a single intravenous of indolinone in rats are presented in Table 27. The pharmacokinetic data indicate short half-life and a relatively high clearance.
The elution started with 90% B then the composition was linearly changed to 30% B over 0.5 minutes and maintained at the level for 1.4 minutes. Finally, the composition was returned to the initial composition over 0.1 minutes and maintained for 1.0 min. The oral bioavailability was found to be 12%. The LLOQ (0.02 and 0.4 ng/mL) was defined as the lowest concentration on the calibration curves. The pharmacokinetic parameters are calculated applying a non-compartmental model. The pharmacokinetic parameters of mangiferin after oral and intravenous administration to rats are presented in Table 28. The oral bioavailability of mangiferin was found to be 1.2%. To improve the oral bioavailability of mangiferin chemical and pharmaceutical modification may be useful.34

5.5. Pueraria lobata (Willd) (大葛藤 dà gé téng)

Kakkalide (KA) is the major isoflavone found in extracts from the dried flower of Pueraria lobata (Willd.). It is one of the TCM herbal remedies for symptoms associated with excessive alcohol intake, such as drunkenness, headache, red face, and liver injury. Three known glucuronide metabolites are irisinolidone-7-O-glucuronide (Ir-7G), tectorigenin-7-O-glucuronide (Te-7G), and 6-OH biochanin A-glucuronide (6-OH BiA-G). A LC-MS/MS was used to determine the pharmacokinetic parameters for KA and its metabolites in rat plasma. LC/MSD (Agilent 1100 Series) Trap was operated at negative ESI interface. The system was equipped with a Kromasil (Tianjin Scientific Instruments Co. Ltd., China) C18 column (4.6 × 200 mm i.d., 5 μm) at 35°C. The mobile phase was composed of acetonitrile containing 0.05% TFA (A) and water containing 0.05% TFA (B), eluted in a gradient way. For the identification of irisolide, the mobile phase consisting of solutions A and B was run in isocratic mode in the ratio of 44:56 (v/v). The known glucuronide metabolites are irisolidone-7-O-glucuronide (Ir-7G), tectorigenin-7-O-glucuronide (Te-7G), and 6-OH biochanin A-glucuronide (6-OH BiA-G) (Table 29). After oral administration of KA in rats, Phase II metabolism occurs in different sites, may occur in different sites, and may be useful.34

Table 25
Pharmacokinetic parameters of the four diterpenoids in six rats plasma after single oral administration of I. rubescens extract 10 mL/kg (n = 6).

| Pharmacokinetic parameter | Compound          | Lasiodamin | Oridonin | Poncinid | Rabdotemin A |
|---------------------------|------------------|------------|----------|----------|--------------|
| Cmax (ng/mL) (means ± SD) | 1300.71 ± 365.53 | 1916.33 ± 307.20 | 1582.83 ± 307.20 | 385.01 ± 58.35 |
| Tmax (min)                | 105              | 105        | 120      | 105      |
| t1/2 (min) (means ± SD)   | 40.98 ± 9.12     | 45.14 ± 11.42 | 40.26 ± 9.05 | 58.04 ± 12.02 |
| K (1/min) (means ± SD)    | 0.0177 ± 0.0045  | 0.0161 ± 0.0037 | 0.0179 ± 0.0035 | 0.0124 ± 0.0024 |
| AUCC0-t (ng/mL) (means ± SD) | 96990.82 ± 26493.23 | 147256.30 ± 34444.80 | 115040.74 ± 15237.04 | 289586.33 ± 55303.37 |
| AUCC0-t (ng/mL) (means ± SD) | 97916.68 ± 5348.35 | 144527.30 ± 33606.69 | 116425.80 ± 15969.54 | 295221.15 ± 5348.35 |

AUC — area under the concentration-time curve; SE — standard deviation; Cmax — maximum blood concentration; Tmax — time to peak concentration; t1/2 — half-life.

Table 26
Lower limit of quantification and limit of detection for given diterpenoids compounds.

| Compound      | LLOQ (ng/mL) | LOD (ng/mL) |
|---------------|--------------|-------------|
| Lasiodamin    | 2.24         | 0.540       |
| Oridonin      | 4.92         | 0.826       |
| Poncinid      | 5.32         | 0.736       |
| Rabdotemin A  | 1.36         | 0.452       |

Data were calculated using non-compartmental analysis. AUC — area under the concentration-time curve; MRT — mean residence time; SE — standard error; Cmax — initial plasma concentration; t1/2 — half-life; CL — total blood clearance and K — elimination rate constant.

Table 27
Pharmacokinetic parameters after a single intravenous dose of 2 mg/kg indololine in rats (n = 4).

| Parameters      | Mean      | SE     |
|-----------------|-----------|--------|
| C0 (ng/mL)      | 5205      | 2232   |
| T1/2 (min)      | 4.30      | 0.14   |
| Ke (1/h)        | 9.53      | 0.21   |
| AUCC0-t (ng h/mL) | 561       | 166    |
| AUCC0-t (ng h/mL) | 568       | 162    |
| MRT (min)       | 5.16      | 0.39   |
| Vz (L/kg)       | 0.39      | 0.15   |
| CL (L/h/kg)     | 3.38      | 1.46   |

Table 28
Pharmacokinetic parameters of mangiferin after oral and intravenous administration to rats.

| Parameter       | Oral administration (n = 6) | Intravenous administration (n = 6) |
|-----------------|-----------------------------|----------------------------------|
| AUCC0-t (μg/L h) | 1855.0 ± 887.7              | 61184.1 ± 22471.4               |
| AUCLC0-t (μg/L h) | 2095.2 ± 942.2              | 62960.2 ± 23013.2               |
| T1/2 (h)        | 3.2 ± 0.6                   | 0.9 ± 0.4                       |
| Tmax (h)        | 2.5 ± 0.8                   | 0.083                           |
| MRT0-t (h)      | 4.3 ± 0.5                   | 1.3 ± 0.2                       |
| Cmax (μg/L)     | 3.01 ± 133.0                | 67798.3 ± 31235.9               |
| CLz (L/h kg)    | (1195 ± 664) × F            | 0.15 ± 0.04                     |

AUC — area under the concentration-time curve; Cmax — peak plasma concentration; MRT — mean residence time; Tmax — time to peak plasma concentration; t1/2 — half-life.

Table 29
Pharmacokinetic parameters for kakkalide (oral 200 mg/kg⁻¹) and its metabolites in rat plasma.

| Parameters      | KA          | Ir-7G          | Te-7G          | 6-OH BiA-G      |
|-----------------|-------------|----------------|----------------|----------------|
| Tmax (h)        | 0.25 ± 0.00 | 3.40 ± 11.8    | 38.0 ± 9.0     | 36.0 ± 7.6     |
| Cmax (μg/mL)    | 0.26 ± 0.17 | 2.73 ± 0.74    | 0.55 ± 0.22    | 2.33 ± 1.29    |
| AUCC0-t (μg h/mL) | 0.24 ± 0.16 | 6.52 ± 11.7    | 17.0 ± 4.7     | 54.9 ± 26.7    |
| AUCC0-t (μg h/mL) | 0.25 ± 0.16 | 10.43 ± 38.2   | 27.2 ± 13.9    | 56.7 ± 25.7    |
| CLz (L/h kg)    | (13833 ± 1061.0) | 55.6 ± 33.4 | 472.9 ± 442.0 | 910 ± 120.4 |

AUC — area under the concentration-time curve; Cmax — peak plasma concentration; MRT — mean residence time; Tmax — time of peak plasma concentration; CLz — apparent plasma clearance; t1/2 — half-life.
in the intestine and then in the liver, and future enterohepatic recirculation prolongs the elimination of these glucuronide metabolites.\textsuperscript{35}

5.6 Pueraria thomsonii (大薔薇 dà gè tèng)

The isoflavone tectoridin is present in large quantities in the flowers of Pueraria thomsonii Benth, a TCM plant. It is useful in the treatment of various disorders such as diabetes, and excessive alcohol intake disorders such as drunkenness, headache, red face, and liver injury. Tectoridin possesses hepatoprotective, estrogenic, antihypolipidemic, antioxidative, and anti-inflammatory properties. The various metabolites of tectoridin are tectorigenin-7-O-glucuronide (Te-7G), and tectorigenin-7-O-sulfate (Te-7S). Pharmacokinetic parameters of paeonol in rat plasma after single oral administration of paeonol alone and paeonol contained in the herbal preparation Qingfu Guanjieshu.

Table 31 Pharmacokinetic parameters of paeonol in rat plasma after single oral administration of paeonol alone and paeonol contained in the herbal preparation Qingfu Guanjieshu.

| Parameters | 35 mg/kg | 70 mg/kg | 140 mg/kg | QFGJS 3.89 g/kg |
|------------|----------|----------|----------|----------------|
| C\textsubscript{max} (µg/mL) | 0.73 ± 0.07 | 2.02 ± 0.23 | 4.16 ± 0.50 | 8.61 ± 1.30** |
| T\textsubscript{max} (min) | 9.00 ± 2.45 | 5.00 ± 0.00 | 7.00 ± 2.00 | 5.00 ± 0.00 |
| T\textsubscript{1/2} E phase (min) | 34.25 ± 3.91 | 34.18 ± 1.77 | 50.13 ± 4.11 | 38.25 ± 2.99 |
| T\textsubscript{1/2} D/A phase (min) | 12.02 ± 1.73 | 12.74 ± 1.69 | 12.79 ± 1.81 | 11.66 ± 0.62 |
| V\textsubscript{d} (mL/kg) | 2.60 ± 0.53 | 1.92 ± 0.44 | 2.51 ± 0.38 | 1.58 ± 0.21 |
| MRT (min) | 51.82 ± 8.66 | 36.65 ± 2.18 | 56.14 ± 3.13 | 37.43 ± 2.58 |
| Vd (mL/kg) | 47.170 ± 598.4 | 48.628 ± 80.8 | 48.329 ± 60.4 | 8.034 ± 1.498* |
| CL/F (mL/min kg) | 1016.8 ± 167.7 | 1003.4 ± 110.5 | 761.0 ± 70.6 | 342.2 ± 39.8** |
| AUC\textsubscript{0-1} (µg min/mL) | 46.06 ± 9.99 | 74.13 ± 8.68 | 188.50 ± 16.35 | 229.64 ± 27.38** |
| AUC\textsubscript{0-2} (µg min/mL) | 40.72 ± 10.01 | 74.38 ± 8.77 | 189.22 ± 16.47 | 229.88 ± 27.46** |

Data are expressed as the mean ± standard error of the mean of 6 to 8 rats. Paeonol contained in QFGJS at dosage of 3.89 g/kg is equivalent to 70 mg/kg pure paeonol to rat. *p is significantly different from that of the paeonol alone [at a dosage of 70 mg/kg] group by Student t test. **p < 0.05; ***p < 0.001.

5.7 Paeonia suffruticosa (牡丹 mǔ dān)

Paeonol (2′-hydroxy-4′-methoxycetophenone) is a major component in the medicinal herb Moutan Cortex, the root cortex of Paeonia suffruticosa A. (Paeoniaceae) (牡丹皮 mǔ dān pi). It is commonly prescribed for the treatment of pain and inflammatory ailments in Chinese medicine. A HPLC-DAD method was used to determine pharmacokinetic profiling of pure paeonol including its metabolites and herbal preparation. The system was equipped with a Phenomenex ODS (250 × 4.6 mm i.d., 5 µm, Phenomenex Inc., USA) protected by a Security Guard Cartridge (C18, 4.0 × 3.0 mm i.d.; Phenomenex Inc.). The mobile phase composed of acetonitrile (A) and aqueous solution containing 0.1% formic acid (B) (pH adjusted to 3.5 ± 0.2 by triethylamine). At normal room temperature flow rate, injection volumes and wavelength for detection are 1.0 mL/min, 50 µL, and 270 nm, respectively. The LLOQ in rat plasma was found to be 0.15 µg/mL of paeonol. Pharmacokinetic parameters are calculated based on the noncompartmental method. The pharmacokinetic parameters of paeonol in rat plasma after single oral administration of paeonol alone and paeonol contained in the herbal preparation Qingfu Guanjieshu (QFGJS) are presented in Table 31. After oral administration of paeonol and QFGJS in rats, five metabolites of paeonol, P1–P5, were identified in rat urine. The relative plasma concentration of these metabolites was found to be significantly higher in rats treated with QFGJS than those treated with pure paeonol at a comparable dose. Four metabolites, P2–P5, appeared as soon as 5 minutes after dosing and reached the maximum plasma concentrations in approximately 20 minutes. This study indicating that paeonol could quickly be metabolized into P2–P5 and circulate in the blood and/or the tissues and organs, but metabolite P1 is not found in plasma.\textsuperscript{37}
5.8. Pulsatilla koreana (白頭翁 bài tóu wēng)

_Pulsatilla koreana_ Nakai (Ranunculaceae) is a traditional Korean herbal medicine used to treat amoebic dysenteries and malaria. A standardized extract of _P. koreana_, SK-PC-B70M, improves scopolamine-induced impairments of memory consolidation and spatial working memory. Oleanolic-glycoside saponins, especially hederacolchiside E, are not only the major constituents but also the marker compounds for the SK-PC-B70M. Hederacolchiside E is an essential saponin that helps facilitate detailed pharmacokinetic study and also future preclinical or clinical investigation of SK-PC-B70M.

A LC-MS/MS with negative EIS was used to determine pharmacokinetic parameters of hederacolchiside E after oral administration. The system was equipped with a Waters Acquity UPLC (Waters Corporation, Milford, MA, USA) consisting of a Waters Acquity I-Class MS Manager and a Waters Acquity UPLC system equipped with a Zorbax SB C18 as the stationary phase. The mobile phase consisted of acetonitrile-water (40:60, v/v) containing 5 mM ammonium acetate and 0.2% glacial acetic acid. The flow rate was 300 μL/min. Solvent (B) was gradually increased to 60% for 0.5 minutes, maintained for 0.5 minutes, and followed by a 15-minute re-equilibration. Injection volume and column oven temperature were 2 μL and 50°C, respectively. LLOQ and LOD are found to be 2 ng/mL in 20 μL of plasma and 0.5 ng/mL, respectively. Plasma concentration data were analyzed using a noncompartmental method. The pharmacokinetic parameters of hederacolchiside E after oral administration of SKPC-B70M in male Sprague Dawley rats are presented in Table 32. The pharmacokinetic data indicate the nonlinear pharmacokinetic pattern.38

5.9. Rhizoma Corydalis Decumbentis (夏天無 xià tiān wú)

Tetrahydropalmatine, protopine, and palmatine are the chemical moieties found in TCM herb, i.e., *Rhizoma Corydalis Decumbentis*. It is commonly used for the treatment of hemiplegia, rheumatoid arthritis, and infantile residual paralysis, to counteract the effects of dementia and hepatotoxicity, and for pain relief.

A LC-ESI-MS with a positive ion mode was used for quantification and to determine the pharmacokinetic profile for the three alkaloids, tetrahydropalmatine, protopine, and palmatine, in rat plasma. The system was equipped with a Diomassil C18 column (250 × 4.6 mm, i.d., 4.6 μm, YMC Co., Ltd., Kyoto, Japan). Nitrogen (99.999%) was used as the nebulizing turbo spray and curtain gas, with the optimum values set at 60, 60, and 20 (arbitrary units), respectively. The HPLC mobile phases consisted of 0.1% formic acid: tetrahydrofuran (FA:THF) (90:10) (A) and acetonitrile:0.1% FA:THF (90:10:10) (B). A linear gradient program was used with flow rate of 0.5 mL/min. Solvent (B) was gradually increased 60% for 0.5 minutes, maintained for 0.5 minutes, and followed by a 1.5-minute re-equilibration. Injection volume and column oven temperature are 2 μL and 50°C, respectively. LLOQ and LOD are found to be 2 ng/mL in 20 μL of plasma and 0.5 ng/mL, respectively. Plasma concentration data were analyzed using a noncompartmental method. The pharmacokinetic parameters of hederacolchiside E after oral administration of SKPC-B70M in male Sprague Dawley rats are presented in Table 32. The pharmacokinetic data indicate the

| Parameter | Tetrahydropalmatine | Protopine | Palmatine |
|-----------|---------------------|-----------|-----------|
| t1/2 (h)  | 6.88 ± 0.64         | 4.98 ± 1.64 | 12.84 ± 4.58 |
| Tmax (h)  | 1.50 ± 1.14         | 3.50 ± 0.55  | 1.92 ± 0.74 |
| Cmax (ng/mL⁻¹) | 435.8 ± 58.5 | 347.9 ± 51.5 | 8.53 ± 2.95 |
| MRT (h)   | 7.21 ± 0.21         | 7.36 ± 0.64  | 8.10 ± 1.07 |
| AUC₁₋₂ (ng/h/mL) | 9.32 ± 0.58 | 8.84 ± 1.88  | 16.89 ± 6.27 |

AUC = area under the concentration-time curve; Cmax = peak plasma concentration; MRT = mean residence time; Tmax = time of peak plasma concentration; t1/2 = terminal elimination half-life.

58. Esterification of the free carboxyl group liberates two ester prodrugs of RE, i.e., rhein methylate; Tmax = time of peak plasma concentration; t1/2 = half life.

6. Rhein

Rhein (RE, 1,8-dihydroxy-3-carboxyxyanthraquinone) is an active ingredient extensively found in plants such as Aloe (薈 lú huì), Rhusbarb (薈 tá huáng), and Cassiator L. It is currently used for treating diabetic nephrosis in clinical practice and for broad pharmacological activities, including anti-tumor, anti-inflammatory, antibacterium, and renal protection properties. Esterification of free carboxyl group liberates two ester prodrugs of RE, i.e., rhein methylate (REM) and rhein ethylate (REE).

A HPLC with Shimadzu RF-10AD fluorescence detector was used to perform the comparative pharmacokinetic study of RE, REM, and REE. The system was equipped with Shimadzu LC-10AT isocratic pump, Shimadzu SIL-10AD auto-injector, HS chromatography integrator, and a Hypersil ODS2 (4.6 × 250 mm, i.d. 5 μm, Dalian Elite Analytical Instruments Co., China). The mobile phase was composed of a mixture of acetonitrile: methanol: 0.3% acetic acid (15:61:24, V/V/V) at a flow rate of 1.2 mL/min. The excitation and emission wavelengths are set at 440 nm and 520 nm, respectively. The retention time of RE, IS, REM, and REE was 4.2, 6.2, 6.8 and 8.6 minutes, respectively. LLOQ for RE, REM, and REE was 0.005, 0.020, and 0.020, respectively. The pharmacokinetic parameters of rhein are provided in Table 34. The carboxyesterification significantly reduced the net exposure amount of rhein in vivo, leading to its inaptitude in the development of drug precursors of RE.40

| Administration route | Parameters | RE | REM | REE |
|----------------------|------------|----|-----|-----|
| i.g.                 | T<sub>max</sub> (h) | 0.9 ± 0.1 | 6.7 ± 2.3* | 10.7 ± 2.3** |
|                     | C<sub>max</sub> (mg/L) | 42.66 ± 14.11 | 0.058 ± 0.035** | 0.95 ± 0.090** |
|                     | t<sub>1/2</sub> (h) | 0.2 ± 0.1 | 4.1 ± 1.6* | 3.0 ± 0.5** |
|                     | t<sub>1/2</sub> (h) | 1.1 ± 0.8 | 5.7 ± 1.6* | 1.5 ± 0.6 |
|                     | t<sub>1/2</sub> (h) | 3.2 ± 0.6 | 6.0 ± 1.7* | 6.4 ± 1.0** |
|                     | CL(1/kg) | 0.78 ± 0.28 | 79.65 ± 66.61** | 5.21 ± 0.51* |
| i.v.                 | AUC<sub>0–t</sub> | 80.28 ± 13.59 | 1.03 ± 0.76** | 12.79 ± 0.96* |
|                     | (h·mg/L) | 0.1 ± 0.04 | 0.6 ± 0.4* | 0.2 ± 0.1 |
|                     | t<sub>1/2</sub> (h) | 0.4 ± 0.1 | 3.8 ± 0.8* | 2.9 ± 1.6* |
|                     | CL<sub>0</sub> (L/h) | 3.6 ± 0.11 | 0.93 ± 0.54 | 1.95 ± 0.68* |
|                     | AUC<sub>0–t</sub> | 2.40 ± 1.15 | 0.84 ± 0.40* | 0.36 ± 0.092* |

AUC = area under the concentration-time curve; C<sub>max</sub> = peak plasma concentration; i.g. = intragastric administration; i.v. = intravenous; RE = rhein; REM = rhein ethylate; REM = rhein methylate; T<sub>max</sub> = time of peak plasma concentration.

Table 33

| Parameter | Mean pharmacokinetic parameters of three alkaloids after oral administration of _Rhizoma Corydalis Decumbentis_ extract at 2.0 g kg⁻¹ to rats (n = 6). |
|-----------|---------------------------------------------------------------|
| Parameter | Tetrahydropalmatine | Protopine | Palmatine |
|-----------|---------------------|-----------|-----------|
| t1/2 (h)  | 6.88 ± 0.64         | 4.98 ± 1.64 | 12.84 ± 4.58 |
| Tmax (h)  | 1.50 ± 1.14         | 3.50 ± 0.55  | 1.92 ± 0.74 |
| Cmax (ng/mL⁻¹) | 435.8 ± 58.5 | 347.9 ± 51.5 | 8.53 ± 2.95 |
| MRT (h)   | 7.21 ± 0.21         | 7.36 ± 0.64  | 8.10 ± 1.07 |
| AUC₁₋₂ (ng/h/mL) | 9.32 ± 0.58 | 8.84 ± 1.88  | 16.89 ± 6.27 |

AUC = area under the concentration-time curve; Cmax = peak plasma concentration; i.g. = intragastric administration; i.v. = intravenous; RE = rhein; REM = rhein ethylate; REM = rhein methylate; Tmax = time of peak plasma concentration.
管,
Reverse phase-HPLC was used to determine the concentrations and pharmacokinetic parameters after oridonin was injected in rat plasma. The system was equipped with analytical DIKMA ODS C18 column (200 × 4.6 mm, 5 μm) with a DIKMA ODS C18 (4.6 × 12.5 mm i.d.) precolumn. The mobile phase was composed of acetonitrile-0.01M ammonium acetate (0.5% acetic acid) (30:70, v/v). The flow rate, column temperature, and UV detector wavelength are 1.0 mL/min, 25°C, and 238 nm, respectively. After tail vein injection of oridonin at 12.5 mg/kg dose in rats, oridonin in plasma are determined for a series of time points within 24 hours. The LOD and LLOQ are found to be 0.025 and 0.05 μg/mL, respectively. The two-compartment open model was used to determine the plasma oridonin concentration-time curve. The pharmacokinetics parameters calculated for intravenous administration of oridonin in rat are presented in Table 38. The oridonin is distributed quickly and was eliminated slowly in rats. The volume of distribution indicates that it might accumulate in certain organs or metabolize in the plasma.43

6.4. Saposhnikovia divaricata (Turcz.) Schischk.

Fangfeng, the root of Saposhnikovia divaricata (Turcz.) Schischk., is listed as a high-grade drug, which means high effectiveness and little toxicity in TCM. It is widely applied for headache, fever, vertigo, and arthralgia due to wind, cold, and dampness in China, Japan, and other Asian countries. Prim-O-glucosylcimifugin and 4-O-D-glucosyl-5-O-methylvisamminol are the two major active chromones isolated from Fanfeng, which possess the analgesic, anti-inflammatory effect and suppression of platelet aggregation, and they may possess potential clinical applications such as treating acute and dull aching, infarction, and anti-inflammatory conditions.

HPLC/MS was used to determine the pharmacokinetic parameters and simultaneous detection of prim-O-glucosylcimifugin and 4-O-D-glucosyl-5-O-methylvisamminol in rat plasma and urine after single oral administration of Fangfeng extract. The system was equipped with an Agilent TC-C18 column (150 × 4.6 mm i.d., 5 μm), and with an ODS security guard column (10 × 4.6 mm i.d., 5 μm, Zhonghuida Co., China). The gradient mobile phase was composed of a methanol-water mixture containing 0.1% formic acid with a flow rate of 0.8 mL/min. The LLOQ of prim-O-glucosylcimifugin and 4-O-D-glucosyl-5-O-methylvisamminol was 1.0 ng/mL and 1.5 ng/mL in plasma, 10 ng/mL and 15 ng/mL in urine, respectively. The percent of two drugs excreted in the urine over the dose administered was 49.42% and 56.69% following oral administration. The pharmacokinetic parameters of prim-O-glucosylcimifugin and 4-O-D-glucosyl-5-O-methylvisamminol in rats after oral administration of Fangfeng extract are presented in Table 39. In this study, other than mentioned chromones two metabolites are also found, which need to be studied in detail.44

6.5. S. japonica, S. mileensis (青葉膽 qing yè dàn), and S. chirata

Different plants of Swertia spp. S. japonica, S. mileensis, and S. chirata (Gentianaceae) are well known in TCM and other Asian countries. These plants exhibit hepatoprotective, anti-edematogenic, antihypolidemic, anti-spastic, anticholinergic, anti-nociceptive, antibacterial, anti-inflammatory, and anti-oxidant properties.

A LC-MS/MS method was used to determine pharmacokinetic parameters and quantification of swertiamarin in rats after oral administration. The system was equipped with a G6410B triple quadrupole mass spectrometer (Agilent), an ESI source, and an Agilent ZORBAX ECLIPSE XDB-C18 (100 × 2.1mm i.d., 1.8 μm) column. The isocratic elution of mobile phase was composed of methanol and water containing 0.1% acetic acid (25:75, v/v). The flow rate, column temperature, and internal standards are 0.2 mL/min, 40°C, and gentiopicroside, respectively. Pharmacokinetic parameters are calculated by using a noncompartmental model. The LLOQ was 5 ng/mL within a linear range of 5–1000 ng/mL (n = 7, r2 ≥ 0.994), and the LOD was 1.25 ng/mL (S/N ≥ 3). The pharmacokinetic parameters of swertiamarin after oral administration in rats are presented in Table 40. The pharmacokinetic data revealed that swertiamarin was rapidly absorbed into the circulation system after oral administration but it showed a short half-life of 1.50 hours. The absolute bioavailability of swertiamarin is around 10.3%. After oral administration to rats, it was rapidly and widely distributed in tissues. High concentrations were found in the liver and kidney, indicating that swertiamarin was possibly absorbed in the liver and eliminated by the kidney.46

6.6. Strychnos nux vomica L. (馬錢子 mà qián zi)

Semen Strychni is the dried mature seed of Strychnos nux vomica L., a tree native in India. In classic Chinese Materia Medica, the herbal drug is listed as a toxic herb and its biological effects (pharmacological and toxic effects) are dose dependent, needing to be processed to reduce the toxicity before clinical uses required by Chinese medicine prescriptions. Processed Semen Strychni is

![Table 38](image1)

| Parameter   | Value |
|-------------|-------|
| Cmax (ng/mL) | 39.92  |
| Tmax (h)    | 0.54   |
| CL (L/kg)   | 66.77  |
| AUC (ng h/mL) | 75.63  |

AUC = area under the concentration-time curve; Cmax = peak plasma concentration; Tmax = time of peak plasma concentration.

| Parameter   | Value |
|-------------|-------|
| T1/2 (h)    | 1.31   |
| Cmax (ng/mL) | 39.92  |
| Tmax (h)    | 0.54   |
| CL (L/kg)   | 66.77  |
| AUC (ng h/mL) | 75.63  |

AUC = area under the concentration-time curve; Cmax = peak plasma concentration; Tmax = time of peak plasma concentration.

![Table 39](image2)

| Parameters | Compounds |
|------------|-----------|
| Prim-O-glucosylcimifugin | 4-O-D-glucosyl-5-O-methylvisamminol |
| T1/2 (h)    | 1.31     |
| Cmax (ng/mL) | 39.92  |
| Tmax (h)    | 0.54     |
| CL (L/kg)   | 66.77    |
| AUC (ng h/mL) | 75.63  |

| Parameters | Value |
|------------|-------|
| CLz/F (L/h/kg) | 5.638 ± 4.322 |
| MRT0e (h)   | 1.929 ± 0.364 |
| Tmax (h)    | 0.945 ± 0.136 |
| Cmax (μg/L) | 1920.1 ± 947.0 |

AUC = area under the concentration-time curve; Cmax = peak plasma concentration; MRT = mean residence time; SD = standard deviation; Tmax = time of peak plasma concentration; CL/F = Apparent clearance; CL = Clearance; T1/2 = Half-life.

![Table 40](image3)

| Parameters | Mean ± SD |
|------------|-----------|
| Prim-O-glucosylcimifugin | 4-O-D-glucosyl-5-O-methylvisamminol |
| T1/2 (h)    | 1.104 ± 0.229 |
| CLz/F (L/h/kg) | 9.637 ± 4.322 |
| MRT0e (h)   | 5.638 ± 2.151 |
| Tmax (h)    | 1.929 ± 0.364 |
| CLz/F (L/h) | 3593.7 ± 985.4 |
| Cmax (μg/L) | 1920.1 ± 947.0 |

AUC = area under the concentration-time curve; Cmax = peak plasma concentration; MRT = mean residence time; SD = standard deviation; Tmax = time of peak plasma concentration; CL/F = Apparent clearance; CL = Clearance; T1/2 = Half-life.

![Table 41](image4)

| Parameters | Value |
|------------|-------|
| CLz/F (L/h/kg) | 5.638 ± 2.151 |
| MRT0e (h)   | 1.929 ± 0.364 |
| Tmax (h)    | 0.945 ± 0.136 |
| Cmax (μg/L) | 1920.1 ± 947.0 |

AUC = area under the concentration-time curve; Cmax = peak plasma concentration; MRT = mean residence time; SD = standard deviation; Tmax = time of peak plasma concentration; CL/F = Apparent clearance; CL = Clearance; T1/2 = Half-life.
clinically used as an important ingredient in various remedies of traditional herbal medicines to treat nervous diseases, vomiting, arthritis, and pain from trauma, and to promote blood circulation and remove blood stasis. The most abundant alkaloids existing in the processed *Semem Strychni* are strychnine and brucine, which have been reported to possess analgesic, anti-inflammatory, and antitumor effects despite their toxicity.

LC-ESI-MS with positive electrospray ionization was used for simultaneous determination of strychnine, brucine, and pharmacokinetic parameters after oral administration of processed *Semem Strychni* to Wistar rats. The system was equipped with a Waters Symmetry TM C18 column (100 × 4.6 mm i.d., 5 µm) kept at 30°C. The mobile phase was composed of methanol, 20mM ammonium formate, and formic acid (32:68:0.68, v/v/v) with a flow rate of 0.4 mL/min. The mean maximum plasma concentrations of strychnine and brucine detected in the rats are 54.93 and 4.95 ng/mL, respectively. Higher sensitivity was offered, with LLOQ of 0.5 ng/mL, respectively. Stricthnine and brucine detected in the rats are 54.93 and 4.95 ng/mL, respectively. Higher sensitivity was offered, with LLOQ of 0.5strapline L. (Thymelaeaceae) is one of the toxic TCM listed in the Chinese Pharmacopeia. In recent years, it has also been used for the treatment of intestinal, gastric, and pulmonary cancers. Chamaechromone is a major biflavone constituent in dried roots of *S. chamaejasme*. The plant also shows anti-inflammatory, antioxidant, cytotoxic, and antioxidative activity because of its biflavones and flavonoids contents.

A LC-MS with a positive ESI in MRM mode was used to determine the pharmacokinetics and absolute bioavailability chamaechromone in rat plasma. The system was equipped with an Xbridge TM C18 column (21.1 × 50 mm i.d., 3.5 µm, Waters). The mobile phase consisted of methanol-water containing 0.1% formic acid with a gradient elution starting at 5% methanol and progressing linearly to 90% methanol over 5.0 minutes, then returning to 5% methanol. Total run time was 6 minutes. The mobile phase was delivered at a flow rate of 0.4 mL/min. Rats receive 100 mg/kg chamaechromone by oral administration or intravenous injection of 5 mg/kg via the tail vein to determine the plasma concentration of chamaechromone in rats. The LLOQ of chamaechromone was 8 ng/mL. The pharmacokinetic parameters of chamaechromone in rats following intravenous and oral administration are provided in Table 41. The absolute bioavailability of chamaechromone was found to be 8.9%. Its poor absorption may be due to poor permeability through the intestinal epithelial membrane and efficient metabolism in the intestine, which is a common reason for low bioavailability of flavanoid compounds.

### 6.7. *Stellera chamaejasme* L. (鹿毒 lăng dû)

*Stellera chamaejasme* L. (Thymelaeaceae) is one of the toxic TCM used for the treatment of intestinal, gastric, and pulmonary cancers. Chamaechromone is a major biflavone constituent in dried roots of *S. chamaejasme*. The plant also shows anti-inflammation, antioxidant, cytotoxic, and antioxidative activity because of its biflavones and flavonoids contents.

6.8. *Salvia miltiorrhiza* Bge (丹参 *dān shēn*)

The Chinese medicine, *dān shēn*, is the dried root and rhizome of *Salvia miltiorrhiza* Bge (Labiatae). Traditionally, *dān shēn* is believed to be effective in eliminating blood stasis, relieving pain, promoting blood flow, and stimulating menstrual discharge as well as easing the mind. Magnesium lithospermate B (MLB) has been found to have strong antioxidative and free-radical scavenging effects.

The LC-MS/MS method was used to determine the pharmacokinetics of MLB after intravenous administration and also detect the serum concentrations of MLB in beagle dogs. The system was equipped with CAPCELL PAK C18 column (50 × 2 mm i.d., 5 µm) and a Phenomenex C18 guard column. The mobile phase composed of 56% water (containing a mass fraction of 0.5% formic acid) and 44% acetonitrile at a flow rate 0.25 mL/min for an isocratic elution at room temperature. The pharmacokinetic parameters of MLB after intravenous administration in beagle dogs are presented in Table 42. This study indicates that MLB is rapidly distributed and metabolized in tissues and at a high dose, it shows saturated distribution. The catechol O-methyltransferase is responsible for formation of four (M1-M4) methylated metabolites in rats. The rapid and high biliary excretion levels of these metabolites suggested that they could undergo enterohepatic circulation and that they might thereby be largely responsible for the pharmacological effects of MLB.

### 6.9. *Salvia miltiorrhiza* Bge (丹参 *dān shēn*)

- **R**-(+)-β-(3,4-dihydroxyphenyl)-lactic acid [named Danshensu (Dhp)] and protocatechuic aldehyde (Pal) have been considered the major active constituents of *Salvia miltiorrhiza* Bge (Labiatae). Danshen (roots) of the plant has been used in TCM to treat coronary diseases, particularly angina pectoris and myocardial infarction. This plant also exhibits anticoagulant, antiarteriosclerotic, anti-inflammatory, and antithyopxic qualities.

The HPLC/UV method was used to determine the pharmacokinetic parameters of Dhp and Pal. The system was equipped with an

### Table 41

| Parameter                  | Oral   | Mean ± SD                  | Intraoral | Mean ± SD                  |
|----------------------------|--------|----------------------------|-----------|----------------------------|
| C_{max} (ng/L)             | 795.9 ± 14.6 | 4300.7 ± 113.6            |           |                            |
| T_{max} (h)                | 11.3 ± 0.8   | 0.47 ± 0.22               |           |                            |
| t_{1/2} (h)                | 30.0 ± 19.3  | 19.5 ± 9.5                |           |                            |
| AUC_{0-∞} (ng h/L)         | 697.67 ± 1026.9 | 1202.1 ± 121.8         |           |                            |
| AUC_{0-∞} (ng h/L)         | 7388.6 ± 940.0 | 3672.1 ± 225.4         |           |                            |
| CL/F (L/(h kg))            | 13.731.8 ± 1871.6 | 4129.2 ± 231.8     |           |                            |
| Vz/F (L/kg)                | 277.476.2 ± 132.126.1 | 0.72 ± 0.66          |           |                            |
| MRT_{0-∞} (h)              | 18.5 ± 0.675 | 1.67 ± 2.34              |           |                            |
| MRT_{0-∞} (h)              | 22.3 ± 4.9   | 0.185 ± 0.261            |           |                            |
| F (%)                      | 8.9 ± 0.58   | 8.1 ± 0.67               |           |                            |
| MRT_{T1/2} (h)             | –        | –                        |           |                            |
| MRT_{T1/2} (h)             | –        | –                        |           |                            |
| All data are expressed as mean ± SD (n = 6). |      |                            |           |                            |

### Table 42

| Parameter                  | Dose/mg/kg | 3       | 6       | 12      |
|----------------------------|------------|--------|--------|--------|
| C_{0} (mg/L)               | 24 ± 4     | 47 ± 12 | 107 ± 15 |
| AUC_{0-∞} (mg min/L)       | 109 ± 24   | 248 ± 55 | 582 ± 84 |
| AUC_{0-∞} (mg min/L)       | 109 ± 24   | 248 ± 55 | 582 ± 84 |
| MRT_{0-∞} (min)            | 16.3 ± 3.8 | 14.8 ± 2.9 | 140.0 ± 68 |
| k_{10} (h)                 | 13.2 ± 2.1 | 11.6 ± 1.5 | 11.2 ± 1.3 |
| k_{12} (h)                 | 5.2 ± 1.6  | 3.9 ± 2.2  | 3.1 ± 0.5  |
| k_{21} (h)                 | 1.5 ± 0.5  | 1.4 ± 0.4  | 1.4 ± 0.3  |
| V/L (kg)                   | 1.7 ± 0.5  | 1.6 ± 0.6  | 1.3 ± 0.3  |
| T_{1/2} (min)              | 2.2 ± 0.2  | 2.7 ± 0.5  | 2.9 ± 0.3  |
| T_{1/2} (min)              | 43 ± 9     | 42 ± 7     | 42 ± 10    |
| CL/mL/min/kg               | 28 ± 5     | 26 ± 7     | 21 ± 3     |

n = 6, Mean ± SD.

AUC – area under the concentration-time curve; MRT – mean residence time; SD – standard deviation; C_{0} – initial plasma concentration; CL – clearance; t_{1/2} – half life.
inertsil ODS-3 C18 reverse-phase column (250 × 4.6 mm i.d., 5 μm) and protected by RP18 (5 μm) guard column (Dikma, Beijing, China). The mobile phase consisted of 0.02% phosphoric acid-acetonitrile (91:9, v/v). The flow rate was 1 mL/min and the UV-vis detector was set at 280 nm. The LOQ for Dhpl and Pal was found to be 1.43 and 0.12 μg/mL, respectively. The pharmacokinetic parameters are determined by using non-compartmental analysis. The pharmacokinetics parameters of Dhpl and Pal after oral administration are presented in Table 43. The double-peak phenomenon was observed in these pharmacokinetic data and it may be due to the hepatenteral circulation and redistribution in tissues phenomenon.52

6.10. Stephania tetrandra (粉防己 fēn fáng jǐ)

Tetrandrine is an important bisbenzyl isoquinoline alkaloid isolated from the bulbous root of Stephania tetrandra S Moore (Menispermaceae) of TCM. It is widely used as an anti-inflammatory, antiallergic, antioxidant, and antifibrogenic agent, as well as in immunomodulation and inhibition of platelet aggregation. In addition to these pharmacological effects, tetrandrine also exhibits liver toxicity in dogs when administered in high doses for a relatively long period.

The LC/MS/MS method was used to determine the pharmacokinetic parameters of tetrandrine in rat plasma when administered as a single oral dose (50 mg/kg) in six Sprague Dawley rats. The system was equipped with a Dikma Diemonsil-C18 analytical column (4.6 × 150 mm i.d., 5 μm, Dikma Technologies, Beijing, China) at 35°C. The mobile phase consisted of acetonitrile-methanol-ammonium formate aqueous solution (20%M) containing 0.3% formic acid (20:30:50, v/v/v). The flow and LLOQ are 0.3 ml/min and 5 ng/ml respectively. The pharmacokinetic parameters after single oral administration standard in female Wister rats are presented in Table 44.53

6.11. Silybum marianum L. (水飛薊 shuǐ fēi jì)

Silybum marianum L., also known as milk thistle, is widely used in traditional medicine. Silymarin, a polyphenolic flavonoid isolated from milk thistle, primarily consists of four isomeric mixtures of active flavonolignans: silychristin, silydianin, and two groups of diasteroisomseric flavonolignans, silybin, and iso-silybin. Silymarin is clinically useful for the treatment of toxic hepatitis, fatty liver, cirrhosis, ischemic injury, radiation toxicity, and viral hepatitis. It is a strong antioxidant capable of scavenging unconjugated radicals.

The LC method was used to measure unconjugated silybinin and total silybinin in rat plasma and bile. The system was equipped with a LiChrosorb RP-18 column (250 × 4 mm i.d., 5 μm, Merck) protected by guard column (Purospher STAR RP-18e, 5 μm) at room temperature (24 ± 1 °C). The mobile phases consisted of acetonitrile-10mM monosodium phosphate (pH 5.45 adjusted with orthophosphoric acid) (50:50, v/v). The flow rate and detection wavelength are 1 mL/min and 288 nm, respectively. The oral bioavailability of silybinin in rats was estimated to be 0.73%. Pharmacokinetic calculations are performed on each individual set of data using noncompartmental method. The AUC was calculated according to the linear trapezoidal method. The pharmacokinetic parameters after silibinin administration are presented in Tables 45 and 46. The polyphenolic silybinin potentially go through Phase II conjugated reaction with glucuronidation. The conjugated metabolites are more water soluble, and they are possible in due course excreted in the urine and bile. It leads to poor bioavailability of silybinin. The absolute oral bioavailability of silybinin in rats was found to be approximately 0.95%. This may be due to the high reactivity with Phase II conjugation and poor absorption rate. The distribution ratio of AUCBile/AUCblood of silybinin suggests that the hepatobiliary elimination of silybinin may be regulated by active transport.54

7. Steroidal glycoalkaloids

Solanum spp. are well known for their steroidal glycoalkaloid properties, and solamargine is one of the steroidal alkaloid glycosides present in them. Solamargine is useful as an antitumor agent in cancers of the colon, lung, and breast.

The HPLC method coupled with Shimadzu LCMS-2010A quadrupole MS by an ESI interface was used to determine the pharmacokinetic parameters of solamargine in rats. The system was

| Parameter | Tetrandrine (50 mg/kg) |
|-----------|------------------------|
| T_max (h) | 6.0 ± 1.8              |
| C_max (ng/mL) | 237.1 ± 95.9         |
| AUC(0→t2) (µg/mL) | 6279.2 ± 2411.5      |
| AUC(→∞) (µg/mL) | 7002.7 ± 2528.0      |
| T_1/2 (h) | 20.6 ± 3.7             |
| ke (h⁻¹) | 0.034 ± 0.006          |

AUC = area under the concentration-time curve; C_max = peak plasma concentration; T_max = time of peak plasma concentration; Ke : elimination rate constant; t_1/2 = half life.

| Parameter | Pharmacokinetic parameters of solamargine after single oral administration of 50 mg/kg in six Sprague Dawley rats. |
|-----------|------------------------------------------------------------------------------------------------------------------|
| Parameter | Unconjugated | Total |
| AUC (min mg/mL) | 5 ± 0.73 | 35.5 ± 5.9 | 0.26 ± 0.07 | 7.17 ± 1.42 |
| C_max (µg/mL) | 256 ± 36 | 239 ± 19 | 8.5 ± 2.6 | 76 ± 15 |
| t_1/2 (min) | 68 ± 7.2 | 105 ± 29 | 12.2 ± 1.8 | 77 ± 3.2 |
| T_max (h) | 0 | 8.2 ± 4.5 | 11 ± 1.8 | 30 ± 4.7 |

Data are expressed as mean ± standard error of the mean (n = 6).

AUC = area under the concentration time curve; C_max = peak plasma concentration; I.V. = intravenous; P.O. = by mouth.

| Parameter | Pharmacokinetic parameters after oral administration (100 mg/kg, intravenously and 500 mg/kg by mouth) for blood. |
|-----------|------------------------------------------------------------------------------------------------------------------|
| Parameter | Unconjugated | Total |
| AUC (min mg/mL) | 11.1 ± 284 | 1202 ± 186 |
| C_max (µg/mL) | 517 ± 85 | 7910 ± 2080 |
| t_1/2 (min) | 33 ± 8.3 | 97 ± 28 |
| T_max (h) | 5.1 ± 1.0 | 50 ± 18 |
| AUC bile/AUC blood | 3.1 ± 0.95 | 30 ± 9.4 |

Data are expressed as mean ± standard error of the mean (n = 6).

AUC = area under the concentration time curve; C_max = peak plasma concentration.
equipped with a Shim-Pack VPODS C18 column (150 × 2.0 mm i.d., 5 μm) with a gradient elution of the mobile phase system consisting of acetonitrile (A) and 0.02% formic acid (B). The temperature of the column and auto-sampler was kept constant at 40°C and 10°C, respectively. Pharmacokinetic parameters in rats are estimated by a compartmental method. The studied method was successfully applied to analyze rat plasma samples after intravenous injection of solamargine at 1.0, 2.0, and 4.0 mg/kg in rats, supporting its applicability to biosample assay. The pharmacokinetic parameters after a single intravenous dose of 1.0, 2.0, and 4.0 mg/kg solamargine in rats are presented in Table 47. The pharmacokinetic data indicate that elimination or biotransformation of solamargine occurred relatively quickly in rats.55

7.1. Stephania cepharantha (金線吊烏龜 jín xiàn diào wū guì)

FK-3000 [6,7-di-O-acetylsinococuline] is isolated from Stephania delavayi Diels (地當Displayed text here.

The LC/MS method was used to determine the pharmacokinetic parameters of triptolide. The system was equipped with a Zorbax Extend-C18 analytical column (4.6 × 150 mm i.d., 5 μm, Agilent Technologies) protected by a ODS guard column (Security Guard, Phenomenex) at 40°C. The mobile phase was composed of acetonitrile/methanol/0.05% triethylamine aqueous solution (20:50:30, v/v/v) at a flow rate of 1 mL/min. Under these conditions, triptolide eluted at approximately 3.2 minutes and the internal standard at 4.0 minutes. All measurements are carried out using the negative ion atmospheric pressure chemical ionization (APCI) mode. LLOQ was found to be 1 ng/mL in rat plasma. The pharmacokinetic parameters of triptolide in rats after oral or intravenous administration of triptolide are presented in Table 49. The current pharmacokinetic data reveal that triptolide was metabolized extensively, eliminated rapidly, and also showed that the toxicity produced by the triptolide was lag behind the exposure concentration.57

7.3. Tripterygium wilfordii (雷公藤 léi gōng téng): Tripterygium wilfordii Hook F (THWF) (雷公藤 léi gōng téng)

Triptolide, a diterpenoid triepoxide compound, isolated from the roots of Tripterygium wilfordii Hook F (Celastraceae, THWF) is also commonly known as Thunder God Vine. In TCM it is used to treat some autoimmune disorders such as rheumatoid arthritis, systemic lupus erythematosus, and skin diseases.

The liquid chromatography with atmospheric pressure chemical ionization mass spectrometry (LC-APCI-MS) method was used to determine the pharmacokinetic parameters of triptolide. The system was equipped with a Zorbax Extend-C18 analytical column (4.6 × 150 mm i.d., 5 μm) protected by a ODS guard column (Security Guard, Phenomenex) at 40°C. The mobile phase composed of acetonitrile/methanol/0.05% triethylamine aqueous solution (30:50:20, v/v/v) at a flow rate of 0.75 mL/min. Triptolide eluted at approximately 3.3 minutes and the internal standard (prednisolone) at 4.0 minutes. The LOQ and total run time are 0.5 ng/mL and 5 minutes, respectively. The pharmacokinetic study of six beagle dogs following intragastric administration at a single dose of 0.05 mg/kg triptolide solution are presented in Table 50.58

7.4. Verbascum sinuatum (毛蕊花 máo ruǐ huā), Orobanche rapum (雷前 liè diǎn), Cistanche salsa G. Beck (肉苁蓉 ròu cōng róng), and Plantago psyllium L. (草前 cǎo qián), Olea europaea (橄欖 gǎn lǎn)

Acteoside is a phenylethanoid glycoside having water-soluble polyphenolic compounds, which are widely distributed in many medicinal plants, including Verbascum sinuatum, Orobanche rapum, Cistanche salsa (C.A. Mey) G. Beck, and Plantago psyllium L. Olea europaea. Acteoside shows neuroprotective action and attenuated scopolamine-induced memory impairments in mice. Acteoside and

Table 48 Pharmacokinetic parameters of FK-3000 [6,7-di-O-acetylsinococuline] isolated from Stephania delavayi.

| Pharmacokinetic parameters | Mean ± SD |
|-----------------------------|-----------|
| Tmax (h)                    | 0.20 ± 0.06 |
| t1/2 (h)                    | 1.79 ± 0.09 |
| Cmax (ng/mL)                | 2519 ± 168.2 |
| MRT (h)                     | 1.61 ± 0.33 |
| AUC0-∞, h (ng h/mL)         | 2093 ± 42.0 |
| AUC0-∞, h (ng h/mL)         | 245.7 ± 40.5 |

AUC = area under the concentration time curve; Cmax = peak plasma concentration; MRT = mean residence time; SD = standard deviation; Tmax = time of peak plasma concentration.

Table 47 Pharmacokinetic parameters after a single intravenous dose of 1.0, 2.0, and 4.0 mg/kg solamargine in rats (n = 5).

| Parameters | Mean ± SD |
|------------|-----------|
| 1.0 mg/kg  | 538.54 ± 278.79 |
| 2.0 mg/kg  | 1994.37 ± 694.87 |
| 4.0 mg/kg  | 2483.40 ± 272.89 |

The plasma concentration at 5min (C5) (ng/mL) CI (L/kg h) 3.81 ± 0.68 4.10 ± 1.23 3.97 ± 0.44 Vd (L/kg) 20.16 ± 10.34 19.78 ± 12.55 15.68 ± 6.19 t1/2 (h) 3.54 ± 1.50 3.29 ± 1.52 2.76 ± 1.10 AUC0-∞, h (ng h/mL) 242.41 ± 65.68 482.36 ± 138.07 947.74 ± 124.76 AUC0-∞, h (ng h/mL) 270.50 ± 54.86 526.92 ± 161.72 1018.91 ± 117.26

AUC = area under the concentration time curve; SD = standard deviation; CI = clearance; Vd = volume of distribution; t1/2 = half life.
its aglycones protect glutamate-induced excitotoxicity in a primary culture of rat cortical cells.

The LC with amperometric detection and microdialysis sampling method was used to determine pharmacokinetic profile protein-unbound acteoside in rat blood. Acteoside and dialysates was separated by using a Phenomenex Gemini column (150 x 2.0 mm i.d., 5 µm) with its guard column (10 x 2.0 mm i.d.). The mobile phase comprised acetonitrile-50 mM monosodium phosphate (pH 2.8, adjusting with 85% orthophosphoric acid) (17:83, v/v), and the flow rate of the mobile phase was 0.2 mL/min.

The LOD and LOQ for acteoside were found to be 2 ng/mL and 5 ng/mL, respectively. The pharmacokinetic parameters of acteoside in rats after 10 mg/kg administration are presented in Table 51. The pharmacokinetic data indicate that acteoside was unable to be detected in the brain dialysate and it also was rapidly distributed in the body.

7.5. Zingiber officinale (薑)

Ginger, the dried rhizome of Zingiber officinale Roscoe (Zingiberaceae), is not only a popular spice and flavoring agent in a variety of foods, but also is an important dietary supplement for nausea and motion sickness. In TCM, fresh or processed ginger has been used for the treatment of many ailments. Ginger mainly contains essential oil and oleoresin. Oleoresin is the nonvolatile pungent component, and the major constituents of oleoresin have been identified as 6-gingerol, 8-gingerol, 10-gingerol, and 6-shogaol, which is the corresponding dehydration product of 6-gingerol.

A HPLC-MS method with positive ionization interface was used to determine the pharmacokinetic parameters of ginger oleoresin. The system was equipped with an Agilent Zorbax StableBond-C18 column (4.6 x 50 mm i.d., 1.8 µm) and the temperature was set at 30°C. The mobile phases consisted of 0.1% formic acid water (A) and acetonitrile (B). The flow rate and injection volume are 1.0 mL/min, and 2 µL, respectively. Pharmacokinetic parameters are estimated using noncompartmental analysis. LLOQ of 6-gingerol 0.0104, 8-gingerol 0.00357, 10-gingerol 0.00920, and 6-shogaol 0.00738 µg/mL. The pharmacokinetic parameters after single oral administration of 300 mg/kg ginger oleoresin in five rats are presented in Table 52. 6-Gingerol shows 90% plasma protein binding in rats and also extensive first-pass metabolism. 6-gingerol could be readily conjugated with glucuronic acid in the alimentary tract in vivo. It is also the reason for the low bioavailability. The 6-gingerol glucuronide was identified from bile and urine as the primary metabolite of rats orally administered 6-gingerol. As per pharmacological and toxicological consideration, Phase II metabolism of gingerols is

**Table 49**

Pharmacokinetic parameters of triptolide in rats after oral or intravenous administration of triptolide.

| Parameter | Oral dose/mg/kg | Intravenous dose/mg/kg |
|-----------|-----------------|------------------------|
|           | 0.6             | 1.2                    | 2.4                     | 6.0                       |
| ka (L/min) | 0.37 ± 0.17     | 0.39 ± 0.16            | 0.251 ± 0.09           | –                         |
| ke (L/min) | 0.03 ± 0.01     | 0.04 ± 0.02            | 0.03 ± 0.01            | –                         |
| Vf (L/kg)  | 0.32 ± 0.34     | 0.33 ± 0.30            | 0.22 ± 0.17            | 1.27 ± 0.25               |
| T1/2 (ka (min) | 2.19 ± 0.92   | 2.06 ± 0.83            | 3.00 ± 0.87            | –                         |
| T1/2 (ke (min) | 21.70 ± 3.00  | 16.81 ± 5.24           | 20.40 ± 3.75           | 15.10 ± 4.44              |
| AUC(0→∞) (mg/L min) | 7057.14 ± 1826.04 | 10456.67 ± 3178.42 | 14538.98 ± 5636.58 | 9791.18 ± 585.88          |
| T1/2 (min) | 11.00 ± 2.24    | 10.00 ± 0.00           | 10.00 ± 0.00           | –                         |
| Cmax (mg/L) | 254.00 ± 47.34 | 446.65 ± 112.86        | 537.33 ± 143.34        | –                         |
| CL/F (L/min/kg) | 0.06 ± 0.02  | 0.06 ± 0.02            | 0.06 ± 0.03            | 0.06 ± 0.01               |

**Table 50**

The pharmacokinetic study of six beagle dogs following i.g. administration at a single dose of 0.05 mg/kg triptolide solution.

| Parameter | Values |
|-----------|--------|
| Cmax      | 28.03 ± 11.76 ng/mL |
| Tmax      | 0.96 ± 0.30 h       |
| MRT0→tn   | 3.00 ± 0.54 h       |
| T1/2(ka)  | 0.50 ± 0.38 h       |

**Table 51**

Pharmacokinetic parameters of acteoside in rats after 10 mg/kg administration.

| Parameters | Estimated |
|------------|-----------|
| A (µg/g)   | 71.9 ± 30.9 |
| B (µg/mL)  | 2.9 ± 0.5   |
| γ (L/min)  | 0.14 ± 0.03 |
| β (L/min)  | 0.02 ± 0.004|
| T1/2 (min) | 5.0 ± 1.2   |
| T1/2(ke) (min) | 28.5 ± 4.7 |
| AUC (min µg/mL) | 592.3 ± 124.7 |
| Vss (mL/kg) | 277.7 ± 185.8 |
| CI (mL/min/kg) | 17.7 ± 4.5 |

Data expressed as mean ± standard deviation (n = 6); T1/2, γ: distribution half-life; T1/2, β: elimination half-life. AUC – area under the concentration-time curve; CI – clearance; Vss – volume of distribution at steady state.

**Table 52**

Estimated pharmacokinetic parameters after single oral administration of 300 mg/kg ginger oleoresin to five rats.

| Parameter | 6-Gingerol | 8-Gingerol | 10-Gingerol | 6-Shogaol |
|-----------|------------|------------|-------------|-----------|
| AUC(0→∞) (µg/mL) | 1.689 ± 0.38 | 0.177 ± 0.025 | 0.222 ± 0.021 | 0.14 ± 0.011 |
| MRT(0→∞) (h)   | 1.776 ± 0.502 | 1.845 ± 0.169 | 1.84 ± 0.263 | 1.932 ± 0.592 |
| Tmax (h)        | 3.574 ± 1.994 | 1.08 ± 0.439 | 1.576 ± 1.03 | 1.127 ± 0.745 |
| Cmax (µg/L)     | 1.167 ± 0.764 | 0.833 ± 0.289 | 0.361 ± 0.141 | 1 ± 0.866 |
| CL/F (Lb/kg)    | 0.933 ± 0.545 | 0.092 ± 0.018 | 0.156 ± 0.012 | 0.111 ± 0.041 |

AUC – area under the concentration-time curve; Cmax – peak plasma concentration; MRT – mean residence time; Tmax – time of peak plasma concentration; CL/F – apparent plasma clearance; T1/2 – half life.
important. In plasma, 6-gingerol was found in its glucuronide form and 8-gingerol, 10-gingerol, and 6-shogaol were distributed into blood in free form.60

8. Conclusion
Numerous herbal medicines as phytoformulations, phytochemicals, nutraceuticals, and functional food currently are available to improve health. Active principle obtained from the plants are the moribund source of treatment against the wide range of the diseases and in near future it may supersede the synthetic moieties. These herbal medicines are not restricted to a particular ailment. Because these medicines are used with increasing frequency to improve health, it is essential to know the pharmacokinetic profile of the aliment being treated. ADME plays a central role in promoting more rational use and to map pharmacological actions of such herbal aliments. This pharmacokinetic profile acts as a blueprint for the medicinal plant. These data help justify the therapeutic, toxicological, and clinical value of herbal medicines. Recent research corroborates traditional claims and justifies use of herbal medicines for the welfare of the human beings. This necessitates further study of the many facets of these wonderful traditional herbal medicines. To support herbal medicine research in the near future and to expand activities, the current review will help those who are involved in natural product research.

Conflicts of interest
All authors have no conflicts of interest to declare.

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