Short Review

Non-clinical pharmacokinetic behavior of ginsenosides

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A B S T R A C T

Ginsenosides, the major active ingredients of ginseng and other plants of the genus Panax, have been used as natural medicines in the East for a long time; in addition, their popularity in the West has increased owing to their various beneficial pharmacological effects. There is therefore a wealth of literature regarding the pharmacological effects of ginsenosides. In contrast, there are few comprehensive studies that investigate their pharmacokinetic behaviors. This is because ginseng contains the complicated mixture of herbal materials as well as thousands of constituents with complex chemical properties, and ginsenosides undergo multiple biotransformation processes after administration. This is a significant issue as pharmacokinetic studies provide crucial data regarding the efficacy and safety of compounds. Moreover, there have been many difficulties in the development of the optimal dosage regimen of ginsenosides and the evaluation of their interactions with other drugs. Therefore, this review details the pharmacokinetic properties and profiles of ginsenosides determined in various animal models administered through different routes of administration. Such information is valuable for designing specialized delivery systems and determining optimal dosing strategies for ginsenosides.

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1. Introduction

Panax ginseng Meyer (P. ginseng) and other ginsengs have long been used medicinally in East Asia and have gradually gained popularity in Western countries over the past several decades. P. ginseng contains various bioactive ingredients, including ginsenosides, polysaccharides, polyacetylenes, and polyphenols; of these, the ginsenosides are considered the main active components [1]. Hence, numerous studies have investigated the beneficial effects of ginsenosides and revealed various pharmacological activities, including antiinflammatory, anticancer, anti diabetic, and antioxidative effects, as illustrated in Fig. 1 [2–34].

However, there have been very few studies reported to date which have investigated the pharmacokinetic characteristics of ginsenosides [35]. This is presumably attributable to the complex nature of biotransformation of ginsenosides during and after their absorption despite the fact that pharmacokinetic studies provide important data that can contribute to the evaluation of the efficacy and safety of ginsenosides and their related compounds [36]. In addition, as ginsenosides have complex chemical structures and as they are subdivided into several groups depending on their chemical forms, the study of their pharmacokinetic behavior is not simple [1]. For these reasons, there have been many complications in the design of the optimal dosage strategies for ginsenosides based on their pharmacokinetic behavior, and the assessment of their interactions with other drugs has been also limited [37]. Moreover, a proper evaluation of the pharmacokinetic properties of ginsenosides is considered to be extremely difficult because of their very low oral bioavailability, which is usually less than 10% (Table 1) [38–45]. As the systemic exposure to ginsenosides impacts their efficacy and side effects, there is also a growing need to determine the optimal dosage regimen of ginsenosides [46].

Therefore, this review comprehensively analyzed the pharmacokinetic behavior of each ginsenoside component, characterized in different animal models after administration through different routes, to provide the essential pharmacokinetic information and background required for the development of ginsenoside-based nutraceuticals and pharmaceuticals. In particular, we have

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specifically discussed the behavior of each ginsenoside component in the processes of absorption, distribution, metabolism, and excretion (ADME).

2. Physicochemical characteristics of ginsenosides

To achieve a better understanding of the pharmacokinetic behaviors of ginsenosides, it is helpful to first examine their physicochemical properties. Ginsenosides, classified as dammarane-type triterpene saponins, typically comprise 17 carbons in a 4-ring structure called the dammarane skeleton, with diverse sugar moieties, such as glucose, rhamnose, xylose, and arabinose, attached to the C-3 and C-20 positions [47]. As presented in Fig. 2, there are two major groups of ginsenosides: the protopanaxadiol (PPD) and protopanaxatriol (PPT) groups. Ginsenoside Rb1, Rb2, Rb3, Rc, and Rd represent the main PPD-type ginsenosides, whereas ginsenoside Rg1 and Re are the main PPT-type ginsenosides. In the PPD group, Rg3 is a metabolite of Rb1, Rb2, Rb3, Rc, and Rd, and Rg3 is subsequently metabolized to Rh2. In the PPT group, Rg2 is a metabolite of Re, and Rh1 is a metabolite of Rg1 and Re [48]. Some minor ginsenosides, such as F0, F11, and 25-OH-PPT, do not belong to either of the two groups mentioned previously and are considered “other” ginsenosides. PPD-type ginsenosides contain sugar moieties attached to the β-OH at the C-3 and/or C-20 position, whereas PPT-type ginsenosides include sugar moieties attached to the α-OH at C-6 and/or the β-OH at C-20 [49].

In general, ginsenosides have low aqueous solubility, poor membrane permeability, and metabolic instability. The aqueous solubility of ginsenosides is dictated by the presence of a hydrophobic functional group comprising triterpenes or steroid aglycones and a hydrophilic functional group consisting of a sugar side chain; therefore, it is considerably affected by the number of attached sugar moieties within the structures. However, most ginsenosides generally exhibit low aqueous solubility as they comprise steroid aglycones and lack sugar moieties. In addition, ginsenosides commonly have low membrane permeability owing to their dammarane-type structure with a large skeleton.

Table 1
Reported oral bioavailabilities of ginsenosides evaluated in animals

| Ginsenosides | Species | Oral dose (mg/kg) | Oral bioavailability (%) | References |
|--------------|---------|------------------|--------------------------|------------|
| Rb1          | Rat     | 10               | 4.35                     | [38]       |
| Rb1          | Rat     | 104              | 1.18                     | [40]       |
| Rb2          | Rat     | 100              | 3.7                      | [39]       |
| Rd           | Rat     | 25               | 2.36                     | [40]       |
| Rh2          | Rat     | 1                | 4.7                      | [41]       |
| Rh2          | Rat     | 3                | 4.0                      | [41]       |
| Rh2          | Rat     | 9                | 6.4                      | [41]       |
| Rh2          | Dog     | 1                | 16.7                     | [41]       |
| Rh2          | Dog (male) | 1            | 17.6                     | [43]       |
| Rh2          | Dog (female) | 1          | 24.8                     | [43]       |
| Rg3          | Rat     | 10               | 2.63                     | [42]       |
| Rg1          | Rat     | 10               | 18.40                    | [38]       |
| Rg1          | Rat     | 79               | 6.06                     | [40]       |
| Rh1          | Rat     | 50               | 1.01                     | [44]       |
| Re           | Rat     | 13               | 7.06                     | [40]       |
| Re           | Rat     | 10               | 0.28                     | [45]       |

Fig. 1. Therapeutic effects of ginsenosides and effective organs.
Ginsenosides are known to be chemically labile in the gastrointestinal (GI) tract because they can be degraded by hydrolytic enzymes [50–52]. Thus, the clinical applications of ginsenosides have been limited by low bioavailability caused predominantly by the unsuitable physicochemical properties of ginsenosides mentioned previously.

3. Pharmacokinetic behavior of ginsenosides

The optimization of drug dosage is significantly affected by its pharmacokinetic properties. After administration, the drug undergoes four major pharmacokinetic processes in the body: ADME. It is hard to evaluate the pharmacokinetic behavior of ginsenosides in these processes as *P. ginseng* contains numerous substances in addition to ginsenosides. Moreover, there are difficulties in the identification of the pharmacokinetic characteristics of ginsenosides due to the fact that ginsenosides have different properties depending on the attached sugar moieties. Despite these complications, we have tried to scrutinize the considerable quantity of pharmacokinetic data for ginsenosides and assessed these data with regard to ADME.

3.1. Absorption

Many pharmacokinetic studies have shown that ginsenosides are very poorly absorbed and exhibit low bioavailability. Xie et al. [42] investigated the pharmacokinetic behaviors of ginsenoside Rg3 and its metabolites in rats. Ginsenoside Rg3 is deglycosylated to ginsenoside Rh2 and then to PPD in vivo [53]. The authors administered an oral dose of 10 mg/kg of Rg3 or an intravenous dose of 1 mg/kg of Rg3 to rats. In the plasma concentration–time curve, Rg3 appeared first, followed by Rh2 and PPD after 1 h and 4 h, respectively. In addition, Rh2 and PPD were present at considerably lower concentrations than Rg3. This observation indicated that Rg3 was metabolized to Rh2 and then to PPD in rats; these metabolic changes are summarized in Fig. 2. The $C_{\text{max}}$ and $T_{\text{max}}$ values of Rg3 were $104.07 \pm 59.95$ ng/mL and $4.40 \pm 1.67$ h, respectively. In this study, the oral bioavailabilities of Rg3 and Rh2 were separately evaluated. The oral bioavailability of Rg3 was 2.63%, and it was not possible to measure the oral bioavailability of Rh2 because of the very low exposure levels to the systemic circulation [42]. Similarly, Ren et al. [54] investigated the pharmacokinetic properties of PPD, the metabolite of ginsenoside Rg3 and Rh2. PPD was administered orally to rats at a dose of 2 mg/kg, and the plasma levels of PPD were measured by HPLC equipped with atmospheric pressure chemical ionization–mass spectrometry. In their study, the $C_{\text{max}}$ and $T_{\text{max}}$ of PPD were $130.2 \pm 41.5$ ng/mL and $73.5 \pm 150.0$ min, respectively. The oral bioavailability of PPD was evaluated as $36.8 \pm 12.4\%$, which was unusually higher than that of ginsenosides Rg3 and Rh2. These results showed that Rg3 and Rh2 were rarely absorbed in the GI tract, whereas PPD was well absorbed. Such results suggest that PPD may be largely responsible for the major pharmacological effects of Rg3 and Rh2.

Several studies have investigated the possible differences in pharmacokinetic profiles and properties among ginsenoside epimers. Peng et al. [53] assigned the rats into four groups and investigated the administration of 20(S)-Rg3 and 20(R)-Rg3 through the oral and intravenous routes. For intravenous administration, a 5 mg/kg dose of 20(S)-Rg3 and 20(R)-Rg3 was injected to the rats. After the intravenous administration, plasma concentrations of 20(S)-Rg3 and 20(R)-Rg3 rapidly decreased from 2 to 30 min; after 1 h, neither epimer was detectable. $C_{\text{max}}$ values were reported to be $70,096.2 \pm 7,204.6$ ng/mL for 20(S)-Rg3 and $46,439.2 \pm 14,365.5$ ng/mL for 20(R)-Rg3, with $T_{\text{max}}$ of 0.033 h for both epimers. As for the oral administration of Rg3 epimers, there were different results from those obtained after intravenous administration. After the oral
administration of 20(S)-Rg3 to rats at a dose of 50 mg/kg, the Cmax and Tmax values were 98.1 ± 40.5 ng/mL and 5.7 ± 2.0 h, respectively, and the oral bioavailability of 20(S)-Rg3 was only 0.17%. In contrast, after the oral administration of 50 mg/kg of 20(R)-Rg3 to rats, traces of 20(R)-Rg3 could not be identified in plasma, which prevented the evaluation of the oral bioavailability of 20(R)-Rg3. However, instead of 20(R)-Rg3, very low levels of 20(S)-Rg3 and 20(R)-PPD could be detected. These results possibly indicated that the majority of 20(R)-Rg3 was converted to 20(S)-Rg3 by chiral inversion and 20(R)-PPD by deglycosylation in vivo. Although the mechanism of chiral inversion of Rg3 is still unknown, it was confirmed to be a single direction inversion from 20(R)-Rg3 to 20(S)-Rg3. The chiral inversion rate was calculated as 7.9% and 9.7% after intravenous and oral administration, respectively, in this study. The study reported that the chiral inversion of ginsenosides could occur in systemic circulation and during the absorption processes in the GI tract.

There were differences in the absorption of ginsenosides depending on their particle size or the animal species. Gu et al [41] examined the pharmacokinetic properties of ginsenoside Rh2 in rats and dogs, which are the rodent and nonrodent species generally used in nonclinical studies. As the oral bioavailability of ginsenosides was known to be very low owing to their poor aqueous solubility and low membrane permeability, the researchers therefore used micronized Rh2 to improve the absorption rate. Micronization reduced the particle size of Rh2 and increased the dissolution rates. Consequently, the absorption rate of Rh2 was greatly enhanced [54]. After the intravenous and oral administration of Rh2 at doses of 0.1 mg/kg and 1 mg/kg, respectively, to dogs, the calculated oral bioavailability of native Rh2 was approximately 16%, whereas that of micronized Rh2 was approximately 32%. These results indicate that the oral bioavailability of Rh2 was doubled by micronization. In addition, the Cmax of micronized Rh2 was approximately twice that of native Rh2. These results showed that the micronization effectively enhanced the oral bioavailability of ginsenosides in dogs. However, as the absorption processes of Rh2 in rats were more complicated than in dogs, the oral bioavailability evaluated in rats was only 4.7% after an oral dose of 1 mg/kg micronized Rh2. Moreover, the measured Tmax values provided an explanation of the difference in the oral bioavailability in dogs and rats. The Tmax values in rats were much longer than those in dogs, which were each 6 h and 1.8 h. In other words, the faster absorption of micronized Rh2 was more prominent in dogs than in rats. Such results were thought to be attributable to the anatomical and physiological differences between rats and dogs [41].

Xu et al [38] performed a study to compare the pharmacokinetic properties of ginsenosides Rb1 and Rg1. Ginsenoside Rb1 is categorized to the PPD group, and ginsenoside Rg1 is classified as the PPT group, as illustrated in Fig. 2. After the oral administration of ginsenosides at a dose of 50 mg/kg in rats, Rb1 was absorbed more slowly than Rg1. The comparison of the calculated pharmacokinetic parameters of Rb1 and Rg1 revealed that the Tmax and oral bioavailability of Rb1 were 1.5 h and 4.35%, respectively, and the Tmax and oral bioavailability of Rg1 were 1 h and 18.40%, respectively [38]. These results showed that the PPT group of ginsenosides exhibited better oral bioavailability than the PPD group. Such results are thought to be related to the slower metabolic changes of PPT-type ginsenosides (i.e., a slower disappearance from systemic circulation) than those of PPD-type ginsenosides [37].

3.2. Tissue distribution

Li et al [55] investigated the pharmacokinetic characteristics of ginsenosides Rg1, Rb1, and Rd in rat tissues after both oral and intravenous administration. The tissue distribution profiles of ginsenosides were evaluated at different time points after the administration of Rg1, Rb1, and Rd. After oral administration, the highest levels of these three ginsenosides were observed in the liver, followed by the lung, kidney, and spleen. On the other hand, when the ginsenosides were administered intravenously, their tissue concentrations varied depending on administration time in all organs other than the liver, which showed the highest distribution of the ginsenosides tested. Ginsenosides were distributed more rapidly after intravenous administration than after oral administration. Similarly, Feng et al [56] examined the tissue distribution profiles of Rg1 after intravenous administration to rats; their study also indicated that the highest levels of ginsenosides were observed in the liver, followed by the lung, spleen, and kidney.

In contrast, very low levels of ginsenosides were detected in the brain. Hao et al [57] reported the pharmacokinetic data of ginsenoside Rb1 evaluated in the plasma and brain after the intravenous administration at 20 mg/kg in rats. The plasma profiles of Rb1 revealed rapid distribution phases and prolonged terminal phases. The brain concentrations of Rb1 increased up to 1 h, and then there was a prolonged decrease in plasma levels of Rb1. The area under the curve (AUCplasma/AUCbrain) of ginsenoside Rb1 was measured as 47.1, which indicated that minimal transport of the ginsenoside occurred from the plasma to the brain. This can be attributed to the role of the well-known blood–brain barrier function.

High plasma protein binding is another important factor that can influence the tissue distribution of ginsenosides and their interactions with other drugs. Plasma protein binding is therefore a crucial factor that should be considered in pharmacokinetic evaluation [58]. Gu et al [41] examined the pharmacokinetic properties of ginsenoside Rh2, including plasma protein binding in rats. In this study, the binding of Rh2 to rat plasma proteins was reported to be 68.4 ± 4.9%, 72.6 ± 3.2%, 72.8 ± 1.2%, and 71.7 ± 4.0% at doses of 50, 100, 200, and 400 ng/mL, respectively. The plasma protein binding rates of Rh2 in rats were similar (approximately 70%) at all doses tested, which presumably indicated saturation of the binding ability of plasma proteins [41]. In another study assessing the plasma protein binding of Rh2, there were significant species-specific differences between plasma protein binding rates in rats and humans. This study found that Rh2 showed considerable species-dependent plasma protein binding rates of approximately 70% in rats and 27% in humans [59].

In general, the tissue distribution of ginsenosides reported tended to be low in most tissues, excluding the liver, and extremely low in the brain. To facilitate the distribution of ginsenosides to the brain, the administration of ginsenosides through routes that can avoid the blood–brain barrier, such as intranasal or intratympanic administration, has been studied [60]. More specifically, the greater distribution of ginsenosides to the liver may be attributable to the existence of the active uptake mechanisms of ginsenosides [49]. Collectively, the distribution of ginsenosides could be altered by their plasma protein binding properties; in addition, there were species-specific differences between plasma protein binding properties in animals and humans.

3.3. Metabolism

Ginsenosides have been known to exert various pharmacological effects in the body. However, the metabolic pathways of ginsenosides have only recently been reported. The typical metabolic processes of ginsenosides were reported to be deglycosylation and oxidation, which mainly occur in the liver. In addition, numerous studies confirmed that the predominant metabolism of ginsenosides occurred in the GI tract. This was thought to occur because
intestinal microorganisms and enzymes are responsible for the metabolic degradation of ginsenosides in the GI tract [61].

Feng et al [56] studied the metabolic pathways of ginsenoside Rg1 in the rat intestine. The researchers demonstrated that ginsenoside Rg1 was easily biotransformed in vivo. They also revealed that Rg1 underwent multiple deglycosylations, which resulted in the formation of PPT via Rh1 or F1. In another study, Yang et al [62] studied the metabolic pathways of ginsenoside Re, one of the PPT-type ginsenosides such as Rg1. Rg1 and Re have similar chemical structures differing only in the C-20-attached rhamnose sugar [62]. In addition, both ginsenosides have common characteristics in that they were converted to Rh1 or F1 in the GI tract and that oxidation and deglycosylation were the major metabolic changes of the ginsenosides in rats. Ginsenosides Rh1, Rh2, Rc, and Rd, which are PPD-type ginsenosides, are all transformed to compound K in the GI tract. The other PPD-type ginsenosides Rg3 and Rg5 were converted to Rh2 and Rh3, respectively [37].

Furthermore, the metabolic pathways of ginsenosides exhibit different patterns depending on their administration routes. Yang et al [63] investigated the influence of administration route on the metabolic profile of ginsenoside Rd in animal models and humans by liquid chromatography–electrospray ionization–tandem mass spectrometry. After oral administration, ginsenosides in the rat GI tract were metabolized in the liver, mostly by oxygenation caused by hepatic cytochrome P450 3A4, the most abundant form of cytochrome P450 [64]. These studies commonly indicated that the GI tract and liver are the major metabolic organs in which ginsenosides are metabolized via the attachment of sugar moieties in the ginsenoside. For example, ginsenoside Rb1, a PPD-type ginsenoside with five sugar moieties, showed slow biliary excretion owing to its large molecular size, which led to a reduced chance of uptake by the biliary transporters. The slow excretion rate of ginsenosides enables their circulation in the plasma for a long time [49].

4. Conclusions

At present, there is a lack of comprehensive studies on the pharmacokinetic characteristics of ginsenosides as they have complicated structures and exist in many different chemical forms which are subdivided into several groups. Furthermore, these characteristics of ginsenosides also result in complex biotransformation pathways in the body. In general, most ginsenosides are poorly absorbed owing to their unsuitable physicochemical properties. Hence, ginsenosides commonly exhibit low oral bioavailability. Although there were slight differences in the pharmacokinetic properties and profiles of ginsenosides depending on the experimental conditions, such as administration routes and animal species, the low bioavailability, which is a common characteristic of ginsenosides, makes the clinical application of ginsenosides difficult. Several studies on the advanced delivery systems of ginsenosides have recently been conducted to facilitate the clinical usefulness of ginsenosides. However, we realized that the scientific information on pharmacokinetic characteristics of ginsenosides is still lacking. Therefore, in this review, we have tried to provide comprehensive information on the pharmacokinetic properties and profiles of ginsenosides, which can be helpful for the development of efficient dosage forms and diverse delivery systems of ginsenosides to improve their bioavailability. The optimized dosage forms and the delivery systems of ginsenosides will certainly maximize the therapeutic potentials of ginsenosides.

Conflicts of interest

The authors have no conflicts of interest to declare.

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References

[1] Park SE, Na CS, Yoo SA, Seo SH, Son HS. Biotransformation of major ginsenosides in ginseng model culture by lactic acid bacteria. J Ginseng Res 2017;41:36–42.

[2] Cheng Y, Shen LH, Zhang JT. Anti-ammotic and anti-aging effects of ginsenoside Rg1 and Rb1 and its mechanism of action. Acta Pharmacol Sin 2005;26:14–23.

[3] Zhu J, Jiang Y, Wu L, Lu T, Xu G, Liu X. Suppression of local inflammation contributes to the neuroprotective effect of ginsenoside Rb1 in rats with cerebral ischemia. Neuroscience 2012;202:34–51.

[4] Park JS, Shin JA, Hyun JW, Le TKV, Kim DH, Park EM, Kim HS. Anti-inflammatory mechanism of compound K in activated microglia and its neuroprotective effect on experimental stroke in mice. J Pharmaco Exp Ther 2012;341:59–67.

[5] Zhang YJ, Wang YL, Zhi X, Li QJ, Bao YJ, Wang GJ, Liu H. Protective effect of ginsenoside Rb1 on acute gastric mucosal lesion induced by intestinal ischemia-reperfusion in rats. Molecules 2013;18:214–26.

[6] Kong SJ, Park JS, Shin JA, Jung JS, Hyun JW, Le TKV, Kim DH, Park EM, Kim HS. Anti-inflammatory effects of ginsenoside Rb1 on JNK in oxidative injury in cardiomyocytes. Arch Pharm Res 2013;36:1299–1306.

[7] Wang J, Qiao LF, Li SS, Yang GT. Protective effect of ginsenoside Rb1 against myocardial ischemia-reperfusion injury in rats. Pharm Biol 2011;49:900–6.

[8] Shi YH, Han B, Yu XF, Qu SC, Sui DY. Ginsenoside Rb3 ameliorates myocardial reperfusion oxidative injury via antioxidant and intracellular calcium homeostasis. J Cell Biochem 2009;108:117–24.

[9] Li J, Zhao SH, Xie JT, Wang CJ, Zhong ZY, Zhao HB, Cui J, Xun SF, Huang XL, et al. Ginsenoside Rg1 protects rats cardiomyocyte from hypoxia/reoxygenation injury via antioxidant and intracellular calcium homeostasis. J Cell Biochem 2009;108:117–24.

[10] Leung KW, Wong AS. Pharmacology of ginsenosides: a literature review. Chin J Biomed Sci 2011;12:818–26.
[54] Ren HC, Sun JG, Wang GJ, A JY, Xie HT, Zha WB, Yan B, Sun FZ, Hao HP, Gu SH, et al. Sensitive determination of 20(S)-protopanaxadiol in rat plasma using HPLC-APCI-MS: application of pharmacokinetic study in rats. J Pharm Biomed Anal 2008;48:1476–80.

[55] Li L, Sheng YX, Zhang JL, Wang SS, Guo DA. High-performance liquid chromatographic assay for the active saponins from Panax notoginseng in rat tissues. Biomed Chromatogr 2006;20:327–35.

[56] Feng L, Wang L, Hu C, Jiang X. Pharmacokinetics, tissue distribution, metabolism, and excretion of ginsenoside Rg1 in rats. Arch Pharm Res 2010;33:1975–84.

[57] Hao K, Gong P, Sun SQ, Hao HP, Wang GJ, Dai Y, Chen YC, Liang Y, Xie L, Li FY, et al. Mechanism-based pharmacokinetic-pharmacodynamic modeling of the estrogen-like effect of ginsenoside Rb1 on neural 5-HT in ovariectomized mice. Eur J Pharm Sci 2011;44:117–26.

[58] Toutain PL, Bousquet-Melou A. Volumes of distribution. J Vet Pharmacol Ther 2004;27:441–53.

[59] Gu Y, Wang G, Sun J, Jia Y, Xu M, Wang W. In vitro assessment of plasma protein binding of 20(R)-ginsenoside Rh2 by equilibrium dialysis and LC-MS analysis: a case of species differences. Biol Pharm Bull 2006;29:951–6.

[60] Zeng MF, Pan LM, Qi SM, Cao YT, Zhu GX, Guo LW, Zhou J. Systematic review of recent advances in pharmacokinetics of four classical Chinese medicines used for the treatment of cerebrovascular disease. Fitoterapia 2013;88:50–75.

[61] Tawab MA, Bahr U, Karas M, Wurglics M, Schubert-Zsilavecz M. Degradation of ginsenosides in humans after oral administration. Drug Metab Dispos 2003;31:1065–71.

[62] Yang L, Xu SJ, Liu CJ, Su ZJ. In vivo metabolism study of ginsenoside Re in rat using high-performance liquid chromatography coupled with tandem mass spectrometry. Anal Bioanal Chem 2009;395:1441–51.

[63] Yang L, Deng Y, Xu S, Zeng X. In vivo pharmacokinetic and metabolism studies of ginsenoside Rg1. J Chromatogr B Analyt Technol Biomed Life Sci 2007;854:77–84.

[64] Hao H, Lai L, Zheng C, Wang Q, Yu G, Zhou X, Wu L, Gong P, Wang G. Microsomal cytochrome P450-mediated metabolism of protopanaxatriol ginsenosides: metabolite profile, reaction phenotyping, and structure-metabolism relationship. Drug Metab Dispos 2010;38:1731–9.

[65] He C, Feng R, Sun Y, Chu S, Chen J, Ma C, Fu J, Zhao Z, Huang M, Shou J, et al. Simultaneous quantification of ginsenoside Rg1 and its metabolites by HPLC-MS/MS: Rg1 excretion in rat bile, urine and feces. Acta Pharm Sin B 2016;6:593–9.

[66] Qian T, Cai Z, Wong RN, Mak NK, Jiang ZH. In vivo rat metabolism and pharmacokinetic studies of ginsenoside Rg3. J Chromatogr B Analyt Technol Biomed Life Sci 2005;816:223–32.

[67] Toutain PL, Bousquet-Melou A. Plasma clearance. J Vet Pharmacol Ther 2004;27:415–25.