Pharmacokinetic properties, potential herb–drug interactions and acute toxicity of oral *Rhizoma coptidis* alkaloids

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**Introduction:** *Rhizoma coptidis* shows various pharmacological activities attributed to its alkaloid constituents. To guide the pharmacological studies, the candidate drug research and development and the clinic applications of these compounds, a review on their pharmacokinetic behavior and toxicity should be beneficial.

**Areas covered:** This article looks at the pharmacokinetic properties and potential herb–drug interactions found with *Rhizoma coptidis* alkaloids. Furthermore, the article also reviews the acute toxicity of these alkaloids.

**Expert opinion:** Generally, the systemic exposures of the alkaloids are extremely low after oral administration. The alkaloids may present their systemic activities via generated metabolites and/or the tissue distributed alkaloids themselves, or by modulating effectors in the gut. The drug transporters and drug-metabolizing enzymes involved in the *in vivo* process, the modulatory effects on both P-glycoprotein and cytochrome P450 isoenzymes and the acute toxicity of the alkaloids were all well documented. However, first, since very significant difference exists between the blood and tissue exposure, to find suitable pharmacokinetic markers of the alkaloids in blood may be challenging but necessary. Second, the dose-systemic exposure–response relationships of the alkaloids should also be determined. Third, in order to improve the oral bioavailability and efficacy, it is important to design derivatives or formulations of the alkaloids with better pharmacokinetic features.

**Keywords:** acute toxicity, ADME, berberine, cytochrome P450 isoenzymes, herb–drug interaction, P-glycoprotein, pharmacokinetics, *Rhizoma coptidis* alkaloid, traditional Chinese medicine, uridine 5-diphosphate glucuronosyltransferase isoenzymes

**Expert Op. Drug Metab. Toxicol.** [Early Online]

1. Introduction

*Rhizoma coptidis* (Huang Lian) is the dried rhizome of several medicinal plants from the family Ranunculaceae, including *Coptis chinensis* Franch, *C. deltoidea* C.Y. Cheng et Hasiao and *C. teeta* Wall. It is usually used in China for the treatment of inflammation-related diseases, digestive tract ulcer, diabetes mellitus, cancer and cardiovascular diseases by oral intake of the extract [1]. The pharmacological properties of *R. coptidis* extract include anti-bacterial [2], anti-fungal [3], anti-oxidant [4], anti-inflammatory [5], anti-diarrheal [6], anti-cancer [7], anti-diabetic [8], anti-Alzheimer [9], anti-lipemic [10] and hepatoprotective [11] activities. It yields alkaloids such as berberine, coptisine, palmatine and jatrorrhizine (Figure 1) [12]. These alkaloids are the effective constituents in *R. coptidis* extract, but berberine is the primary compound. Reports on the pharmacological activities of berberine are even more...
2. Pharmacokinetic properties of the R. coptidis alkaloids

2.1 Blood exposure

Generally, the blood exposures of the R. coptidis alkaloids are extremely low after oral administration (Table 1) despite the fact that they are higher in some pathological conditions, such as diabetes mellitus [14], and lipopolysaccharide (LPS)-related diseases [15].

2.2 Absorption

As for R. coptidis extract, the absorption of the R. coptidis alkaloids in the extract may be somewhat different from that of a pure alkaloid. The alkaloids including berberine and palmatine undergo quick passive absorption by various sections of intestine [16] after oral administration of the R. coptidis extract; the absorption even happens in the upper gastrointestinal tract including the oral cavity, esophagus and stomach [17]. Furthermore, the oral R. coptidis extract is much more toxic than oral berberine [18,19]. These results together suggest that the absorption of the alkaloids in the R. coptidis extract may be better than a pure R. coptidis alkald.

The absolute bioavailability of the oral R. coptidis alkaloids is very low. In terms of berberine, the absolute bioavailability is below 1% [18,20,21]. The bile components or bile salts in intestine do not influence its absorption according to an in vitro transport experiment [22]. After oral administration, about half of berberine is directly excreted in the feces, while other half undergoes extensive first-pass elimination [20]. First, berberine is metabolized by the intestinal drug-metabolizing enzymes during absorption [20], while the intestinal flora is not involved [23]. Second, part of the entered berberine is pumped out of the intestinal epithelial cells since it is the substrate of the intestinal P-glycoprotein (P-gp) [24-27]. Acturally, in the streptozocin-induced diabetic rats or LPS-pretreated rats, both the function and expression of the intestinal P-gp are impaired, the exposure of the R. coptidis alkaloids are thereby increased [14,15,28]. D-α-Tocopheryl polyethylene glycol 1000 succinate (TPGS), a water-soluble form of vitamin E with the biological activity of P-gp inhibition, at a concentration of 2.5% could improve both the maximal concentration (Cmax) and the area under curve (AUC) value of berberine by 2.9 and 1.9 times, respectively [21]. Third, almost a third of the berberine that enters the portal vein is first-pass eliminated in the liver [20].

2.3 Distribution

After absorption, the R. coptidis alkaloids [29-33] are combined with serum albumins due to electrostatic interactions, where a benzene ring and two adjacent methoxy groups are involved [34]. Some metal ions, including Cu²⁺, Ni²⁺, Zn²⁺ and Co²⁺ decreases the binding efficacy and increase the concentration of the free alkaloids simultaneously [35]. The binding rate of berberine with the serum albumins of rabbits is around 38% [36].

The absorbed alkaloids are quickly and widely distributed in tissues, such as brain [37], intestine, stomach, pancreas, heart, kidney, liver, spleen, lung, testicle and uterus [19,20,38]. The tissue concentrations of the R. coptidis alkaloids are generally much more higher than that in the circulation, but liver is the largest organ [19,20], where the concentration of berberine is around 70 times higher than that in the circulation [20]. The dominant tissue distribution suggests that some active transport mechanisms are involved in the
absorption of the alkaloids. For instance, berberine is the substrate of both organic cation transporter 1 and 2 (OCT1/OCT2) [39]. In another experiment, the OCT inhibitor cimetidine could decrease the transport of berberine into the neurons [40]. Since the *R. coptidis* alkaloids are also the substrates of P-gp, which pumps the drugs out of the tissues, therefore, the active transportation of the *R. coptidis* alkaloids must be of high efficiency. The concentration of the tissue distribution of alkaloids are not only higher than that in circulation, but also are eliminated with slower rate [41]. Furthermore, the tissue concentrations of the alkaloids increase non-linearly with higher doses [19].

### 2.4 Metabolism

The *R. coptidis* alkaloids are eliminated mainly by metabolizing in vivo. Up to 11 metabolites were detected in the urine of human after oral administration of a *R. coptidis* extract (groenlandicine 3-O-β-D-glucuronide, dehydrocorydalmine 10-O-β-D-glucuronide, jatrorrhizine 3-O-β-D-glucuronide, corydalmine 2-O-β-D-glucuronide, berberrubine 9-O-β-D-glucuronide, jatrorrhizine 3-O-sulfate, demethyleneberberine 2-O-sulfate, dehydrocorydalmine 10-O-sulfate, 3,10-demethylpalmatine 10-O-sulfate and 2,3,10-trihydroxyberberine 2-O-sulfate), which are mainly the sulfate or glucuronide conjugates of the Phase I metabolites of berberine, which are formed by cleavage of the dioxygenmethene five-membered ring or demethylation of berberine, including berberrubine, thalifendine, demethyleneberberine and jatrorrhizine [23,43,44]. Twelve metabolites were found in rat feces, 13 metabolites in urine, 7 metabolites in plasma and 10 metabolites in intestinal flora after oral administration of palmatine [45]. In rats, jatrorrhizine undergoes the reactions including hydroxylation, methylation, demethylation and dehydrogenation, and finally forms 17, 13, 11 and 17 metabolites in urine, feces, plasma and intestinal flora, respectively [46].

In rat liver microsomes, the Phase I metabolism of berberine is mainly mediated by cytochrome P450 isoenzymes (CYPs) including CYP3A1/2 and CYP2B, while the Phase II metabolism is mainly mediated by uridine 5-diphosphate glucuronosyltransferase isoenzymes (UGT) including UGT1A1 and UGT2B1 [47]. However, in mice and human microsomes, CYP2D6 plays a major role in berberine metabolism, followed by CYP1A2 and CYP3A4 [44,48]. These results suggest potential interspecies variety of the metabolism of berberine. Berberine is mainly metabolized in liver [23,49], but the intestinal flora plays a significant role in the enterohepatic circulation of the metabolites [23], which may be related to the multiple peaks phenomenon of the pharmacokinetics of the *R. coptidis* alkaloids [50].

**Figure 1.** Structures of four *Rhizoma coptidis* alkaloids (berberine, coptisine, palmatine and jatrorrhizine).
Table 1. Pharmacokinetics of the *Rhizoma coptidis* alkaloids after oral administration.

<table>
<thead>
<tr>
<th>Subjects/animals</th>
<th>Drugs administered</th>
<th>Dosages</th>
<th>Detected compounds</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (ng/ml)</th>
<th>T&lt;sub&gt;max&lt;/sub&gt; (h)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rats</td>
<td><em>R. coptidis</em> extract</td>
<td>1.3 g/kg</td>
<td>Berberine</td>
<td>11.4</td>
<td>3.4</td>
<td>[106]</td>
</tr>
<tr>
<td>Rats</td>
<td>Berberine</td>
<td>40 mg/kg</td>
<td>Berberine</td>
<td>10</td>
<td>2</td>
<td>[23]</td>
</tr>
<tr>
<td>Rats</td>
<td>Berberine</td>
<td>100 mg/kg</td>
<td>Berberine</td>
<td>10</td>
<td>4</td>
<td>[20]</td>
</tr>
<tr>
<td>Rats</td>
<td>Berberine</td>
<td>100 mg/kg</td>
<td>Berberine</td>
<td>9.5</td>
<td>2.6</td>
<td>[21]</td>
</tr>
<tr>
<td>Healthy volunteers</td>
<td>Berberine</td>
<td>400 mg/person</td>
<td>Berberine</td>
<td>0.4</td>
<td>10</td>
<td>[107]</td>
</tr>
<tr>
<td>Beagle dogs</td>
<td>Berberine</td>
<td>280 mg/dog</td>
<td>Berberine</td>
<td>15.5</td>
<td>3.2</td>
<td>[108]</td>
</tr>
<tr>
<td>Beagle dogs</td>
<td>Palmatine</td>
<td>300 mg/dog</td>
<td>Palmatine</td>
<td>8</td>
<td>5</td>
<td>[109]</td>
</tr>
</tbody>
</table>

C<sub>max</sub>: Maximum plasma concentration; T<sub>max</sub>: Time to reach maximum plasma concentration.

2.5 Excretion

After intravenous injection, as low as 4.93 and 0.5% of berberine is excreted directly in urine and bile juice, respectively [51]; P-gp is involved in the latter process [49]. In healthy volunteers, only 0.013% of berberine is eliminated directly in urine after oral administration [52]. While the metabolites are mainly eliminated via urine [42], part of them are also eliminated through bile [23].

3. Potential HDIs of the *R. coptidis* alkaloids

3.1 Potential HDIs during absorption and distribution

The *R. coptidis* alkaloids, especially berberine may induce HDIs at ADME (absorption, distribution, metabolism, excretion) process. On the aspect of both absorption and distribution, the potential HDIs are mainly related to P-gp. The *R. coptidis* alkaloids are not only the substrates of the intestinal P-gp [24], but also regulate it. Single dose of berberine has dual effects on modulating the activity of the P-gp in the jejunum of rats, which stimulates at lower concentration and inhibits at higher concentration [53]. After oral administration for 2 weeks, berberine dose-dependently increased the bioavailability of the oral cyclosporine A (CsA) and digoxin in rats via inhibiting the intestinal P-gp [54]. But in an *in vitro* absorption experiment using Caco-2 cell line, the *R. coptidis* alkaloids including berberine, coptisine, palmatine and jatrorrhizine did not influence the efflux of rhodamine-123 (Rho-123), which is a substrate of P-gp [27]. It was also reported that the repeated administration of berberine may up-regulate the function of P-gp in Caco-2 cells [26]. On the aspect of distribution, in an *in vitro* experiment using primary cultured rat brain microvascular endothelial cells (rBMEC), berberine showed a bidirectional effects on the activity of P-gp on blood–brain barrier (BBB), with inhibition from 0.01 to 1 µg/ml and stimulation from 2 to 10 µg/ml [55]. The modulation effect of berberine on P-gp may also influence the curative effect of chemotherapy drugs given that P-gp is involved in the multidrug resistance (MDR) of tumor cells. Single dose of berberine showed P-gp reversal activity similar to verapamil and increased the cytotoxicity of paclitaxel to MDR tumor cells [56]. However, repeated application of berberine up-regulated both the expression and function of P-gp, thus led to reduced response to paclitaxel in digestive track cancer cells [57] and hepatoma cells [58]. To sum up, berberine shows dose-, time- and organ-dependent bidirectional effects on P-gp, more detailed influence involved has yet to be elucidated.

On the other hand, berberine may influence the absorption of victim drugs by modulating the activity of the intestinal drug-metabolizing enzymes, especially for those which undergo extensive intestinal metabolism. For example, berberine can markedly increase the systemic exposure of CsA in both healthy volunteers and renal-transplant recipients, which are speculated to be related with inhibition of intestinal CYP3A4 [59,60]. During transportation in the blood, berberine can displace warfarin, thiopental and tolobutamide from plasma protein, finally increases the blood concentrations of the free drugs as well as their *in vivo* activities [61].

3.2 Potential HDIs during metabolism

On the aspect of metabolism, generally, the *R. coptidis* alkaloids show inhibitory effects on various drug-metabolizing enzymes. Based on *in vitro* experiments, the *R. coptidis* extract shows strong inhibition of CYP2D6, followed by CYP1A2 and CYP3A4 [62]; berberine shows inhibition of CYP1A1 [63-66], CYP2C9 [67], CYP2D6 [62,67,68] and CYP2E1 [69]; coptisine shows inhibition of CYP2D6, and a weak inhibition of CYP1A2 [62]; epiberberine shows inhibition of CYP2D6 [62]; both palmatine and jateorrhizine show inhibition of CYP3A4 [70], and weak inhibition of CYP2D6 [62]. On the other hand, repeated administration of berberine inhibited the activities of CYP2D6, CYP2C9 and CYP3A4 in humans [71] and CYP3A11, and CYP2D22 in mice [72]. Inhibitory effects of berberine on the activities of the drug-metabolizing enzymes may lead to increased systemic exposure of the co-administered drugs such as ketoconazole, a clinical antifungal agent [73]. However, after
For the past decades, the toxicities and related toxic mechanisms of R. coptidis alkaloids have been a matter of concern. The safety issues of R. coptidis were noticed by ancient doctors of China. Both in Ben Cao Gang Mu (Compendium of Materia Medica) and Ben Cao Yan Yi (Augmented Materia Medica), classical works of TCM, the authors have recommended a short period of treatment with R. coptidis for all patients, and this drug was forbidden to use in patients suffering from general debility. Ben Cao Yan Yi also have stated that although the R. coptidis extract is an excellent therapeutic agent for dysentery, the dosage should be adjusted based on the severity of the disease; otherwise, the health of the patient would be endangered. To alleviate the noxious side effects, Ben Cao Gang Mu have recommended R. coptidis be prescribed with other TCMs. Actually, R. coptidis is seldom used alone in clinic.

However, the toxicities and related toxic mechanisms of R. coptidis are still not quite clear. For the past decades, R. coptidis has been banned in Singapore, because berberine, the primary compound in R. coptidis, was believed to induce neonatal jaundice in neonates with glucose-6-phosphate dehydrogenase deficiency. However, the controversy has not stopped up to now [75, 76]. On the other hand, the R. coptidis extract has been reported to cause acute toxicity in animals. Calculated by the weight of the dried herbal pieces, the median lethal dose (LD50) of the oral R. coptidis in mice was 4.9 g/kg [77]; 8.1 g/kg was 100% lethal [78]. The clinical conventional dose of R. coptidis is about 5 – 10 g per adult in China. The equivalent surface area dose of mouse is about 1.50 g/kg. The ratio of the LD50 value to the conventional dose is thus calculated to be about 3 – 6, which suggests that the safety of R. coptidis is not high enough. Oral berberine has caused respiratory failure, extrapyramidal system reactions, severe arrhythmia, liver function injury and even death in clinics in China [79]. These reports suggest that R. coptidis may be acute toxic. Hence, the safety issues of R. coptidis are related to its acute toxicity.

It was concluded that the R. coptidis alkaloids, especially berberine, are the toxic constituents in the R. coptidis extract based on following findings: i) an alkaloid-rich extract of R. coptidis was much more toxic than the R. coptidis extract; ii) relatively high concentration of the R. coptidis alkaloids were detected in the tissues of mice that received the oral R. coptidis extract; iii) phenobarbital sodium, a non-selective CYPs inducer, decreased the tissue concentrations of alkaloids as well as the toxicity of the R. coptidis extract; iv) the R. coptidis alkaloids, especially berberine, presented in vitro cytotoxicity in dose- and time-dependent manners in several cell lines [19].

As for the toxic mechanism, the intravenous injected berberine is able to induce Adams–Stokes syndrome due to cardiac depression [80]. Recently, it was reported that berberine especially dihydroberberine, one of its metabolite, showed inhibitory effect on hERG channel [81], which plays an important role in the electrical activity of the heart. Inhibition of the hERG channel result in a potentially fatal disorder called long QT syndrome which can lead to sudden death. Therefore, cardiac toxicity may be one of the causes of death. On the other hand, the R. coptidis alkaloids show strong acetylcholinesterase (AChE) inhibitory effects [9, 82]. As is known, over-inhibition of AChE is lethal such as organophosphorus pesticides. The authors have reported that neostigmine, an AChE inhibitor, significantly increased the acute toxicity of the R. coptidis extract, whereas pyraloxime methylchloride, a cholinesterase reactivator, significantly decreased the acute toxicity of the extract [28]. Furthermore, given that the R. coptidis extract showed in vitro AChE effects, and the tissue concentrations of the R. coptidis alkaloids in mice received the toxic dosages of the oral R. coptidis extract [19] were higher than the in vitro inhibitory concentration of the R. coptidis alkaloids [9], the authors have drawn a conclusion that the acute toxicity of the oral R. coptidis extract is related to AChE inhibition [28]. Berberine also induces mitochondrial dysfunction through interacting with the adenine nucleotide translocator, which may be related to its organ toxicity [83, 84]. In addition to this, berberine aggravated
R. coptidis alkaloids. Acute toxicity is one of the safety issues of the UGTs (rat UGT1A1 and UGT2B1). On the other hand, (mouse and human CYP2D6, rat CYP3A and CYP2B) and OCT1/OCT2, drug-metabolizing enzymes including CYPs alkaloids: drug transporters such as P-gp and R. coptidis alkaloids may be complicated and remains to be studied. Related to both cardiac depression and AChE inhibition. Following factors are involved in the in vivo process of the R. coptidis alkaloids: drug transporters such as P-gp and OCT1/OCT2, drug-metabolizing enzymes including CYPs (mouse and human CYP2D6, rat CYP3A and CYP2B) and UGTs (rat UGT1A1 and UGT2B1). On the other hand, the R. coptidis alkaloids show bidirectional effects on P-gp and broad inhibition of CYPs, which suggest that they have potential HDIs. Acute toxicity is one of the safety issues of the R. coptidis alkaloids, especially berberine, which may be related to both cardiac depression and AChE inhibition.

6. Expert opinion

6.1 Ways of the R. coptidis alkaloids to present systemic therapeutic actions

As reviewed at the beginning of the article, the R. coptidis extract as well as berberine is commonly used in clinics due to various pharmacological properties. However, researchers have been confused for quite a long time because the plasma concentrations of the R. coptidis alkaloids are too low to produce any efficacy. The alkaloids may present their systemic therapeutic actions via generated metabolites because they are both abundant [23] and active [44,81], or by the relatively dominant tissue distribution of the alkaloids themselves [19,20,41]. Furthermore, in pathological conditions such as diabetes mellitus [14], and LPS-related diseases [15,28], the exposure of the R. coptidis alkaloids are much higher than that detected in normal experimental animals or healthy adult subjects. The alkaloids may also present their systemic therapeutic actions by modulating effectors in the gut. For example, berberine may present its antihyperglycemic activity by inhibiting α-glucosidase and decrease glucose transport through the intestinal epithelium [86], promoting glucagon-like peptide-1amide secretion [87], or modulating gut microbiota [88]. On the other hand, several diseases, where R. coptidis is useful therapy, are associated with endotoxemia, including ulcerative colitis [89], acute gastrointestinal syndrome [90], cardiac-related diseases [91], diabetes [92] and hepatic fibrogenesis [93]. Endotoxemia plays important pathological roles in these diseases. It is induced by systemic exposure to LPS, which may be derived from bacterial and endotoxin translocation from the intestinal lumen [94]. However, intestinal bacteria and endotoxins translocation do not normally occur in the healthy adult subjects and experimental animals, because the gut barrier restricts macromolecular permeation and almost completely restricts macromolecular permeation in normal subjects and experimental animals [95]. Therefore, the protective effects on gut barrier [96,97] may be one of the most important mechanisms of the systemic therapeutic actions of the R. coptidis alkaloids.

6.2 Methods to improve the oral bioavailability of the R. coptidis alkaloids

Anyhow, the absolute bioavailability of the R. coptidis alkaloids is very low. In terms of berberine, the absolute bioavailability is below 1% [20,21]. In order to improve the oral bioavailability and efficacy of the R. coptidis alkaloids, some derivatives with better pharmacokinetic features of the alkaloids were designed [98,99]. By using pharmaceutical preparation technologies, the bioavailability of the R. coptidis alkaloids was significantly improved. The bioavailability of an oral berberine-loaded microemulsion formulation (15 wt.% oleic acid, 17 wt.% Tween-80, 17 wt.% PEG-400 and 51 wt.% water) was 6.47 times greater than that of the berberine tablet suspensions [100]. Chitosan showed enhanced effect on the absorption of berberine due to its ability to improve the berberine paracellular pathway in the intestinal tract; formulations containing 0.5, 1.5 and 3.0% chitosan resulted in improved AUC values of berberine by 1.9, 2.2 and 2.5 times, respectively [101]. Using soy phosphatidylcholine as emulsifier, a berberine-containing water-in-oil (W/O) emulsion enhanced the oral bioavailability of berberine 2.4-fold, and the maximum blood concentration 2.1-fold [102]. These works are very important for further research and development of the R. coptidis alkaloids. It was suggested that only when the oral dosage of berberine is as high as 41.6 g/kg, the blood concentration of berberine could be higher than 0.4 μg/ml [18]. Given that the daily dose of berberine for an adult recommended in China is only 0.3 – 0.9 g, to improve the oral bioavailability to some degree is not only safe but also helpful to promote the effect of berberine. However, one must keep in mind that the tissue concentrations of the alkaloids and the metabolites are already very high; the R. coptidis alkaloids are not only effective but also toxic [19]. The increased bioavailability of the alkaloids may lead to acute toxicity [18,28]. Based on reports and this study, the authors proposed that the acute toxicity is one of the safety issues of the R. coptidis extract, which is related to both cardiac depression and AChE inhibition of the R. coptidis alkaloids, especially berberine. In brief, it is not wise to improve the bioavailability of the alkaloids as much as possible.
6.3 Factors influencing the ADME of the *R. coptidis* alkaloids

The factors that influence the *in vivo* ADME of the *R. coptidis* alkaloids are: drug transporters such as P-gp and OCT1/2 and drug-metabolizing enzymes including CYPs and UGTs. The co-administered drugs which modulate these factors may present significant impact on the pharmacokinetics of the *R. coptidis* alkaloids, and finally lead to changed *in vivo* activities. For example, the pretreatment of *Fructus evodiae* decreased the systemic exposure of the *R. coptidis* alkaloids by inducing hepatic UGT1A1 [50]; LPS increased the acute toxicity of the oral *R. coptidis* extract in mice by increasing the systemic exposure to the *R. coptidis* alkaloids [28], due to the enhancement of their absorption, which was related to the decreased intestinal efflux (mediated by P-gp) and metabolism (mediated by intestinal CYPs and UGTs) [15]. Furthermore, the solubility is the basic and important physicochemical property as well as the fundamental parameter for the absorption properties of a compound. Generally, the pure *R. coptidis* alkaloids are poorly dissolved in water. The poor solubility may be another important reason for the poor bioavailability of the *R. coptidis* alkaloids. By using the complexation technique, the aqueous solubility of berberine improved almost 4.5-fold in the presence of 20% HP-β-CD (2-hydroxypropyl-β-cyclodextrin) [103]. The improved solubility may lead to improved bioavailability as well as *in vivo* activities of the *R. coptidis* alkaloids.

6.4 Potential HDIs of the *R. coptidis* alkaloids

The *R. coptidis* alkaloids show bidirectional effects on P-gp. They also show broad inhibitory effects on CYPs. Both these effects suggest that they have potential HDIs. Unexpected drug-drug interactions (DDIs) always lead to adverse drug reactions (ADRs) or loss of therapeutic efficacy of the victim drugs [104,105]. However, predictable HDIs may be beneficial. For example, berberine can markedly elevate the blood concentration of CsA in renal-transplant recipients, which allows a reduction of the dosages of the expensive CsA [60]. Also, pharmacokinetic interactions between berberine and co-administered ketoconazole may benefit their pharmacodynamic synergism to a certain level [73].

6.5 Future directions

As reviewed above, the authors have concluded that the alkaloids, especially berberine were the toxic constituents of the *R. coptidis* extract. However, reportedly, the oral pure berberine showed only weak acute toxicity in mice due to extraordinary low bioavailability [18]. It is interesting to find that the acute toxicity of pure berberine differs from that of the *R. coptidis* extract, which suggests that at therapeutic dosage, the *in vivo* activities of the oral pure berberine may be weaker than that of the *R. coptidis* extract. This is important for the clinical applications of the *R. coptidis* extract and the pure alkaloid. For example, for a systemic disease, the *R. coptidis* extract may be better than the pure alkaloid; however, for a local gastrointestinal disease, berberine may be a better choice. The authors assumed that the difference may be caused by their pharmacokinetic properties, although the detailed mechanism remains to be elucidated.

Generally, not blood concentration but tissue concentration determine the efficacy of a drug. However, because blood concentration is usually proportional to tissue concentration and it is feasible in clinic, it is usually monitored to reflect the systemic exposure of a drug. But in the case of the *R. coptidis* alkaloids, very significant difference exists between the blood concentration and the tissue concentration. Therefore, to find a suitable pharmacokinetic marker for the *R. coptidis* alkaloids may be challenging but necessary.

As reported previously [19], 4.00, 3.20, 2.56, 2.05 and 1.64 g/kg of a *R. coptidis* extract caused death of 85, 80, 75, 30 and 25% of the mice, respectively. On the other hand, the ratio of the LD₅₀ value to the conventional dose is only about 3 – 6; both data suggest that a small increase in the dose of the *R. coptidis* extract has a big effect on response (steep slope in dose-effect curve). The authors have reported that the tissue concentrations of the alkaloids increase non-linearly with higher doses [19]. However, up to now, the dose-systemic exposure-response relationships of the *R. coptidis* alkaloids are not clear yet. To guide the clinical applications of the *R. coptidis* alkaloids, the related studies are badly needed.

**Declaration of interest**

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B-L. Ma & Y-M. Ma

Bibliography

Papers of special note have been highlighted as either of interest (●) or of considerable interest (◆) to readers.

13. • A comprehensive review discussed the various pharmacological effects of berberine.
15. • An important study on the herb-disease interaction of the R. coptidis alkaloids.
22. Ma BL, Ma YM, Gao CL, et al. • The first report which demonstrated berberine as the substrate of P-gp.
23. Ma BL, Ma YM, Gao CL, et al. Lipopolysaccharide increased the acute
Pharmacokinetic properties, potential herb–drug interactions and acute toxicity of oral *Rhizoma coptidis* alkaloids
toxicity of the *Rhizoma coptidis* extract in mice by increasing the systemic exposure to *Rhizoma coptidis* alkaloids.
J Ethnopharmacol 2011;1:169-74
Biomacromolecules 2009;3:517-21
Mol Biol Rep 2010;8:3827-32
49. Tsai PL, Tsai TH. Hepatobiliary excretion of berberine. Drug Metab Dispos 2004;4:405-12
Table 1: Effects of Berberine on Various Biological Processes

<table>
<thead>
<tr>
<th>Process</th>
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<tr>
<td>Human cytochrome P450 inhibition and metabolic-intermediate complex formation by goldenseal extract and its methylenedioxyphenyl components.</td>
<td>Drug Metab Dispos 2003;11:1391-7</td>
</tr>
<tr>
<td>The in vitro inhibition of human CYP1A2, CYP2D6 and CYP3A4 by tetrahydropalmatine, neferine and berberine.</td>
<td>Phytother Res 2011;2:277-83</td>
</tr>
<tr>
<td>An interesting study which suggested that predictable HDIs may be beneficial.</td>
<td></td>
</tr>
<tr>
<td>The interactions of berberine displace other drug from their plasma proteins binding sites.</td>
<td>Chin Pharmacol Bull 2002;5:576-8</td>
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• The bioavailability of berberine was tremendously improved by using the method introduced.

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