Advance in Pre-Clinical Pharmacokinetics of Paeoniflorin, a Major Monoterpene Glucoside from the Root of *Paeonia lactiflora*

Orleans N. K. Martey¹,², Xiaoyan Shi¹, Xin He¹,³*

¹School of Chinese Materia Medica, Tianjin University of Traditional Chinese Medicine, Tianjin, China; ²Centre for Scientific Research into Plant Medicine, Akwapim-Mampong, Ghana; ³Tianjin State Key Laboratory of Modern Chinese Medicine, Tianjin, China.

Email: ³hexintn@163.com

Received July 27th, 2013; revised August 29th, 2013; accepted September 15th, 2013

Copyright © 2013 Orleans N. K. Martey et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

Paeoniflorin (PF) is one of the main bioactive components of total glucosides of paeony (TGP) extracted from the root of *Paeonia lactiflora* Pall. TGP exhibit various biological activities such as improvement in memory, hepatoprotection, antimutagenic properties and platelet aggregation inhibition. The aim of this paper is to review the pharmacokinetics (PK) of PF as a pure compound and in single or multiple herb(s) of traditional Chinese medicine (TCM) prescriptions. The distribution of PF or PF in TCM fitted one or two compartmental model after oral administration or intravenous injection, respectively. However, PF has a low bioavailability (BA) in rabbit (7.24%) and rat (3.24%) after oral administration. The PK profiles and BA of PF were remarkably improved when co-administered with sinomenine or glycyr rhizic acid. The PK profiles and BA of PF in Radix Paeonia Rubra (RP-R) and Jing-zhi guan-xin were improved, but in co-administration of RP-R with Radix Angelicae Sinensis, the BA was significantly reduced. PK profiles and BA of PF in Shan yao gan-cao tang or Danggui-Shaoyao-San was either remarkably improved or not. However, neither the PK profiles nor the BA of PF in Radix paeonia alba, Huangqin-tang Si ni san or Tang-Min-Ling-Wan was improved. Metabolism in the liver did not play any role in the low oral BA of PF. The low BA was thus attributed to poor permeation due to low lipophilicity, P-glycoprotein mediated efflux, intestinal bacteria and hydrolytic degradation in the intestine by the intestinal brush border lactase phlorizin hydrolase (LPH) and certain esterases. These findings show the *in vivo* course of PF and provide information on the maximum biological actions of PF that may help traditional Chinese herbal medicinal practitioners.

Keywords: Bioavailability; Intestinal Bacteria; Pharmacokinetics; Paeoniflorin (PF); P-glycoprotein (P-gp)

1. Introduction

*Paeonia lactiflora* Pall is a Chinese herb commonly known as Baishao or white peony (*Figure 1*) from the Ranunculaceae family. According to traditional Chinese medicine (TCM), *P. lactiflora* functions either as a single herb or in combination for nourishing blood and Yin, calming the liver to relieve pain and suppressing hyperactive liver-Yang. *P. lactiflora* is used as an analgesic, anti-inflammatory and antispasmodic drug in the treatment of amenorrhea, dysmenorrhea, and pain in the chest and abdomen. Radix Paeniae is also used to treat dementia, headache, vertigo, spasm of the calf muscles, liver disease, and allergies, and as an anticoagulant [1-4].

Chemical compounds isolated from *P. lactiflora* include pentagalloylgucose, paeonilactones A, B and C, paeonol, benzoic acid, trihydroxybenzoic acid, gallic acid and monoterpene glucosides such as paeoniflorin, oxyypaeoniflorin, iso-benzoylpeoniflorin, 4'-O-methyl-paeoniflorin, iso-paeoniflorin, isobenzoylpeoniflorin 3'-O-galloyl-paeoniflorin, 4'-O-galloyl-paeoniflorin, albiiflorin, 4'-O-galloylalbiflorin, 6'-O-beta-D-glucopyranosylalbiflorin, and 6'-O-benzoylalbiflorin [5-9].

Paeoniflorin (PF) (*Figure 2(a)*), the major bioactive monoterpene glucoside from *P. lactiflora* is characterised as a neutral compound (MW 428.47) with good solubility (log P = 2.88) indicating low lipophilicity (http://www. chemnetbase.com). Pharmacological studies have indicated that PF has anti-inflammatory [10], anti-coagulant...
Advance in Pre-Clinical Pharmacokinetics of Paeoniflorin, a Major Monoterpene Glucoside from the Root of Paeonia lactiflora

2. Pharmacokinetics and Poor Oral Bioavailability of PF as a Pure Compound

2.1. Pharmacokinetics of PF as a Pure Compound

The pharmacokinetics of PF as a pure compound has been studied in different species and different routes of administration. The plasma concentration-time curve for dog, rabbit and rat in different papers showed species-independency after intravenous injection [19-23] (Table 1). The logarithmic plasma concentration-time curve of PF (30 mg/kg) in rats after intravenous injection showed a rapid decline initially but then slowed eventually (Wang et al., 2008), thus resulting in a biphasic curve characterized by 

\[ C = C_1e^{-\lambda_1t} + C_2e^{-\lambda_2t}, \]

where, \( C_1 \) and \( C_2 \) refer to the plasma drug concentration given by the corresponding zero-time intercept, and \( \lambda \) is the rate constant with an associated half-life, \( t \). This distribution could therefore be fitted into a two-compartment model as distribution equilibrium is reached between plasma and highly perfused tissues with further redistribution from well-perfused tissues to less-perfused tissues during

<table>
<thead>
<tr>
<th>Parameter (s)</th>
<th>Rabbit (n = 5)</th>
<th>Dog (n = 3)</th>
<th>Rat (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (mg/kg)</td>
<td>25.00</td>
<td>11.25</td>
<td>30.00</td>
</tr>
<tr>
<td>( t_{1/2a} ) (min)</td>
<td>5.93 ± 2.69</td>
<td>6.30 ± 1.80</td>
<td>32.4 ± 16.8</td>
</tr>
<tr>
<td>( t_{1/2b} ) (min)</td>
<td>66.02 ± 27.63</td>
<td>133.4 ± 84.9</td>
<td>280.2 ± 108.6</td>
</tr>
<tr>
<td>( K_{21} ) (1/min)</td>
<td>0.052 ± 0.031</td>
<td>0.019 ± 0.007</td>
<td>0.0025 ± 0.0016</td>
</tr>
<tr>
<td>( K_{10} ) (1/min)</td>
<td>0.035 ± 0.006</td>
<td>0.004 ± 0.008</td>
<td>0.019 ± 0.008</td>
</tr>
<tr>
<td>( K_{12} ) (1/min)</td>
<td>0.069 ± 0.036</td>
<td>0.066 ± 0.024</td>
<td>0.005 ± 0.009</td>
</tr>
<tr>
<td>( V_C ) (mL/kg)</td>
<td>165.4 ± 59.7</td>
<td>84.5 ± 13.6</td>
<td>-</td>
</tr>
<tr>
<td>( V_N ) (mL/kg)</td>
<td>516.8 ± 0.32</td>
<td>539.2 ± 104.2</td>
<td>450 ± 250</td>
</tr>
<tr>
<td>CL (mL/min/kg)</td>
<td>6.11 ± 3.29</td>
<td>3.40 ± 1.00</td>
<td>7.66 ± 0.23</td>
</tr>
</tbody>
</table>

Values represent mean ± SD; \( K_{21} \): Transfer rate constant from the peripheral compartment (2) to the central compartment (1); \( K_{10} \): Elimination rate constant from the central compartment. \( K_{12} \): Transfer rate constant from the central compartment (1) to the peripheral compartment (2).
subsequent decline. However, a logarithmic plasma concentration-time curve of PF (300 mg/kg) after oral administration in rats showed fast absorption with a terminal linear decline of plasma concentration characterised by the monoexponential equation $C = C_{0}e^{-\lambda t}$. This distribution could therefore be fitted into a one-compartmental model as equilibrium is rapidly reached between plasma and highly perfused tissues [22].

PF have a low bioavailability of about (7.24 ± 4.15)% after 250 mg/kg intragastric (ig) dose in rabbits [19], and about (3.12 ± 0.76)% after oral administration in rats [21-23]. Takeda et al. [24] showed that the cumulative urinary and fecal excretions of PF at 5 mg/kg dose after intravenous injection were 50.5% and 0.22% of the dose within 7 h, 1.0% and 0.08% of the dose after oral administration within 48 h, respectively. The cumulative bile excretion after intravenous or oral administration in rats at a dose of 0.5 mg/kg were 6.9% and 1.3% of the doses within 24 h, respectively. The total renal and bile clearance was less than the total clearance value. This conforms to the findings of Chen et al. [20] who found out that after the ig administration of 550 mg/kg of PF, 10% and 1% of PF were removed from rat feces and urine, respectively, and that 8.64% could be recovered from the rat bile within 7 h after 55 mg/kg intravenous administration. PF was also rapidly removed from the blood by the kidney to 36.85% in 20 min and 79.33% in 7h of the accumulated recovery amount of excretion after 11.25 mg/kg total intravenous doses administered to dogs. An accumulated amount of only 3.77% within 7 h was also found in the bile after intravenous administration [19]. These results may be due to poor absorption from the gastrointestinal tract, decomposition in the intestine by bacterial microflora, and/or first-pass elimination in the gut wall or liver.

2.2. Poor Oral Bioavailability of PF in Vivo

PF as a single compound has a wide range of pharmacological actions but low bioavailability. In an in vivo assessment to estimate the first pass elimination by intestinal flora, the extraction ratios of PF in the gut wall, liver and lungs were assessed by comparing the AUCs after various routes of administration [21]. The plasma concentration profile of PF after intraportal administration [(0.5 and 5) mg/kg] was close to that of intravenous administration. The mean pulmonary extraction ratio from the veins and the arteries was also estimated to be 0.06. These findings suggest that PF has a negligible hepatic extraction ratio and that it is not metabolized in liver and lungs. Rather, the unbound fraction is degraded by intestinal flora (Bacteroides fragilis or Lactobacillus brevis) to form the 7S and 7R isomers of paeonimetaboline I as major metabolites, along with the 7R and 7S isomers of paeonimetaboline II as minor metabolites [25,26] (Figure 2).

Liu et al. studied the action of lactase phlorizin hydrolase (LPH, a brush border membrane-associated enzyme in intestinal cells that hydrolyze lactose) to PF using a single-pass four site rat intestinal perfusion model. There was significant decrease of PF to paeoniflorigenin (>80%) in the perfusate in the presence of LPH inhibitor, gluconolactone, with a lower apparent absorption in the upper small intestine. In this region, LPH is more active and esterases catalyse the hydrolysis of PF to form benzoic acid [27] (Figure 2).

3. Pharmacokinetics of PF in TCM Prescriptions

3.1. Pharmacokinetics of PF in a Single-Herb Prescription

Radix paeonia rubra (RP-R) and radix paeonia alba (RP-A) are two independent traditional Chinese herbal medicines, both of which are obtained from the root of P. lactiflora Pall. (Figure 1(b)) and have different pharmacological actions. The former is obtained directly from the dried roots of P. lactiflora Palls. grown wild, while the latter is from a decoction of the dried peeled roots of P. lactiflora Pall. grown domestically. RP-R reportedly exhibits pharmacological actions against coronary diseases (e.g., angina pectoris, chronic-cardiac ischemia, ventricular tachycardia, augmenting blood of coronary artery, anti-acute myocardial ischemia); it also features anti-platelet aggregation, anti-thrombogenesis, activation of fibrinolysis, antihyperlipidaemic effect, improvements in blood hyperviscosity syndrome and decreased blood pressure, anti-atherosclerosis, heart or liver protection, anti-tumor effects, and protection of neurons against kainic acid-induced neurotoxicity [28,29]. RP-A has been reported to exhibit anti-inflammatory, anti-viral, spasmylytic, analgesic and liver protection effects [30,31].

The pharmacokinetic differences of PF have been investigated in RP-R and RP-A with respect to its low bioavailability following oral administration in aqueous PF solution, decoction of RP-R and RP-A at doses of 300 mg/kg PF content by oral gavages in rats using a simple high-performance liquid chromatography (HPLC) method [22]. The oral absorption kinetics of PF in RP-R and RP-A were influenced when compared to PF alone following oral administration (Table 2). The absorption half-life of PF in RP-R was much delayed followed by PF in RP-A and then by PF alone. The peak time (t_{max}) occurred much longer in RP-R followed by RP-A and then by PF alone. This findings indicates that there was a delay in the absorption of PF until it reaches the value at which point the rate of elimination matches the rate of
absorption at maximum concentrations of PF in RP-R, RP-A and PF alone, respectively. However, the significantly decreased Cmax of PF in RP-A with a corresponding decrease in the area under the concentration-time curve (AUC) of (10.61 ± 1.56) µg·h/mL showed that even though there was a delay of absorption of PF in RP-A, there was a decrease in bioavailability when compared to PF in RP-R and PF alone, with AUC of (24.89 ± 7.41) µg·h/mL and (18.87 ± 7.54) µg·h/mL, respectively. These findings correspond to the remarkable improvement in the relative bioavailability of PF alone from 3.26% to 4.26% of PF in RP-R, but a remarkable decrease to 1.82% in RP-A after oral administration of PF solution.

In a similar study using an HPLC-electrospray ionization mass spectrometry, Feng et al. [32] investigated the pharmacokinetic properties of PF following oral administration of aqueous extracts of RP-R and RP-A containing 0.2 g/g crude drug to rats using an HPLC-ESI-MS method. The study also showed a higher Cmax, higher AUC0-\(\infty\) and decreased t\(_{1/2}\), which is consistent with the findings reported by Wu et al. [33] using a UPLC-ESI-MS/MS method. RP-R in the presence of Radix Angelicae Sinensis to rats using HPLC-MS/MS method [33]. RP-R in the presence of Radix Angelicae Sinensis can significantly reduce the bioavailability of PF in RP-R. The kinetic process of paeoniflorin in plasma showed two compartment model after oral administration of RP-A extract at doses of 0.2, 0.4, 0.8 g/kg to rats using an HPLC-MS/MS method [34].

The differences between the plasma concentration profiles of PF in RP-R or RP-A compared to PF alone is evidence of drug-drug interactions as a result of different complex chemical compounds present in herbal medicines. This could occur either by induction of metabolic enzymes, P-glycoprotein, LPH, esterase’s, or degradation by intestinal bacteria. It was reported by Feng et al. [32] that except for PF, the other monoterpene glycosides of albinoflorin, benzoypaeoniflorin and some acids of benzoic acid, trihydroxybenzoic acid were the common components existing in both drugs. Paeonol and paeoniflorin-sulfite were characteristic chemical constituents for RP-R and RP-A, respectively.

Patients are the final users of drugs and it will be interesting if pharmacokinetics studies are considered in animal models compared to normal animals. In a study, Jiang et al. [35], investigated the pharmacokinetics of PF in RP-R following intragastric administration of RP-R powder (low dose: 7 g/kg or high dose: 14 g/kg containing 357 mg/kg or 714 mg/kg PF, respectively) to normal rats (NR) and alpha-naphthylisothiocyanate induced acute cholestasis hepatitis (ACH) rats using Ultra Performance Liquid Chromatography (UPLC)-ESI-MS/MS method. This showed remarkable improvement in absorption kinetics in both low dose (LD) and high dose (HD) administered with increased AUC0-\(\infty\), increased AUC0-\(\infty\), high t\(_{max}\) and reduced CLz/F in the ACH rats compared to that of the normal rats with corresponding parameters shown.
in Table 4. The induced cholestasis is characterized by periportal bile duct epithelial degeneration and necrosis and a pronounced neutrophil infiltration which results in low levels of cytochrome P450 [36,37]. The increase in plasma concentrations and decreased clearance of PF in ACH rats compared to NR may be due to the disease condition. Similar results were observed by He et al. [38] on the effect of cerebral Ischemia-reperfusion (CIR) on pharmacokinetic fate of paeoniflorin after intravenous administration of Paeonia radix extract (at 60 mg/kg PF) to rats using an HPLC method. The CIR significantly, *P* < 0.05, increased, AUC [(9626.00 ± 1053.98) µg·min/mL], decrease CL [(0.0071 ± 0.0013) mg/(kg·min)] and prolong the half-life of distribution \(t_{1/2\alpha} (2.04 ± 0.84)\) min and elimination \(t_{1/2\beta} (24.51 ± 9.23)\) min compared to normal rats with corresponding parameters as (5338.71 ± 467.54) µg·min/mL, (0.0162 ± 0.0023) mg/(kg·min), 0.69 ± 0.19) min and (18.77 ± 3.74) min.

### 3.2. Pharmacokinetics of PF in Multiple-Herb Prescription

The pharmacokinetics of PF in single-herb extracts had been shown to be influenced by the complexity of other phytochemicals that may be present. Most TCM prescriptions are multiple herbal formulations. Thus, knowledge of the pharmacokinetics of marker compounds in the presence of other herbs cannot be overemphasized primarily due to its relevance to the biological actions or otherwise of the herbal prescription. Shao-yao Gancao Tang (SGT), which is composed of Radix *P. lactiflora* and Radix Glycyrrhiza uralensis, is one of the most famous Chinese prescriptions. SGT is widely used in China and Japan for acute abdominal pain and muscles stiffness. The pharmacokinetics of PF following oral administration of 2 mg/ml SGT extract (containing 10 mg/kg PF) to mice using a simple and rapid HPLC method was significantly improved compared to the kinetics data of PF after oral administration of Paeoniae Radix extract alone [39]. The results and the previously reported kinetic data of PF after oral administration of Paeoniae Radix extract alone [39]. The results and the previously reported kinetic data of PF after oral administration of Paeoniae Radix extract alone [39]. The results and the previously reported kinetic data of PF after oral administration of Paeoniae Radix extract alone [39]. The results and the previously reported kinetic data of PF after oral administration of Paeoniae Radix extract alone [39]. The results and the previously reported kinetic data of PF after oral administration of Paeoniae Radix extract alone [39]. The results and the previously reported kinetic data of PF after oral administration of Paeoniae Radix extract alone [39]. The results and the previously reported kinetic data of PF after oral administration of Paeoniae Radix extract alone [39]. The results and the previously reported kinetic data of PF after oral administration of Paeoniae Radix extract alone [39].

#### Table 4. Pharmacokinetics of PF in RP-R following intra-gastric administration of RP-R powder to normal (NR) and alpha-naphthylisothiocyanate induced acute cholestasis hepatitis (ACH) rats.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Normal Rats</th>
<th>ACH Rats</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC∞ (mg·h/L)</td>
<td>8.14 ± 0.62</td>
<td>16.58 ± 0.92</td>
</tr>
<tr>
<td>AUC0-∞ (mg·h/L)</td>
<td>9.64 ± 1.12</td>
<td>20.5 ± 0.61</td>
</tr>
<tr>
<td>t_{max} (h)</td>
<td>0.08 ± 0.00</td>
<td>0.44 ± 0.21</td>
</tr>
<tr>
<td>CLz/F (L/h/kg)</td>
<td>37.40 ± 4.18</td>
<td>34.78 ± 1.05</td>
</tr>
</tbody>
</table>

Values represent: mean ± SD.

looking at the pharmacokinetics of characteristic effective ingredients from individual and combination Shao-yao and Gancao (Glycyrrhiza Radix) treatment in rats using HPLC fingerprinting. In contrast, Gan et al. [41] reported low bioavailability of PF in SGT compared to PF in Radix Paeoniae decoction following oral administration of 60 g/kg SGT and 30 g/kg Radix paeonae decoction (165.7 mg/kg and 182.27 mg/kg PF) to rats using an UPLC method. The results showed decrease in AUC_{0-∞} [(2903 ± 92 vs 3846 ± 477) µg·h/L], AUC_{0-∞} [(2736 ± 164 vs 4046 ± 514) µg·h/L], AUC_{0-∞}/dose [(15.78 ± 0.84 vs 21.05 ± 2.61) µg·h/L/(mg/kg)], and AUC_{0-∞}/dose [(16.51 ± 0.99 vs 22.14 ± 2.81) µg·h/L/(mg/kg)] and high CLz/F [(60.8 ± 3.7 vs 45.9 ± 7.1) L/h/kg] of PF in SGT and Radix paeonae decoction, respectively.

The pharmacokinetic parameters (Table 5) of PF of Jing-Zhi-Guan-Xin (JZGX), composed of Radix *Salviae Miltiorrhizae*, Radix Paeoniae Rubrae, Rhizoma Chuanxiong, *Flos Carthami*, and Lignum Dalbergiae Odoraf erae, were remarkably improved when compared with that of Paeoniae Radix extract along (longer \(t_{max}\), increased \(C_{max}\); increased AUC_{0-∞}, longer MRT and a longer \(t_{1/2}\)) after oral administration, indicating that the absorption of PF after the oral administration of JZGX tablets was significantly greater than that of Paeoniae Radix extract alone and that it occurred with a significant increase in AUC after oral administration of JZGX tablets. These findings suggest that relatively more PF was absorbed [42].

Danggui-Shaoyao-San (DSS), composed of Radix *Angelica sinesis*, Radix *P. lactiflora*, *Sclerotium poriae* Cocos, *Atractylodis macrocephalae*, Rhizoma *Alisma orientalis* and Radix *Linguistici wlichii*, is clinically used for the treatment of vascular dementia (VD). The pharmacokinetics of PF (Table 6), either in pure form (224 mg/kg) or in DSS (3.54 g/kg containing 224 mg/kg PF) following oral administration to VD rats
Table 5. Pharmacokinetics parameters of PF following oral administration of SGT and JZGH to mouse and beagle dogs respectively compared to kinetic data of Radix poeny extracts (RPE).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>RPE</th>
<th>SGT</th>
<th>JZGH</th>
</tr>
</thead>
<tbody>
<tr>
<td>t_{max} (min)</td>
<td>14.0 ± 4.18</td>
<td>17.0 ± 4.47</td>
<td>130.00 ± 30.98*</td>
</tr>
<tr>
<td>C_{max} (ng/mL)</td>
<td>86.34 ± 18.67</td>
<td>111.56 ± 20.83*</td>
<td>210.49 ± 23.89*</td>
</tr>
<tr>
<td>AUC_{0-t} (ng·min/mL)</td>
<td>8126.97 ± 2004.62</td>
<td>12293 ± 1945.96*</td>
<td>-</td>
</tr>
<tr>
<td>AUC_{0-∞} (ng·min/mL)</td>
<td>9746.10 ± 2554.62</td>
<td>16335 ± 3641.46*</td>
<td>43066.50 ± 10119.51*</td>
</tr>
<tr>
<td>t_{1/2} (min)</td>
<td>94.00 ± 12.35</td>
<td>116.17 ± 35.02</td>
<td>147.52 ± 28.98*</td>
</tr>
<tr>
<td>CL/F (mL/min/kg)</td>
<td>1474.44 ± 40.78</td>
<td>103.05 ± 20.45*</td>
<td>-</td>
</tr>
<tr>
<td>Vd/F (L/kg)</td>
<td>135.64 ± 18.51</td>
<td>109.64 ± 50.12</td>
<td>212.87 ± 41.82*</td>
</tr>
</tbody>
</table>

Values represent: mean ± SD; compared with RPE *P < 0.05; **P < 0.01; SGT: Shao-yao Gan-cao Tang; JZGH: Jing-Zhi-Guan-Xin.

Table 6. Pharmacokinetics of PF, either in pure form or in DSS following oral administration to normal and vascular dementia rats.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Normal Rats</th>
<th>Vascular Dementia Rats</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PF</td>
<td>PF-DSS</td>
</tr>
<tr>
<td>t_{1/2} (h)</td>
<td>5.95 ± 1.53</td>
<td>6.94 ± 1.22</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>5.25 ± 1.05</td>
<td>10.47 ± 1.30</td>
</tr>
<tr>
<td>AUC (µg·h/mL)</td>
<td>7.89 ± 1.73</td>
<td>11.95 ± 1.75</td>
</tr>
</tbody>
</table>

Values represent: mean ± SD; PF: Paeoniflorin; DSS: Danggui-Shaoyao-San.

showed significant delay in absorption half life, prolonged mean resident time and an increase AUC compared to normal rats with t_{1/2} and AUC. These observations shows that the bioavailability of PF in DSS in VD was improved compared to PF in DSS and PF alone in NR [43]. Liu et al. also reported that the C_{max} of PF in DSS [(143 ± 65) ng/mL] was significantly lower than PF alone [(659 ± 147) ng/mL], with a corresponding AUC of PF in DSS [(242 ± 126) ng·h/mL] significantly lower than PF alone [(722 ± 158) ng·h/mL]. While a significant higher C_{max} [2132 ± 560 ng/mL.] with a remarkable increase AUC of PF in RP-A [(2259 ± 910) ng·h/mL] after oral administration to rats (calculated at a normalized dose of 20 mg/kg PF) using liquid chromatography-tandem mass spectrometry method. The contradiction of bioavailability of PF in SGT and DSS may be attributed to poor standardization from sourcing of raw material to final product. This may therefore contribute to differences in chemical composition and drug-drug interactions.

Huangqin-Tang, a compound prescription consisting of four medicinal herbs (i.e., Radix Scutellariae baikalensis, Radix P. lactiflora, Radix G. uralensis and Ziziphus jujuba Mill.) showed no significant difference in the pharmacokinetic parameters of PF in compound prescription compared with the single herb extract of P. lactiflora (Table 7) after oral administration containing 10 mg/kg PF content using a simple validated HPLC method [26]. Similarly, the results of a study (Table 8) conducted by Liu et al. [17] on the pharmacokinetics of PF between pure PF and Si Ni San, a TCM formulation composed of Radix Bupleurum falcatum L., Fructus immaqturus, Radix P. lactiflora, and Radix G. uralensis following oral administration were comparable. The pharmacokinetic parameters for PF in Si Ni San and PF alone were C_{max} (250.45 ± 36.17) µg/L, t_{max} (34.38 ± 26.78) min; and C_{max} (640.18 ± 125.86) µg/L, t_{max} (22.31 ± 8.28) min, respectively. The low bioavailability of PF in Si Ni San indicates that instead of PF responsible for the pharmacological effects, possibly its metabolites by intestinal bacteria and liver promoted by other components in Si Ni San [44].

Tang-Min-Ling-Wan (TMLW), another prescription of TCM containing Radix Scutellariae, Radix Paeoniae Alba, Rhizoma Coptidis, Radix et Rhizoma Rhei, Fructus...
Aurantium, Radix Bupleuri, Rhizoma Pinelliae, is used for hyperlipidemia and hyperglycemia and increasing insulin expression and antioxidant enzyme activity. It is used clinically in the treatment of type 2 diabetes mellitus and diabetic complications [45]. An HPLC-MS/MS method was developed and applied to pharmacokinetics of PF after oral administration of 55 mg/kg PF content of TWLW (11.0 g/kg) and RP-A extract (0.63 g/kg extract) by Tong et al. The peak concentration of PF in TWLW occurred more rapidly \[ t_{\text{max}} = (0.28 \pm 0.09) \text{ h} \] but with a higher plasma concentration \[ C_{\text{max}} = (1591 \pm 416.9) \text{ ng/mL} \] whiles the peak concentration of PF in RP-A extract occurred slowly \[ t_{\text{max}} = (0.89 \pm 0.27) \text{ h} \] but with a lower plasma concentration \[ C_{\text{max}} = (301.3 \pm 96.81) \text{ ng/mL} \].

A pharmacokinetic study after intravenous administration of PF alone reported by Wang et al. [22]. However, other compound prescriptions discussed in this review fits one compartmental model. This shows that the use of multiple herbs in a prescription can alter the pharmacokinetic status as well as its pharmacological effects.

4. Influence Factors on PF Absorption

4.1. Using the Everted Rat Gut Sac Model

The everted rat gut sac model [50] has also been used to establish that PF is not metabolised in the intestine. This showed a total recovery rate (in the serosal side, mucosal side and gut side tissue) higher than 97% and an uptake in the sac tissue about 10% with a saturation of PF absorption in the sac content at 80 µM [51]. The possibility that an energy-dependent carrier-mediated transport may be involved in the PF intestinal absorption has been speculated, since in vivo studies with an unrestricted conscious rat demonstrated that with co-administration with sinomenine (90 mg/kg), the peak plasma concentration of PF in rats was elevated, the peak time delayed, AUC0-t increased with prolonged MRT, clearance decreased and volume of distribution declined [52]. A similar outcome was reported upon co-administration of PF and glycyrrhizin acid [53] (Figure 2).

In the everted rat gut system the fraction of PF in the sac content was nearly elevated to 1.5-fold and 2.5-fold, respectively, when the gut sac was treated with 16 µM and 136 µM sinomenine in TC 199 medium for 45 min of incubation. Similarly, treatment of the gut sac with 100 µM verapamil and 1.3 mM quinidine significantly increased PF absorption in the sac content to 2.1-fold and 1.5-fold, respectively. These elevated levels of absorption of PF in the presence of inhibitors were consistent with that of digoxin (113 µM) a P-glycoprotein substrate, which was increasingly absorbed to about 2.5-fold when co-incubated with sinomenine (136 µM) relative to the non-sinomenine treated gut sac [51]. Studies on the effect of glycyrrhizin on the intestinal absorption of PF by the everted rat sac model also showed that PF could be absorbed in the duodenum, jejunum, ileum and colon of rats and glycyrrhizin can improve the efflux of PF from intestinal cells. These findings from the everted rat gut system therefore suggest that PF is not metabolised in the
intestine and that its low bioavailability may be due to P-gp mediated efflux, a hypothesis that was partly in conformity with the findings of Liu et al. [27] who investigated the mechanism for the poor oral bioavailability of PF and the role of intestinal disposition and interaction with sinomenine using a single-pass four site rat intestinal perfusion model and a cultured Caco-2 cell model.

4.2. Using the Rat Perfusion and Caco-2 Cells Models

In both model systems, absorption of PF was shown to be very poor. In the Caco-2 cell model, the apparent permeability from the apical to the basolateral was 0.48 \times 10^{-6} \text{ cm/s}. This value is similar to poorly absorbed compounds such as mannitol at 1.7 \times 10^{-6} \text{ cm/s} and sulfasalazine at 0.34 \times 10^{-6} \text{ cm/s} and is 23 times lower than propranolol at 11.3 \times 10^{-6} \text{ cm/s}, a highly absorbed compound [54,55]. The rat intestinal perfusion model also showed a similar results with \( P^\text{eff} < 0.4 \) in all four intestines lower than propranolol (\( P^\text{eff} > 3.5 \)) but similar to rutin (\( P^\text{eff} < 0.58 \)) and mannitol with \( P^\text{eff} < 0.3 \) [56]. Furthermore, in the perfusate model predominant intestinal metabolites of PF such as paeoniflorigenin and benzoic acid were found. The presence of the metabolites were not affected in the presence of cyclosporine A (5 \( \mu \text{M} \)) or sinomenine (100 \( \mu \text{M} \)), while absorption increased in the jejunum (45% to 55%) and terminal ileum (80% to 86%) but not in the duodenum [27].

Similarly, in the Caco-2 cell model, absorptive transport of PF was significantly (\( P < 0.05 \)) increased 38% by sinomenine, 27% by verapamil and 41% by cyclosporine A. In contrast, its secretory transport was significantly (\( P < 0.01 \)) decreased to 45% by sinomenine, 35% by verapamil and 37% by cyclosporine A. MRP inhibitors MK-571 and leukotriene C4 did not affect transport of PF. Sinomenine was also shown to significantly increase the absorptive transport of digoxin and significantly decrease its secretory transport.

5. Conclusion

PF administered alone has a low bioavailability. However in the presence of other phytochemicals, either in pure form or in single or multiple herb prescriptions, the bioavailability or the pharmacokinetics profiles may or may not be significantly enhanced. This could consequently have direct impact on its pharmacological actions. Different methods to determine the cause of its low bioavailability have shown that PF is poorly absorbed due to low lipophilicity, efflux through P-glycoproteins, hydrolytic degradation in the intestine by intestinal brush border LPH and certain esterases, as well as intestinal bacteria and without hepatic metabolism. However, the bioavailability may be improved with P-gp inhibitors (sinomenine) and LPH inhibitors. Methods that could be used to determine the mechanism of the low bioavailability of a compound needs serious consideration to be able to give good predictions about the in vivo course of the compound. Further work needs to be done to confirm the effect of glycyrrhizin acid on the improvement of the bioavailability of PF using the Caco-2 cell model and/or MDCK II-MDR 1 cells, and the four-site Perfusion model.

6. Acknowledgements

The Project Supported by Natural Science Foundation of Tianjin (No. 12JCZDJC26100); Research Fund for the Doctoral Program of Higher Education [RFDP, No. 20121210110011]; National Basic Research Program of China (973 Program) [No. 2012CB724001]; Program for Changjiang Scholars and Innovative Research Team in University (PCSIRT, No.IRT0973).

REFERENCES


Advance in Pre-Clinical Pharmacokinetics of Paeoniflorin, a Major Monoterpene Glucoside from the Root of *Paeonia lactiflora*


[50] R. Bouver, L. Barthe, C. Philibert, C. Tournarie, J. Wood-


