Recent advances in pharmacokinetics approach for herbal medicine

Kunming Zhang, Guangli Yan, Aihua Zhang, Hui Sun and Xijun Wang

Traditional Chinese Medicine (TCM), an indispensable part of herbal medicine, has been used for treating many diseases and/or symptoms for thousands of years. As we know, the main active components of TCM can account for its therapeutic effects. However, rational use of TCM faces a series of obstacles due to a large diversity of species and inaccurate knowledge of the active components. In recent years, more and more applications of new technologies or methodologies for investigating the active components of TCM have provided us with much additional information on active substances. Pharmacokinetics is an effective tool which can be used to investigate the many components of TCM. A pharmacokinetics approach reveals the dynamic processes of active components in vivo, including their absorption, distribution, metabolism, and excretion which offer guidance for clinical rational uses of TCM. Therefore, the objective of this paper is to review the current status of TCM, application of pharmacokinetics in investigating TCM, and emerging trends.

1. Introduction

Traditional Chinese Medicine (TCM), an indispensable part of herbal medicine, can be defined as the utilization of herbs, animals, and minerals, for prevention and treatment of various diseases or symptoms under the guidance of TCM theory; thus, TCM has been gradually accepted and employed in the world. In 2015, Dr Tu, a Nobel Prize winner in physiology and medicine, attracted more attention of the world to TCM. Worldwide, TCM has been used for protecting the health of mankind for centuries. At present, TCM has effects on curing liver injury, chronic hepatitis B, experimental sepsis, cancer, periodontal pathogens, influenza A, gastric cancer cells, anti-NDV, gastrointestinal disorders, and diabetes mellitus in clinical practices. TCM efficacy relies on its bioactive constituents. However, the kinds of active components or effective fraction of TCM that act on therapeutic effects and dynamic processes of the active components of TCM in vivo are still unclear and ambiguous.

Pharmacokinetics (PK), a new burgeoning technique, which is mainly used for investigating absorption, distribution, metabolism, and excretion of drugs in vivo, has been comprehensively applied to research the main active components of TCM. Currently, according to research data, PK coupled with other separation and identification techniques have important roles in screening the active components of TCM. Pharmacokinetic parameters, especially biological half time ($T_{1/2}$), clearance (CL), area under concentration-time (AUC), etc., indicate the dynamic processes of active components of TCM in vivo. By comparing the pharmacokinetic parameters of the active components of TCM, we can know the characteristics of the active components in vivo. These basic findings will provide evidence for clinical rational and use of TCM.

By deeply investigating TCM, we have learned how active components contained in it exert their therapeutic effects. For example, artemisinin was used to protect against malaria. Dimethylesculetin, geniposide, and rhein were effective fraction of TCM that act on therapeutic effects and dynamic processes of the active components of TCM in vivo are still unclear and ambiguous.

2. The status of TCM

TCM, which possess a history of thousands years of application in clinical practice, is gaining more and more attention and respect in the world. With the development of TCM-based new drugs, treatment of complex diseases becomes more promising.
and realistic. However, a huge number of diseases have weakened human health. Fortunately, a large number of research publications in recent years indicate that the active components of TCM are becoming good choices for curing cancers and minimizing side reactions. For example, report results showed that Xiao-Ai-Tong inhibited pain and adverse reactions following morphine treatment for bone cancer pain.\textsuperscript{31} And bufalin, an effective component in Chansu, was considered as a potential anti-hepatocellular carcinoma therapeutic active component by means of inhibiting hepatoma cell proliferation, migration, invasion and adhesion.\textsuperscript{32} Subamolide A was used to treat human urothelial carcinoma in clinical practice.\textsuperscript{33} Also, Nakamura K. and his colleagues found that cordycepin, an active component of Cordyceps sinensis, has anticancer and anti-metastatic effects.\textsuperscript{34} Currently, breast cancer has become the secondary cause of cancer deaths among women, and approximately 40 450 women died of breast cancer in 2015.\textsuperscript{35} Fortunately, a lot of evidence shows that some active components of TCM will play an important role in treating breast cancer. Paclitaxel, a diterpenoid alkaloid, has been clinically used as therapy for breast cancer.\textsuperscript{36} Polygonatum odoratum extract has an effect on breast cancer by suppressing proliferation of breast cancer cells and inducing its apoptosis.\textsuperscript{37} According to the research of Shen K., cambogin, a bioactive component of Garcinia genus, also has a significant effect on breast cancer.\textsuperscript{38} At the same time, compound Kushen injection, as a candidate, was used to treat MCF-7 human breast cancer cells.\textsuperscript{39} Xue B., et al. found that anti-EV71 components can treat hand-foot-and-mouth disease which results from intestinal virus infection.\textsuperscript{40} Tetramethylpyrazine, an active component in Chuanxiong, might exert beneficial effects in primary open-angle glaucoma patients via regulating CXCR4 expression.\textsuperscript{41} Diammonium glycyrrhizinate liquor extract exerted a significant effect on hepatitis via its anti-inflammatory effects in clinical practice.\textsuperscript{42} And finally, Cortex Moutan showed important in vitro anti-diabetic effects via suppressing glucose uptake.\textsuperscript{43} In recent years, the literature shows that identification of the components of TCM has made great progress, which should help to guide clinical rational drug use of TCM. Application of some analytical technologies makes an investigation of the components of TCM more rapid and accurate. Recent research results indicate that a rapid, sensitive, and effective method, high-performance liquid chromatography [HPLC] combined with mass spectrometry [MS], is useful for screening and identifying the components of a formula (Fig. 1). A total of 169 compounds were simultaneously identified and 11 of them were confirmed by high-performance liquid chromatography combined with mass spectrometry [HPLC-MS] in Xiang-Sha-Liu-Jun-Zi-Jia-Jian granules.\textsuperscript{44} Twenty active components, originating from Zhi-Zi-Da-Huang decoction, were quickly determined using efficient liquid chromatography integrated with mass spectrometry.\textsuperscript{45} In what was the first time to identify chemical constituents in a Shenqi Fuzheng injection, 81 major water-soluble ingredients were identified or accurately characterized by ultra-fast liquid chromatography combined with electrospray ionization quadrupole time-of-flight mass spectrometry.\textsuperscript{46} Twenty-eight components, found in Tianma-Gouteng-Yin, were identified by UHPLC/Q-TOF-MS and HPLC-ELSD methods and 20 of them were quantified.\textsuperscript{47} Ten effective compounds in Dachaiflu Granule were identified by high-performance liquid chromatography combined with a diode array detector.\textsuperscript{48} Zhu F. X., et al. used HPLC-MS to analyze the major constituent in a Danmu injection and the findings indicated that 11 compounds were identified.\textsuperscript{49} At the same time, another method was used to identify the main components in a formula; for instance, the active ingredients of Shixiao San were screened by endothelial cells.\textsuperscript{50} An increasing amount of evidence indicated that another technique for identifying or screening ingredients of a single herb also is making good progress. For example, two main components of the volatile oils from Pogostemon cablin were detected using gas chromatography-flame ionization (GC-FID).\textsuperscript{51} Eighteen compounds in the herb medicine Siegesbeckia pubescens were acquired and identified by column chromatography on silica gel.\textsuperscript{52} In accordance with the investigation of Chen P. Y., we came to the conclusion that eight compounds contained in Cinnamom were identified by liquid chromatography combined with quadruple time-of-flight mass spectrometry and principal component analysis.\textsuperscript{53} Three main anthraquinones in Cassiae Semen were found by principal components analysis which can provide a good reference for quality evaluating of Cassiae Semen medicinal materials.\textsuperscript{54} Additionally, four bound ligands were identified and screened from Radix astragali extract;\textsuperscript{55} incidentally, that was the first time five active triterpenoids which were contained in Rosa davurica Pall were identified. Xie had isolated and identified five flavonoid glycosides and two derivatives from Scorzonera austriaca Wild.\textsuperscript{56} And 36 components were confirmed by HPLC.

Fig. 1 Procedure for components identification of TCM based on LC-MS.
with DAD and MS.\textsuperscript{58} Forty-two compounds, derived from Lamiothomis rotata, were identified by LC/Q-TOF-MS.\textsuperscript{79} Technolo-
gies used to analyze the components of TCM are listed in Table 1.

3. The advantages of pharmacokinetics

The application of PK on TCM has attracted more and more attention of researchers who are devoted to developing TCM. There are three advantages for applying PK on TCM. First, identifying and screening multi-components of TCM could clearly explain its effects. Wang X., et al. screened 9 compounds of Yin-Chen-Hao-Tang as the candidate components to explain Yin-Chen-Hao-Tang pharmacological effects via comparing the dynamic process of each composition \textit{in vivo}.\textsuperscript{66} Ginsenoside Rg1, ginsenoside Rb1, ginsenoside Rb3, and ginsenoside Rc, the potential bioactive components, contributed to the pharmacological effects of Nao Mai Tong formula from its pharmacokinetics behavior.\textsuperscript{64} Twenty-one primary compounds, the active fraction of the Xiao-Xu-Ming decoction, could exert anti-ischemic-stroke effects as determined by investigating their PK behaviors in plasma and brain.\textsuperscript{62} Second, clarifying and explaining the combination mechanism of active components in decoction (Fig. 2). The PK parameters of chrysophanol and physcion, the main effective compounds in Radixet Rhizoma Rhei and Dahuang Fuzi decoction, showed significant differences which were helpful to account for the combination mechanism of Dahuang Fuzi decoction.\textsuperscript{63} Haizao might increase the peak concentration of glycyrrhizic acid, which is contained in Gancao, by investigating PK profiles of different formulas of Haizao Yuhu decoction.\textsuperscript{64} By comparing the PK parameters of 10-deacetylbaccatin III, which is contained in taxane mixtures, Zhang X. et al. found that AUC\textsubscript{0–24}h and concentrations of 10-deacetylbaccatin III were significantly increased and enhanced.\textsuperscript{65} Fan and his colleagues indicated that the absorption of liquiritigenin, isoliquiritigenin, glycyrrhizic acid, and glycyrrhetinic acid were enhanced after oral administration of \textit{Radix Glycyrrhizeae} and \textit{Ramulus Cinnamomomi}.\textsuperscript{66} The time of action of gastrodin could be prolonged in clinical studies by comparing its PK among different administered types of gastrodin.\textsuperscript{67} Third, showing and revealing the dynamic process of active components \textit{in vivo} (Fig. 3). Some ingredients in \textit{Rhizoma chuanxiong} and \textit{Radix puerariae} remarkably influence plasma concentrations of ferulic acid and puerarin, which are the main effective ingredients in Nao-De-Sheng decoction (NDS). This result suggested that the ingredients in NDS enhanced the dissolution and absorption of ferulic acid and puerarin, delaying elimination.\textsuperscript{68} Three major bioactive components, typhaneoside, vanillic acid, and p-coumaric acid, had good absorption \textit{in vivo} as discovered by investigating its \textit{C}_{\text{max}}(\text{max}), \textit{T}_{\text{max}}(\text{max}), \textit{T}_{1(1/2)}\text{ and AUC}_{(0–\infty)}.\textsuperscript{69} Xiang-Fu-Si-Wu decoction essential oil/ß-CD inclusion complex showed higher \textit{C}_{\text{max}}(\text{max}), \textit{T}_{1(1/2)}\text{ and larger AUC}_{(0–24h)} \textit{in vivo}.\textsuperscript{70} Paclitaxe, the \textit{Taxus chinensis} extract, might acquire higher blood concentration and its retention was remarkably improved.\textsuperscript{71}

4. Current research of pharmacokinetics

4.1 Applications in single herb

With the development of PK, several literature references involved application of PK on components research of single herbs. In order to discover the reason that main components in single herb could cure diseases, comparing its PK parameters \textit{in vivo} is a good choice of techniques. Wei B. et al. found that the absorption of six sedative and hypnotic lignans in an insomniac group were all incredibly higher than in a normal group by comparing the PK parameters of them.\textsuperscript{72} At the same time, that study also showed the six lignans were distributed mainly in the hypothalamus and a comparative study of the PK parameters of the six lignans indicated that the absorptions of them in the insomniac group were higher than in the normal group.\textsuperscript{73} After processing a single herb, the PK parameters of active components in TCM were changed. To compare PK parameters of ten alkaloids after oral administration of natural and wine-processed \textit{rhizoma coptidis} aqueous extracts, Qian XC drew the conclusion that the \textit{C}_{\text{max}} of coptisine and 8-oxocoptisine was enhanced as well as the AUC\textsubscript{0–24} of coptisine, palmatine, and 8-oxocoptisine; all were greatly increased after wine-processing.\textsuperscript{74} In addition, a huge number of research papers implied that the dynamic process of active components in a body will be exposed via its PK profile. In terms of the PK parameters of five active isoflavonoids, the active components of \textit{Radix Puerariae}, Xiao B. X. and his colleague’s research indicated that the isoflavonoids can quickly enter the brain and act on neuropharmacological activities.\textsuperscript{75} Columbianetin has rapid oral absorption, quick clearance, and good absolute bioavailability according to its PK properties.\textsuperscript{76} Nine of eleven alkaloids contained in Mahuang-Fuзи combination showed slower elimination by comparing their PKs in single-herb extracts.\textsuperscript{77}

4.2 Applications for decoction

Decoctions (tang in Chinese) are frequently used as a basic herb–herb combination of Chinese formulas for achieving mutual reinforcement and decreasing adverse effects. Currently, many researchers found that investigating PK parameters of TCM could explain synergistic effects of herb medicine which was contained in a formula or recipe. According to the research of Liu R., berberine can prolong the elimination half-life of corynoline which was a component in Shuanghua Baihe tablets, and also increased its bioavailability.\textsuperscript{78} The Nao-De-Sheng decoction (NDS) could further improve ferulic acid and puerarin pharmacological potency \textit{in vivo} by a PK study after oral administration of the monomer, medicinal substance aqueous extract, and NDS.\textsuperscript{79} Ganjiang may promote elimination of aconitine and hyaconitine and enhance the absorption of benzoylalconine, benzoy lhypaconine, and benzoylmesaconine \textit{via} comparing its PK after oral administration of Fuзи and Fuзи-Ganjiang aqueous extracts.\textsuperscript{80} The absorption of rhein was suppressed, and the time of rhein and emodin coming to their peak concentrations was delayed. Besides, the elimination of aloe-emodin and emodin was also
<table>
<thead>
<tr>
<th>Major components</th>
<th>Analytic system</th>
<th>Injection volume</th>
<th>Flow rate</th>
<th>Mobile phase</th>
<th>Technologies</th>
<th>Stationary phase</th>
<th>Prescription</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flavonoids, alkaloids, triterpenic acids, triterpene saponins, lactones, etc.</td>
<td>LTQ-Orbitrap MS</td>
<td>10 μl</td>
<td>1.0 ml min⁻¹</td>
<td>0.1% formic acid in water and acetonitrile</td>
<td>HPLC-MS</td>
<td>Diamonsil C18, column (250 × 4.6 mm, 5 μm)</td>
<td>XiangShaLiJunZijiajian</td>
<td>44</td>
</tr>
<tr>
<td>Iridoid glycosides, flavonoids, anthraquinones, annins.</td>
<td>ESI-Q-MS</td>
<td>10 μl</td>
<td>0.8 ml min⁻¹</td>
<td>Acetonitrile and 0.1% formic acid in water</td>
<td>LC-MS</td>
<td>Phenomenex kinetex C18 column (150 × 4.6 mm, 2.6 μm)</td>
<td>ZhiZiDaHuang decoction</td>
<td>45</td>
</tr>
<tr>
<td>Organic acids, amino acids, oligosaccharides, alkaloids, nucleosides, phenylpropanoids, etc.</td>
<td>ESI-Q-TOF-MS/MS</td>
<td>5 μl</td>
<td>0.2 ml min⁻¹</td>
<td>Methanol-water containing 0.1% formic acid</td>
<td>UFLC-Q-TOF-MS/MS</td>
<td>C18 reversed-phase column (2.1 mm × 100 mm, 1.8 μm)</td>
<td>Shenqi Fuzheng injection</td>
<td>46</td>
</tr>
<tr>
<td>Non-saccharide small molecule components, fructose, glucose and sucrose.</td>
<td>Q-TOF-MS, ELSD</td>
<td>—</td>
<td>0.4 ml min⁻¹</td>
<td>0.1% formic acid in water and 0.1% formic acid in ACN</td>
<td>UHPLC-Q-TOF-MS, HPLC-ELSD</td>
<td>Waters acquity BEH C18 column (2.1 × 100 mm, 1.7 μm)</td>
<td>Tianna-Gouteng-Yin</td>
<td>47</td>
</tr>
<tr>
<td>Paoniflorin, aloe-emodin, rhein, emodin, chrysophanol, physcion, naringin, etc.</td>
<td>DAD</td>
<td>10 μl</td>
<td>1.0 ml min⁻¹</td>
<td>Acetonitrile and 0.2% acetic acid</td>
<td>HPLC-DAD</td>
<td>Phenomenex kinetex C18 column (250 × 4.6 mm, 5.0 μm)</td>
<td>Kromasil C18</td>
<td>48</td>
</tr>
<tr>
<td>Phenolic acid and phenol glycoside, iridoid glycoside and glycoalkaloid</td>
<td>ESI-MS, DAD</td>
<td>20 μl</td>
<td>1.0 ml min⁻¹</td>
<td>Acetonitrile and water containing 0.1% formic acid</td>
<td>LC-DAD-ESI-MS²</td>
<td>Welch material XB-C18 (4.6 mm × 250 mm, 5 μm)</td>
<td>Danmu injection</td>
<td>49</td>
</tr>
<tr>
<td>Quercetin-3-O-(2G-D-glucosyl)-rutinoside, quercetin-3-O-neohesperidoside, etc.</td>
<td>Q-TOF-MS</td>
<td>—</td>
<td>0.2 ml min⁻¹</td>
<td>0.01% formic acid in water and 0.01% formic acid in methanol</td>
<td>C-BC, UHPLC-Q-TOF-MS</td>
<td>Zorbax Eclipse plus C18 column (100 mm × 2.1 mm, 1.8 μm)</td>
<td>Shixiao San</td>
<td>50</td>
</tr>
<tr>
<td>Patchouli alcohol, pogostone</td>
<td>Chemometric techniques</td>
<td>1.3 ml min⁻¹</td>
<td>High-purity (99.99%) nitrogen</td>
<td>GC-FID</td>
<td>—</td>
<td>CC</td>
<td>Siegesbeckia pubescens</td>
<td>52</td>
</tr>
<tr>
<td>3,4’-Dimethoxy quercetin, NMR 3,3’,4’-trimethoxy quercetin, 3,3’-dimethoxy quercetin, etc.</td>
<td>Chemometric techniques</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Coumarin, cinnamaldehyde, cinnamyl alcohol, cinnamic acid, 2-hydroxycinnamaldehyde, etc.</td>
<td>Q-TOF-MS, PCA</td>
<td>5 μl</td>
<td>0.3 ml min⁻¹</td>
<td>Water containing LC-Q-TOF-MS 0.1% formic acid and acetonitrile containing 0.1% formic acid</td>
<td>Agilent Poroshell 120 SB-C18 column (4.6 × 150 mm, 2.7 μm)</td>
<td>Cinnamomum cassia</td>
<td>Cassiae Semen</td>
<td>53</td>
</tr>
<tr>
<td>Aurantio obtusin, rhein, aloe emodin, emodin, chrysophanol and physcion</td>
<td>PCA</td>
<td>20 μl</td>
<td>0.8 ml min⁻¹</td>
<td>Acetonitrile and 0.1% phosphoric acid</td>
<td>HPLC</td>
<td>Kromasil C18, column (4.6 mm × 250 mm, 5 μm)</td>
<td>Cassiae Semen</td>
<td>54</td>
</tr>
<tr>
<td>Genistin, calyosin-7-O-β-D-glucoside, ononin, formononetin</td>
<td>ESI-Q-MS</td>
<td>—</td>
<td>1.0 ml min⁻¹</td>
<td>Water containing HPLC-MS 0.4% v/v acetic acid and acetonitrile containing 0.4% v/v acetic acid 0.05% phosphoric acid aqueous solution and acetonitrile</td>
<td>Waters, SunFire C18 column (250 mm × 4.6 mm, 5 μm)</td>
<td>Radix astragali</td>
<td>Cassiae Semen</td>
<td>55</td>
</tr>
<tr>
<td>Triterpenoids</td>
<td>—</td>
<td>—</td>
<td>1.2 ml min⁻¹</td>
<td>HPLC</td>
<td>Merges C18 column (250 × 4.6 mm, 5 μm)</td>
<td>—</td>
<td>Rosa davurica Pall.</td>
<td>56</td>
</tr>
<tr>
<td>Flavonoid glycosides and derivatives</td>
<td>HR-ESI-MS, NMR</td>
<td>—</td>
<td>3.0 ml min⁻¹</td>
<td>Acetonitrile</td>
<td>SGCC, HPLC, NMR</td>
<td>Scorzoner a austriaca Wild</td>
<td>57</td>
<td></td>
</tr>
</tbody>
</table>

Review

RSC Advances

Table 1 Technologies in analyzing the components of TCM*
found to be postponed in RPD via comparing the PKs of aloe-emodin, rhein, and emodin via oral administration of DaHuang-Mu-Dan-Tang (RPD) and rhubarb extracts. Additionally, some research results indicated that the active ingredients in decoction had no drug-interactions. For example, by comparing PK processes of spinosin, mangiferin, and ferulic acid, which were the main active components in Suan-Zao-Ren decoction, it was seen that the PK parameters of ferulic acid were no different between these two groups. The applications of PK in TCM are listed in Table 2.

Interestingly, one researcher used PK to study the components of formula on animal models. Results showed that the process of components of formula in vivo was significantly different by comparing PK parameters of the components of formula in normal and abnormal animal models. For example, the research of Liu Q. F. indicated that berberine as well as palmatine had higher uptake and slower elimination in rats

Table 1 (Contd.)

<table>
<thead>
<tr>
<th>Major components</th>
<th>Analytic system</th>
<th>Injection volume</th>
<th>Flow rate</th>
<th>Mobile phase</th>
<th>Technologies</th>
<th>Stationary phase</th>
<th>Prescription</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flavonoids, methylapigenin-O-pentoside isomers</td>
<td>DAD - ESI-MS</td>
<td>—</td>
<td>0.2 ml min⁻¹</td>
<td>Methanol and 0.2% formic acid</td>
<td>HPLC - DAD-MS</td>
<td>Agilent Eclipse XDB C18 column (50 mm x 2.1 mm, 1.8 μm)</td>
<td>Egyptian Carob</td>
<td>58</td>
</tr>
<tr>
<td>Iridoids, flavonoids, phenylethanoid glycosides</td>
<td>Q-TOF-MS</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>LC-Q-TOF-MS</td>
<td>—</td>
<td>Lamiopholis rotata</td>
<td>59</td>
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<tr>
<td>Essential oils</td>
<td>MS</td>
<td>10 μl</td>
<td>1.0 ml min⁻¹</td>
<td>Helium</td>
<td>GC-MS</td>
<td>Hewlett Packard HP-20 M polyethylene glycol column (30 m x 0.2 mm, 0.2 μm)</td>
<td>Origanum vulgare L</td>
<td>108</td>
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<tr>
<td>Volatile oils, alkaloids and flavonoids</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>GC-MS, HPLC</td>
<td>—</td>
<td>Fructus Aurantii Immaturus</td>
<td>109</td>
</tr>
<tr>
<td>Lignans, flavones, triterpenoidsaponins, phenolic acids, and other constituents</td>
<td>ESI-MS</td>
<td>0.4 ml min⁻¹</td>
<td>Acetonitrile with 0.1% formic acid and water with 0.1% formic acid</td>
<td>—</td>
<td>UPLC-MS</td>
<td>Waters, ACQUITY BEH C18 column (2.1 mm × 100 mm, 1.7 μm).</td>
<td>Acanthopanax senticosus</td>
<td>110</td>
</tr>
<tr>
<td>Lawson, 2-methoxy-1,4-naphthoquinone</td>
<td>DAD-El-MS, NMR</td>
<td>20 μl</td>
<td>1.0 ml min⁻¹</td>
<td>Acetonitrile-2.5% aqueous acetic acid</td>
<td>HSCCC, HPLC, El-MS, NMR</td>
<td>ZORBAX XDB-C18 column (150 × 4.6 mm, 5 μm)</td>
<td>Impatiens balsamina L</td>
<td>111</td>
</tr>
</tbody>
</table>

*HPLC: high performance liquid chromatography; MS: mass spectrometry; UHPLC: ultra-fast liquid chromatography; Q-TOF: quadrupole time-of-flight mass spectrometry; ELSD: evaporative light scattering detection; DAD: diode array detector; C-BC: cell-based screening; GC: gas chromatography; FID: flame ionization detection; NMR: nuclear magnetic resonance spectrometry; HSCCC: high speed countercurrent chromatography; ESI: electrospray ionization mass spectrometry; PCA: principal component analysis; SGCC: silica gel column chromatography.

Fig. 2  Technical routes of clarifying and explaining the combination mechanism of AC.
with metabolic syndrome.\textsuperscript{83} Besides, plus-minus or absent–present herbs of formula could affect the dynamic process of components of formula \textit{in vivo} by comparing PK parameters of these components in formula. For instance, in view of PK parameters of the main components after oral administration of a Gan-Sui-Ban-Xia Decoction plus–minus Gansui and Gancao anti-drug combination, the research of Zhang Y., \textit{et al.} demonstrated that Gansui may lead to better absorption of glycyrrhizinic acid and liquiritin in Gancao, while Gansui and Gancao may lead to better and faster absorption of albiflorin, but worse absorption of paeoniflorin.\textsuperscript{84} By comparing the PK parameters of cisplatin in the absence or presence of zengmian yiliu granules (ZMYL), it was learned that ZMYL is a potential complementary and alternative medicine for cisplatin chemotherapy.\textsuperscript{85}

In addition, the dynamic process of the main components of TCM \textit{in vivo} would change via comparing its PK profile under the primary herb–herb combination or the formula. Meranzin hydrate and feralic acid were absorbed and distributed rapidly \textit{in vivo} by means of comparing PK parameters.\textsuperscript{86} Platycodon radix could promote PK profiles of marker compounds which were contained in Shengxian decoction.\textsuperscript{87} Correspondingly, a Wuzhi capsule increased the mean plasma concentration of tacrolimus.\textsuperscript{88} In a Kushen–Gancao combination, the absorption of glycyrrhetic acid was significantly lower than in the single herb.\textsuperscript{89} According to Hou and his team’s research, the absorption of rhein was significantly enhanced both in herbal formulae and a single herbal extract over the pure compound \textit{in vivo}.\textsuperscript{89} \textit{Radix Pueraria} flavonoids were able to prolong the absorption of 1-deoxynojirimycin; however, it did not have an effect on the total amount of 1-deoxynojirimycin \textit{in vivo}.\textsuperscript{90} In addition, the bioavailability of geniposide might be more enhanced and heightened in a single herbal extract and Gardenia herbal formulation than in its pure compound administration.\textsuperscript{91}

5. Pharmacokinetics–pharmacodynamics

In early studies, the PK of TCM was just used to investigate absorption, distribution, metabolism, and excretion of active components contained in single or herb–herb combinations, as well as the interaction mechanism between components and formulas.\textsuperscript{92} Whereas the types of active components derived from single herb or complex formula were able to fully represent their pharmacological functions, this was still ambiguous and controversial. With the emerging pharmacokinetic-pharmacodynamic (PK-PD) model,\textsuperscript{94,95} we have a new tool to investigate TCM.

Currently, the PK-PD model is comprehensively used for research with TCM; but it could further explain the compatibility mechanisms for formula and provide comprehensive information for clinical settings.\textsuperscript{96,97} What’s more, increasing numbers of research reports have indicated that using the PK-PD model is a key to explain herb efficacy and herb-herb synergistic effects.\textsuperscript{98,99} A triptolide-loaded liposome hydrogel patch was able to treat rheumatoid arthritis based on its PK and pharmacodynamics study.\textsuperscript{100} The rhubarb–gardenia herb pair exerted enhanced hepatoprotective effects \textit{via} a pharmacodynamic and PK study of five main chemical markers.\textsuperscript{101} Ren \textit{et al.} revealed the mechanism of the anti-inflammatory activity of Huang-Lian-Jie-Du decoction \textit{via} systematic PK and pharmacodynamic data of three major active constituents in Huang-Lian-Jie-Du decoction.\textsuperscript{102} Glycyrrhetic acid combined with paeoniflorin, two primary active compounds in peony-liquorice decoctions, exerted a constant analgesic effect on dysmenorrhea.\textsuperscript{103} Zhan and his colleagues found that ginsenoside Rb1 coupled with schisandrin might delay the elimination of ginsenoside Rg1 and ginsenoside Rg1, Rb1, and schisandrin in a mixture displayed a synergistic effect on NO release.\textsuperscript{104} Rhein was able to influence the PK and pharmacodynamics of clozapine to reduce clozapine-induced constipation.\textsuperscript{105} And Yu and his team revealed the mechanism of borneol’s ability to open the blood–brain barrier \textit{via} its pharmacodynamics and PK research.\textsuperscript{106}

6. Future perspectives

Rapid economic development and a rising focus on health in China has caused TCM to be noticed beyond that of Western countries.\textsuperscript{107} As we know, in order to guarantee the safety and effectiveness of TCM, research using pharmacokinetics is essential. Safety and effectiveness of TCM are key issues in investigating TCM. It is unrealistic that clinical rational use of TCM totally depends on pharmacokinetic parameters of active components that were derived from TCM. Usage and dosage of TCM must originate from a large exploration of clinical practices. Although the PK of TCM has solved some key problems with the application of TCM, it is still in an early stage of exploration. Currently, there are many issues with the PK of...
<table>
<thead>
<tr>
<th>Name of plant</th>
<th>Model</th>
<th>Analytical method</th>
<th>Active components</th>
<th>Compartment model</th>
<th>Process</th>
<th>PK parameters</th>
<th>PK behavior</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schisandra chinensis</td>
<td>Insomnic</td>
<td>UFLC-MS/MS</td>
<td>Schisandrin, schisandrol B, schisantherin A, deoxyshisandrin, γ-schisantherin, gomisin N</td>
<td>Non-compartmental</td>
<td>DAS 2.1</td>
<td>AUC, Cmax</td>
<td>The better absorption of the six analytes in model group</td>
<td>72</td>
</tr>
<tr>
<td>Rhizoma coptidis</td>
<td>Normal</td>
<td>UHPLC-ESI-MS/MS</td>
<td>Berberine, coptisine, palmatine, jatrorrhizine, epiberberine, magnoflorine, columbamine, noroxyhydrastinine, oxyberberine, 8-oxocoptisine</td>
<td>—</td>
<td>DAS 2.0</td>
<td>T1/2, Cmax, Tmax, AUC0-t</td>
<td>Wine-processing did exert limited effects on the absorption of columnbamine, noroxyhydrastinine, oxyberberine and 8-oxocoptisine</td>
<td>74</td>
</tr>
<tr>
<td>Pueraria lobata</td>
<td>Normal</td>
<td>UFLC-MS/MS</td>
<td>Puerarin, 3'-methoxypuerarin, 3'-hydroxyquercetin, daidzein, daidzein-8-C-apiosyl-(1-6)-glycoside</td>
<td>Non-compartmental</td>
<td>WinNonlin6.0</td>
<td>Tmax, C0, AUC0-t, T1/2, etc.</td>
<td>Puerarin, 3'-methoxypuerarin, daidzein and daidzein-8-C-apiosyl-(1-6)-glycoside can quickly penetrate to the brain through the blood brain barrier</td>
<td>75</td>
</tr>
<tr>
<td>Angelica pubescens Maximin</td>
<td>Normal</td>
<td>HPLC</td>
<td>Columbianetin</td>
<td>Optimum compartment</td>
<td>DAS 1.0</td>
<td>Cmax, V/F, T1/2</td>
<td>Columbianetin has rapid oral absorption, quick clearance and good absolute bioavailability</td>
<td>76</td>
</tr>
<tr>
<td>Herba Ephedrae-Radix Aconiti Lateralis</td>
<td>Normal</td>
<td>UPLC-MS</td>
<td>Norephedrine, norpseudoephedrine, ephedrine, pseudoephedrine, methylephedrine, acotin, mesaconitine, hycapontine, benzoylconine, benzoylmesaconine and benzoylhyponacine</td>
<td>Non-compartmental</td>
<td>DAS 3.2</td>
<td>Tmax, Cmax, AUC0-t, T1/2, etc.</td>
<td>Alkaloids (except methylephedrine, benzoylmesaconine and benzoylhyponacine) showed slower elimination</td>
<td>77</td>
</tr>
<tr>
<td>Corydalis bungeana Herba</td>
<td>Normal</td>
<td>LC-MS/MS</td>
<td>Corynoline</td>
<td>Non-compartmental</td>
<td>DAS 3.2</td>
<td>Tmax, T1/2, MRT, AUC0-in</td>
<td>Shuanghua Baihe tablets prolonged the elimination half-life of corynoline and increased its bioavailability</td>
<td>78</td>
</tr>
<tr>
<td>Nao-De-Sheng decoction (NDS)</td>
<td>Normal</td>
<td>RP-HPLC</td>
<td>Ferulic acid, puerarin</td>
<td>Two-compartment</td>
<td>3P97</td>
<td>Tmax, Cmax, AUC0-t, AUC0-in</td>
<td>Some ingredients in NDS may increase dissolution and absorption of ferulic acid and puerarin, delay elimination, and subsequently enhance bioavailability of ferulic acid and puerarin</td>
<td>79</td>
</tr>
<tr>
<td>Radix Aconiti Lateralis</td>
<td>Normal</td>
<td>LC-MS/MS</td>
<td>Aconitine, hycapontine, mesaconitine, benzoylconine, benzoylhyponacine, benzoylmesaconine</td>
<td>—</td>
<td>3P97 1.0</td>
<td>T1/2, AUC0-t, Cmax, Tmax</td>
<td>Ganjiang could promote the elimination of aconitine and hycapontine and enhance the absorption of benzoylconine, benzoylhyponacine and benzoylmesaconine</td>
<td>80</td>
</tr>
</tbody>
</table>
TCM and it still faces many new challenges. For example, the classic PK of TCM can’t explain the overall concept of TCM. Therefore, the PK of TCM should be combined with other effective tools, such as network-pharmacology, network-pharmacy, and metabolic technology, to investigate TCM and provide effective and firsthand evidence for clinical rational use of it.

7. Conclusion

TCM has a long history of protecting human health due to its effective constituents as well as satisfactory pharmacological activities. This review summarized the active components in a single herb or complex formula of TCM. We outlined applications of PK for screening and confirming the active fraction which exerts pharmacological effects of a single herb or a complex formula and explained the mechanisms and interactions of drug-drug or herb-herb via key active component’s PK profiles. Additionally, this review also introduced PK and PD models in investigations of the interactions and pharmacological effects of active components contained in a single herb and in formula. We hope that this review will serve as useful guidance for further investigations of TCM.

Conflict of interest

The authors declare no competing financial interests.

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References


31. Y. Cong, K. Sun, X. He, J. Li, Y. Dong, B. Zheng, X. Tan and J. X. Song, A Traditional Chinese Medicine Xiao-Ai-Tong Suppresses Pain through Modulation of Cytokines and Prevents Adverse Reactions of Morphine Treatment in...


42 C. Feng, H. Wang, C. Yao, J. Zhang and Z. Tian, Diammonium glycyrrhizinate, a component of traditional Chinese medicine Gan-Cao, prevents murine T-cell-mediated fulminant hepatitis in IL-10- and IL-6-dependent manners, *Int. Immunopharmacol.*, 2007, **7**(10), 1292–1298.


54 L. J. Cao, J. Miaoj, J. X. Liu, W. Y. Gao and X. Li, Research on contents of anthraquinones in Cassiae Semen by principal
component analysis, Zhongguo Zhong Yao Za Zhi, 2015, 40(13), 2589–2593.

55 L. Liu, J. Leng, X. Yang, L. Liao, Y. Cen, A. Xiao and L. Ma, Rapid Screening and Identification of BSA Bound Ligands from Radix astragali Using BSA Immobilized Magnetic Nanoparticles Coupled with HPLC-MS, Molecules, 2016, 21(11), pii: E1471.


76 Q. Luo, C. P. Wang, J. Li, W. F. Ma, Y. Bai, L. Ma, X. M. Gao, B. L. Zhang and Y. X. Chang, The pharmacokinetics and oral bioavailability studies of columbiaiet in rats after oral and intravenous administration, *J. Ethnopharmacol.*, 2013, **150**(1), 175–180.


88 H. Wei, X. Tao, P. Di, Y. Yang, J. Li, X. Qian, J. Feng and W. Chen, Effects of traditional chinese medicine Wuzhi capsule on pharmacokinetics of tacrolimus in rats, *Drug Metab. Dispos.*, 2013, **41**(7), 1398–1403.


103 X. Ding, Y. Sun, Q. Wang, T. Pu, X. Li, Y. Pan and Y. Yang, Pharmacokinetics and pharmacodynamics of glycyrrhetinic acid with Paeoniflorin after transdermal administration in dysmenorrhea model mice, *Phytomedicine*, 2016, **23**(8), 864–871.


