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Recent advances in pharmacokinetics approach for herbal medicine

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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,[1] chronic hepatitis B,[2] experimental sepsis,[3] cancer,[4] periodontal pathogens,[5] influenza A,[6] gastric cancer cells,[7] anti-NDV,[8] gastrointestinal disorders,[9] and diabetes mellitus[10] in clinical practices. TCM efficacy relies on its bioactive constituents.[11] 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,[12–14] distribution,[15] metabolism,[16] and excretion[17,18] 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 ($T_{1/2}$),[19–21] clearance (CL),[22,23] area under concentration-time (AUC),[24,25] *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.[26] 6,7-Dimethylesculetin, geniposide, and rhein were effective therapies against hepatic injury syndrome.[27,28] Berberine was applied to treat nonbacterial prostatitis.[29] In addition, we also understand the dynamic processes of active components of TCM *in vivo* from research using PK. For example, 5-hydroxymethyl-2-furoic acid, absorbed into blood from liu wei di huang wan, had rapid absorption and disposition processes, yet its elimination was slow *in vivo*.[30] In order to enhance applications of PK with TCM, the goal of this article is to review the status of TCM, the application of PK on TCM, and to put forward PK application prospects with TCM.

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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.[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.[32] Subamolide A was used to treat human urothelial carcinoma in clinical practice.[33] Also, Nakamura K. and his colleagues found that cordycepin, an active component of *Cordyceps sinensis*, has anticancer and antimetastatic effects.[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.[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.[36] *Polygonatum odoratum* extract has an effect on breast cancer by suppressing proliferation of breast cancer cells and inducing its apoptosis.[37] According to the research of Shen K., cambogin, a bioactive component of *Garcinia* genus, also has a significant effect on breast cancer.[38] At the same time, compound Kushen injection, as a candidate, was used to treat MCF-7 human breast cancer cells.[39] Xue B., *et al.* found that anti-EV71 components can treat hand-foot-and-mouth disease which results from intestinal virus infection.[40] Tetramethylpyrazine, an active component in Chuanxiong, might exert beneficial effects in primary open-angle glaucoma patients *via* regulating CXCR4 expression.[41] Diammonium glycyrrhizinate liquor extract exerted a significant effect on hepatitis *via* its anti-inflammatory effects in clinical practice.[42] And finally, Cortex Moutan showed important *in vitro* anti-diabetic effects *via* suppressing glucose uptake.[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.[44] Twenty active components, originating from Zhi-Zi-Da-Huang decoction, were quickly determined using efficient liquid chromatography integrated with mass spectrometry.[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.[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.[47] Ten effective compounds in Dachaihu Granule were identified by high-performance liquid chromatography combined with a diode array detector.[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.[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.[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).[51] Eighteen compounds in the herb medicine *Siegesbeckia pubescens* were acquired and identified by column chromatography on silica gel.[52] In accordance with the investigation of Chen P. Y., we came to the conclusion that eight compounds contained in *Cinnamon* were identified by liquid chromatography combined with quadruple time-of-flight mass spectrometry and principal component analysis.[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.[54] Additionally, four bound ligands were identified and screened from *Radix astragali* extract;[55] incidentally, that was the first time five active triterpenoids which were contained in *Rosa davurica* Pall[56] were identified. Xie had isolated and identified five flavonoid glycosides and two derivatives from *Scorzonera austriaca* Wild.[57] And 36 components were confirmed by HPLC

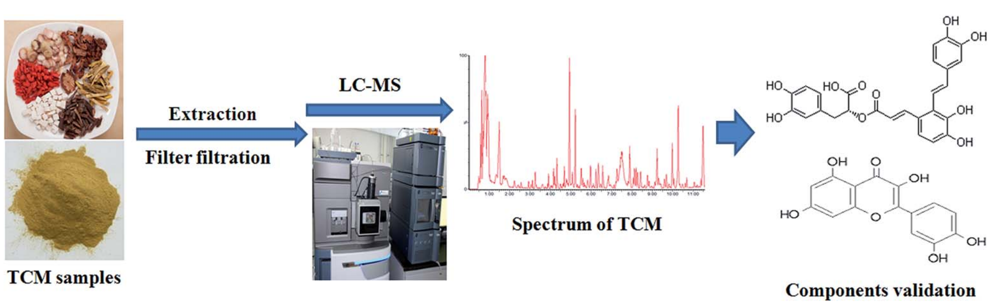

Fig. 1 Procedure for components identification of TCM based on LC-MS.

with DAD and MS.[58] Forty-two compounds, derived from *Lamiophlomis rotata*, were identified by LC/Q-TOF-MS.[59] Technologies 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 *in vivo*.[60] 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.[61] 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.[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.[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.[64] By comparing the PK parameters of 10-deacetylbaccatin III, which is contained in taxane mixtures, Zhang X. *et al.* found that AUC_{0-U} and concentrations of 10-deacetylbaccatin III were significantly increased and enhanced.[65] Fan and his colleagues indicated that the absorption of liquiritigenin, isoliquiritigenin, glycyrrhizic acid, and glycyrrhetinic acid were enhanced after oral administration of *Radix Glycyrrhizae* and *Ramulus Cinnamomi*.[66] The time of action of gastrodin could be prolonged in clinical studies by comparing its PK among different administered types of gastrodin.[67] Third, showing and revealing the dynamic process of active components *in vivo* (Fig. 3). Some ingredients in *Rhizoma chuanxiong* and *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.[68] Three major bioactive components, typhaneoside, vanillic acid, and *p*-coumaric acid, had good absorption *in vivo* as discovered by investigating its $C_{(max)}$, $T_{(max)}$, $T_{(1/2)}$, and $AUC_{(0\sim t)}$.[69] Xiang-Fu-Si-Wu decoction essential oil/β-CD inclusion complex showed higher $C_{(max)}$, $T_{(1/2)}$, and larger $AUC_{(0-24h)}$ *in vivo*.[70] Paclitaxe, the *Taxus chinensis* extract, might acquire higher blood concentration and its retention was remarkably improved.[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 *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.[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.[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 *Rhizoma coptidis* aqueous extracts, Qian XC drew the conclusion that the C_{max} of coptisine and 8-oxocoptisine was enhanced as well as the AUC_{0-t} of coptisine, palmatine, and 8-oxocoptisine; all were greatly increased after wine-processing.[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 *Radix Puerariae*, Xiao B. X. and his colleague's research indicated that the isoflavonoids can quickly enter the brain and act on neuropharmacological activities.[75] Columbianetin has rapid oral absorption, quick clearance, and good absolute bioavailability according to its PK properties.[76] Nine of eleven alkaloids contained in Mahuang-Fuzi combination showed slower elimination by comparing their PKs in single-herb extracts.[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.[78] The Nao-De-Sheng decoction (NDS) could further improve ferulic acid and puerarin pharmacological potency *in vivo* by a PK study after oral administration of the monomer, medicinal substance aqueous extract, and NDS.[79] *Ganjiang* may promote elimination of aconitine and hypaconitine and enhance the absorption of benzoylaconine, benzoylhypaconine, and benzoylmesaconine *via* comparing its PK after oral administration of Fuzi and Fuzi-Ganjiang aqueous extracts.[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 1 Technologies in analyzing the components of TCM[a]

Major components	Analytic system	Injection volume	Flow rate	Mobile phase	Technologies	Stationary phase	Prescription	Reference
Flavonoids, alkaloids, triterpenic acids, triterpene saponins, lactones, *etc.*	LTQ-Orbitrap MS	10 μl	1.0 ml min^{-1}	0.1% formic acid in water and acetonitrile	HPLC-MS	Diamonsil C18, column (250 × 4.6 mm, 5 μm)	XiangShaLiuJunZiJiaJian granules	44
Iridoid glycosides, flavonoids, anthraquinones, annins.	ESI-Q-MS	10 μl	0.8 ml min^{-1}	Acetonitrile and 0.1% formic acid in water	LC-MS	Phenomenex kinetex C18 column (150 × 4.6 mm, 2.6 μm)	ZhiZiDaHuang decoction	45
Organic acids, amino acids, oligosaccharides, alkaloids, nucleosides, phenylpropanoids, *etc.*	ESI-Q-TOF-MS/MS	5 μl	0.2 ml min^{-1}	Methanol-water containing 0.1% formic acid	UFLC-Q-TOF-MS/MS	C18 reversed-phase column (2.1 mm × 100 mm, 1.8 μm)	Shenqi Fuzheng injection	46
Non-saccharide small molecule components, fructose, glucose and sucrose.	Q-TOF-MS, ELSD	—	0.4 ml min^{-1}	0.1% formic acid in water and 0.1% formic acid in ACN	UHPLC-Q-TOF-MS, HPLC-ELSD	Waters acquity BEH C18 column (2.1 × 100 mm, 1.7 μm)	Tianma-Gouteng-Yin	47
Paeoniflorin, aloe-emodin, rhein, emodin, chrysophanol, physcion, naringin, *etc.*	DAD	10 μl	1.0 ml min^{-1}	Acetonitrile and 0.2% acetic acid	HPLC-DAD	Kromasil C18 column (250 × 4.6 mm, 5.0 μm)	Dachaihu granule	48
Phenolic acid and phenol glycoside, iridous glycoside and glycoalkaloid	ESI-MS, DAD	20 μl	1.0 ml min^{-1}	Acetonitrile and water containing 0.1% formic acid	LC-DAD-ESI-MS^n	Welch material XB-C18 (4.6 mm × 250 mm, 5 μm)	Danmu injection	49
Quercetin-3-*O*-(2*G*-α-L-rhamnosyl)-rutinoside, quercetin-3-*O*-neohesperidoside, *etc.*	Q-TOF-MS	—	0.2 ml min^{-1}	0.01% formic acid in water and 0.01% formic acid in methanol	C-BC, UHPLC-Q-TOF-MS	Zorbax Eclipse plus C18 column (100 mm × 2.1 mm, 1.8 μm)	Shixiao San	50
Patchouli alcohol, pogostone	Chemometric techniques		1.3 ml min^{-1}	High-purity (99.99%) nitrogen	GC-FID	HP-5 capillary column (30 m × 0.25 mm, 0.25 μm)	*Pogostemon cablin*	51
3,4′-Dimethoxy quercetin, 3,3′,4′-trimethoxy quercetin, 3,3′-dimethoxy quercetin, *etc.*	NMR	—	—	—	CC	—	*Siegesbeckia pubescens*	52
Coumarin, cinnamaldehyde, cinnamyl alcohol, cinnamic acid, 2-hydroxycinnamaldehyde, *etc.*	Q-TOF-MS, PCA	5 μl	0.3 ml min^{-1}	Water containing 0.1% formic acid and acetonitrile containing 0.1% formic acid	LC-Q-TOF-MS	Agilent Poroshell 120 SB-C18 column (4.6 × 150 mm, 2.7 μm)	*Cinnamomum cassia*	53
Aurantio obtusin, rhein, aloe emodin, emodin, chrysophanol and physcion	PCA	20 μl	0.8 ml min^{-1}	Acetonitrile and 0.1% phosphoric acid	HPLC	Kromasil C18, column (4.6 mm × 250 mm, 5 μm)	*Cassiae Semen*	54
Genistin, calycosin-7-*O*-β-D-glucoside, ononin, formononetin	ESI-Q-MS	—	1.0 ml min^{-1}	Water containing 0.4% v/v acetic acid and acetonitrile containing 0.4% v/v acetic acid	HPLC-MS	Waters, SunFire C18 column (250 mm × 4.6 mm, 5 μm)	*Radix astragali*	55
Triterpenoids	—	—	1.2 ml min^{-1}	0.05% phosphoric acid aqueous solution and acetonitrile	HPLC	Merges C18 column (250 × 4.6 mm, 5 μm)	*Rosa davurica* Pall.	56
Flavonoid glycosides and derivatives	HR-ESI-MS, NMR	—	3.0 ml min^{-1}	Acetonitrile	SGCC, HPLC, NMR	Gemini C18 110A column (250 mm × 10.00 mm, 5 μm)	*Scorzonera austriaca* Wild	57

Table 1 (*Contd.*)

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

[a] 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.

found to be postponed in RPD *via* comparing the PKs of aloe-emodin, rhein, and emodin after oral administration of DaHuang-Mu-Dan-Tang (RPD) and *rhubarb* extracts.[81] Additionally, some research results indicated that the active ingredients in decoction had no drug-interactions. For example, by comparing PK profiles 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.[82] 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

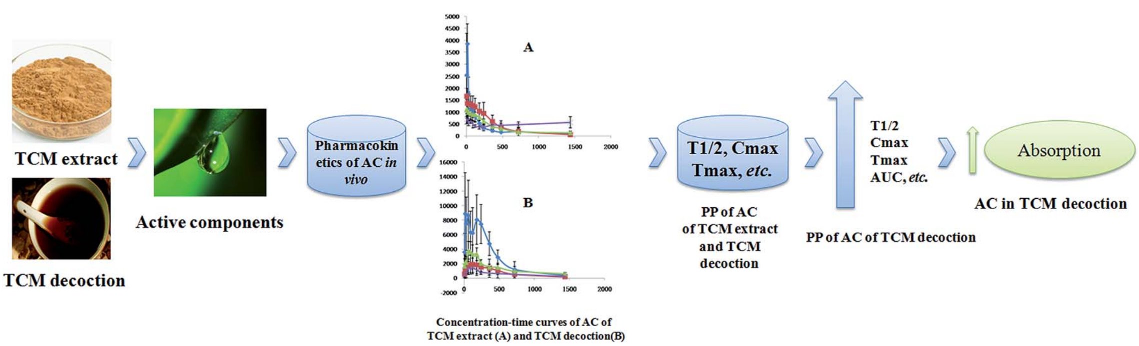

Fig. 2 Technical routes of clarifying and explaining the combination mechanism of AC.

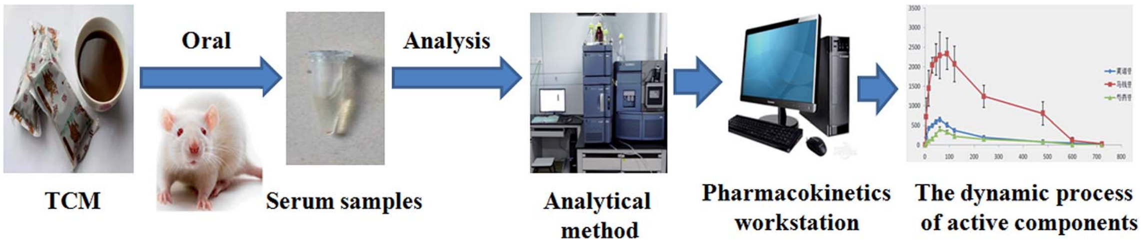

Fig. 3 Pharmacokinetic studies of active components absorbed *in vivo*.

with metabolic syndrome.[83] Besides, plus–minus or absent–present herbs of formula could affect the dynamic process of components of formula *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., *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.[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.[85]

In addition, the dynamic process of the main components of TCM *in vivo* would change *via* comparing its PK profile under the primary herb–herb combination or the formula. Meranzin hydrate and ferulic acid were absorbed and distributed rapidly *in vivo* by means of comparing PK parameters.[86] Platycodonis radix could promote PK profiles of marker compounds which were contained in Shengxian decoction.[87] Correspondingly, a Wuzhi capsule increased the mean plasma concentration of tacrolimus.[88] In a Kushen–Gancao combination, the absorption of glycyrrhetinic acid was significantly lower than in the single herb.[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 *in vivo*.[90] *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 *in vivo*.[91] 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.[92]

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.[93] 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,[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.[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.[98,99] A triptolide-loaded liposome hydrogel patch was able to treat rheumatoid arthritis based on its PK and pharmacodynamics study.[100] The rhubarb–gardenia herb pair exerted enhanced hepatoprotective effects *via* a pharmacodynamic and PK study of five main chemical markers.[101] Ren *et al.* revealed the mechanism of the anti-inflammatory activity of Huang-Lian-Jie-Du decoction *via* systematic PK and pharmacodynamic data of three major active constituents in Huang-Lian-Jie-Du decoction.[102] Glycyrrhetinic acid combined with paeoniflorin, two primary active compounds in peony-liquorice decoctions, exerted a constant analgesic effect on dysmenorrhea.[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.[104] Rhein was able to influence the PK and pharmacodynamics of clozapine to reduce clozapine-induced constipation.[105] And Yu and his team revealed the mechanism of borneol's ability to open the blood–brain barrier *via* its pharmacodynamics and PK research.[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.[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 2 The application of pharmacokinetics in TCM[a]

Name of plant	Model	Analytical method	Active components	Compartment model	Process	PK parameters	PK behavior	Reference
Schisandra chinensis	Insomnic	UFLC-MS/MS	Schisandrin, schisandrol B, schisantherin A, deoxyshisandrin, γ-schisandrin, gomisin N	Non-compartmental	DAS 2.1	AUC, C_{max}, $T_{1/2}$, MRT, CL_Z/F	The better absorption of the six analytes in model group	72
Rhizoma coptidis	Normal	UHPLC-ESI-MS/MS	Berberine, coptisine, palmatine, jatrorrhizine, epiberberine, magnoflorine, columbamine, noroxyhydrastinine, oxyberberine, 8-oxocoptisine	—	DAS 2.0	$T_{1/2}$, C_{max}, T_{max}, AUC_{0-t}	Wine-processing did exert limited effects on the absorption of columbamine, noroxyhydrastinine, oxyberberine and 8-oxocoptisine	74
Pueraria lobata	Normal	UFLC-MS/MS	Puerarin, 3′-methoxypuerarin, 3′-hydroxypuerarin, daidzein, daidzein-8-C-apiosyl-(1-6)-glycoside	Non-compartmental	WinNonlin6.0	T_{max}, C_0, AUC_{0-t}, $T_{1/2}$, *etc.*	Puerarin, 3′-methoxypuerarin, daidzein and daidzein-8-C-apiosyl-(1-6)-glycoside can quickly penetrate to the brain through the blood brain barrier	75
Angelica pubescens Maxim	Normal	HPLC	Columbianetin	Optimum compartment	DAS 1.0	C_{max}, V/F, $T_{1/2}$	Columbianetin has rapid oral absorption, quick clearance and good absolute bioavailability	76
Herba Ephedrae-Radix Aconiti Lateralis	Normal	UPLC-MS	Norephedrine, norpseudoephedrine, ephedrine, pseudoephedrine, methylephedrine, aconitine, mesaconitine, hypaconitine, benzoylaconine, benzoylmesaconine and benzoylhypaconine	Non-compartmental	DAS 3.2	T_{max}, C_{max}, AUC_{0-t}, $T_{1/2}$, *etc.*	Alkaloids (except methylephedrine, benzoylmesaconine and benzoylhypaconine) showed slower elimination	77
Corydalis bungeana Herba	Normal	LC-MS/MS	Corynoline	Non-compartmental	DAS 3.2	T_{max}, $T_{1/2}$, MRT, $AUC_{0-\infty}$	Shuanghua Baihe tablets prolonged the elimination half-life of corynoline and increased its bioavailability	78
Nao-De-Sheng decoction (NDS)	Normal	RP-HPLC	Ferulic acid, puerarin	Two-compartment	3P97	T_{max}, C_{max}, AUC_{0-t}, $AUC_{0-\infty}$	Some ingredients in NDS may increase dissolution and absorption of ferulic acid andpuerarin, delay elimination, and subsequently enhance bioavailability of ferulic acid and puerarin	79
Radix Aconiti Lateralis	Normal	LC-MS/MS	Aconitine, hypaconitine, mesaconitine, benzoylaconine, benzoylhypaconine, benzoylmesaconine	—	3P97 1.0	$T_{1/2}$, AUC_{0-t}, C_{max}, T_{max}	Ganjiang could promote the elimination of aconitine and hypaconitine and enhance the absorption of benzoylaconine, benzoylhypaconine and benzoylmesaconine	80

Table 2 (*Contd.*)

Name of plant	Model	Analytical method	Active components	Compartment model	Process	PK parameters	PK behavior	Reference
Rhubarb peony decoction (RPD)	Normal	LC-MS	Aloe-emodin, rhein, emodin	—	—	$T_{1/2}$, C_{max}, T_{max}	The absorption of rhein in rats was suppressed after oral administration RPD	81
Suan-Zao-Ren decoction (SZR)	Insomnic	UFLC-MS/MS	Spinosin, mangiferin, ferulic acid	Noncompartmental	DAS 2.1	T_{max}, C_{max}, AUC_{0-t}, $T_{1/2}$	The absorptions of spinosin and mangiferin in insomnic group were significantly lower than those in normal group	82

[a] $T_{1/2}$: the half-time; C_{max}: maximum plasma concentration; T_{max}: time to reach the maximum concentrations; AUC_{0-t}: area under concentration–time curve; C_0: extrapolated plasma concentration at 0 min; Vdz/F: apparent volume of distribution; MRT: mean residence time.

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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