Acta Pharmaceutica Sinica B 2023;13(9):3598−3637

Chinese Pharmaceutical Association
Institute of Materia Medica, Chinese Academy of Medical Sciences

Acta Pharmaceutica Sinica B

www.elsevier.com/locate/apsb
www.sciencedirect.com

REVIEW

Potential herb−drug interactions between anti-COVID-19 drugs and traditional Chinese medicine

Ling Ye[a,*,†], Shicheng Fan[a,*,†], Pengfei Zhao[b,†], Chenghua Wu[a,†], Menghua Liu[a,†], Shuang Hu[a,†], Peng Wang[a,†], Hongyu Wang[a], Huichang Bi[a,*]

[a]*NMPA Key Laboratory for Research and Evaluation of Drug Metabolism & Guangdong Provincial Key Laboratory of New Drug Screening, School of Pharmaceutical Sciences, Southern Medical University, Guangzhou 510515, China*
[b]*Guangdong Provincial Key Laboratory of New Drug Design and Evaluation, School of Pharmaceutical Sciences, Sun Yat-sen University, Guangzhou 510006, China*

Received 27 January 2023; received in revised form 21 March 2023; accepted 20 April 2023

KEY WORDS

COVID-19;
Antiviral drugs;
Anti-COVID-19 drugs;
Nirmatrelvir/Ritonavir (Paxlovid™);
Remdesivir;
Molnupiravir;
Traditional Chinese medicine;
Pharmacokinetics;
Herb−drug interaction

Abstract Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread worldwide. Effective treatments against COVID-19 remain urgently in need although vaccination significantly reduces the incidence, hospitalization, and mortality. At present, antiviral drugs including Nirmatrelvir/Ritonavir (Paxlovid™), Remdesivir, and Molnupiravir have been authorized to treat COVID-19 and become more globally available. On the other hand, traditional Chinese medicine (TCM) has been used for the treatment of epidemic diseases for a long history. Currently, various TCM formulae against COVID-19 such as Qingfei Paidu decoction, Xuanfei Baidu granule, Huashi Baidu granule, Jinhua Qinggan granule, Lianhua Qingwen capsule, and Xuebijing injection have been widely used in clinical practice in China, which may cause potential herb−drug interactions (HDIs) in patients under treatment with antiviral drugs and affect the efficacy and safety of medicines. However, information on potential HDIs between the above anti-COVID-19 drugs and TCM formulae is lacking, and thus this work seeks to summarize and highlight potential HDIs between antiviral drugs and TCM formulae against COVID-19, and especially pharmacokinetic HDIs mediated by

*Corresponding authors.
E-mail addresses: yeling623@hotmail.com (Ling Ye), fanshch3@smu.edu.cn (Shicheng Fan), bihchang@smu.edu.cn (Huichang Bi).
[†]These authors made equal contributions to this work.
Peer review under the responsibility of Chinese Pharmaceutical Association and Institute of Materia Medica, Chinese Academy of Medical Sciences.

https://doi.org/10.1016/j.apsb.2023.06.001

metabolizing enzymes and/or transporters. These well-characterized HDIs could provide useful information on clinical concomitant medicine use to maximize clinical outcomes and minimize adverse and toxic effects.

1. Introduction

Coronavirus disease 2019 (COVID-19), a highly infectious respiratory illness caused by a newly discovered coronavirus, namely, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), remains a global pandemic[1]. To date, more than 500 million people have been infected with COVID-19, resulting in six million deaths worldwide[2]. As COVID-19 vaccines have been gradually rolled in the global population, the risk of infection, severe illness, and death has been reduced[3]. However, given the varied efficacy and duration of protection after vaccination in different populations, effective treatments against COVID-19 remain necessary. Angiotensin-converting enzyme 2 (ACE2) is the main target for SARS-CoV-2 to invade the host cell[4]. ACE2-based therapy can be considered as a potential treatment strategy for COVID-19. At present, three antiviral drugs (Paxlovid™, Remdesivir, and Molnupiravir) have been authorized to manage patients with COVID-19[5]. Paxlovid™ (Nirmatrelvir/Ritonavir) is a combination therapy that showed near 90% efficacy in preventing hospitalizations and deaths in high-risk patients[6]. Nirmatrelvir is considered as a SARS-CoV-2 protease inhibitor, and Ritonavir, as an inhibitor of the prominent drug-metabolizing enzyme cytochrome P450 (CYP) 3A4, could slow down the hepatic metabolism and boost the concentration of Nirmatrelvir[7]. Remdesivir, as a prodrug, could selectively inhibit RNA-dependent RNA polymerase (RdRp), then delay viral RNA chain termination, and finally inhibit viral replication[8]. Molnupiravir and its metabolites can also inhibit SARS-CoV-2 transmission by targeting RdRp[9].

Traditional Chinese medicine (TCM) has a long history of being used for the treatment of epidemic diseases and it has good efficacy in treating viral infections including SARS-CoV and MERS-CoV[10,11]. While fighting COVID-19 in China, the National Health Commission of China announced that patients with COVID-19 treated with TCM combined with antiviral drugs had their symptoms effectively relieved and recovered[12]. TCM can inhibit the replication and transcription of SARS-CoV-2 by targeting 3C-like protease (3CLpro) and RdRp, and attenuate cytokine storm and immune deficiency caused by the SARS-CoV-2[13]. Early intervention with TCM in patients with COVID-19 can improve the cure rate, shorten the disease course, delay disease progression, and reduce mortality[14,15]. Among these TCMs, three TCM decoctions and three formulated Chinese medicines, namely Qingfei Paidu decoction (QFPD), Xuanfei Baidu granule (XFBD), Huashi Baidu granule (HSBD), Jinhua Qinggan granule (JHQG), Lianhua Qingwen capsule (LHQW), and Xuebijing injection (XBJ) have been shown to be most effective in treating patients with COVID-19, which are recommended by China's National Health Commission to treat severe and critical cases of COVID-19.

Herb−drug interactions (HDIs) may occur during TCM combined with antiviral drug treatment of patients with COVID-19. HDIs are clinically insignificant, and they do not require any special medical care, but sometimes they may become clinically relevant and require medical intervention. Generally, HDIs have two main types: pharmacodynamic and pharmacokinetic-based interactions. Pharmacodynamic-based HDIs occur when TCM/one drug has an additive, synergistic, or antagonistic effect or has the same drug targets or pathways as co-administrated TCM/drugs[16]. Pharmacokinetic-based HDIs are more frequently reported, where TCM/one drug affects the plasma concentration of the other drug/TCM by modulation of their absorption, distribution, metabolism and excretion (ADME) by affecting the expression and activity of drug-metabolizing enzymes and transporters, which represent a major concern in drug pharmacokinetics[16]. Drug transporters including efflux transporters (*e.g.*, ABC-transporters) and uptake transporters (*e.g.*, SLC-transporters) are expressed in many tissues, such as the intestine, liver, kidney and the brain, and play a crucial role in drug absorption, distribution and excretion[16]. Alterations in the expression and activity of drug transporters will lead to changes in the clearance of drugs and result in varied clinical outcomes. Drug metabolizing enzymes (*e.g.*, CYPs) mainly located in the liver, intestine and kidneys, are responsible for the degradation of drugs. The induction and inhibition of CYPs are predominant mechanisms responsible for PK-based HDIs[16]. For example, St. John's wort (*Hypericum perforatum*) can decrease the bioavailability of numerous conventional drugs that are substrates for CYPs and P-glycoprotein (P-gp) such as warfarin, cyclosporine, digoxin, indinavir, irinotecan, midazolam, and others, resulting in their reduced efficacy[17]. By contrast, grapefruit juice inhibits the catalytic activity of intestinal CYP3A4, thereby altering the pharmacokinetic and pharmacodynamic profiles of cyclosporine and felodipine, thereby enhancing their oral bioavailability[18]. Because of the critical pharmacokinetic effect of the above-mentioned CYP3A4-mediated mechanism for Nirmatrelvir/Ritonavir, co-administration with certain medications that inhibit or induce CYP3A4 is contraindicated and should be a concern in clinical practice. This contraindication reflects concern for potential HDIs with the potential to alter the efficacy or safety of Ritonavir/Nirmatrelvir and/or co-administered drugs metabolized by CYP3A4.

Gut microbiota alterations have been reported in hospitalized COVID-19 patients and are related to poor prognosis through complex interactions with SARS-CoV-2 and host immunity after severe COVID-19[19,20]. More importantly, the composition of the microbial community may not be fully restored in COVID-19 patients after a 3-month recovery[21]. It was reported that ACE2 expression may be regulated by microbiota *via* their metabolites[22]. Numerous studies have demonstrated that TCM formulae are important in the modulation of gut microbiota, and some herbs and Western medicines are closely related to alterations in the gut microbiota[23]. Thus, attention should be paid to gut microbiota-mediated HDIs between anti-COVID-19 drugs and TCM formulae.

However, information on potential HDIs between the above anti-COVID-19 drugs and TCM formulae is lacking, and thus a well-characterized HDI summary is urgently needed. This work seeks to summarize and highlight potential HDIs between antiviral drugs and TCM formulations against COVID-19, and especially pharmacokinetic HDIs mediated by metabolizing enzymes and/or transporters, which provides useful information on clinical concomitant medicine use to maximize clinical outcomes and minimize adverse and toxic effects.

2. Anti-COVID-19 drugs

2.1. *Paxlovid™ (Nirmatrelvir + Ritonavir)*

Paxlovid™ was issued by the US Food and Drug Administration (FDA) and emergency use authorization for the treatment of COVID-19 in 2021. It is a therapeutic combination consisting of two compounds: Nirmatrelvir and Ritonavir[24]. Paxlovid™ reduces the risk of hospitalization or mortality by 89% in non-hospitalized adult patients with COVID-19[24]. Nirmatrelvir, which is designed to prevent viral replication, is a peptidomimetic inhibitor of the SARS-CoV-2 main protease (Mpro), referred to as 3CLpro or nsp5 protease[24]. Co-administration with a low dose of Ritonavir (a potent CYP3A4 inhibitor) can slow down the hepatic metabolism of Nirmatrelvir, leading to longer periods of higher concentrations of Nirmatrelvir to combat the virus[24]. The common adverse events of Paxlovid™ include dysgeusia, diarrhea, nausea, headache, vomiting, and pyrexia. In addition, other adverse reactions are observed such as liver toxicity and allergic reactions[24]. In healthy subjects, the difference in plasma protein binding between Nirmatrelvir (∼69%) and Ritonavir (∼99%) was approximately 30%[24]. Nirmatrelvir is excreted in feces (49.6%) and urine (35.3%), whereas Ritonavir is primarily excreted in feces (86.4%) and to a lesser extent in urine (11.3%)[24].

The metabolism of Nirmatrelvir was qualitatively similar in liver microsomes and hepatocytes from rats, monkeys, and humans, and its prominent metabolic pathway was CYP3A4-mediated oxidation[25]. The oxidative metabolism of Nirmatrelvir is diminished following co-administration of Nirmatrelvir with Ritonavir[26,27]. Nirmatrelvir reversibly inhibits CYP3A4, and it does not reversibly inhibit the activity of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 *in vitro* at clinically relevant concentrations[7,28]. Nirmatrelvir does not induce any CYPs at clinically relevant concentrations[7]. Nirmatrelvir is a substrate for human P-gp but not a substrate for equilibrative nucleoside transporter 1 (ENT1), ENT2, organic anion transporter polypeptide 1B1 (OATP1B1), OATP1B3, OATP2B1, OATP4C1, organic cation transporter 1 (OCT1), OCT2, organic anion transporter 1−3 (OAT1−3), multidrug and toxic compound extrusion protein 1 (MATE1), MATE2K, Na^+/taurocholate cotransporting polypeptide (NTCP), breast cancer resistance protein (BCRP), or peptide transporter 1 (PEPT1)[24]. Nirmatrelvir inhibits the function of several drug transporters, including P-gp, MATE1, OCT1, and OATP1B1 *in vitro*[29]. Relatively weaker inhibition by Nirmatrelvir is noted against OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1, and MATE2K[25].

Ritonavir is primarily metabolized by CYP3A and, to a lesser extent, by CYP2D6. Ritonavir inhibits the activity of CYP3A4, CYP2D6, CYP2C8, CYP2C9, CYP2C19, and CYP2J2[30−33]. In addition, Ritonavir serves as an inducer of several metabolizing enzymes, such as CYP3A, CYP1A2, CYP2B6, CYP2C9, CYP2C19, and UDP-glucuronosyltransferases (UGTs)[30,34]. Ritonavir is a substrate for P-gp, multidrug resistance protein 1 (MRP1), and MRP2[35,36]. Furthermore, it inhibits the function of the intestinal transporters including P-gp, BCRP, OATP, MRP1 and MATE1[37,38] (Table 1).

2.2. *Remdesivir*

Remdesivir, a broad-spectrum antiviral agent, was approved by FDA for emergency use to treat COVID-19 in 2020[39]. Remdesivir (GS-5734) is a prodrug of a nucleoside analog (GS-441524)[40]. Inside the cells, Remdesivir is hydrolyzed to GS-704277 by carboxylesterases (CES), and then GS-704277 is converted to the nucleoside analog monophosphate GS-441524-MP, and GS-441524-MP is consecutively phosphorylated into the active nucleoside triphosphate form GS-443902[41]. GS-443902 serves as an ATP analog to compete with endogenous ATP and selectively inhibit RdRp, which delays viral RNA chain termination and finally inhibits viral replication[39,42,43]. Notably, CES1 (∼80%), cathepsin A (∼10%), and CYP3A (∼10%) are the key metabolizing enzymes involved in the Remdesivir metabolism[44,45]. GS-704277 is hydrolyzed to the monophosphate form by histidine triad nucleotide-binding protein 1[46]. Although the adverse events of Remdesivir are relatively limited, an increase in transaminase was observed in patients treated with Remdesivir[47]. Moreover, an Ebola phase 3 trial reported that one patient treated with Remdesivir experienced hypotension and cardiac arrest that resulted in death[48].

Given its first-pass liver metabolism, Remdesivir is administered *via* intravenous injection rather than oral delivery[44]. Remdesivir has a short plasma half-life (<1 h) of the prodrug, and GS-443902 has a prolonged $t_{1/2}$ (>35 h)[49−51]. Remdesivir shows moderate protein binding in plasma, with a free fraction of 12.1% in humans. However, the metabolite of the Remdesivir, GS-704277 displays low protein binding, with a free fraction ranging from 85% to 127%[50]. Remdesivir is a substrate of CYP3A4, CYP2C8, CYP2D6 and P-gp[40,52]. Remdesivir exhibits an inhibitory effect on the activity of CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, OATP1B1, OATP1B3, MRP4, and NTCP (Table 1)[40]. Remdesivir and its metabolites are primarily excreted through urine (74%) and feces (18%)[40].

2.3. *Molnupiravir*

Molnupiravir, an orally delivered antiviral drug, was approved and developed by Merck for the treatment of COVID-19 in 2021 in the UK[53]. Molnupiravir is an isopropyl ester prodrug, and it is metabolized to β-D-*N*4-hydroxycytidine (NHC or EIDD-1931) by esterases in plasma[54]. Inside the cells, NHC is converted to the active form of NHC-triphosphate (TP)[53]. NHC-TP serves as a substrate instead of cytidine-triphosphate and uridine-triphosphate for RdRp, resulting in mutagenesis during viral RNA replication[55]. Molnupiravir showed excellent efficacy against SARS-CoV-2 infection in mice implanted with human lung tissue[56]. Another study also showed that treatment with Molnupiravir reduced lung viral load and alleviated lung damage in SARS-CoV-2-infected mice[57]. Molnupiravir could also inhibit SARS-CoV-2 transmission in a hamster model[58]. In humans, a clinical Phase III study showed that Molnupiravir was effective for the treatment of unvaccinated adults with COVID-19, which lowered the risk of hospitalization and mortality[59]. The most common side effects of

Table 1 The effect of anti-COVID-19 drugs on metabolizing enzymes and transporters.

Anti-viral drug	Metabolizing enzyme					Transporter						
	CYP1	CYP2	CYP3	UGT	CES	OCT	NTCP	OATP	P-gp	BCRP	MRP	OAT
Nirmatrelvir (Refs. 7,24,25,28,29)	1A2↓	2B6↓ 2C8↓ 2C9↓ 2C19↓ 2D6↓	3A4[a] 3A4↓			OCT1↓ OCT2↓		OATP1B1↓ OATP1B3↓	P-gp[a] P-gp↓			OAT1↓ OAT3↓
Ritonavir (Refs. 30−38)	1A2↑	2B6↑ 2D6[a] 2D6↓ 2C8↓ 2C9↑ 2C9↓ 2C19↑ 2C19↓ 2J2↓	3A[a] 3A↑ 3A4↓	UGTs↑				OATPs↓	P-gp[a] P-gp↓	BCRP↓	MRP1[a] MRP1↓ MRP2[a]	
Remdesivir (Refs. 40,41,52,474)	1A2↓	2C8[a] 2D6[a] 2C9↓ 2C19↓ 2D6↓	3A4[a] 3A4↓		CES1[a]		NTCP↓	OATP1B1↓ OATP1B3↓	P-gp[a]		MRP4↓	
Molnupiravir (Refs. 64,65)					CES1/2[a]							

↑Indicates the induction effect on an enzyme or drug transporter.
↓Indicates the inhibitory effect on an enzyme or drug transporter.
[a]Indicates that the drug is a substrate for an enzyme or drug transporter.

Molnupiravir include headache and diarrhea, and 93.3% of the side effects are well tolerated[60,61].

A low level of Molnupiravir can be detected, but a high level of NHC can be measured in the plasma[60,62,63]. NHC does not bind to plasma protein[53]. Given the rapid conversion into NHC and NHC-TP, Molnupiravir is barely detected in all tissues, however, NHC and NHC-TP are observed in all tissues, primarily in the lungs and spleen, in a dose-dependent manner[63]. Molnupiravir is hydrolyzed to NHC by CES, especially CES2[64,65]. NHC is converted into NHC-TP by host kinases and phosphatases in cells[63]. NHC-TP is ultimately metabolized to endogenous pyrimidine nucleosides (uridine and/or cytidine), and only ≤3% of the administered Molnupiravir is excreted through urine in NHC form[63]. *In vitro*, NHC is a substrate of concentrative nucleoside transporter 1 (CNT1), CNT2, CNT3, and ENT2, whereas Molnupiravir is a comparatively weak substrate of CNT1[63]. Neither Molnupiravir nor NHC is the substrate of human P-gp, or BCRP[66]. *In vitro* studies demonstrated that Molnupiravir is not an inhibitor of major human CYPs (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4), and neither Molnupiravir nor NHC inhibited P-gp, BCRP, OATP1B1, OATP1B3, OCT1[63,66]. Moreover, they are not inhibitors or inducers of major drug-metabolizing enzymes or transporters, which might reduce the risk of drug−drug interactions (DDIs)[63] (Table 1).

3. TCMs for the treatment of COVID-19 infections

3.1. QFPD

3.1.1. Basic pharmacological information of QFPD

QFPD is listed as the first-line prescription of TCM clinical treatment in the latest *Protocol on Diagnosis and Treatment of COVID-19 (Trial Version 9)* issued by China's National Health Commission[67]. Multiple clinical reports have proven that early treatment with QFPD was associated with favorable outcomes, including faster recovery, shorter time to viral shedding, and shorter hospital stay[68−70]. A total of nine trials, including 1108 patients with COVID-19, have revealed that QFPD combined with western medicine treatments reduced the aggravation rate by 71% and decreased the incidence of adverse events by 56%[71].

Previous studies have shown that QFPD acts on several targets associated with its anti-inflammation, immuno-modulation, and anti-viral effects against COVID-19[72−74]. ACE2, SARS-CoV-2 spike protein, and SARS-CoV-2 3CLpro, which are closely relevant to the infectivity and pathogenicity of COVID-19, are also identified as the potential targets of QFPD[75]. Previous study has shown that several kinds of gut microbiota play an important role in the immune function, and QFPD decoction could restore the diversity of gut microbiota and could be used to treat coronavirus-induced pneumonia, reflected in the up-regulation of the relative abundance of *Romboutsia*, *Turicibacter* and *Clostridium_sensu_stricto_1*, and the down-regulation of the relative abundance of *norank_f_Lachnospiraceae*, which is closely related to disease severity and immune dysfunction in COVID-19 patients[76].

QFPD is composed of 20 herbs and one mineral (Ephedrae Herba, Glycyrrhizae Radix et Rhizoma Praeparata Cum Melle, Praeparata Cum Melle, Armeniacae Semen Amarum, Gypsum Fibrosum, Cinnamomi Ramulus, Alismatis Rhizoma, Polyporus, Atractylodis Macrocephalae Rhizoma, Poria, Bupleuri Radix, Scutellariae Radix, Pinelliae Rhizoma Praeparatum Cum Zingibere et Alumine, Zingiberis Rhizoma Recens, Asteris Radix et Rhizoma, Farfarae Flos, Belamcandae Rhizoma, Asari Radix et Rhizoma, Dioscoreae Rhizoma, Aurantii Fructus Immaturus, Citri Reticulatae Pericarpium, Pogostemonis Herba)[67]. It was reported that a total of 195 chemical components, including 104 prototypes and 91 metabolites, were identified in mice serum after oral

administrated with QFPD decoction in mice[77]. Nine of them, including ephedrine, pseudoephedrine, amygdalin, prunasin, liquiritin, hyperoside, hesperidin, baicalin, irisflorentin, were absorbed quickly into the circulation system, subsequently distributed to heart, liver, spleen, lung, and kidney[78].

QFPD exerts regulatory effects on the metabolizing enzymes and drug transporters (Table 2). QFPD shows inhibitory effects on the activities of human CYP1A, CYP2A6, CYP3A, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP2E1[79] by cocktail probe substrates approach, and the potential of HDIs should be considered in the combined therapy against COVID-19. The pharmacodynamic and pharmacokinetic characteristics of each herb of QFPD are summarized below.

3.1.2. Pharmacodynamic and pharmacokinetic feature of each herb in QFPD

Ephedrae Herba (Mahuang in Chinese) is the dried herbaceous stem of *Ephedra sinica*, *Ephedra intermedia*, or *Ephedra equisetina* (Family, Ephedraceae)[80]. Ephedrae Herba could disrupt the interaction between ACE2 and SARS-CoV-2 spike protein receptor-binding domain (RBD), thereby abolishing the infectivity of SARS-CoV-2 pseudoviruses[75]. To date, more than 150 chemical components of Ephedrae Herba have been identified or tentatively characterized, including alkaloids, triterpenoid saponins, flavanone-*O*-glycosides, flavone-*C*-glycosides, and procyanidins[81]. Among them, phenylalkylamine alkaloids including ephedrine, pseudoephedrine, methylephedrine, norephedrine, and norpseudoephedrine are considered as characteristic active compounds[81]. Ephedrine, pseudoephedrine, and methylephedrine are possibly P-gp substrates[82]. Meanwhile, ephedrine and norpseudoephedrin were proved as substrates of OCT2[83]. Ephedrae Herba water decoction could increase CYP1A2 activity characterized by detecting the probe substrate of phenacetin, as well as the expression of mRNA and protein, but it has no effect on the activity of CYP2E1[84]. *In vitro*, it could inhibit MDR1 function in part[85]. Interestingly, pseudoephedrine has an inhibitory effect on the activities of CYP1A1/2 and CYP2E1, whereas ephedrine could induce the activities of CYP2C and CYP1A1/2 by determining their probe substrates[86].

Glycyrrhizae Radix et Rhizoma (Gancao in Chinese) is the dried root and rhizome of *Glycyrrhiza uralensis* Fisch., *Glycyrrhiza inflata* Bat., or *Glycyrrhiza glabra* L.[87], Glycyrrhizae Radix et Rhizoma Praeparata Cum Melle, which is used in QFPD, is processed from Glycyrrhizae Radix et Rhizoma. Studies revealed that Glycyrrhizae Radix et Rhizoma could inhibit ACE2, thereby inhibiting viral infectivity[88] and showing affinity to RdRp of SARS-CoV-2, suggesting its potential efficacy against COVID-19[89]. Based on previous reports, Glycyrrhizae Radix et Rhizoma could modulate gut microbiota, thereby enhancing the immune defensive function of the human body[90]. Numerous bioactive constituents have been found in Glycyrrhizae Radix et Rhizoma, such as triterpene saponins, flavonoids, isoflavonoids and chalcones[91]. Glycyrrhizin, glycyrrhetinic acid, liquiritigenin, isoliquiritigenin, licochalcone A, and glycycoumarin have been isolated from Glycyrrhizae Radix et Rhizoma[91]. Glycyrrhetinic acid, the main bioactive constituent of Glycyrrhizae Radix et Rhizoma, is primarily metabolized by CYP3A4, followed by CYP2C9 and CYP2C19[92]. Glycyrrhetinic acid might be a substrate for P-gp[92]. Studies on rodents and humans demonstrated that glycyrrhizin is poorly absorbed by the gastrointestinal tract but extensively metabolized by the intestinal microflora to glycyrrhetinic acid and monoglucuronyl glycyrrhetinic acid, which are readily absorbed[93]. The transformation of glycyrrhizin in the intestine was mainly catalyzed by the intestinal bacteria *Eubacterium* L-8 and *Streptococcus* LJ-22[94]. Glycyrrhizic acid and glycyrrhetinic acid were mainly excreted *via* bile[95]. Glycyrrhizic acid and glycyrrhetinic acid bind extensively to the plasma albumin in human and rat[96]. The extract of Glycyrrhizae Radix et Rhizoma could inhibit the activity of CYP2B6, CYP2C9, CYP2C19, and CYP3A4 in human liver microsomes[97]. The oral administration of glycyrrhizin or Glycyrrhizae Radix et Rhizoma to mice can induce the activity of CYP3A4, CYP2B1, CYP1A2, CYP3A, CYP2A1 and CYP2B9[98]. Licochalcone A could inhibit the activity of CYP1A2, CYP2D6, CYP2E1, CYP2C19, CYP2C8, CYP2C9 and CYP3A4 in human liver microsomes[99]. Glycyrol, a bioactive compound isolated from Glycyrrhizae Radix et Rhizoma, could inhibit human CYP2C9 activity[100]. Moreover, licochalcone A could inhibit OATP1B1 activity[101]. Studies showed that Glycyrrhizae Radix et Rhizoma could strongly activate human pregnane X receptor (PXR) and induce CYP3A4 expression[102]. Using non-specific probes for UGT isoforms, glycyrrhetinic acid was shown to exhibit strong inhibitory effects towards UGT1A3 and UGT2B7[103]. Additionally, the treatment of Glycyrrhizae Radix et Rhizoma together with Astragali Radix significantly attenuated the decreased diversity, reduced richness, and abnormal composition of intestinal microbiota of cholestatic mice[104].

Armeniacae Semen Amarum (Kuxingren in Chinese) is the dried ripe seed of *Prunus armeniaca* L. var. *ansu* Maxim., *Prunus sibirica* L., *Prunus mandshurica* (Maxim.) Koehne, or *Prunus armeniaca* L.[105]. Previously, Armeniacae Semen Amarum has shown an antiviral effect because of its strong affinity to 3CLpro and ACE2, thereby preventing viral transcription and dissemination[105]. The pharmacokinetic characterization of Armeniacae Semen Amarum was primarily reflected by amygdalin. After oral administration, amygdalin was immediately absorbed and quickly distributed to the heart, liver, spleen, lung, and kidney[106]. However, the absolute bioavailability of amygdalin was low[7]. Amygdalin could be effluxed by P-gp, indicating that it might be a substrate for P-gp[107]. Moreover, amygdalin had evident inhibitory effects on the activity of murine CYP2C9 and CYP2E1[107]. Amygdalin is considered to be toxic due to its metabolite of cyanide *in vivo*[108]. The intestinal microbiota of *Bifidobacterium pseudolongum*, *Marvinbryantia formatexigens*, and *Bacteroides fragilis* were involved in bidirectional regulation of toxicity and detoxification of amygdalin[109].

Gypsum Fibrosum (Shengshigao in Chinese) is a plaster stone of sulfates of the plaster stone group, containing primarily hydrated calcium sulfate[110]. It is a common mineral TCM in *Shennong Bencao Jing* for reducing fever and alleviating thirst[111]. Gypsum Fibrosum might exhibit an inhibitory effect on the activity of rat CYP1A2, which may lead to drug interactions *in vivo*[112].

Cinnamomi Ramulus (Guizhi in Chinese) is the dried young branch of *Cinnamomum cassia* (L.) Presl[113]. Cinnamomi Ramulus could inhibit the activity of Zika virus by inhibiting RdRp activity in the post-entry stage[114]. More than 121 chemical compounds have been isolated from Cinnamomi Ramulus, including volatile oils, organic acids, triterpenoid saponins, coumarins, tannins, flavonoids, flavonoid glycosides, steroids, and polysaccharides[113]. Cinnamic acid is a bioactive compound isolated from Cinnamomi Ramulus[113]. CYP1A is the main enzyme that participates in the metabolism of cinnamic acid[115]. Moreover, cinnamic acid is not a strong substrate for P-gp and MRP in Caco-2 cells[116]. In addition,

Table 2 The effect of QFPD on metabolizing enzymes and transporters.

Herb	Component	Metabolizing enzyme							Transporter					
		CYP1	CYP2	CYP3	UGT1	UGT2	UGT3	CES	OCTs	OAT	OATP	P-gp	BCRP	MRP
Ephedrae Herba (Refs. 82−86)	Water decoction	1A2↑										MDR1↓		
	L-Ephedrine	1A1↑ 1A2↑	2C↑						OCT2[a]			P-gp[a]		
	D-Pseudoephedrine	1A1↓ 1A2↓	2E1↓									P-gp[a]		
	Norpseudoephedrin								OCT2[a]					
	L-Methylephedrine											P-gp[a]		
Glycyrrhizae Radix et Rhizoma (Refs. 92,97−103,477)		1A2↑	2A1↑ 2B1↑ 2B9↑	3A↑ 3A4↑										
	Extract		2B6↓ 2C9↓ 2C19↓	3A4↓										
	Glycyrrhetinic acid		2C9[a] 2C19[a]	3A4[a]	1A3↓	2B7↓		CES1↓				P-gp[a]		
	Glycyrrhizin	1A2↑	2A1↑ 2B1↑ 2B9↑	3A↑ 3A4↑										
	Licochalcone A	1A2↓	2D6↓ 2E1↓ 2C19↓ 2C8↓ 2C9↓	3A4↓							1B1↓			
	Glycyrol		2C9↓											
Armeniacae Semen Amarum (Ref: 107)	Amygdalin		2C9↓ 2E1↓									P-gp[a]		
Gypsum Fibrosum (Ref: 112)		1A2↓												
Cinnamomi Ramulus (Ref: 115)	Cinnamic acid	1A[a]												
Alismatis Rhizoma (Refs. 118,122−126,485)	Alisol acetates			3A2[a]				CES2↓						
	Alisol B 23-acetate			3A4↑								P-gp↓		
	Alisol F 24-acetate											P-gp↓		
	Water etract	1A2↑		3A4↑										
	Alisol B				UGTs↓									
Polyporus (Ref: 133)	Polyporus polysaccharides			3A↑										
Atractylodes Macrocephala Rhizoma (Refs. 137,138,140,141)				3A4↑										
	Atractylenolide I					2B7↓						P-gp[a]		
	Atractylenolide II	1A2[a]	2C9[a]	3A4[a]										
	Atractylenolide III					2B7↓								
Poria (Refs. 146−151)				3A4↑										
	Galactoglucan		2E1↓											
	Polysaccharides		2E1↓											
	Pachymic acid											P-gp↓		
	Dehydrotumulosic acid											P-gp↓		

(*continued on next page*)

Table 2 (*continued*)

Herb	Component	Metabolizing enzyme							Transporter					
		CYP1	CYP2	CYP3	UGT1	UGT2	UGT3	CES	OCTs	OAT	OATP	P-gp	BCRP	MRP
Bupleuri Radix (Refs. 159−161)	Saikosaponin a	1A2↑		3A4↓								P-gp↓		
	Saikosaponin b	1A2↓		3A4↓										
	Saikosaponin b2	1A2↓		3A4↓										
	Saikosaponin c	1A2↓		3A4↓								P-gp↓		MRP2↓
	Saikosaponin d	1A2↑		3A4↓								P-gp↓		MRP2↓
	Saikosaponins		2C9↓	3A4↓										
Scutellariae Radix (Refs. 172,174−182,478)	Aqueous extract of scutellariae radix		2C9↓ 2E1↑											
	Baicalein			3A4↓	1A9[a] 1A10[a]			CES1/2↓				P-gp↓		MRP[a]
	Baicalin		2C9↑ 2C19↑	3A4↑										
	Wogonin	1A2↓			1A9[a]									
	Oroxylin A				1A9[a] 1A10[a]			CES1/2↓		OAT1↓ OAT3↓	1B1[a] 1B1↓ 1B3[a]		BCRP↓	
	Salvigenin				1A8↓ 1A10↓									
	Extract								OCT1↓					
Pinelliae Rhizoma (Ref: 191)				3A↓										
Zingiberis Rhizoma Recens (Refs. 201−205)	Ginger extract	1A2↑	2C9↑ 2C19↓ 2B6↑	3A4↑								P-gp↑		
	6-Shagaol	1A1↑ 1A2↑	2C9↑ 2B6↑	3A4↑	1A1↑							P-gp↑		
	6-Paradoal	1A2↑	2C9↑ 2B6↑	3A4↑								P-gp↑		
	Dihydro-6-6-gingerdione	1A2↑	2C9↑ 2B6↑	3A4↑								P-gp↑		
	6-Gingerol											P-gp↓		
	8-Gingerol		2C9↓ 2C19↓ 2D6↓	3A4↓										
	10-Gingerol		2C9↓ 2C19↓ 2D6↓	3A4↓										
Asteris Radix et Rhizoma (Refs. 209,212)	Astin D		2D6↓	3A4↓										
	Epiifedelanol											P-gp↓		MRP2↓
Farfarae Fos (Refs. 216−218)	Tussilagone	1A2[a]	2B6[a] 2C8[a] 2C9[a] 2C19[a] 2D6[a] 2E1[a]	3A4[a]										

	Isochlorogenic acid	1A2↓	2C9↓		1A6↓	2B↑								
	Chlorogenic acid		2E1↓											
Belamcandae Rhizoma	Isoflavones	1A2↓	2D6↑	3A4[a]										
(Refs. 225−228)	Total isoflavones	1A2↓												
	Iridin	1A7[a]												
		1A8[a]												
		1A9[a]												
		1A10[a]												
	Tectorigenin	1A1[a]												
		1A9[a]												
Asari Radix et Rhizoma	Asarinin	1A1[a]	2C8[a]	3A5[a]										
(Refs. 233−238)	Sesamin			3A4↓								MDR1↑		MRP1↑
														MRP3↑
	Methyleugenol	1A2↓	2C19↓											
	Safrole	1A2↓												
	Myristicin	1A2↓	2E1↓											
			2C19↓											
Dioscoreae Rhizoma	None	None	None	None	None	None	None	None	None	None	None	None	None	None
Aurantii Fructus	Ethanol extract			3A4↑								P-gp↑		
Immaturus (Refs. 246	Hesperetin	1A2[a]			1A1↓							P-gp[a]		
−254)					1A3↓									
					1A4↓									
					1A7↓									
					1A8↓									
					1A9↓									
	Hesperidin											P-gp[a]		MRP1[a]
														MRP2[a] MRP3[a]
	Naringenin	1A2[a]			1A1↓	2B7↓					1B1↓	P-gp[a]		
					1A3↓	2B15↓					1B3↓			
					1A4↓									
					1A7↓									
					1A8↓									
					1A9↓									
					1A10↓									
	Naringin		2E1↓	3A1↓							1A2↓	P-gp[a]↓		MRP1[a]
				3A2↓							1A5↓			MRP2[a] MRP3[a]
				3A4↓										
Citri Reticulatae	Hesperidin	1A↓		3A4↓								P-gp↓		
Pericarpium (Refs.		1B1↓												
257−264)	Nobiletin	1A2↓												
		1A2↑												
		1A1↑												
		1B1↑												

(*continued on next page*)

Table 2 (*continued*)

Herb	Component	Metabolizing enzyme							Transporter					
		CYP1	CYP2	CYP3	UGT1	UGT2	UGT3	CES	OCTs	OAT	OATP	P-gp	BCRP	MRP
Pogostemonis Herba (Refs. 268,269)	Tangeretin	1A2[a]		3A4↑							2B1↓			
	Patchouli alcohol											P-gp[a]		MRP[a]
	Pogostone		2C9↓ 2E1↓	3A4↓										

↑Indicates the induction effect on an enzyme or drug transporter.
↓Indicates the inhibitory effect on an enzyme or drug transporter.
[a]Indicates that the drug is a substrate for an enzyme or drug transporter.

the extract of Cinnamomi Ramulus and lactic acid bacteria could upregulate the alpha diversity of gut microbiota in mice[117].

Alismatis Rhizoma (Zexie in Chinese) is the dried rhizome of *Alisma orientale* (Sam.) Juzep[118]. Alismatis Rhizoma has been reported to inhibit the infection and replication of picornaviridae[119]. A wide range of chemical compounds, including triterpenoids, sesquiterpenoids, and diterpenoids, have been isolated from Alismatis Rhizoma[118]. Among these compounds, alisol acetates are important bioactive triterpenoids that play various pharmacological effects[120]. Under normal physiological conditions the rate of alisol acetate binding to plasma protein is between 70% and 80%[121]. CYP3A2 plays an important role in the metabolism of alisol acetates, which is an important factor leading to the different exposures of alisol A, alisol B, and alisol A 24-acetate between male rats and female rats[122]. Alisol B 23-acetate was identified to be the active compound of Alismatis Rhizoma, and alisol B 23-acetate can transactivate PXR and upregulate the mRNA levels of *CYP3A4 in vitro*[123]. In addition, alisol B 23-acetate could alleviate liver damage by activating farnesoid X receptor (FXR) and inhibiting CYP7A1 expression[124]. Alisol B 23-acetate and alisol F 24-acetate could downregulate P-gp, and Alismatis Rhizoma extract could induce PPARα downstream acyl-CoA oxidase 1[118]. Furthermore, the water extract of Alismatis Rhizoma could induce CYP1A2 and inhibit CYP3A4 activity in rats[125]. Alisol B could moderately inhibit UGT-mediated glucuronidation in human liver microsomes[126]. Alismatis Rhizoma can improve the changes in gut microbial structure caused by diabetes and affect microbiota-associated with lipid metabolism. *Lactobacillus* was decreased significantly by both water and ethanol extract of Alismatis Rhizoma, Lachnospira was increased by its water extract, while Ruminococcus was increased by the ethanol extract[127].

Polyporus (Zhuling in Chinese), a widely used and precious medicinal fungi, has been used as food, antidote, and diuretic for many years in China[128]. Polyporus was reported to exert an antiviral effect by inhibiting SARS-CoV-2[129]. Ergone and ergosterol are the main components of Polyporus[130]. Ergone is primarily excreted in feces *via* bile, and maximum excretion is reached at 6−8 h[131]. As for ergosterol, it is primarily excreted by feces rather than urine and plasma[132]. Pharmacokinetic studies have shown that polyporus polysaccharides could increase the expression of CYP3A in carp liver[133].

Atractylodes Macrocephala Rhizoma (Baizhu in Chinese) is the dried rhizome of *Atractylodes macrocephala* Koidz.[134]. Atractylodes Macrocephala Rhizoma might be a potential herb against SARS-CoV-2 through binding to ACE2[135]. The main constituents isolated from Atractylodes Macrocephala Rhizoma include sesquiterpenoids, triterpenoids, polyacetylenes, coumarins, phenylpropanoids, flavonoids, flavonoid glycosides, steroids, and benzoquinones[136]. Atractylenolide III is rapidly distributed into the body and eliminated[134]. The P-gp inhibitor could increase the absorption rate of Atractylenolide I[137]. CYP1A2, CYP2C9, and CYP3A4 are CYP isoforms involved in the metabolism of Atractylenolide II[138]. Atractylenolide I is primarily absorbed throughout the intestine, and Atractylenolide III metabolites can be detected in feces, urine, and plasma in rats[139]. Studies showed that Atractylodes Macrocephala Rhizoma could strongly activate human PXR and induce CYP3A4 expression[140]. It has been reported that Atractylenolide I and Atractylenolide III could inhibit UGT2B7 activity[141]. Atractylenolide III could significantly regulate the gut microbiota which was downregulated in colitis mice[142].

Poria (Fulin in> Chinese), the dried sclerotia of *Wolfiporia cocos* (F.A. Wolf) Ryvarden & Gilb., has been used as a TCM for over 2000 years[143]. A previous study revealed that Poria exerted an inhibitory effect on the Mpro[144]. The main active components of Poria are triterpenes and polysaccharides[143,145]. It has been reported that Poria polysaccharides could inhibit CYP2E1 expression in mouse liver[146]. Poria (pachymic acid) induced CYP3A4 gene transcription by activating PXR[147]. Poria could also induce transcriptional expression of CYP3A4 in HepG2 cells[148]. A galactoglucan purified from Poria could reduce the expression of constitutive androstane receptor and CYP2E1 in the liver[149]. Pachymic acid and dehydrotumulosic acid isolated from Poria could inhibit P-gp function[150,151]. Poria polysaccharides could affect the gut microbiota and alleviate chronic non-bacterial prostatitis in rat[152]. Poria powder and water-soluble polysaccharides of Poria could regulate the gut microbiota to alleviate the cisplatin-induced intestinal injury in mice[153]. Poria polysaccharides also could affect the diversity of gut microbiota in a non-alcoholic steatohepatitis mouse model[154].

Bupleuri Radix (Chaihu in Chinese) is a traditional herbal medicine derived from the dried roots of *Bupleurum chinense* DC. and *Bupleurum scorzonerifolium* Willd.[155]. The identified bioactive compounds of the Bupleuri Radix primarily focused on essential oils, triterpenoid saponins, polyacetylenes, flavonoids, lignans, fatty acids, and sterols[155]. Among these, triterpenoid saponins, flavonoids, and essential oil are considered as the main bioactive compounds[156,157]. Saikosaponins are potential candidates of Bupleuri Radix for COVID-19 treatment[158]. A previous study showed that saikosaponin b, saikosaponin b2, and saikosaponin c slightly inhibited CYP1A2 activity, whereas saikosaponin a and saikosaponin d increased CYP1A2 activity[159]. Saikosaponin a, saikosaponin b, saikosaponin b2, saikosaponin c, and saikosaponin d slightly inhibited the activity of CYP3A4[159]. Notably, CYP2C9 was strongly inhibited by saikosaponin[159]. Saikosaponin a, saikosaponin c, and saikosaponin d inhibited P-gp activity in P-gp over-expressing HEK293 cells[160]. Saikosaponin c and saikosaponin d inhibited MRP2 activity in HEK293 cells and BRL-3A cell with high MRP2 expression[160]. Saikosaponins and their metabolites also showed a liver meridian guiding effect by inhibiting PXR/CYP3A4[161]. Furthermore, saikosaponin a, saikosaponin c, and saikosaponin d were absorbed rapidly in rats[155]. Saikosaponins are primarily excreted through feces, bile, and urine[162]. It has been reported that saikosaponin d could regulate the gut microbiota in ulcerative colitis mice[163]. Saikosaponin a could upregulate the abundance of *Lactobacilus* and *Prevotella* species in rats[164]. The gut microbiota could affect the biotransformation of Bupleuri Radix[165], and gut microbiota plays an important role in the hydrolysis reaction of Saikosaponins[166].

Scutellariae Radix (Huangqin in Chinese) is the dried root of *Scutellaria baicalensis* Georgi[167]. Over 40 compounds have been isolated and identified from Scutellariae Radix including flavonoids, terpenoids, volatile oils, and polysaccharides[168]. Baicalin, baicalein, wogonin, chrysin and oroxylin A could inhibit H1N1 activity[169]. Baicalin and baicalein could inhibit RdRp of SARS-CoV-2[170]. Wogonin, a bioactive ingredient from Scutellariae Radix, has over 90% serum protein binding rate[171]. The glucuronidation of baicalein, wogonin, and oroxylin A primarily depends on UGT1A9 in the liver, and that of baicalein and oroxylin A primarily depends on UGT1A10 in the intestine[172]. The gut microbiota also plays an important role in the metabolism of baicalin, and baicalin could be metabolized by β-glucuronidase produced by gut microbiota such as *Escherichia coli*[173]. Baicalein is excreted into the intestine by MRP[174]. It has been reported that the aqueous extract of Scutellariae Radix could inhibit CYP2C9 and induce CYP2E1 activity in human[175]. Baicalein could inhibit CYP3A4 activity in human liver microsomes[176]. Baicalin could induce *CYP3A4*, *CYP2C9*, and *CYP2C19* expression in HeLa cells[177]. Wogonin could inhibit CYP1A2 activity in human microsomes[178]. It has been reported that baicalein could inhibit P-gp activity and expression[179]. The extract of Scutellariae Radix could inhibit OCT1 and MATE1 activity *in vitro*[180]. Oroxylin A might be a substrate of OATP1B1 and OATP1B3, and it can also inhibit OATP1B1, OAT1, OAT3 and BCRP activity[181]. The extract of Scutellariae Radix, salvigenin, could downregulate the activity of UGT1A8 and UGT1A10[182]. Polysaccharide isolated from Scutellariae Radix could upregulate the abundance of Firmicutes, Bifidobacterium, Lactobacillus, and Roseburia in mice[183]. Baicalin could also reprogram the gut microbiota in chicken with avian pathogenic *E. coli*-induced lung injury[184].

Pinelliae Rhizoma (Banxia in Chinese) is the dried tuber of *Pinellia ternata* (Thunb.) Breit., family Araceae[185]. Pinelliae Rhizoma Praeparatum Cum Zingibere et Alumine (Jiangbanxia in Chinese) and Pinelliae Rhizoma Praeparatum (Fabanxia in Chinese) are two of its commonly processed forms[185]. Alkaloids, essential oils, amino acids, organic acids, and proteins are the chemical components of Pinelliae Rhizoma[186]. β-Sitosterol is a bioactive compound in Pinelliae Rhizoma[187]. β-Sitosterol could interact with Mpro of SARS-CoV-2[188]. β-Sitosterol is metabolized to bile acid and goose deoxycholic acid, and is excreted in free form through bile[189,190]. Pinelliae Rhizoma showed inhibitory effects on CYP3A activity in rat liver microsomes[191].

Ginger is the rhizome of *Zingiber officinale* Roscoe (Zingiberaceae)[192], and Zingiberis Rhizoma Recens (Shengjiang in Chinese) is the fresh Ginger[193]. More than 100 compounds are identified from Ginger, and its bioactive components include essential oils, gingerols, shogaols, and others[193]. Gingerols and shogaols are recognized as important active ingredients in Ginger[194]. 6-Gingerol is the principal ingredient of Ginger that exerts anti-inflammatory and antioxidant effects[195]. *In silico* and molecular docking studies have revealed that 10-gingerol had an inhibitory effect on COVID-19[196]. 6-, 8-, 10-Gingerol and 6-shogaol are quickly absorbed and detected in the serum as glucuronide and sulfate conjugates, with the majority detected as glucuronide metabolites[197]. Intravenous bolus studies in rats indicated plasma protein binding of 6-gingerol was found to be greater than 90%[198,199]. Over 60% of an oral dose of 50 mg/kg dose of 6-gingerol was excreted as metabolites in the bile (48%) and urine (16%)[200]. Previous studies have shown that Ginger extract could inhibit CYP2C19-mediated drug metabolism[201]. 6-Shaogaol could increase the mRNA levels of *CYP1A1* and *UGT1A1*[202,203]. Ethanolic extract of Ginger activated PXR in LS-174T cells[204]. 6-Paradoal, 6-shagoal, and dihydro-6-6-gingerdione could also activate PXR[204]. The mRNA expression level of *CYP3A4*, *CYP2C9*, *CYP1A2*, *CYP2B6*, and *P-gp* could be increase by the extract, 6-paradoal, 6-shagoal, and dihydro-6-6-gingerdione[204]. 8-, and 10-gingerol could potently inhibit CYP2C9 activity, moderately inhibit CYP2C19 and CYP3A4, and weakly inhibit CYP2D6[203]. 6-Gingerol has been reported to inhibit P-gp activity in L-MDR1 and Caco-2 cells[205]. Ginger polysaccharides may modulate immune function by affecting the diversity of beneficial and harmful gut microbiota in immunosuppressed mice[206].

Asteris Radix et Rhizoma (Ziwan in Chinese) is the dried root and rhizome of *Aster tataricus* L. f.[207]. Shionone, astin D, and

epifriedelinol are three characteristic compounds of Asteris Radix et Rhizoma[208,209]. The content of shionone is low in blood, and it was primarily excreted through the feces[210]. Shionone had a higher protein binding rate in the plasma of rat, human, and bovine (greater than 75%)[211]. Astin D is considered as a potential inhibitor of CYP3A4 and CYP2D6[209]. Epifriedelanol could enhance the adriamycin cytotoxicity by the down-regulating the mRNA and protein expression of P-gp and MRP2[212].

Farfarae Flos (Kuandonghua in Chinese) is the dried flower bud of *Tussilago farfara* L.[213]. Previous study showed that the compounds in Farfarae Flos can bind to SARS-CoV-2 3CLpro and ACE2, thereby exerting a therapeutic effect against COVID-19[214]. Tussilagone is a representative active compound in Farfarae Flos. The absolute bioavailability of tussilagone is only about 1.31%[215] in rats. Eight CYP enzyme subtypes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4) were involved in tussilagone metabolism[216]. Organic acids are considered as active compounds of Farfarae Flos. Isochlorogenic acid demonstrates mild inhibition the activity of human CYP2C9 and a mild suppression on the activity of UGT1A6, while slightly increased UGT2B, but no significant influence UGT1A1 and UGT1A7/8 *in vitro*[217]. Chlorogenic acid, another important organic acid in Farfarae Flos, displayed weak inhibition on human CYP1A2 and CYP2E1 enzymatic activities *in vitro*[218]. Chlorogenic acid could be metabolized by human gut microbiota into caffeic acid, caffeoyl-glycerol, 3-(3,4-dihydroxyphenyl)-propanoic acid, 3-(3,4-dihydroxyphenyl)-propanoyl-glycerol, 3-*O*-(3-(3,4-dihydroxyphenyl)-propanoyl)-quinic acid, 3-*O*-(3-hydroxycinnamoyl)-quinic acid, 2-(3-hydroxyphenyl)-ethanol, 3-(3-hydroxyphenyl)-propanoic acid and phenyl-acetic[219]. On the other hand, chlorogenic acid regulates intestinal homeostasis under various pathological models, thus reducing the inflammatory response of the body[220,221].

Belamcandae Rhizoma (Shegan in Chinese) is the dried rhizome of *Belamcanda chinensis* (L.) DC.[222]. Flavonoids are the main active components for Belamcandae Rhizoma pharmacological effects[222]. Tectorigenin, irigenin, and irisflorentin were absorbed rapidly and they showed double peak phenomena in rat plasma[223]. Tectorigenin is widely distributed in the heart, liver, spleen, kidney, testis, small intestine, and skeletal muscle[224]. Irisflorentin is the compound identified in rat plasma when QFPD is given in rats, and CYP1A2 and CYP3A4 are the major enzymes responsible for its metabolism[225]. Moreover, the total isoflavones have shown an inhibition on the activity of CYP1A2 and an induction on the activity of CYP2D6[226]. The principal metabolic pathway of iridin was glucuronidation after demethylation and was mediated by UGT1A7, 1A8, 1A9 and 1A10[227]. UGT1A1 and UGT1A9 were the main enzymes for tectorigenin metabolism, which could be involved in DDIs[228].

Asari Radix et Rhizoma (Xixin in Chinese) is the dried root and rhizome of *Asarum heterotropoides* Fr. Schmt var. *mandshuricum* (Maxim) Kitag., *Asarum sieboldii* Miq. var. *seoulense* Nakai, or *A. sieboldii* Miq.[229]. Sesamin and asarinin, two active compounds isolated from Asari Radix et Rhizoma, showed inhibitory potential against SARS-CoV-2 3CLpro *in silico*[230,231]. Sesamin is excreted primarily through urine and feces[232]. Asarinin is the index component for the identification and content determination of Asari Radix et Rhizoma. CYP3A5, CYP2C8, CYP1A1, and CYP4F2 are the major CYP enzymes involved in asarinin metabolism[233]. Sesamin could strongly downregulate the mRNA and protein levels of CYP3A4[234], and it could increase significantly the mRNA expression of MDR1, MRP1 and MRP3, but has no effect on the protein of P-gp[235]. Methyleugenol shows an inhibitory effect on the activities of human CYP1A2 and CYP2C19 enzymes[236], and safrole has an inhibitory effect on CYP1A2 activity[237]. Myristicin exerts some inhibitory effect on the activities of human CYP2E1, CYP2C19 and CYP1A2[238]. *In vitro*, sesamin promotes the proliferation and adhesion of intestinal probiotics leading to modulating gut microbiota, which is beneficial for body[239].

Dioscoreae Rhizoma (Shanyao in Chinese) is the dried rhizome of *Dioscorea opposita* Thunb. (Family *Dioscoreaceae*)[240]. Polysaccharides and starch are considered as the main bioactive macromolecule in Dioscoreae Rhizoma[241,242]. Dioscoreae Rhizoma extract could regulate intestinal flora, especially enriching the abundance of *Bacteroides* spp. and *Clostridium* spp.[243]. Dioscoreae Rhizoma starch could inhibit the pathogenic bacteria of *E. coli* and *Helicobacter hepaticus*[244].

Aurantii Fructus Immaturus (Zhishi in Chinese) is the dried young fruit of *Citrus aurantium* L. and its cultivars *Citrus sinensis* Osbeck. Flavanone glycosides were determined as the active compounds in Aurantii Fructus Immaturus[245]. Naringin, naringenin, hesperidin, and hesperetin are the substrates of P-gp, whereas only naringin and hesperidin are extensively transported by the efflux transporters MRP1, MRP2, and MRP3[246]. *In vitro*, naringenin is a potential inhibitor of OATP1B1 and ATP1B3[247]. Naringin is a potential inhibitor of human OATP1A2, rat OATP1A5 and P-gp[248,249]. Naringenin and hesperitin, the hydrolysis products of naringin and hesperidin, respectively, are substrates of CYP1A2[250]. The ethanol extract of Aurantii Fructus Immaturus could upregulate the protein levels of P-gp, CYP3A4, and PXR[251]. Hesperetin strongly inhibits the activities of human UGT1A1, UGT1A3, and UGT1A9 and moderately inhibits the activities of UGT1A4, UGT1A7, and UGT1A8[252]. Naringenin strongly inhibits the activities of UGT1A1, UGT1A3, and UGT2B7 and moderately inhibits the activities of UGT1A4, UGT1A7, UGT1A8, UGT1A9, UGT1A10, and UGT2B15[252]. *In vivo*, naringin showed an inhibitory effect on CYP3A4 activity[253], and it could inhibit CYP3A1/2 activity in rats[254]. Eight flavonoid aglycones showing anti-inflammatory activity, including eriodictyol, naringenin, hesperetin, luteolin, apigenin, chryseriol, isosakuranetin, and diosmetin, are the major metabolites of Aurantii Fructus Immaturus by human gut microbioma[255].

Citri Reticulatae Pericarpium (Chenpi in Chinese) is the dried pericarp of the ripe fruit of *Citrus reticulata Blanco* or its cultivars[256]. Hesperidin, nobiletin, and tangeretin are the quality control index components of Citri Reticulatae Pericarpium. The absolute bioavailability of tangeretin is 27.11% because of its extensive biotransformation *via* CYP1A2 in the liver[257,258]. Hesperidin and its metabolite hesperetin showed an inhibitory effect on the activities of CYP1A, CYP1B1, CYP3A4, and P-gp[259,260]. Tangeretin exerts an inhibitive effect on OATP2B1[261], but can significantly increase the mRNA expression of CYP3A4 by regulating PXR[262]. Nobiletin is both a CYP1A2 inhibitor and inducer, while tangeretin is an inducer of CYP3A4[263]. In addition, nobiletin induces CYP1 enzymatic activity, CYP1A1 protein, and CYP1B1 mRNA levels in MCF7 cells[264]. Citri Reticulatae Pericarpium has a regulatory effect on intestinal microorganisms, especially short chain fatty acids (SCFAs)-producing and anti-inflammatory bacteria, including *Bifidobacterium*, *Lactobacillus* and *Allobaculum*[265].

Pogostemonis Herba (Guanghuoxiang in Chinese) is the dried aerial part of *Pogostemon cablin* (Blanco) Benth. (Family Labiatae)[266]. A study revealed that compounds in Pogostemonis Herba

can bind to the active site of SARS-CoV-2 3CLpro[267]. Patchouli alcohol and pogostone are known as the active compounds in Pogostemonis Herba. P-gp and MRP are involved in the transmembrane process of patchouli alcohol[268]. *In vitro*, pogostone displays inhibitory effects on human CYP3A4, 2C9 and 2E1[269]. Pogostemonis Herba could modulate intestinal microbiota, such as *Anaerostipes butyraticus*, *Butytivibrio fibrisolvens*, *Clostridium jejuense*, *Eubacterium uniforme*, and *Lactobacillus lactis* which are the main producing bacteria for SCFAs[270].

3.2. XFBD

3.2.1. Basic pharmacological information of XFBD

XFBD was the first, newly formulated TCM recipe for COVID-19 treatment, which is derived from classic formulas, including Maxing Shigan decoction[271,272]. XFBD could reduce fever, cough, fatigue, and other symptoms in mild and moderate cases of COVID-19 and prevent the transition of mild/moderate cases into severe cases[273]. In a randomized trial of 42 patients with COVID-19, XFBD (one bag, two times per day for 1 week), combined with conventional therapy, significantly improved the disappearance rate of clinical symptoms, increased the number of white blood cells and lymphocytes, and reduced c-reactive protein and erythrocyte sedimentation rate[274]. In a study of 280 patients with COVID-19 who were treated with XFBD, no case transformed into severe and critical condition[275]. Network pharmacology and molecular docking analysis indicated that XFBD inhibits viral invasion and viral replication by binding to ACE2 and 3CLpro of SARS-CoV-2 through flavonoids and phytosterols. Meanwhile, XFBD could affect 75 operational taxonomic units to improve intestinal flora, such as *Akkermansia*, *Muribaculaceae*, *Lachnospiraceae*, *Enterorhabdus*, and *Bacteroides*[276].

XFBD is composed of 13 herbs including Ephedrae Herba, Armeniacae Semen Amarum, Gypsum Fibrosum, Glycyrrhizae Radix et Rhizoma, Phragmitis Rhizoma, Coicis Semen, Descurainiae Semen Lepidii Semen, Atractylodis Rhizoma, Pogostemonis Herba, Polygoni Cuspidati Rhizoma et Radix, Verbenae Herba, Citri Grandis Exocarpium, and Artemisiae Annuae Herba[276].

Studies have proven that many herbs in XFBD play regulatory roles in CYPs, UGTs, and transporters (Table 3).

3.2.2. Pharmacodynamic and pharmacokinetic characteristics of each herb in XFBD

Coicis Semen (Yiyiren in Chinese) is the dried mature kernel of *Coix lacryma-jobi* L. var. ma-yuen (Roman.) Stapf[277]. Polyphenols and polysaccharides are considered as the major active components of Coicis Semen[277]. Kanglaite, an oily substance, has been reported to induce CYP1A2, but it inhibits CYP2B6, CYP2C9, CYP2C19, and CYP3A4 enzymatic activities[278]. Ethanolic extract of Coicis Semen downregulates the protein expression of CYP1A1, CYP1A2, CYP2C6, CYP2C11, CYP2D1, CYP2E1, CYP3A1, and CYP3A2 in the rat liver[279]. In addition, Coicis Semen extract could change the abundance of bacteria, such as increasing *Bifidobacterium*, reducing *Lactococcus* and further affect lipid accumulation and glycolipid metabolism[280].

Atractylodis Rhizoma (Cangzhu in Chinese) is the dried rhizome of *Atractylodes lancea* (Thunb.) DC. or *Atractylodes chinensis* (DC.) Koidz[281]. The *ex vivo* study in healthy subjects suggests that the immunomodulatory activity of Atractylodis Rhizoma is through decreasing the levels of pro-inflammatory cytokines[282]. Atractylodis Rhizoma contains rich essential oil, including sesquiterpenes and polyethylene alkynes, which are the main active components[283,284]. A high dose of Atractylodis Rhizoma produced an inducing effect on CYP1A2 but an inhibitory effect on CYP3A1 activities in rats[285]. Atractyloside A can significantly induce the expression of CYP1A2, CYP2C, and CYP2E1 proteins[286]. Meanwhile, Atractylodis Rhizoma and atractyloside A could alter the composition of the intestinal flora and eight genera of intestinal flora to regulate intestinal flora homeostasis[287,288].

Artemisiae Annuae Herba (Qinghao in Chinese), an annual herbaceous plant, is the dried aerial part of *Artemisia annua* L.[289]. *A. annua* has an immunomodulatory effect by regulating inflammatory factors[289]. A previous study showed that Artemisiae Annuae Herba extracts significantly inhibit cytopathy caused by SARS-CoV strain BJ001[290] and induce activity against SARS-CoV-2 in Vero-E6 cell-based cytopathic effect screening[272,291]. Artemisiae Annuae Herba is rich in secondary metabolites such as monoterpenes, sesquiterpenes, and phenolic compounds[292]. Artemisinin, a bioactive ingredient of Artemisiae Annuae Herba, was transformed into inactive metabolites in the liver, mediated by CYP2B6 and to a lesser extent by CYP3A4[293]. Meanwhile, artemisinin could induce the enzymatic activities of CYP2B6, CYP2B10, CYP1A2, and CYP2A5[294].

Polygoni Cuspidati Rhizoma et Radix (Huzhang in Chinese) belongs to the Polygonaceae family, and it is the dried rhizome and root of *Polygonum cuspidatum* Sieb. et Zucc[295]. The extract of Polygoni Cuspidati Rhizoma et Radix exhibits anti-inflammatory activities *via* inhibiting NF-κB and downregulating tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6)[296]. The main components of Polygoni Cuspidati Rhizoma et Radix include quinones, stilbenes, and flavonoids[297]. Resveratrol, a primary component of Polygoni Cuspidati Rhizoma et Radix, was primarily metabolized by UGT1A1, UGT1A9, and gut microbiota[298,299]. It can inhibit the activity of CYP3A4, P-gp, MRP2, OAT1, OAT3, OATP1B1/3, OATP1A2 and OATP2B1 *in vitro* and *in vivo*[300–302]. A high dose of resveratrol could theoretically increase bioavailability and the risk of toxicity of drugs that undergo extensive first-pass metabolism by CYP3A4[298]. Resveratrol and emodin in Polygoni Cuspidati Rhizoma et Radix could improve the diversity and structure of the gut microbiota in rats[303–305]

Verbenae Herba (Mabiancao in Chinese) is the dried aerial part of *Verbena officinalis* L. chlorogenic acid and verbascoside[306,307]. Verbenae Herba contains many constituents such as flavonoids, iridoid glycosides, phenylpropanoid glycoside, sterols, triterpenes, and glycoconjugate[308]. Human CYP2A6 and rat CYP2C11 are responsible for the metabolism of (−)-verbenone by liver microsomes[309].

Phragmitis Rhizoma (Lugen in Chinese) is the fresh or dried rhizome of *Phragmites communis* Trin[310]. The chemical constituents of Phragmitis Rhizoma included polysaccharides, flavonoids, steroids, anthraquinones, alkaloids, volatile components, small molecules, and other components[311]. The effects of Phragmitis Rhizoma on the drug-metabolizing enzymes and transporters are rarely reported.

Descurainiae Semen Lepidii Semen (Tinglizi in Chinese) is the dried ripe seed of *Descurainia sophia* (L.) Webb. ex Prantl. and *Lepidium apetalum* Willd[312]. The bioactive components of Descurainiae Semen Lepidii Semen could regulate cytokines and exert anti-inflammatory effects[313]. The main components of Descurainiae Semen Lepidii Semen are thioglycosides, isothiocyanates, flavonoids, lignans, nucleosides, organic acids, and amides[314]. Quercetin in Descurainiae Semen Lepidii Semen was metabolized by gut microbiota, such as *B. fragilis*, *Eubacterium*

Table 3 The effect of XFBD on metabolizing enzymes and transporters.

Herb	Component	Metabolizing enzyme							Transporter					
		CYP1	CYP2	CYP3	UGT1	UGT2	UGT3	CES	OCTs	OAT	OATP	P-gp	BCRP	MRP
Phragmitis Rhizoma	None	None	None	None	None	None	None	None	None	None	None	None	None	None
Descurainiae Semen Lepidii Semen (Refs. 317−320)	Quercetin	1A2↓		3A4↓	1A9↓					OAT3↓	1B1↓ 1B3↓ 2B1↓	P-gp↓	BCRP↓	
Atractylodis Rhizoma (Refs. 285,286)	Extract	1A2↑		3A1↓										
	Atractyloside A	1A2↑	2C↑ 2E1↑											
Pogostemonis Herba (Refs. 268,269)	Patchouli alcohol											P-gp[a]		MRP[a]
	Pogostone		2C9↓ 2E1↓	3A4↓										
Verbenae Herba (Ref: 309)	(−)-Verbenone		2A6[a] 2C11[a]											
Citri Grandis Exocarpium (Refs. 323,325−328)	Extract	1A1↑ 1A2↑	2B↑ 2E1↑											
	Naringin	1A2↓									1A2↓ 2B1↓	P-gp↓		
Artemisiae Annuae Herba (Refs. 293,294)	Artemisinin	1A2↑	2B6↑ 2B10↑ 2A5↑											
Glycyrrhizae Radix et Rhizoma (Refs. 92,97−103,477)		1A2↑	2A1↑ 2B1↑ 2B9↑	3A↑ 3A4↑										
	Extract		2B6↓ 2C9↓ 2C19↓	3A4↓										
	Glycyrrhetinic acid		2C9[a] 2C19[a]	3A4[a]	1A3↓	2B7↓		CES1↓				P-gp[a]		
	Glycyrrhizin	1A2↑	2A1↑ 2B1↑ 2B9↑	3A↑ 3A4↑										
	Licochalcone A	1A2↓	2D6↓ 2E1↓ 2C19↓ 2C8↓ 2C9↓	3A4↓							1B1↓			
	Glycyrol		2C9↓											
Ephedrae Herba (Refs. 82−86)	Water decoction	1A2↑										MDR1↓		
	L-Ephedrine	1A1↑ 1A2↑	2C↑						OCT2[a]			P-gp[a]		
	D-Pseudoephedrine	1A1↓ 1A2↓	2E1↓									P-gp[a]		
	Norpseudoephedrin								OCT2[a]					
	L-Methylephedrine											P-gp[a]		

Armeniacae Semen Amarum (Ref: 107)	Amygdalin		2C9↓ 2E1↓					P-gp[a]	
Gypsum Fibrosum (Ref: 112)		1A2↓							
Polygoni Cuspidati Rhizoma et Radix (Refs. 298–302)	Resveratrol			3A4↓	1A1[a] 1A9[a]	OAT1↓ OAT3↓	1B1↓ 1B3↓ 1A2↓ 2B1↓	P-gp↓	MRP2↓
Coicis Semen (Refs. 278,279)	Kanglaite	1A2↑	2B6↓ 2C9↓ 2C19↓	3A4↓					
	Ethanolic extract	1A1↓ 1A2↓	2C6↓ 2C11↓ 2D1↓ 2E1↓	3A1↓ 3A2↓					

↑Indicates the induction effect on an enzyme or drug transporter.
↓Indicates the inhibitory effect on an enzyme or drug transporter.
[a]Indicates that the drug is a substrate for an enzyme or drug transporter.

ramulus, and *Clostridium perfringens*, and it transported by MATE1[315,316]. It inhibits the activity of CYP3A4, CYP1A2, P-gp, OAT3, OATP1B1, OATP1B3, OATP2B1, BCRP, UGT1A9, and sulfotransferase family 1A member 1 (SULT1A1)[317–320].

Citri Grandis Exocarpium (Huajuhong in Chinese) belongs to the Rutaceae family, and it is the unmature or nearly mature dry exocarp of *Citrus grandis* "*Tomentosa*" and *C. grandis* (L.) Osbeck[321]. The main components of Citri Grandis Exocarpium are flavonoids, including naringin, rhoifolin, and apigenin[322]. Citri Grandis Exocarpium increased the mRNA expression of PXR and peroxisome proliferator activated receptor α (PPARα) and the activities of CYP1A1, 1A2, 2B, and 2E1[323]. Furthermore, naringin in Citri Grandis Exocarpium was metabolized by gut microbiota into a number of metabolites, including 29 flavonoid metabolites and six phenolic catabolites[324]. It inhibits the activities of CYP1A2, P-gp, OATP1A2, and OATP2B1[325–328]. Citri Grandis Exocarpium could increase the abundance of bacterial groups, including *Lactobacillus*, *Bifidobacterium*, and *Bacteroides*, to improve the homeostasis of the gut microbiota composition[329,330].

The information on Ephedrae Herba, Armeniacae Semen Amarum, Gypsum Fibrosum, Pogostemonis Herba, and Glycyrrhizae Radix et Rhizoma is summarized in Section 3.1.

3.3. HSBD

3.3.1. Basic pharmacological information of HSBD

HSBD has a remarkable clinical efficacy in the treatment of acute lung injury and was recommended for treating severe and non-severe patients with COVID-19 by China's National Health Commission[331]. HSBD and its active constituents exert therapeutic effects on COVID-19 through inhibition of ACE2[332], and also could decrease the level of pro-inflammatory factors and decrease cell apoptosis in an inflammatory environment, showing immuno-modulation and anti-inflammation effects against COVID-19[271,333].

HSBD consists of 14 herbs (Ephedrae Herba, Armeniacae Semen Amarum, Gypsum Fibrosum, Glycyrrhizae Radix et Rhizoma, Pogostemonis Herba, Magnoliae Officinalis Cortex, Atractylodis Rhizoma, Tsaoko Fructus, Rhei Radix et Rhizoma, Astragali Radix, Pinelliae Rhizoma Praeparatum, Descurainiae Semen Lepidii Semen, Poria and Paeoniae Radix Rubra)[334].

The herbs and bioactive compounds of HSBD could regulate the expression or activity of CYPs and transporters (Table 4).

3.3.2. Pharmacodynamic and pharmacokinetic features of each herb in HSBD

Magnoliae Officinalis Cortex (Houpo in Chinese), the bark of the stems and roots of *Magnolia officinalis* Rehd. et Wils., belongs to the Magnolia genus of Magnoliaceae[335]. Magnolol and honokiol are the main components of Magnoliae Officinalis Cortex[336]. Honokiol thioethers containing 1,3,4-oxadiazole moieties were considered as SARS-CoV-2 entry inhibitors *via* binding with ACE2[337,338]. Magnoliae Officinalis Cortex extract could markedly reverse the intestinal dysbacteriosis in mice induced by antibiotics[339,340]. Moreover, magnolol potently inhibited the metabolic activity of CYP1A (IC_{50} of 1.62 μmol/L) and CYP2C (IC_{50} of 5.56 μmol/L), while weakly inhibited CYP3A (IC_{50} of 35.0 μmol/L) in human and rat liver microsomes[341]. Honokiol treatment significantly inhibits the activity of hepatic CYP2E1, CYP4A, CYP3A, and CYP1A2[342]. Honokiol could downregulate the expression of *P-gp*, *Bcrp*, and *Mrp4* and significantly upregulate the mRNA expression of hepatic *Oat2* and *Oatp2b1*[343,344].

Table 4 The effect of HSBD on metabolizing enzymes and transporters.

Herb	Component	Metabolizing enzyme							Transporter					
		CYP1	CYP2	CYP3	UGT1	UGT2	UGT3	CES	OCTs	OAT	OATP	P-gp	BCRP	MRP
Ephedrae Herba (Refs. 82−86)	Water decoction	1A2↑												
	L-Ephedrine	1A1↑ 1A2↑	2C↑						OCT2[a]			P-gp[a]		
	D-Pseudoephedrine	1A1↓ 1A2↓	2E1↓									P-gp[a]		
	Norpseudoephedrin								OCT2[a]					
	L-Methylephedrine											P-gp[a]		
Armeniacae Semen Amarum (Ref: 107)	Amygdalin		2C9↓ 2E1↓									P-gp[a]		
Gypsum Fibrosum (Ref: 112)		1A2↓												
Glycyrrhizae Radix et Rhizoma (Refs. 92,97−103,477)		1A2↑	2A1↑ 2B1↑ 2B9↑	3A↑ 3A4↑										
	Extract		2B6↓ 2C9↓ 2C19↓	3A4↓										
	Glycyrrhetinic acid		2C9[a] 2C19[a]	3A4[a]	1A3↓	2B7↓		CES1↓				P-gp[a]		
	Glycyrrhizin	1A2↑	2A1↑ 2B1↑ 2B9↑	3A↑ 3A4↑										
	Licochalcone A	1A2↓	2D6↓ 2E1↓ 2C19↓ 2C8↓ 2C9↓	3A4↓							1B1↓			
	Glycyrol		2C9↓											
Pogostemonis Herba (Refs. 268,269)	Patchouli alcohol											P-gp[a]		MRP[a]
	Pogostone		2C9↓ 2E1↓	3A4↓										
Magnoliae Officinalis Cortex (Refs. 341−344)	Honokiol	1A2 ↓	2E1↓	3A ↓						OAT2↑	2B1↑	P-gp↓	BCRP↓	MRP4↓
	Magnolol	1A↓	2C↓	3A↓				CES1/2↓						
Atractylodis Rhizoma (Refs. 285,286)	Extract	1A2↑		3A1↓										
	Atractyloside A	1A2↑	2C↑ 2E1↑											
Tsaoko Fructus (Refs. 348−350)	Protocatechuic acid	1A2↑	2E1↑						OCT1↑		1A1↑↓	P-gp↑↓		
Pinelliae Rhizoma (Ref: 191)				3A↓										
Poria (Refs. 146−151)				3A4↑										
	Galactoglucan		2E1↓											
	Polysaccharides		2E1↓											
	Pachymic acid											P-gp↓		
	Dehydrotumulosic acid											P-gp↓		

Rhei Radix et Rhizoma (Refs. 352,356−359)								P-gp↓		
	Extract		3A↓							
	Rhein				OCT2↑	OAT1↑		P-gp↑	BCRP↓	MRP2↑
						OAT3↑				
Astragali Radix (Refs. 365,366)		2B6↑	3A4↑	1A↑				P-gp↑	BCRP↑	MRP1↓
		2E1↑		1A6↓						MRP2↑
										MRP3↑
	Astragaloside IV							P-gp↑	BCRP↑	
	Calycosin							P-gp↑	BCRP↑	
	Formononetin							P-gp↑	BCRP↑	
Descurainiae Semen Lepidii Semen (Refs. 317−320)	Quercetin	1A2↓	3A4↓	1A9↓		OAT3↓	1B1↓	P-gp↓	BCRP↓	
							1B3↓			
							2B1↓			
Paeoniae Radix Rubra (Refs. 372,373)	Paeoniflorin	2D6↓	3A4↑↓					P-gp[a]		MRP2↑
	Albiflorin		3A4↑↓							

↑Indicates the induction effect on an enzyme or drug transporter.
↓Indicates the inhibitory effect on an enzyme or drug transporter.
[a]Indicates that the drug is a substrate for an enzyme or drug transporter.

Tsaoko Fructus (Caoguo in Chinese) is the dried ripe fruit of *Amomum tsao-ko* Crevost et Lemaire, which is used as both medicinal material and food additive[345]. Quercetin is an active ingredient in Tsaoko Fructus for the treatment of patients with COVID-19[346,347]. Protocatechuic acid, the other active ingredient, significantly downregulated the mRNA expression of *P-gp* and *Oatp1a1* at a low concentration, whereas it significantly upregulated the mRNA expression level of *P-gp* and *Oatp1a1* at a high concentration[348]. Protocatechuic acid significantly upregulated the mRNA expression level of *Oct1*[349], CYP1A2 and CYP2E1[350].

Rhei Radix et Rhizoma (Dahuang in Chinese) is the dried root and rhizome of *Rheum palmatum* L., *R. tanguticum* Maxim. ex Balf. or *R. officinale* Baill. of the family Polygonaceae[351]. Rhei Radix et Rhizoma shows evident activity against SARS-CoV-2, and it has been applied to the clinical treatment of COVID-19[352]. Notably, anthraquinones are pivotal active components in Rhei Radix et Rhizoma. Free anthraquinones, particularly rhein, emodin, physcion, aloe-emodin, and chrysophanol, are rich in almost all species of Rhei Radix et Rhizoma[353,354]. In addition, rhein treatment could maintain the diversity of gut microbiota[355]. Rhei Radix et Rhizoma treatment inhibits and downregulates P-gp[352,356]. The extract of Rhei Radix et Rhizoma significantly suppressed CYP3A activity in hepatic microsomes[357]. Rhein could inhibit BCRP-mediated efflux transport[358]. Rhein could upregulate the expressions of renal Oat1, Oat3, Oct2, Mrp2, Mate 1 and P-gp[359].

Astragali Radix (Huangqi in Chinese) is derived from the roots of *Astragalus membranaceus* (Fisch.) Bge. or *A. membranaceus* (Fisch.) Bge. var. mongholicus (Bge.) Hsiao[360]. Astragali radix and its active ingredients (SBE, baicalein, and baicalin) could inhibit SARS-CoV-2 replication and its 3CLpro *in vitro*[361−363]. Astragali Radix also had the potential to protect from metabolic perturbation generated by gut microbiotas induced by chronic atrophic gastritis[364]. Astragali Radix considerably increases the expression levels of CYP3A4, CYP2B6, CYP2E1, UGT1A, P-gp, MRP2, BCRP, and MRP3 but decreases the protein levels of UGT1A6, SULT1A1, and MRP1[365]. Astragali Radix and its main bioactive compounds, including Astragaloside IV, calycosin, and formononetin, could induce P-gp and BCRP expression[366].

Paeoniae Radix Rubra (Chishao in Chinese) is the dried root of *Paeonia lactiflora* Pall. and *Paeonia veitchii* Lynch[367]. Paeoniae Radix Rubra could be used for the treatment of patients with COVID-19 complicated with coagulation dysfunction *via* AKT serine/threonine kinase 1, TNF, vascular endothelial growth factor A, epidermal growth factor receptor, and mitogen-activated protein kinase 3[368]. The adverse events of Paeoniae Radix Rubra primarily include gastrointestinal tract disturbances, mostly mild diarrhea[368,369]. Meanwhile, Paeoniae Radix Rubra alleviated gut microbiota disorders in model rats, including upregulating four genera (*Coprococcus*, *Lactobacillus*, etc.) and downregulating four genera (Bacteroides, Escherichia, etc.)[370]. Paeoniae Radix Rubra contains terpenoids and their glycosides, flavonoids and their glycosides, and other chemical components[371]. Paeoniflorin is a major constituent of Paeoniae Radix Rubra. Paeoniflorin and albiflorin at low concentrations could induce CYP3A4 activity; however, the regulation turned into inhibition at high concentration. Paeoniflorin has an inhibitory effect on CYP2D6 activity at high concentration[372]. Paeoniflorin is a substrate of P-gp[372,373].

The information of Ephedrae Herba, Armeniacae Semen Amarum, Gypsum Fibrosum, Glycyrrhizae Radix et Rhizoma, Pogostemonis Herba, Magnoliae Officinalis Cortex, Atractylodis Rhizoma, Tsaoko Fructus, Rhei Radix et Rhizoma, Astragali

Radix, Pinelliae Rhizoma Praeparatum, Praeparatum, Descurainiae Semen Lepidii Semen, Poria and Paeoniae Radix Rubra is summarized in Sections 3.1 and 3.2.

3.4. JHQG

3.4.1. Basic pharmacological information of JHQG

JHQG has been recommended as a medication in the diagnosis and treatment protocol for COVID-19 in China[374]. The active ingredients of JHQG (including 3-methoxy-glycerol, crude-glycerin, glycyrrhizin B, chlorogenic acid, forsythoside A, and ephedrine) have strong binding activity for 3CLpro and ACE2 and suppression of cytokine signaling 1[271], thereby inhibiting viral replication and binding to target cells, reducing host inflammation, and activating antiviral immunity[375].

JHQG consists of 12 herbs including Forsythiae Fructus, Lonicerae Japonicae Flos, Ephedrae Herba, Armeniacae Semen Amarum, Gypsum Fibrosum, Scutellariae Radix, Fritillariae Thunbergii Bulbus, Anemarrhenae Rhizoma, Arctii Fructus, Artemisiae Annuae Herba, Menthae Haplocalycis Herba, and Glycyrrhizae Radix et Rhizoma[376].

Given the effects of JHQG and the bioactive constituents on the CYPs and transporters (Table 5), the potential HDIs should also be of concern.

3.4.2. Pharmacodynamic and pharmacokinetic features of each herb in JHQG

Lonicerae Japonicae Flos, also known as Japanese honeysuckle, Jinyinhua or Rendong, is native in East Asia[377]. In addition, Lonicerae Japonicae Flos could inhibit SARS-CoV-2[375,378] by inhibiting Mpro activity[379]. Phenolic acids were primarily permeated *via* paracellular diffusion and influenced by P-gp, MRP2, and BCRP[380]. Chlorogenic acid is a substrate for P-gp[381]. Chlorogenic acid significantly changed the composition of the gut microbiota and increased the abundance of SCFA-producers (*e.g.*, *Dubosiella*, *Romboutsia, Mucispirillum,* and *Faecalibaculum*) and *Akkermansia*, which can protect the intestinal barrier[382]. In addition, isochlorogenic acid A could inhibit UGT1A6 activity by 25% in mice, and it exhibited a weak inhibitory effect on CYP2C9 activity in human liver microsomes[217]. Moreover, Lonicerae Japonicae Flos had no significant effect on CYP3A activity in rats[383]. Lonicerae Japonicae Flos substantially inhibited MATE1-mediated metformin uptake *in vitro*[384].

Forsythiae Fructus (Lianqiao in Chinese) is widely distributed in China, Korea, and Japan. Forsythoside A, Forsythin, and Phillyrin are major components[385,386]. Forsythoside A showed the strongest docking affinity with the proteins SARS-CoV-2-RBD-hACE2 of COVID-19 and its variants (Alpha (B.1.1.7), Beta (B.1.351), and Delta (B.1.617)), as well as neuropilin-1 and SARS-CoV-2 Mpro to interfere coronavirus entering into the human body[387]. Phillyrin could significantly inhibit SARS-CoV-2 replication *in vitro*[388]. Forsythoside A has inductive effects on the activities of CYP1A2 and CYP2C11[389,390]. Phillyrin has potential inductive effects on rat CYP1A2 and CYP2D1 activities[391]. Phillygenin could ameliorate intestinal epithelial barrier disruption, and reverse the expression of bile acid metabolism-related genes in mice with CCl4-induced liver fibrosis[392].

Fritillariae Thunbergii Bulbus (Beimu in Chinese) is derived from the bulbus of many *Fritillaria* species (family Liliaceae)[393,394]. Peimine inhibited variants of SARS-CoV-2 cell entry *via* blocking the interaction between viral spike protein and ACE2[395]. Peimine is a substrate of P-gp. Alkaloids, including peimine, peimisine, and imperialine, were the active ingredients for inhibiting P-gp activity[396]. Meanwhile, peimine inhibited the activity of CYP3A4, 2E1, and 2D6[397,398].

Anemarrhenae Rhizoma (Zhimu in Chinese), the dried rhizome of *Anemarrhena asphodeloides* Bge[399]. Anemarrhenae Rhizoma suppressed inflammation *via* the regulation of NF-κB and p38 signal transduction pathways in macrophages[400]. *In vitro* studies showed that ethyl acetate extract of Anemarrhenae Rhizoma promoted the proliferation of *Blautia coccoides*, a bacterium with positive implication for diabetes, in a dose-dependent manner[401]. Timosaponin A3 reverses multi-drug resistance *via* the downregulation of MDR1, MRP1, and P-gp expression levels[400–403].

Arctii Fructus (Niubangzi in Chinese), is the dry and mature fruits of *Arctium lappa* L.[404]. Natural lignans from Arctii Fructus could inhibit the activity of P-gp[405]. Furthermore, Arctiin and Arctigenin showed an inhibitory effect on UGTs[406]. UGT1A9, UGT2B7, and UGT2B17 were the major isoforms responsible for the 4′-*O*-glucuronidation of Arctigenin in human intestine microsomes[407]. Furthermore, Arctiin and Arctigenin showed an inhibitory effect on UGT1A9, UGT2B7, and UGT2B17[405,407]. The purified polyphenols from Arctii Fructus could significantly improve the gut microbiota composition and ameliorate DOX-induced heart failure[408].

Menthae Haplocalycis Herba (Bohe in Chinese) is the dry aboveground parts of *Mentha haplocalyx* Briq.[409]. Menthae Haplocalycis Herba could be further developed as plant-derived anti-SARS-CoV-2 agents[410]. It was found that increasing the concentration of menthol could induce the expression of MDR1 and P-gp[411]. Meanwhile, an acidic polysaccharide obtained from the Menthae Haplocalycis Herba modulated the gut microbiota by reducing the ratio of Firmicutes/Bacteroidetes, promoting the proliferation of beneficial bacteria such as Bacteroidaceae and Bifidobacteriaceae, and inhibiting harmful bacteria such as Lachnospiraceae and Enterobacteriaceae[412].

The information on Forsythiae Fructus, Lonicerae Japonicae Flos, Ephedrae Herba, Armeniacae Semen Amarum, Gypsum Fibrosum, Scutellariae Radix, Fritillariae Thunbergii Bulbus, Anemarrhenae Rhizoma, Arctii Fructus, Artemisiae Annuae Herba, Menthae Haplocalycis Herba, and Glycyrrhizae Radix et Rhizoma is summarized in Sections 3.1−3.3.

3.5. LHQW

3.5.1. Basic pharmacological information of LHQW

LHQW is obtained from two well-known Chinese herbal prescriptions, namely, Ma Xing Shi Gan Tang and Yin Qiao San[413]. LHQW is widely used to treat patients with pneumonia caused by the COVID-19[414]. It can effectively reduce the duration of fever, improve chest computed tomography symptoms, and increase the clinical cure rate for patients with COVID-19 by 12.7%[415,416]. The active ingredients of LHQW, including stigmasterol, naringenin, 18β-glycyrrhetinic acid, and quercetin, can bind to ACE2 and inhibit viral replication[271]. Moreover, the active ingredients of LHQW, including quercetin, lignan, baicalin, and kaempferol, showed high binding affinity to Mpro of SARS-CoV-2, which may inhibit the replication of SARS-CoV-2[417,418]. LHQW also alleviates the widespread lung injury in COVID-19 by inhibiting the overexpression of pro-inflammatory factors and exerting immunomodulatory effects[419].

LHQW consists of 13 herbs including Glycyrrhizae Radix et Rhizoma, Forsythiae Fructus, Rhodiolae Crenulatae Radix et

Table 5 The effect of JHQG on metabolizing enzymes and transporters.

Herb	Component	Metabolic enzyme							Transporter					
		CYP1	CYP2	CYP3	UGT1	UGT2	UGT3	CES	OCTs	OAT	OATP	P-gp	BCRP	MRP
Forsythiae Fructus (Refs. 389−391)	Forsythoside A	1A2↑	2C11↑											
	Phillyrin	1A2↑	2D1↑											
Lonicerae Japonicae Flos (Refs. 217, 381, 383)	Phenolic acids											P-gp[a]	BCRP[a]	MRP2[a]
	Chlorogenic acid											P-gp[a]		
	Isochlorogenic acid A		2C9↓		1A6↓									
Scutellariae Radix (Refs. 172, 174−182, 478)	Aqueous extract of scutellariae radix		2C9↓ 2E1↑											
	Baicalein			3A4↓	1A9[a] 1A10[a]			CES1/2↓				P-gp↓		MRP[a]
	Baicalin		2C9↑ 2C19↑	3A4↑										
	Wogonin	1A2↓			1A9[a]									
	Oroxylin A				1A9[a] 1A10[a]			CES1/2↓		OAT1↓ OAT3↓	1B1[a] 1B1↓ 1B3[a]		BCRP↓	
	Salvigenin				1A8↓ 1A10↓									
	Extract								OCT1↓					
Fritillariae Thunbergii Bulbus (Refs. 396−398)	Peimine		2E1↓ 2D6↓	3A4↓								P-gp[a]↓		
	Peimisine											P-gp↓		
	Imperialine											P-gp↓		
Anemarrhenae Rhizoma (Refs. 400−403)	Timosaponin A3											P-gp↓		MRP1↓
Arctii Fructus (Refs. 405−407)												P-gp↓		
	Arctiin				1A9↓	2B7↓2B17↓								
	Arctigenin				1A9↓ 1A9[a]	2B7↓ 2B7[a] 2B17↓ 2B17[a]								
Artemisiae Annuae Herba (Refs. 293,294)	Artemisinin	1A2↑	2B6↑ 2B10↑ 2A5↑											
Menthae Haplocalycis Herba (Ref: 411)	Menthol											P-gp↑		
Ephedrae Herba (Refs. 82−86)	Water decoction	1A2↑												
	L-Ephedrine	1A1↑ 1A2↑	2C↑									P-gp[a]		
	D-Pseudoephedrine	1A1↓ 1A2↓	2E1↓									P-gp[a]		
	Norpseudoephedrin								OCT2[a]					
	L-Methylephedrine											P-gp[a]		
Gypsum Fibrosum (Ref: 112)		1A2↓												
Armeniacae Semen Amarum (Ref: 107)	Amygdalin		2C9↓ 2E1↓									P-gp[a]		

(*continued on next page*)

Table 5 (*continued*)

Herb	Component	Metabolic enzyme						Transporter				
		CYP1	CYP2	CYP3	UGT1	UGT2	UGT3	CES	OCTs	OAT	OATP	P-gp	BCRP	MRP
Glycyrrhizae Radix et Rhizoma (Refs. 92, 97–103, 477)		1A2↑	2A1↑	3A↑										
			2B1↑	3A4↑										
			2B9↑											
	Extract		2B6↓	3A4↓										
			2C9↓											
			2C19↓											
	Glycyrrhetinic acid		2C9[a]	3A4[a]	1A3↓	2B7↓		CES1↓				P-gp[a]		
			2C19[a]											
	Glycyrrhizin	1A2↑	2A1↑	3A↑										
			2B1↑	3A4↑										
			2B9↑											
	Licochalcone A	1A2↓	2D6↓	3A4↓							1B1↓			
			2E1↓											
			2C19↓											
			2C8↓											
			2C9↓											
	Glycerol		2C9↓											

↑Indicates the induction effect on an enzyme or drug transporter.
↓Indicates the inhibitory effect on an enzyme or drug transporter.
[a]Indicates that the drug is a substrate for an enzyme or drug transporter.

Rhizoma, Ephedrae Herba, Armeniacae Semen Amarum, Lonicerae Japonicae Flos, Gypsum Fibrosum, Pogostemonis Herba, Isatidis Radix, l-menthol, Rhei Radix Et Rhizoma, Dryopteridis Crassirhizomatis Rhizoma, and Houttuyniae Herba[271].

LHQW could effectively regulate drug-metabolizing enzymes and transporters[420–423] (Table 6). The pharmacodynamic and pharmacokinetic characteristics of each herb of LHQW are summarized below.

3.5.2. Pharmacodynamic and pharmacokinetic features of each herb in LHQW

Isatidis Radix (Banlangen in Chinese) is the dried root of *Isatis indigotica* Fort[424]. Isatidis Radix can effectively resist COVID-19[425]. The major components of Isatidis Radix include alkaloids, organic acids, nucleosides, amino acids, lignans, and flavonoids, of which epigoitrin is the most important active component[424]. The metabolic pathways of epigoitrin in rats primarily involve methylation, acetylation, hydroxylation, oxidation, reduction reactions, binding to glutathione, and binding to alanine[426]. Moreover, indirubin, another component of Isatidis Radix, could active CYP3A4 gene transcription through the activation of human PXR[422]. Moreover, Isatidis Radix could regulate gut microbiota and restore gut SCFA-derived glucagon-like peptide-1 production and alleviate chronic relapsing colitis in mice[427].

Dryopteridis Crassirhizomatis Rhizoma (Mianmaguanzhong in Chinese) is derived from the dried rhizome and petiole residues of *Dryopteris crassirhizoma* Nakai[428]. Dryopteridis Crassirhizomatis Rhizoma has an inhibitory activity against the Mpro of SARS-CoV-2 and also represses cytokine storm upon COVID-19[420,429]. Previous studies have shown that the major components of Dryopteridis Crassirhizomatis Rhizoma include phloroglucinol, flavonoids, terpenoids, steroids, phenylpropanoids, and aliphatic compounds[430]. Pharmacokinetic studies of dryocrassin ABBA showed good microsomal stability and low CYP450 inhibition. *In vivo* pharmacokinetic properties of dryocrassin ABBA showed a long half-life and high plasma exposure[420].

Houttuyniae Herba (Yuxingcao in Chinese) is derived from the aerial part of *Houttuynia cordata* Thunb[431]. The bioactive compounds of Houttuyniae Herba may exert anti-SARS-CoV-2 effects by targeting SARS-CoV-2 replication and the transcription-related enzyme RdRp[432]. The major components of Houttuyniae Herba include volatile oil, flavonoids, organic acids, alkaloids, and vitamins[432]. Ethyl acetate extract of Houttuyniae Herba would suppress the expression of CYP2E1 and CYP4A[423]. Houttuyniae Herba extract also increased systemic exposure and hepatic concentrations of metformin through OCTs and MATEs in rats[433].

Rhodiolae Crenulatae Radix et Rhizoma (Hongjingtian in Chinese) is derived from the dried roots and rhizomes of *Rhodiola crenulata*[434]. Rhodiolae Crenulatae Radix et Rhizoma may perform anti-inflammatory and immunomodulatory effects in the cytokine storm of COVID-19 by regulating the expression of inflammatory factors[435]. The major components of Rhodiolae Crenulatae Radix et Rhizoma include phenolic glycosides (salidroside), flavonoids, coumarins, and amino acids, of which salidroside is the most important active component[436]. The mechanism of salidroside transport is passive diffusion with no active efflux. Salidroside exhibited inductive effects on CYP1A2, CYP2B6, CYP2C9, and CYP3A4 activities in rats[421]. Meanwhile, salidroside significantly upregulated the expression of genes involved in bile acid synthesis (*Cyp7a1*, *Cyp7b1*, *Cyp8b1*, and *Cyp27a1*) and the uptake transport genes (*Ntcp* and *Oatps*) and downregulated the efflux transport genes (*Bsep*, *Ost-α*, *Ost-β*,

Table 6 The effect of LHQW on metabolizing enzymes and transporters.

Herb	Component	Metabolic enzyme						Transporter						
		CYP1	CYP2	CYP3	UGT1	UGT2	UGT3	CES	OCTs	OAT	OATP	P-gp	BCRP	MRP
Ephedrae Herba (Refs. 82−86)	Water decoction	1A2↑												
	L-Ephedrine	1A1↑ 1A2↑	2C↑						OCT2[a]			P-gp[a]		
	D-Pseudoephedrine	1A1↓ 1A2↓	2E1↓									P-gp[a]		
	Norpseudoephedrin								OCT2[a]					
	L-Methylephedrine											P-gp[a]		
Glycyrrhizae Radix et Rhizoma (Refs. 92,97−103,477)		1A2↑	2A1↑ 2B1↑ 2B9↑	3A↑ 3A4↑										
	Extract		2B6↓ 2C9↓ 2C19↓	3A4↓										
	Glycyrrhetinic acid		2C9[a] 2C19[a]	3A4[a]	1A3↓	2B7↓		CES1↓				P-gp[a]		
	Glycyrrhizin	1A2↑	2A1↑ 2B1↑ 2B9↑	3A↑ 3A4↑										
	Licochalcone A	1A2↓	2D6↓ 2E1↓ 2C19↓ 2C8↓ 2C9↓	3A4↓							1B1↓			
	Glycyrol		2C9↓											
Armeniacae Semen Amarum (Ref: 107)	Amygdalin		2C9↓ 2E1↓									P-gp[a]		
Gypsum Fibrosum (Ref: 112)		1A2↓												
Forsythiae Fructus (Refs. 389−391)	Forsythoside A	1A2↑	2C11↑											
	Phillyrin	1A2↑	2D1↑											
Rhodiolae Crenulatae Radix et Rhizoma (Refs. 421,437)	Salidroside	1A2↑	2B6↑ 2C9↑	3A4↑										MRP2↓ MRP4↓
Lonicerae Japonicae Flos (Refs. 217, 381, 383)	Phenolic acids											P-gp[a]	BCRP[a]	MRP2[a]
	Chlorogenic acid											P-gp[a]		
	isochlorogenic acid A		2C9↓		1A6↓									
Pogostemonis Herba (Refs. 268,269)	Patchouli alcohol											P-gp[a]		MRP[a]
	Pogostone		2C9↓ 2E1↓	3A4↓										
Isatidis Radix (Ref: 422)	Indirubin			3A4↑										
Menthae Haplocalycis Herba (Ref: 411)	Menthol											P-gp↑		
Rhei Radix et Rhizoma												P-gp↓		

(*continued on next page*)

Table 6 (*continued*)

Herb	Component	Metabolic enzyme					Transporter					
		CYP1	CYP2	CYP3	UGT1	UGT2	UGT3	CES	OCTs	OAT	OATP	P-gp	BCRP	MRP
(Refs. 352,356–359)	Extract			3A↓										
	Rhein								OCT2↑	OAT1↑ OAT3↑		P-gp↑	BCRP↓	MRP2↑
Dryopteridis Crassirhizomatis Rhizoma (Ref: 420)	Dryocrassin ABBA		2C9↓											
Houttuyniae Herba (Ref: 423)	Extract		2E1↓											

↑Indicates the induction effect on an enzyme or drug transporter.
↓Indicates the inhibitory effect on an enzyme or drug transporter.
[a]Indicates that the drug is a substrate for an enzyme or drug transporter.

Mrp2, and *Mrp4*)[437]. Salidroside is primarily excreted in the form of the original structure through urine[438]. Studies also found that salidroside could activate FXR and upregulate CYP7A1 expression[439]. Rhodiolae Crenulatae Radix et Rhizoma extract could restore microbial richness and diversity, which were closely correlated with its protective effect against colitis[440].

The associated information of Glycyrrhizae Radix et Rhizoma, Forsythiae Fructus, Ephedrae Herba, Armeniacae Semen Amarum, Lonicerae Japonicae Flos, Gypsum Fibrosum, Pogostemonis Herba, l-menthol, and Rhei Radix et Rhizoma was summarized in Sections 3.1−3.4.

3.6. *XBJ*

3.6.1. *Basic pharmacological information on XBJ*

XBJ injection is based on the well-known Chinese herbal prescription Xue Fu Zhu Yu Tang, combined with the theory of "four evidence and four methods" and "concurrent treatment of bacterial toxicity and inflammation" refined over a period of 30 years[441]. Based on the clinical evidence on XBJ treatment of sepsis, bacterial pneumonia, and acute respiratory distress syndrome, XBJ was recommended by China's National Health Commission to treat severe and critical cases of COVID-19, particularly during systematic inflammatory response syndrome and/or multi-organ failure[442]. XBJ could inhibit inflammation in patients with COVID-19 *via* inhibiting the inflammatory mediator expression and subsequently improving lung injury in patients with severe or critical COVID-19[443]. Network pharmacological analysis showed that XBJ exerts therapeutic potential against SARS-CoV-2 infection *via* modulation of the arachidonic acid metabolic pathway[444]. Administration of XBJ could increase the abundance of the phylum Bacteroides and decrease the phylum Actinobacteria, and subsequently upregulate the pyrimidine metabolic pathway, the pentose phosphate pathway and the glycerophospholipid metabolic pathway in heat-shocked rats[445].

XBJ injection is a five-herb combination, which is composed of Angelicae Sinensis Radix, Salviae Miltiorrhizae Radix et Rhizoma, Paeoniae Radix Rubra, Carthami Flos, and Chuanxiong Rhizoma[271].

Several compounds of XBJ exhibit inhibition of the activity of CYP1A2, CYP2B1, CYP2C11, and CYP2E1[446]. Meanwhile, the compounds of XBJ exhibit inhibition of UGT1A1, UGT1A6, UGT1A9, UGT2B15, and OAT1[446]. Considering the effects of XBJ and the bioactive constituents on CYPs and transporters (Table 7), the potential HDIs should also be of concern. The general overview of each herb in XBJ is summarized below.

3.6.2. *Pharmacodynamic and pharmacokinetic features of each herb in XBJ*

Carthami Flos (Honghua in Chinese) is derived from the dried flowers of *Carthamus tinctorius* L.[447]. Molecular docking showed that safranal, picrocrocin, and crocin molecules found in the composition of Xihonghua might have binding modes with human ACE2 protein[448]. The major components of Carthami Flos include flavonoids, alkaloids, organic acids, and polyacetylenes, of which carthamin yellow is an important active component[449]. Safflower total flavonoids exhibited inhibitory effects on activity of CYP1A2, CYP2B1, CYP2E1, and CYP2C11 and induction effects on CYP2C19 and 2D4[450]. Safflower yellow, the component of Carthami Flos, could enhance liver immune infiltration through the modulation of gut microbiota[451].

Table 7 The effect of XBJ on metabolizing enzymes and transporters.

Herb	Component	Metabolic enzyme							Transporter					
		CYP1	CYP2	CYP3	UGT1	UGT2	UGT3	CES	OCT	OAT	OATP	P-gp	BCRP	MRP
Angelicae Sinensis Radix (Refs. 467,468,481)	Water extract		2D6↑	3A↑				CES1↓						
	Coniferyl ferulate											P-gp↓		
Salviae Miltiorrhizae Radix et Rhizoma (Refs. 446,460−462,482)	Tanshinone I	1A2↓	2C9↓					CES1↓						
	Tanshinone II A	1A2↓	2C9↓	3A4↑								P-gp↓	BCRP↓	MRP1↓
	Cryptotanshinone	1A2↓	2C9↓	3A4↑										
	Dihydrotanshinone	1A2↓	2C9↓	3A4↓										
	Salvianolic acid B				1A1↓ 1A6↓ 1A9↓	2B15↓								
Paeoniae Radix Rubra (Refs. 372,373)	Paeoniflorin		2D6↓	3A4↑↓								P-gp[a]		
	Albiflorin			3A4↑↓										
Carthami Flos (Ref: 450)	Total flavonoids	1A2↓	2B1↓ 2C11↓ 2C19↑ 2D4↑ 2E1↓											
Chuanxiong Rhizoma (Refs. 446,454,455,481)	Ligustrazine			3A4↑				CES1↓				P-gp↓		MRP2↓ MRP3↓ MRP5↓
	Senkyunolide G									OAT1↓ OAT2↓				

↑Indicates induction of an enzyme or drug transporter.
↓Indicates an inhibitory effect on an enzyme or drug transporter.
[a]Indicates that the drug is a substrate for an enzyme or drug transporter.

Chuanxiong Rhizoma (Chuanxiong in Chinese) is derived from the dried rhizome of *Ligusticum chuanxiong* Hort[452]. L. chuanxiong polysaccharide, a major component of Chuanxiong Rhizoma, can significantly enhance the immune function in mice. Polysaccharides play an important role in treating COVID-19[453]. The components of Chuanxiong Rhizoma include essential oil, alkaloids, phenolic acids, and phthalide lactones, of which ligustrazine is the most important active component[452]. Ligustrazine induces the expression of the metabolizing enzyme CYP3A4 *via* PXR[454]. The mRNA and protein levels of MDR1, MRP2, MRP3 and MRP5 were decreased after treatment with ligustrazine[455]. In addition, senkyunolide G inhibited OAT1, OAT2[446]. It has been shown that Puerariae Lobatae Radix with Chuanxiong Rhizoma could remodel gut microbiota to regulate the brain–gut barriers[456].

Salviae Miltiorrhizae Radix et Rhizoma (Danshen in Chinese) is derived from the dried root or rhizome of *Salvia miltiorrhiza* Bge[457]. Salvianolic acids, a component of Salviae Miltiorrhizae Radix et Rhizoma, can inhibit the entry of 2019-nCoV spike pseudovirus into human ACE2 cells by binding to ACE2 protein[458]. The major components of Salviae Miltiorrhizae Radix et Rhizoma include diterpenoids, triterpenoids, phenolic acids, flavonoids, nitrogenous compounds, and lactones, of which tanshinone II A is the most important active component[459]. Tanshinone IIA and cryptotanshinone could activate PXR and induce CYP3A4 expression[460]. Moreover, tanshinone I, tanshinone IIA, and cryptotanshinone were potent human CYP1A2 inhibitors and medium inhibitors of human CYP2C9[461]. Dihydrotanshinone was not only a potent competitive inhibitor of human CYP1A2 and CYP2C9, but also a potent noncompetitive inhibitor of human CYP3A4[460,461]. It has been demonstrated that tanshinone IIA could down-regulate the expression of P-gp, BCRP, and MRP1[462]. Salvianolic acid B, another component of *Salvia*, could inhibit the activity of UGT1A1, UGT1A6, UGT1A9, and UGT2B15[446]. The combination of probiotics and Salviae Miltiorrhizae Radix et Rhizoma could modulate the gut microbiota and improve insulin resistance[463].

Angelicae Sinensis Radix (Danggui in Chinese) is derived from the dried root of *Angelica sinensis* (Oliv.) Diels[464]. The components of Angelicae Sinensis Radix have potential inhibitory effects on SARS-CoV-2 Mpro[465]. The major components of Angelicae Sinensis Radix include Angelica polysaccharides, organic acids, phthalides, and flavonoids, of which ferulic acid is the most important active component[466]. Coniferyl ferulate, isolated from the root of Angelicae Sinensis Radix, could markedly decrease overexpressed P-gp[467]. Moreover, the water extract of Angelicae Sinensis Radix significantly increased the activities of CYP2D6 and CYP3A[468]. Angelicae Sinensis Radix polysaccharide could regulate gut microbiota and improve rheumatoid arthritis[469].

The associated information of Paeoniae Radix Rubra was summarized in Section 3.3.

4. Potential HDI between anti-COVID-19 drugs and the TCM recipes

4.1. Pharmacokinetic HDIs

4.1.1. Potential pharmacokinetic HDI between Paxlovid™ and the TCM recipes

Drug-metabolizing enzymes play a critical role in regulating the drug pharmacokinetic characteristics and thereby is probably a major mechanism causing HDI between Paxlovid™ and the TCM recipes[16]. Nirmatrelvir and Ritonavir are primarily metabolized by CYP3A4[26]. Based on a previous report, the concentration of Nirmatrelvir/Ritonavir will not be increased by any strong CYP3A4 inhibitor because the maximal inhibition of CYP3A4 has been achieved by Ritonavir *per se*[24]. However, strong CYP3A4 inducers may potentially compromise Nirmatrelvir efficacy by accelerating the metabolism of Nirmatrelvir/Ritonavir[24]. It is reported that many ingredients and herbs in the above six TCM recipes have an induction effect on CYP3A4. For example, Glycyrrhizae Radix et Rhizoma is an herb in QFPD, JHQG, XFBD, LHQW, and HSBD. The bioactive ingredient of glycyrrhetinic acid of Glycyrrhizae Radix et Rhizoma could induce the activity of CYP3A4[92]. In addition, Atractylodes Macrocephala Rhizoma, an herb in QFPD, could strongly induce CYP3A4 activity[140]. Poria is an herb in QFPD and HSBD, and it could increase CYP3A4 gene transcription[470]. Furthermore, the bioactive ingredient of Scutellariae Radix (Baicalin) in QFPD and JHQG could induce the activity of CYP3A4[177]. Ligustrazine, an effective component of Chuanxiong Rhizoma in XBJ, could also induce the activity of CYP3A4[454,471]. Tanshinone IIA and cryptotanshinone are the active ingredients of *Salvia*, an herb in XBJ, which could also induce CYP3A4 activity[460]. Collectively, the metabolism of Nirmatrelvir/Ritonavir may be increased, resulting in reduced plasma concentrations of Nirmatrelvir/Ritonavir when Paxlovid™ is co-administrated with TCM recipes (QFPD, JHQG, XFBD, LHQW, and HSBD), leading to the potential loss of antivirotic response. Nevertheless, many herbs in TCM formulations also show an inhibitory effect on CYP3A4 activity[138–140]. Therefore, the "net effects" of the TCM formulations on Paxlovid™ plasma concentration should be further investigated. On the other hand, Nirmatrelvir and Ritonavir are also strong inhibitors of CYP3A4[24], which may increase plasma concentrations of bioactive ingredients of herbs in TCM formulations that are primarily metabolized by CYP3A4. CYP3A4 is involved in the metabolism of glycyrrhetinic acid (the main active ingredient of Glycyrrhizae Radix et Rhizoma)[92], atractylenolide II (the main active ingredient of Atractylodes Macrocephala Rhizoma)[138], irisflorentin (the main active ingredient of Belamcandae Rhizoma)[225]. Apart from as a substrate for CYP3A4, Ritonavir is an inhibitor of CYP2D6, CYP2C8, CYP2C9, CYP2C19, and CYP2J2 and an inducer of several metabolizing enzymes, such as CYP3A, CYP1A2, CYP2B6, CYP2C9, CYP2C19, and UGTs, indicating that the plasma concentrations of the substrates for these metabolizing enzymes may be altered when co-administration of Paxlovid™[30-34]. Several ingredients of Scutellariae Radix are substrates for UGT1A9/10[172]. Asarinin, the main bioactive ingredient of Asari Radix et Rhizoma, is metabolized by CYP1A1, CYP2C8, and CYP3A5[233]. Paeoniflorin and albiflorin, two bioactive ingredients of Paeoniae Radix Rubra, are metabolized by CYP3A4 and CYP2D6[372]. Nevertheless, Nirmatrelvir does not induce any CYPs at clinically relevant concentrations[7]. Thus, based on the effect of Ritonavir on CYPs and UGTs, the plasma concentration of the bioactive ingredients of TCM recipes could be changed and should be considered during TCMs combined use with anti-COVID 19 drugs.

Drug transporters may also trigger HDIs between Paxlovid™ and the TCM recipes, resulting in their fluctuating clinical effects. Given that Nirmatrelvir and Ritonavir are substrates for P-gp[35,472], co-administration with any P-gp inhibitors/inducers may alter their absorption or elimination. Among six TCM recipes, QFPD contains several herbs with ingredients that show inductive effects on P-gp, such as Alismatis Rhizoma (alisol B 23-acetate and alisol F 24-acetate)[118], Bupleuri Radix (saikosaponins a, c, d)[160], and

Citri Reticulatae Pericarpium (hesperidin)[259]. In addition, the herbs in QFPD such as Aurantii Fructus Immaturus could induce the expression of P-gp[251]. The herb Descurainiae Semen Lepidii Semen in XFBD has an inhibitory effect on P-gp[318]. The ingredients of Magnoliae Officinalis Cortex (honokiol)[343], Tsaoko Fructus (protocatechuic acid)[348], Rhei Radix et Rhizoma[352], and Descurainiae Semen Lepidii Semen[318] in HSBD could inhibit the function of P-gp. By contrast, the function of P-gp could be induced by the ingredients of Astragali Radix (astragaloside IV, calycosin, and formononetin) in HSBD[366]. Fritillariae Thunbergii Bulbus[78,398], Anemarrhenae Rhizoma[403], and Arctii Fructus[405] in JHQG could inhibit P-gp function, whereas the herb Menthae Haplocalycis Herba is reported to induce P-gp function[411]. Therefore, the combined use of TCM recipes (QFPD, XFBD, HSBD and JHQG) may change Nirmatrelvir/Ritonavir absorption or elimination *via* altering P-gp function, thereby resulting in alteration of Paxlovid™ therapeutic effects and adverse events including dysgeusia, diarrhea, nausea, headache, vomiting, and pyrexia. On the other hand, the clearance of the bioactive ingredients of TCM recipes may be reduced given that Paxlovid™ has inhibitory effects on several drug transporters including P-gp, BCRP, MATE1, OCT1, and OATP[29,37,38]. It was reported that the bioactive ingredients of Ephedrae Herba (L-ephedrine, D-pseudoephedrine, and L-methylephedrine)[82], Armeniacae Semen Amarum (amygdalin)[107], and Atractylodes Macrocephala Rhizoma (atractylenolide I)[137] in QFPD are substrates for P-gp. Except for QFPD, Ephedrae Herba and Armeniacae Semen Amarum are two herbs that are contained in JHQG, XFBD, LHQW, and HSBD. The ingredients of Paeoniae Radix Rubra in HSBD are substrates for P-gp[372,373]. Lonicerae Japonicae Flos in JHQG has an ingredient (phenolic acids) that is a substrate for P-gp[381]. Many ingredients in TCM formulations are also substrates for BCRP. Collectively, the absorption or elimination of bioactive ingredients that are substrates for P-gp and BCRP in above six TCM recipes may be reduced by Paxlovid™, thereby shifting the plasma concentration and therapeutic effect.

In summary, multiple metabolizing enzymes and transporters-mediated HDI between Paxlovid™ and the TCM recipes (Fig. 1A) should be evaluated.

4.1.2. Potential pharmacokinetic HDI between Remdesivir and the TCM recipes

Alterations in the expression or activity of metabolizing enzymes are of great importance in mediating potential pharmacokinetic HDI between Remdesivir and TCM. CYP3A4 is one of the important metabolizing enzymes responsible for Remdesivir metabolism[44]. Multiple herbs regulate the expression or activity of CYP3A4, potentially affecting the metabolism of Remdesivir. For example, Scutellariae Radix, Asteris Radix et Rhizome and Asari Radix et Rhizoma are commonly used herbs in herbal formulas against COVID-19. These herbs or their bioactive ingredients could inhibit CYP3A4[176,209,234], which might delay the metabolism of Remdesivir and increase its exposure. Although the adverse events of Remdesivir are rare, transaminase increases have been reported in Remdesivir-treated patients[47]. Considering that the suppression of CYP3A4 might increase the exposure of Remdesivir, liver function should be carefully monitored when Remdesivir is co-administered with these herbs and involved formulas. By contrast, some herbs such as Poria, and Astragali Radix could induce CYP3A4[147,365], indicating that the co-

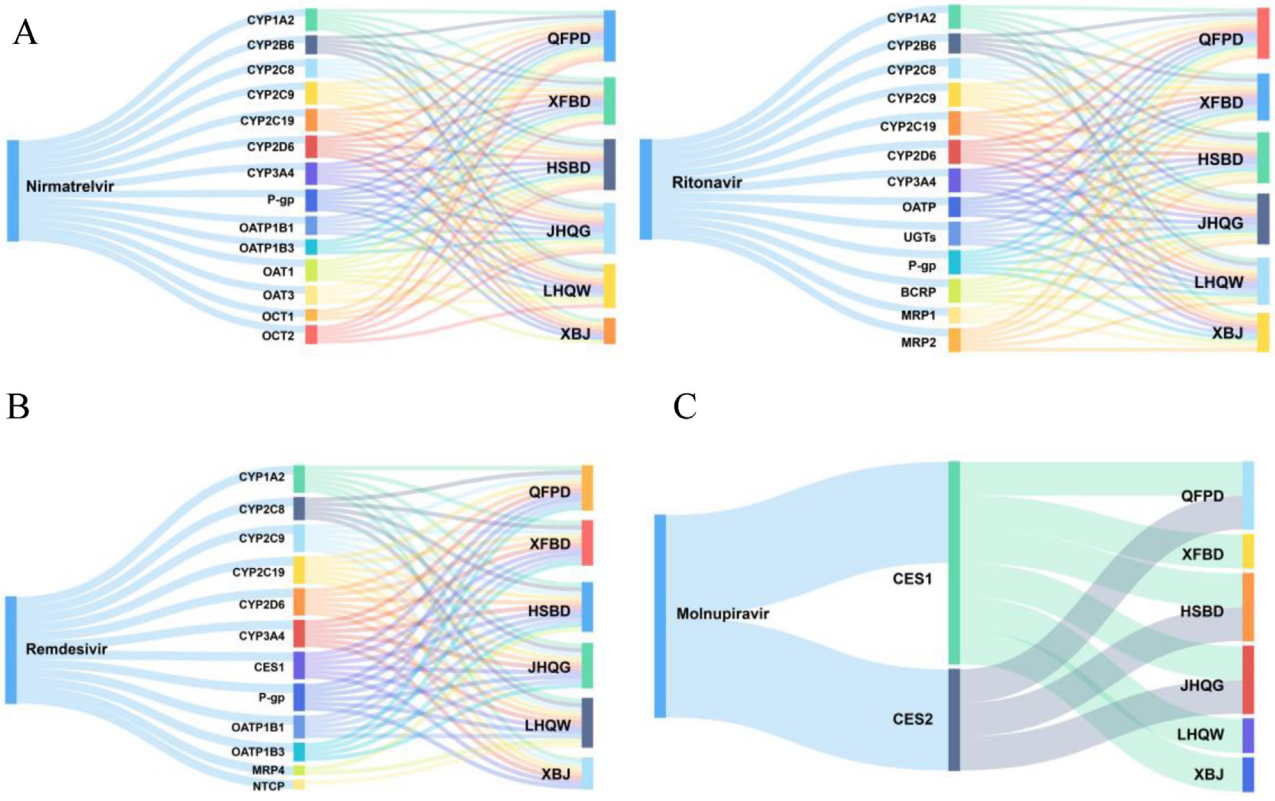

Figure 1 Potential pharmacokinetics HDIs between Paxlovid™ (A)/Remdesivir (B)/Molnupiravir (C) and TCM recipes.

administration with these drugs might accelerate the metabolism of Remdesivir. Glycyrrhizae Radix et Rhizoma is an herb in QFPD, JHQG, XFBD, LHQW, and HSBD. A previous study demonstrated that its extract inhibits CYP3A4 activity in human liver microsomes[97]. However, its bioactive ingredient glycyrrhizin could increase CYP3A4 activity[98]. Apart from CYP3A4, Remdesivir is also a substrate of CYP2C8 and CYP2D6[40,52]. Licochalcone A could inhibit CYP2C8 activity[99]. Licochalcone A, astin D, and peimine could inhibit CYP2D6[99,209,397,398]. These herbal ingredients might also affect Remdesivir metabolism. A previous study showed that QFPD has inhibitory effects on CYP3A, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP2E1 activity[79], indicating that QFPD might increase exposure to Remdesivir. The "net effects" of the herbal formula on the metabolizing enzymes or transporters remain to be further investigated. Thus, studies on the potential effects of herbal formulas on metabolizing enzymes are necessary. On the contrary, many herbs and their bioactive compounds are substrates of CYP3A4. Given that Remdesivir could inhibit CYP3A4 activities, the CYP3A4-mediated metabolism of these herbs might be repressed. CYP3A4 is involved in the metabolism of glycyrrhetinic acid[92], atractylenolide II[138], and irisflorentin[225]. Since these compounds are isolated from Glycyrrhizae Radix et Rhizoma, Atractylodes Macrocephala Rhizome, and Belamcandae Rhizoma. Remdesivir might inhibit the metabolism of these herbs, leading to potential HDIs. For example, the main side effects of Glycyrrhizae Radix et Rhizoma include hypertension and secondary disorders of hypokalemia[473]. Whether the co-administration of Remdesivir would increase the risk of occurrence of adverse events of Glycyrrhizae Radix et Rhizoma should be considered. Moreover, pharmacokinetic studies showed that tangeretin, a bioactive compound in the Citri Reticulatae Pericarpium, is metabolized *via* CYP1A2 in the liver[257,258]. Remdesivir has been shown to inhibit CYP1A2 activity[40], which might delay the metabolism of Citri Reticulatae Pericarpium.

Apart from CYPs, CESs are responsible for the metabolic activation of Remdesivir. Many herbs and their ingredients could inhibit CES, which might repress the CES-mediated hydrolysis of Remdesivir. Remdesivir is normally administered through intravenous infusion, which delivers transient high systemic concentrations and is inheritably related to the development of cytotoxicity. A recent study showed that CES1-based hydrolysis contributes to the activation and cytotoxicity of Remdesivir[474]. A previous study showed that QFPD, Reduning injection, Xiangqin Jiere granules, and Jingyin granules showed weak inhibitory effects on remdesivir hydrolysis, with IC_{50} values larger than 1000 μg/mL, indicating that Remdesivir hydrolysis is hardly affected by these four Chinese medicines[475,476]. Moreover, glycyrrhetinic acid, baicalein, and oroxylin A are bioactive compounds from Glycyrrhizae Radix et Rhizoma and Scutellariae Radix, and these ingredients might serve as CES inhibitors, leading to the inhibition of CES-mediated hydrolysis of substrate prodrugs such as Remdesivir[477,478]. Notably, CES1 was found to be one of the most highly expressed drug-metabolizing enzymes in the liver. CES1 abundance in the liver is ~20- to 30-fold higher than CYP3A4[479,480]. Given that Remdesivir is metabolized by CES1 (~80%), cathepsin A (~10%), and CYP3A (~10%)[44,45], the effect of CYP3A inhibition on the pharmacokinetic behaviors of Remdesivir might be much less compared to that of CES1 inhibition. Thus, potential CES-mediated HDIs between Remdesivir and these herbal medicines should be alerted.

Drug transporters are also important proteins that can affect the absorption or elimination of drugs. Given that Remdesivir is a substrate of P-gp, the compounds that affect P-gp activity might affect the efflux of Remdesivir. For example, herbal medicines and their bioactive ingredients including Alismatis Rhizoma (alisol B 23-acetate and alisol F 24-acetate)[118], Bupleuri Radix (saikosaponins a/c/d)[160], Citri Reticulatae Pericarpium (hesperidin)[259], Descurainiae semen lepidii semen (quercetin)[318], Magnoliae Officinalis Cortex (honokiol)[343,344], Rhei Radix et Rhizoma[352,356], Fritillariae Thunbergii Bulbus (peimisine, imperialine)[396], Anemarrhenae Rhizoma (timosaponin A3)[400–403], Arctii Fructus exerts inhibitory effects on P-gp, which may suppress Remdesivir's absorption or elimination[405]. On the contrary, many herbs such as Aurantii Fructus Immaturus (ethanol extract), Astragali Radix (astragaloside IV, calycosin and formononetin), and Menthae Haplocalycis Herba (menthol) can increase the activity or expression of P-gp[251,366,411]. These herbs and bioactive compounds might accelerate the absorption or elimination of Remdesivir.

Protein binding in plasma is another factor that plays an important role in DDIs. Since Remdesivir has moderate protein binding in plasma and its metabolite GS-704277 displays low protein binding[50], the risk of affecting Remdesivir's exposure *via* influencing plasma protein binding might be relatively low. On the contrary, wogonin, a bioactive ingredient from Scutellariae Radix, has over 90% serum protein binding rate[171]. The plasma protein binding of 6-gingerol, a bioactive ingredient from Ginger, is greater than 90%[198,199]. Scutellariae Radix and Ginger are important herbs in QFPD. Whether HDIs involved in the protein binding process would occur and then affect the exposure of these compounds remains to be investigated.

As indicated in Fig. 1B, the major pathways for the potential pharmacokinetic HDIs between Remdesivir and the TCM recipes involve CES- and CYPs-mediated inhibition or induction and P-gp mediated efflux.

4.1.3. Potential pharmacokinetic HDI between Molnupiravir with the TCM recipes

Molnupiravir is hydrolyzed to NHC (the active metabolite) by CES1 and CES2. The concentration of NHC may be changed when Molnupiravir is co-administrated with drugs that can modulate the expression and activity of CES1 and CES2. It was reported that the ingredients of Salviae Miltiorrhizae Radix et Rhizoma/Radix Puerariae Lobatae in XBJ could decrease the CES1 activity in plasma, and the ingredients of Angelicae Sinensis Radix and Chuanxiong Rhizoma in XBJ could decrease the CES1 activity in the kidneys and lungs, respectively[481,482]. Magnolol, the active ingredient of Magnoliae Officinalis Cortex in HSBD, could inhibit both hCES1 and hCES2[483]. Glycyrrhetinic acid also shows a relatively weak inhibition *in vitro* (IC_{50} > 1 μmol/L) on CES1[484]. A previous study revealed that triterpenoids isolated from Alismatis Rhizoma showed inhibitory activities against human CES2[485]. Baicalein and Oroxylin A could strongly inhibit the hydrolysis of CES-mediated hydrolysis prodrug and CES1 and CES2 activities[478]. A recent study proposed that Molnupiravir is a substrate of CES2 but not CES1, and the hydrolysis of Molnupiravir varies among CES2 natural variants[64]. Future research should be prioritized to estimate CES2-mediated HDI between Molnupiravir with TCM recipes. Therefore, the plasma concentration of NHC may be decreased when TCM is combined with Molnupiravir. On the other hand, neither

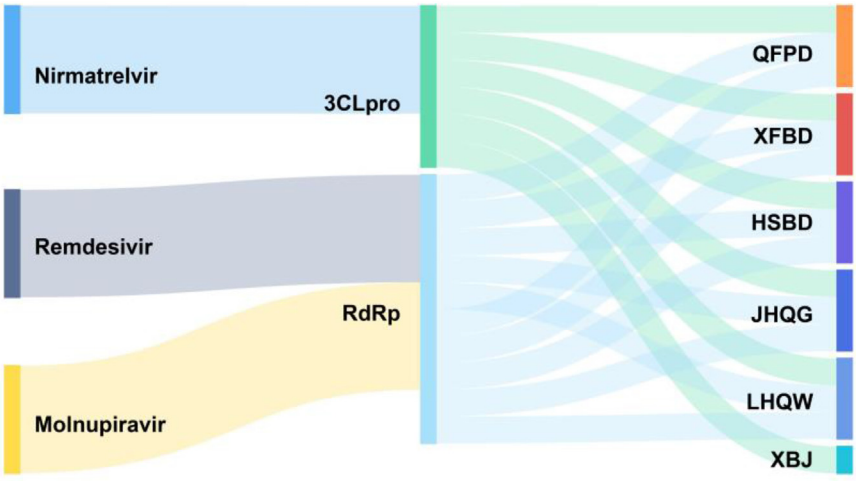

Figure 2 Potential pharmacodynamic HDIs between anti-COVID-19 drugs and TCM recipes.

Molnupiravir nor NHC functioned as substrates/inhibitor/inducer of any important transporters and enzymes that mediate drug−drug interactions[63,65]. Thus, the effect of Molnupiravir on the six TCM recipes through a pharmacokinetic mechanism *via* drug metabolizing enzymes and transporters may not occur.

As indicated in Fig. 1C, the TCM recipes inhibit CES activity, with the potential to cause HDIs during combination of Molnupiravir and the TCM recipes.

4.2. *Pharmacodynamic HDIs*

Compared with the pharmacokinetic HDI, potential pharmacodynamic HDI between antiviral drugs and TCM may also occur because of the complex signaling networks of TCM. Nirmatrelvir is a SARS-CoV-2 Mpro (3CLpro) inhibitor against COVID-19. The active metabolites of Remdesivir and Molnupiravir selectively inhibit RdRp, which delays viral RNA chain termination and inhibits SARS-CoV-2 replication[24]. Previous studies revealed that many herbs and their bioactive ingredients could bind to ACE2, 3CLpro, and RdRp and inhibit their activities[486,487]. Compared with antiviral drug treatment alone, JHQG combined with antiviral drugs was superior in relieving fever and poor appetite in patients with COVID-19[488]. The active ingredients in JHQG such as chlorogenic acid, forsythoside A, and ephedrine have strong binding activity for 3CLpro and ACE2, which significantly relieves fever, cough, fatigue, and anxiety in patients with COVID-19[271,376]. A retrospective study showed that the combination of QFPD with antiviral drugs exerted significantly better anti-inflammatory effects compared with treatment with antiviral drugs alone in patients with mild and moderate COVID-19[69]. The active ingredients including glycyrrhizin, cinnamic acid, baicalin, and baicalein in QFPD can suppress SARS-CoV-2 replication *via* targeting 3CLpro and RdRp[362,486,489]. A meta-analysis indicated that LHQW combined with conventional therapy could effectively reduce the severity in patients with mild or moderate COVID-19[490]. LHQW significantly inhibited SARS-CoV-2 replication in Vero E6 cells, and three ingredients (rutin, forsythoside E, and hyperoside) in LHQW were better bound to 3CLpro than Lopinavir based on the docking scores[271,487]. Baicalein and quercetin, as the top two ingredients of HSBD, have shown high affinity to 3CLpro and ACE2, which was further suggested in a study that showed that HSFD strengthened the efficacy of lopinavir−ritonvir in the treatment of 60 patients with COVID-19[491]. Combined with conventional therapy, XFBD significantly ameliorates the clinical symptoms including fever, cough, and fatigue in 42 patients with COVID-19[271,274]. ACE2 and 3CLpro were also the targets of flavonoids and phytosterols in XFBD by inhibiting viral invasion and replication[271]. XBJ has been shown to effectively treat patients with COVID-19[492], particularly in patients with COVID-19-induced cardiac dysfunction[493]. In a group of 42 patients with COVID-19 treated with XBJ combined with routine treatment, their IL-6 levels and body temperature were significantly reduced[494]. Collectively, the combined use of the TCM recipes might exert synergistic effects and potentiate the efficacy of Nirmatrelvir/Ritonavir, Remdesivir, and Molnupiravir against COVID-19 through "multi-component, multi-target, multi-pathway" pattern (Fig. 2).

5. Conclusions and perspectives

The above-mentioned anti-COVID-19 drugs and the six TCM formulae play important roles in the treatment of COVID-19 infections. As Paxlovid™, Remdesivir and Molnupiravir become more globally available and herbal medicine use varies across different regions, it is critical to clearly demonstrate potential HDIs, particularly through pharmacokinetics-based mechanisms mediated by metabolizing enzyme/transporter induction or inhibition. The present review highlights potential interactions of the six TCM formulae (QFPD, JHQG, XFBD, LHQW, HSBD, and XBJ) and three anti-COVID-19 drugs (Nirmatrelvir/Ritonavir, Remdesivir, and Molnupiravir). Clinical studies and animal experiments have demonstrated that the extract of these TCM recipes, along with their bioactive compounds, exhibit synergistic effects when combined with three antiviral drugs, following a 'multi-component, multi-target, multi-pathway' mechanism. The potential pharmacokinetic HDIs of these TCM recipes with the anti-COVID-19 drugs are mostly *via* the regulation of CYP3A4, CES and/or P-gp. However, additional prospective and retrospective studies, as well as *in vivo* and *in vitro* experiments, are necessary to provide further elucidation on the underlying mechanisms responsible for the changes in plasma concentrations and the subsequent alteration of therapeutic response. Although COVID-19 primarily affects the respiratory system, patients with COVID-19 have shown evidence of microbial dysbiosis.

Preventing ACE2 from binding to SARS-CoV-2 is an effective approach to treat COVID-19. ACE2 plays an important role in maintaining intestinal microecology and intestinal immune regulation. Microbiota and its metabolites may also affect or modulate ACE2 expression. Although no interactions between gut microbiota and anti-COVID-19 drugs have been reported, numerous studies have demonstrated that a bidirectional regulatory relationship between TCM formulae and the gut microbiota. Thus, future studies should focus on the effect of TCM recipes and the anti-COVID-19 drugs on microbiota, which is probably a pathway mediating HDIs between TCM formulae and anti-COVID-19 drugs. Finally, for the wide use of the TCM formulae and the globally available of the anti-COVID-19 drugs, public health authorities should consider well characterizing these HDIs, creating an HDI checklist for these drugs, and raising awareness and better understanding of HDIs in order to maximize clinical outcomes and minimize adverse and toxic effects against COVID-19.

Acknowledgments

The work was supported by the National Natural Science Foundation of China (grants 82025034 and 81973392 to Huichang Bi. And grants 82274193 and 82074110 to Ling Ye), the Open Project of State Key Laboratory of Natural Medicines (grant SKLNMKF202209 to Ling Ye, China), the Shenzhen Science and Technology Program (No. KQTD20190929174023858 to Huichang Bi, China), Guangdong Basic and Applied Basic Research Foundation (2023A1515012859 to Shicheng Fan, China), and Guangdong Medical Research Foundation (A2023109 to Shicheng Fan, China).

Author contributions

Huichang Bi, Ling Ye conceived and designed the project. Ye Ling, Shicheng Fan, Pengfei Zhao, Chenghua Wu, Menghua Liu, Shuang Hu, Peng Wang, Hongyu Wang wrote the manuscript. Huichang Bi, Ling Ye and Shicheng Fan revised the manuscript.

Conflicts of interest

The authors declare no conflict of interest.

References

1. Miyashita K, Hozumi H, Furuhashi K, Nakatani E, Inoue Y, Yasui H, et al. Changes in the characteristics and outcomes of COVID-19 patients from the early pandemic to the delta variant epidemic: a nationwide population-based study. *Emerg Microb Infect* 2023;**12**:2155250.
2. de Andrade SA, de Souza DA, Torres AL, de Lima CFG, Ebram MC, Celano RMG, et al. Pathophysiology of COVID-19: critical role of hemostasis. *Front Cell Infect Microbiol* 2022;**12**:896972.
3. Zeng G, Wu Q, Pan H, Li M, Yang J, Wang L, et al. Immunogenicity and safety of a third dose of CoronaVac, and immune persistence of a two-dose schedule, in healthy adults: interim results from two single-centre, double-blind, randomised, placebo-controlled phase 2 clinical trials. *Lancet Infect Dis* 2022;**22**:483−95.
4. Wang Y, Li X, Zhang JH, Xue R, Qian JY, Zhang XH, et al. Mechanism of Xuanfei Baidu Tang in treatment of COVID-19 based on network pharmacology. *China J Chin Mater Med* 2020;**45**:2249−56.
5. Tiseo G, Barbieri C, Galfo V, Occhineri S, Matucci T, Almerigogna F, et al. Efficacy and safety of nirmatrelvir/ritonavir, molnupiravir, and remdesivir in a real-world cohort of outpatients with COVID-19 at high risk of progression: the PISA outpatient clinic experience. *Infect Dis Ther* 2023;**12**:257−71.
6. Graziani L, Gori L, Manciulli T, Basile G, Campolmi I, Borchi B, et al. Successful use of nirmatrelvir/ritonavir in immunocompromised patients with persistent and/or relapsing COVID-19. *J Antimicrob Chemother* 2023;**78**:555−8.
7. Zhang C, Zhang D, Wang Y, Zhang L, Qi S, Fang Q, et al. Pharmacokinetics and anti-liver fibrosis characteristics of amygdalin: key role of the deglycosylated metabolite prunasin. *Phytomedicine* 2022;**99**:154018.
8. Stevens LJ, Pruijssers AJ, Lee HW, Gordon CJ, Tchesnokov EP, Gribble J, et al. Mutations in the SARS-CoV-2 RNA-dependent RNA polymerase confer resistance to remdesivir by distinct mechanisms. *Sci Transl Med* 2022;**14**:abo0718.
9. Johnson DM, Brasel T, Massey S, Garron T, Grimes M, Smith J, et al. Evaluation of molnupiravir (EIDD-2801) efficacy against SARS-CoV-2 in the rhesus macaque model. *Antivir Res* 2023;**209**:105492.
10. Capodice JL, Chubak BM. Traditional Chinese herbal medicine-potential therapeutic application for the treatment of COVID-19. *Chin Med* 2021;**16**:24.
11. Huang W, Jiang B, Luo J, Luo M, Ding X, Yang Q, et al. Treatment of COVID-19 in hemodialysis patients using traditional Chinese medicine: a single-center, retrospective study. *Front Pharmacol* 2022;**13**:764305.
12. Liu L. Traditional Chinese medicine contributes to the treatment of COVID-19 patients. *Chin Herb Med* 2020;**12**:95−6.
13. Huang Y, Yang C, Xu XF, Xu W, Liu SW. Structural and functional properties of SARS-CoV-2 spike protein: potential antivirus drug development for COVID-19. *Acta Pharmacol Sin* 2020;**41**:1141−9.
14. Zhuang J, Dai X, Zhang W, Fu X, Zhang G, Zeng J, et al. Efficacy and safety of integrated traditional Chinese and Western medicine against COVID-19: a systematic review and meta-analysis. *Phytother Res* 2022;**36**:4371−97.
15. Xing D, Liu Z. Effectiveness and safety of traditional Chinese medicine in treating COVID-19: clinical evidence from China. *Aging Dis* 2021;**12**:1850−6.
16. Li Y, Meng Q, Yang M, Liu D, Hou X, Tang L, et al. Current trends in drug metabolism and pharmacokinetics. *Acta Pharm Sin B* 2019;**9**:1113−44.
17. Mills E, Montori VM, Wu P, Gallicano K, Clarke M, Guyatt G. Interaction of St John's wort with conventional drugs: systematic review of clinical trials. *BMJ* 2004;**329**:27−30.
18. Paine MF, Criss AB, Watkins PB. Two major grapefruit juice components differ in intestinal CYP3A4 inhibition kinetic and binding properties. *Drug Metab Dispos* 2004;**32**:1146−53.
19. de Nies L, Galata V, Martin-Gallausiaux C, Despotovic M, Busi SB, Snoeck CJ, et al. Altered infective competence of the human gut microbiome in COVID-19. *Microbiome* 2023;**11**:46.
20. Li J, Jing Q, Li J, Hua M, Di L, Song C, et al. Assessment of microbiota in the gut and upper respiratory tract associated with SARS-CoV-2 infection. *Microbiome* 2023;**11**:38.
21. Troseid M, Holter JC, Holm K, Vestad B, Sazonova T, Granerud BK, et al. Gut microbiota composition during hospitalization is associated with 60-day mortality after severe COVID-19. *Crit Care* 2023;**27**:69.
22. Gang J, Wang H, Xue X, Zhang S. Microbiota and COVID-19: long-term and complex influencing factors. *Front Microbiol* 2022;**13**:963488.
23. Feng Y, Cao H, Hua J, Zhang F. Anti-diabetic intestinal mechanisms: foods, herbs, and Western medicines. *Mol Nutr Food Res* 2022;**66**:13.
24. US Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization for Paxlovid. Available from: https://www.fda.gov/media/155050/download.
25. Eng H, Dantonio AL, Kadar EP, Obach RS, Di L, Lin J, et al. Disposition of nirmatrelvir, an orally bioavailable inhibitor of SARS-CoV-2 3C-like protease, across animals and humans. *Drug Metab Dispos* 2022;**50**:576−90.
26. Singh RSP, Walker GS, Kadar EP, Cox LM, Eng H, Sharma R, et al. Metabolism and excretion of nirmatrelvir in humans using

quantitative fluorine nuclear magnetic resonance spectroscopy: a novel approach for accelerating drug development. *Clin Pharmacol Ther* 2022;**112**:1201−6.
27. Owen DR, Allerton CMN, Anderson AS, Aschenbrenner L, Avery M, Berritt S, et al. An oral SARS-CoV-2 Mpro inhibitor clinical candidate for the treatment of COVID-19. *Science* 2021;**374**:1586−93.
28. Abraham S, Nohria A, Neilan TG, Asnani A, Saji AM, Shah J, et al. Cardiovascular drug interactions with nirmatrelvir/ritonavir in patients with COVID-19: JACC review topic of the week. *J Am Coll Cardiol* 2022;**80**:1912−24.
29. Wanounou M, Caraco Y, Levy RH, Bialer M, Perucca E. Clinically relevant interactions between ritonavir-boosted nirmatrelvir and concomitant antiseizure medications: implications for the management of COVID-19 in patients with epilepsy. *Clin Pharmacokinet* 2022;**61**:1219−36.
30. Larson KB, Wang K, Delille C, Otofokun I, Acosta EP. Pharmacokinetic enhancers in HIV therapeutics. *Clin Pharmacokinet* 2014;**53**:865−72.
31. Marzolini C, Gibbons S, Khoo S, Back D. Cobicistat *versus* ritonavir boosting and differences in the drug−drug interaction profiles with co-medications. *J Antimicrob Chemother* 2016;**71**:1755−8.
32. Tseng A, Hughes CA, Wu J, Seet J, Phillips EJ. Cobicistat versus ritonavir: similar pharmacokinetic enhancers but some important differences. *Ann Pharmacother* 2017;**51**:1008−22.
33. Kaspera R, Kirby BJ, Sahele T, Collier AC, Kharasch ED, Unadkat JD, et al. Investigating the contribution of CYP2J2 to ritonavir metabolism *in vitro* and *in vivo*. *Biochem Pharmacol* 2014;**91**:109−18.
34. Hsu A, Granneman GR, Bertz RJ. Ritonavir. Clinical pharmacokinetics and interactions with other anti-HIV agents. *Clin Pharmacokinet* 1998;**35**:275−91.
35. Meaden ER, Hoggard PG, Newton P, Tjia JF, Aldam D, Cornforth D, et al. P-glycoprotein and MRP1 expression and reduced ritonavir and saquinavir accumulation in HIV-infected individuals. *J Antimicrob Chemother* 2002;**50**:583−8.
36. Huisman MT, Smit JW, Crommentuyn KM, Zelcer N, Wiltshire HR, Beijnen JH, et al. Multidrug resistance protein 2 (MRP2) transports HIV protease inhibitors, and transport can be enhanced by other drugs. *AIDS* 2002;**16**:2295−301.
37. Olson DP, Scadden DT, D'Aquila RT, De Pasquale MP. The protease inhibitor ritonavir inhibits the functional activity of the multidrug resistance related-protein 1(MRP-1). *AIDS* 2002;**16**:1743−7.
38. Cattaneo D, Cossu MV, Rizzardini G. Pharmacokinetic drug evaluation of ritonavir (*versus* cobicistat) as adjunctive therapy in the treatment of HIV. *Expet Opin Drug Metabol Toxicol* 2019;**15**:927−35.
39. Eastman RT, Roth JS, Brimacombe KR, Simeonov A, Shen M, Patnaik S, et al. Remdesivir: a review of its discovery and development leading to emergency use authorization for treatment of COVID-19. *ACS Cent Sci* 2020;**6**:672−83.
40. Aleissa MM, Silverman EA, Paredes Acosta LM, Nutt CT, Richterman A, Marty FM. New perspectives on antimicrobial agents: remdesivir treatment for COVID-19. *Antimicrob Agents Chemother* 2020;**65**:e01814-e01820.
41. Humeniuk R, Mathias A, Kirby BJ, Lutz JD, Cao H, Osinusi A, et al. Pharmacokinetic, pharmacodynamic, and drug-interaction profile of Remdesivir, a SARS-CoV-2 replication inhibitor. *Clin Pharmacokinet* 2021;**60**:569−83.
42. Wang LY, Cui JJ, Ouyang QY, Zhan Y, Guo CX, Yin JY. Remdesivir and COVID-19. *Lancet* 2020;**396**:953−4.
43. Jordan PC, Liu C, Raynaud P, Lo MK, Spiropoulou CF, Symons JA, et al. Initiation, extension, and termination of RNA synthesis by a paramyxovirus polymerase. *PLoS Pathog* 2018;**14**:e1006889.
44. Deb S, Reeves AA, Hopefl R, Bejusca R. ADME and Pharmacokinetic properties of Remdesivir: its drug interaction potential. *Pharmaceuticals* 2021;**14**:655.
45. VEKLURY® (Remdesivir) Package insert. Available from: https://www.drugs.com/pro/veklury.html.
46. Li R, Liclican A, Xu Y, Pitts J, Niu C, Zhang J, et al. Key metabolic enzymes involved in Remdesivir activation in human lung cells. *Antimicrob Agents Chemother* 2021;**65**:e0060221.
47. Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, et al. Compassionate use of Remdesivir for patients with severe COVID-19. *N Engl J Med* 2020;**382**:2327−36.
48. Mulangu S, Dodd LE, Davey Jr RT, Tshiani Mbaya O, Proschan M, Mukadi D, et al. A randomized, controlled trial of Ebola virus disease therapeutics. *N Engl J Med* 2019;**381**:2293−303.
49. Humeniuk R, Mathias A, Cao H, Osinusi A, Shen G, Chng E, et al. Safety, tolerability, and pharmacokinetics of Remdesivir, an antiviral for treatment of COVID-19, in healthy subjects. *Clin Transl Sci* 2020;**13**:896−906.
50. Summary on compassionate use—remdesivir Gilead. Available from: https://www.ema.europa.eu/en/documents/other/summary-compassionate-use-remdesivir-gilead_en.pdf. Accessed 13 June 2020.
51. Lescure FX, Bouadma L, Nguyen D, Parisey M, Wicky PH, Behillil S, et al. Clinical and virological data of the first cases of COVID-19 in Europe: a case series. *Lancet Infect Dis* 2020;**20**:697−706.
52. Yang K. What do we know about Remdesivir drug interactions?. *Clin Transl Sci* 2020;**13**:842−4.
53. Syed YY. Molnupiravir: first approval. *Drugs* 2022;**82**:455−60.
54. Singh AK, Singh A, Singh R, Misra A. Molnupiravir in COVID-19: a systematic review of literature. *Diabetes Metabol Syndr* 2021;**15**:102329.
55. Malone B, Campbell EA. Molnupiravir: coding for catastrophe. *Nat Struct Mol Biol* 2021;**28**:706−8.
56. Wahl A, Gralinski LE, Johnson CE, Yao W, Kovarova M, Dinnon 3rd KH, et al. SARS-CoV-2 infection is effectively treated and prevented by EIDD-2801. *Nature* 2021;**591**:451−7.
57. Sheahan TP, Sims AC, Zhou S, Graham RL, Pruijssers AJ, Agostini ML, et al. An orally bioavailable broad-spectrum antiviral inhibits SARS-CoV-2 in human airway epithelial cell cultures and multiple coronaviruses in mice. *Sci Transl Med* 2020;**12**:eabb5883.
58. Rosenke K, Hansen F, Schwarz B, Feldmann F, Haddock E, Rosenke R, et al. Orally delivered MK-4482 inhibits SARS-CoV-2 replication in the Syrian hamster model. *Nat Commun* 2021;**12**:2295.
59. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, Kovalchuk E, Gonzalez A, Delos Reyes V, et al. Molnupiravir for oral treatment of COVID-19 in nonhospitalized patients. *N Engl J Med* 2022;**386**:509−20.
60. Painter WP, Holman W, Bush JA, Almazedi F, Malik H, Eraut N, et al. Human safety, tolerability, and pharmacokinetics of Molnupiravir, a novel broad-spectrum oral antiviral agent with activity against SARS-CoV-2. *Antimicrob Agents Chemother* 2021;**65**:e02428-20.
61. Pourkarim F, Pourtaghi-Anvarian S, Rezaee H. Molnupiravir: a new candidate for COVID-19 treatment. *Pharmacol Res Perspect* 2022;**10**:e00909.
62. Khoo SH, Fitzgerald R, Fletcher T, Ewings S, Jaki T, Lyon R, et al. Optimal dose and safety of molnupiravir in patients with early SARS-CoV-2: a Phase I, open-label, dose-escalating, randomized controlled study. *J Antimicrob Chemother* 2021;**76**:3286−95.
63. Food and Drug Administration (Fda). Fact sheet for healthcare providers: emergency use authorization for molnupiravir. Available from: https://www.fda.gov/media/155054/download?utm_medium=email&utm_source=govdelivery.
64. Shen Y, Eades W, Liu W, Yan B. The COVID-19 oral drug Molnupiravir is a CES2 substrate: potential drug−drug interactions and impact of CES2 genetic polymorphism *in vitro*. *Drug Metab DisposHealth Care Sci* 2022;**50**:1151−60.
65. Eisner H, Riegler-Berket L, Gamez CFR, Sagmeister T, Chalhoub G, Darnhofer B, Jazleena PJ, Birner-Gruenberger R, Pavkov-Keller T, Haemmerle G, Schoiswohl G, Oberer M. The crystal structure of mouse ces2c, a potential ortholog of human CES2, shows structural similarities in substrate regulation and product release to human CES1. *Int J Mol Sci* 2022;**23**:13101.

66. Use CfMPfH. molnupiravir_COVID19-MSD−assessment report rev. 1. Availible from: https://www.ema.europa.eu/en/documents/referral/lagevrio-also-known-molnupiravir-mk-4482-covid-19-article-53-procedure-assessment-report_en.pdf.
67. Diagnosis and treatment protocol for COVID-19 patients (Trial Version 9). *Health Care Science* 2022;**1**:14−28.
68. Shi N, Liu B, Liang N, Ma Y, Ge Y, Yi H, et al. Association between early treatment with Qingfei Paidu decoction and favorable clinical outcomes in patients with COVID-19: a retrospective multicenter cohort study. *Pharmacol Res* 2020;**161**:105290.
69. Xin S, Cheng X, Zhu B, Liao X, Yang F, Song L, et al. Clinical retrospective study on the efficacy of Qingfei Paidu decoction combined with Western medicine for COVID-19 treatment. *Biomed Pharmacother* 2020;**129**:110500.
70. Zhang L, Zheng X, Bai X, Wang Q, Chen B, Wang H, et al. Association between use of Qingfei Paidu Tang and mortality in hospitalized patients with COVID-19: a national retrospective registry study. *Phytomedicine* 2021;**85**:153531.
71. Zhang L, Ma Y, Shi N, Tong L, Liu S, Ji X, et al. Effect of Qingfei Paidu decoction combined with Western medicine treatments for COVID-19: a systematic review and meta-analysis. *Phytomedicine* 2022;**102**:154166.
72. Li X, Kang Y, Li W, Liu Z, Xu Z, Zhang X, et al. Comparing the effects of three decoctions for coronavirus disease 2019 on severe acute respiratory syndrome coronavirus 2-related toll-like receptors-mediated inflammations. *J Tradit Chin Med* 2023;**43**:51−9.
73. Yan H, Zou Y, Zou C. Mechanism of Qingfei Paidu decoction for treatment of COVID-19: analysis based on network pharmacology and molecular docking technology. *J South Med Univ* 2020;**40**:616−23.
74. Yang R, Liu H, Bai C, Wang Y, Zhang X, Guo R, et al. Chemical composition and pharmacological mechanism of Qingfei Paidu Decoction and Ma Xing Shi Gan Decoction against coronavirus disease 2019 (COVID-19): *in silico* and experimental study. *Pharmacol Res* 2020;**157**:104820.
75. Mei J, Zhou Y, Yang X, Zhang F, Liu X, Yu B. Active components in *Ephedra sinica* stapf disrupt the interaction between ACE2 and SARS-CoV-2 RBD: potent COVID-19 therapeutic agents. *J Ethnopharmacol* 2021;**278**:114303.
76. Wu G, Zhang W, Zheng N, Zu X, Tian S, Zhong J, et al. Integrated microbiome and metabolome analysis reveals the potential therapeutic mechanism of Qing-Fei-Pai-Du decoction in mice with coronavirus-induced pneumonia. *Front Cell Infect Microbiol* 2022;**12**:950983.
77. Liu W, Huang J, Zhang F, Zhang CC, Li RS, Wang YL, et al. Comprehensive profiling and characterization of the absorbed components and metabolites in mice serum and tissues following oral administration of Qing-Fei-Pai-Du decoction by UHPLC-Q-Exactive-Orbitrap HRMS. *Chin J Nat Med* 2021;**19**:305−20.
78. Liu W, Ge GB, Wang Y, Huang K, Chen J, Wang C, et al. Chemical constituent and tissue distribution of Qingfei Paidu Decotion in mice using UHPLC-Q-Orbitrap HRMS. *Chin Tradit Herb Drugs* 2020;**51**:2035−45.
79. Zhang F, Huang J, Liu W, Wang CR, Liu YF, Tu DZ, et al. Inhibition of drug-metabolizing enzymes by Qingfei Paidu decoction: implication of herb−drug interactions in COVID-19 pharmacotherapy. *Food Chem Toxicol* 2021;**149**:111998.
80. Zheng Q, Mu X, Pan S, Luan R, Zhao P. Ephedrae herba: a comprehensive review of its traditional uses, phytochemistry, pharmacology, and toxicology. *J Ethnopharmacol* 2023;**307**:116153.
81. Chen L, Yao C, Li J, Wang J, Yao S, Shen S, et al. Systematic characterization of chemical constituents in Mahuang decoction by UHPLC tandem linear ion trap-Orbitrap mass spectrometry coupled with feature-based molecular networking. *J Separ Sci* 2021;**44**:2717−27.
82. Zheng M, Zhou H, Wan H, Chen YL, He Y. Effects of herbal drugs in Mahuang decoction and their main components on intestinal transport characteristics of Ephedra alkaloids evaluated by a Caco-2 cell monolayer model. *J Ethnopharmacol* 2015;**164**:22−9.
83. Jensen O, Rafehi M, Gebauer L, Brockmöller J. Cellular uptake of psychostimulants−are high- and low-affinity organic cation transporters drug traffickers?. *Front Pharmacol* 2020;**11**:609811.
84. Tang J, Ji H, Shi J, Wu L. Ephedra water decoction and cough tablets containing ephedra and liquorice induce CYP1A2 but not CYP2E1 hepatic enzymes in rats. *Xenobiotica* 2016;**46**:141−6.
85. Takara K, Horibe S, Obata Y, Yoshikawa E, Ohnishi N, Yokoyama T. Effects of 19 herbal extracts on the sensitivity to paclitaxel or 5-fluorouracil in HeLa cells. *Biol Pharm Bull* 2005;**28**:138−42.
86. Wu W, Liu L, Han F, Chen Y. Effect of pseudoephedrine and ephedrine on the activities of cytochrome P450 enzymes in rat liver microsomes. *China J Tradit Chin Med Pharm* 2011;**26**:804−7.
87. Jiang M, Zhao S, Yang S, Lin X, He X, Wei X, et al. An "essential herbal medicine"—licorice: a review of phytochemicals and its effects in combination preparations. *J Ethnopharmacol* 2020;**249**:112439.
88. Abraham J, Florentine S. Licorice (glycyrrhiza glabra) extracts-suitable pharmacological interventions for COVID-19?. A review. *Plants* 2021;**10**:2600.
89. Bibi N, Farid A, Gul S, Ali J, Amin F, Kalathiya U, et al. Drug repositioning against COVID-19: a first line treatment. *J Biomol Struct Dyn* 2022;**40**:12812−26.
90. Authier H, Bardot V, Berthomier L, Bertrand B, Blondeau C, Holowacz S, et al. Synergistic effects of licorice root and walnut leaf extracts on gastrointestinal candidiasis, inflammation and gut microbiota composition in mice. *Microbiol Spectr* 2022;**10**:e0235521.
91. Asl MN, Hosseinzadeh H. Review of pharmacological effects of *Glycyrrhiza* sp. and its bioactive compounds. *Phytother Res* 2008;**22**:709−24.
92. Zhao K, Ding M, Cao H, Cao ZX. *In-vitro* metabolism of glycyrrhetinic acid by human and rat liver microsomes and its interactions with six CYP substrates. *J Pharm Pharmacol* 2012;**64**:1445−51.
93. Koga K, Kawamura M, Iwase H, Yoshikawa N. Intestinal absorption and biliary elimination of glycyrrhizic acid diethyl ester in rats. *Drug Des Dev Ther* 2013;**7**:1235−43.
94. Kim DH, Hong SW, Kim BT, Bae EA, Park HY, Han MJ. Biotransformation of glycyrrhizin by human intestinal bacteria and its relation to biological activities. *Arch Pharm Res (Seoul)* 2000;**23**:172−7.
95. Krähenbühl S, Hasler F, Krapf R. Analysis and pharmacokinetics of glycyrrhizic acid and glycyrrhetinic acid in humans and experimental animals. *Steroids* 1994;**59**:121−6.
96. Ploeger B, Mensinga T, Sips A, Seinen W, Meulenbelt J, DeJongh J. The pharmacokinetics of glycyrrhizic acid evaluated by physiologically based pharmacokinetic modeling. *Drug Metab Rev* 2001;**33**:125−47.
97. Li G, Huang K, Nikolic D, van Breemen RB. High-throughput cytochrome P450 cocktail inhibition assay for assessing drug−drug and drug-botanical interactions. *Drug Metab Dispos* 2015;**43**:1670−8.
98. Paolini M, Pozzetti L, Sapone A, Cantelli-Forti G. Effect of licorice and glycyrrhizin on murine liver CYP-dependent monooxygenases. *Life Sci* 1998;**62**:571−82.
99. He W, Wu JJ, Ning J, Hou J, Xin H, He YQ, et al. Inhibition of human cytochrome P450 enzymes by licochalcone A, a naturally occurring constituent of licorice. *Toxicol Vitro* 2015;**29**:1569−76.
100. Kim SJ, Kim SJ, Hong M, Choi HG, Kim JA, Lee S. Investigation of selective inhibitory effects of glycyrol on human CYP1A1 and 2C9. *Xenobiotica* 2016;**46**:857−61.
101. Fan X, Bai J, Hu M, Xu Y, Zhao S, Sun Y, et al. Drug interaction study of flavonoids toward OATP1B1 and their 3D structure activity relationship analysis for predicting hepatoprotective effects. *Toxicology* 2020;**437**:152445.
102. Feng D, Tang T, Fan R, Luo J, Cui H, Wang Y, et al. Gancao (Glycyrrhizae Radix) provides the main contribution to Shaoyao-Gancao decoction on enhancements of CYP3A4 and MDR1

expression *via* pregnane X receptor pathway in vitro. *BMC Complement Altern Med* 2018;**18**:345.
103. Huang YP, Cao YF, Fang ZZ, Zhang YY, Hu CM, Sun XY, et al. Glycyrrhetinic acid exhibits strong inhibitory effects towards UDP-glucuronosyltransferase (UGT) 1A3 and 2B7. *Phytother Res* 2013; **27**:1358−61.
104. Zou J, Li W, Wang G, Fang S, Cai J, Wang T, et al. Hepatoprotective effects of Huangqi decoction (Astragali Radix and Glycyrrhizae Radix et Rhizoma) on cholestatic liver injury in mice: involvement of alleviating intestinal microbiota dysbiosis. *J Ethnopharmacol* 2021; **267**:113544.
105. Wang Y, Gu W, Kui F, Gao F, Niu Y, Li W, et al. The mechanism and active compounds of semen armeniacae amarum treating coronavirus disease 2019 based on network pharmacology and molecular docking. *Food Nutr Res* 2021:65.
106. Li XB, Liu CH, Zhang R, Huang XT, Li YY, Han L, et al. Determination and pharmacokinetics of amygdalin in rats by LC−MS-MS. *J Chromatogr Sci* 2014;**52**:476−81.
107. Zhou H, He Y, Yang J, Wan H, Wang L, Wan H. Transport properties of paeoniflorin and amygdalin across caco-2 cell monolayer model and their modulation of cytochrome p450 metabolism. *Pak J Pharm Sci* 2020;**33**:1569−75.
108. Barakat H, Aljutaily T, Almujaydil MS, Algheshairy RM, Alhomaid RM, Almutairi AS, et al. Amygdalin: a review on its characteristics, antioxidant potential, gastrointestinal microbiota intervention, anticancer therapeutic and mechanisms, toxicity, and encapsulation. *Biomolecules* 2022;**12**:1514.
109. Wen Q, Yu S, Wang S, Qin Y, Xia Q, Wang S, et al. Impact of intestinal microbiota on metabolic toxicity and potential detoxification of amygdalin. *Front Microbiol* 2022;**13**:1030516.
110. Ikarashi N, Ogiue N, Toyoda E, Nakamura M, Kon R, Kusunoki Y, et al. Elucidating the mechanism by which *Gypsum fibrosum*, a traditional Chinese medicine, maintains cutaneous water content. *Biol Pharm Bull* 2013;**36**:1615−21.
111. Mei F, Xing XF, Tang QF, Chen FL, Guo Y, Song S, et al. Antipyretic and anti-asthmatic activities of traditional Chinese herb-pairs, Ephedra and Gypsum. *Chin J Integr Med* 2016;**22**:445−50.
112. Meng Y, Shi L, Wang X, Gai L, Zhai C. The influence of Gypsum water decoction on CYP1A2 and CYP2E1 of cytochrome P450. *Inf Tradit Chin Med* 2015;**32**:25−8.
113. Liu J, Zhang Q, Li RL, Wei SJ, Huang CY, Gao YX, et al. The traditional uses, phytochemistry, pharmacology and toxicology of *Cinnamomi ramulus*: a review. *J Pharm Pharmacol* 2020;**72**: 319−42.
114. Chen Y, Li Z, Pan P, Lao Z, Xu J, Li Z, et al. Cinnamic acid inhibits Zika virus by inhibiting RdRp activity. *Antivir Res* 2021;**192**:105117.
115. Li WL, Du J, Ji YB, Yu YY, Hu ZT, Wang XD. Correlation between metabolism of cinnamic acid and CYP450 enzyme. *Chin J Pharm* 2009;**44**:266−70.
116. Yang BK, Wang SJ, Mo LL, Zeng J, Zhong YM, Zang LQ. Studies on the absolute bioavailability of cinnamic acid in rats and its absorption properties. *Pharm J Chin People's Liberation Army* 2013; **29**:185−8.
117. Jeung WH, Nam W, Kim HJ, Kim JY, Nam B, Jang SS, et al. Oral Administration of *Lactobacillus* curvatus HY7601 and *Lac tobacillus plantarum* KY1032 with *Cinnamomi Ramulus* extract reduces diet-induced obesity and modulates gut microbiota. *Prev Nutr Food Sci* 2019;**24**:136−43.
118. Zhang LL, Xu W, Xu YL, Chen X, Huang M, Lu JJ. Therapeutic potential of Rhizoma Alismatis: a review on ethnomedicinal application, phytochemistry, pharmacology, and toxicology. *Ann N Y Acad Sci* 2017;**1401**:90−101.
119. Wang LC, Liao Y, Long RX, Wang JJ, Liu LD, Chen JJ, Li QH, et al. Inhibitory effect of terpene derivative V-54 from *Alisma orientalis* extract on replication of picornaviridae viruses. *Chin J Biologicals* 2010;**23**:25−7.
120. Bailly C. Pharmacological properties and molecular targets of alisol triterpenoids from Alismatis Rhizoma. *Biomedicines* 2022;**10**:1945.
121. Xu F, Wu QN, Chen J, Gu W, Fang F, Zhang LQ, et al. The binding mechanisms of plasma protein to active compounds in Alismaorientale Rhizomes (Alismatis Rhizoma). *Bioorg Med Chem Lett* 2014; **24**:4099−105.
122. Xu W, Li X, Lin N, Zhang X, Huang X, Wu T, et al. Pharmacokinetics and tissue distribution of five major triterpenoids after oral administration of Rhizoma Alismatis extract to rats using ultra high-performance liquid chromatography-tandem mass spectrometry. *J Pharm Biomed Anal* 2017;**146**:314−23.
123. Kanno Y, Yatsu T, Yamashita N, Zhao S, Li W, Imai M, et al. Alisol B 23-acetate from the rhizomes of Alisma orientale is a natural agonist of the human pregnane X receptor. *Phytomedicine* 2017;**26**: 22−7.
124. Meng Q, Chen X, Wang C, Liu Q, Sun H, Sun P, et al. Alisol B 23-acetate promotes liver regeneration in mice after partial hepatectomy *via* activating farnesoid X receptor. *Biochem Pharmacol* 2014;**92**: 289−98.
125. Huang Y, Zheng SL, Xu ZS, Hou Y. Effects of Alismatis rhizome on rat cytochrome P450 enzymes. *Pharm Biol* 2014;**52**:681−7.
126. Koyama M, Shirahata T, Hirashima R, Kobayashi Y, Itoh T, Fujiwara R. Inhibition of UDP-glucuronosyltransferase (UGT)-mediated glycyrrhetinic acid 3-*O*-glucuronidation by polyphenols and triterpenoids. *Drug Metabol Pharmacokinet* 2017;**32**:218−23.
127. Xu X, Li L, Zhang Y, Lu X, Lin W, Wu S, et al. Hypolipidemic effect of *Alisma orientale* (Sam.) Juzep on gut microecology and liver transcriptome in diabetic rats. *PLoS One* 2020;**15**:e0240616.
128. Xing YM, Yin WQ, Liu MM, Wang CL, Guo SX. Oxalic acid and sclerotial differentiation of. *Polyporus umbellatus. Sci Rep* 2015;**5**: 10759.
129. Kwon PS, Oh H, Kwon SJ, Jin W, Zhang F, Fraser K, et al. Sulfated polysaccharides effectively inhibit SARS-CoV-2. *in vitro. Cell Discov* 2020;**6**:50.
130. Zhao YY. Traditional uses, phytochemistry, pharmacology, pharmacokinetics and quality control of *Polyporus umbellatus* (Pers.) Fries: a review. *J Ethnopharmacol* 2013;**149**:35−48.
131. Zhao YY, Qin XY, Cheng XL, Liu XY, Lin RC, Zhang Y, et al. Rapid resolution liquid chromatography-mass spectrometry and high-performance liquid chromatography-fluorescence detection for metabolism and pharmacokinetic studies of ergosta-4,6,8(14),22-tetraen-3-one. *Anal Chim Acta* 2010;**675**:199−206.
132. Zhao YY, Cheng XL, Liu R, Ho CC, Wei F, Yan SH, et al. Pharmacokinetics of ergosterol in rats using rapid resolution liquid chromatography-atmospheric pressure chemical ionization multi-stage tandem mass spectrometry and rapid resolution liquid chromatography/tandem mass spectrometry. *J Chromatogr, B: Anal Technol Biomed Life Sci* 2011;**879**:1945−53.
133. Du JL, Liu YJ, Cao LP, Jia R, Wang JH, Yin GJ. Effects of polyporus polysaccharides on biochemical indexes and CYP3A expression of carbon tetrachloride injured primary hepatocytes of Jiancarp. *J Huazhong Agric Univ* 2014;**33**:78−83.
134. Yang L, Yu H, Hou A, Man W, Wang S, Zhang J, et al. A review of the ethnopharmacology, phytochemistry, pharmacology, application, quality control, processing, toxicology, and pharmacokinetics of the dried rhizome of Atractylodes macrocephala. *Front Pharmacol* 2021; **12**:727154.
135. Sun Y, Yang AWH, Hung A, Lenon GB. Screening for a potential therapeutic agent from the herbal formula in the 4th edition of the Chinese National Guidelines for the initial-stage management of COVID-19 *via* molecular docking. *Evid Based Complement Alternat Med* 2020;**2020**:3219840.
136. Zhu B, Zhang QL, Hua JW, Cheng WL, Qin LP. The traditional uses, phytochemistry, and pharmacology of *Atractylodes macrocephala* Koidz.: a review. *J Ethnopharmacol* 2018;**226**:143−67.
137. Tsuji A, Tamai I. Carrier-mediated intestinal transport of drugs. *Pharm Res (N Y)* 1996;**13**:963−77.
138. Chen XL, Liao ZG, Li C, Huang GY, Song YY, Dong W, et al. Interaction between Atractylenolide II and CYP450 in human liver microsomes. *J Chin Pharmaceut Sci* 2021;**30**:645−56.

139. Deng M, Chen H, Long J, Song J, Xie L, Li X. Atractylenolides (I, II, and III): a review of their pharmacology and pharmacokinetics. *Arch Pharm Res (Seoul)* 2021;**44**:633−54.
140. Yu C, Chai X, Yu L, Chen S, Zeng S. Identification of novel pregnane X receptor activators from traditional Chinese medicines. *J Ethnopharmacol* 2011;**136**:137−43.
141. Zhang Q, Cao YF, Ran RX, Li RS, Wu X, Dong PP, et al. Strong specific inhibition of UDP-glucuronosyltransferase 2B7 by Atractylenolide I and III. *Phytother Res* 2016;**30**:25−30.
142. Ren Y, Jiang W, Luo C, Zhang X, Huang M. Atractylenolide III ameliorates TNBS-induced intestinal inflammation in mice by reducing oxidative stress and regulating intestinal flora. *Chem Biodivers* 2021;**18**:e2001001.
143. Nie A, Chao Y, Zhang X, Jia W, Zhou Z, Zhu C. Phytochemistry and pharmacological activities of wolfiporia cocos (F. A. Wolf) Ryvarden & Gilb. *Front Pharmacol* 2020;**11**:505249.
144. Wu Z, Chen X, Ni W, Zhou D, Chai S, Ye W, et al. The inhibition of Mpro, the primary protease of COVID-19, by *Poria cocos* and its active compounds: a network pharmacology and molecular docking study. *RSC Adv* 2021;**11**:11821−43.
145. Li Q, Ming Y, Jia H, Wang G. Poricoic acid A suppresses TGF-beta1-induced renal fibrosis and proliferation *via* the PDGF-C, Smad3 and MAPK pathways. *Exp Ther Med* 2021;**21**:289.
146. Jiang YH, Zhang Y, Wang YY, Zhang WX, Wang MW, Liu CQ, et al. Extracts of *Poria cocos* polysaccharides improves alcoholic liver disease in mice *via* CYP2E1 and NF-κB inflammatory pathways. *China J Chin Mater Med* 2022;**47**:134−40.
147. Zhang ZQ, Zhang GC, Ruan PP, Lin Y, Tan HL, Xiao CR, Ma ZC, Wang YG, Gao Y. Activating effect of effective components in medicinal and edible substances on human pregnane X receptor and cytotoxicity screening. *Chin J Exp Tradit Med Formulae* 2022;**28**:42−51.
148. Dong HY, Shao JW, Chen JF, Wang T, Lin FP, Guo YH. Transcriptional regulation of cytochrome P450 3A4 by four kinds of traditional Chinese medicines. *China J Chin Mater Med* 2008;**33**:1014−7. 89.
149. Cheng Y, Xie Y, Ge JC, Wang L, Peng DY, Yu NJ, et al. Structural characterization and hepatoprotective activity of a galactoglucan from Poria cocos. *Carbohydr Polym* 2021;**263**:117979.
150. Li Y, Li X, Lu Y, Chaurasiya B, Mi G, Shi D, et al. Co-delivery of *Poria cocos* extract and doxorubicin as an 'all-in-one' nanocarrier to combat breast cancer multidrug resistance during chemot herapy. *Nanomedicine* 2019;**23**:102095.
151. He S, Zhang QL, Xiao FJ, Lu YX, Cheng XC, Han Y. Reversal of multidrug resistance of KBV200 cells by triterpenoids isol ated from Poria cocos. *Planta Med* 2012;**78**:428−33.
152. Liu JS, Liu L, Zhang GW, Peng XC. *Poria cocos* polysaccharides attenuate chronic nonbacterial prostatitis by targeting the gut microbiota: comparative study of *Poria cocos* polysaccharides and finasteride in treating chronic prostatitis. *Int J Biol Macromol* 2021;**189**:346−55.
153. Zou YT, Zhou J, Wu CY, Zhang W, Shen H, Xu JD, et al. Protective effects of *Poria cocos* and its components against cisplatin-induced intestinal injury. *J Ethnopharmacol* 2021;**269**:113722.
154. Tan YY, Yue SR, Lu AP, Zhang L, Ji G, Liu BC, et al. The improvement of nonalcoholic steatohepatitis by *Poria cocos* polysac charides associated with gut microbiota and NF-κB/CCL3/CCR1 axis. *Phytomedicine* 2022;**103**:154208.
155. Yang F, Dong X, Yin X, Wang W, You L, Ni J. Radix Bupleuri: a review of traditional uses, botany, phytochemistry, pharmacology, and toxicology. *BioMed Res Int* 2017;**2017**:7597596.
156. Tian RT, Xie PS, Liu HP. Evaluation of traditional Chinese herbal medicine: chaihu (Bupleuri Radix) by both high-performance liquid chromatographic and high-performance thin-layer chromatographic fingerprint and chemometric analysis. *J Chromatogr A* 2009;**1216**:2150−5.
157. Huang HQ, Zhang X, Xu ZX, Su J, Yan SK, Zhang WD. Fast determination of saikosaponins in *Bupleurum* by rapid resolution liquid chromatography with evaporative light scattering detection. *J Pharm Biomed Anal* 2009;**49**:1048−55.
158. Bahbah EI, Negida A, Nabet MS. Purposing saikosaponins for the treatment of COVID-19. *Med Hypotheses* 2020;**140**:109782.
159. Yu T, Chen X, Wang Y, Zhao R, Mao S. Modulatory effects of extracts of vinegar-baked Bupleuri Radix and saikosaponins on the activity of cytochrome P450 enzymes in vitro. *Xenobiotica* 2014;**44**:861−7.
160. Feng L, Liu L, Zhao Y, Zhao R. Saikosaponins A, C and D enhance liver-targeting effects of anticancer drugs by modulating drug transporters. *Oncotarget* 2017;**8**:110092−102.
161. Liu QW, Xue YW, Liu JJ, Ren SQ, Xu JN, Yang JN, Xing YY, Zhang ZJ, Song Rui. Saikosaponins and the deglycosylated metabolites exert liver meridian guiding effect through PXR/CYP3A4 inhibition. *J Ethnopharmacol* 2021;**279**:114344.
162. Liu G, Tian Y, Li G, Xu L, Song R, Zhang Z. Metabolism of saikosaponin a in rats: diverse oxidations on the aglycone moiety in liver and intestine in addition to hydrolysis of glycosidic bonds. *Drug Metab Dispos* 2013;**41**:622−33.
163. Li PZ, Wu MN, Xiong WC, Li JS, An YY, Ren J, Xie YG, Xue HF, Yan D, Li M, Zhong GS. Saikosaponin-d ameliorates dextran sulfate sodium-induced colitis by suppressing NF-κB activation and modulating the gut microbiota in mice. *Int Immunopharm* 2020;**81**:106288.
164. Li J, Han JF, Lv J, Wang SJ, Qu L, Jiang YF. Saikosaponin A-induced gut microbiota changes attenuate severe acute pancreatitis through the activation of Keap1/Nrf2-ARE antioxidant signaling. *Oxid Med Cell Longev* 2020;**2020**:9217219.
165. Tang C, Fu Q, Chen X, Hu Y, Renaud H, Ma C, et al. The biotransformation of Bupleuri Radix by human gut microbiota. *Xenobiotica* 2020;**50**:1011−22.
166. Shimizu K, Amagaya S, Ogihara Y. Structural transformation of saikosaponins by gastric juice and intestinal flora. *J Pharmacobio-Dyn* 1985;**8**:718−25.
167. Hu QC, Zhang WW, Wu Z, Tian X, Xiang JB, Li LX, et al. Baicalin and the liver-gut system: pharmacological bases explaining its therapeutic effects. *Pharmacol Res* 2021;**165**:105444.
168. Zhao T, Tang H, Xie L, Zheng Y, Ma Z, Sun Q, et al. Scutellaria baicalensis Georgi. (Lamiaceae): a review of its traditional uses, botany, phytochemistry, pharmacology and toxicology. *J Pharm Pharmacol* 2019;**71**:1353−69.
169. Ji S, Li R, Wang Q, Miao WJ, Li ZW, Si LL, et al. Anti-H1N1 virus, cytotoxic and Nrf2 activation activities of chemical constituents from Scutellaria baicalensis. *J Ethnopharmacol* 2015;**176**:475−84.
170. Zandi K, Musall K, Oo A, Cao D, Liang B, Hassandarvish P, et al. Baicalein and baicalin inhibit SARS-CoV-2 RNA-dependent-RNA polymerase. *Microorganisms* 2021;**9**:893.
171. Talbi A, Zhao D, Liu Q, Li J, Fan A, Yang W, et al. Pharmacokinetics, tissue distribution, excretion and plasma protein binding studies of wogonin in rats. *Molecules* 2014;**19**:5538−49.
172. Li C, Lin G, Zuo Z. Pharmacological effects and pharmacokinetics properties of Radix Scutellariae and its bioactive flavones. *Biopharm Drug Dispos* 2011;**32**:427−45.
173. Noh K, Kang Y, Nepal MR, Jeong KS, Oh DG, Kang MJ, et al. Role of intestinal microbiota in baicalin-induced drug interaction and its pharmacokinetics. *Molecules* 2016;**21**:337.
174. Akao T, Sakashita Y, Hanada M, Goto H, Shimada Y, Terasawa K. Enteric excretion of baicalein, a flavone of Scutellariae Radix, *via* glucuronidation in rat: involvement of multidrug resistance-associated protein 2. *Pharm Res (N Y)* 2004;**21**:2120−6.
175. Yi S, Cho JY, Lim KS, Kim KP, Kim J, Kim BH, et al. Effects of Angelicae tenuissima radix, Angelicae dahuricae radix and Scutellariae radix extracts on cytochrome P450 activities in healthy volunteers. *Basic Clin Pharmacol Toxicol* 2009;**105**:249−56.
176. Kim JY, Lee S, Kim DH, Kim BR, Park R, Lee BM. Effects of flavonoids isolated from Scutellariae radix on cytochrome P-450 activities in human liver microsomes. *J Toxicol Environ Health* 2002;**65**:373−81.

177. Lan F, Haitang X, Zhi L, Dongli H, Dong G, Guo W. Effects of baicalin on CYP3A4,CYP2C9 and CYP2C19 expressions in chang liver cells. *China J Mod Med* 2009;**19**:3546−50.
178. Shao YX, Zhao P, Li Z, Liu M, Liu P, Huang M, et al. The molecular basis for the inhibition of human cytochrome P450 1A2 by oroxylin and wogonin. *Eur Biophys J* 2012;**41**:297−306.
179. Miao Q, Wang Z, Zhang Y, Miao P, Zhao Y, Zhang Y, et al. *In vitro* potential modulation of baicalin and baicalein on P-glycoprotein activity and expression in Caco-2 cells and rat gut sacs. *Pharm Biol* 2016;**54**:1548−56.
180. Yim S, You BH, Chae HS, Chin YW, Kim H, Choi HS, et al. Multidrug and toxin extrusion protein 1-mediated interaction of metformin and Scutellariae radix in rats. *Xenobiotica* 2017;**47**:998−1007.
181. Ren G, Qin Z, Yang N, Chen H, Fu K, Lu C, et al. Interactions between Oroxylin A with the solute carrier transporters and ATP-binding cassette transporters: drug transporters profile for this flavonoid. *Chem Biol Interact* 2020;**324**:109097.
182. Chang CF, Chang YC, Lin JT, Yu CW, Kao YT. Evaluation of inhibitors of intestinal UDP-glucuronosyltransferases 1A 8 and 1A10 using raloxifene as a substrate in Caco-2 cells: studies wi th four flavonoids of *Scutellaria baicalensis*. *Toxicol Vitro* 2021;**72**:105087.
183. Cui L, Guan X, Ding W, Luo Y, Wang W, Bu W, et al. *Scutellaria baicalensis* Georgi polysaccharide ameliorates DSS-induced ulcerative colitis by improving intestinal barrier function and modula ting gut microbiota. *Int J Biol Macromol* 2021;**166**:1035−45.
184. Peng LY, Shi HT, Tan YR, Shen SY, Yi PF, Shen HQ, et al. Baicalin inhibits APEC-induced lung injury by regulating gut microbiot a and SCFA production. *Food Funct* 2021;**12**:12621−33.
185. Zhang X, Cai Y, Wang L, Liu H, Wang X. Optimization of processing technology of Rhizoma Pinelliae Praeparatum and its antitumor effect. *Afr Health Sci* 2015;**15**:101−6.
186. Bai J, Qi J, Yang L, Wang Z, Wang R, Shi Y. A comprehensive review on ethnopharmacological, phytochemical, pharmacological and toxicological evaluation, and quality control of Pinellia ternata (Thunb.) Breit. *J Ethnopharmacol* 2022;**298**:115650.
187. Tang X, Zhao H, Jiang W, Zhang S, Guo S, Gao X, et al. Pharmacokinetics and pharmacodynamics of citrus peel extract in lipopolysaccharide-induced acute lung injury combined with Pinelliae Rhizoma Praeparatum. *Food Funct* 2018;**9**:5880−90.
188. Sharma S, Sharma A, Bhattacharyya D, Chauhan RS. Computational identification of potential inhibitory compounds in Indian medicinal and aromatic plant species against major pathogenicity determinants of SARS-CoV-2. *J Biomol Struct Dyn* 2021;**40**:140961. 14114.
189. Salen G, Ahrens Jr EH, Grundy SM. Metabolism of beta-sitosterol in man. *J Clin Invest* 1970;**49**:952−67.
190. Su T, Tan Y, Tsui MS, Yi H, Fu XQ, Li T, et al. Metabolomics reveals the mechanisms for the cardiotoxicity of Pinelliae Rhizoma and the toxicity-reducing effect of processing. *Sci Rep* 2016;**6**:34692.
191. Wu J, Cheng Z, He S, Shi J, Liu S, Zhang G, et al. Pinelliae rhizoma, a toxic Chinese herb, can significantly inhibit CYP3A activity in rats. *Molecules* 2015;**20**:792−806.
192. Haniadka R, Saldanha E, Sunita V, Palatty PL, Fayad R, Baliga MS. A review of the gastroprotective effects of ginger (Zingiber officinal e Roscoe). *Food Funct* 2013;**4**:845−55.
193. Li X, Ao MY, Zhang CL, Fan SM, Chen ZM, Yu LY. Zingiberis Rhizoma Recens: a review of its traditional uses, phytochemistry, pharmacology, and toxicology. *Evid Based Complement Alternat Med* 2021;**2021**:6668990.
194. Li LL, Cui Y, Guo XH, Ma K, Tian P, Feng J, et al. Pharmacokinetics and tissue distribution of gingerols and shogaols from ginger (*Zingiber officinale* Rosc.) in rats by UPLC−Q-Exactive−HRMS. *Molecules* 2019;**24**:512.
195. Hong MK, Hu LL, Zhang YX, Xu YL, Liu XY, He PK, et al. 6-Gingerol ameliorates sepsis-induced liver injury through the Nrf2 pathway. *Int Immunopharm* 2020;**80**:106196.
196. Unuofin JO, Masuku NP, Paimo OK, Lebelo SL. Ginger from farmyard to town: nutritional and pharmacological applications. *Front Pharmacol* 2021;**12**:779352.
197. Zick SM, Djuric Z, Ruffin MT, Litzinger AJ, Normolle DP, Alrawi S, et al. Pharmacokinetics of 6-gingerol, 8-gingerol, 10-gingerol, and 6-shogaol and conjugate metabolites in healthy human subjects. *Cancer Epidemiol Biomarkers Prev* 2008;**17**:1930−6.
198. Ding GH, Naora K, Hayashibara M, Katagiri Y, Kano Y, Iwamoto K. Pharmacokinetics of [6]-gingerol after intravenous administration in rats. *Chem Pharm Bull (Tokyo)* 1991;**39**:1612−4.
199. Naora K, Ding G, Hayashibara M, Katagiri Y, Kano Y, Iwamoto K. Pharmacokinetics of [6]-gingerol after intravenous administration in rats with acute renal or hepatic failure. *Chem Pharm Bull (Tokyo)* 1992;**40**:1295−8.
200. Nakazawa T, Ohsawa K. Metabolism of [6]-gingerol in rats. *Life Sci* 2002;**70**:2165−75.
201. Kim IS, Kim SY, Yoo HH. Effects of an aqueous-ethanolic extract of ginger on cytochrome P450 enzyme-mediated drug metabolism. *Pharmazie* 2012;**67**:1007−9.
202. Yoshida K, Satsu H, Mikubo A, Ogiwara H, Yakabe T, Inakuma T, et al. 6-Shogaol, a major compound in ginger, induces aryl hydrocarbon recept or-mediated transcriptional activity and gene expression. *J Agric Food Chem* 2014;**62**:5492−9.
203. Li M, Chen PZ, Yue QX, Li JQ, Chu RA, Zhang W, Wang H. Pungent ginger components modulates human cytochrome P450 enzymes *in vitro*. *Acta Pharmacol Sin* 2013;**34**:1237−42.
204. Husain Islam AZ, Amar G, Khan Ikhlas A, Noonan Gregory O, Khan Shabana I. *Modulation of PXR activity by ginger and its constituents*. Available from: https://www.fda.gov/science-research/fda-science-forum/modulation-pxr-activity-ginger-and-its-constituents.
205. Zhang W, Lim LY. Effects of spice constituents on P-glycoprotein-mediated transport and CYP3A4-mediated metabolism *in vitro*. *Drug Metab Dispos* 2008;**36**:1283−90.
206. Liu JP, Wang J, Zhou SX, Huang DC, Qi GH, Chen GT. Ginger polysaccharides enhance intestinal immunity by modulating gut microbiota in cyclophosphamide-induced immunosuppressed mice. *Int J Biol Macromol* 2022;**223**:1308−19.
207. Rho J, Seo CS, Park HS, Jeong HY, Moon OS, Seo YW, et al. Asteris Radix et Rhizoma suppresses testosterone-induced benign prostatic hyperplasia in rats by regulating apoptosis and inflammation. *J Ethnopharmacol* 2020;**255**:112779.
208. Yin DF, Zhou K, Liu JT, Hu L, Liu Y, Deng J, et al. Development and validation of an LC/MS/MS method for simultaneous determination of shionone and epi-friedelinol in rat plasma for pharmacokinetic study after oral administration of Aster tataricus extract. *Biomed Chromatogr* 2016;**30**:1112−7.
209. Zhao Y, Chen Y, Chen X, Qiao L, Zhang J, Cai L, et al. Discovery of cytochrome P450 enzymes-inhibiting components in traditional Chinese medicine. *China J Chin Mater Med* 2020;**45**:923−31.
210. Tian Y, Jiang Y, Wang Y, Liu H, Shan J, Liu Y. The excretion of shionone in rats by RP-HPLC method. *Anim Husb Vet Med* 2015;**47**:81−4.
211. Tian Y, Qi H, Zheng X, Wang Q, Zhang L. Determination of protein binding rates of shionone by HPLC. *Chin J Pharm* 2008;**39**:838−41.
212. Li Y, Liao Z, Wei X, Xiao X, Hu J. Epifriedelanol enhances adriamycin-induced cytotoxicity towards K562/ADM cells by down regulating of P-gp and MRP2. *Xenobiotica* 2022;**52**:389−96.
213. Liu C, Wu H, Wang L, Luo H, Lu Y, Zhang Q, et al. Farfarae Flos: a review of botany, traditional uses, phytochemistry, pharmacology, and toxicology. *J Ethnopharmacol* 2020;**260**:113038.
214. Fan J, Qin X, Li Z. Mechanism of Farfarae flos in Qingfei Paidu decoction against COVID-19 based on network pharmacology and molecular docking. *Chin Tradit Herb Drugs* 2020;**51**:2317−25.
215. Liu YF, Yang XW, Lu W, Xin XL. Determination and pharmacokinetic study of tussilagone in rat plasma by RP-HPLC method. *Biomed Chromatogr* 2008;**22**:1194−200.
216. Zhang XS, Ren W, Bian BL, Zhao HY, Wang S. Comparative metabolism of tussilagone in rat and human liver microsomes using ultra-high-performance liquid chromatography coupled with high-resolution LTQ-Orbitrap mass spectrometry. *Rapid Commun Mass Spectrom* 2015;**29**:1641−50.

217. Wang J, Wang H, Peng Y, Wang GJ, Hao HP. Isochlorogenic acid A affects P450 and UGT enzymes *in vitro* and *in vivo*. *Chin J Nat Medicines* 2016;**14**:865−70.
218. Pang C, Sheng YC, Jiang P, Wei H, Ji LL. Chlorogenic acid prevents acetaminophen-induced liver injury: the involvement of CYP450 metabolic enzymes and some antioxidant signals. *J Zhejiang Univ - Sci B* 2015;**16**:602−10.
219. Tomas-Barberan F, García-Villalba R, Quartieri A, Raimondi S, Amaretti A, Leonardi A, et al. *In vitro* transformation of chlorogenic acid by human gut microbiota. *Mol Nutr Food Res* 2014;**58**: 1122−31.
220. Shi A, Li T, Zheng Y, Song Y, Wang H, Wang N, et al. Chlorogenic acid improves NAFLD by regulating gut microbiota and GLP-1. *Front Pharmacol* 2021;**12**:693048.
221. Yang L, Yu S, Qin X, Li Z. Analysis of inter-individual variability of antitussive effect of Farfarae Flos and its fecal metabolites based on gut microbiota. *J Pharm Biomed Anal* 2022;**217**:114836.
222. Woźniak D, Matkowski A. Belamcandae chinensis rhizome−a review of phytochemistry and bioactivity. *Fitoterapia* 2015;**107**:1−14.
223. Zhang WD, Yang WJ, Wang XJ, Gu Y, Wang R. Simultaneous determination of tectorigenin, irigenin and irisflorentin in rat plasma and urine by UHPLC−MS/MS: application to pharmacokinetics. *J Chromatogr, B: Anal Technol Biomed Life Sci* 2011;**879**:3735−41.
224. Qu J, Gao J, Sun J, Zhang L, Makino T, Yuan D. Pharmacokinetics of conjugated metabolites in rat plasma after oral administration of tectoridin. *J Chromatogr, B: Anal Technol Biomed Life Sci* 2012;**902**:61−9.
225. Zhang X, Qiao GX, Zhao GF, Zhao SF. Characterization of the metabolites of irisflorentin by using ultra-high performance liquid chromatography combined with quadrupole/orbitrap tandem mass spectrometry. *J Pharm Biomed Anal* 2021;**203**:114222.
226. Zhang Q, Wang G, Kang Y, You X, Zou G, Xia L, et al. Study on effect of effective components of isoflavones from Belamcandae Rhizoma on liver drug enzyme. *Liaoning J Tradit Chin Med* 2019;**46**: 796−9.
227. Hu T, Ge X, Wang J, Zhang N, Diao X, Hu L, et al. Metabolite identification of iridin in rats by using UHPLC−MS/MS and pharmacokinetic study of its metabolite irigenin. *J Chromatogr, B: Anal Technol Biomed Life Sci* 2021;**1181**:122914.
228. Li J, Xu Z, Gu J. UGT1A1 and UGT1A9 are responsible for phase II metabolism of tectorigenin and irigenin *in vitro*. *Molecules* 2022;**27**: 4104.
229. Li C, Xu F, Cao C, Shang MY, Zhang CY, Yu J, et al. Comparative analysis of two species of Asari Radix et Rhizoma by electronic nose, headspace GC−MS and chemometrics. *J Pharm Biomed Anal* 2013; **85**:231−8.
230. Kumar A, Mishra DC, Angadi UB, Yadav R, Rai A, Kumar D. Inhibition potencies of phytochemicals derived from sesame against SARS-CoV-2 main protease: a molecular docking and simulation study. *Front Chem* 2021;**9**:744376.
231. Lakhera S, Devlal K, Ghosh A, Rana M. *In silico* investigation of phytoconstituents of medicinal herb 'Piper Longum' against SARS-CoV-2 by molecular docking and molecular dynamics analysis. *Results Chem* 2021:100199.
232. Tomimori N, Rogi T, Shibata H. Absorption, distribution, metabolism, and excretion of [^{14}C]sesamin in rats. *Mol Nutr Food Res* 2017;**61**:1600844.
233. Sakaki T, Yasuda K, Nishikawa M, Ikushiro S. Metabolism of sesamin and drug−sesamin interaction. *Yakugaku Zasshi* 2018;**138**: 357−63.
234. Lim YP, Ma CY, Liu CL, Lin YH, Hu ML, Chen JJ, et al. Sesamin: a naturally occurring lignan inhibits CYP3A4 by antagonizing the pregnane X receptor activation. *Evid Based Complement Alternat Med* 2012;**2012**:242810.
235. Okura T, Ibe M, Umegaki K, Shinozuka K, Yamada S. Effects of dietary ingredients on function and expression of P-glycoprotein in human intestinal epithelial cells. *Biol Pharm Bull* 2010;**33**:255−9.
236. Yu Q, Chen H, Ju H, Shen R, Kou X, Yang A. Molecular docking of volatile oily constituents of Chinese herbal medicine Asari Radix et Rhizoma and CYP1A2 Enzyme. *Chin J Exp Tradit Med Formulae* 2020;**26**:202−7.
237. Yang AH, Zhang L, Zhi DX, Liu WL, Gao X, He X. Identification and analysis of the reactive metabolites related to the hepatotoxicity of safrole. *Xenobiotica* 2018;**48**:1164−72.
238. Yang AH, He X, Chen JX, He LN, Jin CH, Wang LL, et al. Identification and characterization of reactive metabolites in myristicin-mediated mechanism-based inhibition of CYP1A2. *Chem Biol Interact* 2015;**237**:133−40.
239. Wang M, Liu P, Kong L, Xu N, Lei H. Promotive effects of sesamin on proliferation and adhesion of intestinal probiotics and its mechanism of action. *Food Chem Toxicol* 2021;**149**:112049.
240. Shi Z, Deng Z, Peng X, Tian Y. Study on the pharmacodynamic effect of Rhizoma Dioscoreae polysaccharides on cerebral ischemia-reperfusion injury in rats and the possible mechanism. *J Ethnopharmacol* 2022;**296**:115517.
241. Zhang L, Wang M. Optimization of deep eutectic solvent-based ultrasound-assisted extraction of polysaccharides from *Dioscorea opposita* Thunb. *Int J Biol Macromol* 2017;**95**:675−81.
242. Chen H, Hu Z, Liu D, Li C, Liu S. Composition and physicochemical properties of three Chinese Yam (*Dioscorea opposita* Thunb.) starches: a comparison study. *Molecules* 2019;**24**:2973.
243. Sun Y, Liu T, Si Y, Cao B, Zhang Y, Zheng X, et al. Integrated metabolomics and 16S rRNA sequencing to investigate the regulation of Chinese yam on antibiotic-induced intestinal dysbiosis in rats. *Artif Cell Nanomed Biotechnol* 2019;**47**:3382−90.
244. Xu Z, Liu W, Zhang Y, Zhang D, Qiu B, Wang X, et al. Therapeutic and prebiotic effects of five different native starches on dextran sulfate sodium-induced mice model of colonic colitis. *Mol Nutr Food Res* 2021;**65**:e2000922.
245. Li P, Zeng SL, Duan L, Ma XD, Dou LL, Wang LJ, et al. Comparison of Aurantii Fructus Immaturus and Aurantii Fructus based on multiple chromatographic analysis and chemometrics methods. *J Chromatogr A* 2016;**1469**:96−107.
246. Guo X, Cao X, Fang X, Guo A, Li E. Involvement of phase II enzymes and efflux transporters in the metabolism and absorption of naringin, hesperidin and their aglycones in rats. *Int J Food Sci Nutr* 2022;**73**:480−90.
247. Mandery K, Balk B, Bujok K, Schmidt I, Fromm MF, Glaeser H. Inhibition of hepatic uptake transporters by flavonoids. *Eur J Pharmaceut Sci* 2012;**46**:79−85.
248. Glaeser H, Bujok K, Schmidt I, Fromm MF, Mandery K. Organic anion transporting polypeptides and organic cation transporter 1 contribute to the cellular uptake of the flavonoid quercetin. *Naunyn-Schmiedeberg's Arch Pharmacol* 2014;**387**:883−91.
249. Shirasaka Y, Kuraoka E, Spahn-Langguth H, Nakanishi T, Langguth P, Tamai I. Species difference in the effect of grapefruit juice on intestinal absorption of talinolol between human and rat. *J Pharmacol Exp Therapeut* 2010;**332**:181−9.
250. Androutsopoulos VP, Papakyriakou A, Vourloumis D, Tsatsakis AM, Spandidos DA. Dietary flavonoids in cancer therapy and prevention: substrates and inhibitors of cytochrome P450 CYP1 enzymes. *Pharmacol Ther* 2010;**126**:9−20.
251. Okada N, Murakami A, Urushizaki S, Matsuda M, Kawazoe K, Ishizawa K. Extracts of immature orange (Aurantii fructus immaturus) and Citrus unshiu peel (Citri unshiu pericarpium) induce P-glycoprotein and cytochrome P450 3A4 expression *via* upregulation of pregnane X receptor. *Front Pharmacol* 2017;**8**:84.
252. Liu D, Wu J, Xie H, Liu M, Takau I, Zhang H, et al. Inhibitory effect of hesperetin and naringenin on human UDP-glucuronosyltransferase enzymes: implications for herb−drug interactions. *Biol Pharm Bull* 2016;**39**:2052−9.
253. Yeum CH, Choi JS. Effect of naringin pretreatment on bioavailability of verapamil in rabbits. *Arch Pharm Res (Seoul)* 2006;**29**: 102−7.
254. Lim SC, Choi JS. Effects of naringin on the pharmacokinetics of intravenous paclitaxel in rats. *Biopharm Drug Dispos* 2006;**27**: 443−7.

255. Liu XY, Fan ML, Wang HY, Yu BY, Liu JH. Metabolic profile and underlying improved bio-activity of Fructus aurantii immaturus by human intestinal bacteria. *Food Funct* 2017;**8**:2193−201.
256. Yu X, Sun S, Guo Y, Liu Y, Yang D, Li G, et al. Citri Reticulatae Pericarpium (Chenpi): botany, ethnopharmacology, phytochemistry, and pharmacology of a frequently used traditional Chinese medicine. *J Ethnopharmacol* 2018;**220**:265−82.
257. Breinholt VM, Rasmussen SE, Brøsen K, Friedberg TH. *In vitro* metabolism of genistein and tangeretin by human and murine cytochrome P450s. *Pharmacol Toxicol* 2003;**93**:14−22.
258. Lei J, Xue Y, Liu YM, Liao X. Characterization of major metabolites of polymethoxylated flavonoids in Pericarpium Citri Reticulatae using liver microsomes immobilized on magnetic nanoparticles coupled with UPLC/MS-MS. *Chem Cent J* 2017;**11**:13.
259. Roohbakhsh A, Parhiz H, Soltani F, Rezaee R, Iranshahi M. Neuropharmacological properties and pharmacokinetics of the citrus flavonoids hesperidin and hesperetin−a mini-review. *Life Sci* 2014;**113**:1−6.
260. Doostdar H, Burke MD, Mayer RT. Bioflavonoids: selective substrates and inhibitors for cytochrome P450 CYP1A and CYP1B1. *Toxicology* 2000;**144**:31−8.
261. Bajraktari-Sylejmani G, Weiss J. Potential risk of food-drug interactions: citrus polymethoxyflavones and flavanones as inhibitors of the organic anion transporting polypeptides (OATP) 1B1, 1B3, and 2B1. *Eur J Drug Metab Pharmacokinet* 2020;**45**:809−15.
262. Satsu H, Hiura Y, Mochizuki K, Hamada M, Shimizu M. Activation of pregnane X receptor and induction of MDR1 by dietary phytochemicals. *J Agric Food Chem* 2008;**56**:5366−73.
263. Weiss J, Gattuso G, Barreca D, Haefeli WE. Nobiletin, sinensetin, and tangeretin are the main perpetrators in clementines provoking food−drug interactions *in vitro*. *Food Chem* 2020;**319**:126578.
264. Surichan S, Androutsopoulos VP, Sifakis S, Koutala E, Tsatsakis A, Arroo RR, et al. Bioactivation of the citrus flavonoid nobiletin by CYP1 enzymes in MCF7 breast adenocarcinoma cells. *Food Chem Toxicol* 2012;**50**:3320−8.
265. Zheng Y, Zeng X, Chen P, Chen T, Peng W, Su W. Integrating pharmacology and gut microbiota analysis to explore the mechanism of Citri Reticulatae Pericarpium against reserpine-induced spleen deficiency in rats. *Front Pharmacol* 2020;**11**:586350.
266. Xu F, Cai W, Ma T, Zeng H, Kuang X, Chen W, et al. Traditional uses, phytochemistry, pharmacology, quality control, industrial application, pharmacokinetics and network pharmacology of Pogostemon cablin: a comprehensive review. *Am J Chin Med* 2022;**50**:691−721.
267. Zrieq R, Ahmad I, Snoussi M, Noumi E, Iriti M, Algahtani FD, et al. Tomatidine and patchouli alcohol as inhibitors of SARS-CoV-2 enzymes (3CLpro, PLpro and NSP15) by molecular docking and molecular dynamics simulations. *Int J Mol Sci* 2021;**22**:10693.
268. Yan P, Peng C, Zhang L, Zhang R. Transmembrane transport mechanism of patchouli alcohol in MDCK cell model. *Chin J New Drugs Clin Remedies* 2017;**36**:24−9.
269. Zhang G, Zhang Y, Ma X, Yang X, Cai Y, Yin W. Pogostone inhibits the activity of CYP3A4, 2C9, and 2E1 *in vitro*. *Pharm Biol* 2021;**59**:532−6.
270. Leong W, Huang G, Khan I, Xia W, Li Y, Liu Y, et al. Patchouli essential oil and its derived compounds revealed prebiotic-like effects in C57BL/6J mice. *Front Pharmacol* 2019;**10**:1229.
271. Huang K, Zhang P, Zhang Z, Youn JY, Wang C, Zhang H, et al. Traditional Chinese medicine (TCM) in the treatment of COVID-19 and other viral infections: efficacies and mechanisms. *Pharmacol Ther* 2021;**225**:107843.
272. Nair MS, Huang Y, Fidock DA, Polyak SJ, Wagoner J, Towler MJ, et al. *Artemisia annua* L. extracts inhibit the *in vitro* replication of SARS-CoV-2 and two of its variants. *J Ethnopharmacol* 2021;**274**:114016.
273. Pan X, Dong L, Yang L, Chen D, Peng C. Potential drugs for the treatment of the novel coronavirus pneumonia (COVID-19) in China. *Virus Res* 2020;**286**:198057.
274. Xiong WZ, Wang G, Du J, Ai W. Efficacy of herbal medicine (Xuanfei Baidu decoction) combined with conventional drug in treating COVID-19:A pilot randomized clinical trial. *Integr Med Res* 2020;**9**:100489.
275. Wang H, Song HX, Wang DF, Ma XR, Zhou DX, Miao JX, et al. Potential mechanism of Xuanfei Baidu Formula intreating new coronavirus pneumonia based on network pharmacology and molecular docking. *J Hainan Med Univ* 2020;**26**:1361−72.
276. Ma L, Zhao X, Liu T, Wang Y, Wang J, Kong L, et al. Xuanfei Baidu decoction attenuates intestinal disorders by modulating NF-κB pathway, regulating T cell immunity and improving intestinal flora. *Phytomedicine* 2022;**101**:154100.
277. Zhu R, Xu X, Shan Q, Wang K, Cao G, Wu X. Determination of differentiating markers in coicis semen from multi-sources based on structural similarity classification coupled with UPCC-Xevo G2-XS QTOF. *Front Pharmacol* 2020;**11**:549181.
278. Du X, Ye H, Zhang C, Ye L, Lin G. Effect of kanglaite on rat cytochrome P450. *Pharm Biol* 2015;**53**:995−1001.
279. Yao HT, Lin JH, Chiang MT, Chiang W, Luo MN, Lii CK. Suppressive effect of the ethanolic extract of adlay bran on cytochrome P-450 enzymes in rat liver and lungs. *J Agric Food Chem* 2011;**59**:4306−14.
280. Zhang W, Jia X, Xu Y, Xie Q, Zhu M, Zhang H, et al. Effects of coix seed extract, bifidobacterium BPL1, and their combination on the glycolipid metabolism in obese mice. *Front Nutr* 2022;**9**:939423.
281. Deng AP, Li Y, Wu ZT, Liu T, Kang LP, Nan TG, et al. Advances in studies on chemical compositions of *Atractylodes lancea* and their biological activities. *China J Chin Mater Med* 2016;**41**:3904−13.
282. Kulma I, Panrit L, Plengsuriyakarn T, Chaijaroenkul W, Warathumpitak S, Na-Bangchang K. A randomized placebo-controlled phase I clinical trial to evaluate the immunomodulatory activities of *Atractylodes lancea* (Thunb) DC. in healthy Thai subjects. *BMC Complement Med* 2021;**21**:61.
283. Chang XW, Liu YQ, Cai Q. Fingerprints of raw and processed Atractylodis rhizoma by HPLC. *Chin J Exp Tradit Med Formulae* 2015;**21**:40−3.
284. Chang XW, Xu CX, Liu YQ, Cai Q. Determination and pharmacokinetic comparisons of atractylodin after oral administration of crude and processed Atractylodis Rhizoma. *Phcog Mag* 2016;**12**:80−3.
285. Muhamad N, Plengsuriyakarn T, Na-Bangchang K. Atractylodes lancea for cholangiocarcinoma: modulatory effects on CYP1A2 and CYP3A1 and pharmacokinetics in rats and biodistribution in mice. *PLoS One* 2022;**14**:e0277614.
286. Xu HM, Zhang XY, Wang DJ, Wang K, Sui DJ, Wang D, et al. Effect of atractyloside a on the expression of major CYP450 Subtypes in mice. *Chin Tradit Pat Med* 2017;**39**:398−401.
287. Xu J, Liu C, Shi K, Sun X, Song C, Xu K, et al. Atractyloside-A ameliorates spleen deficiency diarrhea by interfering with TLR4/MyD88/NF-κB signaling activation and regulating intestinal flora homeostasis. *Int Immunopharm* 2022;**107**:108679.
288. Pang J, Ma S, Xu X, Zhang B, Cai Q. Effects of rhizome of atractylodes koreana (Nakai) kitam on intestinal flora and metabolites in rats with rheumatoid arthritis. *J Ethnopharmacol* 2021;**281**:114026.
289. Efferth T. From ancient herb to modern drug: *Artemisia annua* and artemisinin for cancer therapy. *Semin Cancer Biol* 2017;**46**:65−83.
290. Fuzimoto AD. An overview of the anti-SARS-CoV-2 properties of artemisia annua, its antiviral action, protein-associated mechanisms, and repurposing for COVID-19 treatment. *J Integr Med* 2021;**19**:375−88.
291. Yang BF, Luo DL, Bao LH, Zhang YC, Wang HZ. Artemisinin blocks activating and slowly activating K^+ current in Guinea pig ventricular myocytes. *Acta Pharm Sin* 1998;**19**:269−72.
292. Mohyeldin MM, Tarbah AFS, El NM, Ghazy NM, Amr EH. Comparative anti-herpes simplex virus type 1 and chemical profiling of thymus capitatus and artemisia herba-alba collected from North Africa. *Nat Prod Res* 2023:1−4.
293. Kane NF, Kiani BH, Desrosiers MR, Towler MJ, Weathers PJ. Artemisia extracts differ from artemisinin effects on human hepatic CYP450s 2B6 and 3A4 *in vitro*. *J Ethnopharmacol* 2022;**298**:115587.

294. Medhi B, Patyar S, Rao RS, Byrav DSP, Prakash A. Pharmacokinetic and toxicological profile of artemisinin compounds: an update. *Pharmacology* 2009;**84**:323−32.
295. Hu WH, Chan GK, Lou JS, Wu QY, Wang HY, Duan R, et al. The extract of Polygoni Cuspidati Rhizoma et Radix suppresses the vascular endothelial growth factor-induced angiogenesis. *Phytomedicine* 2018;**42**:135−43.
296. Han JH, Koh W, Lee HJ, Lee HJ, Lee EO, Lee SJ, et al. Analgesic and anti-inflammatory effects of ethyl acetate fraction of *Polygonum cuspidatum* in experimental animals. *Immunopharmacol Immunotoxicol* 2012;**34**:191−5.
297. Liu S, Zhang R, Zhang X, Zhu S, Liu S, Yang J, et al. The invasive species reynoutria japonica houtt. as a promising natural agent for cardiovascular and digestive system illness. *Front Pharmacol* 2022;**13**:863707.
298. Ji SB, Park SY, Bae S, Seo HJ, Kim SE, Lee GM, et al. Comprehensive investigation of stereoselective food drug interaction potential of resveratrol on nine P450 and six UGT isoforms in human liver microsomes. *Pharmaceutics* 2021;**13**:1419.
299. Chaplin A, Carpéné C, Mercader J. Resveratrol, metabolic syndrome, and gut microbiota. *Nutrients* 2018;**10**:1651.
300. Li J, Liu Y, Zhang J, Yu X, Wang X, Zhao L. Effects of resveratrol on P-glycoprotein and cytochrome P450 3A *in vitro* and on pharmacokinetics of oral saquinavir in rats. *Drug Des Dev Ther* 2016;**10**:3699−706.
301. Jia Y, Liu Z, Wang C, Meng Q, Huo X, Liu Q, et al. P-gp, MRP2 and OAT1/OAT3 mediate the drug−drug interaction between resveratrol and methotrexate. *Toxicol Appl Pharmacol* 2016;**306**:27−35.
302. Poór M, Kaci H, Bodnárová S, Mohos V, Fliszár-Nyúl E, Kunsági-Máté S, et al. Interactions of resveratrol and its metabolites (resveratrol-3-sulfate, resveratrol-3-glucuronide, and dihydroresveratrol) with serum albumin, cytochrome P450 enzymes, and OATP transporters. *Biomed Pharmacother* 2022;**151**:113136.
303. Bird JK, Raederstorff D, Weber P, Steinert RE. Cardiovascular and antiobesity effects of resveratrol mediated through the gut microbiota. *Adv Nutr* 2017;**8**:839−49.
304. Luo S, He J, Huang S, Wang X, Su Y, Li Y, et al. Emodin targeting the colonic metabolism *via* PPARγ alleviates UC by inhibiting facultative anaerobe. *Phytomedicine* 2022;**104**:154106.
305. Dou Z, Rong X, Zhao E, Zhang L, Lv Y. Neuroprotection of resveratrol against focal cerebral ischemia/reperfusion injury in mice through a mechanism targeting gut-brain axis. *Cell Mol Neurobiol* 2019;**39**:883−98.
306. Casanova E, García-Mina JM, Calvo MI. Antioxidant and antifungal activity of *Verbena officinalis* L. leaves. *Plant Foods Hum Nutr (Dordr)* 2008;**63**:93−7.
307. Speroni E, Cervellati R, Costa S, Guerra MC, Utan A, Govoni P, et al. Effects of differential extraction of *Verbena officinalis* on rat models of inflammation, cicatrization and gastric damage. *Planta Med* 2007;**73**:227−35.
308. Müller A, Ganzera M, Stuppner HJC. Analysis of the aerial parts of *Verbena officinalis* L. by micellar electrokinetic capillary chromatography. *Chromatographia* 2004;**60**:193−7.
309. Miyazawa M, Sugie A, Shimada T. Roles of human CYP2A6 and 2B6 and rat CYP2C11 and 2B1 in the 10-hydroxylation of (−)-verbenone by liver microsomes. *Drug Metab Dispos* 2003;**31**:1049−53.
310. Kim NS, Shin S, Shin GG, Bang OS. Genotoxicity evaluation of a Phragmitis rhizoma extract using a standard battery of *in vitro* and *in vivo* assays. *J Ethnopharmacol* 2019;**241**:112025.
311. Cao LH, Zhao YY, Miao JX, Bai M, Kang L, Miao MS, et al. Effect of fresh Phragmitis Rhizoma on airway inflammation in chronic bronchitis based on TGF-β signaling pathway. *China J Chin Mater Med* 2021;**46**:5887−94.
312. Zhou XD, Tang LY, Zhou GH, Kou ZZ, Wang T, Wang ZJ. Advances on lepidii semen and Descurainiae semen. *China J Chin Mater Med* 2014;**39**:4699−708.
313. Kim BY, Lee J, Park SJ, Bang OS, Kim NS. Gene Expression profile of the A549 human non-small cell lung carcinoma cell line following treatment with the seeds of descurainia sophia, a potential anticancer drug. *Evid Based Compl Alt* 2013;**2013**:584604.
314. Zhang J, Zhou N, Wang Y, Liu T, Cao Y, Feng W, Zheng X. Protective effects of *Descurainia sophia* seeds extract and its fractions on pulmonary edema by untargeted urine and serum metabolomics strategy. *Front Pharmacol* 2023;**14**:1080962.
315. Lee JH, Lee JE, Kim Y, Lee H, Jun HJ, Lee SJ. Multidrug and toxic compound extrusion protein-1 (MATE1/SLC47A1) is a novel flavonoid transporter. *J Agric Food Chem* 2014;**62**:9690−8.
316. Shabbir U, Rubab M, Daliri EB, Chelliah R, Javed A, Oh DH. Curcumin, quercetin, catechins and metabolic diseases: the role of gut microbiota. *Nutrients* 2021;**13**:206.
317. Yim SK, Kim K, Chun S, Oh T, Jung W, Jung K, et al. Screening of human CYP1A2 and CYP3A4 inhibitors from seaweed *in silico* and in vitro. *Mar Drugs* 2020;**18**:603.
318. Batiha GE, Beshbishy AM, Ikram M, Mulla ZS, El-Hack MEA, Taha AE, et al. The pharmacological activity, biochemical properties, and pharmacokinetics of the major natural polyphenolic flavonoid: quercetin. *Foods* 2020;**9**:374.
319. Wang M, Qi H, Li J, Xu Y, Zhang H. Transmembrane transport of steviol glucuronide and its potential interaction with selected drugs and natural compounds. *Food Chem Toxicol* 2015;**86**:217−24.
320. Mohos V, Fliszár-Nyúl E, Ungvári O, Kuffa K, Needs PW, Kroon PA, et al. Inhibitory effects of quercetin and its main methyl, sulfate, and glucuronic acid conjugates on cytochrome P450 enzymes, and on OATP, BCRP and MRP2 transporters. *Nutrients* 2020;**12**:2036.
321. Jiang K, Song Q, Wang L, Xie T, Wu X, Wang P, et al. Antitussive, expectorant and anti-inflammatory activities of different extracts from Exocarpium Citri grandis. *J Ethnopharmacol* 2014;**156**:97−101.
322. Liu G, Li S, Zhang N, Wei N, Wang M, Liu J, et al. Sequential grade evaluation method exploration of Exocarpium Citri Grandis (Huajuhong) decoction pieces based on "network prediction → grading quantization → efficacy validation". *J Ethnopharmacol* 2022;**291**:115149.
323. Li ML, Huang CY, Chen SH, Lee CN, Yao HT. Citrus depressa Hayata peel ameliorates nonalcoholic fatty liver and modulates the activity of hepatic drug-metabolizing enzymes and transporters in rats fed a high-fat diet. *Food Funct* 2022;**13**:3353−67.
324. Zeng X, Zheng Y, He Y, Zhang J, Peng W, Su W. Microbial metabolism of naringin and the impact on antioxidant capacity. *Nutrients* 2022;**14**:3765.
325. Moon YJ, Wang X, Morris ME. Dietary flavonoids: effects on xenobiotic and carcinogen metabolism. *Toxicol Vitro* 2006;**20**:187−210.
326. Sama V, Pagilla B, Chiluka R, Alvala R, Pola RK, Mullangi R. Bioenhancing effects of naringin on atorvastatin. *Admet Dmpk* 2019;**7**:174−82.
327. Araki N, Morita T, Akiyoshi T, Kataoka H, Yajima K, Katayama K, et al. Comparison of the inhibitory properties of the fruit component naringenin and its glycosides against OATP1A2 genetic variants. *Drug Metabol Pharmacokinet* 2022;**46**:100464.
328. Schäfer AM, Meyer Zu Schwabedissen HE, Bien-Möller S, Hubeny A, Vogelgesang S, Oswald S, et al. OATP1A2 and OATP2B1 are interacting with dopamine-receptor agonists and antagonists. *Mol Pharm* 2020;**17**:1987−95.
329. Hu H, Zhang S, Liu F, Zhang P, Muhammad Z, Pan S. Role of the gut microbiota and their metabolites in modulating the cholesterol-lowering effects of citrus pectin oligosaccharides in C57BL/6 mice. *J Agric Food Chem* 2019;**67**:11922−30.
330. Hu M, Zhang L, Ruan Z, Han P, Yu Y. The Regulatory effects of citrus peel powder on liver metabolites and gut flora in mice with non-alcoholic fatty liver disease (NAFLD). *Foods* 2021;**10**:3022.
331. Han L, Wang Y, Hu K, Tang Z, Song X. The therapeutic efficacy of huashi baidu formula combined with antiviral drugs in the treatment

of COVID-19: a protocol for systematic review and meta-analysis. *Medicine* 2020;**99**:e22715.
332. Cai Y, Zeng M, Chen YZ. The pharmacological mechanism of huashi baidu formula for the treatment of COVID-19 by combined network pharmacology and molecular docking. *Ann Palliat Med* 2021;**10**: 3864−95.
333. Tao Q, Du J, Li X, Zeng J, Tan B, Xu J, et al. Network pharmacology and molecular docking analysis on molecular targets and mechanisms of huashi baidu formula in the treatment of COVID-19. *Drug Dev Ind Pharm* 2020;**46**:1345−53.
334. Liu J, Yang W, Liu Y, Lu C, Ruan L, Zhao C, et al. Combination of hua shi Bai du granule (Q-14) and standard care in the treatment of patients with coronavirus disease 2019 (COVID-19): a single-center, open-label, randomized controlled trial. *Phytomedicine* 2021;**91**: 153671.
335. Kim JY, Kim KH, Kwag EH, Seol YJ, Lee YM, Ku Y, et al. Magnoliae Cortex and maize modulate porphyromonas gingivalis-induced inflammatory reactions. *J Periodontal Implant Sci* 2018; **48**:70−83.
336. Yin Y, Peng F, Zhou L, Yin X, Chen J, Zhong H, et al. The chromosome-scale genome of *Magnolia officinalis* provides insight into the evolutionary position of magnoliids. *iScience* 2021;**24**: 102997.
337. Xu T, Meng JR, Cheng W, Liu JZ, Chu J, Zhang Q, et al. Discovery of honokiol thioethers containing 1,3,4-oxadiazole moieties as potential alpha-glucosidase and SARS-CoV-2 entry inhibitors. *Bioorg Med Chem* 2022;**67**:116838.
338. Guo Y, Meng JR, Liu JZ, Xu T, Zheng ZY, Jiang ZH, et al. Synthesis and biological evaluation of honokiol derivatives bearing 3-((5-phenyl-1,3,4-oxadiazol-2-yl)methyl)oxazol-2(3*H*)-ones as potential viral entry inhibitors against SARS-CoV-2. *Pharmaceuticals* 2021; **14**:885.
339. Niu L, Hou Y, Jiang M, Bai G. The rich pharmacological activities of magnolia officinalis and secondary effects based on significant intestinal contributions. *J Ethnopharmacol* 2021;**281**:114524.
340. Tian H, Zhao L, Zhang Q, Zhang Y, Mao X, Wang J, et al. The therapeutic effects of magnolia officinalis extraction on an antibiotics-induced intestinal dysbacteriosis in mice. *Curr Microbiol* 2020;**77**:2413−21.
341. Kim SB, Kang HE, Cho HJ, Kim YS, Chung SJ, Yoon IS, et al. Metabolic interactions of magnolol with cytochrome P450 enzymes: uncompetitive inhibition of CYP1A and competitive inhibition of CYP2C. *Drug Dev Ind Pharm* 2016;**42**:263−9.
342. Wang J, Zhai T, Chen Y. Effects of honokiol on CYP450 activity and transporter mRNA expression in type 2 diabetic rats. *Int J Mol Sci* 2018;**19**:815.
343. Han HK, Van Anh LT. Modulation of p-glycoprotein expression by honokiol, magnolol and 4-*O*-methylhonokiol, the bioactive components of Magnolia officinalis. *Anticancer Res* 2012;**32**:4445−52.
344. Yu CP, Li PY, Chen SY, Lin SP, Hou YC. Magnolol and honokiol inhibited the function and expression of BCRP with mechanism exploration. *Molecules* 2021;**26**:739.
345. Yang S, Xue Y, Chen D, Wang Z. Amomum tsao-ko Crevost & Lemarié: a comprehensive review on traditional uses, botany, phytochemistry, and pharmacology. *Phytochemistry Rev* 2022;**21**: 1487−521.
346. Dong SY. Professor wang qi's network pharmacology discussion on the mechanism of COVID-19 prevention formula to prevent novel coronavirus pneumonia. *World Sci Technol Mod Tradit Chin Med Mater Med* 2021;**23**:1063−75.
347. Liu JZ, Lyu HC, Fu YJ, Cui Q. Amomum tsao-ko essential oil, a novel anti-COVID-19 Omicron spike protein natural products: a computational study. *Arab J Chem* 2022;**15**:103916.
348. Meng MR. Effect of protocatechuic acid on the expression of membrane transporter mRNA in hepG2.2.15 cells and rat primary hepatocytes. *Chin J Tradit Chin Med Pharm* 2011;**26**:2555−8.
349. Wang Z, Wu WD, Ci XY, Cui T, Zhang HB, Li YZ, et al. The role of organic anion transporters 1 and 3 in transmembrane transport of traditional Chinese medicine components with different pharmacological properties. *Chin J Clin Pharmacol* 2019;**35**:372−6.
350. Zhang XY, Xu HM, Wang DJ, Wang K, Sui DJ, Wei Y. Effects of protocatechuic acid and protocatechuic aldehyde on the expression of cytochrome P450 in mouse liver. *Chin Wild Plant Resource* 2017;**36**: 18−21+25.
351. Xie HC, Shang J. Study on the extraction process of total anthraquinones in Radix et Rhizoma Rhei and their antilipemic effects. *Afr J Tradit, Complementary Altern Med* 2014;**11**:358−62.
352. Ren X, Shao XX, Li XX, Jia XH, Song T, Zhou WY, et al. Identifying potential treatments of COVID-19 from traditional Chinese medicine (TCM) by using a data-driven approach. *J Ethnopharmacol* 2020;**258**:112932.
353. Qi JH, Dong FX, Wang K, Zhang SY, Liu ZM, Wang WJ, et al. Feasibility analysis and mechanism exploration of Rhei Radix et Rhizome-Schisandrae Sphenantherae Fructus (RS) against COVID-19. *J Med Microbiol* 2022;**71**:10.
354. Zhuang T, Gu X, Zhou N, Ding L, Yang L, Zhou M. Hepatoprotection and hepatotoxicity of Chinese herb Rhubarb (Dahuang): how to properly control the "general (jiang jun)" in Chinese medical herb. *Biomed Pharmacother* 2020;**127**:110224.
355. Wu J, Wei Z, Cheng P, Qian C, Xu F, Yang Y, et al. Rhein modulates host purine metabolism in intestine through gut microbiota and ameliorates experimental colitis. *Theranostics* 2020;**10**:10665−79.
356. Zhu YQ, Yan F, Di B, Yan J, Li JC, Li YM. The inhibitory effect of emodin on doxorubicin resistance in K562/ADM cells. *J China Pharm Univ* 2014;**45**:462−8.
357. Yokooji T, Kida M, Mori M, Akashi H, Mori N, Yoshihara S, et al. Interaction of Rhei Rhizoma extract with cytochrome P450 3A and efflux transporters in rats. *Pharmazie* 2010;**65**:367−74.
358. Zhang Y, Zhang M, Hu G, Zhang Z, Song R. Elevated system exposures of baicalin after combinatory oral administration of rhein and baicalin: mainly related to breast cancer resistance protein (ABCG2), not UDP-glucuronosyltransferases. *J Ethnopharmacol* 2020;**250**: 112528.
359. Zhu Y, Jin H, Huo X, Meng Q, Wang C, Sun P, et al. Protective effect of Rhein against vancomycin-induced nephrotoxicity through regulating renal transporters and Nrf2 pathway. *Phytother Res* 2022;**36**: 4244−62.
360. Guo Z, Lou Y, Kong M, Luo Q, Liu Z, Wu J. A systematic review of phytochemistry, pharmacology and pharmacokinetics on Astragali Radix: implications for Astragali Radix as a personalized medicine. *Int J Mol Sci* 2019;**20**:1463.
361. Zhang RP, Zhang XP, Ruan YF, Ye SY, Zhao HC, Cheng QH, et al. Protective effect of Radix Astragali injection on immune organs of rats with obstructive jaundice and its mechanism. *World J Gastroenterol* 2009;**15**:2862−9.
362. Liu H, Ye F, Sun Q, Liang H, Li C, Li S, et al. Scutellaria baicalensis extract and baicalein inhibit replication of SARS-CoV-2 and its 3C-like protease in vitro. *J Enzym Inhib Med Chem* 2021;**36**: 497−503.
363. You J, Li H, Fan P, Yang X, Wei Y, Zheng L, et al. Inspiration for COVID-19 treatment: network analysis and experimental validation of baicalin for cytokine Storm. *Front Pharmacol* 2022;**13**:853496.
364. Liu Y, Cai C, Qin X. Regulation of gut microbiota of Astragali Radix in treating for chronic atrophic gastritis rats based on metabolomics coupled with 16S rRNA gene sequencing. *Chem Biol Interact* 2022; **365**:110063.
365. Zhang G, Ou R, Li F, Wu J, Zheng L, Tong Y, et al. Regulation of drug-metabolizing enzymes and efflux transporters by Astragali radix decoction and its main bioactive compounds: implication for clinical drug−drug interactions. *J Ethnopharmacol* 2016;**180**:104−13.
366. Lou Y, Guo Z, Zhu Y, Zhang G, Wang Y, Qi X, et al. Astragali radix and its main bioactive compounds activate the Nrf2-mediated signaling pathway to induce P-glycoprotein and breast cancer resistance protein. *J Ethnopharmacol* 2019;**228**:82−91.
367. Lu Z, Ye Y, Liu Y, Yang X, Ding Q, Wang Y, et al. Aqueous extract of Paeoniae Radix Rubra prevents deep vein thrombosis by

ameliorating inflammation through inhibiting GSK3beta activity. *Phytomedicine* 2021;**92**:153767.
368. Deng QK. Exploring the mechanism of Radix Paeoniae Rubra in treating COVID-19 with coagulation dysfunction based on network pharmacology. *Acad J Guangzhou Med Univ* 2021;**49**:6−12.
369. He DY, Dai SM. Anti-inflammatory and immunomodulatory effects of paeonia lactiflora pall., a traditional Chinese herbal medicine. *Front Pharmacol* 2011;**2**:10.
370. Xu JJ, Xu F, Wang W, Wang PP, Xian J, Han X, et al. Paeoniae Radix Rubra can enhance fatty acid beta-oxidation and alleviate gut microbiota disorder in alpha-naphthyl isothiocyanate induced cholestatic model rats. *Front Pharmacol* 2022;**13**:1002922.
371. Ohta H, Ni JW, Matsumoto K, Watanabe H, Shimizu M. Peony and its major constituent, paeoniflorin, improve radial maze performance impaired by scopolamine in rats. *Pharmacol Biochem Behav* 1993;**45**:719−23.
372. Gao LN, Zhang Y, Cui YL, Akinyi OM. Comparison of paeoniflorin and albiflorin on human CYP3A4 and CYP2D6. *Evid Based Complement Alternat Med* 2015;**2015**:470219.
373. Shen C, Shen B, Zhu J, Wang J, Yuan H, Li X. Glycyrrhizic acid-based self-assembled micelles for improving oral bioavailability of paeoniflorin. *Drug Dev Ind Pharm* 2021;**47**:207−14.
374. Yang Z, Liu Y, Wang L, Lin S, Dai X, Yan H, et al. Traditional Chinese medicine against COVID-19: role of the gut microbiota. *Biomed Pharmacother* 2022;**149**:112787.
375. Zhuang W, Fan Z, Chu Y, Wang H, Yang Y, Wu L, et al. Chinese patent medicines in the treatment of coronavirus disease 2019 (COVID-19) in China. *Front Pharmacol* 2020;**11**:1066.
376. Zhu Y, Han Q, Wang L, Wang B, Chen J, Cai B, et al. Jinhua qinggan granules attenuates acute lung injury by promotion of neutrophil apoptosis and inhibition of TLR4/MyD88/NF-κB pathway. *J Ethnopharmacol* 2023;**301**:115763.
377. Shang X, Pan H, Li M, Miao X, Ding H. Lonicera japonica thunb.: ethnopharmacology, phytochemistry and pharmacology of an important traditional Chinese medicine. *J Ethnopharmacol* 2011;**138**:1−21.
378. Lee YR, Chang CM, Yeh YC, Huang CF, Lin FM, Huang JT, et al. Honeysuckle aqueous extracts induced let-7a suppress EV71 replication and pathogenesis *in vitro* and *in vivo* and is predicted to inhibit SARS-CoV-2. *Viruses* 2021;**13**:308.
379. Gu L, Xie X, Wang B, Jin Y, Wang L, Yin G, et al. Chemical pattern recognition for quality analysis of Lonicerae Japonicae Flos and Lonicerae Flos based on ultra-high performance liquid chromatography and anti-SARS-CoV2 main protease activity. *Front Pharmacol* 2021;**12**:810748.
380. Zhou W, Shan J, Wang S, Cai B, Di L. Transepithelial transport of phenolic acids in Flos Lonicerae Japonicae in intestinal caco-2 cell monolayers. *Food Funct* 2015;**6**:3072−80.
381. Tu MP. The effect of honeysuckle on CYP3A enzyme activity and gene expression in rats. *J Chengdu Med Coll* 2020;**15**:204−207+31.
382. Ye X, Liu Y, Hu J, Gao Y, Ma Y, Wen D. Chlorogenic acid-induced gut microbiota improves metabolic endotoxemia. *Front Endocrinol* 2021;**12**:762691.
383. Xu W, Sun SH, Liu T, Ma M, Sui ZG. Study on the inhibitory effect of honeysuckle extract and its main components on the activity of drug metabolizing enzyme CYP3A4. *Chin J Rational Drug Use* 2012;**9**:3−5+15.
384. Han SY, Chae HS, You BH, Chin YW, Kim H, Choi HS, et al. Lonicera japonica extract increases metformin distribution in the liver without change of systemic exposed metformin in rats. *J Ethnopharmacol* 2019;**238**:111892.
385. Piao XL, Cho EJ, Jang MH, Cui J. Cytoprotective effect of lignans from Forsythia suspensa against peroxynitrite-induced LLC-PK1 cell damage. *Phytother Res* 2009;**23**:938−42.
386. Yan X, Chen T, Zhang L, Du H. Protective effects of Forsythoside A on amyloid beta-induced apoptosis in PC12 cells by downregulating acetylcholinesterase. *Eur J Pharmacol* 2017;**810**:141−8.
387. Fu Y, Pan F, Zhao L, Zhao S, Yi J, Cai S. Interfering effects on the bioactivities of several key proteins of COVID-19/variants in diabetes by compounds from Lianqiao leaves: *in silico* and *in vitro* analyses. *Int J Biol Macromol* 2022;**207**:715−29.
388. Ma Q, Li R, Pan W, Huang W, Liu B, Xie Y, et al. Phillyrin (KD-1) exerts anti-viral and anti-inflammatory activities against novel coronavirus (SARS-CoV-2) and human coronavirus 229E (HCoV-229E) by suppressing the nuclear factor kappa B (NF-κB) signaling pathway. *Phytomedicine* 2020;**78**:153296.
389. Cheng Y, Liang X, Feng L, Liu D, Qin M, Liu S, et al. Effects of phillyrin and forsythoside A on rat cytochrome P450 activities *in vivo* and. *in vitro*. *Xenobiotica* 2017;**47**:297−303.
390. Hu N, Guo C, Dai X, Wang C, Gong L, Yu L, et al. Forsythiae Fructuse water extract attenuates liver fibrosis *via* TLR4/MyD88/NF-kappaB and TGF-beta/smads signaling pathways. *J Ethnopharmacol* 2020;**262**:113275.
391. Wei JB, Yang GY, Chen H, Ye F, Zhang CN, Du SM, et al. Research progress in extraction method, pharmacology, toxicology and pharmacokinetics of forsythin. *China Pharm* 2015;**18**:2144−8.
392. Wang C, Ma C, Fu K, Liu Y, Gong L, Peng C, et al. Hepatoprotective effect of phillygenin on carbon tetrachloride-induced liver fibrosis and its effects on short chain fatty acid and bile acid metabolism. *J Ethnopharmacol* 2022;**296**:115478.
393. Wu X, Chan SW, Ma J, Li P, Shaw PC, Lin G. Investigation of association of chemical profiles with the tracheobronchial relaxant activity of Chinese medicinal herb Beimu derived from various Fritillaria species. *J Ethnopharmacol* 2018;**210**:39−46.
394. Wei CB, Chen J, Zhang QY, Shi YH, Lin L, Zheng HY, et al. A new potyvirus from Thunberg fritillary (Fritillaria thunbergii Miq.) in Zhejiang, China. *Arch Virol* 2005;**150**:1271−80.
395. Wang WJ, Chen Y, Su WC, Liu YY, Shen WJ, Chang WC, et al. Peimine inhibits variants of SARS-CoV-2 cell entry *via* blocking the interaction between viral spike protein and ACE2. *J Food Biochem* 2022;**46**:e14354.
396. Liu W, Wei L, Kanai Y, He X. Studies on the incompatibility between bulbus Fritillariae and radix aconiti Praeparata based on the p-gp. *Evid Based Complement Alternat Med* 2021;**2021**:8351717.
397. Li M, Liu X, Wang Y, Ju X. In vitro effects of peimine on the activity of cytochrome P450 enzymes. *Xenobiotica* 2020;**50**:1202−7.
398. Chen L, Lu X, Liang X, Hong D, Guan Z, Guan Y, et al. Mechanistic studies of the transport of peimine in the Caco-2 cell model. *Acta Pharm Sin B* 2016;**6**:125−31.
399. Xia YG, Wang TL, Sun HM, Liang J, Kuang HX. Gas chromatography-mass spectrometry-based trimethylsilyl-alditol derivatives for quantitation and fingerprint analysis of Anemarrhena asphodeloides Bunge polysaccharides. *Carbohydr Polym* 2018;**198**:155−63.
400. Kim BR, Cho YC, Le HTT, Vuong HL, Lee S, Cho S. Suppression of inflammation by the rhizome of *Anemarrhena asphodeloides via* regulation of nuclear factor-kappaB and p38 signal transduction pathways in macrophages. *Biomed Rep* 2017;**6**:691−7.
401. Yan D, Fan P, Sun W, Ding Q, Zheng W, Xiao W, et al. *Anemarrhena asphodeloides* modulates gut microbiota and restores pancreatic function in diabetic rats. *Biomed Pharmacother* 2021;**133**:110954.
402. Lin N, Liu B, Zhang J, Long Y, Dong G, Jin H, et al. Acute toxicity, 28-day repeated-dose toxicity and toxicokinetic study of timosaponin BII in rats. *Regul Toxicol Pharmacol* 2017;**90**:244−57.
403. Chen JR, Jia XH, Wang H, Yi YJ, Wang JY, Li YJ. Timosaponin A-III reverses multi-drug resistance in human chronic myelogenous leukemia K562/ADM cells *via* downregulation of MDR1 and MRP1 expression by inhibiting PI3K/Akt signaling pathway. *Int J Oncol* 2016;**48**:2063−70.
404. Skowronska W, Granica S, Dziedzic M, Kurkowiak J, Ziaja M, Bazylko A. Arctium Lappa and Arctium Tomentosum, sources of Arctii radix: comparison of anti-lipoxygenase and antioxidant activity as well as the chemical composition of extracts from aerial parts and from roots. *Plants* 2021;**10**:78.
405. Su S, Cheng X, Wink M. Natural lignans from Arctium lappa modulate P-glycoprotein efflux function in multidrug resistant cancer cells. *Phytomedicine* 2015;**22**:301−7.

406. Zhang H, Zhao Z, Wang T, Wang Y, Cui X, Zhang H, et al. Inhibition of UDP-glucuronosyltransferase (UGT) isoforms by Arctiin and arctigenin. *Phytother Res* 2016;**30**:1189−96.
407. Xin H, Xia YL, Hou J, Wang P, He W, Yang L, et al. Identification and characterization of human UDP-glucuronosyltransferases responsible for the *in-vitro* glucuronidation of arctigenin. *J Pharm Pharmacol* 2015;**67**:1673−81.
408. Wu X, Zhang N, Kan J, Tang S, Sun R, Wang Z, et al. Polyphenols from Arctium lappa L ameliorate doxorubicin-induced heart failure and improve gut microbiota composition in mice. *J Food Biochem* 2022;**46**:e13731.
409. Xu DB, Ma YN, Qin TF, Tang WL, Qi XW, Wang X, et al. Transcriptome-wide identification and characterization of the JAZ gene family in *Mentha canadensis* L. *Int J Mol Sci* 2021;**22**:8859.
410. Jan JT, Cheng TR, Juang YP, Ma HH, Wu YT, Yang WB, et al. Identification of existing pharmaceuticals and herbal medicines as inhibitors of SARS-CoV-2 infection. *Proc Natl Acad Sci U S A* 2021;**118**:e2021579118.
411. Yang B, Du S, Lu Y, Jia S, Zhao MD, Bai J, et al. Influence of paeoniflorin and menthol on puerarin transport across MDCK and MDCK-MDR1 cells as blood−brain barrier *in vitro* model. *J Pharm Pharmacol* 2018;**70**:349−60.
412. Fang C, Chen G, Kan J. Characterization and *in vitro* simulated gastrointestinal digestion and fermentation of *Mentha haplocalyx* polysaccharide. *Int J Biol Macromol* 2022;**222**:360−72.
413. Wang CH, Zhong Y, Zhang Y, Liu JP, Wang YF, Jia WN, et al. A network analysis of the Chinese medicine Lianhua-Qingwen formula to identify its main effective components. *Mol Biosyst* 2016;**12**:606−13.
414. Jin YH, Zhan QY, Peng ZY, Ren XQ, Yin XT, Cai L, et al. Chemoprophylaxis, diagnosis, treatments, and discharge management of COVID-19: an evidence-based clinical practice guideline (updated version). *Mil Med Res* 2020;**7**:41.
415. Hu K, Guan WJ, Bi Y, Zhang W, Li L, Zhang B, et al. Efficacy and safety of Lianhuaqingwen capsules, a repurposed Chinese herb, in patients with coronavirus disease 2019: a multicenter, prospective, randomized controlled trial. *Phytomedicine* 2021;**85**:153242.
416. Wagner KC, Byrd GD. Evaluating the effectiveness of clinical medical librarian programs: a systematic review of the literature. *J Med Libr Assoc* 2012;**100**:J.
417. Zhang X, Gao R, Zhou Z, Tang X, Lin J, Wang L, et al. A network pharmacology based approach for predicting active ingredients and potential mechanism of Lianhuaqingwen capsule in treating COVID-19. *Int J Med Sci* 2021;**18**:1866−76.
418. Li RF, Hou YL, Huang JC, Pan WQ, Ma QH, Shi YX, et al. Lianhuaqingwen exerts anti-viral and anti-inflammatory activity against novel coronavirus (SARS-CoV-2). *Pharmacol Res* 2020;**156**:104761.
419. Ding Y, Zeng L, Li R, Chen Q, Zhou B, Chen Q, et al. The Chinese prescription lianhuaqingwen capsule exerts anti-influenza activity through the inhibition of viral propagation and impacts immune function. *BMC Compl Alternative Med* 2017;**17**:130.
420. Jin YH, Jeon S, Lee J, Kim S, Jang MS, Park CM, et al. Anti-coronaviral activity of the natural phloroglucinols, Dryocrassin ABBA and Filixic acid ABA from the rhizome of by targeting the main protease of SARS-CoV-2. *Pharmaceutics* 2022;**14**:376.
421. Wei YL, Du HJ, Lin YP, Wu ML, Xu RA. Effects of salidroside on rat CYP enzymes by a cocktail of probe drugs. *Iran J Basic Med Sci* 2018;**21**:422−6.
422. Kumagai T, Aratsu Y, Sugawara R, Sasaki T, Miyairi S, Nagata K. Indirubin, a component of Ban-Lan-Gen, activates CYP3A4 gene transcription through the human pregnane X receptor. *Drug Metabol Pharmacokinet* 2016;**31**:139−45.
423. Kang H, Koppula S. Houttuynia cordata alleviates high-fat diet-induced non-alcoholic fatty liver in experimental rats. *Pharm Biol* 2015;**53**:414−22.
424. Zhou W, Zhang XY. Research progress of Chinese herbal medicine Radix isatidis (banlangen). *Am J Chin Med* 2013;**41**:743−64.
425. Yu B, Lin F, Ning H, Ling B. Network pharmacology study on the mechanism of the Chinese medicine Radix Isatidis (Banlangen) for COVID-19. *Medicine (Baltim)* 2021;**100**:e26881.
426. Li J, Shi Y, Xu Y, Yang L, Wang Z, Han H, et al. Metabolic profiles and pharmacokinetics of goitrin in rats through liquid chromatography combined with electrospray ionization-tandem mass spectrometry. *Biomed Chromatogr* 2019;**33**:e4606.
427. Peng J, Li X, Zheng L, Duan L, Gao Z, Hu D, et al. Ban-Lan-Gen granule alleviates dextran sulfate sodium-induced chronic relapsing colitis in mice *via* regulating gut microbiota and restoring gut SCFA derived-GLP-1 production. *J Inflamm Res* 2022;**15**:1457−70.
428. Yuk HJ, Kim JY, Sung YY, Kim DS. Phloroglucinol derivatives from as potent xanthine oxidase inhibitors. *Molecules* 2020;**26**:122.
429. Ren Y, Yao MC, Huo XQ, et al. Study on treatment of "cytokine storm" by anti-2019-nCoV prescriptions based on arachidonic acid metabolic pathway. *China J Chin Mater Med* 2020;**45**:1225−31.
430. Jia YY, Zhao JT, Han XY, Li SS. Research progress on chemical compositionand pharmacological activities of Dryopteridis Crassirhizomatis Rhizoma. *Asia-Pac Trad Med* 2017;**13**:53−6.
431. Kim HG, Jeong HU, Hong SI, Oh MS. Houttuyniae Herba attenuates kainic acid-induced neurotoxicity *via* calcium response modulation in the mouse hippocampus. *Planta Med* 2015;**81**:1697−704.
432. Bahadur Gurung A, Ajmal Ali M, Lee J, Abul Farah M, Mashay Al-Anazi K, Al-Hemaid F. Identification of SARS-CoV-2 inhibitors from extracts of Thunb. *Saudi J Biol Sci* 2021;**28**:7517−27.
433. You BH, Chin YW, Kim H, Choi HS, Choi YH. Houttuynia cordata extract increased systemic exposure and liver concentrations of metformin through OCTs and MATEs in rats. *Phytother Res* 2018;**32**:1004−13.
434. Panossian A, Wikman G, Sarris J. Rosenroot (Rhodiola rosea): traditional use, chemical composition, pharmacology and clinical efficacy. *Phytomedicine* 2010;**17**:481−93.
435. Wang L, Wang Y, Yang W, He X, Xu S, Liu X, et al. Network pharmacology and molecular docking analysis on mechanisms of Tibetan Hongjingtian (Rhodiola crenulata) in the treatment of COVID-19. *J Med Microbiol* 2021;**70**:001374.
436. Tao H, Wu X, Cao J, Peng Y, Wang A, Pei J, et al. Rhodiola species: a comprehensive review of traditional use, phytochemistry, pharmacology, toxicity, and clinical study. *Med Res Rev* 2019;**39**:1779−850.
437. Wang Z, Liu H, Li L, Li Y, Yan H, Yuan Y. Modulation of disordered bile acid homeostasis and hepatic tight junctions using salidroside against hepatocyte apoptosis in furan-induced mice. *J Agric Food Chem* 2022;**70**:10031−43.
438. Fan F, Yang L, Li R, Zou X, Li N, Meng X, et al. Salidroside as a potential neuroprotective agent for ischemic stroke: a review of sources, pharmacokinetics, mechanism and safety. *Biomed Pharmacother* 2020;**129**:110458.
439. Yuan Y, Wu X, Hong Y, Zhang X, Wang Z, Yan H. Salidroside ameliorates liver metabonomics in relation to modified gut-liver FXR signaling in furan-induced mice. *Food Chem Toxicol* 2020;**140**:111311.
440. Wang Y, Tao H, Huang H, Xiao Y, Wu X, Li M, et al. The dietary supplement *Rhodiola crenulata* extract alleviates dextran sulfate sodium-induced colitis in mice through anti-inflammation, mediating gut barrier integrity and reshaping the gut microbiome. *Food Funct* 2021;**12**:3142−58.
441. Li C, Zhang X, Liu S, Shang H. Current evidence and research prospects of xuebijing injection in treating novel coronavirus-infected pneumonia(COVID-19). *World Sci Technol Mod Tradit Chin Med Mater Med* 2020;**22**:242−7.
442. Song Y, Zhang M, Yin L, Wang K, Zhou Y, Zhou M, et al. COVID-19 treatment: close to a cure? A rapid review of pharmacotherapies for the novel coronavirus (SARS-CoV-2). *Int J Antimicrob Agents* 2020;**56**:106080.
443. Ma Q, Qiu M, Zhou H, Chen J, Yang X, Deng Z, et al. The study on the treatment of Xuebijing injection (XBJ) in adults with severe or

critical corona virus disease 2019 and the inhibitory effect of XBJ against SARS-CoV-2. *Pharmacol Res* 2020;**160**:105073.
444. Ren JL, Zhang AH, Wang XJ. Traditional Chinese medicine for COVID-19 treatment. *Pharmacol Res* 2020;**155**:104743.
445. Qiang W, Xuan H, Yu S, Hailun P, Yueli Z, Zhiguo P, et al. Impact of the gut microbiota on heat stroke rat mediated by Xuebijing metabolism. *Microb Pathog* 2021;**155**:104861.
446. Li J, Olaleye OE, Yu X, Jia W, Yang J, Lu C, et al. High degree of pharmacokinetic compatibility exists between the five-herb medicine XueBiJing and antibiotics comedicated in sepsis care. *Acta Pharm Sin B* 2019;**9**:1035−49.
447. Qiao Y, Shi Y, Wu C, Hou X, Pan X, Deng Z, et al. Rapid screening and identification of anticoagulation component from carthami flos by two-dimensional thrombin affinity chromatography combined with HPLC−MS/MS. *J Separ Sci* 2021;**44**:3061−9.
448. Madikyzy M, Tilegen M, Nazarbek G, Mu C, Kutzhanova A, Li X, et al. Honghua extract mediated potent inhibition of COVID-19 host cell pathways. *Sci Rep* 2022;**12**:14296.
449. Zhang LL, Tian K, Tang ZH, et al. Phytochemistry and pharmacology of *Carthamus tinctorius* L. *Am J Chin Med* 2016;**44**:197−226.
450. Li Y, Lu YY, Meng YQ, Du ZY, Gao P, Zhao MB, et al. Evaluation of the effects of notoginseng total saponins (NS), safflower total flavonoids (SF), and the combination of NS and SF (CNS) on the activities of cytochrome P450 enzymes using a cocktail method in rats. *Biomed Chromatogr* 2021;**35**:e5171.
451. Fu H, Liu X, Jin L, Lang J, Hu Z, Mao W, et al. Safflower yellow reduces DEN-induced hepatocellular carcinoma by enhancing liver immune infiltration through promotion of collagen degradation and modulation of gut microbiota. *Food Funct* 2021;**12**:10632−43.
452. Chen Z, Zhang C, Gao F, Fu Q, Fu C, He Y, et al. A systematic review on the rhizome of Ligusticum chuanxiong Hort. (Chuanxiong). *Food Chem Toxicol* 2018;**119**:309−25.
453. Cao P, Wu S, Wu T, Deng Y, Zhang Q, Wang K, et al. The important role of polysaccharides from a traditional Chinese medicine-lung cleansing and Detoxifying Decoction against the COVID-19 pandemic. *Carbohydr Polym* 2020;**240**:116346.
454. Zhang YW, Bao MH, Wang G, Qu Q, Zhou HH. Induction of human CYP3A4 by huperzine A, ligustrazine and oridonin through pregnane X receptor-mediated pathways. *Pharmazie* 2014;**69**:532−6.
455. Wang XB, Wang SS, Zhang QF, Liu M, Li HL, Liu Y, et al. Inhibition of tetramethylpyrazine on P-gp, MRP2, MRP3 and MRP5 in multidrug resistant human hepatocellular carcinoma cells. *Oncol Rep* 2010;**23**:211−5.
456. Chen R, Wu P, Cai Z, Fang Y, Zhou H, Lasanajak Y, et al. Puerariae Lobatae Radix with chuanxiong Rhizoma for treatment of cerebral ischemic stroke by remodeling gut microbiota to regulate the brain-gut barriers. *J Nutr Biochem* 2019;**65**:101−14.
457. Ren YJ, Cao YG, Zeng MN, Zhang QQ, Liu YL, He C, et al. Ten undescribed diterpenoid quinones derived from the. *Salvia miltiorrhiza. Phytochemistry* 2022;**200**:113224.
458. Hu S, Wang J, Zhang Y, Bai H, Wang C, Wang N, et al. Three salvianolic acids inhibit 2019-nCoV spike pseudovirus viropexis by binding to both its RBD and receptor ACE2. *J Med Virol* 2021;**93**:3143−51.
459. Liang YY, Wan XH, Niu FJ, Xie SM, Guo H, Yang YY, et al. Salvia plebeia R. Br.: an overview about its traditional uses, chemical constituents, pharmacology and modern applications. *Biomed Pharmacother* 2020;**121**:109589.
460. Yu C, Ye S, Sun H, Liu Y, Gao L, Shen C, et al. PXR-mediated transcriptional activation of CYP3A4 by cryptotanshinone and tanshinone IIA. *Chem Biol Interact* 2009;**177**:58−64.
461. Wang X, Cheung CM, Lee WY, Or PM, Yeung JH. Major tanshinones of Danshen (*Salvia miltiorrhiza*) exhibit different modes of inhibition on human CYP1A2, CYP2C9, CYP2E1 and CYP3A4 activities in vitro. *Phytomedicine* 2010;**17**:868−75.
462. Li K, Liu W, Zhao Q, Wu C, Fan C, Lai H, et al. Combination of tanshinone IIA and doxorubicin possesses synergism and attenuation effects on doxorubicin in the treatment of breast cancer. *Phytother Res* 2019;**33**:1658−69.
463. Wang W, Xu AL, Li ZC, Li Y, Xu SF, Sang HC, et al. Combination of probiotics and salvia miltiorrhiza polysaccharide alleviates hepatic steatosis *via* gut microbiota modulation and insulin resistance improvement in high fat-induced NAFLD mice. *Diabetes Metab J* 2020;**44**:336−48.
464. Long Y, Li D, Yu S, Shi A, Deng J, Wen J, et al. Medicine-food herb: , a potential therapeutic hope for Alzheimer's disease and related complications. *Food Funct* 2022;**13**:8783−803.
465. Antonopoulou I, Sapountzaki E, Rova U, Christakopoulos P. The inhibitory potential of ferulic acid derivatives against the SARS-COV-2 main protease: molecular docking, molecular dynamics, and ADMET evaluation. *Biomedicines* 2022;**10**:1787.
466. Wei WL, Zeng R, Gu CM, Qu Y, Huang LF. Angelica sinensis in China-A review of botanical profile, ethnopharmacology, phytochemistry and chemical analysis. *J Ethnopharmacol* 2016;**190**:116−41.
467. Chen C, Wu C, Lu X, Yan Z, Gao J, Zhao H, et al. Coniferyl Ferulate, a strong inhibitor of glutathione *s*-transferase isolated from radix angelicae sinensis, reverses multidrug resistance and downregulates p-glycoprotein. *Evid Based Complement Alternat Med* 2013;**2013**:639083.
468. Tang JC, Zhang JN, Wu YT, Li ZX. Effect of the water extract and ethanol extract from traditional Chinese medicines Angelica sinensis (Oliv.) Diels, *Ligusticum chuanxiong* Hort. and *Rheum palmatum* L. on rat liver cytochrome P450 activity. *Phytother Res* 2006;**20**:1046−51.
469. Hu Q, Wu C, Yu J, Luo J, Peng X. Angelica sinensis polysaccharide improves rheumatoid arthritis by modifying the expression of intestinal Cldn5, Slit3 and Rgs18 through gut microbiota. *Int J Biol Macromol* 2022;**209**:153−61.
470. Hao DC, Wang F, Xiao PG. Impact of drug metabolism/pharmacokinetics and its relevance considering traditional medicine-based anti-COVID-19 drug research. *Curr Drug Metab* 2022;**23**:374−93.
471. Liu Y, Zhang J, Wu D, Cui L. Pharmacokinetic interaction study between ligustrazine and valsartan in rats and its potential mechanism. *Pharm Biol* 2020;**58**:1290−3.
472. Hau RK, Wright SH, Cherrington NJ. PF-07321332 (Nirmatrelvir) does not interact with human ENT1 or ENT2: implications for COVID-19 patients. *Clin Transl Sci* 2022;**15**:1599−605.
473. Nazari S, Rameshrad M, Hosseinzadeh H. Toxicological effects of Glycyrrhiza glabra (licorice): a review. *Phytother Res* 2017;**31**:1635−50.
474. Shen Y, Eades W, Yan B. The COVID-19 medicine Remdesivir is therapeutically activated by carboxylesterase-1, and excessive hydrolysis increases cytotoxicity. *Hepatol Commun* 2021;**5**:1622−3.
475. Zhang F, Li HX, Zhang TT, Xiong Y, Wang HN, Lu ZH, et al. Human carboxylesterase 1A plays a predominant role in the hydrolytic activation of remdesivir in humans. *Chem Biol Interact* 2022;**351**:109744.
476. Jia WW, Lu C, Lin G, Ge GB. Editorial: pharmacokinetics of herbal medicines and herb−drug interactions. *Front Pharmacol* 2022;**13**:1107777.
477. Zou LW, Li YG, Wang P, Zhou K, Hou J, Jin Q, et al. Design, synthesis, and structure-activity relationship study of glycyrrhetinic acid derivatives as potent and selective inhibitors against human carboxylesterase 2. *Eur J Med Chem* 2016;**112**:280−8.
478. Zhang J, Xiao M, Ji X, Lai YS, Song Q, Zhang Y, et al. Inhibition of Radix Scutellariae flavones on carboxylesterase mediated activations of prodrugs. *Life Sci* 2022;**305**:120743.
479. Achour B, Russell MR, Barber J, Rostami-Hodjegan A. Simultaneous quantification of the abundance of several cytochrome P450 and uridine 5′-diphospho-glucuronosyltransferase enzymes in human liver microsomes using multiplexed targeted proteomics. *Drug Metab Dispos* 2014;**42**:500−10.
480. Boberg M, Vrana M, Mehrotra A, Pearce RE, Gaedigk A, Bhatt DK, et al. Age-dependent absolute abundance of hepatic carboxylesterases (CES1 and CES2) by LC−MS/MS proteomics:

application to PBPK modeling of oseltamivir *in vivo* pharmacokinetics in infants. *Drug Metab Dispos* 2017;**45**:216−23.
481. Zhang J, Wang D, Zou L, Xiao M, Zhang Y, Li Z, et al. Rapid bioluminescence assay for monitoring rat CES1 activity and its alteration by traditional Chinese medicines. *J Pharm Anal* 2020;**10**:253−62.
482. Hatfield MJ, Binder RJ, Gannon R, Fratt EM, Bowling J, Potter PM. Potent, irreversible inhibition of human carboxylesterases by tanshinone anhydrides isolated from *Salvia miltiorrhiza* ("Danshen"). *J Nat Prod* 2018;**81**:2410−8.
483. Song YQ, Weng ZM, Dou TY, Finel M, Wang YQ, Ding LL, et al. Inhibition of human carboxylesterases by magnolol: kinetic analyses and mechanism. *Chem Biol Interact* 2019;**308**:339−49.
484. Qian Y, Markowitz JS. Natural products as modulators of CES1 activity. *Drug Metab Dispos* 2020;**48**:993−1007.
485. Mai ZP, Zhou K, Ge GB, Wang C, Huo XK, Dong PP, et al. Protostane triterpenoids from the rhizome of *Alisma orientale* exhibit inhibitory effects on human carboxylesterase 2. *J Nat Prod* 2015;**78**:2372−80.
486. Zhang Y, Gu X, Zhou Y, Si N, Gao W, Sun B, et al. An integrative analysis of Qingfei Paidu Decoction for its anti-HCoV-229E mechanism in cold and damp environment based on the pharmacokinetics, metabolomics and molecular docking technology. *Phytomedicine* 2023;**108**:154527.
487. Cao JF, Gong Y, Wu M, Xiong L, Chen S, Huang H, et al. Molecular docking and molecular dynamics study Lianhua Qingwen granules (LHQW) treats COVID-19 by inhibiting inflammatory response and regulating cell survival. *Front Cell Infect Microbiol* 2022;**12**:1044770.
488. An X, Xu X, Xiao M, Min X, Lyu Y, Tian J, et al. Efficacy of Jinhua Qinggan Granules combined with Western medicine in the treatment of confirmed and suspected COVID-19: a randomized controlled trial. *Front Med* 2021;**8**:728055.
489. Chen L, Hu C, Hood M, Zhang X, Zhang L, Kan J, et al. A novel combination of vitamin C, curcumin and gycyrrhizic acid potentially regulates immune and inflammatory response associated with coronavirus infections: a perspective from system biology analysis. *Nutrients* 2020;**12**:1193.
490. Shi C, Wu M, Yang K, Wang X. Lianhua Qingwen Capsules reduced the tate of severity in patients with COVID-19: a system review and meta-analysis of randomized controlled trials. *Evid Based Complement Alternat Med* 2022;**2022**:9617429.
491. Shi N, Guo L, Liu B, Bian Y, Chen R, Chen S, et al. Efficacy and safety of Chinese herbal medicine *versus* Lopinavir-Ritonavir in adult patients with coronavirus disease 2019: a non-randomized controlled trial. *Phytomedicine* 2021;**81**:153367.
492. Luo Z, Chen W, Xiang M, Wang H, Xiao W, Xu C, et al. The preventive effect of Xuebijing injection against cytokine storm for severe patients with COVID-19: a prospective randomized controlled trial. *Eur J Integr Med* 2021;**42**:101305.
493. He DD, Zhang XK, Zhu XY, Huang FF, Wang Z, Tu JC. Network pharmacology and RNA-sequencing reveal the molecular mechanism of Xuebijing injection on COVID-19-induced cardiac dysfunction. *Comput Biol Med* 2021;**131**:104293.
494. Guo H, Zheng J, Huang G, Xiang Y, Lang C, Li B, et al. Xuebijing injection in the treatment of COVID-19: a retrospective case-control study. *Ann Palliat Med* 2020;**9**:3235−48.