Chinese Herbal Medicines for Sepsis Treatment

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Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection; the pathophysiology of sepsis is complex. The incidence of sepsis is steadily increasing, with worldwide mortality ranging between 30% and 50%. Current treatment approaches mainly rely on the timely and appropriate administration of antimicrobials and supportive therapies, but the search for pharmacotherapies modulating the host response has been unsuccessful. Chinese herbal medicines, i.e., Chinese patent medicines, Chinese herbal prescriptions, and single Chinese herbs, play an important role in the treatment of sepsis through multicomponent, multipathway, and multitargeting abilities and have been officially recommended for the management of COVID-19.

Keywords: Chinese herbal medicines ; sepsis

1. Introduction

Based on the characteristics of emergency medicine in China, the Preventing Sepsis Campaign in China (PSCC) was initiated in May 2018 [1]. It was advocated by experts that the prevention, diagnosis, and treatment of sepsis should be performed as early as possible to decrease morbidity and mortality, and the principle of the prevention of sepsis was introduced to prevent its occurrence. Several Chinese treatment guidelines for sepsis management and expert consensus—e.g., the Chinese guidelines for the emergency management of sepsis and septic shock 2018, the clinical practice guidelines on traditional Chinese medicine therapy alone or combined with antibiotics for sepsis, and the Chinese emergency medicine expert consensus on the diagnosis and treatment of sepsis complicated by disseminated intravascular coagulation—have been successively released for the management of sepsis [2][1][3]. In these treatment guidelines and expert agreements, CHMs are recommended as add-on therapies to complement the conventional treatment of sepsis, e.g., a XueBiJing injection (XBJ) for sepsis, a ShenFu injection (SF) for septic shock, the ShengMai formula (SMF) for sepsis with the qi and yin exhaustion pattern, the Xuanbai Chengqi decoction (XBCQ) for sepsis with acute respiratory distress syndrome (ARDS), the Qingwen Baidu decoction (QWBD) for sepsis with the internal exuberance of toxins and heat pattern, etc. [4]. The diagnosis and treatment protocol for COVID-19 (the revised eighth version) released by China's National Health Commission also recommends the use of CHM in accordance with different degrees of severity of COVID-19 [5]. XueBiJing, ShenFu, and ShengMai injections are typical herbal injections officially recommended for the management of COVID-19 when patients with a severe case of the disease develop SIRS and/or MODS [5].

2. Chinese Patent Medicines - XueBiJing Injection

The XueBiJing injection (XBJ), derived from the Xuefu Zhuyu decoction, is an injectable licensed in China since 2004 for sepsis and MODS, with a National Medical Products Administration (NMPA) drug ratification number of GuoYaoZhunZi-Z20040033. It is exclusively manufactured by Tianjin Chasesun Pharmaceutical (Tianjin, China). The herbal injection is prepared from a combination of *Carthamus tinctorius* flower (Honghua in Chinese), *Paeonia lactiflora* root (Chishao), *Salvia miltiorrhiza* root (Danshen), *Ligusticum chuanxiong* rhizome (Chuanxiong), and *Angelica sinensis* root (Danggui). Several meta-analyses have suggested that the addition of XBJ to routine sepsis care could further reduce the 28-day mortality of patients and incidence of complications, and improve patient prognosis [6][7][8][9][10]. The 28-day mortality is the primary clinical outcome of sepsis care. In a prospective, randomized controlled trial in 710 patients with severe community-acquired pneumonia, adding XBJ to the conventional treatment reduced the 28-day mortality from 24.6% (conventional treatment) to 15.9% (conventional treatment + XBJ), increased the percentage of patients with improved pneumonia severity indices from 46.3% to 60.8%, and improved their Sequential Organ Failure Assessment (SOFA) scores from 4.44 to 3.65 and Acute Physiology and Chronic Health Evaluation (APACHE) II scores from 11.12 to 9.19 ($p < 0.01$ for all) [11]. In a single-center, randomized, double-blinded, prospective trial in 60 patients with severe COVID-19, significant improvements in the rates of septic shock and mechanical ventilation, as well as the proportion of patients severely affected, the duration until the main clinical symptoms improved ($p < 0.05$ for all), and the lengths of ICU hospitalization ($p < 0.01$), were observed for the XBJ group (routine medication + XBJ) after 14 days of treatment, compared with the control group (routine medication + saline) [12]. A large-scale survey involving 31,913 hospitalized patients indicated that the incidence of adverse drug reactions (ADRs) to XBJ was at the occasional level (0.3%); most of these reactions were mild or nonserious [13]. Another analysis of data from the Hospital Information System indicated that the ADRs to XBJ were mainly correlated with age, dosage, vehicle type, and drug combination [14]. A recent investigation

by our group suggested that the herbal compounds in XBJ have a low potential to participate in therapeutic pharmacokinetic interactions with antibiotics when coadministered with XBJ in sepsis care [15].

Many pharmacological studies have suggested that the antisepsis action of XBJ is correlated with the modulation of the host response, i.e., inhibiting the uncontrolled release of inflammatory mediators, relieving an early overabundant innate immune response and potentially cumulative immunosuppression, attenuating crosstalk between inflammation and coagulation, protecting endothelial cells, and maintaining the physiologic functions of vital organs [16][17][18][19]. Zhou et al. identified four biological functional actions of XBJ in sepsis: the regulation of inflammation, immune activity, cell apoptosis, and coagulation [20]. XBJ can significantly alleviate liver injury in cecal ligation and puncture (CLP) rats via downregulating tumor necrosis factor-α (TNF-α) and interleukin 6 (IL-6) expression while upregulating IL-10 expression and promoting the suppression of cytokine signaling 1 (SOCS1) expression [21]. XBJ played a protective role in methicillin-resistant *Staphylococcus aureus* (MRSA)-challenged mice by downregulating the inflammatory response (IL-6, TNF-α, IL-1β, and IL-12) and signaling pathways (NF-κB, MAPK, and PI3K/Akt) activated by Pam3CSK4 (a synthetic tripalmitoylated lipopeptide mimicking bacterial lipoproteins) [22]. A study based on a sepsis rat model indicated that adding XBJ to antibiotics could improve renal perfusion and oxygenation and suppress renal inflammation, as well as ameliorate kidney dysfunction [23]. A rat- and cell-based study indicated that XBJ may improve pulmonary vascular barrier function by upregulating claudin-5 expression in a rat model with acute lung injury (ALuI) [24]. A GC/MS-based metabonomics approach revealed that XBJ reduced multiorgan dysfunctions in septic rats and increased their survival rate: serum biochemistry indicators including blood urea nitrogen (BUN), creatinine (Cr), alanine aminotransferase (ALT), and aspartate aminotransferase (AST); cytokines (TNF-α and IL-6); and morphologic changes all decreased [25].

XBJ may improve the clinical symptoms and alleviate the disease severity of COVID-19. By using network pharmacology and molecular docking analysis approaches, the active ingredients, potential molecular targets, and mechanisms of XBJ have been investigated [26][27]. Similarly, to explore the multicomponent, multipathway, and multitarget mechanisms of XBJ in sepsis, a drug–target–pathway network and a drug–ingredients–targets–disease network of XBJ were constructed by Zuo et al. and Feng et al., respectively, to identify major active ingredients, targets, and signaling pathways [28][29].

XBJ is a chemically complex herbal injection; more than 100 constituents, including Honghua flavonoids, Chishao monoterpene glycosides, Danshen catechols, Chuanxiong/Danggui phthalides, and other types of constituents, have been detected and characterized in XBJ [15][30]. Additionally, several analytical assays have been developed for the quantification of the multiple constituents in XBJ [30][31][32][33][34]. Based on the comprehensive chemical composition analysis of XBJ, the human pharmacokinetics of XBJ (by dosing with labeled doses) were systematically investigated by Li et al., and the disposition of major circulating XBJ compounds was well characterized with supportive rat studies and in vitro metabolism and transport studies [15][35][36][37]. Accordingly, 13 major circulating XBJ compounds originating from the five component herbs were identified, i.e., hydroxysafflor yellow A from Honghua; paeoniflorin, oxypaeoniflorin, and albiflorin from Chishao; senkyunolide I, senkyunolide I-7-*O*-â-glucuronide, senkyunolide G, and ferulic acid from Chuanxiong and Danggui; tanshinol, 3-*O*-methyltanshinol, protocatechuic acid, salvianolic acid B, and 3-*O*-methylsalvianolic acid B from Danshen. Among these compounds, senkyunolide I-7-*O*-â-glucuronide, 3-*O*-methyltanshinol, protocatechuic acid, and 3-*O*-methylsalvianolic acid B are the in vivo metabolites of senkyunolide I, tanshinol, protocatechuic aldehyde, and salvianolic acid B, respectively; the unchanged compound protocatechuic aldehyde could not be detected in human plasma samples [15][35][36][37]. Several other research groups also measured circulating herbal compounds in their unchanged forms in rats receiving XueBiJing based on developed bioanalytical assays [38][39][40][41]. Zuo et al. investigated the tissue distributions of several bioactive compounds in rats after they intravenously received XBJ, and the levels of exposure to four compounds (i.e., hydroxysafflor yellow A, paeoniflorin, ferulic acid, and benzoylpaeoniflorin) were found to be high in the kidneys, liver, stomach, and intestines [38]. Hydroxysafflor yellow A, despite its poor membrane permeability, could partly cross the damaged blood–brain barrier in patients with traumatic brain injury after the intravenous administration of XBJ [42].

The antisepsis-related activities—i.e., anti-inflammatory, anticoagulant, endothelium-protective, immune-regulatory, antioxidant, and organ-protective activities—of the aforementioned unchanged circulating compounds from XBJ, based on animal or cellular studies, have been widely reported [43][44][45][46][47][48][49][50]. However, the experimental doses or concentrations of the test XBJ compounds were poorly related to their systemic exposure levels. Therefore, the antisepsis-related activities of the major pharmacokinetically identified circulating compounds were systematically evaluated at the concentrations of their systemic exposure levels after dosing XBJ in in vitro studies and for individual doses of XBJ in a CLP rat study. Finally, six XBJ compounds (hydroxysafflor yellow A, paeoniflorin, oxypaeoniflorin, albiflorin, tanshinol, and senkyunolide I; **Figure 1**) were identified to be the material basis of XBJ: the survival rate of CLP rats receiving the intravenous injection of the combination of the six XBJ compounds proved to be comparable to that of CLP rats receiving XBJ. The survival rates of both groups were significantly lower than that of CLP control rats receiving 0.9% saline ($p < 0.05$; pending publication). **Table 1** lists some potential target pathways of the bioavailable and bioactive XBJ compounds.

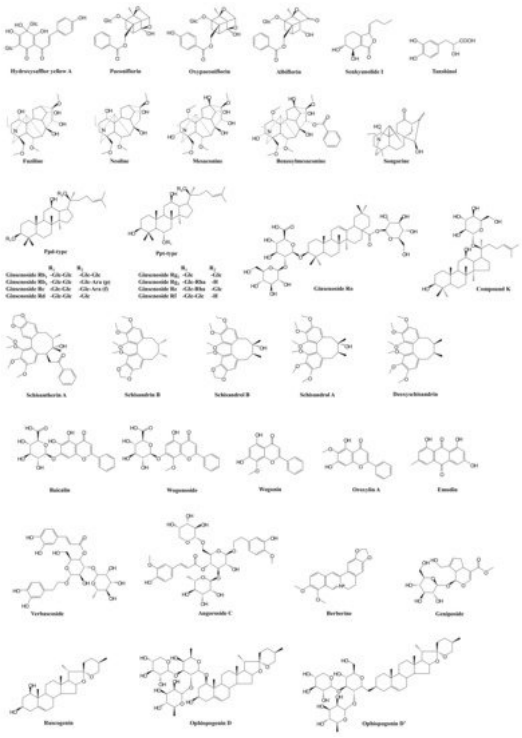

Figure 1. Chemical structures of bioactive and bioavailable herbal compounds from antisepsis Chinese herbal medicines.

Table 1. Chemical compositions, pharmacological actions, bioactive compounds, and mechanisms of action of representative antisepsis Chinese herbal medicines.

Prescription	Component Herbs	Chemical Composition	Pharmacological Actions	Bioactive and Bioavailable Compounds	Potential Target Pathway	Potential DDI Target
XueBiJing injection	*Carthamus tinctorius* flower (Honghua in Chinese), *Paeonia lactiflora* root (Chishao), *Ligusticum chuanxiong* rhizome (Chuanxiong), *Angelica sinensis* root (Danggui), and *Salvia miltiorrhiza* root (Danshen)	Flavonoids, monoterpene glycosides, catechols, phthalides, organic acids, etc.	Exhibit anti-inflammatory, anticoagulant, endothelium-protective, immunoregulatory, antioxidant, and organ-protective activities; inhibit ox-LDL-induced apoptosis; improve microcirculation and myocardial ischemia/reperfusion injury	Hydroxysafflor yellow A	TLR4/NF-κB; NLRP3; Rac1/Akt; NF-κB/ICAM-1	—
				Paeoniflorin Oxypaeoniflorin Albiflorin	SIRT1; IRAK1-NF-κB; IκB; PI3K/Akt; TLR2; Sirt1/Foxo1	—
				Senkyunolide I	p-Erk1/2; Nrf2/HO-1; Caspase 3; MAPK; TLRs	As victim: UGT2B15
				Tanshinol	cAMP-PKA	As victim: OAT1/2
ShenFu injection	*Panax ginseng* steamed root (Hongshen) and processed *Aconitum carmichaelii* root (Fuzi)	Ginsenosides, aconitum alkaloids, organic acids, etc.	Regulate oxidative stress and inflammatory responses, inhibit HMGB1-mediated severe inflammatory response, restore endothelial integrity, attenuate the proinflammatory response, enhance innate immunity, preserve adaptive immunity, alleviate neuropathic pain	Ginsenosides Rb_1, Rc, Rb_2, Rf, Rd, Rg_1, etc.	TLR4; PXR/NF-κB; TLRs/IRAK-1; TBK-1/IκB kinase ε/IRF-3; p38/ATF-2	As substrate: OATP1B3 (for Ginsenosides Rg_1, Rf) As perpetrator: OATP1B1/1B3 (for Ginsenosides Rb_1, Rc, Rb_2, Rd)
				Benzoylmesaconine Fuziline Mesaconine Neoline Songorine	TLR4/NF-κB; Nrf2	As victim: P-gp (for benzoylmesaconine)

Prescription	Component Herbs	Chemical Composition	Pharmacological Actions	Bioactive and Bioavailable Compounds	Potential Target Pathway	Potential DDI Target
ShengMai formula	*Panax ginseng* root (Renshen), *Ophiopogon japonicus* root (Maidong), and *Schisandra chinensis* fruit (Wuweizi)	Ginsenosides, lignans, steroidal saponins, and homoisoflavanones	Exhibit anti-inflammatory or antioxidant, hepatoprotective activities	Ginsenosides Rb_1, Rb_2, Rc, Rd, Re, Rg_1, Rh_1, Compound K, Rf, and Rg_2	TLR4; PXR/NF-κB; TLRs/IRAK-1; TBK-1/IκB kinase ε/IRF-3; p38/ATF-2	As substrate: OATP1B1/1B3 (for Ginsenoside Rg_2) OATP1B3 (for Ginsenosides Rg_1, Rf, Re) As perpetrator: OATP1B1/1B3 (for Ginsenosides Rb_1, Rc, Rb_2, Rd) NTCP (for Rg1) CYP3A (for Rd)
				Ophiopogonin D Ophiopogonin D' Ruscogenin	PPARα; NF-κB/IκBα; SIRT1; TLR4; TLR4/NF-κB/MyD88	As perpetrator: CYP3A4, 2C9, and 2E1 (for Ophiopogonin D) UGT1A6/1A8 (for Ophiopogonin D) UGT1A6/1A10 (for Ophiopogonin D') NTCP (for Ophiopogonin D') CYP3A (for Ophiopogonin D) As victim: OATP1B1/1B3 (for Ophiopogonin D)
				Schisandrol A Schisandrol B Schizandrin A Schizandrin B Deoxyschisandrin	iNOS; COX-2; PGE2; MAPK; TLR4/NF-κB/MyD88	As perpetrator: NTCP (for Schizandrin A)
Qingwen Baidu decoction	*Rehmannia glutinosa* root (Dihuang), *Rhinoceros unicornis* horn (Xijiao), *Coptidis chinensis* rhizome (Huanglian), *Gardenia jasminoides* fruit (Zhizi), *Platycodon grandiflorum* root (Jiegeng), *Scutellaria baicalensis* root (Huangqin), *Anemarrhena asphodeloides* rhizome (Zhimu), *Paeonia lactiflora* root (Chishao), *Scrophularia ningpoensis* root (Xuanshen), *Forsythia suspense* fruit (Lianqiao), *Lophatherum gracile* stem and leaf(Danzhuye), *Glycyrrhiza uralensis* root and rhizome (Gancao), *Paeonia suffruticosa* root cortex (Danpi), and *Gypsum Fibrosum* (Shigao)	Alkaloids, iridoids, flavonoids, etc.	Reduce LPS-induced intestinal damage; treat inflammation; alleviate LPS-induced acute kidney injury; alleviate liver injury in sepsis; exhibit anti-inflammatory, antioxidant, and cardioprotective effects	Berberine	TLRs; NF-κB; STAT3; Wnt/β-catenin; PI3K/Akt; MAPK/JNK/p38/ERK	As perpetrator: CYP3A4, CYP2D6 As victim: P-gp
				Geniposide Genipin	NF-κB; MAPK; PPARγ; AMPK; NLRP3; AKT-mTOR	—
				Baicalin	iNOS; COX-2; NF-κB; HMGB1	As perpetrator: CYP1A2/3A/2E1, OATP1B1, P-gp
				Wogonoside Wogonin	TLR4; NF-κB; Nrf2; NLRP3	As perpetrator: CYP1A2 (for Wogonin)
				Oroxylin A	JAK/STAT; IRF2BP2-NFAT1; NF-κB	As perpetrator: CYP1A2, OATP1B1, OAT1/3 and BCRP
				Verbascoside	iNOS	—

Prescription	Component Herbs	Chemical Composition	Pharmacological Actions	Bioactive and Bioavailable Compounds	Potential Target Pathway	Potential DDI Target
XuanBai Chengqi decoction	*Rheum palmatum* rhizome and root (Dahuang), *Gypsum Fibrosum* (Shigao), *Prunus armeniaca* seed (Kuxingren), and *Trichosanthes kirilowii* fruit (Gualou)	Anthraquinones, etc.	Attenuate LPS-induced microcirculatory disturbance	Emodin	TLR4/NF-κB/ICAM-1; JAK1/STAT3; MAPK; cAMP-PKA; NLRP3; PPARγ	As victim: CYP1A2, UGT1A8/1A10/12B7

3. Chinese Herbal Prescriptions-ShengMai Formula

The ShengMai formula (SMF), which was first recorded in Yi Xue Yuan Li, consists of *P. ginseng* root (Renshen), *Ophiopogon japonicus* root (Maidong), and *Schisandra chinensis* fruit (Wuweizi) with a dosage proportion of 5:3:1.5. It is normally prepared as ShengMai powder (SMP; or ShengMai san, SMS), ShengMai yin (SMY), ShengMai injection (SMI), etc., for clinical use. SMF is a classic tonic prescription for the treatment of tuberculosis, chronic bronchitis, cough due to neurasthenia, and heart failure [127]. SMI, an intravenous dosage form of SMF, is used to treat acute myocardial infarction, cardiogenic shock, toxic shock, hemorrhagic shock, coronary heart disease, endocrine disorders, and other diseases due to a deficiency of qi and yin, with low toxicity [128][129]. SMI is highly recommended for use in combination with antibiotics for community-acquired pneumonia in clinical guidelines [2]. A meta-analysis including 17 randomized controlled trials (RCTs) and 860 patients with septic shock suggested that adding SMI to conventional Western medicine treatment further reduced the number of ineffective shock treatments ($p < 0.0001$) and reduced the blood lactate concentration at 12 h ($p < 0.001$), 24 h ($p < 0.0001$), and 72 h ($p = 0.002$) [130].

SMI protects multiple organs by regulating immunity, inflammation, apoptosis, and energy metabolism. SMI also protected the intestinal mucosal barrier of mice mainly through regulating the NF-κB–pro-inflammatory factor–myosin light-chain kinase (MLCK)–TJ cascade. Decreasing trends for inflammatory factors including interferon-γ (IFN-γ), TNF-α, and IL-2 were observed in the sera of mice receiving SMI at 1.5 mL/kg. The content of occludin increased and MLCK protein decreased in SMI-treated mice compared with the endotoxemia mouse model group ($p < 0.05$ or $p < 0.01$) [131]. SMI could induce myocardial mitochondrial autophagy via the caspase-3/Beclin-1 axis to protect myocardial mitochondria in septic mice [132]. A study by Chai et al. on CLP rats suggested that the regulation of taurine and taurine metabolism, as well as arginine and proline metabolism, etc., could be the key mechanism in the treatment of sepsis [133].

Zheng et al. recently reviewed, in Chinese, the material composition, preclinical pharmacokinetic, and pharmacodynamic studies of SMI [134]. Several research groups have analyzed the chemical compositions of SMF preparations and identified the main constituents as ginsenosides (originating from *P. ginseng*), steroidal saponins (from *O. japonicus*), lignans (from *S. chinensis*), and flavonoids (mainly from *O. japonicus*). Using LC-IT-TOF/MS and a diagnostic fragment-ion-based extension strategy, Zheng et al. detected and identified more than 30 ginsenosides and 20 lignans from SMI [135]. Zhao et al. identified or partially characterized 87 herbal compounds in SMI and selected 6 bioactive constituents (four ginsenosides (i.e., Rg_1, Re, Rb_1, and Rd) and 2 lignans (i.e., schisandrol A and schisandrol B) with high content levels as quality markers (Q-markers). The total content range for these selected Q-markers in 10 batches of SMI was 13.8–22.5 mg/mL [136]. Wu et al. identified 92 compounds (i.e., 49 ginsenosides, 31 lignans, 5 steroidal saponins, and 7 homoisoflavanones) in SMP and discovered a class of 25-hydroxyginsenosides for the first time [137]. In a study by Cheng et al., 10 compounds (the ginsenosides Rb_1, Rb_2, Rc, Rd, Re, Rg_1, and Rh_1; compound K; ophiopogonin D; and schisandrol A) were measured in SMP, and the contents of these herbal constituents were found to vary by up to several hundredfolds among five pharmaceutical manufacturers [138]. In their study, Zheng et al. selected eight compounds (the ginsenosides Rf, Rb_1, Rg_2, and Rb_2; schisandrol A; schisandrol B; methylophiopogonanone A; and schisandrin B) as Q-markers to evaluate the batch-to-batch consistency of SMF; ginsenoside Rb_1, ranging from 2046.1 μg/g (1.84 μmol/g) to 5975.8 μg/g (5.39 μmol/g), was found to be the dominant component in SMF, followed by ginsenoside Rg_2 (838.3–2091.64 μg/g; 1.07–2.66 μmol/g) and ginsenoside Rb_2 (567.2–1989.9 μg/g; 0.53–1.84 μmol/g). The batch-to-batch chemical variation among 10 batches of SMF ranged from 27.9% (for ginsenoside Rf) to 113.95% (for schisandrol B) [139]. Li et al. established a seven-marker-based quality standard to quantify seven ginsenosides (i.e., the ginsenosides Rf, Rd, Rc, Re, Rb_1, Rb_2, and Rg_1) in SMI, which was then used to evaluate the quality consistency of 22 batches of SMI [140]. Li et al. detected 62 compounds in SMI and established a quantitative assay for the determination of 21 main components, including 14 saponins, 6 lignans, and 1 pyranoglucoside, and found the contents of these 21 components to vary widely amongst 10 batches [141].

Lu et al. established a TCM–components–core targets–key pathway network platform to investigate the mechanism of SMI's effects in sepsis. SMI was found to mainly affect several signaling pathways, suggesting that SMI could regulate immunity, inflammation, apoptosis, and energy metabolism for the protection of multiple organs. Gene ontology (GO) enrichment analysis further indicated that the bioactive SMI constituents altered the pathophysiology of sepsis through the regulation of various biological processes [142]. SMP protected against I/R-induced blood–brain barrier (BBB) dysfunction by significantly upregulating ZO-1 and claudin-5 under oxygen-glucose deprivation/reoxygenation (OGD/R), as well as reducing matrix metalloproteinase 2/9 (MMP-2/9) levels and the phosphorylation of myosin light-chain (MLC) through the ROCK/cofilin signaling pathway [143].

Zhan et al. developed and validated a sensitive LC-MS/MS method for the simultaneous quantification of 11 SMI compounds in rat serum and applied it to a pharmacokinetic study in rats after a single intravenous administration of SMI. The 11 constituents were ppt-type ginsenosides (i.e., the ginsenosides Rg_1, Re, Rf, and Rg_2), ppd-type ginsenosides (i.e., the ginsenosides Rb_1, Rd, and Rc), ophiopogonin (ophiopogonin D), and lignans (i.e., schisandrol A, schisandrol B, and schisandrin B) [144][145]. A total of 30 compounds (23 prototype components and 7 metabolites) were detected and characterized in the plasma of rats after they received SMS (8 g/kg) [146][147]. Further, ppt-type ginsenosides were eliminated rapidly through urinary, biliary, and fecal excretions (plasma $t_{1/2â}$, 0.60–0.82 h; MRT, 0.22–0.46 h), whereas the ppd-type ginsenosides Rb_1, Rd, and Rc exhibited slow elimination through biliary and urinary excretions (MRT, 23.0–28.6 h). Ophiopogonin D was mainly excreted in bile in the metabolized forms. Schisandrol A, schisandrol B, and schisandrin B, with low contents in SMI, were found to be eliminated quickly (plasma $t_{1/2â}$, 0.51–1.98 h; MRT, 0.51–2.50 h) and accumulated in these tissues. Lignans were mainly excreted in their metabolized form, as indicated by the very low biliary, urinary, and fecal excretion of the unchanged forms [144][145]. SMI, within the concentration range of 30% (volume percentage), showed an inhibitory effect on the activities of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4, with IC_{50} values of 6.12%, 2.72%, 10.00–30.00%, 14.31%, 12.96%, 12.26%, and 3.72%, respectively, and had an inhibitory effect on the activities of the transporters MDR1, BCRP, and organic anion transporting polypeptide (OATP)1B1, with IC_{50} values of 0.15%, 0.75%, and 2.03%, respectively. This suggested a high risk of drug interactions of SMI when clinically combined with the use of the transporters MDR1 and BCRP substrate [148]. SMS selectively suppressed intestinal, but not hepatic, nifedipine oxidation (a CYP3A marker reaction) activity in a dose- and time-dependent manner. Three-week SMS treatment decreased the maximal velocity of intestinal nifedipine oxidation by 50%, while the CYP3A protein level remained unchanged; among the SMS component herbs, the decoction of *Ophiopogonis Radix* decreased the intestinal nifedipine oxidation activity [149]. Based on an inhibition kinetic investigation of various UGT isoforms, ophiopogonin D was found to noncompetitively inhibit UGT1A6 (K_i, 20.6 μmol/L) and competitively inhibit UGT1A8 (40.1 μmol/L); ophiopogonin D' noncompetitively inhibited UGT1A6 (5.3 μmol/L) and UGT1A10 (9.0 μmol/L); and ruscorectal competitively inhibited UGT1A4 (0.02 μmol/L) [81]. The ginsenoside Rg_1, ophiopogon D', and schisandrin A are potential inhibitors of sodium taurocholate co-transporting polypeptide (NTCP) and probably interact with NTCP-modulating clinical drugs. The ginsenoside Re and schisandrin B are potential NTCP substrates, and their NTCP-mediated uptake could be inhibited by other ingredients in SMF [75]. The ginsenosides Rb_2, Rc, Rg_2, Rg_3, Rd, and Rb_1 are P-gp substrates, and *Schisandra Lignans* extract (SLE) was found to significantly enhance the uptake and inhibit the efflux ratio of the ginsenosides Rb_2, Rc, Rg_2, Rg_3, Rd, and Rb_1 in Caco-2 and L-MDR1 cells. Additionally, a rat study showed that a single dose and multiple doses of SLE at 500 mg/kg could significantly increase the $AUC_{0-\infty}$ of Rb_2, Rc, and Rd without affecting the $t_{1/2}$ [150]. The chemical structures of the major circulating SM compounds are shown in **Figure 1**, and their potential action target pathways are summarized in **Table 1**.

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