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Salvia miltiorrhiza in thorax and abdomainal organ fibrosis: A review of its pharmacology

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Organ fibrosis is a common pathological change that finally results in organ failure, which involves the destruction of parenchyma cells, the activation of mesenchymal cells and the imbalance of immunological cells. In recent years, although some breakthroughs have been made in understanding the pathogenesis and therapeutics of organ fibrosis, no registered drugs could directly target the fibrotic process, which constitutes a major biomedical challenge. *Salvia miltiorrhiza* (SM) is a well-known medicinal plant in China, which has been widely applied because of its pharmacological effects on anti-oxidative, anti-myocardial infarction, anti-fibrotic, anti-inflammatory, and anti-neoplastic properties. Accumulated evidence suggested that SM played critical roles against organ fibrosis *in vivo* and *in vitro* experiments by its multiple biological compounds. In this review, we discussed the recent advances on the phytochemistry and pharmacological mechanisms of SM and its active ingredients in liver, lung, kidney, and heart fibrosis, which might help to promote the treatment of fibrotic diseases in thorax and abdomainal viscera in clinic.

KEYWORDS

organ fibrosis, *Salvia miltiorrhiza*, ingredients, pharmacological mechanism, review

Introduction

Fibrosis, defined as fibroblast proliferation and excessive accumulation of extracellular matrix (ECM) in the broadest sense, was associated with a high cost in morbidity and mortality at a global level (Wynn and Ramalingam, 2012). In solid organ fibrosis, such as thorax and abdomainal organ fibrosis, activated fibroblasts presented overwhelming proliferating and invasion capacities, which could accelerate the development of fibrosis pathogenesis (Deng et al., 2021). Myofibroblasts, differentiated from fibroblasts, were then accumulated dramatically while ECMs were simultaneously synthesizd and deposited. Thus, these abnormal cell populations could contribute to the induction of fibrosis in major organs.

To date, many human diseases, including those of lung, heart, liver, kidney, bone marrow, brain blood vessels, and skin, correlated strongly with fibrosis. The main

characteristics of organ fibrosis were typically presented with the chronic inflammation, the microvascular disturbances, the missing organ parenchyma and the loss-off function (Eddy, 2005). Therefore, fibrosis is a common pathway that might finally lead to organ failure. It was clear that organ fibrosis was a major clinical challenge. Currently, no registered drugs could directly target the fibrotic process. In contrast, traditional Chinese medicine (TCM) and its active ingredients had potential to target fibrosis in one organ or synchronously reversing fibrosis in multiple other fibrotic organs, which were increasingly recognized as effective therapies for fibrosis.

Herbal medicine and its active ingredients were believed to treat disease as a trusted source of medicine from ancient times. *Salvia miltiorrhiza* (SM) Bunge (Lamiaceae), known as danshen (Chinese), is a widely used medicinal plant in TCM (Figure 1). It has been used in China with a long history of two thousand years, which was recorded in the oldest materia medica book "Shen Nongs Classic of Materia Medica" (Shen Nong Ben Cao Jing, 100 BCE to 200 CE). Historically, SM was used to promote blood circulation for removing blood stasis, improving microcirculation and assuaging pain. In addition, SM was demonstrated to exert numerous pharmacological effects, including anti-oxidative, myocardial infarction, anti-fibrotic (Su et al., 2015), anti-inflammatory (Ma et al., 2016), anti-hypertension (Lee et al., 2009), and anti-neoplastic (Chen et al., 2014) and anti-bacterial (Lee and Kim, 2016) properties.

Salvia miltiorrhiza Bunge contains ethanol-soluble compounds (such as various tanshinone analogues) and water-soluble active components (such as salvianolic acids) (Li et al., 2009; Pang et al., 2016). Accumulated evidence suggested that SM played critical roles against organ fibrosis in both animal experiments and clinical studies by its multiple biological ingredients, including anti-inflammation, anti-fibrosis, anti-oxidation and anti-apoptosis. In order to adequately define and elucidate the pharmacological functions of SM in organ fibrosis, pharmacology, phytochemistry, and safety of SM in organ fibrosis were hereby reviewed. For better understanding the pharmacological actions of SM against organ fibrosis, phytochemistry of SM were firstly summarized (Figures 2, 3).

Phytochemistry of *Salvia miltiorrhiza*

There are more than 100 ingredients that were identified from SM so far, including lipid-soluble tanshinones and water-soluble phenolic compounds (Ma et al., 2015). Over 30 phenolic acids had been isolated from SM(Pang et al., 2016), including salvianolic acid A/B/C/D/E/F/G/H/I/J/K/N, rosmarinic acid, danshensu, protocatechuic acid, caffeic acid, lithospermic acid, caffeic acid, etc and other derivatives. Most of the phenolic acids had been conventionally isolated by continuous refluxing extraction and sonication in different solvents such as methanol, aqueous methanol (75%–95%, *v*/*v*) and aqueous ethanol (60%–95%, v/v) (XD et al., 2019). However, these methods also have some shortcomings. Most of them were time-consuming, which might promote phenolic acids converted into another kinds of compounds. In the last few years, novel emerging methods have been applied to extract phenolic acids, including microwave-assisted extraction (Gallo et al., 2010), supercritical fluid extraction (SFE) (Li et al., 2002), ultrasonic extraction (UAE) (Li et al., 2009), tissue-smashing based ultra-rapid extraction (Fan et al., 2014) and microsphere resin chromatography combined with microbial biotransformation (Kan et al., 2009).

Besides the hydrophilic salvianolic acids, the lipophilic terpenoids were also the major bioactive constituents of SM. Until now, at least 40 liposoluble compounds had been isolated from SM. Tanshinones and their analogues, including tanshinone I, tanshinone IIA, tanshinol A, tanshinol B, cryptotanshinone, dihydrotanshinone, danshenxinkun A, przewaquinone A, etc, were the main

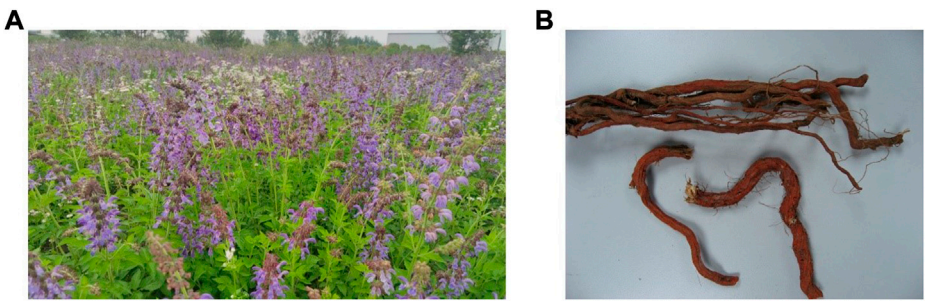

FIGURE 1
Overall appearance of *Salvia miltiorrhiza* Bunge (SM). **(A)**The aerial parts of SM. **(B)** The raw herb of SM.

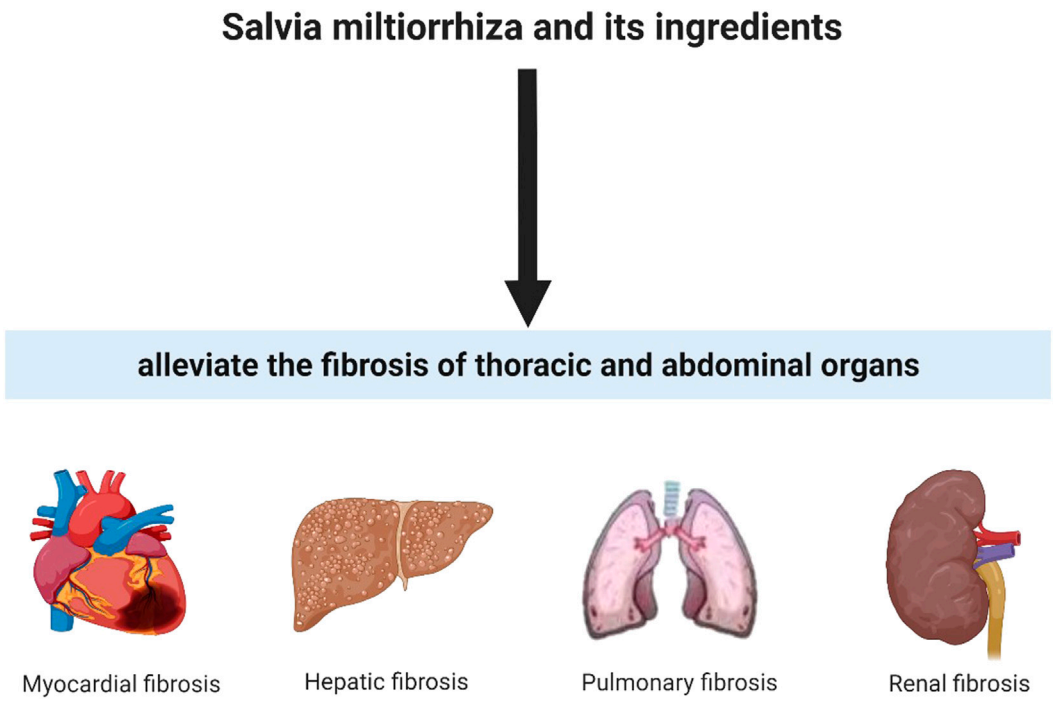

FIGURE 2
Salvia miltiorrhiza and its ingredients could alleviate fibrotic condition in thoracic and abdominal organs.

active diterpenoids in SM (Su et al., 2015). Some conventional extraction reagents, such as CHCl3, ethyl acetate, or petroleum ether, were used as the initial extraction solvent to isolate the tanshinones (XD et al., 2019). Besides these, extraction techniques such as soaking, percolation, reflux as well as ultrasound were generally applied for the extraction of tanshinones. However, tanshinones were present at lower concentrations than in the original SM, and many liposoluble constituents were instability, eg. cryptotanshinone and tanshinone IIA, etc (Li et al., 2008). Nowadays, these problems could be solved by a wide range of technique or approach, including infrared-assisted extraction (Chen et al., 2010), UAE (Li et al., 2009), surfactant-assisted extraction (Bi et al., 2011), SFE (Li et al., 2002) and pressurized-liquid extraction (Jiang et al., 2010).

Apart from the above, as SM was cultivation is scattered all over the country, the contents of main active constituents of SM might be influenced by environmental, altitude and cultivars factors (Wang et al., 2013; Zhao et al., 2016a). In addition, the active constituents might differ in intrinsically because of the various germplasms (Zhang et al., 2013; Zhao et al., 2016b). And the different genotypes of SM possessed their own specific ethylene responsive element binding protein gene (Cui et al., 2010).

Pharmacological actions of *Salvia miltiorrhiza* in treatment for organ fibrosis

Liver fibrosis

Liver fibrosis is a key pathological hallmark of various chronic liver diseases, including auto-immune liver disease, viral hepatitis, alcohol, and non-alcoholic fatty liver disease (Friedman, 2010; Tsochatzis et al., 2014). Although significant achievements have been made in our understanding of the pathogenenic actions of hepatic fibrosis and cirrhosis, effective anti-fibrotic agents and therapies remain the unconquered areas in the fields of drug research and development (Schuppan and Kim, 2013). "Deficiency of vital essential and blood stasis" was response in development of liver fibrosis and cirrhosis, which was the basic TCM pathogenesis of this condition. Among these, blood stasis was a central component. In TCM theory, SM was considered to promote blood circulation for removing blood stasis and resolving microcirculation (Sun et al., 2005). SM was applied in treating splenomegaly due to schistosomiasis in the fifties of the last century in China. Since then, many Chinese patent medicines, typified by Fuzheng Huayu tablet/capsule, contained SM as an integral part against liver fibrosis and cirrhosis. Both *in vitro* and *in vivo* experiments confirmed

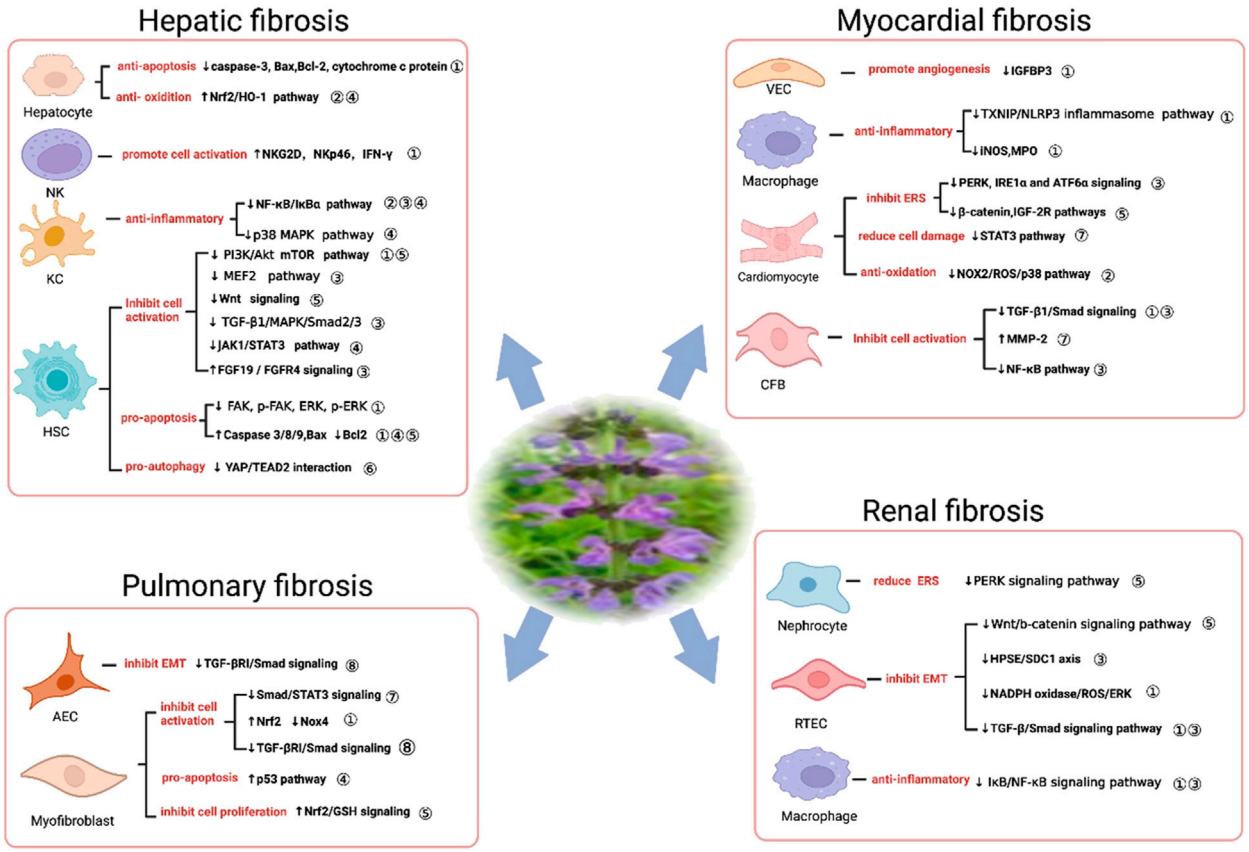

FIGURE 3
Pharmacological mechanisms of SM and its active ingredients in liver, lung, kidney and heart fibrosis. Ingredients in SM, ① *Salvia miltiorrhiza*; ② Tanshinol; ③ Salvianolic acid B; ④ Salvianolic acid A; ⑤ Tanshinone IIA; ⑥ Dihydrotanshinone I; ⑦ Cryptotanshinone; ⑧ Magnesium Lithospermate B. Abbreviations, NK, natural killer cells; KC, Kupffer cell; HSC, Hepatic stellate cell; VEC, vascular endothelial cell; CFB, myocardial fibroblast; AEC, alveolar epithelial cell; RTEC, renal tubular epithelial cell; Bax, B-cell lymphoma-2-associated X protein; BCL2, B-cell lymphoma-2; Nrf2, nuclear factor-erythroid 2-related factor 2; HO-1, heme oxygenase-1; NKG2D, natural killer cell group 2D; NF-κB, nuclear factor kappa-B; IκB, inhibitor of nuclear factor kappa-B; MAPK, mitogen-activated protein kinase; PI3K, phosphatidylinositol-3-kinase; Akt, protein kinase B; mTOR, molecular target of rapamycin; MEF2, myocyte enhancer factor 2; TGFβ1, transforming growth factor β1; Smad, *drosophila* mothers against decapentaplegic protein 2/3; JAK1, Janus kinase one; STAT3, signal transducer and activator of transcription three; FGF19, fibroblast growth factor 19; FGFR4, fibroblast growth factor receptor 4; FAK, focal adhesion kinase; p-FAK, phosphorylated focal adhesion kinase; ERK, extracellular regulated protein kinases; p-ERK, phosphorylated extracellular regulated protein kinases; YAP, yes-associated protein; TEAD2, TEA domain family member two; IGFBP3,insulin-like growth factor-binding protein 3; TXNIP, thioredoxin interacting protein; NLRP3, Nucleotide-binding oligomerization domain; leucine-rich repeat and pyrin domain-containing three; iNOS, inductible nitric oxide synthase; MPO, myeloperoxidase; PERK, protein kinase R-like endoplasmic reticulum kinase; IRE1α, Inositol requiring enzyme1α; ATF6α, activating transcription factor 6α; IGF-2R, insulin-like growth factor 2 receptor; NOX2, nicotinamide adenine dinucleotide phosphate oxidase two; ROS, reactive oxygen species; MMP-2, matrix metalloproteinase-2; EMT, epithelial-mesenchymal transition; TGF-βRI, transforming growth factor β receptor I; GSH, glutathione; ERS, endoplasmic reticulum stress; HPSE, heparinase; SDC1,syndecan-1; NADPH oxidase, reduced nicotinamide adenine dinucleotide phosphate oxidase; ↑ activate; ↓ inhibit).

that SM played anti-fibrotic roles in liver fibrosis and cirrhosis (Peng et al., 2018). These hepatoprotective mechanisms of SM were shown to be attributed to inhibiting inflammation, reducing oxidant stress, enhancing apoptosis of HSCs, decreasing hepatocellular injury and suppressing the functions of activation of HSCs without damaging the hepatocytes. In addition to the direct effects of inhibiting the activated HCSs, SM could indirectly enhance the activities of NK cell to reduce liver fibrosis (Peng et al., 2018). Several experimental studies had reported that SM could couple with some herbal medicines, such as radix astragali (Yang et al., 2008; Cao et al., 2020), stephania tetrandra (Chor et al., 2009), ligusticum chuanxiong and glycyrrhiza glabra (Lin et al., 2008), to exert the antifibrotic effects *via* alleviating collagen deposition and reducing inflammation in the liver. Moreover, the active anti-fibrotic ingredients from SM have gained an increasing amount of attention. Salvianolic acid A/B/C, danshensu, tanshinone IIA and dihydrotanshinone I were reported to have noticeable pharmacological activities and were also representative active ingredients in SM. The anti-fibrotic activities of these

TABLE 1 Effects of SM and its active ingredients against liver fibrosis *in vivo* and *in vitro*.

Animals/ Cells	Inducer	Drug and dose	Mechanism	References
In vivo				
C57BL/6 mice	10% CCl_4 2 ml/kg i.p	SM extract 3.0 g/kg i.g	NKG2D, Nkp46, IFN-γ↑	Peng et al. (2018)
SD rats	TAA 350 mg/kg i.p	PF2401-SF 1 or 2.5 mg/kg i.g	collagen 1(α), TIMP1, α-SMA↓	Parajuli et al. (2015)
SD rats	BDL	IH764-3 40 mg/kg i.p	α-SMA, FAK, p-FAK, ERK, p-ERK↓	Liu et al. (2012)
SD rats	50% CCl_4 1 ml/kg i.g	tanshinol 20 or 40 mg/kg i.g	SOD, GSH-Px, HO-1, NQO-1, GCLC, NF-κB, IκBα ↑ HA, LN, IV-C, PIIIP, MDA, Cox-2, TGF-β, TNF-α, IL-1β, IL-6, NF-κB in the nucleolus↓	Wang et al. (2018b)
SD rats	BDL	hot-water extract of SM 100 mg/kg i.g	TCHO, MDA, Hyp, α-SMA↓	Nan et al. (2001)
Kunming mice	0.1% DEN 10 ml/kg i.p	salvianolic acid B 10 or 30 mg/kg i.g	p-Smad3C↑ α-SMA,CollagenI, p-Smad2C, p-Smad2L,p-Smad3L↓	Wu et al. (2019)
SD rats	CCl_4 0.75 ml/kg i.g	PF2401-SF 50 mg/kg i.g	α-SMA↓	Parajuli et al. (2013)
Wistar rats	CCl_4 1 ml/kg i.p	Tanshinone IIA 10 mg/kg i.g	α-SMA, COL1A2, c-Jun, p-c-Jun, c-Myc, CCND1, MMP9, P65, p-P65, PI3K, P38↓	Shi et al. (2020)
Wistar rats	CCl_4 0.5 ml/kg i.p	SM extract 25 or 50 mg/kg i.g	GSH↑ GST, TGFβ1, TIMP-1, procollagen I↓	Lee et al. (2003)
SD rats	BDL	dihydrotanshinone I 25 mg/kg i.p	γ-GT, COL1A1¸ ACTA2, TGFβ1, MMP-2, TIMP-1, TIMP-2↓	Ge et al. (2017)
SD rats	CCl_4	tanshinol 20 or 40 mg/kg i.g	MMP-13, MMP-1,Bax, Caspase- 3↑ PIIINP, HA, CollagenIV, LN, HOP, TIMP-1, Collagen I, Collagen II, α-SMA, TGFβ, Cox-2, TNF-α, IL-1, IL-6, Bcl-2, β-FGF, PD-ECGF↓, PI3K/AKT/mTOR/p70S6K1↓	Peng et al. (2017)
Wistar rats	CCl_4 0.5 ml kg i.p	water-soluble extract of SM 50 mg/kg i.g	GSH↑ caspase-3, Bax, Bcl-2, cytochrome c protein, calpain-μ↓	Lee et al. (2006)
SD rats	CCl_4 1 ml/kg i.g	salvianolic acid B 10 or 20 mg/kg i.g	NF-κB, IκBα in the cytoplasm↑ HA, LN, IV-C, PIIIP, NF-κB in the nucleolus↓	Wang et al. (2012)
In vitro				
JS-1 cell line	TGF-β1 5 ng/ml	SM extract 12.5–50 μg/ml	RAE-1ε↑ α-SMA↓	Peng et al. (2018)
T6 and LX-2 cell lines	TGF-β1 9p.m.	salvianolic acid B 25, 50 and 100 μM	p-ERK1/2, p-JNK1/2, p-P38, p-Smad2C, p-Smad2L, p-Smad3C, p-Smad3L, PAI-1↓	Wu et al. (2019)
LX-2 cell line	LPS 100 ng/ml	salvianolic acid B 1, 2.5 and 5 μM	FGF19, FGFR4 ↑ α-SMA, COL1A1↓	Tian et al. (2021)
t-HSC/Cl-6 cell line	Null	PF2401-SF 20 μg/ml	Caspase -3, Caspase -8, Caspase- 9, Bax↑ Bcl2↓	Parajuli et al. (2013)
LX-2 cell line	TGF-β1 2 ng/ml	dihydrotanshinone I 1, 5 and 10 μM	MAP1LC3B, LC3B↑ TGFβ1, α-SMA, COL1A1, pHSCs, ACTA2, CTGF, SOX4, p62↓	Ge et al. (2017)
LX-2 cell line	7-days culture	salvianolic acid B (6 μM, 48 μM), caffeic acid (6 μM, 48 μM) and rosmarinic acid (48 μM)	α-SMA↓	Yang et al. (2013)
human primary HSCs	TGF-β1 10 ng/ml	salvianolic acid B 1 μM	MEF2, α-SMA, Collagen I↓	Zhang et al. (2019a)
T6 cell line	acetaldehyde 200 μM	danshensu 100, 125 and 150 μM	uPA↑ TGF-β1, PAI-1↓	Zhang et al. (2012)
t-HSC/Cl-6 cell line	null	tanshinone IIA 20 μM	Caspase -3, cytochrome c, cyclin E, cyclin A, cdk2, Bax/Bcl-2↑	Che et al. (2010)
primary rat HSCs	TGF-β1 1 ng/ml	salvianolic acid B 280 μM	DPPH, MDA, ROS, α-SMA↓	Lin et al. (2006b)
T6 cell line	PDGF-BB	salvianolic acid A 10 mM	Caspase -3↑ Bcl-2, p21, p27, Akt, cyclinsD1/E, PDGF↓	Lin et al. (2006a)
primary rat HSCs	24-h culturing	salvianolic acid A 1 and 10 μM	Collagen I↓	Liu et al. (2000)

Note: i.p: intraperitoneal injection; i.g.: intragastric administration.

TABLE 2 Effects of SM and its active ingredients against renal fibrosis *in vivo* and *in vitro*.

Animals/ Cells	Inducer	Drug and dose	Mechanism	References
In vivo				
SD rats	adenine 150 mg/kg i.g	Ethanol extract of SM 0.46 g/kg i.g. and water extract of SM 1.03 g/kg i.g	UP, Scr, BUN, ISF, E-cadherin, α-SMA, FN, p-ERK, NOX1, NOX2, NOX4, TGF-β↓	Cai et al. (2018b)
C57BL/6 mice	UUO model	protocatechualdehyde (PCA) 10 or 40 mg/kg i.g	Smad7↑	Yang et al. (2021)
			KIM-1, BUN, SCR, α-SMA, collagenI, fibronectin, TNF-α, IL-1β, MCP-1, COX2, iNOS, NF-κB, Smad3↓	
C57BL/6 mice	UUO model	salvianolic acid B 6.25–25 mg/kg i.g	SDC1, E-cadherin↑	Hu et al. (2020)
			BUN, CR, HPSE, α-SMA, TGF-β1, FGF-2↓	
SD rats	streptozotocin 60 mg/kg i.p	tanshinone IIA 2, 4, 8 mg/kg i.p	SOD↑	Xu et al. (2020)
			TGF-β1, TSP-1, Grp78, CHOP, p-PERK, p-elf2α, ATF4 ↓	
SD rats	5/6 nephrectomy	tanshinone IIA 10 mg/kg i.g	Ang II, TGF-β1, collagen IV↓	Ahn et al. (2010)
SD rats	streptozotocin 60 mg/kg i.p	danshen injection 0.5–1 ml/kg i.p	SOD↑	Xu et al. (2016)
			ROS, MDA, TGF-β1,Smad2/3, TNF-α, IL-1β, IL-6, p-IκBα, p-NF-κB p65 ↓	
	streptozotocin 55 mg/kg i.p	danshen injection 0.78 ml/kg i.p	GSH-Px, SOD↑	Yin et al. (2014)
			AGEs, LPO, TGF-β1↓	
In vitro				
HK-2 cell line	ISF 250 μM	Ethanol or water extract of SM, 5–100 μM	α-SMA, FN, E-cadherin↑	Cai et al. (2018b)
			NOX1, NOX2, NOX4, p-ERK ↓	
			TGF-β, TGF-βRI, TGF-βRII, Smad2, Smad3, Smad7 ↓	
primary renal TECs	TGF-β1 2 ng/ml	protocatechualdehyde 20–80 μM	LRNA9884, iNOS, COX2, IL-6, MCP-1, NF-κB, IL-6, α-SMA, collagen I, fibronectin↓	Yang et al. (2021)
HK-2 cell line	AngII 1 μM	salvianolic acid B 0.1–10 μM	SDC1, E-cadherin↑	Hu et al. (2020)
			TGF-β1, FGF-2, HPSE, α-SMA↓	
HK-2 cell line	glucose 30 mM	Tanshinone IIA 5 or 10 μM	VDR, E-cadherin↑ a-SMA, b-catenin, GSK-3b↓	Zeng and Bao, (2021b)
HK-2 cell line	glucose 30 mM	Tanshinone IIA 1–50 μM	E-cadherin↑	Cao et al. (2017)
			α-SMA, vimentin, fibronectin, Snail↓	

compounds were exhibited significantly, especially inhibiting the activation of HSCs which was a stromal cell in the liver well known for its role in triggering the fibrogenic process both *in vitro* and *in vivo*. These results indicated that SM alone or in combination with other herbs were highly effective in anti-fibrotic therapeutic strategy. And the inhibitory effect of the ingredients from SM might be a continuation of its anti-fibrotic effect. More details were shown in Table 1.

Renal fibrosis

Renal fibrosis is a common feature of a range of chronic kidney diseases (CKDs) with the progressive and irreversible declines in renal functions. Renal tubulointerstitial fibrosis, glomerulosclerosis, and arteriosclerosis with perivascular fibrosis are the established characteristic of renal fibrosis (Liu, 2011). Excessive deposition of ECM, inflammatory cell infiltration, fibroblast accumulation, and myofibroblast expansion disrupt the local vasculature and impede the tissue repair, which accelerates the development of renal fibrosis in CKDs and eventually leads to kidney failure. Therefore, renal fibrosis is a hallmark of end-stage kidney disease.

Currently, despite remarkable progress in preclinical animal experiments, very limited therapeutics could inhibit or even reverse renal fibrosis effectively and safely. Haemodialysis, peritoneal dialysis and kidney transplantation are largely to the symptomatic approaches and palliation of symptoms, but cannot fundamentally improve the condition. In contrast, TCM can provide an alternative approach for treating renal fibrosis. SM and its main ingredients were demonstrated to have nephroprotective activities and anti-fibrotic functions via multiple pathways in adenine diet, streptozotocin (STZ) injection, 5/6 nephrectomy and unilateral urethral obstruction (UUO) induced renal fibrosis models (Table 2). Both water and ethanol extracts of SM presented protections in nephropathy and renal fibrosis *via* inhibiting the elevation of renal functions, improving the clinical symptoms of glomerular and tubular atrophy, alleviating focal calcium deposits, altering metabolites and reversing renal interstitial fibrosis and inflammation.

Furthermore, it was revealed that SM suppressed renal fibrosis and epithelial trans-differentiation by inhibiting TGF-β/Smad and NADPH oxidase/ROS/ERK signaling pathways (Cai et al., 2018a). Beyond that, therapeutic application of SM was effective in combination with other agents. Astragalus membranaceus and SM could alleviate collagen deposition and metabolism, especially Tryptophan metabolism and Butanoate metabolism, in cyclosporin A-induced chronic nephrotoxicity and renal fibrosis. The further underlying mechanism might be lied in regulating the "gut-kidney axis" and modulating the disorder of miRNA-mRNA interaction profiles (Han et al., 2021).

In addition, active compounds in SM, such as protocatechualdehyde, salvianolic acid B, and tanshinone IIA, were also exert effects against renal fibrosis (Hu et al., 2020; Xu et al., 2020; Yang et al., 2021) in several renal fibrosis models. Protocatechualdehyde, a natural compound in the root of SM, was reported to decrease renal inflammation and fibrosis via mediating NF-κB/TGF-β1/Smad3/lncRNA9884/MCP-1 signaling pathway (Yang et al., 2021). Salvianolic acid B could notably reduce the renal injury and fibrosis in murine UUO model *in vivo*. The mechanism was confirmed to be related with the downregulation of HPSE/FGF-2/TGF-β1/α-SMA expression and upregulation of SDC1/E-cadherin levels *in vitro* (Hu et al., 2020). Tanshinone IIA was demonstrated to have excellent anti-fibrotic properties in streptozotocin-induced and 5/6 nephrectomy models, respectively (Ahn et al., 2010; Xu et al., 2020). More importantly, the mechanism for SM against renal fibrosis might be related to reducing endoplasmic reticulum stress to attenuate PERK signaling activities, decreasing expressions of Ang II, TGF-β1 and collagen IV, attenuating high glucose-induced EMT by up-regulating VDR levels on Wnt/β-catenin pathway and inhibiting HG-induced the epithelial-myofibroblast trans differentiation pathway (Ahn et al., 2010; Cao et al., 2017; Xu et al., 2020; Zeng and Bao, 2021a).

Pulmonary fibrosis

Pulmonary fibrosis is a chronic interstitial pulmonary disease caused by a diversity of insults, including smoke, chemical materials, microbial infection, and environment contamination (Noble et al., 2012). Pulmonary fibrosis (rather difficult to reverse), consisting of progressive and irreversible destruction of lung architecture caused by scar formation, could ultimately lead to organ malfunction, disruption of gas exchange, and death from respiratory failure (Wynn, 2011). Till now, no effective therapy could prevent or reverse the development of pulmonary fibrosis. Nintedanib and pirfenidone are proved by FDA to alleviate lung function and lung fibrosis, however, neither of these drugs are able to reverse pulmonary fibrosis. Currently, the only life-saving treatment available for patients with progressive lung fibrosis is lung transplantation. Thus, identifying drugs to ameliorate the pulmonary fibrogenesis is urgently needed.

Recently, TCM has played an indispensable role in the treatment of pulmonary fibrosis *via* its multi-components, multi-targets and multi-pathways. SM and its ingredients were demonstrated to have effects in extenuating pulmonary fibrosis (Peng et al., 2019). The effect of SM for treatment in pingyangmycin-induced experimental model, was reported for the first time in 1987 in China (Chen, 1987). In Table 3, we summarized the available literatures related to the mechanisms of SM and its ingredients against pulmonary fibrosis during the past 35 years. Among these, bleomycin (BLM) and silica were commonly used to induce pulmonary fibrosis in rats and mice. And TGF-β1-stimulated cultured lung fibroblast, such as HLFs and MRC-5, exerted as an excellent model for evaluating anti-fibrotic compounds *in vitro*.

Peng et al. (2019) found that ethyl acetate extract of SM could alleviate bleomycin-induced lung fibrosis. The mechanism was associated with the reduction of ROS generation in fibroblasts, activation of Nrf2 pathway and inhibition TGF-β1/Smad3 pathway *in vivo* and *in vitro*. Single use of SM significantly ameliorated experimental lung fibrosis, and such effect was also exerted when combined with other herbal medicine. Combination of SM and ligustrazine were viewed to attenuate bleomycin-induced pulmonary fibrosis in rats *via* modulating TNF-α and TGF (Huang et al., 2018). Both the lipophilic ingredients (tanshinone IIA and cryptotanshinone) and hydrophilic ingredients (salvianolic acid A, salvianolic acid B, and magnesium lithospermate B) from SM have protective effects against pulmonary fibrosis, including reducing the proliferation of lung fibroblasts and protecting the alveolar epithelial integrity (Pan et al., 2014; Liu et al., 2018; Zhang Y. et al., 2019; Luo et al., 2021a).

Salvianolic acid B (SAB) was the most well studied active hydrophilic compound of SM against lung fibrosis. SAB had potent anti-fibrotic effects via blocking proliferation of lung fibroblasts, trans-differentiation and oxidative stress levels (Liu et al., 2018; Jiang et al., 2020). The pharmacological mechanisms of SAB were mainly related to the inhibition of TGF-βRI/Smad signaling in activated pulmonary fibroblasts. Tanshinone IIA were also weakened the myofibroblast proliferation by activating Nrf2/GSH signaling pathway to limit glutaminolysis (An et al., 2019).

Myocardial fibrosis

Myocardial fibrosis (MF) is characterized by excessive deposition of ECM in the cardiac interstitium, which is a pathophysiologic component of many chronic myocardial diseases. Although the pathological processes of MF involved the complex interaction of multiple cell types, activated fibroblasts and myofibroblasts are the major contributors, serving as the main source of collagen fibres in cardiac fibrosis (Gonzalez et al., 2018). Clinically available drugs for

TABLE 3 Effects of SM and its active ingredients against pulmonary fibrosis *in vivo* and *in vitro*.

Animals/Cells	Inducer	Drug and dose	Mechanism	References
In vivo				
SD rats	intratracheal instillation of bleomycin 5 mg/kg	Cryptotanshinone 7.5–60 mg/kg	E-cadherin↑ Fibronectin, COL-I, COL-III, α-SMA, PAI-1, IL-6, TNF-α, p-STAT3Tyr705, p-STAT3Ser727↓	Zhang et al. (2019b)
C57BL/6 mice	intratracheal injection of bleomycin 1.25 U/kg	ethyl acetate extract of SM(EASM) 20, 40, 80 mg/kg	Nrf2↑ TGF-β, p-Smad3, α-SMA, Col-I, Nox4, acid-soluble collagen↓	Peng et al. (2019)
SD rats	intratracheal instillation of bleomycin 2 mg/kg	Magnesium Lithospermate B 50 mg/kg i.p	Col1A1, α-SMA, Col3A1, IL-4, IL-6, IL-13, TGF-β1↓	Luo et al. (2021b)
Wistar rats	intratracheal injection of bleomycin 5 mg/kg	salvianolic acid A 2.5, 5, and 10 mg/kg i.v	TGF-β mRNA↓	Pan et al. (2014)
C57BL/6 mice	intratracheal injection of bleomycin 0.025U/mice	tanshinone IIA 5, 10, 20 mg/kg, i.g	Nrf2↑ Nox4, Smad3, TGF-β1, fibronectin, Col-I, Col-III, α-SMA↓	An et al. (2019)
SD rats	intratracheal instillation of bleomycin 3.5 U/kg	Salvianolic Acid B 10 mg/kg i.p	Col1a1, Col1a2, Ctgf, PAI-1, α-SMA↓	Liu et al. (2016)
Wistar rats	intratracheal injection of bleomycin 5 mg/kg	Salvianolic acid B 20 mg/kg i.v	GSH, Nrf2↑ α-SMA, MDA↓	Liu et al. (2018)
Human fetal lung fibroblasts (HLFs)	TGF-β1 5 ng/ml	Cryptotanshinone 1.5–6 mg/L	E-cadherin↑ Fibronectin, COL-I, COL-III, α-SMA, PAI-1↓ TGF-βR I, TGF-βR II, Smad2, Smad3 ↓	Zhang et al. (2019b)
Mice embryo fibroblasts (NIH-3T3)	TGF-β1 10 ng/ml	EASM 0.1, 1, 3 μg/ml	Nrf2↑ TGF-β1, Nox4, PKC-δ, p-Smad3, α-SMA↓	Peng et al. (2019)
Human lung fibroblasts (MRC-5)	TGF-β1 10 ng/ml	salvianolic acid B 20 μg/ml or sodium tanshinone IIA sulfonate 50 μg/ml	IL-1β, TNF-α, COL1A1, α-SMA, ACTA2↓	Jiang et al. (2020)
Human type II alveolar epithelial cell line (A549) or MRC-5 cell	TGF-β1 10 ng/ml	Magnesium Lithospermate B 30 or 50 μM	Col 1A1, Col 3A1, α-SMA↓ TGF-βRI, Smad3 ↓	Luo et al. (2021b)
Murine 3T6 fibroblasts	null	salvianolic acid A 6.25–25 μg/ml	p21, p53, caspase-3↑ cyclin D1, cyclin E1, cyclin B1, Bcl-2↓	Pan et al. (2014)
NIH-3T3	TGF-β1 10 ng/ml	tanshinone IIA 1–10 μM	Nrf2, GSH↑ Nox4, α-SMA, Col-I, Smad3, Col-III, PKCδ↓	An et al. (2019)
A549 cell line	TGF-β1 10 ng/ml and TNF-α 10 ng/ml	salvianolic acid B 50 μg/ml	CDH1↑ FN1, p-Smad3, p-ERK1/2, p-JNK↓	Liu et al. (2016)
MRC-5 cell line	TGF-β1 10 ng/ml	salvianolic acid B 40 μM	GSH, Nrf2↑ α-SMA, vimentin, fibronectin, ROS, MDA↓	Liu et al. (2018)

treating MF were applied including angiotensin-converting enzyme inhibitors (lisinopril) (Brilla et al., 2000), type1 angiotensin II-receptor antagonists (losartan) (Diez et al., 2002) and mineralocorticoid-receptor antagonists (spironolactone) (Izawa et al., 2005), which target renin-angiotensin-aldosterone system. Besides, loop diuretics (torasemide) were also applied in clinical practice that targeting extracellular collagen processing (Lopez et al., 2004). However, no specific drugs exist for reversing myocardial fibrosis to the present date.

SM has been used in Chinese folk medicine to treat heart diseases for a long history in China. In recent years, multiple SM preparations such as compound Danshen tablets, compound Danshen Dripping Pill, Danshen injections, Danshen tablets and Danshen capsules have been used in treatment of cardiovascular problems. According to Chinese medicine theory, SM is considered to promote blood circulation and alleviate blood stasis so as to relieve pain, eliminate blood stasis and promote blood flow in treatment of MF. Similar to PF, SM, and its ingredients (e.g., Salvanic acid B) restrained fibroblasts activation and inhibited collagen deposition through suppressing oxidative stress and TGF-β1/smad signaling pathway in MF, especially blocking cardiac fibroblast proliferation and ECM synthesis (Zhang

TABLE 4 Effects of SM and its active ingredients against myocardial fibrosis *in vivo* and *in vitro*.

Animals/Cells	Inducer	Drug and dose	Mechanism	References
In vivo				
Kunming mice	Iron Dextran Injection 50 mg/kg i.p	SM injection 3 g/kg and 6 g/kg i.p	SOD↑ Hyp,MDA,COL-I,COL-III,TGF-β1, MMP-9↓	Zhang et al. (2015)
C57BL/6J mice	Streptozotocin (STZ) 60 mg/kg i.p	Salvianolic acid B (Sal B) 15 or 30 mg/kg i.p	VEGFA, VEGFR2, p-AKT, p-ERK↑ Collagen I, Collagen Ⅲ, IGFBP3↓	Li et al. (2020)
Kunming mice	Isoproterenol hydro-chloride injection (ISO) 2.5 mg/kg i.p	Salvanic acid B	Smad7↑ TGF-β1, Smad2/3↓	Gao et al. (2019b)
SD rats	left anterior descending (LAD) ligation	Danshen Injection (DSI) 1.5 ml/kg/d i.m	Bcl-2, Bax↑ MMP-2, iNOS, MPO↓	Wang et al. (2017)
SD rats	left aortic descending coronary artery ligation	Cryptotanshinone (CTS) 30 and 60 mg/kg i.g	FN, COX-2, NOX-2,NOX-4↓	Ma et al. (2014)
SD rats	left anterior descending coronary artery ligation	Salvianolate 10, 20 and 40 mg/kg i.p	TGFβ1, p-Smad2/Smad2, p-Smad3/ Smad3, Collagen I, Collagen III, MMP9, TIMP1, TXNIP, IL-1β, IL-18, NLRP3, Caspase-1, CRP, IL-6, BNP↓	Qiu et al. (2018b)
SD rats	left and right renal artery ligation	Tanshinone II-A 35 and 70 mg/kg i.g	MMP-9, TIMP-1, TIMP-2↓	Fang et al. (2010)
Wistar rats	Streptozotocin 65 mg/kg i.v	Cryptotanshinone 10 mg/kg i.g	STAT3, CTGF, MMP-9↓	Lo et al. (2017)
SD rats	isoprenaline 0.25 mg/kg i.p	isopropyl 3-(3,4-dihydroxyphenyl)-2-hydroxylpropanoate (IDHP) 50 mg/kg	Collagen I, Collagen III↓	Yin et al. (2015)
C57BL/6 mice	Isoprenaline 3 mg/kg s.c	Cryptotanshinone 20 mg/kg i.g	MMP-2↑	Ma et al. (2012)
In vitro				
Rat embryonic ventricular H9c2 cardiomyocytes	oxygen-glucose deprivation/ reoxygenation (OGD/R) condition	PCA 1.25, 2.5 and 5.0 μM	Caspase-3, Bax↓ CHOP, BiP, PERK, Ero1-Lα, IRE1α, ATF6, HIF-1α↓	Wan et al. (2021)
Mouse cardiac fibroblasts (CFs) cells	TGF-β1 20 ng/ml	Sal B 5, 10, and 20 ng/ml	Smad7↑ Smad2/3, MMP-2, MMP-9↓	Gao et al. (2019b)
primary rat cardiac fibroblasts (CFs)	Ang II 100 nM	Cryptotanshinone (CTS) 2.5–20 mM	FN, CTGF, p-ERK1/2, ROS, NOX-2, NOX-4, COX-2↓	Ma et al. (2014)
primary neonatal rat cardiac fibroblasts	Ang II 1 μM	Salvianolic acid B (SalB) 12.5–50 μM	Collagen I, FN, CTGF, p-IκB, p-p65, α-SMA↓	Wang et al. (2018a)
Primary neonatal rat cardiomyocytes	D-glucose 30 mM	cryptotanshinone 3 μM	STAT3, CTGF, MMP-9↓	Lo et al. (2017)
neonatal rat cardiac fibroblasts (NRCFs)	isoprenaline	isopropyl 3-(3,4-dihydroxyphenyl)-2-hydroxylpropanoate (IDHP) 1–100 μM	ROS, p-p38, NOX2↓	Yin et al. (2015)
H9c2 cardiomyoblast cell	AngII 10^{-8}M	Tanshinone IIA 40 μM	ERα, ERβ↑ β-catenin, p-ERK1/2, IGF-2R, LEF-1, MMP-9, MMP-2, TGF-β1, p-Smad2/3, SP-1,CTGF↓	Chen et al. (2017b)
Primary cardiac myocytes and cardiac fibroblasts from neonatal rats	endothelin-1 (ET-1) 10–8 M, phenylephrine (PE) 10–6 M, or insulin-like growth factor-1 (IGF-1) 10^{-8} M	tanshinone VI (tsh) 10^{-5} M	ET-1, PE, IGF-1↓	Maki et al. (2002)

et al., 2015; Qiu et al., 2018a; Gao et al., 2019a). The mechanisms were mainly associated with inhibiting TGF-β1 expression and Smad2/3 phosphorylation, as well as restraining the release of myeloperoxidase (MPO) (Wang et al., 2017). In addition, tanshinone IIA, the main lipophilic bioactive components of SM, reduced the Ang II-induced activation of β-catenin and IGF-2R pathways, apoptosis and cardiac remodeling via ERs (Chen et al., 2017a). More details were shown in Table 4.

Conclusions and outlooks

Organ fibrosis was a common endpoint of diverse chronic diseases with progressive tissue scarring and organ dysfunction that eventually led to organ failure and significant mortality world-wide (Wynn, 2004). Pulmonary fibrosis, cardiac fibrosis, hepatic fibrosis, and renal fibrosis were the most common four types of organ fibrosis in thorax and abdomainal viscera, which shared the same histopathological features, including the destruction of parenchyma cells, the activation of mesenchymal cells, and the imbalance of immunological cells. Fibrosis is a highly dynamic process in various organ systems. Indeed, despite certain achievements were made in clinic treatment, no specific drug for reversing fibrosis of either organ was approved by Food and Drug Administration. Numerous anti-fibrotic drugs against single-target and single-pathway single target have failed in clinical experiments, which revealed that the candidate drug against organ fibrosis should shift to multi-target and multi-pathway.

SM has been regarded as the most frequent used hepatoprotective and cardioprotective drug in TCM practice. Accumulated evidence suggests that SM and its active ingredients exerted protective effects on fibrotic diseases in thorax and abdomainal viscera. The mechanism of how SM and its ingredients benefit fibrosis treatment including but not limited to decreasing inflammation, alleviating oxidative stress, regulating collagen production and degradation, and preventing tissue injury through different signaling pathways (Figures 2, 3). In fibrotic diseases, SM and its ingredients exerted anti-fibrotic functions in different organs via different mechanisms. But they share the same core aim: to lower the fibrous septa in the viscera. It has been known that the activated fibroblasts and myofibroblasts, mainly activated by TGF-β1, are the principal cells of producing ECM (Henderson et al., 2020). On the one hand, SM and its ingredients could inhibit the activation of fibroblasts and myofibroblasts through TGF-β/Smad signaling pathway in fibrotic organs, which contributed the acceleration of ECM degradation, decrease of collagen cross-linking and inhibition of collagen/ECM deposition. And on the other hand, ECM degradation, blocked by SM and its ingredients, could alleviate the cell-ECM interactions to limit the excessive activation of fibroblasts and myofibroblasts.

However, despite of the encouraging progress in our understanding of the efficacy of SM in organ fibrosis, a nonnegligible translational gap remained between bioactive novel constituents extracted form SM and conversion into effective patient therapies and pharmacological agents. Besides, most of the known mechanisms were explored from *in vitro* experiments with a single cell line. Some advanced experimental designs, such as 3D culture system of co-culturing with a diverse array of cells *in vitro* and transgenic mice experiments *in vivo*, were urgent needed to verity the above discoveries. And although the efficacy of Chinese patent medicine from SM and its ingredients have been repeatedly tested in clinical treatment of organ fibrosis, more further studies are needed to better understand the mechanism and to serve the patients. In addition, because of the insufficient bioavailability of SM and its ingredients in poor solubleness, which leads to low oral bioavailability and delivery problems, advanced drug carriers are meaningful to develop, so as to enhance the tissue targeting, expand the clinical applications for the patients suffering from organ fibrosis.

In summary, though many shortcomings exist in the current studies, pharmacological studies and clinical practices have demonstrated that SM and its ingredients are considered to have good clinical efficacy and widespread application prospects. With the implementations of further research, it is believed that more systematic molecular mechanisms and anti-fibrotic targets of SM and its ingredients could be identified and elucidated to improve the treatment for patients with organ fibrosis.

Author contributions

ZY and YP wrote the manuscript; JQ, DP, and XS assisted with the data collection; CL, YT, and YP made critical revision for the manuscript; CL and YP co-correspond for the whole project.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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