Research progress on the molecular mechanisms of Saikosaponin D in various diseases (Review)

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Abstract. Bupleurum, a Traditional Chinese Medicine (TCM) herb, is widely used in China and other Asian countries to manage chronic liver inflammation and viral hepatitis. Saikosaponin D (SSD), a triterpenoid saponin extracted from Bupleurum, exhibits extensive pharmacological properties, including anti-inflammatory, antioxidant, anti-apoptotic, anti-fibrotic and anti-cancer effects, making it a therapeutic candidate for numerous diseases. Clarifying the targets and molecular mechanisms underlying TCM compounds is essential for scientifically validating TCM's therapeutic roles in disease prevention and treatment, as well as for identifying novel therapeutic targets and lead compounds. This analysis comprehensively examines SSD's mechanisms across various conditions, such as myocardial injury, pulmonary diseases, hepatic disorders, renal pathologies, neurological disorders, diabetes and cancer. In addition, challenges and potential solutions encountered in SSD research are addressed. SSD is posited as a promising monomer for multifaceted therapeutic applications and this article aims to enhance researchers' understanding of the current landscape of SSD studies, offering strategic insights to guide future investigations.

Contents

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1. Introduction

As awareness of health and wellness grows, the benefits of Traditional Chinese Medicine (TCM) in health care and disease treatment are increasingly recognized. TCM compounds, valued for their targeted therapeutic effects and minimal adverse reactions (1-3), are gaining market traction. Guided by TCM principles, researchers employ modern scientific and technological methods to investigate the pharmacodynamics, pharmacology, toxicology and clinical applications of TCM compounds. Extensive studies have elucidated the active ingredients and mechanisms of these compounds (2), leading to significant advancements. For instance, Qinggan Huoxue Recipe has been shown to mitigate alcoholic liver disease (ALD) progression by inhibiting the liver X receptor-lysophosphatidylcholine acyl-transferase 3 signaling pathway (4). In addition, Danggui Buxue Decoction may improve diabetic nephropathy by modulating insulin resistance, chronic inflammation, and lipid accumulation (5). In Jiangzhi Granule, Xiang *et al* (6) identified that kaempferol, a monomer from lotus leaf, alleviates liver damage in non-alcoholic steatohepatitis mice by reducing endoplasmic reticulum stress. Ginsenosides from ginseng have been demonstrated to exhibit anti-inflammatory, antioxidant and anti-tumor activities (7,8), alongside neuroprotective effects through the protein kinase B (AKT)/cyclic adenosine monophosphate (cAMP) response element-binding protein (CREB)/brain-derived neurotrophic factor (BDNF) pathway (9). Such findings support the development of innovative therapeutics.

Bupleurum, a widely used TCM herb in China and other Asian countries for managing chronic liver inflammation and viral hepatitis (10,11), is a key component in classic TCM formulas such as Xiao-Chai-Hu-Tang (12), Chaihu-Shugan-San (13) and Xiaoyaosan (14). Known for its anti-inflammatory, anti-infective and hepatoprotective effects (15-18), Bupleurum has yielded >100 triterpene saponins, including saikosaponin (SS)A, B, C and D, with SSA and SSD as primary bioactive components (11). Studies have demonstrated SSD's diverse pharmacological effects, including anti-inflammatory, antioxidant, anti-apoptotic, anti-fibrotic

and anti-cancer properties (19), underscoring its therapeutic potential across a spectrum of conditions such as myocardial injury (20), lung injury (21), non-alcoholic fatty liver disease (NAFLD) (22), liver fibrosis (23), glomerulonephritis (24), diabetes (25), depression (26), Alzheimer's disease (AD) (27) and various cancers (28,29).

Elucidating the action targets and molecular mechanisms of TCM compounds is instrumental in scientifically validating their roles in disease prevention and treatment, as well as in identifying novel therapeutic targets and lead compounds. Our team has dedicated extensive research to understanding SSD's mechanisms in liver fibrosis (30-33), while valuable studies by other researchers on SSD in additional diseases also deserve close examination. This review synthesizes the mechanisms of SSD across a range of diseases from its discovery to the present, highlighting current challenges and proposing strategic solutions in SSD research. SSD emerges as a promising monomer with multifaceted therapeutic potential. This article will enhance researchers' understanding of SSD's current research status and offer strategic guidance for future studies.

2. Chemical structure of SSD

SSD, a triterpene saponin compound, dissolves well in methanol and ethanol but has limited solubility in water. Structurally, it resembles steroids (Fig. 1) (34,35) and possesses a chemical formula of $C_{42}H_{68}O_{13}$ with a molecular weight of 780.98 (35). The extracted SSD is a white powder, which will be considered for oral administration in the future. The main administration methods of SSD in existing animal experimental studies are gastric lavage and intraperitoneal injection (24,25).

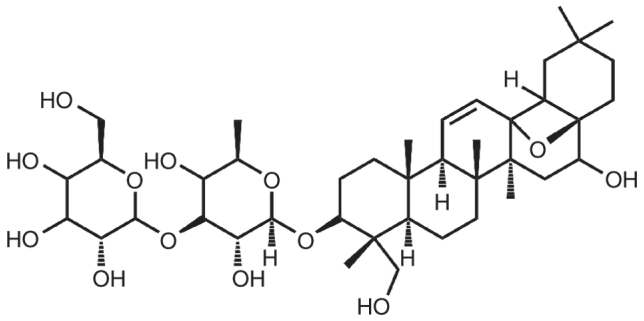

Figure 1. Chemical structure of SSD. SSD is a triterpene saponin with a steroid-like structural framework. Its chemical formula is $C_{42}H_{68}O_{13}$, with a molecular weight of 780.98 g/mol. SSD, Saikosaponin D.

3. Pharmacological effects of SSD

SSD possesses diverse therapeutic properties, including anti-inflammatory, antipyretic, analgesic, antioxidant, anti-apoptotic, antiviral, antifibrosis, immune-regulation and anti-tumor activities (19), with specific mechanisms supported by studies (Fig. 2).

Investigations into SSD's anti-inflammatory mechanisms reveal its potent inhibition of lipopolysaccharide (LPS)-induced inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2) and pro-inflammatory cytokines (TNF-α and IL-6) in RAW264.7 cells by blocking nuclear factor-κB (NF-κB) activation (36). Furthermore, SSD was reported to significantly reduce cerulein-induced apoptosis and inflammation in pancreatic AR42J cells by modulating the mitogen-activated protein kinase (MAPK) signaling pathway (37). Heat stress, a trigger for reactive oxygen species (ROS) production, leads to oxidative tissue damage (38). Zhang *et al* (39) reported that SSD mitigated heat stress-induced oxidative damage in LLC-PK1 cells by promoting antioxidant enzymes and heat shock protein 72. The imbalance between cellular defense mechanisms and free radical production is known as oxidative stress (OS). Research by Lin *et al* (40) demonstrated that SSD significantly reduces H_2O_2-induced malondialdehyde (MDA) and lactate dehydrogenase (LDH) release, while enhancing superoxide dismutase (SOD) activity and antioxidant capacity, thereby protecting against PC12-cell apoptosis. The primary mechanism involves SSD's ability to eliminate ROS and disrupt MAPK-mediated oxidative injury, which prevents H_2O_2-induced PC12-cell death (40). An additional study showed SSD's ability to reduce OS through the phosphatidylinositol-3 kinase (PI3K)/AKT/nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, improving muscle atrophy in chronic kidney disease (CKD) models (41).

SSD has shown antiviral activity against enterovirus A71 (EV-A71), which causes hand, foot and mouth disease, a virus known to trigger autophagy (42). Li *et al* (43) found that SSD inhibits EV-A71 infection by effectively suppressing viral RNA replication and subsequent viral protein synthesis, preventing EV-A71-induced cell death.

In anti-fibrosis research, Sun *et al* (44) demonstrated that SSD inhibits human embryonic lung fibroblast proliferation and collagen production by modulating the transforming growth factor β (TGF-β1)/Smads signaling pathway, exerting a significant antifibrotic effect.

SSD has also shown immunomodulatory benefits, as it regulates Type 1 T-helper cell (Th1)/Th2 and Th17/T-regulatory cell (Treg) imbalances and alleviates Hashimoto's thyroiditis (HT) severity in mice by promoting M2 macrophage differentiation (45).

Among saikosaponins, SSD displays the strongest anti-tumor activity, targeting various cancers through multiple pathways (46-48). For instance, SSD inhibits non-small cell lung cancer cell proliferation and induces apoptosis by disrupting the signal transducer and activator of transcription 3 (STAT3) pathway (48) and also suppresses triple-negative breast cancer cell growth through β-catenin signaling inhibition (49).

These pharmacological insights underscore SSD's promising potential as a therapeutic agent.

4. Research progress on SSD in various diseases

SSD demonstrates a wide range of therapeutic properties, including anti-inflammatory, antipyretic, analgesic, antioxidant, anti-apoptotic, antiviral, antifibrotic, immune-regulation and anti-tumor activities. Consequently, its pharmacological effects of inhibiting inflammation, oxidative stress, fibrosis and so on are related to the treatment of various diseases, such as myocardial injury (20), lung damage (50), NAFLD (22), liver fibrosis (23), glomerulonephritis (51), diabetes (25),

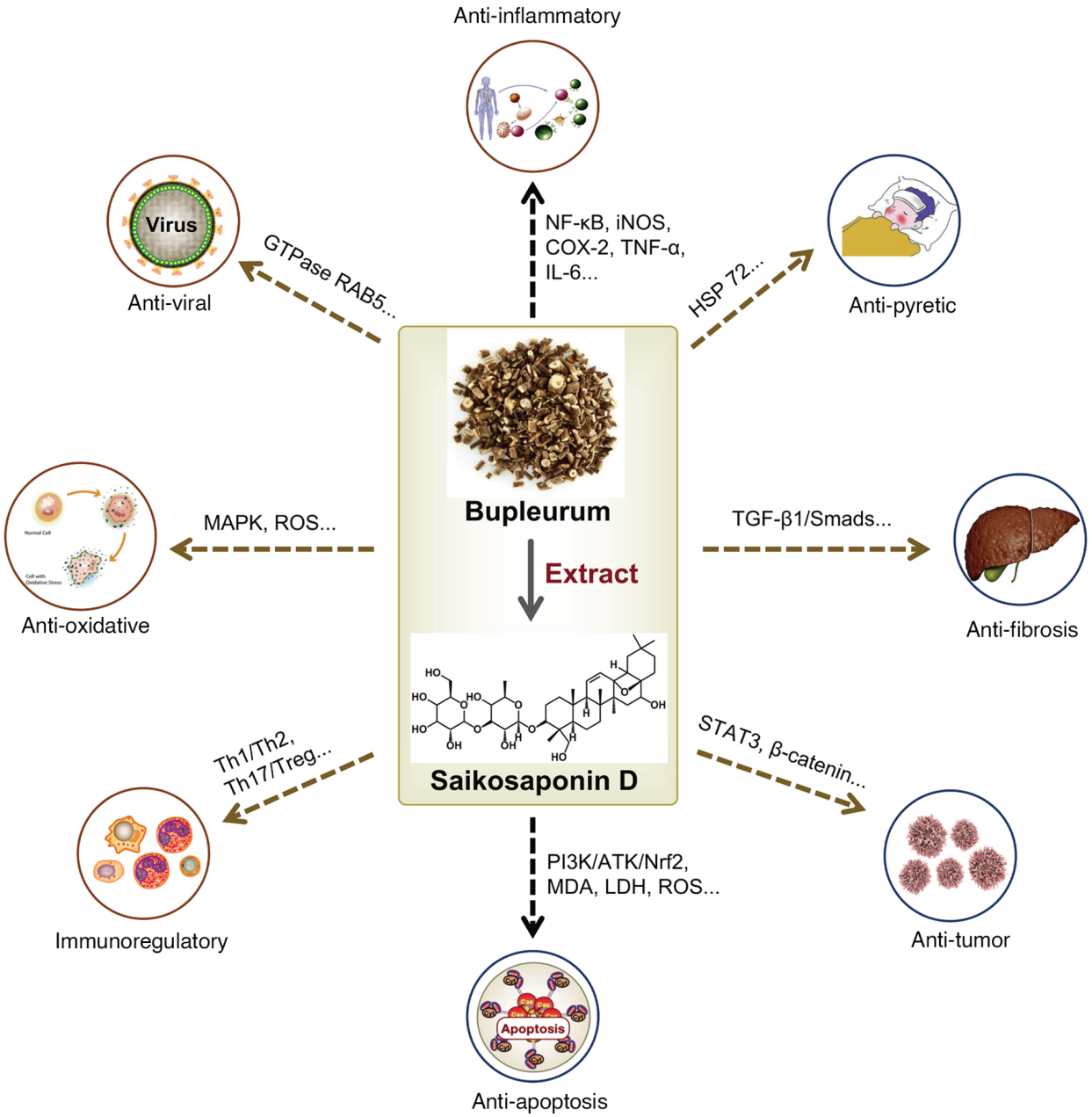

Figure 2. Pharmacological effects of SSD. SSD exhibits a broad range of therapeutic activities, including anti-inflammatory, antipyretic, analgesic, antioxidant, anti-apoptotic, antiviral, antifibrotic, immune-regulatory and antitumor effects. AKT, protein kinase B; COX-2, cyclooxygenase-2; HSP72, heat shock protein 72; IL-6, interleukin-6; iNOS, inducible nitric oxide synthase; LDH, lactate dehydrogenase; MAPK, mitogen-activated protein kinases; MDA, malondialdehyde; NF-κB, nuclear factor-κB; Nrf2, nuclear factor erythroid 2-related factor 2; PI3K, phosphatidylinositol-3 kinase; ROS, reactive oxygen species; SSD, Saikosaponin D; STAT3, signal transducer and activator of transcription 3; TGF-β1, transforming growth factor β; TNF-α, tumor necrosis factor-α.

depression (26), AD (27) and cancers (52,53) (Fig. 3). Specific molecular mechanisms are detailed in Tables I and II.

Myocardial damage. The oxidative damage induced by anticancer drugs such as doxorubicin (DOX) can result in irreversible cardiotoxicity (54). Zhang *et al* (20) found that DOX administration led to cardiac damage and dysfunction, as well as reduced survival in mice. In H9c2 cells, DOX treatment increased LDH leakage, cardiomyocyte apoptosis, myocardial fibrosis and reduced cardiomyocyte volume. SSD protects cardiomyocytes from DOX-induced cardiotoxicity by inhibiting excessive OS through the p38-MAPK signaling pathway (20).

Lung-related diseases

Lung damage. In a rat model of ventilator-induced lung injury (VILI), SSD reduced pulmonary neutrophil infiltration, myeloperoxidase levels and pro-inflammatory cytokines (MIP-2, IL-6 and TNF-α), while elevating anti-inflammatory mediators (TGF-β1 and IL-10) (21). SSD also reduced OS and apoptosis in lung tissue by downregulating caspases-3 and pro-apoptotic protein Bax, while upregulating the anti-apoptotic protein Bcl-2. These effects suggest that SSD may alleviate VILI by suppressing inflammation, OS and apoptosis (21). Another study demonstrated that SSD reduced LPS-induced inflammation and apoptosis in MLE-12 lung epithelial cells and, *in vivo*, decreased pathological damage, inflammation and apoptosis

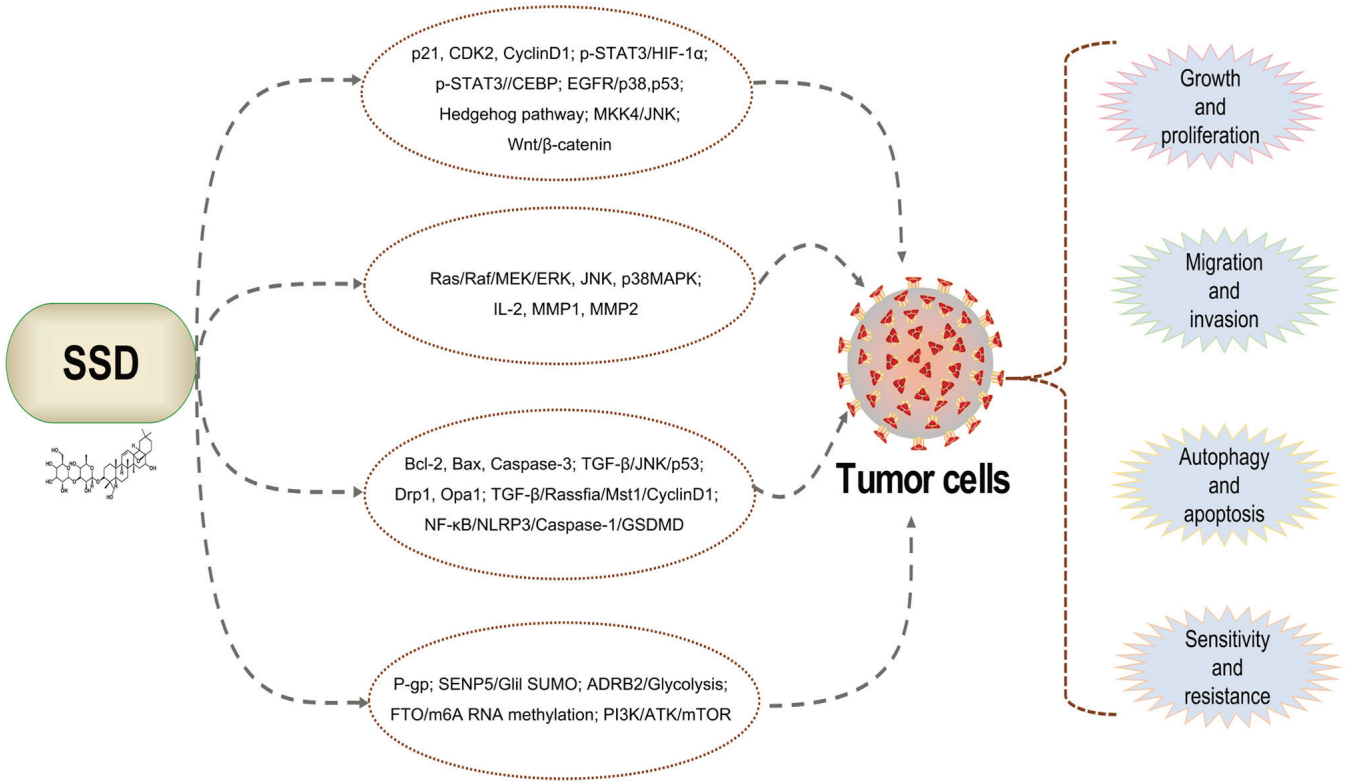

Figure 3. Antitumor mechanisms of SSD. SSD exerts antitumor effects by inhibiting tumor-cell growth and proliferation through molecules such as P21, CDK1, cyclin D1, STAT3, HIF-1α, EGFR and P53. It suppresses migration and invasion by targeting pathways including Ras/Raf/MEK/ERK, JNK, P28MAPK and MMPs. SSD promotes autophagy and apoptosis in tumor cells through the modulation of Bcl-2, Bax, Caspase-1, TGF-β/JNK/P53, Drp1 and the NF-κB/NLRP3/Caspase-1 axis. Additionally, SSD affects drug sensitivity and resistance by modulating pathways such as P-gp, SENP5/Gli SUMO, ADRB2/Glycolysis and PI3K/AKT/mTOR. ADRB2, β2-adrenergic receptors; CDK2, cyclin-dependent kinase 2; CREB, cyclic adenosine monophosphate (cAMP) response element-binding protein; EGFR, epidermal growth factor receptor; Drp1, dynamin-related protein 1; FTO, fat mass and obesity-associated protein; GSDMD, gasdermin D; HIF-1α, hypoxia-inducible factor-1α; MMP-1, matrix metalloproteinase-1; m6A, mRNA N6-methyladenosine; NF-κB, nuclear factor-κB; NLRP3, NLR family pyrin domain containing 3; Opa1, optic atrophy 1; PI3K, phosphatidylinositol-3 kinase; P-gp, P-glycoprotein; SENP5, sentrin-specific proteases; SSD, Saikosaponin D; STAT3, signal transducer and activator of transcription 3; TGF-β1, transforming growth factor β.

in cecum ligation and perforation-induced mouse septic acute lung injury model (55).

Pulmonary fibrosis. Idiopathic pulmonary fibrosis, a group of heterogeneous parenchymal lung disorders characterized by chronic progressive fibrosis, represents one of the most severe interstitial lung diseases (56). Sun *et al* (44) reported that SSD inhibits human embryonic lung fibroblast proliferation and collagen production [Collagen-1 (Col-1), α-smooth muscle actin (α-SMA)] via modulation of the TGF-β1/Smads pathway, exerting an antifibrotic effect. A recent study revealed that SSD reduces the expression of angiotensin-1 (Ang-1), Ang-2 and Tie-2 (tyrosine kinase receptors with immunoglobulin and epidermal growth factor homology domains-2) in the angiopoietin/Tie2 pathway, which may help alleviate pulmonary inflammation in bleomycin-induced mice (administered via intratracheal injection) by inhibiting angiogenesis and fibrosis (57).

Liver diseases

Acute liver injury. Excessive acetaminophen (APAP) intake can lead to acute liver injury, which can be fatal and necessitates effective pharmacological intervention (58). Liu *et al* (59) found that SSD protected mice from APAP-induced hepatotoxicity by primarily inhibiting NF-κB and STAT3-mediated inflammatory signaling pathways (IL-6, C-C motif chemokine ligand 2, IL-10). Another study indicated that SSD mitigated carbon tetrachloride-induced acute hepatocyte damage by suppressing OS and NLR family pyrin domain containing 3 (NLRP3) inflammasome activation in HL-7702 cells (60). Similar protective effects were observed in animal models (61), where SSD administration led to reduced MDA and superoxide production in carbon tetrachloride-treated mouse liver tissue while enhancing SOD, glutathione peroxidase (GPx) and catalase activities. In addition, protein levels of caspase 1, NLRP3, apoptosis-associated speck-like protein, IL-1β and IL-18 were diminished (61), supporting conclusions drawn from *in vitro* experiments.

ALD. ALD, encompassing a range of liver damage due to chronic excessive alcohol intake, has become a significant global health concern (62). Hepatic stellate cells (HSCs) play a pivotal role in ALD progression, with activated HSCs acting as a primary source of extracellular matrix (ECM) in the liver (63). Jiang *et al* (64) demonstrated that SSD suppressed proliferation and promoted apoptosis in acetaldehyde-activated rat HSC-T6 cells by stimulating autophagosome formation. SSD treatment increased caspase-3 and Bax expression while reducing Ki67 and Bcl-2 levels. Despite its therapeutic potential, SSD has poor bioavailability, stability and solubility, which limits its clinical application. A promising study aimed to enhance SSD's efficacy by formulating SSD-loaded liposomes using a

Table I. SSD inhibits the molecular mechanisms underlying the development of several diseases.

Disease	Mechanism	(Refs.)
Myocardial damage	SSD → p38MAPK↓ → CAT, GPx↑, MDA, ROS↓ → OS↓	(20)
Lung damage	SSD → neutrophils, MPO, MIP, IL-6, TNF-α↓, TGF-β1, IL-10↑ → inflammation↓; SSD → caspase-3, bax↓, bcl-2↑ → apoptosis↓	(21,55)
Pulmonary fibrosis	SSD → TGF-β1/Smads↓ → Col-1, α-SMA↓ → fibrosis↓; SSD → angiopoietin/Tie2 pathway↓ → ANG-1, ANG-2, Tie2↓ → Angiogenesis↓	(44,57)
Acute liver injury	SSD → NF-κB, STAT3↓ → IL-6, CCL2↓, IL-10↑ → inflammation↓; SSD → NLRP3 inflammasome, OS↓ → NLRP3, ASC, IL-1β, IL-18↓; SOD, GPx, CAT↑, MDA, MSP↓ → inflammation and OS↓	(59-61)
Alcoholic liver disease	SSD → ALT, AST, TG, TC, TNF-α, MDA↓ GPx, T-SOD↑ → inflammation and OS↓	(63-65)
NAFLD	SSD → INSIG/SREBP1c, Fas, Acaca↓ → fatty acid synthesis↓; SSD → PPARα, COX1, CPT1α↑ → fatty acid oxidation↑	(22,67, 68)
Liver fibrosis	SSD → GPER1/autophagy → Col-1, α-SMA↓ → fibrosis↓; SSD → ERβ↑ → ROS/NLRP3 pathway↓ → inflammation↓	(32,73)
Functional dyspepsia	SSD → ghrelin, SP↑, caspases-3, bax↓, bcl-2↑ → autophagy and apoptosis↓	(74)
Ulcerative colitis	SSD → NF-κB↓ → IL-6, TNF-α, IL-1β↓, IL-10↑ → inflammation↓	(75)
Chronic pancreatitis	SSD → PI3K/AKT/mTOR↑ → autophagy↓ → fibrosis↓; SSD → MAPK → inflammation and apoptosis↓	(37,77)
Nephritis	SSD → TGF-β1, macrophages, CD8+T↓ → inflammation↓; SSD → TCF7/FOSL1/ MMP-9 → inflammation and apoptosis↓	(24,51)
Chronic kidney disease	SSD → PI3K/AKT/Nrf2↑ → ROS↓	(41)
Nephrotoxicity	SSD → MAPK, NF-κB↓ → TNF-α, IL-1β, IL-6, NO, iNOS↓ → inflammation↓	(82)
Renal failure	SSD → TGF-β1/BMP7/Gremlinl/Smad↓ → fibrosis↓	(84)
Alzheimer's disease	SSD → NF-κB↓ → amyloid β, astrocytes, hippocampal microglia↓; SSD → Nrf2 pathway↑ → OS↓	(27,87)
Depression	SSD → p-CREB, BDNF↑ → neuron generation↑; SSD → NF-κB, miR-155↓, FGF-2↑, Homer1-mGluR5 and mTOR pathways↑ → depressive behavior↓; SSD → MGB1/TLR4/NF-κB↓ → inflammation, microglia↓ → depressive behavior↓	(91-94)
Diabetes complications	SSD → SIRT3↑ → OS↓ → DN↓; SSD → AQP1/RhoA/ROCK↓ → inflammation (IL-6, TNF-α, IL-1β)↓, NVC↑ → DPN↓	(25,79)
Thyroiditis	SSD → TPOAb, IFN-γ(Th1), IL-17(Th17)↓ M2 macrophage polarization↑ → HT↓	(45)
Osteoarthritis	SSD → PI3K/AKT/mTOR↓ → inflammation and autophagy↓; SSD → Nrf2/HO-1/ROS↑ → inflammation and ECM damage↓; SSD → microRNA-199-3p↑ → TCF4↑ → inflammation↓	(98-100)

ADRB2, β2-adrenergic receptors; ANG, angiotensin; ASC, adapter protein apoptosis associated speck-like protein containing a CARD; ALT, alanine aminotransferase; AKT, protein kinase B; AST, aspartate aminotransferase; BDNF, brain-derived neurotrophic factor; CAT, catalase; COX-2, Cyclooxygenase-2; C/EBPβ, CCAAT enhancer binding protein beta; CPT1α, carnitine palmitoyltransferase-1 alpha; CREB, cyclic adenosine monophosphate (cAMP) response element-binding protein; ERβ, estrogen receptor β; FOSL1, Fos-like antigen 1; FTO, fat mass and obesity-associated protein; GPx, glutathione peroxidase; IL-6, interleukin-6; iNOS, inducible nitric oxide synthase; LDH, lactate dehydrogenase; MAPK, mitogen-activated protein kinases; MDA, malondialdehyde; MPO, myeloperoxidase; MMP-9, matrix metalloproteinase-9; m6A, mRNA N6-methyladenosine; MSP, MDA and superoxide production; NCV, nerve conduction velocity; NF-κB, nuclear factor-κB; NLRP3, NLR family pyrin domain containing 3; Nrf2, nuclear factor erythroid 2-related factor 2; OS, oxidative stress; PI3K, phosphatidylinositol-3 kinase; ROS, reactive oxygen species; SOD, superoxide dismutase; SP, substance P; SSD, Saikosaponin D; STAT3, signal transducer and activator of transcription 3; TCF4, transcription factor-4; TC, total cholesterol; TG, triglycerides; TGF-β1, transforming growth factor β; TLR4, Toll-like receptor 4;TNF-α, tumor necrosis factor-α; TPOAb, thyroid peroxidase antibody; T-SOD, total superoxide dismutase.

thin-film hydration method (65). Compared to the group treated with SSD alone, mice administered SSD liposomes showed significantly lower serum alanine aminotransferase, aspartate aminotransferase, MDA, TNF-α, total cholesterol and triglyceride levels in liver homogenates, while GPx and total SOD levels were significantly elevated. These observations suggest that SSD liposomes exhibit enhanced hepatoprotective effects in alleviating alcoholic hepatitis in mice, likely due to their improved antioxidative and anti-inflammatory properties (65).

NAFLD. Adipogenesis is the developmental process by which preadipocytes differentiate into mature adipocytes, leading to fat accumulation (66). Research has shown that SSD suppresses adipogenesis in 3T3-L1 adipocytes by promoting AMP-activated protein kinase phosphorylation and

Table II. SSD inhibits the molecular mechanisms underlying the development of cancers.

Disease	Mechanism	(Refs.)
Thyroid cancer	SSD → P53, bax↑, bcl-2↓ → apoptosis↑; SSD → P21↑, CDK2, cyclin D1↓ → cell cycle inhibition↑	(101)
Lung cancer	SSD → TGFα-JNK-p53, TGFα-Rassfia-Mst1↑; NF-κB/NLRP3/caspase-1/GSDMD↑; STAT3/Bcl-2 pathway↓ → apoptosis↑; SSD → TGFβ-p53/p21/p27/p15/p16, TGFα-Rassfia-cyclin D1↑ → cell proliferation↓	(46,50, 103)
Breast cancer	SSD → β-catenin↓ → apoptosis↑; SSD → P-gp↓ → drug resistance↓	(49,105)
Liver cancer	SSD → p-STAT3/HIF-1α, p-STAT3/C/EBPβ↓ → COX-2↓ → proliferation↓, apoptosis↑; SSD → P53, bax↑, bcl-2, HIF-1α↓ → radiosensitivity and apoptosis↑; SSD → SENP5↑ → Glil SUMO↓ → chemosensitivity↑	(111-116)
Intrahepatic cholangiocarcinoma	SSD → ADRB2/Glycolysis pathway → drug resistance↓	(130,131)
Gastric cancer	SSD → IKKβ/NF-κB pathway↓ → apoptosis and autophagy↓; SSD → caspase-3, bcl-2, IL-2↑, MMP1, MMP2 ↓ → apoptosis↑, migration and invasion↓	(28,133)
Pancreatic cancer	SSD → MKK4/JNK pathway↑ → proliferation↓; SSD → PI3K/AKT/mTOR↓ → M2 polarization↓ → immunosuppression↓	(47,135)
Kidney cancer	SSD → EGFR/p38↓ → p53↑ → cell cycle arrest and apoptosis↑	(136)
Prostate cancer	SSD → GSK3β↓ → Wnt/β-catenin↓ → EMT, CSC↓; SSD → p53, p21 ↑ → cell cycle arrest↑; SSD → caspaes3 ↑ → apoptosis↑	(138,139)
Ovarian cancer	SSD → Drp1, Opa1 ↑, MMP↓ → mitochondrial division and cell cycle arrest↑ → apoptosis↑	(141)
Endometrial cancer	SSD → p21, cyclin B↑ → G2/M cycle arrest↑; SSD → ROS, bcl-2↑, mitochondrial membrane potential↓ → apoptosis↑; SSD → Ras/Raf/MEK/ERK, JNK and p38 MAPK pathway → tumor metastasis↓	(142)
Osteosarcoma	SSD → p53, p21, p27↑, cyclin D1↓ → proliferation↓; SSD → cytochrome C, bax/bcl-2 ratio, caspase-3, caspase-8, caspase-9↑ → apoptosis↑	(144,145)
Glioblastoma	SSD → JNK, caspase-3↑, AKT, ERK↓ → apoptosis↑	(146)
Medulloblastoma	SSD → Hedgehog pathway↓ → tumor growth↓	(151)
Acute myeloid leukemia	SSD → FTO↓ → m6A RNA methylation↑ → tumor drug resistance↓	(155)

ADRB2, β2-adrenergic receptors; AKT, protein kinase B; CDK2, cyclin-dependent kinase 2; COX-2, cyclooxygenase-2; CSC, cancer stem cell; Drp1, dynamin-related protein 1; EGFR, epidermal growth factor receptor; EMT, epithelial-to-mesenchymal transition; FTO, fat mass and obesity-associated protein; GSK3β, glycogen synthase kinase 3β; GSDMD, gasdermin D; HIF-1α, hypoxia-inducible factor-1α; IL-6, interleukin-6; MAPK, mitogen-activated protein kinases; MMP, mitochondrial membrane potential; m6A, mRNA N6-methyladenosine; NF-κB, nuclear factor-κB; NLRP3, NLR family pyrin domain containing 3; Nrf2, nuclear factor erythroid 2-related factor 2; Opa1, optic atrophy 1; PI3K, phosphatidylinositol-3 kinase; P-gp, P-glycoprotein; ROS, reactive oxygen species; SENP5, sentrin-specific proteases; SSD, Saikosaponin D; STAT3, signal transducer and activator of transcription 3; TGF-β1, transforming growth factor β; UCMS, unpredictable chronic mild stress.

its substrate acetyl-CoA carboxylase during the early stage of adipogenesis, while concurrently inhibiting the phosphorylation of the ERK1/2 and p38 MAPK pathways (67). In a study focused on SSD's effects on NAFLD, SSD was found to significantly reduce fatty acid biosynthesis by downregulating fatty acid synthase (FASN) and acetyl-CoA carboxylases α (ACACA) expression and to enhance fatty acid degradation through increased expression of COX1 and carnitine palmitoyltransferase-1α (CPT1α) (22). Building on these outcomes, Gu *et al* (68) conducted further investigations using a high-fat diet (HFD)- and fructose water-induced metabolic dysfunction-associated fatty liver disease mouse model along with HepG2 cells, primary mouse hepatocytes and adipocytes. They discovered that SSD acts as a potent peroxisome proliferator-activated receptor α (PPARα) activator, promoting fatty acid oxidation in hepatocytes and adipocytes while upregulating insulin-induced genes 1 and 2 (INSIG1/2) expression, which inhibits sterol regulatory element-binding protein 1c (SREBP-lc) maturation and thereby reduces fatty acid production. Of note, the lipid-regulating effects of SSD were nullified by the PPARα inhibitor GW6471, indicating that SSD mitigates metabolism-related fatty liver disorder via coordinated modulation of the PPARα and INSIG/SREBP-1c pathways (68).

Liver fibrosis. Previous studies highlighted SSD's protective effects against CCl_4-induced liver fibrosis (23,69-71), though detailed mechanisms were initially unclear. Recent research has provided deeper insights. *In vitro* experiments

demonstrated that SSD induced apoptosis in HSC-T6 and LX-2 cells through both caspase-3-dependent and -independent pathways, promoting Bax and Bak translocation to mitochondria, which disrupts mitochondrial function and membrane potential, ultimately releasing apoptotic factors (72). Further investigations using TGF-β and CCl_4 to establish liver fibrosis models *in vitro* and *in vivo* revealed that SSD significantly reduced fibrosis markers Col-1 and α-SMA. Importantly, SSD inhibited fibrosis progression in primary HSCs and TGF-β-treated LX-2 cells by modulating the G protein-coupled estrogen receptor 1/autophagy pathway (73). An additional study noted that SSD attenuated oxidative stress-induced HSC-T6 activation and fibrosis progression through regulation of estrogen receptor β (Erβ), suggesting that SSD may act as a novel phytoestrogen with estrogen-like effects (31). Lin *et al* (32) demonstrated that SSD combats liver fibrosis via the ERβ/NLRP3 inflammasome (NLRP3, IL-18 and IL-1β) pathway. Further supporting this, Zhang *et al* (33) found that SSD reduces liver fibrosis by stimulating the ERβ pathway and downregulating the ROS/NLRP3 inflammasome. Collectively, these outcomes underscore SSD's strong potential as an anti-liver fibrosis agent.

Intestinal diseases

Functional dyspepsia (FD). FD ranks among the most prevalent digestive tract disorders. Zeng *et al* (74) developed a model to investigate SSD's impact on apoptosis, autophagy and the morphology of Cajal intestinal cells in FD. Their findings showed that SSD administration in FD rats prevented inflammatory cell infiltration, restored the normal gastric mucosal structure and significantly upregulated light chain 3 I/II, ghrelin and substance P (SP) protein expression, while reducing apoptosis rates. SSD also markedly improved the ultrastructure and clarity of intestinal Cajal cells (ICCs), suggesting it enhances ICC morphology, regulates excessive autophagy and alleviates gastrointestinal motility disorders in FD by modulating ghrelin and SP levels (74).

Ulcerative colitis (UC). In a separate study on DSS-induced UC in mice, SSD significantly decreased pro-inflammatory cytokines (TNF-α, IL-6 and IL-1β) and elevated mRNA levels of the anti-inflammatory cytokine IL-10 (75). The primary mechanism involves SSD's suppression of NF-κB activation and modulation of the gut microbiota to mitigate DSS-induced intestinal inflammation (75).

Chronic pancreatitis (CP). CP is a progressive fibro-inflammatory syndrome where acinar cell injury initiates inflammation and pancreatic stellate cell (PSC) activation (76). Cui *et al* (77) found that SSD alleviates pancreatic fibrosis by inhibiting PSC autophagy through the PI3K/AKT/mTOR pathway. Their subsequent research showed that SSD further reduces pancreatic injury by inhibiting acinar cell apoptosis and inflammation via the MAPK signaling pathway (37).

Kidney diseases

Nephritis. Prior research has shown that SSD can prevent aminonucleoside-induced proteinuria in rats (78). Another study indicated that SSD protects renal tubular epithelial cells from high-glucose-induced injury through modulation of SIRT3 (79). Li *et al* (51) demonstrated that SSD hinders the progression of mesangial proliferative glomerulonephritis in rats by downregulating TGF-β1 and reducing macrophages and $CD8^+$ T lymphocytes. Additionally, it has been suggested that SSD reduces renal inflammation and apoptosis in a sepsis mouse model by inhibiting the transcription factor-7 (TCF7)/Fos-like antigen 1/matrix metalloproteinase (MMP)-9 axis (24), supporting its protective role in renal inflammation.

CKD. In CKD, skeletal muscle atrophy diminishes quality of life and increases morbidity and mortality (80). Huang *et al* (41) developed a muscle atrophy model using 5/6 nephrectomized mice and dexamethasone-treated C2C12 myotubes. Their results revealed that SSD activates the PI3K/AKT/Nrf2 pathway, reducing OS and alleviating CKD-induced muscle atrophy (41).

Nephrotoxicity. Cisplatin (DDP)-induced nephrotoxicity significantly limits the efficacy of this widely used anticancer drug (81), with inflammation and apoptosis likely contributing to the observed renal damage. Ma *et al* (82) examined the anti-apoptotic, anti-inflammatory and antioxidant effects of SSD in DDP-induced injury in human renal cortex and HK-2 human proximal tubular epithelial cells. Their findings indicated that SSD substantially increased the survival rate of DDP-treated HK-2 cells, improved nuclear morphology and reduced vesicle-3 activation and apoptosis. In addition, SSD treatment significantly lowered TNF-α, IL-1β and IL-6 secretion, NO generation and iNOS expression. The underlying mechanism suggests that SSD mitigates DDP-induced nephrotoxicity by inhibiting the MAPK and NF-κB signaling pathways (82).

Renal failure. Peritoneal dialysis has the potential to enhance life quality and prolong survival in patients with renal failure; however, peritoneal fibrosis can frequently lead to treatment discontinuation (83). Liu *et al* (84) found that SSD may alleviate peritoneal fibrosis in renal failure rats by modulating the TGF-β1/BMP7/Gremlin1/Smads pathway, though further research is needed to confirm SSD's mechanism in renal failure.

AD. AD, a neurodegenerative disorder, manifests primarily through dementia, memory loss and language deficits (85). As elevated ROS levels are implicated in OS in AD (86). Du *et al* (87) showed that SSD alleviates glutamate-induced oxidative cytotoxicity in SH-SY5Y human neuroblastoma cells by activating the Nrf2 pathway, underscoring SSD's neuroprotective effects. However, it has been reported that SSD may impair cognitive function in mice by inhibiting hippocampal neurogenesis through the AKT/forkhead box G1 pathway (27). Another study found that SSD decreases the viability of neural stem/progenitor cells by disrupting neurotrophic factor receptor signaling, thus impairing hippocampal neurogenesis and potentially leading to cognitive deficits (88). These observations suggest a complex role for SSD in AD, with both protective and adverse effects, highlighting the need for further research to clarify SSD's impact on neurodegeneration.

Depression. Depression is a severe, recurrent disorder characterized by persistent low mood, anhedonia and impaired cognitive function (89). Early studies indicated that SSD therapy significantly increased hippocampal neurogenesis in rats exposed to unpredictable chronic mild stress (UCMS), as

evidenced by elevated doublecortin levels. In addition, SSD treatment boosted hippocampal neuromolecule levels, such as p-CREB and BDNF, in UCMS rats, suggesting that SSD may counter CMS-induced depressive behaviors partly by enhancing hypothalamic-pituitary-adrenal axis function and supporting hippocampal neurogenesis (90). Further research demonstrated that SSD alleviates depressive-like behavior in UCMS rats by reducing NF-κB and microRNA (miR)-155, while upregulating the fibroblast growth factor 2 (91), homer protein homolog 1-metabotropic glutamate receptor 5 and mTOR signaling pathways (92). A recent study found that SSD alleviates depression in UCMS mice by promoting NLRP3 ubiquitination and suppressing inflammasome activation (26). SSD also reduced LPS-induced depression-like behavior in mice by inhibiting microglial activation and neuroinflammation, potentially through downregulation of the mammaglobin 1/Toll-like receptor 4/NF-κB pathway (93). These insights suggest SSD as a promising candidate for treating depressive disorders.

Diabetes. Diabetes complications include diabetic nephropathy (DN) and diabetic peripheral neuropathy (DPN) (94). Zhao *et al* (79) showed that SSD protects renal tubular epithelial cells (NRK-52E) from high glucose-induced OS by upregulating SIRT3, elucidating its protective mechanism against DN. Another study revealed that SSD improved body weight, lowered blood glucose levels, alleviated mechanical and thermal hyperalgesia, enhanced nerve conduction velocity and reduced pro-inflammatory cytokines (TNF-α, IL-1β and IL-6) in streptozotocin/HFD-induced DPN in rats. Of note, SSD mitigated DPN by inhibiting the aquaporin 1/Ras homolog family member A/Rho-associated protein kinase signaling pathway (25).

Thyroiditis. HT is an autoimmune condition (95). Du *et al* (45) reported that SSD therapy reduced lymphocyte infiltration in the thyroid tissue of HT mice, lowered reduced serum thyroid peroxidase antibody levels and suppressed the expression of Th1-type cytokine interferon-γ and Th17-type cytokine IL-17. SSD also shifted the M1/M2 macrophage balance in the spleen toward M2 polarization. These observations suggest that SSD could modulate Th1/Th2 and Th17/Treg imbalances and mitigate HT severity in murine models by promoting M2 macrophage differentiation (45).

Osteoarthritis. Osteoarthritis is the most prevalent joint disease among the elderly, characterized by inflammation and autophagy dysregulation (96). A literature survey by Jiang *et al* (97) indicated that SSD may inhibit inflammation and modulate autophagic processes by downregulating the PI3K/AKT/mTOR signaling pathway, positioning SSD as a promising treatment option for osteoarthritis. Wu *et al* (98) demonstrated in their experimental investigation that SSD inhibited IL-1β-induced apoptosis in differentiated ATDC 5 chondrocytes *in vitro*. Furthermore, SSD effectively prevented cartilage degeneration in the knee joints of mice and reduced the number of osteochondrocytes in the subchondral bone. Of note, SSD activates the Nrf2/heme oxygenase-1/ROS axis, suppresses the production of inflammatory mediators and protects against ECM degradation, thereby delaying the progression of osteoarthritis in destabilization of the medial meniscus model mice (98). A recent study also reported that SSD reduces inflammatory responses in osteoarthritis mice and chondrocytes and mediates autophagy by upregulating miR-199-3p, which targets TCF4 (99). These insights collectively support the notion that SSD mitigates the development of osteoarthritis through its anti-inflammatory and autophagic effects.

Cancer

Thyroid cancer. In thyroid cancer, SSD has been shown to enhance p53 and Bax expression while reducing Bcl-2 levels, promoting apoptosis in thyroid cancer cells. In addition, SSD notably elevates p21 and inhibits cyclin-dependent kinase 2 and cyclin D1, leading to the suppression of human thyroid cancer cell growth (100).

Lung cancer. Prior research has established that SSD inhibits growth and induces programmed cell death in non-small cell lung cancer (NSCLC) cells (A549 and H1299), primarily by inhibiting STAT3 phosphorylation and activating caspase 3 (52). Chen *et al* (46) further elucidated the anti-cancer mechanism of SSD, revealing that it induces apoptosis in A549 cells through two pathways: TGFα-JNK-p53 and TGFα-Rassfia-Mst1. SSD also inhibits A549 cell proliferation by activating two pathways: TGF-β-p53/p21/p27/p15/p16 and TGF-α/Rassfia/cyclin D1 (46). Drug resistance remains a significant challenge in lung cancer treatment (101). *In vivo* and *in vitro* studies by Tang *et al* (102) indicated that SSD reduced p-STAT3 levels and increased Bcl-2 expression. Downregulation of STAT3 enhanced lung cancer cell responsiveness to gefitinib, suggesting that the combination of SSD and gefitinib may yield improved anti-tumor effects in NSCLC cells, linked to the inhibition of the STAT3/Bcl-2 signaling pathway. Recent investigations have also demonstrated that SSD induces apoptosis in HCC827 and A549 NSCLC cells by increasing ROS levels and activating the NF-κB/NLRP3/caspase-1/gasdermin D pathway (50). These outcomes provide a strong rationale for the use of SSD in the treatment of NSCLC.

Breast cancer. Elevated expression of P-glycoprotein (P-gp) in multidrug-resistant (MDR) cells poses a significant barrier to effective cancer chemotherapy (103). Research indicates that SSD effectively counteracts P-gp-mediated multidrug resistance in MCF-7/adriamycin breast cancer cells (104). Another study corroborated these findings, revealing that the combination of DOX and SSD yielded a stronger anti-cancer effect compared to either DOX or SSD alone (105). Furthermore, Wang *et al* (49) demonstrated that SSD significantly inhibits β-catenin and its associated downstream target genes, leading to programmed cell death in various triple-negative breast cancer cell lines (HCC1937, MDA-MB-468 and MDA-MB-231 and MCF-7). Fu *et al* (106) expanded on the mechanisms underlying SSD's anti-breast cancer activity, showing that it inhibits autophagosome-lysosome fusion and induces autophagy-independent apoptosis via caspase-3 activation in MDA-MB-231 cells. A recent untargeted metabolomic analysis highlighted that SSD exerts anti-breast cancer effects by regulating basal metabolism (107), with changes in serum metabolites observed in breast cancer mice

following SSD treatment, including alterations in sphingolipid metabolism, glycerophospholipid metabolism and the biosynthetic pathways for phenylalanine, tyrosine and tryptophan (107).

Liver cancer. Hepatocellular carcinoma (HCC) ranks among the most common malignancies (108). In an earlier study utilizing an diethyl nitrosamine (DEN)-induced rat HCC model, SSD was found to inhibit the expression of syndecan-2, MMP-2, MMP-13 and TIMP-2 in liver tissue, suggesting its potential anti-HCC effects (109). COX-2 (110) and C/EBPβ (111) are known to be associated with inflammation and carcinogenesis. One investigation revealed that SSD inhibited the proliferation of HCC SMMC-7721 cells and induced apoptosis by downregulating COX-2 expression and reducing prostaglandin E2 synthesis (112). In addition, SSD was shown to impede DEN-induced liver cancer in rats by suppressing C/EBPβ and COX-2 levels (113). Two further studies indicated that SSD inhibits COX-2 expression via the p-STAT3/HIF-1α pathway (114) and the p-STAT3/C/EBPβ signaling pathway (115), thereby exerting an anti-HCC effect.

The integration of SSD and radiotherapy demonstrates superior efficacy in the treatment of liver cancer compared to their individual applications. Research indicates that SSD enhances the radiosensitivity of SMMC-7721 liver cancer cells by regulating the G0/G1 and G2/M cell cycle checkpoints, which correlates with the upregulation of p53 and Bax and the downregulation Bcl-2 (116). A similar study confirmed that SSD also increases the radiosensitivity of liver cancer cells (SMMC-7721 and HepG2) under hypoxic conditions by suppressing hypoxia-inducible factor-1α, thereby triggering the upregulation of p53 and Bax and the downregulation of Bcl-2 (117). The activation of glioma-associated oncogene (GLI) family proteins and significant protein assimilation are characteristic of HCC cells. Hypoxia activates the sonic hedgehog pathway, which promotes epithelial-to-mesenchymal transition (EMT), invasion and chemosensitivity in HCC cells, with hypoxia-dependent GLI protein activation requiring SUMOylation (118-120). Zhang *et al* (121) demonstrated that SSD inhibited liver cancer cells (Hep3B) and enhanced chemotherapy sensitivity through sentrin-specific protease 5-dependent inhibition of Gli1 SUMOylation in hypoxic environments. Furthermore, SSD significantly increased radiation-induced apoptosis in SMMC-7721 and MHCC97L liver cancer cells while concurrently inhibiting cell proliferation (122). The introduction of the autophagy inhibitor chloroquine or the mTOR agonist MHY1485 attenuated the pharmacodynamic effects of SSD, suggesting that SSD enhances radiation-induced apoptosis in HCC cells by promoting autophagy through the inhibition of mTOR phosphorylation (123).

Ongoing investigations into the anti-HCC mechanisms of SSD have included a non-targeted metabolomics study revealing that SSD, in combination with neuropilin (NRP)-1 gene knockout, exerts anti-liver cancer effects *in vitro*, primarily by modulating lipid transport and phospholipid metabolism (124). In addition, the potential interactions between SSD and its hypothetic target, NRP-1, are under investigation. Li *et al* (125) found that SSD significantly induced the expression and enzyme activity of cytochrome P 450 enzyme (CYP)1A2 and CYP2D6 in HepaRG cells. Another study utilizing molecular docking indicated that SSD substantially suppressed the expression and enzyme activity of CYP3A4 protein in HepaRG cells; however, experimental validation is still required (126).

Intrahepatic cholangiocarcinoma (ICCA). ICCA is a highly lethal malignant tumor, with systemic chemotherapy using gemcitabine as the primary clinical treatment option (127,128). Norepinephrine (NE) and epinephrine (E) have been shown to promote ICCA cell growth and diminish the efficacy of gemcitabine through stimulation of the β 2-adrenergic receptors (ADRB2) receptor (129). A 2023 study demonstrated that SSD can reverse the adverse effects of gemcitabine in ICCA cells by reducing ADRB2 levels. Furthermore, SSD inhibited drug efflux and glycolysis in ICCA cells by modulating the expression of multidrug resistance 1, ABC subfamily G, isoform 2 protein, hexokinase 2 and glucose transporter 1. This suggests that SSD may counteract NE- and E-induced gemcitabine resistance in intrahepatic cholangiocarcinoma via downregulation of ADRB2 and glycolytic signaling pathways (130).

Gastric cancer (GC). GC remains a significant contributor to cancer-related mortality, with drug resistance being a critical factor in its poor prognosis (131). Research by Hu *et al* (28) indicated that SSD enhances the efficacy of DDP by inhibiting the growth and invasiveness of SGC-7901 and SGC-7901/DDP-resistant cells, thereby increasing DDP-induced apoptosis. SSD appears to enhance the sensitivity of GC cells to DDP, potentially through inhibition of the IKKβ/NF-κB pathway, which induces apoptosis and autophagy in GC cells (28). A recent network pharmacology study identified six key targets linking SSD to gastric cancer: VEGFA, IL-2, CASP3, BCL2L1, MMP2 and MMP1. Experimental results demonstrated that SSD induces apoptosis in cancer cells by enhancing caspase-3 activity and elevating Bcl-2 levels, while also inhibiting migration and invasion through upregulation of IL-2 and downregulation of MMP1 and MMP2 (132). These findings indicate that SSD may play a role in overcoming drug resistance in GC treatment.

Pancreatic cancer. Pancreatic cancer remains one of the deadliest malignancies with limited therapeutic options (133). SSD has been shown to inhibit the growth of pancreatic cancer cells (BxPC3, PANC1 and Pan02) and enhance the cleavage of apoptotic proteins caspase-3 and caspase-9 by activating the MAPK kinase 4-JNK signaling cascade (47). An additional *in vivo* and *in vitro* study found SSD directly suppresses pancreatic cancer cell apoptosis and invasion while modulating the immunosuppressive microenvironment to reactivate local immune responses. The primary mechanism involves reducing M2 macrophage polarization by downregulating phosphorylated STAT6 levels and the PI3K/AKT/mTOR signaling pathway (134). These findings suggest that SSD holds promise as a potential treatment for pancreatic cancer.

Kidney cancer. Cai *et al* (135) reported that SSD induces apoptosis in human renal cell adenocarcinoma cells (769-P and 786-O) by upregulating the p53 protein and arresting the cell cycle in the G0/G1 phase, primarily through inhibition of the EGFR/p38 signaling pathway.

Prostate cancer (PC). PC ranks among the most prevalent malignancies affecting males (136). Research by Yao *et al* (137) demonstrated that SSD induces apoptosis in DU145 cells via

the intrinsic apoptotic pathway. The primary mechanism involves SSD causing cell cycle arrest in G0/G1 phase through upregulation of p53 and p21, along with regulation of Bcl-2 family proteins, dissipation of mitochondrial membrane potential, release of cytochrome into the cytosol and activation of caspase-3, leading to apoptosis. Another study revealed that SSD suppresses the growth, migration and invasion of prostate cancer (DU145 and CWR22Rv1) by reversing EMT and inhibiting the expression and activity of MMP2/9 (138). In addition, SSD impedes the self-renewal capacity of cancer stem cell phenotypes by reducing glycogen synthase kinase 3β phosphorylation, thereby blocking the Wnt/β-catenin signaling pathway (138). These findings position SSD as a promising therapeutic agent for PC.

Ovarian cancer. DDP and its derivatives serve as first-line anticancer drugs for ovarian cancer (139). Studies indicate that SSD sensitizes drug-resistant ovarian cancer cells to DDP-induced apoptosis by promoting mitochondrial fission and causing G2/M phase arrest. The specific mechanism involves the enhancement of calcium signaling, upregulating of mitochondrial fission proteins dynamin-related protein 1 and optic atrophy 1 and inhibition of MMPs (140).

Endometrial cancer. Research conducted by Tang *et al* (141) revealed that SSD upregulates p21 and Cyclin B, leading to G2/M phase retention in endometrial cancer Ishikawa cells. Furthermore, SSD increased ROS levels, reduced the mitochondrial membrane potential, activated Bcl-2 and caspase family cascades, and mediated both endogenous and exogenous apoptosis pathways in Ishikawa cells. In addition, SSD influences three classic MAPK pathways (Ras/Raf/MEK/ERK, JNK and p38-MAPK pathways) to inhibit cell metastasis (141).

Osteosarcoma. Although human osteosarcoma has a low incidence rate, its prognosis is often poor compared to other cancers (142). A study assessing SSD's therapeutic potential in osteosarcoma demonstrated that it significantly suppresses the proliferation of 143B and MG-63 cells. The underlying mechanism includes the upregulation of tumor protein 53 (p53) and its downstream targets (p21, p27, Bcl-2-like protein 4 and cleaved caspase-3), along with the downregulation of cyclin D1 expression levels (143). Another study within the same year indicated that SSD, either alone or in combination with the JNK inhibitor SP600125, inhibits proliferation, induces apoptosis, and suppresses migration and invasion in human osteosarcoma U2 cells. However, SP600125 alone did not show a significant effect on U2 cells. The mechanism involves enhancement of cytochrome release, elevation of the Bax/Bcl-2 ratio, and activation of caspases -3, -8 and -9, indicating that apoptosis is triggered via both mitochondrial and death receptor pathways (144). These findings provide a theoretical basis for the use of SSD in osteosarcoma treatment.

Glioblastoma (GBM). An earlier study demonstrated that SSD can inhibit apoptosis in human GBM U87 cells, primarily by significantly suppressing the phosphorylation of AKT and ERK while promoting the expression of phosphorylated JNK and cleaved caspase-3 (145). A subsequent investigation revealed that SSD notably impedes the growth of RG-2, U87-MG and U251 cells in a sugar-dependent manner, leading to a marked increase in the proportion of apoptotic cells. Further research has indicated that SSD induces apoptosis and autophagy by activating endoplasmic reticulum stress in GBM cells, thereby exerting anti-GBM effects (146). Chemotherapy remains a critical adjunctive treatment for glioblastoma; however, resistance to chemotherapy presents an urgent clinical challenge for neuro-oncologists (147). Liang *et al* (148) discovered that SSD partially suppressed the migration, invasion and apoptosis of LN-229 cells. When combined with temozolomide (TMZ), SSD enhanced the chemotherapeutic efficacy of TMZ by increasing the apoptosis rate and LDH release in LN-229 cells, while also inhibiting the expression of stem cell factors (octamer-binding transcription factor 4, SRY-box transcription factor 2, myelocytomatosis viral oncogene homolog and Kruppel-like factor 4 at both gene and protein levels (148). These insights lay the groundwork for the potential application of SSD in overcoming GBM chemotherapy resistance, although further research is required for a more comprehensive understanding.

Medulloblastoma (MB). MB is a highly malignant embryonic tumor and the most common primary tumor of the posterior fossa in children (149). A 2021 study demonstrated that SSD inhibits tumor progression in MB-transplanted mice by suppressing the Hedgehog signaling pathway (150). However, further investigations are necessary to elucidate the mechanisms underlying SSD's anti-MB effect.

Acute myeloid leukemia (AML). AML remains an uncommon but potentially devastating condition with persistently elevated mortality rates (151). The fat mass and obesity-associated protein (FTO), an mRNA N6-methyladenosine (m6A) demethylase, functions as an oncogene that facilitates leukemic oncogene-driven cellular transformation and leukemogenesis (152,153). Research by Sun *et al* (154) demonstrated that SSD significantly suppressed AML cell proliferation, induced apoptosis and caused cell cycle arrest both *in vivo* and *in vitro*. At the molecular level, SSD specifically targets FTO, thereby enhancing m6A RNA methylation, which reduces the stability of downstream gene transcripts and inhibits associated pathways. Notably, SSD also mitigates FTO/m6A-mediated resistance to tyrosine kinase inhibitors in leukemia (154). This investigation reveals promising therapeutic avenues for the treatment of leukemia.

5. Conclusion and prospects

TCM monomers are single components extracted from TCM, characterized by a clear chemical structure and established pharmacological activity. Compared to compound formulas and proprietary Chinese medicines, TCM monomers offer advantages such as well-defined ingredients, clear mechanisms of action and straightforward quality control. Consequently, they exhibit promising applications in the treatment of various diseases (155-158). SSD is a prominent bioactive component of Bupleurum, demonstrating pharmacological activities that include hepatoprotective, anti-inflammatory, antiviral and anti-tumor effects (15,18,159). The mechanisms underlying these pharmacological actions involve inflammation, OS, immune modulation, autophagy and apoptosis, thereby influencing the progression of numerous diseases (Fig. 4). An unpublished study by our group also identified that SSD can exert anti-hepatic fibrosis effects by modulating the expression of biological clock genes in liver tissue, with findings set for

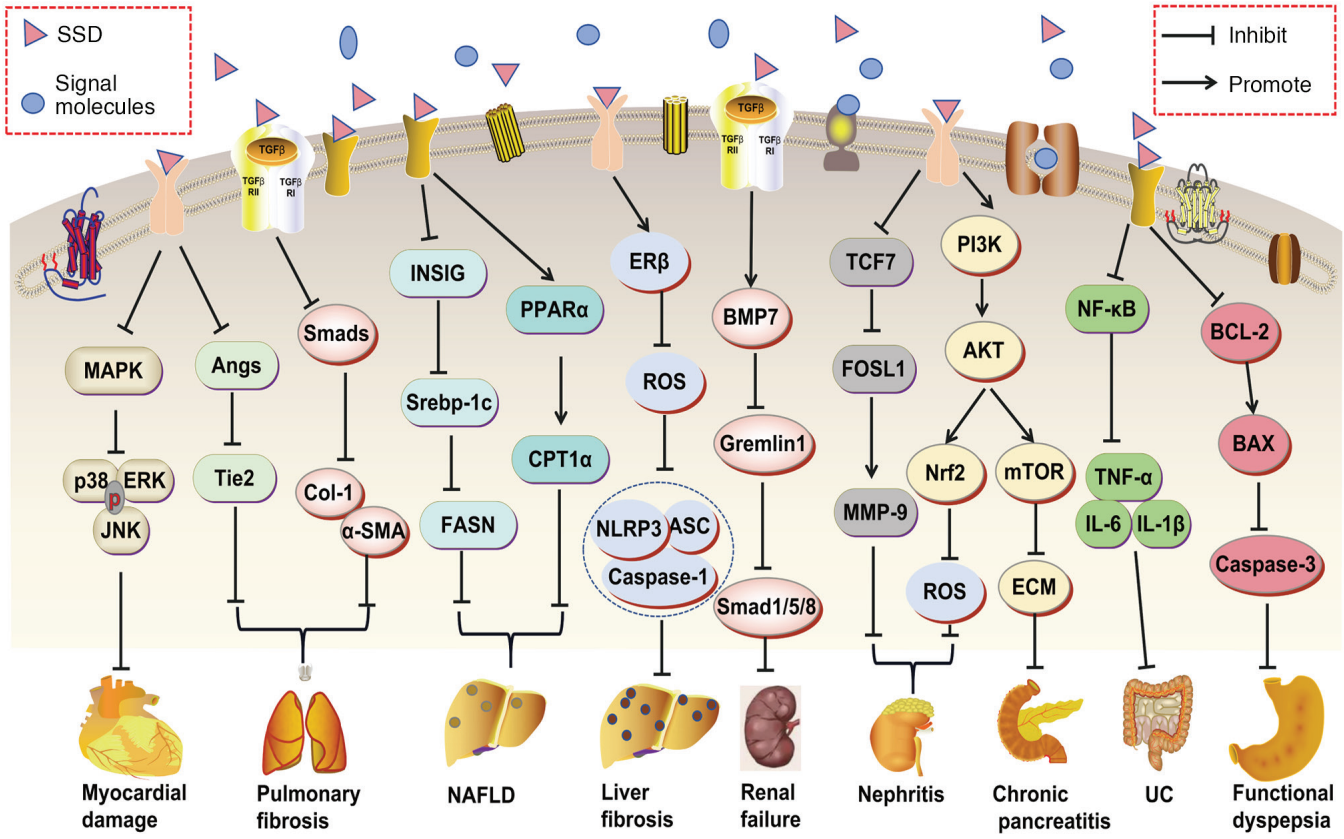

Figure 4. Role of SSD in disease regulation through multiple pathways. SSD participates in disease modulation via multiple pathways: It reduces myocardial damage by inhibiting the MAPK pathway, mitigates pulmonary fibrosis by targeting the Ang/Tie and TGF-β/Smads pathways, and slows non-alcoholic fatty liver disease progression by inhibiting the INSIG/SREBP-1c/FASN and activating the PPARα/CPT1α pathway. SSD also alleviates liver fibrosis by inhibiting the ERβ/ROS/NLRP3 inflammasome pathway, mitigates renal failure through the TGF-β/BMP7/Gremlin1/Smads pathway and reduces renal inflammation via the TCF7/FOSL1/MMP-9 and PI3K/AKT/Nrf2/ROS pathways. In chronic pancreatitis, SSD activates the PI3K/AKT/mTOR/ECM pathway, while in ulcerative colitis, it suppresses inflammation by inhibiting the NF-κB pathway. SSD also alleviates functional dyspepsia through inhibition of the BCL-2/BAX/Caspase-3 pathway. AKT, protein kinase B; Ang, angiotensin; ASC, adapter protein apoptosis associated speck-like protein containing a CARD; BMP7, bone morphogenetic protein 7; Col-1, collagenol-1; α-SMA, α-smooth muscle actin; FASN, fatty acid synthase; CPT1α, carnitine palmitoyltransferase-1 α; ECM, extracellular matrix; FOSL1, Fos-like antigen 1; IL-6, interleukin-6; MAPK, mitogen-activated protein kinases; mTOR, mechanistic target of rapamycin; MMP-9, matrix metalloproteinase-9; NF-κB, nuclear factor-κB; NLRP3, NLR family pyrin domain containing 3; Nrf2, nuclear factor erythroid 2-related factor 2; PI3K, phosphatidylinositol-3 kinase; PPARα, peroxisome proliferator-activated receptor α; ROS, reactive oxygen species; SREBP-lc, sterol regulatory element-binding protein 1c; SSD, Saikosaponin D; TCF7, transcription factor-7; TGF-β1, transforming growth factor β; Tie, angiopoietin/tyrosine kinase with immunoglobulin-like and epidermal growth factor homology; TNF-α, tumor necrosis factor-α.

forthcoming publication. These investigations indicate that SSD is a potential monomer for addressing lung diseases, kidney diseases, liver diseases and tumors.

Natural products and botanical sources serve as vital reservoirs for anti-cancer agents. Several natural compounds and their derivatives, such as Matrine (160), ginsenosides (161), strychnine (162) and berbamine (163), have demonstrated anti-cancer effects. While SSD is a natural substance with significant anti-tumor potential, it is essential to thoroughly understand its possible adverse effects to ensure pharmaceutical safety during its application. Research has identified toxic effects of SSD, including hepatotoxicity, neurotoxicity, hemolysis and cardiotoxicity (88,164,165). Natural compounds derived from plants are generally considered less toxic to normal cells than chemically synthesized drugs, thus offering greater potential safety as anti-cancer therapies (166-169).

Despite its potential, several challenges remain in the research surrounding SSD. Firstly, pharmacokinetic studies are insufficient. Although SSD is categorized as a triterpenoid saponin with poor water solubility, its bioavailability may exceed current expectations. Modern research indicates that bioavailability can be enhanced through methods such as nanoparticle encapsulation and liposomal formulations (65,170). In addition, investigations into SSD metabolism reveal its conversion into specific metabolites (e.g., prosaikogenins and saikogenins) within the body, influenced by various transformation factors including the intestinal flora, gastric acid and enzymes (171,172). However, a comprehensive understanding of the pharmacokinetics of SSD after systemic administration is currently lacking. For instance, while SSD excretion has been documented, the specific metabolic pathways and resulting metabolites are not fully elucidated, hindering a complete grasp of its pharmacokinetic properties. Secondly, the mechanistic research on SSD is limited. Current therapeutic mechanisms attributed to SSD in treating diseases are primarily associated with specific proteins and pathways, with insufficient exploration of the complete upstream and downstream pathways and the interactions between multiple pathways. Although evidence supports SSD's significant preventive and

therapeutic effects on liver disease, the precise mechanisms of action are not fully characterized. For instance, despite SSD's recognized therapeutic efficacy for liver diseases, comparative analyses of its mechanisms across various liver conditions are sparse, complicating the differentiation and effective treatment of specific liver diseases in clinical settings. Thirdly, the synergistic effects of SSD with other compounds are underexplored. The treatment of tumors poses significant challenges and the integration of traditional Chinese and Western medicine is becoming increasingly prevalent in oncological therapies (173,174). SSD has shown promise as an anti-cancer monomer; however, research on its application, either alone or in combination with other TCM monomer saponins, remains limited. Furthermore, investigations into the synergistic effects of SSD alongside other compounds, such as SSA and SSC, are scarce. While studies have optimized the extraction processes for SSA and SSD, the interactions among these components within the body and their influence on therapeutic efficacy warrant further examination. Lastly, there is a notable deficiency in clinical application research. Although SSD has demonstrated significant pharmacological activity in preclinical animal studies, there are relatively few investigations into its clinical application. This lack of research restricts its broader clinical utilization and necessitates additional clinical trials to ascertain its safety and efficacy.

In summary, future research on SSD should prioritize pharmacokinetic studies, explore the complex interactions of multiple proteins and pathways and foster collaborative investigations between traditional Chinese and Western medicine. Furthermore, *in vivo* and *in vitro* experimental studies on SSD have shown that it is a promising drug in the treatment of various diseases, but to the best of our knowledge, there have been no reports of clinical trials. There should be an increased emphasis on animal studies and clinical trials. Integrating these research approaches will effectively translate basic research findings into clinical practice.

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Authors' contributions

SG: Conceptualization, validation, writing-original draft. YZ and CC: Software, visualization, writing-review & editing. JL: Investigation, methodology. YaW: Visualization, project administration. JuW and YL: Funding acquisition, project administration, formal analysis. All authors have read the manuscript and approved it for publication. Data authentication is not applicable.

Ethics approval and consent to participate

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Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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