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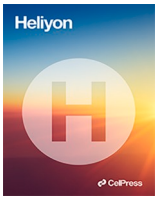

Review article

Pharmacology, medical uses, and clinical translational challenges of Saikosaponin A: A review

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ABSTRACT

Saikosaponin A (SSA), the primary active monomer derived from the Radix bupleuri, demonstrates a diverse array of pharmacological activities, including anti-inflammatory, antitumor, analgesic, anti-fibrotic, antidepressant, and immune-modulating properties. Despite its potential therapeutic impact on various human diseases, comprehensive studies exploring SSA's efficacy in these contexts remain limited. This review synthesizes the current research landscape regarding SSA's therapeutic applications across different diseases, highlighting critical insights to overcome existing limitations and clinical challenges. The findings underscore the importance of further investigations into SSA's mechanisms of action, facilitating the development of targeted therapeutic strategies and their translation into clinical practice.

1. Introduction

The radix bupleurum is obtained from the root of Bupleurum Chinese DC, which belongs to the Umbelliferae family, it typically grows mainly in the subtropical regions of the Northern Hemisphere [1],Chaihu contains abundant natural metabolites, such as phenolics, lignans, flavonoids, terpenoids (triterpenoids and sterols), mono- and sesquiterpenes (essential oils), and polyacetylenes, Pharmacological studies have confirmed that radix bupleurum exhibits various biological functions, including hepatoprotective, antitumor, anticonvulsant, antidepressant, antipyretic, analgesic, antibacterial, antiviral, anti-inflammatory, antioxidant, and immunomodulatory effects [2,3]. It is primarily utilized for the treatment of colds, fevers, cold, imbalances in cold and heat, and stagnation of liver qi. In clinical practice, a range of patented traditional Chinese medicines or herbal formulations containing Bupleurum are frequently utilized in China. These include Xiao-Yao-Wan tablets, Xiao-Chai-Hu-Tang, Da-Chai-Hu-Tang, Chai-Hu-Shu-Gan tablets, and Chai-Hu-Shu-Gan-San [4]. Saikosaponins (SSs) are one of the major active components of radix bupleurum and a triterpenoid saponin extracted only from Bupleurum plants, known for their diverse pharmacological characteristics [5]. Saikosaponins can be further categorized as Saikosaponin A, B1, B2, B3, B4, C, D, E, F, G, H, and I [6]. It demonstrates various effects, including anti-endotoxin and corticosterone hormone properties. It has the ability to inhibit the activity of sodium-potassium ATPase and is extensively used as a widely recognized medicinal herb [7,8]. In recent decades, these herbal medicines have attracted considerable scholarly attention owing to their potential therapeutic properties,including anti-inflammatory, antiviral, anticancer, and hepatoprotective effects [4,9,10]. Among these, SSA and SSD have exhibited biological activity [11]. SSD has been observed to demonstrate antitumor and anti-inflammatory effects through various mechanisms [4,12–14]. The molecular formula of SSA is

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Abbreviations

SSA	Saikosaponin A
NF-κB	nuclear factor kappa-B
MAPK	mitogen-activated protein kinases
ROS	reactive oxygen species
CKD	chronic kidney disease
P-gp	P-glycoprotein
CRH	corticotropin-releasing hormone
CUMS	chronic unpredictable mild stress
PPAR	peroxisome proliferator-activated receptor
LPS	lipopolysaccharide
CREB	cyclic response element binding protein
BDNF	brain-derived neurotrophic factor
ALI	acute lung injury

$C_{42}H_{68}O_{13}$. It is a triterpenoid saponin compound with a molecular mass of 781. SSA has a melting point that ranges between 224 and 230 °C and is soluble in both water and alcohol [15]. Pharmacological investigations of SSA have predominantly concentrated on its anti-inflammatory properties, particularly through the modulation of nuclear factor activation within signaling pathways, including nuclear factor kappa-B (NF-κB) and mitogen-activated protein kinases (MAPK). In a study involving mice with chronic kidney disease, SSA treatment markedly improved renal histomorphology, evidenced by reduced inflammatory cell infiltration, decreased vacuolization of renal tubular epithelial cells, and repair of interstitial dilatation and renal fibrosis, alongside the modulation of extracellular regulated protein kinases (ERK) in B cells [16–18]. Additionally,SSA has demonstrated significant efficacy in antitumor, neuroprotective, and organ damage prevention [4,19,20]. The development of SSA-based therapeutics could have profound implications for the treating of various human diseases, including tumors, inflammation, depression, and organ damage. This article aims to provide a comprehensive review of SSA research, emphasizing its application in these context. It will also address the limitations and challenges encountered in SSA research and its potential future clinical applications.

2. Search strategy

I conducted searches in online academic databases, namely PubMed, Web of Science, Google Scholar, and CNKI, using the search terms "Saikosaponin A″ OR "Radix Bupleuri" OR "Bu-pleurum" AND "Cancer" OR "Tumor" OR "Inflammatory" OR "Depression" OR "Neuroprotective" OR "Organ Protective". We have included relevant literature for the research topic.

3. Anti-inflammatory activity of SSA

The anti-inflammatory activity of SSA has garnered extensive interest due to its significant therapeutic potential. Evidence suggests that SSA inhibits inflammatory response in chronic kidney disease (CKD) models by reducing levels of pro-inflammatory cytokines such as IL-6, IL-1β, and TNF-α, while increasing IL-10. Treatment with SSA has demonstrated improvements in renal histomorphology, notably decreasing inflammatory cell infiltration, tubular epithelial cell vacuolization, and alleviating interstitial dilatation and fibrosis [21]. These beneficial effects can be attributed to SSA's potent antioxidant properties, which counteract oxidative stress that exacerbates inflammation, thereby reducing the risk of oxidative damage in CKD models [22]. These findings suggest that SSA effectively reduces oxidative damage in mice with CKD. Prolonged oxidative stress in the kidneys results in chronic inflammation and renal insufficiency, both of which can be significantly alleviated by SSA treatment [23]. Similarly, SSA decreases the inflammatory response in acute pancreatitis, a condition often exacerbated by heightened oxidative stress. This oxidative stress worsens pancreatic injury by elevating glutathione levels. SSA mitigates inflammation in acute pancreatitis by modulating gut microbiota and enhancing antioxidant signaling. Furthermore, SSA enhances antioxidant and anti-inflammatory properties, leading to improved lesions associated with acute pancreatitis in rat models [24]. It has been proposed that SSA inhibits the secretion of inflammatory cytokines through the enhancement of lipid metabolism and modulation of NF-κB signaling, thus reducing the severity of hyperlipidemic pancreatitis in animal models. These alterations in gut microbiota induced by SSA may offer protective effects against acute pancreatitis and contribute to the prevention of inflammatory diseases overall [25].

In vitro studies demonstrate that SSA exhibits anti-inflammatory effects in autoimmune conditions such as ulcerative colitis, characterized by an exaggerated mucosal immune response [26]. The pathogenesis of ulcerative colitis involves a complex interplay of inflammatory responses [27], with elevated levels of cytokines like TNF-α and IL-1β stimulating mucosal immune activation [28]. SSA enhances antioxidant enzyme activity, yielding neuroprotective effects in a mouse model of 5-fluorouracil-induced intestinal mucositis [29]. It also provides protection against dextran sodium sulfate-induced colitis by inhibiting TNF-α and IL-1β levles [30]. Moreover, SSA effectively suppresses chemically induced hepatic inflammation and fibrosis in rats by downregulating pro-inflammatory factors and modulating the NF-κB signaling pathway [10]. The inhibition of pro-inflammatory cytokine expression and the modulation of inflammation via signaling pathways, particularly NF-κB, are recognized mechanisms underlying SSA's anti-inflammatory activity

[31]. Experimental evidence supports SSA's regulation of inflammation-related cytokines and signaling pathways, including NF-κB and MAPK [32,33]. Notably, Lu et al. first identified SSA as an NF-κB activation inhibitor, reducing NF-κB target gene expression in macrophages. They also reported that SSA directly inhibits COX2 protein expression, potentially linked to mRNA stability rather than transcriptional effects [31]. Additionally, SSA regulates lipid metabolism and promotes cholesterol efflux in early atherosclerosis stages. It may act as a peroxisome proliferator-activated receptor (PPAR)-γ agonist, enhancing PPAR-γ expression [34]. PPAR-γ interacts closely with NF-κB, inhibiting its signaling and the release of pro-inflammatory factors [35]. Animal studies suggest that SSA stimulates PPAR-γ expression and suppresses NF-κB signaling in pancreatic tissues, ultimately mitigating hyperlipidemic pancreatitis in rats through improved lipid metabolism and reduced pro-inflammatory cytokine release [36]. These findings suggest SSA's potential as a therapeutic agent for pancreatitis, highlighting its multifaceted role in regulating inflammatory responses and metabolic processes. The alterations in gut microbiota induced by SSA may also provide protective effects against acute pancreatitis and contribute to the prevention of various inflammatory diseases.

In a mouse model of pneumonia, SSA exhibited protective effects against lung inflammation induced by cigarette smoke, attributed to its capacity to suppress both inflammation and oxidative stress. The mechanisms for SSA's suppression of cigarette smoke-induced lung inflammation include the activation of Nrf2 and inhibition of the NF-κB signaling pathway [37]. Conversely, SSA induced apoptosis and suppressed the proliferation of HEKa cells through reactive oxygen species (ROS) production [16]. Previous research

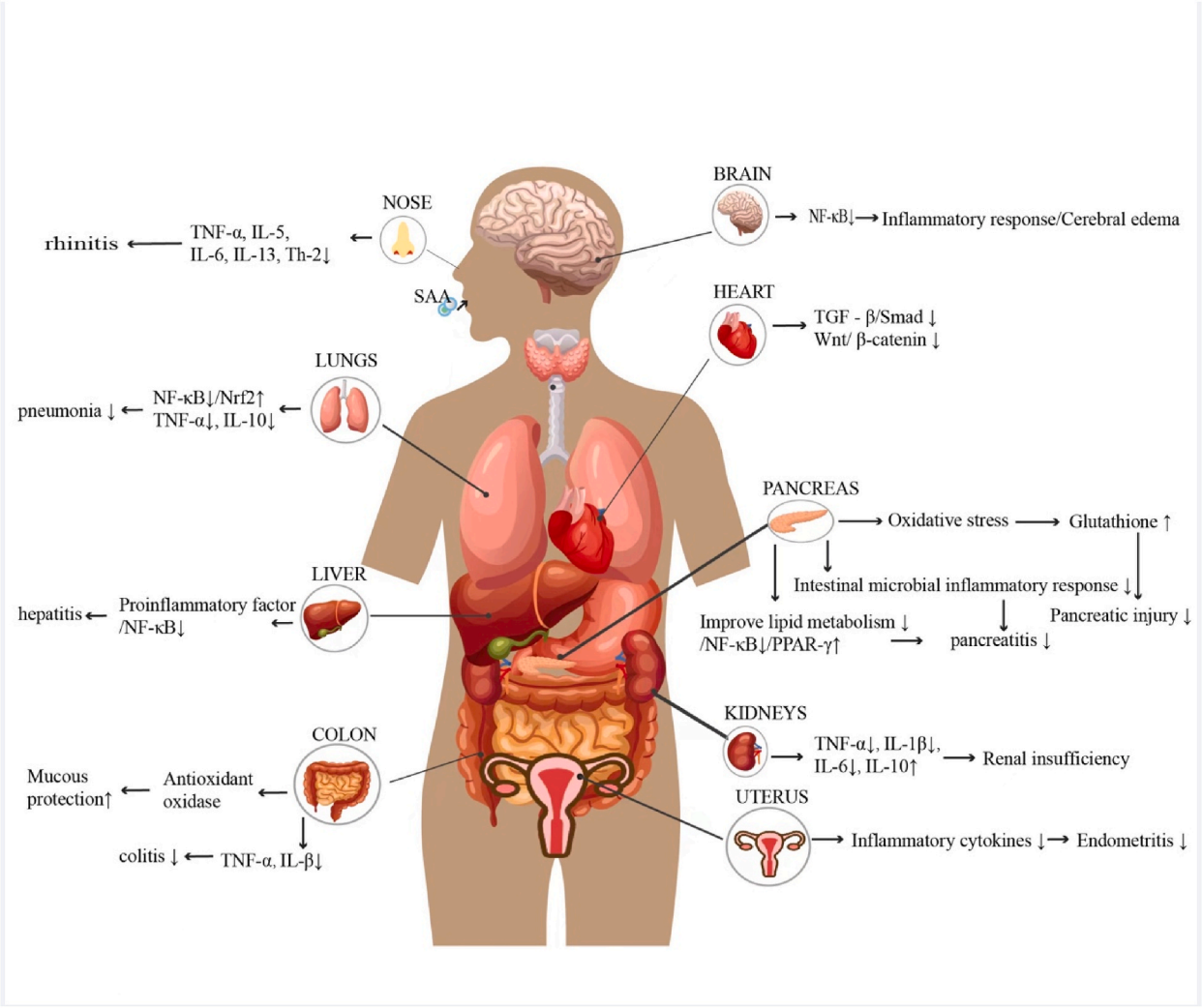

Fig. 1. SSA exhibits protective effects across multiple organs, including the alleviation of inflammatory responses, preservation of organ function, reduction of oxidative stress, and improvement of metabolic processes. It mitigates rhinitis, brain edema, and inflammation by inhibiting the NF-κB signaling pathway. In cardiac protection, SSA acts through the suppression of TGF-β/Smad and Wnt/β-catenin pathways. For pulmonary inflammation, it reduces symptoms by inhibiting the NF-κB/Nrf2 signaling pathway. In liver inflammation, SSA similarly alleviates symptoms via NF-κB inhibition. It protects the pancreas by reducing oxidative stress and improving lipid metabolism, thereby minimizing pancreatic damage. In cases of renal dysfunction, SSA decreases inflammatory factors such as TNF-α, IL-1β, IL-6, and IL-10. It also alleviates endometrial inflammation by suppressing inflammatory cytokines and reduces colitis symptoms through its antioxidant properties and inhibition of TNF-α and IL-1β.

indicates that ROS can modulate NF-κB activity bidirectionally [38]. While NF-κB influences ROS production by regulating antioxidant protein expression [39]. Thus, the interaction between SSA-induced ROS production and NF-κB inhibition may be significant. In vitro studies have demonstrated that SSA inhibits the expression of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 while simultaneously increasing IL-1 levels via the NF-κB pathway in macrophages and adipocytes treated with lipopolysaccharide (LPS) [17,40]. In vivo, SSA has been shown to prevent sepsis by inhibiting nucleotide-binding oligomerization domain 2 (NOD2)-mediated NF-κB activation [41].

In allergic rhinitis, the levels of TNF-α, IL-5, IL-6, and IL-13 are upregulated. However, SSA administration significantly down-regulates these cytokines, indicating its potential to reduce inflammation by inhibiting Th2 cytokines, which are instrumental in eosinophil recruitment [42,43]. Studies have shown a decrease in mast cells, eosinophils, and cup cells in SSA-treated mice, emphasizing SSA's role in preventing inflammatory cell infiltration into nasal tissues [44]. These findings indicate that SSA plays a role in reducing inflammation in allergic rhinitis by regulating the levels of pro-inflammatory cytokines. Moreover, pro-inflammatory cytokines play a crucial role in the progression of endometritis [45], characterized by inflammatory cell infiltration during LPS-induced endometritis [46]. The suppression of these cytokines lessens LPS-induced endometritis, with SSA demonstrating a protective effect likely due to its inhibition of inflammatory responses. This mechanism may involve the activation of the Nrf2 signaling pathway and the inhibition of the NF-κB signaling [47]. Liu et al. highlighted the beneficial effects of SSA on cardiac fibrosis through its inhibition of TGFβ/Smad signaling at higher doses and Wnt/β-cyclin signaling at lower doses [48]. Increasing evidence

Table 1
Anti-inflammatory activity of SSA.

Disease Type	Model	SSA dosage	Findings	Suggested mechanism	Ref.
Chronic kidney disease	5/6 nephrectomized mice in vivo and in vitro with Dexamethasone (Dex)-managed C2C12 myotubes.	5 mg/kg; 1uM	decreasing oxidative stress, reduced CKD-related muscle atrophy.	activated the PI3K/AKT/Nrf2 signaling pathway	[21]
Chronic inflammatory pain	rats were initially treated intraplantarly with complete Freund's adjuvant for induction of hyperalgesia	2 mg/kg	Analgesic, anti-inflammatory	/	[33]
Atopic dermatitis	HaCaT cells; BALB/c mice challenged with 2,4-dinitrochlorobenzene	1uM; 0.5 %	Inhibits production of multiple inflammatory cytokines and chemokines	Inhibition of MAPK signaling-mediated transcriptional activation of EGR1	[55]
Obesity	3T3-L1 cells	1.875–15uM	Inhibition of lipogenesis	Activated AMPK-ERK-JNK-p38 signaling pathway	[56]
Severe acute pancreatitis	Sprague-Dawley (SD) rats through the injection of sodium taurocholate into the biliopancreatic duct	10–40 mg/kg	Inhibition of oxidative stress, Anti-inflammatory, Improved gut microbiota composition	Activated Keap1-Nrf2-ARE signaling pathway	[24]
Acute pancreatitis	a rat model of hyperlipidemic pancreatitis	10,20 mg/kg	Suppressing the inflammatory response, regulating the release of proinflammatory cytokines	Inhibition of NF-κB signaling pathway	[36]
Allergic rhinitis	Mice were sensitized by intraperitoneal injection of OVA with aluminum hydroxide adjuvant	2,10 mg/kg	improved epithelial disruption and interstitial edema, reduce inflammatory factors.	inhibition of IL-6/STAT3/ROR-γt and NF-κB pathway	[44]
Chronic pancreatitis and pancreatic fibrosis	Pancreatic stellate cells	5-10μg/ml	reduced viability, proliferation, migration, and autophagy, promoted apoptosis, promotes collagen degradation and inhibits matrix deposition	regulated the AMPK/mTOR pathway	[57]
Psoriasis	HEKa cells and imiquimod (IMQ)-induced mice	5-20μM; 37.5,75 mg/kg	Promotes apoptosis and promotes ROS production	inhibiting activation of NF-κB signaling	[16]
Ulcerative colitis	dextran sulfate sodium-induced colitis in C57BL/6 mice	5,10,20 mg/kg	Inhibition of inflammatory response	Activation of LXRα	[30]
Intestinal mucositis	5-FU-induced intestinal mucositis in mice	1,5,10 mg/kg	Protection against intestinal injury, inhibits oxidative stress, inhibits inflammatory factors	inhibiting activation of NF-κB signaling	[29]
Chronic obstructive pulmonary disease	mice were exposed to cigarette smoke	5,10,20 mg/kg	Inhibits inflammatory mediators, inhibits oxidative stress	Activating Nrf2 and inhibiting NF-κB signaling pathway	[37]
Endometritis	lipopolysaccharide (LPS)-induced endometritis in mice	5,10,20 mg/kg	Inhibits production of inflammatory cytokines	Activating Nrf2 and inhibiting NF-κB signaling pathway	[47]
Obesity	3T3-L1 adipocytes	100 nM	Inhibition of inflammatory factors	Inhibition of ERK and NF-κB signaling	[40]
Sepsis	cecal ligation and puncture	1,2.5,5 mg/kg	Decreased secretion of pro-inflammatory mediators	inhibition of the NOD2-mediated NF-κB signaling pathway	[41]
Inflammation	LPS-stimulated mouse RAW 264.7	3.125–25uM	Suppression of pro-inflammatory cytokines	Inhibition of NF-κB and MAPK signaling pathway	[17]

suggests that SSA exerts strong antioxidant and anti-inflammatory effects on cardiac remodeling [49,50]. In a study of LPS-induced acute lung injury (ALI) in mice, SSA notably reduced TNF-α and IL-1β expression while inhibiting the NF-κB and NLRP3 signaling pathway [51]. Additionally, SSA diminished the inflammatory response and reduced brain edema in rats with craniocerebral trauma, alleviating neuropathic pain via NF-κB inhibition [52,53]. Finally, in human umbilical vein endothelial cells, SSA suppresses oxidative stress and inflammation by reducing TLR4 translocation to lipid rafts [54]. Overall, SSA's ability to reduce inflammatory pathways across various models—including chronic kidney disease, acute pancreatitis, ulcerative colitis, and endometritis—highlights its potential as a therapeutic agent in treating inflammatory diseases. Its dual actions of promoting apoptosis and exerting anti-inflammatory effects necessitate further exploration to fully elucidate their interconnection and therapeutic implications.(Fig. 1, Table 1).

4. Antitumor activity of SSA

Natural medicines derived from plants, foods, and fruits are often regarded as low in toxicity and considered safe, making them attractive options for enhancing anticancer activity [58,59]. There is growing interest to exploring natural compounds for cancer treatment. A study found that the aqueous extract of Radix bupleurum alleviated DNA damage induced by 5-fluorouracil in HepG2 hepatocellular carcinoma cells, promoting cancer cell death while sparing normal human lymphocytes. Co-treatment with 5-fluorouracil and Radix bupleurum extract increased the expression of the apoptotic protein BAX and decreased the mitochondrial membrane potential in HepG2 cells, indicating potential for targeted hepatocellular carcinoma therapy [60]. Active components in Radix bupleurum, particularly SSA and SSD, have been extensively studied for their potential anticancer properties. SSA inhibits the growth of HepG2 cells by activating ERK and its downstream cell cycle regulators, p15 (INK4b) and p16 (INK4a), inducing growth arrest [61]. Wang et al.'s research suggests that SSA may inhibit the proliferation of hepatocellular carcinoma cells through a dose-time effect. This is achieved by decreasing the expression of COX-2 and down-regulating the levels of prostaglandin E2 (PGE2). This mechanism could potentially contribute to the anticancer effects of SSA in hepatocellular carcinoma [61,62]. Additionally, SSA induces cell death in

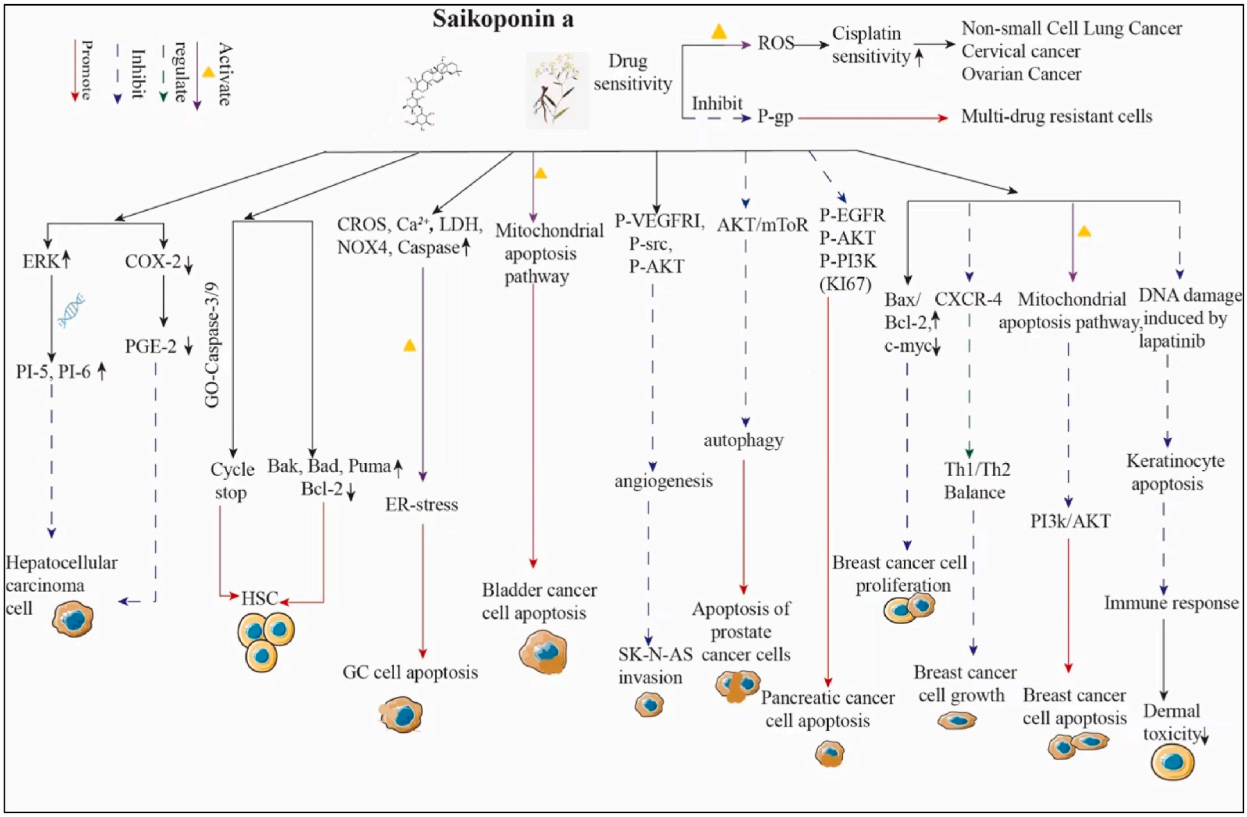

Fig. 2. SSA significantly impacts cancer by inhibiting cell proliferation, inducing apoptosis, suppressing invasion, reducing cell growth, and alleviating skin toxicity. It inhibits hepatocellular carcinoma proliferation via ERK pathway suppression and COX-2 expression. In gastric cancer, SSA activates CROS, Ca2+, LDH, NOX4, and Caspase pathways to induce apoptosis. It triggers mitochondrial apoptosis in bladder cancer and inhibits neuroblastoma invasion by targeting P-VEGFR1, P-src, and P-AKT. In prostate cancer, SSA induces apoptosis through AKT/mTOR pathway inhibition, and in pancreatic cancer by suppressing P-EGFR, P-AKT, and P-PI3K signaling. In breast cancer, it inhibits proliferation via Bax/Bcl-2, c-myc, and CXCR-4 modulation, while reducing growth by affecting Th1/Th2 balance and the PI3K/AKT pathway. SSA also induces breast cancer cell apoptosis through mitochondrial pathways and DNA damage and promotes keratinocyte apoptosis by inhibiting the PI3K/AKT pathway, alleviating skin toxicity by suppressing immune responses.

hematopoietic stem cells via caspase-dependent and independent pathways, as well as through a mitochondria-dependent intrinsic pathway [63]. SSA, a novel inhibitor of sarcoplasmic/endoplasmic reticulum Ca2+-ATPase, induces ER stress and apoptotic cell death in gastric cancer cells through the generation of ROS, elevation of intracellular calcium levels, increase in LDH activity, upregulation of Nox4 expression, and activation of cysteine asparaginase activity. Both in vivo and in vitro studies have shown that SSA suppresses the proliferation of bladder cancer cells by triggering the mitochondrial apoptotic pathway and promoting apoptosis [64]. The combination of SSA and radiotherapy (2Gy) was discovered to effectively overcome radioresistance by suppressing the EMT phenotype. However, in PERK knockdown radioresistant AGSR cells, the use of SSA/2 Gy hindered apoptotic cell death by suppressing the PERK-ATF4-CHOP axis [65]. In breast cancer research, SSA inhibits the proliferation of MDA-MB-231 and MCF-7 cells by enhancing the Bax/Bcl-2 protein ratio and upregulating c-myc expression [66]. It has been shown to regulate the balance between Th1 and Th2 immune responses by reducing the expression of CXCR4 [67,68]. Furthermore, SSA inhibits the PI3K/AKT signaling pathway, leading to apoptosis through mitochondrial and ER stress pathways [69]. Additionally, SSA holds promise in counteracting the reduction in HMGB1 transcription induced by lapatinib, thereby mitigating lapatinib-induced DNA damage, preventing apoptosis in keratinocytes, and alleviating dermatological toxicity observed in murine models of breast cancer [70]. This potential suggests that the combination of SSA with lapatinib could offer a more effective therapeutic strategy for breast cancer by reducing toxicity while enhancing efficacy [67]. Furthermore, SSA exhibits significant inhibitory effects on the proliferation and DNA synthesis of hepatocellular carcinoma cell lines, specifically PLC/PRF/5 and Hep-G2 cells, as well as pancreatic cancer BxPC-3 cells [71]. SSA treatment resulted in a marked decrease in levels of phosphorylated EGFR, Akt, and PI3K across these pancreatic cancer models. Xenograft studies corroborated these findings, demonstrating SSA's capability to reduce pancreatic tumor weight and downregulate the expression of Ki67, a marker

Table 2
Antitumor activity of SSA in vitro vivo.

Disease Type	Model	SSA dosage	Findings	Suggested mechanism	Ref.
Pancreatic cancer	BxPC-3 and MIA PaCa-2; xenograft mouse model	5,10,20uM	Pro-apoptotic	Inhibition of the EGFR/PI3K/Akt signaling pathway	[72]
Gastric Cancer	Gastric Cancer Cells; GC xenograft mouse model	1-20μM; 5,10 mg/kg	Pro-apoptotic, enhancing radiation sensitivity	Activates ER stress and Ca^{2+} release	[65]
Prostate cancer	prostate cancer cells; xenograft mouse model	2-30μM; 7.5 mg/kg	Induction of apoptosis, activation of autophagy, enhances chemosensitivity of Docetaxel	Inhibition of Akt/mTOR activity	[73]
Colorectal cancer	HCT 116 cells	2-16uM	Promoting apoptosis	NR	[79]
Bladder cancer	T24 and 5637, orthotopic xenograft mice model	3.75–15uM; 2,5,10 mg/kg	Inhibits proliferation, promotes apoptosis	NR	[64]
Cutaneous adverse reactions	HaCaT and NHEK cells; lapatinib-induced cutaneous toxicity	15μM; 20 mg/kg	Inhibition of skin toxicity of lapatinib	mitigates lapatinib-induced cutaneous toxicity by restoring HMGB1 expression	[70]
Antiangiogenesis	umbilical vein endothelial cells; chick embryo chorioallantoic membrane (CAM) and Matrigel plug model	1-100uM	Inhibition of migration and angiogenesis	Suppressing VEGFR2 Signaling Pathway and Its Downstream Proteins	[75]
Neuroblastoma	SK-N-AS cells	2.5–20uM	Inhibition of migration and invasion, promoting apoptosis	Inhibition of VEGFR/Src/Akt pathway	[76]
Cervical cancer	HeLa cells; cervical cancer xenograft model	5-20μM; 15 mg/kg	Inhibits growth and promotes apoptosis	Inhibition of PI3K/AKT signaling	[69]
Breast cancer	SUM149 and MDA-MB-231 cells; MDA-MB-231-Luc injected orthotopically into left mammary fat pads	0.625–30μM; 12 mg/kg	Inhibition of migration and invasion, inhibition of lung metastasis	Inhibition of PI4K/Akt/mTOR and MMP signaling pathways	[67]
Breast cancer	7,12-dimethyl-benz[a]anthracene induces breast cancer by gavage	35 mg/kg	Inhibits growth and regulates immune infiltration	Activated the IL-12/STAT4 Pathway	[68]
Breast cancer	MCF, MCF-7/ADR	2.5,5uM	Enhancing chemosensitivity and promoting apoptosis	Inhibition of P-glycoprotein-mediated multidrug resistance	[78]
Colon carcinoma	human colon carcinoma cell lines	5-20uM	Promotes apoptosis and increases release of LDH	proteolytic caspase-2 activation and the caspase-8/Bid pathway	[71]
Cervical cancer, ovarian cancer, non-small cell lung cancer	human cancer cells	2,6,10uM	Enhances cisplatin sensitivity, promotes apoptosis, and increases ROS accumulation	NR	[77]
Breast cancer	MDA-MB-231 and MCF-7 cell lines	2-10μg/ml	Inhibits proliferation and promotes apoptosis	Activation of p53/p21 signaling	[66]
Liver cancer	HepG2	12.5ug/ml	Inhibited growth	Activation of ERK signaling pathway by induction of p15INK4b/p16INK4a expression	[61]

associated with cell proliferation [72]. Similarly, SSA has been shown to significantly inhibit the Akt/mTOR pathway, which plays a crucial role in negatively regulating autophagy. The cytotoxic effects of SSA on quiescent prostate cancer cells were nearly abolished with the overexpression of Akt,underscoring the necessity of the Akt/mTOR pathway in mediating these effects. Although the AKT inhibitor MK-2206 exhibited cytotoxic properties against quiescent prostate cancer cells, it was less effective compared to SSA [73]. Moreover, SSA has been reported to inhibit the proliferation of rat C6 glioma cells [74], promote their differentiation into astrocytes, and diminish macrophage immune function by targeting the PI3K/AKT pathway [34]. It notably inhibits tumor angiogenesis, displaying enhanced sensitivity in primary human umbilical vascular endothelial cells compared to tumor cells (4T1 and HCT-15). Additionally, SSA inhibits primary human umbilical vascular endothelial cell migration and tube formation in a dose-dependent manner. This antiangiogenic property of SSA was further validated in vivo experiments involving chick embryos [75]. The expression levels of p-VEGFR2, p-Src, and p-Akt were found to increase during angiogenesis, with SSA regulating the VEGFR2/Src/Akt pathway, thereby mitigating the invasion and migration of neuroblastoma (SK-N-AS) cells [76]. In addition, SSA demonstrates potent efficacy in overcoming tumor resistance mechanisms. It triggers an accumulation of ROS, which leads to apoptosis. Notably, SSA enhances the efficacy of the chemotherapeutic agent cisplatin across various cancer lines, including non-small cell lung cancer A549, cervical cancer (HeLa and Siha), and ovarian cancer (SKOV3) cell lines [77]. The association between P-glycoprotein (P-gp) expression and multidrug resistance in tumor cells is well-documented. Importantly, SSA has been observed to induce apoptosis in P-gp-overexpressing MCF-7 and HepG2 multidrug-resistant cells while decreasing P-gp expression, thereby augmenting the sensitivity of these chemotherapy-resistant cells to conventional treatments [78]. Thus, SSA holds promise as a sensitizer for drug-resistant cancer cells and exhibits noteworthy anticancer properties, suggesting its potential utility as an adjuvant therapy in combination with existing anticancer drugs to enhance treatment efficacy (Fig. 2, Table 2).

5. Antidepressant effects of SSA

Depression is a mental disorder characterized by persistent low mood and is often accompanied by various physical symptoms, including reduced appetite, bodily discomfort, and various physiological dysfunction. It is associated with high rates of prevalence, relapse, and disability [80]. Currently, four primary hypotheses have been proposed regarding the etiology of depression: the monoamine neurotransmitter hypotheses, the hypothalamus-pituitary-adrenal (HPA) axis hypothesis, the cytokine hypothesis, and the excitatory amino acid and endocrine hormone hypothesis [81–84]. The prevailing consensus in research indicates that depression is primarily attributed to insufficient or dysregulated activity of neurotransmitters, particularly 5-hydroxytryptamine (5-HT) and noradrenaline (NE) in the central nervous system. Consequently, investigations targeting potential antidepressant drug mechanisms frequently concentrate on NE or 5-HT [85]. Recently, SSA has emerged as an compound exhibiting antidepressant properties [86]. Chronic elevation of HPA axis mediators, such as corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and glucocorticoids, has been linked to depressive-like behaviors, including impairments in memory, cognition, and neurogenesis [87]. However, the administration of SSA over four weeks resulted solely in the reversal of corticosterone elevation without significant changes in CRH levels in conditions of chronic unpredictable mild stress (CUMS) or serum following SSA treatment. Analysis of CRH mRNA and protein levels in the hypothalamus demonstrated increased CRH expression in the CUMS group and a decrease in the SSA group, aligning with clinical findings that suggest that perimenopausal depression does not correlate with altered basal hormone concentrations of the HPA axis [88]. This observation implies that SSA primarily exerts its influence on the HPA axis through central effects rather than peripheral modulation. Within the HPA circuit, the activity of the axis is primarily regulated by feedback mechanisms activated by glucocorticoid receptors in the hippocampus [89]. Although reduced glucocorticoid receptors have been associated with responses to persistently high glucocorticoid levels in depression [90], related studies indicate that CUMS can increase glucocorticoid receptor mRNA levels in the hippocampus —a response that is reversed by SSA [91]. A recent study supports this notion, showing that both mRNA and protein expression of glucocorticoid receptors were upregulated by CUMS [92]. In CUMS mice, however, glucocorticoid sensitivity is diminished due to the previously noted association where glucocorticoid receptor down-regulation reflects an increase in function rather than a decrease [93]. Consequently, down-regulation of glucocorticoid receptors by SSA suggests heightened sensitivity to glucocorticoids, illustrating the modulatory effect of SSA on HPA axis dysfunction. In conclusion, SSA seems to exert antidepressant-like effects, partially by enhancing neuroendocrine responses. Evidence suggesting that intracerebroventricular administration of SSA does not directly modify CRH and ACTH levels supports the inference that SSA does not directly impact the HPA axis [94]. Instead, SSA treatment appears to alleviate depressive symptoms by modulating the neuroendocrine, neuroinflammatory, and neurotrophic systems within the hippocampus of perimenopausal rats [94]. Therefore, it is hypothesized that the restoration of the HPA axis may arise indirectly through the suppression of neuroinflammation or enhancement of neurotrophic factors. Furthermore, SSA is proposed to exert antidepressant effects by elevating levels of proline-rich transmembrane protein 2 (PRRT2) and dopamine (DA) in the hippocampus of rats suffering from CUMS-induced depression [95]. Studies have demonstrated that SSA can effectively mitigates depressive symptoms in CUMS rats by augmenting PRRT2 expression and elevating DA levels in the hippocampus while simultaneously reducing the neurotoxic effects of excessive corticosterone on neural cells. Thus, PRRT2 is positioned as a promising target protein through which SSA mediates its antidepressant effects. Long-term administration of SSA at a dose of 50 mg/kg may upregulate PRRT2 expression levels, potentially increasing the likehood of PRRT2 and subsequent DA release [95]. The hippocampus is known to plays a significant role in the pathophysiology of depression [96], with reduced hippocampal volume recognized a reliable structural marker for the disorder [97]. CUMS has been found to induce hippocampal volume reduction by activating neuronal apoptotic pathways and diminishing neurogenesis [98]. The combination of postischemic separation and CUMS stimulation has been found to significantly increase the expression of neuronal apoptotic and pro-apoptotic proteins in the hippocampus, while SSA has been shown to reverse this effect [91]. Additionally, neurotrophic transcription factor phosphorylated

cyclic response element binding protein (CREB) and brain-derived neurotrophic factor (BDNF) are crucial in the prevention and treatment of post-stroke depression [99,100]. Notably, nearly all treatments for depression, including antidepressants, exercise, and electroconvulsive therapy, have been shown to increase BDNF levels in both clinical and experimental contexts [101–103]. Therefore, the neurotrophic hypothesis emphasizes the role of BDNF and its function in neuronal survival and synaptic plasticity [104]. Parallel to this hypothesis, it has been demonstrated that CUMS reduces BDNF expression, which is subsequently reversed four weeks of SSA administration. Additionally, CUMS was found to diminish phosphorylated tropomycin receptor kinase B (TrkB) receptor levels, with SSA reversing this decline. These findings suggest that SSA induces antidepressant-like effects by upregulating the BDNF signaling pathway in the perimenopausal hippocampus [94]. Phosphorylated CREB, representing the active form of CREB, stimulates BDNF expression, which, conversely, promotes CREB activation through TrkB [105]. Repeated administration of antidepressants has been observed to enhance CREB activity and BDNF expression, leading to the protection of damaged nerves in depressed mice [106]. Additionally, rapid BDNF release has been associated with the reversal of stress-induced depressive behavior in mice [107]. Such findings emphasize the potential role of CREB and BDNF in the mechanisms underpinning antidepressant treatments and stress-related depressive behaviors. The involvement of p-CREB in neuronal apoptosis, partially mediated through BDNF, has been documented, revealing that various stimuli that alter CREB expression levels intricately influence the progression of neuronal apoptotic pathways [108,109]. Studies indicate that SSA treatment significantly upregulates p-CREB and BDNF expression while concurrently down-regulating Bax and Caspase-3 levels. Consequently, the prevention of hippocampal neuronal apoptosis ultimately results in the improvement of depression-like behaviors in rats with post-stroke depression [110].

In conclusion, the therapeutic effect of SSA on depression may align more closely with the neurotrophic hypothesis rather than the direct modulation of the HPA axis. It is suggested that SSA may indirectly impact the HPA axis by influencing neurotrophic factors, thereby exerting an antidepressant effect (Table 3, Fig. 3).

6. Organ protective effects of SSA

The preservation of organs function following injury is crucial for the recovery of the affected tissues. Chinese medicine has garnered considerable interest due to its extensive clinical experience in addressing organ injuries [114]. Inflammation plays a pivotal role in the pathophysiology ALI [115],with research demonstrating that the inhibition of inflammatory cytokines such as TNF-α and IL-1β can attenuate ALI induced by LPS [116]. Additionally, previous research has shown that inhibition of NF-κB activation can also attenuate LPS-induced ALI in mice models [117]. Interestingly, treatment with SSA has been shown to significantly reduce the lung wet-to-dry weight ratio in a dose-dependent manner compared to LPS-treated controls. Furthermore, SSA treatment has alleviated LPS-induced pulmonary edema in mice, suggesting a potential protective effect against ALI-induced lung injury [118]. Histological analyses have demonstrated a visible reduction in lung injuries, including inflammatory cell infiltration, cell proliferation, and bleeding, following treatment with SSA [119]. Additionally, previous studies have proposed that the activation of the Nrf2 signaling pathway can mitigate renal injury. Observations indicate that SSA increases the expression of catalase and heme oxygenase-1(HO-1) in a dose-dependent manner, thereby providing a protective effect against kidney injury [120]. Furthermore, SSA has been demonstrated to protect against renal injury by activating the Nrf2 signaling pathway in response to lead-induced oxidative stress [121]. In the context of traumatic brain injury, SSA treatment has been associated with the attenuation of blood-brain barrier disruption and improved functional recovery, potentially through the suppression of inflammation via inhibition of the MAPK signaling pathway [52]. Moreover, in studies involving cerebral ischemia-reperfusion injury, SSA has been shown to attenuate the extent of cerebral infarction in rats subjected to middle cerebral artery occlusion while minimizing cerebral edema and neurological deficits [122,123]. These findings highlight the potential multi-organ protective effects of SSA in various injury and disease models. LXRα, a member of the nuclear hormone receptor superfamily, has been implicated in the regulation of inflammatory responses [124]. Activated LXRα has been shown to compete with IRF3 for binding and inhibit LPS-induced NF-κB transcriptional activity induced by LPS Kupffer cells. Additionally, SSA has been found to increase LXRα expression in a dose-dependent manner in LPS/D-GalN-induced liver injury [125].

Table 3
Mechanism of action of SSA in antidepressants.

Disease Type	Model	SSA dosage	Findings	Suggested mechanism	Ref.
Depression	CUMS combined with solitary confinement establish a depression model	1-8uM	Increased 5-HT levels, decreased cortisol levels, antidepressant effects	NR	[111]
Post-stroke depression	middle cerebral artery occlusion + isolation + CUMS model	5 mg/kg	Improving neurological function, inhibition of neuronal apoptosis	Activates p-CREB/ BDNF signaling	[110]
Stress-induced depression	CUMS depression model	50 mg/kg	Increased body weight, increased sucrose consumption, increased dopamine	Regulates expression levels of PRRT2	[95]
Perimenopausal depression	depression model induced by CUMS	25,50,100 mg/kg	Reduce inflammatory factors, corticosterone decreased	Upregulated BDNF-TrkB signaling pathway	[94]
Depression	PC12 cells	0.156-5uM	Regulation of metabolic disorders, inhibition of apoptosis	Inhibits NF-κB signaling pathway	[112]
Attention deficit hyperactivity disorder	spontaneously hypertensive rat	12.5,25,50 mg/kg	DA levels in prefrontal cortex and striatum	Increased protein levels of BDNF	[113]

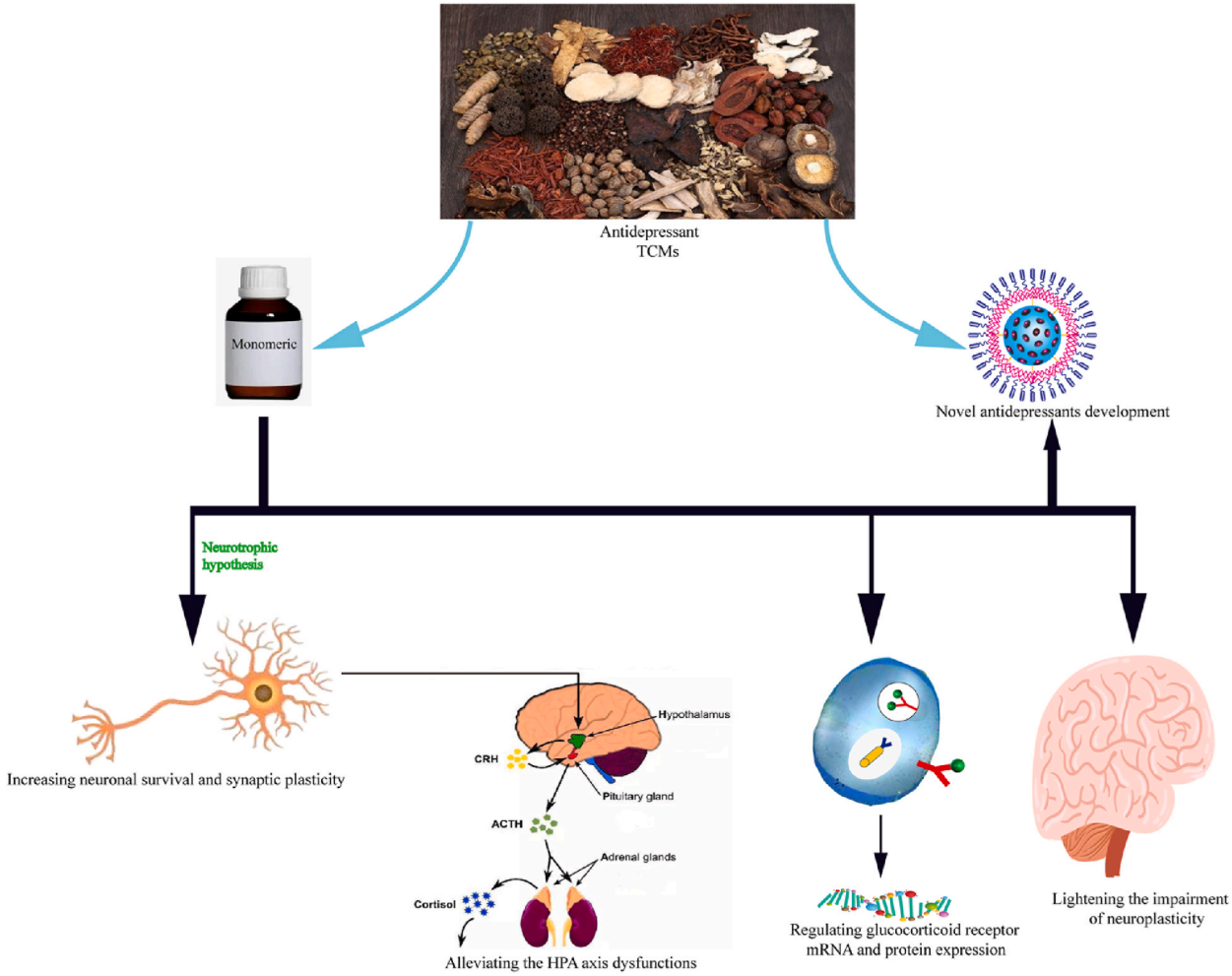

Fig. 3. Mechanism of action of SSA in antidepressants. SSA exerts its antidepressant effects by enhancing neuronal survival and synaptic plasticity, alleviating dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis, regulating the expression of glucocorticoid receptor mRNA and proteins, and mitigating neuroplasticity damage, thereby paving the way for novel antidepressant therapies.

Furthermore, supplementation with SSA has been demonstrated to improve hepatic antioxidant status and inhibit the formation of malondialdehyde, thereby protecting the liver by attenuating hepatic lipids and lipid peroxidation while enhancing antioxidant defense [126]. Thus, SSA may provide protection against liver injury by inhibiting the inflammatory response mediated by the NF-κB signaling pathway (Table 4).

7. Neuroprotective effects of SSA

Saikosaponin, particularly its primary component SSA, has been associated with both antidepressant and neuroprotective properties [52,95]. A direct correlation has been established between scar formation, the release of inflammatory cytokines, and Saikosaponin 's activity [130]. Pro-inflammatory cytokines such as tumor necrosis factor-alpha and interleukin-6 have been shown to facilitate neural scarring, while anti-inflammatory factors like IL-10 have been observed to inhibit this process [131]. In a study by Ngeow et al. [132], the local administration of IL-10 peptide fragments at the site of sciatic nerve injury in C57/B6 mice significantly reduced nerve scarring and enhanced nerve regeneration. These findings suggest that SSA and Saikosaponin may have a potential role in modulating the inflammatory response and promoting neural regeneration. In further investigations, it has been shown that following sciatic nerve injury in rats, SSA promotes the recovery of motor and nerve conduction functions by increasing the expression of the anti-inflammatory cytokine IL-10 and inhibiting nerve scar formation [127]. Preconditioning with SSA appears to reduce the nuclear accumulation of NF-κB, which may lead to enhanced anti-inflammatory responses and contribute to the neuroprotective effects of SSA in the context of cerebral ischemia-reperfusion injury [123]. Inflammation often triggers the release of glutamate from glial cells into the extrasynaptic gap. This excess glutamate can activate extrasynaptic N-methyl-D-aspartate receptors, resulting in the disruption of synaptic integrity and, ultimately, neuronal loss [133]. Conversely, treatment with SSA can modulate glutamate

Table 4
Organ-protective and neuroprotective effects of SSA.

Disease Type	Model	SSA dosage	Findings	Suggested mechanism	Ref.
Peripheral nerve injury	sciatic nerve injury model	10 mg/kg	Inhibits nerve scarring, promoted recovery of lower extremity motor function and neurophysiological function	NR	[127]
Acute lung injury	LPS-induced ALI mice	2.5,10 mg/kg	Inhibition of pulmonary edema, reduce pro-inflammatory cytokine levels, reduce lung tissue injury	Inhibition of TLR4/NF-κB pathway	[119]
Acute lung injury	LPS-induced ALI mice	5,10,20 mg/kg	Decrease MPO activity, decreased lung W/D ratio, inhibition of inflammatory factors	Inhibits NF-κB and NLRP3 signaling pathways	[118]
Drug-induced liver injury	L-02 cells; ICR mice	1-20μM; 75,150,300 mg/kg	Causing autophagy	up-regulate autophagy by triggering ER stress	[128]
Kidney injury	Lead-Induced Fish Kidney Injury Model	5,10,20 mg/kg	Suppression of inflammatory factor levels, decreases SOD and MPO activity	Inhibits NF-κB signaling pathway and activates Nrf2 signaling pathway	[121]
Brain damage	Rat middle cerebral artery occlusion (MCAO) model	0.001 %,0.01 %,0.1 %	Enhancing motor function, decreases brain water content, reduce inflammatory cytokine levels	Inhibits HMGB1 release and attenuates NF-κB activation	[123]
Liver injury	LPS/ D-galactosamine -induced mice liver injury model	5,10,20 mg/kg	Decreases SOD and MPO activity, decreased AST and ALT levels, suppression of inflammatory factor levels	Inhibits NF-κB signaling pathway	[125]
Liver injury	CCl(4)-induced liver injury model in rats	0.004 %	Decreased AST and ALT levels, improving liver fibrosis	NR	[126]
Insomnia	C57BL/6J mice	0.625,1.25, 2.5 mg/kg	Increased sleep duration, improving sleep quality	Decreases neuronal activity in LH	[129]

metabolic disorders by inhibiting glutaminase activity, thereby exerting neuroprotective effects through mechanisms that regulate metabolic disturbances and attenuate neuroinflammation. These findings collectively underscore the potential of SSA and Saikosaponin in therapeutic strategies aimed at neural repair and inflammation modulation [112] (Table 4).

8. Other

Current research predominantly concentrates on the exploration of the anti-inflammatory, antitumor, antidepressant, post-organ injury protection, and neuroprotective properties of SSA, however, recent studies have revealed additional pharmacological effects. Notably, SSA exhibits properties as an analgesic, antiepileptic agent, as well as a modulator of osteoclast differentiation to a certain extent. Saikosaponin has demonstrated efficacy in mitigating neuropathic pain in rats with chronic contraction injury by modulating the p38-MAPK and NF-κB signaling pathways within the spinal cord [53]. The alleviation of neuropathic pain induced by chronic constriction injury may not solely be attributed to the anti-inflammatory effects of SSA but also to its antagonistic properties on TRPA1 channels. This idea is supported by previous research highlighting the role of TRPA1 in the development of neuropathic pain in mice models [134]. The analgesic activity of SSA has been demonstrated in thermal pain and formalin-induced pain tests conducted on mice [135]. In this context, thermal hyperalgesia, which is characterized by acute pain elicited by a thermal stimuli, involves signal transmission to the central nervous system through the spinal cord [136]. While SSA demonstrated an ability to inhibit thermal hyperalgesia, its analgesic effects did not exhibit a dependence on dosage. In the formalin-induced pain test, SSA did not exhibit significant inhibitory effects in phase I, however, it did demonstrated a concentration-dependent inhibition of formalin-induced pain in phase II [135]. Notably, SSA displayed a marked inhibitory effect on inflammatory pain by suppressing nitric oxide synthase, cyclooxygenase-2, and pro-inflammatory cytokines, effectively reducing inflammatory pain through the NF-κB pathway in rats [137]. Recent investigations have also indicated that SSA can prevent and treat osteoporosis and cancer-induced bone loss through its inhibitory effects on osteoclast formation [138,139]. The data suggest that SSA not only promotes the differentiation of BMSC into osteoblasts both in vitro and in vivo settings but also helps counteract bone loss caused by estrogen deficiency. Notably, SSA enhances osteogenic differentiation of BMSCs during both early and mature stages, possibly through the WNT/β-linker signaling pathway [50]. Additionally, SSA has been found to inhibit osteoclastogenesis and mediate osteoclast activity in vitro. These effects occur through the inhibition of NF-κB and MAPK activation [138]. Moreover, SSA exhibits anticonvulsant and antiepileptic effects in a model of electroshock-induced epilepsy [140]. These effects may be achieved by inhibiting glial fibrillary acidic protein expression and glutamate-induced activation of rat hippocampal astrocytes. These findings highlight the diverse pharmacological properties of SSA [141]. It has been demonstrated that treatment with SSA significantly reduces the frequency and duration of recurrent seizures and enhances the production of voltage-gated potassium currents over an eight-week period [142,143]. However, further investigation is needed to fully elucidate the underlying mechanisms. In line with this, Yu et al. [144] have shown that SSA alleviates pentylenetetrazole-induced seizures and modulates the expression of inflammatory cytokines by inhibiting the activation of the p-mTOR/p-70S6K pathway. This suggests that SSA plays a role in mediating inflammatory cytokines in the context of analgesia, osteoblast differentiation, and antiepilepsy. The multifaceted effects of SSA highlight its potential as a versatile pharmacological agent.

9. Conclusions and perspectives

The research on traditional Chinese medicines (TCM) has received considerable attention in recent years, especially regarding their potential effectiveness and lower occurrence of adverse reactions compared to Western medicines for various difficult-to-treat diseases [145]. SSA, a crucial pharmacological component of traditional Chinese medicine, has been extensively investigated for its pharmacological effects and mechanisms of action, particularly in the fields of anti-inflammation, antitumor effects, organ protection, neuroprotection, and antidepressant properties [4]. The dual mechanisms of apoptosis mediated by SSA, which in involve the up-regulation of pro-apoptotic proteins and the concurrent down-regulation of Bcl-2, suggest that SSA may have a multifaceted impact on cellular apoptosis pathways. Such complexity in its mode of action could contribute to its potential effectiveness in targeting various types of cells and diseases [63]. The combination of SSA with conventional chemotherapeutic agents such as adriamycin, vincristine, or paclitaxel has shown promising results in overcoming chemoresistance by downregulating P-gp in multidrug-resistant (MDR) cells. Furthermore, the combination of these drugs has demonstrated significant induction of prostate cancer cell death and reduction of tumor volume compared to using doxorubicin or SSA alone. These findings underscore the potential synergistic effects of combining SSA with conventional chemotherapeutic agents for enhanced anticancer activity [73,78]. The anti-inflammatory properties of SSA have received significant attention for potential clinical application due to its low toxicity [146]. SSA has demonstrated the ability to inhibit the secretion of pro-inflammatory cytokines and promote the production of anti-inflammatory cytokines, thereby mitigating inflammatory responses [36]. Moreover, its modulation of the NF-κB signaling pathway suggests a protective role in inflammation by reducing the expression of pro-inflammatory cytokines. While existing studies have provided insights into its effectuveness against various diseases and clearer understanding of its molecular mechanisms, these findings are primarily based on cell and cell line xenograft models. To validate these observations, further exploration using preclinical organoid models and human tumor xenograft models is necessary.

Traditional Chinese prescriptions that are made from or contain Radix bupleuri, such as Xiao-Yao-Wan tablets, Chai-Hu-Shu-Gan tablets, and Chai-Hu-Shu-Gan-San, have been utilized in clinical settings. However, the clinical application and development of these prescriptions have been restricted due to the toxic side effects they may have on organs such as the liver, kidneys, and lungs when used excessively or for prolonged periods of time [4,147]. However, recent studies have found that the use of SSA in Radix bupleuri not only does not rsult in hepatotoxicity, but also helps to reduce acute liver injury. SSA is considered a crucial compound that exerts hepatoprotective effects. The protective effects are observed in a dose-dependent manner, with concentrations of the drug ranging from 10 to 100μM. Additionally, in in vivo experiments, the oral administration of Radix bupleuri significantly reduced CCL4-induced liver injury [148]. In addition, SSA has been found to attenuate LPS-induced acute lung injury [119]. A growing body of research has demonstrated that SSA has an anti-tumor effect in various types of cancer, including breast cancer, gastric cancer, liver cancer, and leukemia [149–152]. Interestingly, SSA has also been shown to alleviate skin toxicity induced by chemotherapeutic drugs [70,153], and to attenuate a model of heart failure induced by Adriamycin [154]. These findings suggest that SSA may hold promise as a potential treatment option for depression, tumors, inflammation with comorbidities, or in cases where toxic side effects of treatment are present, thereby providing patients with optimized therapeutic choices.

Through a comprehensive review of the research advancements concerning SSA in various domains, including anti-inflammatory, anti-tumor, neuroprotective, and anti-depressant effects, this study delves into the mechanistic actions of SSA via the inhibition of inflammatory signaling pathways such as NF-κB and MAPK. It further explores SSA's functions in apoptosis, antioxidant activity, and immune modulation, highlighting its potential as a therapeutic agent in clinical applications, particularly in diseases such as cancer, inflammation, depression, and organ injury. As a compound derived from traditional Chinese medicine, SSA exhibits extensive biological activity and therapeutic potential for the treatment of a variety of conditions. The research elucidates specific mechanisms by which SSA exerts its anti-inflammatory and anti-tumor effects, providing a theoretical foundation for the development of novel therapeutics based on SSA. Moreover, studies conducted in animal models and cell lines lay the groundwork for future clinical trials, with the promise of yielding more effective treatment modalities. The findings indicate that SSA possesses low toxicity, offering significant safety assurance for its clinical applications as a therapeutic intervention. In addition, the study delineates future research directions, including further pharmacokinetic and toxicological studies, as well as in vivo and clinical application research, to facilitate the clinical translation of SSA. In conclusion, this research not only summarizes the progress of SSA across multiple disease areas but also emphasizes its importance and novelty as a potential therapeutic agent, providing valuable references for subsequent research and clinical applications.

SSA, which is the primary active ingredient found in Radix bupleuri, has the potential to be an effective and relatively safe natural compound for treating various diseases including inflammation, tumors, depression, and organ protection. However, the transition of SSA from basic experiments to clinical applications is a time-consuming process, particularly due to the contradictory experimental evidence regarding the toxicity of Radix bupleuri to the liver and kidney, as well as its hepatorenal protective effect [4,147], SSA demonstrates a broad spectrum of pharmacological activities, encompassing anti-inflammatory, anti-tumor, analgesic, anti-fibrotic, anti-depressant, and immunomodulatory effects, thereby positioning it as a promising candidate for the treatment of various diseases. Nonetheless, the current body of research regarding SSA as a therapeutic modality remains insufficiently systematic and comprehensive. Furthermore, investigations into the pharmacokinetic properties of SSA—such as its metabolism, distribution, and excretion—as well as toxicological assessments are markedly limited. While SSA has exhibited favorable activity in vitro, its application in animal models and clinical trials is still constrained, particularly due to a lack of long-term safety and efficacy data. Additionally, the exploration of SSA's metabolic pathways and its metabolites is not sufficiently thorough, which restricts our holistic understanding of its pharmacodynamic and toxicological profiles.

To address these deficiencies, future work should prioritize enhancing the pharmacokinetic and toxicological research of SSA to

ensure its safety and efficacy. Additionally, there is a pressing need for more in vivo and clinical studies to validate the effectiveness and safety of SSA, as well as to determine optimal dosing regimens and routes of administration. Furthermore, further investigation into the metabolic pathways of SSA and its metabolites is essential for a comprehensive understanding of its pharmacodynamics and toxicity. Finally, building upon the existing research findings, the development of novel therapeutics based on SSA should be pursued, alongside the formulation of more precise and personalized treatment strategies, with the aim of achieving broader clinical application.

In summary, despite the extensive pharmacological activities and potential therapeutic value of SSA, several challenges must be addressed to facilitate its translation into practical clinical applications. Future research should focus on bridging these knowledge gaps to optimize the utilization of SSA's potential in the treatment of human diseases.

CRediT authorship contribution statement

Xiao-Hong Sun: Writing – original draft. **Yi-Hong Chai:** Writing – original draft. **Xiao-Teng Bai:** Software. **Hong-Xing Li:** Data curation. **Ya-Ming Xi:** Writing – review & editing.

Informed consent

For this type of study formal consent is not required.

Data availability statement

All data reported are included and represented in the manuscript.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

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