Role, mechanisms and effects of *Radix Bupleuri* in anti-breast cancer (Review)

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Abstract. The prevalence of breast cancer among women has led to a growing need for innovative anti-breast cancer medications and an in-depth investigation into their molecular mechanisms of action, both of which are essential tactics in clinical intervention. In the clinical practice of Traditional Chinese Medicine, *Radix Bupleuri* and its active components have shown promise as potential anti-breast cancer agents due to their ability to target multiple pathways, exhibit synergistic effects and reduce toxicity. These compounds are considered to enhance the prognosis of patients with cancer, prolong survival and combat chemotherapy resistance. The present review aimed to delve into the anti-breast cancer properties of *Radix Bupleuri* and its active ingredients, highlighting their mechanisms, such as inhibition of cell proliferation, promotion of apoptosis, metastasis prevention, microenvironment improvement and synergy with certain chemotherapeutic agents. These findings may provide a scientific rationale for combining *Radix Bupleuri* and its active components with traditional chemotherapy agents for the management of breast cancer.

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Abbreviations: SSA-D, saikosaponin A-D; TME, tumor microenvironment; CDK, Cyclin-dependent kinase; DOX, doxorubicin; MAPK, mitogen-activated protein kinase; ERS, excessive endoplasmic reticulum stress; TNBC, Triple-negative breast cancer; EMT, epithelial-mesenchymal transition; MMP, matrix metalloproteinase; ECM, extracellular matrix; p-STAT3, phosphorylated STAT3; VASP, vasodilator stimulated phosphoprotein; STAT3, signal transducers and activators of transcription 3; PI3K, phosphatidylinositol-3-kinase; AKT, protein kinase B; mTOR, mammalian target of rapamycin; SDF-1, stromal cell-derived factor-1; CXCR4, C-X-C chemokine receptor type 4; MDA, malondialdehyde; SIRT1, sirtuin 1; Nrf2, nuclear factor erythroid 2-related factor 2; HO-1, heme oxygenase 1; ΔΨm, mitochondrial membrane potential; ATP, adenosine triphosphate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TAM, tumor associated macrophage; VEGF, vascular endothelial growth factor; VEGFR2, VEGF receptor 2; MDR, multidrug resistance; P-gp, p-glycoprotein; ADR, adriamycin; PGC-1α, peroxisome proliferator-activated receptor γcoactivator-1 α; ROS, reactive oxygen species; GSH, glutathione; NADPH, reduced nicotinamide adenine dinucleotide phosphate; NADH, nicotinamide adenine dinucleotide; NQO1, NAD(P)H:quinone oxidoreductase 1

Key words: breast cancer, *Radix Bupleuri*, saikosaponins, polysaccharides, flavonoids

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1. Introduction

Breast cancer is the most prevalent form of cancer among women and its incidence and mortality rates are rising annually (1). The initial symptoms of breast cancer can be subtle, resulting in a majority of cases being diagnosed in the advanced stages of the disease, which exhibit aggressive characteristics and often a poor prognosis (2). Surgical excision and endocrine therapy are the mainstays in clinical practice (2,3). However, these treatment methods can lead to an inadequate response to chemotherapeutic drugs, side effects, susceptibility to drug resistance (4), recurrence, metastasis (5,6) and higher levels of patient suffering and economic burden (7). Therefore, the development of new

anticancer medications is imperative to hinder tumor growth and enhance the quality of life and survival for patients with cancer.

Traditional Chinese Medicine has been utilized in patients with a poor prognosis treated with radiotherapy and chemotherapy, offering a potential novel approach to anticancer treatment (8-10). The anticancer mechanism of active ingredients found in Traditional Chinese Medicine have previously been reported (11,12). According to a previous study, 18/247 anticancer drugs approved by the U.S. Food and Drug Administration from 1981-2019 were derived from natural products (13). Increasing numbers of Traditional Chinese Medicines, such as curcumin and *Salvia miltiorrhiza*, have been used for anti-breast cancer treatment and as adjuvant treatments that exhibit enhanced efficacy and reduced toxicity (14,15).

Radix Bupleuri has been used as a traditional medicine for >2,000 years. *Radix Bupleuri* can relieve fever (16) and depression (17,18), and is often used to treat cold, fever, depression and liver-related diseases (16,19,20). Pharmacological studies have shown that *Radix Bupleuri* has a variety of biological activities such as anti-inflammatory, anticancer, antipyretic, antiviral, hepatoprotective, neuroprotective and immunomodulatory effects (21-25). The active components of *Radix Bupleuri*, including saikosaponins, polysaccharides and flavonoids, have been reported to significantly slow down the growth and inhibit the development of breast cancer by affecting the characteristics of tumor cells, such as the proliferative, invasive, migratory and apoptotic properties (25,26). Moreover, *Radix Bupleuri* has a broad-spectrum antitumor effect through multiple targets and channels (27,28). It is well established that chronic psychological stress serves as a significant risk factor in the development of breast cancer (29-31). Thus, the liver detoxifying and anti-depressant properties of *Radix Bupleuri* can target the pathogenesis of breast cancer. Consequently, the present review aimed to report an overview of the research progress on the effects and mechanisms of action of *Radix Bupleuri* and its active ingredients against breast cancer.

2. Main active ingredients of *Radix Bupleuri* and their pharmacological effects

Radix Bupleuri has a long history of medicinal use in China and is the main ingredient in numerous types of compound decoctions that are used in clinical practice. Various active ingredients, such as saikosaponins, polysaccharides and flavonoids, have been extracted from *Radix Bupleuri* (Fig. 1 and Table I) (32,33).

Pharmacological actions of saikosaponins. A total of 18 saikosaponins have been discovered in the roots of *Radix Bupleuri*, including saikosaponins A-D (SSA-D), which primarily exist as isomers (33). Saikosaponins serve as the primary bioactive compound in *Radix Bupleuri*, exhibiting various pharmacological properties, including antitumor (25,26), anti-inflammatory (34), anti-oxidant (35), antifibrotic (36), antiviral (37,38) and immunomodulatory effects (39). The main saikosaponins with antitumor effects are SSA and SSD (40).

Pharmacological effects of polysaccharides. Polysaccharides are complex sugar chains composed of galactose, glucose, xylose, arabinose, rhamnose and other monosaccharides. These monosaccharides link to form a higher-order structure (41). Among these, glucose and arabinose are particularly notable monosaccharides that influence the activity of *Radix Bupleuri*. Polysaccharides extracted from *Radix Bupleuri* have been reported to enhance the functionality of macrophages and natural killer cells, boost the body's immune response and exhibit antioxidant, anti-inflammatory and immunomodulatory properties (42-45).

Pharmacological effects of flavonoids. Flavonoids such as kaempferol, isorhamnetin and quercetin have been identified as possessing the ability to suppress the release and expression of certain pro-inflammatory factors, such as TNF-α, inducible nitric oxide synthase, IL-1β, IL-6 and IL-12p70 (46,47). Furthermore, flavonoids are capable of inhibiting the generation of free radicals in the body, scavenging free radicals, activating the body's anti-oxidant system (48) and regulating inflammation (49,50).

3. Anti-breast cancer mechanisms of action

Traditional anticancer tools, such as surgery, radiotherapy, chemotherapy, targeted therapy, hormonal therapy and immunotherapy, aim to eliminate malignant cells, arrest disease progression, alleviate symptoms and enhance patients' quality of life. At present, small molecule therapeutic strategies are gradually shifting towards the regulation of the tumor microenvironment (TME) (51), as well as targeted interventions of metabolic pathways (52) and protein lipidation modifications (53), while delving into the mechanisms of drug resistance formation (54) and potential for immunotherapy (55). This section will focus on the analysis of the regulatory mechanisms of tumor cells and their microenvironment, with special attention to the effects of *Radix Bupleuri* and its effective ingredients on breast cancer cell stemness and metabolism. The present section is not only limited to the cancer cells themselves but also reviewed the cells and signaling molecules in the TME, as well as the inhibition of tumor angiogenesis and drug resistance. In addition, the present section explored novel ways in which *Radix Bupleuri* and its effective ingredients may induce breast cancer cell death, such as through ferroptosis and mitochondrial damage, to enhance the overall effect of *Radix Bupleuri* against breast cancer. The present section reviewed the anticancer effects of the *Radix Bupleuri* and its effective ingredients in breast cancer, but most of the studies on the main active components of *Radix Bupleuri* against breast cancer are *in vitro* experimental studies, while *in vivo* studies were limited (Table II).

Regulation of tumor cell proliferation and apoptosis. The eukaryotic cell growth and proliferation process encompasses replication and division, collectively referred to as the cell cycle, consisting of the G1, S, G2 and M phases. The advancement of the cell cycle is typically linked to an escalation in proliferative proteins, such as Cyclin, Cyclin-dependent kinase (CDK) and CDK inhibitor (56). Disturbances in any of the regulatory factors can result in abnormal cell cycle activity

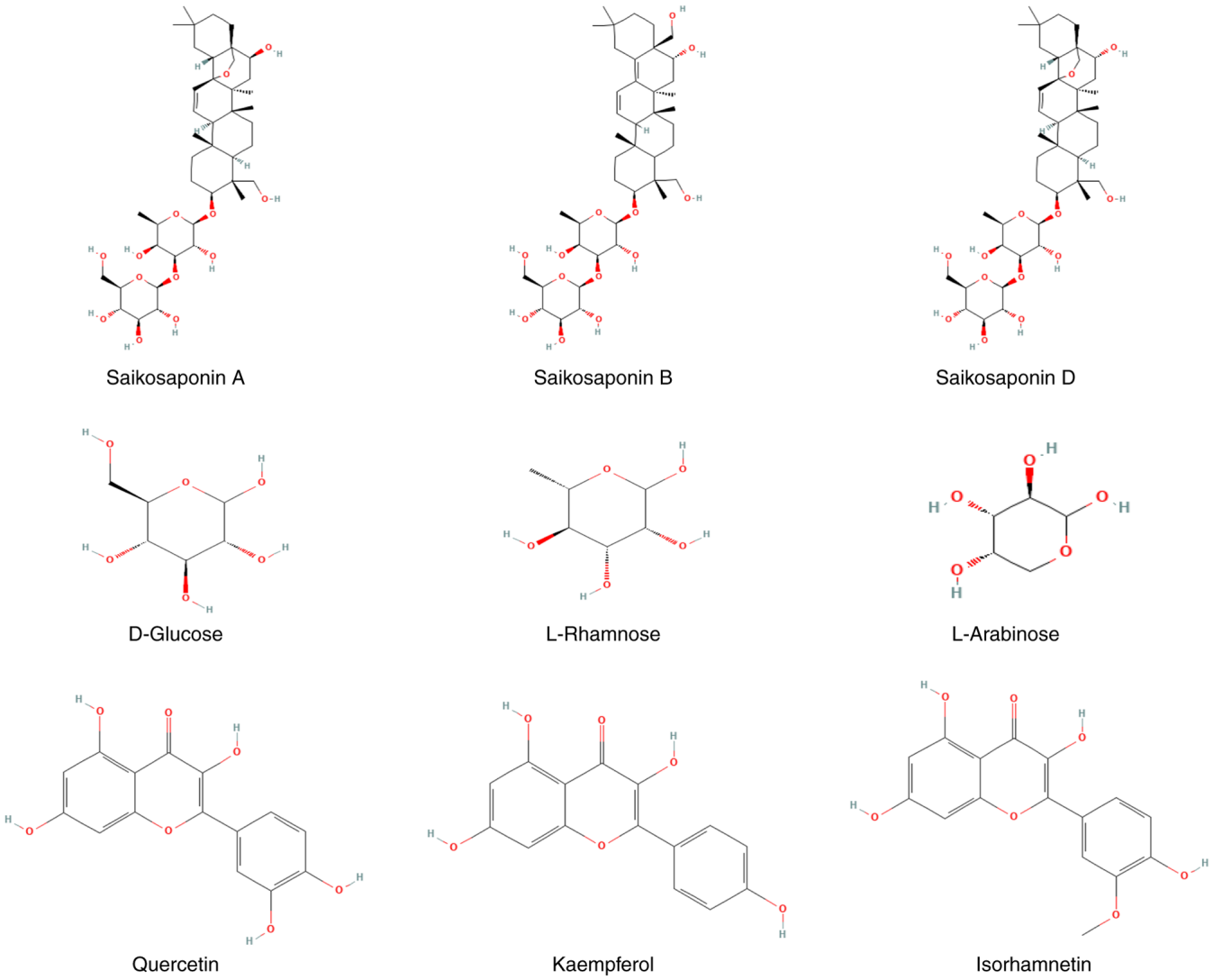

Figure 1. Active chemical constituents of *Radix Bupleuri*.

and uncontrolled cell proliferation, leading to tumor formation (57). SSD was shown to induce a G0/G1 phase blockade in doxorubicin (DOX)-resistant cells by decreasing the protein expression levels of Cyclin D1 and CDK4, while promoting DOX-induced apoptosis *in vitro* and *in vivo* by increasing cleaved Caspase 3 expression levels (58). p21 and p27 act as negative regulators of the cell cycle in coordination with cell cycle-associated kinases. Specifically, p21 halts cell cycle progression through the G/S phase and corrects abnormal centrosome replication, while p27 suppresses CDK expression, causing cell cycle arrest in the G0/G1 phase, inhibiting centrosome separation and impeding breast cancer cell proliferation (59). SSA induces apoptosis in the breast cancer cell lines, MDA-MB-231 and MCF-7, through p53/p21-independent and -dependent mechanisms (60). DNA synthesis during the S phase and mitosis in the G2/M phase are crucial for sustaining malignant tumor cell proliferation. Antitumor drugs primarily inhibit the progression of these cell cycle phases (61,62). The flavonoid, isorhamnetin, exhibits high anticancer activity, downregulating the protein expression levels of Cyclin B1 and CDK1 and inducing G2/M phase blockade, thus preventing the proliferation of MCF-7 cells (63).

Mitogen-activated protein kinase (MAPK) serves a crucial role in apoptosis induction. The downregulation of the p38 MAPK signaling pathway reduces the metastasis of breast cancer cells in the bone-tropic mouse mammary tumor virus-driven polyoma virus middle T oncoprotein transgenic (MMTV-PyMT) Bo1 mouse model (64-66). Additionally, SSD induces the apoptosis of MDA-MB-231 cells through the p38 MAPK signaling pathway by enhancing the p38its phosphorylation level and expression levels (67).

Excessive endoplasmic reticulum stress (ERS), or ER dysfunction, results in the persistent accumulation of unfolded and misfolded proteins in the ER, leading to an imbalance in cellular homeostasis, which can induce apoptosis (68). Calnexin monitors intracellular Ca^{2+} homeostasis by assisting in folding misfolded proteins and serving an essential role in ERS (69). SSD acts as an adenosine triphosphate (ATP) ase sarcoplasmic/ER Ca^{2+} transporting inhibitor in apoptosis-deficient cancer cells, such as MCF-7, and induces ERS and autophagic cell death by disrupting intracellular Ca^{2+} homeostasis via the Ca^{2+}/calmodulin-dependent protein kinase 2/mammalian target of rapamycin (mTOR) pathway (70). Wnt/β-catenin signaling pathway-related genes are highly

Table I. Pharmacological effects of the main active components of *Radix Bupleuri*.

Compound classification	Compound	Pharmacological action
Saikosaponins	Saikosaponin A	Anticancer (25,26,60,90,122), anti-inflammatory (34), anti-oxidative damage (35) and immune system regulation (39).
	Saikosaponin B	Anti-inflammatory (19), antifibrotic (36), anticancer (80).
	Saikosaponin D	Anticancer (58,67,70,72,121,137).
Polysaccharides	D-Glucose, L-rhamnose and L-arabinose	Anti-inflammatory (43,45) and immunomodulatory (42,44).
Flavonoids	Isorhamnetin	Anticancer (63) and reversal of drug resistance (63).
	Quercetin	Anti-inflammatory (47) and immune system regulation (91).
	Kaempferol	Anti-inflammatory (47).

expressed in triple-negative breast cancer (TNBC) (71). After incubation with SSD, the protein and mRNA expression levels of β-catenin in the cytoplasm and nucleus of the TNBC cells, SUM-159, HCC1937, MDA-MB-468 and MDA-MB-231, were significantly decreased, as well as the expression of downstream target genes, such as c-myc and CyclinD1, indicating that SSD inhibits the proliferation of TNBC cells by significantly inhibiting β-catenin and its downstream target genes. SSD also induces Caspase-dependent apoptosis and inhibits the proliferation of SUM-159, HCC1937, MDA-MB-468 and MDA-MB-231 cells (72).

Therefore, saikosaponins and flavonoids inhibit the development of breast cancer cells by negatively regulating cell cycle-related proteins. Saikosaponins also regulate apoptosis-related genes, downregulate the Wnt/β-catenin and p38 MAPK signaling pathways, reduce the expression levels of calnexin, serve a vital role in inhibiting the proliferation and promoting the apoptosis and autophagy of breast cancer cells and exhibit a concentration and time dependent-effect compared with the clinical breast cancer drug, paclitaxel, in which saikosaponins have a higher potency (72).

Inhibition of tumor cell invasion and metastasis. Invasive metastatic recurrence is the leading cause of death in patients with breast cancer (73). Epithelial-mesenchymal transition (EMT) is an important mechanism for initiating the process of malignant phenotypic transformation and the development of metastasis in breast cancer (74). Matrix metalloproteinases (MMPs) degrade the extracellular matrix (ECM) and promote the metastatic process of tumors, particularly MMP-2 and MMP-9 (75,76). SSA was shown to inhibit TNBC invasive metastasis by downregulating the MMP-9 and MMP-2 expression levels in SUM-149 and MDA-MB-231 cells (26). Phosphorylated signal transducers and activators of transcription 3 (p-STAT3) promotes the invasive metastasis of TNBC by mediating the EMT (77). Vasodilator stimulated phosphoprotein (VASP) can modulate actin polymerization and promote breast cancer development (78,79). SSB-2 suppresses the proliferation and migration of MCF-7 cells by inhibiting the STAT3 signaling pathway and reducing the expression levels of VASP, MMP-2 and MMP-9 (80).

The phosphatidylinositol-3-kinase (PI3K)/protein kinase B (AKT)/mTOR pathway can regulate tumor cell growth, proliferation, survival, angiogenesis and other processes (81). The stromal cell-derived factor-1 (SDF-1)/chemokine receptor (CXCR4) axis is involved in the invasion and migration of MDA-MB-231 cells (82), and the crosstalk between the CXCR4/SDF-1 axis and the AKT/mTOR pathway occurs in circulating tumor cells (83). CXCR4 expression is associated with breast cancer growth, angiogenesis and distant metastasis and is an important indicator of infiltrative metastasis and poor prognosis (84,85). When compared with normal breast cancer cells, CXCR4 is highly expressed in TNBC cell lines (86). Results from an animal study showed that SSA downregulates the expression of CXCR4 in mouse lung high metastatic breast cancer luciferase cells (4T1-LUC cells) and exhibits anti-growth and anti-metastatic effects on TNBC through multiple signaling pathways, including PI3K/AKT/mTOR and MMPs (26).

Accordingly, different saikosaponins can inhibit the invasive and metastatic potential of breast cancer cells and prevent the occurrence and development of breast cancer through various signal transduction pathways such as the STAT3, VASP, MMPs, CXCR4/SDF-1, PI3K/Akt and Akt/mTOR pathways.

Regulation of glycolipid metabolism in tumor cells. Solid tumor cells have the potential to proliferate indefinitely, and to support cell proliferation and survival, tumor cells rewire their metabolism to a glycolytic phenotype to satisfy their escalating bioenergetic demands, with TNBC being the breast cancer subtype most reliant on glycolysis for energy gain (87). Through the Warburg effect, the breakdown of glucose into lactic acid allows efficient access to the ATP required for unlimited proliferation of tumor cells, the raw material for the synthesis of tumor cell biomolecules and the precursors essential for other metabolic pathways, ultimately promoting tumor progression (88,89). SSA reduces the upregulation of p-STAT3 and p-AKT in MDA-MB-231 and MCF-7 cells and decreases lactate and ATP production and glucose uptake in tumor cells through downregulation of the AKT/STAT3 signaling pathway, inhibiting the proliferation of tumor cells (90).

Table II. Pharmacological effects of the main active compounds of *Radix Bupleuri*.

Compound	Animal/cell	Stimulation	Dosage	Time	Effects	(Refs.)
SSA	MDA-MB-231	N/A	5 μg/ml	3 h	Bax/Bcl-2↑, c-myc↑, Caspase 3↑, proliferation or viability ↓, sub-G1 population of cell cycles.	(60)
	MCF-7	N/A	5 μg/ml	2 h	Apoptosis depend on p53/p21 mechanism, c-myc↑, proliferation or viability of cells↓, sub-G1 population of cell	
SSA	SUM-149 MDA-MB-231 BALB/c nude mice (4T1-luc) BALB/c nude mice (MDA-MB-231-Luc cell)	N/A Xenografts	2.5-10 μM 12 mg/kg	48 h 24 h 14 days	CXCR4↓, by the PI3K/Akt/mTOR and MMP signaling pathways, anti-growth and anti-metastasis effects.	(26)
SSA	MDA-MB-231 or MCF-7	N/A	10 μM	48 h	p-STAT3↓, p-Akt↓, Akt/STAT3 pathway aerobic glycolysis process of cells↓, ATP↓, causes cell death.	(90)
SSA	Female SD rat	DMBA	35 mg/kg	56 days	IFN-γ↑, IL-12↑, IL-4↓, IL-10↓, activation of the IL-12/STAT4 pathway mediated differentiation of Th1 cells, promoting Th1/Th2 balance towards Th1 response, inhibits cancer development and progression.	(25)
SSA	Female BALB/c mice (4T1 cell)	N/A	10 mg/kg	24 h	Inhibits tumor growth by suppressing angiogenesis and notably reduced the Ki-67-positive tumor cells.	(85)
SSA	MCF-7/ADR	ADR	5 μM	24-48 h	Reduces the IC_{50} of drug-resistant cells to DOX VCR, and PTX, thereby enhancing their sensitivity to	(122)
SSB-2	MCF-7	NSC74859	5 μM	48 h	c-myc↓, cyclin D1↓, p-STAT3↓, VASP↓, inhibition of cancer cell proliferation and metastasis.	(80)
	Kunming mice (MCF-7)	N/A	30 mg/kg	30 days	No liver or kidney toxicity.	
SSD	MCF-7 HCC1937 MDA-MB-468 SUM159 MDA-MB-231	N/A	5-20 μM	2-24 h	β-catenin and its downstream targets genes↓, resulting in caspase-dependent cell apoptosis	(72)
SSD	MDA-MB-231	N/A	2-8 μM	24 h	Induces apoptosis in MDA-MB-231 cells through activation of the p38 MAPK. signaling	(67)
SSD	MCF-7	N/A	10 μM	24 h	Induces autophagy by direct inhibition of SERCA, CaMKKβ-AMP-AMPK-mTOR↑, ER↑, UPR↑, cytosolic calcium level, autophagy induction, disruption of calcium homeostasis↑	(70)
SSD	MCF-7	N/A	10 μM	24 h	Acts as an agonist of the estrogen receptor, ERα↑, inhibits proliferation by affecting the cell cycle.	(133)
SSD	MCF-7/ADR	ADR	1-5 μg/ml	24-48 h	Sensitivity to ADR↑, P-gp-mediated efflux↓	(121)

Table II. Continued.

Compound	Animal/cell	Stimulation	Dosage	Time	Effects	(Refs.)
SSD	MCF-7/DOX MDA-MB-231/DOX	DOX	1, 7 and14 μM	24 h	The redox imbalance or oxidative stress caused by the STAT1/ NQO1/PGC-1α signaling pathway, increasing ROS accumulation, and decreasing GSH, NADPH and NADH concentrations, is responsible for inhibiting cell growth and stimulating apoptosis.	(58)
	BALB/c nude mice (MCF7/DOX cell)		10 mg/kg	3 days		
Isorhamnetin	MCF-7/ADR	ADR	10-50 μM	24 h	p-AMPK↑, mTOR↓, p-p70S6K↓, Bcl-2↓, induces cell cycle arrest and apoptosis by triggering DNA damage and regulating the AMPK/mTOR/p70S6K signaling pathway.	(63)

SSA-D, saikosaponin A-D; c-myc, myelocytomatosis oncogene; CXCR4, C-X-C chemokine receptor type 4; PI3K, phosphatidylinositol 3-kinase; Akt, protein kinase B; mTOR, mechanistic target of rapamycin; MMP, matrix metalloproteinase; p-, phosphorylated; STAT1/3/4, signal transducers and activators of transcription 1/3/4; IFN-γ, interferon-γ; IL-4/10/12, interleukin-4/10/12; Th1-2, T helper type 1-2; P-gp, p-glycoprotein; ADR, adriamycin; IC_{50}, half maximal inhibitory concentration; DOX, doxorubicin; VCR, vincristine; PTX, paclitaxel; VASP, vasodilator stimulated phosphoprotein; p38 MAPK, p38 mitogen-activated protein kinases; SERCA, sarcoplasmic endoplasmic reticulum calcium ATPase; ER, estrogen receptor; UPR, unfolded protein response; NQO1, NAD(P)H:quinone oxidoreductase 1; PGC-1α, peroxisome proliferator-activated receptor-γ coactIvator-1α; ROS, reactive oxygen species; GSH, glutathione; NADPH, reduced nicotinamide adenine dinucleotide phosphate; NADH, nicotinamide adenine dinucleotide.

Bioinformatics and network pharmacology analyses have shown that flavonoids and saikosaponins can regulate lipid metabolism-related genes and improve the depressive symptoms of patients with breast cancer (91,92). Saikosaponins can increase hepatic uptake of circulating fatty acids, promote mitochondrial respiration in fatty acid oxidation, repair imbalanced lipid metabolism and promote intracellular cholesterol efflux, high-density lipoprotein (HDL) remodeling and the clearance of low-density lipoprotein (LDL) particles and bile acid synthesis, significantly modulating cholesterol clearance (93,94). Certain commonly used drugs for the treatment of breast cancer, such as exemestane and chloroquine, are hepatotoxic and have major adverse effects (95,96). Saikosaponins have been reported to be effective liver protectants and Chaihu Liver Protection Tablets have been clinically used to combat oxidative stress and lipid peroxidation reactions associated with lipid overload (97).

The main component of the breast is adipose tissue and mammary glands, in which cancer-associated adipocytes can promote the proliferation and metastasis of breast cancer cells (98-100). SSA and SSD inhibit adipocyte 3T3-L1 production via the AMP-activated protein kinase (AMPK) and MAPK signaling pathways (101). Disorders of glucose and lipid metabolism predispose individuals to insulin resistance, abnormal glucose tolerance and altered lipid metabolism, all of which are risk factors for the development of breast cancer (102,103). It has been previously reported that SSA can be used to reduce the levels of blood glucose, triglyceride, free fatty acid, total cholesterol, LDL and HDL in mice, significantly reduce liver weight and fat accumulation, downregulate the expression of TNF-α and NF-κB, and upregulate the expression of fibroblast growth factor-21 and recombinant autophagy related protein 7, which stimulates the autophagy of cells and improves insulin resistance (104).

Therefore, saikosaponins can affect the glucose metabolism of breast cancer cells by regulating the production of aerobic enzymolysis products and inhibiting the activity of cytokines. Together with flavonoids, they can also serve a role in lipid regulation. Targeting the regulation of the AMPK and the MAPK signaling pathway and other aspects could enable treatments to target multiple breast tumors. The pharmacological effects of the active ingredients of *Radix Bupleuri* are shown in Table II.

Regulating the TME. The TME consists of cancer cells, stromal cells, cytokines, chemokines and other factors that serve a crucial role in breast cancer development, progression and drug resistance (105). Tumor-associated macrophages (TAMs) are the most abundant immune cell group in breast cancer, participate in every stage of cancer progression and are associated with tumor malignant progression (105,106). TAMs are typically divided into M1 and M2 types, with M1 TAMs contributing to the dormancy of metastatic breast cancer cells and M2 TAMs promoting tumor growth (105). Polysaccharides can upregulate the activity of macrophages, effectively inhibit the release of key factors of inflammatory response and immune regulation, exert anti-inflammatory activity, prevent tissue damage caused by excessive inflammation and may enhance the TME in breast cancer (43,44). SSD can significantly enhance the phagocytic ability of

macrophages, increase their acid phosphatase levels and promote the expression of immune-related antigens on the cell surface (107).

Tumor infiltrating T cells are associated with improved clinical prognosis and survival in patients with breast cancer. As a crucial component of the TME, T cells serve a significant role in the immune response to cancer (108). The balance between T helper (Th)1 and Th2 cells is particularly important, as a shift from Th1 to Th2 promotes breast cancer progression (109). SSA activates the IL-12/STAT4 pathway, leading to a significant increase in the infiltration of $CD8^+$ and $CD4^+$ T cells in tumors. This activation occurs through the upregulation of IL-12, IL-12R and STAT4 gene expression, as well as the increased expression levels of IL-12, IL-12R and p-STAT4 proteins (25). $CD8^+$ T cells exert tumor-killing activity by interacting with tumor antigens and releasing perforin, granzyme and cytokines, which directly or indirectly kill tumor cells. Additionally, this process promotes a shift in the Th1/Th2 balance towards a Th1 response, thereby inhibiting the development and progression of breast cancer (25).

Therefore, polysaccharides and saikosaponins jointly regulate the TME, which are important components of *Radix Bupleuri* for immune regulation.

Inhibition of tumor angiogenesis. The process of tumor angiogenesis includes endothelial cell activation, ECM degradation and endothelial cell migration, angiogenesis and extension into the tumor and is regulated by various cytokines in the TME (110). Vascular endothelial growth factor (VEGF) is an important angiogenesis factor and blocking VEGF is a potential strategy for the treatment of invasive breast cancer (111). The VEGF receptor 2 (VEGFR2) signaling pathway and its downstream proteins are an important signaling pathway that regulates endothelial cell function during angiogenesis (112). Clinically, patients with breast cancer who experience lymph node metastasis often harbor high expression levels of hypoxia inducible factor 1 subunit α (HIF-1α) and VEGF. The recurrence and metastasis of breast cancer may be related to the upregulation of HIF-1α and VEGF, promoting the angiogenesis of breast cancer and other related factors (113,114). SSA inhibits the phosphorylation of VEGFR2 and the activity of downstream protein kinases, phospholipase C-γ-1, focal adhesion kinase, Src and AKT, reducing tumor angiogenesis and subsequently inhibiting the growth of mouse breast cancer 4T1 cells (115). Thus, by downregulating the expression level or activity of angiogenesis-related proteins, saikosaponins inhibit tumor angiogenesis and limit the growth and metastasis of breast tumors.

Improving the efficacy of chemotherapy drugs. At present, surgical resection is still the main treatment option for patients with breast cancer and postoperative radiotherapy or chemotherapy are often used to further improve patient prognosis (116). Radiotherapy and chemotherapy both non-selectively kill cancer cells and can cause toxic side effects (117). Traditional Chinese Medicine has been used for the prevention and treatment of breast cancer (118). Traditional Chinese Medicine has been reported to target tumors and can be combined with Western medicine to enhance the efficacy of these medicines and reduce potential toxicity (119).

During or after chemotherapy, the expression levels of multidrug resistance protein (MDR)1 and breast cancer resistance protein, ABCG2, can increase significantly (120). A mechanism of action of MDR is the upregulation of p-glycoprotein (P-gp), and the direct inhibition of P-gp upregulation by SSA and SSD *in vitro* reverses MDR in MCF-7 cells (121,122). Isorhamnetin mediates the inhibition of proliferation and the induction of apoptosis in MCF7/adriamycin (ADR) and MDAMB-231/DOX cells by enhancing the phosphorylation of AMPK, decreasing the phosphorylation levels of mTOR and p70S6K, inhibiting the expression levels of B-cell lymphoma-2 and increasing the cleavage of Caspase 3 (63). In addition, isorhamnetin also downregulates the expression level of P-gp, leading to increased intracellular DOX accumulation, increased toxicity, promotion of apoptosis and the restriction of tumor growth *in vivo* (63).

Moderate levels of reactive oxygen species (ROS) can activate various signaling pathways to promote tumor development (123,124). However, excessive ROS levels that cannot be effectively balanced by the antioxidant system can lead to oxidative stress, promoting apoptosis and the death of cancer cells. Drug-resistant cells produce higher levels of ROS compared with non-drug-resistant cells. To maintain redox homeostasis in an environment with high ROS levels, drug-resistant cancer cells enhance their antioxidant capacity by increasing the synthesis of reduced glutathione (GSH) and upregulating antioxidant enzymes, including NAD(P)H:quinone oxidoreductase 1 (NQO1) (125). NQO1 is significantly upregulated in various types of solid tumors, suggesting its potential involvement in cellular defense during oncogenesis (126). NQO1 is reported to be a STAT1-regulated gene in MCF-7/DOX and MDA-MB-231/DOX-resistant strain cells, as STAT1 expression levels are positively correlated with NQO1 expression levels (58). Molecular docking has shown that SSD may interact with the active site of NQO1, forming two hydrogen bonds with the Leu103 and Tyr128 residues, suggesting that SSD has a strong binding affinity with the NQO1 protein (58). Subsequently, *in vitro* and *in vivo* experiments have been performed to confirm that SSD downregulates the STAT1/NQO1/peroxisome proliferator-activated receptor γcoactivator-1 α (PGC-1α) signaling pathway (58). After SSD inhibits NQO1, the consumption of nicotinamide adenine dinucleotide phosphate (NADPH) and nicotinamide adenine dinucleotide (NADH) decreases (58). The redox imbalance in the cell is in a high ROS state, and the antioxidants, GSH, NADPH and NADH, are consumed in large quantities in response to oxidative stress, which ultimately leads to a decrease in their levels (58), which leads to an increase in intracellular oxidative stress levels and ultimately induces MCF-7/DOX and MDA-MB-231/DOX apoptosis (58).

Patients with breast cancer treated with radiation and chemotherapy may have adverse reactions, such as insomnia, bone marrow suppression, leukopenia and depression (127). *Radix Bupleuri*, as the main ingredient of *Xiao Chaihu Tang*, *Jia Wei Chaihu Gui Jiang Tang* and other Traditional Chinese Medicine compound tonics, has been reported to clinically improve the postoperative adverse effects in patients with breast cancer, reduce or slow down the secretion of tumor markers and improve the efficacy of certain chemotherapeutic agents such as paclitaxel and cisplatin (27,128).

A variety of components of *Radix Bupleuri* can slow down the progression of breast cancer, reverse the MDR of tumor cells to chemotherapeutic drugs including ADR, vincristine and paclitaxel and alleviate postoperative adverse reactions (122).

Additional anticancer mechanisms. The stability of subcellular organelles and metal ions is essential for various physiological and biochemical processes, such as homeostasis of the internal environment, regulation of cellular metabolism, substance synthesis, signal transmission and energy conversion (129). *Staphylococcus aureus* infection can cause an increase in inflammatory markers such as myeloperoxidase, TNF-α and IL-1 β in mice, as well as an accumulation of Fe^{2+}; it significantly increases the expression levels of malondialdehyde (MDA) and reduces the expression levels of GSH, indicating that *S. aureus* induces ferroptosis in normal breast cells, leading to the development of mastitis. Additionally, *S. aureus* reduces the expression levels of sirtuin 1 (SIRT1), nuclear factor erythroid 2-related factor 2 (Nrf2) and heme oxygenase 1 (HO-1); however, SSA treatment increases the expression levels of SIRT1, Nrf2 and HO-1 in a dose-dependent manner, indicating that SSA inhibits *S. aureus*-induced mastitis by activating the SIRT1/Nrf2 signaling pathway (34).

Mitochondria are the metabolic centers and energy factories of cells (130). During respiration and oxidation, mitochondria store the generated energy as electrochemical potential energy in the inner mitochondrial membrane, causing an asymmetric distribution of protons and other ions on both sides of the inner membrane to form the mitochondrial membrane potential (ΔΨm) (130). Normal ΔΨm is a prerequisite for mitochondria to carry out oxidative phosphorylation and produce ATP, and ΔΨm instability promotes the development of cancer cells (131). With increasing SSD concentrations, the ΔΨm levels of MCF-7/DOX and MDA-MB-231/DOX cells decrease, the PGC-1α protein expression levels decrease and the protein expression levels of the double-stranded DNA breakage marker, γ-H2AX, increase, suggesting that SSD leads to the oxidative stress of drug-resistant cells by amplifying the ΔΨm loss, mitochondrial dysfunction and DNA damage to exert antitumor effects (58). Estrogen receptor 2 (ERβ) serves a key role in maintaining mitochondrial homeostasis in breast epithelial cells, but decreased expression levels of ERβ in some patients with breast cancer after surgical treatment leads to tumor recurrence and metastasis, suggesting that ERβ abnormalities are related to mitochondrial dysfunction. ERβ inhibits the invasive properties of EMT and TNBC cells and patients with ERβ deficiency are prone to tumorigenesis (132). SSD has weak estrogen-like effects and activates ERβ expression at high doses (133). The role of saikosaponins in inhibiting ferroptosis in normal breast cells in mastitis and in affecting the ΔΨm of drug-resistant cells provides a potential basis for the investigation of saikosaponin-induced ferroptosis in breast cancer and may suggest the feasibility of this approach for the future treatment of patients with this disease.

The study of signaling pathways has implications for the treatment of certain diseases and future biotechnological innovations. A number of relevant signaling pathways activated by *Radix Bupleuri* active ingredients cause anti-breast cancer effects (Fig. 2).

4. Mechanisms of action against other types of cancer

In other tumor types, *Radix Bupleuri* and its active ingredients also serve an anticancer role. In aggressive B-cell lymphoma hematopoietic stem cell, SSA inhibits cell activation, promotes apoptosis and reduces cell migration, and its derivative, SSB1, reduces collagen deposition, ultimately alleviating liver fibrosis (134). In the human hepatocellular carcinoma cell line, Huh-7, and the human hepatoblastoma cell line, HepG2, SSA promotes fat mobilization, increases MDA and Fe^{2+} accumulation, mediates ferroptosis in liver cancer cells and significantly reduces the viability of cells in a concentration- and time-dependent manner (135). SSA can also induce the EGFR/PI3K/AKT signaling pathway to target pancreatic cancer (136). SSD induces ROS accumulation and activates the NF-κB/NLR family pyrin domain-containing 3/Caspase 1/Gasdermin D pathway to induce apoptosis in lung cancer cells (137). SSD also directly binds to the SH2 domain of STAT3, significantly downregulates the expression level of p-STAT3, inhibits the Janus kinase/STAT pathway and reduces the expression of the inflammatory cytokines, IL-6 and IL-1β, which can serve a therapeutic role in cancer cachexia (21).

In summary, *Radix Bupleuri* and its active ingredients can serve an anticancer role in hepatocellular carcinoma, lung cancer and pancreatic cancer through modulating oxidative stress. This could provide a reference for the in-depth study of the potential anti-breast cancer effects of *Radix Bupleuri* and its active ingredients and its mechanism of action in the treatment of breast cancer, through studies investigating its impact on ferroptosis, cuproptosis and pyroptosis.

5. Discussion and future perspectives

The incidence and mortality rates of breast cancer continue to rise on a global scale (1). Current treatment approaches focus on precise treatment methods, minimizing the extent of breast resection (138) and utilizing a combination of radiotherapy, chemotherapy and immunotherapy post-surgery to enhance patient quality of life and extend survival duration. However, there are several issues with these treatments, such as adverse reactions and drug resistance. Traditional Chinese Medicine may exhibit anticancer properties that target various cellular signaling pathways (139,140). For instance, *Radix Bupleuri*, a component of Traditional Chinese Medicine, contains a diverse array of active ingredients with promising anticancer applications. Saikosaponins, polysaccharides and flavonoids found in *Radix Bupleuri* have been shown to regulate cell cycle proteins, inhibit breast cancer cell proliferation and induce apoptosis. Furthermore, *Radix Bupleuri* and its constituents have been reported to prevent tumor cell invasion and metastasis, influence tumor cell metabolism, modulate TAMs, enhance the TME, reduce MDR protein expression levels in tumor cells and aid in the efficacy of radiotherapy and chemotherapy by boosting immune system activity.

Nevertheless, current research is focused on identifying changes in protein expression levels and signaling pathways, with specific targets of this treatment yet to be fully understood. New technologies such as multi-omics studies, network pharmacology and molecular docking, offer novel perspectives

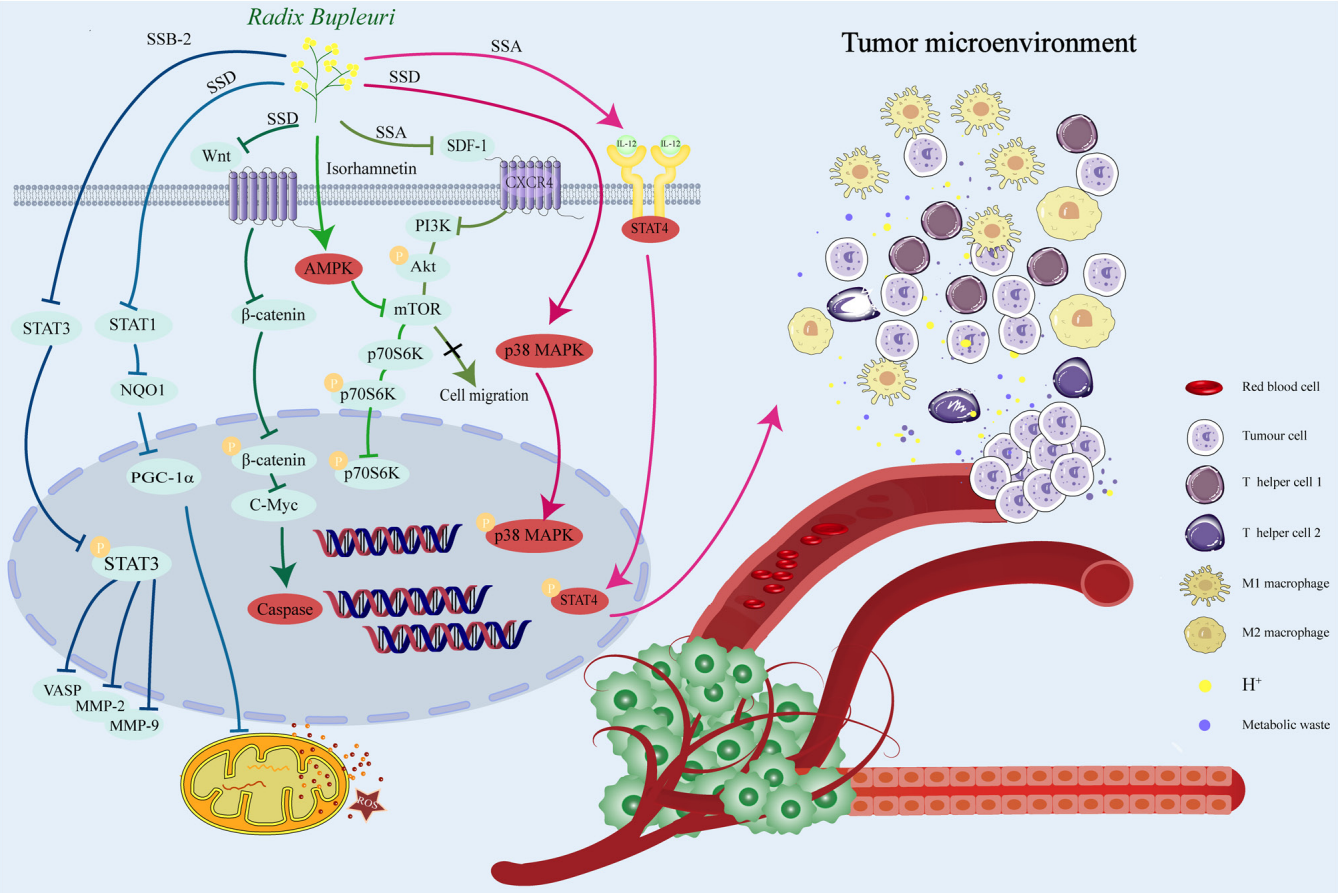

Figure 2. Relevant signaling pathways of the *Radix Bupleuri* active ingredients in anti-breast cancer. SSA-D, saikosaponin A-D; STAT1/3/4, signal transducers and activators of transcription 1/3/4; p-STAT3, phosphorylated STAT3; VASP, vasodilator stimulated phosphoprotein; MMP, matrix metalloproteinase; NQO1, NAD(P)H:quinone oxidoreductase 1; PGC-1α, peroxisome proliferator-activated receptor-γ coactivator-1α; ROS, reactive oxygen species; c-myc, myelocytomatosis oncogene; AMPK, AMP-activated protein kinase; mTOR, mechanistic target of rapamycin; p70S6K, 70 kDa ribosomal protein S6 kinase; SDF-1, stromal cell-derived factor; CXCR4, C-X-C chemokine receptor type 4; PI3K, phosphatidylinositol 3-kinase; Akt, protein kinase B; p38 MAPK, p38 mitogen-activated protein kinase.

for gaining a deeper insight into the mechanism of action of *Radix Bupleuri* as an adjuvant chemotherapy agent. While combining *Radix Bupleuri* with conventional chemotherapy drugs shows potential in reversing drug resistance, rigorous clinical trials are essential to assess the safety and efficacy of this treatment approach. The adoption of modern ultrafine grinding technology and nanotechnology can improve the efficient utilization and absorption of herbal components, reduce toxicity, enhance chemotherapeutic efficacy and improve the acceptance of herbal medicines by young patients.

Future studies on the toxicological and pharmacokinetic effects of *Radix Bupleuri* and its active ingredients are required to elucidate the biological activities of metabolites, establish dose-time-pharmacology/toxicity relationships and to determine its biological targets and mode of action (141-143). These studies are not only important for the development and discovery of novel *Radix Bupleuri*-based drugs and treatment strategies, but also crucial for the clinically safe use and improvement of medicines containing *Radix Bupleuri*.

6. Conclusion

Existing reviews (144,145) on *Radix Bupleuri* typically discuss the full range of pharmacological effects of this compound, such as its anti-pyretic, anti-inflammatory, anti-bacterial, anti-viral and anti-depressant effects, or, alternatively, focus only on the pharmacological effects of saikosaponins. However, most compound components are widely used in clinical practice in the form of herbal compound formulations, and compound preparations of *Radix Bupleuri* have been used clinically for the treatment of breast nodules and for recovery from breast cancer surgery. Compared with previous studies, the present review has further expanded, in both scope and depth, the anti-breast cancer effects and mechanisms of *Radix Bupleuri* and its active ingredients. Various active ingredients, such as SSA, SSB-2, SSD and isorhamnetin, show synergistic anti-breast cancer effects when combined with chemotherapy drugs. In addition, *Radix Bupleuri* compound decoction may have the potential to reduce certain side effects caused by chemotherapy drugs. These findings support the use of *Radix Bupleuri* and its components, especially saikosaponins, as a potential future clinical candidate for anti-breast cancer drugs.

However, current studies in this area have a number of limitations. First, according to bibliometric analysis, SSD is the most studied *Radix Bupleuri* monomer as an anti-breast cancer drug, but there are no detailed reports on the safety and toxicology of SSD, which may limit its clinical

development. Second, current research is limited to *in vitro* cell and *in vivo* animal experiments and there is little clinical trial data. Third, the current research on the mechanism of action of *Radix Bupleuri* is lacking in depth, especially the study of the targets of compounds, and there are no consistent reports on the concentrations and treatment durations of these compounds that are required to induce anticancer effects.

In conclusion, *Radix Bupleuri* and its effective ingredients could potentially be used clinically in the future to alleviate the symptoms of breast cancer, improve immunity and prolong survival times. However, further research is required to provide a theoretical basis for the development and application of *Radix Bupleuri* and its active ingredients for the treatment of patients with this disease.

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Availability of data and materials

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Authors' contributions

Conceptualization was conducted by SJ and WY; formal analysis and data interpretation of the literature were conducted by SJ, CL, TH and WY; literature analysis was conducted by SJ, CL, DL, FZ and WW; writing of the original draft was conducted by SJ, CL, TH and WY; reviewing and editing of the manuscript was conducted by SJ, TH and WY; construction of the figures was conducted by SJ and CL; supervision was conducted by SJ, TH and WY; project administration was conducted by FZ, TH and WY. Data authentication is not applicable. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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