Anticancer effects of salvianolic acid A through multiple signaling pathways (Review)

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Abstract. *Salvia miltiorrhiza* Bunge (*Salvia miltiorrhiza*), commonly referred to as Danshen, is a well-known herb in traditional Chinese medicine, the active ingredients of which are mostly categorized as water soluble and lipid soluble. Salvianolic acids are the major water-soluble phenolic acid constituents of Danshen; salvianolic acid B is the most prevalent, with salvianolic acid A (SAA) being the next most predominant form. SAA offers a wide array of pharmacological benefits, including cardiovascular protection, and anti-inflammatory, antioxidant, antiviral and anticancer activities. SAA is currently undergoing phase III clinical trials for diabetic peripheral neuropathy and has shown protective benefits against cardiovascular illnesses; furthermore, its safety and effectiveness are encouraging. By targeting several signaling pathways, preventing cell cycle progression, tumor cell migration, invasion and metastasis, normalizing the tumor vasculature and encouraging cell apoptosis, SAA can also prevent the growth of malignancies. In addition, it enhances sensitivity to chemotherapeutic drugs, and alleviates their toxicity and side effects. However, the broad therapeutic use of SAA has been somewhat limited by its low content in *Salvia miltiorrhiza* Bunge and the difficulty of its extraction techniques. Therefore, the present review focuses on the potential mechanisms of SAA in tumor prevention and treatment. With the anticipation that SAA will serve a notable role in clinical applications in the future, these discoveries may offer a scientific basis for the combination of SAA with conventional chemotherapeutic drugs in the treatment of cancer, and could establish a foundation for the development of SAA as an anticancer drug.

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Abbreviations: mTOR, mammalian target of rapamycin; c-MET, mesenchymal-to-epithelial transition factor; MDR1, multidrug resistance-1, Cyto C, cytochrome *c*; PTEN, phosphatase and tensin homolog; ETAR, endothelin A receptor; DLBCL, diffuse large B-cell lymphoma; p-, phosphorylated; Chk-2, checkpoint kinase-2; EMT, epithelial-mesenchymal transition; HGF, hepatocyte growth factor; PRMT1, protein arginine methyltransferase 1; PXR, pregnane X receptor; GRP78, glucose-regulated protein 78; DOX, doxorubicin hydrochloride; TAMs, tumor-associated macrophages; FA, folic acid; TCM, traditional Chinese medicine; SAA, salvianolic acid A

Key words: *Salvia miltiorrhiza* Bunge, *Salvia miltiorrhiza*, SAA, anticancer activity, pro-apoptosis

1. Introduction

Global statistics indicate that there were ~20 million newly diagnosed cases of cancer and ~10 million cases of cancer-associated mortality in 2022 (1). Projections based on demographics indicate that the yearly incidence of new cancer cases might increase to 35 million by 2050, representing a 77% increase compared with 2022 (1). Current cancer treatments, including surgery, radiation and chemotherapy, have shown promising results; however, recurrence and metastasis due to chemotherapy resistance remain the leading causes of death in patients (2-4). Over the last few years, global interest in traditional Chinese medicine (TCM) as cancer treatment has rapidly increased (5-7). TCM is favored by an increasing number of patients due to its holistic approach and possibility for individualized treatment, as well as fewer side effects and its applicability to long-term treatment. TCM has become an indispensable part of comprehensive tumor therapy, and has been shown to aid the relief of symptoms and improve the quality of life of patients (8). The therapeutic effects of the active

ingredients of TCM on malignant growth, including liver, lung and breast cancer growth, have been reported, providing new potential for cancer therapy (9-11). Furthermore, active ingredients of natural Chinese herbal medicines have extensive use in the treatment of cancer due to their high efficacy, lack of resistance, low toxicity and minimal side effects (12,13). It is anticipated that they may work around the disadvantages of currently available anticancer medications, and serve as adjuvants to chemotherapy by enhancing their effects and reducing toxicity. Consequently, they are gaining increasing attention in cancer prevention and treatment.

The present review focuses on the anticancer effects and mechanisms of the small molecule SAA from the traditional Chinese medicine *Salvia miltiorrhiza* Bunge *(Salvia miltiorrhiza)*, also known as Danshen.

2. Source, structure and bioactivity of SAA

As a widely used traditional Chinese herb, Danshen contains various active ingredients that can be categorized into different groups according to their chemical and structural characteristics (14). These components are separated into two primary categories: Lipid-soluble tanshinones and water-soluble phenolic acids (15). Salvianolic acid and rosmarinic acid B make up the water-soluble phenolic acids, whereas the lipid-soluble tanshinones include tanshinone I and II, dihydrotanshinone I and cryptotanshinone (16). The salvianolic acids in Danshen include many compounds, namely salvianolic acids A-H, J-N, T/U and Y (17). Among these, SAA and salvianolic acid B are particularly regarded as having the highest antioxidant activity (18). Chemically, SAA is identified as (R)-3-(3,4-dihydroxyphenyl)-2-(((E)-3-(2-((E)-3,4-dihydroxystyryl)-3,4-dihydroxyphenyl)acryloyl)oxy) propanoic acid, with a molecular formula of $C_{26}H_{22}O_{10}$ (19,20). Structurally, SAA is a trimer consisting of danshensu and caffeic acid as its fundamental units. The molecular structure of SAA is depicted in Fig. 1 (21).

A principal water-soluble component of *Salvia miltiorrhiza* Bunge, salvianolic acid A (SAA), has been recognized for its pharmacological activities, including antioxidant (22), anti-inflammatory (23), antiviral (24), antitumor (25,26), vascular endothelial protective (27) and myocardial protective (28) properties.

3. Anticancer activity of SAA

The main water-soluble active ingredient in Danshen, SAA, influences cell migration, invasion, apoptosis and proliferation, all of which notably impact the occurrence and development of tumors (29,30). Unlike most chemotherapeutic drugs currently used in clinical settings, which typically target a single pathway and are susceptible to drug resistance (31), small-molecule components derived from natural products often exhibit antitumor effects by modulating multiple signaling pathways (32,33). For example, natural compounds can influence pathways that are critical for regulating tumor cell proliferation and growth, such as PI3K/Akt (34,35), Wnt/β-catenin (36-38) and NF-κB (39) pathways, thus providing a multifaceted approach to cancer treatment (40-42). In several tumor cells, including MCF-7 breast cancer cells, SCC-9 oral squamous cell carcinoma cells, and KG-1 and Kasumi-1 acute myeloid leukemia cells, SAA exerts its antitumor effects by inhibiting cell invasion, migration and proliferation, and promotes apoptosis by targeting different signaling pathways, including the PI3K/Akt, Raf/extracellular signal-regulated kinase (ERK) kinase (MEK) and mammalian target of rapamycin (mTOR) pathways (43-45). Through its electrophilic α,β-unsaturated ester moiety, SAA functions as a covalent ligand to alter biological proteins (46). The protein targets of SAA have been identified using chemoproteomics and phosphoproteomics (47). According to chemoproteomics analysis, SAA covalently alters a minimum of 46 proteins, including the mTOR complex 1 (mTORC1) subunit Raptor to inhibit mTORC1 (47). According to the phosphoproteomics profile, SAA primarily interferes with the PI3K/Akt/mTOR signaling pathway (47). SAA exhibits multifaceted antitumour properties. These include the regulation of intracellular energy dynamics [e.g., induction of endogenous apoptosis (48) and suppression of mitochondrial membrane potential (49)], inhibition of tumour cell proliferation (50), suppression of tumour cell migratory and invasive (51), enhancement of chemotherapy sensitivity (49,52) or reversal of chemotherapy resistance (53), inhibition of tumour angiogenesis (54) and modulation of genomic instability and mutations (55) (Fig. 2).

4. Anticancer mechanism of SAA

Research has indicated that the anticancer effect of SAA is multifaceted and involves several molecular mechanisms. A key aspect is activation of the caspase family, which is crucial for the execution of apoptosis (48). In addition, the levels of proteins that inhibit apoptosis have been shown to be decreased by SAA, such as those of anti-apoptotic Bcl-2, while pro-apoptotic proteins such as Bak and Bax are simultaneously activated (49). Furthermore, SAA may inhibit the c-mesenchymal-to-epithelial transition factor (c-MET) and reduce the activity of matrix metalloproteinases (MMPs), such as MMP-2 and MMP-9, which are implicated in tumor invasion and metastasis (50,51). In a previous study, SAA has been shown to decrease the expression of drug-resistant proteins, specifically P-glycoprotein and multidrug resistance-1 (MDR1) (43). Finally, SAA has been found to regulate critical signaling pathways, including PI3K/Akt/MAPK and c-Raf/MEK/ERK pathways, which are essential for cell survival and proliferation.

Regulation of tumor cell apoptosis by SAA. The process through which a cell stops growing and dividing, and enters a phase that eventually leads to regulated cell death, is called apoptosis or programmed cell death (56). The impairment of a series of processes in cell apoptosis, as well as defects in death receptor signaling, impacts the growth of tumor cells (57,58). Notably, promoting cancer cell apoptosis is a strategy for treating tumors, whereas inhibiting apoptosis or other cell death mechanisms can directly impact tumor cell sensitivity to chemotherapy (56,59).

Two mechanisms underlie apoptosis: The intrinsic mechanism, which depends on mitochondrial components, and the extrinsic mechanism, which is regulated by death receptors (56,60,61). A key event in intrinsic apoptosis is the release

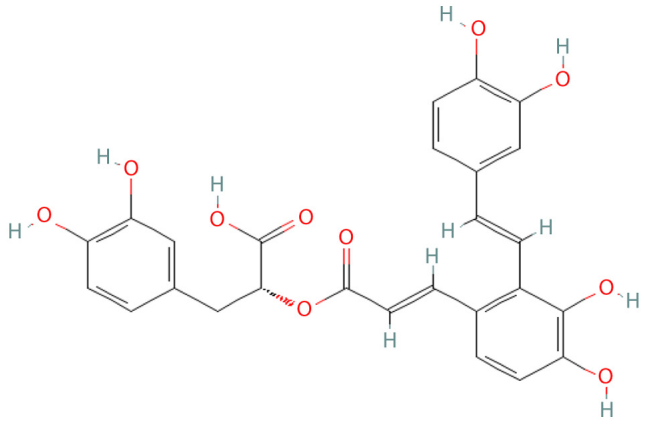

Figure 1. Chemical structure of salvianolic acid A (PubChem CID: 5281793).

of cytochrome *c* (Cyto C) from the mitochondria, which is regulated by the Bcl-2 family (62). This family consists of anti-apoptotic proteins, such as Bcl-2 and Bcl-xl, as well as pro-apoptotic proteins, such as Bax, Bad, Bim and Bid. Bax forms oligomers on the mitochondrial outer membrane, promoting Cyto C release (61); this activates the caspase family, which is split into initiators such as caspases 8, 9 and 10, and effectors such as caspases 3, 6 and 7 (63). Caspase 9 and apoptotic peptidase activating factor 1 form apoptotic bodies, activating caspase 3 to induce apoptosis (64). By contrast, Bcl-2 inhibits apoptosis by sequestering Bax and preventing Cyto C release (65-68). After treating esophageal cancer cells with SAA, caspase 9, a protease that causes DNA fragmentation, receives an upstream apoptosis signal and activates downstream caspase 3, leading to apoptosis (69). After treating the esophageal cancer cell line KYSE-150 with SAA, while Bcl-2 expression levels were much lower, those of Bax, as well as cleaved-caspase 9 and 3, were substantially greater (48). By upregulating Bak and downregulating Bcl-xl, SAA therapy causes KG-1, THP-1 and Kasumi-1 acute myeloid leukemia cells to undergo apoptosis through the intrinsic apoptotic pathway. Subsequently, poly ADP-ribose polymerase is cleaved, which activates caspase 3 (Fig. 3) (45). In doxorubicin hydrochloride (DOX)-resistant breast cancer cells (MCF-7/MDR), SAA causes intrinsic apoptosis by caspase activation, Bax upregulation, Bcl-2 downregulation and a decrease in mitochondrial membrane potential (49). Furthermore, SAA treatment enhances Bax and decreases Bcl-2 expression in KYSE-150 esophageal cancer cells, thereby inducing apoptosis (48). The aforementioned mechanisms likely involve the inhibition of c-MET gene transcription and protein expression in HepG-2 liver cancer cells, which in turn reduces the degree of Akt phosphorylation in the downstream PI3K/Akt signaling cascade (70) (Table I). These studies have suggested that SAA mediates the intrinsic apoptotic pathway in various tumor cells; however, whether SAA induces apoptosis via an extrinsic pathway has not yet been reported, to the best of our knowledge.

SAA inhibits tumor cell proliferation. Tumor cells exhibit the hallmark characteristic of unlimited proliferation. Capitalizing on this advantage, they not only evade growth-inhibitory signals but also resist cell death, often through the loss of tumor suppressor gene function (71). Phosphatase and tensin homolog (PTEN) is a widely studied gene that suppresses tumor growth and encodes a phosphatase that dephosphorylates phosphatidylinositol (3,4,5)-trisphosphate, leading to the inactivation of downstream effectors, particularly Akt (72). Essential for regulating various biological functions, the PI3K/Akt signaling pathway is particularly important for cell cycle progression, cell proliferation and apoptosis prevention. This signaling cascade is frequently found to be disrupted in cancer (73-75). By reducing the expression of PI3K and Akt, cell cycle arrest and effective inhibition of tumor cell growth can be accomplished (76). Treatment of A549 lung cancer cells with different concentrations of SAA (10, 20 and 30 μg/ml) for different durations (6, 12 and 24 h) has been shown to significantly increase PTEN protein expression levels and consistently reduce AKT^{S473} phosphorylation (Fig. 3). These findings indicate how suppressing tumor cell proliferation and encouraging apoptosis have concentration- and time-dependent effects (77).

Endothelin-1, a small vasoactive peptide that is upregulated in the plasma and tissue specimens of various patients with solid tumors, can activate endothelin A receptor (ETAR) and endothelin B receptor through autocrine and paracrine interaction, thereby regulating the proliferation of tumor cells (78). SAA, an ETAR antagonist, significantly inhibits spontaneous tumor cell proliferation and exhibits concentration-dependent effects (79). Furthermore, SAA and oxymatrine together have been reported to exert a synergistic impact on immortalized H8 cervical epithelial cells in a study of precancerous lesions in cervical cancer (80). This combination effectively halts the cell cycle in the G_2/M phase in H8 cells, thereby suppressing proliferation (80). *In vitro* experiments have revealed that SAA suppresses diffuse large B-cell lymphoma (DLBCL) proliferation though regulating the MAPK signaling pathway; specifically, SAA upregulates c-Jun N-terminal kinase, and downregulates phosphorylated (p-)ERK and p-p38 MAPK (81). *In vivo* studies employing xenograft mouse models have supported these findings, further confirming that SAA can suppress the tumor growth of DLBCL OCI-Ly01 and SUDHL-8 cells (81). In addition, the intermediate metabolite of SAA, S-3-1, inhibits the spread of various types of cancer, including small cell lung cancer, lung adenocarcinoma, oral squamous cell carcinoma, colon cancer, gastric cancer and pancreatic cancer (82). The cell cycle is arrested at the G_2/M phase by SAA, which can also dose-dependently reduce the proliferation of the human melanoma A2058 and A375 cell lines. Notably, SAA causes checkpoint kinase (Chk)-2 phosphorylation to be selectively induced without impacting Chk-1; this results in the degradation of the genes cell division cycle (CDC)25A and CDC2, which are controlled by Chk-2, but has no effect on the Chk1-CDC25C axis (29).

SAA inhibits the migration and invasion of tumor cells. One major factor in cancer-associated mortality is tumor metastasis, which is a complex and multidimensional process (83). This progression is marked by genetically unstable cancer cells that adapt to and thrive within tissue microenvironments distant from the primary tumor site (84). When cells with the ability to metastasize invade new tissues, they undergo a selection process that favors traits for survival and proliferation (85).

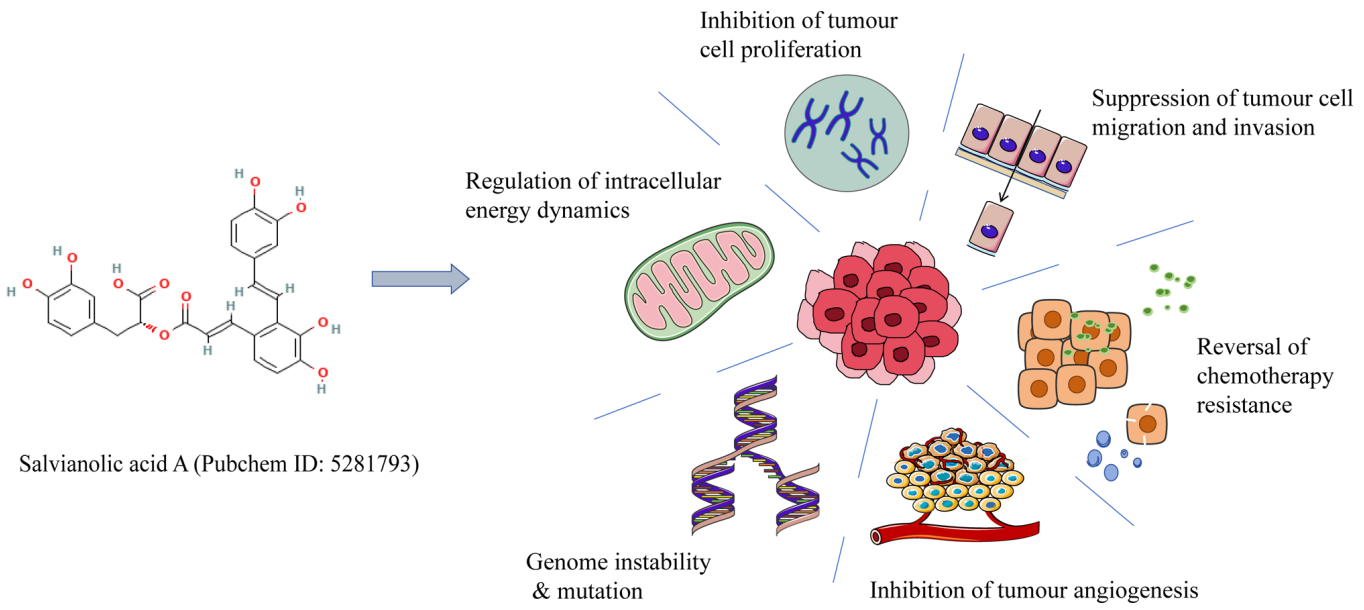

Figure 2. Antitumor effects of salvianolic acid A. SAA exerts antitumor effects through multiple mechanisms, including the regulation of intracellular energy dynamics (e.g., induction of endogenous apoptosis and suppression of mitochondrial membrane potential), inhibition of tumour cell proliferation, suppression of tumour cell migration and invasion, enhancement of chemotherapy sensitivity and reversal of chemotherapy resistance, inhibition of tumour angiogenesis and modulation of genomic instability and mutations. SAA, salvianolic acid A.

Concurrently, recruitment of a distinctive tumor stroma occurs, which serves a vital role in facilitating the invasion and establishment of metastatic cells in distant organs (86). A mechanism known as epithelial-mesenchymal transition (EMT) causes epithelial cancer cells to change from their standard epithelial phenotype to a mesenchymal phenotype. Cancer cells that undergo EMT exhibit a greater ability to migrate and invade, making them more likely to metastasize (87). EMT is a pivotal step towards invasiveness, orchestrated by many cell adhesion molecules and intermediate filaments, including E-cadherin, N-cadherin and vimentin (88-90).

MMPs are responsible for degrading the components of the basement membrane and the extracellular matrix (91). Through interactions with a series of cell adhesion molecules, they participate in altering the adhesive properties between tumor cells and their environment, facilitating the movement of tumor cells through the extracellular matrix (92). Therefore, MMPs such as MMP-2 and MMP-9 are required for cancer cell metastasis (93-95). Targeting these crucial mediators of metastasis can aid in inhibiting cancer cell migration and invasion. SAA has been reported to reduce MMP-2 expression in SCC-9 oral squamous cell carcinoma cells through the Raf/MEK/ERK pathway to regulate cell migration (44). Similarly, SAA treatment can inhibit MMP-2 protein expression and activity in HONE-1 and NPC-39 nasopharyngeal carcinoma cells in a concentration-dependent manner, preventing migration and invasion (96). SAA also inhibits MCF-7 cell migration and invasion by preventing EMT, leading to higher E-cadherin expression, and reduced vimentin and N-cadherin levels (30). Previous studies have indicated that SAA inhibits cancer metastasis by regulating MMP-2 levels and important EMT markers, such as E-cadherin, vimentin and N-cadherin; however, further research is required to ascertain whether SAA can also impede tumor migration and invasion through the modulation of additional EMT markers, such as zinc finger e-box binding homeobox 1, snail family transcriptional repressor (Snail) 1, Snail 2, twist family bHLH transcription factor 1 and fibronectin.

SAA promotes chemotherapy sensitization and reverses chemotherapy resistance. Resistance to chemotherapeutic drugs poses a notable challenge for cancer therapy (97); therefore, it is essential to overcome tumor resistance and enhance tumor cell sensitivity to these drugs (98). c-MET is a receptor tyrosine kinase that becomes activated upon binding to its ligand, hepatocyte growth factor (HGF) (48). The HGF/c-MET axis is frequently abnormally activated in gastric (99), lung (100) and pancreatic (101) cancer. This abnormal activation is often associated with c-MET gene mutations, overexpression of the c-MET protein and gene amplification (102). The activation of several downstream signaling pathways, including PI3K/Akt, Ras/MAPK, JAK/STAT, SRC and Wnt/β-catenin, can drive tumor progression and enhance the resistance of tumor cells to therapeutic agents (103-105). Thus, c-MET could potentially serve as a crucial target for overcoming tumor cell resistance. Drugs or small molecules that target c-MET can help overcome chemotherapy resistance in tumor cells (106).

SAA is capable of partially reversing cisplatin resistance in A549/DDP lung cancer cells by blocking the c-MET/Akt/mTOR signaling axis (50). SAA has been shown to downregulate MDR1 in A549 cells, while simultaneously upregulating the expression of microRNAs (miRNAs) associated with this gene. This dual action suggests that SAA may influence MDR1 expression by regulating tumor cell miRNAs. Consequently, this regulatory mechanism could potentially lead to the reversal of multidrug resistance in A549 cells (107). Furthermore, SAA may reverse drug resistance in lung cancer cells through regulation of the PI3K/Akt signaling pathway (108). In MCF-7 breast cancer cells, SAA decreases transgelin 2 (TAGLN2) and Bcl-2 levels, and increases

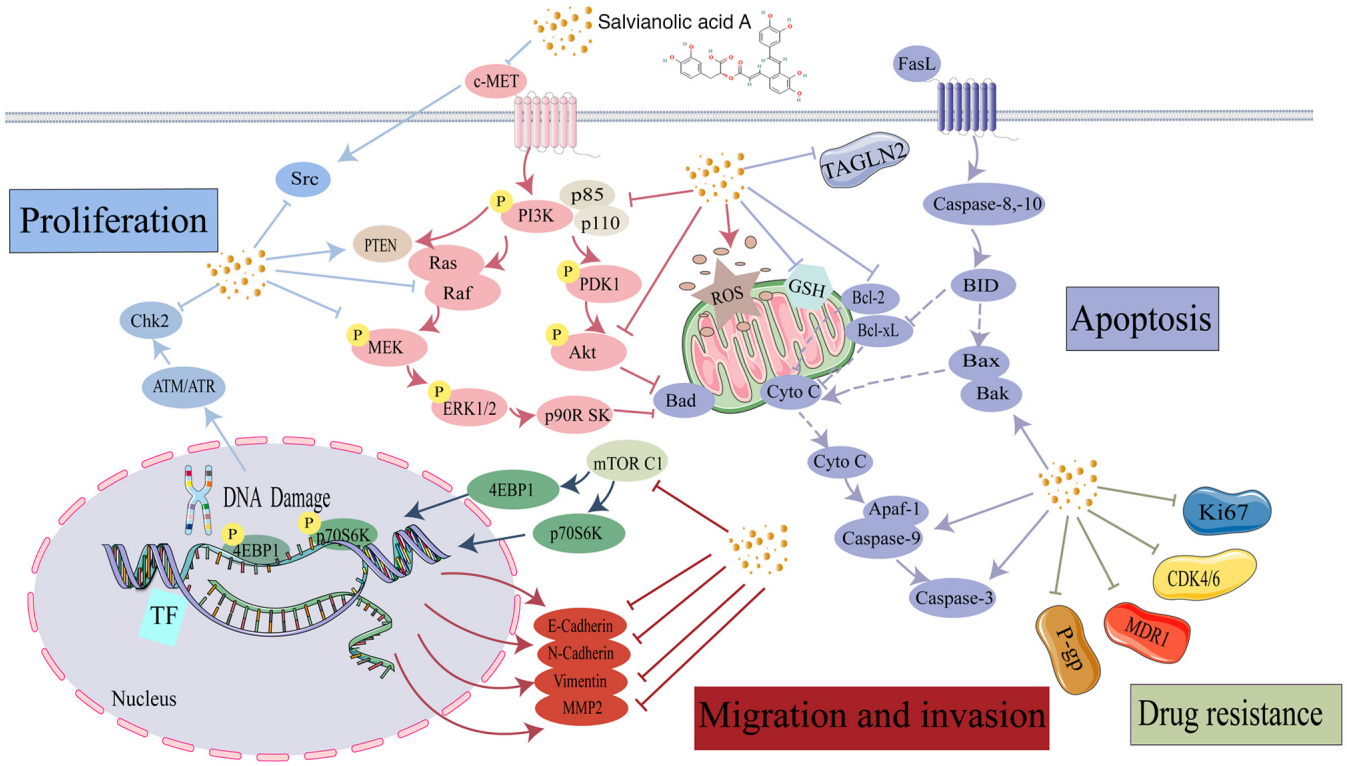

Figure 3. Schematic diagram of the membrane, cytoplasmic and nuclear targets of salvianolic acid A. Akt (PKB), protein kinase B; Apaf-1, apoptotic protease activating factor 1; ATM, Ataxia-telangiectasia mutated; ATR, Ataxia telangiectasia and Rad3-related protein; Bad, Bcl-2 associated agonist of cell death; Bak, Bcl-2 homologous antagonist/killer; Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma-2; Bcl-xl, B-cell lymphoma extra large; BID, Bcl-2 homology 3 interacting domain death agonist; c-MET, cellular-mesenchymal epithelial transition factor; Raf, serine/threonine kinase; Caspase-3/8/9/10, cysteinyl aspartate specific proteinase; CDK4/6, cyclin-dependent kinase 4/6; Chk 2, checkpoint kinase-2; Cyto C, cytochrome C; ERK1/2, extracellular-signal-regulated kinase 1/2; GSH, glutathione; Ki67, marker of proliferation Ki-67; MDR1, multidrug resistance-1; MEK, MAPK kinase; MMP2, matrix metallopeptidase 2; mTOR, mammalian target of rapamycin; mTOR C1, mechanistic target of rapamycin complex 1; p-, phosphorylated; p90R SK, the 90 kDa ribosomal s6 kinases; p70S6K, 70 kDa ribosomal protein S6 kinase; PDK1, pyruvate dehydrogenase kinase 1; P-gp, P-glycoprotein; PI3K, phosphoinositide 3-kinase; PTEN, phosphatase and tensin homolog; ROS, reactive oxygen species; Ras, rat sarcoma; SAA, salvianolic acid A; Src, steroid receptor coactivator; TAGLN2, transgelin 2; 4EBP1, eIF4E-binding protein.

levels of PTEN, Bax, cleaved-PAPR, cleaved-caspase 3 and cleaved-caspase 9. SAA enhances MCF-7 breast cancer cell sensitivity to paclitaxel by inhibiting the PI3K/Akt signaling pathway and activating the mitochondrial apoptosis pathway (43,49). Furthermore, SAA can suppress the migration and invasion of paclitaxel-resistant MCF-7 breast cancer cells by downregulating TAGLN2 expression, thereby reversing paclitaxel resistance in these cells (30). Furthermore, by blocking the TAGLN2/PI3K/Akt signaling pathway, SAA can inhibit the malignant growth of U87 glioma cells and increase their susceptibility to temozolomide; therefore, SAA could potentially serve as an adjunctive medication in clinical chemotherapy for glioma cells (109). In adriamycin-resistant MCF-7 breast cancer cells, protein arginine methyltransferase 1 (PRMT1) potentially contributes to the upregulation of MDR1, which is activated by the pregnane X receptor (PXR). In addition, a PRMT inhibitor may suppress MDR1 by interfering with the PRMT1 and PXR interaction. Notably, SAA can act as a PRMT1 inhibitor to increase the anticancer effects of DOX by increasing the sensitivity of drug-resistant breast cancer cells to it (52). A previous study indicated that, compared with the use of DOX alone, SAA alone or the SAA/DOX combination, E-[c(RGDfK)2]/folic acid (FA) co-modification of nanostructured lipid carriers (NLC) in conjunction with SAA and DOX exhibit the most effective antitumor activity. These findings suggested that SAA and DOX may have a synergistic effect in breast cancer treatment (53). Furthermore, the renal toxicity levels of E-[c(RGDfK)2]/FA-NLC-SAA/DOX were revealed to be low, with no abnormalities observed in the *ex vivo* kidney pathology examination at the end of the study. In addition, SAA is capable of antagonizing the nephrotoxic effects of DOX, highlighting its significant potential in enhancing the tolerance of cancer patients to chemotherapy (110).

SAA is involved in tumor angiogenesis. Angiogenesis is the process through which endothelial cells migrate and proliferate within preexisting small blood vessels, or venules, to produce new blood vessels, mostly capillaries (111). For tumors, this mechanism is essential, as it provides the oxygen and nutrients needed for development and spread (112). Furthermore, the blood circulation makes it easier for tumor cells to spread to different areas of the body (113). As a result, most cancers promote tumor angiogenesis, the process through which new capillaries grow in the surrounding tissue. Notably, not all cancers depend on the development of new blood vessels, as some can endure and proliferate by altering their metabolism (114,115). Therefore, inhibiting capillary formation during tumor treatment can indirectly block the development and metastasis of tumor cells (116). When it comes to inhibiting tumor-secreted glucose-regulated protein

Table I. Targets of SAA in various cancer cells.

Cancer type	Cell line(s)	Treatment time	Dosage	Molecular targets	(Refs.)
Breast cancer	MCF-7	12, 24 and 48 h or 24 h	12 μM or 40 and 80 μM	TAGLN2, E-cadherin, vimentin, N-cadherin, ROS, GSH, Bcl-2, Bax, P-gp	(30,49)
Breast cancer	MCF-7	48 h	3, 6 and 12 μM	TAGLN2, P-gp, MRP1, BCRP, PTEN, Akt, Bcl-2, Bax, cleaved-caspase 9, cleaved-PARP	(43)
Lung cancer	A549	24 h	4 μg/ml (103), 10, 20, 40 μg/ml (49), 10, 20 and 30 μg/ml (72), 40 mg/l (102)	c-MET, MDR1, p-mTOR, p-Akt, PTEN, cleaved-caspase 3, p-Akt, MDR1	(50,77, 107,108)
Glioma	U87	24 h	25, 50 and 100 μM	Bcl-2, Bax, TAGLN/PI3K/Akt$^{\perp}$	(109)
Oral squamous cell carcinoma	SCC-9 and SCC-25	24 h	12.5, 25 and 50 μM	MMP2, c-Raf/MEK/ERK$^{\perp}$, p-Src, p-FAK	(44)
Nasopharyngeal carcinoma	HONE-1 and NPC39	24 h	12.5, 25 and 50 μM	MMP2, p-ERK, p-Src, p-FAK, p-JNK	(96)
Esophageal cancer	KYSE-150	24 h	10, 25 and 50 μM	Ki-67, cyclin D1, CDK4, Bax, CDK6, Bcl-2, cleaved-caspase 9, cleaved-caspase 3, PI3K/Akt/mTOR$^{\perp}$	(48)
Melanoma	A2058 and A375	48 h	50 μM	Chk 2, CDC25A	(29)
Acute myeloid leukemia	KG-1, THP-1 and Kasumi-1	6, 12 and 24 h	50 μM (*in vitro*) 5 and 20 mg/kg (*in vivo*)	Bax, Bcl-xl, caspase 3	(45)
Human ovarian carcinoma, human cervical cancer, human prostate, human non-small cell lung cancers carcinoma, human lung adenocarcinoma	SKOV3, HeLa, DU145 NCI-H1975, A549	72 h	1.56, 6.25, 25 and 100 μM	ETAR$^{\perp}$	(79)
Cervical cancer	H8	24 h	SAA/OSR=1:2; 0.5, 1 and 2 μM SAA	G_2/M phase$^{\perp}$, cyclin B1, CDK1	(80)
DLBCL	OCI-Ly01 and SUDHL-8	6 and 12 h	10, 50 and 100 μM	p-JNK, p-p38, p-ERK	(81)
Colon cancer	HCT-116 and DLD1	48 h	10, 20 and 30 μM	GRP78$^{\perp}$	(54)
Mouse Lewis lung carcinoma	LLC	3 weeks (*in vivo*)	10, 15 and 20 μM	PKM2, β-catenin/Claudin-5	(118)
Triple-negative breast cancer tumor-associated macrophages	Murine macrophages RAW264.7 coculture with conditional medium from Triple-negative breast cancer cells SUM159 and 4T1	24 h	15 and 30 μM	CD86, IL-1β, iNOS, Arg-1, CD206	(120)
Immortalized human cerebral microvascular endothelial cells	HCMEC/D3	6 h	10 μM	PKB/Src/p-Caveolin-1	(123)

$^{\perp}$ signifies suppression. Arg-1, arginase 1; Akt(PKB), protein kinase B; Bax, BCL-2-associated X protein; Bcl-2, B-cell lymphoma-2; Bcl-xl, B-cell lymphoma extra large; BCRP, breast cancer resistance protein; c-MET, cellular-mesenchymal epithelial transition factor; c-Raf, serine/threonine kinase; CDC25A, cell division cycle 25A; CDK1, cyclin-dependent kinase 1; Chk 2, checkpoint kinase-2; DLBCL, diffuse large B-cell lymphoma; ERK, extracellular-signal-regulated kinase; ETAR, endothelin A receptor; FAK, focal adhesion kinase; JNK, c-Jun N-terminal kinase; IL-1β, interleukin-1 β; MET, mesenchymal-to-epithelial transition factor; GSH, glutathione; GRP78, glucose-regulated protein 78; iNOS, inducible nitric oxide synthase; MDR1, multidrug resistance-1; MEK, MAPK kinase; MMP2, matrix metallopeptidase 2; MRP1, multidrug resistance protein 1; mTOR, mammalian target of rapamycin; OSR, oxysophoridine; p-, phosphorylated; p38, p38 mitogen-activated protein kinase; P-gp, P-glycoprotein; PI3K, phosphoinositide 3-kinase; PKM2, pyruvate kinase isozyme typeM2; PTEN, phosphatase and tensin homolog; ROS, reactive oxygen species; SAA, salvianolic acid A; Src, steroid receptor coactivator; TAGLN2, transgelin 2.

78 (GRP78) in DLD1 and HCT-116 colon cancer cells, SAA has been shown to be the most successful among Diosmin, Quertruicin, Vitexin, Baicain, SAA, Isovitexin, Narigin and Platycodin D; SAA can encourage the breakdown of GRP78 through the lysosomal pathway and prevent its release into the tumor microenvironment (54). Furthermore, SAA has been shown to specifically interact with GRP78 and inhibit tumor angiogenesis (54). DOX, as one of the anthracycline antibiotics, is extensively used in cancer therapy (117). In a mouse lung cancer model, it has been demonstrated that SAA is able to normalize the tumor vasculature by targeting PKM2. This focused strategy affects alterations to the shape and function of the tumor vasculature, enabling the effective delivery of DOX and thereby enhancing its therapeutic efficacy. Concurrently, SAA is capable of reducing the cardiotoxicity caused by DOX (118).

5. Additional anticancer effects of SAA

Nucleotide biosynthesis involves two pathways: *De novo* and salvage synthesis. Given the elevated nucleoside transport activity in tumor cells, targeting nucleoside transport provides a potential opportunity for combating cancer (119). SAA inhibits nucleoside transport activity in murine Ehrlich ascites carcinoma cells, and it enhances the antitumor effects of chemotherapeutic drugs, such as 5-fluorouracil, on KB human oral squamous cell carcinoma cells (55). Therefore, combining SAA with chemotherapeutic drugs may be promising for improving the efficiency of cancer treatment (55). Furthermore, SAA can exert antitumor effects in the Paca human pancreatic cancer cell line by enhancing gap junctional intercellular communication and inhibiting RAS function (82). In a previous study, E-[c(RGDfK)2]/FA-modified NLCs were co-loaded with DOX and SAA to create E-[c(RGDfK)2]/FA-NLC-SAA/DOX; this multipurpose drug delivery system based on nanotechnology is distinguished by its high encapsulation efficiency and compact size. In the 4T1 animal tumor model, this formulation was able to markedly increase the antitumor actions of SAA/DOX by encouraging tumor cell death and inhibiting cell proliferation (107). To the best of our knowledge, this was the first study to show that SAA alone inhibits the polarization of macrophages into M2-like tumor-associated macrophages (TAMs) by suppressing the ERK pathway and promoting the re-polarization of M2-like TAMs into M1-like TAMs; this modulation of M1/M2 TAM polarization may underlie the antitumor effects of SAA (120).

The expression levels of two well-known hypoxia indicators, hypoxia-inducible factor 1α and carbonic anhydrase IX (121,122), have been shown to be significantly reduced in mouse Lewis lung carcinoma cells LLC and mouse melanoma high metastatic cells B16F10 following SAA treatment. These findings suggested that SAA may have a marked impact in lowering tumor hypoxia (118). Furthermore, the lactate levels in LLC and B16F10 tumors from an SAA-treated group have been shown to be significantly reduced compared with those in a vehicle control group (118). These findings collectively suggested that SAA could be essential in reducing tumor growth by improving the hypoxic microenvironment (118). Through a caveolae-dependent mechanism, SAA has been reported to increase the transcellular permeability of the tumor blood-brain barrier while decreasing its paracellular permeability; this can enhance the ability of DOX to treat HCMEC/D3 immortalized human cerebral microvascular endothelial cells and make it easier for the drug to enter brain tumor tissues. Thus, SAA and DOX together might provide a new method of treating glioma cells (123). In conclusion, SAA has shown considerable promise as a drug monomer. Preclinical and experimental studies have demonstrated its potential to enhance the efficacy of antitumor drugs, providing new possibilities for cancer treatment. The unique mechanism of action of SAA makes it a strong candidate as an effective adjunctive antitumor agent, offering new perspectives for future therapeutic strategies.

6. Conclusions and perspectives

Chinese medicine has garnered notable attention from experts and scholars, both domestically and internationally, due to its distinctive characteristics and advantages in treating tumors. Notably, it operates through multiple targets, effects and pathways, contributing to its precise efficacy. Chinese medicine is also widely available and well known for having few adverse effects and low toxicity, which makes it a good substitute in oncology.

Research on drug delivery carriers has advanced, particularly in the domain of specialized delivery systems. These systems have attracted considerable attention due to their enhanced *in vivo* stability, improved bioavailability, increased drug efficacy, enhanced tissue targeting, reduced off-target adverse reactions and ability to co-deliver drugs. For example, research has shown that specific ligands, such as E-[c(RGDfK)2]/FA, can effectively deliver drugs to target tissues, thereby enhancing the therapeutic effects of the drugs (110).

In the field of TCM, as research into active ingredients develops, it has been shown that terpenoids, alkaloids, flavonoids, quinones, polysaccharides and other active ingredients of TCM not only possess notable pharmacological activity but also show potential as drug delivery nanocarriers (124). SAA, as a type of salvianolic acid, is also seen as a promising candidate in drug delivery systems; however, the extraction methods for SAA have certain shortcomings (125). By developing new extraction technologies and optimizing extraction conditions, its extraction efficiency and safety can be improved. In practice, the use of nanoparticles for targeted medication delivery can minimize side effects, improve therapeutic benefits and decrease toxicity, in addition to increasing the effectiveness of SAA.

Notably, E-[c(RGDfK)2]/FA-NLC-SAA/DOX exhibits low renal toxicity, as no abnormalities have been found in *ex vivo* kidney pathology examinations. SAA is also capable of antagonizing the nephrotoxic effects of DOX, further demonstrating its low toxicity and lack of side effects (107). The pharmacological mechanisms of SAA must be thoroughly studied to support widespread therapeutic application. Currently, most studies on the use of SAA for tumor treatment are in the preliminary stages, and many of the underlying

mechanisms of action have yet to be fully elucidated. A comprehensive awareness of the antitumor mechanisms of SAA is crucial for advancing TCM and improving tumor treatment strategies.

Clinical trials of SAA have shown promise in the fields of diabetic microangiopathy (CTR20210544) and acute myocardial infarction (CTR20213269) (126). The clinical trial for diabetic microangiopathy has progressed to phase III. The results of the phase II trial (CTR20210544) have indicated that SAA tablets are effective in alleviating the symptoms of diabetic peripheral neuropathy, such as limb numbness and tingling, with good safety. However, the current trials are subject to certain limitations, such as strict inclusion and exclusion criteria (e.g., excluding patients with severe cardiovascular and cerebrovascular diseases, or abnormal liver and kidney function), which may restrict its application in a broader population. In the field of acute myocardial infarction, the phase II clinical trial (CTR20213269) of Salvianolic acid A sodium salt monohydrate for injection is ongoing, aiming to assess its efficacy and safety in myocardial protection after percutaneous coronary intervention. The trial, which follows a randomized, double-blind, placebo-controlled and multicenter design, has shown that SAA sodium has potential advantages in suppressing inflammatory responses and reducing myocardial injury. However, the trial also had strict participant selection criteria, such as excluding patients with severe liver and kidney dysfunction, a history of malignant tumors or allergies to other drugs, which may affect its clinical promotion. Future research should focus on expanding the sample size, extending the trial duration and further exploring the mechanism of action of SAA to better advance its clinical application.

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Availability of data and materials

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Authors' contributions

CXL and WLY conceptualized the review and wrote the original draft. CXL, QX, STJ, DL, CT and WLY reviewed and edited the review, and were involved in visualization. WLY was responsible for supervision, project administration and funding acquisition. 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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