Salvianolic acid monomers against metastasis: Decoding the multilayered interception of EMT, angiogenesis and immune evasion (Review)

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Abstract. Salvianolic acids (SAs), a water-soluble active component extracted from the traditional Chinese herb *Salvia miltiorrhiza*, have attracted considerable attention as an anti-tumor agent. Accumulating evidence demonstrates that SAs potently inhibit tumor-cell migration, invasion and metastasis through multiple signaling pathways and molecular targets. First, SAs remodel the extracellular matrix and suppress matrix metalloproteinase activities, thereby attenuating the epithelial-mesenchymal transition and the associated stem-like properties of cancer cells. Second, SAs block tumor angiogenesis, depriving tumors of essential nutrients and routes for metastasis. Third, SAs reprogram the tumor microenvironment by modulating immune cells, enhancing immune cell infiltration and relieving immunosuppression, ultimately curbing tumor progression. Fourth, SAs target metastatic cellular plasticity and therapy resistance by disrupting cytoskeletal reorganization, impairing cell motility and reversing drug-resistant phenotypes, thereby enhancing cancer treatment efficacy with reduced toxicity. At the molecular level, SAs suppress the PI3K/AKT, MAPK and TGF-β1/Smad signaling cascades, thereby diminishing the invasive and migratory capacity of tumor cells. In this review, recent advances in understanding the anti-metastatic effects and underlying mechanisms of SAs were systematically summarized, the challenges hindering their clinical translation were discussed and future directions that may facilitate their development as a promising anti-metastatic therapeutic agent were outlined.

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Abbreviations: TCM, traditional Chinese medicine; SA, salvianolic acid; SAA, salvianolic acid A; SAB, salvianolic acid B; EMT, epithelial-mesenchymal transition; MMP, matrix metalloproteinase; ECM, extracellular matrix; TNBC, triple-negative breast cancer; RECK, reversion-inducing cysteine-rich protein with Kazal motifs; PEG-SAB-Lip, nanoparticle and PEGylated-liposome; SAB@HMON-PDA, dopamine-functionalized hollow mesoporous organosilica nanoparticles; PEG-DTX-Lip, docetaxel-loaded nanoparticles; GRP78, glucose regulated protein 78; EndMT, endothelial to mesenchymal transition; DOX, doxorubicin; GEC, glomerular endothelial cell; TEC, tumor endothelial cell; MLC2, myosin light-chain 2; DDP, cisplatin; TME, tumor microenvironment; TAM, tumor-associated macrophage; CD, cluster of differentiation; TAF, tumor-associated fibroblast; PTX, paclitaxel; ROS, reactive oxygen species; VCR, vincristine

Key words: salvianolic acids, salvianolic acid A, salvianolic acid B, EMT, tumor angiogenesis, tumor microenvironment

Contents

1. Introduction

Metastasis remains the leading cause of cancer-related mortality worldwide (1). Despite advances in surgical techniques and systemic therapies, treatment efficacy is often poor due to resistance and drug toxicity (2,3). Metastasis commonly involves vital organs, significantly worsening patient prognosis and reducing survival rates (4,5). Recently, traditional Chinese medicine (TCM) has shown promising results in patients with poor outcomes after conventional therapy, thus highlighting its potential anticancer properties (6,7). Medicinal botanicals, including *Salvia miltiorrhiza* and *Astragalus*, are particularly

valued due to their favorable safety profile, low toxicity and multi-target pharmacological effects, which may offer advantages in overcoming cancer recurrence and resistance to therapy (8,9).

Salvia miltiorrhiza is a well-known medical herb, traditionally used to invigorate blood circulation, promoting blood flow through meridians to relieve pain and calming the mind. Additionally, it is commonly used in TCM to 'clear heat', a concept associated with the reduction of inflammation, and to resolve abscesses (10,11). Emerging evidence has suggested that *Salvia miltiorrhiza* also exerts significant effects in treating cardiovascular diseases and possesses promising therapeutic potential in oncology (12-14). SAs from *Salvia miltiorrhiza* have received considerable attention due to their antitumor (15,16), antioxidant (17), anti-inflammatory (18) and antithrombotic effects (19). However, their specific mechanisms and clinical applicability warrant further investigation.

The present review article provides a systematic and up-to-date overview of the effects of SAs on tumor behavior and uncovers their underlying molecular mechanisms of action. It also discusses the current challenges limiting their clinical translation, including issues associated with drug development. Furthermore, potential future directions are highlighted, including structural optimization, novel drug-delivery systems and multi-omics integration, to promote translational advancement of TCM in oncology.

2. SAs

Common monomers. SAs, derived from *Salvia miltiorrhiza*, are polyphenolic compounds and include methyl tanshinonate, caffeic acid, 3,4-dihydroxybenzaldehyde, lithospermic acid, rosmarinate, as well as SA A-G (20). Methyl tanshinonate, also known as β-(3,4-dihydroxyphenyl) lactic acid, is the core scaffold contained in all Sas (21). Salvianolic acid A (SAA) consists of one Danshensu unit and two caffeic acid molecules, while SAB is formed of three Danshensu units and one caffeic acid molecule (22,23). The most common SA monomers identified in *Salvia miltiorrhiza* are illustrated in Fig. 1.

Pharmacological effects. It has been reported that SA monomers from *Salvia miltiorrhiza* can induce apoptosis and autophagy in cancer cells (24,25), as well as inhibit cell proliferation, cell-cycle progression and angiogenesis (24), then suppress metastasis (24,26) and enhance the sensitivity of tumor cells to chemotherapy while mitigating its adverse effects (27,28). Beyond their anticancer effects, SAs exhibit antioxidant capacity through free radical scavenging (29), inhibit thrombus formation and platelet aggregation (30,31), downregulate inflammatory mediators (32), attenuate oxidative-stress-related injury (29,33), improve microcirculation (32) and protect cardiovascular and cerebrovascular health (33). The most common pharmacological effects of SAs from *Salvia miltiorrhiza* are summarized in Fig. 2.

3. Role and mechanism of SAs from *Salvia miltiorrhiza* in inhibiting metastasis

Inhibition of the epithelial-mesenchymal transition (EMT). EMT is a key biological process that enables tumor cells to invade surrounding tissues and metastasize to other organs, including the lungs and liver, while also increasing tumor aggressiveness and therapeutic resistance (34,35). During EMT, the expression levels of matrix metalloproteinases (MMPs) are increased, thus leading to the degradation of the extracellular matrix (ECM) and adhesion molecules, disruption of intercellular junctions and acquisition of mesenchymal properties, thereby enhancing tumor cell migration and invasion (36,37). MMPs are key participants in EMT. Among the members of the MMPs family, MMP-2 and MMP-9 can promote tumor angiogenesis through the release of factors such as vascular endothelial growth factor (VEGF) and transforming growth factor β (TGF-β) (38-42).

Network pharmacology and experimental studies have demonstrated that SAs can inhibit the EMT process by downregulating the expression of MMPs and mesenchymal-related markers (19,43-46). In a previous study, SAA, the principal bioactive component of the high-dose *Salvia miltiorrhiza*-ginseng formula (47,48) could suppress spontaneous lung metastasis in a murine triple-negative breast cancer (TNBC) 4T1 model by reducing the protein and mRNA expression levels of both MMP-9 and VEGFA (47). Similarly, SAB induced a concentration- and time-dependent reduction in MMP-9 expression in human highly invasive TNBC (MDA-MB-231 cells), thereby significantly inhibiting tumor cell invasion and migration (43). Mechanistically, SAB targets mortalin to promote its degradation, thereby upregulating the reversion-inducing cysteine-rich protein with Kazal motifs (RECK) and suppressing signal transducer and activator of transcription 3 (STAT3), collectively leading to reduced MMP-2 and MMP-9 activity (49). This mortalin/RECK/STAT3 regulatory axis has been validated in hepatocellular carcinoma cells (HCCLM3), in which SAB could reverse EMT and attenuate cell migration and invasion (49).

In addition to direct MMP inhibition, SAs could modulate multiple signaling pathways to inhibit EMT. In nasopharyngeal carcinoma (HONE-1 and NPC-39 cells) and oral squamous cell carcinoma (SCC-9 and SCC-25 cells), SAA inhibited the extracellular signal-regulated kinase (ERK) pathway, thereby suppressing MMP-2 expression and blocking tumor cell invasion and migration (46,50). In non-small cell lung cancer (NSCLC) cells (A549), SAB could suppress the mitogen-activated protein kinase (MAPK) signaling pathway and inhibit small mothers against decapentaplegic (Smad)2/3 activation, and thereby repressing EMT (24). In gastric cancer (AGS and GES-1 cells) (51) and melanoma (A375 and B16 cells) (51,52), SAB attenuated the phosphorylation of the protein kinase B (AKT)/mammalian target of rapamycin (mTOR) axis and interacted with β-actin, respectively, ultimately resulting in N-cadherin (N-cad) and vimentin downregulation, while simultaneously restoring E-cad expression (51,52).

Yes1-associated transcriptional regulator (YAP1) promotes EMT via inducing the expression of several factors such as twist-related protein 1 (TWIST1), Snail1 and SRY-box transcription factor 9 (SOX9), thus shifting gene expression profiles from epithelial to mesenchymal phenotypes (53). In human clear cell renal cel carcinoma (786-O and Caki-2 cells), SAB time-dependently reduced YAP1 expression, thereby inhibiting E-cad downregulation and N-cad upregulation, while reducing the mRNA expression levels of Snail1

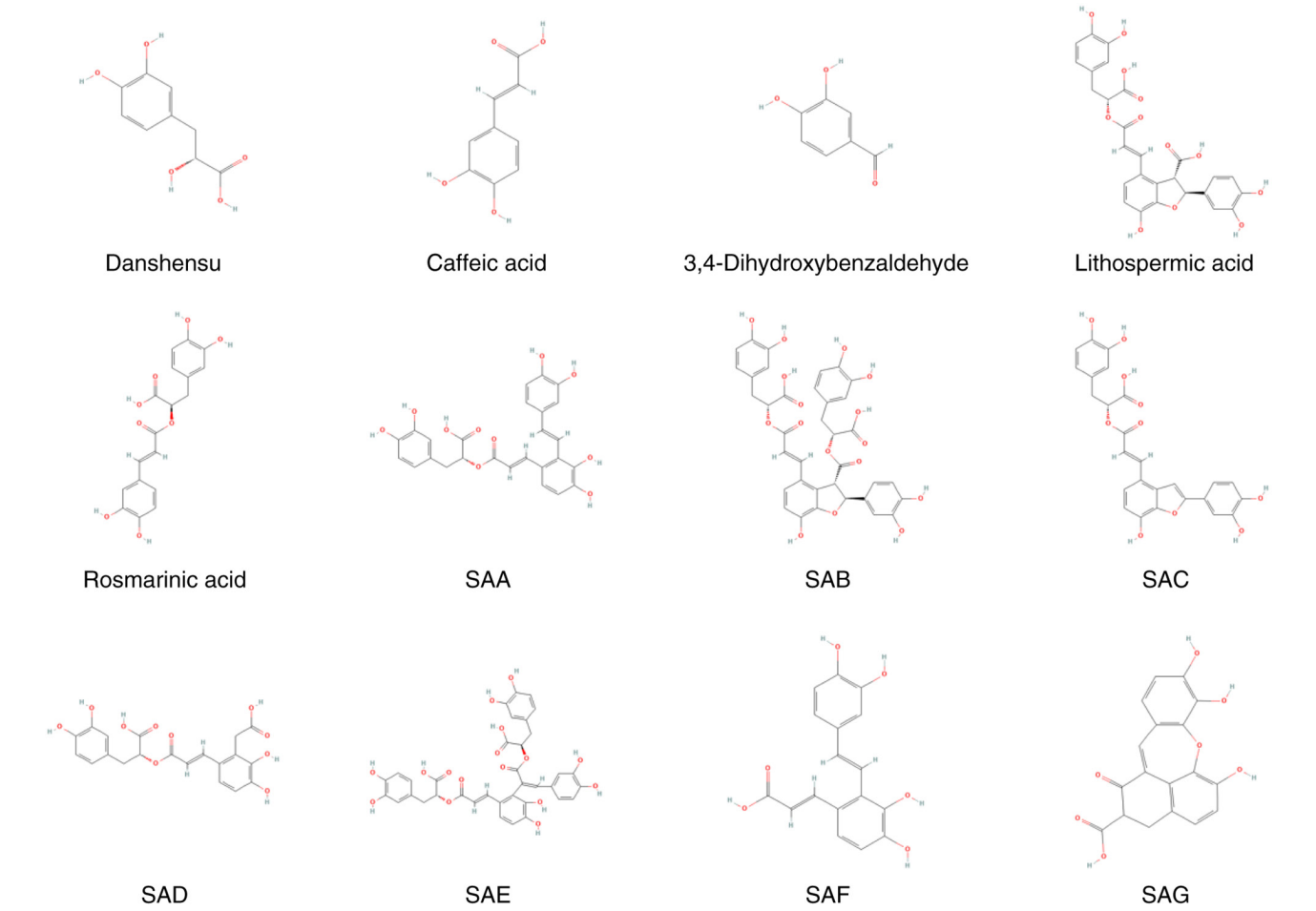

Figure 1. Structure of the mainly SA monomers in *Salvia miltiorrhiza*. 2-D chemical structures of the SAs: Danshensu (PubChem CID, 11600642), caffeic acid (PubChem CID, 689043), 3,4-dihydroxybenzaldehyde (PubChem CID, 8768), lithospermic acid (PubChem CID, 6441498), rosmarinic acid (PubChem CID 5281792), SAA (PubChem CID 5281793), SAB (PubChem CID 6451084), SAC (PubChem CID 13991590), SAD (PubChem CID 75412558), SAE (PubChem CID 86278266), SAF (PubChem CID 10903113) and SAG (PubChem CID 11530200) (142). SAA, salvianolic acid A.

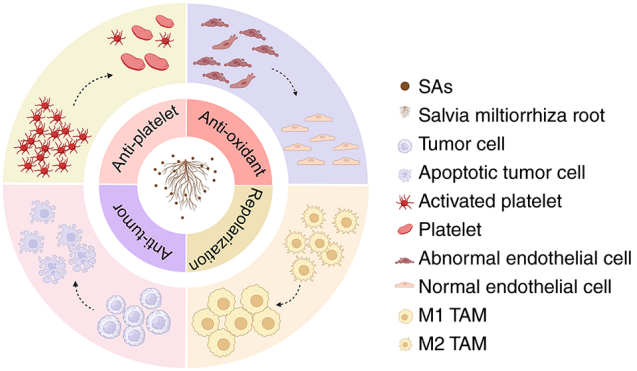

Figure 2. Pharmacology of SAs from *Salvia miltiorrhiza*. These salvianolic acid metabolites isolated from dried *Salvia miltiorrhiza* roots exhibit multiple pharmacological effects: i) Inducing apoptosis in tumor cells. ii) Restoring hyperactivated/aggregated platelets to a quiescent state. iii) Normalising endothelial cells damaged by oxidative stress. iv) Repolarization of TAMs from M2 (promote tumor growth) to M1 (anti-tumor). SAs, salvianolic acids; TAM, tumor-associated macrophage.

and TWIST1, thus restraining EMT (53). RNA-sequencing analysis of SAB-treated 4T1 cells further identified enhancer of zeste homolog 2 (EZH2), a key EMT-promoting factor, as a significantly downregulated transcript (54). Consistently, SAB decreased EZH2 expression while increasing E-cad levels and decreasing N-cad and vimentin expression in TNBC (4T1 and MDA-MB-231 cells) (55).

To further enhance the antitumor efficacy of SAB, several nanodelivery systems have been developed. Nanoparticle-based and polyethylene glycol (PEG)ylated liposome (PEG-SAB-Lip) delivery systems markedly enhance the bioavailability and antitumor activity of SAB (56,57). In a study, dopamine-functionalized hollow mesoporous organosilica nanoparticles loaded with SAB (SAB@HMON-PDA) could more effectively downregulate vimentin and upregulate E-cad compared with free SAB, thereby inhibiting EMT and lung metastasis in 4T1 cells (56). In addition, co-administration of PEG-SAB-Lip with docetaxel-loaded nanoparticles (PEG-DTX-Lip) substantially reduced ECM deposition and restrained TNBC growth and progression (57).

Collectively, EMT can promote tumor cachexia and metastasis through MMP-mediated basement-membrane degradation, cadherin switching (58) and transcription factors such as Snail1, zinc finger e-box binding homeobox and TWIST1 (59,60), which integrate TGF-β, Wnt/β-catenin and Hippo-YAP/transcriptional coactivator with PDZ-binding motif signaling pathways (61-65). The dysregulation of the aforementioned pathways has been strongly associated with

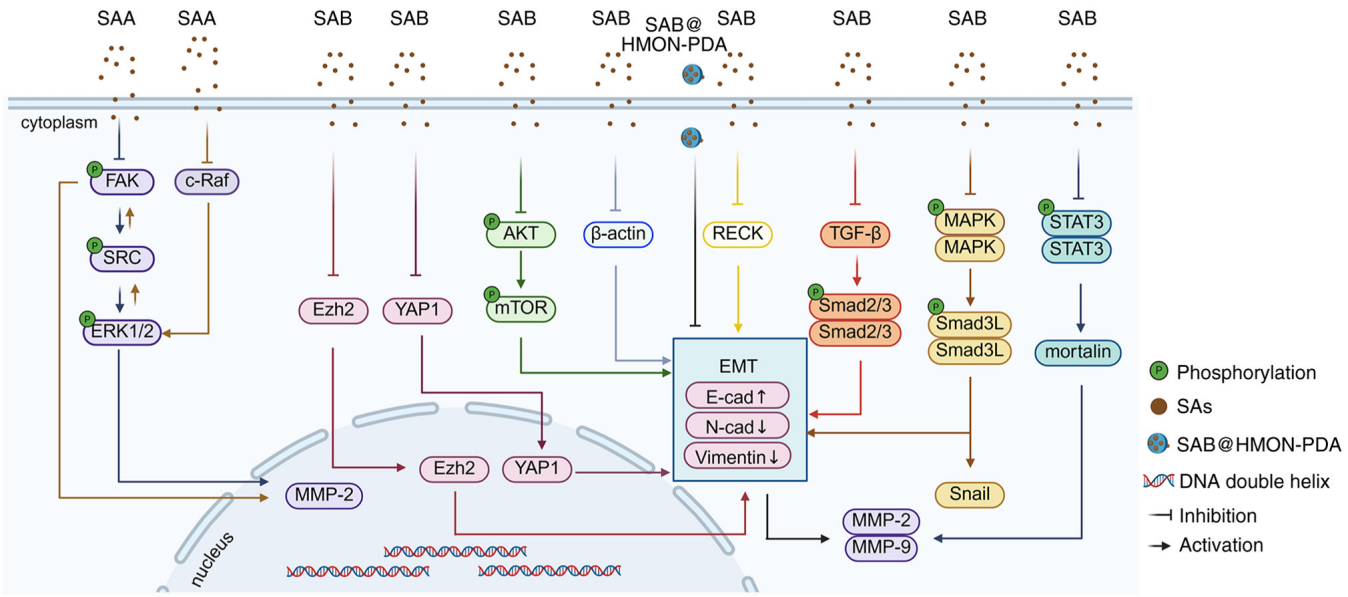

Figure 3. The mechanisms of SAA and SAB in inhibiting the EMT. SAA and SAB curb tumor-cell invasion and migration by silencing MMP-2/9 via the STAT3, MAPK and AKT/mTOR cascades, and by directly repressing EMT-driving transcription factors to lower both the mRNA and protein levels of key motility genes. SAB, salvianolic acid B; SAB@HMON-PDA, SAB@dopamine-functionalized hollow mesoporous organosilica; FAK, focal adhesion kinase; SRC, sarcoma; ERK, extracellular signal-regulated kinase; c-RAF, cellular rapidly accelerated fibrosarcoma; EZH2, enhancer of zeste homolog 2; YAP1, yes-associated protein 1; AKT, protein kinase B; mTOR, mammalian target of rapamycin; RECK, reversion-inducing cysteine-rich protein with Kazal motifs; EMT, epithelial to mesenchymal transition; N-cad, neural cadherin; E-cad, epithelial cadherin; TGF-β, transforming growth factor-β; Smad, small mothers against decapentaplegic; MAPK, mitogen-activated protein kinase; MMP, matrix metalloproteinase; STAT3, signal transducer and activator of transcription 3.

aggressive disease and poor prognosis (4,66,67). SAs act through a 'multi-target, multi-pathway and multi-disease' blockade strategy, including direct inhibition of MMP-2 and MMP-9 activity, suppression of YAP1 and EZH2, and inhibition of the c-Raf/MEK/ERK signaling pathway and Smad2/3 phosphorylation, thus upregulating E-cad and downregulating N-cad. Notably, the aforementioned multi-target suppression extends beyond oncology and has been implicated in inflammatory diseases and renal fibrosis (68-71), thus underscoring the broad pathological relevance of EMT modulation and providing a molecular rationale for the development of EMT-targeted combination therapies to overcome metastatic barriers (Fig. 3).

Inhibition of tumor angiogenesis and promotion of vascular normalization. Tumor neovasculature, a critical structure for malignant cells, acts via providing oxygen and nutrients while ensuring waste removal. The disorganized architecture of tumor blood vessels facilitates tumor-cell movement and distant micrometastasis (72,73). Tumor angiogenesis is a crucial process involving endothelial cell proliferation, migration, lumen formation and ECM degradation (74). MMP-2 and MMP-9 degrade type IV collagen, thereby releasing angiogenic signals and promoting vessel sprouting (75,76). By contrast, SAA, SAB and SAC dose-dependently inhibit MMP-2 and MMP-9 expression, thereby suppressing tumor angiogenesis (77-79). Mechanistically, a study in NSCLC (A549 cells) demonstrated that SAA abolished the phosphorylation of the phosphatidylinositol 3-kinase (PI3K)/AKT/mTOR signaling, downregulated erythropoietin-producing hepatocellular A2, vascular endothelial cadherin (VE-Cad) and MMP-2, and disrupted vasculogenic mimicry networks in NSCLC cells (A549), ultimately preventing the formation of new tumor blood vessels and distant metastasis (80). Glucose-regulated protein 78 (GRP78) is upregulated in tumor and endothelial cells under stress conditions, thus contributing to tumor angiogenesis (81). A previous study showed that the interaction between secreted GRP78 and VEGF enhanced angiogenic signaling, thus promoting endothelial cell survival and proliferation (82). In addition, treatment of colorectal cancer (DLD1 and HCT-116 cells) with SAA suppressed GRP78 secretion, with low SAA concentrations offering therapeutic advantages for formulation development and clinical application (83). Furthermore, co-culturing pancreatic cancer cells (PANC-1) and human umbilical vein endothelial cells (HUVECs) induced endothelial-to-mesenchymal transition (EndMT) (84,85), a process crucial for vascular network shaping. The above study also revealed that combined treatment with *Formononetin* and SAB suppressed abnormal tube formation, upregulated platelet endothelial cell adhesion molecule-1, downregulated vimentin and reversed EndMT, thereby inhibiting PANC-1 migration and neovascularization (84). In a 7,12-dimethylbenzanthracene-induced hamster cheek pouch carcinogenesis model, SAB treatment markedly reduced abnormal endothelial cell proliferation (86). Additionally, SAB also decreased circulating tumor cells and lung metastases in TNBC models (4T1 and MDA-MB-231 cells) without significantly affecting primary tumor volume, thus supporting the potential role of SAB in inhibiting metastasis via preventing tumor cell shedding into the circulation (55).

Collectively, these findings indicated that SAs could inhibit tumor angiogenesis through three main mechanisms. First, they directly suppress endothelial cell proliferation and migration. For example, SAA can inhibit HUVEC proliferation, metastasis and new blood vessel sprouting (84,85). Second, they rebalance angiogenic signaling via suppressing

tumor-derived GRP78 signaling (83) and modulating the PI3K/AKT pathways (80), thereby inhibiting endothelial cell proliferation, migration and lumen formation (87). Third, they inhibit MMP-2 and MMP-9 activity, thereby attenuating ECM degradation and limiting endothelial cell migration and vascular formation (77-79,88).

Although antiangiogenic therapy aims to inhibit or destroy newly formed vessels, vascular normalization represents a distinct therapeutic strategy that restores abnormal tumor vasculature into a more organized and functional state, thereby alleviating tumor hypoxia to enhance drug delivery (89,90).

Tumor-associated endothelial cells exhibit a unique metabolic profile characterized by enhanced glycolysis triggered by tumor-derived factors and hypoxia, resembling the Warburg effect (91). SAA directly binds to the type M2 pyruvate kinase (PKM2) and suppresses glycolysis in HUVECs, triggering nuclear translocation of PKM2 and β-catenin, reducing β-catenin phosphorylation and stabilizing claudin-5. The aforementioned effects could improve endothelial barrier integrity and promote tumor vascular normalization, thereby enhancing doxorubicin (DOX) delivery in melanoma and lung carcinoma models (92). In BALB/c mice bearing CT-26 colon carcinoma xenografts combined with femoral artery ligation-induced hind-limb ischemia, *Salvia miltiorrhiza* extract normalized tumor vasculature, enhancing pericyte coverage and vascular integrity while reducing vascular leakage, alleviating hypoxia and inhibiting tumor growth (48). In this model, angiopoietin-1 (Ang1) expression increased while Ang2 and forkhead box O1 expression decreased in both normal glomerular endothelial cells (GECs) and tumor endothelial cells (TECs). Concurrently, Ang1 increased and Ang2 decreased in mouse serum, muscle and tumor tissue, accompanied by elevated tyrosine kinase with immunoglobulin-like and EGF-like domains 2 (Tie2) phosphorylation in GECs and TECs and activation of the PI3K/AKT pathway (48). The extract also inhibited Ras homolog family member A (RhoA) and Rho-associated coiled-coil-containing protein kinase 2 (ROCK2) in GECs and TECs, thereby reducing myosin light-chain 2 (MLC2) phosphorylation and regulating the Ang/Tie2/MLC2 signaling axis to restore tumor vasculature and blood flow in ischemic limbs (48). SAA, an active component of the extract, further improved tumor vascular perfusion via targeting Ang2, enhancing Tie2 phosphorylation and stabilizing blood vessel integrity in both ischemic areas and tumors (48,93). Furthermore, EZH2-related cytokines could disrupt endothelial junction integrity and reduce VE-Cad expression, thus affecting tumor vasculature. However, this effect was abrogated following SAB treatment, eventually normalizing tumor vasculature, improving vascular perfusion and enhancing sensitivity to cisplatin (DDP) (55).

Mechanistically, SA-induced tumor vascular normalization includes combined regulation of endothelial cell metabolism and vascular structural integrity. Unlike their anti-angiogenic effects that suppress endothelial cell proliferation, tumor vascular normalization primarily focuses on metabolic reprogramming and stabilization of endothelial junctions. SAA can restore endothelial barrier function via targeting PKM2-mediated glycolysis and β-catenin/claudin-5 signaling (92). By contrast, *Salvia miltiorrhiza* extracts can modulate the Ang/Tie2/MLC2 axis to improve pericyte coverage and reduce vessel leakage (48,93). Notably, SAs exhibit context-dependent effects. Therefore, SAs can inhibit tumor angiogenesis (84,92), while simultaneously exerting protective effects on ischemic vessels in cardiovascular diseases. In particular, specific peptide-modified SAB could target ischemic areas to promote endothelial cell growth and the formation of new blood vessels (94). However, the SAB-mediated regulation of GRP78 could protect human endothelial cells against oxidative stress- induced damage (95). This dual role underscores the importance of distinguishing antiangiogenic activity from tumor vascular normalization mechanisms in therapeutic applications. Tumor vascular normalization enhances chemotherapeutic drug penetration and improves the efficacy of combination therapies (55,92). Given their multi-target activity and low toxicity, SAs represent promising vascular-targeting agents. However, optimization of dosage and treatment scheduling is critical for maintaining the balance between antiangiogenic and normalization effects, thus enhancing therapeutic efficacy. The mechanisms by which SAs inhibit tumor angiogenesis and promote tumor vascular normalization are illustrated in Fig. 4.

Regulation of the immunosuppressive metastatic microenvironment. The tumor microenvironment (TME) is a dynamic metastatic niche composed of tumor cells, myeloid cell populations, stromal fibroblasts, platelets and ECM, which collectively promote immune evasion, metastatic dissemination and therapeutic resistance (96-99). Rather than targeting a single cellular compartment, SAs appear to modulate several interconnected inflammatory and stromal signalling pathways that maintain the immunosuppressive TME.

A recurring observation across multiple tumor models is the suppression of TGF-β-associated myeloid reprogramming. In TNBC models, co-culture with tumor cells (SUM159PT and 4T1 cells) could drive macrophages toward an M2-like phenotype characterized by elevated TGF-β1 expression and activation of ERK signalling. However, SAA could reverse this transition, reduce macrophage migration and promote M1-like polarization, thereby attenuating tumor invasion (100). Similar findings have been reported in gastric cancer (MKN45 and BGC823 cells) (101), in which SAB inhibited sarcoma kinase (SRC)/focal adhesion kinase (FAK)/ERK signaling and reduced M2 tumor-associated macrophage (TAM) infiltration, together with reduced IL-4 and IL-10 expression in metastatic xenografts (MKN45 cells) (101). Notably, cyclase-associated protein 2 (CAP2), a cytoskeleton-regulatory protein associated with lymph-node metastasis in gastric cancer (101,102), could also be involved in this process. Computational molecular docking analyses suggested a potential interaction between SAB and the N-terminal domain of CAP2 (101), whereas Transwell assays, western blot analysis and functional recovery experiments further demonstrated that CAP2 contributed to SAB-mediated inhibition of gastric cancer cell proliferation, migration and invasion (101). *In vivo*, SAB also suppressed tumor growth and reduced M2-like macrophage polarization in xenograft models (101). Collectively, the aforementioned findings indicated that SAB could inhibit gastric cancer metastasis by targeting both tumor cell motility - via SRC/FAK/ERK inhibition and putative CAP2 binding - and the pro-tumorigenic microenvironment through suppression

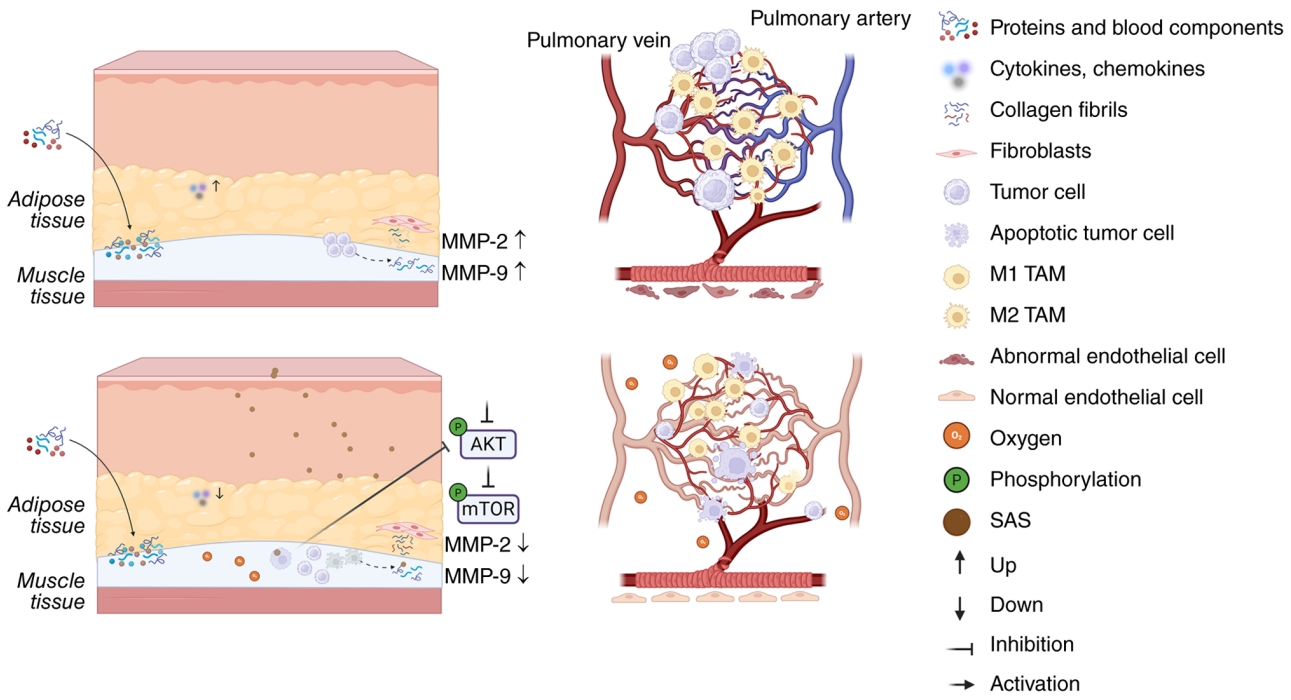

Figure 4. SAs inhibit tumor angiogenesis and promote vascular normalization. SAs (SAA, SAB) selectively neutralize MMP-2/9, halting collagenolysis within the tumor extracellular matrix. The resulting vascular pruning curtails perfusion deficits, relieves intratumoral hypoxia and ultimately drives a phenotypic switch toward functionally normalized, drug-permissive vasculature. MMP, matrix metalloproteinases; PI3K, phosphatidylinositol 3-kinase; AKT, protein kinase B; mTOR, mammalian target of rapamycin; SAA, salvianolic acid A; M1 TAM, classically activated tumor-associated macrophage; M2 TAM, alternatively activated TAM.

of M2-TAM polarization (101). Beyond macrophage polarization, SAs also can attenuate broader inflammatory cytokine and chemotactic signaling networks within the TME. Isodanolic acid A-1 suppressed inflammatory cytokine pathways associated with nuclear factor κB (NF-κB)/STAT3 activation, including interleukin-6 (IL-6) and tumor necrosis factor-α, suggesting broader inhibition of tumor-associated myeloid inflammation (18). In the colorectal cancer model (MC38 cells), *Salvia miltiorrhiza* root extract suppressed the cyclooxygenase 2/prostaglandin E2 inflammatory axis and reduced the expression of chemotactic mediators, including colony-stimulating factor (CSF)1, C-C motif chemokine ligand 2, monocyte chemoattractant protein 1 and granulocyte-macrophage-CSF, thereby limiting TAM recruitment and partially restoring cluster of differentiation (CD)8$^+$ T-cell infiltration (103,104). These findings suggest that SAs can suppress not only macrophage phenotype maintenance, but also the upstream inflammatory gradients required to sustain myeloid-dominant immune exclusion.

Concomitantly, SA derivatives target matrix and vascular components that provide both physical and functional protection to migrating tumor cells. It has been reported that the SAB, PEG-SAB-Lip and SAB@HMON-PDA can suppress TGF-β1/Smad and downregulate α-smooth muscle actin in tumor-associated fibroblasts (TAFs) (56,57), thereby reducing ECM deposition and improving immune-cell penetration in TNBC models (16,56,57). These interventions can also enhance the expression of type 1 T-helper cell (Th1)-type cytokines and promote the recruitment of CD4$^+$ T cells, CD8$^+$ T cells and M1-like TAMs (57), while reducing immunosuppressive Th2-associated cytokines (55). In hepatocellular carcinoma (Hep-3B and HCCLM3 cells), SAB-mediated inhibition of gap junction protein β2 (GJB2) signalling enhanced sensitivity to anti-programmed cell death protein 1 (PD-1) therapy, further supporting a role for SAB in reversing stromal-mediated immune resistance (93).

Additionally, nanoparticle-based delivery systems can further enhance these effects via improving intratumoral accumulation and immune cell infiltration (16,56,57). A previous study demonstrated that magnetic nanoparticle-coated SAB could enable magnetic field-guided tumor targeting, suppress TAF-derived ECM production and promote T-cell infiltration (16). Similarly, injection of desferrioxamine-loaded ferrum-sulfur hydride nanoparticles enabled controlled SAB release, suppressed TGF-β signaling, enhanced macrophage M1 polarization and increased cytotoxic T-cell activation, thereby partially converting immune-excluded tumors into a more immune-permissive microenvironment (105). Combination therapy with anti-PD-1/programmed cell death ligand 1 (PD-L1) antibodies further improved suppression of both primary and metastatic TNBC lesions (16,56,105). Furthermore, SAB combined with anti-PD-L1 could elevate interferon-γ and granzyme B expression in resistant 4T1 tumor models, thus indicating that SAB could activate cytotoxic T cells and synergize with immune checkpoint blockers (55). However, these findings remain primarily preclinical and whether stromal normalization represents a direct pharmacological mechanism of SAs or a secondary consequence of reduced inflammatory signaling remains elusive.

Another important component of metastatic niche regulation involves platelet activation. DOX could dose-dependently activate platelets by increasing P-selectin/glycoprotein

membrane protein-140 and fibrinogen binding (106). DOX also elevated CD41 expression in platelets and promoted platelet-tumor microaggregation in TNBC (4T1 and MDA-MB-231 cells) (106), thereby enhancing platelet-mediated immune shielding, endothelial adhesion, angiogenesis and EMT-associated metastatic signaling (106-112). Another study revealed that SAC could markedly inhibit the aforementioned processes and showed greater efficacy compared with aspirin and ticagrelor in suppressing DOX-induced platelet activation (106). Given that activated platelets contribute to both metastatic dissemination and thrombotic complications during chemotherapy (106,113), the antiplatelet activity of SAs may represent an additional mechanism limiting thrombo-inflammatory support for tumor progression (106). Consequently, clinical regimens have evaluated the combination of antiplatelet agents with DOX to reduce recurrence and treatment-associated toxicity (114,115). SAA, SAB and SAC exhibit strong antiplatelet and antithrombotic abilities, while they can reverse DOX-induced platelet dysfunction and attenuate DOX-related cardiotoxicity (28,116,117), with SAC showing the strongest activity (106). Combining SAC with DOX lowers drug-induced immune thrombocytopenia and venous thromboembolism incidence and reduces tumor-related platelet pathology (106).

Collectively, current evidence suggests that SAs do not act on a single cellular compartment within the TME, but rather coordinately remodel interconnected inflammatory, stromal and thrombo-immunological networks that sustain metastatic progression and immune exclusion. Through convergent regulation of inflammatory signaling, macrophage polarization, stromal activation, ECM remodeling, platelet-assisted metastatic protection and immune checkpoint responsiveness, SAs collectively enhance immune-cell infiltration and improve sensitivity to chemotherapy and immune checkpoint blockade in preclinical tumor models. The interconnected cellular and signaling interactions underlying this proposed TME-remodeling framework are summarized in Fig. 5. However, most current evidence is derived from murine transplantation systems, particularly TNBC models, and mechanistic convergence across different tumor types remains incompletely resolved. Future studies integrating spatial transcriptomics, single-cell profiling and clinically relevant treatment models will be necessary to determine whether these apparently coordinated effects reflect a unified mechanism of TME remodeling or multiple context-dependent pharmacological activities.

Targeting metastatic cellular plasticity and therapy resistance. Metastatic dissemination requires continuous cellular adaptation to mechanical stress, therapeutic pressure and microenvironmental remodeling (113). Increasing evidence suggests that cytoskeletal plasticity, EMT, stemness acquisition and drug-tolerant survival states are mechanistically interconnected processes that collectively sustain metastatic progression and relapse (118-121).

Cytoskeletal remodeling constitutes a central biomechanical driver of tumor-cell migration and invasion (122,123). Actin polymerization dynamics, focal adhesion turnover and actomyosin contractility are tightly regulated by Rho GTPases, cofilin and PI3K/AKT-associated signaling pathways, enabling tumor cells to acquire invasive plasticity (124-127). SAA suppresses transgelin-2 (TAGLN2), attenuating the migratory and invasive capacity of paclitaxel (PTX)-resistant MCF-7/PTX cells (127), and SAB limits PANC-1 migration and invasion by targeting RhoA and inhibiting PI3K/AKT phosphorylation (84). Given the established role of the RhoA/ROCK axis in stress-fiber formation and force generation, these findings suggest that SAs may impair the mechanical adaptability required for metastatic dissemination.

Emerging evidence also implicates cytoskeletal-associated signaling in chemotherapy resistance. PTX suppresses tumor progression by stabilizing microtubules and disrupting mitotic dynamics (128-130), yet adaptive cytoskeletal remodeling frequently contributes to taxane resistance. In PTX-resistant MCF-7/PTX breast cancer cells, SAA restored chemosensitivity by targeting TAGLN2 and suppressing PI3K/AKT signaling, while simultaneously reducing migratory capacity (126,127). As TAGLN2 is closely associated with actin stabilization, EMT-related plasticity and survival signaling, these findings suggest that SAs may interfere with the coupling between cytoskeletal adaptation and therapy-resistant phenotypes.

Beyond migratory plasticity, SAs also appear to suppress metastatic persistence and stemness-associated therapeutic resistance (27,126,127). Therapy-resistant clones and cancer stem cells (CSCs) are increasingly recognized as major drivers of metastatic relapse, owing to their capacity for adaptive survival, dormancy and re-initiation of tumor growth (131-134). In DDP-resistant A549/DDP lung cancer cells, SAA downregulateed c-met/AKT/mTOR signaling, prevented multidrug-resistance protein 1 (MDR1) upregulation and restored cisplatin sensitivity (27). Similarly, SAA lowered MDR expression and inhibited P-glycoprotein (P-gp) activity in MCF-7/PTX breast cancer cells, accompanied by increased reactive oxygen species (ROS) accumulation and apoptosis (126,127). Tumor-derived exosomal GRP78 further contributes to chemoresistance and angiogenesis (135), whereas SAA inhibited GRP78 secretion, suggesting potential interference with resistance-supportive intercellular signaling (135).

Comparable effects were observed with SAB in multiple resistant tumor models. In AGS/DDP gastric cancer cells, SAB reduces viability and migration while suppressing AKT/mTOR signaling and enhancing ROS-associated cytotoxicity, thus decreasing DDP resistance (51). In vincristine (VCR)-resistant HCT-8/VCR colorectal cancer cells, SAB lowers MDR expression and P-gp levels, triggering apoptosis (136). Importantly, SAB also reduced stemness-associated markers, including CD44, SOX2, and ATP binding cassette transporter G2 in LoVo and HCT-116 xenograft models (134), supporting a potential role in limiting CSC-like persistence and metastatic recurrence.

Notably, several signaling pathways implicated in drug resistance - including PI3K/AKT, cytoskeletal remodeling and EMT-associated survival programs - substantially overlap with those governing metastatic plasticity. This raises the possibility that SAs may not simply enhance chemotherapy sensitivity, but more broadly suppress adaptive cellular states required for metastatic survival and re-colonization. However, current evidence remains largely derived from *in vitro* resistance models and subcutaneous xenografts, with limited investigation of spontaneous metastasis, dormant disseminated tumor cells or organ-specific metastatic recurrence.

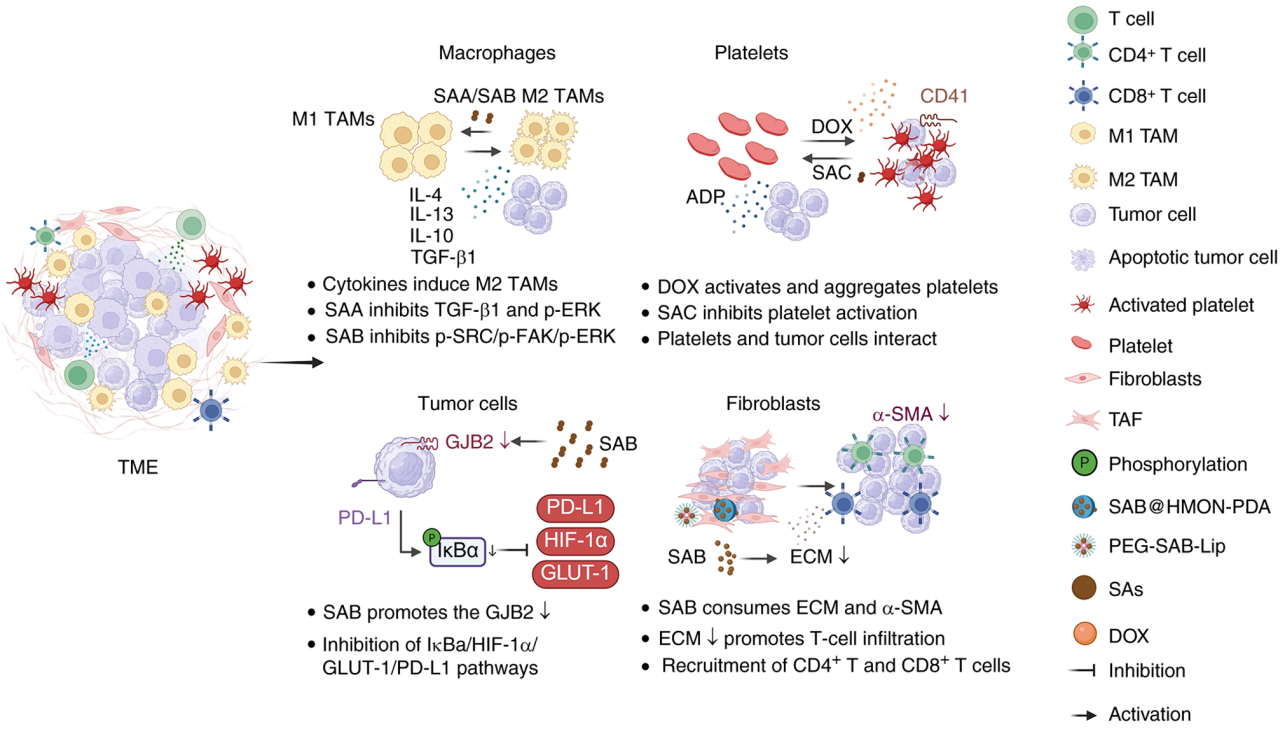

Figure 5. SAs suppress tumor progression through coordinated remodeling of the immunosuppressive metastatic microenvironment. SAA, SAB and SAC act as 'phenotype switchers' within the TME: They repolarize macrophages from M2 to M1, drive platelets from a pro-coagulant to a quiescent state, convert exhausted T cells into cytotoxic effectors and trans-differentiate cancer-associated fibroblasts toward a non-activated phenotype. Concurrently, the compounds silence GJB2 and α-SMA while blocking PD-L1, dismantling physical and immune barriers that otherwise suppress anti-tumor immunity. IL, interleukin; SAA, salvianolic acid A; TGF-β1, transforming growth factor β1; ERK, extracellular signal-regulated kinase; SRC, sarcoma kinase; FAK, focal adhesion kinase; ADP, adenosine diphosphate; DOX, doxorubicin; CD41, cluster of differentiation 41; GJB2, gap junction protein β2; PD-L1, programmed cell death ligand 1; HIF-1α, hypoxia-inducible factor 1α; IκBα, inhibitor of nuclear factor κB α; GLUT1, glucose transporter 1; T cell, thymus-derived lymphocyte; $CD4^+$ T, T helper cells; CD^{8+}T, cytotoxic T lymphocyte; ECM, extracellular matrix; SAB@HMON-PDA, SAB@Dopamine-functionalized hollow mesoporous organosilica; SMA, smooth muscle actin; PEG-SAB-Lip, nanoparticles or polyethylene glycol-modified liposomes as drug carriers for SAB; TAM, tumor associated macrophage; TAF, tumor-associated fibroblast; TME, tumor microenvironment; M1 TAM, classically activated tumor-associated macrophage; M2 TAM, alternatively activated TAM.

Current evidence indicates that SAs suppress multiple features associated with therapy-resistant and stem-like tumor phenotypes. In parallel, inhibition of TAGLN2-associated cytoskeletal signaling and reduction of migratory capacity in resistant tumor cells further support a functional link between cytoskeletal plasticity and therapy-resistant metastatic behavior. These findings collectively suggest that SAs may coordinately restrict invasive dissemination and adaptive persistence, two central processes underlying metastatic relapse.

However, most current studies rely on *in vitro* resistance models and subcutaneous xenografts, with limited investigation of spontaneous metastasis, dormant disseminated tumor cells or organ-specific metastatic recurrence. Furthermore, whether the observed suppression of stemness-associated phenotypes reflects direct targeting of CSC programs or secondary consequences of altered survival signaling and oxidative stress remains unresolved. Future studies integrating patient-derived metastatic models, lineage tracing and spatially resolved analyses will be necessary to determine whether SAs can durably suppress metastatic persistence in clinically relevant settings. Collectively, SAs appear to interfere with metastatic cellular plasticity through coordinated modulation of cytoskeletal dynamics, survival signaling, stemness-associated programs and therapy-resistant phenotypes, thereby representing a potential strategy for limiting metastatic relapse and improving long-term therapeutic responsiveness (Fig. 6).

4. Conclusions and future perspectives

Metastasis is a dynamic and adaptive process involving tumor-cell dissemination, stromal remodeling, immune evasion, vascular adaptation and metastatic colonization (137). Although multiple anti-metastatic strategies have been developed, including MMP inhibition, stromal targeting and anti-angiogenic therapy, their clinical benefits remain limited by biological heterogeneity, compensatory signaling and context-dependent effects (138,139). For example, while MMPs are generally considered pro-metastatic, certain family members such as MMP-8 may exert tumor-suppressive functions in specific contexts (140,141). Similarly, therapies targeting platelet-derived growth factor receptor signaling or TAFs have yielded inconsistent outcomes, reflecting the functional heterogeneity of stromal populations and the dual tumor-promoting vs. tumor-restraining roles of fibroblasts. These observations highlight a central challenge in anti-metastatic therapy: Metastasis is governed not by isolated pathways, but by highly adaptive and interconnected cellular ecosystems.

Within this framework, SAs emerge as potential modulators of metastatic plasticity rather than conventional

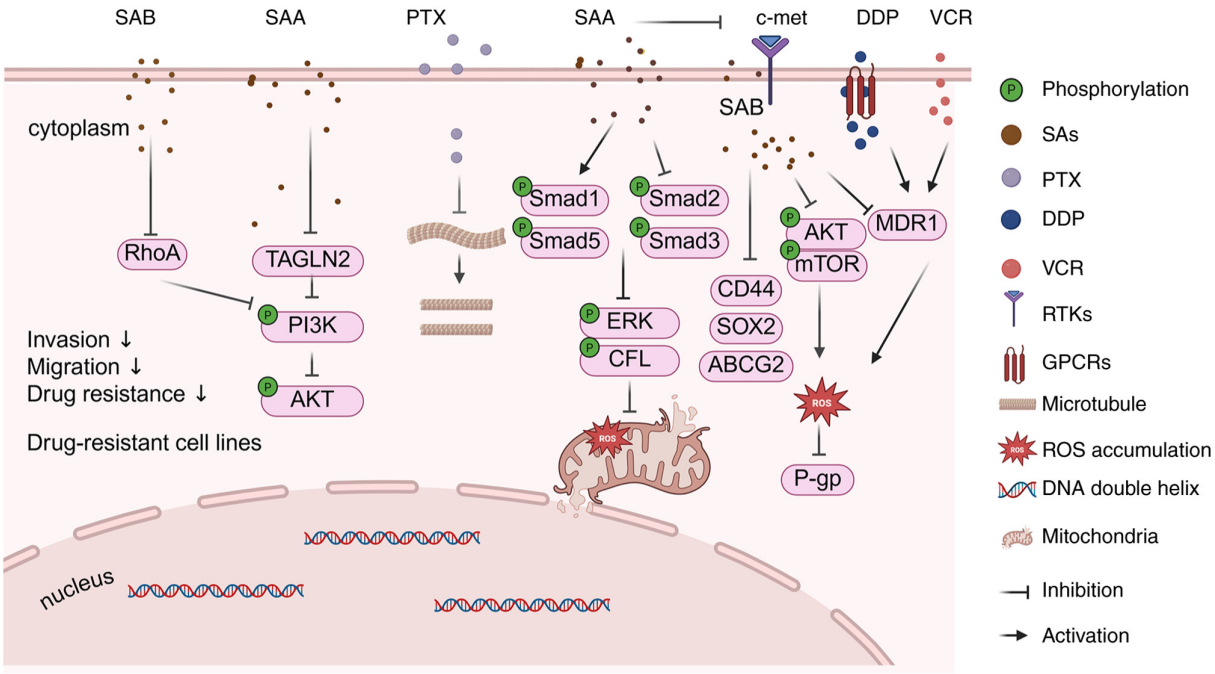

Figure 6. SAs suppress metastatic cellular plasticity and therapy-resistant tumor states. Schematic of molecular pathways activated in drug-resistant cell lines, illustrating crosstalk between cytoplasmic and nuclear effectors. SAA and SAB directly disrupt cytoskeletal proteins and resensitize resistant cells to PTX, DDP and VCR by inhibiting the PI3K/AKT/mTOR axis, boosting ROS production and driving lethal damage. SAA, salvianolic acid A; PTX, paclitaxel; DDP, cisplatin; VCR, vincristine; AKT, protein kinase B; Smad, small mothers against decapentaplegic; mTOR, mammalian target of rapamycin; TAGLN2, transgelin-2; PI3K, phosphatidylinositol 3-kinase; ERK, extracellular signal-regulated kinase; CFL, cofilin; MDR1, multidrug-resistance protein 1; RhoA, Ras homolog gene family, member A; SOX2, SRY-related HMG-box 2; CD44, cluster of differentiation 44; ABCG2, ATP-binding cassette sub-family G member 2; P-gp, P-glycoprotein; MDR1, multi-drug resistance 1; RTKs, receptor tyrosine kinases; GPCRs, G protein-coupled receptors; ROS, reactive oxygen species.

single-target inhibitors. Across different tumor models, recurrent involvement of PI3K/AKT, MAPK/ERK, TGF-β/Smad and NF-κB signaling suggests partial mechanistic convergence on broader programs regulating EMT, inflammatory remodeling, cytoskeletal adaptation, stemness-associated persistence and therapy-resistant survival states. Notably, these pathways collectively govern cellular adaptability within metastatic ecosystems, raising the possibility that SAs primarily function by disrupting adaptive stress integration and microenvironmental remodeling rather than selectively targeting metastasis-specific drivers.

However, substantial limitations remain. Most evidence derives from short-term *in vitro* assays, induced resistance systems and subcutaneous xenograft models - particularly TNBC-derived models such as 4T1 cells - which incompletely recapitulate spontaneous metastasis, organotropism, metastatic dormancy, immune heterogeneity and evolutionary selection under therapeutic pressure. Furthermore, numerous proposed mechanisms rely primarily on signaling alterations without rigorous causal validation, making it difficult to distinguish direct anti-metastatic activity from nonspecific cytotoxic or oxidative stress responses.

Several translational barriers also require careful consideration. Pharmacokinetic properties of SAs, including bioavailability, metabolic stability, tissue penetration and achievable intratumoral exposure, remain insufficiently characterized in oncology settings. Importantly, effective concentrations reported *in vitro* may exceed clinically attainable plasma levels. In addition, SAA, SAB and SAC exhibit distinct physicochemical and metabolic properties, yet are often discussed collectively despite potentially different pharmacological behaviors. Strategies such as liposomal or nanoparticle-based delivery systems may improve drug stability, tumor accumulation and sustained exposure, while combination approaches with chemotherapy or immune checkpoint blockade may enhance therapeutic responsiveness by simultaneously targeting metastatic plasticity and microenvironmental adaptation. Nevertheless, these approaches remain largely unvalidated in clinically relevant metastatic models.

Future studies should therefore prioritize clinically relevant metastasis models, including patient-derived organoids, spontaneous metastasis systems, lineage tracing approaches, spatial transcriptomics and single-cell multi-omics analyses. Greater emphasis should also be placed on pharmacokinetics, dose-exposure relationships, treatment scheduling and combinatorial therapeutic design, particularly in the context of chemotherapy and immune checkpoint blockade. Combinatorial strategies with SAs may be expanded along the following dimensions: First, synergy with chemotherapeutic agents: SAA, SAB and SAC have demonstrated the capacity to reverse DOX-induced platelet activation and cardiotoxicity (106,116,117), suggesting that SAs may enhance antitumor efficacy while mitigating chemotherapy-associated adverse effects. Second, combination with immune checkpoint inhibitors: SAB can enhance anti-PD-1 therapy sensitivity through GJB2 inhibition (93), while nanoparticle-delivered SAB combined with anti-PD-L1 elevates interferon-γ and granzyme B expression to activate cytotoxic T cells (57); furthermore, new biomaterials loaded with SAB suppress

TAFs and M2 macrophage activation, and thereby remodel the immune microenvironment to augment antitumor immune responses (56,57). Beyond immunotherapy sensitization, engineered nano- or liposomal carriers may improve tumor-targeted accumulation and sustained exposure of SAs, while sequential or synchronous administration with targeted agents (e.g., anti-angiogenics) or epigenetic modulators may address the spatiotemporal heterogeneity and adaptive evolution of metastatic tumors. These findings indicate that engineered delivery systems not only enable tumor-targeted accumulation of SAs but also synergistically enhance the efficacy of immune checkpoint inhibitors through stromal remodeling, indicating that SAs may serve as sensitizers for immunotherapy. Third, metronomic chemotherapy regimens: Low-dose sustained administration can maintain the vascular normalization window, suppress tumor vascular regrowth and reduce opportunities for metastatic dissemination during treatment intervals, forming mechanistic complementarity with the microenvironment-remodeling effects of SAs. Collectively, it is indicated that SAs may function as immunotherapy sensitizers, while advanced delivery systems - exemplified by SAB@HMON-PDA - can synergistically enhance therapeutic efficacy through concurrent stromal remodeling and precise tumor targeting. It should be acknowledged that these combinatorial strategies remain largely preclinical and rigorous validation in patient-derived models and prospective clinical trials will be essential to realize their translational potential.

In conclusion, SAs, used for cardiovascular issues, are now seen as anti-cancer agents affecting metastasis in various diseases, highlighting their potential to prevent tumor relapse. They require more research as adjuvants to inhibit processes like EMT and immune evasion, with rigorous studies needed for their integration into oncology and standardization of botanical therapies.

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Availability of data and materials

Not applicable.

Authors' contributions

STJ and WLY were involved in the conceptualization of the study. STJ, DL, TTW, STJ, QWS, HWW and YDG were responsible for literature search, study selection and data curation. STJ, TTW, QWS, HWW and YDG performed visualization. STJ and DL participated in writing - review and editing. PSM and WLY were responsible for data interpretation, critical revision of the manuscript for important intellectual content, writing - review and editing and funding acquisition. Data authentication is not applicable. All authors have read and approved the final 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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