Breast Cancer: Targets and Therapy

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REVIEW

Salidroside-Based Nanomedicines for Triple-Negative Breast Cancer: From Molecular Mechanisms to Clinical Translation

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Abstract: Triple-negative breast cancer (TNBC) presents a substantial therapeutic challenge due to its aggressive biological characteristics and the absence of actionable molecular targets. Salidroside, the principal bioactive compound of *Rhodiola rosea*, demonstrates significant anticancer potential; however, its clinical application is severely constrained by poor bioavailability (less than 12%) and a short half-life (2.3 hours). This review contributes to the field in three key ways. Firstly, it systematically elucidates the molecular mechanisms of salidroside in TNBC, emphasizing its distinctive dual role in redox homeostasis: inducing ferroptosis in cancer cells while safeguarding normal tissues. Secondly, it critically assesses advanced nanomedicine strategies such as PLGA-PEG nanoparticles, lipid-polymer hybrid nanoparticles, and biomimetic RBC membrane-camouflaged carriers-designed to address pharmacokinetic limitations. Thirdly, and most importantly, it proposes a biomarker-driven framework, centered on BRCA1 methylation and HIF-1α, along with a three-phase translational roadmap to advance salidroside into a precision nanomedicine for TNBC.

Keywords: salidroside, triple-negative breast cancer, nanomedicines, tumor immune microenvironment, ferroptosis

Introduction

Triple-negative breast cancer (TNBC) approximately accounts for 15–20% of all breast cancer cases and presents a formidable therapeutic challenge due to its aggressive clinical progression and lack of targetable estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2).[1] Triple-negative breast cancer (TNBC) is not a singular entity; rather, it represents a highly heterogeneous group of diseases characterized by several distinct molecular subtypes, including basal-like 1 (BL1), basal-like 2 (BL2), immunomodulatory (IM), mesenchymal (M), mesenchymal stem-like (MSL), and luminal androgen receptor (LAR) subtypes. These subtypes demonstrate varying sensitivities to different therapeutic agents and possess unique immune microenvironment profiles. The standard therapeutic regimen for triple-negative breast cancer (TNBC) typically involves the administration of anthracyclines (eg., epirubicin), taxanes (eg., paclitaxel), and platinum-based agents, often followed by adjuvant capecitabine. Recent developments have highlighted the potential of antibody-drug conjugates, such as sacituzumab govitecan, especially when combined with immune checkpoint inhibitors like pembrolizumab, as promising strategies for the treatment of advanced TNBC. These findings are supported by data from the ASCENT-04 trials. Conventional endocrine and HER2-targeted therapies have proven ineffective in treating triple-negative breast cancer (TNBC). Furthermore, immune checkpoint inhibitors demonstrate limited efficacy, with clinical response rates below 20%.[2,3] Within this evolving therapeutic landscape, salidroside emerges as a compound of interest due to its potential synergistic roles: it may mitigate epirubicin-induced cardiotoxicity, counteract paclitaxel resistance, and enhance the efficacy of anti-PD-1 immunotherapy. Consequently, salidroside is positioned as a potential adjunct to existing treatment regimens rather than as a replacement.

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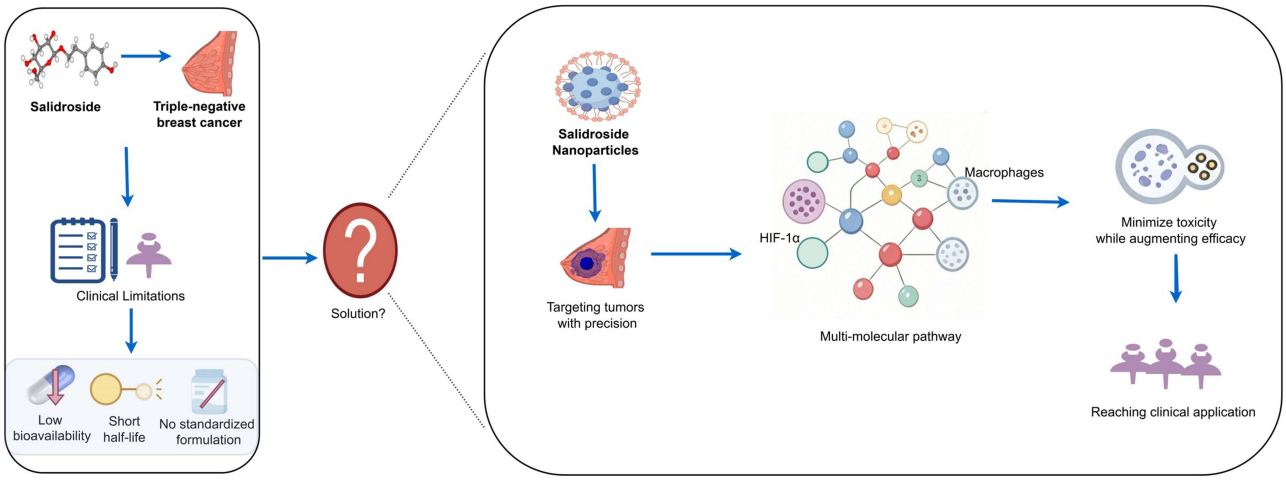
Graphical Abstract



Salidroside ($C_{14}H_{20}O_7$), the primary bioactive component of *Rhodiola rosea* L. (Figure 1), has emerged as a promising polypharmacological candidate. In addition to its extensively documented antioxidant and anti-inflammatory properties,[4–12] it demonstrates multifaceted antitumor efficacy against breast cancer by inhibiting cellular

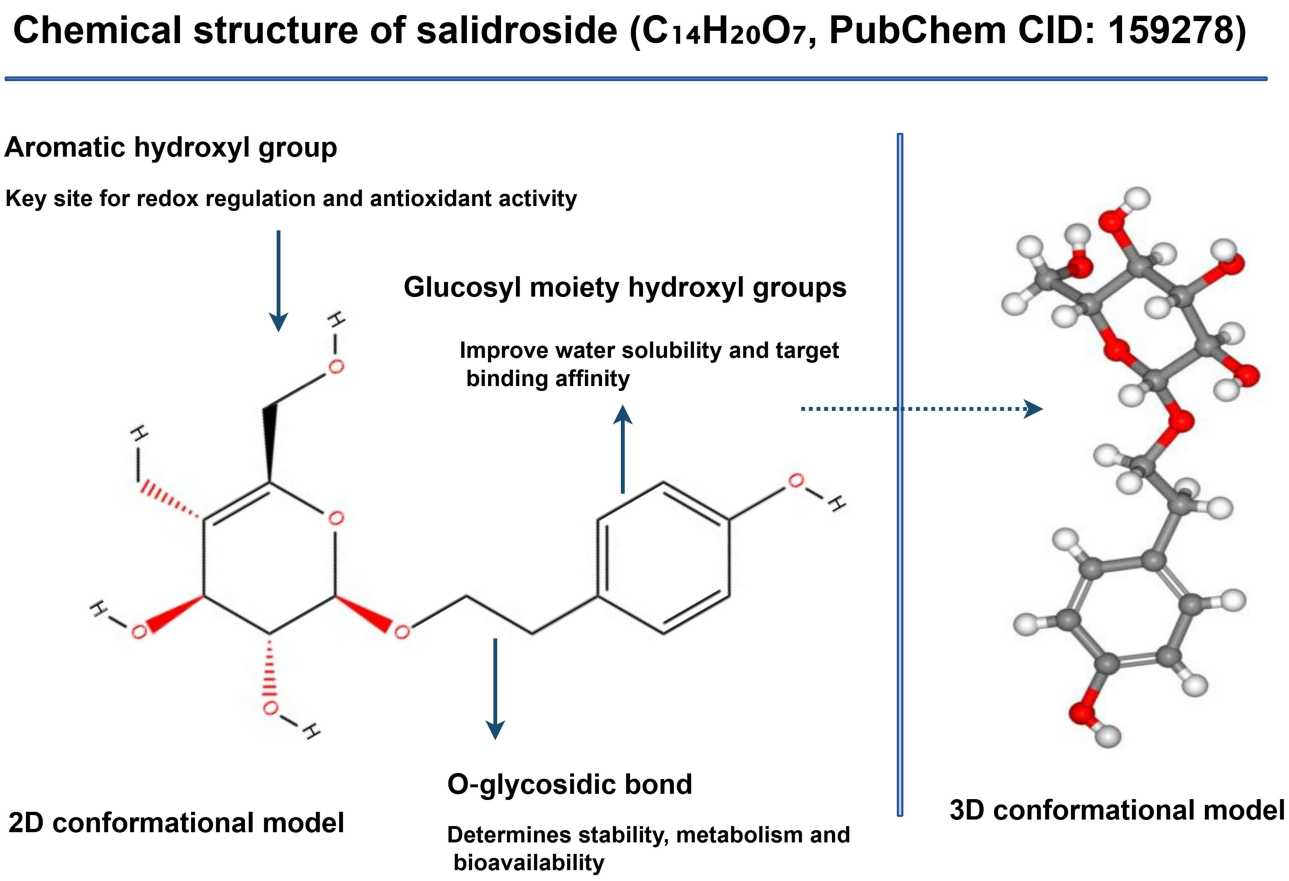


Figure 1 Chemical structure of salidroside ($C_{14}H_{20}O_7$). The two-dimensional and three-dimensional chemical structures of salidroside are depicted, illustrating a benzene ring connected to a glucose moiety through a glycosidic bond. This configuration includes hydroxyl groups at critical positions, where the aromatic hydroxyl group is associated with redox regulation and antioxidant activity, while the glucosyl moiety hydroxyl groups contribute to water solubility and target binding affinity. Additionally, the O-glycosidic bond plays a role in the compound's stability, metabolism, and bioavailability. This information has been adapted from PubChem (CID: 159278) with permission (https://pubchem.ncbi.nlm.nih.gov/).

proliferation, reprogramming metabolism pathways, and modulating the immune microenvironment. Elucidating how salidroside's multi-targeted mechanisms-specifically its modulation of the Wnt/β-catenin and PI3K-AKT-mTOR pathways, as well as its induction of ferroptosis-may differentially impact specific TNBC subtypes is essential for the development of biomarker-driven therapeutic strategies. Nevertheless, similar to numerous natural compounds exhibiting pleiotropic anticancer properties, salidroside encounters a prevalent translational challenge: its high in vitro potency does not effectively translate into clinical efficacy, primarily due to suboptimal pharmacokinetic characteristics and the absence of standardized formulations. This gap presents an opportunity that nanomedicine is particularly well-suited to address.

Despite strong preclinical evidence supporting its efficacy, the translational potential of salidroside is significantly constrained by its dependence on non-physiological experimental conditions, the use of supraphysiological concentrations in vitro, and limited clinical bioavailability, which is less than 12%.[2] Nanomedicine presents a strategic approach to overcoming these limitations. The concept of "nanotheranostics" pertains to nanoscale platforms that amalgamate therapeutic and diagnostic (imaging) capabilities, facilitating the real-time monitoring of drug delivery and treatment efficacy. Advanced nanodelivery systems have the potential to enhance the pharmacokinetic properties of salidroside, facilitate targeted delivery, and enable real-time therapeutic monitoring, thereby establishing a foundation for precision therapy in TNBC.

To ensure a comprehensive synthesis, this review systematically incorporates 87 relevant studies. The foundational mechanistic literature encompasses the period from 2009 to 2023, while significant advancements in nanodelivery strategies and clinical translational frameworks from 2024 to 2025 have been included to maintain contemporary relevance. Relevant studies were identified through systematic searches of the PubMed, Web of Science, and Scopus databases (up to March 2025), employing combinations of keywords such as "salidroside," "*Rhodiola rosea*," "breast cancer," "TNBC," "nanomedicine," "nanoparticle," "ferroptosis," and "tumor microenvironment." The inclusion criteria were restricted to peer-reviewed, English-language original articles and reviews.

Building on foundational evidence, this review initially elucidates the complex molecular mechanisms and subtype-specific pharmacological effects of salidroside in breast cancer. Subsequently, it identifies critical translational barriers and proposes the use of integrated nanomedicine approaches-merging advanced nanodelivery systems with real-time imaging-as a pivotal strategy to address pharmacokinetic limitations and enhance personalized therapy for triple-negative breast cancer (TNBC). Overall, our analysis provides a comprehensive roadmap for the development of salidroside as a precision oncology agent, offering novel insights to overcome existing therapeutic challenges in TNBC.

Molecular Mechanisms of Salidroside in Breast Cancer

Salidroside demonstrates a wide range of antitumor effects in breast cancer by influencing a complex network of molecular pathways that regulate uncontrolled proliferation, tumor metastasis, metabolic reprogramming, epigenetic dysregulation, immune evasion, and regulated cell death, including ferroptosis and apoptosis (Figure 2). These mechanisms display distinct specificity across different subtypes, offering a robust basis for pharmacological development. However, core translational limitations are primarily associated with non-physiological experimental conditions and insufficient disease models, which are central to the ongoing optimization of nanotheranostic approaches.

Regulation of Cell Proliferation and Apoptosis

Salidroside influences sustained proliferation and apoptosis resistance through subtype-specific mechanisms in breast cancer. In TNBC cell line MDA-MB-231, salidroside induced G1 phase cell cycle arrest by upregulating cyclin-dependent kinase inhibitors p21 and p27, while inhibiting the CDK4-cyclin D1 signaling pathway, resulted in 65% arrest in the G1 phase.[13] Conversely, in luminal A breast cancer cell line MCF-7, it impeded proliferation by targeting the phosphatidylinositol 3-kinase (PI3K)-protein kinase B (AKT)-mammalian target of rapamycin (mTOR) signaling pathway, leading to a 58% reduction in malignant cell growth.[14] The induction of apoptosis was consistently facilitated by caspase activation: salidroside activated caspase-3 in MCF-7 xenografts and caspase-9 in MDA-MB-231 cells by modulating Bcl-2 family proteins, thereby increased the apoptotic index by up to 3.1-fold.[13,14]

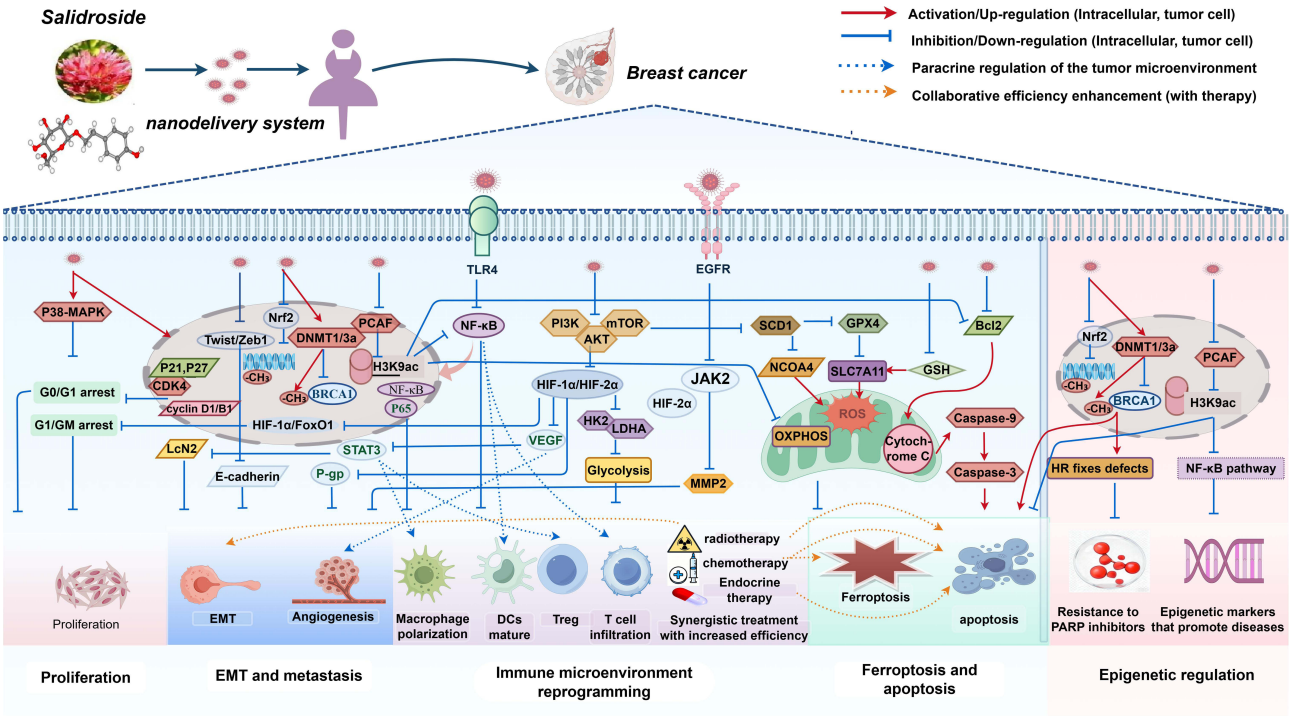


Figure 2 Integrated molecular mechanisms of salidroside in breast cancer. Schematic diagram illustrating salidroside's core molecular targets and pathways in breast cancer, including proliferation inhibition (PI3K-AKT-HIF-1α axis), ferroptosis induction (SCD1-NCOA4 pathway), angiogenesis suppression (HIF-1α/VEGF/STAT3 axis), EMT inhibition (Twist1/Zeb1-E-cadherin pathway), immune microenvironment remodeling (Treg/DC regulation), and epigenetic modulation (DNMT3B-BRCA1 axis). Note: Solid arrows are used to denote promotional regulatory effects, while T-shaped arrows signify inhibition. Blue dashed arrows illustrate indirect paracrine modulation of the tumor microenvironment, encompassing macrophages, dendritic cells, and regulatory T cells (Tregs). Orange dashed arrows indicate synergistic therapeutic effects. Notably, all solid arrows represent the direct regulatory impact of salidroside on intracellular signaling pathways within breast cancer cells.

It is noteworthy that the effective in vitro concentrations (50–200 μM) exceeded clinically achievable plasma levels (1–5 μM) by a factor of 10–4010,16. Furthermore, the majority of studies are constrained by a limited selection of cell lines, such as MDA-MB-231, MCF-7, and 4T1, which do not adequately represent the heterogeneity of breast cancer.[14,15] These limitations underscore the need for the development of nanodelivery systems to enhance in vivo bioavailability and targeted accumulation.

Inhibition of Epithelial-Mesenchymal Transition (EMT) and Metastasis

Salidroside interfered with tumor angiogenesis, adaptation to hypoxia, EMT, and metastatic spread in breast cancer. Under experimentally induced hypoxic conditions (1–2% O_2), *Rhodiola rosea* extract reduced hypoxia-inducible factor 1α (HIF-1α)/HIF-2α expression by 51% in MCF-7 cells, which was associated with reduced cellular proliferation.[16] In human umbilical vein endothelial cells (HUVECs), the extract inhibited the phosphorylation of signal transducer and activator of transcription 3 (STAT3) and subsequent matrix metalloproteinase 2 (MMP2) activity, leading to a 65% reduction in tube formation.[17] Concurrent studies in MDA-MB-231 cells demonstrated suppression of the EGFR/Jak2/STAT3-MMP2 signaling pathway, thereby impaired migration, invasion, and angiogenic potential.[17] Research conducted in a non-oncological setting, specifically utilizing a rat model of cerebral small vessel disease (CSVD), has demonstrated that the administration of salidroside (24 mg/kg, intraperitoneally) enhanced vascular integrity and function. This effect is associated with the upregulation of Notch1, Hes1/5, and ITGB1 signaling pathways.[18] Though derived from non-breast cancer models, this finding offer mechanistic insights likely applicable to TNBC due to the conserved nature of these pathways. These findings collectively indicate that salidroside may have dual effects on tumor vasculature, potentially combining anti-angiogenic properties with vascular stabilization. Furthermore, Salidroside directly influences cellular plasticity and metastasis. In hypoxic MDA-MB-231 cells (1% O_2), treatment with 50 μM salidroside results in a 62% reduction in Twist1 expression and a 58% reduction in Zeb1 expression, while simultaneously inducing a 2.1-fold

increase in E-cadherin expression. This modulation leads to a 73% decrease in Transwell invasion.[19,20] Beyond these cell-intrinsic effects, salidroside also disrupted the pre-metastatic niche by significantly reducing nicotine-induced N2 neutrophil infiltration by 81% and inhibiting STAT3-mediated LCN2 release by 75%, thereby decreased the lung metastatic burden by 69% in hormone receptor-negative breast cancer models.[21]

A significant translational challenge is that the experimental hypoxic conditions (1–2% O_2) employed are more severe than those observed in clinical breast tumor hypoxia (5–10% O_2).[22] Furthermore, current metastasis models do not accurately replicate the organotropic metastasis of human triple-negative breast cancer (TNBC), particularly to bone and brain.[23] The development of nanocarriers with tumor microenvironment-responsive targeting capabilities offers a potential solution by enabling the targeted delivery of salidroside to hypoxic tumor regions, thereby enhancing its anti-metastatic efficacy in clinically relevant settings.

Metabolic Reprogramming & Ferroptosis

Metabolic reprogramming is a critical adaptive mechanism in breast cancer, facilitating malignant proliferation and survival. Salidroside disrupted the metabolic reprogramming of breast cancer cells and induced ferroptosis, a form of iron-dependent regulated cell death intricately linked to metabolic processes. Preclinical studies have demonstrated that salidroside exerts dual modulation of energy metabolism and cell death pathways. At a concentration of 100 μM in vitro treatment, salidroside decreased the expression of HIF-1α by 62% and reduces the levels of glycolytic enzymes hexokinase 2 (HK2) and lactate dehydrogenase A (LDHA) by 45–58%, resulting in a 68% reduction in lactate production.[24–27] Simultaneously, it enhanced the activity of mitochondrial complexes I and III, thereby promoting a metabolic shift towards oxidative phosphorylation and mitigating the Warburg effect.[24–27] These metabolic changes were mechanistically associated with the suppression of the PI3K/AKT/mTOR signaling pathway, activation of AMPK, and engagement of the SIRT1-mediated PGC-1α/NRF-1/TFAM axis, which collectively promote mitochondrial biogenesis.[28,29] This metabolic reprogramming induces ferroptosis in triple-negative breast cancer (TNBC) by inhibiting stearoyl-CoA desaturase-1 (SCD1) through salidroside, leading to a 73% reduction in oleic acid synthesis, and by activating nuclear receptor coactivator 4 (NCOA4)-mediated ferritinophagy, resulting in a 3.1-fold increase in lipid peroxidation.[27] Notably, the induction of ferroptosis significantly enhances sensitivity to oxaliplatin by 30% through the inhibition of the SLC7A11/GPX4 pathway, demonstrating substantial chemosynergistic effects.[27]

In addition to its role in chemosensitization, the SLC7A11/GPX4 axis serves as a pivotal component of the ferroptotic defense network. SLC7A11, also referred to as xCT, acts as the light chain subunit of system Xc^-, a cystine-glutamate antiporter responsible for importing cystine in exchange for intracellular glutamate. Once imported, cystine is reduced to cysteine, a rate-limiting precursor for glutathione (GSH) synthesis. GPX4 subsequently employs GSH as a cofactor to reduce phospholipid hydroperoxides, thereby averting lethal lipid peroxidation and ferroptosis. Salidroside disrupts this antioxidant defense by inhibiting SLC7A11/GPX4 signaling, resulting in the accumulation of lipid reactive oxygen species (ROS) and the induction of ferroptotic cell death. This mechanism is particularly pertinent in triple-negative breast cancer (TNBC), which frequently exhibits increased system Xc^- activity and GSH biosynthesis as an adaptive resistance strategy against oxidative stress. Recent studies have independently corroborated that pharmacological inhibition of SLC7A11 sensitizes TNBC cells to ferroptosis inducers, underscoring the therapeutic potential of targeting this axis.[27,30]

It is important to note that the quantitative data on SCD1 inhibition (73% reduction in oleic acid synthesis) and NCOA4-mediated ferritinophagy (3.1-fold increase in lipid peroxidation) are primarily derived from a single research group and require independent validation. The precise molecular interaction between salidroside and SLC7A11/GPX4, whether it is direct or indirect, has yet to be comprehensively elucidated. This represents a significant avenue for future mechanistic research.[27,30]

The principal obstacle in translation is that the effective in vitro concentration (≥100 μM) significantly surpasses the pharmacologically achievable levels in humans.[30] This issue can be mitigated through the utilization of nanodelivery systems, which enhance intracellular drug accumulation within tumor cells.

Epigenetic Regulation and Immunomodulation of the Tumor Immune Microenvironment (TIME)

Salidroside modulates epigenetic dysregulation and remodels the immunosuppressive TIME to enhance the therapeutic efficacy against triple-negative breast cancer (TNBC). Specifically, in the context of epigenetic regulation, salidroside inhibits DNA methyltransferase 3B (DNMT3B) in MDA-MB-231 cells, leading to a reduction in BRCA1 promoter methylation. This results in a 5.1-fold increase in sensitivity to the poly (ADP-ribose) polymerase (PARP) inhibitor olaparib, representing a promising mechanism for overcoming resistance to PARP inhibitors in TNBC.[31] Salidroside inhibits the histone acetyltransferase PCAF, reducing H3K9 acetylation.[32] Though derived from non-breast cancer models, this finding offer mechanistic insights likely applicable to TNBC due to the conserved nature of the pathway. Recent studies have identified BPHL as a promoter of TNBC stemness through the resolution of R-loops.[33] However, the potential influence of salidroside on this pathway has yet to be elucidated.

In the context of TIME remodeling, salidroside exerts its effects by inhibiting STAT5 phosphorylation in regulatory T cells (Tregs) and facilitating the maturation of dendritic cells (DCs) within humanized TNBC models. This process results in a 1.8-fold increase in CD80/CD86 expression and enhances the efficacy of programmed cell death protein 1 (PD-1) inhibitors by 37%.[34] Additionally, salidroside influences macrophage polarization by decreasing NF-κB p65 expression, while liposomal salidroside activates the TLR4-NF-κB pathway, leading to an upregulation of co-stimulatory markers by 42–37% and a 1.78-fold improvement in antigen presentation.[35] In preclinical models, salidroside promotes a 2.9/2.5-fold increase in $CD8^+/CD4^+$ T cell infiltration, reduces $FOXP3^+$ Tregs by 43.5%, and achieves a tumor inhibition rate of 64.9% ± 5.1%.[36] While this finding is derived from model not specific to breast cancer or triple-negative breast cancer (TNBC), they offer mechanistic insights that are likely applicable to TNBC, considering the conserved nature of these pathways. Moreover, clinical validation is sparse; a randomized trial indicated only modest peripheral immune alterations without direct evidence of enhanced intratumoral immunity in breast cancer patients.[37,38] Salidroside enhances immune activity at concentrations up to 20 μM but may suppress T cell function at 50 μM or higher, with limited clinical evidence of its effects within tumors.[34] Nanocarriers targeting tumors can sustain optimal salidroside levels for immune activation in the tumor microenvironment, minimizing systemic side effects.

Pharmacological Effects of Salidroside in Breast Cancer

Leveraging its molecular mechanisms, salidroside demonstrates three principal pharmacological effects in triple-negative breast cancer (TNBC) that are well-suited for integration with nanodelivery systems: enhancement of chemotherapy sensitivity and reduction of toxicity, radiosensitization, and synergy with immunotherapy and endocrine therapy. These effects are substantiated by preclinical evidence and initial findings from clinical randomized controlled trials (RCTs). The incorporation of nanodelivery systems further augments these effects by overcoming pharmacokinetic limitations (Figure 3 and Table 1).

Chemotherapy Sensitization and Toxicity Mitigation

Salidroside had been shown to counteract chemotherapy resistance in triple-negative breast cancer (TNBC) by down-regulating drug efflux pumps and modulating pathways associated with resistance. Specifically, it decreased the half-maximal inhibitory concentration (IC_{50}) of cisplatin from 18.6 μM to 11.2 μM by reducing HIF1α -mediated P-glycoprotein (P-gp) expression by 45%.[47,48] Furthermore, it enhanced paclitaxel sensitivity by 78%, lowering the IC_{50} from 189 nM to 45 nM, through the suppression of the Wnt/β-catenin pathway and downregulation of ABCG2.[39] While derived from non-breast cancer models, these findings offer mechanistic insights likely applicable to TNBC due to the conserved nature of these pathways. Salidroside also induced iron depletion via inhibition of the SLC7A11/GPX4 pathway, enhancing oxaliplatin sensitivity and reducing the IC_{50} by 30%.[49] For anthracyclines, combining salidroside with epirubicin significantly enhances tumor cell apoptosis by 2.2-fold via caspase-3 activation.[44]

Concurrently, salidroside's antioxidant and anti-inflammatory properties help mitigate chemotherapy-induced toxicities. In a cohort of 60 breast cancer patients, a daily dose of 600 mg salidroside in combination with epirubicin preserved left ventricular function (ΔSR +0.19) and maintained stable serum reactive oxygen species (ROS) levels.[44]

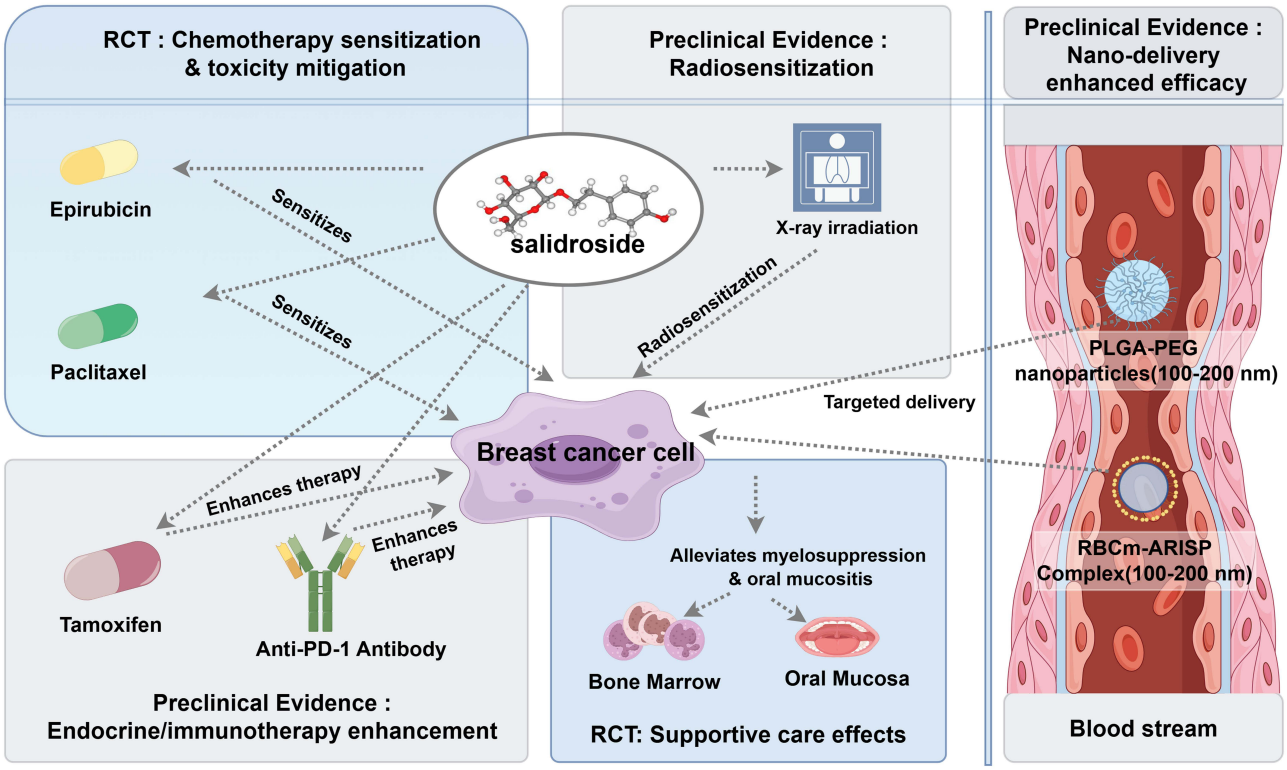


Figure 3 Pharmacological effects and nanodelivery optimization of salidroside in TNBC. Therapeutic Effects: Chemosensitization utilizing epirubicin and paclitaxel; Radiosensitization via X-ray irradiation; Immuno/endocrine synergy achieved through anti-PD-1 and tamoxifen. Nanodelivery Advantages: Improved targeting and pharmacokinetics facilitated by PLGA-PEG and RBCm-ARISP. Evidence Level: Blue denotes clinical evidence from randomized controlled trials (RCTs), while Gray indicates preclinical evidence. Abbreviations: PLGA-PEG refers to poly(lactic-co-glycolic acid)-polyethylene glycol; RBCm-ARISP denotes red blood cell membrane-camouflaged salidroside/indocyanine green nanovesicles.

Additionally, in a group of 42 patients, *Rhodiola rosea* injection was found to reduce serum cardiac troponin I (cTnI) levels and improve left ventricular ejection fraction (LVEF), thereby alleviating anthracycline-induced cardiotoxicity.[46] Salidroside also reduced the incidence of Grade III–IV myelosuppression by 57% and facilitates the recovery of white blood cell counts in patients undergoing chemotherapy.[49] Additionally, an RCT (130 patients with various tumors) indicated *Rhodiola rosea* extract accelerated white blood cell recovery and reduced oral ulcer size and number.[45]

Radiosensitization and Immuno/Endocrine Therapy Synergy

Salidroside enhances the radiosensitivity of triple-negative breast cancer (TNBC) by modulating hypoxia and DNA repair pathways. At a concentration of 40 μM, salidroside decreases HIF-1α levels by 58%, elevates tumor partial oxygen pressure (pO_2) by 2.3-fold, induces a 3.1-fold increase in reactive oxygen species (ROS) production, and inhibits nuclear factor erythroid 2-related factor 2 (Nrf2) nuclear translocation by 62%, resulting in a sensitizer enhancement ratio (SER) of 2.8.[41] In the context of immunotherapy, salidroside synergized with anti-programmed cell death protein 1 (anti-PD-1) antibodies to transform "cold" TNBC tumors into "hot" tumors, as evidenced by a 2.9-fold increase in $CD8^+$ T cell infiltration and a 43.5% reduction in regulatory T cells (Tregs), culminating in 64.9% tumor inhibition.[36] For endocrine therapy, nanocarriers co-loaded with salidroside and tamoxifen overcame tamoxifen resistance by inhibiting the PI3K-AKT signaling pathway, resulting in a 2.8-fold increase in the area under the curve (AUC) and a 53% improvement in tumor inhibition compared to free tamoxifen.[42]

Nanodelivery Strategies for Salidroside in TNBC Therapy

Advanced nanodelivery systems constitute a fundamental strategy to address the challenges of salidroside's limited bioavailability, short half-life, and inadequate targeting capability. In this study, we conduct a systematic evaluation of

Table 1 Core Molecular Mechanisms and Pharmacological Effects of Salidroside in Breast Cancer

Category	Model System	Key Targets/Pathways	Key Effect	Evidence Type	Ref.
Direct evidence from TNBC models					
Molecular Mechanism	MDA-MB-231 (TNBC)	p21/p27 upregulation; CDK4-cyclin D1 inhibition	65% G1 phase arrest	Preclinical	[13]
	MDA-MB-231 (TNBC)	Caspase-9/Bcl-2 family; mitochondrial apoptosis	3.1-fold increase in Bax/Bcl-2 ratio	Preclinical	[13]
	TNBC xenograft	SCD1 inhibition; NCOA4-mediated ferritinophagy	3.1-fold increase in lipid ROS	Preclinical	[27]
	4T1 metastasis model	Twist1/Zeb1 downregulation; restoration of E-cadherin	Lung metastatic nodules ↓86%	Moderate	[19]
	MDA-MB-231 (TNBC)	DNMT3B inhibition; BRCA1 demethylation	5.1-fold increase in olaparib sensitivity	Preclinical	[31]
	TNBC humanized PDX	Treg p-STAT5 inhibition; DC maturation	37% increase in PD-1 inhibitor efficacy	Preclinical	[34]
Pharmacological Effect	Paclitaxel-resistant TNBC	Salidroside + paclitaxel	78% reduction in paclitaxel IC_{50}	Preclinical	[39]
	TNBC humanized PDX model	Salidroside + anti-PD-1 antibody	$CD8^+$ T cell infiltration ↑2.9-fold; 64.9% tumor inhibition rate	Preclinical	[40]
	MDA-MB-231 (TNBC)	Salidroside + X-ray irradiation	SER=2.8; prolonged γH2AX foci retention	Preclinical	[41]
	4T1 tumor-bearing mice	Sal-Tam PLGA-PEG NPs	53% increase in tumor volume inhibition vs. free Tam	Preclinical	[42]
	4T1 lung metastasis model	RBCm-ARISP (Sal/ICG)	78% reduction in lung metastatic nodules	Preclinical	[43]
Evidence from other breast cancer subtypes (for context)					
Molecular Mechanism	MCF-7 (Luminal A)	PI3K-AKT-mTOR inhibition	58% proliferation reduction	Preclinical	[14]
	MCF-7 nude mouse model	Bcl-2 downregulation; Activation of caspase-3/p53	Apoptosis index ↑2.2-fold	Moderate	[14]
Pharmacological Effect	60 breast cancer patients (mix of subtypes)	Salidroside (600 mg/day) + epirubicin	Preserved left ventricular function; stabilized ROS	Clinical (RCT)	[44]
	130 patients (mixed tumors)	*Rhodiola algida* extract (salidroside-rich) + chemotherapy	Faster WBC recovery; reduced oral ulcer size/number	Clinical	[45]
	42 patients (breast cancer)	Chemotherapy + *Rhodiola rosea* injection (1 month)	Reduced serum cTnI; improved LVEF	Clinical	[46]

three types of salidroside-based nanoplatforms that exhibit significant translational potential for the treatment of triple-negative breast cancer (TNBC). Our analysis emphasizes their design principles, key performance metrics, and therapeutic efficacy, as detailed in Table 1.

Polymeric Nanoparticles: Poly(Lactic-Co-Glycolic Acid)-Polyethylene Glycol (PLGA-PEG)

PLGA-PEG polymeric nanoparticles represent the most advanced nanodelivery system for salidroside, utilizing FDA-approved materials that ensure excellent biocompatibility. Employing an optimized emulsion-solvent evaporation method, PLGA-PEG-PLGA (with a lactic acid to glycolic acid ratio of 3:1 and a molecular weight of 15 kDa) successfully co-encapsulates salidroside and tamoxifen. This results in nanoparticles with an average diameter of 275.3 ± 44.0 nm,[42,50,51] encapsulation efficiencies of 32.63% for salidroside and 49.18% for tamoxifen, and a cumulative release of 82.3% over a 72-hour period.[52] This delivery platform significantly extends the half-life of salidroside from 2.3 hours to 17.2 hours,[10] enhances the area under the curve (AUC), and reduces the IC_{50} of tamoxifen by 1.7-fold through the enhanced permeability and retention (EPR) effect and targeted tumor accumulation.[42] It demonstrates substantial efficacy in tamoxifen-resistant triple-negative breast cancer (TNBC) models, achieving a 53% greater inhibition of tumor volume compared to free tamoxifen. The system's translational potential relies on the safety of FDA-approved materials like PLGA and PEG,[53–55] but clinical translation is hindered by data gaps, such as the need for comprehensive in vivo safety assessments and manufacturing validation.

Lipid-Polymer Hybrid Nanoparticles (LPNPs)

LPNPs integrate the structural stability of polymeric cores with the biocompatibility of lipid shells, facilitating chemo-photothermal synergistic therapy for triple-negative breast cancer (TNBC). These nanoparticles are synthesized through the co-assembly of poly(lactic-co-glycolic acid)-polyethylene glycol/polypropylene glycol-polyethylene glycol (PLGA-PEG/PPG-PEG) with lecithin and cholesterol, resulting in a core-shell architecture capable of co-loading chemotherapeutic agents and photosensitizers. A notable example included cetuximab-targeted LPNPs, with an average size of 99.88 ± 2.51 nm, a polydispersity index (PDI) of 0.15 ± 0.03, and a zeta potential of −29.17 ± 3.09 mV, which encapsulated irinotecan (CPT-11) with an efficiency of 51.72% and indocyanine green (ICG) at 65.13%.[56] These nanoparticles exhibited dual-responsive release triggered by pH and near-infrared (NIR) light; NIR irradiation significantly accelerates drug release, achieving 59.29% irinotecan release within 24 hours, and enhances synergistic chemo-photothermal effects.[56] Moreover, surface modification using folate[57] or cetuximab[56] enhanced the specificity for cancer cells, especially in those overexpressing epidermal growth factor receptor (EGFR) antibodies or folate receptors, such as SW480 and MCF-7 cells. This modification increased specificity towards TNBC cells. Additionally, the enhanced permeability and retention (EPR) effect facilitated passive tumor targeting, thereby mitigating systemic toxicity.[56]

Biomimetic Nanocarriers: Red Blood Cell Membrane-Camouflaged Nanocarriers (RBCm-ARISP)

The RBCm-ARISP biomimetic nanocarriers proficiently incorporate mechanisms for immune evasion, active targeting of hypoxic environments, and controlled drug release. These features result in improved pharmacokinetics and notable anti-metastatic efficacy relative to traditional nanocarriers, thereby addressing the challenges associated with the limited in vivo circulation and insufficient accumulation of salidroside in hypoxic tumors. These nanocarriers encapsulate salidroside and indocyanine green (ICG) within poly(lactic-co-glycolic acid) (PLGA) cores, are camouflaged with rat red blood cell membranes achieving a coating efficiency of 92.3%, and are further modified with low-density lipoprotein receptor (LDLR) ligands to specifically target hypoxic triple-negative breast cancer (TNBC).[43] The nanoparticles exhibited a mean size of 180 ± 15 nm, a zeta potential of −18.5 ± 3.2 mV, and demonstrated a 78% release of salidroside over a 72-hour period, with accelerated release at pH 6.5, simulating the tumor microenvironment.[43] The RBC membrane coating significantly reduces macrophage uptake by 76% and extends the circulation half-life to 28.6 hours, compared to 4.2 hours for non-coated nanovesicles, thereby enhancing tumor targeting by a factor of 6.3. In 4T1 TNBC models, these nanocarriers reduce lung metastases by 78%, compared to 69% with free salidroside, demonstrating superior anti-metastatic efficacy. In addition to its therapeutic efficacy, the indocyanine green (ICG) component facilitates real-time near-infrared fluorescence imaging, which permits non-invasive monitoring of nanoparticle biodistribution and tumor accumulation. This theranostic capability establishes a feedback loop for optimizing dosing regimens and assessing treatment response, thereby offering a significant advantage over traditional nanotherapeutics.[43]

Despite demonstrating promising efficacy in preclinical studies, these nanoplatforms encounter several common challenges in translation to clinical application: (1) Scalable manufacturing: the intricate preparation processes, such as red blood cell membrane coating, result in batch inconsistencies and variable encapsulation efficiency.[58–60] (2) Long-term safety: there is a lack of sufficient data regarding in vivo biodegradation, tissue accumulation, and immunogenicity.[58] (3) Targeting specificity: the ligands currently in use, such as LDLR and folate, do not possess specificity for triple-negative breast cancer (TNBC), necessitating optimization with anti-EGFR/HER2 antibodies.[56,59]

Translational Challenges and Future Directions

Salidroside's accumulation in *Rhodiola rosea* affects DNA methylation based on altitude (38.18% at 2594 meters vs. 25.00% at 763 meters).[61] However, the link between altitude-dependent methylation in Rhodiola and salidroside accumulation is indirect and unproven in breast cancer models.

Salidroside demonstrates significant anticancer potential in preclinical breast cancer models; however, the transition of salidroside from preclinical success to clinical use in TNBC faces three main obstacles: The absence of validated

predictive biomarkers presents a significant hurdle. Although salidroside demonstrates subtype-specific effects, clinically actionable thresholds for potential biomarkers such as BRCA1 methylation, p-STAT3, and HIF-1α are yet to be established, and there is a lack of composite signatures for synergistic therapy.[17,31,62] Machine learning frameworks have facilitated the discovery of biomarkers in breast cancer,[63] and analogous methodologies could be employed to investigate salidroside-responsive subtypes of triple-negative breast cancer (TNBC). Additionally, the issue of non-standardized formulations is evident. The challenge of standardization is further complicated by the fact that the salidroside content in *Rhodiola rosea* is influenced by environmental factors, such as altitude. For instance, one study found a methylation level of 38.18% at an altitude of 2594 meters, compared to 25.00% at 763 meters.[61] While this botanical variation does not directly apply to human breast cancer, it highlights the essential requirement for stringent quality control in the sourcing of raw materials, which is a fundamental prerequisite for any clinical formulation. Native salidroside is characterized by poor solubility (<1 mg/mL), a short half-life (2.3 hours in rats), and low bioavailability (<12%), which hinder the attainment of effective therapeutic concentrations.[42,64] Current research often employs non-standardized Rhodiola extracts with varying salidroside content (5–30%), resulting in inconsistent experimental outcomes.[45] Furthermore, there is insufficient clinical evidence to support its efficacy. Most available data are derived from simplistic cell lines and xenografts that do not adequately replicate the clinical heterogeneity of triple-negative breast cancer (TNBC). Preliminary clinical data suggest only a potential for toxicity mitigation, without robust evidence of direct antitumor efficacy.

Consequently, this study suggests a three-phase translational roadmap for salidroside-based nanomedicines (Figure 4), following a framework of formulation standardization → biomarker-driven trials → clinical therapy positioning.

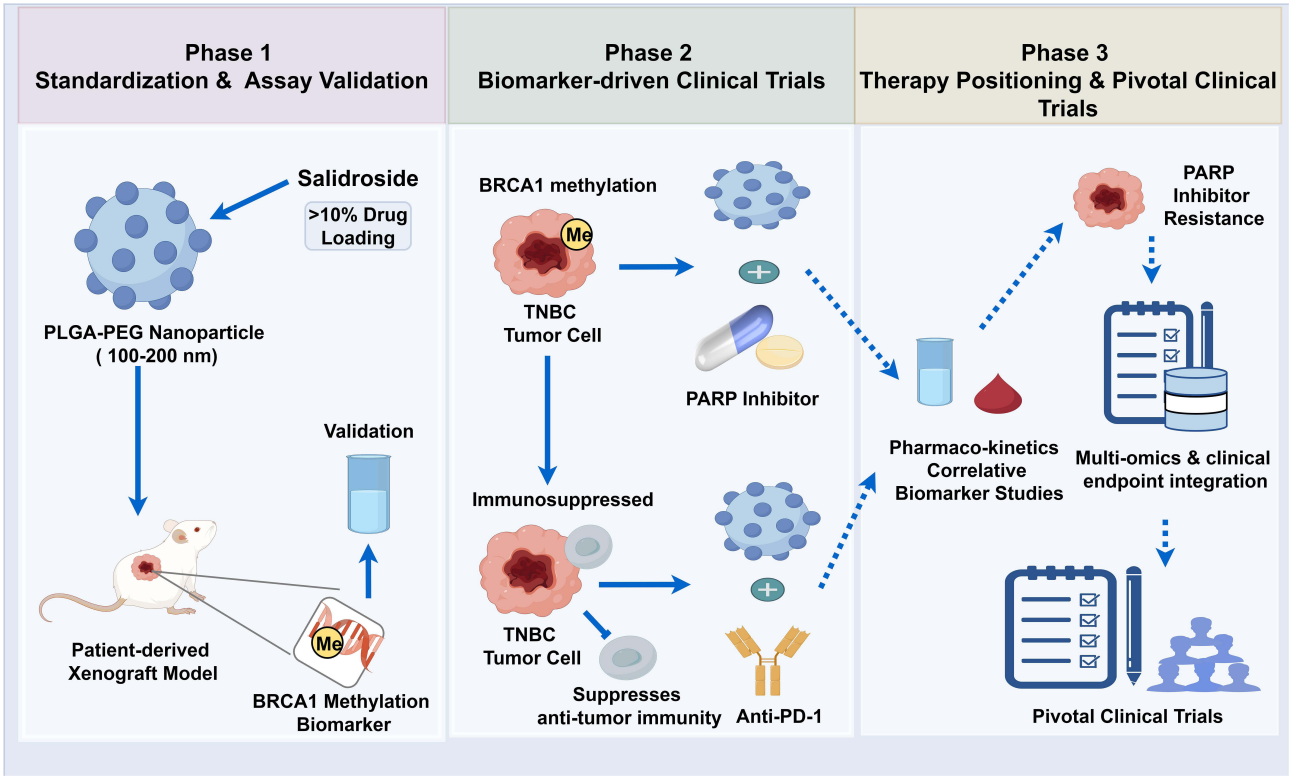


Figure 4 Three-phase translational roadmap for salidroside-based nanomedicines in TNBC. This schematic delineates a sequential clinical development strategy for salidroside-loaded nanomedicines in TNBC, with BRCA1 methylation serving as the central predictive biomarker. The yellow circle labeled "Me" represents the BRCA1 methylation biomarker, while the blue circles marked with a plus sign (+) signify combination treatment regimens, specifically nanoparticles in conjunction with PARP inhibitors or anti-PD-1 therapies. All arrows are standardized: solid arrows indicate direct, validated relationships; dashed arrows represent indirect or data-flow relationships; and T-shaped bars (—|) signify inhibition. Phase 1 (Preclinical Standardization and Validation): involves the formulation of PLGA-PEG nanoparticles with over 10% drug loading and a size range of 100–200 nm, validation using PDX models, and the identification of BRCA1 methylation as a biomarker. Phase 2 (Biomarker-Driven Adaptive Clinical Trials): focuses on BRCA1-driven adaptive trials that combine PARP inhibitors with anti-PD-1 therapy to address immunosuppressive TNBC. Phase 3 (Pivotal Trials and Clinical Positioning): encompasses pivotal trials that integrate pharmacokinetics/pharmacodynamics (PK/PD), correlative biomarkers, and multi-omics approaches to overcome resistance to PARP inhibitors.

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Three-Phase Translational Roadmap for Salidroside-Based Nanomedicines.

Phase 1 (Preclinical Standardization and Validation): This phase involves the development of standardized salidroside nanodelivery formulations, ensuring a drug loading efficiency greater than 10%.[42,43] Concurrently, biomarker assays, specifically BRCA1 methylation and HIF-1α, would be validated using patient-derived xenograft (PDX) models that accurately represent the heterogeneity of TNBC.

Phase 2 (Biomarker-Driven Adaptive Clinical Trials): This phase could implement basket trials to assess the efficacy of salidroside nanomedicines in biomarker- defined subsets of TNBC, such as BRCA1-methylated TNBC resistant to PARP inhibitors[31] and immunosuppressed TNBC with elevated p-STAT3 levels.[3,65] The trials will incorporate pharmacokinetic monitoring and correlative biomarker studies.

Similarly, computational models that incorporate various cell death modalities have been developed for ovarian cancer.[66] Adapting these models for TNBC could facilitate the rational design of combination treatment regimens.

Phase 3 (Pivotal Trials and Clinical Positioning): Based on data from early-phase studies, pivotal trials will be designed to establish the role of salidroside nanomedicines in overcoming resistance to PARP and PD-1 inhibitors in TNBC.[67,68] This phase will also integrate multi-omics data to optimize personalized therapeutic strategies.

Conclusions

Salidroside emerges as a promising and versatile molecular regulator for triple-negative breast cancer (TNBC), demonstrating antitumor efficacy through its modulation of cellular proliferation, metabolic pathways, metastasis, epigenetic mechanisms, and the immune microenvironment. Importantly, its unique dual role in maintaining redox homeostasis-promoting ferroptosis in cancer cells while protecting normal tissues from oxidative damage-may reduce off-target toxicity. This potential advantage warrants further clinical investigation. However, the primary obstacle to its translational application lies in the misalignment between its polypharmacological actions and the prevailing single-target validation frameworks. This challenge is further compounded by suboptimal pharmacokinetic properties and the lack of standardized formulations.

Integrated nanomedicine represents a promising strategy to current challenges, as advanced nanoplatforms such as PLGA-PEG, LPNPs, and RBCm-ARISP significantly enhance the bioavailability and targeted delivery of salidroside. These platforms also facilitate real-time in vivo monitoring of its mechanistic effects, including hypoxia modulation and immune remodeling, thereby validating its polypharmacological potential in clinically relevant settings. In future research, salidroside-based precision nanomedicines, guided by predictive biomarkers like BRCA1 methylation and HIF-1α, in conjunction with standardized formulations, could offer promising therapeutic strategies. These approaches merit further clinical investigation, particularly for biomarker-defined subsets of triple-negative breast cancer (TNBC) that demonstrate resistance to PARP and PD-1 inhibitors. Furthermore, the translational framework delineated in this review provides a generalizable model for the clinical advancement of other pleiotropic natural products, facilitating the integration of phytochemistry with systems-based precision oncology. This methodology has the potential to address unmet therapeutic needs in breast cancer treatment and to advance the development of natural product-based nanomedicine within the oncology domain.

Abbreviations

TNBC, triple-negative breast cancer; PI3K, phosphatidylinositol 3-kinase; AKT, protein kinase B; HIF-1α, hypoxia-inducible factor 1α; SCD1, stearoyl-CoA desaturase 1; NCOA4, nuclear receptor coactivator 4; VEGF, vascular endothelial growth factor; STAT3, signal transducer and activator of transcription 3; MMP2, matrix metalloproteinase 2; ECM, extracellular matrix; EMT, epithelial-mesenchymal transition; Treg, regulatory T cell; DC, dendritic cell; DNMT3B, DNA methyltransferase 3B; PDX, patient-derived xenograft; RCT, randomized controlled trial; PARP, poly (ADP-ribose) polymerase; RBCm, red blood cell membrane; ICG, indocyanine green; PD-1, programmed cell death protein 1; ROS, reactive oxygen species; Wnt/β-catenin, Wingless/Integrated-β-catenin; ABCG2, ATP-binding cassette subfamily G member 2; IC_{50}, half-maximal inhibitory concentration; Nrf2, nuclear factor erythroid 2-related factor 2; SER, sensitizer enhancement ratio; PLGA, poly(lactic-co-glycolic acid); PEG, polyethylene glycol; AUC, area under the curve; WBC, white blood cell; cTnI, cardiac troponin I; LVEF, left ventricular ejection fraction; MTD, maximum

tolerated dose; PLGA-PEG, poly(lactic-co-glycolic acid)-polyethylene glycol; RBCm-ARISP, red blood cell membrane-camouflaged salidroside/ICG co-loaded.

Data Sharing Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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