Tanshinone IIA in breast cancer: Molecular mechanisms, structural optimization and translational challenges (Review)

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Abstract. Tanshinone IIA (Tan IIA), a lipophilic abietane-type diterpenoid isolated from *Salvia miltiorrhiza*, exhibits a set of mechanistic features that distinguish it from numerous other natural products. Recent studies in breast cancer models have revealed that Tan IIA not only induces apoptosis but also targets several cancer-relevant vulnerabilities, including the stabilization of G-quadruplex (G4) DNA structures, the disruption of mitochondrial oxidative phosphorylation and the inhibition of estrogen receptor α/human epidermal growth factor receptor 2-driven signaling. Tan IIA further modulates epigenetic regulators such as lysine demethylase 1A and promotes ferroptosis by disturbing redox homeostasis. These mechanisms support the multifaceted anticancer potential of Tan IIA; however, their relative contribution appears to be highly dependent on concentration, formulation, derivative structure and breast cancer subtype. Nevertheless, Tan IIA suffers from poor aqueous solubility, rapid metabolic conversion and low oral bioavailability, reported to be ~2-6% in rats, which hinder its translational prospects. Recent efforts involving structural optimization and nanoscale delivery systems have partially addressed these limitations. Overall, this review integrates current mechanistic and pharmacological evidence and highlights both the therapeutic promise and the critical barriers that must be overcome for the successful development of Tan IIA-based interventions in breast cancer. High-micromolar *in vitro* findings, particularly those related to reactive oxygen species-dependent cytotoxicity, ferroptosis or G4 stabilization, should be interpreted cautiously unless supported by pharmacokinetic, tumor-exposure and *in vivo* target-engagement data.

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Abbreviations: ABC, ATP-binding cassette; ADC, antibody-drug conjugate; ADME, absorption, distribution, metabolism and excretion; AKT, protein kinase B; AMPK, AMP-activated protein kinase; ATA, acetyltanshinone IIA; BCSCs, breast cancer stem cells; Bcl-2, B-cell lymphoma 2; Bcl-xL, B-cell lymphoma-extra large; BCRP, breast cancer resistance protein; BrdU, 5-bromo-2'-deoxyuridine; CD44+/CD24-, cluster of differentiation 44 positive/cluster of differentiation 24 low or negative; CHOP, C/EBP homologous protein; CM, celastrol; Dox, doxorubicin; EGFR, epidermal growth factor receptor; EMT, epithelial-mesenchymal transition; ERα, estrogen receptor α; ERK, extracellular signal-regulated kinase; ESR1, estrogen receptor 1; FES, fluoroestradiol; G4, G-quadruplex; GADD153, growth arrest and DNA damage-inducible protein 153; GPER, G protein-coupled estrogen receptor; GREB1, growth regulating estrogen receptor binding 1; HER2, human epidermal growth factor receptor 2; HIF-1α, hypoxia-inducible factor 1α; HTA, hydroquinone tanshinone IIA; IC_{50}, half-maximal inhibitory concentration; IL-6, interleukin 6; JNK, c-Jun N-terminal kinase; KDM1A, lysine demethylase 1A; MAPK, mitogen-activated protein kinase; MRP1, multidrug resistance-associated protein 1; MSN, mesoporous silica nanoparticles; MYC, MYC proto-oncogene; NF-κB, nuclear factor κB; PARP, poly(ADP-ribose) polymerase; PD, pharmacodynamic; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PET/CT, positron emission tomography/computed tomography; P-gp, P-glycoprotein; PI3K, phosphoinositide 3-kinase; PIAS4, protein inhibitor of activated STAT 4; PK, pharmacokinetic; PTEN, phosphatase and tensin homolog; ROS, reactive oxygen species; SAR, structure-activity relationship; SLC7A11, solute carrier family 7 member 11; STAT3, signal transducer and activator of transcription 3; STS, sodium tanshinone IIA sulfonate; SUMOylation, small ubiquitin-like modifier conjugation; TA01-TA12, imidazole-substituted tanshinone IIA derivatives; Tan IIA, tanshinone IIA; Tan-Dox-MSN, tanshinone IIA-doxorubicin-loaded mesoporous silica nanoparticles; Tan-NH_2, amino-modified tanshinone IIA; Taxol, paclitaxel; TNBC, triple-negative breast cancer; TWIST, TWIST family basic helix-loop-helix transcription factor; VEGF, vascular endothelial growth factor

Key words: tanshinone IIA, breast cancer, structure-activity relationship, molecular mechanisms, drug delivery

1. Introduction

Breast cancer remains the most commonly diagnosed cancer and the leading cause of cancer-related mortality among women worldwide. According to GLOBOCAN 2022 estimates, ~2.3 million new female breast cancer cases and 666,000-670,000 deaths occurred globally in 2022, accounting for ~11.6% of all new cancer cases and 6.9% of all cancer deaths (1). Despite substantial advances in surgery, radiotherapy, chemotherapy, endocrine therapy and targeted agents, therapeutic resistance, recurrence and treatment-related toxicities continue to limit long-term clinical outcomes (2-4). These challenges underscore the need for mechanistically rational and clinically translatable therapeutic strategies that improve efficacy without adding unacceptable systemic toxicity (5,6).

Natural products have historically contributed to anticancer drug discovery; however, their role in contemporary drug development has become more limited due to challenges such as structural complexity, low drug-likeness and difficulties in optimization and formulation (7). Nevertheless, bioactive phytochemicals remain valuable as mechanistic probes or scaffolds for structural modification, particularly when they exhibit unique biochemical properties not easily replicated by synthetic molecules. Therefore, natural products should be evaluated not only for biological activity but also for pharmacokinetic (PK) feasibility, target selectivity and safety margins.

Salvia miltiorrhiza (Danshen), a widely used traditional medicinal herb, contains a series of lipophilic diterpenoid quinones known as tanshinones, among which tanshinone IIA (Tan IIA) is the major and most extensively studied constituent (8-11). Beyond its well-recognized cardiovascular and anti-inflammatory activities (12-15), Tan IIA has attracted attention in oncology due to its ability to interfere with cancer-associated vulnerabilities, including mitochondrial dysfunction, epigenetic regulation and oncogenic signaling networks (16,17). However, native Tan IIA has poor aqueous solubility, extensive first-pass metabolism, low oral bioavailability of reportedly ~2-6% in rats and a short plasma half-life after intravenous administration (18). These limitations raise a critical question as to whether the concentrations required for many *in vitro* anticancer mechanisms can be achieved and sustained *in vivo*.

Studies have expanded the mechanistic understanding of Tan IIA in breast cancer, demonstrating effects on apoptosis, proliferation, angiogenesis, redox homeostasis and hormone- and growth factor-driven pathways (19,20). At the same time, substantial efforts have been devoted to improving its PK profile through structural modification and advanced delivery technologies, including acetyltanshinone derivatives (21), nanoscale formulations (22) and other rationally designed analogues (23). Nevertheless, most of these findings remain preclinical and are derived from heterogeneous cell-line systems, exposure durations and formulations, which limits direct comparison across mechanisms.

The present review focuses specifically on Tan IIA research in breast cancer and explicitly links mechanistic insights to translational constraints. Recent studies are incorporated and the mechanistic evidence is systematically organized according to key cancer vulnerabilities and clinically relevant pathway contexts, including hormone- and growth factor-driven signaling. Particular emphasis is placed on integrating structure-activity relationships with mechanistic readouts to clarify how chemical modifications reshape antitumor efficacy. In parallel, formulation and delivery strategies are critically assessed in light of current progress and the practical barriers to clinical development, including PK limitations and translational feasibility. By aligning mechanistic claims with druggability realities, this review delineates what is supported by existing *in vitro* and *in vivo* evidence, what remains uncertain, and what will be required to advance Tan IIA-derived strategies toward credible and clinically meaningful applications in breast cancer therapy.

2. Chemical and pharmacological basis of Tan IIA

Chemically, Tan IIA is a highly lipophilic diterpene quinone derived from *Salvia miltiorrhiza*. It is essentially insoluble in water and dissolves only in organic solvents (11,24). These properties contribute to its low systemic availability (oral bioavailability, ~2-6% in rats). Tan IIA also has a short plasma half-life (~0.3 h in rats after i.v. administration) (18). Together, its high first-pass metabolism and poor absorption mean that native Tan IIA requires special formulation to achieve therapeutic levels. Consequently, extensive efforts have focused on developing delivery systems (e.g., nanoparticles, liposomes) and derivatives to overcome these PK challenges. These PK features have direct implications for interpreting mechanistic studies. Concentrations that are readily achieved *in vitro* may not reflect tumor exposures attainable *in vivo*, particularly for native Tan IIA without formulation support. Therefore, mechanisms reported at high micromolar concentrations should not be considered equally translatable unless accompanied by PK/pharmacodynamic (PD) evidence, tumor accumulation data or *in vivo* target-engagement validation.

Beyond cancer, Tan IIA has cardiovascular, anti-inflammatory and metabolic activities (24-33). These pleiotropic effects may be beneficial in some contexts but may also complicate anticancer development, because systemic exposure could affect non-tumor tissues and interact with cardiovascular or inflammatory homeostasis (34,35). Therefore, the present review focuses on breast cancer-related evidence while also considering PK feasibility and potential safety liabilities.

3. Mechanisms of Tan IIA in breast cancer

In breast cancer models, Tan IIA and its derivatives have been associated with several mechanistic effects, including estrogen receptor α (ERα) modulation, chemosensitization, apoptosis, breast cancer stem cell (BCSC) inhibition, ferroptosis and G-quadruplex (G4) stabilization (Table SI). However, these effects should not be interpreted as parallel mechanisms occurring with equal relevance. For example, ERα-related effects have been reported at low micromolar concentrations, whereas ferroptosis and chemosensitization studies often employed different concentration ranges and experimental contexts (Table SI), highlighting the heterogeneity of the available evidence.

The mechanisms summarized below differ in pharmacological plausibility. ERα degradation has been mainly

characterized in ER-positive models treated with acetyltanshinone IIA (ATA) or its active metabolite hydroquinone Tan IIA (HTA) at low micromolar concentrations. BCSC inhibition and chemosensitization have been reported in defined resistant or stem-like cell populations over relatively broad but model-specific concentration ranges. By contrast, reactive oxygen species (ROS)-dependent apoptosis, ferroptosis and G4 stabilization are often observed at higher concentrations or with structurally optimized derivatives. Accordingly, these mechanisms should be viewed as context-dependent rather than interchangeable. In particular, high-micromolar *in vitro* effects require cautious interpretation in light of the poor bioavailability and short systemic half-life of native Tan IIA.

Modulation of ER signaling in ER-positive and ER-context-dependent models. ER signaling plays a pivotal role in the proliferation and survival of ER^+ breast cancers (36). In specific ER^+ cell-line models, ATA showed stronger antiproliferative activity than tamoxifen under the tested experimental conditions (21).

In vitro studies demonstrate that ATA inhibits ER^+ breast cancer cell growth in a dose-dependent manner over a concentration range of 1.56-25 μM, with selective suppression of ER^+ cells observable at ~3 μM. The half-maximal inhibitory concentration (IC_{50}) of ATA against ER^+ breast cancer cell lines is ~1.4-1.5 μM, markedly lower than that of tamoxifen, while 6 μM has been established as a standard effective concentration for downstream mechanistic investigations. Mechanistically, the active ATA metabolite HTA directly binds to ERα and promotes its nuclear degradation via a ubiquitin-proteasome-dependent pathway, while simultaneously downregulating the transcription of estrogen receptor 1 (ESR1), the gene encoding ERα. This dual mechanism distinguishes ATA from classical selective ER degraders such as fulvestrant. In addition, ATA suppresses the transcription of ER-responsive genes, including growth regulating estrogen receptor binding 1, thereby effectively inhibiting ER-driven proliferation in breast cancer cells (21). Consistent with these findings, combination treatment with Tan IIA and fulvestrant produces synergistic antitumor effects in ER^+ breast cancer models. In ER^+ ZR-75-1 xenograft tumors, combined therapy significantly inhibited tumor growth and elicited earlier therapeutic responses compared with either agent alone. Importantly, ^{18}F-fluoroestradiol positron emission tomography/CT imaging enabled real-time monitoring of treatment response, with quantitative imaging signals closely correlating with intratumoral ERα expression, further validating the synergistic interaction between Tan IIA and fulvestrant *in vivo* (37). Thus, ERα degradation represents one of the more pharmacologically plausible and subtype-defined mechanisms, but it is primarily supported by ATA/HTA data in ER^+ models rather than by evidence that native Tan IIA produces identical ERα target coverage *in vivo*.

Tan IIA has also shown antiproliferative effects in ER^- models, suggesting that ER-independent mechanisms may contribute under certain experimental conditions. Both *in vitro* and *in vivo* studies demonstrate that Tan IIA exhibits greater antitumor efficacy than tamoxifen in ER^- models, potentially through downregulation of p53 and Bcl-2 expression and suppression of genes involved in cell cycle progression, proliferation, apoptosis and DNA synthesis (38). Tan IIA displays an IC_{50} value of ~0.25 μg/ml in both ER^+ and ER^- breast cancer cell lines, reflecting potent and relatively non-subtype-restricted antiproliferative activity. *In vitro*, Tan IIA inhibits cell growth in a dose-dependent manner over a concentration range of 0.0625-1.0 μg/ml, with 0.25 μg/ml commonly used for mechanistic studies. *In vivo*, subcutaneous administration of Tan IIA at 30 mg/kg significantly suppresses tumor growth and induces apoptosis, supporting its antitumor efficacy in animal models (38). Advances in nanomedicine have further expanded the therapeutic potential of Tan IIA by addressing its PK limitations and enhancing tumor targeting. Given that ER is overexpressed in various tumor cells, it has been explored as a target receptor for nanoparticle-based drug delivery. Molecular docking studies suggest that Tan IIA, acting as a phytoestrogen, possesses high ER-binding affinity and can be effectively incorporated into engineered nanocarriers. A modified derivative, Tan IIA-NH_2, demonstrates favorable biocompatibility, enhanced tumor-targeting capability, robust antitumor efficacy and anti-metastatic potential. Furthermore, mesoporous silica nanoparticles co-loaded with Tan IIA and doxorubicin (Dox) (Tan-Dox-MSN) exhibit uniform particle size distribution, good dispersion and high drug-loading capacity. Both *in vitro* and *in vivo* experiments show that Tan-Dox-MSN achieves superior tumor accumulation and antitumor effects while significantly reducing systemic toxicity to normal tissues. These findings highlight the potential of leveraging high-ER-affinity phytoestrogens such as Tan IIA to improve nanodelivery systems for breast cancer therapy (22). However, ER-mediated targeting strategies should be evaluated carefully because ER expression is not restricted to tumor tissues, and systemic ER modulation may affect endocrine and inflammatory homeostasis in normal tissues (Fig. 1).

Chemosensitization and reversal of drug resistance. Dox and paclitaxel (taxol) remain frontline chemotherapeutic agents for breast cancer; however, their long-term use often results in drug resistance and severe dose-dependent toxicities, including cardiotoxicity, myelosuppression and weight loss (39,40). Because BCSCs contribute to drug resistance and relapse (41), this section focuses on chemosensitization in resistant models, whereas BCSC-specific mechanisms are discussed separately below. Accumulating evidence demonstrates that Tan IIA markedly enhances the sensitivity of breast cancer cells, including both parental MCF-7 cells and drug-resistant sublines such as MCF-7/Dox, to Dox and taxol (42-47). These chemosensitizing effects involve multiple complementary mechanisms, including inhibition of drug efflux transporters, modulation of oncogenic signaling pathways and enhancement of the overall efficacy of combination chemotherapy.

Mechanistically, Tan IIA downregulates key ATP-binding cassette transporters, including P-glycoprotein, breast cancer resistance protein and multidrug resistance-associated protein 1, thereby increasing intracellular accumulation of Dox and effectively eliminating both drug-sensitive and drug-resistant breast cancer cells (42,46). In parallel, Tan IIA suppresses activation of the PTEN/AKT pathway and inhibits β-catenin nuclear translocation, further restoring chemosensitivity in resistant cells (42,43). Consistent with these observations, Li *et al* (42) reported that Tan IIA, at concentrations described

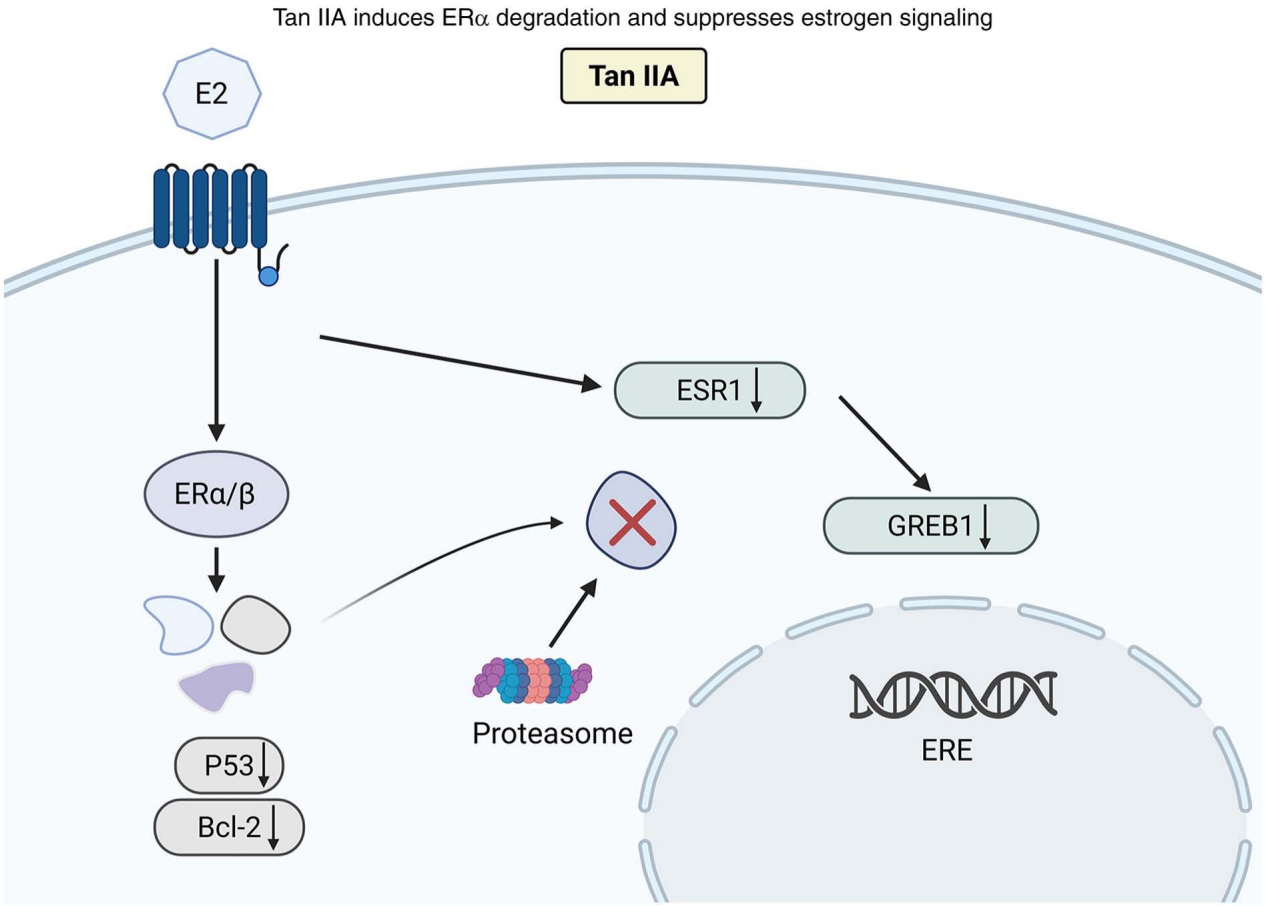

Figure 1. Tan IIA promotes ubiquitin-mediated proteasomal degradation of ERα and suppresses ESR1 transcription, thereby inhibiting the growth of ER$^+$ breast cancer cells. Tan IIA, Tanshinone IIA; ERα/β, estrogen receptor α/β; ESR1, estrogen receptor 1; GREB1, growth regulating estrogen receptor binding 1; E2, estradiol; P53, protein 53; Bcl-2, B-cell lymphoma 2; ERE, estrogen response element; ↑, increase; ↓, decrease.

as non-toxic in the tested cell models (≤20 μg/ml), significantly potentiated the cytotoxicity of Dox, particularly in resistant breast cancer cells, by enhancing intracellular drug accumulation. However, these concentrations remain relatively high from a translational PK perspective and therefore require *in vivo* exposure confirmation. Combination treatment markedly reduced the IC_{50} of Dox, resulting in an ~3.9-4.4-fold increase in chemosensitivity compared with Dox alone (42).

Tan IIA also enhances the efficacy of taxol in resistant breast cancer models. In taxol-resistant MCF-7 cells, Tan IIA suppresses the expression of the microtubule-associated protein Tau, a known mediator of taxol resistance, thereby potentiating taxol-induced cytotoxicity (44). Notably, Tan IIA itself exhibits stronger antiproliferative activity than taxol in this model, with IC_{50} values of 8.4 μM for Tan IIA vs. 23.7 μM for taxol. Combination treatment within concentration ranges of 1-20 μM (Tan IIA) and 5-100 μM (taxol) predominantly produced additive effects, indicating that Tau suppression may contribute to improved taxol responsiveness in this resistant model. These data support an additive interaction in this model rather than a universally synergistic effect (44).

Beyond tumor-specific chemosensitization, Tan IIA exerts dual regulatory effects on ERK1/2 signaling that contribute to both efficacy enhancement and toxicity mitigation. In breast cancer cells, Tan IIA suppresses ERK1/2 activation to promote apoptosis, whereas in cardiomyocytes, it activates ERK1/2 signaling, thereby alleviating Dox-induced cardiotoxicity (45). Another study further revealed that Tan IIA can reverse hypoxia-induced Dox resistance and suppress epithelial-mesenchymal transition (EMT). Under hypoxic conditions, breast cancer cells such as MCF-7 and HCC1937 exhibit reduced E-cadherin expression and elevated vimentin levels, consistent with EMT and acquired chemoresistance. Treatment with Tan IIA restores these markers toward basal levels, significantly reduces cell viability and proliferation, and likely mediates these effects through downregulation of hypoxia-inducible factor 1α and TWIST family basic helix-loop-helix transcription factor-dependent signaling pathways. Notably, under hypoxic conditions, Tan IIA at 10 μM effectively reverses resistance to Dox (0.2 μg/ml), restoring drug sensitivity in breast cancer cells (47). The opposite regulation of ERK1/2 in tumor cells and cardiomyocytes also illustrates the context-dependent pharmacology of Tan IIA and supports the need to evaluate tissue-specific responses rather than assuming uniform pathway inhibition.

Collectively, available preclinical evidence suggests that Tan IIA can enhance the activity of Dox and taxol in selected breast cancer models, particularly resistant cell populations (42-47). However, the magnitude and nature of the interaction vary across models, ranging from additive to synergistic effects, and require confirmation at pharmacologically achievable exposures (Fig. 2).

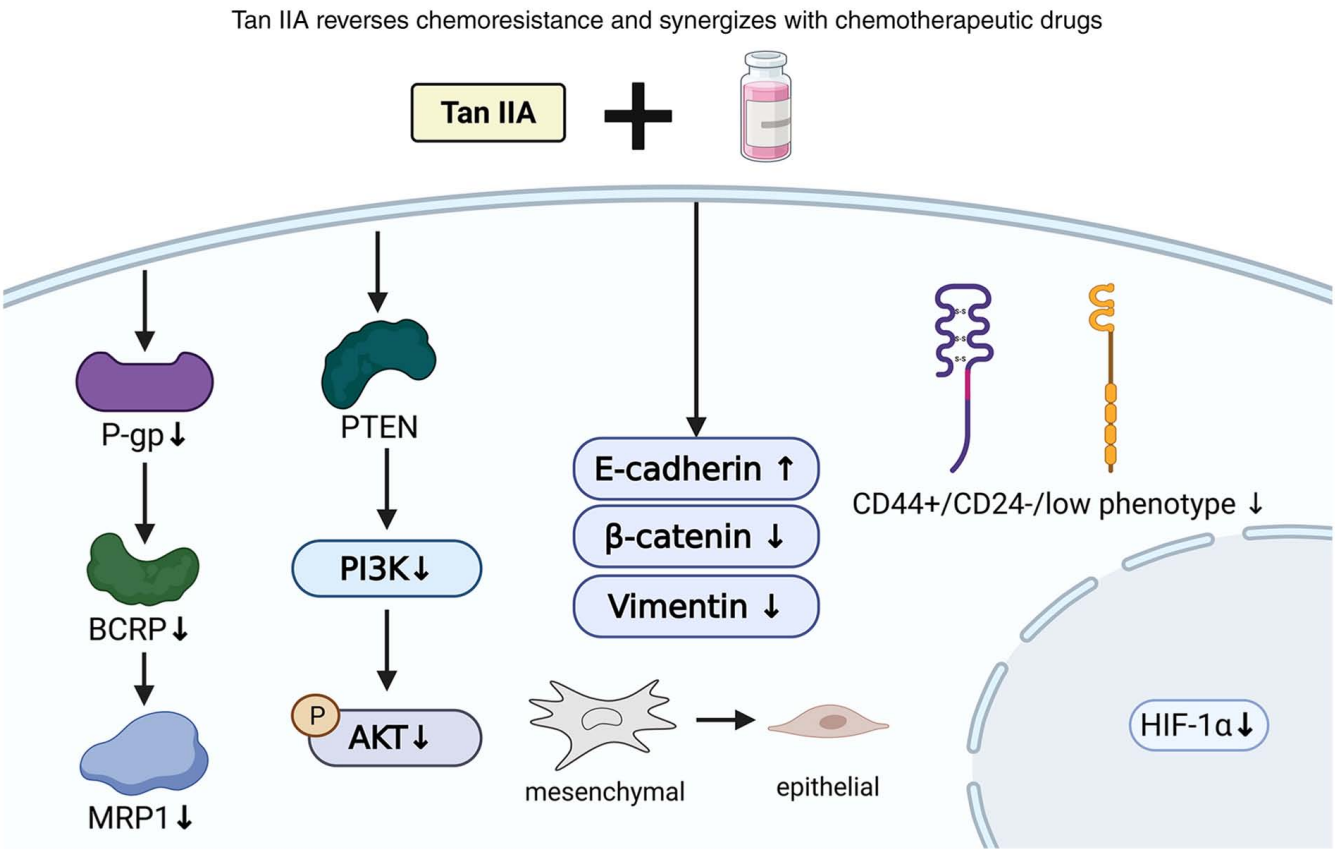

Figure 2. Tan IIA may attenuate multidrug resistance by inhibiting drug efflux pumps, suppressing survival signaling, reversing EMT and targeting BCSCs, thereby improving chemotherapy responses in selected models. Tan IIA, tanshinone IIA; AKT, protein kinase B; BCRP, breast cancer resistance protein; E-cadherin, epithelial cadherin; HIF-1α, hypoxia-inducible factor 1α; MRP1, multidrug resistance-associated protein 1; P-gp, P-glycoprotein; PI3K, phosphoinositide 3-kinase; PTEN, phosphatase and tensin homolog; ↑, increase; ↓, decrease.

Induction of apoptosis and cell cycle arrest. Apoptosis and cell-cycle arrest are best interpreted as convergent downstream phenotypes rather than a single uniform mechanism, because the effective concentrations and upstream triggers vary considerably among derivatives and cell lines. Aberrant proliferation and dysregulated apoptosis in breast cancer cells are major contributors to tumor progression and therapeutic resistance (48,49). Tan IIA and its derivatives exert antitumor effects predominantly through the induction of apoptosis and cell cycle arrest across multiple breast cancer subtypes. Among these compounds, 1-hydroxy-Tan IIA has been identified as one of the most active derivatives. These relatively high concentrations suggest that this derivative may be useful as a mechanistic probe, but its direct pharmacological relevance requires further optimization. In MCF-7 and MDA-MB-231 breast cancer cells, 1-hydroxy-Tan IIA promotes DNA fragmentation, upregulates the pro-apoptotic protein Bax, downregulates the anti-apoptotic protein Bcl-2 and induces poly(ADP-ribose) polymerase cleavage, thereby triggering apoptosis (19). Consistent with these mechanistic findings, tanshinone derivatives isolated from *Stachys parviflora* exhibit measurable *in vitro* antitumor activity, with 1-hydroxy-Tan IIA showing the strongest cytotoxicity, characterized by an IC_{50} of ~22 μg/ml over a concentration range of 2.5-100 μg/ml (19). In addition to mitochondrial apoptosis, Tan IIA can induce cell death through ER stress-mediated pathways. In human breast cancer BT-20 cells, Tan IIA inhibits cell proliferation in both dose- and time-dependent manners, significantly increases the proportion of sub-G1 cells and activates ER stress-related apoptotic signaling, including caspase-12, growth arrest and DNA damage-inducible protein 153/C/EBP homologous protein, phosphorylated c-Jun N-terminal kinase (p-JNK) and phosphorylated p38 MAPK. Concurrently, Tan IIA suppresses the expression of anti-apoptotic Bcl-xL and phosphorylated ERK, collectively indicating the involvement of ER stress and MAPK pathway modulation in apoptosis induction (50). Quantitatively, Tan IIA exhibits time-dependent cytotoxicity in BT-20 cells, with IC_{50} values of 3.3 μg/ml at 24 h, 1.87 μg/ml at 48 h and 0.67 μg/ml at 72 h, within an effective concentration range of 0.25-8 μg/ml (50). In TNBC MDA-MB-231 cells, Tan IIA similarly suppresses proliferation in a dose- and time-dependent manner, markedly increases the sub-G1 population and activates apoptotic signaling by upregulating Bax and downregulating Bcl-2 (20).

Additionally, Tan IIA inhibits breast cancer cell proliferation and migration through modulation of the G protein-coupled estrogen receptor (GPER)/EGFR/ERK/c-Fos/c-Jun pathway. Flow cytometry and Transwell assays demonstrate that Tan IIA induces apoptosis and suppresses migration in MDA-MB-231 cells, accompanied by reduced expression of c-Fos, c-Jun and cell cycle-associated proteins. These effects are partially reversed by GPER inhibitors, implicating GPER as a key mediator. *In vivo*, oral administration of Tan IIA significantly reduced xenograft tumor volume and weight, with concomitant

NF-κB downregulation and caspase-3 upregulation in tumor tissues (51). In MDA-MB-231 xenograft models, long-term oral treatment with Tan IIA (20 or 60 mg/kg, 90 days) inhibited tumor growth, decreased NF-κB p65 and increased caspase-3 expression, underscoring apoptosis activation as a central mechanism (52). In the 4T1 breast cancer model, Tan IIA showed antiproliferative and pro-apoptotic effects associated with changes in key molecules, including p53, NF-κB, AKT, MYC and BCL-2, as well as enrichment of the p53, PI3K/AKT, MAPK and mTOR pathways. Molecular docking further suggested possible interactions between Tan IIA and proteins such as p53, Bcl-2 and NF-κB; however, these docking results should be considered hypothesis-generating unless validated by biochemical binding or *in vivo* target-engagement assays (53).

To overcome its poor water solubility and bioavailability, imidazole groups were introduced to generate a series of derivatives (TA01-TA12), which significantly inhibited proliferation, migration and invasion of MDA-MB-231 cells, with TA12 showing the most potent activity. In zebrafish xenograft models, TA12 effectively blocked cancer cell metastasis, potentially through S-phase arrest, ROS generation and DNA damage induction (54). Further *in vitro* and *in vivo* experiments demonstrate that Tan IIA inhibits breast cancer cell proliferation in a dose- and time-dependent manner, markedly reduces colony formation and BrdU incorporation, and regulates a broad genetic network. Gene expression profiling revealed that Tan IIA upregulated 41 and downregulated 24 genes associated with cell cycle regulation, proliferation, apoptosis, signal transduction, transcriptional regulation and cell adhesion. In a nude mouse xenograft model of invasive ductal carcinoma, intraperitoneal administration of Tan IIA (30 mg/kg) reduced tumor volume by 44.91%, with concomitant caspase-3 upregulation, indicating that its antitumor effects are mediated by multi-gene network regulation and apoptosis signaling activation. These findings collectively support the broad-spectrum antitumor activity of Tan IIA in both ER-positive and ER-negative breast cancers (55) (Fig. 3).

Targeting BCSCs. BCSCs are critical drivers of drug resistance and tumor relapse, with inflammatory cytokines and associated signaling pathways playing key roles in their maintenance (56). The IL-6/STAT3/NF-κB axis is therefore discussed here as a BCSC-maintenance pathway, while its contribution to drug resistance is cross-referenced in the chemosensitization section. Tan IIA, owing to its combined anticancer and anti-inflammatory activities, has been shown to markedly inhibit BCSC proliferation and mammosphere formation. *In vitro*, Tan IIA treatment significantly reduced BCSC proliferation and sphere-forming capacity, accompanied by decreased proportions of $CD24^-/CD44^+$ and aldehyde dehydrogenase 1^+ subpopulations. Expression levels of inflammatory signaling proteins, including IL-6, STAT3, phosphorylated STAT3 (Tyr705), nuclear NF-κB p65 and cyclin D1, were also significantly suppressed. *In vivo*, Tan IIA administration inhibited tumor growth and reduced average tumor weight in xenograft models, confirming its capacity to effectively target and suppress BCSC-like populations (57). Quantitatively, Tan IIA exhibits stronger inhibitory activity against BCSCs than against parental breast cancer cells, with an IC_{50} of ~0.40 μg/ml for BCSCs compared with 0.65 μg/ml for bulk tumor cells, and an effective *in vitro* concentration range of 0.125-2.0 μg/ml (57). In the study by Li *et al* (58), Tan IIA effectively inhibited BCSC-associated traits within a concentration range of 2.5-20 μM (~0.74-5.92 μg/ml). Mechanistic analyses further demonstrated that Tan IIA attenuates BCSC stemness through modulation of the microRNA (miR)-125b/StAR-related lipid transfer domain protein 13 (STARD13) regulatory axis. Specifically, Tan IIA downregulates miR-125b while concomitantly upregulating its target gene STARD13, thereby suppressing miR-125b/STARD13 signaling, reducing stem-like properties and enhancing Dox sensitivity in breast cancer cells (58). Overexpression of miR-125b or knockdown of STARD13 reversed the inhibitory effects of Tan IIA on BCSC stemness, further validating the central role of this regulatory axis. Collectively, these findings indicate that Tan IIA suppresses BCSC properties and tumor-initiating capacity through inhibition of IL-6/STAT3/NF-κB signaling and modulation of the miR-125b/STARD13 axis, underscoring its therapeutic potential in overcoming drug resistance and preventing tumor recurrence (Fig. 4). These findings suggest that Tan IIA may suppress BCSC-like traits in selected models, but the durability of this effect and its contribution to relapse prevention remain to be validated in clinically relevant *in vivo* systems.

Induction of ferroptosis. Ferroptosis is an iron-dependent form of programmed cell death that has emerged as a novel anticancer strategy (59,60). Tan IIA has recently been linked to ferroptosis regulation in breast cancer models. Mechanistic studies showed that Tan IIA downregulated lysine-specific histone demethylase 1A (KDM1A) expression, thereby reducing the transcriptional activity of protein inhibitor of activated STAT 4 (PIAS4) and inhibiting PIAS4-mediated SUMOylation of solute carrier family 7 member 11 (SLC7A11). Destabilization of SLC7A11 impaired cystine uptake and antioxidant defense, leading to lipid peroxide accumulation, increased labile iron and ferroptotic cell death in breast cancer cells (61).

In vitro, Tan IIA treatment suppressed breast cancer cell proliferation, colony formation and migration, while *in vivo* xenograft and lung metastasis models further supported its tumor-suppressive activity (61). However, ferroptosis-related effects have been reported over a broad concentration range, including high micromolar exposures. Therefore, ferroptosis should currently be regarded as a mechanistically interesting pathway but with PK-related uncertainty for native Tan IIA, particularly in light of its poor bioavailability, rapid metabolism and limited evidence of sustained tumor exposure.

Collectively, these findings identify the KDM1A/PIAS4/SLC7A11 axis as a potential mechanistic link between Tan IIA and ferroptotic vulnerability in breast cancer. Nevertheless, further PK/PD studies are required to determine whether this pathway can be engaged at achievable tumor concentrations and whether ferroptosis contributes substantially to the *in vivo* antitumor effects of Tan IIA or its optimized derivatives (Fig. 4).

Suppression of HER2-positive breast cancer through HER2/EGFR and metabolic signaling. HER2-overexpressing breast cancer cells frequently depend on HER2/EGFR

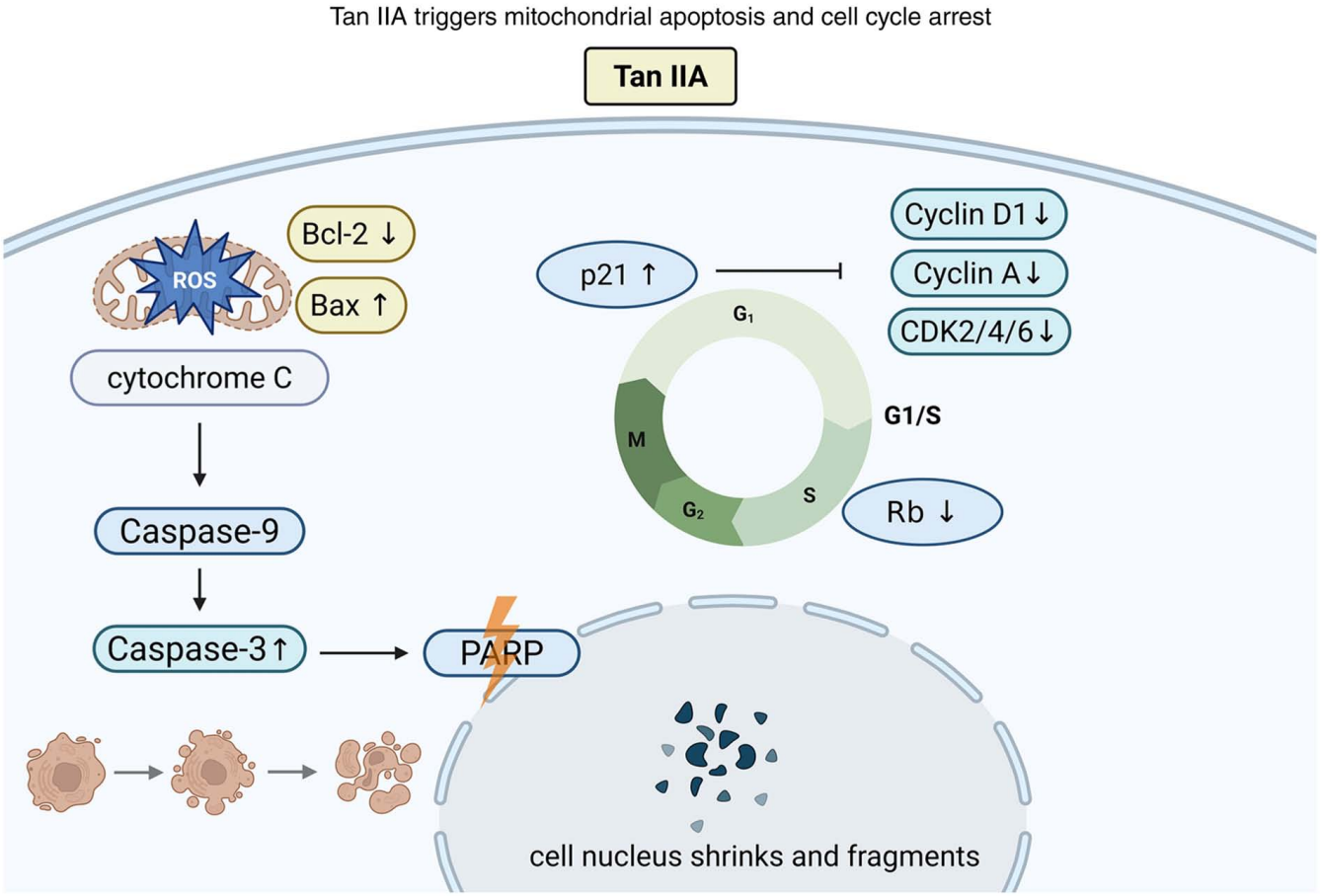

Figure 3. Tan IIA induces intrinsic apoptosis via mitochondrial dysfunction and arrests the cell cycle at G1/S phase by modulating cyclins, CDKs and p21. Tan IIA, tanshinone IIA; Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma 2; CDK2/4/6, cyclin-dependent kinase 2/4/6; PARP, poly(ADP-ribose) polymerase; Rb, retinoblastoma protein; ROS, reactive oxygen species; ↑, increase; ↓, decrease.

signaling and downstream anabolic pathways, including lipid synthesis and protein biosynthesis (62,63). These metabolic pathways have thus emerged as attractive therapeutic targets. ATA, a derivative of Tan IIA, demonstrates superior antitumor activity compared with its parent compound in HER2-overexpressing breast cancer. In cell lines such as MDA-MB-453, SK-BR-3 and BT-474, ATA induced G1/S phase arrest and apoptosis, associated with marked downregulation of EGFR/HER2 receptor tyrosine kinases and inhibition of downstream prosurvival signaling. Furthermore, ATA triggered oxidative stress and endoplasmic reticulum stress, while activating the AMP-activated protein kinase (AMPK) signaling pathway, thereby inactivating key enzymes involved in lipid and protein biosynthesis and disrupting metabolic dependencies of tumor cells. *In vivo*, intraperitoneal administration of ATA significantly suppressed xenograft tumor growth in MDA-MB-453 models without inducing body weight loss or overt toxicity. Functional assays further demonstrated that ATA inhibited breast cancer cell migration, invasion and angiogenesis *in vitro* (64) (Fig. 4). Whether these findings are relevant to HER2-low or HER2-ultralow breast cancer remains unknown. Given the clinical expansion of HER2-directed ADCs, future studies should determine whether Tan IIA derivatives influence ADC sensitivity or resistance by altering HER2 expression, endocytosis, EMT oxidative stress or payload susceptibility.

Emerging evidence from non-breast cancer models suggests that Tan IIA may enhance anti-programmed cell death 1 (PD-1) efficacy by modulating tumor vasculature, endoplasmic reticulum stress, JNK signaling and immune-cell infiltration (28,29). However, direct evidence in breast cancer remains limited, and these findings should be regarded as hypothesis-generating. Future studies should evaluate whether Tan IIA-derived compounds can remodel the breast tumor microenvironment, enhance checkpoint blockade or influence PD-1/PD1 ligand 1 responsiveness in TNBC or other immunologically active breast cancer subtypes.

Stabilization of G4 DNA. Because of their planar heterocyclic scaffold, certain Tan IIA derivatives have been investigated as G4 stabilizers. G4 DNA structures represent promising anticancer targets due to their regulatory roles in oncogene transcription and translation (65,66). A series of imidazole-modified Tan IIA derivatives (compounds 1-8), particularly compound 4, exhibited strong selectivity and binding affinity toward G4 DNA. These derivatives effectively stabilized multiple G4 structures, including those in c-Myc, K-ras and VEGF, leading to DNA damage and suppression of TNBC cell growth, metastasis and angiogenesis. Molecular docking and interaction studies further confirmed that these derivatives preferentially bind G4 DNA over duplex DNA, highlighting their specificity. These results provide a rationale

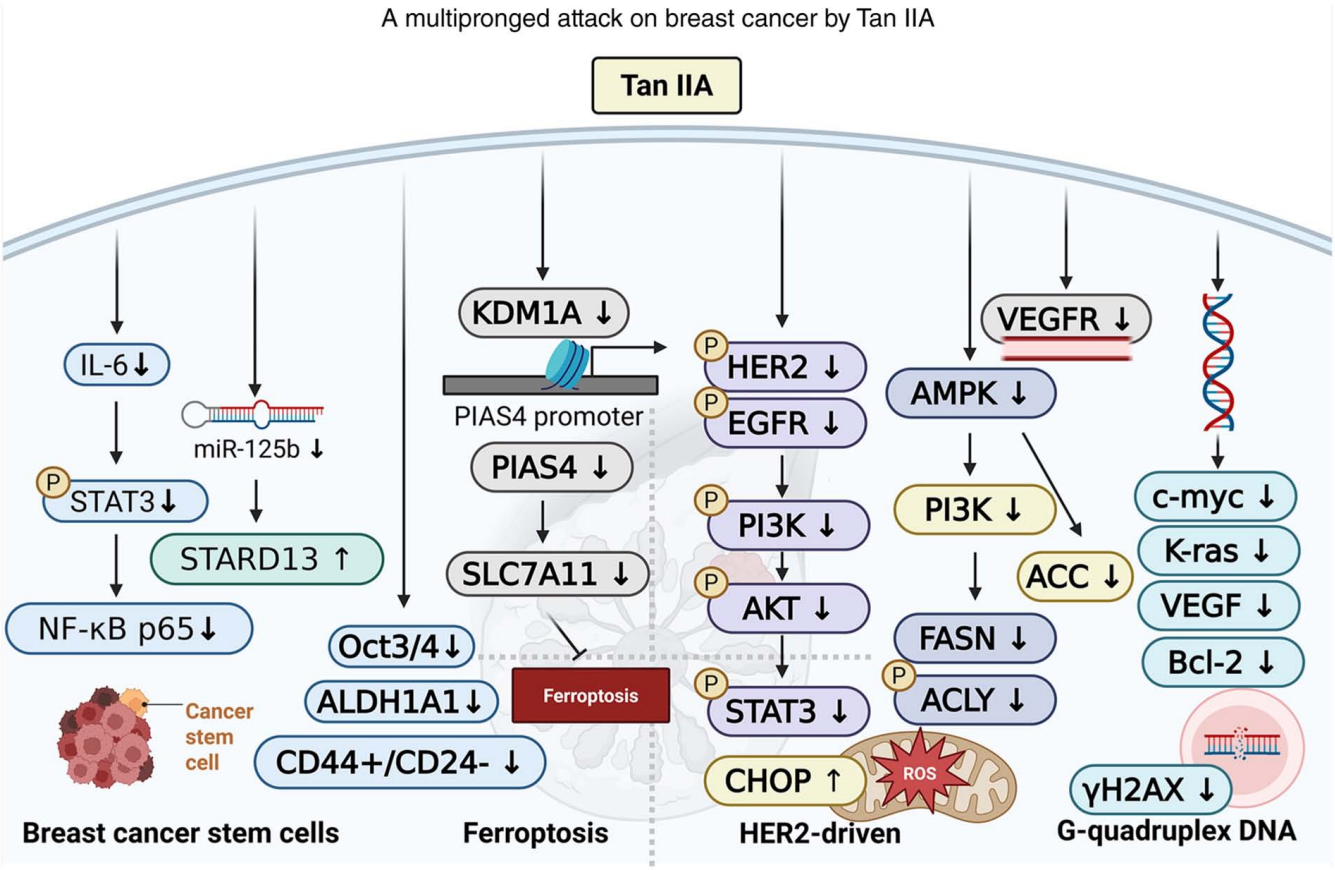

Figure 4. Tan IIA combats breast cancer through four reported mechanisms: Targeting breast cancer stem cells, inhibiting HER2 signaling and metabolic pathways, inducing ferroptosis and stabilizing G-quadruplex DNA to suppress oncogene expression. Together, these actions lead to tumor growth inhibition, enhanced cancer cell death and reduced metastasis. ACLY, ATP-citrate lyase; AKT, protein kinase B; ALDH1A1, aldehyde dehydrogenase 1 family member A1; AMPK, AMP-activated protein kinase; Bcl-2, B-cell lymphoma 2; CHOP, C/EBP homologous protein; EGFR, epidermal growth factor receptor; FASN, fatty acid synthase; HER2, human epidermal growth factor receptor 2; IL-6, interleukin-6; KDM1A, lysine-specific histone demethylase 1A; Kras, Kirsten rat sarcoma viral oncogene homolog; miR-125b, microRNA-125b; NF-κB p65, nuclear factor-κB p65 subunit; Oct3/4, octamer-binding transcription factor 3/4; PI3K, phosphoinositide 3-kinase; PIAS4, protein inhibitor of activated STAT 4; ROS, reactive oxygen species; SLC7A11, solute carrier family 7 member 11; STAT3, signal transducer and activator of transcription 3; STARD13, StAR-related lipid transfer domain protein 13; Tan IIA, tanshinone IIA; VEGFR, vascular endothelial growth factor receptor; ↑, increase; ↓, decrease.

for developing selected Tan IIA derivatives as G4-targeting leads, although their pharmacological relevance requires further PK/PD and target-engagement validation (67) (Fig. 4). Importantly, G4 stabilization is currently best supported for structurally optimized derivatives rather than for native Tan IIA itself. Therefore, this mechanism should be interpreted as a derivative-specific optimization strategy.

4. Optimization of derivatives and delivery systems

Tan IIA and its derivatives have demonstrated significant pharmacological activity against breast cancer. However, their poor water solubility, limited bioavailability and insufficient tumor-targeting capacity remain major obstacles to clinical application. To address these challenges, researchers have focused on derivative design and the development of optimized nanodelivery systems. The objective of these strategies is not merely to increase cytotoxic potency, but to improve aqueous stability, systemic exposure, tumor accumulation, target engagement and therapeutic index. The chemical structures of Tan IIA derivatives discussed above are summarized in Fig. 5.

Regarding derivatives, ATA represents one of the best-characterized Tan IIA analogues and has shown stronger inhibitory activity than native Tan IIA in ER-positive breast cancer models. Its active metabolite, HTA, binds to ERα, promotes ubiquitin-proteasome-dependent ERα degradation in the nucleus and downregulates ESR1 transcription, thereby distinguishing this mechanism from that of classical endocrine agents such as tamoxifen and fulvestrant (21). ATA has also demonstrated activity in HER2-overexpressing breast cancer cells, where it induces G1/S cell-cycle arrest and apoptosis through downregulation of EGFR/HER2 and downstream survival pathways, together with ER stress and AMPK activation (64). Other semisynthetic Tan IIA derivatives have exhibited IC_{50} values ranging from 1.3 to 18.7 μM across breast cancer cell lines including SUM149, MDA-MB-231, T47D and MCF-7 cells (68,69). Imidazole-substituted derivatives, particularly TA12, further inhibited proliferation, migration and invasion of MDA-MB-231 cells and suppressed metastasis in zebrafish xenograft models, with effects associated with S-phase arrest, ROS accumulation and DNA damage activation (54). In addition, selected imidazole-modified derivatives have been reported to stabilize G4 structures within oncogene

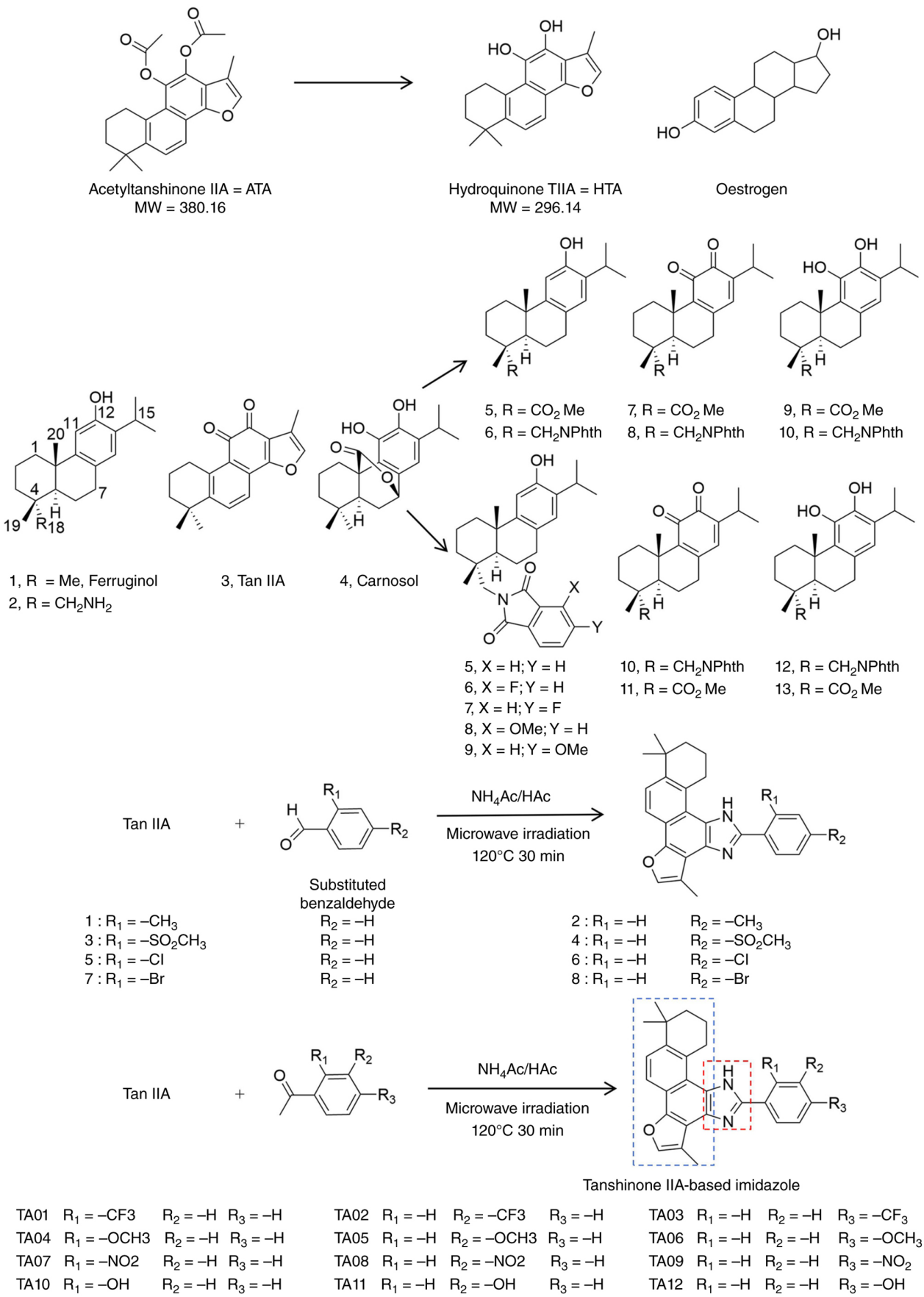

Figure 5. Chemical structures and structure-activity relationships of Tan IIA derivatives. Chemical structures of Tan IIA and its representative derivatives are discussed in this review, including ATA, its major metabolite HTA and optimized TA01-TA12. Key modification sites on the Tan IIA scaffold, such as acetylation, oxidation state changes and side-chain substitutions, are highlighted to facilitate structure-activity relationship analysis. In the lower-right structure, the blue dashed box indicates the Tan IIA-derived core scaffold and the red dashed box indicates the introduced imidazole ring. Tan IIA, tanshinone IIA; ATA, acetyltanshinone IIA; HTA, hydroquinone tanshinone IIA; TA01-TA12, imidazole-substituted Tan IIA derivatives; MW, molecular weight.

promoters such as MYC, KRAS and VEGF, leading to DNA damage and suppression of TNBC-associated proliferation, migration, invasion and angiogenesis (67). However, these findings should be interpreted as derivative-specific optimization strategies rather than uniform evidence that all Tan IIA analogues share the same mechanism or translational potential. Table SII summarizes representative Tan IIA derivatives and delivery systems, showing that ATA exhibits low-micromolar activity in ER-positive and HER2-overexpressing breast cancer cells, while optimized derivatives such as TA12 and compound 4 show selective activity in MDA-MB-231 models (21,54,64,67). Delivery systems such as T/CM-L and Tan-Dox-MSN further improved formulation performance and tumor inhibition *in vivo*, although further pharmacokinetic, safety and target-engagement validation remains necessary before clinical translation (22,23).

With respect to delivery systems, several innovative strategies have been developed to enhance the therapeutic efficacy of Tan IIA. A multi-component liposomal system co-loaded with sodium Tan IIA sulfonate (STS) and celastrol (CM) was designed to achieve sequential release: STS first modulated the tumor microenvironment, followed by CM-mediated tumor cell killing. This dual-delivery approach produced synergistic anticancer effects, significantly reducing tumor volume while minimizing systemic toxicity (23). In another approach, a phytoestrogen-modified nanodelivery system (Tan-Dox-MSN) was constructed to co-deliver Tan IIA derivatives and Dox. This platform exhibited excellent tumor-targeting properties and biocompatibility, improved Dox loading efficiency, and markedly suppressed breast cancer growth and metastasis (22). Although these systems improve tumor delivery in preclinical models, carrier-related immunogenicity, reticuloendothelial uptake, organ accumulation and long-term tolerability remain insufficiently characterized.

Together, these findings suggest that molecular modification and delivery optimization may improve the therapeutic feasibility of Tan IIA-based strategies. However, their clinical relevance remains dependent on quantitative PK/PD validation, safety assessment and demonstration of target engagement *in vivo*.

5. Structure-activity relationships of Tan IIA and its derivatives

Systematic structural modification of Tan IIA has revealed several recurrent structure-activity relationship (SAR) patterns that critically determine its anticancer potency, selectivity and mechanistic profile in breast cancer models. At the core scaffold level, acetylation of Tan IIA to generate ATA markedly enhances subtype-selective activity, particularly against ER-positive and HER2-overexpressing breast cancer cells, while maintaining lower toxicity toward non-malignant mammary epithelial cells (21,64). This minor modification confers a dual mechanism involving ERα protein degradation and transcriptional suppression, as well as inhibition of EGFR/HER2 signaling and downstream metabolic and survival pathways, highlighting acetylation as an effective strategy to modulate both target engagement and pharmacological behavior. Beyond core modifications, the oxidation state at the C11-C12 positions of the C ring emerges as a dominant determinant of cytotoxic potency. Conversion of phenolic hydroxyl groups to ortho-quinone structures consistently enhances antiproliferative activity, particularly in TNBC cell lines, likely through redox cycling, ROS generation and mitochondrial dysfunction (68). Side-chain modifications at the C18 position further fine-tune activity and selectivity, with bulky substituents such as phthalimide groups synergizing with ortho-quinone or catechol cores to improve solubility, therapeutic index and induction of intrinsic apoptosis (68,69). In parallel, aromatic substitution patterns in imidazole-fused and phenyl-substituted derivatives demonstrate that para-oriented substituents-either electron-withdrawing or electron-donating, depending on the scaffold-can enhance molecular planarity, optimize electronic distribution and promote selective targeting of aggressive TNBC cells through mechanisms such as G4 DNA stabilization or suppression of migration- and invasion-related signaling axes (54,67).

Despite these encouraging SAR trends, several important limitations must be acknowledged when interpreting the current data and translating them into rational drug design strategies. Most SAR conclusions are derived from heterogeneous *in vitro* systems, with limited consistency in cell lines, exposure durations and dose reporting, restricting direct quantitative comparison across studies. Furthermore, while specific structural motifs-such as ortho-quinone cores, C18 side-chain extensions and para-substituted aromatic rings-are recurrently associated with enhanced activity, their precise molecular targets and off-target liabilities remain insufficiently defined. The chemical instability of Tan IIA derivatives in aqueous environments and the lack of comprehensive PK and metabolic profiling further constrain their clinical translatability. Consequently, existing SAR insights should be regarded as guiding principles rather than definitive design rules. Future efforts should integrate rational structural optimization with systematic PK evaluation, multi-omics-based target deconvolution and *in vivo* validation to balance potency, selectivity and drug-likeness, thereby enabling the development of next-generation, patentable Tan IIA-derived candidates for difficult-to-treat breast cancer subtypes (21,54,64,68,69). Therefore, future SAR studies should routinely report IC_{50} values in malignant and non-malignant cells, solubility, microsomal stability, plasma exposure, tumor accumulation and preliminary safety margins.

6. Conclusion, safety considerations and perspectives

In conclusion, while Tan IIA displays numerous anticancer actions in cell and animal experiments, its practical drug potential is severely limited. Its intrinsic drawbacks, including poor solubility, rapid metabolism and low bioavailability, mean that native Tan IIA is unlikely to be developed as a standalone anticancer drug (70). Instead, the value of Tan IIA lies in its scaffolding: Derivatives and formulations built on its structure can achieve potent activity. Furthermore, no well-controlled clinical studies have validated Tan IIA's efficacy in cancer patients. Because unmodified Tan IIA is a natural compound, patent protection for it is weak, further reducing incentives for costly drug development (71). Going forward, research should prioritize optimized analogues (with better ADME profiles) and advanced delivery systems, while rigorously testing these in preclinical models (72-74).

It must be emphasized that Tan IIA's anticancer data are entirely preclinical. Most studies have used cell lines or mouse models (75-77). To move forward, rigorous PK and toxicology studies in animals are needed, followed by early-phase human trials to determine whether any benefit translates to patients. In addition, the multiplicity of Tan IIA's purported targets (from ERα to KDM1A to G4 DNA) raises the possibility of off-target pharmacology and unintended pathway perturbation, particularly at exposures required for anticancer efficacy. Future development should therefore define a feasible therapeutic window and systematically evaluate safety liabilities, including potential endocrine-related effects given its ER-binding and phytoestrogen-like properties, mitochondrial and oxidative stress-related toxicity, quinone-associated electrophilic reactivity, cardiovascular interference and drug-drug interactions when combined with chemotherapeutic, endocrine, HER2-targeted or immune checkpoint inhibitors. For advanced delivery systems, carrier-related immunogenicity, reticuloendothelial uptake, organ accumulation and long-term tolerability also warrant careful assessment. Finally, even with derivatives, Tan IIA analogues tend to remain chemically challenging because of poor solubility and stability issues. Without highly potent lead compounds or delivery systems capable of achieving sustained tumor exposure, it may be difficult to reach therapeutically relevant concentrations in humans. In short, Tan IIA highlights how a natural scaffold can inspire drug design, but also why its direct clinical utility remains constrained (78).

Pathways inhibited in tumor cells may also have essential physiological functions in normal tissues. ER signaling contributes to reproductive, skeletal, cardiovascular and immune-inflammatory homeostasis; therefore, systemic ER-modulating activity may have consequences in female subjects beyond tumor inhibition. Similarly, suppression of NF-κB, STAT3, PI3K/AKT or redox signaling may affect immune competence, hematopoietic function, tissue repair and inflammatory balance. These risks may be amplified in combination with chemotherapy, endocrine therapy, HER2-targeted therapy or immunotherapy.

In summary, Tan IIA serves as a valuable pharmacological probe but is not itself a drug candidate without significant improvement. Any clinical application will depend on developing semisynthetic analogues with truly drug-like properties (much greater potency and stability) and robust delivery methods. Given its low patentability in native form, future efforts will likely focus on novel derivatives. Meanwhile, caution is warranted: Claims of 'promising anticancer potential' should be tempered by the compound's PK realities and the absence of clinical proof. Only compounds or formulations that demonstrate achievable tumor exposure, target engagement, acceptable safety margins and reproducible efficacy in clinically relevant breast cancer models should be advanced toward clinical development.

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Authors' contributions

XL was responsible for manuscript writing and figure preparation, and conducted the literature review and data collection. LF contributed to manuscript revision and proofreading, supervised the overall study design, provided guidance on the research direction, oversaw the manuscript drafting and provided final approval of the submitted version. 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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