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Resveratrol as an immune checkpoint inhibitor to enhance the efficacy of breast cancer immunotherapy

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ABSTRACT

A major goal in cancer treatment is to convert "cold" tumors into "hot" ones by altering the tumor microenvironment (TME). Breast cancer is often a cold tumor and is resistant to immunotherapy. Resveratrol is a polyphenolic compound found in grapes, with antioxidant, anti-inflammatory, and potential cardioprotective and anti-aging properties. Resveratrol promotes the conversion of immunologically cold breast tumors into hot tumors, thereby increasing the efficacy of immunotherapy. This article reviews the potential of resveratrol to convert immunologically "cold" breast tumors into "hot" tumors by modulating the TME and enhancing the efficacy of immunotherapy. A comprehensive literature search was conducted in PubMed, Scopus, Web of Science, and Google Scholar to identify English-language articles investigating the effects of resveratrol on immune checkpoints in breast cancer. The results showed that resveratrol suppresses key cancer-promoting pathways (PI3K/Akt/mTOR, MAPK/ERK, STAT/NF-κB, and Wnt/β-catenin) and modulates the immune system. It boosts anti-tumor immunity by activating immunostimulatory cells (such as M1-TAMs, NKs, and CTLs) while simultaneously inhibiting immunosuppressive cells (such as Tregs and MDSCs). It also acts as a natural immune checkpoint inhibitor by targeting the PD-1/PD-L1 pathway. Resveratrol prevents T-cell exhaustion in "cold" tumors and reduces PD-L1 expression in "hot" tumors, thereby enhancing cytotoxic T cells' ability to attack cancer. However, its effectiveness is limited by poor bioavailability and differences in the biological activity of its metabolites. Future clinical studies are needed to confirm these results and determine optimal therapeutic protocols for resveratrol-mediated breast cancer immunotherapy.

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Introduction

Breast cancer, which is highly prevalent in women, is characterized by remarkably diverse malignancy (1). Breast cancer contains a range of biological subtypes with various treatment responses and clinical outcomes. Despite the availability of targeted therapies, treatment resistance remains a significant challenge (2). The tumor microenvironment (TME) is a complex and active system of tumor cells, stromal cells, and extracellular matrix. The TME influences tumor progression and treatment efficacy through environmental signals, including chemokines, growth factors, tumor-related cytokines, and metabolic products (3). Immune cells play a pivotal role in organizing anti-tumor immune responses in TME (4, 5). Immune cells often include innate immune cells such as macrophages, neutrophils, adaptive immune cells (T and B cells), dendritic cells (DCs), natural killer cells (NK cells), and bone marrow-derived suppressor cells (6). Nevertheless, in some cases, immune cells can have two distinct roles: they can either stimulate anti-tumor responses or facilitate immunosuppressive responses. This duality depends on the complex interactions among signals in the TME (7, 8). This novel view of immune evasion has improved approaches to cancer therapy, particularly by using immune cells to combat cancer cells (9). Tumors based on the presence of tumor-infiltrating lymphocytes (TILs) are categorized as "hot" (inflamed) or "cold" (non-inflamed). A significant challenge in oncology is converting immunologically cold tumors into hot ones to sensitize them to immunotherapy. This transformation requires a multi-faceted approach targeting key mechanisms within the TME (Figure 1).

Cancer immunotherapy has revolutionized oncology by providing novel therapeutic approaches. The major cancer immunotherapies include adoptive cell therapy (ACT), chimeric antigen receptor T-cells (CAR-T), T-cell receptor (TCR) engineering, monoclonal antibodies (mAbs), bispecific antibodies (BsAbs), and immune checkpoint inhibitors (ICIs) (10). Cancer immunotherapy works by boosting the immune system's innate ability to fight cancer and to target tumor cells (11, 12). A pre-existing anti-tumor immune response is critical to the

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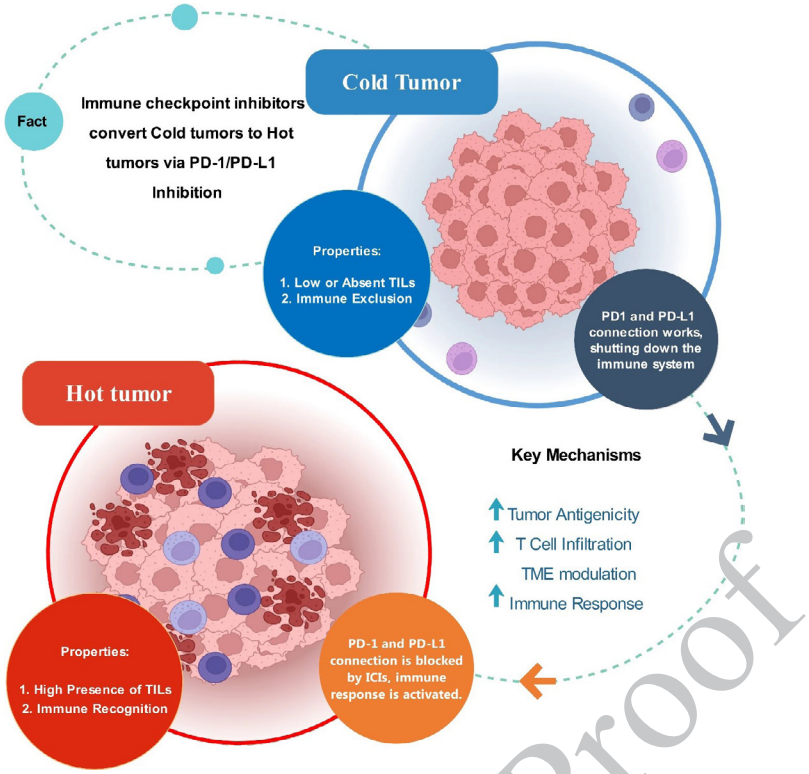

Figure 1. Impact of ICIs and the PD-1/PD-L1 pathway on converting cold tumors to hot tumor
ICIS: Immune checkpoint inhibitors; PD-1: Programmed cell death protein 1; PD-L1: Programmed death-ligand 1; TMB: tumor mutational burden; ICIs: immune checkpoint inhibitors

efficacy of cancer immunotherapy and immune checkpoint inhibitors (ICIs). Immune checkpoints are regulators of the immune system. Certain tumors can activate immune checkpoint pathways and evade the immune response. ICIs have demonstrated critical therapeutic effects on a diverse range of malignancies. Currently approved ICIs primarily inhibit the T-lymphocyte-associated antigen-4 (CTLA-4) and programmed cell death protein 1/programmed death ligand 1 (PD-1/PD-L1) pathways. PD-1 is a receptor on the surface of immune cells, primarily T-cells. PD-1 prevents T cells from attacking healthy cells, thereby inhibiting autoimmune diseases. PD-L1 is a ligand on the surface of healthy cells, tumor cells (in cancer), and other cells in the TME. PD-L1 acts as the signal that tells the T-cell to shut down. Cancer cells exploit PD-L1 to evade the immune response. Cancer cells exploit immune checkpoint pathways by overexpressing PD-L1 on their surface. This ligand binds to the PD-1 receptor on activated T-cells. This interaction suppresses T-cell effector functions and enables tumor cells to evade immune-mediated destruction (13). Several immunotherapy strategies have been explored for breast cancer, with a focus on ICIs (14). Cancers that respond well to ICIs generally display at least one of the following three important properties: a significant number of tumor-infiltrating lymphocytes (TILs), elevated PD-L1 expression, and a high tumor mutational burden (TMB) (15).

Despite the potential of immunotherapy for cancer treatment, its success in breast cancer has been limited, especially for patients with metastatic breast cancer (16). The complexity of TME signaling is a key challenge in developing effective cancer immunotherapy (17). Moreover, combining chemotherapy and radiotherapy can enhance the efficacy of immunotherapy (18).

A novel strategy for improving immunotherapy efficacy in breast cancer involves the use of natural products with immunomodulatory properties (19-22). Various natural compounds have shown significant effects in breast cancer immunotherapy by inhibiting Epithelial-Mesenchymal Transition (EMT) and PD-L1 (23, 24).

Resveratrol (3,4′,5-trihydroxystilbene) is a stilbene polyphenol naturally synthesized in plants such as red grapes, berries, and nuts (25). Resveratrol regulates immune responses through direct effects on innate and adaptive immunity and indirect effects by sensitizing tumor cells to immune cells (20, 26, 27). Resveratrol is a promising candidate for breast cancer therapy due to its ability to modulate immune responses (21, 26). Combining resveratrol with standard treatments that target the PD-1/PD-L1 pathway is a promising approach to enhance anti-tumor effects in breast cancer therapy (28-30).

This review explains the role of immunotherapy in breast cancer and investigates the impact of resveratrol on TME and immunotherapy. Additionally, it discusses the potential of resveratrol to act synergistically with anti-PD-1/PD-L1 immunotherapy to improve treatment outcomes for breast cancer patients.

Research methods

A comprehensive literature search was conducted in 2025 using the databases PubMed, Scopus, Web of Science, and Google Scholar. The search strategy employed the following keywords combined with operators: ("Resveratrol") AND ("Breast Cancer") AND ("Immune Checkpoint Inhibitors" OR "PD-1" OR "PD-L1" OR "CTLA-4"). All English-language articles investigating the effects of resveratrol on immune checkpoints in the context of breast cancer were included in the review.

Results

Common breast cancer therapies such as chemotherapy, radiation, and surgery often yield limited results and cause

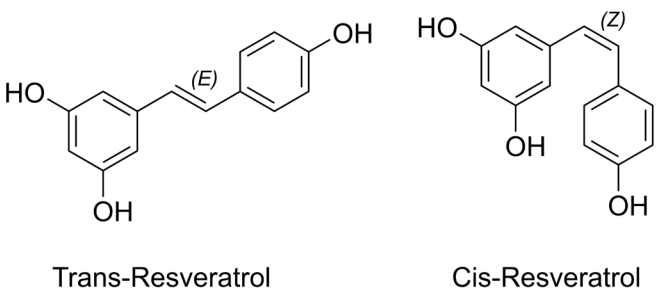

Figure 2. *trans-* and *cis*-configurations of resveratrol

considerable side effects (13). Additionally, metastatic breast cancer remains incurable (31). Immunotherapy could be a new approach to treating breast cancer. Several immunotherapy strategies have been investigated for the treatment of breast cancer, including adoptive T-cell therapy, tumor-targeting antibodies, cytokine/chemokine-based immunotherapies, vaccines, and innate immune agonists. Notably, PD-1/PD-L1 inhibitors represent the most widely studied strategy (14, 32).

A key challenge is that breast tumors are typically non-immunogenic (cold tumors). This means they have a low number of mutations (low TMB), few lymphocytes (low TILs), and low PD-L1 levels. Consequently, they typically respond poorly to immunotherapies, including ICIs (15).

Many studies investigating breast cancer immunotherapy have focused on PD-1/PD-L1 inhibition (33-35).

Clinically, the monoclonal antibody pembrolizumab (a PD-1 inhibitor) has been approved for metastatic triple-negative breast cancer (TNBC). However, its use is typically limited to cases with high PD-L1 expression (32, 36). It is also demonstrated that the combination of antiestrogen with pembrolizumab has shown promise in treating hormone receptor (HR)-positive metastatic breast cancer (37). Moreover, atezolizumab is Food and Drug Administration (FDA)- approved, in combination with chemotherapy, to treat metastatic PD-L1-positive TNBC (34).

ICIs for breast cancer can cause significant side effects. The most common are skin rash (38%), infusion reactions (12%), and hypothyroidism (12%) (38, 39).

Researchers are seeking new ways to make breast tumors more responsive to immunotherapy (40, 41). There is growing interest in natural compounds such as resveratrol, which may help modulate the immune system, improve long-term outcomes, reduce side effects, and prevent therapy resistance (21, 26, 26).

Immunomodulatory effects of resveratrol

Resveratrol is a natural polyphenolic compound (42). Resveratrol is present in grapes, berries, plums, and even peanuts, but it was originally identified in white hellebore (*Veratrum grandiflorum*) (25). This compound exists primarily in two configurations: *cis-* and *trans*-resveratrol (Figure 2). The more stable isomer is *trans*-resveratrol, which is stable in visible light, high temperature, and low pH (43). The bioavailability of resveratrol is generally low due to rapid metabolism by phase II enzymes in both the intestine and liver, which convert it into 3- and 4′-O-sulfate and 3-O-glucuronide conjugates (44).

Resveratrol has demonstrated various biological effects, including neuroprotective, antibacterial, cardioprotective, anti-diabetic, anti-aging, and estrogenic/anti-estrogenic effects, as well as the prevention and management of obesity and obesity-related metabolic syndrome (43, 45). Anti-tumor properties of resveratrol influence multiple stages of cancer development, including initiation, promotion, and progression. These anti-tumor effects are related to the regulation of various signal-transduction pathways that control cell growth and division, inflammation, apoptosis, metastasis, and angiogenesis (45).

The inflammasome, a multiprotein complex that activates pro-inflammatory cytokines and initiates immune responses, is a critical regulator of inflammation. Resveratrol can act as NLR family pyrin domain containing 3 (NLRP3) inflammasome modulator, an inhibitor of inflammatory signals (nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), interleukin-1β (IL-1β), tumor necrosis factor α (TNF-α)), and an activator of the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, which is a protective pathway against oxidative stress (46).

Resveratrol enhances immunotherapy efficacy through multiple mechanisms. It promotes the release of anticancer cytokines (e.g., interferon γ (IFN-γ), TNF-α) and inhibits immunosuppressive factors like transforming growth factor β (TGF-β). Furthermore, it stimulates the polarization of $CD4^+$ T cells and macrophages towards an anticancer response and reduces the presence of immunosuppressive cells. Finally, resveratrol increases cancer cells' susceptibility

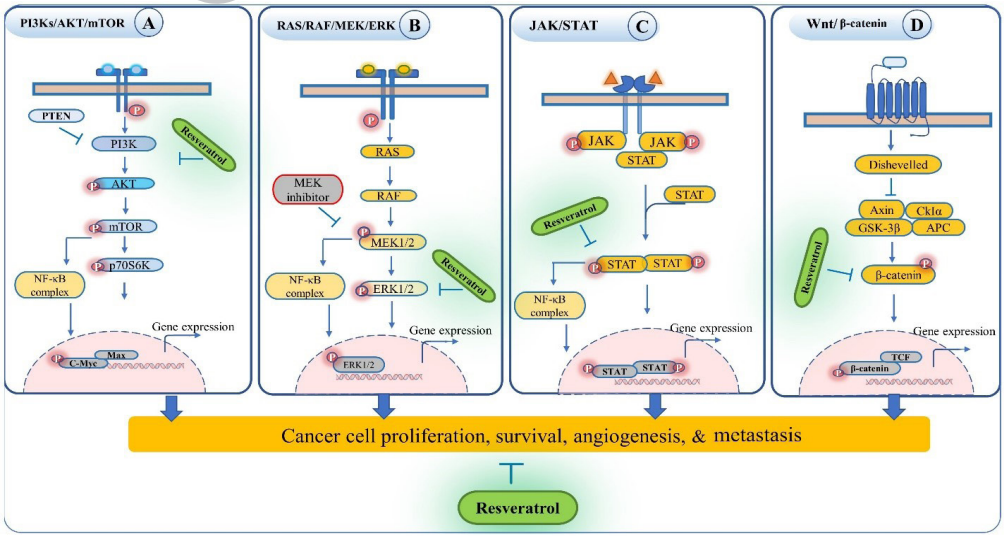

Figure 3. Inhibitory mechanisms of resveratrol on key oncogenic signaling pathways (A) PI3K/Akt/mTOR, (B) RAS/RAF/MEK/ERK, (C) JAK/STAT, (D) Wnt/β-catenin

to the immune response (20).

Current research shows that resveratrol can influence immune cells and PD1/PD-L1 signaling pathway in breast cancer. Resveratrol, through its immunomodulatory effects in the TME (26), can enhance the effectiveness of immunotherapy in breast cancer treatment. This can lead to more effective and less toxic treatments for this disease.

Resveratrol's effect on oncogenic signaling pathways

Resveratrol has been shown to influence the most important signaling pathways related to breast cancer proliferation and metastasis (Figure 3).

Ras/Raf/MEK/ERK (MAPK) signaling pathway

The Ras/Raf/MEK/ERK pathway, or mitogen-activated protein kinase (MAPK) pathway, has been shown to regulate PD-L1 expression in numerous cancer cell types (47-49). A critical effector of the MAPK pathway during cancer progression is extracellular signal-regulated kinase (ERK) (50).

Research using mouse models of breast cancer shows that combining mitogen-activated protein kinase (MEK) inhibitors with PD-1/PD-L1-targeted immunotherapy may improve treatment outcomes. It suggests that the Ras–MAPK pathway helps tumors avoid the immune system in TNBC. Additionally, the activity of the Ras/MAPK pathways and major histocompatibility complex (MHC) expression might help predict how well patients respond to ICIs (51). It was shown that high doses of resveratrol reduced ERK1/2 phosphorylation, however, a study by Lee *et al.* found that resveratrol increased protein kinase B (Akt) signaling but had no effect on phosphorylation of STAT5 or ERK pathways (52). Chen et al. found that treating cells with both resveratrol and the drug PD98059 significantly reduced the activity of Ras/Raf/MEK/ERK signaling pathway. By inhibiting this pathway, apoptosis in tumor cells was increased (53).

PI3Ks/Akt/mTOR signaling pathway

Phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) is an important signaling pathway that plays a critical role in cell growth, division, metabolism, suppression of apoptosis, and angiogenesis. The PI3K/AKT/mTOR pathway is a complex intracellular signaling pathway involved in the pathogenesis of various diseases, and its activation contributes to protective effects against cancer and inflammatory diseases (54). The reduction of phosphatase and tensin homolog (PTEN), a crucial tumor suppressor protein, plays a significant role in cancer progression. When PTEN is lost or inactivated, it leads to the oncogenic activation of the PI3K/Akt/mTOR signaling pathway. When PD-L1 is expressed on tumor cells, it can inhibit T-cell activation and allow cancer cells to escape from immune detection. Therefore, the loss of PTEN not only disrupts normal cellular signaling but also enhances tumors' ability to express PD-L1, thereby promoting immune evasion (55).

Messeha *et al.* knocked down the PTEN gene in MDA-MB-231 breast cancer cells, causing the cells to produce more PD-L1 than even after the addition of IFN-γ, a potent inducer of PD-L1 production (23).

Wnt signaling pathway

Wnt signaling is another important pathway in human breast cancer, as it is associated with elevated nuclear and cytoplasmic levels of β-catenin (56). The Wnt signaling pathway involves two main cellular compartments: (i) the cytoplasmic segment includes Disheveled (DVL), adenomatous polyposis coli (APC), glycogen synthase kinase 3 β (GSK3β), casein kinase 1 (CK1), and axis inhibition protein (AXIN). This complex constantly breaks down β-catenin and prevents it from building up. (ii) The nucleus mainly contains translocated β-catenin. When Wnt ligands bind to Frizzled receptors, the canonical Wnt signaling pathway is activated, leading to β-catenin-mediated gene transcription (57).

When the Wnt/β-catenin signaling pathway is overactive in a tumor, it often makes the cancer "cold or non-immunogenic". Overactivation of the Wnt/β-catenin pathway promotes immune evasion by shielding cancer cells from recognition and attack by T cells in the TME. This leads to poor responses to immunotherapies that try to engage the immune system against the tumor (56).

Resveratrol and related stilbenoids can exert cytotoxic effects on the MCF-7 cell line via the Wnt signaling pathway (58). Resveratrol works by inhibiting cell migration and invasion through dual targeting of the PI3K/Akt and Wnt/β-catenin pathways, and by reducing matrix metalloproteinase-9 (MMP-9) activity (59, 60).

JAK/STAT signaling pathway

The JAK/STAT pathway is a pivotal signaling mechanism activated by growth factors and cytokines. In this pathway, Janus kinases (JAKs) phosphorylate signal transducers and activators of transcription (STATs) to regulate gene expression. This pathway influences cell growth, survival, differentiation, and immune function, playing a crucial role in cancer progression and immune regulation (61, 62). Specifically, STATs modulate the immune response by regulating PD-L1 expression in TNBC (63). Ma *et al.* hypothesized that resveratrol could suppress JAK/STAT signaling pathways and exhibit anti-inflammatory potential. Their investigation revealed that resveratrol removes the translocation of high mobility group box 1 (HMGB1) from the nucleus to the cytoplasm and NF-κB (p65) from the cytoplasm to the nucleus (64). Sun *et al.* indicated that STAT3 activation is a crucial regulator of cancer cell proliferation. Resveratrol has been shown to reduce STAT3 activity both *in vitro* and *in vivo* (65).

In most breast cancers, NF-κB is always active. In normal conditions, NF-κB stays inactive in the cytoplasm by binding to inhibitor of kappa B (IκB) proteins, which are controlled by the IκB kinase (IKK) complex. When IκB proteins are phosphorylated and degraded, NF-κB is released and moves to the nucleus. There, it binds to specific DNA sequences, and the p65 subunit activates the transcription of target genes (66). Sustained NF-κB activation in the TME can lead to chronic inflammation, which promotes tumor growth, survival, metastasis, and resistance to hormone therapy (67).

Based on promising results, it is recommended to use resveratrol, which may inhibit NF-κB and pro-inflammatory cytokines, in combination with immunotherapeutic agents to treat breast cancer (30, 64). Evidence suggests that resveratrol can inhibit NF-κB-regulated inflammatory gene products, including MMP-3, MMP-9, cyclooxygenase-2 (COX-2), and vascular endothelial growth factor (VEGF). It also targeted anti-apoptotic proteins B-cell lymphoma-extra large (Bcl-xL), B-cell lymphoma 2 (Bcl-2), and TNF receptor-associated factor 1 (TRAF1), and stimulated cleaved caspase-3 activation (68). Thus, targeting the JAK/STAT and NF-κB signaling pathways by resveratrol can be a promising therapeutic strategy to improve the prognosis of highly inflammatory TNBC, potentially in combination with other effective inhibitors (66, 69).

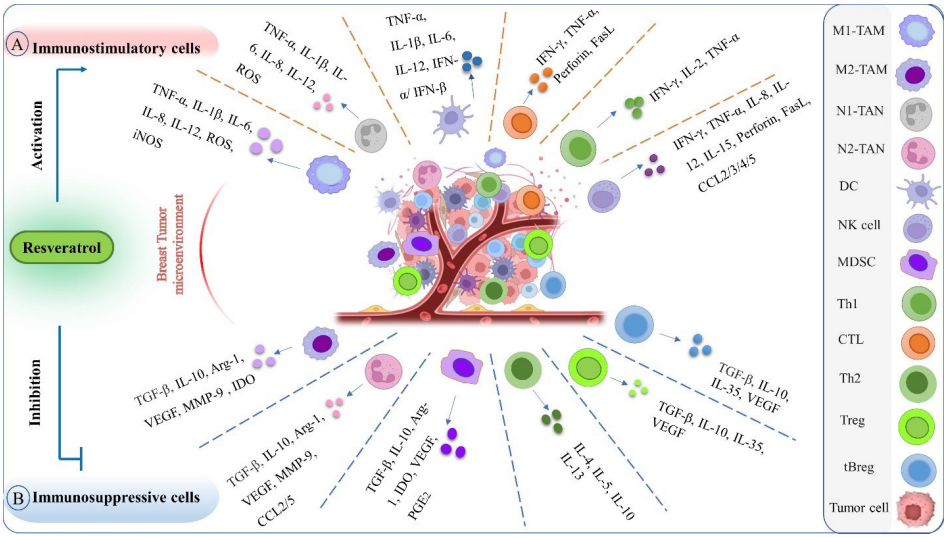

Figure 4. Bifunctional modulatory effects of resveratrol on immune cells
(A) Resveratrol has the potential to activate immunostimulatory cells, including M1-TAM, N1-TANs, DCs, NKs, CTLs, and Th1. (B) Resveratrol inhibits the function of immunosuppressive cells, including tBregs, Tregs, Th2 cells, MDSCs, M2-TAMs, and N2-TANs.
tBregs: Tumor-evoked bregs; Tregs: Regulatory T cells; MDSCs: Myeloid-derived suppressor cells

Table 1. Summary of resveratrol anti-cancer and immunomodulatory effects

Treatment	Tumor cell type/ Animal model	Results	Ref.
	Study model: Anti-breast cancer effects of resveratrol *in vitro*		
Resveratrol: 25 μM for 3 days	MDA-MB-231 MDA-MB-231-cisplatin resistance T47D	Significant IL-6/pSTAT3 pathway inhibition Modulation of M1/M2 macrophage polarization to increase M1 markers ↓ Breast cancer cell growth	(71)
Resveratrol: 100 μmol/l for 24 hr	Basal-like/HER2⁺ highly aggressive breast cancer cells (JIMT-1, MDA-MB-231 cell line)	Promotion of anti-tumor T cell response by altering PD-L1 glycosylation and dimerization Lowering the cytotoxicity threshold of tumors for T cell attack Preventing the suppression and exhaustion of anti-tumor immunity	(100)
Resveratrol: 6.25 μM or 25 μM for 48 hr	MDA-MB-231, BT-474, BCap37, MDA-MB-468, Hs 578T, SK-BR-3, & MCF-7 cell lines	Induction of MICA/B expression through suppression of the c-Myc/miR-17 regulatory pathway Increased cytolytic activity of NK cells demonstrated safety in murine models ↑Anti-tumor immunity in breast cancer patients	(107)
Resveratrol: 0.625-1280 μM for 24 or 48 hr + Curcumin: 0.625-1280 μM for 24 or 48 hr	MDA-MB-231 and MCF7	Resveratrol (IC_{50}:134.10 μM) and Curcumin (IC_{50}:12.60 μM) Resveratrol and curcumin inhibit breast cancer cells growth Downregulating the oncogenic lncRNA MAPT-IT1 pathway Autophagy and ferroptosis pathways activation Resveratrol and curcumin inhibit breast cancer cell proliferation	(126)
Resveratrol: 6.25 μM, 12.5 μM, and 25 μM for 48 hr	MDA-MB-231, BCap37, MCF7, MDA-MB-468 and HeLa	Resveratrol treatment significantly upregulates ULBP(NKG2D receptor activator) Resveratrol downregulates miR-17-5p and induces MINK1gene Resveratrol increased MINK1 protein and activates the JNK/c-Jun signaling pathway Resveratrol activates NK cell immune response	(127)
Resveratrol: 2-128μg/ml for 1-3 days	BT-549	Resveratrol (IC_{50}:40.55±3.39 μg/ml) Breast cancer cell growth, invasion, and metastasis inhibition apoptosis induction PGK1 enzyme expression reduction by regulating the transcription factor c-Myc Breast cancer treatment through the PGK1 glycolytic pathway	(128)

Continued Table 1.

Resveratrol: 0-200 μM for 24 and 48 hr	SK-BR-3 (HER2+), MCF-7, and MDA-MB-231	Fatty Acid Synthase (FASN) downregulation with siRNA Apoptosis induction Focal adhesion kinase (FAK)/Akt/ERK1/2 inhibition Induces apoptosis in different breast cancers by FASN pathway inhibition	(129)
Study model: Anti-breast cancer effects of resveratrol (*in vivo*)			
Resveratrol + Curcumin + Quercetin in different concentrations intragastric administration before (15/30 days) and after inoculation (30 days)	4T1- breast cancer-bearing	Resveratrol (IC_{50}: 69.62 mg/ml), Curcumin (IC_{50}: 79.32 mg/ml), Quercetin (IC_{50}: 114.3 mg/ml) Elevation of ROS-mediated apoptosis in cancer cells Elevated levels of $CD4^+$ and $CD8^+$ T cells in the TME Inhibition of Th2 cells, M2 macrophages, and N2 neutrophils ↑ Immune response in the breast TME	(29)
Resveratrol: 12.5 mg/kg or 25 mg/kg per body weight via IP for 21 days	4T1- tumor-bearing mice	Enhancement of the cytotoxicity of $CD8^+$ T cells and Th1 immune responses Elevated secretion of IFN-γ, IL-2, perforin, granzyme B Promotion of macrophage polarization Lower the PD-1 expression on lung-resident $CD8^+$ and $CD4^+$ T cells No impact observed on cytokines IL-10 and TGF-β or pulmonary MDSCs Suppression of TNBC lung metastasis and growth	(90)
Resveratrol: 50 μg/mouse via IP every other day from days 3 to 11	4T1-tumor-bearing mice	STAT3 inactivation Blocking tBreg formation and function Reducing TGF-β synthesis to inhibit tBreg-induced Treg conversion No impact on MDSC function Facilitating PPAR-α inactivation and blocking B cell conversion to tBregs ↓ tBreg-mediated breast cancer progression and metastasis	(103)
Resveratrol: 0, 25 or 100 mg/kg/day IP for 28 days	BCa-J27 tumor-bearing mice	Induction of MICA/B expression through suppression of the c-Myc/miR 17 regulatory pathway Increased cytolytic activity of NK cells demonstrated safety in murine models ↑Anti-tumor immunity in breast cancer patients	(107)
Resveratrol: 25 mg/kg/day and 100 mg/kg/day IP for 28 days	MDA-MB-231 cells were inoculated into female BALB/c immunodeficient mice	Resveratrol treatment significantly upregulates ULBP (NKG2D receptor activator) Resveratrol downregulates miR-17-5p and induces MINK1gene Resveratrol increased MINK1 protein and activates the JNK/c-Jun signaling pathway Resveratrol activates NK cell immune response Breast cancer cell growth, invasion, and metastasis inhibition	(127)
Resveratrol: 20, 50, and 100 mg/kg body weight/day IP for 21 days	4T1-tumor-bearing mice	apoptosis induction PGK1 enzyme expression reduction by regulating the transcription factor c-Myc Breast cancer treatment through the PGK1 glycolytic pathway	(128)
Study model: Anti-cancer effects of resveratrol through immunomodulation (*in vitro* studies)			
Resveratrol: 20 μM for 48 hr	A549 & H1299 (Human lung cancer cell) HMDMs	Reduction of M2 polarization & activation Decrease in TCM-stimulated IL-10 production and other M2 markers Reduction of STAT3 phosphorylation Enhancement of IL-12 and TNF-α secretion ↓ Tumor proliferation and invasion *in vitro*/*in vivo*	(65)
Resveratrol: 5-50 μM for 24 hr	Human monocyte THP-1 cells, M2-polarized THP-1 macrophages, lymphatic endothelial cells (HLECs)	Decrease in of M2-polarized THP-1 macrophages STAT3, IL-10 & MCP-1 inhibition Reduction of VEGF- stimulated HLEC motility, invasion, and lymphangiogenesis ↓ Tumor invasion and angiogenesis *in vitro*/*in vivo*	(74)

Continued Table 1.

Resveratrol: 25–50 μM for 2 hr	Bone marrow-derived dendritic cells (BMDCs)	Downregulation of IFN-γ-mediated IDO expression and function Reduction of JAK/STAT and PKCδ-dependent mechanisms in BMDCs Elevation of $CD8^+$ T cell polarization and CTL activity Suppression of tumor growth and IDO-mediated immune tolerance	(83)
Resveratrol: 0- 100 μmol/l for 6 and 12 hr	Myeloid-derived suppressor cells (MDSCs)	Reduction of the immunosuppressive functions of G-MDSCs through decreased ROS and Arg-1 levels Enhancing CTL activity Stimulation of M-MDSC maturation Blocking HMGB1-induced immune suppression in MDSCs Significant inhibition of MDSC-mediated proliferation and tumor immune evasion	(87)
Resveratrol: 20 μM, 100 μM for 1-3 days	$CD4^+$ T cells	Induction of TCR-dependent cell cycle progression at 20 μM and 100 μM Resveratrol acts as a strong activator of Sirt1 deacetylase Promotion of cell cycle arrest in the S phase (100 μM) or G2 phase (20 μM) in $CD4^+$ T cells Activation of cell cycle arrest via p53 pathway (20 μM) Stimulation of $CD4^+$ cell activation activity and IFN-γ production ↑ Anti-tumor immune response driven by $CD4^+$ T cell	(92)
Resveratrol: 20 μM for 36 hr	Human NK cell line (NK92)	Enhancement of NK cell cytotoxicity through Up-regulation of Akt-related transcription factors (e.g., c-Myb) in NK cells Increase in IL-2-Induced IFN-γ secretion from NK Cells Overexpression of NK cell-activating receptor CD107a ↑ IL-2 secretion in NK cells and inhibition of tumor growth	(52, 106)
Resveratrol: 12.5μM for 4 hr	NK92 cells, K562, HepG2, and A549 cells	Up-regulation of perforin expression and NK92 cell cytotoxicity via NKG2D-dependent ERK-1/2 and JNK-MAPK signaling pathways in cancer cells No observed effect on STAT3 or STAT5 protein expression Dose-dependent anti-tumor responses	(108)
4 – 32 μmol/l for 24-72 hr	HL60 human leukemia cells, T47D breast carcinoma cells	Selective activation of the CD95 (FasL) pathway to induce apoptosis in cancer cells without affecting normal cells acts as both a chemopreventive and a chemotherapeutic agent through the CD95 pathway	(109)
Resveratrol: 0.6 – 10 μg/mL for 18 hr to 6 days	PBMC	At low concentrations: enhanced the differentiation of $CD8^+$ and $CD4^+$ T cells into IL-2, IL-4, and IFN-γ producers after anti-CD3/anti-CD28 stimulation, and increased secretion of cytokines At higher concentrations, it suppressed cytokine production and T-cell proliferation cell activity increased at low concentrations and suppressed at higher concentrations dose-dependent immunomodulator, through cytokine production and T-cell proliferation	(110)
Resveratrol: 10^{-5} M to 3×10^{-3} M for 5 min to 2.5 hr	K562, PBMC	Platelet aggregation inhibition through downregulation of integrin gpIIb/IIIa expression on platelet surfaces Increased tumor cell susceptibility to NK cell-mediated cytotoxicity Reduction in TXA_2 production via inhibition of COX1-dependent pathways Increased NK cell-mediated cytotoxicity	(130)
Study model: Anti-cancer effects of resveratrol through immunomodulation (*in vivo* studies)			
100 mg/kg /day IP for 4 weeks	LLC tumor xenografts	Reduction of M2 polarization & activation Decrease in TCM-stimulated IL-10 production and other M2 markers Reduction of STAT3 phosphorylation Enhancement of IL-12 and TNF-α secretion ↓ Tumor proliferation and invasion *in vitro*/*in vivo*	(65)

Continued Table 1.

25 mg/kg twice daily, orally for 30 days	LM8-bearing mice	Decrease in of M2-polarized THP-1 macrophages STAT3, IL-10 & MCP-1 inhibition Reduction of VEGF- stimulated HLEC motility, invasion, and lymphangiogenesis ↓ Tumor invasion and angiogenesis *in vitro*/*in vivo*	(74)
50 mg/kg every 2 days for 3 weeks	EG7 thymoma-bearing mice	Downregulation of IFN-γ-mediated IDO expression and function Reduction of JAK/STAT and PKCδ-dependent mechanisms in BMDCs Elevation of $CD8^+$ T cell polarization and CTL activity Suppression of tumor growth and IDO-mediated immune tolerance	(83)
50 mg/kg /day for 3 weeks	LLC-bearing mice	Reduction of the immunosuppressive functions of G-MDSCs through decreased ROS and Arg-1 levels Enhancing CTL activity Stimulation of M-MDSC maturation Blocking HMGB1-induced immunosuppression in MDSCs Significant inhibition of MDSC-mediated proliferation and tumor immune evasion	(87)
4 mg/kg IP (single dose)	EG7 tumor-bearing mice (T lymphoblast)	Reduction the Treg cell population Suppressed secretion of TGF-β Increased IFN-γ expression in $CD8^+$ T cells ↑ Anti-tumor immune response both ex vivo and *in vivo*	(97)
Resveratrol (0.5 mg/kg) IV in the presence of IL-2	Murine models bearing B16F10 metastatic melanoma	Enhancement of NK cell cytotoxicity through Up-regulation of Akt-related transcription factors (e.g., c-Myb) in NK cells Increase in IL-2-Induced IFN-γ secretion from NK Cells Overexpression of NK cell-activating receptor CD107a ↑ IL-2 secretion in NK cells and inhibition of tumor growth	(52, 106)
0.03% and 0.06% resveratrol	HFD-induced obese & diet-resistant mice	Elevated numbers of Tregs (as negative regulators of inflammation) Suppression of long-term oxidative stress and pro-inflammatory gene activity Marked transition from Th1 to Th2 cytokine profiles ↓ Inflammation and oxidative stress	(124)
(< 5 mg/kg /day IP)	Renal tumor model	Induction of $CD8^+$ T cell-mediated anti-tumor immunity via increased MHC-I expression on APCs Increased levels of Th1 cells and Th1-associated cytokines (IFN-γ) Reduction in Th2-associated cytokines IL-6 and IL-10 Notable decrease in Tregs in the TME Lower levels of the angiogenesis factor VEGF ↓ Tumor progression and angiogenesis	(131)

MCP-1: Monocyte chemoattractant protein-1; HLECs: Human lymphatic endothelial cells; HMDMs: Human monocyte derived macrophage; LCC: Lewis lung cancer cell; IP: Intraperitoneal; BMDCs: Bone marrow-derived dendritic cells; IDO: Indoleamine 2,3-dioxygenase; PKCδ: Protein kinase Cδ; CTL: Cytotoxic T lymphocyte; G-MDSC: Granulocytic MDSCs; M-MDSC: Monocytic MDSC; LUAD: Lung adenocarcinoma; IV: Intravenously; MICA/B: Major histocompatibility complex class I chain-related proteins A and B; PBMC: Peripheral blood mononuclear cells

Interaction of resveratrol with TME immune cells

The modulatory effects of resveratrol on immune cells in the breast TME are shown in Figure 4, with Table 1 summarizing its immunological and anti-cancer effects across different experimental models. Also, Table 2 summarizes clinical studies on the anticancer and anti-inflammatory effects of resveratrol.

Tumor-associated macrophages

In the TME of a breast tumor, a type of immune cell called a tumor-associated macrophage (TAM) is the most abundant. In over 80% of breast cancer cases, high levels of tumor-associated macrophages (TAMs) are associated with a worse prognosis (70). Resveratrol significantly reduces breast cancer cell growth in MDA-MB-231 and cisplatin-resistant MDA-MB-231 cell lines by modulating the M1/M2 macrophage polarization ratio, leading to overexpression of the C-X-C motif chemokine ligand 10 (CXCL10) gene, an M1 marker. This effect is enhanced by a strong inhibition of the IL-6/pSTAT3 pathway, suggesting a mechanism by which resveratrol modulates immune responses and tumor growth (71).

Table 2. Clinical studies about the anti-cancer and anti-inflammatory effects of resveratrol

Treatment	Type of study	Results	Ref.
5 g orally for 2.5 and 5 hr after overnight fasting	Randomized, single-dose pilot trial involving 10 healthy male volunteers	Substantial elevation of IDO activity Notable reduction of tryptophan levels Significant modulation of immune function	(84)
1000 mg/day for 28 days	Phase 1 randomized trial involving 9 healthy Japanese participants	Resveratrol was well tolerated with a favorable safety profile Marked increase in circulating γδ T cells and Tregs Stable levels of $CD8^+$ T cells, $CD4^+$ T cells, and $CD19^+$ B cells Lower plasma concentrations of the proinflammatory cytokines TNF-α and MCP-1 Significant increase in plasma anti-oxidant activity ↓ Inflammation and oxidative stress	(98)
5 or 50 mg of trans-resveratrol/ twice daily for 12 weeks	Randomized, double-blind, placebo-controlled clinical trial involving 39 adult women at increased risk of breast cancer	Reduction of RASSF-1α methylation (key tumor suppressor gene) Reduction of PGE_2 Resveratrol can induce RASSF-1α demethylation and reduce inflammation	(132)

Tregs: Regulatory T cells; CD8+: Cluster of differentiation 8 positive; CD4+: Cluster of differentiation 4 positive; CD19+: Cluster of differentiation 19 positive; TNF-α: Tumor necrosis factor α, MCP-1: Monocyte chemoattractant protein-1; IDO: Indoleamine 2,3-dioxygenase; PGE_2: Prostaglandin E2; RASSF-1α: Ras association domain family member 1α

Resveratrol may reduce the cancer-promoting activity of TAMs by blocking the NF-κB pathway (72). A major factor in the metastasis of breast cancer to the lungs is the EMT, which TAMs trigger through changes in the JAK/STAT3 signaling pathway (73). Resveratrol (50 μM) suppresses M2-polarized ToHoku Hospital Physician-1 (THP-1) macrophages, leading to reduced tumor invasion and angiogenesis by decreasing STAT3 activity, IL-10 secretion, and expression of monocyte chemoattractant protein-1 (MCP-1). It also diminishes the movement, infiltration, and network formation of human lymphatic endothelial cells (HLEC) driven by VEGF. *In vivo*, administering resveratrol (25 mg/kg twice daily) inhibits tumor growth and lung metastasis in mice with highly metastatic osteosarcoma (LM8). It reduces the area of lymphatic endothelial cells within the tumors (74).

In advanced-stage breast cancer, tumor cells use transforming growth factor β (TGF-β) to modify the TME and evade immune detection. The immunosuppressive effects of TGF-β reduce the effectiveness of immunotherapy, particularly ICIs (75, 76).

Resveratrol (0-100 μM for 24 hr) can help by increasing the levels of macrophage inhibitory cytokine 1 (MIC-1), which is part of the TGF-β superfamily, in human pancreatic cancer cell lines (12). Although TGF-β promotes immune evasion, resveratrol increases MIC-1 protein expression (via p53), which promotes anti-cancer activity. This effect is linked to the tumor suppressor p53, which promotes MIC-1 expression. Consequently, it demonstrates both anti-cancer properties and potential as a diagnostic biomarker and treatment target (77, 78). Li *et al.* investigated the effects of a combination of three natural polyphenols, including resveratrol, curcumin, and quercetin (RCQ), in mice with 4T1 breast cancer. RCQ treatment showed a dual effect by reducing immunosuppressive cells (such as Th2 cells, M2 macrophages, and N2 neutrophils) and increasing CD4+ and CD8+ T cells, ultimately leading to enhanced cancer cell death via ROS-induced apoptosis (29).

Dendritic cells

DCs are known to exhibit immune-suppressive characteristics, one of which is the expression of indoleamine 2,3-dioxygenase (IDO) (79). IDO is an enzyme that can inhibit T cell activation and promote immune tolerance. The overexpression of IDO creates a barrier to effective immunotherapy (79, 80). Recent studies have identified phytochemicals such as resveratrol as promising therapeutic agents that can target JAK/STAT signaling and modulate IDO expression in cancer cells, particularly in the breast TME (81, 82). Resveratrol modulates the immune response mediated by DCs by regulating IDO expression (83).

Resveratrol, at concentrations of 25-50 μM, effectively inhibits the expression and function of IDO in bone marrow-derived dendritic cells (BMDCs) through JAK/STAT signaling and protein kinase C δ (PKCδ) mechanisms. This inhibition enhances anti-tumor responses by promoting $CD8^+$ T cell polarization and increasing cytotoxic T lymphocyte (CTL) activity. *In vivo*, administration of resveratrol (50 mg/kg every 2 days for 3 weeks) has reduced tumor growth and modified IDO-mediated immune tolerance in mice with EG7 thymoma (83).

A pilot study with 10 healthy male participants evaluated the Kynurenine/ Tryptophan (Kyn/Trp) ratio as an indicator of IDO activity after administering 5 g of resveratrol. The results showed a significant reduction in tryptophan levels and a corresponding increase in IDO activity at 2.5 and 5 hr post-treatment compared to the placebo group. Despite the limited sample size, which characterizes this study as preliminary, the findings highlight resveratrol's effect on tryptophan metabolism, with implications for immune function, cancer progression, and cardiovascular health (84). In this study, resveratrol acutely increased IDO activity in healthy humans as an anti-inflammatory measure. Still, in long-term studies of cancer models, resveratrol inhibited IDO expression, thereby reversing immunosuppression and restoring anti-tumor immunity.

Myeloid-derived suppressor

Today, researchers are interested in how myeloid-derived suppressor cells (MDSCs) can promote tolerance in cancer, particularly regarding their contribution to peripheral tolerance in breast cancer (85, 86).

In vitro studies show that resveratrol induces apoptosis in granulocytic MDSCs (G-MDSCs). Resveratrol may reduce their immunosuppressive effects by decreasing ROS and Arg-1 levels while enhancing CTL activity. *In vivo*, administration of resveratrol (50 mg/kg daily for 3 weeks) has decreased G-MDSCs levels and promoted the expansion of $CD8^+$ IFN-γ^+ cells in mice with LLC tumors (87). Resveratrol has promoted the maturation of monocytic-MDSCs (M-MDSC) into $CD11c^+$ and $F4/80^+$ cells *in vitro*, but did not significantly alter M-MDSC levels in living organisms after treatment (87). Notably, the reduction in MDSC accumulation appears linked to lower HMGB1 levels after resveratrol treatment, highlighting the crucial role of HMGB1 in MDSC growth and tumor evasion (87, 88).

T lymphocytes

Resveratrol is being explored as a potential adjunct therapy for lung metastasis in TNBC due to its ability to enhance local anti-tumor immune responses. It promotes the activation of $CD8^+$ T cells and increases the production of IFN-γ and IL-2 (89). Furthermore, resveratrol treatment (12.5 or 25 mg/kg for 21 days) improved $CD8^+$ T cell cytotoxicity and Th1 responses while reducing PD-1 expression on pulmonary $CD8^+$ and $CD4^+$ T cells. This intervention reduced lung metastasis in TNBC by decreasing PD-1 levels and polarizing macrophages toward the M1 phenotype in tumor-bearing mice (90).

Sirtuins (SIRTs), classified as Class III histone deacetylases, are NAD^+-dependent enzymes that are critically involved in regulating cellular metabolism. SIRTs manage cellular responses to stress and play a crucial role in T cell metabolism and functions (91).

Craveiro *et al.* show that both low (20 μM) and high (100 μM) doses of resveratrol influence the cell cycle progression of T-cell receptor-stimulated $CD4^+$ T cells, leading to different types of cell cycle arrest. At low doses, resveratrol enhances IFN-γ secretion by activating SIRT1 deacetylase. This induces genotoxic stress and DNA damage, which subsequently activate p53 in $CD4^+$ T cells. Conversely, high concentrations disrupt antigen receptor signaling and cause cell cycle arrest in the G_1 phase. In contrast, the low-dose genotoxic stress response connects metabolic reprogramming to improved $CD4^+$ T cell effector function (92).

According to Yang *et al.*, resveratrol at concentrations under five μM suppresses anti-tumor immunity through PD-L1 modulation and the Wnt signaling pathway. Resveratrol activates SIRT1 which promotes the deacetylation and stabilization of Snail. This process represses Axin2 transcription, thereby increasing the binding of the β-catenin/TCF complex to the PD-L1 promoter in lung adenocarcinoma cells. Conversely, higher resveratrol concentrations (>40 μM) lead to a gradual decrease in PD-L1 expression (93).

SIRT2 may help attract different T cell types, such as $CD8^+$ and $CD4^+$ T cells, regulatory T cells (T_{regs}), and NK cells, and its expression is positively linked to PD-1 levels (91, 94). Triacetyl-resveratrol, a resveratrol analog, is the most effective activator of SIRT2, with an EC_{50} of 142.79 nM (94). This indicates its potential as an immunomodulatory agent that could improve overall survival in lung adenocarcinoma patients when combined with anti-PD-1 therapy (94, 95). A negative correlation between increased T_{reg} numbers in the TME and patient survival outcomes has been established (96). A single intraperitoneal dose of resveratrol (4 mg/kg) in tumor-bearing mice reduced T_{regs} and TGF-β secretion while increasing IFN-γ expression in $CD8^+$ T cells. These findings suggest that resveratrol could serve as a beneficial adjunct therapy to enhance the anti-tumor immune response (97). It was reported that resveratrol-based compounds could influence immune responses by regulating lymphocyte expansion and T_{reg} dynamics in breast cancer models (21).

A pilot randomized trial investigated the immunomodulatory effects of resveratrol in nine healthy Japanese participants, administering 1000 mg/day for 28 days. The study found that resveratrol was safe and well-tolerated, significantly increasing gamma delta (γδ) T cells and Tregs, while minimally affecting CD8+ T cells, CD4+ T cells, and CD19+ B cells. Additionally, compared with both baseline levels and control participants, plasma TNF-α and MCP-1 levels decreased significantly, while plasma antioxidant activity increased significantly (98).

In another study, resveratrol was shown to reduce oxidative stress, decrease pro-inflammatory gene expression, and increase T_{reg} numbers, which help regulate inflammation. Furthermore, the study highlighted a notable shift in cytokine production from a Th1 profile (TNF-α) to a Th2 profile (IL-10) in the splenocytes of mice (99).

The increase of PD-L1 in the TME, upregulated by T_{regs} and cancer cells, causes CTLs to become exhausted. Research shows that resveratrol can block the effects of PD-L1 on CTLs, helping to maintain anti-tumor immunity (100). Overall, resveratrol influences T-cell activation in distinct mechanisms. It suppresses $CD4^+$ T-cell activation and diminishes the inhibitory role of T_{regs} that serve to control tumor growth (101).

Tumor-evoked B_{regs} (tB_{reg})

To effectively block lung metastasis in breast cancer, it is essential to regulate T_{regs} and tB_{regs} (Tumor-evoked B_{regs}) (102). Resveratrol, administered intraperitoneally at 50 μg/mouse, has been shown to prevent breast cancer progression and metastasis by STAT3 and tB_{regs} suppression. Furthermore, by reducing TGF-β production, it prevents the conversion of tB_{regs} to T_{regs}, without influencing MDSC populations in 4T1-tumor-bearing mice (103).

Additionally, resveratrol targets PPAR-α, a nuclear receptor involved in various cellular processes, to prevent cancer cells from converting B cells into tB_{regs}. Blocking tB_{regs} suppressed T-cell proliferation, tumor progression, and lung metastasis. This intervention highlights the critical role of PPAR-α in the generation of tB_{regs} (104).

Natural killer cells

Resveratrol is emerging as a promising adjuvant in cancer immunotherapy due to its ability to enhance NK cell activity (52). It has dual effects; low doses activate NK cells, while high doses induce apoptosis through the caspase signaling pathway (105). A combination of resveratrol (20 μM) with IL-2 (5 ng/ml) significantly boosts NK cell cytotoxicity, increases IFN-γ secretion, and activates receptor expression. This effect is mediated by the activation of cellular Myeloblastosis viral oncogene homolog (c-Myb), a key transcription factor for NK cell activation (52). In an *in vivo* study in mice with B16F10 metastatic melanoma, a combination of intravenous resveratrol (0.5 mg/kg) and IL-2 resulted in a notable reduction in tumor growth and

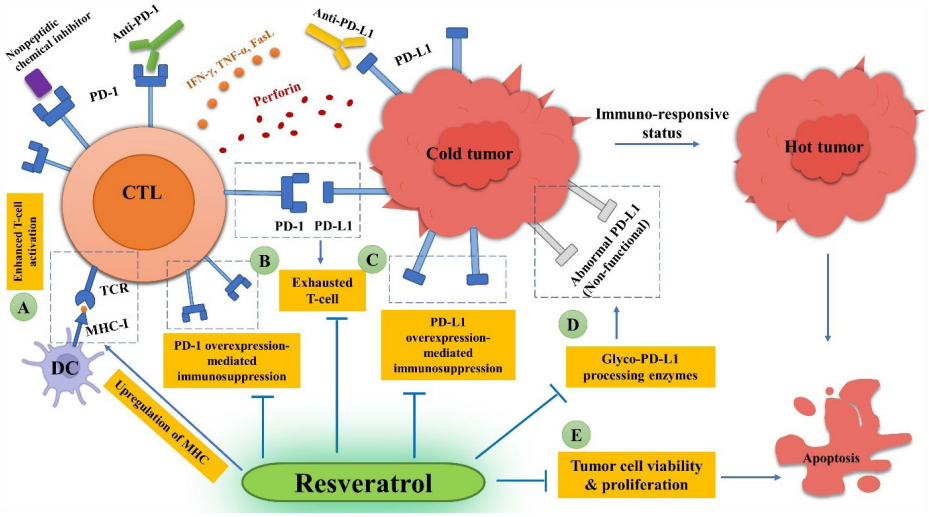

Figure 5. Dual strategies of resveratrol to enhance immunity and combat tumors via PD-1/PD-L1 regulation
(A) Enhanced immune cell activation: Resveratrol activates CTLs, critical effectors in breast tumor immunity, by upregulating MHC-I on DCs, thereby enhancing tumor cell recognition and targeting. (B &C) Immune checkpoint inhibition. Resveratrol functions as an ICI by counteracting PD-1 overexpression-mediated immunosuppression in cold tumors. It reduces the interaction between PD-1 and its ligand, PD-L1, on tumor cells, preventing T cell exhaustion. Conversely, in hot tumors, which exhibit high immune activity, resveratrol lowers PD-L1 expression, thus enhancing CTL activation and their anti-tumor effectiveness. (D) Tumor cell viability and proliferation. Resveratrol interferes with tumor cell viability by targeting glyco-PD-L1 processing enzymes, thereby affecting PD-L1 maturation, which contributes to tumor resistance to immune attack. (E) Apoptosis promotion: In addition to rendering cancer cells more susceptible to apoptosis, resveratrol directly modulates apoptotic signaling pathways.

metastasis compared with IL-2 alone (106).

Pan *et al.* conducted research on various breast cancer cell lines, treating them with resveratrol at 6.25 μM and 25 μM for 48 hr. They also administered resveratrol intraperitoneally to BCap37 tumor-bearing mice at doses of 0, 25, or 100 mg/kg/day for 28 days. The findings indicated that resveratrol significantly reduced the inhibitory effects of miR-17 on MHC class I polypeptide-related sequence A and B (MICA and MICB). This potentially enhances the cytotoxic activity of NK cells and suggests a promising therapeutic approach to improve anti-tumor immunity in breast cancer patients (107).

Humans express eight cell surface glycoproteins that act as ligands for natural killer group 2 member D (NKG2D), an activating receptor on NK cells. At a concentration of 12.5 μM, resveratrol significantly enhances the cytotoxic activity of NK cells, primarily via NKG2D-mediated ERK-1/2 and JNK-MAPK signaling pathways. Additionally, it promotes Up-regulation of perforin expression without affecting STAT3 and STAT5 protein expression levels in myeloid leukemia (K562), hepatocellular carcinoma (HepG2), and human lung adenocarcinoma (A549) cell lines (108). Resveratrol (32 μmol/l) has been shown to uniquely boost the Factor Associated with Suicide ligand (FasL) expression on human leukemia cells and breast carcinoma cells, enabling NK cells to induce apoptosis through signaling pathways (109).

Falchetti *et al.* found that low concentrations of resveratrol (up to 0.3 μg/ml) enhanced the cytotoxic activity of NK cells, whereas higher concentrations (5 and 20 μg/ml) significantly reduced it. Additionally, when peripheral blood mononuclear cells were stimulated with anti-CD3/anti-CD28 antibodies, low resveratrol concentrations (0.625-2.5 μg/ml) increased the frequency of $CD8^+$ T cells that produced IFN-γ, IL-2, and IL-4, and $CD4^+$ T cells that produced IFN-γ. However, the highest concentration of resveratrol (10 μg/ml) suppressed cytokine production (110). Resveratrol enhances the cytotoxic activity of NK cells against myeloid leukemia tumor cells, thereby increasing their susceptibility to NK cell-mediated cytotoxicity.

In summary, resveratrol shows promise as an adjuvant in cancer immunotherapy due to its ability to modulate NK cell activity. At low doses, it enhances NK cell activation, while at higher concentrations, it can induce apoptosis in NK cells. Research indicates that combining resveratrol with IL-2 boosts NK cell cytotoxicity and cytokine secretion, resulting in reduced tumor growth and metastasis. Additionally, resveratrol inhibits miR-17 expression and enhances NKG2D signaling, thereby improving anti-tumor immunity. However, its effects are concentration-dependent, as high doses may suppress NK cell function.

Dual effects of resveratrol on PD1/PD-L1 pathway

Resveratrol may enhance the effectiveness of immunotherapy by converting "cold" tumors into "hot" ones via mechanisms involving the PD-1/PD-L1 pathway (Figure 5, Table 3). Resveratrol has demonstrated pleiotropic effects on immune response. The effect of resveratrol on PD-L1 expression varies with cancer type, exposure duration, and concentration. An initial cellular stress response might activate pathways like NF-κB, leading to Up-regulation of PD-L1. With prolonged exposure, direct inhibitory mechanisms, such as the disruption of PD-L1 glycosylation and stability, may dominate, leading to a net reduction in functional PD-L1 on the cell surface (111).

Evidence from animal models suggests that combining resveratrol with immunotherapy strategies, such as intravenous immunocytokine (112) and/or ICIs, leads to better tumor control and longer survival than either treatment alone (21, 111).

Up-regulation of PD-L1

Resveratrol and one of its metabolites, piceatannol (3′,4′,3,5-*trans*-trihydroxystilbene), can increase PD-L1 levels in the human TNBC cell line (Cal51) and colon cancer cells (SW620). In addition, the synergistic effect of resveratrol and piceatannol reduces tumor cell viability. This effect was marked by increased DNA damage signals and

Table 3. Different effects of resveratrol in immunotherapy through PD1/PD-L1 pathway

Mechanism of action	Study model	Findings of study	Resveratrol's effect on immunotherapy
Inhibits Glyco-PD-L1	*In vitro* basal-like/HER2+ breast cancer cells	↑ Cytotoxic T-lymphocyte immune-surveillance in TME of breast tumor De-localization of PD-L1 through disruption in N-glycan branching PD-L1 maturation disruption (99)	Resveratrol makes tumors more vulnerable to immune attack
PD-L1 Up-regulation	*In vitro* Cal51 triple-negative breast cancer	↑ level of PD-L1 ↓ Tumor cell survival ↑DNA-damaging marker Activation of caspase-3 Inhibition of p38-MAPK/c-Myc pathways (112)	Resveratrol behaves like radiotherapy through stress response induction in tumors, making the tumor more visible to the immune system
Lowers PD-L1 expression	*In vitro* A549 and H1299 (Human lung adenocarcinoma)	Dose-dependently upregulates PD-L1 expression through snail-driven activation of the Wnt pathway (92)	
	In vitro Human oral epidermoid carcinoma cell line	Resveratrol inhibits thyroxine related PD-L1 accumulation in cancer cells Removes "off switch" signal (132)	Resveratrol decreases immune exhaustion
	TNBC with lung metastasis	↑ Anti-tumor activity of CD8+ T cells ↓ PD-1 expression on CD8+ & CD4+ T cells ↑ Macrophages to M1 phenotype (89)	Resveratrol prevents immune resistance
PD-L1 inhibition	*In vitro* Cancer stem-like cells in oral cancer cells	Nano-formulated resveratrol inhibited PD-L1 through IL-6/JAK2/STAT3 axis (133)	Resveratrol improves immunotherapy efficacy through PD-L1 inhibition
	In vitro pair ELISA & surface plasmon resonance	Inhibition of PD-1/PD-L1 Selectively bind to PD-L1 (114)	

PD-L1: Programmed death-ligand 1; HER2: Human epidermal growth factor receptor 2; TME: Tumor microenvironment; MAPK: Mitogen-activated protein kinase; c-Myc: Cellular myelocytomatosis; Wnt: Wingless-related integration site; IL-6: Interleukin 6; JAK2: Janus kinase 2; STAT3: Signal transducer and activator of transcription 3; ELISA: Enzyme-linked immunosorbent assay; PD-1: Programmed cell death protein 1; TNBC: Triple-negative breast cancer; DNA: Deoxyribonucleic acid; CD8: Cluster of differentiation 8; CD4: Cluster of Differentiation 4

caspase-3 activation via suppression of p38-MAPK/c-Myc. This research suggests that the combination of resveratrol and piceatannol, along with anti-PD-L1 immunotherapy, could be beneficial for breast cancer patients with low or no PD-L1 levels (113).

In a study by Hsieh and Wu, the synergistic effects of resveratrol and piceatannol on PD-L1 overexpression were investigated. Their combination strategy enhances the efficacy of anti-PD-1/PD-L1 immune checkpoint blockade. The goal is to enhance the detection and destruction of cold tumors with low PD-L1 expression by targeting and eliminating them via the host anti-tumor immune mechanisms (114).

Inhibition of PD-L1

Verdura *et al.* introduced a novel approach using resveratrol to combat aggressive breast cancer by targeting PD-L1 in HER2+ cells. Resveratrol directly inhibits glyco-PD-L1 processing enzymes, leading to a build-up of the abnormal glycosylated form of PD-L1. It also prevented PD-L1/PD-1 interaction and reduced PD-L1 expression on the cell surface (100). This is a direct, post-translational mechanism for downregulating functional PD-L1, thereby acting as a natural checkpoint inhibitor.

In another study, Li *et al.* conducted additional investigations into the inhibitory effects and binding capabilities of natural compounds, including resveratrol, on PD-L1. This study used a combination of two tests, including i) measuring the ability to block PD-1/PD-L1 interaction and ii) measuring the binding of compounds to PD-1 and PD-L1. The compounds were classified into four groups: PD-1/PD-L1 inhibitors, selective PD-L1 inhibitors, non-binding PD-1/PD-L1 inhibitors, and non-inhibiting PD-1/PD-L1 binders. Resveratrol is a PD-1/PD-L1 inhibitor that selectively binds to the PD-L1 protein (115). In conclusion, resveratrol functions as a multi-target agent that bridges oncogenic and immunomodulatory pathways. Its paradoxical effects on PD-L1 emphasize its biological complexity.

Challenges and future directions

In vivo and *in vitro* studies have demonstrated the anti-inflammatory and immunomodulatory effects of resveratrol; however, translating these findings into clinically significant outcomes in breast cancer treatment remains challenging

(116). The most commonly administered dose of resveratrol in clinical trials is 500 mg, followed by 1 g daily. Resveratrol is usually well-tolerated at daily doses of up to 1 g (117). It is essential to conduct a specialized, well-designed, double-blinded randomized trial (117, 118). These trials should measure appropriate biomarkers, such as serum cytokine levels, immune cell subsets, or gene expression profiles, to accurately assess immune responses (99).

One of the major challenges in using resveratrol in cancer immunotherapy is the influence of the gut microbiota on its metabolism and efficacy. Studies have shown that microbiota can significantly affect the efficacy of the PD-L1/PD-1 pathway (119) and the biological activity of resveratrol (120). This can lead to variations in resveratrol efficacy for treating breast cancer among different patients. Resveratrol, in combination with an anti-PD-1 monoclonal antibody, enhances anti-tumor effects via the gut microbiome and increases the abundance of *Desulfovibrio fairfieldensis*. Notably, prostaglandin D2 acts as a key mediator of this process by promoting CD8+ T cell infiltration into tumor tissue (121).

Resveratrol is generally well-tolerated (122), but may cause nephrotoxicity, gastrointestinal issues, and hypersensitivity reactions in some individuals (123). Its efficacy depends on dosage: low concentrations confer antioxidant benefits for cancer prevention (124), whereas high doses may induce DNA damage and oxidative stress due to pro-oxidant activity (123). The *in vivo* pharmacokinetics of resveratrol is challenged by low bioavailability, metabolic turnover, and complex metabolic pathways, including phase II hepatic detoxification and intestinal bacterial metabolism (123). Also, resveratrol stability is influenced by factors such as UV radiation, pH, and temperature (42). To optimize the therapeutic benefits of resveratrol, it is necessary to enhance its poor bioavailability and stability by developing advanced delivery systems (e.g., liposomes, cyclodextrin, solid lipid nanoparticles) and synthesizing resveratrol derivatives (125, 126). Collaborations among researchers, industry experts, and regulatory agencies are crucial for the development of advanced resveratrol-based delivery systems for clinical applications.

Conclusion

Based on the presence of TILs, tumors are classified as "hot" or "cold". A significant challenge in oncology is converting cold tumors into hot ones, thereby sensitizing them to immunotherapy. This transformation requires a multi-faceted approach targeting key mechanisms within TME. The complex interactions between immune cells and the breast cancer TME are pivotal in disease progression and resistance to immunotherapy. The inhibitory effect of resveratrol on key oncogenic pathways (PI3K/Akt/mTOR, MAPK/ERK, STAT, NF-κB, and β-catenin) not only reduces cancer cell proliferation and survival but also fundamentally reprograms the TME to facilitate immune attack. Resveratrol promotes the conversion of immunologically "cold" breast tumors to "hot" tumors through the synergistic integration of three mechanisms, i.e., immune reprogramming, oncogenic signaling disruption, and checkpoint blockade, which collectively remodel the TME.

The first aspect is the effects of resveratrol on oncogenic pathways. It inhibits the PI3K/Akt/mTOR pathway by reducing Akt phosphorylation and the activity of its downstream target mTOR, and it blocks NF-κB activation. This inhibition decreases cancer cell proliferation and promotes apoptosis. Additionally, resveratrol modulates the MAPK/ERK pathway by reducing ERK phosphorylation, thereby decreasing cancer cell survival and stimulating apoptosis. By blocking STAT phosphorylation and NF-κB activation, resveratrol prevents the nuclear translocation of STATs and the expression of pro-oncogenic genes. Therefore, invasion, migration, and metastasis of cancer cells are significantly reduced. Furthermore, resveratrol inhibits the accumulation of β-catenin in the cytoplasm, which prevents its nuclear translocation. This disruption suppresses transcription of target genes critical for cell proliferation, survival, and metastasis.

The second aspect concerns resveratrol's effect on immunomodulatory cells. Resveratrol has the potential to activate immunostimulatory cells, including M1-TAMs, N1-TANs, DCs, NKs, CTLs, and Th1. This activation boosts anti-tumor immunity through increased cytokine production, antigen presentation, and cytotoxicity. Simultaneously, resveratrol inhibits the function of immunosuppressive cells that support tumor progression, including tBregs, Tregs, Th2 cells, MDSCs, M2-TAMs, and N2-TANs.

The third aspect is the dual effects of resveratrol on PD1/PD-L1 pathway. Resveratrol combats tumors through a dual strategy focused on the PD-1/PD-L1 immune checkpoint. It enhances immunity by activating $CD8^+$ cytotoxic T cells (CTLs) through improved antigen presentation on DCs. Concurrently, it acts as a natural immune checkpoint inhibitor. In cold tumors, it blocks the PD-1/PD-L1 interaction to prevent T-cell exhaustion, whereas in hot tumors, it directly downregulates PD-L1 expression on cancer cells to enhance CTL attack.

Furthermore, resveratrol damages tumor defenses by inhibiting PD-L1 maturation and inducing apoptosis in cancer cells. Beneficial effects include inhibiting PD-L1 expression on tumor cells, reducing PD-1 expression on T cells, enhancing $CD8^+$ T cell infiltration, and suppressing EMT. In some studies, resveratrol upregulated PD-L1 expression but still decreased tumor cell survival. It seems that in these cases, resveratrol behaves like radiotherapy, inducing a stress response in tumors that makes them more visible to the immune system.

However, its effectiveness is limited due to poor bioavailability, and the biological activity of its metabolites differs. Future clinical trials are essential to validate these findings, assess safety, and optimize therapeutic protocols in breast cancer treatment. Such advancements could ultimately expand the arsenal against breast cancer, offering patients more effective and personalized therapeutic options.

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Authors' Contributions

N A was responsible for conceptualization, data curation, investigation, validation, visualization, and both the original draft writing and the review and editing. B H managed supervision, validation, review, and editing. F M and MB assisted with supervision, validation, and review and editing.

Conflicts of Interest

The authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

Declaration

We have not used any AI tools or technologies to prepare this manuscript.

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