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Review

Targeting Receptor Tyrosine Kinase–Driven Drug Resistance in Breast Cancer Using Dietary Polyphenols: Molecular Crosstalk Between EGFR, HER2, VEGFR2, and Downstream Survival Pathways

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Abstract

Breast cancer progression and therapeutic resistance are strongly influenced by aberrant receptor tyrosine kinase (RTK)–mediated signaling transduction, particularly involving epidermal growth factor receptor (EGFR), human epidermal growth factor receptor-2 (HER2), and vascular endothelial growth factor receptor-2 (VEGFR2). Although RTK-targeted therapies have significantly improved patient outcomes, their long-term efficacy is frequently compromised by adaptive resistance arising from receptor crosstalk, pathway redundancy, and downstream survival signaling. Increasing attention has therefore been directed toward multitarget strategies capable of disrupting RTK signaling networks rather than individual receptors. Naturally occurring dietary polyphenols have emerged as promising candidates in this context due to their pleiotropic molecular actions, favorable safety profiles, and ability to modulate multiple oncogenic pathways simultaneously. Accumulating in-vitro and in-vivo evidence indicates that polyphenol combinations can inhibit RTK activation, suppress PI3K/AKT/mTOR and MAPK/ERK signaling, attenuate angiogenesis, reverse multidrug resistance, and promote apoptosis in breast cancer models. This review systematically examines the molecular crosstalk among EGFR, HER2, and VEGFR2 in breast cancer progression and resistance, and critically evaluates the mechanistic basis by which polyphenol combinations interfere with RTK-driven signaling transduction. Emphasis is placed on translational insights derived from experimental studies and the potential integration of polyphenol-based strategies into future precision oncology frameworks.

Keywords: Breast cancer, receptor tyrosine kinase signaling, polyphenol combinations, therapeutic resistance, in-vitro and in-vivo studies

1. Introduction: RTK Signaling and Therapeutic Resistance in Breast Cancer

Breast cancer is a biologically complex and clinically heterogeneous disease that encompasses multiple molecular subtypes with distinct pathological features, prognostic outcomes, and therapeutic responses. Advances in molecular classification have revealed that breast cancer is not a single disease entity but rather a spectrum of tumors driven by diverse genetic, epigenetic, and signaling abnormalities [1,2]. This heterogeneity underlies the variable response to therapy observed in clinical practice and represents a major obstacle to durable disease control. Among the molecular determinants that critically influence tumor progression and treatment resistance, receptor tyrosine kinases (RTKs) have emerged as central regulators of oncogenic signaling networks in breast cancer.

RTKs are transmembrane proteins that transmit extracellular growth factor signals into intracellular biochemical cascades controlling cell proliferation, survival, differentiation, migration, and angiogenesis. Aberrant RTK activation in breast cancer occurs through multiple mechanisms, including gene amplification, receptor overexpression, ligand overproduction, and constitutive kinase activation [3]. Once activated, RTKs initiate complex signaling programs that rewire cellular homeostasis toward a malignant phenotype. Importantly, these signaling programs are not linear but are highly interconnected, allowing tumor cells to adapt dynamically to therapeutic pressure.

The molecular heterogeneity of breast cancer is strongly reflected in RTK expression and signaling dependency. HER2 overexpression or amplification defines a clinically aggressive subtype accounting for approximately 15–20% of breast cancers and is associated with increased tumor proliferation and poor prognosis in the absence of targeted therapy [4]. EGFR is frequently overexpressed in basal-like and triple-negative breast cancers (TNBC), a subgroup characterized by the absence of estrogen receptor, progesterone receptor, and HER2 expression, and associated with limited treatment options and high rates of recurrence [5]. In parallel, VEGFR2-mediated signaling plays a crucial role in tumor angiogenesis, supporting tumor growth, invasion, and metastatic dissemination by ensuring sustained vascular supply [6].

Targeted therapies against RTKs have transformed the clinical management of specific breast cancer subtypes. The introduction of HER2-targeted agents significantly improved survival outcomes in HER2-positive disease, while EGFR and VEGF pathway inhibitors have been explored as therapeutic strategies in aggressive and treatment-refractory tumors [7]. Despite these advances, the long-term success of RTK-targeted therapies remains limited by the development of drug resistance. Many patients who initially respond to targeted treatment eventually experience disease progression, underscoring the adaptive capacity of breast cancer cells.

One of the primary limitations of single-target RTK inhibitors is their inability to fully suppress the complexity of oncogenic signaling networks. RTKs rarely function in isolation; instead, they engage in extensive crosstalk with other receptors and downstream pathways. Inhibition of a single RTK often results in compensatory activation of alternative receptors or signaling routes, allowing tumor cells to maintain survival signaling despite pharmacological blockade [8]. This phenomenon, commonly referred to as pathway redundancy, represents a major mechanism of therapeutic resistance in breast cancer.

Adaptive resistance is further driven by dynamic reprogramming of downstream survival pathways such as PI3K/AKT/mTOR and MAPK/ERK. These pathways serve as central signaling hubs integrating input from multiple RTKs and controlling critical cellular processes including apoptosis suppression, metabolic adaptation, and DNA damage repair [9]. Even when upstream RTK activity is effectively inhibited, persistent activation of these downstream pathways can sustain tumor viability and limit therapeutic efficacy. As a result, resistance to RTK-targeted therapy is often multifactorial and difficult to overcome with conventional monotherapies.

The emergence of adaptive resistance has prompted a shift in therapeutic paradigms from highly selective single-target inhibition toward multi-target and network-based strategies. In this context, dietary polyphenols have gained increasing attention as potential modulators of complex signaling networks in cancer. Polyphenols are naturally occurring bioactive compounds abundant in fruits, vegetables, tea, and medicinal plants, and are known to exert a wide range of biological effects, including antioxidant, anti-inflammatory, antiproliferative, and anti-angiogenic activities [10].

Unlike synthetic tyrosine kinase inhibitors that are designed to selectively target a single receptor, polyphenols exhibit pleiotropic molecular actions and can interact with multiple RTKs and intracellular signaling proteins simultaneously. This multitarget capability enables polyphenols to disrupt signaling crosstalk and suppress compensatory pathway activation, thereby addressing key mechanisms underlying RTK-driven drug resistance [11]. Importantly, accumulating in-vitro and in-vivo evidence suggests that dietary polyphenols can inhibit EGFR, HER2, and VEGFR2 signaling, modulate downstream survival pathways, reverse multidrug resistance, and enhance the efficacy of conventional chemotherapeutic agents [12].

The rationale for exploring dietary polyphenols as multi-target modulators in breast cancer is further supported by their favorable safety profile and long history of dietary exposure in humans. While challenges related to bioavailability and pharmacokinetics remain, advances in formulation strategies and combination approaches have renewed interest in their translational potential [13]. Collectively, these observations provide a strong scientific foundation for investigating dietary polyphenols as novel adjuncts in targeting RTK-driven drug resistance in breast cancer.

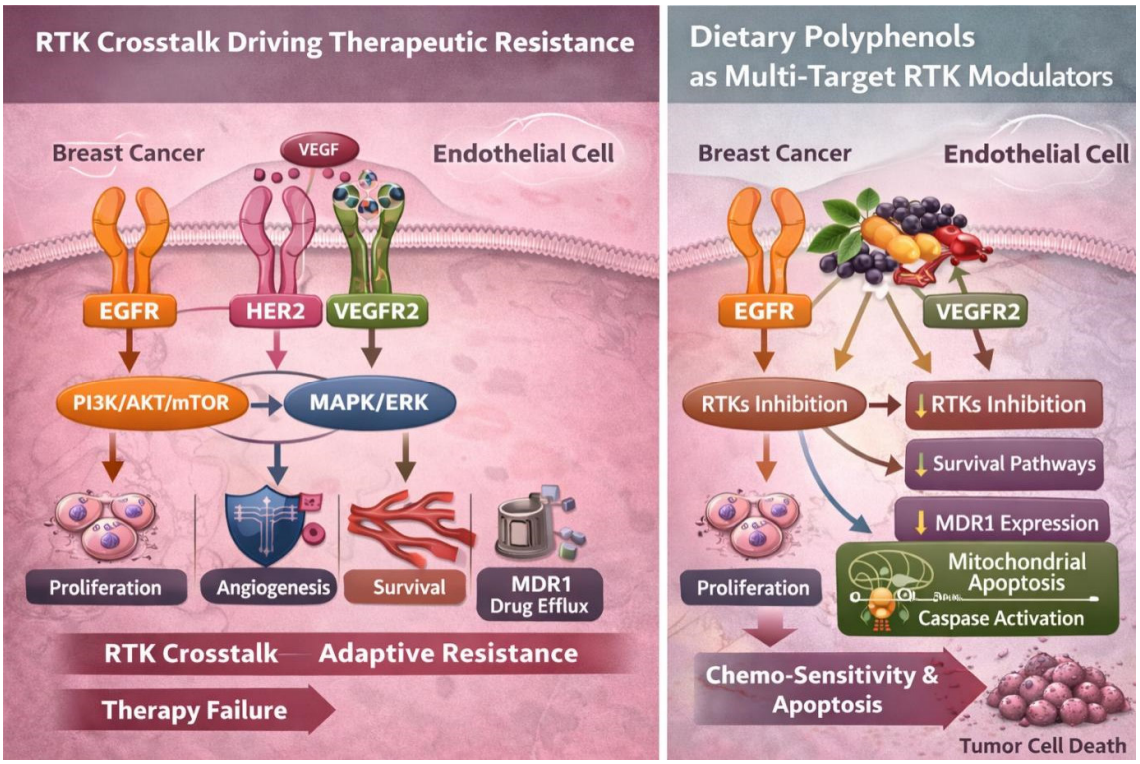

Figure 1. RTK network crosstalk (EGFR–HER2–VEGFR2) driving downstream PI3K/AKT/mTOR and MAPK/ERK activation and therapeutic resistance in breast cancer.

2. Receptor Tyrosine Kinase Crosstalk in Breast Cancer Progression

Receptor tyrosine kinase signaling in breast cancer is governed by extensive molecular crosstalk rather than linear, receptor-specific pathways. This interconnected signaling architecture enables tumor cells to integrate multiple extracellular stimuli into coordinated intracellular responses that promote proliferation, survival, angiogenesis, and resistance to therapy. Among the various RTKs implicated in breast cancer, EGFR, HER2, and VEGFR2 form a highly cooperative signaling network that reinforces malignant behavior and undermines the efficacy of targeted therapies [14,15]. Understanding the mechanistic basis of RTK crosstalk is therefore essential for identifying vulnerabilities that can be exploited therapeutically.

One of the most extensively characterized interactions in breast cancer is EGFR–HER2 heterodimerization. HER2 is unique among the ErbB family members in that it lacks a known ligand and adopts a constitutively active conformation, making it the preferred dimerization partner for ligand-activated EGFR [16]. Formation of EGFR–HER2 heterodimers results in enhanced kinase activity, prolonged receptor phosphorylation, and sustained downstream signaling compared to EGFR homodimers. This amplified signaling output drives increased cell proliferation, survival, and migratory capacity, contributing to aggressive tumor phenotypes and poor clinical outcomes [17].

EGFR–HER2 heterodimerization also plays a critical role in therapeutic resistance. In HER2-positive breast cancers treated with HER2-targeted therapies, residual or compensatory EGFR signaling can maintain downstream pathway activation despite effective HER2 blockade [18]. Conversely, inhibition of EGFR can lead to increased reliance on HER2-mediated signaling. This reciprocal compensation highlights the inherent limitation of single-receptor targeting strategies and underscores the importance of targeting RTK networks rather than individual receptors.

VEGFR2-mediated signaling adds another layer of complexity to RTK crosstalk in breast cancer progression. Although VEGFR2 is primarily expressed on endothelial cells, its activation is tightly regulated by tumor cell–derived VEGF, the expression of which is stimulated by EGFR and HER2 signaling [6,19]. This indirect cross-activation establishes a paracrine signaling loop in which tumor cells promote angiogenesis through VEGFR2 activation, while enhanced vascularization, in turn, supports tumor growth, invasion, and metastatic spread.

Angiogenic signaling mediated by VEGFR2 is not merely a supportive process but actively contributes to therapeutic resistance. Increased tumor vascularization enhances nutrient and oxygen delivery, facilitates waste removal, and promotes a microenvironment conducive to tumor survival under therapeutic stress [20]. Furthermore, VEGFR2 signaling has been shown to activate survival pathways such as PI3K/AKT and MAPK/ERK in endothelial cells, contributing to resistance against anti-angiogenic therapies and indirectly sustaining tumor cell viability [21]. Through these mechanisms, VEGFR2 functions as a critical amplifier of RTK-driven malignancy.

At the intracellular level, RTK crosstalk converges predominantly on two major signaling hubs: the PI3K/AKT/mTOR and MAPK/ERK pathways. These pathways act as central integrators of growth factor signaling and regulate a wide array of cellular processes essential for tumor progression. Activation of PI3K/AKT/mTOR signaling promotes cell survival by inhibiting pro-apoptotic factors, enhancing protein synthesis, and supporting metabolic reprogramming [9,22]. Persistent activation of this pathway is frequently observed in breast cancers with aberrant EGFR or HER2 signaling and is strongly associated with poor prognosis and therapeutic resistance.

Similarly, the MAPK/ERK pathway plays a pivotal role in driving cell proliferation and differentiation downstream of RTKs. Sustained ERK activation promotes uncontrolled cell cycle progression, enhances transcription of oncogenic genes, and facilitates epithelial–mesenchymal transition, a process linked to invasion and metastasis [23]. Importantly, MAPK/ERK signaling can remain active even when upstream RTKs are inhibited, due to compensatory signaling through alternative receptors or mutations in downstream components. This signaling plasticity contributes significantly to resistance against RTK-targeted therapies.

The convergence of multiple RTKs on shared downstream pathways creates a robust signaling network capable of maintaining oncogenic signaling under diverse conditions. When one RTK is pharmacologically inhibited, alternative RTKs can activate the same downstream pathways, preserving critical survival signals [8,24]. This redundancy explains why inhibition of a single RTK often produces only transient clinical responses and highlights the need for strategies that disrupt signaling convergence points rather than individual receptors alone.

Table 1. Molecular Crosstalk Between EGFR, HER2, and VEGFR2 and Their Contribution to Drug Resistance in Breast Cancer

RTK	Primary Activation Mechanism	Downstream Pathways Activated	Role in Tumor Progression	Mechanism of Drug Resistance
EGFR	Ligand binding (EGF, TGF-α); overexpression in TNBC	PI3K/AKT/mTOR; MAPK/ERK	Promotes proliferation, migration, invasion	Compensatory HER2 activation; persistent downstream signaling despite EGFR inhibition
HER2	Gene amplification; constitutive activation; heterodimerization with EGFR	PI3K/AKT/mTOR; MAPK/ERK	Aggressive growth phenotype; enhanced survival signaling	EGFR-mediated bypass signaling; activation of PI3K mutations; downstream pathway reactivation
VEGFR2	VEGF-mediated activation (tumor-derived VEGF)	PI3K/AKT; MAPK/ERK	Angiogenesis; vascularization; metastatic facilitation	Increased tumor vascular supply; microenvironment-mediated survival support
EGFR–HER2 Heterodimer	Receptor heterodimerization	Amplified AKT and ERK signaling	Sustained proliferative signaling	Reduced sensitivity to single RTK inhibitors
RTK Convergence Node	Multiple RTKs activating shared pathways	PI3K/AKT/mTOR; MAPK/ERK	Network-level oncogenic maintenance	Pathway redundancy; adaptive signaling rewiring

RTK crosstalk also fuels therapeutic resistance by promoting adaptive rewiring of signaling networks. Exposure to RTK inhibitors can induce upregulation of compensatory RTKs, increased ligand production, or activation of parallel pathways, allowing tumor cells to bypass the inhibited receptor [25]. These adaptive responses are facilitated by the intrinsic plasticity of RTK signaling networks and are further reinforced by interactions with the tumor microenvironment.

Collectively, EGFR–HER2 heterodimerization, VEGFR2-mediated angiogenic signaling, and convergence on PI3K/AKT/mTOR and MAPK/ERK pathways form a tightly interconnected network that drives breast cancer progression and therapy resistance. This network-level organization underscores the inadequacy of single-target therapeutic approaches and provides a strong rationale for exploring multi-target strategies capable of disrupting RTK crosstalk and downstream survival signaling.

3. Dietary Polyphenols as Multi-Target RTK Modulators

Dietary polyphenols comprise a large and structurally diverse class of naturally occurring phytochemicals widely distributed in fruits, vegetables, whole grains, tea, wine, and medicinal plants. These compounds are characterized by multiple phenolic rings and hydroxyl substitutions, which confer strong redox activity and enable diverse molecular interactions with proteins involved in oncogenic signaling [10,26]. Unlike conventional tyrosine kinase inhibitors (TKIs), which are designed for high specificity against individual receptor tyrosine kinases, polyphenols exhibit pleiotropic biological activities and can simultaneously modulate multiple signaling molecules within interconnected pathways. This multitarget property positions dietary polyphenols as attractive candidates for addressing RTK-driven signaling redundancy and adaptive resistance in breast cancer.

At the molecular level, the structural features of polyphenols enable promiscuous binding to RTKs and intracellular kinases. The presence of planar aromatic rings allows π–π stacking interactions with amino acid residues within kinase domains, while hydroxyl groups facilitate hydrogen bonding with ATP-binding pockets and regulatory regions [27]. These interactions do not necessarily result in complete kinase inhibition but rather lead to partial and sustained suppression of receptor activation. Such

modulation is particularly advantageous in the context of complex signaling networks, as it reduces selective pressure for resistance while dampening oncogenic signaling output across multiple nodes.

Extensive in-vitro evidence demonstrates that dietary polyphenols inhibit EGFR activation in breast cancer cell lines. Polyphenol treatment has been shown to reduce EGFR phosphorylation, suppress downstream signaling, and promote receptor internalization and degradation [28,29]. These effects translate into decreased cell proliferation, reduced migratory potential, and enhanced sensitivity to cytotoxic agents. Importantly, EGFR inhibition by polyphenols has been observed in triple-negative breast cancer models, where EGFR signaling plays a dominant role in tumor aggressiveness and therapeutic resistance [5,30].

HER2 signaling is similarly susceptible to modulation by dietary polyphenols. Several polyphenolic compounds attenuate HER2 kinase activity and disrupt HER2-driven downstream signaling cascades, particularly PI3K/AKT/mTOR and MAPK/ERK pathways [31,32]. In HER2-positive breast cancer models, polyphenol-mediated suppression of HER2 signaling reduces oncogenic dependence on this receptor and limits compensatory signaling through alternative RTKs. These findings suggest that polyphenols may enhance the durability of HER2-targeted therapies by interfering with resistance-associated signaling adaptations.

VEGFR2 inhibition represents another critical mechanism through which dietary polyphenols exert anticancer effects. Polyphenols suppress VEGFR2 phosphorylation and downstream angiogenic signaling, leading to impaired endothelial cell proliferation, migration, and tube formation in in-vitro angiogenesis models [19,33]. By limiting VEGFR2-mediated angiogenesis, polyphenols indirectly restrict tumor growth and metastasis while simultaneously enhancing the efficacy of cytotoxic therapies through improved drug penetration and reduced tumor hypoxia.

When compared with conventional TKIs, dietary polyphenols exhibit distinct pharmacological profiles. TKIs are designed to achieve potent and selective inhibition of specific RTKs, often resulting in rapid tumor regression but also promoting the emergence of resistance through pathway bypass mechanisms [7,8]. Polyphenols, in contrast, exert moderate but broad-spectrum inhibition across multiple RTKs and downstream pathways. This network-level modulation reduces compensatory signaling and may delay or prevent adaptive resistance. Moreover, the favorable safety profile of polyphenols allows their long-term use as adjuncts to standard therapies, an advantage not always feasible with synthetic TKIs due to dose-limiting toxicities [34].

Among dietary polyphenols, flavones, flavanones, and phenolic acids have been most extensively studied for their RTK-modulatory properties. Flavones, such as luteolin and apigenin, possess planar structures that facilitate interaction with kinase domains and effectively suppress EGFR and HER2 signaling [16,35]. Flavanones, including naringenin and hesperetin, exhibit flexible conformations that support anti-angiogenic activity through VEGFR2 inhibition and modulation of redox-sensitive pathways [21,36]. Phenolic acids, such as caffeic and gallic acid, indirectly suppress RTK signaling by modulating oxidative stress, inflammatory mediators, and transcriptional regulators involved in growth factor signaling [37].

Table 2. Dietary Polyphenols Targeting RTK Signaling and Downstream Resistance Mechanisms in Breast Cancer

Polyphenol Class	Representative Compounds	Primary RTK Target(s)	Downstream Effects	Anti-Resistance Mechanisms
Flavones	Luteolin, Apigenin	EGFR, HER2	↓ AKT phosphorylation; ↓ ERK activation	Inhibits compensatory RTK signaling; induces apoptosis

Flavanones	Naringenin, Hesperetin	VEGFR2, EGFR	↓ Angiogenic signaling; ↓ PI3K activation	Suppresses tumor vascularization; enhances drug penetration
Catechins	EGCG	EGFR, HER2	↓ RTK phosphorylation; ↓ mTOR activity	Restores chemosensitivity; inhibits MDR1 expression
Stilbenes	Resveratrol	HER2, PI3K	↓ AKT signaling; mitochondrial depolarization	Induces caspase activation; overcomes apoptosis resistance
Phenolic Acids	Caffeic acid, Gallic acid	Indirect RTK modulation	↓ Oxidative stress–mediated signaling	Reduces inflammatory survival signals; enhances cytotoxic drug response
Polyphenol Combinations	EGCG + Resveratrol; Luteolin + Quercetin	Multi-RTK network suppression	Broad inhibition of PI3K/AKT/mTOR & MAPK/ERK	Synergistic apoptosis induction; MDR1 downregulation; reduced adaptive resistance

The complementary molecular actions of these polyphenol classes form the basis for combination-based approaches targeting RTK-driven signaling networks. By simultaneously modulating EGFR, HER2, and VEGFR2, dietary polyphenols disrupt receptor crosstalk and attenuate convergence on downstream survival pathways. This multitarget strategy offers a mechanistically sound approach to overcoming the limitations of single-target therapies and provides a strong rationale for further investigation of polyphenols as modulators of RTK-driven drug resistance in breast cancer.

4. Downstream Survival Pathways and Resistance Modulation

The oncogenic impact of receptor tyrosine kinase signaling in breast cancer is largely mediated through downstream survival pathways that integrate inputs from multiple receptors and translate them into cellular programs favoring proliferation, stress tolerance, and resistance to therapy. Among these, the phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR) pathway and the mitogen-activated protein kinase/extracellular signal–regulated kinase (MAPK/ERK) pathway represent central signaling hubs that sustain malignant phenotypes even when upstream receptors are pharmacologically inhibited [9,13]. Persistent activation of these pathways is a defining feature of RTK-driven breast cancers and a major determinant of therapeutic failure.

The PI3K/AKT/mTOR axis is one of the most frequently dysregulated signaling cascades in breast cancer and is strongly associated with poor prognosis, disease progression, and resistance to systemic therapy. Activation of this pathway downstream of EGFR, HER2, and VEGFR2 promotes cell survival by inhibiting pro-apoptotic signaling, enhancing protein synthesis, and supporting metabolic reprogramming required for rapid tumor growth [22]. Even in the presence of effective RTK inhibition, constitutive or compensatory activation of PI3K/AKT/mTOR signaling can maintain oncogenic output, thereby limiting the clinical efficacy of targeted therapies.

Dietary polyphenols have demonstrated a robust capacity to suppress PI3K/AKT/mTOR signaling through both indirect and direct mechanisms. By inhibiting upstream RTKs, polyphenols reduce the initiation of PI3K signaling, while additional evidence suggests that certain polyphenols can directly modulate PI3K and AKT activity through interactions with regulatory domains [26,31]. In-vitro studies across multiple breast cancer cell lines show that polyphenol treatment decreases AKT phosphorylation, inhibits mTOR complex activation, and suppresses downstream effectors involved in protein translation and cell growth [35]. These molecular effects translate into reduced proliferation and enhanced susceptibility to apoptotic stimuli.

Suppression of PI3K/AKT/mTOR signaling by polyphenols is particularly relevant in the context of therapeutic resistance. Hyperactivation of this pathway has been implicated in resistance to HER2-targeted therapies, endocrine agents, and chemotherapeutic drugs [15]. Polyphenol-mediated inhibition of PI3K/AKT/mTOR signaling restores apoptotic sensitivity and enhances the cytotoxic effects of conventional therapies, suggesting a role for polyphenols as chemosensitizing agents in resistant breast cancer models [24,30]. Importantly, these effects have been observed at concentrations achievable through dietary supplementation or optimized formulations, supporting their translational relevance.

In parallel with survival signaling, RTK activation contributes to multidrug resistance through upregulation of ATP-binding cassette transporters, particularly multidrug resistance protein-1 (MDR1/P-glycoprotein). MDR1 functions as an efflux pump that reduces intracellular accumulation of chemotherapeutic agents, thereby diminishing their cytotoxic efficacy [23]. Transcriptional regulation of MDR1 expression is closely linked to RTK-driven signaling pathways, including PI3K/AKT and MAPK/ERK, which activate downstream transcription factors involved in drug resistance [38].

Dietary polyphenols have been shown to inhibit MDR1 expression and function, thereby counteracting one of the most clinically relevant mechanisms of chemotherapy resistance. In-vitro studies demonstrate that polyphenol treatment downregulates MDR1 gene expression and reduces efflux activity, leading to increased intracellular drug retention and enhanced cytotoxicity [24,39]. These findings are supported by in-vivo evidence showing improved therapeutic response and reduced tumor burden when polyphenols are combined with standard chemotherapeutic agents [22]. By targeting both signaling-mediated and transporter-mediated resistance mechanisms, polyphenols exert a dual resistance-modulating effect.

Beyond their impact on survival pathways and drug efflux, polyphenols also modulate key regulators of cell cycle progression downstream of RTK signaling. Aberrant activation of EGFR and HER2 promotes cell cycle progression through upregulation of cyclins and cyclin-dependent kinases, facilitating unchecked proliferation [25]. Polyphenols disrupt this process by downregulating cyclins, inhibiting cyclin-dependent kinase activity, and inducing cell cycle arrest at critical checkpoints [27]. This growth-inhibitory effect complements their pro-apoptotic and chemosensitizing actions.

Polyphenols further influence the balance between pro- and anti-apoptotic proteins downstream of RTK signaling. RTK-driven activation of PI3K/AKT and MAPK/ERK pathways enhances expression of anti-apoptotic members of the Bcl-2 family, thereby raising the threshold for programmed cell death [26]. Polyphenol treatment reduces expression of these anti-apoptotic proteins while promoting pro-apoptotic signaling, effectively lowering the apoptotic threshold of breast cancer cells [34]. This coordinated modulation of survival and death pathways enhances the overall vulnerability of tumor cells to therapeutic intervention.

The link between polyphenol-mediated pathway suppression and chemotherapy sensitization has significant clinical implications. Resistance to chemotherapy remains a major challenge in breast cancer management, particularly in advanced and metastatic disease. By inhibiting PI3K/AKT/mTOR signaling, suppressing MDR1/P-glycoprotein expression, and reprogramming cell cycle and apoptotic regulators, polyphenols create a cellular environment more permissive to cytotoxic drug action [29,31]. This multifaceted modulation addresses several resistance mechanisms simultaneously, offering a strong mechanistic rationale for incorporating polyphenols into combination therapeutic strategies.

Collectively, dietary polyphenols target critical downstream survival pathways that lie at the intersection of RTK signaling networks. Through suppression of PI3K/AKT/mTOR activity, inhibition of drug efflux mechanisms, modulation of cell cycle regulators, and enhancement of apoptotic sensitivity, polyphenols effectively dismantle key resistance programs in breast cancer. These properties underscore their potential as adjunct agents in overcoming RTK-driven drug resistance and improving therapeutic outcomes.

5. Polyphenol-Induced Apoptosis and Anti-Angiogenic Mechanisms

Evasion of apoptosis and sustained angiogenesis are fundamental hallmarks of breast cancer progression and are tightly regulated by receptor tyrosine kinase–mediated signaling networks. Aberrant activation of EGFR, HER2, and VEGFR2 promotes tumor cell

survival by suppressing intrinsic apoptotic pathways and simultaneously fostering a pro-angiogenic tumor microenvironment that supports growth, invasion, and metastatic dissemination [25,28]. Consequently, therapeutic strategies that can reactivate apoptosis while concurrently inhibiting angiogenesis are critical for effectively targeting RTK-driven breast cancers.

Dietary polyphenols have demonstrated a strong capacity to induce apoptosis in breast cancer cells through modulation of mitochondrial integrity. The intrinsic apoptotic pathway is primarily regulated by mitochondrial membrane potential, which determines the release of pro-apoptotic factors such as cytochrome c into the cytosol. RTK-driven activation of PI3K/AKT signaling stabilizes mitochondrial membranes and suppresses pro-apoptotic proteins, thereby raising the threshold for programmed cell death [26]. Polyphenols counteract this effect by disrupting mitochondrial membrane potential, leading to mitochondrial outer membrane permeabilization and initiation of apoptosis.

In-vitro studies consistently show that treatment with dietary polyphenols results in mitochondrial depolarization in breast cancer cell lines, an effect closely associated with inhibition of upstream RTK signaling and downstream survival pathways [27,34]. Loss of mitochondrial membrane potential facilitates the release of cytochrome c and other apoptogenic factors, triggering activation of initiator caspases and downstream executioner caspases. This mitochondrial-mediated apoptosis represents a key mechanism through which polyphenols overcome resistance to cell death in RTK-overexpressing tumors.

Activation of the caspase cascade is a defining feature of polyphenol-induced apoptosis. Following mitochondrial depolarization, polyphenols promote activation of caspase-9, which in turn activates caspase-3 and other executioner caspases responsible for DNA fragmentation and cellular dismantling [26,27]. Importantly, this caspase activation occurs alongside suppression of anti-apoptotic Bcl-2 family proteins and upregulation of pro-apoptotic mediators, reflecting a coordinated reprogramming of apoptotic signaling. Such comprehensive modulation is particularly significant in breast cancers that exhibit strong RTK-driven apoptosis resistance.

Beyond direct induction of tumor cell apoptosis, dietary polyphenols exert potent anti-angiogenic effects that further inhibit breast cancer progression. Tumor angiogenesis is primarily driven by VEGFR2 signaling in endothelial cells and is essential for maintaining tumor vascularization, nutrient delivery, and metastatic potential [28,29]. Activation of EGFR and HER2 in tumor cells enhances VEGF production, thereby indirectly stimulating VEGFR2-mediated angiogenesis and reinforcing RTK crosstalk within the tumor microenvironment.

Polyphenols interfere with this process by inhibiting VEGFR2 phosphorylation and downstream angiogenic signaling pathways. In-vitro angiogenesis models demonstrate that polyphenol treatment suppresses endothelial cell proliferation, migration, and tube formation, indicating direct inhibition of VEGFR2-dependent angiogenic responses [19,33]. This anti-angiogenic activity limits the formation of new blood vessels required for tumor expansion and contributes to growth suppression.

In-vivo studies further corroborate the anti-angiogenic effects of dietary polyphenols. Experimental breast cancer models show that polyphenol administration reduces microvessel density within tumors and impairs tumor vascularization, leading to restricted tumor growth and enhanced sensitivity to cytotoxic therapies [22,29]. Reduced angiogenesis also alleviates tumor hypoxia, a condition known to promote therapy resistance and aggressive tumor behavior. By targeting VEGFR2-mediated angiogenesis, polyphenols disrupt the supportive role of the tumor microenvironment in sustaining RTK-driven malignancy.

The dual capacity of dietary polyphenols to induce apoptosis and inhibit angiogenesis underscores their therapeutic versatility. By simultaneously targeting tumor cell survival mechanisms and the vascular infrastructure that supports tumor growth, polyphenols exert a multifaceted anticancer effect that addresses multiple hallmarks of cancer. This integrated action is particularly valuable in the context of RTK-driven breast cancers, where redundancy and adaptability of signaling networks undermine the efficacy of single-target therapies.

Collectively, polyphenol-induced mitochondrial membrane depolarization, caspase cascade activation, and VEGFR2-mediated angiogenesis inhibition represent critical mechanisms through which dietary polyphenols suppress breast cancer progression. These effects complement their ability to modulate RTK signaling and downstream survival pathways, reinforcing the rationale for incorporating

polyphenols into multi-target therapeutic strategies aimed at overcoming drug resistance.

6. Synergistic Polyphenol Combinations and Translational Implications

The complex and redundant nature of receptor tyrosine kinase–mediated signaling networks in breast cancer necessitates therapeutic strategies that extend beyond single-agent interventions. While individual polyphenols exhibit measurable anticancer activity, increasing evidence indicates that **polyphenol combinations outperform monotherapy** by exerting synergistic effects across multiple molecular targets simultaneously. This synergy arises from the ability of different polyphenols to modulate distinct yet interconnected components of RTK signaling networks, downstream survival pathways, and mitochondrial apoptotic machinery, resulting in a more comprehensive disruption of oncogenic signaling [30,31].

One of the primary reasons polyphenol combinations demonstrate superior efficacy is their capacity to **simultaneously suppress multiple RTKs**, including EGFR, HER2, and VEGFR2. Whereas inhibition of a single RTK often leads to compensatory activation of alternative receptors, combined polyphenols reduce the overall signaling output of the RTK network, thereby minimizing pathway bypass mechanisms [8,24]. Experimental studies have shown that combined polyphenols produce greater inhibition of RTK phosphorylation and more sustained suppression of downstream PI3K/AKT/mTOR and MAPK/ERK signaling compared with individual compounds [26,35]. This network-level inhibition is particularly effective in attenuating signaling plasticity, a hallmark of therapy-resistant breast cancers.

Molecular synergy among polyphenols also extends to **mitochondrial and apoptotic pathways**. Different polyphenols modulate distinct aspects of mitochondrial homeostasis, including reactive oxygen species balance, mitochondrial membrane potential, and expression of Bcl-2 family proteins. When used in combination, these effects converge to amplify mitochondrial dysfunction, promote cytochrome c release, and enhance caspase activation [26,27]. This coordinated engagement of intrinsic apoptotic pathways lowers the threshold for programmed cell death and overcomes the apoptosis resistance commonly associated with chronic RTK activation.

The translational relevance of polyphenol combinations is particularly evident in **triple-negative breast cancer (TNBC)**. TNBC is characterized by high EGFR expression, elevated angiogenic signaling, and limited availability of molecularly targeted therapies, resulting in poor prognosis and high rates of recurrence [5]. Polyphenol combinations that suppress EGFR signaling, inhibit VEGFR2-mediated angiogenesis, and sensitize tumor cells to chemotherapy offer a promising adjunct strategy in this aggressive subtype. Preclinical studies demonstrate that TNBC cells exhibit enhanced sensitivity to combined polyphenol treatment, with marked reductions in proliferation, invasion, and survival signaling [30,32].

Similarly, **HER2-positive breast cancer** represents a clinically important context in which polyphenol combinations may provide added benefit. Although HER2-targeted therapies have substantially improved outcomes, resistance frequently develops due to compensatory RTK signaling and downstream pathway reactivation [18]. Polyphenols can complement HER2-targeted agents by suppressing parallel signaling routes, inhibiting PI3K/AKT/mTOR activation, and promoting apoptotic sensitivity, thereby delaying or overcoming resistance [31,34]. These observations support the integration of polyphenols into combination regimens designed to enhance the durability of targeted therapy responses.

Despite their promise, several **limitations** must be addressed to facilitate clinical translation of polyphenol-based strategies. A major challenge is **bioavailability**, as many polyphenols exhibit poor absorption, rapid metabolism, and limited systemic exposure following oral administration [32,33]. Additionally, **dose optimization** remains critical, as effective concentrations observed in preclinical studies may not be readily achievable through diet alone. Interindividual variability in metabolism and gut microbiota composition further complicates standardization of polyphenol-based interventions.

Future research should prioritize **rational design of polyphenol combinations** informed by molecular profiling of tumors and RTK signaling dependencies. Advances in formulation science, including nano-delivery systems and targeted carriers, offer promising avenues to enhance bioavailability, stability, and tumor-specific accumulation of polyphenols [35]. Moreover, integration of polyphenols as **adjuvant agents** alongside standard therapies, rather than as

standalone treatments, may provide the greatest clinical benefit by exploiting their resistance-modulating properties while minimizing toxicity.

In summary, synergistic polyphenol combinations represent a biologically grounded and translationally relevant approach to targeting RTK-driven drug resistance in breast cancer. By concurrently disrupting RTK crosstalk, suppressing downstream survival pathways, and amplifying mitochondrial apoptotic signaling, polyphenols address multiple mechanisms of therapeutic failure. Continued validation through well-designed in-vitro, in-vivo, and early-phase clinical studies will be essential to define their role within precision oncology frameworks.

7. Conclusion and Future Perspectives

Receptor tyrosine kinase–driven signaling networks represent a central axis in breast cancer progression, therapeutic resistance, and disease recurrence. The molecular crosstalk among EGFR, HER2, and VEGFR2, together with their convergence on downstream survival pathways such as PI3K/AKT/mTOR and MAPK/ERK, creates a highly adaptable signaling architecture that enables tumor cells to withstand pharmacological pressure and evade cell death. Accumulating experimental and clinical evidence demonstrates that this signaling redundancy and plasticity fundamentally limit the long-term efficacy of single-target RTK inhibitors, despite their initial therapeutic success [7–9,15].

This review highlights that breast cancer should be viewed not as a disease driven by isolated oncogenic receptors, but rather as a malignancy sustained by **interconnected RTK signaling networks**. EGFR–HER2 heterodimerization amplifies proliferative and survival signaling, VEGFR2-mediated angiogenesis reinforces tumor–microenvironment interactions, and downstream pathway convergence ensures continuity of oncogenic signaling even under targeted inhibition. Together, these mechanisms explain the frequent emergence of adaptive resistance and underscore the need for **network-oriented therapeutic strategies** rather than receptor-specific monotherapies [14,18,24].

Dietary polyphenols emerge as compelling multi-target modulators within this framework. Unlike conventional tyrosine kinase inhibitors, polyphenols possess structural features that enable promiscuous yet biologically meaningful interactions with multiple RTKs and intracellular kinases. Through simultaneous modulation of EGFR, HER2, and VEGFR2 signaling, polyphenols disrupt RTK crosstalk and attenuate convergence on PI3K/AKT/mTOR and MAPK/ERK pathways. In-vitro and in-vivo studies consistently demonstrate that polyphenols suppress tumor cell proliferation, reverse apoptosis resistance, inhibit angiogenesis, and sensitize breast cancer cells to chemotherapy and targeted agents [10,26,30].

A key strength of polyphenol-based strategies lies in their ability to target **downstream survival mechanisms** that underlie drug resistance. Suppression of PI3K/AKT/mTOR signaling restores apoptotic competence, while inhibition of MDR1/P-glycoprotein reduces drug efflux and enhances intracellular accumulation of cytotoxic agents. In parallel, modulation of cell cycle regulators and anti-apoptotic proteins lowers the threshold for programmed cell death. These coordinated effects dismantle multiple resistance mechanisms simultaneously, providing a strong mechanistic rationale for the use of polyphenols as resistance-modulating agents in breast cancer therapy [22,24,31].

The capacity of dietary polyphenols to induce mitochondrial dysfunction and activate caspase-dependent apoptosis further reinforces their anticancer potential. By promoting mitochondrial membrane depolarization and triggering intrinsic apoptotic pathways, polyphenols overcome one of the most formidable barriers in RTK-driven malignancies—evasion of cell death. Concurrent inhibition of VEGFR2-mediated angiogenesis disrupts tumor vascularization, depriving tumors of essential nutrients and oxygen while enhancing the efficacy of systemic therapies. This dual targeting of tumor cells and the tumor microenvironment distinguishes polyphenols from many conventional targeted agents [26–29].

Importantly, growing evidence indicates that **polyphenol combinations outperform monotherapy**, owing to molecular synergy at both RTK and mitochondrial levels. Different polyphenols modulate complementary signaling nodes, resulting in broader and more sustained suppression of oncogenic networks. This approach is particularly relevant for aggressive breast cancer subtypes such as triple-negative breast cancer, where EGFR overexpression and angiogenic signaling dominate, and for HER2-positive disease, where compensatory pathway activation undermines targeted therapy durability. In these contexts, polyphenol combinations offer a

promising adjunct strategy to enhance therapeutic response and delay resistance onset [5,30–32].

Despite compelling mechanistic and preclinical evidence, several challenges must be addressed before dietary polyphenols can be fully integrated into clinical practice. Limited bioavailability, rapid metabolism, and variability in systemic exposure remain major obstacles. Additionally, optimal dosing strategies and standardization of polyphenol combinations require careful investigation. Advances in drug delivery technologies, including nano-formulations and targeted carriers, hold significant promise for improving bioavailability and tumor-specific accumulation of polyphenols, thereby bridging the gap between experimental efficacy and clinical applicability [32–35].

Future research should focus on **rational, mechanism-guided integration of polyphenols into existing therapeutic regimens**, supported by molecular profiling of RTK signaling dependencies. Well-designed in-vitro, in-vivo, and early-phase clinical studies will be essential to define optimal combinations, dosing schedules, and patient populations most likely to benefit. Moreover, incorporation of polyphenols into precision oncology frameworks may enable personalized modulation of RTK signaling networks while minimizing toxicity.

In conclusion, targeting RTK-driven drug resistance in breast cancer using dietary polyphenols represents a biologically sound and translationally relevant strategy. By simultaneously disrupting RTK crosstalk, suppressing downstream survival pathways, inhibiting angiogenesis, and reactivating apoptotic signaling, polyphenols address multiple hallmarks of cancer in an integrated manner. Continued multidisciplinary efforts integrating molecular biology, pharmacology, and clinical oncology are warranted to fully realize the potential of polyphenol-based network therapeutics in improving outcomes for patients with breast cancer [36–40].

References

1. Harbeck N, Penault-Llorca F, Cortes J, Gnant M, Houssami N, Poortmans P, et al. Breast cancer. Nat Rev Dis Primers. 2019;5:66.
2. Loibl S, Poortmans P, Morrow M, Denkert C, Curigliano G. Breast cancer. Lancet. 2021;397:1750–69.
3. Yarden Y, Pines G. The ERBB network: at last, cancer therapy meets systems biology. Nat Rev Cancer. 2012;12:553–63.
4. Arteaga CL, Engelman JA. ERBB receptors: from oncogene discovery to basic science to mechanism-based cancer therapeutics. Cancer Cell. 2014;25:282–303.
5. Baselga J, Swain SM. Novel anticancer targets: revisiting ERBB2 and discovering ERBB3. Nat Rev Cancer. 2009;9:463–75.
6. Foulkes WD, Smith IE, Reis-Filho JS. Triple-negative breast cancer. N Engl J Med. 2010;363:1938–48.
7. Holohan C, Van Schaeybroeck S, Longley DB, Johnston PG. Cancer drug resistance: an evolving paradigm. Nat Rev Cancer. 2013;13:714–26.
8. Gottesman MM, Lavi O, Hall MD, Gillet JP. Toward a better understanding of the complexity of cancer drug resistance. Annu Rev Pharmacol Toxicol. 2016;56:85–102.
9. Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015;15:7–24.
10. Samatar AA, Poulikakos PI. Targeting RAS–ERK signalling in cancer: promises and challenges. Nat Rev Drug Discov. 2014;13:928–42.
11. Miller TW, Rexer BN, Garrett JT, Arteaga CL. Mutations in the phosphatidylinositol 3-kinase pathway: role in therapeutic resistance in breast cancer. Oncogene. 2011;30:4345–53.
12. Apte RS, Chen DS, Ferrara N. VEGF in signaling and disease: beyond discovery and development. Cell. 2019;176:1248–64.
13. Ellis LM, Hicklin DJ. VEGF-targeted therapy: mechanisms of anti-tumour activity. Nat Rev Cancer. 2008;8:579–91.
14. Ferrara N, Adamis AP. Ten years of anti-vascular endothelial growth factor therapy. Nat Rev Drug Discov. 2016;15:385–403.

15. Carmeliet P, Jain RK. Angiogenesis in cancer and other diseases. Nature. 2000;407:249–57.

16. Scalbert A, Johnson IT, Saltmarsh M. Polyphenols: antioxidants and beyond. Am J Clin Nutr. 2005;81:215S–7S.

17. Manach C, Scalbert A, Morand C, Rémésy C, Jiménez L. Polyphenols: food sources and bioavailability. Am J Clin Nutr. 2004;79:727–47.

18. D'Archivio M, Filesi C, Vari R, Scazzocchio B, Masella R. Bioavailability of the polyphenols: status and controversies. Int J Mol Sci. 2010;11:1321–42.

19. Vauzour D, Rodriguez-Mateos A, Corona G, Oruna-Concha MJ, Spencer JPE. Polyphenols and human health: prevention of disease and mechanisms of action. Nutrients. 2010;2:1106–31.

20. Aggarwal BB, Shishodia S. Molecular targets of dietary agents for prevention and therapy of cancer. Biochem Pharmacol. 2006;71:1397–421.

21. Russo M, Spagnuolo C, Tedesco I, Bilotto S, Russo GL. The flavonoid quercetin in disease prevention and therapy: facts and fancies. Biochem Pharmacol. 2012;83:6–15.

22. Tang SM, Deng XT, Zhou J, Li QP, Ge XX, Miao L. Pharmacological basis and new insights of quercetin action in cancer. Food Chem Toxicol. 2020;136:111014.

23. Chen AY, Chen YC. A review of the dietary flavonoid, kaempferol on human health and cancer chemoprevention. Food Chem. 2013;138:2099–107.

24. Pan MH, Lai CS, Ho CT. Anti-inflammatory activity of natural dietary flavonoids. Food Funct. 2010;1:15–31.

25. Singh BN, Shankar S, Srivastava RK. Green tea catechin, epigallocatechin-3-gallate (EGCG): mechanisms, perspectives and clinical applications. Biochem Pharmacol. 2011;82:1807–21.

26. Salehi B, Mishra AP, Nigam M, Sener B, Kilic M, Sharifi-Rad M, et al. Resveratrol: a double-edged sword in health benefits. Biomedicines. 2018;6:91.

27. Shanmugam MK, Lee JH, Chai EZ, Kanchi MM, Kar S, Arfuso F, et al. Cancer prevention and therapy through the modulation of transcription factors by bioactive natural compounds. Semin Cancer Biol. 2016;40–41:35–47.

28. Pratheeshkumar P, Kuttan G. Flavonoids as antiangiogenic agents. Biomed Pharmacother. 2011;65:578–87.

29. Szakács G, Paterson JK, Ludwig JA, Booth-Genthe C, Gottesman MM. Targeting multidrug resistance in cancer. Nat Rev Drug Discov. 2006;5:219–34.

30. Gillet JP, Gottesman MM. Mechanisms of multidrug resistance in cancer. Methods Mol Biol. 2010;596:47–76.

31. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011;144:646–74.

32. Kroemer G, Galluzzi L, Brenner C. Mitochondrial membrane permeabilization in cell death. Physiol Rev. 2007;87:99–163.

33. Elmore S. Apoptosis: a review of programmed cell death. Toxicol Pathol. 2007;35:495–516.

34. Newman DJ, Cragg GM. Natural products as sources of new drugs over the nearly four decades from 01/1981 to 09/2019. J Nat Prod. 2020;83:770–803.

35. Zhang L, Li J, Hao C, Guo X. Polyphenols and breast cancer therapy: molecular mechanisms and clinical applications. Front Oncol. 2023;13:1159214.

36. Yang CS, Landau JM, Huang MT, Newmark HL. Inhibition of carcinogenesis by dietary polyphenolic compounds. Annu Rev Nutr. 2001;21:381–406.

37. Nabavi SM, Russo GL, Daglia M, Nabavi SF. Role of quercetin as an alternative for cancer therapy: updated evidence. Food Chem. 2015;173:305–12.

38. Khan N, Mukhtar H. Dietary agents for prevention and treatment of cancer. Cancer Lett. 2015;359:155–64.

39. Loibl S, Gianni L. HER2-positive breast cancer. Lancet. 2017;389:2415–29.

40. O'Shaughnessy J. Extending survival with chemotherapy in metastatic breast cancer. Oncologist. 2005;10 Suppl 3:20–9.