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Flavonoids as Anti-Metastatic Agents: Targeting the Epithelial-Mesenchymal Transition (EMT) in Breast Cancer Treatment

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ABSTRACT:

Breast cancer locoregional invasion and metastasis are the main reasons for patient mortality, being driven by the malignant tumor cell development. One of the main processes of their formation is the epithelial–mesenchymal transition (EMT), initially described in embryonic development, during which it facilitates cell migration and differentiation. In breast cancer, EMT is a key process mediating metastasis, therapeutic resistance, and cancer stem cell renewal. Flavonoids, a broad class of naturally derived polyphenols known for their strong antioxidant and anti-inflammatory effects, have attracted considerable interest because of their promising therapeutic applications in breast cancer. Extensive in vitro and in vivo studies demonstrate that flavonoids modulate EMT by inhibiting key regulatory molecules such as TWIST1, CD44, SNAI1/2, N-cadherin, ZEB1, integrins, matrix metalloproteinases (MMPs), and vimentin, while upregulating the epithelial marker E-cadherin. These effects are mediated through the suppression of pivotal oncogenic signaling pathways, such as NF-κB p65, PI3K/AKT, and JAK2/STAT3, which are critically involved in breast cancer progression. EMT is also regulated by some families of transcription factors, notably the Zn-finger family (e.g., ZEB1, ZEB2, SNAI2), which suppress E-cadherin transcription by binding to E-boxes. Given their multitargeted mechanism of action and ability to disrupt EMT processes specifically in breast cancer, flavonoids represent promising candidates for anti-metastatic therapy. This review summarizes the mechanistic roles of flavonoids in EMT suppression within the context of breast cancer and explores their translational relevance as adjuncts in targeted breast cancer therapy. Incorporating flavonoid-based strategies may improve therapeutic outcomes in aggressive breast cancer subtypes by mitigating metastatic progression and enhancing patient prognosis.

Keywords: Breast cancer; Epithelial–mesenchymal transition (EMT); Flavonoids; Oncogenic signaling pathways; Tumor metastasis.

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1. Introduction

Metastasis, the process of invasion by cancer cells from the primary tumor to distant organs, remains the most common reason for cancer death, such as in breast cancer. The epithelial–mesenchymal transition (EMT) ability of breast cancer cells is a critical process in breast cancer growth, metastasis, drug resistance, and the acquisition of stem-like features [1]. Though EMT imposes physiological roles in wound healing, fibrosis, and embryogenesis, in breast cancer it involves alteration of the epithelial junctions such as tight junctions, desmosomes, adherens junctions, and gap junctions as well as the polarity complexes including

Crumbs, Scribble (SCRIB), and partitioning defective (PAR) leading to suppression of epithelial genes and induction of mesenchymal genes [2-8].

In breast cancer, EMT is triggered by several factors within the tumor microenvironment, including hypoxia, cytokines, growth factors, stromal interactions, metabolic reprogramming, inflammatory responses, and anti-cancer therapies [9, 10]. EMT is orchestrated by transcription factors such as SNAI1, SNAI2, ZEB1, ZEB2, and TWIST, whose aberrant activation correlates with poor prognosis and higher metastatic potential in breast cancer patients [11, 12]. Various signaling pathways are involved in regulating this transition. For instance, Wnt/β-catenin pathway activation inhibits GSK3β, stabilizing β-catenin and promoting the expression of EMT-associated transcription factors SNAI1/SNAI2. The Notch signaling pathway, through ligand-receptor binding and subsequent γ-secretase-mediated cleavage of the Notch intracellular domain (NICD), activates nuclear transcription of EMT-promoting genes such as SNAIL, ZEB, and TWIST. TGF-β signaling, notably elevated in aggressive subtypes of breast cancer, induces EMT through both SMAD-independent and SMAD-dependent mechanisms (13). In the SMAD-dependent pathway, activation of TβRI and TβRII leads to SMAD2/SMAD3 phosphorylation, forming a complex with SMAD4 that translocates to the nucleus and initiates EMT-associated gene transcription. Additionally, receptor tyrosine kinases (RTKs) activate downstream pathways including PI3K, PAK1, and STAT3, further enhancing EMT progression in breast cancer. Dysregulated JAK/STAT signaling has also been implicated in promoting EMT and metastasis, specifically in triple-negative breast cancer [13-16]. Given the pivotal role of EMT in breast cancer metastasis and therapy resistance, targeting EMT represents a promising strategy for improving treatment outcomes in patients [17]. However, further research is needed to fully elucidate its mechanisms, regulatory networks, and therapeutic reversibility within the context of breast cancer (Figure 1) [18, 19].

Flavonoids, a diverse group of naturally occurring polyphenolic compounds found abundantly in fruits, vegetables, and plant-based beverages, possess potent antioxidant, anti-inflammatory, and anti-cancer properties [20, 25].

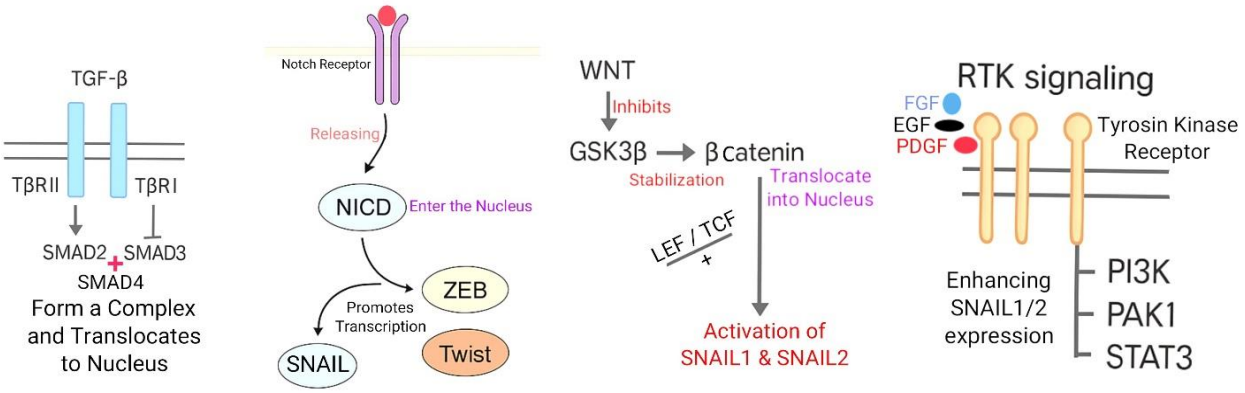

Figure 1. Regulation of Key Transcription Factors Driving EMT. This illustration outlines the principal signaling events *that control EMT transcription factors and their associated* signaling pathways. Several signaling mechanisms control the activation of these key transcription factors, including SNAIL, ZEB, and bHLH, which are critical drivers of EMT. WNT signaling inhibits GSK3β, leading to the stabilization of β-catenin. This stabilized β-catenin translocates to the nucleus and recruit's transcription factors LEF and TCF, promoting the expression of SNAIL1 and SNAIL2, key regulators of EMT. The interaction of Notch ligands with Notch receptors triggers the γ-secretase complex, which cleaves the receptor, releasing the NICD (Notch intracellular domain). NICD then translocates to the nucleus, where it regulates the transcription of EMT-related factors such as ZEB, SNAIL, and Twist. TGFβ induces EMT through both SMAD-dependent and non-SMAD-dependent signaling pathways. In the SMAD pathway, TβRI and TβRII receptors activate SMAD2 and SMAD3, which form a trimeric complex with SMAD4. This complex then moves to the nucleus to initiate the expression of EMT transcription factors. *Growth factors, including EGF, FGF, and PDGF, activate receptor tyrosine kinases (RTKs)*. Which dimerize and undergo autophosphorylation. This triggers downstream signaling cascades through proteins such as PI3K, PAK1, and STAT3, ultimately enhancing the expression of SNAIL1 and SNAIL2. This diagram highlights the interplay of signaling pathways that converge to regulate key transcription factors involved in the initiation and progression of EMT. These factors are crucial for cellular plasticity, tissue remodeling, and cancer metastasis.

In vitro and in vivo studies focusing on breast cancer models demonstrate that flavonoids can significantly reduce metastasis by targeting critical molecules such as matrix metalloproteinases (MMPs), transforming growth factor-beta (TGF-β), and urokinase-type plasminogen activator (uPA), which are key players in tumor invasion and EMT processes [20, 25]. Flavonoids offer a cost-effective, environmentally sustainable, and well-tolerated approach, with minimal toxicity even during prolonged usage [26].

This review examines the molecular mechanisms by which flavonoids regulate EMT pathways in breast cancer, focusing on their interactions with transcription factors, microRNAs, and novel molecular modulators [27]. More understanding of these mechanisms may lead to the development of flavonoid-based therapeutic strategies to inhibit metastasis and improve treatment outcomes specifically for breast cancer patients.

2. Molecular and Cellular Mechanisms of EMT

The epithelial-to-mesenchymal transition is a fundamental cellular reprogramming process in which epithelial cells gradually acquire mesenchymal-like characteristics [28, 29]. EMT is a highly dynamic and reversible process. Initially identified as a mechanism facilitating gastrulation and neural crest migration [2, 3]. EMT is frequently hijacked by tumor cells to promote metastasis, and EMT is considered a hallmark of cancer progression, aiding tumor dissemination, apoptosis resistance, and secondary lesion formation [30]. EMT is classified into three types: Type I (embryonic development), Type II (tissue repair and fibrosis), and Type III (tumor metastasis). This process allows epithelial cells to transform into a fibroblastoid phenotype [31]. This transition enhances cell motility, survival, and invasion [32, 33].

Regulation of EMT is orchestrated by a complex interplay of molecular mechanisms, including microRNAs (miRNAs), epigenetic modifications, post-translational modifications, and alternative splicing events [34]. During EMT, epithelial cell junctions are disrupted, and cytoskeletal remodeling occurs, leading to the downregulation of cell adhesion molecules such as E-cadherin and claudins [35, 36]. In contrast, mesenchymal markers, including N-cadherin, vimentin, fibronectin, α-smooth muscle actin (α-SMA), and MMPs, are upregulated, facilitating tumor invasion and extracellular matrix degradation [37]. The EMT program is primarily driven by a network of transcription factors, including ZEB1, Snail1, Snail2, and Twist, which repress epithelial gene expression while inducing mesenchymal-associated genes [38]. Snail1-induced EMT is characterized by vimentin and fibronectin upregulation, along with E-cadherin suppression [39]. Notably, Snail2 deficiency has been linked to delayed mammary gland development, which may impact breast cancer progression to delayed mammary gland tubulogenesis and early branching morphogenesis in animal models (Table 1) [40].

EMT is also regulated by β-catenin signaling, which is activated when β-catenin dissociates from the cell membrane and translocates into the nucleus [41].

Table 1. Summary of Key Mechanisms and Regulatory Proteins Involved in EMT and MET.

Stage	Description	Mechanisms/Proteins Involved
Epithelial to Mesenchymal Transition (EMT)	Epithelial cells lose their epithelial characteristics and acquire mesenchymal properties, becoming motile and invasive.	Loss of junctions (tight, adherens, desmosomes), downregulation of epithelial markers (e.g., E-cadherin), upregulation of mesenchymal markers (e.g., vimentin, N-cadherin). Disruption of polarity complexes such as DLG, LGL, PALS1, PATJ, and aPKC.
Mesenchymal to Epithelial Transition (MET)	After migration, mesenchymal cells can transition back to an epithelial state by re-establishing cell junctions and polarity. In cancer, cells that have undergone EMT may reverse this process through MET, resulting in the formation of secondary tumors that closely resemble the primary carcinoma.	Re-formation of junctions (tight junctions, adherens junctions), re-expression of epithelial markers (e.g., E-cadherin), and restoration of polarity complexes. Restoration of polarity through proteins like PALS1, PATJ, aPKC, with re-expression of epithelial markers.
Regulatory Proteins During EMT/MET	Key polarity and junction-related proteins maintain epithelial integrity. Their disruption or restoration can drive either EMT or MET.	Key regulators of cell polarity include DLG (Discs large), LGL (Lethal giant larvae), PALS1 (Protein associated with Lin-7), PATJ (a tight-junction protein interacting with PALS1), and aPKC (Atypical protein kinase C).

Within the nucleus, β-catenin interacts with transcription factors of the T-cell factor (TCF) and lymphoid enhancer-binding factor (LEF) families, driving the expression of EMT-related genes [41, 42]. During gastrulation, β-catenin forms a complex with LEF-1, which binds to the CDH1 promoter, repressing E-cadherin transcription and reinforcing the EMT phenotype (Figure 2) [43].

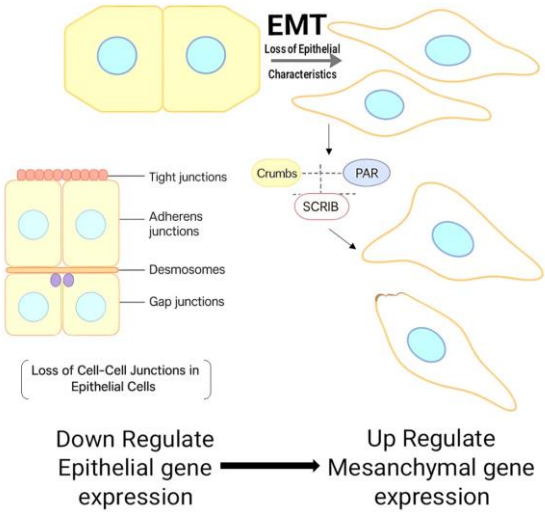

Figure 2. During the early phases of epithelial–mesenchymal transition (EMT), epithelial cell-cell junctions, such as tight junctions, adherens junctions, desmosomes, and gap junctions, begin to break down. At the same time, cell polarity is disrupted due to interference with polarity complexes like Crumbs, PAR (partitioning defective), and Scribble (SCRIB). These events are accompanied by the suppression of epithelial gene expression and the upregulation of mesenchymal markers.

3. The role of EMT in Cancer Invasion and Metastasis

Approximately 90% of malignant solid tumors originate from epithelial tissues, underscoring the crucial role of EMT in cancer metastasis [30, 44]. In breast cancer, EMT plays a pivotal role in facilitating tumor cell dissemination and metastasis formation. EMT facilitates the acquisition of migratory and invasive traits by epithelial tumor cells and is also linked to immunosuppression and resistance to therapy [45, 46]. Both tumor-intrinsic and tumor-extrinsic factors from the microenvironment modulate EMT plasticity, contributing to tumor heterogeneity and disease progression [47, 48]. Activation of EMT leads to the loss of epithelial polarity and cell-cell adhesion, promoting a mesenchymal phenotype with enhanced metastatic potential [49]. This transition has been extensively implicated in breast malignancies, where it contributes to aggressive behavior and poor clinical outcomes [50]. This transition has been implicated in a variety of cancers, including breast, lung, liver, pancreatic, and prostate malignancies [51]. EMT also contributes to the emergence of cancer stem cells (CSCs), particularly metastatic CSCs (MCSCs), which possess the ability to initiate tumors. Cytoskeletal remodeling, especially through actin fiber formation and cofilin activity, facilitates cellular elongation and motility [52]. Depending on the tumor microenvironment, migrating cells adopt varied invasion strategies: they may move collectively as sheets, clusters, or linear chains, guided by leader cells that maintain intercellular communication [53]. However, when intercellular connections break, individual tumor cells, either in a mesenchymal or amoeboid state, can migrate independently [54]. In breast cancer, MCSCs actively penetrate adjacent tissues, contributing to lymphovascular invasion and early metastasis [55].

During intravasation, MCSCs penetrate the endothelial barrier via VEGF, Notch, and TGF-β regulatory signaling [56]. Enzymes such as urokinase-type plasminogen activator (uPA) and matrix metalloproteinases (MMPs) degrade the basement membrane and extracellular matrix (ECM), facilitating tumor invasion and activating oncogenic signaling pathways like EGFR, thereby promoting neoangiogenesis and sustaining tumor progression [57-60]. Once in circulation, MCSCs evade immune surveillance by recruiting platelets, which shield them from immune attack. The Notch and SMAD pathways help sustain their mesenchymal phenotype and survival during transit. Upon reaching distant organs such as the lungs, liver, or brain, breast cancer MCSCs extravasate, colonize new tissues, and establish secondary tumors, contributing to recurrence and therapy resistance (Figure 3) [61-64].

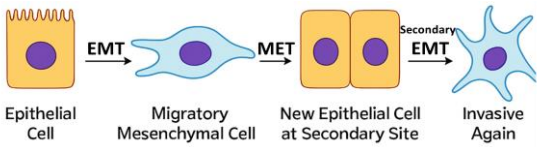

Figure 3. Epithelial Cell → (EMT) → Migratory Mesenchymal Cell → (MET) → New Epithelial Cell at Secondary Site → (Secondary EMT) → Invasive Again.

4. Cellular Stress Responses: Oxidative Stress and Endoplasmic Reticulum Stress

Oxidative stress and endoplasmic reticulum (ER) stress are crucial mechanisms of cellular damage in various diseases, especially cancer. Reactive oxygen species

(ROS), including H_2O_2, ·OH, HOCl, $^1O_2$, $O_2\cdot^-$, RO·, and ROO·, influencing physiological and pathological processes. Their primary sources are mitochondrial respiration and metal-catalyzed oxidation [65]. Excessive ROS induces oxidative stress, damaging proteins, lipids, and DNA, leading to genomic instability and functional impairment [66, 67]. Elevated ROS, driven by the Warburg effect, is a hallmark of cancer, promoting rapid growth via sustained oxidative pressure [68, 69]. ROS-induced nuclear and mitochondrial DNA damage activates oncogenic signaling, supporting tumorigenesis [70]. Epigenetic ROS modulation alters the expression of tumor suppressors and oncogenes, influencing proliferation, angiogenesis, and metastasis through the PI3K-AKT and MAPK-ERK pathways. ROS also drives neovascularization, enhancing tumor progression [70-73]. Diet-derived bioactive, notably plant-based organosulfur compounds, mitigate ROS via redox modulation. These compounds reduce the risk of cancer by enhancing antioxidant responses. They can induce ROS-dependent cytotoxicity in cancer cells, characterized by G2/M arrest that is reversible with N-acetylcysteine, underscoring redox-driven cell cycle disruption [74-79]. In vitro research using hormone-sensitive ER+ human breast cancer cell lines such as T47D and MCF-7 has demonstrated that flavonoids present in wine, including quercetin and resveratrol, can reduce cell proliferation by counteracting the effects of hydrogen peroxide [80]. Flavonoids not only possess antioxidant properties but can also act as pro-oxidants in certain situations, promoting cancer cell death. Some flavonoids, like myricetin and naringenin, induce ROS production in cancer cells, triggering apoptosis by activating stress responses that lead to cell cycle arrest [81, 82]. This dual role, acting as antioxidants in normal cells and inducing ROS in cancer cells, makes flavonoids a promising option for targeted cancer therapies. Additionally, flavonoids such as apigenin and luteolin reduce ROS-induced DNA damage and genomic instability, preventing mutations that contribute to cancer progression [83]. They also influence critical pathways, such as PI3K/Akt and FOXO3a, which regulate the cell cycle and apoptosis, further supporting their potential as chemopreventive agents. In summary, oxidative stress plays a key role in breast cancer by causing DNA damage and altering the tumor microenvironment [84]. Flavonoids by modulating ROS levels offer a dual approach to combating cancer, neutralizing excess ROS while selectively inducing ROS-dependent toxicity in tumor cells [84]. This makes flavonoids a promising strategy for both treatment and prevention. Alongside oxidative stress, ER stress is a key mechanism in the cellular response to damage [85]. Under conditions where protein synthesis or calcium regulation in the ER is disrupted, unfolded or misfolded proteins accumulate, activating the Unfolded Protein Response (UPR). The UPR can lead to autophagy or apoptosis, depending on the severity and duration of the stress [86-88]. C/EBP-homologous protein (CHOP) mediates ER stress-induced apoptosis by regulating apoptotic genes such as GADD34, DR5, and ERO1α [89]. CHOP enhances the expression of growth arrest and DNA damage-inducible protein 34 (GADD34), death receptor-5 (DR5), and ER oxidase 1α (ERO1α), all of which contribute to the stress response [90]. ERO1α amplifies ROS production and triggers calcium (Ca^{2+}) release from the ER via inositol-1,4,5-triphosphate receptors (IP3Rs), leading to mitochondrial dysfunction and CHOP-mediated apoptosis [91, 92]. GADD34 facilitates the dephosphorylation of eukaryotic initiation factor 2 alpha (eIF2α), a process that can either restore protein synthesis or initiate apoptosis. Additionally, tumor necrosis factor receptor-associated factor 2 (TRAF2) interacts with caspase-12, an ER-associated protein [93]. Under prolonged ER stress, caspase-12 detaches from TRAF2, activating caspase-9/3 to drive apoptosis. Recent studies emphasize the function of bioactive compounds in inducing ER stress and cancer cell death. Saxifragifolin D induces ER stress in MCF-7 and MDA-MB-231 cells via ROS and Ca^{2+} modulation [94]. In cancer, this stress not only promotes cell survival and resistance to therapy but also contributes to metabolic changes in cancer cells, enhancing tumor progression.

4.1. Inflammation and cancer progression

Chronic inflammation is a crucial factor in both the initiation and progression of cancer, influencing critical stages of tumorigenesis such as cellular transformation, growth, and metastasis [95]. Inflammatory signaling pathways have emerged as important therapeutic targets in cancer treatment, with transcription factors playing a pivotal role in regulating the genes that contribute to tumor development and progression, thus making them vital in cancer therapies [96]. Nuclear Factor Kappa B (NF-κB) is a central transcription factor in cancer, responsible for controlling inflammation, cell survival, and proliferation. Typically inactive in the cytoplasm, NF-κB translocates to the nucleus upon activation by proinflammatory signals, stimulating tumor cell growth. Activation of NF-κB is closely associated with the progression of breast cancer, where it promotes tumor cell survival and proliferation. Bioactive compounds, such as curcumin, have been shown to inhibit NF-κB signaling, thereby limiting tumor growth. At the same time, celastrol blocks the NF-κB/Notch 1 pathway, which is critical for hematopoietic cancer cell proliferation [97-100]. Another key transcription factor, Signal Transducer and Activator of Transcription 3

(STAT3), is persistently activated in several cancers, including gastric and pancreatic cancers. STAT3 facilitates abnormal cell growth and metastasis by inducing the expression of genes such as Bcl2 and c-Myc, which promote cell survival and proliferation. Upon phosphorylation, STAT3 moves to the nucleus, activating proinflammatory pathways that drive tumorigenesis [101-103]. In addition to NF-κB and STAT3, transcription factors such as FoxM1, PPARγ, Nrf2, and HIF-1α are modulated by bioactive compounds in cancer cells. These factors regulate key processes like oxidative stress response, cell cycle progression, and tumor metabolism. Their modulation represents promising therapeutic strategies for cancer treatment [104]. These findings underline the therapeutic potential of targeting inflammation-related transcription factors with bioactive compounds to disrupt oncogenic signaling. However, in vivo studies are necessary to verify their clinical efficacy and translational potential.

4.2. Cancer Stem Cells (CSC) and Therapeutic Targeting

CSCs play a crucial role in how tumors develop, grow, and resist treatment [105]. CSCs possess the ability to self-renew and differentiate into various cancer cell types, maintaining tumor complexity. They divide asymmetrically, with one daughter cell remaining a stem cell. Although CSCs are highly aggressive, resistant, and crucial in cancer recurrence [106-109]. CSCs sustain tumor growth through key signaling pathways, such as Wnt/β-catenin, Notch, and Hedgehog (Hh). The dysregulation of these pathways promotes cancer progression and the spread of tumor cells [110]. Research suggests that natural compounds can disrupt key signaling pathways and directly target CSCs, for example, flavonoids and polyphenols, found in plant-based foods, slow CSC growth and invasion. Sulforaphane, from cruciferous vegetables like broccoli, inhibits EMT and blocks Wnt signaling, both crucial for CSC survival [111, 112]. Similarly, epigallocatechin gallate (EGCG), a powerful antioxidant in green tea, has been shown to reduce CSC survival and stem-like traits in human cancer models [113, 114]. Retinoic acid, another naturally occurring substance, plays a role in regulating Notch signaling, helping to push CSCs toward differentiation while limiting their ability to self-renew [115]. Matcha, a concentrated form of green tea, suppresses mitochondrial function, key glycolytic enzymes, and mTOR signaling in breast CSCs, inducing a dormant state [116]. These findings underscore the potential of bioactive compounds in targeting CSCs, offering promising avenues for more effective cancer treatments.

4.3. Natural Phytochemicals and Angiogenesis

Angiogenesis, the formation of new blood and lymphatic vessels from existing vasculature, is a key process in both normal and malignant tissues [117]. Angiogenesis plays a crucial role in physiological processes. Dysregulated angiogenesis is linked to various pathological conditions, including cancer, where it supports tumor growth and metastasis by supplying nutrients, oxygen, and removing metabolic waste [118, 119]. Dietary phytochemicals, natural plant-based compounds, have been shown to block angiogenesis, highlighting their potential as alternative or complementary cancer treatments [120]. A well-known example is EGCG, a polyphenol in green tea [121]. Studies in animal models of endometrial cancer show that EGCG reduces VEGFA secretion by inhibiting key signaling pathways like PI3K/Akt and mTOR/HIF-1α, thereby limiting blood vessel growth [122, 123]. A modified form of EGCG, pro-EGCG, reduces stromal cell-derived factor 1 (SDF-1) levels in tumor-supporting cells, limiting the movement and development of tumor-associated macrophages. Since TAMs enhance VEGFA production, their reduction disrupts the tumor's ability to form new blood vessels [124, 125]. Other natural compounds also show promise in blocking angiogenesis. Certain herbal extracts have been found to reduce the movement of aggressive breast cancer cells by downregulating MMP-9, an enzyme involved in cancer spread [126]. These extracts prevent new blood vessel formation in human umbilical vein endothelial cells, cutting off the tumor's blood supply [127]. Nobiletin, a flavonoid in citrus fruits, suppresses MMP and VEGF expression, reducing angiogenesis and colorectal cancer spread. Delphinidin, an anthocyanidin in pomegranates, inhibits EGF-induced VEGF production and lowers HIF-1α expression, preventing blood vessel formation in tumors [128, 129]. Luteolin, another bioactive flavonoid, directly blocks VEGF production and its interaction with its receptor, exerting strong antiangiogenic effects in breast cancer [130]. Curcumin, the active compound in turmeric, has also demonstrated antiangiogenic properties in gastric tumors by stimulating cancer cell apoptosis and interfering with VEGF, STAT3, and HIF-1α signaling pathways [131].

Furthermore, resveratrol (found in grapes and red wine) and 3-O-acetyloleanolic acid have been identified as potential antiangiogenic agents, acting by targeting VEGF receptors and modulating key signaling pathways such as PI3K/Akt and ERK1/2 [131-133]. These findings suggest that natural compounds could provide strategies for restricting tumor growth by cutting off their blood supply. While further research, especially in clinical settings, is needed, these bioactive substances

show promise as complementary cancer treatments (Figure 4).

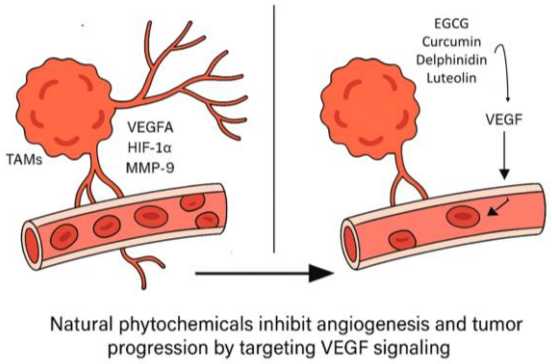

Figure 4. Antiangiogenic Effects of Natural Phytochemicals in Tumor Progression.

5. Flavonoids as Modulators of EMT in Breast Cancer

5.1. Breast Cancer

Flavonoids can modulate EMT in breast cancer by targeting key signaling pathways, thereby inhibiting tumor progression and metastasis. Recent studies have revealed that exposure of MDA-MB-231 breast cancer cells to baicalein or baicalin leads to an increase in E-cadherin expression [134, 135]. Moreover, baicalein and baicalin reduce TGF-β-driven invasion in normal breast epithelial cells by downregulating SNAI2 expression through inhibition of the NF-κB pathway, while leaving Smad2/3 phosphorylation largely unaffected. These findings highlight their potential to hinder breast cancer development by interfering with the epithelial–mesenchymal transition (EMT) process [136]. TGF-β induces EMT in breast cancer cells by upregulating SNAI1, TWIST, SNAI2, and N-cadherin, while suppressing E-cadherin. Co-treatment with 3,6-dihydroxyflavone reverses these changes, restoring E-cadherin and reducing EMT markers in MCF-7, MDA-MB-231, and rodent models. Similarly, hispidulin combined with TGF-β1 suppresses cancer cell growth and EMT in vitro and in vivo [137, 138].

The flavonoid 2′-hydroxyflavanone inhibits ERK signaling in breast cancer xenograft models, reducing phosphorylated ERK, AKT1, JAK2, and STAT3 levels, thereby affecting the JAK-STAT pathway. It downregulates cell cycle proteins (CDK4, cyclin B1) and anti-apoptotic markers (Bcl2, survivin), while upregulating pro-apoptotic proteins (Bax, Bim, PARP). Additionally, it decreases fibronectin and vimentin expression and enhances E-cadherin, suggesting EMT inhibition [139-142].

Chrysin inhibits metastasis in triple-negative breast cancer cells by reducing p-AKT levels. This anti-metastatic effect is confirmed through experiments using a PI3K inhibitor (LY294002), which also suppresses cell invasion and migration. However, restoring AKT activity via adenoviral expression reverses chrysin's effects, indicating that AKT downregulation is central to its anti-metastatic mechanism [143-145].

EGCG and quercetin, particularly when delivered via gold nanoparticles, suppress breast cancer growth and metastasis by targeting key signaling pathways, including EGFR, VEGFR-2, PI3K/AKT, and GSK-3β. Notably, nanoparticle-based delivery enhances their therapeutic effects [146, 147].

Additionally, research by Ma et al. demonstrated that baicalein inhibits Wnt1 expression in MDA-MB-231 breast cancer cells, a critical ligand in the Wnt/β-catenin signaling pathway. It also downregulated key downstream effectors of the pathway, such as cyclin D1 and Axin2. In an in vivo xenograft model, baicalein treatment led to reduced expression of Wnt1, β-catenin, and SATB1, thereby impairing metastatic potential and highlighting baicalein's promise as a therapeutic candidate for breast cancer metastasis prevention (Table 2) [148-150].

5.2. Animal Models

Flavonoids have anti-cancer properties in various animal models, notably through the inhibition of EMT, in tumor invasion and metastasis. In vivo studies highlight the ability of these compounds to modulate signaling pathways and transcription factors that regulate EMT, leading to suppressed tumor growth and metastatic potential. In murine xenograft models of breast cancer, baicalein reduced tumor invasiveness by downregulating mesenchymal markers (vimentin, N-cadherin) and upregulating E-cadherin, indicating reversal of EMT [151]. Similarly, fisetin has been shown to reduce tumor volume and inhibit EMT in melanoma, colorectal, and prostate cancer models by suppressing EMT-associated transcription factors such as SNAI1 and TWIST1 [152]. Luteolin has been tested in both aggressive breast and gastric cancer xenograft models, inhibiting tumor progression by targeting oncogenic pathways such as YAP/TAZ, Notch1, and Akt/β-catenin, resulting in EMT inhibition and enhanced apoptosis [153]. In prostate cancer PC3 xenografts, myricetin suppressed STAT3 signaling and its downstream targets, leading to decreased EMT, invasion, and metastasis [26].

Table 2. Effects of Various Flavonoids on EMT in Breast Cancer and Their Underlying Molecular Mechanisms.

Cancer Type	Flavonoid Treatment	Effects on EMT	Mechanisms Involved
Breast	Baicalein/Baicalin	Increased E-cadherin, reduced invasion, blocked TGF-β-induced EMT	Reduced SNAI2, inhibited NF-κB activation, and did not affect Smad2/3 phosphorylation
	3,6-Dihydroxyflavone (DHF)	Restored E-cadherin, reduced EMT markers in MCF-7 and MDA-MB-231	Inhibited SNAI1, TWIST, SNAI2, N-cadherin
	Hispidulin	Downregulated EMT markers, suppressed cancer growth, and EMT	Modulated TGF-β1 signaling
	2′-Hydroxyflavanone	Enhanced E-cadherin, reduced fibronectin/vimentin, modulated apoptotic proteins	Inhibited ERK, AKT, JAK2, STAT3
	Chrysin	Reduced p-AKT, inhibited metastasis	AKT suppression, PI3K/AKT pathway interference
	Epigallocatechin gallate (EGCG)	Suppressed growth/metastasis, modulated EGFR, AKT, and laminin receptor pathways	Inhibited p-EGFR, p-PI3K, p-AKT, p-GSK-3β
	Isorhamnetin	Inhibited cell proliferation	Inhibited AKT/PI3K signaling, reduced tumor growth
	Kaempferol	Reduced metastasis, induced apoptosis	Inhibited NF-κB, PI3K/AKT, and MAPK pathways
	Eriocitrin	Inhibited phosphorylation of p38 MAPK, GSK-3β, reduced mesenchymal markers	Inhibition of p38 MAPK, GSK-3β, reduced vimentin and fibronectin expression
	Apigenin	Reduced integrin β1, FAK, increased E-cadherin, and blocked hypoxia-induced EMT.	Hypoxia signaling modulation inhibited FAK-integrin interaction.
	Icariin	Reduced migration, inhibited EMT	Inhibited ERK and PI3K/AKT pathways, downregulated MMPs
	Silibinin	Suppressed metastasis, upregulated E-cadherin	Inhibited PI3K/AKT pathway, increased E-cadherin expression, reduced MMPs

In glioma-bearing mice, eriodictyol inhibited EMT by modulating p38 MAPK and GSK-3β pathways, reducing tumor progression and migration [154]. These findings from diverse animal models provide strong evidence for the therapeutic potential of flavonoids in suppressing EMT and metastasis, supporting their advancement toward clinical applications in cancer management.

5.3. Therapeutic Doses of Flavonoids

Flavonoids are generally safe and well-tolerated, with low toxicity observed in both animal and human studies. In rodent models, compounds like quercetin, EGCG, and baicalein showed anti-cancer effects without hepatotoxicity at doses up to 100 mg/kg. Clinical trials have similarly reported good safety profiles for quercetin and genistein, with oral doses up to 1,000 mg/day causing only mild gastrointestinal issues. However, high doses may affect cytochrome P450 enzymes, necessitating careful dosing and monitoring, especially when combined with chemotherapy [155-157].

5.4. Flavonoid-Derived Drugs in Breast Cancer Therapy

While natural flavonoids have long been renowned for their diverse array of bioactivities, research in the last decade has enabled scientists to design and synthesize synthetic and semi-synthetic flavonoid analogues with enhanced pharmacokinetics, bioavailability, and target affinity [158-160]. These designed analogues address many of the natural flavonoid's limitations, including poor solubility, metabolic instability, and inefficient cellular permeability. They are the best candidates for the development of drugs for breast cancer, particularly for recalcitrant subtypes such as TNBC [161-163]. Structural optimization of these compounds, quercetin, luteolin, and apigenin, leading to derivatives increasing

cytotoxicity, metabolic stability, and reduced off-target effects [164-166]. Synthetic quercetin analogues with increased lipophilicity and resistance to metabolic conjugation, which have exhibited more effective inhibition of the Akt/mTOR and EGFR signaling pathways in TNBC cells with lower cardiotoxic effects characteristic of anthracycline-based drugs [167, 168]. Similarly, luteolin derivatives glycosylated and methylated exhibit increased cell permeability and sustained inhibition of EMT by stabilized β-catenin and YAP/TAZ complex interaction [153, 169, 170].

Halogenated or hydroxyl-substituted baicalein derivatives have exhibited potent MMP and EMT-regulatory transcription factor inhibition in metastatic breast cancer models. 7-O-glucuronide and acetate conjugates have improved pharmacokinetics and selectivity against the PI3K/Akt pathway, a critical pathway in TNBC development [171]. Baicalin analogue treatment regimens, when used alone with conventional chemotherapeutic drugs such as doxorubicin, are synergistic, partly by reducing the expression of efflux transporters and re-sensitizing resistant TNBC phenotypes [172].

Synthetic flavonolignan hybrids and conjugates, including silybin and genistein-derived compounds, were engineered to modulate epigenetic modulators and cell cycle checkpoints [173, 174]. Multitarget agents of this type, typically engineered using methodologies involving bioisosteric replacement and scaffold hopping, have shown impressive efficacy in rescuing BRCA1 expression and reversing hormone receptor silencing, thereby re-sensitizing ER-negative breast cancer to endocrine therapy [174, 175].

Isoliquiritigenin analogs, particularly chalcone-type compounds, have been discovered to be promising angiogenesis inhibitors [176, 177]. Site-directed modifications of the α,β-unsaturated carbonyl scaffold enhance reactivity with cysteine residues on VEGFR2 and JAK2, leading to inhibited vascularization in TNBC xenograft models [177]. The compounds have also been demonstrated to have improved pharmacodynamics in microfluidic tumor-on-a-chip assays, pointing towards their translational potential [178].

Semi-synthetic conjugates, such as quercetin-doxorubicin hybrids and rutin-platinum complexes, are dual-action platforms that have the potential to couple the DNA-damaging action of cytotoxic with the anti-inflammatory and anti-metastatic action of flavonoids. Such conjugates not only augment killing in tumor cells but also bypass systemic toxicity and oxidative stress, enhancing the therapeutic index of chemotherapeutic regimens [179, 180].

Additionally, nano-formulation strategies such as flavonoid-loaded liposomes, dendrimers, and polymeric nanoparticles have been used to deliver highly tumor-targeting synthetic baicalein and apigenin flavonoid derivatives [181-183]. In particular, pH-sensitive carriers loaded with baicalein and apigenin derivatives target the tumor microenvironment preferentially and dramatically suppress the growth of TNBC in orthotopic mouse models [184].

Synthetic flavonoid derivatives, optimized for bioavailability and target specificity, offer promising strategies for combating resistant breast cancers, such as TNBC. Advances in computational design now enable their development as precision therapies targeting tumor-specific vulnerabilities.

5.5. Clinical Trials of Flavonoids in Cancer Therapy

Flavonoids such as quercetin, genistein, EGCG, and apigenin have been investigated in Phase I/II clinical trials for their anti-cancer properties. Quercetin, administered up to 1,000 mg/day, demonstrated good tolerability and tyrosine kinase inhibition in cancer patients (NCT00003365). Genistein has shown the ability to enhance chemo- and radiosensitivity, particularly in prostate and bladder cancers (NCT00244933). EGCG, derived from green tea, has been evaluated in trials such as NCT00917735, showing biomarker modulation and tumor-suppressive effects in breast and prostate cancers. Apigenin has exhibited early-phase anti-cancer activity in colorectal and cervical cancers, though clinical data remain limited. While early results are promising, larger randomized trials are needed to confirm efficacy, establish standardized formulations, and assess long-term safety [185]. Flavonoids may offer added benefit when integrated with conventional therapies, particularly in cancers involving epithelial–mesenchymal transition and inflammation [186, 187]. Despite these results in preclinical studies, the successful translation of these findings into clinical applications remains challenging due to interspecific differences, tumor heterogeneity, and complexities in drug metabolism and resistance mechanisms in humans.

6. Conclusion

Flavonoids are a diverse group of naturally occurring polyphenolic compounds. They have emerged as potent inhibitors of epithelial-mesenchymal transition in breast cancer, offering significant therapeutic potential in combating metastasis and therapy resistance, key drivers of breast cancer mortality. Through their antioxidant and anti-inflammatory properties, flavonoids modulate critical regulatory molecules involved in EMT, such as TWIST1, N-cadherin, ZEB1, SNAI1/2, and vimentin, while promoting the upregulation of the epithelial marker E-cadherin. These effects are driven by the

inhibition of pivotal oncogenic signaling pathways, including PI3K/AKT, NF-κB p65, and JAK2/STAT3, which are integral to breast cancer progression. Given the central role of EMT in driving metastasis, therapy resistance, and the maintenance of cancer stem cells, flavonoids offer a multitargeted approach to halting the metastatic cascade. Their ability to disrupt multiple stages of carcinogenesis, including invasion and migration, makes them a promising adjunct to conventional therapies. Moreover, flavonoids present an advantage over standard anti-cancer treatments by offering a safer, environmentally friendly option with minimal side effects, unlike traditional therapies that often cause toxicity and harm to healthy cells. Advances in nanotechnology and structural modifications further enhance the bioavailability and clinical efficacy of flavonoids, facilitating their potential translation into clinical practice. By integrating flavonoid-based strategies with existing treatment regimens, it is possible to target aggressive breast cancer subtypes more effectively, mitigate metastatic progression, and improve overall patient outcomes. Ultimately, the incorporation of flavonoids into cancer therapy could revolutionize the way metastatic breast cancer is treated, offering a safer, more effective means of managing this devastating disease while enhancing patient quality of life.

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Conflict of interest

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