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Article *in* Nutrition and Cancer · June 2025

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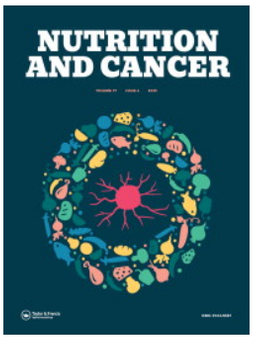

Nutrition and Cancer

ISSN: 0163-5581 (Print) 1532-7914 (Online) Journal homepage: www.tandfonline.com/journals/hnuc20

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To cite this article: Adil Farooq Wali, Siajunisa Talath, Mohamed El Tanani, Imran Rashid Rangraze, Rasha Babiker, Sadat Shafi & Ruby Bansal (23 Jun 2025): PI3K/AKT/mTOR Pathway in Breast Cancer Pathogenesis and Therapy: Insights into Phytochemical-Based Therapeutics, Nutrition and Cancer, DOI: 10.1080/01635581.2025.2521884

To link to this article: https://doi.org/10.1080/01635581.2025.2521884

Published online: 23 Jun 2025.

NUTRITION AND CANCER
https://doi.org/10.1080/01635581.2025.2521884

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PI3K/AKT/mTOR Pathway in Breast Cancer Pathogenesis and Therapy: Insights into Phytochemical-Based Therapeutics

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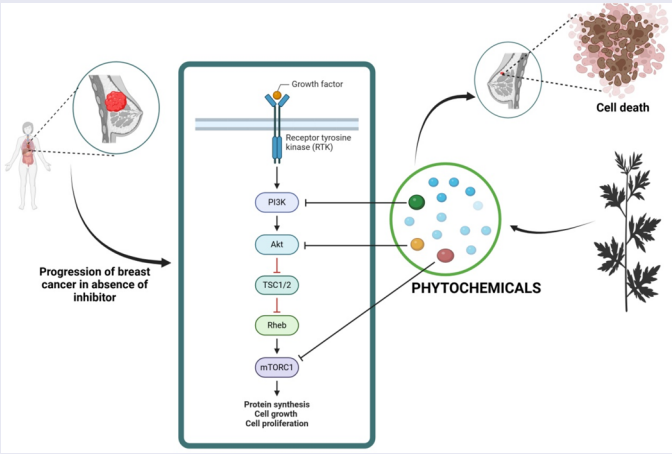
ABSTRACT

Breast cancer (BC) is listed as the most prevalent cancer form in women worldwide, with major subtypes classified by hormone receptor (HR) and HER2 status including, HR+/HER2– (~65–70%), HER2+ (~15–20%), Triple-Negative-HR–/HER2– (~10–15%) and rare sybtypes (<5%). Scientific evidence has revealed that PI3K/AKT/mTOR signaling cascade plays an important role in the development and progression of BC, contributing to key cellular processes including cell growth, proliferation, angiogenesis, and metastasis. Dysregulation of the components of this cascade including functional loss of Phosphatase and TENsin homolog (PTEN), PI3K hyperactivation, and gain-of-function of AKT, are frequently observed in BC subtypes, making it a promising target for therapeutic intervention. A myriad of studies have documented the potential of phytochemicals, including curcumin, chrysin, fisetin, genistein, resveratrol and lycopene as modulators of the PI3K/AKT/mTOR axis. These phytochemicals exhibit multifaceted mechanisms of action, including inhibition of key kinases, induction of apoptosis, suppression of angiogenesis, and reversal of resistance to chemotherapy. This review aims to provide a detailed overview about the role of PI3K/AKT/mTOR alteration in BC development and the current research on phytochemicals that modulate the PI3K/AKT/mTOR pathway in BC. We documented the molecular mechanisms through which these compounds exert their effects, their potential synergistic interactions with conventional therapies, and the challenges and prospects for their clinical application. The evidence presented underscores the promise of phytochemicals as novel, less toxic adjuncts to traditional BC therapies, warranting further exploration and development for clinical use.

ARTICLE HISTORY
Received 20 March 2025
Accepted 13 June 2025

GRAPHICAL ABSTRACT



Therapeutic application of phytochemicals in BC by modulating PI3K/AKT/mTOR axis. Created in https://BioRender.com

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Introduction

Breast cancer (BC) is a heterogeneous cancer form exhibiting significant variability in molecular features, morphology, and clinical outcomes (1). It is the most commonly diagnosed type of cancer and the primary cause of cancer-related mortality among women globally (2). In 2022, around 2.3 million BC cases causing 670,000 deaths were reported worldwide (3). Clinically, BC is categorized into three primary subtypes based on the status of progesterone receptor (PR), estrogen receptor (ER), and human epidermal growth factor receptor 2 (HER2): hormone receptor (HR)-positive, HER2-positive, and triple-negative BC (TNBC, which don't express PR, ER or HER-2) (4). Interestingly, various risk factors have been associated with the incidence of BC, including obesity, diabetes, age, increased hormone production, genetic predisposition and familial history of BC (5). Multiple therapeutic strategies are available for the management of BC, and accurate patient stratification is essential to ensure the selection of the most effective treatment regimen. g. Clinically, BC is managed through a combination of chemotherapy, radiation therapy, hormonal therapy and surgery (6). BC sub-types that expresses PR and/or ER are more likely to respond to hormonal therapies such as aromatase inhibitors or tamoxifen (7,8). Subsequently, BC type that independently over-express HER-2/neu oncogene (HER-2 positive) are amenable to treatment with targeted biological agents such as trastuzumab (9). Certain subtypes of BC such as TNBC, are more aggressive, difficult to manage and has higher rates of recurrence than others (10). Recently, different immunotherapeutic modalities, including immune checkpoint blockade, vaccination, and adoptive cell transfer, have been studied extensively in managing BC in the clinical settings, specifically in TNBC patients (11). Despite significant advancements in BC treatment, mortality rates remain high, mainly due to the incidence of tumor recurrence and resistance to therapy (12)… Approximately 30% of the early-stage BC cases experience recurrence, primarily through metastasis (13). Therefore, it is essential to develop new therapeutic strategies tailored to each BC subtype. Efforts to improve BC treatment involve gaining deeper scientific understanding of pathological mechanisms and altered pathways, and exploring novel bio-molecule classes which have been studied in relation to numerous biological specimens.

In recent years, the Phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/mechanistic target of rapamycin (mTOR) axis, which mediates various vital cellular processes, has been identified as a critical regulator of BC occurance and progression (14,15). Additionally, various studies have documented a correlation between the activation of this pathway and resistance to endocrine therapy in BC (16). Mechanistically, alteration of PI3K/AKT/mTOR pathway results in increased PI3K activity and/or loss of PI3K inhibitory functions as well as mutation in tumor suppressor genes Phosphatase and TENsin homolog (PTEN), and downstream molecular players including Akt, TSC1, or mTOR, which initiate enhanced cell proliferation, suppress apoptosis, and promote autophagy and aberrant cell differentiation, resulting in tumor formation and metastasis (17). This molecular pathway, is abnormally altered in over 70% of BC, including TNBC, thereby serves as a critical mechanism for cell survival and resistance development in BC, making it a potential target for therapeutic interventions (18,19). Investigating the PI3K/AKT/mTOR axis has led to the identification of inhibitors targeting one or more components within this pathway. Although various studies demonstratred great perspectives for a series of PI3K and AKT inhibitors to limit BC in preclinical studies, however the adverse events associated with these compounds have led to the limitation of clinical usage to only one mTOR inhibitor: everolimus. Interestingly, tumor cell mutations, significant toxicity and compensatory feedback mechanisms have hindered the success of these synthetic agents (20). Therefore, identification and development of small molecule compounds modulating PI3K/AKT/mTOR pathway, with better efficacy and lesser side effects, is crucial for improving the survival outcomes of BC patients.

Phytochemicals represent one of the promising therapeutic options to intercept BC induction and development, improve treatment efficiency in BC patients and limit adverse reactions associated with the conventional therapy (21,22). These natural compounds have been used for decades to prevent and treat a variety of illnesses, and recent research suggests that phytochemicals possesses substantial anticancer potential for bench to bedside drug development (21,23). Notably, several natural phytochemicals and their derivatives have been shown to disrupt PI3K signaling and its downstream regulatory components, resulting in anticancer and anti-metastatic effects (24,25). For instance, well-studies phytochemicals including curcumin, chrysin, fisetin, genistein and resveratrol have demonstrated potential antiproliferative effect on BC by modulating PI3K/AKT signaling axis.Since, BC exhibit alteration of PI3K/AKT/mTOR signaling pathway (26), natural compounds targeting this axis have considerable therapeutic promise in the treatment of BC.

PI3K/AKT/mTOR Axis and Molecular Mutations Associated with Breast Cancer

Cells communicate with each other through a mechanism known as extracellular signaling. They generate

specialized chemicals that attach to specific receptors on neighboring cells and trigger intracellular signaling pathways (27). Interestingly, PI3K/AKT/mTOR cascade is a signaling system that plays a critical role in cellular functions such as cell growth, and proliferation is reported to be one of the most frequently dysregulated pathways in various cancers including BC (28,29). It regulates hallmarks of cancer, including cell proliferation, metastasis, angiogenesis and metabolism (27).

Activation of PI3K/AKT/mTOR Pathway

The PI3K heterodimer, a member of the class IA PI3K family, plays a pivotal role in this signaling pathway (15). It is composed of two subunits: a regulatory subunit (p85) and a catalytic subunit (p110). The p85 subunit modulates the activation of p110 in response to upstream signals, particularly those mediated by growth factor receptor tyrosine kinases (RTKs) (17). Each subunit has different isotopes in mammals and their respective genes encode these. Namely, p110α, p110β and p110δ subunits are encoded by PIK3CA, PIK3CB and PIK3CD, while the regulatory subunit is encoded by PIK3R1, PIK3R2, PIK3R3 (30). A ligand, such as insulin or insulin-like growth factor, interacts to a cell membrane receptor. This extracellular ligand binding activates the particular receptor (RTK), subsequently triggering the activation of PI3K. The stimulated PI3K promote the phosphorylation of Ptdlns-4,5-p2 (PIP2) at three positions on the inositol ring to produce PIP3, inititating PI3K pathway (31). Interestingly, PTEN, an important tumor suppressor has the opposite action and dephosphorylates PIP3 into PIP2 (32). PIP3recruits two oncogenic signaling protein kinases, AKT and PDK1 (phosphoinositide-dependent protein kinase 1), to the plasma membrane through their PH domains (33,34). Upon membrane association, mTORC2 (mTOR complex 2) phosphorylates AKT at Ser473, inducing a conformational change that enables PDK1 to phosphorylate AKT at Thr308. The phosphorylated AKT then activates target proteins at the cell membrane before detaching and phosphorylating additional targets in the cytosol and nucleus. AKT signaling facilitates cancer cell survival, proliferation and metabolism by activating its downstream effectors. mTOR, one of the most common downstream effectors of AKT, integrates many proteins to promote cancer progression (14). Notably, members of the PI3K/AKT/mTOR pathway are often mutated and activated in BC (27) (Figure 1).

Dysregulation of PI3K/AKT/mTOR Axis in Breast Cancer and Its Clinical Relevance

The PI3K/AKT/mTOR signaling cascade is commonly dysregulated in BC through various mechanisms, resulting in elevated PI3K activity and/or disruption of its negative regulation. This dysregulation often involves mutations in tumor suppressor genes such as PTEN, which normally inhibit this pathway (35). Among the PI3K isoforms, PIK3CA is one of the most frequently mutated genes, with alterations typically occurring at two hotspot regions: an acidic cluster within the helical domain (residues E542, E545, and Q546) and a conserved histidine (H1047) within the kinase domain. Helical domain mutations primarily act by disrupting the inhibitory control exerted by the p85 regulatory subunit, whereas kinase domain mutations enhance the intrinsic lipid kinase activity of p110α by promoting conformational changes essential for membrane-associated catalysis (36). Notably, breast, prostate, colon, and endometrial cancers have been reported to exhibit highest prevalence of PIK3CA mutations (37). Mutations within the catalytic domain of PIK3CA represent the most prevalent genetic alterations in early-stage BC, occurring in over one-third of cases. These mutations are particularly enriched in specific molecular subtypes, being detected in up to 47% of HR-positive/HER2-negative (luminal A), 33% of HR+/HER2+ (luminal B), 39% of HR–/HER2+ (HER2-enriched), and approximately 8–25% of basal-like or TNBC subtypes (14,38–40). In addition to PIK3CA mutations, loss-of-function alterations frequently occur in PTEN. While the mutation rates of PTEN in HER2-positive and luminal BC types are comparable to those of PIK3CA (up to 22% and 44% respectively), PTEN alterations are particularly prevalent in (TNBC, with frequencies exceeding 65% (41,42). Notably, PTEN loss is associated with a more aggressive genomic subtype of ER+ BC, often correlating with poor clinical outcomes and resistance to conventional therapies (43). Among the most characterized cancer-associated mutations within the PTEN catalytic domain are C124S and G129E, both of which abolish its phosphatase activity (43). Furthermore, activating mutations in AKT1 are found in approximately 4% of luminal tumors (44), while gene amplifications of PDK1 and AKT2 occur across all BC subtypes, with reported frequencies of 20–38% and 3%, respectively (45,46).

The clinical significance of PIK3CA and related molecular alterations in BC remains unclear, with studies on their prognostic value yielding inconsistent findings (47–49). Some analyses have shown that PIK3CA mutations are significantly associated with improved invasive disease-free survival (IDFS), particularly in older patients with HR+, low-grade tumors; however, no consistent correlation has been observed with distant disease-free survival (DDFS) or overall survival (OS) (50,51). In operable primary BC,

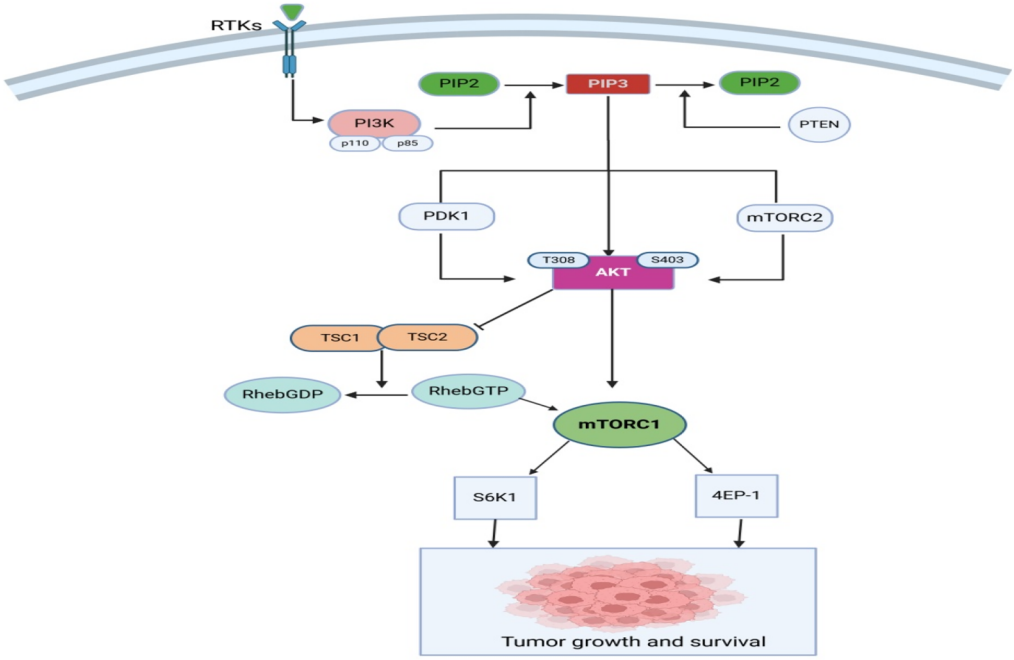

Figure 1. Overview of PI3K/AKT/mTOR pathway in cancer. The interaction of a growth factor with its tyrosine kinase receptor triggers receptor activation, facilitating the conversion of PIP2 to PIP3 through the enzymatic activity of phosphoinositide 3-kinase (PI3K). This molecular event initiates a downstream signaling cascade that enhances cellular processes linked to growth and proliferation. Created in https://BioRender.com.

PIK3CA mutations have been linked to favorable disease-free survival (DFS) and improved recurrence-free survival, especially within the Luminal A subtype (52). In contrast, in advanced or metastatic BC, these mutations are often associated with resistance to chemotherapy and poorer clinical outcomes (53). In HER2-positive BC, PIK3CA mutations correlate with unfavorable prognosis in both early and advanced disease stages (54). A meta-analysis found that breast cancer tissues have a higher rate of PTEN deletion when compared with normal tissues and that these mutations are associated with breast cancer invasiveness and metastatic potential. Patients with such mutations also have poor overall survival (OS) and disease-free survival (55). Collectively, these findings underscore the need for more comprehensive clinical studies to clarify the prognostic and predictive implications of mutations in PIK3CA, PTEN and AKT across different BC contexts.

Phytochemicals Modulating PI3K/AKT/mTOR Signalling in Breast Cancer

Plants are intriguing producers of novel molecules, known as phytochemicals which are being explored for their potential health advantages because of their proven therapeutic efficacy, easy availability and suitability for in human consumption (56). Phytochemicals exhibit a wide spectrum of protective and disease-preventive properties. Historically, they have been utilized to address various health conditions, including diabetes, cancer, cardiovascular diseases, neurological disorders, inflammation, and skin ailments (57–61). Epidemiological research has consistently revealed a reduced incidence of BC associated with the consumption of phytochemicals (62–64). A plethora of studies have demonstrated that phytochemicals exert anti-cancer effect by altering various oncogenic and oncosuppressive cell signaling pathways, including PI3K/AKT/mTOR. These natural bioactives have been explored in relation to their ability to influence the PI3K/AKT signal transduction by interacting with key drivers of the pathway, thereby serving as promising therapeutic agents in BC treatment. Among the phytochemicals, flavonoids, carotenoids and stilbenes have been found to be most effective in limiting the BC proliferation in preclinical models (65–67). Specifically, phenolic compounds or flavonoids (curcumin, chrysin and quercetin) inhibit the activation of AKT by increasing phosphatases activity and decreasing kinases activity, resulting in the suppression of mTOR signaling, cell growth, and evasion of apoptosis (68). Carotenoids and stilbenes have also been reported to modulate the PI3K/AKT/mTOR pathway by interaction with the AKT, mTOR, and PI3K proteins, among others (69,70). This could be as a result of their high antioxidant, anti-inflammatory, anti-proliferative, and anticancer properties. Here we documented the pre-clinical

development and efficacy of different phytochemicals as PI3K/AKT/mTOR modulators for BC treatment.

Flavonoids

Flavonoids represent the predominant class of polyphenolic secondary metabolites present in human diets. They have garnered significant scientific interest due to their diverse pharmacological properties, particularly their anti-cancer potential (71,72). Recent research has linked the anti-cancer effects of flavonoids to their ability to modulate key cellular pathways, including the PI3K/AKT/mTOR axis (73,74). Additionally, emerging evidence revealed that flavonoids increase the sensitivity of cancer cells to conventional therapeutic agents through the modulation of PI3K/AKT signaling (75). The anti-cancer effects of various flavonoids through modulation of the PI3K/AKT/mTOR pathway in breast cancer are summarized in Table 1.

Curcumin

Curcumin (CuRC), a flavonoid isolated from the rhizomes of *Curcuma longa*, possess a number of pharmacological activities, including neuroprotective, anti-inflammatory, antioxidant, immunomodulatory, and anti-cancer effects (76,77). Extensive research has highlighted its potential as a chemotherapeutic agent for various cancers (77). Experimental studies, both *in vitro* and *in vivo*, documented that CuRC influences multiple intracellular signaling pathways involved in cancer progression, survival, metastasis and angiogenesis (78). Among these, the PI3K/AKT/mTOR pathway has been identified as a key target of CuRC's activity. CuRC interacts directly with key factors of the PI3K/AKT/mTOR cascade, including AKT, mTORC1, PI3K, and growth factors such as EGFR (79–81). Additionally, CuRC modulates this pathway indirectly by targeting critical upstream regulators, such as AMP-activated protein kinase (AMPK) and IκB kinase B (IKKβ). Specifically, CuRC inhibits IKKβ, an upstream activator of mTORC1, leading to suppressed cancer growth in BC and human adenoid cystic carcinoma cells (82). Furthermore, CuRC enhances the activation of AMPK, a kinase involved in cellular metabolism, which in turn downregulates mTORC1. CuRC-induced AMPK activation is involved in the activation of autophagy and the suppression of AKT levels, thereby inhibiting the proliferation and migration of BC cells (77). This mechanism contributes to its anticancer effect in different tumors, including those of the lung, breast and prostate (78,83,84).

CuRC has demonstrated anti-proliferative activity across various BC cell lines, with distinct effects observed in hormone-dependent (MCF-7) and hormone-independent (MDA-MB-231) cells, as reported by Jia *et al.* (85). In MDA-MB-231 cells, CuRC inhibited AKT phosphorylation in both time and dose dependent manner. Conversely, in MCF-7 cells, the modulation of AKT phosphorylation by CuRC was more complex. At lower concentrations, CuRC enhanced AKT activation, while higher concentrations reduced AKT phosphorylation. Notably, co-treatment with CuRC and an inhibitor of AKT sensitized CuRC-resistant BC cells, increasing their susceptibility to the compound (85). A similar study by Kizhakkayil et al. demonstrated that co-treatment of MCF-7 cells with PI3K inhibitor (LY294002) and CuRC triggered apoptosis by reducing CuRC-induced

Table 1. Flavnoids exert anti-cancer effect by modulating PI3K/AKT/mTOR axis in breast cancer .

Flavonoid	Mechanism of action in BC	Therapeutic outcome	References
Curcumin	suppressed AKT levels, inhibited AKT phosphorylation, upregulated PTEN, modulated AMPK and IκB kinase B, inhibited mTOR	Decreased cancer cell proliferation, promoted apoptosis and cell cycle arrest, sensitized resistant cells to treatment	(77,79, 85,86)
Chrysin	downregulate PI3K/AKT expression, decreased MMP-10, slug, snail and vimentin levels and increased E-cadherin,	suppressed cancer proliferation, inhibited TNBC cell migration and invasion, reversed EMT	(94–96,101)
Fisetin	downregulated expression of AKT, P_{70}, and mTOR, modulated PTEN/AKT/GSK-3β signaling	suppressed proliferation, inhibited metastasis, and reversed EMT	(106,107)
Epigallocatechin Gallate	inhibited AKT and telomerase activity, reduced EGFR and ErbB receptor activity, induction of pro-apoptotic genes including p21, p53, caspase-3, Bax, PTEN, and caspase-9	impeded cell proliferation, induced apoptosis,	(112,145)
Genistein	downregulated PI3K/AKT levels, decreased AKT phosphorylation, and increased PTEN and E-cadherin expression	suppressed growth and induced apoptosis, suppresses mammosphere formation,. enhanced chemotherapeutic effectiveness of chemotherapeutic agents	(122–124)
Quercetin	downregulated AKT, upregulated PTEN	suppressed BC growth and induced apoptosis	(127–129)
Apigenin	blocked HGF-mediated AKT phosphorylation	inhibited cell proliferation, migration and invasion	(133)
Formononetin	downregulated, p-AKT, p-IGF-1 R, cyclin D1 levels and reduced MMP-2 and MMP-9 expression levels	reduced BC proliferation and invasion, enhanced cytotoxic effect of the mTOR inhibitor (everolimus).	(136)

phosphorylation of AKT and activating GSK3β (86). Subsequently, Hu et al. explored the cytotoxic potential of CuRC on various BC cell lines in the context of PI3K/AKT/mTOR signaling modulation. Using seven different cell lines, their findings revealed differential sensitivity to CuRC treatment, with ER+ BC cells, such as T47D, MDA-MB-415, and MCF-7 exhibiting greater susceptibility compared to HER2-, ER-, PR-, cell lines like BT-20 and MDA-MB-231. Furthermore, CuRC was observed to promote apoptosis and cell cycle arrest by inhibiting mTOR and AKT phosphorylation, thereby suppressing their downstream targets, including protein S6 (87).

Lai et al. investigated the impact of CuRC on HER-2-overexpressing BC cell lines, specifically BT-474 and SKBR3. Study results revealed that CuRC treatment caused a significant downregulation of EGFR and HER-2, which was closely associated with the suppression of key signaling pathways, including PI3K/AKT (evidenced by reduced AKT phosphorylation), NF-κB and MAPK (88). Furthermore, the anticancer potential of CuRC in human BC cells also involves its regulatory effects on microRNAs, particularly miR-21. Wang et al. demonstrated that CuRC dose-dependently reduced miR-21 expression in MCF-7 cells. This was accompanied by inhibition of AKT phosphorylation and elevated PTEN expression. Given the established inverse relationship between PTEN and miR-21, the anticancer activity observed in this study was likely mediated through the AKT/PTEN/miR-21 signaling axis (89,90). Subsequently, Li et al. investigated the interaction of CuRC with PI3K/AKT and microRNA-axis in MCF-7 cells. Their findings revealed that CuRC decreased the oncogenic miR-19 expression, upregulated PTEN, and suppressed AKT phosphorylation, thereby mitigating the tumor-facilitating effects of Bisphenol A, a known endocrine disruptor (91). Overall, these studies demonstrate the potential of CuRC in impeding BC proliferation by modulating PI3K/AKT/mTOR axis.

Chrysin

Chrysin (CRY), a naturally occurring flavonoid found in propolis, honey and various plant extracts exhibits a range of pharmacologcal activities, including notable anti-cancer effects. Research has demonstrated its therapeutic potential against various cancer forms, including lung, hepatic, cervical, prostate and breast carcinomas (92,93). CRY exerts its anti-proliferative effect by selectively regulating key cell-signaling pathways mediating cancer cell survival, progression, invasion, angiogenesis, and metastasis (94). Various studies have investigated the cytotoxic potential of CRY in *in vitro* and *in vivo* BC models, by altering various cellular pathways including PI3K/AKT/mTOR axis (95,96). Mechanistically, CRY has been reported to downregulate the expression of PI3K/AKT, thereby inhibiting cell proliferation and inducing apoptosis (94).

Yang et al. explored the anti-metastatic potential of CRY using metastatic TNBC cell lines. Study results revealed that pretreatment of cells with CRY extensively inhibited TNBC cell migration and invasion. Mechanistically, CRY decreased MMP-10, downregulated the expression of slug, snail and vimentin, increased E-cadherin expression, and suppressed the AKT signaling pathway (96). These results suggest that CRY may reverse epithelial-mesenchymal transition (EMT), highlighting its prospective usage as a chemotherapeutic agent for advanced or metastatic BC. Similarly, Zhao and colleagues demonstrated that 5,7-dihydroxy-8-nitrochrysin, a synthetic analog of CRY, influenced cell fate in MDA-MB-453 cells by activating caspase pathways and modulating the AKT/FOXO3a signaling axis (97). Moreover, structural modifications of CRY, by incorporating dimethylamino, benzyloxy, fluoro and nitro groups, led to the synthesis of potent cytotoxic agents with significant activity against BC cells (98). Beyond its inherent anticancer properties, CRY has been shown to enhance the efficacy of chemotherapeutic drugs. For instance, a CRY-ruthenium complex modulated the VEGF, mTOR, and p53 signaling pathways in MCF-7 cells (99). Furthermore, CRY nanoparticles inhibited MDA-MB-231 cell proliferation *via* the PI3K/JNK pathway and induced apoptosis through the p53-mediated pathway, ultimately delaying tumor progression in MDA-MB-231 models (100). Mohammadi et al reported that CRY loaded PEG/PLGA nanoparticles effectively altered expression of PI3K, MMP2, MMP9 and TIMPs in 4T1 induced BC murine model (101). Although the documented results highlighted the potential of CRY in suppressing BC growth in pre-clinical models, however, more studies to elucidate its exact therapeutic mechanisms are required.

Fisetin

Fisetin (FST), a well-known flavonoid present in a number of vegetables and fruits, such as cucumber, strawberries, grapes, apples, persimmons, and onions, has been documented to possess anti-cancer activity (102). The anti-proliferative effect of FST on cancer cells has been linked to apoptosis induction, lowering oxidative stress, suppressing cell migration, and blocking angiogenesis (103). Mechanistically, the anticancer

effect of FST is attributed to its interaction with various molecules and signaling cascades, such as vascular endothelial growth factor (VEGF), mitogen-activated protein kinase (MAPK), nuclear factor-kappa B (NF-κB), the PI3K/AKT/mTOR pathway, and the Nrf2/HO-1 pathway (104). Notably, FST was found to act as a dual inhibitor of the AKT and mTOR. This PI3K/AKT/mTOR modulatory effect of FST is significant in cancer considering the fact that hyperactivation of AKT and mTOR is more frequent in tumors with overexpression of PI3K/AKT/mTOR. FST mediated modulation of PI3K/AKT/mTOR pathway resulted in decreased PI3K protein expression, inhibition of AKT, mTOR, 4E-BP1 and 4E-BP1 phosphorylation, thereby impeding cancer cell proliferationm (105).

Sun et al. investigated the PI3K/AKT/mTOR signaling mediated cytotoxic effect of FST in BC. Treatment of BC cells (MCF-7, MDA-MB-231 and 4T1) with FST inhibited *in vitro* progression of BC cells by blocking their proliferation, invasion and migratory potential. Moreover, FST administration in BC induced mice suppressed tumor growth and enhanced tumor cell death (106). FST significantly suppressed the expression of AKT, P70, and mTOR. Additionally, levels of p-AKT, p-AKT/AKT, p-P70, p-P70/P-70, p-PI3K, p-PI3K/PI3K, and p-mTOR were notably decreased, while Bax was upregulated and Bcl-xL was downregulated following FST treatment compared to the untreated group (106). Li et al. also reported that FST effectively suppressed proliferation, inhibited metastasis, and reversed the epithelial-to-mesenchymal transition (EMT) process in TNBC cells by modulating PTEN/AKT/GSK-3β signaling network (107). These results predict that FST could offer a therapeutic rationale for the management of BC by modulating PI3K-AKT axis.

Epigallocatechin Gallate

Epigallocatechin gallate (EGCG) is a catechin derivative resulting from the esterification of gallic acid and epigallocatechin. It is primarily present in the dried leaves of white and green tea. EGCG has been widely investigated for its potential as a bioactive dietary compound with anti-cancer properties (108). Its mechanisms of action, in suppressing BC progression, are thought to involve the alteration of several signaling cascades, including the PI3K, MAPK, and NF-κB pathways (109,110). Mechanistically, EGCG inhibits PI3K/AKT pathway by acting as an ATP-competitive inhibitor of both PI3K and mTOR, and studies have shown it can reduce AKT phosphorylation, resulting in decreased proliferation and induction of apoptosis in cancer cells (111).

Moradzadeh et al. identified that EGCG caused apoptosis in human BC cells by inhibiting PI3K/AKT and telomerase receptors (112). EGCG altered the PI3K/AKT signaling in BC (T47D) cells by down-regulating protein and gene expression. This suppression was followed by the induction of pro-apoptotic genes including p21, p53, caspase-3, Bax, PTEN, and caspase-9, as well as the down-regulation of anti-apoptotic genes like AKT, PI3K, and Bcl-2. These modifications lead to an increase in the expression ratio of Bax/Bcl-2 proteins, which encourages apoptosis. Moreover, EGCG suppresses the formation of hTERT, the catalytic component of the telomerase enzyme, which causes cellular senescence. Research by Hong et al documented that EGCG suppressed the canonical pathway of B-catenin signaling in BC cells by de-phosphorylation or deactivation of the AKT protein, important for cell proliferation, survival and metabolism (113). Moreover, the anti-cancer effect of EGCG on BC cells has also been related to its interaction to epidermal growth factor receptors (ErbB or EGFR) (114). ErbB receptors, upon ligand binding, undergo conformational changes that facilitate their organization into heterodimers, thereby promoting transmembrane signaling pathways. This process is often upregulated in cancer cells, leading to enhanced proliferation through pathways such as PI3K/AKT and Ras/Raf/MAPK, which activate transcription factors involved in cell proliferation and survival. EGCG has been observed to reduce the expression of these receptors. This reduction may result from alterations in the organization of lipid rafts within the plasma membrane, interference with their interaction to epidermal growth factor or increased internalization *via* endocytosis (115,116). These effects of EGCG could be exploited, especially when the quest for developing novel chemotherapeutics is increased.

Genistein

Genistein (GST), a natural isoflavone isolated from soybeans, fava, and lupine has been shown to reduce the BC progression (117). According to epidemiological finding, it is also speculated to be related with a reduced incidence of BC in Asian women (118). GST, an intriguing phytoestrogen, has a dual impact on cell development, binding to ER to stimulate growth at dietary doses achievable with a soy-rich diet and inhibiting growth at higher experimental concentrations (119). The modulation of PI3K/AKT/mTOR signaling is one of the molecular mechanism by which GST demonstrated its capacity to induce apoptosis and cell cycle arrest, alongside exhibiting anti-angiogenic, anti-metastatic, and anti-inflammatory

activities. Specifically, GST caused downregulation of PI3K/AKT levels, decreased AKT phosphorylation, and increased PTEN in cancer cells (120,121).

A study conducted by Satoh et al. explored the anti-cancer potential of GST against HER-2-overexpressing BC cells (122). The results revealed that low doses of GST enhanced the cytotoxic effect of adriamycin (ADR), primarily by increasing necrotic-like cell death. The combination of GST and ADR led to significant inactivation of HER2 and AKT in BC cells, indicating that GST may promote necrotic-like cell death in these cells (122). Kaushik et al. discovered that GST enhanced centchroman's anti-neoplastic activity in BC by altering the PI3K/AKT signaling pathway. GST treatment to BC (MDA-MB-231) cells suppressed growth and induced apoptosis *via* down-regulating NF-κB and AKT signaling pathways (123). Similarly, combination of GST with another isoflavone, calycosin, reduced BC cell growth by blocking the PI3K/AKT axis, and lowering the expression of the downstream target HOTAIR (124). Additionally, GST was reported to suppress mammosphere development in BC-stem cells (BCSC). The tumoricidal effect of GST on mammospheres was correlated with increased expression of mammary tumor suppressors E-cadherin and PTEN, thereby alterating PI3K/AKT signaling (125). Although, GST has demonstrated a potent anti-proliferative effect against BC, however, more research exploring the mechanistic role of GST could yield a potential phytochemical based chemotherapeutic agent.

Quercetin

Quercetin (QRT) is a natural bioactive flavonoid found in different plant species, including, *Allagopappus viscosissimus*, *Opuntia ficus-indica var. Saboten, Lychnophora staavioides*, *Semecarpus anacardium*, *Rhamnus* species, and *Larrea divaricate* (126). QRT has shown anti-carcinogenic properties against a variety of tumors, including BC. A number of studies have correlated the anti cancer effect of QRT by modulating PI3K/AKT/mTOR signaling pathway. QRT was reported to inhibit AKT activity and increase the activity of AMPK, a negative regulator of mTOR. These effects suppressed the activity of the downstream mTOR effector proteins, ribosomal protein S6 kinase beta-1 (p70S6K), and eukaryotic translation initiation factor 4E-binding protein 1 (4EBP-1) suppressing cell migration thereby impeding BC development (127).

Specifically, exposure of BC cells to QRT impeded their growth dose dependently and induced apoptosis by modulating pro-and anti-apoptotic markers. QRT treated cells demonstrated increased PTEN and reduced AKT, PI3K, and mTOR levels, hence suppressing this signaling pathway (128). Similar result were reported by Zhu et al. where QRT suppressed cell viability and induced apoptosis in MCF-7 cells, by up-regulating the PTEN expression and down-regulating PI3K/AKT and JNK pathways (129). Cao et al reported a significant reduction in cell proliferation and migratory potential as well as induction of apoptosis and cell cycle arrest in BC cells exposed to QRT. Moreover, QRT also decreased the EMT process as indicated by the increased E-cadherin expression, and the concomitant decreased expression of MMP-2 and vimentin. Mechanistically, QRT markedly hampered the constitutive activation of the PI3K/AKT/mTOR signaling cascade and the IGF-1-induced phosphorylation of AKT, PI3K, and GSK-3β in BC cells, which resulted in the down-regulation of proteins related to cell cycle, apoptosis, stem cell pluripotency, and self-renewal (130). Additionally, QRT enhances the chemosensitivity of BC to doxorubicin (DOX) by altering critical components of the PI3K/AKT signaling. QRT up-regulated the expression of PTEN and down-regulated the expression of p-AKT, making cancer cells more susceptible to DOX treatment (131). This synergy between QRT and DOX boosts the anticancer effects of DOX, indicating that QRT may be a promising drug for bypassing chemotherapy resistance in BC cells by targeting the PI3K/AKT pathway.

Apigenin

Apigenin (AGN) is a natural dietary flavonoid molecule found in many fruits and vegetables that has a number of pharmacological effects, including antibacterial, anti-inflammatory and antioxidant properties (132). Scientific studies demonstrated the cytotoxic potential of AGN in various cancers including colon, breast, cervical and prostate. Notably, the anti-proliferative mechanism of AGN has been correlated with the modulation of PI3K/AKT/mTOR axis. Treatment of BC (HER2/neu-over-expressing) cells with AGN inhibited PI3K activity by interacting with its ATP-binding domain, and subsequently restricted AKT kinase activity (133). Lee and coworkers demonstrated the anti-invasion and anti- migration effect of AGN on HGF/Met-mediated tumor metastasis and invasion of BC cells. AGN suppressed the HGF-induced cell scattering and motility and inhibited the HGF-mediated cell invasion and migration in a concentration-dependent manner. AGN treatment impeded HGF-induced AKT phosphorylation and clustering of beta 4 integrin at actin-rich adhesion sites and lamellipodia *via* PI3K pathways (134). These results suggest that AGN may have a significant potential for being tested as PI3K/AKT modulator for BC chemoprevention.

Formononetin

Formononetin (FMT) is a natural isoflavone present in the roots of *Glycyrrhiza glabra, Astragalus membranaceus, Pueraria lobata,* and *Trifolium pratense*. FMT exerted anticancer effect by increasing cell death, producing cell cycle arrest, inhibiting angiogenesis, and reversing multidrug resistance by targeting various signaling cascades (135). FMT decreased MCF-7 cell growth and efficiently produced cell cycle arrest by altering PI3K/AKT pathway. Treatment of BC cells with FMT down-regulated, p-AKT, p-IGF-1 R, cyclin D1 mRNA and protein expression, thereby suggesting its potential application in restricting BC proliferation. FMT also decreased the expression of cyclin D1, one of the downstream target proteins of AKT, which enhanced the G0/G1 phase in MCF-7 cells thereby decreasing proliferation (136). Zhou et al. demonstrated that FMT reduced the invasive capabilities of BC (MDA-MB-231 and 4T1) cells, including migration and invasion, by reducing MMP-2 and MMP-9 expression levels. This impact might be due to the inactivation of the PI3K/AKT pathway, because MMP-2 and MMP-9 expression are mediated by the PI3K/AKT pathway (137). Moreover, the *in vivo* administration of FMT in combination with everolimus (mTOR inhibitor), an FDA approved chemotherapeutic agent, caused a 2-fold suppression in tumor volume compared to everolimus alone (138). Mechanistically, FMT and everolimus alone decreased p-mTOR and p-P70S6K expression while increasing p-4EBP-1 and PTEN activity. However, FMT alone decreased the amount of p-AKT, whereas everolimus did not. Moreover, FMT effectively reversed the expressions of p-P70S6K and p-4EBP-1 in the presence of AKT siRNA. These findings indicated that FMT inhibited the mTOR pathway by decreasing AKT expression (138). These results predict FMT a promising new therapeutic agent as anti-invasive agent for BC management.

Miscellaneous

A myriad of studies have demonstrated the cytotoxic effect of various flavonoids and correlated it with the modulation of PI3K/AKT/mTOR pathway. For instance, Myricetin (MRT), a polyhydroxyflavonol organic compound found largely in the bark of waxberry (*Myrica rubra*), exerted anticancer effect against a variety of malignancies including breast, colon, bladder, prostate and pancreatic cancers (139). Notably, MRT treatment to TNBC cells resulted in both early and late apoptotic cell death, as well as inhibited cell growth. Subsequently, MRT was reported to affect cell cycle, angiogenesis, and invasion activities of BC cells by modulating MAPK and PI3K/AKT signaling pathways (140). Similarly, naringenin (NGN) has been documented to suppress the migration of BC cells (MDA-MB-231) by inhibiting the activation of PI3K, thereby reducing downstream AKT signaling (141). This suppression interferes with key cellular processes vital for cancer progression. By modulating PI3K/AKT signaling, NGN prevents EMT and diminishes the invasion and migration of BC cells. Additionally, its influence on the PI3K/AKT pathway extends to the regulation of mTOR, a downstream molecule regulating protein synthesis and cell proliferation, further restricting cancer development (142). Wu et al. demonstrated the cytotoxic potential of luteolin on tamoxifen-resistant BC cells. Luteolin treatment to BC cells induced apoptosis by suppressing PI3K/AKT/mTOR cascade (143). The combination of luteolin plus AKT, PI3K, or mTOR inhibitors synergistically promoted apoptosis in ER-positive (tamoxifen-resistant) BC cells (143). Genkwanin (GKN), a non-glycosylated flavone, was reported to induce authophagy and apoptosis in BC cells by interacting with ATP binding domain of PI3K, thereby blocking its activity. GKN significantly reduced the amounts of phospho-PI3K, PI3Kγ-p110, phospho-AKT, phospho-ULK, phospho-mTOR and phospho-p70S6K. Moreover, pretreatment with the PI3Kγ-specific inhibitor AS605240, improved GKN-mediated inhibition of p70S6K, mTOR, AKT, ULK and apoptosis level (144). Although, these compounds were effective in suppressing BC growth and development *in vitro*, however further research is needed to elucidate their detailed mechanism of action.

Stilbenes

Stilbenes are a significant class of polyphenolic, non-flavonoid compounds, distinguished by the presence of a 1,2-diphenylethylene core (146). These compounds exhibit remarkable potential in the treatment and prevention of various diseases, including cancer, owing to their antioxidant, anti-inflammatory and pro-apoptotic properties (147).

Resveratrol

Resveratrol (RVT) is a naturally existing polyphenol that offer a variety of anti-aging health advantages such as better metabolism, cardiovascular protection, and prevention against cancer (148). RVT functions as a chemopreventive compound across the four key stages of carcinogenesis including cancer initiation, progression, invasion and metastasis and has demonstrated therapeutic effectiveness in pre-clinical models of cancer (149). A myriad of studies have revealed the

anti-proliferative potential of RVT in BC and correlated it with modulation of various pathways and mechanism crucial for cancer proliferation (150,151). RVT reduced the growth of BC cells (MCF-7) by modulating ERα-associated PI3K/AKT pathway. Notably, ERα was reported to interact and modulate activity of PI3K in MCF-7 cells. Exposure of BC cells to RVT (10 μM) enhanced the PI3K activity, whereas RVT concentration above 50 μM inhibited the activity of PI3K suggesting that RVT could have estrogenic or anti-estrogenic properties (152). Interestingly, RVT has been reported to downregulate the expression of fatty acid synthase (FASN) and HER2 in a dose-dependent manner, and upregulated the expression of polyoma enhancer activator 3 (PEA3) (targeting the HER2 promoter to downregulate its transcriptional activity), thereby suppressing the proliferation of HER2-overexpressing BC cells (157). Previously, Kumar-Sinha et al. reported that HER2 triggered FASN expression by activating the FASN promoter through the PI3K pathway (158). Therefore, it is speculated that RVT decreases the proliferation of BC cells by inhibiting the PI3K–AKT signaling pathway. Notably, Nair et al. evaluated the combinatorial potential of RVT and docetaxel (DCX) on HER-2-overexpressing BC cells. RVT, when introduced as a chemosensitizer in DCX chemotherapy, inhibited the up-regulation and activation of HER-2, while also interfering with downstream signaling pathways like AKT (153). In a similar research study, Chen et al. also demonstrated the chemosensitive potential of RVT in multi-drug resistant BC cells. Researchers observed that combination of doxorubicin (DOX) and RVT synergistically improved DOX-induced chemo-sensitivity and cytotoxicity in MDR-BC cell lines. Mechanistically, RVT restored DOX resistance in BC and suppressed DOX-resistant BC cell proliferation and metastasis and induced cell apoptosis by altering PI3K/AKT/mTOR signaling pathway (154). RVT also demonstrated a mild inhibitory impact on the mTOR/p70S6K pathway activation in two PTEN-expressing BC cells (MDA-MB-231 and MCF-7). The combination of RVT and rapamycin (RPY) had minor additive inhibitory effects on the growth of BC cells, mostly by inhibiting RPY-induced AKT activation. RVT suppressed the phosphorylation and activation of the PI3K/AKT pathway in both the RPY-sensitive (MCF-7) and -resistant (MDA-MB-231) cells (155). RPY-PVT treatment also inhibited the downstream target of mTOR p70S6K resulting in S-phase cell cycle arrest in BC cells (155). These results support the further evaluation of RVT in conjugation with conventional anti-cancer drugs for management of BC.

Pterostilbenes

Pterostilbene (PTS), a stilbenoid phytochemical found in grapes, blueberries, and *Pterocarpus marsupium* wood, is recognized as one of the most potent stilbenes (156). It has a structural resemblance to RVT but has better pharmacokinetic properties (157). Wakimoto and coworkers demonstrated the anti-proliferative effect of PTS on three subtypes of BC cell lines. PTS significantly impeded proliferation and induced cell-cycle arrest (G_0/G_1 phase) and apoptosis in TNBC (MDA-MB-468) cells. PTS triggered a robust and prolonged stimulation of extracellular signal-regulated kinase (ERK) 1/2, accompanied by suppression in cyclin D1 levels and enhancement in p21 expression. Additionally, it inhibited the mTOR and AKT phosphorylation, leading to a subsequent up-regulation of BAX, while leaving B-cell lymphoma-extra large (BCL-xL) unaffected (158). Elsherbini et al. reported the effect of PTS on signaling pathways regulating the apoptosis of mutant p53-BC cell lines. PTS reduced the proliferation capacity of BC cells (T47-D and MDA-MB-231). Mechanistically, PTS up-regulated the level of pro-apoptotic protein (Bax), and caspase-3 activity and down-regulated, mTOR, cyclin D1, and β-catenin protein expression (159). These results indicate the further pre-clinical evaluation of PTS as a natural chemotherapeutic agent.

Carotenoids

Carotenoids include fat-soluble pigments that give plants and animals their colors. Carotenoids are characterized by a C40 isoprenoid backbone, which can either remain acyclic or undergo modifications, resulting in one or both ends forming rings with various structural alterations (160). The distinctive polyene structure of carotenoids underlies their antioxidant properties and is implicated in their ability to modulate cancer-associated signaling pathways, including the PI3K/Akt/mTOR axis. Evidence suggests that carotenoids can suppress the expression or function of key proteins within this pathway, thereby attenuating signaling events that promote cellular proliferation and survival (161). Among the various carotenoids studied, β-carotene and lycopene have garnered considerable scientific interest due to their potential anticancer properties. β-carotene has been reported to inhibit PI3K activity and reduce AKT phosphorylation in cancer cells, leading to suppressed tumorigenesis and downregulation of the mTOR signaling pathway (162,163). Likewise, lycopene has

demonstrated the ability to inhibit AKT activation and mTOR signaling, thereby contributing to the suppression of cancer cell proliferation. The PI3K/AKT/mTOR mediated anti-proliferative effect of carotenoids on BC is still under infancy, more research to evaluate their impact on BC is needed.

Lycopene

Lycopene (LCP), a carotenoid found in tomatoes and other orange or red fruits and vegetables, has been researched for its potential anticancer properties, specifically in relation to BC (164). Preclinical studies in *in vitro* and *in vivo* BC models revealed that LCP inhibited the proliferation of BC cells and induced apoptosis, potentially through the modulation of PI3K/AKT/mTOR pathway (24,165). Takishema et al. demonstrated the molecular mechanism facilitating the anticancer activity of LCP against three subtypes of BC (ER/PR +, HER2+ TNBC) cells. LCP dose-dependently and time dependently suppressed the proliferation of BC cells by halting the cell cycle at sub-G0/G1 phase. In TNBC, LCP blocked the phosphorylation of mTOR and AKT, and subsequently increased pro-apoptotic protein (Bax) without influencing anti-apoptotic protein (Bcl-xl) (165). Soo et al. demonstrated the inhibitory effect of LCP on the migratory and invasive behavior of two highly aggressive BC cell lines, (MDA-MB-231 and H-Ras MCF10A). LCP effectively inhibited the proliferation, migration and invasion of these cells. Moreover, LCP suppressed ERK and AKT activation in H-Ras MCF10A cells, indicating that the ERK and AKT signaling pathways may be implicated in LCP'S anti-invasive/migratory and/or anti-proliferative activities in these cells (166). These results, provide a crucial mechanistic impact regarding the application of LCP in management of the BC and necessitates the evaluation of PI3K/AKT mediated anti cancer effect of other carotenoids.

Factors Limiting the Clinical Translation of Phytochemicals in Breast Cancer Therapy: possible Solutions

Recently, phytochemicals have gained significant attention for their potential therapeutic applications in BC treatment. Scientific evidence has shown an increasing interest in the use of phytochemicals as standalone agents or as adjuncts to conventional chemotherapeutic agents. Despite the promising preclinical results, their translation into effective and clinically approved treatments remains a major challenge (59). One of the most significant obstacle limiting the clinical use of phytochemicals is their pharmacokinetic instabilities, such as poor aqueous solubility, limited bioavailability, low stability, and short circulation duration (23,167). For instance, phytochemicals such as curcumin, quercetin, apigenin and lycopene have low solubility in water, which decreases their oral bioavailability by limiting their absorption in the gastrointestinal tract. Furthermore, some of them (resveratrol,chrysin) are often rapidly metabolized and eliminated, reducing their effectiveness (168,169). One promising strategy to overcome these limitations is the use of nanoparticle-based drug delivery systems, which passively target tumor sites through the enhanced permeability and retention (EPR) effect—a phenomenon that allows nanoparticles to accumulate in tumor tissue due to leaky vasculature and poor lymphatic drainage (136). Nano-phytomedicine, an emerging field that integrates phytochemicals and nanotechnology, provides an innovative solution by improving the pharmacokinetic and pharmacodynamic profiles of these compounds. Encapsulating phytochemicals in nanoparticles enhances their stability, bioavailability, and retention in the body, potentially leading to more effective cancer therapies with reduced systemic toxicity and side effects (137). This approach not only maximizes the therapeutic potential of phytochemicals but also opens new avenues for precision medicine in cancer treatment. Off-target effects and poorly understood mechanisms of action poses another hurdle in clinical applicability of natural compounds. Phytochemicals often interact with multiple molecular targets, which, while contributing to their broad-spectrum activity, can also lead to unintended biological effects. These off-target interactions may result in toxicity, adverse drug reactions, or interference with essential cellular pathways, particularly in non-diseased tissues (168). For example, flavonoids have been shown to affect cytochrome P450 enzymes, leading to altered drug metabolism and potential drug–drug interactions (170). A plethora of studies have demonstrated the acute toxicity of phytochemicals in pre-clinical models however, concerns about their long-term safety, and toxicity at higher doses and interactions with other drugs remain to be fully elucidated in pre-clinical and clinical models (171). To overcome challenges associated with molecular targets and signaling pathways, *in silico* approaches such as molecular docking should be utilized to elucidate the binding interactions of phytochemicals within key cellular pathways. These computational predictions can then be substantiated through comprehensive validation using appropriate *in vitro* and

in vivo experimental models. Most preclinical studies involving phytochemicals are conducted at doses much higher than what is achievable in humans. This discrepancy raises concerns about potential adverse effects when these compounds are administered at clinical doses. Interestingly, the complexity and heterogeneity of BC is an important constraint limiting their effectiveness (172). The efficacy of phytochemicals varies substantially depending on the kind of phytochemicals and the individual BC subtype, making the ideal dosage and delivery protocol problematic. Another major barrier is the lack of quality control and standardization protocol in the production of phytochemical-based therapies. This variability makes it difficult to ensure consistent therapeutic outcomes in clinical settings (173). Addressing these issues requires multidisciplinary efforts, including advancements in formulation technologies, safety profiling, and standardization of natural products. Moreover, personalized treatment strategies and large-scale clinical trials are important to validate the therapeutic potential of phytochemicals in the clinical settings.

Nanocarriers Mediated Delivery of Phytochemicals Targeting the PI3K/AKT/mTOR Pathway in Breast Cancer

Phytochemicals such as curcumin, quercetin, apigenin, lycopene, epigallocatechin gallate (EGCG) and resveratrol have been researched extensively for their ability to mediate dysregulated PI3K/AKT signaling in pre-clinical models of BC (25,174). These compounds targeted the key components of this cascade, including catalytic activity of PI3K, AKT phosphorylation, and downstream effectors such as mTOR, PDK1, FOXO and GSK-3β, However, their clinical translation has been limited primarily due to their pharmacokinetic concerns. Nanotechnology- based delivery presents a novel solution to tackle these obstacles simply by encapsulating these natural drugs in biocompatible carriers that increase their solubility, stability, and target specificity while minimizing off-target toxicity (23).

Nano-delivery platforms used for delivering phytochemical include lipid nanoparticles (NPs) (liposomes), polymeric nanoparticles, dendrimers, micelles, and inorganic nanoparticles such as silver, silica or gold based platforms. Among them, polymeric nanoparticles made of biodegradable components like PEG (polyethylene glycol) or PLGA (poly(lactic-co-glycolic acid)) have demonstrated significant success in encapsulation of hydrophobic phytochemicals and achieving controlled drug release profiles. For instance, CuRc-loaded PLGA NPs have revealed decreased AKT phosphorylation in BC cells (MCF-7/MDA-MB-231), resulting in apoptosis and cell cycle arrest (175,176). Similarly, RVT delivered through PEGylated liposomes has shown enhanced suppression of the PI3K/AKT/mTOR axis compared to free RVT, along with improved tumor accumulation and reduced systemic clearance in xenograft models (177).

Liposomes and nanostructured lipid carriers have also gained interest due to their high drug-entrapment capacity for lipophilic phytochemicals. QRT-loaded liposomes have been reported to alter PI3K/AKT signaling and restore sensitivity to tamoxifen in resistant BC cells by downregulating AKT phosphorylation and Bcl-2 expression (178). Notably, EGCG was found to inhibit PI3K/AKT signaling in HER2-positive BC cells; its delivery using chitosan nanoparticles improved its cellular uptake and bioactivity, reducing tumor growth in murine models more significantly than the free drug (179). These examples underscore the value of nanophytomedicine for enhancing the anti-PI3K/AKT activity of phytochemicals. However, despite the significant promise of phytonanomedicine, several challenges must be addressed to enable their clinical translation. These include ensuring reproducible large-scale production, assessing tumor-NPs interactions, elucidating long-term safety and immunogenicity, and understanding complex regulatory pathways. Furthermore, patient-specific tumor heterogeneity and differential PI3K/AKT activation states necessitate personalized approaches.

Discussion

Over the past few decades, extensive research into the PI3K/AKT/mTOR signaling pathway has elucidated its intricate networks, including its activation mechanisms, upstream and downstream targets, and various types of inhibitors. At the core of its oncogenic potential lies the pathway's ability to integrate diverse extracellular signals (e.g., growth factors, hormones, cytokines) and translate them into intracellular responses that promote cell survival and metabolic reprogramming. Mutations or amplifications in PI3K subunits (especially PIK3CA), loss of the tumor suppressor PTEN, and hyperactivation of AKT or mTOR are commonly observed across a wide variety of cancers (14) Numerous studies have demonstrated that the PI3K/AKT/mTOR pathway is frequently altered in BC, particularly in hormone receptor-positive (HR+) tumors, where it plays a key role in promoting resistance to treatment. This growing knowledge of the PI3K/AKT/mTOR pathway offers new insights

into the management of BC. While the development of targeted inhibitors has advanced cancer treatment, challenges remain, particularly concerning their toxicity and side effects, such as hyperglycemia, rashes, and other symptoms, which must be carefully considered in patient care. In light of the PI3K/AKT/mTOR pathway's significant role, efforts are underway to discover novel drugs targeting this pathway. Phytochemicals, including flavonoids, carotenoids, and stilbenes, have shown promising chemotherapeutic potential against BC by modulating this pathway, with many still in preclinical development stages. Researchers are also exploring combinatorial therapies, combining phytochemicals with conventional treatments, to enhance synergistic effects and improve the solubility and bioavailability of active compounds. However, one of the key challenges in targeting the PI3K/AKT/mTOR pathway is its complex feedback regulation and cross-talk with other oncogenic pathways, such as RAS/RAF/MEK/ERK and JAK/STAT. Inhibition at one node (e.g., mTOR) often leads to compensatory activation upstream (e.g., AKT or PI3K) or lateral activation of alternative survival pathways (180). Alteration of feedback-loops or compensatory pathways by modulating PI3K/AKT/mTOR axis can pose an unintended consequence of drug resistance to phytochemicals, a thought which needs to be addressed. To date, only a few natural products have advanced to clinical trials, with the majority, such as paclitaxel, being well-established for cancer treatment. Therefore, a deeper understanding of the specific molecular targets of natural products is essential to facilitate the translation of their potential anticancer effects into clinical practice in the near future.

Conclusion

The PI3K/AKT/mTOR signaling pathway is a central regulator of cell survival, proliferation, angiogenesis and metabolism, and its disruption is a hallmark of BC. Therapeutic exploitation of this pathway has revealed considerable therapeutic promise, yet challenges such as feedback activation, drug resistance, and systemic toxicity limit the long-term efficacy of traditional inhibitors. Notably, phytochemicals offer a complementary therapeutic approach with the potential to modulate this pathway through multi-targeted mechanisms, often with lower toxicity profiles. Various preclinical studies have indicated the ability of phytochemicals such as curcumin, quercetin, resveratrol, and genistein to inhibit key nodes within the PI3K/AKT/mTOR axis, leading to impeded tumor growth and increased chemosensitivity. However, their clinical translation remains hindered by low bioavailability and inadequate target specificity. Emerging technologies, including *in silico* modeling, nano-formulation, and combination therapy approaches, are paving the way to overcome these limitations. Future research should focus on pharmacokinetic optimization, mechanistic validation and controlled clinical trials to fully elucidate the therapeutic potential of phytochemicals targeting the PI3K/AKT/mTOR pathway in BC.

Acknowledgment

We extend our deepest appreciation to all contributors to this manuscript. We are particularly grateful to our VP-Research at RAK Medical and Health Sciences University for their insightful comments and feedback. Additionally, we acknowledge the support from our institutions, which was instrumental in facilitating this research.

Author Contribution

Conceptualization, A.F.W. and M.E.-T.; Software, A.F.W., S.T., S.S. and M.E.-T.; Writing—original draft preparation, A.F.W., S.T., M.El-T., I.R.R., R.Bk., S.S. and R.B- writing—review and editing, A.F.W., S.T., M.El- and S.S. All authors have read and agreed to the published version of this manuscript.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The author(s) reported there is no funding associated with the work featured in this article.

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