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REVIEW

Targeting Molecular Pathways in Breast Cancer Using Plant-Derived Bioactive Compounds: A Comprehensive Review

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Abstract: Breast cancer remains one of the most prevalent and life-threatening diseases worldwide, affecting millions of individuals and their families. While current treatments such as chemotherapy, radiation, and targeted therapies have improved survival rates, they often come with severe side effects and limitations. This has led to a growing interest in natural compounds derived from medicinal plants as safer and potentially more effective alternatives. These plant-based compounds have shown promise in targeting key cancer pathways, including EGFR, PI3K/AKT/mTOR, NF-κB, JAK-STAT3, RAF/MEK/ERK, BCL-2, p53, and SKP/p21, helping to inhibit tumor growth, induce cancer cell death, and prevent metastasis. Research combining computational, in vitro, and in vivo studies has revealed that bioactive compounds such as flavonoids, alkaloids, and phenolics can provide meaningful therapeutic benefits. However, challenges such as ensuring proper absorption, stability, and clinical application remain. By addressing these limitations through advanced drug formulations and integration into existing treatment plans, plant-based therapies could play a vital role in improving outcomes for breast cancer patients. This review sheds light on the potential of natural compounds to offer hope for more effective and less harmful cancer treatments in the future.

Keywords: breast cancer, phytochemicals, natural compounds, targeted therapy, molecular pathways

Introduction

Breast cancer remains one of the most prevalent and challenging malignancies worldwide, with significant morbidity and mortality among women in 2022, there were approximately 2.3 million new breast cancer cases and 670,000 deaths.[1] According to GLOBOCAN (2021), in 2020, the number of new breast cancer cases in Indonesia reached 68,858, accounting for 16.6% of the total 396,914 new cases, with the death toll exceeding 22,000 cases.[2–4]Breast cancer arises due to a combination of internal and external factors.[5–7]Breast cancer arises from genetic mutations in key tumor suppressor genes such as BRCA1, BRCA2, and TP53, resulting in uncontrolled cellular proliferation, resistance to apoptosis, and genomic instability. Several signalling pathways are implicated in breast cancer progression, including EGFR, RAF/MEK/ERK, NF-κB, JAK-STAT3, BCL-2, p53, and SKP/p21, each of which regulates critical cellular processes such as growth, differentiation, and metastasis. Research also indicates that poor lifestyle habits, environmental exposures, and socio-psychological influences contribute to its development.[8,9] Approximately 5% to 10% of breast cancer cases are linked to genetic mutations and family history, while 20% to 30% can be attributed to modifiable risk factors.[10]

Conventional treatments, including surgery, chemotherapy, radiation, and hormone therapy, have improved survival rates but are often accompanied by severe side effects and limitations.[11,12] Consequently, there is an increasing interest in exploring alternative and complementary therapies that are both effective and less harmful.[13] Among these, natural compounds derived from plants have garnered substantial attention due to their bioactive properties and potential anti-cancer activities.[14,15] Plants provide a rich source of bioactive compounds such as flavonoids, alkaloids, terpenoids, and phenolics, which have shown promise in fighting cancer by triggering apoptosis, slowing cell proliferation, and inhibiting angiogenesis and metastasis.[16–18]Their ability to

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target multiple pathways makes them valuable in cancer treatment.[19] Research on plant-derived compounds includes in vitro, in silico, and in vivo studies. In silico methods use computational techniques to predict how these compounds interact with cancer-related targets, optimizing their structures and assessing pharmacokinetics.[20–22] In vitro studies test their effects on cancer cells, evaluating cytotoxicity, apoptosis, and cell cycle impact.[23,24] In vivo studies conducted on animal models help determine their effectiveness, safety, and bioavailability, bridging the gap to clinical application.[24–26]

However, the safety profiles of many plant-derived agents remain under-characterized, with limited data on their potential off-target toxicity and optimal dosing parameters.[27,28] In contrast, conventional cancer therapies possess well-defined therapeutic insights and dosing guidelines, underscoring the need for comprehensive toxicity and pharmacokinetic studies of novel botanical candidates prior to clinical application.[29,30] The safety profiles of many plant-derived agents remain under-characterized, with scarce data on their off-target toxicity and safe dosing ranges. Without standardized toxicity testing (eg acute and sub-chronic LD_{50} or NOAEL assays), the translational potential of crude extracts and fractions is difficult to assess[28,31]. This gap underscores the need for comprehensive pharmacokinetic and toxicological evaluations prior to clinical application.

This review explores the potential of plant-based compounds in breast cancer treatment, summarizing key findings from different study approaches. By understanding their mechanisms, identifying promising candidates, and addressing challenges, we aim to contribute to developing effective, natural therapies that could improve patient outcomes and quality of life.

Materials and Methods

At the start, the reference was limited to published from 2014 to 2025. The search for papers was conducted using Scopus. The search technique employed synonyms and related concepts interchangeably as keywords. The Boolean operators "AND", "AND NOT", and "OR" were used to combine and exclude terms in the following way: (1) A search was performed in the Scopus database using the terms Breast cancer AND Herbal medication OR Plant extract OR natural Compound AND route OR Signalling pathway, AND NOT preclinical study OR Clinical trial. The search was restricted to the Article title, Abstract, and Keywords. The search yielded a total of 1034 articles. (2) All papers identified through these searches were subsequently assessed to ascertain whether they satisfied the review's criteria for inclusion. Eligible studies were original, peer-reviewed research articles published in English from 2014 onward that focused specifically on breast cancer and evaluated the molecular mechanisms of action of individual plant-derived compounds, whether by in silico modeling, in vitro assays, and in vivo experiments, within defined signaling pathways such as EGFR, PI3K/AKT/mTOR, or NF-κB. We excluded any publications before 2014, non-English articles, studies that did not address breast cancer, investigations of multi-component extracts or mixtures without isolating a single bioactive agent, reports lacking a clear examination of pathway-specific mechanisms, and non-original literature types such as reviews, editorials, conference abstracts, or commentaries (Figure 1).

Results

EGFR Pathway

The EGFR, or epidermal growth factor receptor, belongs to a family of receptor tyrosine kinases that also includes three other members (erbB2/HER-2, erbB3/HER-3, and erbB4/HER-4) [67]. The receptors are located within the cytoplasmic membrane and share a similar structure, including an extracellular domain that binds to ligands, a short hydrophobic region that crosses the membrane, and an intracellular domain with a tyrosine kinase.[32,33] EGFR is triggered through receptor overexpression, which is frequently observed in cancer. Furthermore, it can be activated through both ligand-dependent and ligand-independent pathways. Six known ligands can bind to the EGFR, including EGF and transforming growth factor-α. Upon ligand binding, EGFR undergoes dimerization and then phosphorylates particular tyrosine residues within its intracellular domain. This initiates a sequence of signaling cascades, which involve the RAS/RAF/MEK/ERK and PI3K/AKT pathways.[33] EGFR triggers the activation of the RAS/RAF/MEK/ERK pathway, leading to the phosphorylation of ERK.[34] Subsequently, ERK translocates to the nucleus and regulates gene expression associated with cell proliferation and survival. Concurrently, the initiation of the PI3K/AKT pathway results in the phosphorylation

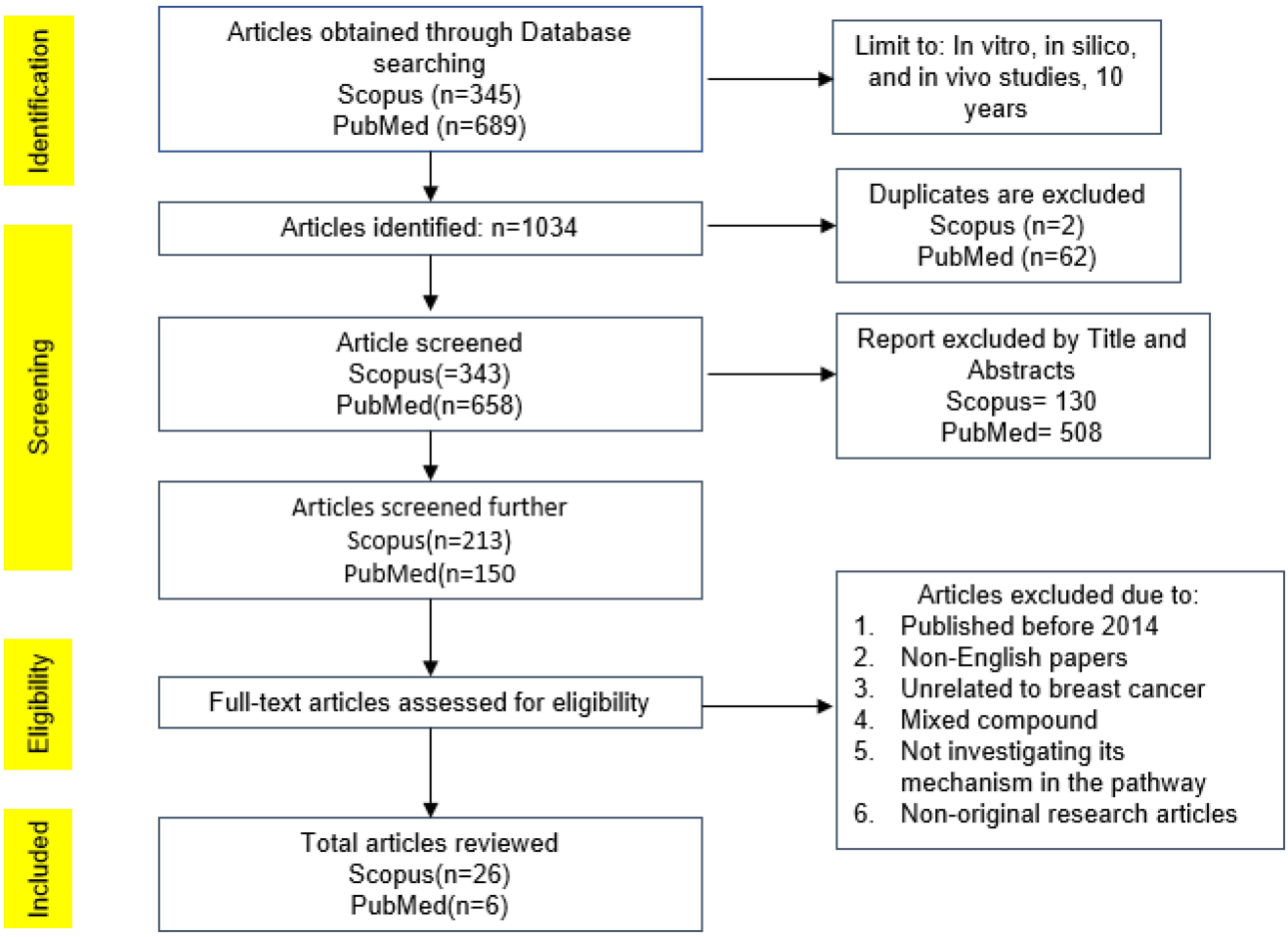

Figure 1 A search strategy flow diagram.

and stimulation of AKT, which enhances cell survival and growth by inhibiting programmed cell death and enhancing protein production via mTOR signaling.[35]

Based on in silico assay, *Terminalia chebula* has shown promise in blocking the EGFR by directly binding to its active site, stabilizing it in an inactive state, and preventing downstream oncogenic signaling (Table 1). Saccharopine, a bioactive compound from *Terminalia chebula*, directly binds to EGFR (PDB ID: 3W2S) with a high binding affinity of −9.7 kcal/mol, which is stronger than the standard reference ligand 17β-estradiol (−4.4 kcal/mol). Molecular docking simulations showed that saccharopine interacts with key EGFR active site residues, including GLN-791, MET-793, CYS-797, THR-854, and ASP-855, stabilizing the receptor in an inactive conformation and preventing autophosphorylation. Molecular dynamics (MD) simulations also confirmed the structural stability of the EGFR-saccharopine complex, with RMSD values ranging between 0.13 and 0.23 Å, indicating minimal fluctuations and a stable binding pose. Binding free energy calculations using MM-PBSA analysis further showed a high binding affinity (−87.74 kcal/mol), with electrostatic interactions contributing significantly (−133.567 kcal/mol), confirming a strong inhibitory interaction with EGFR.

The bioactive compounds from *Abrus precatorius* target the epidermal growth factor receptor (EGFR) pathway by directly binding to the receptor's kinase domain, thereby preventing its activation and subsequent signaling. Stigmasterol, in particular, exhibits the strongest binding affinity to EGFR (−9.9 kcal/mol) (Table 1). This suggests that stigmasterol can effectively compete with ATP, blocking EGFR's phosphorylation and disrupting its downstream signaling. The *A. precatorius* compounds interfere with this process by occupying the ATP-binding pocket, inhibiting the phosphorylation of tyrosine residues required for signal transduction.[36]

Based on in vitro assay, saccharopine in *Terminalia chebula* leads to suppression of breast cancer cell proliferation and induction of apoptosis (see Figure 2). Western blot analysis confirmed that saccharopine treatment significantly

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Table 1 In Silico Assay of Plants

Medicinal Plants	Phytoconstituent Name	Macromolecule (PDB Code)	Binding Energy (kcal/mol)	Inhibition Constant (Ki) (μM)	Hydrogen Bond Interactions at Catalytic Site (Amino acid residues)	Hydrophobic Bond Interactions at Catalytic Site (Amino acid residues)	Interpretation	Reference
Phaleria macrocarpa	Ageratriol (1)	Bcl-2 (PDB Code: 1GJH)	−5.4	N/A	Asn39, Glu13	N/A	Corymboside Suggests Bcl-2 inhibition, promoting apoptosis	[1]
	Apigenin (2)		−6.3	N/A	Asn39, Gly46	N/A		
	Betulin (3)		−6.4	N/A	Asn39, Glu13	N/A		
	Cafestol (4)		−6.1	N/A	Asn39, Glu13	N/A		
	Carvone (5)		−4.4	N/A	Ser49	Gly8		
	Corymboside (6)		−7.3	N/A	Asn39, Glu13, Gly8	Lys17		
	Fraxetine (7)		−5.2	N/A	Ser49, Glu13	N/A		
	Glycitein (8)		−5.5	N/A	Asn39, Glu13	N/A		
	Matairesinol (9)		−6.4	N/A	Asn39, Glu13	N/A		
	Nootkatone (10)		−4.4	N/A	Ser49	Gly8		
	Sakuranetin (11)		−6.4	N/A	Asn39, Glu13	N/A		
	Sesamin (12)		−6.9	N/A	Gly46	Pro44		
	Sterubin (13)		−6.7	N/A	Asn39, Glu13	N/A		
	Trigoneline (14)		N/A	N/A	N/A			
Curcuma zedoaria (Christm). Roscoe	Curcumol (15)	Erα (PDB Code: 1A52)	−8.0	1.36	N/A	Met343, Leu346, Thr347, Ala350, Leu384, Leu387, Phe404, Met421, Leu428	Isocurcumenol was the most potent ERα inhibitor	[2]
	Curcumenol (16)		−7.9	1.61	Leu346	Leu346, Ala350, Leu384, Leu387, Met388, Leu391, Phe404, Leu428		
	Isocurcumenol (17)		−8.5	0.58	N/A	Leu349, Ala350, Leu384, Leu387, Met388, Phe404, Leu525		

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Brassica oleracea var. italica	Sulforaphane (18)							
Abrus precatorius L.	Abrin (19)	EGFR (1XKK)	−7.3		LEU788.	MET766, PHE856, LEU788, LEU858, LEU777	Stigmasterol exhibited the strongest binding energy. it may be a more potent EGFR inhibitor	[3]
	Abruroside A (20)		−7.7		CYS797, VAL717, ASP800	PHE856		
	Stigmasterol (21)		−9.9		N/A	LEU718, VAL726, ALA743, LEU844, CYS775, LEU777.		
	Glycyhrhizin (22)		−4.1		CYS797, ASP855, ARG841, PHE856, LEU718	N/A		
Terminalia chebulata	Phthalamic acid (23)	EGFR (3W25)	−8.4		N/A	N/A		[4]
	Saccharopine (24)		−9.7		GLN-791, MET-793, CYS-797, THR-854, ASP-855	VAL-726, ALA-743, and LEU-844	Saccharopine showed the highest binding energy, surpassing 17β-estradiol (−4.4 kcal/mol), suggesting it could inhibit EGFR signaling	
	Mauritianin (25		−8.1		GLN-791, MET-793, and THR-854	VAL-726, ALA-743, and LEU-844,		
	Carbetamide (26)		−7.3		LYS-745 and MET-793	ALA-722, VAL-726, and LEU-718,		
	Silibinin (27)		−5.4		THR-854	VAL-726 and ALA-743,		

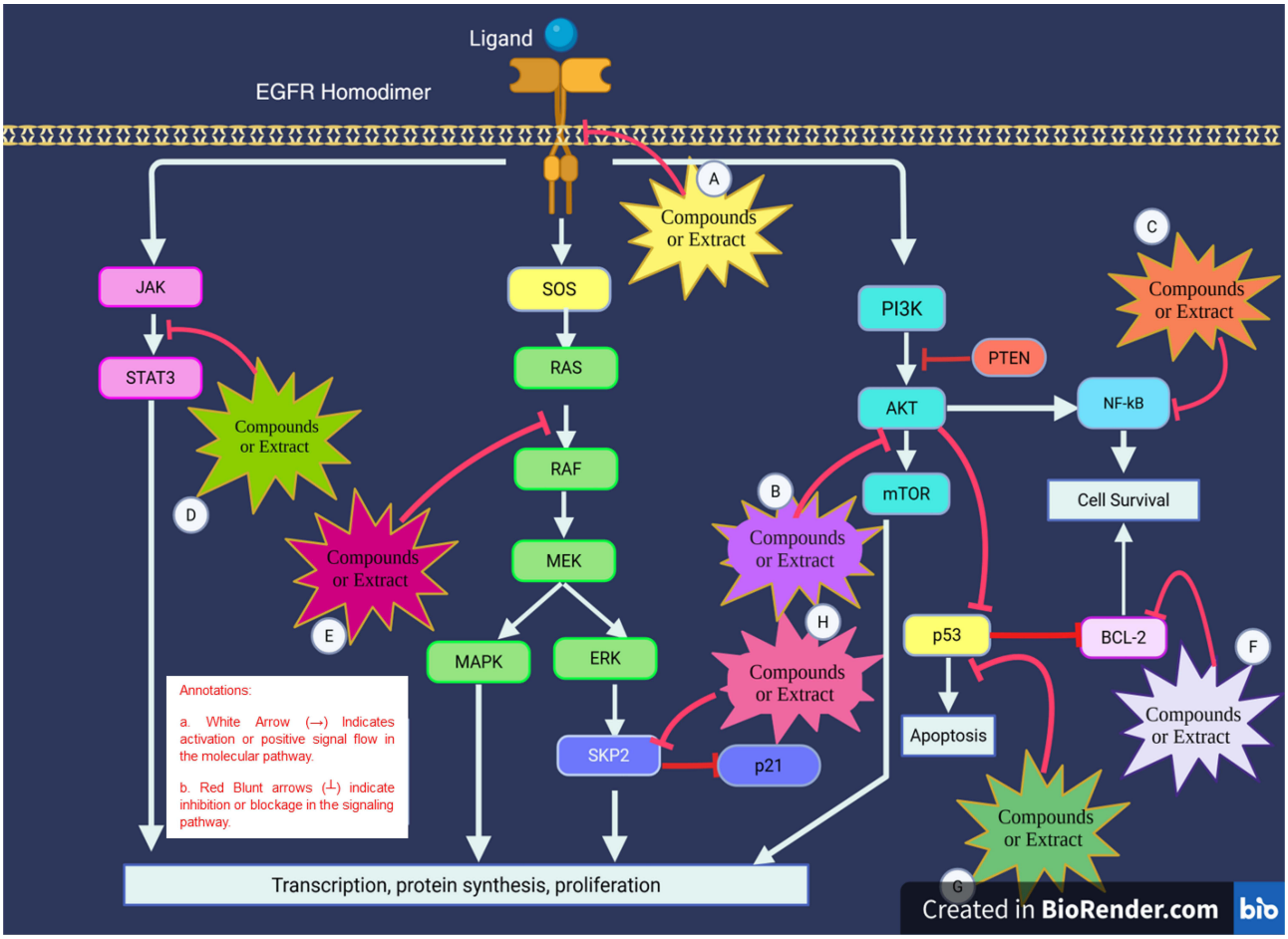

Figure 2 Breast Cancer Signaling Pathway Mechanism and Compound or Extract Intervention in Cell Regulation.

reduced EGFR phosphorylation, preventing its activation and blocking downstream signaling pathways. Additionally, MTT cytotoxicity assays revealed that saccharopine dose-dependently reduced MCF-7 breast cancer cell viability, with a value of 103.2 µg/mL, indicating strong antiproliferative effects. Flow cytometry-based cell cycle analysis showed that saccharopine-induced G2/M phase arrest, preventing uncontrolled cancer cell division. Moreover, Annexin V/PI staining and caspase activation assays demonstrated that saccharopine significantly increased apoptosis, as confirmed by upregulation of Bax and cleaved caspase-3, and downregulation of Bcl-2, indicating its ability to induce programmed cell death via EGFR inhibition.

Extracts derived from *Strobilanthes crispus* that contains lutein, campesterol, stigmasterol, β-sitosterol, pheophytin a, 132 -hydroxy-pheophytin a, and 131 -hydroxy-132 -oxo-pheophytin also demonstrate encouraging outcomes in the treatment of breast cancer. The bioactive subfraction F3 effectively suppresses the movement and infiltration of MDA-MB-231 cells by reducing the expression of metastasis-associated markers like MMP-9, VEGF, and MUC1. This suppression is similar to the effects of established anticancer drugs such as curcumin and metformin, indicating its promise in stopping the spread of cancer cells (metastasis).[37,38]

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PI3K/AKT/mTOR Pathway

The PI3K/Akt/mTOR pathway is a critical intracellular signaling cascade that responds to nutrients, hormones, and growth factors, playing a significant role in tumor growth and proliferation. Central to this pathway is the PI3K heterodimer, consisting of a regulatory subunit (p85) and a catalytic subunit (p110), which is activated by receptor tyrosine kinases (RTKs).[39,40] Activated Akt, through phosphorylation by PDK1 and mTORC2, phosphorylates downstream targets, enhancing cell survival and growth, such as blocking pro-apoptotic factors (Bad, caspase-9) and activating mTORC1, which promotes protein synthesis and cell growth through S6 kinase and 4E-BP1 phosphorylation.[41] Disruptions in the PI3K/Akt/mTOR pathway are common in cancer, often due to PI3K mutations, loss of the tumor suppressor PTEN, or overactivation of growth factor receptors, leading to increased PI3K activity and Akt activation. Activation in uncontrolled cell growth, tumor progression, metastasis, and treatment resistance.[42]

Phaleria macrocarpa has the ability to inhibit the PI3K/Akt/mTOR pathway utilizing its bioactive components, which were identified using Liquid Chromatography–High-Resolution Mass Spectrometry (LC-HRMS). Computational investigations (Table 1) demonstrated that twelve out of fourteen compounds exhibit anticancer characteristics, namely affecting the PI3K/Akt signaling pathways. Apigenin strongly inhibits PI3K (−7.2 kcal/mol) and Akt (−7.2 kcal/mol), showed hydrogen bonding between apigenin and key residues in PI3K, preventing its activation, making it a potent candidate for targeting this pathway.[43]

A study examined the impacts of Gallic acid (GA), a compound from *Terminalia chebula*, a polyphenol molecule that is recognized for its anti-tumor activities discovered to inhibit the advancement of triple-negative breast cancer (TNBC) HCC1806 cells via regulating the PI3K/AKT/EGFR and MAPK signaling pathways (Table 1). Gallic acid has a strong binding affinity with PI3K (PDB ID: 3APC), with a binding energy of −7.32 kcal/mol, indicating a stable interaction. GA formed hydrogen bonds with key residues GLN-1071 and GLU-981 which are crucial for PI3K activity. The formation of these bonds suggests that GA may interfere with PI3K phosphorylation, thereby preventing downstream activation of

Akt. GA also exhibited a binding affinity toward Akt (PDB ID: 1GZK), with a binding energy of −5.61 kcal/mol. The docking analysis revealed that GA interacted with the TYR-417 residue of Akt through hydrogen bonding (1.9 Å). This interaction may lead to the suppression of Akt phosphorylation, thereby inhibiting its pro-survival signaling in cancer cells.[44]

Ent-abietane diterpenoids such as Jolkinolide A and B, extracted from *Euphorbia fischeriana*, have strong anti-breast cancer properties. These compounds inhibit AKT phosphorylation, a key step in the PI3K/AKT/mTOR pathway (see Figure 2). By blocking this pathway, they reduce cancer cell proliferation and induce apoptosis.[45] The study also showed that GA from *Terminalia chebula* effectively inhibits the PI3K/Akt pathway in TNBC HCC1806 cells by reducing cell viability through cytotoxic effects, inducing apoptosis via caspase activation and mitochondrial dysfunction. Suppressing PI3K, Akt, and mTOR phosphorylation, leading to pathway inhibition and downregulating EGFR, preventing further activation of PI3K/Akt signaling[44] β-sitosterol (Table 2) inhibits glucose uptake in cancer cells by reducing GLUT1 localization on the membrane and suppressing hexokinase activity, leading to impaired glycolysis. Additionally, β-sitosterol downregulated key oncogenic proteins, including AKT, pAKT, mTOR, and HIF1α, while inhibiting PKC activity, thereby disrupting tumor cell metabolism and survival. Moreover, β-sitosterol increased TXNIP expression and reduced fibronectin levels, which contributed to decreased cancer cell migration and invasion, highlighting its potential as an anticancer agent.[46]

Isorhamnetin (Table 3) found in *Antenoron filiforme* significantly reduced tumor volume and weight, with the DOX + IS combination group exhibiting the most significant tumor suppression compared to the control and DOX-only groups. Immunohistochemistry (IHC) analysis confirmed that mTOR phosphorylation (p-mTOR) was markedly reduced in tumor tissues from the Isorhamnetin-treated group, correlating with decreased expression of p70S6K and 4E-BP1, key downstream effectors of mTOR signaling. Additionally, γ-H2AX expression was elevated, indicating increased DNA damage and apoptosis, which further contributed to tumor regression.[47] *Strobilanthes crispus*, a medicinal plant from Malaysia, exhibits anticancer properties its potent fraction, F3, derived from the leaves was analyzed in high-performance liquid chromatography (HPLC) and nuclear magnetic resonance (NMR) and six bioactive components in F3, namely lutein, β-sitosterol, and stigmasterol (Table 3). The chemicals suppressed glycolysis and the PI3K/Akt pathway, resulting in decreased expression of AKT, pAKT, mTOR, and HIF1α. Additionally, it reduced the migratory ability of MDA-MB-231 cells, indicating their anti-glycolytic and anti-metastatic properties.[37,38]

Taraxacum mongolicum extract exhibited significant anticancer properties when tested against triple-negative breast cancer (TNBC) cells. Dandelion extract disrupts the metabolic processes of glycerophospholipids and unsaturated fatty acids. Luteolin can inhibit the PI3K/AKT signaling pathway by reducing CHKA expression. This suppression leads to decreased phosphorylation levels of AKT, which is crucial for tumor cell proliferation and survival (see Figure 2). Studies conducted in living organisms demonstrated a decrease in tumor size and mass directly proportional to the dosage administered, with no impact on overall body weight.[48]

NF-Kb Pathway

The NF-κB pathway is crucial for breast cancer progression, modulating inflammation, immunity, cell proliferation, and survival. NF-κB is a protein complex composed of Rel family proteins (p65/RelA, RelB, c-Rel, p50, and p52) that control the transcription of several genes involved in the immune response and cell survival. In the setting of breast cancer, the NF-κB pathway is frequently and continuously active, which leads to the development of tumors and the survival of cancer cells. This activation occurs through the control of genes that produce proteins that prevent cell death (anti-apoptotic proteins), as well as substances that regulate inflammation (cytokines and chemokines) and the cell division process (cell cycle regulators).[49–51] The main function of this route is to primarily participate in the development of lymphoid organs and adaptive immune responses. However, it also plays a role in the advancement of breast cancer by controlling the activity of genes involved in cell movement and the spread of cancer cells to other parts of the body.[52]

Russelioside A, a pregnane glycoside derived from the plant *Caralluma tuberculata*. The researchers extracted Russelioside A and examined its impact on NF-κB activity (see Figure 2) using the 4T1-NFκB-luciferase reporter cell line. It was found that Russelioside A effectively inhibited NF-κB transcriptional activity and the phosphorylation of p65, which is a crucial subunit of NF-Kb.[53]

Table 2 In vitro Assay on Plants

Plants	Active compounds	Origin	Parts of plants/ extraction	Pathway	Method	Result	Interpretation	Reference
Brassica oleracea var. italica	Sulforaphane (1)		Sprouts, ethanol	RAF/ MEK/ ERK	Cck assay; wound healing assay; transwell invasion assay; proteomic and phosphoproteomic assay; Western blot	SFN inhibited TGF-β1-induced migration and invasion of TNBC cells	Sulforaphane inhibits metastasis in TNBC cells by targeting the RAF/MEK/ERK pathway and reducing actin cytoskeleton reorganization, indicating its potential as an anti-metastatic agent	[5]
Strobilanthes crispus (L). Blume	Lutein (2)	Malaysia	Leaves, Dichloromethane fraction	PI3K/ AKT/ mTOR	Immunofluorescence Analysis (GLUT1 and Fibronectin Localization), Western blot, flow cytometry, protein kinase c assay, transwell migration	GLUT1 localization to the membrane was inhibited sitosterol. PKC activity is reduced, PI3K/AKT/mTOR pathway was inhibited, reducing glucose metabolism and metastasis Cell migration decreased, Lutein 20 μM	Lutein inhibit PI3K/AKT/ mTOR reducing glucose metabolism and metastasis	[6,7]
	β; Sitosterol (3)	–	Pure compound	PI3K/ AKT/ mTOR		PKC activity is reduced, PI3K/AKT/mTOR pathway was inhibited, reducing glucose metabolism and metastasis Cell migration decreased,;GLUT1 localization to the membrane was inhibited IC50 β-Sitosterol= 25 μM	β; Sitosterol inhibit PI3K/ AKT/mTOR reducing glucose metabolism and metastasis	
	Stigmasterol					PKC activity is reduced, PI3K/AKT/mTOR pathway was inhibited, reducing glucose metabolism and metastasis Cell migration decreased,;GLUT1 localization to the membrane was inhibited Stigmasterol 90 μM	Stigmasterol inhibit PI3K/ AKT/mTOR reducing glucose metabolism and metastasis	
Tussilago farfara	7β-(3-Ethyl-cis-crotonoyloxy)-1α-(2-methylbutyryloxy)-3,14-dehydro -Z-notonipetranone (ECN)	Korea	Flower/ acetonitrile, hplc. Countercurrent chromatography	PI3K/ AKT/ mTOR	MTT assay; Western blot Analysis; Flow cytometry	IC50 P18-2 (ECN: 7β-(3-Ethyl-cis-crotonoyloxy)-1α-(2-methylbutyryloxy)-3,14-dehydro -Z-notonipetranone)= 6.85 ± 0.03 μM	ECN inhibits JAK–STAT3 signaling and activation of apoptotic pathways	[8]

(*Continued*)

Table 2 (Continued).

Plants	Active compounds	Origin	Parts of plants/ extraction	Pathway	Method	Result	Interpretation	Reference
	Rutin	–	Pure compound	NF-κB	ROS: DCFH-DA staining, flow cytometry Western Blot: p65, p-p65, IκBα, p-IκBα qRT-PCR: NF-κB, HSP90, iNOS; Wound-Healing: Annexin V/PI staining, flow cytometry Crystal violet	Cell viability: Hyperoside decreased viability.IC50 MCF-7= 49.3 μM, IC50 4T1= 54.7 μM at 24 hours. ROS levels= Reduced by hyperoside.Apoptosis= Induced in MCF-7 and 4T1 cells.Protein expression= Decreased IκBα and p65 phosphorylation, inhibiting NF-κB pathway.Gene expression= Downregulated NF-κB,	Inhibit NF-κB pathway by Downregulated NF-κB	[9]
Zanthoxylum bungeanum	Hyperoside	China	Pure compound, DMSO	NF-KB	CCK-8 Assay, Annexin V/PI Staining, Wound Healing Assay, Western Blot, qRT-PCR	Hyperoside inhibited proliferation and migration of breast cancer cells IC50= 100 μM Apoptosis=100 μM	Hyperoside suppresses breast cancer growth by inducing apoptosis through ROS reduction and NF-κB inhibition	[10]
Euphorbia fischeriana Steud	17-hydroxy jolkinolide B	Qiqihar, China	Roots; acetonitrile		MTT assay	IC50 MCF-10A= 3.4 ± 0.1 μg/mLIC50 MCF-7:= 4.7 ± 0.2 μg/mLIC50 ZR-75-1= 2.2 ± 0.1 μg/mLIC50 MDA-MB-231= 1.1 ± 0.1 μg/mL	Very high cytotoxicity, indicating strong anti-cancer activity	[11]
	jolkinolide B,		Roots; acetonitrile			IC50 MCF-10A= 83.3 ± 0.9 μg/mLIC50 MCF-7= 94.4 ± 1.6 μg/mLIC50 ZR-75-1: 73.1 ± 0.9 μg/mLMDA-MB-231= 43.6 ± 1.6 μg/mL	More potent than compounds 1, particularly in MDA-MB-231	
	17-hydroxyjolkinolide A		Roots; acetonitrile			IC50\/MCF-10A: 39.4 ± 0.4 μg/mLMCF-7: 41.0 ± 0.7 μg/mLZR-75-1: 44.9 ± 0.5 μg/mLMDA-MB-231: 71.5 ± 2.5 μg/mL	Higher potency compared to previous compounds	
	jolkinolide A		Roots; acetonitrile			MCF-10A: 114.6 ± 1.7 μg/mLMCF-7: 169.4 ± 2.2 μg/mLZR-75-1: 104.8 ± 1.9 μg/mLMDA-MB-231: 162.5 ± 3.2 μg/mL	Lower activity	

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Eleutherine bulbosa	N-hexane extracts	Medan, Indonesia.	Bulb, n-hexane; extraction	MAPK pathway	MTT assay; Flow cytometry	– IC50= 265.023 µg/mL; Likely inhibition of Cyclin D; CDK4/6 activityLeads to G0-G1 phase arrest; Potential apoptosis	NESO has some anti-cancer potential	[12]
	Ethyl acetate extract		Bulb, ethyl acetate; extraction			– IC50 value= 147.124 µg/ mLcaused G0-G1 phase cell cycle arrest.- 40.88% of cells in G0-G1 phase compared to 36.18% in control.- Induced apoptosis with a 7.22% increase in sub-G1 phase (M1 phase) cell population.	EAESO is the most potent extract, effective in halting cancer cell proliferation	
	Methanol extract		Bulb, ethanol; extraction			– IC50= 3782.29 µg/mLcaused significant G0-G1 phase cell cycle arrest (40.88%).- Indicates effective inhibition of the cell cycle at G0-G1 phase.- Induced apoptosis: increased sub-G1 phase cells (7.22%) compared to control (0.55%).	EESO is the least effective extract,	
Terminalia chebula	Saccharopine	Bengaluru, India	Fruits, ethanol; extraction	EGFR	Cell cytotoxicity analysis using the MTT assay, hemolysis assay, G2M phase studies, apoptosis studies, LDH activity assay, AO/EtBr staining, and ROS determination	– (IC50= 103.2 µg/mL).- Induced G2/M phase cell cycle arrest= 16.81% (10 µg/mL), 23.62% (15 µg/ mL). – Induced apoptosis: Early apoptotic cells at 0.03% and 47.22%, late apoptotic cells at 15.0% and 52.38%. – No hemolysis in hemolysis assay.- Increased ROS production dose-dependently. –Significant LDH activity at high concentrations,	Induced apoptosis, Blocking cell cycle progression at the G2/M phase.	[13]
	Gallic acid		Pure compounds; DMSO	PI3K/ AKT/ EGFR and MAPK	MTT assay; Colony Formation Assay; Flow cytometry; Hoechst 33258 staining and flow cytometry for apoptosis rate; JC-1 staining method; DCFH-DA fluorescent probe; Quantitative Real-Time PCR (QRT-PCR); Western Blotting	IC50 gallic acid = 200–300 µM; S-phase arrest in HCC1806 cells; 2–3x increase in ROS, MMP depolarization (40–53%)	Moderate cytotoxicity in TNBC cells; Blocks cancer cell proliferation; Moderate cytotoxicity in TNBC cells	[14]

(*Continued*)

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Table 2 (Continued).

Plants	Active compounds	Origin	Parts of plants/ extraction	Pathway	Method	Result	Interpretation	Reference
Caralluma tuberculate	Russelioside A	Al-Sheffa, Saudi Arabia	Herbaceous parts, ethanol	NF-κB	Cell Counting Kit-8 Assay. Luciferase reporter assays.NF-κB p65 phosphorylation: Western blot. Trans-well migration, invasion assays, wound healing assays.: RT-PCR and ELISA.	IC50 (4T1 Cells) 88.0 μM IC50 (MDA-MB-231 Cells) NF-κB Inhibition (200 μM) ~70% inhibition	Has anticancer properties	[15]
Antenoron Filiforme	Ethyl Acetate Extract	Mountain E Mei, China	Herbaceous parts, ethyl acetate	SKP/P21	Cells treated with varying concentrations of kaempferol.MTS Assay:Assessed cell proliferation. Flow Cytometry:Analyzed cell cycle distribution using propidium iodide staining.Western Blotting:Detected protein levels of p-ATM, gH2AX, cleaved caspase 3, and cleaved caspase 9.DAPI Staining:Observed nuclear morphology for apoptosis. Annexin V/PI Staining:Evaluated apoptosis using flow cytometry.	IC50 MDA-MB-231=149.7 μM IC50 LM2=166.9 μM IC50 MDA-MB-453= 34.26 μM IC50 hCC1806 = 119.1μM IC50 hCC38 =71.02 μM IC50 hS-578= 129.6 μM IC50 BT-549= 154.5 μM	The extract effectively inhibits TNBC cell growth via the Skp2/p21 pathway	[16]
	Kaempferol		Pure compound; DMSO		MTS Assay; Flow Cytometry; Western Blotting; DAPI Staining; Annexin V/PI Staining	IC50 MDA-MB-231 = 43 μmol/ LIC50 BT474= >100 μmol/L; Cell Cycle Arrest; G1 phase: 85.48% to 51.35%; G2 phase: 9.27% to 37.5%; Increased annexin V+ cells; Increased cleaved caspase 9 and caspase 3; z-VAD attenuated apoptosis; Increased gH2AX levels; Increased p-ATM levels	Kaempferol inhibits TNBC proliferation through G2/M arrest, apoptosis, and DNA damage,	[17]
	β-sitosterol		Pure compound; DMSO	Akt/ MTOR	Proliferation assay	EC50 Value= 196.28 ± 4.45 μMInhibition of Migration/ Invasion:β-Sitosterol: 15.67%	Inhibition of Migration/ Invasion	[18]

	Isorhamnetin		Pure compound; DMSO	mTOR	Cell Viability Assays: MTS assayMigration Assay: Transwell migration assayThree-Dimensional Tumor Spheroid Model:Flow Cytometry Analysis:Assays: Apoptosis (Annexin V-FITC/ PB450), Cell Cycle (DAPI staining), Intracellular ROS (DCFH-DA staining)Western Blot Analyses: Nuclear Staining: DAPI stainingEdU Proliferation Assays:	Increased G2/M phase cell cycle arrest from 35.84% to 50.64% in MCF7/ADR cells; enhanced ROS production 6.78-fold, leading to DNA damage and AMPK/mTOR/ p70S6K inhibition.	Activated AMPK/mTOR/ p70S6K signaling pathway	[19]
Viscum album	Ethanolic extract	Wonju, Republic of Korea	Leaves, ethanol	ER	MTT assay, Annexin V/PI staining, Western blot, Flow cytometry	MCF-7 cells=IC50 ≈ 250 μg/mL BT-474 cells= IC50 ≈ 500 μg/mL HCC-1428 cells= IC50 ≈ 500 μg/ mL Induced apoptosis via caspase-3/ PARP cleavage.- Caused G1/S phase arrest by downregulating Cyclin D1, Cyclin E1, and CDK6.- Suppressed STAT3 phosphorylation, leading to inhibition of its oncogenic function.	Inhibited cell viability and proliferation, induced apoptosis,	[20]
Chloroxylon swietenia (Roxb).	Ethanolic extract 4-methoxy-7H-furo[3,2-g]chromen-7-one, 7-methoxy-8-(3-methylbut-2-en-1-yl)-2H-chromen-2-one, 1-(4-methoxyphenyl)-2,5-dimethyl-1H-pyrrole-3-carbaldehyde, 1,4-di-tert-pentylbenzene, 7-methoxy-6-(3-methyl-2-oxobutyl)-2H-chromen-2-one, 4,7,8-trimethoxyfuro[2,3-b] quinoline, (E)-5-methyl-1-(2,6,6-trimethylcyclohexa-2,4-dien-1-yl)hexa-1,4-dien-3-one, and 4-hydroxy-9-(3-methylbut-2-en-1-yl)-7H-furo[3,2-g]chromen-7-one	India (Kinwat city, Nanded district)	Leaves; methanol	NF-KB	MTT assay, Annexin V-FITC, Western blot, Flow cytometry	Inhibited proliferation, induced apoptosis, cell cycle arrest at G2/M phase, IC50 = 20 μg/mL	Inhibit proliferation, induced apoptosis, cell cycle arrest at G2/M phase,	[21]

(*Continued*)

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Table 2 (Continued).

Plants	Active compounds	Origin	Parts of plants/ extraction	Pathway	Method	Result	Interpretation	Reference
Ruellia tuberosa	Methanolic extracts	Kolkata, India	Flowers; methanol	Bcl-2	MTT assay, Wound Healing, Migration Assay, Cell Cycle Analysis, Apoptotic Nuclear Morphology Study, Annexin V/PI, Mitochondrial Membrane Potential Estimation, Western Blot, qRT-PCR	Significant reduction in TNBC cell viability (IC_{50} = 23.84 μg/mL), inhibition of cell migration, increased ROS generation, G0/G1 cell cycle arrest, nuclear fragmentation, loss of mitochondrial membrane potential, downregulation of Bcl-2, upregulation of Bax, increased caspase-3 and caspase-9 levels,	Extracts inhibit anti-cancer potential against TNBC by inducing ROS production, DNA damage, and apoptosis via mitochondrial pathways.	[22]
Syzygium samarangense (Blume) Merr.	Quercetin	Barangai, The Philippines	Methanolic extracts		MTT assay; caspase-3 activation; DNA fragmentation analysis; annexin V/PI staining (fluorescent microscopy)	IC50 MCF-7 = 7.2 μg/mL μg/mL); extract not toxic to normal cells (IC50 >1 mg/mL); triggers apoptosis (DNA fragmentation, caspase-3 activation)		[23]
Annona cherimola Mill	Ethanolic	Awkar, Lebanon	Leaves; ethanol; maceration	BCL-2	MTS cell viability assay; PI staining and flow cytometry (cell cycle); Cell Death ELISA (DNA fragmentation); Annexin V–FITC staining (fluorescence microscopy and flow cytometry); Western blot for cytochrome c, p21, Bax, Bcl-2	Selective anti-proliferative effect on IC_{50} MDA-MB-231: = 390.2 μg/mL at 48 h; minimal effect on MCF-7 and no cytotoxicity on rat MSCs; Dose-dependent ↑ pre-G0/G1 cells (fragmentation) to 28.65% at 522 μg/mL; DNA fragmentation enrichment 3.07- and 5.22-fold at 261/522 μg/mL; Annexin V^+ cells ↑ from 17.4% control to 56.5% at 522 μg/mL• ↑ p21 and cytochrome c, ↑ Bax/Bcl-2 ratio indicative of mitochondrial apoptosis	Extract cytotoxicity selectively against triple-negative MDA-MB-231 cells via induction of mitochondrial apoptosis—triggering cytochrome c release, upregulating p21 and Bax/Bcl-2 imbalance	[24]

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Radix Tetrastigma	Ethanolic extracts	Jiangxi province, China	Roots; ethanol, maceration	PI3K/ Akt/ mTOR-	CCK-8 viability assay; EdU proliferation assay • Annexin V/PI apoptosis (flow cytometry) • Western blot for PI3K, AKT, mTOR, LC3I/II, cleaved caspase-3	In Taxol-resistant MDA-MB-468 cells, RTEs + Taxol ↓ LC3II/LC3I ratio (ie, autophagy), ↑ cleaved caspase-3 and apoptosis (% Annexin V^+ cells ↑ vs Taxol alone; $P < 0.001$), ↓ viability and proliferation (CCK-8, EdU; $P < 0.01$) • mTOR protein level preserved by RTEs + Taxol (vs Taxol-only decrease) • Inhibition of PI3K/Akt (wortmannin) reverses RTEs effect (↑ autophagy, ↓ apoptosis, ↑ viability)	Extract sensitize Taxol-resistant TNBC cells by activating PI3K/Akt/mTOR signaling to suppress protective autophagy and trigger caspase-3–dependent apoptosis, reducing proliferation	
MeLia toosendan Sieb.et Zucc	Toosendanin		Pure compound, dissolved in DMSO	Caspase-3	MTT assay (IC_{50} determination); PI staining (necrosis); Annexin V-FITC/PI flow cytometry (apoptosis); Western blot	IC_{50} MDA-MB-231 ≈ 0.095 μM • Rapid ↑ PI^+ cells (12–48 h) • Annexin V^+ cells markedly ↑; strong caspase-9 → caspase-3 cleavage; Bcl-xL ↓ signi ficantly • Abundant autophagosomes; LC3B II/I and Beclin-1 up; p62 ↓ sharply	Toosendanin potently induces multimodal cell death—necrosis, mitochondrial apoptosis and autophagy—in TNBC cells at sub-micromolar levels, highlighting its high anticancer efficacy.	[25]
	Isotoosendanin		Pure compound, dissolved in DMSO	Caspase-3	MTT assay (IC_{50} determination); PI staining (necrosis); Annexin V-FITC/PI flow cytometry (apoptosis); Western blot	IC_{50} MDA-MB-231 ≈ 7.42 μM; Slower, less intense ↑ PI^+ cells; Moderate Annexin V^+ increase; weaker caspase activation; modest Bcl-xL reduction Fewer autophagosomes; moderate LC3B II/I and Beclin-1 up; p62 ↓ mildly	Isotoosendanin exhibits anticancer activity via the same multimodal pathways but requires ~80× higher concentration and induces weaker necrosis, apoptosis, and autophagy	

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Table 3 In vivo Assay on Plants

Plant	Parts of Plants	Compounds	Origin	Pathway	Model Category	Dose	Duration of Treatment (days)	Result	Reference
Murraya koenigii	Leaves	Hydroethanolic extracts	Botanical garden of Panjab University, Chandigarh, India	ER	Female SD rats	200 mg/kg body weigh	22 days	Tumor incidence & volume, ↑ Pro-apoptotic genes, ↓ Anti-apoptotic genes; ↓ Estrogen levels, ↑ Antioxidant markers, ✓Histopathological improvement	[26]
Farfarae Flos	Flower buds	7β-(3-ethyl-cis-crotonoyloxy)-1α-(2-methylbutyryloxy)-3,14-dehydro-Z-notonipetranone (ECN	Korea	JAK–STAT3 signaling inhibition	BALB/c nude mice	1 mg/kg	21 days	↓ tumor growth, ↑ apoptosis (extrinsic & intrinsic), ↓ STAT3 target genes	[8]
		Chlorogenic acid	–	NF-κB pathway	Female Balb/C mice	(20 and 40 mg/kg)	Not specified in the study	Tumor growth, ↑ survival, ↓ metastasis, ↑antitumor immunity	[27]
Xanthium spinosum	Aerial parts	Chloroform fraction ethanol extracts n-hexane extracts aqueous extract	South America	Apoptotic pathway and immune modulation	Female Balb/C mice	100 mg/kg to 7500 mg/kg	10 days	↓ Tumor size, ↑apoptosis, modulated cytokines, no liver/kidney toxicity	[28]
Chloroxylon swietenia	Leaves	Ethanolic extracts	Kinwat city, India	NF-κB	NOD-SCID mice	25 mg/kg	17 days	↓ tumor volume, ↑ apoptosis, ↓ migration & angiogenesis	[21]
Taraxacum mongolicum	Whole plant	Ethanol extracts;	China	tnbc	BALB/c nude female mice,	Not specified in the study	Not specified in the study	↓TNBC proliferation; ↓CHKA expression, regulated lipid metabolism	[29]
Antenoron filiforme	Leaves	Ethyl acetate extract	China	Skp2/p21	BALB/c nude female mice	Not specified in the study	Not specified in the study	↓ TNBC proliferation, G1/S cell cycle arrest	[16]

Terminalia chebula	Ethanol extract	Ethanol extracts	India	EGFR	Sprague Dawley rats	Not specified in the study	Not specified in the study	↑ apoptosis, ↓ proliferation	[30]
Caralluma tuberculate	Herbaceous parts, ethanol	Russelioside A	Taif, Saudi Arabia	NF-Kb	Female BALB/c mice	100 µL	3 day	↓ NF-κB activity; ↓p65 phosphorylation; ↓ tumor proliferation & metastasis in breast cancer cells; ↓ expression of VEGF-b, MMP-9, IL-6= ↓ lung metastasis in mice	[15]
Sthrobilantes Crispus		Dichloromethane fraction	Malaysia	EGFR	Female Balb/c mice	Not specified in the study	30 days	Tumor growth ($p < 0.01$) and ↓ migration ↓ invasion	[6]
Radix Tetrastigma		Ethanolic extracts	Jiangxi province, China	Pi3k/Akt/ mTOR	Female Balb/c mice		16 days	Tumor growth ↓ ($P < 0.01$), ↓ autophagy, ↑ caspase-3–mediated apoptosis	[31]

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The second investigation conducted by Kamble et al, methanol extract derived from *Chloroxylon swietenia* (Table 2). The mechanism of action of its extract was associated with the induction of apoptosis via DNA fragmentation, actin cytoskeleton disorganization, and cell cycle arrest at the G2/M phase. Another notable study was around hyperoside a glycoside of the flavonoid class that is found in *Zanthoxylum bungeanum*. The study demonstrated that Hyperoside demonstrated its potential as a powerful inhibitor of the NF-κB pathway (see Figure 2) by causing mitochondrial malfunction and triggering apoptosis, triggering programmed cell death, and suppressing cell division in MCF-7 and 4T1 breast cancer cells.[54]

α-Pinene in *Tussilago farfara L*. inhibits tumor invasion in highly metastatic MDA-MB-231 breast cancer cells by targeting the NF-κB signaling pathway (see Figure 2) and suppressing MMP-9 expression. 3D spheroid invasion assays confirmed that 50 μM. α-Pinene significantly reduced TNF-α-induced cancer cell invasion, while RT-PCR and MMP-9 promoter assays showed that α-Pinene dose-dependently downregulated MMP-9 transcription, preventing extracellular matrix degradation. Furthermore, Western blot and luciferase assays revealed that α-Pinene inhibited IKK phosphorylation, suppressed IκB degradation, and reduced p65/RelA activation, thereby blocking NF-κB-dependent transcription of pro-metastatic genes.[55] α-Phellandrene also in *Tussilago farfara L*. inhibits the NF-κB signaling pathway (see Figure 2) in MCF-7 breast cancer cells by suppressing TNF-α-induced NF-κB activation through inhibition of IκB degradation and reduced IKK phosphorylation, preventing NF-κB nuclear translocation.[56] Additionally, α-Phellandrene-induced G2/M cell cycle arrest and promoted apoptosis in a dose-dependent manner. Rutin in *Tussilago farfara L*. also suppresses DMBA-induced breast carcinogenesis by inhibiting the IL-6/NF-κB signaling pathway, which plays a key role in inflammation, tumor progression, and cancer cell survival significantly reduced IL-6, IL-1β, and TNF-α levels, thereby preventing NF-κB activation and downregulating oncogenic proteins Src1 and HSP90, which contribute to cancer cell survival and chemoresistance.[57]

Eugenol, which demonstrated that this substance regulates the NOD1-NF-κB signaling pathway (see Figure 2) in triple-negative breast cancer cells. Eugenol inhibits the NF-κB signaling pathway in triple-negative breast cancer (TNBC) cells by suppressing NOD1 expression, an upstream activator of NF-κB, thereby reducing phosphorylated IκBα (p-IκBα) and NF-κB p65 levels, preventing its nuclear translocation. CCK8 and colony formation assays confirmed that eugenol dose-dependently inhibited TNBC cell proliferation, with IC_{50} values of 16.84 μM in MDA-MB-231 and 27.25 μM in MDA-MB-453 cells, while transwell and wound healing assays revealed that eugenol reduced cell migration and invasion rates by up to 75.38%. Furthermore, DARTS-LC-MS/MS analysis confirmed that eugenol directly binds to NF-κB, stabilizing it in an inactive state.[58]

Another study focused on chlorogenic acid, which is obtained from *Euphorbia fischeriana* (Table 1). This study showed that chlorogenic acid can trigger apoptosis and hinder breast cancer cell metastasis by inhibiting NF-κB activation in breast cancer cells by blocking IκBα phosphorylation, preventing NF-κB nuclear translocation, and reducing NF-κB target gene expression. Western blot analysis confirmed that CGA significantly downregulated NF-κB p65 expression and prevented IκBα degradation, leading to reduced transcription of MMP-9, COX-2, and VEGF, which are involved in metastasis and inflammation. Additionally, MTT and Annexin V/PI assays revealed that CGA selectively reduced breast cancer cell viability, increased apoptosis (via Bax and cleaved caspase-3 upregulation), and suppressed anti-apoptotic Bcl-2 expression.[59]

An in vivo study of chlorogenic acid conducted by Zeng et al (Table 3) [59] demonstrated that chlorogenic acid (CGA) inhibits NF-κB-mediated tumor progression in a BALB/c mouse model injected with 4T1 breast cancer cells, where CGA was administered intraperitoneally at doses of 20 mg/kg and 40 mg/kg every two days. Western blot analysis of tumor tissues confirmed that CGA downregulated NF-κB p65 and phosphorylated IκBα (p-IκBα), leading to reduced expression of metastatic markers such as MMP-9 and VEGF, which are critical for cancer cell invasion and angiogenesis. Additionally, flow cytometry analysis showed that CGA treatment increased CD4+ and CD8+ T-cell populations in the spleen, enhancing antitumor immunity, suggesting that CGA suppresses NF-κB activation while boosting immune-mediated tumor suppression in breast cancer.

JAK STAT3

The Janus kinase-signal transducer and activator of transcription 3 (JAK–STAT3) pathway is a pivotal signaling cascade that conveys information from extracellular chemical signals to the cell nucleus, culminating in the transcription of specific genes

and subsequent cellular responses 43. The pathway is initiated when cytokines or growth factors bind to their corresponding receptors, causing the activation of receptor-associated Janus kinases (JAKs). Activated JAKs then phosphorylate specific tyrosine residues on the receptor, creating docking sites for STAT3 44. Upon binding, STAT3 is phosphorylated by JAKs, leading to its dimerization. The phosphorylated STAT3 dimers translocate into the nucleus, where they bind to particular DNA sequences, regulating the transcription of target genes involved in critical cellular processes such as proliferation, differentiation, apoptosis, and immune responses[60–62] In cancer, the JAK/STAT3 pathway is frequently overactive due to mutations, the absence of negative regulators such as SOCS3, or an increase in cytokine production. This leads to unregulated cell proliferation and the spread of cancer cells to other parts of the body.

7β-(3-Ethyl-cis-crotonoyloxy)-1α-(2-methylbutyryloxy)-3,14-dehydro-Z-notonipetranone(ECN), which is a sesquiterpenoid derived from *Tussilago farfara L*. (Table 3) The cytotoxic effects of ECN effectively suppressed cell viability in a way that depended on the dosage. Western blot analysis revealed that ECN suppressed STAT3 phosphorylation at tyrosine 705, hence inhibiting dimerization and nuclear translocation. ECN inhibited STAT3 phosphorylation (p-STAT3) and downregulated JAK1, JAK2, and Src expression, leading to the suppression of the JAK-STAT3 signaling pathway. The inhibition resulted in reduced activation of STAT3 target genes, such as Bcl-2, Cyclin D1, and COX-2, and triggered programmed cell death through both external and internal routes ECN effectively suppressed tumor growth in a BALB/c nude mouse xenograft model injected with MDA-MB-231 breast cancer cells, where ECN was administered intraperitoneally at 1 mg/kg every two days for 21 days.[57]

RAF/MEK/ERK Pathway

Proliferation, differentiation, survival, and apoptosis are regulated by the mitogen-activated protein kinase (MAPK) pathway, also known as the RAF/MEK/ERK signaling system. Extracellular growth factors or mitogens bind to receptor tyrosine kinases (RTKs), triggering the activation of RAS, a small GTPase. RAS, once activated, recruits and activates RAF kinases, including ARAF, BRAF, and CRAF. RAF kinases subsequently phosphorylate and stimulate the activity of MEK1 and MEK2, which are dual-specificity kinases. These kinases, in turn, phosphorylate and activate ERK1 and ERK2.[63,64]

Sulforaphane, a naturally occurring chemical extracted from *Brassica oleracea var. italica*, as a powerful inhibitor of this specific pathway (Table 1).[65] The in silico study revealed that sulforaphane (SFN) directly interacts with RAF kinases (ARAF, BRAF, and CRAF), preventing their activation and downstream signaling in the RAF/MEK/ERK pathway. Molecular docking simulations demonstrated that SFN binds ARAF at Thr34 and Lys36, BRAF at Ser536, and CRAF at Lys399, Tyr340, and Tyr341, forming hydrogen bonds that stabilize these kinases in an inactive conformation. This binding disrupts the catalytic activity of RAF kinases, inhibiting MEK and ERK phosphorylation, thereby blocking proliferation and migration signals in breast cancer cells. Molecular dynamics simulations also confirmed that SFN binding alters the conformational flexibility of RAF kinases, further preventing MEK and ERK activation. Proteomic and phosphoproteomic analysis revealed that SFN affects the actin cytoskeleton by reducing the expression of focal adhesion and migration-related proteins, including paxillin, focal adhesion kinase (FAK), IQGAP1, ROCK, and PAK2, which play essential roles in cytoskeletal remodeling and tumor cell motility.

The in vitro study demonstrated that sulforaphane (SFN) inhibits the RAF/MEK/ERK signaling pathway (see Figure 2 and Table 2), leading to reduced proliferation and migration in triple-negative breast cancer (TNBC) cells. Western blot analysis confirmed that SFN significantly decreased RAF activation, which subsequently led to reduced MEK and ERK phosphorylation, preventing downstream signaling required for tumor progression. The inhibition of RAF/ERK signaling resulted in the suppression of oncogenic gene transcription, including MYC and Cyclin D1, thereby impairing cancer cell division and survival.

BCL-2 Pathway

The BCL-2 pathway is a major factor in cell survival and oncogenesis, particularly in breast cancer. This pathway involves a family of proteins, including Bcl-2, Bcl-X L, Bcl-w, Mcl-1, Bfl1/A-1, and Bcl-B, which interact with BH3-domain pro-apoptotic proteins, hence controlling the balance between cell survival and death.[66] In breast cancer, the overexpression of Bcl-2 has been associated with treatment resistance and poor[67,68] The mechanism of the BCL-2 pathway in breast cancer relies on enhancing cell survival by blocking apoptosis. Overexpression of anti-apoptotic Bcl-2

proteins, such as Mcl-1, can result in apoptotic escape and treatment resistance in breast cancer.[69] Targeting BCL-2 has shown potential in enhancing vulnerability to therapy in estrogen receptor-positive breast cancer.[70] Moreover, the BCL-2 pathway can be efficiently targeted in combination with ionizing radiation to increase apoptotic cell death in breast cancer cells.[71]

The in silico study demonstrated that three lead phytochemicals from *Ruellia tuberosa* methanolic extract (RTME) directly interact with Bcl-2, potentially inhibiting its anti-apoptotic function and promoting apoptosis in breast cancer cells. Molecular docking analysis using Bcl-2 (PDB ID: 1G5M) revealed that 5-Hydroxymethylfurfural (−4.3 kcal/mol), n-Hexadecanoic acid (−4.4 kcal/mol), and Linoelaidic acid (−5.2 kcal/mol) exhibited strong binding affinities, stabilizing Bcl-2 in an inactive conformation. Further ligand–receptor interaction analysis showed that these compounds formed hydrogen bonds and hydrophobic interactions with key Bcl-2 residues (Table 1).

In vitro assay of the methanolic extract of *Ruellia tuberosa* extract also explains how the extract suppresses the Bcl-2 pathway in triple-negative breast cancer (TNBC) cells, leading to apoptosis (Table 2). The in vitro study demonstrated that the methanolic extract of *Ruellia tuberosa* (RTME) suppresses the Bcl-2 pathway in TNBC cells, leading to apoptosis (see Figure 2). Western blot and qRT-PCR analysis confirmed significant Bcl-2 downregulation, while JC-1 staining revealed mitochondrial destabilization and cytochrome c release, triggering apoptosis. Additionally, RTME increased the Bax/Bcl-2 ratio, activated caspase-9 and caspase-3, confirming intrinsic apoptosis. These findings suggest that RTME induces apoptosis in TNBC cells by inhibiting Bcl-2, promoting mitochondrial dysfunction, and activating caspase signaling.

Toosendanin (TSN) from *MeLia toosendan Sieb.et Zucc* activates caspase-3 via the mitochondrial apoptotic pathway by the following mechanisms: First, TSN decreases the expression of anti-apoptotic Bcl-xL and increases pro-apoptotic Bax, thereby triggering changes in mitochondrial membrane permeability and the release of cytochrome c to the cytosol. Cytochrome c then binds to Apaf-1 to form apoptosomes, which recruit and activate pro-caspase-9. Active caspase-9 further cleaves pro-caspase-3 into active caspase-3, which executes cell death by breaking down substrates such as PARP, causing chromatin condensation and DNA fragmentation. This activation of caspase-3 is measurable as an increase in the number of Annexin V^+ cells and an increase in the level of activated caspase-3 in MDA-MB-231 cells.

Isotoosendanin (ITSN) in *MeLia toosendan Sieb.et Zucc* induced apoptosis through the mitochondrial-cas¬pase pathway, but with less intensity than Toosendanin. Mechanistically, ITSN decreased the expression of Bcl-xL and slightly increased Bax, thus causing mitochondrial membrane permeability and the release of cytochrome c. Cytochrome c combines with Apaf-1 to form apoptosomes that activate pro-caspase-9, and active caspase-9 then cleaves pro-caspase-3 into active caspase-3. Activation of caspase-3 by ITSN was detected as an increase in the number of Annexin V^+ cells and an increase in the level of activated caspase-3, but at a much more moderate level, corresponding to the IC_{50} value of ITSN (~7.42 μM).

The in vivo study (Table 3) also demonstrated that RTME suppresses the Bcl-2 pathway, induces apoptosis, and reduces tumor growth in a Balb/C mouse model without causing significant toxicity. Blood biochemical analysis confirmed that liver, kidney, and lung function markers remained within normal ranges, while histopathological examination of major organs showed no structural damage, indicating that RTME is safe at therapeutic doses. Furthermore, mice treated with RTME exhibited a significant reduction in tumor volume and weight.

p53 Pathway

The p53 pathway is a significant pathway for suppressing tumors by controlling DNA repair, cell cycle progression, cell death, and senescence which hinders the spread of aberrant cells. p53 is a transcription factor that is present in both the nucleus and cytoplasm.[72] It has the ability to bind DNA in a specific manner and control the activity of certain genes. Cellular levels of the p53 protein are kept relatively low due to stringent regulation by its negative regulators MDM2 and MDMX.[73] These regulators encourage the breakdown of p53 through a process called ubiquitination. In response to DNA damage, p53 induces the expression of p21, a cyclin-dependent kinase inhibitor blocking CDK2 and CDK1, leading to a cell cycle arrest at the G1/S and G2/M checkpoint, allowing time for DNA repair or enabling cellular senescence and preventing the proliferation of damaged cells.[74] When p53 induces senescence, this elevates the p21 and PAI1 genes, leading cells to permanently stop proliferating in response to irreparable DNA damage or other stressors.[75]

Senescence acts as a tumor suppressor process by inhibiting the growth of damaged cells.[76] P53 exhibits control over cellular metabolism by suppressing glycolysis and enhancing oxidative phosphorylation via the transcriptional activation of genes.[77] P53 can stimulate the expression of autophagy-related genes (Atgs) and suppress mTOR, a vital controller of autophagy. Autophagy promotes cell survival during periods of limited nutrients, while excessive autophagy results in cell death.[78]

The in vitro study (Table 2) shows moringin, an isothiocyanate from *Moringa oleifera*, activates the p53 pathway (See Figure 2) in MCF-7 and MDA-MB-231 breast cancer cells with IC50 value of 20.75 μM and: 23.04 μM after 72 hours, leading to apoptosis and cell cycle arrest. Western blot analysis confirmed that moringin significantly increased p53 expression, which in turn activated its downstream pro-apoptotic targets, including Bax, NOXA, and PUMA, promoting programmed cell death. Additionally, p53 upregulation was associated with increased expression of p21, a key cyclin-dependent kinase (CDK) inhibitor, resulting in G1-phase cell cycle arrest and preventing uncontrolled cancer cell proliferation.

SKP/p21

The SKP/p21 signaling pathway plays a crucial role in controlling the progression of the cell cycle and programmed cell death (apoptosis), which are vital events in the development and progression of breast cancer.[79] The SCF complex, composed of the SKP1-CUL1-F-box protein, acts as an E3 ubiquitin ligase, promoting the ubiquitination and subsequent proteasomal destruction of certain target proteins.[80] This degradation is crucial for the regulation of the cell cycle. P21, also called Cip1/Waf1, is a protein that inhibits the activity of cyclin-dependent kinase 2 (CDK2) and cyclin-dependent kinase 4 (CDK4) complexes.[81,82] Additionally, it acts as a tumor suppressor, preventing the formation and growth of tumors. The interaction between SKP2 and p21 holds great significance in the setting of breast cancer, especially in aggressive subtypes like triple-negative breast cancer (TNBC).[83] SKP2, an F-box protein found in the SCF complex, is commonly upregulated in breast cancer, resulting in increased ubiquitination and breakdown of p21.[84] The decrease in p21 levels reduces its ability to inhibit cyclin-CDK complexes, leading to uncontrolled cell proliferation and poor programmed cell death. This ultimately promotes tumor growth and advancement.[85]

Recent studies have emphasized the considerable capacity of plant extracts to hinder the growth of breast cancer cells.[86] Eleutherine bulbosa (Mill). Urb (Table 2). The ethyl acetate extract inhibit transcription of TCF/β-catenin (Table 2).[87] The ethyl acetate extract (EAESO) shown high potency by effectively interrupting the cell cycle at the G0-G1 phase. The ethyl acetate increases the expression of p21 and p27 proteins and becomes a complex bond with Cyclin D and Cyclin Dependent Kinase 4/6 (CDK), which would inhibit the phosphorylation PRB (retinoblastoma protein). This suggests that EAESO has the potential to be used as a therapeutic agent for breast cancer by arresting the cell cycle and inducing apoptosis.

A study conducted on the ethyl acetate extract of *Antenoron filiforme*. showed promising results in blocking the SKP2/p21 pathway. The in silico analysis (Table 1) demonstrated that quercetin and its analogs in *Antenoron filiforme* could directly bind to Skp2, potentially inhibiting its function and stabilizing p21. Molecular docking simulations revealed strong interactions between quercetin and Skp2 (PDB ID: 2ASS), with key hydrogen bonds forming at Ser343, Ser391, Arg344, and Ser238, ensuring high binding affinity (Glide scores < −6 kcal/mol). Molecular dynamics (MD) simulations were conducted over 20 ns, confirming that the quercetin-Skp2 complex remained structurally stable, with an RMSD of ~4.76 Å and strong interactions within the 240–320 residue region of Skp2. The root-mean-square fluctuation (RMSF) analysis showed that quercetin maintained stable binding throughout the simulation. These results indicate that quercetin and its analogs may function as Skp2 inhibitors, preventing p21 degradation and thereby reinforcing G1/S cell cycle arrest in TNBC cell.

The in vitro assay (Table 2) shows that ethyl acetate extract induces G1/S cell cycle arrest in TNBC cells via the Skp2-p21 pathway (see Figure 2). AF-EAE upregulate p21 (CDKN1A) expression, leading to CDK6 and CCND1 downregulation, thereby inhibiting Rb phosphorylation and E2F-mediated S-phase entry. Concurrently, AF-EAE suppressed Skp2, preventing p21 ubiquitination and stabilizing its function as a CDK inhibitor.

The in vivo study (Table 3) demonstrated that *Antenoron filiforme* ethyl acetate extract effectively suppresses TNBC tumor growth in a xenograft mouse model. Tumor volume measurements revealed that the extract significantly inhibited

tumor growth compared to the control group ($p < 0.05$). Histological analysis (H&E staining) confirmed extensive tumor cell membrane and nuclear disruption, suggesting apoptosis or reduced proliferation. Notably, body weight and major organ histology (heart, liver, spleen, lung, kidney) showed no significant toxicity, indicating AF-EAE's safety profile.

Discussion

Several bioactive compounds from medicinal plants have shown significant anticancer properties by targeting key molecular pathways involved in cancer progression. Among pure phytoconstituents, 17-Hydroxy-jolkinolide B showed the greatest potency with an IC_{50} of 1.1 μg/mL against MDA-MB-231 cells, while the Toosendanin achieved an IC_{50} of 0.095 μM in the same line, and Kaempferol exhibited an IC_{50} of 43 μM in MDA-MB-231 cells by triggering G_2/M arrest and caspase-mediated apoptosis. In parallel, the ethyl acetate fraction of Syzygium samarangense leaves demonstrated an IC_{50} of 7.2 μg/mL in MCF-7 cells while sparing normal breast epithelial cells. The ethyl acetate extract of Eleutherine bulbosa bulbs attained an IC_{50} of 147.1 μg/mL and induced G_0/G_1 arrest and apoptosis, and the dichloromethane fraction of *Strobilanthes crispus* leaves effectively inhibited PI3K/AKT/mTOR signaling to reduce cell migration and metastatic potential.

Limitations

Breast cancer remains one of the most challenging diseases to treat, with conventional therapies often coming with severe side effects and limited long-term success. This has fueled interest in plant-derived compounds as potential alternative or complementary treatments. Despite these encouraging findings, translating these compounds into viable treatments presents challenges. Many plant-based molecules struggle with bioavailability, metabolic stability, and consistency in effectiveness. Most of the studies compiled in this review used crude extracts or fractions as test materials, while data on pure compounds are still minimal. Only a few studies evaluated isolated molecules, so we cannot yet isolate the specific contribution of each component to antiproliferative activity. This limitation hinders understanding the molecular mechanism of action and the pharmacokinetic hurdles associated with the selected compounds. The absence of acute/sub-chronic toxicity (LD_{50}) and safe-dose (NOAEL) data hinders our ability to judge therapeutic windows and anticipate off-target effects.

Despite potent in vitro anticancer activity, translation of these agents is hampered by significant pharmacokinetic and safety barriers. 17-Hydroxy-jolkinolide B, though highly cytotoxic (IC_{50} = 1.1 μg/mL), is essentially insoluble in water and exhibits very low oral bioavailability with rapid hepatic clearance, necessitating specialized nanoparticle formulations to achieve meaningful plasma levels and raising concerns about a narrow therapeutic window. Toosendanin demonstrates sub-micromolar efficacy (IC_{50}=0.095 μM) but is limited by well-documented neurotoxicity—blockade of synaptic transmission—and hepatotoxicity in rodent studies, compounded by poor aqueous solubility that complicates reliable dosing. Kaempferol, despite inducing G_2/M arrest and apoptosis at 43 μM, suffers from extensive first-pass glucuronidation and sulfation, yielding oral bioavailability below 2% and rapid renal elimination, which precludes achieving therapeutic concentrations without supraphysiological dosing. The flavonoid-rich ethyl acetate fraction of S*yzygium samarangense* (IC_{50} = 7.2 μg/mL) remains an unstandardized botanical extract: its complex, variable composition and unknown ADME/Tox profile mean batch-to-batch inconsistencies and undefined safety margins hamper in vivo assay. Similarly, the *Eleutherine bulbosa* ethyl acetate fraction (IC_{50}= 147.1 μg/mL) has only modest potency and lacks any pharmacokinetic or systemic toxicity data, making its therapeutic index and metabolic stability wholly speculative. Finally, the *Strobilanthes crispus* dichloromethane fraction, though effective in suppressing PI3K/AKT/mTOR signaling in vitro, is a hydrophobic mixture with no solubility enhancement, absorption studies, or safety evaluations, leaving its in vivo feasibility untested and its translational readiness very low.

Future Research

In addition to biological effectiveness, drug formulation and delivery advancements will play a key role in the future of plant-derived cancer therapies.[88] Nanotechnology and other innovative drug delivery systems may help improve the absorption and targeted action of these natural compounds, overcoming their current limitations.

Many of these plant compounds suffer from poor solubility or stability, which can be mitigated by nanoformulation. For example, folate-modified PLGA–PEG nanoparticles carrying apigenin achieved much more potent cytotoxicity against breast cancer cells: the IC_{50} of folate–PLGA–PEG–apigenin was ~13.3 μM versus ~50.2 μM for free apigenin (ie, ~3.8× enhanced potency). Similarly, polymer–lipid hybrid nanoparticles (PLGA + lecithin) loaded with apigenin (100–175 nm size) showed rapid initial release followed by sustained delivery, improved antioxidant activity. They significantly increased the killing of MCF-7 and MDA-MB-231 cells compared.[89] Phytosterols have also been nano-engineered: stigmasterol was co-encapsulated with doxorubicin in hyaluronic acid-coated PEGylated liposomes targeting the CD44 receptor. The HA-PEG–Liposome–doxorubicin–stigmasterol (HA-DOX-STS-lipo) particles (~174 nm) released DOX in acidic tumor-mimicking conditions and selectively accumulated in $CD44^+$ MDA-MB-231 tumors, greatly enhancing antitumor efficacy in vitro and in vivo.[90]

Other targeted carriers include isorhamnetin: it was loaded into carboxymethyl chitosan nanoparticles with a polydopamine coating, forming Iso/CMC-PDA nanospheres. This formulation targeted tumor cells and inhibited cervical cancer growth in vitro[91] (suggesting it might be adapted to breast or other tumors). Likewise, the diterpenoid 17-hydroxy-jolkinolide B (17-HJB) was formulated in hyaluronic-acid–coated liposomes (HA-Lip-HJB) of ~130 nm. The HA-targeted liposomes greatly increased uptake via CD44, inhibited breast cancer cell migration (via blocking EMT), and suppressed lung metastasis in 4T1 tumor-bearing mice.[92] Polymeric nanoparticles have also improved delivery of flavonoids like kaempferol: for instance, PLGA NPs carrying kaempferol selectively killed ovarian (and by extension likely breast) cancer cells while sparing normal cells.[93] In that study, PLGA-kaempferol NPs had potent cytotoxicity on tumor cells without harming normal cells, outperforming free kaempferol.[93]

Several studies have explored combining these phytocompounds with standard drugs to achieve potentiatism or to overcome resistance. Toosendanin, a triterpenoid from *Melia toosendan*, blocked late-stage autophagy in triple-negative breast cancer (TNBC) cells. When Toosendanin was combined with the topoisomerase-I inhibitor irinotecan (or its metabolite SN-38) in MDA-MB-231 xenografts, it prevented chemotherapy-induced protective autophagy and significantly increased apoptosis and tumor shrinkage compared to irinotecan alone.[94] Likewise, apigenin has been shown to modulate anthracycline efficacy: co-treatment with apigenin altered doxorubicin-induced lipid metabolism and is predicted to interact at drug-efflux transporters (ABC proteins) via AKT/MYC pathways,[95] hinting that apigenin might sensitize specific breast cancer cells to doxorubicin. Stigmasterol and doxorubicin were co-formulated in the same targeted liposome,[90,96] yielding synergistic killing of $CD44^+$ cancer cells. Although not yet tested in breast cancer, other flavonoid–drug combinations (eg, kaempferol with sorafenib) have shown additive effects in model studies.

For complex extracts, standardization is crucial. *Syzygium samarangense* ethyl acetate extract has been thoroughly profiled: researchers used TLC, FTIR, LC-MS/MS, and total phenol/flavonoid assays to confirm a high flavonoid content.[97] The extract is shown to have potent antioxidant capacity (comparable to ascorbic acid) and cytotoxicity ($IC_{50} \approx 7.2$ μg/mL) against MCF-7 cells, inducing apoptosis (DNA fragmentation, caspase-3 activation) without harming normal breast epithelial cells. Such phytochemical fingerprinting ensures consistency and helps link active constituents to bioactivity. Similarly, *Eleutherine bulbosa* bulb extracts have been investigated: network-pharmacology and in vitro assays showed *E. bulbosa* extract triggers ~93.6% apoptosis in T47D breast cancer cells and causes cell-cycle arrest[98] These efforts identify key pathway effects (p53, MAPK, PI3K/Akt) and support dose standardization. Although formal phytochemical standardization of Russelioside A (a purified pregnane glycoside) has not been reported, its anti-TNBC activity has been documented in cell and animal models. Fractionation studies identified a potent anticancer sub-fraction from the DCM extract. One sub-fraction, SC/D-F9, killed both ER^+ (MCF-7) and TNBC (MDA-MB-231) cells at low concentrations while sparing normal MCF-10A breast cells SC/D-F9 was even more cytotoxic than tamoxifen or doxorubicin at comparable doses, and it induced caspase-3/7–mediated apoptosis.[99] Such fractionation and bioactivity-guided isolation effectively "standardize" the extract by defining an active component, which can then be further characterized (eg by LC-MS) and used in targeted delivery.

Various solubilization strategies have been used to improve oral uptake and circulation time. A recent study formulated apigenin as a self-nanoemulsifying drug delivery system (SNEDDS) using bioactive excipients (Gelucire 44/14, Tween 80, PEG 400). This SNEDDS dramatically increased apigenin's C_max and AUC: relative oral bioavailability in rats was ~3.3–3.8× higher than crude apigenin.[89] Likewise, formulating apigenin into polymeric nanoparticles both solubilized the drug and provided controlled release, enhancing in vitro activity. Similar approaches (lipid NPs,

cyclodextrins, micronization) could boost the bioavailability of other hydrophobic compounds here. For instance, kaempferol–like flavonols often undergo rapid Phase II metabolism; encapsulation in PEGylated carriers or use of prodrug linkers might extend their half-life (strategies successful for taxanes or resveratrol[100]). Although not yet reported for Russelioside A or Toosendanin, glycosylated triterpenoids might benefit from pH-sensitive polymeric NPs or inclusion complexes to improve solubility and protect against premature degradation. By refining extraction methods, optimizing bioavailability, and conducting rigorous clinical trials, we can unlock the full potential of these natural compounds. Ultimately, the goal is not only to develop more effective treatments but also to provide safer, less toxic alternatives that improve both survival rates and quality of life for breast cancer patients.

Conclusions

This review underscores the therapeutic potential of plant-derived compounds in targeting key oncogenic pathways in breast cancer, including EGFR, PI3K/AKT/mTOR, NF-κB, and RAF/MEK/ERK. Several compounds such as saccharopine, apigenin, isorhamnetin, russelioside A, and sul demonstrate promising in vitro and in vivo activity through induction of apoptosis, inhibition of metastasis, and cell-cycle arrest. However, translation into clinical application remains limited due to poor bioavailability, metabolic instability, and lack of compound-specific pharmacokinetic data.

Most studies rely on crude extracts or semi-purified fractions, hindering the delineation of specific molecular mechanisms. To address these limitations, future research should focus on isolating active constituents, standardizing extract profiles, and applying advanced delivery systems such as nanoparticle-based formulations. These strategies may significantly improve pharmacological performance and safety, facilitating the development of plant-based therapeutics as effective alternatives or adjuncts in breast cancer management. While these compounds exhibit remarkable anticancer properties, further research is needed to enhance their bioavailability, stability, and clinical application. Developing advanced drug delivery systems, optimizing combination therapies, and conducting rigorous clinical trials will be essential to integrating these natural compounds into mainstream breast cancer treatment. By leveraging the power of plant-derived bioactives, future therapies may offer safer and more effective alternatives for patients worldwide.

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