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REVIEW

Exploring the anti-cancer potential of dietary phytochemicals for the patients with breast cancer: A comprehensive review

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Abstract

Background: The most common and deadly cancer in female is breast cancer (BC) and new incidence and deaths related to this cancer are rising.

Aims: Several issues, that is, high cost, toxicity, allergic reactions, less efficacy, multidrug resistance, and the economic cost of conventional anti-cancer therapies, has prompted scientists to discover innovative approaches and new chemopreventive agents.

Materials: Numerous studies are being conducted on plant-based and dietary phytochemicals to discover new-fangled and more advanced therapeutic approaches for BC management.

Result: We have identified that natural compounds modulated many molecular mechanisms and cellular phenomena, including apoptosis, cell cycle progression, cell proliferation, angiogenesis and metastasis, up-regulation of tumor-suppressive genes, and down-regulation of oncogenes, modulation of hypoxia, mammosphere formation, onco-inflammation, enzymatic regulation, and epigenetic modifications in BC. We found that a number of signaling networks and their components such as PI3K/Akt/mTOR, MMP-2 and 9, Wnt/-catenin, PARP, MAPK, NF-κB, Caspase-3/8/9, Bax, Bcl2, Smad4, Notch1, STAT3, Nrf2, and ROS signaling can be regulated in cancer cells by phytochemicals. They induce up-regulation of tumor inhibitor microRNAs, which have been highlighted as a key player for ani-BC treatments followed by phytochemical supplementation.

Conclusion: Therefore, this collection offers a sound foundation for further investigation into phytochemicals as a potential route for the development of anti-cancer drugs in treating patients with BC.

KEYWORDS

anti-cancer mechanism, breast cancer, cancer treatment, natural products, phytochemicals, resistance

1 | INTRODUCTION

Breast cancer (BC) is the most common and frequent malignancy among females, and it is the second most frequent carcinoma and a significant cause of cancer-associated death worldwide. This cancer is a multifactorial disease and various factors, including demographic, oxidative stress, bacterial infection, reproductive, hormonal, hereditary, and lifestyle contribute to its occurrence.[1] A number of conventional therapeutic options such as surgical resection, radiotherapy, chemo-radiotherapies (e.g., adjuvant chemotherapies and neoadjuvant therapy), hormonal therapies, monoclonal antibodies, immunotherapy, and small molecular inhibitors are available for the patients with BC.[2,3] However, these therapeutic modalities have drawbacks, bearing side effects and toxicities. Thus, new approaches and strategies are needed to manage patients with BC effectively to minimize the limitations, such as increasing resistance to conventional therapeutics, side effects, and toxicities of existing treatment modalities. Interestingly, alternative medicines (with fewer side effects) for patients with BC, especially metastatic cancer, have been developed.

Phytochemicals are an essential natural resource for anti-cancer medicine. They are safe, non-toxic, cost-effective, and readily available sources from villages to cities and underdeveloped to developed countries.[4] Currently, medicinal plants or their derivatives account for about 70% of the anti-cancer compounds, thus, playing the lead role in developing anti-cancer drugs.[5,6] Initially, natural plant extracts have showed higher anti-tumor responses and better pharmacological or bioactivity with less toxicity in patients with advanced BC (Table 1).[37–40] For example, anti-cancer compounds from *Curcuma longa*, *Piper longum*, *Nigella sativa*, *Murrayakoenigii*, *Amora rohituka*, *Withania somnifera*, and *Dimocarpus longan* possess anti-cancer activity against various cancers, especially anti-BC properties.[8,25,36,41–44] Latter specific phytochemicals have been identified as a new source of anti-cancer agents from plant extract to decrease the negative effects of cancer chemotherapies in recent research.[45–48] These natural agents can target several BC-related pathways and provide protective activity against breast malignancies, which play a significant role in preventing and managing patients with BC.[46,49] Several individual studies exhibited phytochemicals had anti-cancer property through several mechanisms.[50–52] However, a comprehensive summary on precise anti-cancer mechanisms including apoptosis induction, cell cycle, and cell proliferation regulation, inhibition of angiogenesis and metastasis, regulating hypoxia-inducible factor, suppressed mammosphere formation, onco-inflammation inhibition, controlling enzyme activity, signal transduction regulation, epigenetic and immune regulation have not been reported collectively. Therefore, in this review, we have discussed various phytochemicals with their major sources, structure, and their possible anti-cancer pathways in the BC, thereby providing an aggregative source of information on potential natural anti-cancer resources.

2 | SOURCE OF ENLISTED DIETARY PHYTOCHEMICAL

Phytochemicals are plant-based compounds founds in vegetables, fruits, beans, grains, and other parts of plants. Bioactive phytochemicals protect cells from cancer-causing injury.[53] For instance, daidzein, genistein, epigallocatechin gallate (EGCG), epigallocatechin, and formononetin-A are phytoestrogen in nature and found in the form of flavonoids in soy and soy products.[54–57] Lutein, 3,3-Diindolylmethane, benzyl isothiocyanate, kaempferol, and quercetin are available in green leafy vegetables including spinach, broccoli, peas, and herbs such as dill, chives, onion, leeks, and egg yolks.[9,58–60] In addition, vegetables such as tomatoes, potatoes, and fruits such as citruses, watermelon, apples, pink guava, pink grapefruit, papaya, passion flower fruit, and dried apricots, are the significant source of 2-hydroxychalcone,[61] lycopene,[62] naringenin.[63] Also, natural compounds such as nimbolide, sanguinarine, withaferin A, α-Mangostin, arctigenin, calycosin, curcumin, and flavopiridol are present abundantly in medicinal plants such as *Azadirachta indica* (leaves and seed), *Sanguinaria canadensis* (rhizome), *W. somnifera*, *Tripterygium wilfordix* (roots), *Garcinia mangostana* L.(pericarps), *Arctium lappa* L. (seeds), *Radix astragali* (dry root), *C. longa* (rhizome), and *Dysoxylum binectariferum* (stem and bark), respectively.[36,64–68] Furthermore, punicalagin, sesamin, shikonin, silibinin, taiwanin A, and wogonin are found in *Punica granatum*, *Cuscuta palaestina* (seed), *Sesamum indicum*, *Lithospermum erythrorhizon* (roots), *Silybum marianum*, *Taiwania cryptomerioides* (bark), *N. sativa* (seeds), and *Anodendron affine* (stems) plants.[69–74] EGCG, and epigallocatechin are known catechin phytochemicals, widely distributed in tea with several health benefits.[75,76] The source and structure of these phytochemicals are presented in Table 2.

3 | PHYTOCHEMICALS TARGETING BC CELLS

Therapeutic strategies against BC include surgery chemoradiotherapies, adjuvant/neoadjuvant therapies, hormonal therapies, monoclonal antibodies, immunotherapy, nanomedicines, and small molecular inhibitors.[99]

TABLE 1 Summary of plants extract and their anti-cancer activity in human breast cancer cell line.

		Working protocol					
Source/plant	**Parts used**	**Methods**	**Extract used**	**Cell line**	**Anti-cancer mechanism**	**Efficacy/dose**	**Ref.**
Ailanthus altissima	Bark	Flow cytometry, RT-PCR, western blot	Petroleum, dichloromethane	MCF-7	↓ Cell proliferation ↑ Cell cycle arrest, apoptosis	0.5–8.0 μg/mL	[7]
Amoora rohituka	Leaf	FTIR analysis, phytochemical screening methods	Petroleum ether, ethyl acetate, methanol	MCF-7	↓ Cell migration ↑ Apoptosis ↑ Cytotoxic effect	9.81 mg/mL	[8]
Ardisia crispa	Leaves	MTT assay, DPPH, ABTS assay	Ethyl acetate, aqueous	MCF-7, MDA-MB-231	↓ Glucose uptake	57–100 μg/mL	[9]
Baeckea frutescens	Leaves extracts	Cytotoxity, glucose consumption assay	Ethanol, aqueous	MCF-7 MDA-MB-231, MCF10A	↓ Cell viability, cell motility ↑ Cell cycle arrest, apoptosis	53 μg/mL	[10]
Bryonia dioica	Roots	Extracted, flow cytometry, staining, western blot	Aqueous	BL-41	↑ Cell cycle arrest, apoptosis	15–63 g/mL	[11]
Bulbine frutescens	Bulb	Membrane potential, ROS, Notch promoter, western blot	Methanol, hexane	MDA-MB-231, T47D	↑ Cell cycle arrest, DNA repair, scavenge free radical	4.8–28.4 μg/mL	[12]
Butea monosperma	Bark fractions	MTT, clonogenic, neutral comet assay, flow cytometry	Methanol, hexane, chloroform, ethyl acetate	MCF-7	↑ Inhibit proliferation, cell cycle arresting effect	44–213 mg/mL	[13]
Cimicifuga dahurica	Rizhomes	Extraction NMR, BrdU	70% ethanol	MCF-7	↓ Oncogene expression cell proliferation ↑ Apoptosis induction	30 μM	[14]
Decatropis bicolor	Leaves	MTT assay, cell morphology analysis, western blot	Water, ethanol, acetone, hexane	MDA-MB-231	↑ Apoptosis induction	53.81 μg/mL	[15]
Fagonia indica	flower	Cytotoxicity, PARP, DNA fragmentation assay	EtOH	MCF-7, MDA-MB-468	↑ Apoptosis	50–100 μM	[16]
Garcinia oblongifoli	Fruits, leaves	Cell viability, antioxidant	Methanol	MCF-7	↑ Cytotoxic effect	1000 μg/mL	[17]
Glycyrrhiza glabra	Root	qRT-PCR, western blots, DNA methylation analysis, immunostaining	Glabridin	Multiple cell line	↑ Anti-tumor activity	0 or 20 mg/kg	[18]
Hedyotis diffusa	Leaves and shoots	Mitochondrial membrane potential, western blot	Methylanthraquinone	MCF-7	↓ Cell growth ↑ Apoptosis	18.62 μM	[19]
Lawsonia nermis	Leaves	Chromatography, dynamic light scattering, UV–Vis spectroscopy	Alcoholic solution	MCF-7	↑ Apoptosis, autophagy	1.5 μM	[20]
Lotus corniculatus	Leaves	MTT, PCR, wound healing assay	Ethyl acetate, methanol, water	MDA-MB-231, MCF-7	↓ Cell migration, cancer-related enzymatic activity	21.13 mg RE/g	[21]
Lycium barbarum	Fruit	Signaling mechanism test	NA	MCF-7 cells	↓ Cancer-related signaling, hypoxia condition	0.50 mg/mL	[22]
Malus domestica	Fruit	Western blot, cell cycle analysis	Acetone	MCF-7, MDA-MB-231	↓ Enzyme activity, cell growth	10–80 mg/mL	[23]
Morus alba	Leaves	Anti-proliferative radical scavenging assay	Methanol	MCF-7	↑ Morphology change ↓ Cell proliferation	350 μg/mL	[24]
Nigella sativa	Seed	UV–visible spectroscopy, FT-IR, SEM, EDX	Aqueous	MCF-7	↑ Apoptosis ↓ Migration, adhesion, metastasis	1–200 μg/mL	[25]

TABLE 1 (Continued)

Source/plant	Parts used	Working protocol			Anti-cancer mechanism	Efficacy/dose	Ref.
		Methods	Extract used	Cell line			
Platycodon grandiflorus	Root	Cytotoxicity, flow cytometry, western	Platycodin D	MCF-7	↑ Apoptosis	8 μg/mL	26
Premna odorata	Leaves	NMR, extraction, molecular modeling, proliferation, migration assay	70% ethanol	MCF-7, BT- 474	↑ Cytotoxicity activity	13.3 μM	27
Rabdosiae rubescens	Whole part	Western blot analysis, immunohistochemistry analysis	Ethanol, water extract	MDA-MB-231 In vivo	↓ Growth migration, apoptosis	12 μg/mL	28
Salpichroascandens	Aerial parts	Extraction, cytotoxicity assay	Dichloromethane	MCF-7, T47D	↓ Growth, cytotoxic activity	29–646 μM	29
Salvia sclarea	Plant	In vivo mice	n-hexane/ethylacetate/ methanol (1:1:1)	MCF-7, T47D, ZR-75-1	↑ Anti-proliferative, cytotoxicity activity	7.85 μg/day	30
Salvia species	N/A	Sulforhodamine B assay, chromatography	Ethanol	T47D, ZR-75-1, BT 474	↓ Aromatase enzyme	30 μg/mL	31
Schisandra chinensis	Seeds, leaves, and stems	Western blotting, Immunohistochemistry	Schisandrin A	MDA-MB- 231, BT-549	↑ Apoptosis induction, cell cycle arrest, cell cytotoxicity	134.21 ± 6.85 μM	32
Scrophularia variegat	Aerial parts	MTT assay, ELISA, annexin V-FITC/PI staining	Ethanol	MCF-7	↑ Apoptosis induction, cell cycle arrest	31–299 mg/L	33
Scutellaria baicalensis	Root	HPLC, staining	Ethanol, ethyl acetate, 1-butanol, water	MCF-7	↑ Cytotoxicity ↓ Hypoxic conditions	100 mg/mL	34
Senecio graveolens	Flower, leaves, stems	Extraction, cytotoxic assays, western blot	Ethanol	ZR-75-1, MDA-MB- 231	↑ Cell death, cell cycle arrest ↓ Proliferation	200 μg/mL	35
Withania somnifera	N/A	Flow cytometry, microarray data analysis, PCR, invasion assay, western blotting	70% ethanol	MDA-MB- 231, MCF-7	↑ Apoptosis induction, cell cycle arrest	853.6 nM	36

TABLE 2 Source and structure of common phytochemicals with anti-cancer properties.

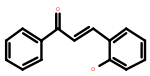
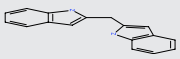
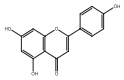
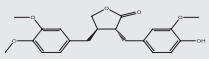
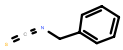
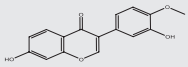
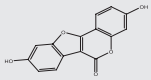
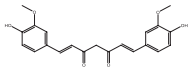
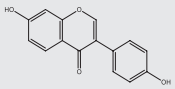
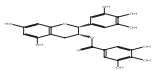
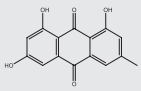
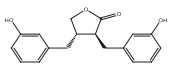
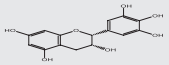
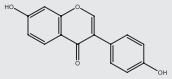
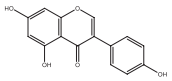
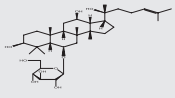
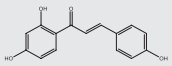
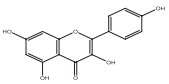
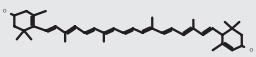
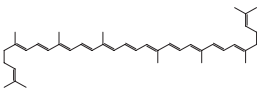
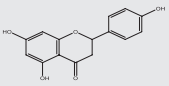
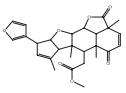
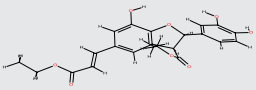
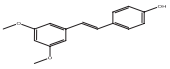
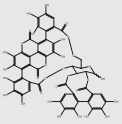
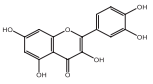
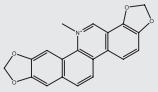
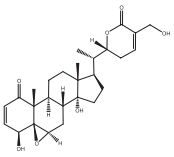
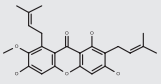
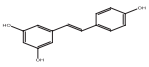
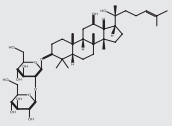
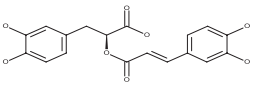
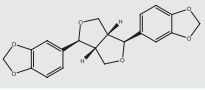
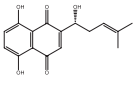
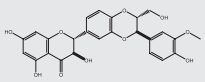
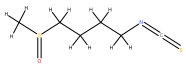
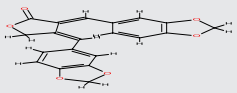
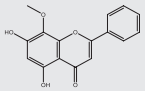
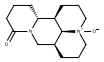
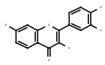
Compounds	Structure	Source	Ref.
2-Hydroxychalcone		Tomatoes, potatoes, licorice, citruses, apples (*Humulus lupulus* L.)	61
3,3-Diindolylmethane		Cruciferous vegetables, that is, brussels sprouts, cauliflower, cabbage, and broccoli	59
Apigenin		Parsley, chamomile, celery, vine-spinach, and oregano	77
Arctigenin		Present in the seeds of *Arctium lappa* L.	67
Benzyl isothiocyanate		Cruciferous vegetables like 3,3-diindolylmethane source	9
Calycosin		Dry root extract of *Radix astragali*	68
Celastrol		The root extract of *Tripterygium wilfordi* plant	78
Coumestrol		Clover, Kala Chana, Alfalfa sprouts	79
Curcumin		Rhizome of turmeric (*Curcuma longa*)	80
Daidzein		Soybeans and soy products, that is, beans, peas, nuts, coffee, tea, and specific herb like red clover	54
EGCG		Green tea	81
Emodin		Herbs, that is, *Polygonum cuspidatum*, *Aloe vera*, *Rheum palmatum*, and *Cassia obtusifolia*	82
Enterolactone		Flaxseed, sesame seed	
Epigallocatechin		Green tea	83
Flavopiridol		The stem and bark of *Dysoxylum binectariferum* plant	84
Formononetin		Red clovers, soya bean, milk vetch (*Astragalus mongholicus*)	55
Genistein		Soybeans and soy products	56
Ginsenoside Rh1		Red ginseng, root	85
Ginsenosides		*Panax* species (roots, leaves, stems, flower, fruits)	86
Isoliquiritigenin		Licorice, extract of *Sinofranchetia chinensis*	87

TABLE 2 (Continued)

Compounds	Structure	Source	Ref.
Kempferol		Green leafy vegetables such as broccoli, spinach, and kale, and herbs such as dill, chives, and tarragon, onion, leeks	60
Lutein		Green leafy vegetables such as broccoli, spinach peas, lettuce, and egg yolks	58
Lycopene		Tomato, watermelon, pink guava, papaya, pink grapefruit, and dried apricots passionflower fruit	62
Naringenin		Fruits like citrus species and tomatoes	63
Nimbolide		Leaves and flowers of neem (*Azadirachta indica*)	64
Pharbilignan C		Pharbitidis semen, the seed of morning glory (*Pharbitis nil*)	88
Pterostilbene		Blueberries, grapes, and tree wood	89
Punicalagin		Pomegranate (*Punica granatum*)	69
Quercetin		Nuts, apples, onions, olive oil green tea, broccoli, red grapes, dark cherries	90
Sanguinarine		Rhizome of bloodroot (*Sanguinaria canadensis*)	65
Withaferin A		*Withania somnifera*	36
α-Mangostin		Pericarps of mangosteen	66
Resveratrol		Grapes, peanuts, and soy	57
Rg3		Red ginseng root (*Panax ginseng* C.A. Meyer)	91
Rosmarinic acid		Boraginaceae species and Nepetoideae of the Lamiaceae subfamily	92
Sesamin		Sesame seeds, *Cuscuta palaestina* plant extract	48
Shikonin		Roots of *Lithospermum erythrorhizon*	93

(Continues)

TABLE 2 (Continued)

Compounds	Structure	Source	Ref.
Silibinin		*Silybum marianum* plant	72
Sulforaphane		Broccoli, cauliflower, radish, cabbage and arugula	94
Taiwanin A		Bark of *Taiwania cryptomerioides*	73
Thymoquinone		*Nigella sativa* (seeds)	95
Wogonin		*Scutellaria baicalensis* (dried root), *Scutellaria rivularis, Andrographis paniculata* (wall, leaves)	74
Oxymatrine		*Sophora flavescens* (quinazine alkaloid extracted)	96
Jasmonates		*Camellia sasanqua L.*, *Camellia sinensis L.* (anther and pollen)	97
Fisetin		*Fragaria ananassa*, *Malus domestica* (fruit)	98

However, limitations such as resistance, compromised efficacy, and side effects of conventional therapies limit their clinical applications. Thus, plant-derived anti-cancer agents with less or no toxic effects can be an alternative chemotherapeutic option. Anti-cancer activity of phytochemicals is dependent on their multi-targeted mechanism of action. Since carcinogenesis is a multistep process involving multiple signaling mechanisms, numerous phytochemicals targeting the altered signaling in cancer are considered promising anti-cancer therapeutics.[100] Phytochemicals targeting signaling pathways in cancer are summarized (Table 3). The following sections outline the role of potentially bioactive compounds against BC cells with their possible molecular mechanism.

3.1 | Inhibition of cell proliferation

Cellular proliferation is essential for all multicellular organisms to develop bodies and organs during embryogenesis. However, in the case of cancer, abnormal cell proliferation is due to changing the expression or activity of protein associated with cell proliferation or cell cycle regulation. Phytochemicals and their derivatives can inhibit the growth and expansion of BC cells by targeting cell cycle regulatory proteins.[172] For example, the naturally active compound formononetin (25 μM) suppresses tumor growth and angiogenesis in MCF-7 and MDA-MB-231 tumor models by targeting the FGFR2-mediated Akt signaling pathway.[101] Treatment of MCF-7 cells by silibinin (50–200 μmol) prevented cell proliferation through modulating the expression of apoptosis-related proteins such as Bcl-xl, bak, p53, p21,[107] whereas sesamin (100 μM) could inhibit MCF-7 cell proliferation by down-regulating cyclin D1 expression.[102] Curcumin mediated its anti-proliferative activity against BC (MDA-MB-231 and BT-483) cells by regulating the expression of NF-κB, cyclin D1, CDK4, and MMP1.[103] Chen et al. noted that Genistein (40–100 μM) exhibited anti-proliferative activity by deactivating the IGF-1R-PI3K/Akt signaling pathway along with increasing Bax/Bcl-2 expressions in MCF-7 cells,[104] whereas lycopene showed similar activities by increasing Bax expression without changing Bcl-xL in MDA-MB-468 cancer cells.[105] Scheckel KA reported that the anti-proliferative activity of rosmarinic acid (20 μmol/L) is associated with a decrease in COX-2 expression and activation of AP-1 and ERK1/2 in MCF-7 cells.[106] Harrison et al. reported that apigenin arrests the cell cycle at the G2/M phase, followed by down-regulation p-Akt in MDA-MB-468 cancer cells.[108] Furthermore, enterolactone (ENL) has been shown to suppress cell proliferation by lowering uPA-mediated plasmin activation and down-regulation of MMP-2 and MMP-9 in MDA-MB-231 cells.[109] Therefore, phytochemicals could act as potent inhibitors of cell proliferation in BC cells by suppressing cell survival signaling, cell cycle regulatory protein, and regulating apoptosis-related proteins.

TABLE 3 Summary of selected particular phytochemical and their anti-cancer activity in human breast cancer cell line.

Phytochemical	Dose	Study type	Target	Macular mechanism	Ref.
Effects of phytochemicals on cell proliferation					
Formononetin-A	25 μM	MCF-7 and MDA-MB-231	↓ Tumor growth ↓ Angiogenesis	↓ FGFR2-mediated Akt signaling	101
Sesamin	100 μM	MCF-7	↓ Proliferation	↓ Cyclin D1 expression	102
Curcumin	1.25–5 mg/mL	MDA-MB-231 and BT-483 cell	↓ Proliferation	↓ NF-κB, and more importantly cyclin D1, CDK4 MMP1 mRNA	103
Genistein	40–100 μM	MCF-7	↓ Proliferation	↓ IGF-1R-PI3K/Akt ↓ Bcl-2/Bax mRNA	45,104
Lycopene	100 μM	MDA-MB-468	↓ Proliferation ↑ Apoptosis	↓ Akt, mTOR ↑ Bax	105
Rosmarinic acid	20 μmol/L	MCF-7	↓ Proliferation	↓ COX-2 expression, AP-1 activation, and antagonized the ERK1/2 activation	106
Silibinin	50–200 μmol	MCF-7	↑ Apoptosis ↓ Proliferation	↓ Bcl-xl ↑ p53, p21, BRCA1, Bak, ATM	107
Apigenin	30 μM	MDA-MB-468	↓ Proliferation	↑ ROS production ↓ p-Akt	108
Enterolactone	75 μM	MDA-MB-231	↓ Proliferation ↓ Migration	↓ PA-induced plasmin activation ↓ MMP-2 and MMP-9	109
Effects of phytochemicals on apoptosis induction					
Ginsenoside Rh1	50 μM	In vitro MCF-7, HCC1428	↑ Apoptosis, autophagy	↓ ROS-mediated PI3K/Akt pathway ↑ ROS production ↑ LC3B and cleaved caspase-3	110
Daidzein	25–100 μM	In vitro MCF-7	↑ Apoptosis	↑ Bax, cyt c, caspases 9 and 3 ↓ Bcl-2	111
Nimbolide	1.97–5 μM	In vitro MDA-MB-231 MCF-7	Apoptosis autophagy	↓ Bcl2, mTORp62 Beclin 1, LC3B protein	112
Lycopene	2–16 μM	In vitro MCF-7	↓ Proliferation ↑ Apoptosis	↑ p53 and Bax	113
Pharbilignan C	5–20 μM	In vitro MDA-MB-231	↑ Apoptosis	↑ Bax, caspases 9 and 3 ↓ Bcl-2	88
EGCG	0–80 μM	In vitro T47D	↑ Apoptosis	↓ Telomerase and P13K/AKT ↑ Bax/Bcl-2, CASP3, CASP9, and PTEN	83
Sanguinarine	0–1.5 μM	In vitro MDA-MB-231	↑ Apoptosis	↑ ROS generation ↑ cytochrome *c* ↑ caspase-3 and caspase-9 ↓ XIAP, cIAP-1	114

(Continues)

TABLE 3 (Continued)

Phytochemical	Dose	Study type	Target	Macular mechanism	Ref.
Lutein	N/A	In vivo BALB/c mice	↑ Apoptosis ↓ angiogenesis	↑ p53 and Bax ↓ Anti-apoptotic gene, Bcl-2	115
Kaempferol	20–80 μM	In vitro MCF-7 cells	↑ Apoptosis	↑ PARP cleavage, Bax ↓ Bcl-2	116
Emodin	40 μM	In vitro Bcap-37 and ZR-75-30	↓ Growth ↑ Apoptosis	↑ Cleaved caspase-3, PARP, p53 ↑ Bax/Bcl-2 ratio	117
Withaferin A	2.5–5 μM	In vitro MDA-MB-231 and MCF-7	↑ Apoptosis	ROS production, Bax and Bak mitochondrial membrane potential	118
Celastrol	1–10 μM	In vitro MDA-MB-231 and MCF-7	Apoptosis	↑ TNF-α, caspase-8, caspase-3, PARP cleavage ↓ Cellular cIAP1 and cIAP2, FLIP, Bcl-2	119
Effects of phytochemicals on cell cycle regulator					
Quercetin	5–20 μM	In vitro MCF-7	↓ Cell cycle progression	↓ Cdc2-cyclin B1 ↑ p21CIP1/WAF1	120
Taiwanin A	5 μg/mL	In vitro MCF-7	↑ DNA damage ↑ Cell cycle arrest at G(2)/M ↑ Apoptosis	↑ p53, p-p53, p21, p27	121
Coumestrol	50 μM	In vitro MCF-7	↑ G1/S phase arrest	↑ CDKI p21 and p53	122
Ginsenosides	100 μM	In vitro MCF-7	↓ Proliferation	↓ CDK4, cyclin E2, cyclin D1 ↑ p21WAF1/CIP1, p53 p15INK4B	123
Kaempferol	10–6 μM	In vitro MCF-7	↓ Proliferation ↑ Apoptosis	↓ Capthepsin D, cyclin E and cyclin D1 ↑ Bax and p21	124
Thymoquinone	100–200 μM	In vitro MCF-7, T47D, MDA-MB231	↓ Proliferation, viability	↓ Cyclin D1, cyclin E, p27, survivin	125
Naringenin	0.05–4 μM	In vitro HTB26 and HTB132	↓ Cell growth ↑ Cell cycle arrest at S- and G2/M-phases ↑ Apoptotic cell death ↓ Cell survival factors	↑ p18, p19, p21 ↓ Cdk4, Cdk6, Cdk7, NF-κB p65	126
Effects of phytochemicals on angiogenesis and metastasis					
Shikonin	5 μM	In vitro MCF-7	↓ Migration and invasion	↓ MMP-9	127
Flavopiridol	70 nM	MDA-MB-231	↓ Metastasis	↓ MMPs 2 and 9, c-erbB-2	128
Silymarin	100 μg/mL	MCF-7 and MDA-MB-468	↓ Migration and invasion	↓ VEGF secretion, MMP-9, AP-1 activation	129
Curcumin	20–100 μM	MCF-7	↓ Metastasis and migration	↓ uPA, NF-κB activation	130

TABLE 3 (Continued)

Phytochemical	Dose	Study type	Target	Macular mechanism	Ref.
Arctigenin	10–200 μM	MCF-7 and MDA-MB-231	↓ Cell migration	↓ MMP-9, urokinase-type plasminogen activator	131
2-hydroxychalcone and xanthohumol	4.6–18.1 μM	MDA-MB-231	↓ Invasive phenotype	↓ MMP-9 ↓ Bcl-2	132
Enterolactone	25–5 μM	MDA-MB-231 cells	↓ Migration and invasion	↓ MMP-2 and MMP-9 expressions ↑ MMPs inhibitor	109
Quercetin	34 mg/kg	MCF-7	↓ Angiogenesis	↓ VEGF, VEGFR2, NFATc3, calcineurin pathway	133
Rg3	5 mg/kg Rg3, 1 time/2 day	MCF-7	↓ Invasion and angiogenesis	↓ MMP-2, MMP-9, VEGFA, VEGFB, VEGFC, p62, Beclin-1, P13K, mTOR, Akt and JNK	134
Sulforaphane	10 μM	MCF10	↓ Migration, invasion	↓ TNF-α, MMP-2, MMP-9, MMP-13	135
Silibinin	50 μg/mL	MDA-MB-468 xenograft model	↓ Metastasis and migration ↓ Tumor volume	↓ EGFR phosphorylation VEGF, MMP-9, and COX-2	136
Isoliquiritigenin	25–50 μM	MDA-MB-231	↓ Migration ↓ Angiogenesis	↓ VEGF, HIF-1α, MMP-2, MMP-9 ↓ p38, Akt, NF-κB, P13K	137
Thymoquinone	100 μL	MCF7 and MDA-MB-231	↓ Migration, invasion	↑ TGF-b, E-cadherin, cytokeratin 19 ↓ MMP-2, MMP-9, Ysnail, Twist, Smad2, NF-κB	138
Punicalagin	N/A	MDA-MB-231	↓ Invasion and angiogenesis	↓ VEGF expression ↑ MIF regulation	139
Effects of phytochemicals on hypoxia-inducible factor					
EGCG	50–100 mg/kg/day for 4 weeks	In vivo C57BL/6J mice	↓ Growth ↓ Migration ↓ Angiogenesis ↓ Proliferation	↓ HIF-1α ↓ NFκB and VEGF expression	140
Isoliquiritigenin	25–50 μM	In vitro MDA-MB-231	↓ Proliferation	↓ HIF-1α	137
3,3-Diindolylmethane	50 μM	In vitro MDA-MB-231	↓ Angiogenesis	↓ Furin, glucose transporter-1 ↓ VEGF, enolase-1 ↓ Phosphofructokinase in hypoxic	141
Lyciumbarbarum polysaccharides	0.50 mg/mL	In vitro MCF-7	↓ Angiogenesis	↓ HIF-1α mRNA levels	22
Wogonin	40 μM	In vitro and vivo MCF-7, MDA-MB-231 Xenograft mouse	↓ Angiogenesis	↑ HIF-1α degradation ↓ HIF-1α protein aggregation and translation ↓ Hsp90 client proteins EGFR, Cdk4, and survivin	142
Effects of phytochemicals on mammosphere formation					
Pterostilbene	25–50 μM	MCF-7	↓ bCSCs ↓ Mammospheres	↓ CD44, hedgehog, Akt, GSK3b signaling, cyclin D1, c-Myc ↑ β-Catenin	143
Sulforaphane	50 mg/kg	SUM-149 and SUM-159 Y	↓ bCSCs ↓ Mammospheres	↓ NF-κB p65 subunit, p52	144

(Continues)

TABLE 3 (Continued)

Phytochemical	Dose	Study type	Target	Macular mechanism	Ref.
Benzyl isothiocyanate	3 μmol/g	MDA-MB-231, MCF-7 and SUM159	↓ bCSCs ↓ Mammospheres	↓ Ron, sfRon, ALDH1 ↑ SOX-2, Nanog, [Oct-4]	145
Resveratrol	100 mg/kg/day	MCF-7, SUM159	↓ bCSC proliferation ↓ Mammospheres	↓ Wnt, β-catenin	146
Curcumin	5 μM	MCF-7, MCF10A, SUM149	↓ bCSCs self-renewal	↓ SCD, CD49f, LDH1A3, TP63	147
EGCG	40 μM	MDA-MB-231 and MDA-MB436	↓ bCSCs growth	↓ ER-a36, MAPK/ERK, EGFR, PI3K/AKT	148
Effects of phytochemicals on inflammation					
Pomegranate juice	20–80 μmol/L	ApoE-KO mice J774.A1 macrophage	↓ Pro-inflammatory state	↓ TNF-α and IL-6 secretion ↑ IL-10	149
Curcumin	10–20 μM	In vitro MCF-7	↓ Inflammation ↓ Cell proliferation ↑ Apoptosis	↑ Blocked the TNF-α-induced NF-κB ↓ Proteasomal activities	150
Resveratrol	10 ppm	In vivo Sprague Dawley rats	↑ Cell cycle arrest at S-G(2)-M phase ↓ Ductal carcinoma	↓ NF-κB, cyclooxygenase-2, and matrix metalloprotease-9 expression	151
Resveratrol, EGCG, curcumin	–	In vivo Sprague Dawley rats	↑ Pro-inflammatory mediators in macrophage ↓ Stearic acid-mediated activation	↓ TNF-α, IL-1β, COX-2, phospho-Akt, phospho-p65, NF-κB	152
Effects of phytochemicals on enzymatic activity					
Curcumin	20 μM	In vitro MCF-7	↓ GSTP1 methylation	↑ Glutathione S-transferase Pi 1	153
Resveratrol	25 μM	In vitro MCF-7	↑ Enzymatic inhibition	↓ Aromatase mRNA expression ↓ CYP19 promoters activity and II transactivation	154
Sulforaphane	25 μM	In vitro MCF10A	Block signaling pathways	↓ COX-2 expression ↓ ERK1/2-IKK and NAK-IKK	155
Rosmarinic acid	10 μmol/L	In vitro MCF10A	↓ Pro-inflammatory gene ↓ Cell proliferation	↑ AP-1 activation ↓ COX-2 expression	106
Silibinin	200 μM	In vitro MCF-7 and MDA-MB231	↓ Cell viability ↓ Tumor inducing genes	↓ COX-2 expression ↓ TPA-arbitrated MMP-9 expression	156
Isoliquiritigenin	10–40 μM	In vitro MDA-MB-231, BT-549	↓ Metastasis ↑ Apoptosis	↓ COX-2, CYP 4A activity ↓ PGE2, PLA2 expression and activity	157
Quercetin and epigallocatechin	0.01–500 μM and 0.01–1000 μM	In vitro MCF-7 and MDA-MB231	↓ Metabolic process	↓ Glucose uptake ↓ Lactate production	158

TABLE 3 (Continued)

Phytochemical	Dose	Study type	Target	Macular mechanism	Ref.
Effects of phytochemicals on cell signaling pathways					
Genistein	100 μM	MCF-7 and MCF-7 HER2	Signal inhibition	↓ IκBα, p65 nucleus phosphorylation ↓ NF-ŚB transcription	159
Formononetin	10–100 μM	MCF-7	↓ Proliferation ↓ Cyclin D1 mRNA expression	↓ IGF1/IGF1R-PI3K/Akt phosphorylation	160
Calycosin	0–100 μM	MCF-7, T-47D, MDA-231 and MDA-435	↓ Growth and induce apoptosis	↓ IGF-1R, MAPK, (PI3K)/Akt pathways	161
Arctigenin	200 μM	MCF-7, MDA-MB-231	↓ Metastasis	↓ Akt, NF-κB phosphorylation ↓ MAPK (ERK 1/2 and JNK 1/2) signaling	.[131]
Resveratrol	100 mg/kg	MCF-7	↑ Autophagy ↑ Cytotoxicity	Wnt/β-catenin	146
Apigenin	50 μM	MCF-7/HER2 and MCF-7 vec	↑ Apoptosis ↓ Proliferation	↓ p-JAK1, p-STAT3, NF-κB, p-IκBa	162
Silibinin	50 μM	MDA-MB-231	↑ Apoptosis	↓ ERK, Akt, Notch-1	163
Pterostilbene	0–100 μM	MDA-MB-468	↑ Apoptosis ↓ Proliferation	↑ ERK1/2 ↓ p21, YAkt, mTOR	164
Naringenin	250 μM	MCF-7	↑ Apoptosis ↓ Proliferation	↓ P13K, MAPK, ERK1/2, AKT	165
α-Mangostin	30 μM	T47D, MDA-MB-468, SKBR3, and AU565	↑ Apoptosis ↓ Proliferation	↓ P13K, ERK1/2, ERa, Akt, ERK1/2, MAPK ↑ p-p38, p-JNK1/2	166
Effects of phytochemicals on epigenetic regulator					
Genistein	80 μM	In vitro MDA-MB-231	↑ Epigenetic stability	↑ $p21^{WAF1}$ (p21) and $p16^{INK4a}$ ↓ BMI1 and c-MYC expression	167
Lycopene	3.125 μM, 2 μm/week)	In vitro MCF-7 and MDA-MB-468, MCF10A	↑ Epigenetics stability	↑ Demethylases the GSTP1, RARbeta2 and the HIN-1 genes	168
Curcumin	40 μM	In vitro MDA-MB-361	↓ Cell growth ↑ Repression tumor suppressor gene	↓ Sp1 expression, DLC1 methylation	169
EGCG	15 μM	In vitro MCF7 and MDA MB 231	↓ Cell viability	↓ RARb2, cyclin D2 methylation, TMS1 methylation, MGMT methylation	170
Sulforaphane	5 μM	In vitro MDA-MB-231	↑ Cell death ↓ Proliferation	↓ HDAC demethylation	171

(Continues)

3.2 | Apoptosis inductions

Apoptosis, a programmed cell death mechanism, plays a crucial role in cancer pathogenesis and maintenance by regulating cell death and survival based on specific signals.[173] Apoptosis can be executed via two mechanisms, that is, the extrinsic and intrinsic mitochondrial pathways.[174] Both of these pathways are regulated through several regulatory proteins.[175] The extrinsic pathway, for instance, is associated with the Fas ligand, Fas-associated protein with death domain initiator pro-caspase-8, and many caspases contributing to the cascade amplification.[176] In contrast, the intrinsic pathway involves apoptosis-related proteins such as Bax, Bak, Bcl2, Cyto-c, adaptor protein Apaf-1, and active caspases.[177] Thus, regulating these proteins by phytochemicals could be an alternative for better management of patients with BC. Ginsenoside Rh1 (50 μM, 24 h) exerted a potential anti-cancer effect against BC (MCF-7 and HCC1428) cells through induction of apoptosis and autophagy.[110] Nimbolide (1.97–5 μM) and pharbilignan C (5–20 μM) are associated with the down-regulation of Bcl-2/Bax along with up-regulation of caspases (caspases 9 and 3), thereby leading to induced apoptosis of MDA-MB 231 and MCF-7 cells through mitochondrial-dependent intrinsic pathways.[88,112] Furthermore, nimbolide induces cancer cell autophagy by inhibiting mammalian target of rapamycin (mTOR) and p62 expression and increasing two essential proteins, Beclin 1, and LC3B expression.[112] Jin et al. reported that daidzein (25–100 μM) treatment of MCF-7 BC cells caused up-regulation of Bax protein and down-regulation of Bcl-2 protein expression, leading to cytochrome *c* release, which in turn induced apoptosis via activating caspases-9 and 7.[111] Choi et al. reported that treatment of BC cells (MDA-MB 231) with sanguinarine (0–1.5 μM) caused apoptosis by generating ROS, leading to the transfer of cytochrome-*c* into cytosol followed by caspase-3 and caspase-9 activation and inactivation of anti-apoptosis factor XIAP and cIAP-1.[114] Chew et al. noted that lutein regulated the apoptosis pathway by increasing tumor suppressors (and apoptosis genes) such as p53 and Bax and decreasing anti-apoptosis genes such as *Bcl-2* expression in female BALB/c mice.[115] Zu et al. reported that emodin (40 μM) inhibits growth by inducing apoptosis through up-regulating cleaved Bax/Bcl2, p53, caspase-3, PARP cleavage in human BC (ZR-75-30 and Bcap-37) cells.[117] Another phytochemical, withaferin A (2.5–5 μM) induced apoptosis through ROS production by modulating the expression of Bax/Bak in MDA-MB 231 and MCF-7 BC cells.[118] Furthermore, Mi et al. reported that celastrol (1–10 μM) induced apoptosis by modulating the expression of TNF-α, caspase-8, caspase-3, and PARP cleavage along with inhibition of anti-apoptotic proteins such as cellular cIAP1 and cIAP2, FLIP, and Bcl-2 expression in MCF-7 and MDA-MB 231 cells.[119] Also, lycopene and EGCG induced apoptosis by up-regulating the expression of p53 and Bax/Bcl-2 ratio with down-regulating telomerase and P13K/AKT in MCF-7 and T47D cancer cells.[83,113] Furthermore, curcumin and resveratrol can induce apoptosis through the regulation of Bax/Bcl2, whereas thymoquinone, apigenin, pterostilbene, and sulforaphane are associated with apoptosis by regulating caspases cascade and signal transduction mechanism in multiple human BC cells.[144,164,178–181] Therefore, phytochemicals inhibit BC progression by apoptosis induction, which mediates either intrinsic or extrinsic, and sometimes both pathways.

3.3 | Inducing cell cycle arrest

The cell cycle is a principal physiological mechanism regulating tissue homeostasis and development in multicellular organisms. Therefore, alterations in the cell cycle cause cancer. Thus, novel strategies have been developed targeting altered cell cycles or components. Checkpoints in the cell cycle arrest cell cycle progression in the case of DNA damage, allowing time for DNA repair.[182,183] In numerous breast carcinomas, phytochemicals inhibit the passage of the cell cycle by modulating checkpoints components such as lowering cyclins (D1 and E) levels and cyclin-dependent CDKs etc., and by up-regulating the expression of proteins such as CDK inhibitors (p21 and p27). For example, quercetin halts the cell cycle at the G2/M phase by raising Cdk-inhibitor, especially p21CIP1/WAF1 and its associated protein Cdc2-cyclin B1 complex in MCF-7 cancer cells.[120] Treatment of coumestrol (50 μM) caused cell cycle arrest at the G1/S phase, followed by upregulations of regulatory protein CDKI and p21 and p53 in MCF-7 cells.[122] Also, taiwanin A treatment was associated with the up-regulation of p21, p27, p53, and p-p53 in MCF-7 cells in a dose-dependent manner.[121] Kim et al. reported that ginsenosides (100 μM) had arrested the cell cycle at G0/G1 phase via inhibiting Cyclin D1, Cyclin E2, and their associated enzyme CDK4, along with up-regulating p15INK4B, p21WAF1/CIP1 and p55 level in MCF-7 cells.[123] Another phytochemical, kaempferol, reduced MCF-7 cell growth by down-regulating cathepsin D, cyclin E, and cyclin D1 expressions and up-regulating Bax and p21.[124] Furthermore, thymoquinone (100–200 μM) significantly inhibited the expression of cyclin D1 and E, resulting in promoting the survival of multiple BC (MCF-7, T47D, and MDA-MB-231) cells.[125] Moreover, naringenin is an essential plant chemical that can regulate cell cycle checkpoints by suppressing CDK4, CDK6, and CDK7 with up-regulating p18, p19, and p21 in BC (HTB26 and HTB132) cells.[126] Altogether, phytochemicals halt the

progression of the cell cycle of BC cells by either inhibiting the expression and activity of cyclins (B1, D1, and E) and CDKs (4, 6, 7) or increasing the expression of CDKs inhibitors (p18, p21, p27, and p53).

3.4 | Inhibition of angiogenesis and metastasis

Angiogenesis is closely associated with metastasis. These processes are acquired at a critical density of arteries and occur as the tumors expand, spread, or become less differentiated.[184] Growth factors (VEGF, PDGF, FGF, and EGF), matrix metalloproteinase (MMP-2, MMP-9), intracellular adhesion molecules-1(ICAM-1), etc., are associated with these processes. Thus, they can be a potential target for cancer therapeutics development. It was reported that phytochemicals have significant anti-metastatic and anti-angiogenesis effects by inhibiting MMP-9 and MMP-2 and suppressing VEGFR-2 expression, thereby inhibiting the growth and invasiveness and adhesion of cancer cells.[185,186] Flavopiridol, a phytochemical (70nM), inhibited secretion of metalloproteinase, especially MMPs (MMP 2 and 9) and c-erbB-2 in MDA-MB-231 cells, which is associated with the reduction of cell invasion inhibition.[128] Nobel phytochemicals such as 2-hydroxy chalcone and xanthohumol exerted potent inhibitory effects on the invasive phenotype of MDA-MB-231 cells by inhibiting MMP-9 expression with Bcl-2 down-regulation and shikonin showed a similar result in MCF-7 cells.[127,132] The reduced level of MMP-9 and urokinase-type plasminogen activator was observed in MDA-MB-231, TPA-induced MCF-7 cells followed by a lower dose of arctigenin (10–200 μM) treatment in turn inhibited cells' movement.[131] Similarly, plant-derived silymarin decreased VEGF secretion, blocked PMA-induced inhibition of MMP-9, and blocked AP-1 activation, thus, modulating MAP signaling in MCF-7 and MDA-MB- 468 cells in a dose-dependent manner.[129] In addition, it could downregulate VEGF activity in MDA-MB-231 cells, inhibiting angiogenesis.[139] Mali et al. reported that ENL (2–25 μM) could downregulate MMP-2 and MMP-9 activity while up-regulating tissue inhibitors, that is, metalloproteinases 1 and 2 (TIMP-1 and TIMP-2), in MDA-MB-231 cells.[109] Another phytochemical Rg3 (5 mg/kg/2 day) suppressed cell migration and angiogenesis while promoting autophagy through decreasing angiogenesis factors (VEGFA, VEGFB, VEGFC), metastatic factors (MMP-2, MMP-9), signaling molecules (P13K, Akt, mTOR, JNK, p62, and Beclin-1) in MCF-7 cells.[134] Treatment with quercetin (34 mg/kg) inhibits angiogenesis by reducing the activity of VEGF, VEGFR2, and NFATc3 in human BC xenografted nude mice. Also, it defeats calcineurin activity and its mediated pathway.[133] Kil et al. reported that silibinin (50 μg/mL) could inhibit metastasis and migration by inhibiting EGFR phosphorylation and suppressing VEGF, MMP-9, and COX-2 in MDA-MB-468 cells, resulting in decreased tumor volume in the triple-negative BC xenograft model.[136] Isoliquiritigenin (25–50 μM) treatment inhibited signaling molecules such as NF-κB, P13K/Akt, and p38, decreasing MMP-2, MMP-9, VEGF, and HIF-1α expressions leading to reduce the motility of MDA-MB-231 cancer cells.[137] Another phytochemical, thymoquinone, could modulate the expression of epithelial markers such as E-cadherin, cytokeratin 19, and mesenchymal markers such as MMP-2, MMP-9, integrin-aV, TGF-b in MCF-7 and MDA-MB-231 cells.[138] Thus, the suppression of angiogenesis and metastasis in BC cells can be achieved by treating with plant products or plant-derived bioactive compounds, which could suppress matrix metalloproteinases, growth factor expressions, and signaling mechanisms (Figure 3).

3.5 | Inhibition of hypoxia-inducible factor

Tumor hypoxia refers to cells being deprived of normal oxygen due to low oxygen levels in the tumor microenvironment. Hypoxia induces multiple signaling cascades such as MAPK, phosphatidyl-inositol 3-kinase (PI3K), HIF, and NF-κB pathways in cancer cells, leading to feedback loops of both positive and negative, and enhancing or diminishing hypoxic effects.[187] It was also found that hypoxia regulates several cellular phenomena, such as the expression of drug efflux proteins, apoptosis, DNA damage, the efficiency of chemotherapy, angiogenesis, and metastasis.[187] Therefore, targeting hypoxia-inducible factor 1 (HIF-1), a crucial component of hypoxia, could be a potential strategy against hypoxia-induced cancer cell growth and progression. Several phytochemicals can directly inhibit HIF-1-related genes, including *GLUT-1*, *CDKN1A*, and *VEGF*. This inhibition ultimately results in a decrease in tumor angiogenesis, migration, and chemotaxis. According to Wang et al. isoliquiritigenin (25–50 μM) treatment suppressed P13K/Akt, NF-κB signaling pathways via modulating the expression of VEGF, HIF-1α, and MMP-2, MMP-9 expressions, leading to limit the migration of MDA-MB-231 cells.[137] Riby et al. demonstrated that 3,3-diindolylmethane (50 μM) exhibited anti-cancer activity by decreasing the expression of hypoxia-responsive factors such as furin, and glucose transporter-1, VEGF, enolase-1, and phosphofructokinase in hypoxic specific MDA-MB-231 cells.[141] In addition, lyciumbarbarum polysaccharides inhibit HIF-1α protein aggregation by altering mRNA levels and VEGF mRNA expression leading to inhibit the nuclear translocation of HIF-1α in MCF-7 cells.[142] Another study showed that EGCG (50 μg/mL) inhibits

breast tumor formation, proliferation, migration, and angiogenesis by inhibiting HIF-1α in MCF-7 and MDA-MB-231 cells.[140] Wang et al. noted that shikonin (10 μM) suppresses the expression of HIF-1α in MDA-MB-231 cells in hypoxic conditions.[188] Thus, phytochemicals inhibit cancer progression by regulating hypoxia-inducible factors by aggregation or degradation (Figure 3).

3.6 | Inhibition of oxidative stress and redox signaling

Reactive oxygen species (ROS) such as hydroxyl radical, superoxide anion radical, hydrogen peroxide, oxygen singlet, nitric oxide radical, and peroxynitrite extreme play essential roles in the initiation and development of tumors.[189] These species contribute to harmful genomic material, making them genetically unstable. Also, they act as intercessors in mitogenic and survival signaling using adhesion molecules and receptors of growth factors. Enzymes involved in an antioxidant system, such as catalase (CAT), superoxide dismutase (SOD), peroxiredoxins (PRXs), glutathione peroxidase (GPX) and glutathione reductase, are essential for maintaining cellular redox system.[190] However, it is not easy to mitigate the excessive production of ROS by cellular antioxidant enzymes.[191] It was noted that phytochemicals could modulate oxidative stress and redox signaling by regulating the expression of these enzymes. For example, Singh et al. reported protective roles of resveratrol via increasing Nrf-2 expression, which could up-regulate the expression of antioxidant genes such as SOD3, NQO1, and 8-oxoguanine DNA glycosylase 1 (OGG1).[192] In addition, biochanin A (500 μg/g) has shown anti-cancer activity in oxidative stress-mediated cancer by up-regulating CAT, DT-diaphorase, GST, GPx, and SOD, along with the reduction of lipid peroxidation and lactate dehydrogenase activities significantly.[193] Nadal-Serrano et al. reported the protective effects of Genistein on oxidative stress, redox signaling, and mitochondria, followed by up-regulation of ERβ in T47D BC cells.[194] Moreover, Fan et al. reported that 3,3′-diindolylmethane (1 μmol/L) protects BC cells against oxidative stress by stimulating the expression of nuclear factor erythroid 2 in BC cells.[195] Therefore, phytochemicals regulate oxidative-mediated cancer progression by controlling potent oxidative markers, including Nrf-2 expression and antioxidant gene expression in both in vitro and in vivo models.

3.7 | Inhibition of mammosphere formation

The formation of the mammosphere is an essential characteristic of cancer progression, mainly cancer stem cells (CSCs). Several studies reported that BC cells, including non-adherent, non-differentiating CSC, form the mammosphere.[196] CSCs are believed to be associated with cancer reappearance, metastasis, and resistance to anticancer drugs. Thus, targeting breast CSCs by inhibiting mammosphere formation can be an alternative approach for managing BC. Naturally occurring plant-based compounds can prevent cancer cells and CSCs by decreasing mammosphere formation.[197] For example, Wu et al. demonstrated that pterostilbene suppressed mammosphere formation BCSCs growth by reducing $CD44^+$ surface antigen expression and stimulating β-catenin phosphorylation.[143] The pterostilbene also modulates the hedgehog/Akt/GSK3b signaling pathway via the down-regulation of cyclin D1 with c-Myc expression.[143] Another phytochemical, sulforaphane (SFN), reduced the number and size of ALDH1-positive (BCSC) cells, resulting in the inhibition of mammospheres formation in both in vitro and in vivo models.[198] In addition, SFN-pretreated $ALDH^+$ cells showed enhanced sensitivity to taxane, thereby blocking mammospheres formation significantly.[144] Fu et al. noted that resveratrol (100 mg/kg/day) treatment against BCSCs induces autophagy by suppressing the Wnt/β-catenin signaling pathway in MCF-7 and SUM159 cells.[146] Colacino et al. found that curcumin downregulates the expression of CD49f, ALDH1A3, PROM1, and TP6 in MCF-7, MCF10A, SUM149-derived stem cells' growth and proliferation.[147] Benzyl isothiocyanate (3 μmol BITC/g) treatment suppressed the expression of both Ron and sfRon in cultured MCF-7 derived stem cells and tumor xenografts, indicating that benzyl isothiocyanate treatment caused inhibition bCSCs in vitro and in vivo.[145] Piperine (10 μM) significantly decreased mammosphere formations in stem cells derived from BC.[199] Therefore, phytochemicals showed anti-cancer activities by inhibiting mammosphere formation in multiple breast carcinomas by suppressing signaling pathways or their components (Figure 3).

3.8 | Inhibition of inflammation

Inflammation is a biological reaction to cellular injury produced due to infections, chronic irritation, and other inflammatory responses.[200] Information suggests that inflammatory cells, including neutrophils, macrophages, dendritic cells, eosinophils, and lymphocytes were associated with tumor formation, development, angiogenesis, and progression.[201,202] Interestingly, significant research demonstrated that natural compounds prevent inflammation by regulating antioxidant defence mechanisms via modulating Phase I, and Phase II enzymes or inflammatory cells or factors in cancer.[203] An in vitro study reported the therapeutic advantage of polyphenols on the

inflammatory phenotype of macrophages.[149] In this study, supplemented pomegranate juice polyphenols reduced M1-macrophages mediated pro-inflammatory stimulation in the J774.A1 macrophage-like cells in a dose-depended manner.[149] Curcumin also exhibited anti-cancer properties against inflammation-associated carcinogenesis by inhibiting TNF-α mediated NF-κB activation and inhibiting the proteasomal activity of IκB kinase in MCF-7 cells.[150] Synergistically, using Sprague Dawley rats, curcumin with resveratrol inhibits inflammation by lowering NF-κB and reducing inflammatory markers such as COX-2 and MMP-8 expression animal model.[151] In addition, Dharmappa et al. reported that genistein had anti-inflammatory properties in cancer by inhibiting sPLA activity in a concentration-dependent manner.[204] Furthermore, multiple dietary polyphenols combination from zyflamend, (e.g., resveratrol, curcumin, and EGCG), decreased the expression of pro-inflammatory markers such as COX-2, IL-1β, TNF-α, phospho-Akt, phosphor-p65, and NF-κB-binding activity in C57BL/6J female mouse model.[152] Therefore, natural phytochemicals are potent oncogenic inhibitors by regulating inflammation through regulating TNF-α mediated NF-κB, IκB kinase, COX-2 and MMP-8, IL-1β, TNF-α, phospho-Akt, phosphor-p65, and NF-κB-binding activity in numerous cancer models.

3.9 | Enzymatic inhibition

Interfering the enzymatic functionality associated with cancer pathogenesis potentially prevents BC development. Phytochemical treatment could inhibit Phase I enzymes, inducible nitric oxide synthase, cyclooxygenase-2, xanthine oxide, aromatase, and many more in cancer.[205] Supplementation of curcumin (20 μM) is associated with reversing hypermethylation of the Glutathione S-Transferase Pi 1 (GSTP1) gene, resulting in reactivation via modulation of epigenetics mechanism in MCF-7 cells.[153] It is also reported that curcumin (35 μM) inhibited MCF-7 cell proliferation by Nrf2 arbitrated Flap endonuclease-1 (Fen1) expression,[206] whereas resveratrol (25 mM) inactivates the aromatase enzyme by removing the CYP19 promoters I.3 and II transactivation.[154] Furthermore, resveratrol regulates other cancer-associated enzymes such as COX-2, NQO-2, and GSTP 1.[207] In addition, Barbara E reported that cabbage juice inhibits BC (MCF10 and MDA-MB-231) cells by inhibiting aromatase expression.[208] Similarly, rosmarinic acid (10 μM) acts as an essential COX-2 inhibitor through AP-1 activation in MCF-7 cells in a dose-dependent manner.[106] Furthermore, another natural product, isoliquiritigenin (10–40 μM), showed chemopreventive actions by targeting metabolic enzymes such as COXs, PLA2s, LOXs, and PGE2, cytochrome P450 4 (CYP 4A) activity in MDA-MB-231, BT-549 BC cells.[157] Quercetin and epigallocatechin could decrease glucose consumption and lactate production in MCF-7 and MDA-MB231 cells, inhibiting cancer-related metabolic pathways.[158] Thus, phytochemicals showed anti-cancer efficacy through regulation of enzymatic functions, that is, by regulating estrogen synthesizing enzymes such aromatase, estrogen metabolizing enzymes CYP 4A, CYP19 suppressing COX-2 expression, or regulating GSTP1 in BC cells. Therefore, natural phytochemicals are potent oncogenic inhibitors by regulating several enzymes, including hypermethylation of the GSTP1, Flap endonuclease-1, aromatase expression, CYP19 promoters I.3 and II transactivation, and numerous enzymes in different cell lines.

3.10 | Natural compounds targeting cell signaling pathways

mTOR, PI3K, protein kinase B (Akt), MAPK/ERK, Wnt, Notch, and hedgehog signaling pathways are associated with the regulation of cell proliferation, differentiation, survival, apoptosis, invasion, migration, angiogenesis, and metastatic spread of cancer cells.[209,210] Phytochemicals elicit anti-cancer actions by regulating these pathways or components.[159] For example, Seo et al. reported that genistein (100 μM) inhibited IκBα phosphorylation and maintained its association with p65–p50 heterodimer, which blocked their nuclear translocations, and p65 phosphorylation, which in turn prevented the transcription of NF-κB targeted genes.[159] Also, genistein inhibited MAPK signaling by suppressing MEK5, ERK5, and p-ERK5 levels in MDA-MB231 cells,[211] whereas apigenin inhibited ERK 1/2 and JNK 1/2 phosphorylation via inhibiting MAPK signaling in MCF-7 cells.[131] Calycosin and formononetin, two phytochemicals, regulated PI3K/Akt pathways through IGF-1R protein expression along with the inhibition of Akt phosphorylation in T47D and MCF-7 cells.[160,161] In addition, Fu et al. reported that resveratrol (100 mg/kg) down-regulates Wnt/β-catenin signaling, inducing autophagy in MCF-7 cells[146] and inhibiting cell proliferation of SKBR-3 BC cells through down-regulation of various signaling pathways such as p-Akt, PI3K, Akt, mTOR.[212] Apigenin inhibited MCF-7 cells by inducing apoptosis by inhibiting NF-κB, STAT3, and p53 signaling.[162] Silibinin is associated with the death of MDA-MB-231 cells by regulating Notch-1 signaling pathways.[163] Pterostilbene regulates ERK1/2 activation, decreased cyclin D1, p-AKT, mTOR, and increased p21, Bax protein, but not Bcl-xL.[164] Hatkevich showed that naringenin inhibits PI3K, thus disrupting proliferation signaling in MCF-7 cells through ERK1/2, AKT, and MAPK signaling pathways,[165] whereas α-Mangostin mediated its anti-tumor effect through

decreasing HER2, Akt, and P13K along with increasing p-p38 and p-JNK1/2 phosphorylation.[166] Therefore, phytochemicals inhibit NF-κB, PI3K/Akt, MAPK/ERK, p-mTOR, Wnt, Notch-1, and hedgehog signaling pathways by modulating their components or upkeep/downstream molecules in BCs (Figure 4).

3.11 | Natural compounds targeting epigenetic control

Accumulating information suggests that previous studies have shown that phytochemicals can modulate the epigenetics of cancer cells by regulating the methylation of DNA via DNA methyltransferase activity and histone modifications, resulting in inhibiting the oncogenic miRNA expression and increasing tumor-suppressing miRNA expression.[213–215] Studies have shown that genistein could inhibit primary breast carcinogenesis by increasing some tumor suppressor protein i,e and p16, p16 (INK4a), p21, p21 (WAF1) expression, along with decreasing expression oncogene, that is, BMI1, and c-MYC in estrogen negative MDA-MB-231 cell line.[167] Moreover, genistein attributed its anti-cancer activity in BC cells by demethylating and reactivating methylation-silenced tumor suppressor genes via direct contact with inhibition of both DNA methyltransferase 1 (DNMT1) catalytic domain activation and DNMT1 expression.[213] Furthermore, genistein decreased the oncogenic miR-155 expression with increasing expression of miR-155 targets such as Forkhead box O3 and casein kinase, p27, phosphatase, and tensin homolog (PTEN), which in turn that promote apoptosis and antiproliferation of MDA-MB-435 cells.[162,216] Lycopene up-regulated glutathione S-transferase pi gene (GSTP1) expression and demethylases the GSTP1 in MCF-7, MDA-MB-468 cells, whereas induced RARbeta2 and HIN-1 genes demethylation in BC (MCF10A) cells in a dose-dependent manner.[168] Similarly, SFN (5 μM) significantly inhibits HDAC through demethylation in MDA-MB-231 cells.[171] Liu et al. reported that curcumin activated the promoter of deleted in liver cancer 1 by suppressing methylation status, with the help of down-regulating the Sp1 transcription factor in MDA-MB-361 cells.[169] Also, EGCG (15 μM) treatment is associated with epigenetic changes that can increase DNMTs transcripts expressions such as DNMT1, DNMT3a, and DNMT3b in both MCF-7 and MDA-MB-361 cells.[170] Thus, phytochemicals have the potential to modulate the epigenetic make-up of BC cells via regulating DNA methylation and histone modification; therefore, they could control the expression of oncogenes and tumor suppression genes in BC cells. The summary of phytochemicals that act against epigenetics regulation is summarized in Figure 2.

3.12 | Natural compounds targeting the immune system

Phytochemicals include substances found in nature that can be bioactive and possess an immune system-stimulating effect.[217] For example, curcumin, a clinically naturally occurring compound, has immunomodulatory properties that suppress PHA-induced T cell proliferation, IL-2, NO, and NF-κB while increasing NK cell cytotoxicity in mouse macrophage cells RAW.264.7.[218] A study involving C57BL/6 mice found that apigenin may influence the alteration of dendritic cells and other immune cell functions.[219] Daidzein, has a modulatory function on nonspecific immunity in Swiss mice when given in high doses since it enhances the phagocytic response of peritoneal macrophages.[220] Additionally, in male Kunming mice exposed to 60Coγ radiation, EGCG significantly reduced immune system destruction by inducing macrophage phagocytosis, boosting the activity of the antioxidant enzymes, that is, SOD and GSH-Px (glutathione peroxidase), raising glutathione level, and preventing lipid peroxidation.[221] Conversly, genistein regulates immunological response in female Sprague Dawley, promoting IL-4 synthesis while inhibiting IFN-γ release and balancing Th1/Th2 cells.[222] Furthermore, kaempferol had immune-suppressive effects on cold-stressed, 6-7-week-old SPF mice, decreasing the levels of activated pro-inflammatory cytokines like IL-9 and IL-13, $CD8^+$ T cells and raising anti-inflammatory cytokines and $CD4^+$ T cells.[223] Therefore, selected phytochemicals have the potential to activate immune system including numerous immune cells including NK cell, $CD8^+$ T, $CD4^+$ T and cytokines like IL-9 and IL-13 to fight against BC cells. A summary of the anti-cancer mechanism of phytochemicals in BC treatment is presented in Table 3 and Figures 1–4.

4 | THE ABILITY OF PHYTOCHEMICALS TO ALLEVIATE THE RESISTANCE OF ANTI-CANCER DRUGS

Due to numerous significant challenges, such as multidrug resistance, treating cancer patients is becoming more difficult.[224] Drug efflux, drug inactivation, drug detoxification, drug target modification, involvement of CSCs, miRNA dysregulation, epigenetic alteration, and other numerous irregular DNA damage/repair mechanisms, tumor microenvironment, and ROS modulation are just a few potential defensive processes that could result in this resistance mechanism.[40,225,226] P glycoprotein (P-GP), MRP 1, MRP 1–9, BCRP, and changes in beta-tubulin are a few proteins that are connected to

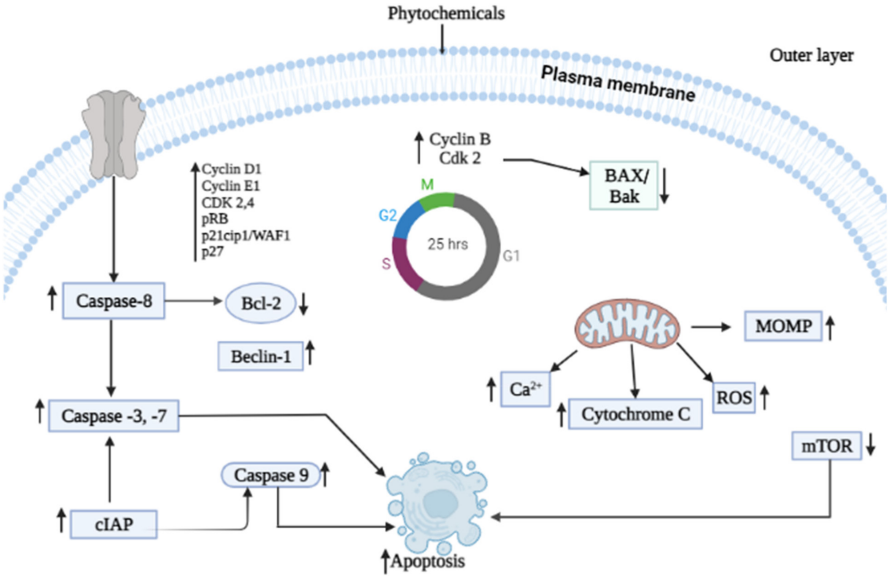
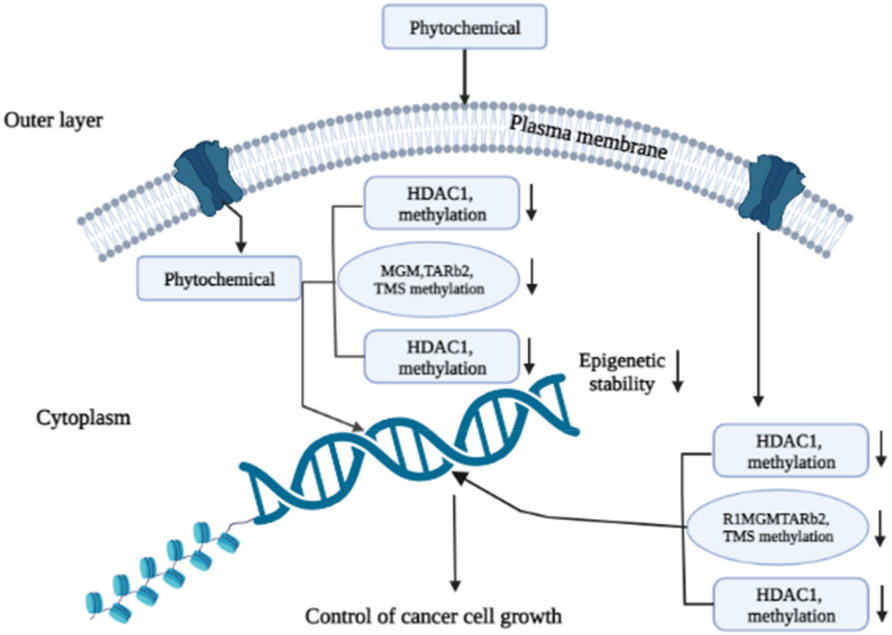


FIGURE 1 Breast cancer management by dietary phytochemicals through apoptosis and cell cycle: Phytochemicals activate caspase-8 through modulating TRAIL- and FAS-associated receptors. Activated caspase-8 mediated activation of some effector caspase-3 and caspase-7 attributed to the extrinsic pathway of apoptosis. Moreover, the anti-apoptotic protein BCL2 mediates activation of BAK, BAX. These powerful mechanisms increase cytosolic Ca^{2+}, cytochrome *c*, and reactive oxygen species (ROS). Cytochrome *c* sequentially activates caspase-9, which is simultaneously activated by effector caspase-3 and caspase-7 attribute to apoptosis. Activation of tumor suppressor protein (p21CIP1/W, p27, p53, pRB, and AF1) and suppression of cyclin (cyclin B, D1, E1) with associating enzymes (CDK 2, 4) by phytochemicals regulated cell cycle and cell proliferation.

FIGURE 2 Breast cancer management by dietary phytochemicals through enzymatic control of epigenetics factors: Breast cancer can regulate epigenetics factors. The key epigenetic regulatory protein R1MGMTARb2, TMS methylation, BMI1, c-MYC, HDAC1 methylation, histone modification can be regulated by dietary phytochemicals; leading to show anti-cancer effect.



drug resistance in cancer.[227] The multi-drug resistance protein P-glycoprotein (P-gp) is overexpressed in the membrane of cancer cells, where it commonly increases drug efflux and contributes to the emergence of treatment resistance in malignancies.[228] Hence, inhibiting MDR-efflux proteins may help improve cancer therapy's effectiveness. For example, Biochanin A exhibits this type of action. Soo et al. demonstrated that Biochanin A treatment increased [3H]-DNM accumulation by reducing DNM efflux and caused MDR to be reversed by suppressing P-gp activity in MCF-7/ADR BC cells.[225] The effects of phloretin on P-gp activity were examined (HTB26) by measuring the uptake of rhodamine 123 in a variety of cancer cells, including human MDR1 gene-transfected mouse lymphoma cells (L1210) and human BC cells MDA-MB-231 expressing the MRP1 pump.[226]

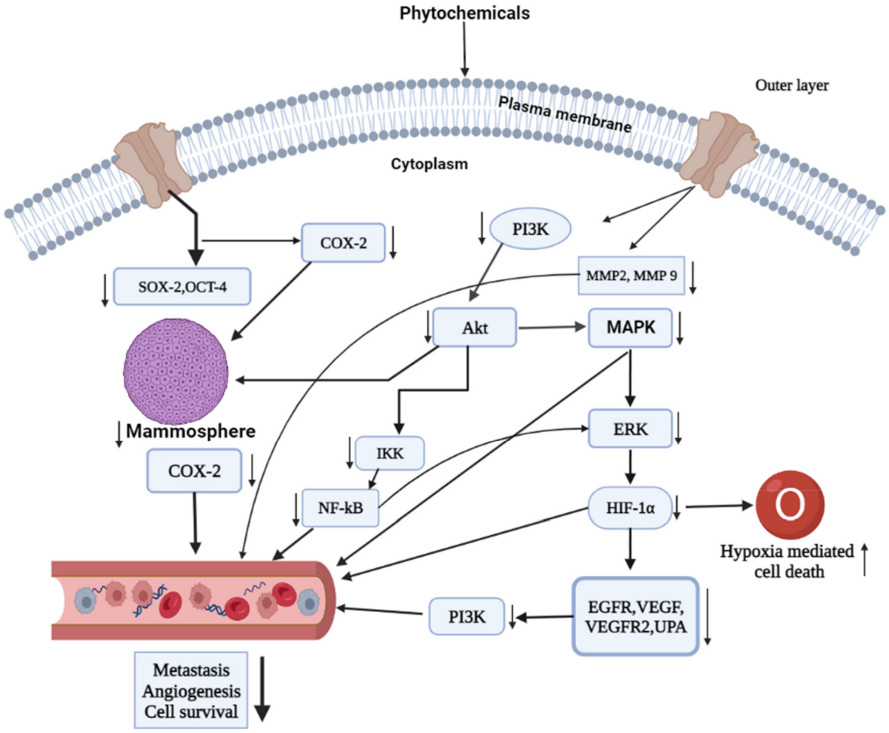


FIGURE 3 Control of breast cancer by dietary phytochemicals targeting multiple patways: Targeting the multiple signal transduction, phytochemicals can suppress some cell signaling pathways, that is, PI3k/Akt/mTOR, MAPK/ERK, NF-κB, HIF-1α, leading to a decrease cancer cell metastasis, angiogenesis, and survival. Followed by the signal transductions, phytochemicals can mitigate important metastatic and angiogenic factors including EGFR, VEGF, VEGFR2, NF-κB, MMP2, MMP9, COX-2, and ERK in breast cancer cell line.

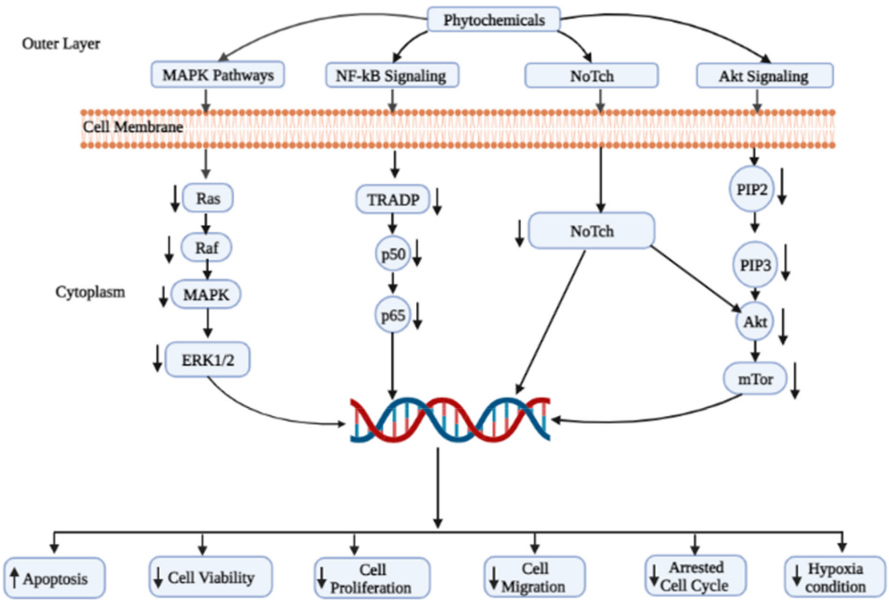


FIGURE 4 Phytochemicals targeted signaling pathways associated with breast cancer treatment: The schematic diagram represents the overview of molecular mechanisms of phytochemicals mediated inhibition of breast cancer cell growth through the Notch, MAPK, NF-κB, and Akt pathways.

Genistein indirectly raises intracellular drug concentration, including doxorubicin concentration, but does not directly alter P-gp activity in a BC cell lines. In a study, Castro and Altenberg reported that genistein reduced the photo-affinity labeling of P-gp with [3H] azidopine, a P-gp substrate, indicating that genistein might suppress rhodamine123 efflux in human MCF-7 cells by directly interacting with P-gp to impede P-gp-mediated drug efflux.[229] The other component that stimulates the formation of BC is human epidermal growth factor receptor 2 (HER2), a tyrosine kinase (TK) receptor that belongs to the EGFR family. Curcumin was reported to have the capacity to alter the EGFR signaling pathway, which is linked to the growth, differentiation, adhesion, and migration of cancer cells.[230,231] According to Chandrika et al. hesperetin at 10-500 μM promotes apoptosis in MDA-MB-231 and SKBR3 BC cells and inhibits their ability to proliferate. Dietary flavonoid hesperetin reduces the development of MDA-MB-231 BC cells by inhibiting the activity of HER2 Tyrosine Kinase (HER2-TK), causing MMP loss, chromatin condensation, and activating caspase-8 and-3, which causes cell cycle arrest at the G2 phase.[232] Sesamin inhibited cell migration at the same dosage and cells by delaying the G1 phase and down-regulating PDL-1, MMP-9, and MMP-2. Sesamin's ability to inhibit cell proliferation was demonstrated by

Yokota et al. in BC cells. They discovered that sesamin inhibited growth at doses of 1–100 M by increasing retinoblastoma protein dephosphorylation and decreasing cyclin D1 gene expression, which mediates cyclin D1 degradation.[102] The co-treatment of resistant (MCF-7R) cells with Apigenin, which reduced MDR1 expression at the mRNA and protein levels in both resistant and non-resistant cells, significantly reduced DOX resistance in the MCF-7 cell line. In both the MCF-7 and MCF-7R cell lines, apigenin strongly inhibited the phosphorylation and activation of the JAK2 and STAT3 proteins.[233] By lowering Bcl-2, Nimbolide induces the expression of the proteins Bax and caspases with a modulation of the expression of HDAC-2 and H3K27Ac, and stopping the progression of the cell cycle, as well as reduced the growth of MDA-MB-231 and MCF-7 cells. Increasing Beclin 1 and LC3B and decreasing p62 and mTOR protein expression in BC cells. Nimbolide also activated autophagy signaling.[112] Combining Sanguinarine with TRAIL therapy may break BC cells' resistance caused by overexpression of Akt or Bcl-2. In human BC MDA-231 cells, Sanguinarine triggered apoptosis, which resulted in decreased pro-caspase-3, Bcl-2, cIAP2, XIAP, and c-FLIPs protein levels and increased ROS production.[234] When Emodin was applied to the BC cells Bcap-37 and ZR-75-30, it was shown to suppress proliferation, induce apoptosis, and decrease Bcl-2 while increasing levels of cleaved caspase-3, PARP, p53, and Bax.[117] In MCF-7 and MDA-MB-231 cells, Isoliquiritigenin lowered cell survival and clonogenic potential, triggered apoptosis, suppressed mRNA expression of many AA-metabolizing enzymes, including PLA2, COX-2, and CYP-4A, and reduced production of PGE2 and 20-HETE. Moreover, it reduced the expression of phospho-PI3K, phospho-PDK, phospho-Akt, phospho-Bad, and Bcl-xL, triggering caspase cascades that ultimately led to the cleavage of PARP.[235] The expression pattern of β-catenin in BC tissue are high than the normal tissue. EGCG thus decreased the viability of MDA-MB-231 cells by lowering the levels of β-catenin, cyclin D1, and p-AKT. Moreover, pretreatment of MDA-MB-231 cells with PI3 kinase inhibitors, such wortmannin or LY294002, enhanced the suppressive effect of EGCG, given after 24 h, on the production of β-catenin.[236] By transfecting the plasmid and inducing cytotoxicity and autophagy in BCSCs derived from MCF-7 and SUM159, Resveratrol inhibits the Wnt/β-catenin signaling pathway and excessive production of the β-catenin protein.[146] The impact of Wogonin supplementation on cell survival and proliferation has been shown to be effective against a variety of BC cell lines, including TNBC and its related cell lines, BT-549 and MDA-MB-231. Additionally, wogonin inhibits the cell cycle of cancer cell lines by inhibiting the expression of cyclin D1, cyclin B1, and CDK1, inducing apoptosis, improving the Bax/Bcl-2 ratio, and increasing caspase-3 cleavage.[237] In ER-positive BC cells like MCF-7 and T-47D cells, Calycosin tends to suppress proliferation and trigger apoptosis. This effect is caused by ER-induced inhibition of IGF-1R as well as the targeted control of the MAPK and (PI3K)/Akt pathways.[161]

5 | LIMITATIONS AND PROSPECTS OF PHYTOCHEMICALS IN BREAST CANCER THERAPY DEVELOPMENT

Several factors interfere with the conventional therapeutic options used to treat BC. Phytochemicals offer a broad spectrum of pharmacological effects, which might benefit the clinical management of patients with BC. Phytochemicals are an effective therapeutic agent due to their several biological properties. Though phytochemicals have enormous benefits, there are significant constraints in achieving the actual effectiveness of phytochemicals-based therapeutic for the management of patients with BC due to the lack of systematic and proper information in this field. In addition, to develop a clinically useful drug, a series of preclinical and clinical it must pass in vitro, in vivo, and clinical trials (Phase I–IV) studies must be accomplished with clinical benefit. Furthermore, long-term studies are still required to determine therapeutic interactions, in vivo pharmacokinetic attributes, effective doses, suitable administration routes, and defined mass and/or nanoformulation of these phytochemicals. To estimate bioactivities, the structure–activity relationship must be established. Gathering additional information regarding phytochemicals' synergistic actions when combined with other phytochemicals, it is possible to boost their activity and prevent the anti-cancer profile by modifying conventional medications. Moreover, these phytochemicals could be used in computational chemistry research, such as docking, neural networking, and pharmacophore-based virtual screening programs for the drug development sector. Therefore, these phytochemicals could potentially become a potent chemotherapeutic anti-cancerous substance in managing BCs, at least at the cellular level and could be formulated for clinical applications if all of the strategies are accomplished.

6 | CONCLUSION

Although the complete molecular mechanisms for BC pathogenesis are yet to be established, whereas the mortality rates associated with this cancer are still rising

worldwide. Thus, developing an effective therapeutic, especially from natural resources, that is, phytochemical-based therapeutic, could provide significant clinical benefit in the management of patients with BC. The details mechanism of anti-cancer activity from in vitro, preclinical and clinical studies suggested that phytochemicals mediate their anti-cancer efficacy through targeting apoptosis proteins, including anti-apoptotic proteins (Bcl-2) and apoptotic proteins (Bax, Bak, Bad, and Caspase), arresting cell cycle and proliferation. They modulate the expression of growth-related genes, for instance, inhibiting expression and activity of cyclins (B1, D1, E) and CDKs (4, 6, 7) or increasing the expression of CDKs inhibitors (p18, p21, p27, and p53). Inhibits metastasis and angiogenesis by controlling the expression of MMP-2,8 and 9, Wnt/-catenin, PARP, oxidative markers, including Nrf-2, antioxidant-related gene, inhibiting mammosphere formation, regulating inflammation via modulating TNF-α, NF-κB, IκB kinase, COX-2, IL-1β, TNF-α, phospho-Akt, phospho-p65. Also, regulation enzymatic functions (i.e., aromatase, estrogen metabolizing enzymes CYP 4A, CYP19 suppressing COX-2 expression, or regulating GSTP1), targeting cell signaling (NF-κB, PI3K/Akt, MAPK/ERK, p-mTOR, Wnt, Notch-1, hedgehog), epigenetics control (regulating DNA methylation and histone modification), activate immune system (NK cell, $CD8^+$ T, $CD4^+$ T, cytokines like IL-9 and IL-13) in BC cell lines.

To conclude, phytochemicals may be used as an alternative and complementary therapeutic option in BC treatments due to their therapeutic benefits. However, further studies are needed to conduct before taking phytochemicals as a food supplement to manage and prevent BC until clinically proven standard drugs are not available in pharma-markets.

AUTHOR CONTRIBUTIONS

Md Sohel: Conceptualization (supporting); data curation (lead); resources (lead); validation (lead); visualization (supporting); writing—original draft (lead); writing—review and editing (supporting). **Suraiya Aktar:** Resources (supporting); writing—original draft (supporting). **Partha Biswas:** Resources (supporting); visualization (supporting). **Md. Al Amin:** Resources (supporting); writing—original draft (supporting). **Md. Arju Hossain:** Data curation (supporting); resources (supporting). **Nasim Ahmed:** Resources (supporting); writing—original draft (supporting). **Md. Imrul Hasan Mim:** Visualization (supporting). **Farhadul Islam:** Supervision (supporting); validation (supporting); writing—review and editing (supporting). **Md. Abdullah Al Mamun:** Conceptualization (lead); resources (supporting); supervision (lead); validation (supporting); visualization (lead); writing—original draft (supporting); writing—review and editing (lead).

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